THE KNOWLEDGE REPRESENTATION AND ALGORITHM FOR PERSONALIZED INFECTIOUS DISEASE RISK PREDICTION

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DECLARATION

I, the undersigned, declare that this work has not been previously submitted as an exercise for a degree at this or any other University, and that, unless otherwise stated, it is entirely my own work.

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“To expect the unexpected shows a thoroughly modern intellect.”

– Oscar Wilde

ABSTRACT

Infectious diseases are a major cause of human morbidity. However, in the EU in 2014 more than 40 thousand deaths caused by infectious diseases were considered preventable. Information about infection risk based on personal and environmental attributes, as well as up-to-date infectious disease risk knowledge is expected to make lay people aware of their infection risks. With the emergence of APIs and GPS technology, surrounding location features and weather information can be inferred from a person's position. This offers an opportunity to create a system for personalized infectious disease risk prediction.

This thesis presents research towards a system that can predict personalized infectious disease risk (IDR) based on a person's attributes and geo-position by utilizing infectious disease risk knowledge (entitled **PROSPECT-IDR**: Personalised Prediction of Infectious Disease Risk). A knowledge representation was designed to facilitate epidemiologists to encode infectious disease risk knowledge in a form familiar to them. The *generic IDR ontology* represents personal and environmental risk factors for all human infectious diseases (n=234). Quantifications for the risk factors (e.g. odds ratios) are encoded using *five IDR rule types*. This IDR knowledge representation (ontology and rule types) allows encoding of knowledge about risk of infectious diseases prevalent in a region.

The IDR ontology can never be complete, as new risk factors for existing diseases, and new diseases, are constantly discovered. The initial generic ontology contains all risk factors found in the Atlas of Human Infectious Diseases, and in factsheets from the CDC and WHO. Each instantiation of knowledge for a specific disease in a region comprises of a subset of risk factors from the generic ontology plus any new risk factors not found there, along with a set of risk quantification rules (instantiations of the five rule types). An algorithm (entitled **BN-Builder**) converts the knowledge-base into a fully functioning and *consistent* risk prediction model, a Bayesian Network, which is the core of the PROSPECT-IDR prediction system.

The *usefulness* and *completeness* of the IDR knowledge representation (initial generic ontology and five rule types) were evaluated using 22 published case-control studies that encode infectious disease risk knowledge. Each case-control study was encoded as one evaluation knowledge-base. With regard to completeness, more than 3/4 of the ontology

objects needed to encode the knowledge in the evaluation case-control studies were found in the initial generic ontology. With regard to usefulness, more than 3/5 were used to encode evaluation case-control studies. With regard to completeness and usefulness of the five rule types, all infectious disease risk knowledge in the 22 evaluation case-control studies can be encoded with just those five rule types, and all five rule types were used.

To evaluate BN-Builder algorithm, the *consistency* between the generated BN and the knowledge-base was measured. Chi-square tests for differences were carried out for two evaluation knowledge-bases that covered all functions of the algorithm and all data ranges allowed by the rule types. There was no significant difference between the resulting infectious disease risk prediction and the encoded knowledge ($p > .05$).

Evaluation results suggest that the IDR knowledge representation is useful. Further, statistical findings indicate that the BN-Builder algorithm generates infectious disease risk predictions that are consistent with the encoded risk knowledge. The PROSPECT-IDR system that this IDR-KB and BN-Builder algorithm is designed for is expected to give information about personalized infectious disease risk prediction to lay people. So, the relevant preventive actions can be tailored based on this personalized information, and thus, hopefully will reduce the incidence number of infectious diseases in the world.

RESEARCH OUTPUTS

Published

R. A. Vinarti and L. Hederman, “Personalization of Infectious Disease Risk Prediction: Towards Automatic Generation of a Bayesian Network,” in ***Proceedings – IEEE Symposium on Computer-Based Medical Systems***, 2017, vol. 2017 - June (see Appendix 3 for full paper).

R. Vinarti and L. Hederman, A knowledge-base for a personalized infectious disease risk prediction system, ***Book Section – Studies in Health Technology and Informatics***. vol. 247. 2018 (see Appendix 4 for full paper).

R. A. Vinarti and L. Hederman, “Introduction of a Bayesian Network Builder Algorithm - Personalized Infectious Disease Risk Prediction,” ***Proceedings – 11th International Joint Conference on Biomedical Engineering Systems and Technologies***, vol. 5, no. Biostec, pp. 115–126, 2018 (see Appendix 5 for full paper).

The form of Knowledge Representation is available in R. A. Vinarti, “IDR Ontologies”, https://osf.io/p6qv8/, Open Science Framework, 2018.

The BN-Builder algorithm is available in R. Vinarti, "Thesis Code", https://github.com/retnor/ThesisCode

Submitted

R. A. Vinarti and L. Hederman, “A Personalized Infectious Disease Risk Prediction System”, ***International Journal of Expert Systems with Applications*** (see Appendix 6 for full paper).

R. A. Vinarti and L. Hederman, “Infectious Disease Risk knowledge representation for use in a personalized IDR prediction system”, ***BMC - Journal of Biomedical Semantics*** (see Appendix 7 for full paper).

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ABBREVIATIONS

AHID	Atlas of Human Infectious Diseases
AIDS	Acquired Immunodeficiency Syndrome
ANN	Artificial Neural Networks
API	Application Programming Interface
ASP	Answer Set Programming
BFO	Basic Formal Ontology
BKB	Bayesian Knowledge-base
BN	Bayesian Network
CARRE	Cardiorenal Risk Factor Ontology
CDC	Centre for Disease Control and Prevention
CPT	Conditional Probability Tables
DALY	Disability-adjusted life year
FCM	Fuzzy Cognitive Maps
GPS	Global Positioning System
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
IDO	Infectious Disease Ontology
IDR	Infectious Disease Risk
KB	Knowledge-base
LR	Logistic Regression
OBO	Open Biomedical Ontologies
OntoQA	Ontological Quality Assessment
OR	Odds Ratios
OWL	Web Ontology Language (WOL), an honor for William A. Martin's knowledge representation project named One World Language (OWL)
PKB	Probabilistic Knowledge-base
PRM	Probabilistic Relational Model
PROSPECT-IDR	Personalized Prediction of Infectious Disease Risk
PR-OWL	Probabilistic – OWL
RDF	Resource Description Framework
RR	Relative Risk
SARS	Severe Acute Respiratory Syndrome
SEIR	Susceptible – Exposed – Infected – Recovered
SN	Semantic Networks
SIRS	Susceptible – Infected – Recovered – Susceptible
SPARQL	SPARQL Protocol and RDF Query Language
STI	Sexual Transmitted Infections
SWRL	Semantic-web Rule Language
TB	Tuberculosis
UNSD	United Nations Statistics Division
URL	Uniform Resource Locator
WHO	World Health Organization
XML	Extensible Markup Language
XPath	XML Path Language

1. INTRODUCTION

1.1 Background

Infectious disease is a major cause of human morbidity. The measure of human morbidity is disability-adjusted life year (DALY). DALY is a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death [1]. Global leading causes of DALYs for the year 2015 are shown in **Table 1.1**. The items in bold letters are top five infectious diseases listed in top 20 leading causes: lower respiratory infections (e.g. pneumonia), diarrheal diseases (e.g. cholera), HIV/AIDS, tuberculosis, malaria, from which it is clear that infectious disease is a significant cause of morbidity even though it is not the first rank cause.

Table 1.1: Top 20 leading causes of DALYs globally in 2015 [1]

Rank	Cause	% DALYs
0	All Causes	100.0
1	Ischaemic heart disease	7.2
2	**Lower respiratory infections** (e.g. pneumonia)	5.3
3	Stroke	5.2
4	Preterm birth complications	3.8
5	**Diarrhoeal diseases** (e.g. cholera)	3.2
6	Road injury	2.8
7	Chronic obstructive pulmonary disease	2.7
8	Diabetes mellitus	2.6
9	Birth asphyxia and birth trauma	2.5
10	Congenital anomalies	2.4
11	**HIV/AIDS**	2.4
12	**Tuberculosis**	2.1
13	Depressive disorders	2.0
14	Iron-deficiency anaemia	2.0
15	Back and neck pain	1.9
16	Cirrhosis of the liver	1.6
17	Trachea, bronchus, lung cancers	1.5
18	**Malaria**	1.4
19	Kidney diseases	1.4
20	Self-harm	1.4

Looking in more detail at causes of infectious disease morbidity, the number of new cases of infectious disease morbidity (i.e. incidence) in 2014 per WHO region is given in **Table 1.2**. From this table, two things can be deduced. First, based on the number of WHO incidence report, the top three infectious diseases are diarrheal disease (e.g. cholera),

lower respiratory infections (e.g. pneumonia), and malaria. Second, based on the incidence distributions across WHO regions, infectious diseases are spread worldwide: diarrheal disease, and lower respiratory infections. Also, there are infections that are predominant in specific regions (e.g. malaria, dengue fever).

Table 1.2: Incidence report of infectious diseases in 2014 per WHO region (in millions) [2]

	World	Africa	The Americas	Eastern Mediter-ranean	Europe	South-East Asia	Western Pacific
Tuberculosis[a]	7.8	1.4	0.4	0.6	0.6	2.8	2.1
HIV infection[a]	2.8	1.9	0.2	0.1	0.2	0.2	0.1
Diarrhoeal disease[b]	4 620.4	912.9	543.1	424.9	207.1	1 276.5	1 255.9
Pertussis[b]	18.4	5.2	1.2	1.6	0.7	7.5	2.1
Measles[a]	27.1	5.3	0.0[e]	1.0	0.2	17.4	3.3
Tetanus[a]	0.3	0.1	0.0	0.1	0.0	0.1	0.0
Meningitis[b]	0.7	0.3	0.1	0.1	0.0	0.2	0.1
Malaria[b]	241.3	203.9	2.9	8.6	0.0	23.3	2.7
Dengue[b]	9.0	0.1	1.4	0.5	0.0	4.6	2.3
Lower respiratory infections[b]	429.2	131.3	45.4	52.7	19.0	134.6	46.2

Though infectious diseases are a major cause of human morbidity, they are largely preventable. In 2013, 47,480 deaths in European countries were considered preventable through better public health interventions (see **Table 1.3**).

Table 1.3: The number of preventable deaths in EU countries in 2013 (infectious disease mortality only)

Infectious Diseases	Number of preventable deaths
Selected invasive bacterial and protozoal infections	12,593
Tuberculosis	2,725
Hepatitis C	3,057
HIV	3,825
Influenza (including swine flu)	1,190
Pneumonia	24,090

Personalized information to lay people about their infection risk based on the up-to-date knowledge should increase their awareness of their infection risks. Thereafter, relevant, personalized and actionable preventive recommendations could be provided from the predicted risks. The envisaged situation from people knowing their risks and taking the preventive recommendations is the reduction of incidents of infection disease mortality.

Important elements of the process of generating personalized information related to the personal and location facts are (1) submission of the personal attributes (including the

geo-location), (2) mechanism to yield infectious disease risk prediction based on the submitted attributes, (3) the prediction should be based on recent knowledge, (4) the personalized recommendations that depends on the predicted infectious disease risk.

Quantitative prediction techniques are widely available to achieve the second element, including (infectious) disease risk modelling [3]–[5], (infectious) disease risk factor analysis [6]–[8], and (infectious) disease outbreak prediction based on geo-location [9]. However, attention needs to be paid to developing a holistic framework that captures the role of the disease risk factors, from *demography, behavioral risk factors, land use* and *atmospheric factors*. At the same time, there is still considerable room for *communicating with domain experts* and *users* with the aim to *improve the prediction modelling* [10].

By involving *communication with domain experts,* up-to-date knowledge can be acquired and documented (this is relevant to the third element). As research in infectious diseases develops, a repository of the acquired knowledge needs to be updated, so the knowledge is relevant to the current predicted infectious disease risk [11]. Thus, a knowledge repository (i.e. knowledge-base) that is able to store infectious disease knowledge that is continuously updated by experts is an essential component.

From the general epidemiology theory for human infectious diseases [12], the risk of human infection is affected by the pathogens that emerge in an environment where the person lives, and the immunity level when the person is exposed to the pathogen. Some pathogens are weather-dependent or found in a specific location feature (e.g. vegetation) [13]. Through *communication with users,* detailed personal attributes (e.g. gender, habit) can be obtained to personalize the infection risk information (this can be used to answer the first element). Also, users' geolocation can be gathered to retrieve the weather and the surrounding location feature to infer the infections on that day at that location [9] [14].

From the envisaged framework, an example query asking for the personalized information from an individual is *"what is my risk of contracting tuberculosis here now?"* and (for future research) *"what precautions should I take to reduce the predicted tuberculosis risk?"*.

To address the personalization in the query (*my*, *here*, *now*), APIs that provide that kind of data can be used. For example, *location-related APIs* (e.g. Google Places, Google Elevation) supply terrain features and altitudes of a person which can be used to expand

on the concept of *here* [9], [15]. *Weather-related APIs* (e.g. OpenWeather) provide atmospheric conditions of a city in a country at a given date and time, this can be used to expand on *now* in the query above [16]–[18]. WHO reports can be used to give the latest tuberculosis incidence in *here* [19]. The basic personal attributes are required to be submitted by the users to explain *my*.

To sum up, the background of this thesis is in public health and epidemiology, and, to be more specific, is epidemiology of human infectious diseases. Meanwhile, in the context of computer systems, the thesis background is in knowledge representation, (infectious) disease risk prediction systems, and personalization systems.

1.2 Motivation

Started by a concern about infectious disease burden in the world, informing lay people about their personal infection risk is achievable through designing a framework (e.g. system, service) that allows communication with both experts and the users (whose risk are being predicted) and capable of predicting the infectious disease risk based on the weather, location, personal attributes, and recent knowledge.

In the public health area, there is a type of study (i.e. case-control study) that provides knowledge about risk of an infectious disease along with a measure of the extent to which a person with observed attributes is at risk relative to a baseline case (e.g. odds ratio) [20]. The output of case-control studies is the risk factors, along with their odds ratios, for the observed population. The output of such studies can be used to inform lay people about their infectious disease risk (see **Figure 1.1**).

To transform the knowledge given in **Figure 1.1** into information about personal risk of infectious disease based on the recent knowledge, a computation that incorporates the risk factors with their odds ratios and yields a risk prediction is needed. For example, if the client is a 32-year old lady living in Africa, then the personalized tuberculosis risk based in **Figure 1.1** should be tailored based on the risk ratios of *25-34 years* and *female* only.

	All cases versus healthy population			HIV-positive cases versus population
	Cases	Population	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)[c]
Demographic data				
Sex				
Male	166	11557	2.37 (1.82, 3.10)	2.09 (1.24, 3.52)
Female	81	13385	1.00	1.00
Age group (years)				
15–24	58	10005	1.00	1.00
25–34	51	7042	1.25 (0.86, 1.82)	3.02 (1.45, 6.28)
35–44	51	4134	2.13 (1.46, 3.11)	8.28 (4.12, 16.7)
45–54	44	1996	3.80 (2.56, 5.64)	9.76 (4.60, 20.7)
55+	43	1765	4.20 (2.82, 6.26)	6.16 (2.65, 14.3)

Figure 1.1: Extract of an output of a case-control study for tuberculosis in African population [21]

Besides encoding from published case-control studies, broader and deeper understanding of the related infectious disease risk knowledge can be acquired directly from experts (e.g. epidemiologists). Another motivation of this thesis is to facilitate more than one epidemiologists to encode their knowledge. Thus, the designed knowledge representation is intended for to be a generic approach, which can later be instantiated for each infectious disease. Each infectious disease will contain detailed risk factors and ratios that are specific for that particular condition in a certain environment context.

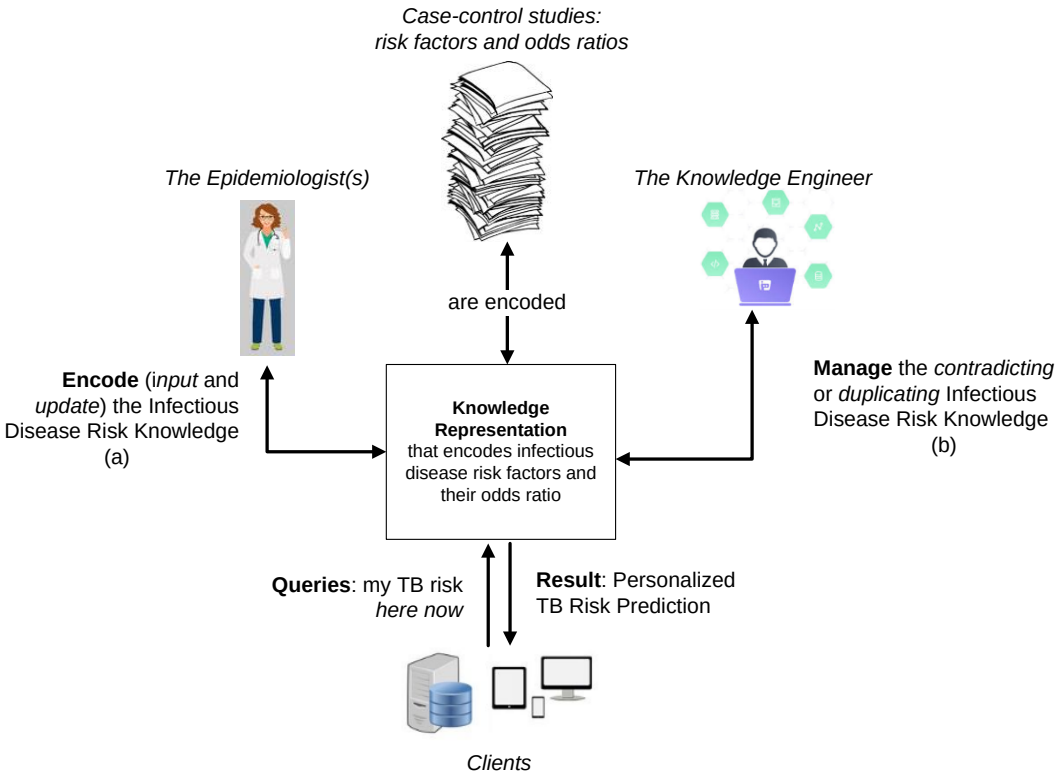

Figure 1.2: An early version of the knowledge representation

Since it is possible to have *conflicting* (*contradicting* or *duplicating*) knowledge across the experts, a knowledge manager is then required to resolve the conflicting knowledge by using prioritization. The illustration of the incorporated roles and the personalized query is shown in **Figure 1.2**.

The following paragraphs outline the gap that this research aims to fill which motivates this research. The existing knowledge representations (e.g. IDO [22], IDOBRU [23], IDOSchisto [24]) related to infectious diseases and risk factors do not allow the odds ratio encoding. Other knowledge representations for non-infectious disease risk factors such as CARRE [25], ORC [26], HEPO [27] are available, but, these ontologies do not provide a placeholder to put the odds ratio to be bound with the represented risk factors. Another form of knowledge representation, rules [28], [29], allows (1) the binding of numerical variables (e.g. odds ratios, prevalence values) with risk factors in the context of causal relationships, and (2) the priority encoding for each piece of knowledge. From studies carried out for this thesis (explained in section 3.2), there is no form of knowledge representation that represents the infectious disease risk knowledge and allow the experts to encode their knowledge and update it as the knowledge develops.

To get kinds and characteristics of the infectious disease risk knowledge to be encoded in the knowledge representation, a study of the Atlas of Human Infectious Diseases (AHID) [13], the Center for Disease Control and Prevention (CDC) [30], and the World Health Organization (WHO) [31] is conducted. The (infectious) disease risk factors are usually presented as categorical variables: *nominal*, *ordinal*, and *binary*. Meanwhile the odds ratios are presented as *numeric* with certain meaning of range [32]. Approaches that represent the knowledge and calculate the risk probability are available (e.g. Probabilistic-OWL [33], BayesOWL [34], [35], BNTab [36]). These approaches provide the ontology modelling and calculate the risk using a Bayesian Network technique. But, since these approaches are not specially built for infectious disease risk knowledge encoding, they only provide binary encoding. The detailed explanation of the investigation results will be given in section 3.3. These approaches cannot handle odds ratios to be involved in the conditional probability table population.

Another approach to dealing with (infectious) disease risk prediction is to separate the knowledge modelling from risk prediction model. Risk prediction models that are commonly used for disease-related prediction are available (e.g. Fuzzy Cognitive Maps

(FCM) [37], [38], Bayesian Networks (BN) [3], [39], Logistic Regression (LR) [40], [41]). Knowledge about infectious disease risk factors has characteristics (mix between nominal, ordinal, binary states) which are compatible with the BN technique. A version of Bayes chain rule [42], [43] is available to be utilized. However, none of the existing algorithms populate a CPT by utilizing this version of Bayes chain rule. A detailed explanation of each risk prediction model will be elaborated in section 2.2.1.

Taking all previous into consideration, a knowledge-base that (1) represents infectious disease risk knowledge (as in **Figure 1.1**), (2) allows infectious disease risk prediction, (3) is usable by the epidemiologists and manageable by knowledge manager continuously as the knowledge develops (illustrated in **Figure 1.2**), is the goal of this thesis.

1.3 Research Questions

The research question posed in this thesis is,

> 'can a *useful* knowledge representation be designed to encode infectious disease risk knowledge, and can this the encoded knowledge be *correctly* availed of to yield personalized infectious disease risk prediction?'

1.4 Objectives and Goals

In answering the research question presented in the preceding section, the main goal of the *useful* knowledge representation is that it -

G1. allows epidemiologists to encode infectious disease risk knowledge continuously as the knowledge develops.
G2. can be availed to yield personalized infectious disease risk prediction.

To achieve those main goals, the objectives of this thesis is

O1. to **comprehend** the characteristics of the infectious disease risk knowledge that are relevant to predict a person's infectious disease risk from declarative knowledge sources (e.g. AHID [13], CDC [30], WHO [31]).
O2. to **search** and **review** the state of the art in (infectious) disease risk prediction systems and the used techniques.

O3. to **search** and **review** the state of the art of knowledge representation specific for (infectious) disease knowledge.
O4. to **design** a form of knowledge representation that fits the knowledge characteristics and meets the goals G1 and G2.
O5. to **evaluate** the consistency between the resulting personalized infectious disease risk prediction and the encoded knowledge.

As a placeholder of the knowledge representation and the needed tools, a system is also designed in this thesis that,

G3. facilitates the clients to submit their personal queries and personalize their infectious disease risks
G4. facilitates the knowledge manager to resolve the conflicting knowledge (e.g. contradicting and duplicating)
G5. retrieves relevant contexts from live data sources (e.g. APIs) and disease morbidity from WHO reports

However, since the main focus of this thesis is the form of the knowledge representation that is capable of encoding infectious disease risk knowledge which allows risk prediction, thus, the design of the system that utilizes the knowledge-base and allows communication to the experts and the clients is adequate. Therefore, the system development is not included in this thesis.

1.5 Contribution to the State of the Art

This thesis proposes a contribution, **a format of knowledge representation** that allows domain experts to continuously encode the knowledge related to a personalized infectious disease risk prediction. The form of knowledge representation is published in a a conference proceeding and uploaded to the Open Science Framework repository (see Appendix 4 for early development and Appendix 7 for the later version). Together with **a tool** (as an algorithm) to make sure that the encoded knowledge is consistent with the risk prediction results. The Java packages of the algorithm are published in a conference proceeding (see Appendix 5 for early development) and uploaded in a GitHub repository. This thesis also proposes a minor contribution related to the **design of a system architecture**. The system is where the knowledge representation and the tool interact

with the other components (e.g. APIs) to serve personalized requests from clients. The request is to calculate a person's risk of contracting of an infectious disease at a time at a certain place. The system also facilitates a knowledge manager to resolve conflicting knowledge as the epidemiologists continuously update the knowledge-base. We call this system PROSPECT-IDR (Personalised Prediction of Infectious Disease Risk).

1.6 Methodology

To answer the research question posed in section 1.3 and achieve goals listed in section 1.4, this section explains how this research is conducted. Basically, this section is an elaboration of the objectives listed in section 1.4.

The contexts of this thesis are infectious diseases, risk prediction, knowledge representation, and personalization. To retrieve existing research, projects, apps, web services in these contexts, a search on the peer-reviewed article repository, and app and web stores is conducted. For the journal repository search, the relevant topics are *infectious disease informatics, public health informatics, global health informatics, computational epidemiology,* and *digital epidemiology*. The search results are then analyzed based on two focuses: (1) the risk prediction techniques that they use, and (2) how they model their risk factors (i.e. predictors). Any related data stores (e.g. APIs, reports, patient admission records) that may be reused for the system are also investigated during this search.

The first part of the research question of this thesis is *whether a useful knowledge representation can be designed to encode the infectious disease risk knowledge*. This part has two concentrations, first, on the *characteristics* of the infectious disease risk knowledge (e.g. the risk factors, and odds ratios) and second, on the *form of knowledge representation* (e.g. ontology, rules) that fits to the (infectious) disease risk knowledge characteristics (e.g. ordinal (smoking habit), binary (gender), nominal (nationality)). To find the characteristics of the knowledge, key declarative knowledge sources are consulted (e.g. AHID, CDC, WHO). From these knowledge sources, all risk factors mentioned for all human infectious diseases are collated. This collation includes the personal risk factors and relationships between (infectious) disease risk and the climate or location features. For the form of (infectious) disease risk knowledge representation, a

search in journal and knowledge repositories is conducted with specific key search on ‘disease’. The search aims to find the concepts, objects, or structure of existing knowledge representation that can be reused partially or wholly.

The next part of the research question is *whether the knowledge representation is usable by the epidemiologists*. To make this knowledge representation usable, a user interface that facilitates inputting knowledge into the knowledge representation is designed. The characteristics of the epidemiological knowledge are represented as input controls of the user interface. The process of inputting knowledge details obtained from case-control studies is then designed as features in the user interfaces.

The last part of the research question is *whether the encoded knowledge can be correctly availed to yield personalized infectious disease risk prediction*. This part of the question adds another focus to the knowledge representation search by investigating a way or a tool that allows the encoded knowledge to support the infectious disease risk prediction.

The system that serves the personalized queries from clients asking for their infectious disease risk prediction, PROSPECT-IDR, is then designed. In this system design, the reusable and relevant data sources that were obtained, the forms of knowledge representation and the prediction techniques that were reviewed, the facilitations of the communication to experts, knowledge manager and clients, are all included. At this stage, a decision of the risk prediction technique that meets all requirements is made. Following this decision, the form of knowledge representation that is compatible with the risk prediction technique is chosen. Two involving activities: time to encode knowledge, and prediction time, are also described at this stage.

After finding the infectious disease risk knowledge characteristics and quantifications, a form of knowledge representation is designed by taking influences from the existing concepts, objects, or structures. Besides that, the design of the knowledge representation is also affected by the prediction technique that allow infectious disease risk prediction from the encoded knowledge. The *usefulness* and the *completeness* of the (initial version) knowledge representation are evaluated. The evaluation involves selected case-control studies that discovered knowledge of infectious diseases prevalent in several countries.

The algorithm that makes sure the encoded knowledge is used correctly by the risk prediction technique is then constructed. The various characteristics and quantifications

found in the infectious disease risk knowledge are the main focus of the tool development. Evaluation cases (in the form of a knowledge-base) are intentionally built (including the *contradicting* and *duplicating* knowledge) with aim to test the *consistency* of the resulting infectious disease risk prediction with the encoded knowledge, and the ability to handle different priority levels that are set by the knowledge manager to resolve the conflicts.

The outcome of the PROSPECT-IDR as a holistic system is the infectious disease risk prediction that is personalized based on personal attributes (including the inferred environment condition at a time in a place). The correctness of the resulting personalized infectious disease risk prediction can be evaluated using *reliability* testing [43]. However, the infectious disease risks depend on the quality of the case-control studies' outputs (risk factors, and the associated risk ratios). The better the case-control studies were researched, the more qualified the risk factors and odds ratios that are encoded in the knowledge-base, thus, the more reliable the infectious disease risk prediction. However, the tool that is designed in this thesis only makes sure that the resulting risk prediction results are *consistent* with the encoded knowledge in the designed form of knowledge representation. This means that the tool is not responsible for the quality of the encoded knowledge which can impact the reliability of the end results. Therefore, even though a reliability evaluation for the risk prediction results is related, this evaluation is not included in this thesis. An article that evaluates the reliability of the resulting infectious disease risk prediction for three infectious diseases prevalent in three different countries has been submitted to a journal. See Appendix 6 to read this submission.

1.7 Thesis Overview

The preceding section described the thesis methodology that covers review of the state-of-the-art, design and evaluation of the knowledge representation (including the required tool). The search related to literature, apps, web services, projects, forms of knowledge representation resulted in two thesis chapters.

Chapter 2 reviews existing projects, web services, systems, proposals, or apps related to human (infectious) disease risk prediction systems. In this chapter, the information of the reusable data sources, risk prediction techniques, and predictor modelling of the human (infectious) disease risk prediction are identified.

Chapter 3 describes the domain knowledge that explains how a person is at risk of an infectious disease based on personal and environment risk factors. This kind of knowledge is available in epidemiology for infectious diseases provided by CDC. Thereafter, the reviews of the disease knowledge representations are discussed and reviewed. Other articles about the risk prediction models that also serve as knowledge-base, or a knowledge-base that also models probabilistic knowledge are investigated. Advantages and limitations for each model are outlined in this chapter. An example of declarative infectious disease risk knowledge is also shown in each model with aim to give a fair comparison for the discussion.

From the state-of-the-art review chapters above, data sources, forms of knowledge representation, the way the projects, web services, systems, proposals, or apps model their predictors and their prediction techniques were gathered. The relevant features or concepts were taken for inspiration to create the components of PROSPECT-IDR system.

Chapter 4 explains the influences taken from the literature review chapters (chapter 2 and 3) to design the PROSPECT-IDR system. All required data sources and components are described in this chapter. The system is designed to achieve goals G3 to G5 in section 1.4. In this chapter, the explanation about decisions of the knowledge representation and the risk prediction technique that fit the system is elaborated. The further details of the knowledge representation are elaborated in chapter 5.

Taking two decisions made in chapter 4, the design and evaluation of the covered components are elaborated in chapter 5 and chapter 6 as the main chapters of this thesis.

Chapter 5 describes the design of the form of knowledge representation that encodes the infectious disease risk knowledge taken from declarative knowledge sources (e.g. AHID, WHO, CDC). The form of knowledge representation is designed to allow the encoded knowledge to be used for predicting personalized infectious disease risk using the chosen risk prediction technique. In the evaluation, knowledge of several infectious diseases prevalent in several countries is encoded in the designed knowledge representation. This encoding activity aims to test the *usefulness* and *completeness* of the initial design of the knowledge representation.

Chapter 6 explains the required tool to keep the knowledge *consistent* between the encoded knowledge and the resulting personalized infectious disease risk prediction. To

make sure the *consistency* of this algorithm, test cases (i.e. knowledge-bases) that touch the boundaries of the requirements (including conflicting knowledge) are chosen. Thereafter, the algorithm is executed to transform the encoded knowledge into a BN. The resulting BN and the encoded knowledge are then compared and analyzed whether they are consistent or not.

Chapter 7 concludes the thesis. It summarizes the thesis contributions made to the state-of-the-art together with the limitations. Some discussion related to long-term vision and the continuation of research from this thesis is also provided in this chapter.

2. STATE OF THE ART – INFECTIOUS DISEASE RISK PREDICTION SYSTEM

This chapter reviews the state of the art in infectious disease risk prediction systems, focusing on context-specific and personalized prediction. This chapter describes projects, apps, ongoing research that is related to infectious disease risk prediction and personalization. This chapter informs us about the basic definition and typical research in "personalization", "infectious disease" and "risk prediction" in the context of the areas of medicine and computer science. The domains that cover this kind of research are *Computational Epidemiology*, *Public Health Informatics, Infectious Disease Informatics, Digital Epidemiology,* and *Global Health Informatics*. The review yields the prediction models that are usually used for (infectious) disease risk prediction, the kind of the inputs and outputs for each model, and what kind of data in what form is available for person and environment modelling relevant to (infectious) disease risks.

Together with the following chapter (chapter 3 – the domain knowledge and its representation), the prediction models and obtainable data found in this chapter will influence the design decisions (explained in chapters 4, 5, and 6).

2.1 Definition of Personalized Infectious Disease Risk Prediction System

Based on the Merriam-Webster dictionary, *prediction* is an act to declare or indicate in advance; foretell on the basis of observation, experience or scientific reason [44].

Risk prediction is an estimation of future outcomes for individuals based on one or more underlying predictors (characteristics) [45]. Risk prediction has application in many domains. Based on Scopus search using “risk prediction” or “risk estimation” keywords, the distribution of such articles across subject areas is presented in **Figure 2.1**. Medicine, the subject area of this research, is the most common.

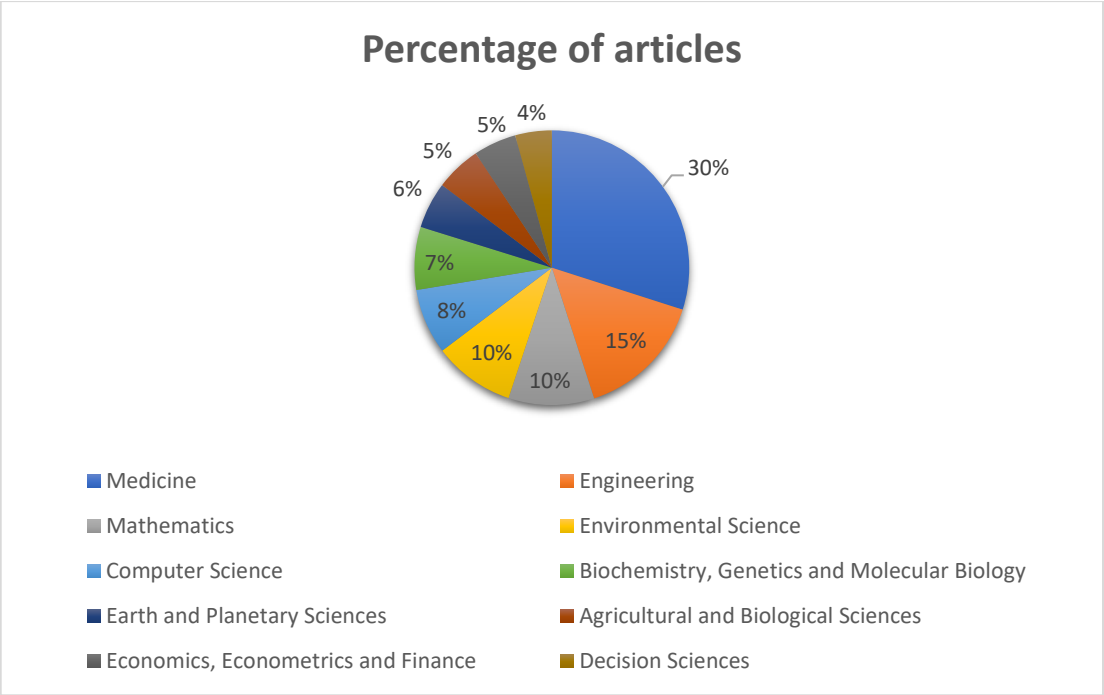

Figure 2.1: Distribution across subject areas of articles in Scopus containing "risk prediction" terminology

Infectious disease risk prediction is a risk estimation of specific infectious disease for individuals. In medicine, the subject area of this research, most risk prediction articles focus on finding predictors of disease risk using data mining approaches and measure how precise and accurate the prediction results are against real observations (i.e. 'ground truth') [46], [47], [48] either using historical data [4], [49]–[52] or rare events which are largely unknown [47], [53], [54]. Usually, they predict the mortality rate [46], or the probability of an event, such as suicide [55], contracting a disease [4], [50]–[52] or prematurity [54].

The term *personalized* or *individualized* in general domains mean to make personal or individual, or tailor something to suit the individual needs [56]. Based on Scopus search using "personalization" keyword, the percentages of the subject areas that contain this term are presented in **Figure 2.2**. The figure shows that articles on personalization are common in computer science (40%) and medicine (8%), the subject areas of this research.

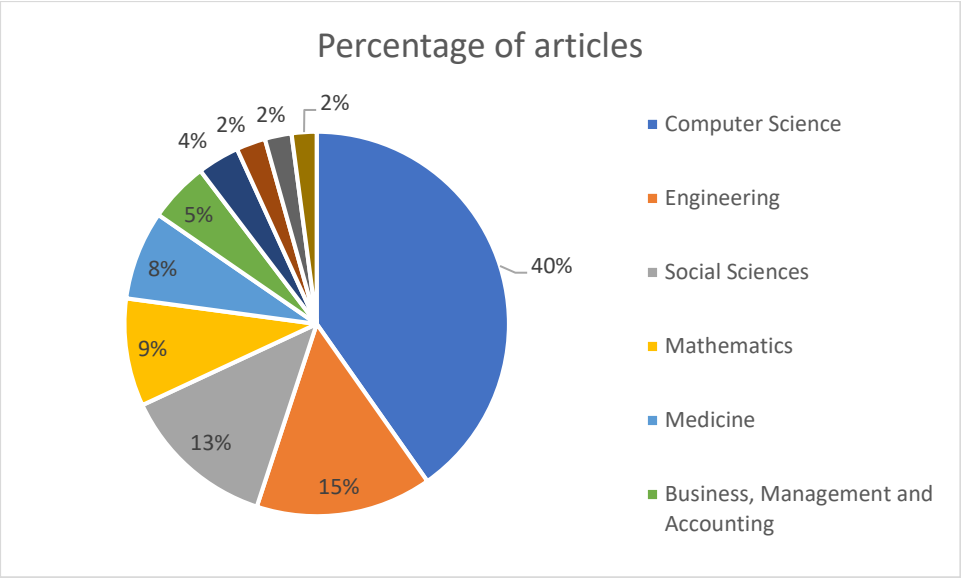

Figure 2.2: Distribution across subject areas of Scopus articles matching "personalization"

Personalization in *medicine* is a model that allows customization of health-care to the individual person by use of genetic, proteins, personality traits, behavior, environment or other information to prevent, diagnose, and treat disease using therapy [57]–[61]. *Personalized medicine* is able to improve the safety of patients [62], reduce unnecessary expenses for medical procedures by providing early diagnosis and optimal therapies (e.g. for cancer, and diabetes cases) [63], or help avoiding adverse drug reactions [64]. Mostly, *personalized medicine* yields the same outputs for the same users with the same characteristics, or for different users with the same characteristics (e.g. hyper-tailoring) [65]. Therefore, the concept of personalization is centralized to the user's attributes.

Even though personalized medicine for cancer or diabetes started in 2005, personalized medicine for infectious diseases is first mentioned in 2016 [14], [66]. This late issue of personalized for infectious disease is caused by the complexity of the predictors. Personalized medicine for cancer or diabetes is mostly researched from the genetic and risky habits, thus, the predictors in the personalization model are almost known. Whereas, a person's risk of contracting of infectious diseases are determined by the 'invisible' variable: the *pathogen* (e.g. virus, bacteria) which the emergence only known when there are reported incidences in the area. Some of the pathogen survival depends on the availability of the reservoir (e.g. nature, land use), and the climate (e.g. weather, season). Besides that, the *host* (e.g. human, animal) attributes also have certain 'role' in infection

risk [14]. Host susceptibility is affected by the host's immunity level which is, in turn, influenced by weather, genetic factors, demographic factors, behavior, or pre-existing illness [66], [67].

These personal and environmental risk factors become the definition of an extended personalization concept. The personalization is not only focused on the user attributes but also the environment (e.g. weather and location) of the user. This extended personalization definition was used to search for articles that relate to the PROSPECT-IDR system developed for this research.

2.2 Existing Research on Infectious Disease Risk Prediction and its Predictor Modelling

In order to find state of the art in personalized infectious disease risk prediction systems, the first step was to identify relevant domain topics. These were gathered from the titles of journals, conferences, and book chapters; the names of laboratories, research centers, and course disciplines at the intersection between informatics, computer science, public health, and (infectious) diseases. The following domains recurred in multiple titles: *computational epidemiology, public health informatics, infectious disease informatics, digital epidemiology,* and *global health informatics*.

Computational epidemiology is a multidisciplinary field that harnesses computer science, mathematics, geographic information science and public health to understand the spread of (infectious) diseases, or human behavior patterns that contribute to (infectious) disease risk [68].

Informatics synthesizes the theory and practices of computer science, information sciences, and behavioral and management sciences into methods, tools and concepts [69]. An effective informatics application is able to transform raw data into usable information. In the public health domain, informatics can be used for monitoring and surveillance, to support improved decision-making, and to improve population health [70]. *Public health informatics* empowers disease interventions and prevention – leading to better health of individuals and the community where they live [71].

Infectious disease informatics is a multidisciplinary field of science that is extended from research on the public health laboratory data to find potential infectious disease vectors and more robust to surveillance and computational of epidemiological factors. This domain is intersected with *computational epidemiology* and *public health informatics* but have more focus at vectors of infectious diseases [72].

Digital epidemiology is epidemiology that uses digital data to find the patterns (using machine learning) which are used to understand and mitigate or preventing the disease. The source of the data generation can be from inside, or outside the public health system in a region [73].

Global health informatics is a multidisciplinary field between computer science, medicine, engineering, public health, policy, and business that aims to improve healthcare systems and outcomes. Admittedly, the global health informatics focus on specific vector-borne diseases (e.g. Ebola, zika) in specific region.

Having identified the relevant domains, search queries were submitted to two types of repository: (1) repository of established mobile or web apps (including the general-purpose search engines such as Google, app store, and web store). The resulting information from this kind of research is usually used to find the terminologies, general concepts, and current technology which may not registered to peer-reviewed publications, (2) repository of scientific articles (mainly referred from index citation database, such as Scopus); the results from this repository usually follow a valid research methodology and thus the information is more credible and qualified as the basis of the state-of-the-art of this research.

The search keys used to obtain the supporting articles for this chapter are presented in **Table 2.1** and **Table 2.2**. The keywords of the resulting articles in the upper rows determine the search keys of the lower rows. **Table 2.1** and **Table 2.2** list the search key(s) that is submitted to academic and non-academic type of repository, respectively. The resulting publication types are news articles, WHO/CDC web pages, thesis books, articles that are not peer-reviewed, lecture notes, book chapters. The search keys in the last two rows were submitted to the second, scientific, type of repository related to health and sciences (e.g. Science Direct, PLOS one, omics online, Nature, Google Scholar, Academia).

Table 2.1: Search aim and keys submitted to the academic repositories, and the resulting articles

#	Aims of the search	Samples of search keys	Samples of scope of the resulting articles
1	To find the domain(s) of this research	"public health informatics", "infectious disease informatics", "computational epidemiology", "global health informatics", "digital epidemiology"	Published articles about - (infectious) disease risk prediction - early warning system - (infectious) disease outbreak prediction
2	To find the epidemiology knowledge for infectious diseases which allows risk prediction	"epidemiology knowledge infectious diseases", "infection risk", "infectious disease stages"	Published articles that explain - the concepts that affect (infectious) disease risk in a person: knowledge of the infection stages in a person, infection chain, risk factors of (infectious) diseases - relations between climate and location features with the infectious disease risk emergence
3	To find the common risk prediction approaches and methods	"(infectious) disease risk (prediction/ estimation/assessment)", "case-control studies", "statistics disease risk prediction (methods/models/ techniques)", "(infectious) disease risk (factors/groups) magnitudes",	Published articles that discover - how the causal relationship of risk factors is represented to allow disease risk prediction: network, tree, function - risk prediction tools/methods: Bayesian Network, FCM, variants of Regression, SEIR models, PR-OWL, Probabilistic Relational Model, Bayesian Knowledge-base, Probabilistic Knowledge-base, Bayes-OWL, BNTab - kinds of inputs/variables: time-series data, population statistical parameters, metrics, risk ratios - kinds of disease risk prediction evaluations: calibration (or reliability), accuracy, discrimination
4	To find the input knowledge for predicting infectious disease risk probability in a person	"risk ratios", "odds ratios", "(infectious) disease (prevalence/incidence)", "relative risk", "pooled OR", "Bayesian network", "fuzzy cognitive maps", "(logistic) regression model"	Published articles that find about - (infectious) disease risk factors: personal attributes, environmental attributes, others - details of personal attributes: demographic, genetic, biomedical, behavioral personal attributes - details of environmental attributes: weather, season, climate, geo-position, location features - examples of miscellaneous: natural disasters, bird migration, academic term/holiday

Table 2.2: Search aim and keys submitted to the non-academic repositories, and the resulting articles

#	Aims of the search	Samples of search keys	Samples of scope of the resulting articles
1	To find current information technology related to infectious disease risk prediction	"public health risk monitoring (mobile/web) application", "(infectious) disease risk prediction system", "expert system (infectious) disease risk estimation projects"	Published articles that present kinds of projects, computer systems, mobile and web applications or services in disease risk and public health.

The search results of the queries listed in **Table 2.1** and **Table 2.2** are then used in section 2.2.1 and 2.2.2. The results are either scientific articles or web pages that explain certain web services, apps, or projects that exist or in development or planned. Some of the projects in **Table 2.1** and **Table 2.2** are reviewed below.

The *VBD-AIR tool* [74] enables the user to explore the interrelationships among distributions of vector-borne infectious diseases (malaria, dengue, yellow fever and chikungunya) and international air service routes to quantify seasonally changing risks of vector and vector-borne disease importation and spread by air travel. It uses Climatic Euclidean Distances (CEDs) to measure similarity in climatic regime between one airport and another. The incorporated atmospheric attributes are rainfall (r), temperature (t) and humidity (h) recorded for each airport location for each month. From this tool, the current research adopted way of retrieving atmospheric attributes from weather API.

HealthMap [75], [76] is an internet-based system designed to collect and display information about new infectious disease outbreaks according to geo-location, time, and infectious agents. HealthMap integrates outbreak data from multiple electronic sources such as UN data, news websites, WHO and CDC websites.

The *AIME.Life* (Artificial Intelligence in Medical Epidemiology) project [9] aims to predict dengue outbreak 3 months in advance based on geo-position and date/time, by incorporating public health data, weather, and geographical data. Both HealthMap and AIME.Life projects are using Google Map APIs as a geo-position locator; their way of converting the geo-position into location for other purposes influenced the PROSPECT-IDR system. Even though this AIME.Life used the same inputs with this thesis to predict an infectious disease: geo-position, public health data, weather, and geographical data, AIME.Life does not contain the knowledge-base for infectious diseases. Thus, it cannot be replicated to other infectious diseases because it might need different knowledge and lead to different inputs.

CAIDE (Cardiovascular Risk Factors, Aging, and Incidence of Dementia) [77] is an app based on the Dementia Risk Score that has two aims: (1) allowing users (lay people) to detect their individual risk, and (2) allowing practitioners to discuss preventive measures and monitor risk reduction. To achieve the first aim, lay people are asked to enter personal attributes (e.g. age, educational level, blood pressure, obesity, and physical inactivity)

from which the Dementia risk is calculated using a logistic regression model. To achieve the second aim, health care providers and practitioners are asked to communicate with each other using the provided features. From this app, features to facilitate communication with users and domain experts are adopted.

This section reviews the existing research on prediction of the infectious disease risk and the way they model the predictors. From the reviewed systems, apps, or projects, some APIs and data sources, that are beneficial to this research are adopted. The next section will review the same retrieved articles with **Table 2.1** and **Table 2.2** based on their risk prediction techniques.

2.2.1 Previous research related to risk prediction techniques

From articles retrieved from Table 2.1 and Table 2.2, there are three approaches that are used to predict the (infectious) disease risk from person or environment models: *data-driven, knowledge-driven*, and *compartmental model* approach. The data-driven and knowledge-driven approach to classification is known in the computer science area, whereas the compartmental model appears in the public health area. A list of articles that lead to this classification can be seen in Table 2.3. Quartile Scores (Q1-Q4) are derived based on Impact Factor (IF). Q1 (high) denotes top 25% of the IF distribution; Q2 (middle-high) denotes between top 50% and top 25%; Q3 (middle-low) denotes from 75% to 50%; and Q4 (low) denotes bottom 25% of the IF distribution.

Table 2.3: Summary of risk prediction approaches and techniques

No	Article	Type of publications / Project Name	Knowledge-driven Methods	Data-driven Methods	Compartment Model	Other
1	[78]	Journal - Q2			SIRS	
2	[79]	Journal - Q1			SEIR	
3	[80]	Journal - Q1			SEIR	
4	[81]	Proceeding			SEIR	
5	[82]	Proceeding			SEIR	
6	[83]	Journal - Q1 / CA - MRSA			SEIR	
7	[84]	Journal - Q1	BN			
8	[85]	Journal - Q1	BN			
9	[38]	Journal - Q1 / Diagnosis Support System	BN, FCM			
10	[37]	Journal - Q1	FCM			

11	[42]	Journal - Q1	BN		
12	[86]	Journal - Q2	BN		
13	[87]	Journal - Q1	BN		
14	[74]	Journal - Q1 / VBD - AIR	Distance-based Risk Metric		
15	[77]	Journal - Q2 / CAIDE	Scoring Method		
16	[88]	Journal - Q1	Preference Similarity Computation (PSC)		
17	[89], [90]	Book Chapters	Probabilistic Relational Model (PRM)		
18	[91], [92]	Journal - Q3	Bayesian Knowledge-base		
19	[93], [94]	Journal - Q1	Probabilistic Knowledge-base		
20	[33], [95]	Journal - Q2	Probabilistic-OWL		
21	[35], [96]	Book Chapters	Bayes-OWL		
22	[36]	Journal - Q1	BNTab		
23	[97]	Proceeding		Generalized Linear Mixed Model	
24	[98]	Journal - Q1		Logistic Regression	
25	[99]	Journal – Q2		Regression	
26	[100]	Journal – Q2		Time Series Regression	
27	[101]	Journal – Q1		Time Series Regression	
28	[102]	Journal – Q1		Time Series Regression	
29	[103]	Journal - Q1		Logistic Regression	
30	[104]	Journal - Q2		Regression	
31	[105]	Journal - Q1			Citizen Scientist Crowdsourcing
32	[106]	Journal - Q1			Lomb-Scargle Periodograms (LSP)

The example **knowledge-driven** approaches are (some of) Bayesian Network (BN) and Fuzzy Cognitive Maps (FCM). Other knowledge-driven approaches utilize a distance formula to measure similarity between data in the knowledge-base and data in the actual data (e.g. distance-based risk metric [74], preference similarity computation [77]). Generally, the knowledge-driven approach requires input knowledge that expresses a *causal relationship* between predictors (e.g. age, gender) and predicted object (e.g. risk

of malaria). A *basis of predictive reasoning* that explains correlation between predictors and predicted object is also needed (e.g. conditional probability table for BN, adjacency matrix for FCM, and risk metric for distance-based risk metric or preference similarity computation).

Data-driven approaches to risk prediction include mostly variants of Regression, variant of Generalized Mixed Model, and (some of) Bayesian Network. The data-driven approach, essentially machine learning, requires structured data (e.g. time-series Electronic Health Record (EHR) [107], [108], sales record [85], prescription record [104]) for building the prediction model. The regression technique has two outputs: the *risk prediction model* (e.g. regression equation), and the *magnitude of the risk factors* (e.g. odds ratio, or r correlation).

In the epidemiology theory, a person's risk of contracting infectious diseases is determined by the state of the health of the person at the time he is exposed to the infectious pathogen. A technique that is used to calculate the infectious disease risk is the *compartmental model*. This technique categorizes human population into several compartments based on the generic infection stages: Susceptible, Exposed, Infected and Resistant [78], [101], [109]–[111] (see section 3.1.1 for details of these stages). Some implementations of this compartmental model can have a modified infection flow, for example, SIR, SIRS, SEIRS.

The **SEIR model** has been used for simulating several infectious diseases (e.g. H1N1 influenza [79], Ebola [80], dengue [81], tuberculosis [82], hepatitis B [112]). These simulations are used to predict the *prevalence* of an infectious disease in a population or to estimate an epidemic duration in a region. To achieve the simulation aims, these articles make use of historical data about *who got what diseases* which is reported regularly from health centers and accumulated in a central organization. This data is then aggregated to provide SEIR proportions in a population at a time. One of the outputs of this SEIR research, *prevalence value*, is an important variable to predict infectious disease risk in a person [42], [77], [85]–[87], [97], [113].

2.2.2 Previous research related to person and environmental modelling

Based on the extended definition of *personalization* in the context of (infectious) disease risk prediction, this thesis needs both *person* and *environmental* (climate and location) modelling. User modelling in (infectious) disease risk prediction [37], [38] includes personal attributes such as age [83], [98], race [84], [114], occupation [115], and fields specified in health records [106], [107]. These attributes can be used to determine a person's immunity level. For example, *infants* and *elderly* are at lowest immunity level compared to *adults*. Other elements of the user model allow inference of the possibility that a person can be exposed to a certain pathogen through a specific transmission mode. For example, *aquatic athletes* are vulnerable to pathogens which live in water-related habitat or water-borne infectious diseases.

Previous articles that includes person, climate (season or weather), and location in their (infectious) disease risk prediction models were retrieved using the search keys listed in the row of **Table 2.1** and **Table 2.2**. The collected articles from **Table 2.1** are presented in rows 1-22 of **Table 2.4**. Whereas the collected projects, apps, or web-services from **Table 2.2** are presented in rows 23-27 of **Table 2.4**. **Table 2.4** only includes articles that focus on infectious disease risk prediction. From these articles, the predictors of the risk prediction model are identified. The tick (√) symbol marks articles that model the associated column to predict the infectious disease risk. From **Table 2.4**, it can be seen that none article that include both person and environment (location/climate) attributes.

Table 2.4: Summary of articles about predictor model of infectious disease risk prediction

No.	Article	Type of publications / Project Name	Inclusion of person attributes	Inclusion of location or climate attributes	Other predictors
1	[106]	Journal – Q2	√		
2	[80]	Journal - Q1	√		
3	[81]	Proceeding	√		
4	[82]	Proceeding	√		
5	[38]	Journal - Q1 / Diagnosis Support System	√		
6	[83]	Journal - Q1 / CA – MRSA	√		

7	[98]	Journal - Q1	√			
8	[84]	Journal - Q1	√			
9	[86]	Journal – Q2			√	
10	[87]	Journal - Q1			√	
11	[97]	Proceeding			√	
12	[88]	Journal - Q1			√	
13	[105]	Journal - Q1			√	
14	[99]	Journal – Q2			√	
15	[100]	Journal – Q2			√	
16	[101]	Journal – Q1			√	
17	[78]	Journal – Q2			√	
18	[102]	Journal – Q1			√	
19	[74]	Journal - Q1 / VBD – AIR			√	
20	[79]	Journal - Q1			√	
21	[85]	Journal - Q1				Thermometer sales
22	[104]	Journal - Q2				Prescription record

	Name of web serv./ app./ project		Inclusion of person attributes	Inclusion of location or climate attributes
23	[116]	Healthians: Android	√	
24	[117]	Smart Health Care: Android	√	
25	[118]	Framingham Heart Disease Risk Prediction	√	
26	[119]	Infectious Disease Advisor: Android, iOS		√
27	[120]	iCheqult		√

Published research that includes weather or season model in their infectious disease risk prediction [78], [88], [97], [99]–[102] usually make use of the data of *when the disease occurred*, as well as the number of disease cases to deduce what atmospheric attributes may affect the pathogen occurrence and spread of a disease by a vector. For example, a windy day accelerates the spread of air-borne infectious diseases (e.g. anthrax). Besides that, the data about the changes of the weather in a period of time (e.g. hour, day) is also observed. This kind of research usually focuses on research about *person's susceptibility* which is affected by weather changes.

Research in infectious disease risk models that incorporate location features of a region (e.g. terrain, altitude, land-use) usually discover the relationship between location features and the emergence of the infectious diseases from *where the disease occurred* data [74], [79], [86], [87], [105]. In the chain of infection, the emergence of the infectious diseases

is determined by whether a person lives close to the pathogen's reservoir, or vector's natural habitat. For example, the natural habitat of a chikungunya mosquito's eggs is a stagnant water pool; thus, the people who are infected are found to live near locations that contain such water-related features (e.g. lake, basin).

From **Table 2.4**, it can be seen that no one risk prediction article includes person, climate, and location attributes for predicting infectious disease risk. However, there are research articles that include person, climate, and location attributes in disease-related studies but are not about **infectious disease** risk personal **prediction** (e.g. disease outbreak prediction research, early warning system). Outbreak detection systems [9], [39], [121]–[125] do include all those attributes in their prediction models. The outputs of these articles can tell the user *when* and *where* the pathogen will be active and cause an outbreak. Some knowledge can be taken from these outbreak detection articles:

(1) Even though the possibility of contracting of an infectious disease is higher during an outbreak period, not all people living in the location of the outbreak will have the same risk of contracting the disease; the risk also depends on the person's susceptibility level, and the transmission modes of the infectious diseases.
(2) The exact GPS location of someone yields atmospheric attributes that infer weather at a location. The weather information can be an indicator whether pathogens or vectors are active or not in a location.
(3) The sources of infectious disease data, the methods to get odds ratios and prevalence from the data, the prediction evaluation methods and risk prediction models that these articles use to predict the location of the outbreak can be reused. To be more specific, the location features can be used to identify the reservoir of a particular pathogen.

2.3 Conclusion

In the beginning, this chapter gave the definition of the personalized infectious disease risk prediction which lies in a multidisciplinary area between medicine and computer science area. The specific disciplines in the *medicine area* that are relevant to this research

are *public health* and *human infectious diseases*. Whereas the relevant disciplines in the *computer science area* are *knowledge representation* and *personalization*.

Referring back to the aim of this chapter outlined in the methodology (section 1.6), this chapter focuses on the risk prediction techniques that are common in (infectious) disease research, and from the way they model the predictors (person and environment). From queries given in **Table 2.1**, three categories of prediction techniques are retrieved: *knowledge-driven, data-driven,* and *compartment model*.

From knowledge-driven approach, two important components that appear in most methods are *causal relationship* between predictors and predicted object and the *basis of predictive reasoning*. From data-driven approach, other two essential elements are the risk prediction *equation* and the magnitude of the predictors (i.e. *risk ratios*). From compartment model, two concepts used to simulate infection in a person were obtained: *infection stages* (susceptible-exposed-infected-recovered) and *prevalence* value.

From the collected articles on infectious disease risk prediction, no article involves both person and environment in their risk prediction model. However, from the outbreak detection articles that include person and environment models, some important and relevant information are gathered:

(1) To estimate a person's susceptibility level, personal attributes (e.g. age, occupation) and health records can be used.
(2) To deduce when the disease occurred, atmospheric attributes can be used to infer weather-dependent pathogen or vector.
(3) To discover where the disease emerges, specific location features that become reservoir of specific pathogens can be availed.

3. STATE OF THE ART – THE DOMAIN KNOWLEDGE AND ITS REPRESENTATION

The previous chapter reviewed the risk prediction techniques, and predictor modelling (i.e. person and environment models) from scientific articles and non-academic projects, services or apps. From chapter 2, information about how to represent the (infectious) disease risk knowledge and what kind of data that influences the infectious disease risk prediction were obtained.

This chapter reviews the existing forms of disease knowledge representation. Before searching for disease knowledge representation, the scope of domain knowledge that is relevant to explain a person's risk of contracting infectious diseases is first comprehended. The domain knowledge is gathered from the epidemiology for human infectious disease discipline. This knowledge elaborates more the attributes relevant to the person and environment model, and SEIR compartment model (section 3.1.1).

Thereafter, the kinds of knowledge representation related to the domain knowledge are searched. Techniques used to encode (infectious) disease risk, and similar knowledge in computer interpretable form are explored (section 3.2). Besides that, the ability of using the represented knowledge to predict the infectious disease risk is also investigated. As none of these techniques meet the needs of the research, section 3.3 presents approaches that combine risk prediction techniques and knowledge-bases, but not related to disease or health.

Some information in this chapter will influence the design of the system, and the knowledge representation in chapters 4 and 5, respectively.

3.1 The Domain of Knowledge: Human Infection Risk

This section describes relevant knowledge to estimate a person's risk of contracting infectious diseases in epidemiology domain. The knowledge in this section is the detailed explanation of the susceptibility of a person, climate-dependent pathogen[1] and vector[2],

[1] an infectious agent that causes illnesses

[2] agent that carries and transmits pathogen into another host

and pathogen reservoir[3] in specific location features. The etiology of infectious diseases in human is explained in section 3.1.1, whereas, the quantifications that are common in the epidemiology domain related to risk factor are presented in section 3.1.2. This section concludes the scope of infectious disease risk knowledge (risk factors and their quantifications) that relevant to personalized infectious disease risk prediction (section 3.1.3).

3.1.1 Etiology of Infectious Diseases

Three kinds of knowledge are included in this section: *chain of infection* that explains the basic cycle of how infections are transmitted and infect humans; *infection flow in a person* (SEIR compartment model) that describes stages of infection in a person; and the knowledge that shows *correlation between environment and infectious diseases*.

Chain of Infection

Infectious disease is an ailment caused by a *pathogen* which is transmitted from an infected person, animal or *reservoir* to a susceptible human (i.e. host) directly or indirectly using a *vector* or *vehicle* [67], [126].

A pathogen is an agent causing an infectious disease (e.g. bacteria, virus, parasite, prion). Based on their activity, the pathogens are divided into two: *active* and *dormant* pathogen. Active pathogens multiply in their natural habitat (i.e. reservoir) and are ready to attack hosts (e.g. human, plant, animal). Some pathogens require specific atmospheric conditions to survive and multiply in the reservoir (i.e. climatic-dependent pathogen). For example, *Campylobacter spp.* was found prefer to live in water surface during winter; warmer temperature supports other bacteria to out-compete *Campylobacter spp.* and ultraviolet light prohibits the survival of this bacteria [127]. Even though pathogens cannot be seen with the naked eye, some developing projects can be used to estimate the pathogen emergence in a location (e.g. Pathosphere.org [128]), country-based morbidity reports can also be an indicator of the activity of pathogens of notifiable diseases [19].

[3] person, animal, plant, or substance in which pathogen lives and multiplies

A reservoir is a habitat in which the infectious agent is able to survive and multiply. There are three kinds of human infectious diseases reservoir: *humans, animals*, and *environment*. *Human* or *animal* reservoirs may not show the symptoms of illnesses but can still transmit the pathogen to other hosts [67]. For example, a nurse may harbor a virus from the patient she visited beforehand and unintentionally infect other patients without infecting herself because she does not have an open wound for the virus' entrance, but the other patients have. *Plants, soil*, and *water* are examples of the environment reservoir for some pathogens. For example, *Legionnaires* disease is often traced to water supplies in cooling towers and evaporative condensers, because those are the reservoirs for the agent *Legionella pneumophila*.

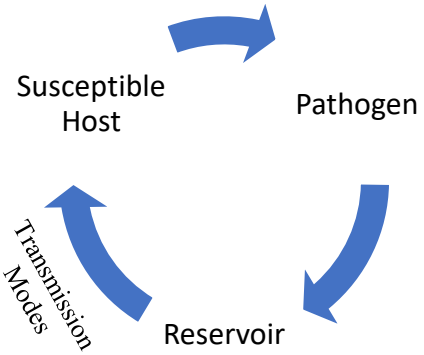

Figure 3.1: Diagram of chain of infection

A pathogen is transmitted from a reservoir to a host in two ways, directly and indirectly (see **Figure 3.2** for the summary of infection transmission). *Direct* transmission means the pathogen is transmitted to the host from the reservoir without intermediaries. Direct transmission includes direct contact and droplet spread. *Direct contact* occurs through skin-to-skin contact, kissing, sexual intercourse, and contact with soil or vegetation harboring infectious agents. *Droplet spread* usually occurs when the infected person sneezes or coughs, the air can carry the infectious droplets for a while before contracting to other human hosts. Therefore, some sources consider this droplet transmission as air-borne diseases. *Indirect* transmission needs a medium to transfer the pathogen. The medium that transmits the pathogen from reservoir to hosts indirectly is *air* (e.g. dust, spore, pollen), *vehicles* (e.g. food, water, blood, fomites) and *vectors* (e.g. mosquitos, flies, fleas). An example of an air-borne pathogen in this category is *Bacillus anthracis*

which the agent of anthrax disease. The agent lives on animal hides, hair, and wool, and is unconsciously inhaled by a person host during shearing. Its spores can germinate outside an animal under appropriate weather conditions.

Vehicle-borne infectious diseases are divided into three: *food and water-borne* infectious diseases, *blood-borne* infectious diseases, and via *fomites*. The food and water-borne transmission (including *fecal-oral*[4] transmission) occurs when a susceptible person ingests contaminated food/water, or the ingested food/water is clean, but the person's hand is contaminated because of improper hand washing after visiting toilets.

Vector-borne infectious diseases usually bite or lick the susceptible person to transmit the infectious agents inside their body (e.g. malaria, dengue fever). These vectors are limited to certain regions and altitudes; for example, the *Aedes aegypti* mosquito that is a vector of dengue fever can only live below 1000m altitude where the climate is usually warm (above 20^{o}C) between the latitudes 35^{o}N and 35^{o}S. *Aedes aegypti* is an example of climate and location-dependent vectors.

Fomites are objects which are likely to carry infectious agents, such as, clothes, tooth brush, coins. Examples of people at increased risk of infectious diseases transmitted by fomites are travelers, who usually share apartments and their utilities such as towels, and people that have unhygienic tattoo services (through sharing needles).

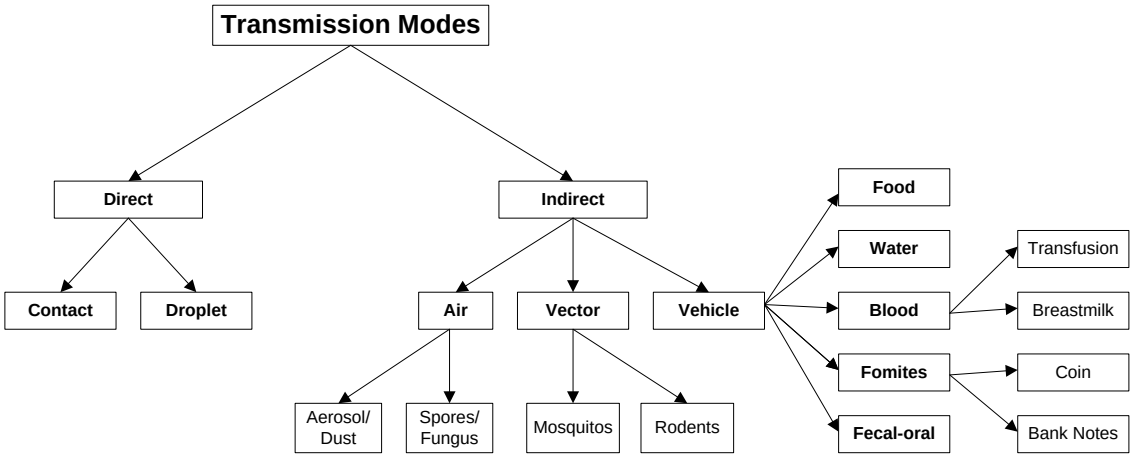

Figure 3.2: Infection transmission modes

[4] Fecal-oral route means that contaminated feces from an infected person are somehow ingested by another person.

As described above, infectious diseases result from the interaction between *pathogen*, *host*, and *environment*. More specifically, transmission occurs when the pathogen leaves its reservoir using a specific mode of transmission, then enters to a susceptible human host. From this host, the *infection* can be transmitted to other human directly, depending on the disease transmission mode. This sequence is called the *chain of infection*.

Infection flow in a person

In epidemiology, there is a well-known mathematical modelling of infectious diseases. This model divides the human population into compartments: Susceptible – Exposed – Infected – Recovered (SEIR) [109] [129]. This division assumes that individuals belonging to the same compartment have the same characteristics. The flow of these compartments reflects the infection stages in a person.

Susceptible is a state of the targeted host (human) with low or declining immunity system. The human susceptibility is affected by many factors: *life stages, genetic, nutrition intake, pre-existing diseases, tobacco smoking and alcohol consumption,* and *hygiene* [130].

- *Life stages* refer to ages and developmental stages throughout human life. Early life development stage from age of 3 – 24 months (infant, toddler) is a critical period when a human has the lowest immune system. The human immunity then increases with age. The peak of immunity is at adult development stage. Thereafter, immunity declines (elderly). Most articles in case-control studies that explain (infectious) disease risk prediction include age, and development stage as personal risk factors [4], [131], [132].
- *Genetic* factors may confer susceptibility or resistance to particular diseases. Usually in a population, genetic factors are identified through the parents' medical history, nationality, or ethnicity. For example, infectious diseases that are transmitted vertically from a pregnant mother to her unborn baby (e.g. Rubella) [133]–[135].
- *Nutrition intake* is determined by a person's consumption habits (e.g. eating and drinking habits). Improper nutrition intake can result in obesity or malnutrition both of which are risk factors for any diseases [136], [137].

- Those who have *pre-existing diseases* (such as cardiovascular disease, diabetes, or renal dysfunction) may be more vulnerable to any infectious disease. For example, people with positive HIV/AIDS are six-fold more susceptible to Tuberculosis than people who do not have HIV/AIDS [21], [41], [138]–[140].
- *Tobacco smoking and alcohol drinking* are associated with numerous infectious diseases, such as tuberculosis. Despite this, some articles may show no correlation between these habits and tuberculosis. In fact, these habit increase dual exposure to arsenic and ethanol which weaken the function of liver, heart, and kidneys [141]. Thereafter, the weak body organs can result in a susceptible person to any diseases, including tuberculosis [6], [142]–[144].
- *Low hygiene* is related with high risk of food and water-borne infectious diseases (e.g. cholera). Also, low hygiene can be an indicator of a person's low social class (poverty); poverty is positively correlated with any infectious disease risks [145]–[147].

Exposed is a state when a host (human) has been attacked by the infectious pathogen of a particular disease. The exposure can be traced from the infectious disease transmission modes. There are four transmission modes: *direct contact* (person-to-person), *air-borne, vehicle-borne,* and *vector-borne*. From previous section, personal attributes, and the surrounding environments of a person can determine whether the person is at risk of certain infectious disease that are transmitted in some way [81], [109].

Infected is a state where a pathogen is already inside a human body. Most articles in epidemiology and clinical domains identify whether a person is infected or not based on his reported symptoms. However, the infection may still occur even though the host does not show any symptoms, but he is still able to carry and transmit the pathogen to other humans. Therefore, the majority of the case-control studies test serum samples for certain antibodies to conclude whether a person is infected or not [87], [148], [149].

Recovered is a state where the infected human regains his immunity and health. This state is related with nutrition intake, exercise habits, tobacco smoking and alcohol consumption, and current atmospheric condition (e.g. solar exposure).

By understanding this infection flow, the definition of a person's risk of contracting an infectious disease can be deduced, mainly from the probability of S and E compartments. While to validate whether the person is infected or not, the I compartment is included.

Correlation between environment and infectious diseases

To find the correlation between environment (climate, and location) and infectious disease risk, published articles were identified using search keys: "climate dependent (pathogen/vector)", "geographical distribution infectious diseases", "seasonal infectious diseases", "weather season infections", "environmental risk factors" to search engines, and scientific journal repositories in public health and medical-related journal repositories such as NCBI, and PubMed.

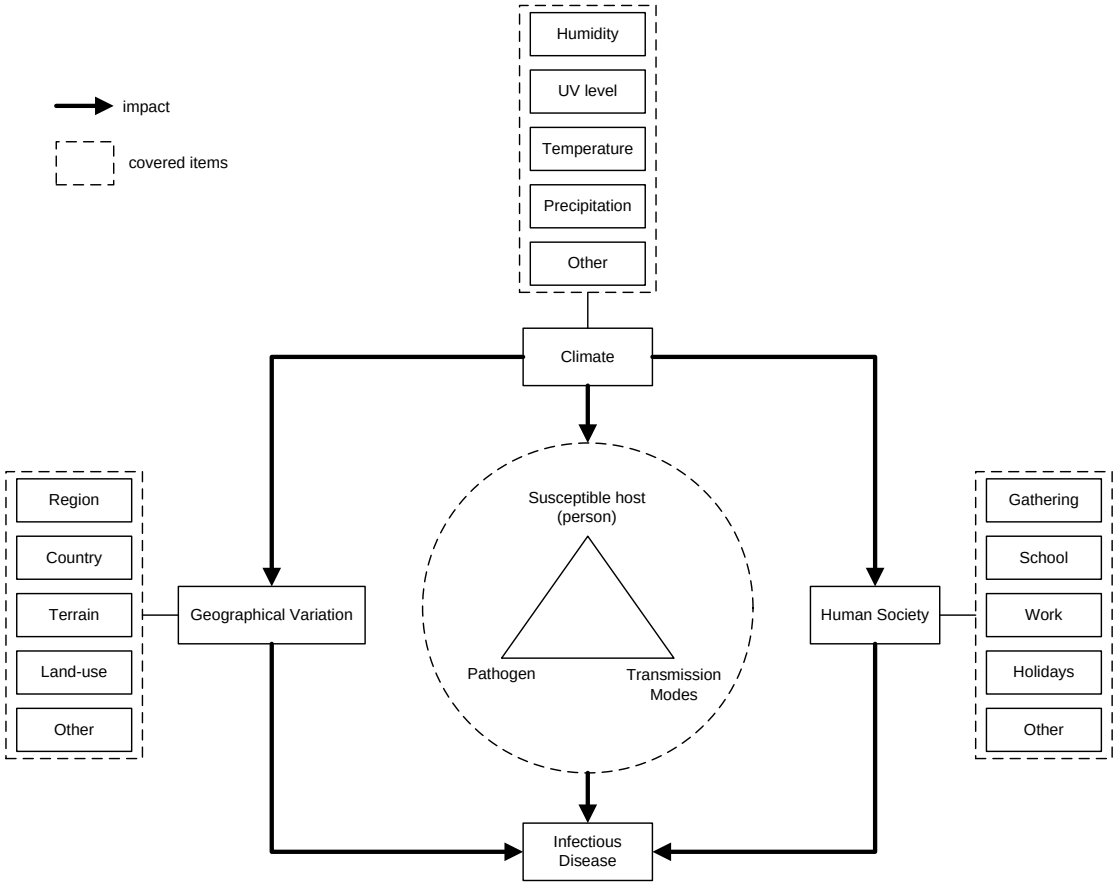

Figure 3.3: The correlation between environment and infectious diseases (redrawn from [127])

Climate in this context is defined by atmospheric condition that occur in an area for certain period. Climate is usually observed over a long period in a wide region. Climate covers *season* and *climate*. Season is divisions of the time based on weather patterns and

daylight hours (e.g. spring, summer, autumn, winter). Weather is a dynamic state that describes atmosphere at a particular location in a short-time (e.g. rainy, cloudy).

Seasons and time in calendar affect certain *human activities in their societies* which can enable some person-to-person infectious disease transmission during special occasion (e.g. summer camps). For example, the outbreak of cryptosporidiosis is frequently reported during summer especially at summer camps [150]. This season effects on the infection risks are illustrated as a rectangular at the right-side of **Figure 3.3**.

Certain temperature, humidity, or precipitation conditions (i.e. weather) that occur in a special land-use at a location can activate or inactivate some *pathogens* (e.g. anthrax pathogen is dormant during low temperature, but, becomes active on hot and dry days at livestock farms). Besides pathogen, the climate also affects the availability of the *vehicle* or *vector* that carries the pathogen (e.g. strong wind distributes anthrax spores from its reservoir). The weather also has impact to the susceptibility level of a person due to the solar exposure level, or certain allergy that lower a person's *susceptibility* level that is triggered by weather changes. The pathogen, transmission modes, and the hosts' susceptibility level are visualized as a triangle in the middle of **Figure 3.3**.

The geographical variation also has impacts to the infectious disease risk through the vector or pathogen. For example, *the Lassa fever* occurs in two geographical variations in two different seasons. In the dry season, the Lassa fever occurs in houses, residences, or building blocks because multi-mammate rat (i.e. vector) usually gathers in houses. In the rainy season, the fever occurs at surrounding fields because the rat forages in the surrounding fields. But, in general, the fever usually occurs at area around the river [13].

However, there are other risk factor sources not be covered by the list above. For example, the relation between a country where a person lives (including a geo-location of the country) and the infection risks. Other knowledge is then searched to explain the relation.

The Atlas of Human Infectious Diseases (AHID) [13] contains (1) the *infection drivers* for infectious disease in general (a sample is presented in **Figure 3.4**), and (2) *brief and general explanation* of each infectious diseases' pathogen, reservoir, transmission mode, clinical findings, epidemiology, prevention (see **Figure 3.5**), and its distribution map (see **Figure 3.6**). The infection drivers in the AHID are given as declarative knowledge; the

highlighted words in **Figure 3.4** shows the brief explanation, and the influenced infectious diseases. **Table 3.1** summarizes all infection drivers found in the AHID based on these brief explanations, and the infectious diseases these drivers influence.

Subject: Global Peace Index

Definition: The Global Peace Index (GPI) is a composite measure of 23 different quantitative and qualitative measures intended to give an overall, relative measure of *peacefulness*. The measures are broadly categorized into (a) societal safety and security (internal peace), such as violent crime, political, stability respect of human rights, displaced persons; and (b) militarization (external peace). The 2010 GPI ranks 149 countries using data from 2008 and 2009.

Trends: Western Europe (and Scandinavia in particular) is the most peaceful region; followed by North America and then central and eastern Europe. Sub-Saharan Africa is the region least at peace while nations in a chronic state of war or internal conflict – such as Iraq, Afghanistan, Somalia, and Sudan – are, unsurprisingly, the lowest ranked. Although the GPI has only been in existence for four years, it suggests that over this period the world has become slightly less peaceful. Over a longer time-scale the overall level of conflict has declined since the end of the Cold War in the early 1990s but there are predictions that climate change, population growth, resource scarcity, ideological movements, and shifts in global power will result in an increase in conflicts in the coming decades.

Poor healthcare infrastructure and a lack of infection control is repeatedly associated with outbreaks of blood-borne viruses such as Ebola hemorrhagic fever and a low GPI is correlated with shorter life expectancy and increased infant mortality. Poorly functioning immunization programs lead to inadequate control of vaccine preventable diseases such as polio, diphtheria, pertussis, measles, and yellow fever, while a breakdown of vector control can lead to resurgences of vector-borne diseases such as malaria. Conflict also results in disrupted public health surveillance systems, making it difficult to quantify the impact of conflict on infectious disease risks. However, specific studies of the health impacts of chronic crises, such as those in Darfur, Sudan, and the Democratic Republic of Congo, have shown that, following an initial peak in violent deaths, more deaths are caused by preventable, largely infectious, diseases than violence.

On an international scale, war spreads disease, with historical examples including influenza, typhus, and dysentery. Unconventional global conflict by non-state actors and the specter of the deliberate release of pathogens, such as anthrax and smallpox, have in the past decade added a new dimension to the international infectious risks of conflict.

Figure 3.4: A sample of peacefulness as an infection driver from AHID [13]

Disease: Tuberculosis

Classification: ICD-9 010-018; ICD-10 A15–A19

Syndromes and synonyms: Consumption, white plague, TB.

Agent: *Mycobacterium tuberculosis* complex, including *M. tuberculosis*, *M. africanum*, *M. canetti*, and *M. bovis*, slow growing acid-fast rods. *M. bovis* is not discussed further.

Reservoir: Mainly humans; rarely non-human primates and other mammals.

Transmission: Person-to-person via inhalation of infectious aerosols from cases with pulmonary TB, particularly after prolonged exposure over time. Extrapulmonary tuberculosis is generally not communicable. HIV-infected individuals are more likely to develop TB.

Incubation period: 2–10 weeks to primary lesion or tuberculin-positive skin test; around 10% progresses to active disease annually, but it may remain latent for decades to lifelong,. This percentage is higher in children and in HIV-infected or otherwise immune-suppressed individuals.

4 months of rifampicin plus isoniazid. If resistance to rifampicin or isoniazid is suspected, treatment must continue with second-line drugs for at least 18 months. Drug-resistant tuberculosis (MDR and XDR-TB) require special regimens.

MDR-TB is defined as resistance to two main first-line TB drugs: isoniazid and rifampicin. XDR-TB (Extensive Drug Resistant TB) is defined as MDR-TB with resistance to fluoroquinolones and one second-line injectable drug.

Prevention: Primary: BCG vaccination of children protects against disseminated disease. Secondary: intensive search for and treatment of source cases; contact investigation and treatment of positive cases with chemoprophylaxis. WHO has established a 'Stop TB Partnership' program to control TB world wide.

Epidemiology: TB is a major cause of death and disability world wide, especially in developing countries. Morbidity and mortality rates increase with age, and are higher in males. In regions of high incidence, morbidity peaks in adults of working age. Morbidity is higher in urban populations, among the poor, and in closed institutions such as prisons and military barracks. There were an estimated 9.27 million incident cases of TB in the world in 2007 (14% HIV positive),

Figure 3.5: A sample of Tuberculosis brief explanation from AHID [13]

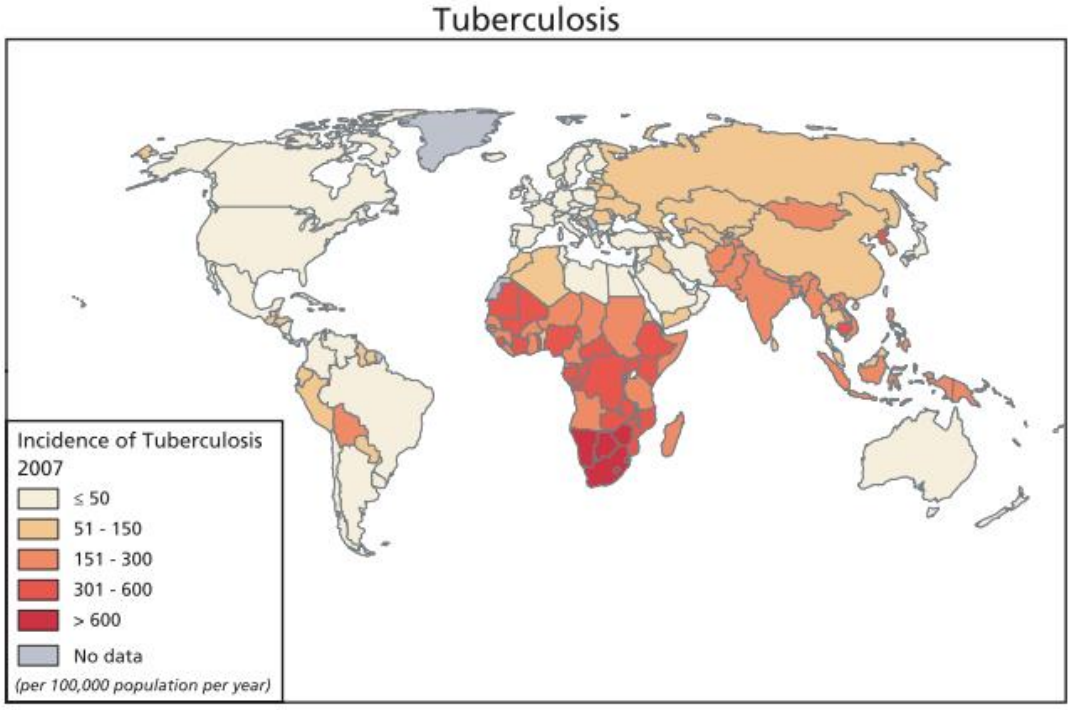

Figure 3.6: A distribution map of Tuberculosis from AHID [13]

Table 3.1: The infection drivers summarized from [13]

#	**Drivers** (brief definition)	Influenced infectious diseases

1	**Emerging Infectious Diseases** (first temporal emergence of a pathogen in a population)	HIV, SARS, influenza A (H5N1)
2	**Human population** (related to size and demographic profile of a country)	Air-borne infections, STI
3	**Urbanization** (the proportion of people living in rural and urban areas)	Influenza, SARS, STI, blood-borne viruses, anthrax, imported food-borne infections, tuberculosis
4	**Global Connectivity** (connectedness of people in space and time, e.g. access to road, terrain)	HIV, SARS, influenza A (H5N1), STI
5	**Human Developments** (number of people meeting the standard of living)	All infectious diseases which are related to poverty, sanitary, nutritional, behavioral, environmental and healthcare access components.
6	**Peacefulness** (social safety and security, militarization, e.g. crime rates)	cholera, dysentery, measles, respiratory infections, Ebola hemorrhagic fever, polio, diphtheria, pertussis
7	**Life Expectancy** (the number of years that a person can expect to live from birth in a population) **and Child Mortality** (number of children who die before the age of 5 years per 1,000 live births)	HIV/AIDS, hepatitis B, C, H. Pylori, HPV, pneumonia, diarrhea, malaria.
8	**Water and Sanitation** (the proportion of population using an improved drinking water source and sanitation facility)	Water-borne infections: typhoid, cholera, hepatitis A. Water-based infections: dracunculiasis, schistosomiasis. Water-washed infections: trachoma, scabies.
9	**Undernutrition** (the proportion of population that is underweight, wasted, and stunted)	tuberculosis, pneumonia, measles, malaria.
10	**Climate** (defined by average weather and season)	Vector-borne and animal reservoir infections, climate-dependent pathogen survival.
11	**Forest Cover Change** (e.g. deforestation)	Vector-borne infectious diseases, the infection results of human predation on animals (e.g. Ebola), and environmental sources (e.g. *Cryptococcus gattii*)
12	**Natural Disaster** (natural hazards, e.g. cyclones, droughts, earthquakes)	pneumonia, blood-borne viruses, tuberculosis, cholera, vector-borne infectious diseases
13	**Antibiotic Use** (average dose per day for a drug used for its main indication in adults)	tuberculosis, carbapenem-resistant bacteria.
14	**Inherited blood disorders** (e.g. sickle HbS, G6PD deficiency, and thalassemia)	malaria

15	**Immunization** (active or passive vaccines that have been injected to a person since birth)	Vaccine-preventable infectious diseases
16	**Vector Presence** (terrain and climatic conditions that affect vector emergence e.g. *Anopheles, P. vivax*)	Vector-borne infectious diseases
17	**Bird Migration** (seasonal event in which certain bird species travel between breeding and overwintering grounds)	influenza A, west nile virus, western equine encephalitis, St. Louis encephalitis, Japanese encephalitis, Lyme disease.
18	**Livestock Density** (the population of cattle, poultry, sheep and goats per kilometer square)	leptospirosis, fascioliasis, tuberculosis, brucellosis, African trypanosomiasis, Q fever, campylobacter, listeria.

From several rows in the *infection drivers* (in **Table 3.1**), a deeper understanding of a country's infection risks can be comprehended. Rows number 2 (human population), 5 (human developments), 6 (peacefulness), and 7 (life expectance and child mortality), show the infection driver attributes that can be inferred from a *country*. This is because these drivers can be deduced from certain indicators which are usually surveyed for country scope; for example, the Global Peace Index is a measure of peacefulness. Whereas, the infection drivers that are related to a *specific location* in a country (including terrain and land-use) are in rows numbered 3 (urbanization), 4 (global connectivity), 8 (water and sanitation), 11 (forest cover), 16 (vector presence), 18 (livestock density).

Infection drivers (in **Table 3.1**) that are related to a *person's* health or medical status are 9 (undernutrition), 13 (antibiotic use), 14 (inherited blood disorder), and 15 (immunization). For example, a person who has less body mass index (i.e. undernutrition) would be likely to have a higher risk to any infections. The *climate* related infection disease drivers are 10 (climate) and 16 (vector presence). These two drivers can be used to explain the effect of climate on the presence of some vectors. But, driver #12 (natural disaster) and #17 (bird migration) cannot be classified into person, climate or location.

However, the eighteen infection drivers are not enough to get the details of the infection risk factors. Therefore, to get detailed risk factors, all mentioned risk factors for all human infectious diseases in those declarative sources (AHID, WHO, CDC) was collated. 105 infectious diseases are mentioned in AHID; another 129 infectious diseases not listed in AHID but mentioned in WHO and CDC are also gathered (e.g. yersiniosis, trichuriasis). In total, 234 distinct infectious diseases were collated from three sources (AHID, WHO,

CDC). **Figure 3.7** shows a sample of WHO factsheet about malaria, and **Figure 3.8** gives a sample of a CDC factsheet about cholera.

From AHID, WHO, and CDC, person, climate, location risk factors for all 234 human infectious diseases were collated. Later, the collation is used to design the ontology objects and structure for encoding infectious disease risk knowledge (see section 5.3).

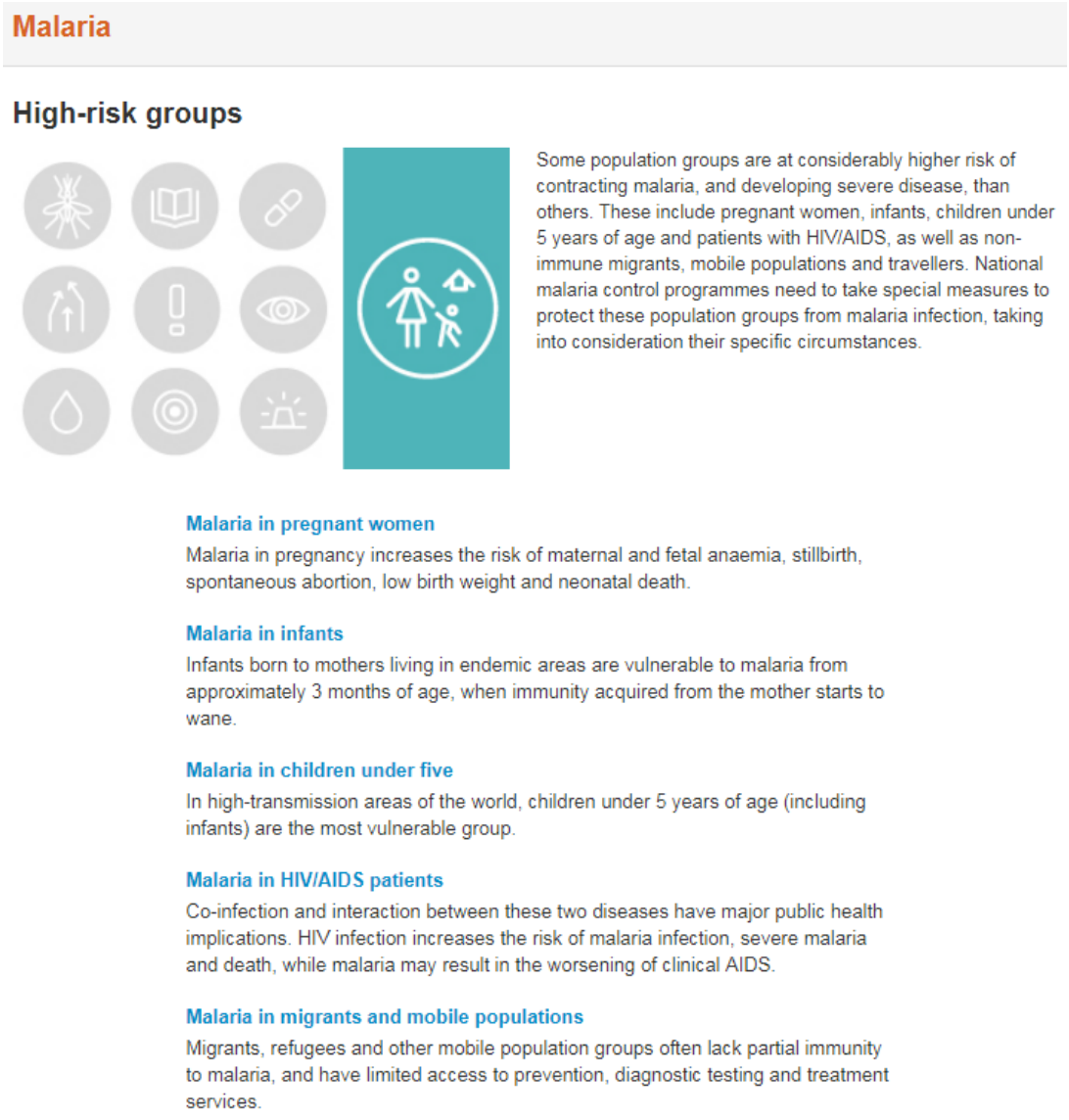

Figure 3.7: A WHO factsheet that explains malaria risk factors [31]

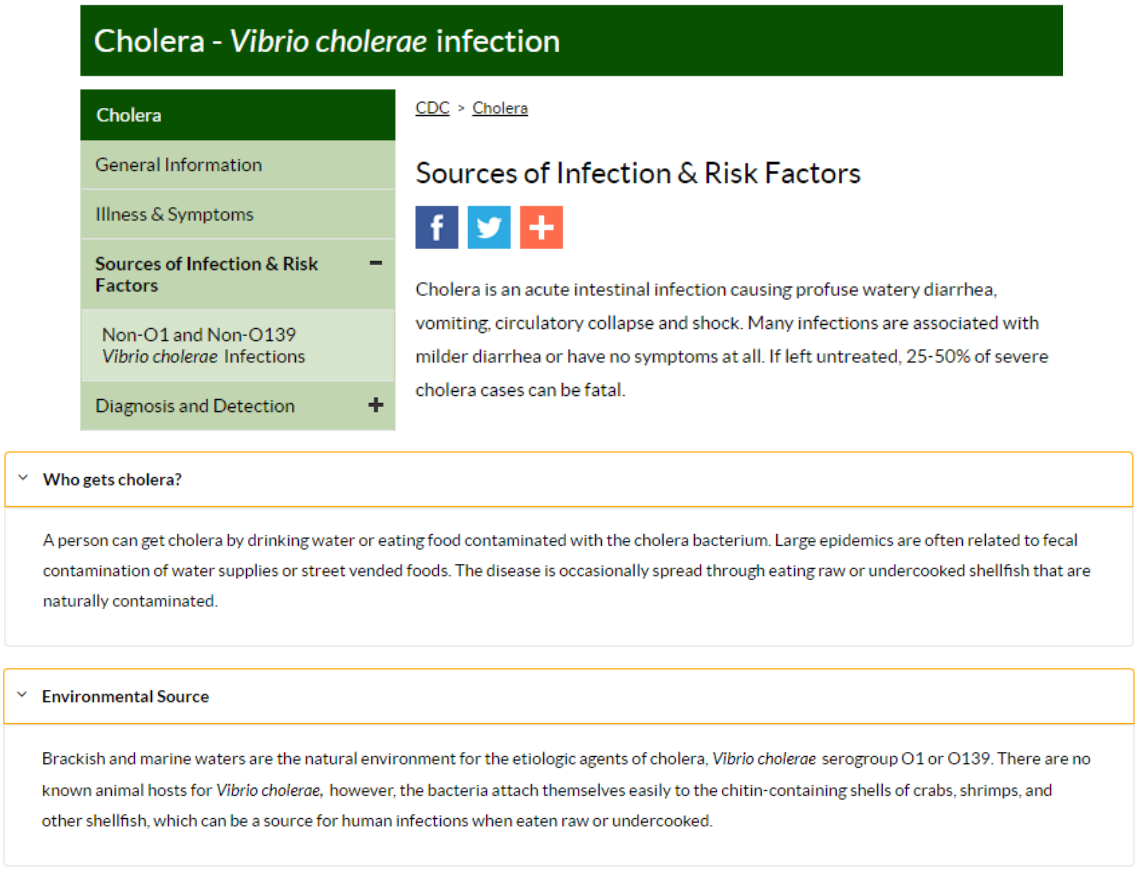

Figure 3.8: A CDC factsheet that explains cholera risk factors [30]

In this section, the fundamental knowledge of infection risk started from the pathogen (e.g. virus, bacteria, parasite, or mix), pathogen habitats (i.e. reservoir), and how pathogens attack human (i.e. transmission modes) was explained. Human as hosts, has four stages of infection: susceptible – exposed – infected – recovered. The personal infection risk factors are usually derived from S and E compartments, whereas the climate risk factors are related with the pathogen and vector life requirements. Besides that, the weather also affects human immunity level which can alter the risk of a person contracting infectious disease, either increase or decrease the risk. The infection risk factors related to specific location features are related to pathogen's reservoir, and vector's distribution. Whereas the urbanization, human development status, social-economic factors are related to infection risk factors that can be deduced from a country.

3.1.2 Disease Risk Quantifications

Previous section presented the information about the infectious risk factors gathered from reservoir and transmission modes, and then categorized into person, climate, and location. Since AHID, WHO, and CDC present the infection risk knowledge in declarative form, the magnitude of each found risk factor is not always provided.

This section aims to collect the form of risk quantifications used to measure the magnitude of risk factor in the epidemiology context which is usually exhibited in case-control studies (see **Figure 1.1**). Case-control studies can be found by submitting these keywords to search engines: `"disease risk", "infection risk", "risk prediction", "estimating risk", "personal (risk) factors", "environmental (risk) factors", "human infectious diseases", "risk ratio", "odds ratio", "relative risk", "demographic"`. Journal articles are preferred to be included in the review rather than the ones that are published in conference proceedings.

From knowledge books [32], [151], it is apparent that the probability of someone contracting a disease depends on the personal attributes he/she has, the surrounding environment he/she lives in, and the commonness of the disease in the region he/she lives in. Besides risk ratios, those books mention disease *prevalence* or *incidence* as another parameter that is commonly used to quantify the commonness of disease morbidity in a population. Therefore, identification of disease risk quantification is not only the risk ratio but also morbidity frequency (e.g. prevalence and incidence).

Table 3.2 shows the selected journal articles for human (infectious) diseases. Relevant quantifications (risk ratios, morbidity frequency, and other quantification mentioned in each retrieved article) to predict the personalized infectious disease risk are identified. In **Table 3.2**, the diseases are not only limited to infectious diseases. Only 20 out of 234 infectious diseases are presented in this table.

Table 3.2: Retrieved articles that contain the risk quantifications

No.	Name of Disease [Citation]	Risk Ratios	Morbidity Frequency	Other Variables	Rank of Journal
1	Schistosomiasis [86]	OR	Prevalence	Confidence Interval per OR	Q2
2	Diabetes Mellitus, Heart Failure [152]	OR	Prevalence		Q2
3	Respiratory Diseases [153]	OR	Prevalence		Q1/Q2

4	Yersinia enterocolitica [87]	OR	Prevalence	Sero-prevalence (prevalence in serum), Confidence Interval per OR	Q1
5	Ross River Virus [154]	NA	Incidence	Descriptive Statistics of each personal risk factor in total case	Q1/Q2
6	Gastric Cancer [4]	OR	Incidence	Confidence Interval per incidence per year	Q1
7	Vector-borne Diseases [74]	NA	Prevalence		
8	Atherosclerotic Cardiovascular Disease (ASCVD) [155]	OR	Incidence	Confidence Interval per OR	Q1/Q2
9	Tuberculosis [21]	OR	Incidence	Confidence Interval per OR	Q1
10	Tuberculosis [132]	OR	Prevalence		Q3
11	Acute Endophthalmitis [5]	OR, RR, Pooled OR	Incidence		Q1
12	Obesity [114]	OR	Prevalence	P-value per OR	Q1
13	Cardiovascular Disease (ASCVD) [156]	NA	Prevalence	Framingham Cohort, Descriptive Statistics of each personal risk factor in total case	Q1
14	Dengue Disease [157]	OR	Incidence	P-value per OR	Q1
15	Norovirus [158]	OR	Incidence		Q2
16	Influenza [159]	NA	Incidence	Descriptive Statistics of each personal risk factor in total case	Q2
17	Lyme Disease [160]	NA	Incidence	R square	Q1
18	Anthrax [161]	OR	Incidence		Q1
19	Coronary Heart Disease (CHD), Gastric Cancer, Thrombosis, Pancreatic Cancer, Malaria [162]	OR	Prevalence, Incidence	Confidence Interval per OR	Q2/Q3
20	Escherichia coli [163]	OR, RR	NA	Confidence Interval and P-value per OR	Q2
21	Rare disease: Kaposi sarcoma, Toxoplasmosis, Kawasaki disease [107]	OR	Prevalence, Incidence	False Discovery Rate (FDR) and P-value per OR	Q1
22	Parkinson's disease [164]	RR	Incidence	P-value per RR, Descriptive Statistics of each personal risk factor	Q1
23	Herpes Zoster [165]	OR	Incidence	Confidence Interval per OR	Q1
24	Colorectal Cancer [142]	OR	Incidence		Q3/Q4
25	Intrahepatic cholangiocarcinoma [166]	Pooled OR	Incidence	Confidence Interval per OR	Q1
26	Bacterial Infections [167]	NA	Incidence	Descriptive Statistics of each personal risk factor	Q1
27	Tuberculosis [6]	OR	Prevalence		Q1
28	Spinal Tuberculosis [136]	OR	Prevalence	P-value per OR	Q1

29	Meningococcal disease [8]	OR	Prevalence	Confidence Interval and P-value per OR	Q1
30	Meningitis, Herpes Zoster [168]	OR	Prevalence	Confidence Interval and P-value per OR	Q2
31	Meningococcal disease [169]	OR	Prevalence	Confidence Interval per OR	Q1
32	Meningitis [170]	OR	Prevalence	Confidence Interval and P-value per OR	Q3
33	Dengue Fever [148]	OR	Prevalence	Confidence Interval and P-value per OR	Q1
34	Dengue Fever [49]	OR	Prevalence	Confidence Interval per OR	Q1
35	Dengue Fever [149]	OR	Prevalence	Confidence Interval and P-value per OR	Q1
36	Dengue Fever [171]	OR	NA	Descriptive Statistics of each personal risk factor, Confidence Interval per OR	Q1/Q2
37	Dengue Fever [41]	OR	Prevalence	Confidence Interval per OR	Q1
38	Dengue Fever [7]	OR	Prevalence	Confidence Interval per OR	Q1
39	Cholera [172]	NA	Prevalence	Raw morbidity case data, Descriptive Statistics	Q4
40	Cholera [147]	OR	Prevalence	Confidence Interval and P-value per OR	Q1
41	Cholera [173]	OR	Prevalence	Descriptive Statistics, P-value	Q1/Q2
42	Cholera [146]	OR	Prevalence	Confidence Interval per OR	Q2
43	Crohn's disease [42]	RR	Prevalence		Q1

From **Table 3.2**, in the scope of risk ratios, besides odds ratios (OR), there is another measure used to quantify the magnitude of a risk factor: relative risk (RR). The definition of OR and RR are given in the following section. After knowing the measures relevant to quantify infection risk factors, the format they are usually presented in the scientific articles is studied.

From 43 reviewed articles in **Table 3.2**, two formats of risk quantifications are shown: *numerical* and *ordinal* values. 36 articles present the risk ratios in *numerical* forms (e.g. OR, RR, pooled OR). 3 articles present the risk ratios as *ordinal* values (e.g. high, moderate, low risk). 7 articles do not contain any risk ratio, but present the raw data (1 article), descriptive statistics (5 articles) of the surveyed data, and R-square (1 article). From the 36 articles that mention *numerical* risk ratios, 34 articles use OR; 4 articles use RR; 2 articles use both OR and RR; 2 articles use pooled OR[5]. The meaning of these measures is explained below.

[5] Pooled-OR is an odds ratio that is calculated from a combination of multiple surveys.

For morbidity frequency, 24 and 15 articles provide prevalence and incidence, respectively; 2 articles provide both, and 2 articles do not contain information about morbidity frequency.

Risk Ratios

A risk ratio is a measurement that is used to describe the magnitude of a risk factor. The risk ratio is usually presented as either an odds ratio (OR) or a relative risk (RR); both measures the same thing, only slightly different in precision [174]. The OR is used to determine whether an exposure is a risk factor for an outcome, and to compare the magnitude of various risk factors for that outcome. In this research, the outcome is the risk of a person contracting an infectious disease; examples of exposures of interest in this research are gender, or temperature of the day [32].

OR=1 means exposure does not affect odds of outcome
OR>1 means exposure is associated with higher odds of outcome
OR<1 means exposure is associated with lower odds of outcome

Another representation of risk ratios uses addition or reduction by a certain percentage. For example, by consuming 1 cup of milk per day, the tuberculosis risk is reduced 29%; or by smoking one pack of cigarette per day, the tuberculosis risk is increased by 10%. To convert such risk additions and reductions by a certain percentage into risk ratios, the formulae eq. 1 and eq. 2 can be used [32].

$$OR = 1 + \frac{percentage}{100} \quad \text{eq. 1}$$

$$OR = 1 - \frac{percentage}{100} \quad \text{eq. 2}$$

Table 3.3 shows a contingency table that observes whether a person's gender affect a person's risk of being infected by an infectious disease. The observation involves counting how many females and males are infected (**a** and **c**, respectively). These numbers are then compared with the number of females and males that are not infected (**b** and **d**, respectively). This comparison gives a sense that the person's risk of being infected by an infectious disease is not solely caused by their gender, but also other factors. By using eq. 1 the magnitude of a person's gender to the predicted infection risk is measured.

Table 3.3: An example of a table for calculating the magnitude of a risk factor (i.e. contingency table)

Hypothesized Risk Factor (e.g. gender – E_1)	Number of people that are infected by an infectious disease (D)	Number of people that are not infected by an infectious disease
Male	a	b
Female	c	d

$$OR = \frac{a/c}{b/d} \quad \text{eq. 3}$$

By using the risk ratios, the probability of a person's risk of contracting (infectious) diseases can be deduced. For example, from a tuberculosis case-control study, the odds ratios for smoker is 2.3, and for male is 1.34. Then, a male smoker's risk of contracting tuberculosis is 3.082 (product of 2.3 and 1.34) [43]. But, this 3.082 cannot be used to infer how many people with the same attributes are at risk for tuberculosis in the same location he lives in. A measure in the following section is used to project the infection risk per population.

Another definition of the odds ratio besides eq.3 is given below,

$$OR(D|E) = \frac{O(D|E)}{O(D|\bar{E})} = \frac{\lambda_{E|D}}{\lambda_{\bar{E}|D}} \quad \text{eq. 4}$$

The definition above is used when the odds of contracting disease D given evidence E $O(D|E)$ are known.

Morbidity Frequency

In general, morbidity encompasses disease, injury, and disability. This research is concerned only with morbidity frequency for infectious disease. There are two measures that are relevant to infectious diseases: *prevalence* and *incidence* rates. *Prevalence* is the proportion of persons who have a particular disease, both new and pre-existing cases, in a population at a specific time period, whereas *incidence* is limited to new cases only. Both have same units, per 10,000 or 100,000 population depending on the disease [151]. Some morbidity case reports are obtainable from the WHO website [19].

The formulae below are used to calculate the incidence and prevalence,

$$Prevalence = \frac{all\ new\ and\ pre{-}existing\ cases\ during\ a\ given\ time\ period}{population\ during\ the\ same\ period} \quad \text{eq. 5}$$

$$Incidence = \frac{new\ cases\ during\ a\ given\ time\ period}{population\ during\ the\ same\ period\ or\ at\ start\ of\ period} \quad \text{eq. 6}$$

Since the measure that is usually reported to public health agencies (e.g. WHO, CDC) is the number of reported cases (the numerator of eq. 4 and eq. 5), the population of a country where a client lives is used to calculate the prevalence or incidence.

3.1.3 Summary

In summary, three concepts are needed to predict infectious disease risk in a person: (1) the chain of infection for general human infectious diseases, (2) the SEIR concept of infection flow in a person, (3) the correlation between environment (climate, location) and the infectious disease emergence. Chain of infection shows that infectious diseases are the result of interaction between three elements: *pathogen*, *host*, and *environment*. Pathogen or vectors of infectious diseases have specific *reservoir* and *transmission modes* where the environmental risk factors can be deduced. By understanding the SEIR model, the host susceptibility and the possibility to get pathogen exposure can be used to explain the *personal* risk factors. Whereas from the correlation between *environment* and infection risks, there are three components that are influential: geographical variation (e.g. terrain, land-use, country), climate (e.g. weather and season), human social interaction (e.g. gathering, work, school), and human immunity changes affected by certain atmospheric conditions (e.g. winter-immunosuppression). The characteristics of the infectious disease risk knowledge can be binary, nominal, and ordinal. Meanwhile the infectious disease risk quantifications are continuous (e.g. risk ratios, morbidity frequencies).

The further explanation about country and location features were reviewed from AHID infection drivers. Human and livestock density population, human developments, peacefulness are the examples of infection drivers which are usually observed from a nation. Whereas the urbanization, water and sanitation are the examples of infection drivers from a specific region of a nation. Furthermore, all mentioned risk factors from all human infectious diseases that ever existed are collated from declarative knowledge sources: Atlas of Human Infectious Diseases (AHID), World Health Organization (WHO), and Centre for Disease Control and Prevention (CDC). The infection risk

drivers' can be categorized into risk factors that related to *person*, *climate* (weather or season), *location* (country or location features). For accommodating infection risk factors that cannot be classified into aforementioned categories, a *miscellaneous* can be used.

Thereafter, the quantifications of the risk factors were reviewed from case-control studies in epidemiology domain. The common measurements are *risk ratios* and *morbidity frequency*. *Risk ratios*, either as odds ratios (OR) or relative risk (RR), are used to quantify the magnitude of the impact of risk factors on a disease. Whereas the commonness of disease *morbidity* in a region is usually presented in numeric form with certain population units, either as prevalence or incidence. By using these two measurements, the person's risk of contracting of infectious diseases can be estimated based on her/his risk ratios of the personal and environmental risk factors and morbidity frequency of the location.

The collected information about risk factor and quantifications will be used to design the knowledge representation for infectious disease risk knowledge. The design will be presented in chapter 5.

3.2 Disease Knowledge Representation

In section 1.4, research objectives and goals were explained. A knowledge representation that encodes the infectious disease risk knowledge and usable by the epidemiologists is needed. In section 3.1, the infectious disease risk knowledge, risk factors and risk ratios, was explained. This section investigates the existing knowledge representation for human (infectious) disease in *medical* and *computer science* areas that help the domain experts. Thereafter, the required efforts and adjustments of the domain experts to encode their knowledge using the selected knowledge representation are identified.

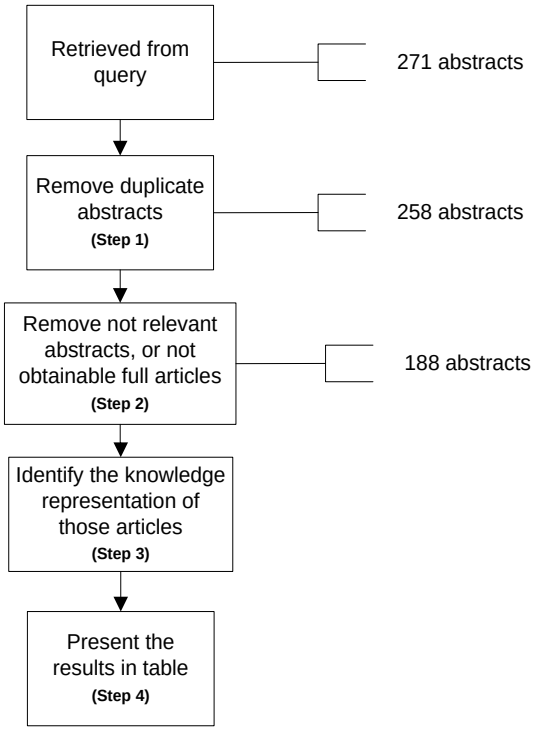

Figure 3.9 Procedure to select documents about knowledge representation for this review.

The investigation aims to find how (infectious) disease risk factors in both areas are represented for achieving various purposes, not limited to risk prediction only. Using this query `TITLE-ABS-KEY (disease "knowledge representation") AND (LIMIT-TO (SUBJAREA, "MEDI") OR LIMIT-TO (SUBJAREA, "COMP")) AND (LIMIT-TO (LANGUAGE, "English"))` in Scopus[6] repository, 401 abstracts are retrieved. 271 of 401 abstracts that are published 10 years from now (within 2008 to 2018) are selected. Further selection procedure is presented in **Figure 3.9**.

Several abstracts were removed from the list because they were duplicate or anonymous abstracts. The anonymous was removed because the author's eligibility in this topic cannot be searched. Thereafter, further abstracts were removed due to irrelevancy (abstracts and keywords did not match, or there is no knowledge representation in the full article despite being mentioned in the abstract). Another situation is when the abstract is not well written, usually the full article will be searched to clarify the meaning of the abstract, but it turns out that full article cannot be downloaded. The full article can help

[6] Scopus is Elsevier's abstract and citation database, https://www.scopus.com

the reader to conclude whether the article is relevant to the research or not. So, that in such cases, abstracts will be removed from the list.

At the end of the process, there are 188 articles left. Most of the retrieved articles are about building an expert system for diagnosing a particular (infectious) disease or syndrome in a person by representing the knowledge using case-base reasoning, fuzzy cognitive maps [175]–[177]. Another stream of the articles are about supporting a specific medical decision by representing patient data using a knowledge representation (e.g. ontology) [178], [179]. Some other articles are conflict and knowledge discovery which are related to medical decisions [180], [181]. Only few articles that assessing risk of certain (infectious) diseases or rare syndrome in a person [182], [183].

All 188 articles were studied, and the used knowledge representation for achieving their own purpose was identified and summarized in **Table 3.4**.

Table 3.4: Summary of disease-related knowledge representations from articles published from 2008 until mid-2018[7].

No	Knowledge Representation	Number of articles that are published in										
		2017-June 2018	2016	2015	2014	2013	2012	2011	2010	2009	2008	Overall
1	Ontologies (OWL)	10	8	12	8	5	4	6	5	6	8	72
2	Fuzzy (incl. Fuzzy Cognitive Map)	2	3	6	2	1	2	3	3	2	0	24
3	Rules (excl. semantic-web rules, belief rule-based)	1	2	5	6	2	4	0	0	2	0	22
4	Artificial Neural Networks and its variants (e.g. Radial Basis Function)	2	0	7	2	1	2	0	1	0	1	16
5	Semantic Networks	3	0	2	0	2	0	3	1	3	0	14
6	Bayesian Networks	2	0	2	0	2	1	0	2	0	0	9
7	Case-based Reasoning	2	1	2	1	1	0	0	0	0	1	8
8	Graph and its variants (e.g. Bipartite Graph)	0	0	1	3	2	0	1	1	0	0	8

[7] The author names, article title, and published year of the retrieved abstract can be seen at Appendix 1

9	Data-driven temporal model	3	2	0	0	0	0	1	1	0	0	7
10	Belief rule-based	1	1	0	2	1	0	0	0	0	0	5
11	Answer Set Programming	1	1	0	1	1	0	0	0	0	1	5
12	Semantic-Web Rules (SWRL)	1	0	0	0	0	1	1	0	0	0	3
13	Decision Tree	1	0	0	0	0	0	1	0	0	0	2
14	Other (e.g. Lazy reasoning, Hybrid model, Lattice model, frame)	5	2	3	1	2	2	1	0	2	0	18

The number of articles mentioning each knowledge representation in each year is shown, to show the development over the decade. The knowledge representations in the table are ordered by decreasing frequency (right-most column in **Table 3.4**). Since each article may avail more than knowledge representation to achieve their aims, thus, the total of *overall* column is more than 188.

The process of identifying knowledge representation for each article was easy. If the abstract of the article is good, then, only by reading the *methodology* or *result* section of the abstract, the knowledge representation of each article can be obtained. For some articles, the full articles are needed to clarify the knowledge representation they used; they usually present them in their main section.

Related to the term they used for the knowledge representation, the ones which do not have many strains (e.g. ontology, Bayesian network, or case-base reasoning) are easily to spot. But, for artificial neural network, fuzzy, rules that have many specifications where for each strain they different term (such as *radial basis function* is a strain of *artificial neural network*), more works to find out the parent technique are needed.

Mixed models or new models are also tricky, for example, belief-rule based that is a combination between belief (like in the Bayesian network) and if-then rules. Thus, these kind of models, both Bayesian network and rules are identified as knowledge representation of this article.

There are several knowledge visualizations encompassed in **Table 3.4**: network, tree, if-then statement, map, graph, and ontology. For *network* visualizations, the knowledge

representation #4 (Artificial Neural Networks), #5 (Semantic Networks), and #6 (Bayesian Networks). *Artificial Neural Networks (ANN)* is a deep learning technology by training large data to create an adaptive map that consists of layers of nodes where nodes between layers are connected by a weighted edge. *Bayesian Networks (BN)* is a knowledge model that contains node which represents a random variable, and edges between the nodes representing probabilistic dependencies among the corresponding random variables. *Semantic Network (SN)* is a form of knowledge representation between concepts, objects, features, events in a network. Unlike the ANN and BN that are executable approach to yield the numerical prediction, SN is more as a conceptual approach, hence, need other executable approach to formalize the SN. Some articles include *frame* (#14) into SN. However, SN is good at conceptualizing knowledge that needs clarity on object-to-object relationships, while frame focus on the conceptualization of object-to-attribute relationships.

An ontology (i.e. knowledge graph) is a representation of formal naming, definition of the categories, properties, and relations by explicitly conceptualizing the data and entities in one, many, or all domains. Ontology allows sharing conceptualization (e.g. vocabulary) which can be used to model a specific knowledge for a particular purpose.

For *tree* visualizations, *decision trees* (#13) is a knowledge model learned from observations about an item which represented as a branch. A tree can be used to represent if-then rules.

Rules (#3) is a conditional statement that represents causality between antecedent and consequent, which denoted by $p \rightarrow q$. A set of rules is a rule-base which is commonly used as a knowledge representation. Rules that is implemented in an ontology environment is called *semantic-web rules* (#12). Rules that incorporate uncertainty like BN is called *belief rule-based* (#10). In **Table 3.4**, these three types of rules are separated since they have different feature and environment of implementation. More discussion about these three kinds of rule will be provided in section 3.2.4.

A set of rules is called as rule-base. The rule-base is commonly used to predict desired outcome(s). Rule-base is built from historical data or observations, thus, mostly it can only solve the problem that has already known before. For a new problem that is not contained in the observations, the *case-based reasoning* (#7) model can be used. A

technique to measure distance between the new problem and the cases is utilized, which then can be used to infer the estimation of the results.

Besides rules, a knowledge visualization that using a statement is *Answer Set Programming* (#11) (ASP). ASP is a form of declarative programming which is categorized constraint programming languages. Group of logics and AND or OR operators are used to create the ASP.

For map representation, *Fuzzy Cognitive Maps (FCM)* (#2) is a combination of *fuzzy logic* and cognitive mapping. *Fuzzy logic* itself is a form of multi-valued logic which the values may be any real number between 0 and 1. Fuzzy logic are represented by if-then statement. *Cognitive maps* (i.e. mental map or mental model) is a representation which allows the users to look for a cause-effect in the ideas of the mapping. Since there is no cognitive map appear as standalone knowledge model in the collected articles, thus, FCM is merged with fuzzy logic knowledge representation.

From the review, it is apparent that there are two approaches to acquiring knowledge in the context of artificial intelligence systems. First, the knowledge is induced from observational data; this approach is known as *data-driven* [106], [184], [185]. The knowledge representations that are used in data-driven cases are Fuzzy Cognitive Maps, Artificial Neural Networks, Data-driven temporal models, and Decision Trees.

Second, approach to knowledge acquisition is from domain experts directly or from their knowledge documentations; this approach is known as *knowledge-driven* [186], [187]. The knowledge-driven representations that are used for knowledge-driven systems are in **Table 3.4** are Ontologies, (some of) Fuzzy, (some of) Rules, (some of) Bayesian Network, Semantic Network, etc.

Whereas, based on the characteristic of the knowledge representation, there are two representation types: (1) using *node-link structures*, and (2) using *antecedent and consequent*. Of the knowledge representation listed in **Table 3.4**, Ontologies, Semantic Networks, Bayesian networks, Fuzzy Cognitive Maps, Artificial Neural Networks, Decision Trees and Graphs are categorized in the first type. The advantage of node-link structures is they easily represent properties of an object, and illustrate the relationship between objects [188]. Whereas the second type, *antecedent-consequent* (if-then rules),

comprises of Semantic-web rules, Belief rule-based, Answer Set Programming. This kind of representation emphasizes the causal relationship between antecedent and the consequent [189]–[191].

From **Table 3.4**, it can be seen that the most used knowledge representation in these areas is *ontologies* (discussed in section 3.2.1). For node-link structures, the most used data-driven approach is, *Fuzzy Cognitive Map*; and, the most used knowledge-driven approach is, *Bayesian Network*. These methods are described in section 3.2.2 and 3.2.3, respectively. Also, all kinds of *rules* are explained in section 3.2.4.

To answer the research question, two types of approaches can be used. The first type is approaches that represent knowledge related to diseases mentioned in risk prediction articles. This type is explained in section 3.2.1 to 3.2.4. Whereas, the following section presents the second type of approaches that combine both risk prediction and knowledge representation as a single model but not related to disease or health. This second type will be described in section 3.3.

3.2.1 Ontology

As described in section 1.6, the knowledge representation for this research is expected to encode the infectious disease risk knowledge. From section 3.1, the personal attributes related to infectious disease risk knowledge can be presented as risk factors, and quantified by risk ratios, whereas some the environmental attributes (e.g. country as a location) to infectious disease risk knowledge can be quantified by morbidity frequency. In this section, relevant ontologies are explored with a view to identifying an existing ontology which can be reused to encode infectious disease risk factors for both personal and environmental attributes.

An ontology is a formalization of knowledge using classes and properties. From **Table 3.4**, ontology is the most used knowledge representation for encoding the domain knowledge in computer science and medical areas. Several of the reviewed articles provide URLs of ontology repositories. Thus, they lead to further search in repositories such as BioPortal [192], OBO Foundry [193], or Google Code Archive [194].

19 ontologies are found with various focuses depending on the research purposes. To give a glance review for each ontology, **Table 3.5** presents those 19 ontologies along with the abbreviation and a citation.

Table 3.5: A list of the found ontologies

No.	Name of ontology (abbreviation) [source]
1	Network of Epidemiology-related Ontologies (NERO) [195]
2	Vaccine Ontology (VO) [196]
3	Human Disease Ontology (DOID) [197]
4	Infectious Disease Ontology (IDO) [22]
5	Epidemiology Ontology (EPO) [195]
6	Diabetes Mellitus Diagnosis Ontology (DDO) [198]
7	Bacterial Clinical Infectious Disease Ontology (BCIDO) [199]
8	Cigarette Smoke Exposure Ontology (CSEO) [200]
9	Apollo [201]
10	Traditional Chinese Medicine (TCM) [202]
11	Tibb Al-Nabawi Medicine (TibbOnto) [203]
12	Ontology of Psychiatry (OntoPsychia) [204]
13	PCP for Thalassemia (PCPThalOnto) [205]
14	Infectious Disease Ontology for Schistosomiasis (IDOSchisto) [24]
15	Infectious Disease Ontology for Brucellosis (IDOBru) [23]
16	CardioRenal Risk Factor Ontology (CARRE) [25]
17	Hepatitis Ontology (HEPO) [27]
18	Ontology Reasoning Component for Diabetes (ORC) [206]
19	Ontology based expert system for thyroid disease diagnosis (OBESTDD) [207]

Ideally, all ontologies are inherited from the basic formal ontology (BFO) [208], a generic ontology that does not contain any domain-related terminologies. The ontologies #3 (DOID) and #5 (EPO) are inherited from BFO with specific concentration on human diseases and epidemiology domain, respectively [195]. Therefore, these ontologies focus on providing general vocabularies and their semantic relationships (e.g. synonym).

DOID and EPO ontologies allow other research to reuse some or all of their ontology objects with more detailed focus (i.e. disease-specific ontology). The ontologies #4 (IDO), #6 (DDO), #8 (OBESTDD), #16 (CARRE), #17 (HEPO), #18 (ORC) are inherited from ontology #3 (DOID) with more focus on a particular disease. While the ontology #1 (NERO) is inherited from #5 (EPO). Ontologies #7 (BCIDO), #14 (IDOSchisto) and #15 (IDOBru) are instantiations of IDO. The tree diagram that showing the which ontologies are inherited from which foundation ontologies (e.g. BFO, DOID, EPO) is given in

Figure 3.10. The arrows show which ontologies are parents of other ontologies. For example, the EPO is the parent of NERO. The grey rectangular on the left shows ontologies that are containing risk factors as their ontology objects. The yellow squares show the ontologies that are related to human diseases. The patterned squares show the ontologies related to human infectious diseases.

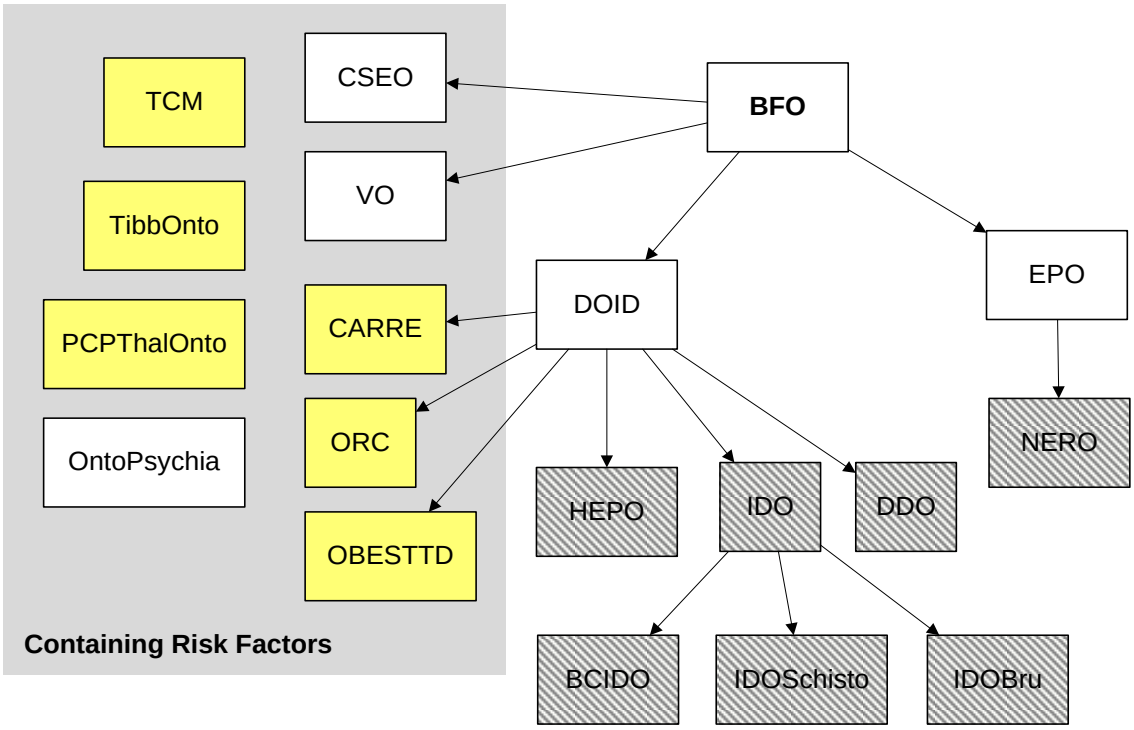

Figure 3.10: A tree explaining the relationship between ontologies given in **Table 3.5**

The DOID, IDO, and EPO do not represent causal relationships between risk factors and the disease risk. However, their instantiations provide the reusable vocabularies and semantic relationships for explaining the causal relationship for the detailed disease risk. For example, CARRE is instantiated from DOID, CARRE specifies the detail characteristics of cardiorenal diseases in which the basic concept is inherited from human disease in DOID.

From the obtained information from the associated articles, the existing ontologies that are inherited from the infectious disease ontology (IDO) only describe characteristics of the particular infectious diseases (e.g. IDOBru, IDOSchisto); they don't encode the infectious disease risk factors.

Therefore, a new investigation to find disease-specific ontologies that inherit objects from different generic ontology is conducted. Now, the ontologies in **Table 3.5**, that encode risk factors, inherited from DOID or from BFO are investigated. This investigation aims to find reusable terminologies, measures, annotations to encode infectious disease risk factors. As a result, there are 5 ontologies that represent disease risk factor knowledge in the context of epidemiology: #2 (VO), #8 (CSEO), #16 (CARRE), #18 (ORC), #19 (OBESTDD). CARRE is built to find the risk prediction of the cardiorenal disease, therefore, the CARRE contains some personal risk factors. Same with CARRE, ORC is designed to model domain and operational knowledge for understanding diabetes risk factor. The OBESTDD focuses on obesity risk factor for thyroid disease only. Whereas, CSEO defines the cigarette smoking effects to general health, not specific to disease risk. Even though those ontologies are not specific to infectious diseases, but some of ontology objects can be reused to further design of knowledge representation.

From 19 ontologies provided in **Table 3.5**, ontologies that are not instantiated from DOID, IDO, EPO nor BFO but encode the risk factor knowledge are investigated. The result is #10 (TCM), #11 (TibbOnto), #12 (OntoPsychia), and #13 (PCPThalOnto). These ontologies do not reuse vocabularies or properties from BFO or DOID but create their own ontology objects. TCM, TibbOnto, and PCPThalOnto are specific for describing Traditional Chinese Medicine, Prophetic Medicine (‘Al-Tibb al-nabawi), and Thalassemia, respectively. Whereas, OntoPsychia is an ontology that explains mental illness and its treatment (i.e. psychiatric).

Again, none of these ontologies are specific for encoding the risk factors (personal or environmental) specific for infectious diseases. In **Figure 3.10**, only three ontologies that are related to infectious diseases (BCIDO, IDOSchisto, IDOBru), but none of them is covered by grey area, regardless they are instances of the BFO or not. However, some of the ontology objects (classes and properties) of these ontologies (yellow boxes) can still be reused.

3.2.2 Fuzzy Cognitive Map

From **Table 3.4**, *Fuzzy Cognitive Map* (FCM) is the second-most used knowledge representation after ontologies. FCM is a map-based representation to capture the domain expert knowledge and conduct what-if analysis. FCM mostly use learning algorithms to populate the adjacency matrix, however, the simple formula regression can be used to infer the values in the adjacency matrix [209].

Even though the main purpose of the adjacency matrix is for what-if analysis and simulation, it can be used to predict the disease risk. FCM is capable of representing magnitude of *drivers* that have *positive* (+), *negative* (-) or *unknown* (?) effect to the *receiver*. In the context of this thesis, the driver can be used to model the risk factors, the magnitude of drivers can represent the risk ratios, and the receiver can symbolize the predicted infection risk. The driver magnitude ranges from -1 to +1. To represent certainty, the FCM also provides a specific feature named *confidence rating*.

The declarative anthrax risk knowledge that is encoded in **Figure 3.12** is presented in **Figure 3.11**. This declarative anthrax risk knowledge is taken from AHID [13].

There are three kinds of anthrax transmissions: (1) contact with infected animal tissue, *cutaneous anthrax*, direct skin inoculation during processing of contaminated animal hides, hair, wool, or animal hide products, (2) *gastro-intestinal anthrax*: consuming meat from infected livestock, (3) *inhalation anthrax*: inhalation of anthrax spores by tanning/shearing sheep or processing contaminated hair/wool or intentional during a bioterrorist attack. There is no direct person-to-person transmission. Anthrax occurs mainly in rural areas in countries where there is no livestock vaccination and no veterinary control of slaughtered animals. There is a seasonal variation in animal disease with an increase in cases during hot dry weather. Anthrax is an occupational hazard for people who process contaminated animal tissues, this makes anthrax cases are prevalent more in adult instead of children, and more in men instead of women.

Figure 3.11: A piece of declarative anthrax risk knowledge

For an encoding example, **Figure 3.12** shows the knowledge of anthrax risk factors that is summarized from AHID [13]. *Age* and *temperature* have positive relationships (+) to anthrax risk; the more the *age*, the higher the anthrax risk. *Humidity* have negative relationship (-) to anthrax risk; the less the *humidity*, the higher the anthrax risk. The relationship between eating habit, gender, season, location feature and anthrax risk cannot

be identified (?). The dummy adjacency matrix of this anthrax risk factor knowledge is presented in **Figure 3.13**.

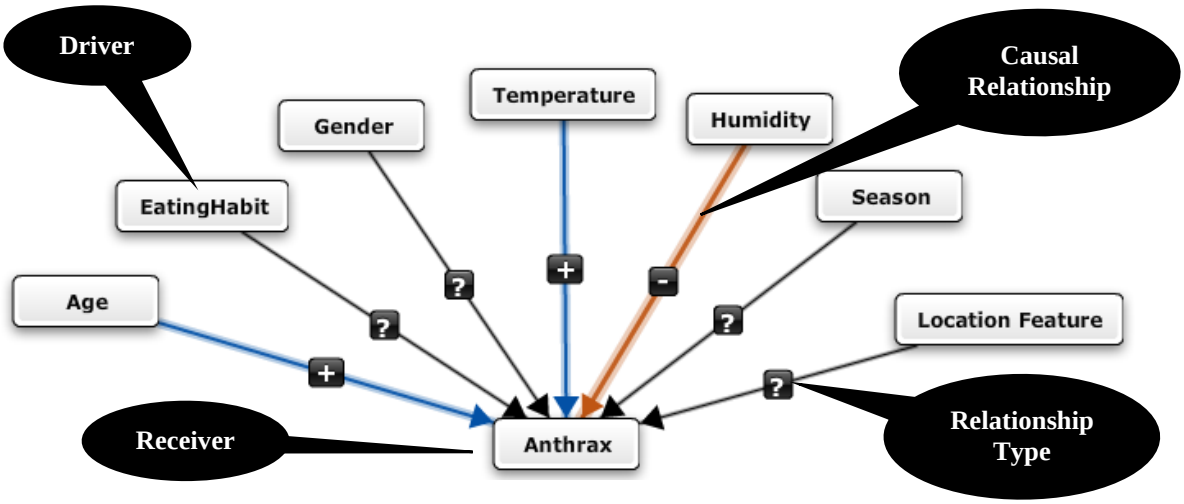

Figure 3.12: Fuzzy Cognitive Map to represent the example of anthrax risk. Blue and brown arrows indicate positive and negative relationships, respectively. Black arrows indicate unknown relationships.

From **Figure 3.12**, only *age*, *temperature*, and *humidity* are applicable the FCM, it is because age and atmospheric conditions (temperature and humidity) are presented in continuous form. Even though the *eating* habit (vegetarian, meatatarian), *gender* (female, male), *season* (winter, spring, summer, fall), and *location feature* (forest, river) are illustrated in the FCM, but their relationships are unknown. Therefore, the adjacency matrix for those kind of relationship cannot be filled in.

Component	Indegree	Outdegree	Centrality	Preferred State	Type
Age	0	0.44	0.44		driver
EatingHabit	0	0	0		none
Occupation	0	0	0		none
Temperature	0	0.25	0.25		driver
Humidity	0	0.64	0.64		driver
Season	0	0	0		none
Location Feature	0	0	0		none
Anthrax	1.33	0	1.33		receiver

Figure 3.13: Dummy adjacency matrix that represents anthrax risk

To fill the adjacency matrix, two ways can be used: *a learning algorithm*, or using a *simple regression formula* [209]. Outputs from a simple regression can be used to fill up the magnitude. For example, from a dummy regression formula below,

$$DF_t = 0.73\, Temperature_{t-1} - 0.8\, Humidity_{t-1}$$

The dengue fever (DF) case in month (t) depends on temperature (Celsius) and humidity (%) in preceding month (t-1). From the coefficient it can be seen that each 1^{o}C increase in temperature, the dengue fever case will increase 0.73. Thus, the type relationship is positive for *temperature*. Same goes to the other variable, each 1% increase in humidity, the dengue fever case will decrease 0.8. Then, the type of relationship is negative for the *humidity*. Since the variables that can be encoded in FCM are only continuous ones, the categorical data type (nominal or ordinal) cannot be encoded using FCM. For example, *gender* which may contain *female* or *male* only.

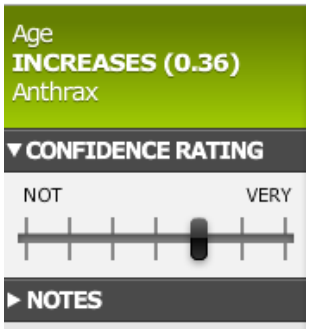

Figure 3.14: Confidence Rating for each link in the FCM

Therefore, the domain expert effort is linear with the number of the risk factors. Besides that, to encode certainty, FCM has special placeholder, *confidence rating*, for experts to indicate their confidence and include that in the outcome calculation (see **Figure 3.14**).

FCM only facilitates continuous numerical attribute from -1 to +1 for each predictor. This helps the decision makers for simulating the sensitivity analysis[8] better than other models (e.g. BN, Regression) [37], [38]. In this research, the decision makers are the one who use the FCM to solve their problems which is the person who is looking for his risk of contracting infectious diseases. For analysis like finance, market sales, or other domains

[8] Sensitivity analysis is a kind of study that adjusting the independent variables will affect a particular dependent variable under given set of assumptions. Usually the study objective is to find the maximum profits or minimum resources.

that present their knowledge in continuous variable type and demands sensitivity analysis, FCM address these problems well.

However, to encode infectious disease risk knowledge, with the characteristics and quantifications presented in sections 3.1.1 and 3.1.2, respectively, two adjustments are needed. First, the odds ratios and prevalence values need to be converted into the acceptable range for the adjacency matrix. Second, the categorical risk factors (binary, nominal, ordinal) need to be mapped into continuous numerical form.

3.2.3 Bayesian Network

The prediction model that is needed by this research is one that (1) represents causal relationship, (2) encodes the infectious disease risk factors, and (3) yields risk prediction. From section 3.1, it becomes apparent that the infectious disease risk factors can be continuous, binary, nominal, or ordinal. The previous section, section 3.2.2, shows that the FCM fits knowledge modelling for continuous risk factors (e.g. humidity, temperature). Whereas, the Bayesian Network is more flexible to model (mixed) categorical risk factors and (recent development of Bayesian also allows continuous variable incorporation). This section elaborates the Bayesian network in relation to disease risk prediction.

There are two types of dependency in Bayesian Network: *conditionally independent* and *conditionally dependent*. The conditionally dependent, depicted by a blue square in **Figure 3.15**, means that the result of D (Disease) depends on the *k* evidences ($E_1 \ldots E_k$), but the relationship between evidence is independent. This blue square usually depicts the relationship between risk factors and the probability of contracting a disease. Whereas, the yellow square represents conditional independence; this means that the values of symptoms ($S_1 \ldots S_k$) depends on whether a person has contracted disease D.

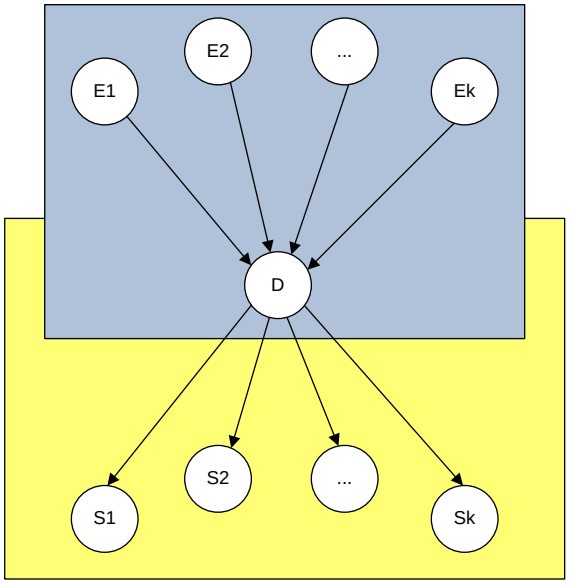

Figure 3.15: Illustration of conditionally dependent and conditionally independent in BN graph

Since this thesis focused on encoding risk factors quantifications and making them useful for predicting the disease risk, thus the blue square is the underlying assumption for this thesis. **Figure 3.16** represents this BN with E_1...E_n as risk factors, while D is an infectious disease risk that is going to be predicted.

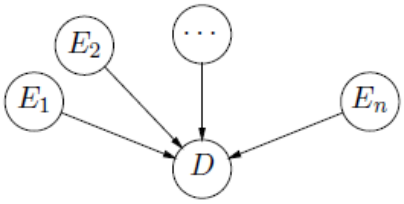

Figure 3.16: A conditionally dependent Bayesian Network graph

A Bayesian Network is a set of variables and a set of direct edges between variables which are built from probability distributions for diagnostic, decision making under uncertainty and prediction [210], [211]. A challenge with using the BN as a prediction model is: populating the basis of predictive reasoning (conditional probability table), especially if the domain knowledge requires many predictors. The CPT is a table that contains probabilities for combinations of states for each node in a BN. There are two types of CPT, the one that contains conditional probabilities (i.e. main CPT), and another one that contains marginal/joint probabilities.

To illustrate the challenge, the declarative anthrax risk knowledge (shown in **Figure 3.11**) is encoded as a BN. The BN and a sample of its CPT are presented in **Figure 3.17** and **Figure 3.18**, respectively. However, the encoded number in **Figure 3.17** is uniformly distributed, while number in **Figure 3.18** is randomized.

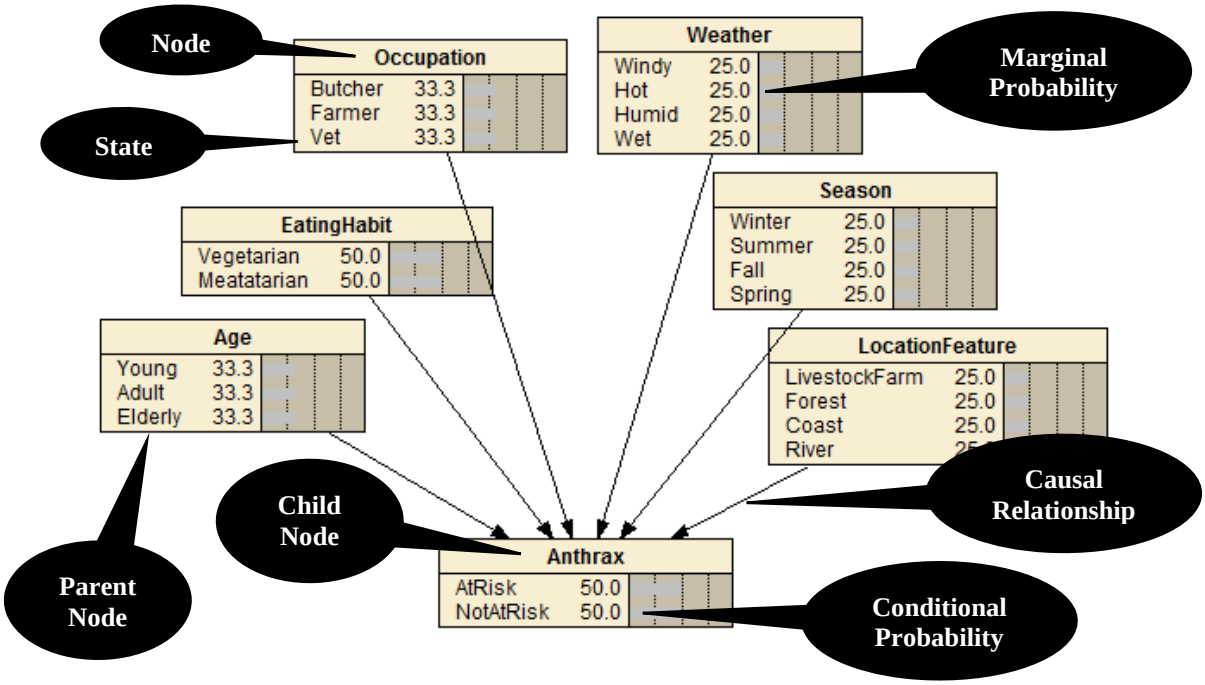

Figure 3.17: The example of BN representing Anthrax risk

The full CPT contains all combinations of the states for all parent nodes. In the anthrax example above, the CPT consists of 1,152 rows (as a result of 3 x 2 x 3 x 4 x 4 x 4 – the number of attributes for each predictor). Each row requires two joint probabilities for *AtRisk* and *NotAtRisk* condition. This CPT illustrates a simplified case of one infectious disease risk (anthrax) that is defined by personal risk factors (age, eating habit, occupation), climate risk factors (weather, season), and a location feature, with 20 attributes in total.

Age	EatingHabit	Occupation	Weather	Season	LocationFeature	AtRisk
Young	Vegetarian	Butcher	Windy	Winter	LivestockFarm	99.976
Young	Vegetarian	Butcher	Windy	Winter	Forest	47.477
Young	Vegetarian	Butcher	Windy	Winter	Coast	52.414
Young	Vegetarian	Butcher	Windy	Winter	River	60.523
Young	Vegetarian	Butcher	Windy	Summer	LivestockFarm	59.734
Young	Vegetarian	Butcher	Windy	Summer	Forest	18.517
Young	Vegetarian	Butcher	Windy	Summer	Coast	70.312
Young	Vegetarian	Butcher	Windy	Summer	River	35.143

Figure 3.18: Sample extract of the CPT of the BN that represents anthrax risk

Unlike FCM for which the encoding effort is linear with the number of risk factors, to populate the CPT of a BN, the domain expert effort is exponential with the network size [212]. As a comparison, from the anthrax risk knowledge above that contains 6 predictors, the CPT of the BN needs 1,152 x 2 cells (for *AtRisk* and *NotAtRisk*), while adjacency matrix of the FCM needs only 6 x 2 (for +/-) cells to fill.

The solution of a CPT auto-population method using a computer program was introduced in 1985 by Judea Pearl [213]. Noisy-OR was the first algorithm that populates a conditional probability table containing binary attributes from n parent nodes. In 1987, Max Henrion [214] extended the Noisy-OR to become Noisy-MAX which is able to generate a CPT for multivalued attributes instead of binary only. A recent development of Noisy-OR for a CPT containing continuous variables was built by Logan Perreault in 2016 [215].

Another approach is developed by Balaram Das in 2004 [212]. Balaram Das used a combination of Noisy-MAX and weight-sum algorithm to populate a CPT of a BN with multivalued attributes. He reduced the number of iterations by identifying the possibility of a condition's occurrence. Several levels of the condition's possibility are introduced: *impossible, unlikely possible,* and *likely possible*. The impossible conditions are eliminated, and weights are given to the other two levels. The conditions with the same weights will have the same conditional probability.

Since the Noisy-OR, Noisy-MAX, and weight-sum algorithms are general-purpose (not built for a specific domain), then they require the general input knowledge: the probability of two events occurring together at the same time (i.e. joint probability).

To encode the infectious disease risk knowledge only one adjustment is needed: convert the odds ratios into conditional probabilities. This is because the BN allows the categorical (e.g. binary, ordinal, nominal) knowledge encoding already.

3.2.4 Rules

Table 3.4 listed several representations that use rules of some sort to represent disease risk knowledge. In disease knowledge representation, rules are mostly used to represent the causal relationship between attributes in an object for a specific knowledge context.

The causes are placed in the *antecedent*, while the effects are placed on the *consequent*. The numerical measure can be either placed in the antecedent or consequent [189], [191], [216].

Early version of rules that are used to encode experts' knowledge was introduced by the MYCIN system. These rules were built using a form of if *condition* then *action* [189], [217]. An example of a MYCIN rule that is used in Bayesian diagnosis programs encoding a conditional probability (X) is shown in **Figure 3.19**. These examples show that experts' knowledge including conditional probabilities in the medical domain can be encoded using a rule-based approach. For the approach presented in this thesis, the (X) can be replaced with other numerical values (e.g. odds ratio, prevalence).

$P(h|e) = X$ means
IF: e is known to be true
THEN: conclude that h is true with probability X

Figure 3.19: MYCIN rule that encodes conditional probability (X) [217]

Abstraction Level

RULE-SCHEMA: MENINGITIS.COVERFOR.CLINICAL
RULE-MODEL: COVERFOR-IS-MODEL
KEY-FACTOR: BURNED
DUAL: D-RULE577

Performance Level

D-RULE578

IF: 1) The infection which requires therapy is meningitis, and
2) Organisms were not seen on the stain of the culture, and
3) The type of the infection is bacterial, and
4) The patient has been seriously burned
THEN: There is suggestive evidence (.5) that pseudomonas-aeruginosa is one of the organisms (other than those seen on cultures or smears) which might be causing the infection

UPDATES: COVERFOR
USES: (TREATINF ORGSEEN TYPE BURNED)

Figure 3.20: Sample MYCIN rules in the context of infectious disease domain [217]

The kind of rules presented in **Figure 3.20** help to find out the infection based on evidences (IF clause #1 to #4). However, these evidences can be substituted with risk

factors for an infectious disease. Thus, these MYCIN rules containing risk factors become an inspiration for designing rules in this thesis.

Though *rules*, *semantic-web rules*, and *belief rule-based* representations contain similar structure (having antecedent and consequent), in this review they are discussed separately. *Semantic-web rules* (encoded using Semantic-Web Rule Language – SWRL) are only implemented together with ontology representation. Whereas, the *belief rule-based* is a general rule representation that has ability to include uncertainty as in FCM or BN representation.

SWRL can encode belief rule-based and general rules using specific notation, however, SWRL has limitations in expressing OR and negation logical operators either in antecedent or consequent [218]. These limitations result in numerous rules to represent single general rule statement for which other rule approaches only need one rule.

The following examples show encoding of certainty, incorporating fuzziness and encoding a negation operator. The SWRL notation of the general rule and belief rule-based are presented for each example, so the differences between them can be seen.

The first example contains **crisp** and **certain** knowledge: if a person is above 10 years old then he/she must have an *adult* travel card; a person aged 10 and below may have a *child* travel card or none at all. The following rule encoding covers rules and SWRL notation. Since the required knowledge is crisp and certain, the belief rule-based is not applicable for encoding this example.

Rules:

```
IF age > 10 years THEN travel card = adult
```

SWRL notation:

```
Person(?x) ^ hasAge(?x, >10) -> ownTravelCard(adult)
```

Rules:

```
IF age <= 10 years THEN travel card = child or travel card = none
```

SWRL notation:

```
Person(?x) ^ hasAge(?x, <=10) -> ownTravelCard(child)
Person(?x) ^ hasAge(?x, <=10) -> ownTravelCard(none)
```

The second example contains **crisp** and **uncertain** knowledge: person aged 10 and below may have a *child* travel card or none at all.

Belief rule-based:

```
IF age <= 10 THEN travel card {(none, 0.5), (child, 0.5), (adult, 0)}
```
SWRL notation:
```
Person(?x) ^ hasAge(?x, <=10) -> ownTravelCard(child, 0.5)
Person(?x) ^ hasAge(?x, <=10) -> ownTravelCard(none, 0.5)
```

The next example encodes **fuzzy** and **non-negation** knowledge: if a *young* person lives around a livestock farm then he is at *high* risk of Anthrax.

Rules:
```
IF age = young AND liveAround = livestock farm THEN AnthraxRisk = high
```
SWRL notation:
```
Person(?x) ^ hasAge(?x, young) ^ liveAround(?x, livestockFarm) ->
Anthrax(high)
```

The next example of **uncertain** and **negation** knowledge encoding: livestock farmers in other than Winter season are at medium-high risk of Anthrax.

Rules:
```
IF occupation = livestock farmer AND season != Winter THEN AnthraxRisk
= medium or high
```

SWRL notation:
```
Person(?x) ^ hasOccupation(?x, livestock farmer) ^ inSeason(?x,
Summer) -> Anthrax(medium)
Person(?x) ^ hasOccupation(?x, livestock farmer) ^ inSeason(?x, Fall)
-> Anthrax(medium)
Person(?x) ^ hasOccupation(?x, livestock farmer) ^ inSeason(?x,
Spring) -> Anthrax(medium)
Person(?x) ^ hasOccupation(?x, livestock farmer) ^ inSeason(?x,
Summer) -> Anthrax(high)
Person(?x) ^ hasOccupation(?x, livestock farmer) ^ inSeason(?x, Fall)
-> Anthrax(high)
Person(?x) ^ hasOccupation(?x, livestock farmer) ^ inSeason(?x, Spring)
-> Anthrax(high)
```

The rules below is the encoding example of **uncertain** and **negation** using belief-rule based: livestock farmers in other than Winter season are at medium-high risk of Anthrax.

Belief rule-based:
```
IF occupation = livestock farmer AND season != Winter THEN AnthraxRisk
{(low, 0), (medium, 0.5), (high, 0.5)}
```
SWRL notation:
```
Person(?x) ^ hasOccupation(?x, livestock farmer) ^ season(?x, Summer ->
AnthraxRisk(medium, 0.5)
Person(?x) ^ hasOccupation(?x, livestock farmer) ^ season(?x, Fall ->
AnthraxRisk(medium, 0.5)
```

```
Person(?x) ^ hasOccupation(?x, livestock farmer) ^ season(?x, Spring ->
AnthraxRisk(medium, 0.5)
Person(?x) ^ hasOccupation(?x, livestock farmer) ^ season(?x, Summer ->
AnthraxRisk(high, 0.5)
Person(?x) ^ hasOccupation(?x, livestock farmer) ^ season(?x, Fall ->
AnthraxRisk(high, 0.5)
Person(?x) ^ hasOccupation(?x, livestock farmer) ^ season(?x, Spring ->
AnthraxRisk(high, 0.5)
```

From the examples above, SWRL can be used to represent certainty of the antecedent and consequent. However, more semantic-web rules are needed to encode one rule or belief rule-based that contain uncertainty.

However, without any structural knowledge representation (e.g. Ontology, BN, FCM), none of the rule encoding give the complete attributes of an object in a whole knowledge context. This is because the rules only state the IF-Then relationship of attributes. The attributes which are not explained by IF-Then relationship will not appear in the rules. An example is given below,

Rules: `IF age = children AND liveAround = farm THEN AnthraxRisk = high`

By seeing only the rule above, the users will not know if there are 2 other attributes (*adult, elderly*) or 3 other attributes (*infant, adult, elderly*) or even 4 other attributes (*infant, adolescent, adult, elderly*) in the age object since the rule above only mention *children*. Or how many location features are related to anthrax risk, that is because the rule above only mention *farm*. To clarify the big picture of knowledge, the structural knowledge representation can be implemented together with the rules.

3.2.5 Summary

This section presented knowledge representations used for disease related knowledge in the area of *computer science* and *medicine*. To sum up, this section has three aims: (1) to find existing representation that can be reused (partially or wholly) for encoding the infectious disease risk knowledge which was presented in section 3.1, (2) to sense the required efforts of the domain experts to encode their knowledge using the existing representation, (3) to identify the needed adjustments of the existing representation to fit the infectious disease risk knowledge.

The most used knowledge representation (ontology), a data-driven representation (FCM), a knowledge-driven representation (BN), and a representation for causal relationship (rules) were investigated based on those three aims. Ontologies are useful for encoding the infectious disease risk knowledge since they allow sharing resources (e.g. vocabulary, concept) and able to encode the characteristics of the infectious disease risk knowledge and the quantifications. However, there are no existing *ontologies* that can be instantiated with aim to encode the infectious disease risk factors and their risk quantifications (risk ratios, prevalence). Therefore, some of the objects (classes and properties) of the existing ontologies that encode concepts of disease risk factors can be reused to design the knowledge representation.

The gathered articles show that *FCM* has a feature, confidence rating, that can be reused to represent uncertainty across domain experts in a knowledge-base. The efforts of the domain experts in encoding knowledge in FCM is linear with the size of the map (number of the risk factors). But, from section 3.1, infectious disease risk factors are likely to contain a mixture of nominal, binary, ordinal variables. Until the recent development of the FCM, it can only encode the continuous variable; in fact, the continuous variable in the infectious disease risk knowledge is very few (e.g. temperature and humidity affect mumps risk). Thus, using FCM to encode the infectious disease risk knowledge is not much useful.

Articles that use *BN* to model disease risk factors show that categorical knowledge representation fits the characteristics of the infectious disease risk factors. However, the required effort to encode knowledge using BN is exponential with the size of the network (multiplication results of the number attributes for each risk factor). Some approaches to automate these efforts are available. For these automated approaches, the risk ratios and prevalence should be presented in a way that can be converted into conditional probabilities.

From the reviewed articles, *rules* are versatile to represent crisp, fuzzy, certain, uncertain, negation, or non-negation knowledge. *Semantic-web rules* are able to express causal relationship in an ontology environment. The encoding examples of declarative knowledge show that semantic-web rules are useful to capture *uncertainty* and *quantifications* (e.g. odds ratios, prevalence) that may appear on the domain knowledge.

Some limitations of semantic-web rules were identified: may require more semantic-web rules than general rules to represent OR logical operator, and unable to encode knowledge with negation. These limitations may result in numerous rules for encoding a simple negative rule.

To sum up, the node-link representation (ontology, FCM, and BN) needs some adjustments to fit infectious disease risk quantifications with their requirements of the basis of predictive reasoning (e.g. fit the range OR with the range of adjacency matrix). If the ontology is chosen to represent the infectious disease risk factors, the semantic-web rules can be utilized to encode the risk quantifications.

This section explains the first type of approach, while the next section elaborates the second type of approach that combine both risk prediction technique and knowledge representation as a single model.

3.3 Approaches that combine knowledge representation and risk prediction as a single model

From previous section, existing knowledge representations for encoding disease risk knowledge were obtained. Ontologies represent the knowledge without an ability to yield a prediction, whereas the FCM and BN are prediction models with some limitations for modeling the domain knowledge. Rules are a representation for causal relationships and facilitate numerical encoding but are not specific for prediction nor knowledge representation. Models that combine knowledge representation as an ontology, but which are also able to yield risk predictions as a probability do exist. This kind of model is investigated and explained in this section.

To find this kind of model, a search was conducted using these search terms: `"ontology for prediction", "probabilistic modelling ontology", "knowledge-base for risk prediction", "probabilistic knowledge model".`

Based on the number of steps required to avail of this kind of model, this literature review divides them into: *one-step*, and *two-step* modelling. The first three models: Probabilistic Relational Model, Bayesian Knowledge-base, and Probabilistic Knowledge-base are *one-*

step modelling. The *one-step* means that the users only need to represent the knowledge and their parameters, then the models predict the risk probability as the outcomes.

The last three models: Probabilistic-OWL, Bayes-OWL, and BNTab require *two-step* modelling. The *two-step* means the users need to encode the domain knowledge and its parameters, then the user still needs to fire 'something' to generate the encoded knowledge into an equivalent prediction model.

3.3.1 Probabilistic Relational Model

A Probabilistic Relational Model (PRM) combines a frame-based logical representation with probabilistic semantics based on a directed graphical model (Bayesian Network) [89]. PRM is an extension of the BN by allowing uncertainty not only on the objects but also in the relationships [219]. To induce the dependency structure of a PRM, *parameter estimation* and *structure learning* are used. The *structure learning* is used to construct the directed graphical structure from large datasets. The *parameter estimation* is employed to estimate the dependency of a structure [219].

To illustrate, a PRM is built for the anthrax risk knowledge presented in **Figure 3.11**. Six objects are created with two types of relationship: *directed* and *undirected* links. The directed links (thicker lines) show the causal relationship, while the undirected links show the first-order-logic of a person with *person risk factor*, living near a location near with a *location feature*, under *climate* condition, is infected by a *pathogen* of an *infectious disease*. The dashed lines show the referred tables that contain the uncertainty for relationships or objects. See **Figure 3.21** for the knowledge encoding result.

In a PRM building process, large datasets are needed to populate the CPT. The PRM is a suitable solution for representing a first-order-logic that requires probabilistic encoding not only on the objects, but also in the relationships between objects [90]. If the datasets are not available, then the PRM cannot be built automatically. Other ways to build PRM from other knowledge sources (e.g. from domain experts or given as odds ratios) are not yet available.

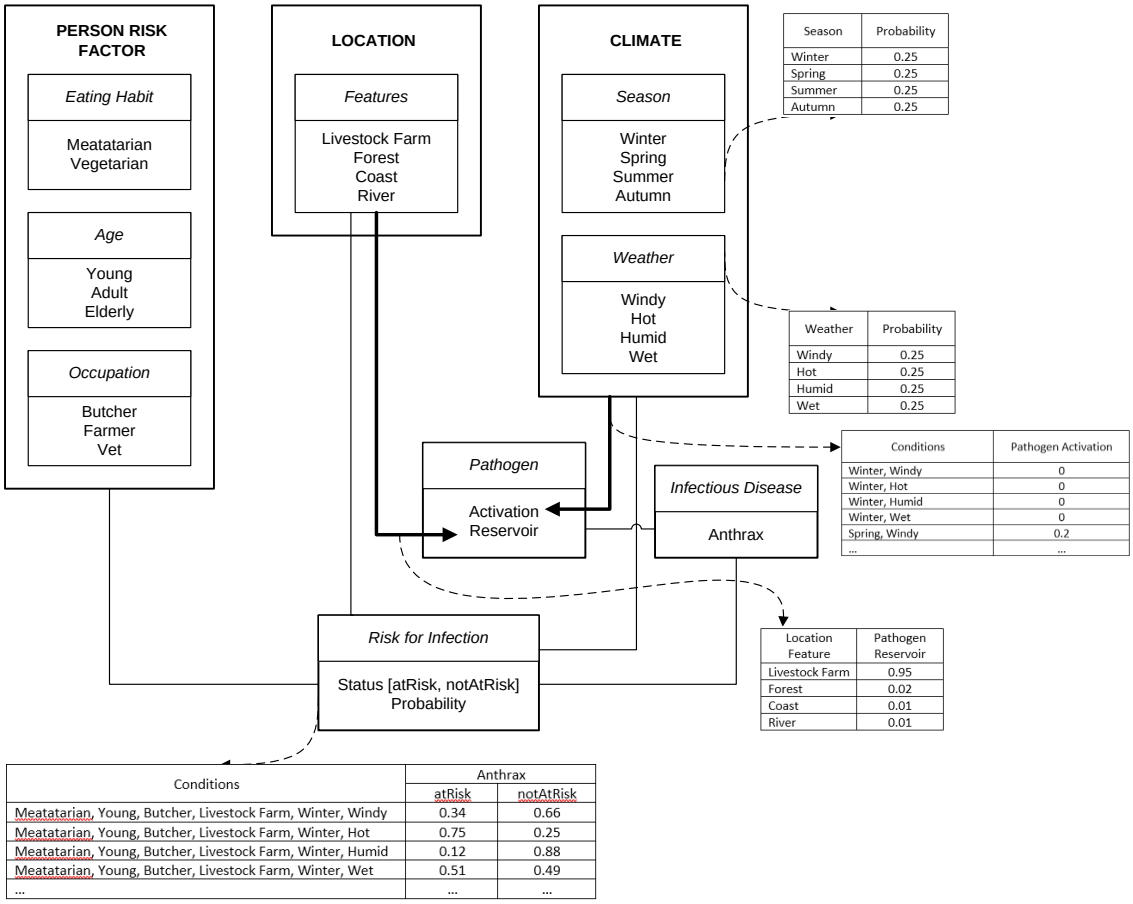

Figure 3.21: Probabilistic Relational Model for Anthrax risk knowledge

3.3.2 Bayesian Knowledge-base

As with PRM, a Bayesian Knowledge-base (BKB) is represented as a directed graph which has BN as its basis. But, the BKB is built from experts' knowledge rather than learnt from datasets. BKB can be used to represent a rule-base in a diagrammatic model.

As mentioned in section 3.2.3, BN demands the experts to populate the CPT, and can be cumbersome. The BKB facilitates the experts to express their knowledge by organizing the values of conditional probabilities. By using the BKB, the experts can write these IF-Then statements *IF a person is a meatatarian and lives around a livestock farm, then the Anthrax risk of that person is 0.7; IF a person is a vegetarian farmer, then the Anthrax risk of that person is 0.45* to fill parts of the CPT in a directed graph. The BKB model for Anthrax risk knowledge is shown in **Figure 3.22**.

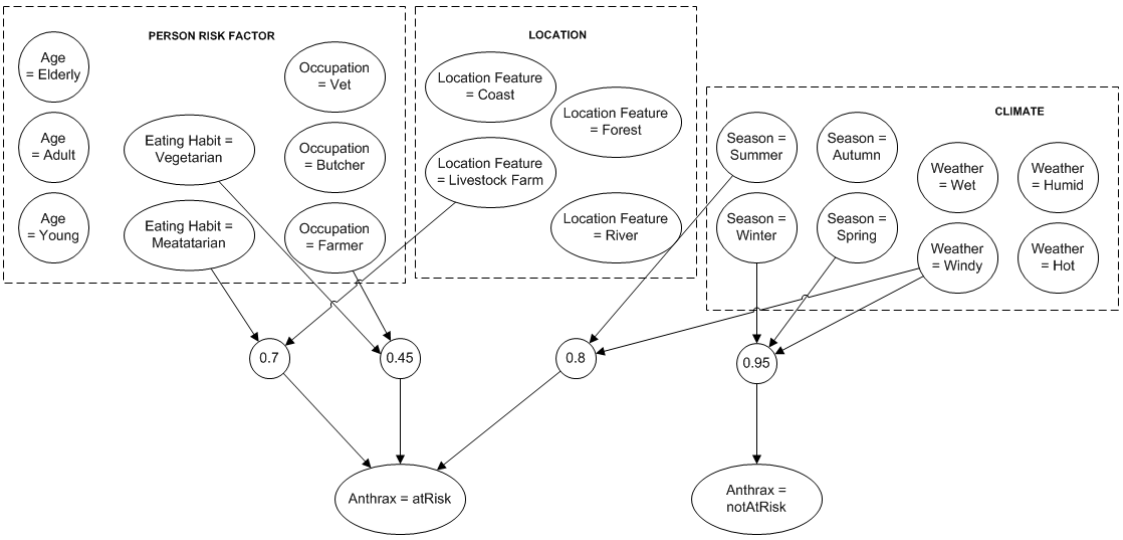

Figure 3.22: Bayesian Knowledge-base for Anthrax risk knowledge

The advantage of using BKB is that experts can express their knowledge in a simple way (rules), and are able to populate (part of) the CPT automatically [91]. BKBs allow incompleteness in the knowledge they represent. The BKB is useful for large CPT and could encourage more than one epidemiologists to contribute to the contextual knowledge-base partially.

As an example of BKB in this research, the epidemiologist A encoded *a meatatarian and live around a livestock farm*, he does not have to specify the other knowledge, for example, *a vegetarian who live around a livestock farm*, or *a meatatarian who live near a river*. Other epidemiologists can contribute to fill this knowledge.

Another benefit of using BKB is that users can still understand the big picture of the represented domain knowledge by seeing the graph. The graph contains all risk factors and all their attributes even though they are not used to populate the CPT yet.

However, since BKB allows partial knowledge to populate the CPT, it still requires a method to infer the rest CPT under incompleteness [220]. Also, an identifier is needed if two possible rules refer to the same conditional probability. For example, there is no difference on the right-hand side of **Figure 3.22** whether the represented rules are **a)** the probability of not contracting anthrax on a *windy* day in *winter* season is 0.95; the probability of not contracting anthrax in *spring* season is 0.95, or **b)** the probability of not

contracting anthrax on a *windy* day in *spring* season is 0.95; the probability of not contracting anthrax in *winter* season is 0.95.

3.3.3 Probabilistic Knowledge-base

In contrast with BKBs which represent all disease risk knowledge in a diagram, Probabilistic Knowledge-base (PKB) represents all the disease risk knowledge as a set of rules. In the recent development of probabilistic knowledge-base, the *context* is incorporated by inputting the additional atoms in the antecedent. A PKB for representing the anthrax risk knowledge presented in **Figure 3.11** is shown below. For example, in S1, the *context* is livestock farm.

```
KB = {
(S1) P(Anthrax(X, atRisk)) = 0.7 ← hasEatingHabit(X, meatatarian),
liveAround(X, livestockFarm)
(S2) P(Anthrax(X, atRisk)) = 0.45 ← hasEatingHabit(X, vegetarian),
hasOccupation(X, farmer)
(S3) P(Anthrax(X, atRisk)) = 0.8 ← actualSeason(X, Summer), actualWeather(X,
Windy)
(S4) P(Anthrax(X, notAtRisk)) = 0.95 ← actualSeason(X, Winter)
(S5) P(Anthrax(X, notAtRisk)) = 0.95 ← actualSeason(X, Spring),
actualWeather(X, Windy)
(S6) P(Anthrax(X, atRisk)) = 0.7 ← hasEatingHabit(X, meatatarian),
liveAround(X, Forest)
(S7) P(Anthrax(X, atRisk)) = 0.7 ← hasEatingHabit(X, meatatarian),
liveAround(X, River)
(S8) P(Anthrax(X, atRisk)) = 0.7 ← hasEatingHabit(X, meatatarian),
liveAround(X, Coast)
…
}
```

The advantage of this approach is the ability to give the big picture of contextual knowledge using a set of rules. In the example above, the attributes of EatingHabit node can be deduced from (S1) and (S2), whereas the attributes of LocationFeature can be deduced from (S1), (S6), (S7), and (S8). An equivalent BN can be generated successfully using a backward-chaining algorithm [94].

The numerical values that are encoded in the 8 rules above showing the joint probabilities. However, from section 3.1.2, it is known that in the case-control studies, the magnitude of risk factor is rarely presented in joint probabilities, but in risk ratios. Therefore, a slight modification in the numerical encoding influence the designed form of knowledge

representation. This influence is explained in section 5.2.2. A knowledge structure of the probability knowledge-bases is somehow not visible. A knowledge representation that visualize the structure of knowledge is required to make the knowledge-base *usable* by the epidemiologists.

3.3.4 Probabilistic-OWL (PR-OWL)

Now, moving on to models that involve *two-step* modelling, wherein knowledge representation is separated from prediction model and, thus, someone still needs to fire 'something' to generate the prediction model.

Probabilistic-OWL (PR-OWL) is a language for defining probabilistic ontologies. PR-OWL allows knowledge encoding in three hierarchies of knowledge: *context level* (wider scope, represented by MEBN[9]); – *basic level* (the main structure of the knowledge, represented by MFragments[10]); – *detail level* (the probability numbers, represented by SSBN[11]) [33], [95], [221], [222].

PR-OWL introduces granularity of the knowledge encoding level. This granularity approach brings some benefits and drawbacks. By using this granularity, knowledge that is used for operational purposes is separate from the domain knowledge definition and assumptions. However, because of this granularity the PR-OWL implements the MFrag for each random variable for each class. The PR-OWL is more complex than ordinary ontology [33].

Figure 3.23 and **Figure 3.24** below shows comparison between an ordinary ontology and PR-OWL to represent one rdf:property: *a person has an eating habit*. The ontology only contains two classes: *Person*, and *EatingHabit*. To model the complete anthrax risk knowledge that contains six anthrax risk factors, it will need 5 more rdf:property.

[9] Multi-Entity Bayesian Network is a first-order language that specifies probabilistic knowledge bases as parameterized fragments of Bayesian networks

[10] Part of MEBN which is relevant to a particular context

[11] Situation-specific BN which answers the requested query to MEBN

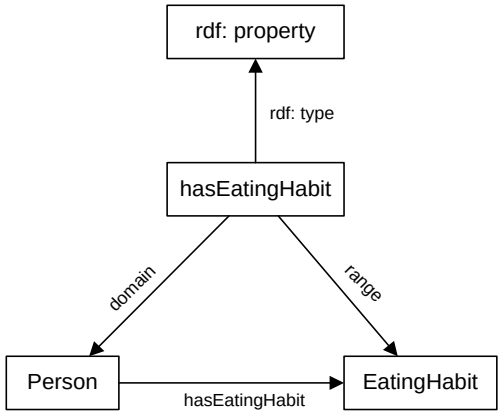

Figure 3.23: An OWL schema for representing one predicate of Anthrax risk knowledge

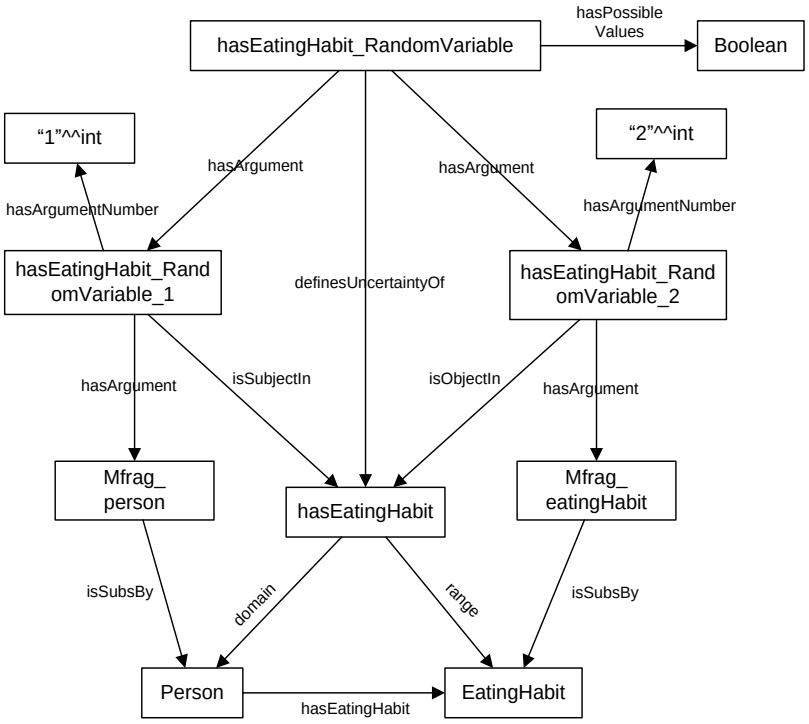

Figure 3.24: A PR-OWL schema for representing the same predicate as **Figure 3.23**

An algorithm, Multi-entity Bayesian Network (MEBN), is then needed to transform this PR-OWL into a BN that contains several Situation-Specific Bayesian Networks (SSBN) [95]. The number of generated SSBNs is same as the number of CPT rows in an ordinary BN (1,152 rows for the same example of the Anthrax risk knowledge). Each SSBN has one small CPT that consists of one condition that is populated using random variables specified in the PR-OWL.

Table 3.6: A CPT example of a generated SSBN

Eating Habit	Age	Occupation	Location Feature	Season	Weather	Anthrax	
						atRisk	*notAtRisk*
Meatatarian	Young	Butcher	Livestock Farm	Winter	Windy	0.34	0.66

3.3.5 BayesOWL and BNTab

This section explains BayesOWL and BNTab that allow a user to model the domain knowledge and generate a risk prediction model from an ontology as a knowledge representation. BayesOWL converts ontology *classes* into BN *child nodes*, and *sub-classes* into BN *parent nodes*. This conversion uses a table that contains several ontology constructors (e.g. rdfs:subClassOf) that map the ontology objects into desired objects of the BN. By using this conversion table, the fixed mapping from ontology objects to BN objects can be stored and reused anytime when the conversion is needed. Any new constructor can be added in the table when needed.

For encoding the anthrax risk knowledge (see **Figure 3.11**), each attribute of the anthrax risk factors is represented as an ontology sub-class of an *AnthraxAtRisk* class (see **Figure 3.25**). However, since this BayesOWL does not involve the generation of states in a BN node, then it uses default binary states (true, false) for all BN nodes [34], [35]. After generating the binary BN, the Noisy-OR algorithm (as described in section 3.2.3) is used to populate the CPT of the child node (*AnthraxAtRisk*).

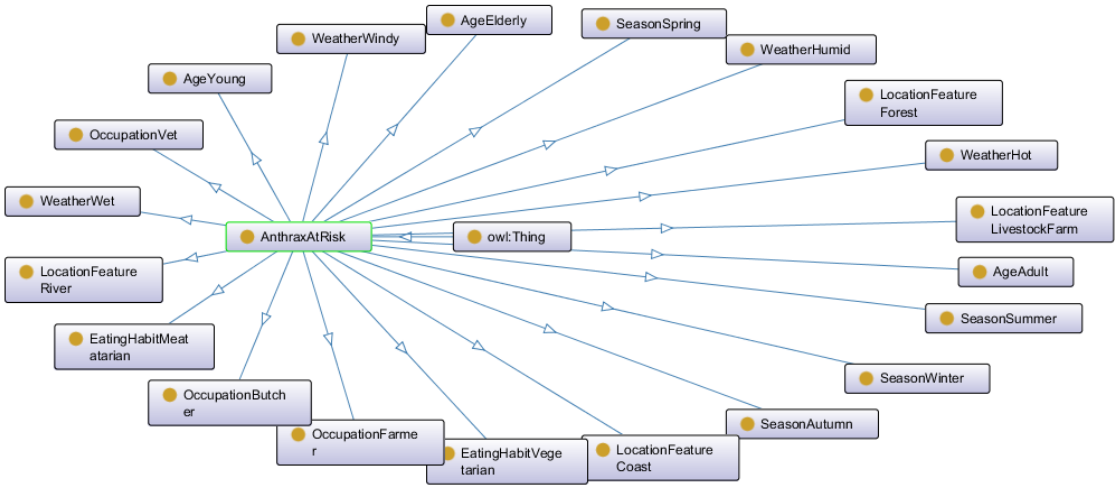

Figure 3.25: An ontology to represent the anthrax risk knowledge

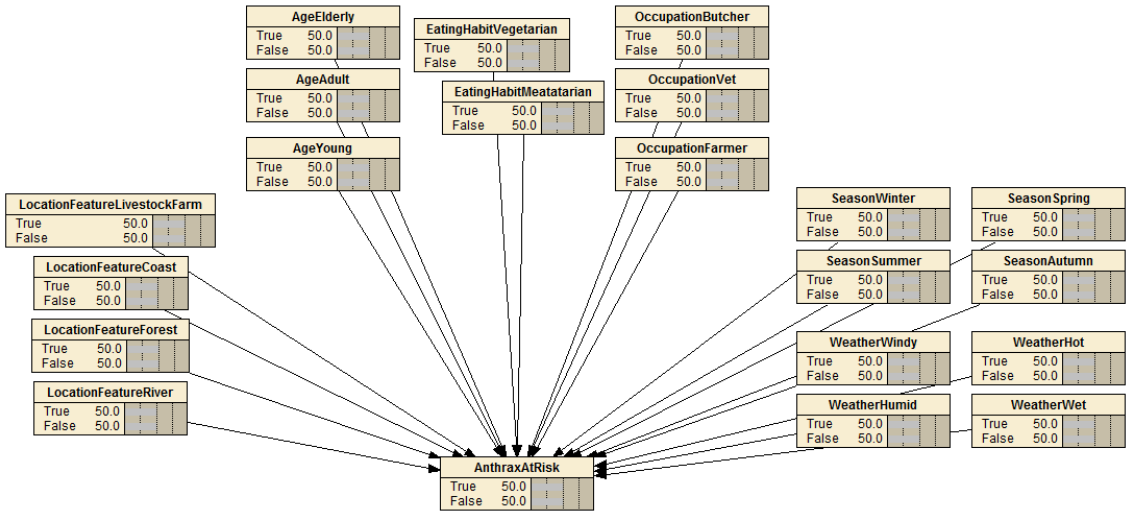

Figure 3.26: The generated binary BN

From the BayesOWL model, the use of a conversion table is learned. Even though the generated BN is binary which can limit the knowledge expression to some extent, BayesOWL shows the possibility of generating a BN from an ontology using some semantic-web query language. See **Figure 3.26** for the generated BN of the designed ontology structure **Figure 3.25**.

Another interesting tool that interfaces between ontology and BN is BNTab, a plugin of a knowledge model editor (Protégé) which is connected to a Bayesian network application and transforms ontology objects into a BN network. Unlike BayesOWL which generates binary BN, BNTab converts the ontology *classes*, *individuals*, and *properties* to become *nodes*, *states*, and *links*, respectively.

BNTab extends the expressivity of the generated BN, not only limited to binary but any individuals that are assigned to a class will become states of a BN node. However, since the Noisy-OR (limited for binary nodes) and Noisy-AND (limited for multivalued node) algorithms cannot be used to generate the resulting CPT of the generated BN, the BNTab generates an empty BN (only BN structure without populating the CPT).

From BayesOWL and BNTab, it can be concluded that an ontology is transformable to a BN with certain limitations. There are several paths, along with their drawbacks and benefits, which can be reused conceptually and learned from.

3.3.6 Summary

Information about six models that combine the knowledge representation and risk prediction in two approaches, *one-step* and *two-step*, were presented. Three *one-step* models (e.g. PRM, BKB, PKB) were reviewed. Probabilistic Relational Model (PRM) is able to encode a probabilistic table in an object or in a relationship between objects by learning from large dataset. Bayesian Knowledge-base (BKB) can represent both rules and the big picture of the knowledge, and also allow more than one epidemiologist to collaborate together on one knowledge-base. Probabilistic Knowledge-base (PKB) generates a Bayesian network from a rule-base using a backward-chaining algorithm.

Three *two-step* models (e.g. PR-OWL, BayesOWL, BNTab) were also included in this review. Probabilistic-OWL (PR-OWL) provides levelling on knowledge modelling: context – basic – detail. But from a comparison with basic OWL, PR-OWL is rather complex even for modelling a simple triple. BayesOWL uses a conversion table to map the ontology objects to become the Bayesian network objects; however, BayesOWL can only generate a binary BN (*true* and *false* states). A Protégé plug-in, BNTab, is able to model categorical knowledge and generate an isomorphic BN, but the conditional probability table is blank.

3.4 Conclusion

Based on the collected knowledge in section 3.1, infections happen when a susceptible host (human) is exposed to the pathogen of an infectious disease through direct or indirect transmission. From SEIR mathematical modelling in epidemiology, a person's risk of contracting of infectious diseases can be deduced from the person's susceptibility (S) and pathogen exposure (E) level under specific atmospheric condition in a location.

The susceptibility of a person is identified from the demography, genetic, nutrition intake, habits, and pre-existing illness (e.g. diabetes, cancer). In this thesis, these factors are called *personal risk factors*. Besides the personal risk factors, climate and location are found to have implications on the infectious disease risk, specifically on human immunity level (e.g. wintertime-immune suppression). In this thesis, these factors are called *environmental risk factors*. These factors are quantified by risk ratios (either odds ratios,

or relative risks). Most risk factors presented in categorical (nominal, ordinal, binary), and very few risk factors are presented in numerical (continuous) variable type.

The infectious disease exposure can be deduced from the climate (weather and season), and specific location features. Some climate-dependent pathogen and vector (e.g. Aedes Aegypti) are multiply and attack hosts only under certain weather and season. Whereas some pathogen's reservoir is associated with some location features (e.g. cave, river), or geographical variations (e.g. altitude). In the context of diseases, this exposure level can be recognized through prevalence or incidence (the number of reported infection cases divided by total population of a country). The prevalence or incidence are presented in specific units (100,000 population or 1,000 population) depending on the diseases.

Thereafter, existing knowledge representation that fits the disease risk knowledge characteristics were investigated. *Ontologies* turned out the most used representation in the medical and computer science subject areas for the last 10 years. However, to represent the infectious disease risk knowledge that contains causal relationship and numerical encoding, the *semantic-web rules* should be used together with the ontology. Also, since the ontology is not intended for prediction but representing knowledge, current ontological model that can yield risk prediction were searched.

Six models were gathered, and their mechanisms were learned. All of them is able to encode categorical knowledge for general-purpose. However, since these models are not specific for disease related knowledge, thus, none of them that capable of encoding infectious disease risk factors from epidemiologists and provide an automatic way to generate their basis of predictive reasoning from risk ratios and prevalence.

To predict the personalized infectious disease risk from recent knowledge, besides an *ontology* and *semantic-web rules*, a formula that uses risk ratios and prevalence to populate a basis of predictive reasoning is required. Material presented in this chapter will inform design decisions for PROSPECT-IDR, as presented in the following chapters.

4. DESIGN OF PROSPECT-IDR SYSTEM ARCHITECTURE AND THE USER INTERFACES

4.1 Introduction

The introduction to this thesis outlined the need for a system that is capable of encoding, updating, managing input knowledge about infectious disease risk, and of calculating a person's personalized infectious disease risk from the inputted knowledge. With such a system, infectious disease risk knowledge can be encoded by domain experts as the knowledge itself develops. This chapter presents the design of the PROSPECT-IDR system, which was informed by several existing models, explained in the state-of-the-art chapters (chapter 2 and 3). Those chapters examine the relevant use of mathematical modelling, prediction modelling, and knowledge representation in this system context, thus, some parts of them influence the design of this system.

This chapter begins with the taken influences from the state-of-the-art chapters (chapter 2 and 3). The influences are related to characteristics of infectious disease risk knowledge, available and relevant data sources that can be used to personalize the resulting infectious disease risk prediction, the reusable ontology objects (conceptually), and the mechanism that allows a knowledge-base to yield risk prediction as probabilities. Thereafter, some decisions related to system components will be made based on the influences.

4.2 Influences from the State of the Art

From review of the projects, apps, systems given in chapter 2, there are some existing information that can be useful to achieve those three aims. The review about the availability of data, prediction models, system or specific requirements is gathered in the context of the PROSPECT-IDR.

4.2.1 Data Sources, Reports, APIs

This section mentions the existing data sources that can be obtained using the available APIs or reports. This information was collected from section 2.2.

- From case-control studies, the *who got what diseases* can be inferred to become magnitude of a risk factor (risk ratio) using eq. 3 or using a machine learning approach (e.g. Logistic Regression). The risk ratios are widely available in case-control studies published in epidemiology domain.
- There is a WHO report that exhibits *number of reported cases* for some notifiable infectious diseases for some countries for a specific period. Together with the number of *total populations* of each country in the world for specific year, which provided by UNSD report, a *prevalence value* of an (infectious) disease in a country for a certain period can be calculated using eq. 4.
- Several weather *APIs* can yield the atmospheric attributes (e.g. temperature, humidity) based on the given city and country name (e.g. OpenWeather API).
- Several location-based *APIs* can yield the surrounding location features (e.g. river, forest, market) based on a person's geo-location (e.g. Google Place API).

4.2.2 Reused Concepts and Objects

In section 3.2.1, the disease related ontologies were collected. Since there are no existing ontologies able to represent infectious disease risk knowledge, a knowledge representation will be designed (explained in chapter 5). From the existing ontologies, the containing concepts and categorizations relevant to infectious disease risk knowledge are reused to design further knowledge representation.

From the conclusion of chapter 3, there are two types of risk factors included in this thesis, *personal risk factors* that describe the relation of personal attributes with infection risks (e.g. pre-existing illness, occupation), and *environmental risk factors* that explain the relationship between climate (weather and season), location (country and location features) and infection risks. **Table 4.1** is a summary of the reusable concepts found in the existing ontologies to be adopted as the content of personal and environmental risk factors in the context of personalization of infectious disease risk prediction.

Table 4.1: The reused concepts from existing ontologies

Existing ontology names	Reused concepts	Adopted as
Epidemiology Ontology (EPO) [195]	*Spatio-temporal* objects which represents the time and location of the usual occurrence	Region as a country and specific location features (i.e. terrain)
Infectious Disease Ontology (IDO) [223]	*Biomedical* and *clinical* aspects for infectious diseases in general	Personal risk factors: biomedical history
CARRE risk factor ontology [224]	Human susceptibility concept in three aspects: *demography*, *biomedical*, *behavioral* risk factors in cardiorenal diseases	Personal risk factors: demography, behavioral risk factors

The reused objects (e.g. literals, terminologies) to encode (infectious) disease risk factors are found in DOID [197], IDO [223], CARRE [224], HEPO [27], ORC [26], CSEO [200] and OBESTDD [207]. For example, the derivation of *behavioral risk factors* of *alcohol consumption*, and *tobacco smoking* can be reused from CARRE [224].

4.2.3 Required Tools and Activities

From the motivation of this thesis, in chapter 1, the main aims of the PROSPECT-IDR system are (1) **facilitating** infectious disease risk knowledge provided by case-control studies to be encoded, including **allowing** the *domain experts* to continuously modify, and the *knowledge manager* to resolve conflicting knowledge as the infection risk knowledge develops, (2) **calculating** the infectious disease risk prediction based on the knowledge, including **personalizing** the calculated infectious disease risk prediction based on the submitted personal and environmental risk factors. Based on the reviewed articles in chapter 2 and chapter 3,

- To achieve the first aim, **a knowledge-base** can be used. The scope of the infectious disease risk knowledge is the *risk factors*, *risk ratios*, and *prevalence* value of an *infectious disease* in a particular *country*. **User interfaces** is designed to acquire knowledge from the experts and store them in the knowledge-base. In this user interface, a feature to retrieve current infectious disease cases in some countries are retrieved from WHO data repositories.

  In this thesis, the time when the experts encode the infectious disease risk knowledge using the user interfaces before **run-time** system is called **knowledge-**

encoding time. In this knowledge-encoding time, the knowledge engineer is also allowed to manage the knowledge using the same user interfaces designed for domain experts, if there are *contradicting* or *duplicating* knowledge.

- To reach the second aim, **an algorithm** that makes sure the recent knowledge encoded in the knowledge-base be *consistent* with a predictive reasoning of a prediction model is required. For example, the encoded knowledge is consistent with the conditional probability table of the generated Bayesian network. The algorithm is designed to take categorical (*nominal, ordinal, binary*) and numerical (*continuous*) as inputs, then, it converts them into the prediction model.

  To facilitate communication between the system and the users (lay people), a **user interface** to submit their personal attributes is needed. The submitted personal attributes are then used to personalize the infectious disease risk prediction. Then, several **packages** might be needed to parse the given *facts* in order to get the *context* of the given geo-position and submit them (both *facts* and *context*) to personalize the calculated infectious disease risk prediction.

The focus of the **knowledge-encoding time** is inputting, modifying, and managing knowledge in the knowledge-base. The focus of the **run-time** system is the collection of personal *facts* (including the associated environmental *contexts*) and personalization the prediction results based on the collected *facts* and *contexts*. In the run-time, the developed algorithm ensures the encoded knowledge is consistent with the predicted infectious disease risk. By putting the algorithm in charge every time the knowledge-base is updated, then, this PROSPECT-IDR system is designed as a *two-step* approach. This means that, in the system design, the knowledge-base is separated from the risk prediction model.

The needed components mentioned in the paragraphs above are then designed to become a system architecture like that in **Figure 4.1**. The detailed explanation of the system design and activity are given in section 4.3.

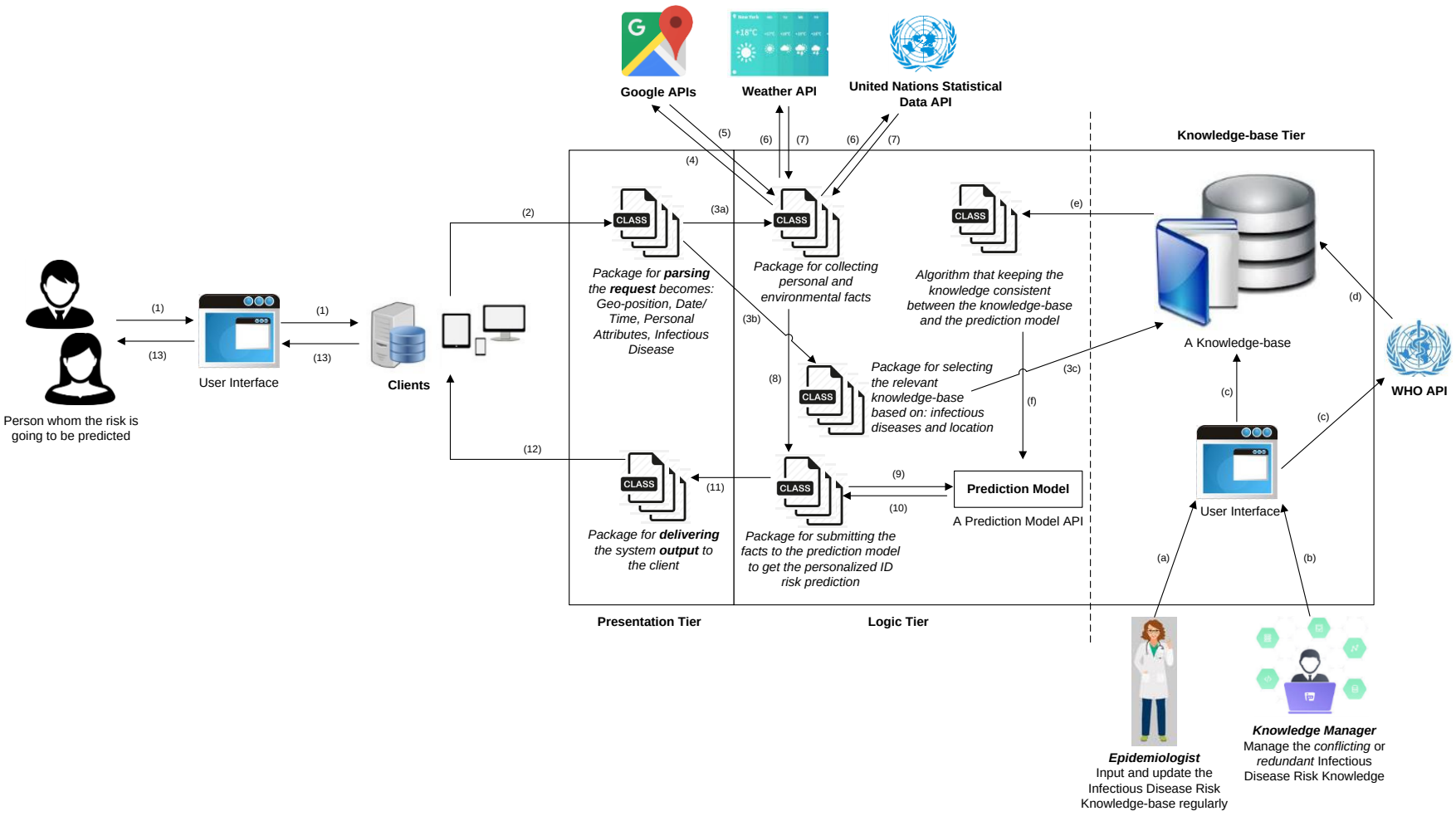

Figure 4.1: Draft of PROSPECT-IDR system architecture

4.3 The PROSPECT-IDR system

In **Figure 4.1**, there are three tiers: presentation tier, logic tier, and knowledge-base tier. The *presentation* tier and *logic* tier work at run-time, while the *knowledge-base* tier work at knowledge-encoding time. The decision whether a separate package is needed is based on the function; different function will be designed to have different package. *The presentation tier* aims to facilitate communication between the clients and the PROSPECT-IDR system. The presentation tier consists of *two packages*: one for receiving requests from the client and parsing them to the logic tier (this package sits between arrows number **2** and **3**), and one for delivering the end result of the system to the client (this package sits between arrows number **11** and **12**).

The logic tier is the main processor of the PROSPECT-IDR system; it consists *the algorithm*, *the prediction model*, and *three packages*. *The algorithm* keeps the knowledge between knowledge-base and the prediction model is consistent. *The prediction model* calculates the infectious disease risk prediction for all combinations of the knowledge from knowledge-base. *The first package* aims to communicate with the APIs to get the contexts of the parsed client's request. *The second package* sends the facts and the contexts (i.e. beliefs) to the prediction model as inputs of prediction. *The third package* selects the relevant knowledge-base based on the submitted infectious disease and inferred location.

The knowledge-base tier stores the infectious disease risk knowledge and the user interfaces that facilitate communication between the knowledge-base and the epidemiologists and the knowledge manager.

Since the prediction model depends on the knowledge encoded in the knowledge-base, the sequence of the system started with the knowledge-encoding time, and then run-time system. The ***run-time*** flows are denoted by numerical arrows, while the ***knowledge-encoding*** time flows are denoted by alphabetical arrows in **Figure 4.1**. A dashed line separates the run-time and knowledge-encoding time of the PROSPECT-IDR.

The activity flows of the *knowledge-encoding time* are,

a. The epidemiologist(s) input the risk knowledge for an infectious disease prevalent in a country. For example, risk ratio for children of contracting of dengue fever in Indonesia is twice higher than adults.
b. When there are anomalies: *contradicting* or *duplicating* rules, the knowledge manager (in collaboration with domain expert) will resolve it by assigning different priority for each anomaly rule. So, there is only one risk factor that has the highest priority which will be taken by the algorithm to be included in calculation of risk prediction.
c. When needed, the infectious disease *prevalence value* can be retrieved from the WHO API. Otherwise, the epidemiologist can input the prevalence and send to the knowledge base directly as in activity **a**.
d. If required, the retrieved *prevalence value* of the specific infectious disease in a region is submitted to the knowledge base.
e. When the knowledge-base is updated, the algorithm that making sure that the encoded knowledge in the knowledge-base is consistent with the prediction model is executed.
f. This execution will renew the basis of predictive modelling of the prediction model.

Those activities above will result in one knowledge-base that contains a set of rules for encoding risk factors, risk ratios, prevalence values of one infectious disease. As the dengue fever infection does not only prevalent in Indonesia, but also in other countries, then, in knowledge-base tier could modify the prevalence value. For example, dengue fever in Indonesia and in Malaysia have almost same risk factors and risk ratios, however, the prevalence values of the dengue fever between those countries are different. This is because the number of population in Malaysia and Indonesia is quite different (see eq. 4 for the prevalence formula). Therefore, a decision of whether a separate knowledge-base is needed or not, will be explained in following section.

After the algorithm makes sure that the encoded knowledge in a particular knowledge-base is consistent with the basis of predictive reasoning in the prediction model, then the

prediction model is ready to answer queries from clients at the *run-time system*. Based on the numerical notation in **Figure 4.1**, the activity flows of the run-time system are,

1. A person is going to find prediction of his risk for an infectious disease at a time at his current geo-position. For example, the *dengue fever* risk prediction for *a 4-year old female living in [-7.2759, 112.8083] at 13:55 on 4th of July 2018*.
2. The person requests from an app or web as a client of the system and sends all her personal attributes (age, gender, geo-position, request for dengue fever risk prediction) into the system through presentation tier.
3. A package inside the tool parses the request based on the **geo-position**, **date and time**, **personal attributes**, and name of **infectious disease** that is requested to be predicted for the client. The parsing result is *[-7.2759, 112.8083], 13:55 on 04/07/2018, female, 4, dengue fever.*
4. A package for collecting the personal and environment contexts from the given facts. First, converting the geo-position *[-7.2759, 112.8083]* become the city and country names.
5. The city and country names are retrieved back for example *Surabaya* city in *Indonesia*. (5a) A package is designed for selecting the relevant knowledge-base (5b), based on parsed **infectious disease** and **location** (*country*).
6. Then, *Surabaya* and *Indonesia* are then sent to Weather API to retrieve the weather [humidity, precipitation, temperature] for city = Surabaya, and country = Indonesia. The detail human population of [gender = *female*, development stage = *children*] for country = Indonesia is sent to UNSD API to get the population context in the Indonesia. Whereas the geo-position of the user [-7.2759, 112.8083] is sent to Google API to retrieve the location feature [altitude].
7. The package retrieves the environmental contexts from Weather API, Google API, and UNSD API. The results from Weather API are *[80%, 20mmHg, 30C]*; the results from Google API are *[7.234m]*; the results from UNSD API are *[51.09%, 25.29%]*.
8. The package then pre-processes the *[80%, 20mmHg, 30C], [7.234m], 04/07/2018* to become the environmental context: weather *[hot, humid]*, season *[rainy]*, location feature *[below 1000m]*.

9. Submitting the collected personal facts and environmental contexts: weather *[hot, humid]*, season *[rainy]*, altitude *[below 1000m]*, gender *[female]*, development stage *[children]*, infectious disease *[dengue fever]* to a relevant prediction model. To select which prediction model is relevant to the client request, the infectious disease which is being predicted (*dengue fever*), and country name where the client is (*Indonesia*) are used as selection parameters. As a result, the knowledge-base for dengue fever in Indonesia is selected.
10. The prediction model calculates the personalized dengue fever risk based on the given facts.
11. The prediction result for example 0.00135 (or 135 people per 100,000 population). This result is sent back to the presentation tier using a package labelled by *'package for delivering the system output to the client'*.
12. The package inside the presentation tier delivers the result to the client.
13. Then, it is sent to the person who requested it through the client.

These activities above aim to personalize dengue fever risk prediction given the person's facts, and the associated environmental contexts based on the person's geo-position.

4.4 The System Components

This section clarifies which components of the system are included in this thesis and which are not. In chapter 3, it is concluded that there are no existing ontologies for encoding infectious disease risk knowledge. But, there are some concepts and objects that can be reused for designing a new form of knowledge representation. The knowledge representation will become the main reference of the knowledge-base, therefore, it is an essential part of the system and covered by the thesis scope. A knowledge-base that inherits some relevant objects from the knowledge representation is then used for evaluating the knowledge encoding process in the scope of this system. The knowledge-base is designed to store one infectious disease risk knowledge prevalent in one projected population. The design and evaluation of the knowledge-base, Infectious Disease Risk (IDR), is covered in chapter 5.

Besides that, from the conclusion of chapter 3, there is no existing algorithm that is able to encode categorical (mixed between binary, nominal, ordinal), and continuous risk ratios and convert them into a basis of predictive reasoning of a prediction model. However, there is a version of Bayes chain rule that is common in breast and lung cancer risk prediction [42], [43]. The logic flow of Bayes chain rule is learned, however, there is no formula which is ready to be implemented as a code program. Therefore, an equation is written (eq. 7), and the resulting conditional probabilities are compared. The conditional probability results from eq. 7 are exactly matched with the original Bayes chain flow. In Appendix 3, there is a published article that showed that the rewritten BN [42] can yield accurate predictions.

$$\mathrm{p}\left(\mathrm{H}\middle|\mathrm{E}_1^{\mathrm{s}_1}, \mathrm{E}_2^{\mathrm{s}_2}, \ldots, \mathrm{E}_\mathrm{n}^{\mathrm{s}_\mathrm{n}}\right) = \mathrm{prev}(\mathrm{H}).\prod_{\mathrm{i}=1;\,\mathrm{j}=1}^{\mathrm{n}} \mathrm{OR}^{\mathrm{E}_\mathrm{i}^{\mathrm{s}_\mathrm{j}}} \qquad \text{eq. 7}$$

where $p(H|E_1^{s_1}, E_2^{s_1})$ is the risk probability for contracting an infectious disease H given the conditions $E_1^{s_1}, E_2^{s_1}$; $prev(H)$ is the prevalence of the disease H in a specific region during a particular time; $OR^{E_i^{s_j}}$ is the risk ratio for attribute ($E_i^{s_j}$) of a condition (E_i).

For example, risk of contracting anthrax for youngsters on a windy day in Indonesia is $(Anthrax - Indonesia|age^{young}, weather^{windy})$. To obtain the conditional probability of that risk $p(H|E_1^{s_1}, E_2^{s_1})$, the following information is needed: first, *prevalence* or *incidence* of Anthrax in Indonesia during a year, denoted by $prev(Anthrax - Indonesia)$; second, *risk ratios* for Indonesian youngsters of contracting of Anthrax, denoted by $(OR^{age^{young}})$; on a windy day, denoted by $(OR^{weather^{windy}})$.

The existence of the version of Bayes rule (given in eq. 7) leads to a decision to use Bayesian network as the prediction model for this system. By utilizing this equation, the conditional probability table can be populated. Furthermore, the equation is suitable for the characteristics of the infectious disease risk factors which contain *categorical* risk factors (mixed nominal, ordinal, binary) and *continuous* numerical risk ratio.

Besides that, the Bayesian network is chosen because it is compatible with the ontology structure – proven by three approaches that combine knowledge representation with the risk prediction which all use ontology as basic representation and Bayesian network as prediction model (i.e. BKB, BayesOWL, BNTab).

An algorithm aims to make sure that the encoded knowledge is developed based on this equation (eq. 6). This algorithm, *BN-Builder algorithm,* sits in the logic tier and converts the chosen knowledge-base into Bayesian network. This algorithm will be the subject of chapter 6. From the eq. 6, the decision of whether a new separate knowledge-base is needed is whether the risk factors are same within one infectious disease. Dengue fever in Indonesia and in Nepal have the same risk factors (e.g. weather, age), therefore, the knowledge-base that contains dengue fever risk factors can be reused for different countries, even if both countries have different prevalence values. In the long-term vision, a collection of prevalence values that are retrieved from WHO regularly are stored separately with a collection of the risk factors. By storing this separately, it allows to use different prevalence value for the same infectious disease risk factors.

In some cases, the risk factors of an infectious disease could be different if the attacked organ is different, for example, the tuberculosis risk knowledge. The pulmonary tuberculosis (the attacked organ is lung) and spinal tuberculosis (the attacked organ is spine) have different risk factors. Pulmonary tuberculosis risk factors are smoking, and gender, but spinal tuberculosis risk factors are related to vitamin D intake (meat, egg, milk consumption) [132], [136]. Thus, two separate knowledge-base are needed even though the infectious disease name is same (tuberculosis): one knowledge-base for pulmonary tuberculosis, and one knowledge-base for spinal tuberculosis. The design of the user interfaces that facilitate communication between system and the domain experts and knowledge engineer is also given as Appendix 2 of this thesis. **Figure 4.1** shows the arrangement of the needed components that mentioned in the previous discussions. However, several components in **Figure 4.1** but not renamed in **Figure 4.2** means that they are not included as the scope of this thesis.

Only three system components are renamed from **Figure 4.1** to **Figure 4.2**: (1) the algorithm that keeps the knowledge consistent between the knowledge-base and the prediction model is relabeled as *BN-Builder algorithm,* (2) a prediction model is renamed into Bayesian network; it avails of built-in functions provided by the Netica-J API, (3) the knowledge-base is now labeled *Infectious Disease Risk (IDR) Ontology and Rules*. The blue boxes in **Figure 4.2** depict components contributed by this thesis: *BN-Builder algorithm,* and *IDR Ontology and Rules*.

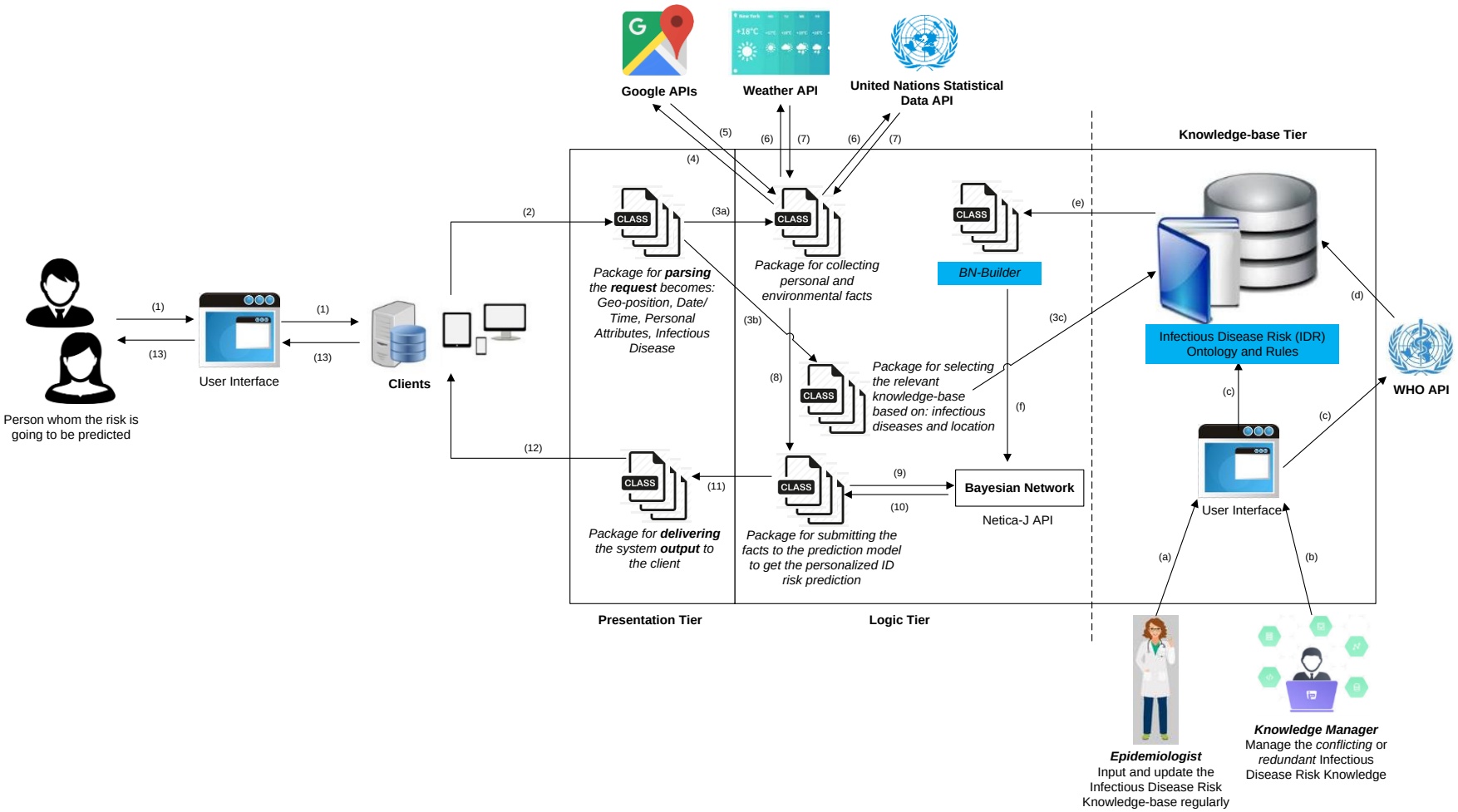

Figure 4.2: The design of PROSPECT-IDR system

5. DESIGN AND EVALUATION OF THE INFECTIOUS DISEASE RISK (IDR) KNOWLEDGE-BASE (KB)

The previous chapter provided an overview of the PROSPECT-IDR system and indicated that the essential parts of it that are the subjects of this thesis are **the knowledge-base** that contains representation of infectious disease risk knowledge, and **the algorithm** that keeps the encoded knowledge in the knowledge-base consistent with the Bayesian network. Early design of the knowledge-base (ontology and rule types) was published (the article is attached in the Appendix 4). This chapter explains the process of designing the knowledge-base, Infectious Disease Risk (IDR), and presents several evaluations to assess the *usefulness* and *completeness* of the IDR knowledge-base through encoding knowledge published in several case-control studies.

5.1 Introduction

This chapter presents the design and evaluation of a knowledge representation for encoding declarative infection risk knowledge. Section 5.2 presents the influences from previous chapters (chapters 2, 3, and 4), on the knowledge *contents* to be encoded, the *frequency* with which different kinds of encoding activities will occur, and *how to encode* that contents. The following section, section 5.3 and 5.4, explains the *design* of the knowledge representation that is fit to encode the contents. Thereafter the *usefulness* and *completeness* of the designed representation are *evaluated* in section 5.5. Conclusions are drawn in section 5.6.

5.2 Influences from the State of the Art

Chapter 3 reviewed the domain knowledge that is relevant for the IDR knowledge-base of the PROSPECT-IDR system. This section categorizes them into ***what*** knowledge to represent, ***how*** to represent the knowledge and yield the personalized risk prediction from the represented knowledge.

5.2.1 What knowledge to represent

Based on the Bayes chain rule written specially for predicting (infectious) disease risk (eq. 6), two types of knowledge need to be encoded in a form of representation,

- Infectious disease risk factors

  The infectious disease risk factors include *personal* and *environmental* risk factors. The *personal* risk factors cover demography (e.g. age, gender, occupation, ethnicity, etc.), genetic, nutrition intake, habits (e.g. tobacco smoking, alcohol consumption, pets), and pre-existing illness (e.g. diabetes, cancer, HIV). These personal risk factors deduce the susceptibility of a person and getting exposed to a pathogen through specific transmission.

  The *environmental* risk factors include climate and location factors deduced from a person's current geolocation and access date/time. The climate risk factors incorporate the atmospheric attributes (e.g. temperature, humidity, precipitation), weather condition (e.g. windy, hot), and season (e.g. winter, spring). The location risk factors comprise of geographical attributes (e.g. altitude), land-use (e.g. farming), or features (e.g. cave, forest).
- Infectious disease risk quantifications

  Risk ratios (OR and RR) are used to describe the magnitude of a risk factor using a numerical ratio from 0 to ~. For example, *females risk of tuberculosis is twice than males*. The odds ratio for gender (male) in this knowledge is 2 compared with gender (female). The baseline (basis of comparison) in this statement is *female* and the odds ratios of the baseline is always one [12].

  Morbidity frequency (prevalence and incidence) is used to quantify how common the disease is in a region in a time period (yearly). For example, *the prevalence of tuberculosis in Indonesia in 2015 is 354 per 100,000 population*.

The knowledge above need to be inputted by epidemiologists through the user interfaces in the knowledge-base tier at knowledge-encoding time of the PROSPECT-IDR system (see **Figure 4.2**). An example of risk factors and their risk ratios is presented in **Figure 5.1**. The illustration gives tuberculosis (TB) risk factors (smoking, gender, and HIV) example. For each risk factor, there are several attributes that are depicted by patterned

[12] Refer to the case-control studies learned using logistic regression.

lines. The attributes may be added or removed as the knowledge develops. For example, at first, the smoking attributes relevant to TB risk are only whether a person is a *smoker* or *non-smoker*, but as knowledge of TB risk develops, now, the attributes become four: *active smoker, passive smoker, non-smoker*, and *ex-smoker*.

The most frequent activity in the infectious disease risk knowledge encoding is updating a risk ratio for a risk factor. For example, at first the odds ratio of the passive smoker is 0.5, but the recent study shows that the odds ratio 0.47 is more accurate than 0.5, then the epidemiologist updates the number for the associated risk factor attribute.

Besides adding and removing the attributes of the smoker, the risk factor itself can be updated. Now the TB risk factors are *smoking*, *gender*, and *HIV*, in case there is a new risk factor that is found in the future, for example, *alcohol drinking habits* (regular consumer, once in a week, never), then the *alcohol drinking habits* can be added.

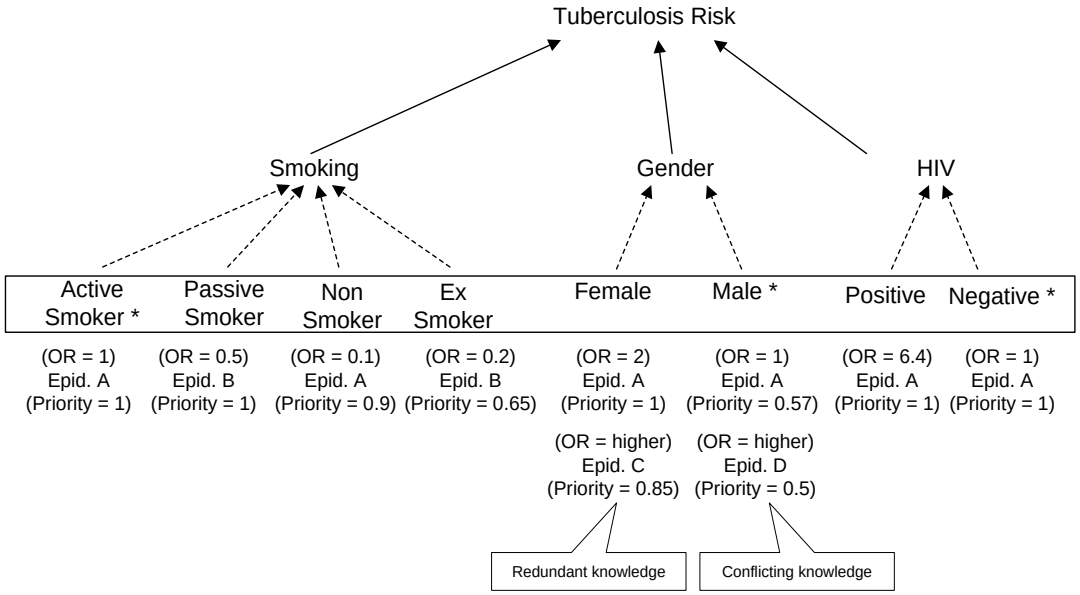

Figure 5.1: An illustration of sample risk factors and their ratios for tuberculosis.

The illustration in **Figure 5.1** gives an example of the *redundant* and *conflicting* knowledge that may happen in a knowledge-base. An example of the *redundant* knowledge is presented between epidemiologist A and C for determining the TB risk ratios for females. Epidemiologist A says that *females risk of TB is twice that of males.* Epidemiologist C also says that *females risk of TB is higher than males*. C's statement is redundant as the risk ratio given by epidemiologist A is more precise than epidemiologist

C. An example of conflicting knowledge is presented between epidemiologist A and D for determining the TB risk ratios for male. Epidemiologist A says that *females risk of TB is twice that of males.* Epidemiologist D says that *males supposed to have higher risk than females*. D's statement is conflicting, in the presence of A's.

From this section, we conclude that the contents that need to be encoded in the knowledge representation are the *categorical* risk factors, *numerical* risk ratios, and *numerical* prevalence value. The encoding activities that the knowledge representation should support, ordered from least to most frequent, are: modifying the risk factors, modifying the risk factor attributes, and modifying the risk ratio for the associated attribute.

5.2.2 How to represent the knowledge and yield personalized prediction from it

From section 3.2, *ontologies* are the commonly used knowledge representation for (infectious) disease risk knowledge. Further, ontologies can represent the risk factor knowledge. To bind the risk factors with their quantifications, rules that compatible with ontology environment are needed (i.e. semantic-web rules). *Semantic-web rules* are needed to express (infectious) disease risk quantifications (risk ratios and prevalence) in a causal relationship.

However, from section 3.2.4, it is apparent that semantic-web rules are unable to express negation and OR logical operator. An example of encoding infectious disease risk knowledge that contains negation operator is given, for the following rule: *anthrax virus is dormant during winter, therefore there is no anthrax risk found in winter.*

To encode this kind of knowledge using semantic-web rules, instead of using the following rule, in which "-" denotes "NOT":

```
EnvironmentRiskFactor(?all) ^ hasSeason(?all, -Winter) ->
setPathogen(Anthrax, active)
```

The following set of rules is needed,

```
EnvironmentRiskFactor(?all) ^ hasSeason(?all, Spring) ->
setPathogen(Anthrax, active)
```

```
EnvironmentRiskFactor(?all) ^ hasSeason(?all, Summer) ->
setPathogen(Anthrax, active)

EnvironmentRiskFactor(?all) ^ hasSeason(?all, Autumn) ->
setPathogen(Anthrax, active)
```

As there is no OR operator, the three non-winter seasons have to be represented as separated rules. As can be seen form this example, the semantic-web rule-base will contain more rules than it would if the SWRL allowed negation and OR logical operator.

Ontologies for representing disease risk factors include CARRE (ontology for cardiorenal disease), ORC (ontology for diabetes), and OBESTTD (ontology for obesity) ontologies. Some vocabulary from these ontologies can be used for representing infectious disease risk factors for PROSPECT-IDR system.

Bayesian Networks are a prediction model that can work with ontology structures. This is proven by PR-OWL, Bayesian Knowledge-base, BNTab, and BayesOWL reviewed in section 3.3. Since the characteristics of personal or environmental infectious disease risk factors are not only binary, then, since BNTab allows ontology classes and individuals to encode nominal, ordinal, and binary, it is more suitable than BayesOWL for encoding infectious disease risk knowledge.

A Probabilistic Knowledge-base allows to encode risk quantifications using rules whose structure is the same as semantic-web rules. *Fuzzy Cognitive Maps* allow the uncertainty degree encoding in using the belief rule-based; this method can be used to resolve conflicts between rules such as the redundant and duplicate rules illustrated in **Figure 5.1**.

To sum up, the way the ontology encodes the risk factors (including their attributes) and the semantic-web rules to encode the risk ratios (including prevalence value) are partially taken from the existing approaches.

5.3 Ontology Construction

To facilitate the declarative infectious disease risk knowledge encoding, all required knowledge is gathered. From previous section there are three levels based on the update frequency.

In **Figure 5.1**, the tuberculosis risk factors are *smoking*, *age*, and *HIV*. These risk factors can be obtained from the collation table which was constructed to help reviewing infectious disease risk factors in section 3.1.1. The contents of the collation table are list of all human infectious diseases and their risk factors mentioned in AHID, CDC, and WHO, classified into *person*, *climate*, and *location* related. However, since there are some differences and overlap in the infectious diseases explained in those three sources, AHID is prioritized as the knowledge source. 107 infectious diseases are described in the AHID. Then, 57 infectious diseases which are not covered by the AHID but mentioned in CDC are added. Lastly, 70 infectious diseases that are notified by WHO but not explained in both AHID and CDC are added. In total, there are 234 distinct infectious diseases as accumulation from those three knowledge sources. The risk factors for each infectious disease are obtained from the associated knowledge sources.

Besides risk factors, there are attributes of risk factors, such as *active smoker*, *non-smoker*, *passive smoker*, and *ex-smoker* are attributes of *smoking* risk factor. Default attributes can generally be found in the AHID, CDC, and WHO. For example, the attributes of *gender* are *male* and *female*, and these apply to all infectious diseases for which *gender* is a risk factor. However, some of them cannot be found in those sources. The detailed attributes, along with the information of which attributes are treated as baseline, can be obtained from case-control studies. This means that detailed risk factors depend on the population characteristics of a location.

Besides the detailed risk factors' attributes, the risk ratios for each attribute can be retrieved from case-control studies. Sometimes, the magnitude of an attribute explained in the associated study is not presented as numerical ratio but given either as an addition or reduction in percentage or in ordinal value (high, medium, low) as a declarative form. The ordinal quantifications usually appear to present the environment conditions that trigger the activity of the pathogen or vector of a specific infection. For example, malaria cases are *high* in the *rainy* season since the *Anopheles* mosquitos thrive and multiple during *hot* days with *high* precipitation [225]. The prevalence values sometimes are revealed in the case-control studies, and sometimes not. If it is not given through the article text, then it can be calculated by using eq.4 (section 3.1.2) using the number of cases (obtained from WHO) and total population for the associated country (obtained from UNSD).

Since these risk factors (e.g. *smoking, HIV, age*) are not frequently updated and these can be risk factors for another infectious disease, then these risk factors are designed as something reusable as ontology objects (either classes, sub-classes or individuals). Whereas the *active smoker, non-smoker, passive smoker,* and *ex-smoker* are designed as attributes of the risk factors. Thus, there are two hierarchy options of how to encode the risk factors and their associated attributes.

(1) if the risk factors are represented as *classes*, then the attributes are designed as their *sub-classes*.
(2) if the risk factors are represented as *sub-classes*, then the attributes can be designed as their *individuals*.

The decision whether an attribute will be implemented as a class or an individual is influenced by the decision as to what ontology objects will be converted as what BN objects (i.e. nodes and states). Whereas the decision of BN nodes and states is affected by whether the represented events can occur at the same time or not (this will be explained in detail with examples in section 6.3). In short, if two events can occur at the same time, for example high *temperature* and high *precipitation* that occur on the same day resulting in a hot and rainy day, then the two risk factors, in this case the *temperature* and *precipitation* cannot be represented as ontology individuals.

5.3.1 Generic ontology

From this stage, two ontology levels are designed. The generic ontology is initially designed for formalizing the all mentioned risk factors and their default attributes for all collected human infectious diseases from AHID, CDC, and WHO. These risk factors are specified in the collation table in **Table 5.1**. The generic ontology facilitates the risk factors to be categorized into: *person* and *environment*, also, an object to put the *infectious disease*. These three objects are represented as main classes. Under the *person risk factor* class, there are dozens of sub-classes that represent risk factors related to person attributes found in the collation table. The *environment risk factor* class similarly has many sub-classes to represent the many environmental risk factors. Under the *infectious disease* class, there are 234 infectious diseases as specified in the collation table. Further hierarchy

of *environment risk factor* main class, *climate* and *location*, is designed. This decision is based on the life dependency of the pathogen and vector that are found to be related with weather, season, and specific location features.

An extract of the collation table for two infectious diseases, dengue fever and tuberculosis, is given in **Table 5.1**. Their risk factors, *development stage, age, gender, pregnancy status, smoking habits, blood types, BMI* are represented as sub-classes of the *person risk factor* class. Whereas, items inside brackets, *children, below 5 years, pregnant, active smoker, passive smoker, O, A, low* are represented as individuals of the associated sub-class. *Drinking habits, pre-existing illness*, and *immunization* are also formalized as sub-classes. But, since it is possible for a person to have multiple pre-existing illness, both *HIV* and *pulmonary disease*, thus, *HIV* and *pulmonary disease* are designed as separate sub-classes of a *pre-existing illness* sub-class instead of designed as individuals of *pre-existing illness* sub-class. This design decision is affected by the requirements of the BN that will be generated by BN-Builder algorithm from the IDR knowledge-base. The detail of this design decision will be explained in the next chapter (section 6.3).

Table 5.1: Extract of the collation table (2 of 234 human existing infectious diseases)[13]

Disease Name	**Person Risk Factor** (known attribute from AHID, CDC, WHO)	**Environment Risk Factor** (attribute)	
		Location	**Climate**
Dengue Fever	Development Stage (children), pregnancy status (pregnant), blood types (O, A), drinking habits (beer)	Between 35ºN and 35ºS, altitudes below 1000m, close to stagnant water, dense vegetation	Weather (above 10C, humid), season (rainy)
Tuberculosis	Age (below 5 years), gender (males), pre-existing illness (HIV, pulmonary diseases), smoking habits (active and passive smoker), immunization (BCG), drinking habits (milk), BMI (low)	Development status (developing), Country (Russia, China, Indonesia, India)	Season (spring), Weather (high temperature, less sunshine)

[13] The full collation table is available at Appendix 8 or the online version can be seen in https://is.gd/IDcompletelist

Table 5.2: Ontology encoding of infection drivers into the main classes of IDR generic ontology [13]

No.	**Drivers** (brief definition)	Significance for infectious diseases	Ontology main **class**: subclass encoding
1.	**Emerging Infectious Diseases** (first temporal emergence of a pathogen in a population)	HIV, SARS, Influenza A (H5N1)	**Location**: Country, Region
2.	**Human population** (related to size and demographic profile of a country)	Air-borne infections, STI	**Location**: Population Density
3.	**Urbanization** (the proportion of people living in rural and urban areas)	Influenza, SARS, STI, blood-borne viruses, Anthrax, imported food-borne infections, Tuberculosis	**Location**: Urbanization Status
4.	**Global Connectivity** (connectedness of people in space and time, e.g. access to road, terrain)	HIV, SARS, Influenza A (H5N1), STI	**Location**: Terrain, Region
5.	**Human Developments** (number of people meeting the standard of living)	All infectious diseases which are related to poverty, sanitary, nutritional, behavioral, environmental and healthcare access components.	**Person**: Employment status, Habits, BMI, Behavioral, Personal conditions. **Location**: Development status
6.	**Peacefulness** (social safety and security, militarization, e.g. crime rates)	Cholera, Dysentery, Measles, Respiratory infections, Ebola hemorrhagic fever, Polio, Diphtheria, Pertussis	**Location**: Country, Continent, Region
7.	**Life Expectancy** (the number of years that a person can expect to live from birth in a population) **and Child Mortality** (number of children who die before the age of 5 years per 1,000 live births)	HIV/AIDS, Hepatitis B, C, H. Pylori, HPV, Pneumonia, Diarrhea, Malaria.	**Location**: Country, Continent, Region
8.	**Water and Sanitation** (the proportion of population using an improved drinking water source and sanitation facility)	Water-borne infections: Typhoid, Cholera, Hepatitis A. Water-based infections: Dracunculiasis, Schistosomiasis. Water-washed infections: Trachoma, Scabies.	**Location**: Terrain, **Person**: Employment: Workplace, Object to deal with, Hobby.
9.	**Undernutrition** (the proportion of population that is underweight, wasted, and stunted)	Tuberculosis, Pneumonia, Measles, Malaria.	**Person**: BMI
10.	**Climate** (defined by average weather and season)	Vector-borne and animal reservoir infections, climate-dependent pathogen survival.	**Climate**: Weather, Season

11.	**Forest Cover Change** (e.g. deforestation)	Vector-borne infectious diseases, the infection results of human predation on animals (e.g. Ebola), and environmental sources (e.g. Cryptococcus gattii)	**Location**: Vegetation Density, Location Features
12.	**Natural Disaster** (natural hazards, e.g. cyclones, droughts, earthquakes)	Pneumonia, blood-borne viruses, Tuberculosis, Cholera, vector-borne infectious diseases	**Miscellaneous**: Natural Disaster
13.	**Antibiotic Use** (average dose per day for a drug used for its main indication in adults)	Tuberculosis, carbapenem-resistant bacteria.	**Person**: Habits: Drug
14.	**Inherited blood disorders** (e.g. sickle HbS, G6PD deficiency, and thalassemia)	Malaria	**Person**: Medical history
15.	**Immunization** (active or passive vaccines that have been injected to a person since birth)	Vaccine-preventable infectious diseases	**Person**: Vaccination records
16.	**Vector Presence** (terrain and climatic conditions that affect vector emergence e.g. *Anopheles*, *P. vivax*)	Vector-borne infectious diseases	**Location**: Terrain. **Climate**: Weather, Season.
17.	**Bird Migration** (seasonal event in which certain bird species travel between breeding and overwintering grounds)	Influenza A, West Nile virus, Western equine encephalitis, St. Louis encephalitis, Japanese encephalitis, Lyme disease.	**Miscellaneous**: Bird migration season
18.	**Livestock Density** (the population of cattle, poultry, sheep and goats per kilometer square)	Leptospirosis, Fascioliasis, Tuberculosis, Brucellosis, African Trypanosomiasis, Q Fever, Campylobacter, Listeria.	**Location**: Livestock density, Location features.

The generic ontology contains all risk factors for 234 infectious diseases. These risk factors are categorized into three main classes *person risk factor*, *environment risk factor*, *miscellaneous* in the generic ontology. This ontology design is a continuation of the reviewed discussion in section 3.1.1 about eighteen infection drivers found in AHID which can be categorized into those three main classes. Detailed categorization for each driver can be seen in **Table 5.2**.

In **Table 5.2**, the ontology encoding as main classes and its sub-classes for each driver is presented in the right-most column. Inside *person risk factor* main class, there are employment, habits, BMI, behavioral, personal conditions, workplace, object to deal with, hobby, medical history, vaccination. *Environment risk factor* main class has two sub-classes: *location* and *climate*. *Location* sub-class is used to encode the prevalence value for an infectious disease in a country. Also, the location sub-class encodes the pathogen reservoir related to specific terrain and location feature, such as, near water or forestry. *Climate* sub-class is used to encode the atmospheric condition required for pathogen or vectors which are dependent to certain weather or season. Therefore, the pathogen activation status is encoded using individuals in the climate sub-class. Inside the *miscellaneous* main class, there are *bird migration* and *natural disaster* sub-classes, or other sub-classes that do not fit into *person* and *environment* main classes.

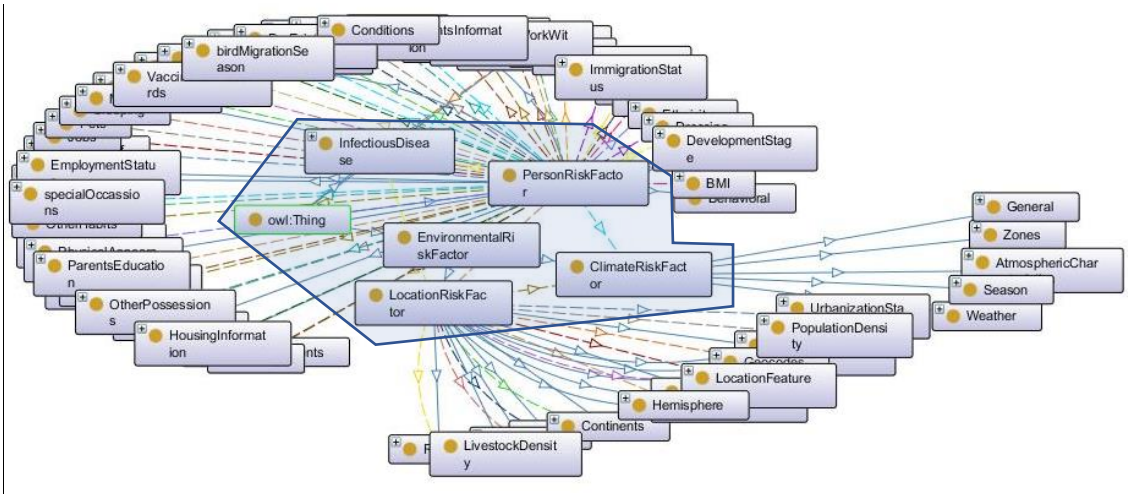

Figure 5.2: The IDR generic ontology (without individuals); the main classes are inside the polygon

At the end of generic ontology design, the main classes are *person risk factor*, *environment risk factor*, and *infectious disease*. The sub-classes of the *environment risk factor* main class, *location* and *climate* risk factors are also represented as a blue polygon (**Figure 5.2**). Sub-classes of person risk factors which represent a person's attributes are represented as squares outside the polygon.

The ontology specified in **Figure 5.2** is called as the *infectious disease risk* (IDR) generic ontology. The IDR generic ontology is constructed using Protégé and its graph is presented using the OntoGraf plugin [226]. The IDR generic ontology consists of 207 distinct risk factors that are formalized as sub-classes (e.g. gender), and 246 risk factor values that are formalized as individuals (e.g. female, male).

The aim of the generic ontology construction is to facilitate the epidemiologists to select the relevant infectious disease risk factors. So, this ontology is designed to capture as much as possible distinct risk factors and their attributes. However, this is an initial design of the IDR generic ontology[14], any additions of the risk factors and attributes are expected to be accommodated with minimum changes on the main classes.

An annotation for marking an individual that becomes a baseline for each risk factor is added to some individuals in the IDR generic ontology. This annotation will affect behavior of the user interfaces for epidemiologists when selecting the relevant risk factors for an infectious disease prevalent in a country (see Appendix 2 for the design of the user interface). Also, the annotation will give information that the epidemiologists are not allowed to put any risk ratios to the baseline, because the risk ratio is always one. The information about which individuals that become the baseline is obtained at knowledge-encoding time.

These risk factors that are unable to be classified as either person, climate, or location are included in *miscellaneous* main class. Under *miscellaneous* main class, there are currently 4 sub-classes: *social gathering, post-natural disaster, harvest time,* and *bird migration* sub-classes. The lower hierarchy sub-classes of the social gathering class are *funeral, wedding,* and *bachelorette parties.*

[14] RDF of the complete IDR generic ontology can be downloaded in [249]

Besides the classes and instances (i.e. ontology individuals), there are object properties that connect between individuals. For example, consider "a *person* who has age *below 5 years* old is at triple risk of *tuberculosis* than *above 5 years*". The object properties are denoted by underlining (e.g. has age, at risk). In this example, has age is an object property whose domain class is *person risk factor* and whose range class is *age (below 5, above 5 years)*. The at triple risk is a data range of the property of the object whose range class is *infectious disease* (*tuberculosis*) and the data range is [*double*].

In addition to that, the ontology formalizes different object properties that are possible between the same individuals that appear in the AHID, CDC, and WHO. For example, there are two possible relations between *person* (as domain class) and *education* (as range class). The first relation is *person* who has education is in *primary* level, and the second relation is *person* who has parent's education is in *primary* level. Thus, two possible object properties are included in the IDR generic ontology.

5.3.2 Disease-specific ontology

After the IDR generic ontology is constructed, the epidemiologists encode their knowledge by (1) creating an instantiation of the generic ontology for an infectious disease prevalent in a country (i.e. disease-specific ontology), (2) encoding the risk quantifications using semantic-web rules, at **knowledge-encoding time** of the PROSPECT-IDR system.

The disease-specific ontology is constructed by reusing some of generic ontology objects (classes, individuals, properties) that are relevant for an infectious disease. The disease-specific ontology is the part of the *knowledge-base* that is going to generate the prediction model at the end of knowledge-encoding time (stage **e** and **f** in **Figure 4.1**). Thus, the epidemiologist decision whether he/she is going to reuse an ontology object or not is based on the availability of their quantifications in the published case-control studies or the quantifications given by herself/himself.

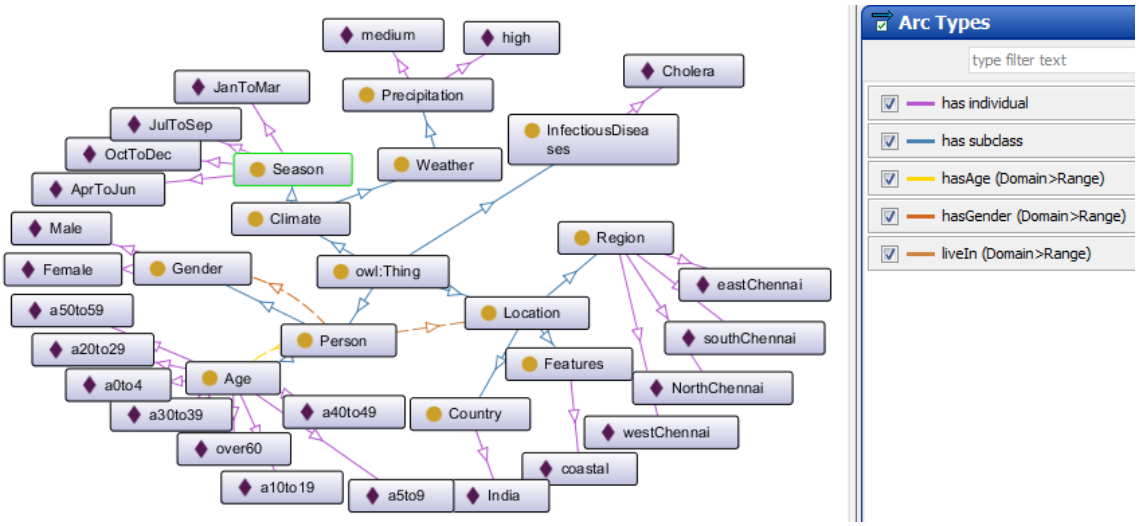

Figure 5.3: The disease-specific ontology for cholera risk in India

Since the IDR generic ontology's risk factors and their attributes were taken from AHID, CDC, and WHO, while the case-control studies are mostly specific to one (infectious) disease prevalent at a population in a location for a particular period, so, there are some chances that during instantiation time, epidemiologists may need to encode risk factors that are not found in the IDR generic ontology. In this case, there are two options for adding these risk factors: (1) the needed risk factors can be added to the disease-specific ontology which is being created at the instantiation time; this is performed by the epidemiologists, (2) the risk factors that are constantly needed to build several disease-specific ontologies can be added to the initial version of the IDR generic ontology; this is performed by the knowledge manager. So, the individuals and sub-classes of the IDR generic ontology will continue to evolve as the knowledge in case-control studies develops.

Therefore, at the end of this chapter (section 5.5), an evaluation for assessing how many risk factors (sub-classes), and risk factors' attributes (individuals) found in the IDR generic ontology will be carried out (a measure of *usefulness* of the generic ontology). Also, the sub-classes and individuals that reused from the IDR generic ontology during the instantiation process are compared with the total ontology objects per disease-specific ontology (measuring the *completeness* of the generic ontology).

5.4 Rule Type Design

The IDR generic ontology aims to encode the infectious disease risk factors found during collating infectious diseases from AHID, WHO, and CDC factsheets. Whereas, the semantic-web rules are designed to bind the risk factors with their risk quantification. Therefore, the IDR rule types are designed to specify the characteristics of the risk quantifications, so they can be used anytime when the epidemiologists need as the knowledge develops. In designing the rule types, observations made during collating the infectious disease risk factors are taken into account.

Quantifications for most of the risk factors related to *person* attributes are represented as numerical, either as *risk ratios* or as a *percentage* (addition/reduction). These numerical quantifications are represented by using *real* rule types. The risk ratios, either OR or RR, are represented by *real direct* rule type; the addition/reduction in percentage are represented by *real indirect* rule type. These are rules type 3 and 4 in **Table 5.3**.

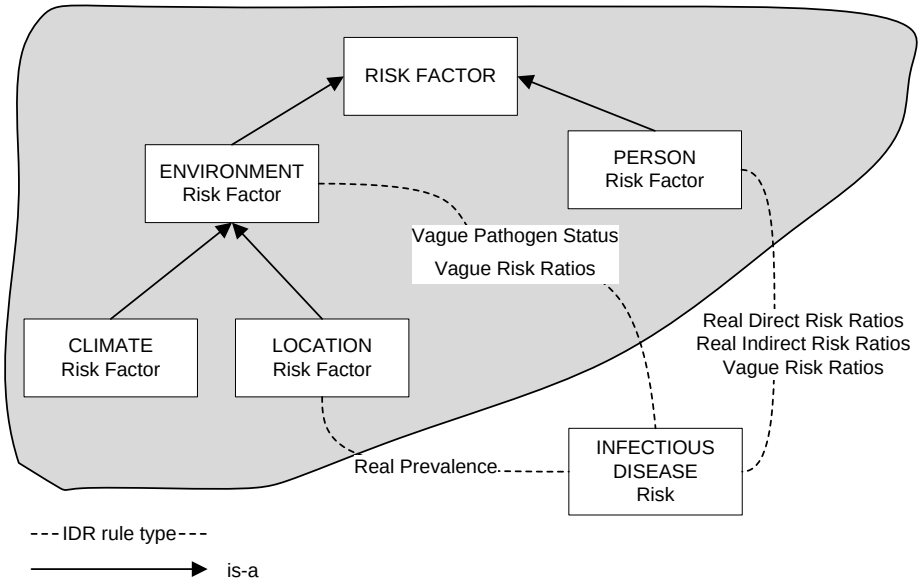

Figure 5.4: The correlation between IDR generic ontology main classes and the IDR rule types

The risk factors related to environment are usually quantified as *ordinal* values. Some environmental risk factors explain the pathogen or vector activity, others describe the human immunity level that is influenced by certain weather or season. This ordinal quantification is represented using *vague* rule types. In section 3.1.1, there are two contributions of the climate (weather and season) in the context of infectious disease risk

knowledge: describe pathogen activation status, and human immunity level that depends on the climate.

Quantifications that represent climate attributes to describe pathogen activity are represented using *vague pathogen status* rule type. Whereas the quantifications that explain human immunity level or other than pathogen information are represented using *vague risk ratio* rule type. These are rule types 2 and 5 in **Table 5.3**.

In order to fulfil the Bayes chain rule to populate the conditional probability table of a BN, the knowledge-base should contain at least one *risk ratio* (either person or environment risk factor) and one *prevalence value* (for the contextual country). The main classes together with the associated rule types are illustrated in **Figure 5.4**.

Table 5.3: The IDR rule types and their encoding examples

IDR Rule Type Number	IDR Rule Type Names	IDR Rule Properties	IDR class category to encode	Value in data forms	Examples of declarative knowledge to encode
#1	#2	#3	#4	#5	#6
1	Real Prevalence	setRisk	location	Prevalence rate in %	TB prevalence in Indonesia is 391 per 100,000 population [227]
	IDR Rule: Environment(?all) ^ hasCountryName(?all, Indonesia) -> setRisk(TB, 0.395)				
2	Vague Pathogen Status	setPathogen	weather, season	Pathogen Activity in inactive, less active, active, more active	*Mycobacterium tuberculosis* is more active during humid condition [136]
	IDR Rule: Environment(?all) ^ during(?all, humid) -> setPathogen(TB, MoreActive)				
3	Real Direct Risk Ratios	alterRisk	person, (weather, season, location)	Risk ratio in $0 < \mathbb{R} < \infty$	Males have 2.37 times more TB risk than females [21]
	IDR Rule: Person(?all) ^ hasGender(?all, Male) -> alterRisk(TB, 2.37)				
4	Real Indirect Risk Ratios	addRisk, reduceRisk	person, (weather, season, location)	Risk ratio in %	Fish intake can reduce the TB risk by 50% [136]
	IDR Rule: Person(?all) ^ hasEatingHabits(?all, fish) -> reduceRisk(TB, 50%)				
5	Vague Risk Ratios	estimateRisk	person, weather, season, location	Risk ratio in high, low, medium, around n	People who have low body mass index are at a high TB risk [136]
	IDR Rule: Person(?all) ^ hasBMI(?all, low) -> estimateRisk(TB, high)				

There are 10 IDR rule examples that are given along with the IDR generic ontology (see **Figure 5.5**). S1 is an example of a *real prevalence* rule type, this rule example follows the first rule type at **Table 5.3**. S2 is an example of environment risk factor for *vague pathogen status* rule type; this rule example explains the more activation of the IDname's pathogen during humid day. S3 and S4 are examples of person risk factor (e.g. male gender) and location feature (e.g. rice fields) for *real direct risk ratio* rule type, respectively. S5 and S6 are examples of person risk factor for reduction and addition of risk with certain percentage, respectively. S7 and S8 are examples of person risk factor and location feature for *vague risk ratio* rule type, respectively.

Name	Rule	Comment
S1	EnvironmentRiskFactor(?all) ^ hasCountryName(?all, aCountryName) -> setRisk(IDname, 0.395)	Priority: 1
S10	PersonRiskFactor(?all) ^ hasDevelopmentStage(?all, Children) -> alterRisk(IDname, 0.34)	Priority: 1
S2	EnvironmentRiskFactor(?all) ^ isHumid(?all, Yes) -> setPathogen(IDname, "MoreActive")	Priority: 1
S3	PersonRiskFactor(?all) ^ hasGender(?all, Male) -> alterRisk(IDname, 2.37)	Priority: 1
S4	EnvironmentRiskFactor(?all) ^ nearWith(?all, RiceFields) -> alterRisk(IDname, 1.07)	Priority: 1
S5	PersonRiskFactor(?all) ^ hasEatingHabits(?all, Fish) -> reduceRisk(IDname, "50%")	Priority: 1
S6	PersonRiskFactor(?all) ^ hasHabits(?all, Fishing) -> addRisk(IDname, "10%")	Priority: 1
S7	PersonRiskFactor(?all) ^ hasBMI(?all, Low) -> estimateRisk(IDname, "Low")	Priority: 0.8
S8	EnvironmentRiskFactor(?all) ^ nearWith(?all, LivestockFarms) -> estimateRisk(IDname, "high")	Priority: 0.92
S9	PersonRiskFactor(?all) ^ hasGender(?all, Male) ^ hasDevelopmentStage(?all, Children) -> alterRisk(IDname, 6.12)	Priority: 1

Figure 5.5: IDR examples written in SWRL

Every risk ratio for a risk factor's attribute has a baseline of comparison. For example, tuberculosis risk for an adult is *twice* that of a child; tuberculosis risk for an active smoker is *six times* that of a non-smoker. The italic words show the risk ratio; the underlined words show the baseline whose risk ratios are always one. One of the attributes for each risk factor must be a baseline to make the risk ratio becomes make sense. However, the baseline can be different from one case-control study to another case-control study depending on the purpose of the research.

Identification of the baseline should be accommodated as part of the ontology design in order to provide clarity of the risk ratios that are going to be inputted by more than one epidemiologists using semantic-web rules. However, this information was not found during collating infectious diseases from AHID, WHO, and CDC, but appeared in each case-control study. This finding affects the evolution of the initial IDR generic ontology. More specifically, change on defining attributes for each risk factor.

Most of the risk quantification studies assume risk factors are independent. Independence of risk factor means for example, that the risk probability for *male children* of contracting of an infectious disease is the product of risk ratio for *male* and risk ratio for *children*. However, 3 articles discover dependent risk factors [8], [21], [49], meaning that the risk probability for *male children* of contracting of an infectious disease may not be equal to the products of risk ratio for *male* and risk ratio for *children*. The instantiation examples for the dependent rules is shown by S9 in **Figure 5.5**. The risk ratio in the dependent rule S9 (for *male children*) shows that the value is different with the product results of the independent rules: S3 (for *male*) and S10 (for *children*). The impact of the inclusion of dependent risk factors to different parts of this research is to the algorithm that is going to populate the CPT from rules that have more than one object properties. See section 6.3.4 for the design of the CPT population procedure.

To resolve the conflicts between rules, a numerical value is assigned for each rule to indicate the priority of the containing infectious disease risk knowledge. The numeric value (i.e. priority) is encoded in the *comment* column (see **Figure 5.5**); the range of a priority is designed to have a value between 0 and 1. The priorities are inputted by the epidemiologists for specifying their confidence level of their inputted knowledge via user interfaces (see Appendix 2). By default, the *real* rule types have higher priorities than *vague* rule types since the *real* rule types can be directly processed to Bayes chain rule without using random distribution. The impact of the inclusion of the priority is to the algorithm populates the CPT from rules that have the highest priority level. See section 6.3.4 for the design of the CPT population procedure related to the priority. However, it is possible to have the same priority values for more than one duplicating and contradicting IDR rule. In this case, the knowledge manager will be asked to assign different priority values for the conflicting rules before firing the algorithm.

5.5 Knowledge-base Evaluation

5.5.1 Evaluation Plan

In this chapter, there are two knowledge representations proposed to encode infectious disease risk knowledge: the IDR generic ontology, and the IDR rule types. Both are used to instantiate an IDR knowledge-base in the knowledge-building time. To evaluate the goodness of the IDR generic ontology and the IDR rule types, several infectious diseases prevalent in several countries that are published in case-control studies will be selected carefully with some criteria. Thereafter, the selected case-control studies will be encoded to evaluate how *useful* and how *complete* the IDR generic ontology and the IDR rule types are. Some of the evaluation presented in this section has been submitted to a journal article which the full manuscript is given in Appendix 7.

The case-control studies are selected based on these criteria: (1) The infectious diseases cover the known *reservoir types*, the known *transmission modes* and cover both *personal* and *environmental* risk factors (e.g. climate and location). This criterion makes sure that the chosen infectious diseases can represent the whole 234 human infectious diseases. So, in order to test the *usefulness* and the *completeness* of the IDR generic ontology, it doesn't have to encode every infectious disease. (2) The infectious diseases are preferred to prevalent in more than one regions. This criterion makes sure that there could be another prevalence values to compare with. Also, to show that even though the infectious disease is same, the risk factors and risk factor's attributes could be different, thus, a different knowledge-base is still needed to encode each contextual knowledge (e.g. one infectious disease – one country).

Using the infectious disease risk encoded in the selected case-control studies based on the criteria above, the IDR generic ontology and IDR rule types are evaluated by measuring their *completeness* and *usefulness* to instantiate the IDR knowledge-base.

The *degree of usefulness* of the IDR rule types is investigated by counting how many of the five rule types are used to bind risk factors with their risk quantifications. Whereas, the degree of the usefulness IDR generic ontology usefulness is assessed by counting how many ontology objects (individuals and sub-classes) are used to encode risk factors compared with the total ontology objects for each IDR disease-specific ontology. This

counting methodology in ontological evaluation is inspired by OntoQA [228]. However, since the purpose of the evaluation is different with the OntoQA, thus, the used measure is not entirely same with OntoQA evaluation.

As with the degree of usefulness, the *degree of completeness* is also used to evaluate both IDR rule types and IDR generic ontology. The complete IDR rule types is when there are no other rules needed to encode the infectious disease risk knowledge specified in the case-control studies. Whereas, the complete IDR generic ontology is more than half ontology objects (sub-classes and individuals) in the IDR disease-specific ontology are found in the IDR generic ontology. The addition usually occurs when the risk factors are too specific and not found in the initial version of the IDR generic ontology, hence, they should be added as new ontology objects. The ontology objects that are found in the IDR generic ontology are counted and divide it with the all of contained ontology objects for each ontology objects in the disease-specific ontologies.

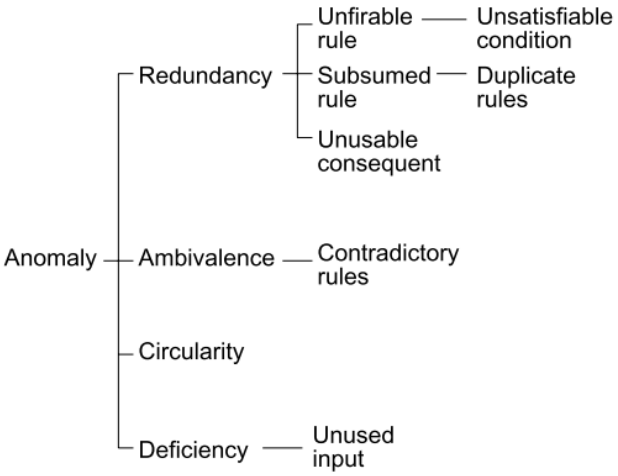

Figure 5.6: COVER anomaly types [229]

Besides these two measures, the evaluation whether there are anomalies appear on the IDR rule-base is conducted. To evaluate the anomalies on the IDR knowledge-base, a *logical-based* approach that verifies a knowledge-base containing rule-base is used. COVER [229] evaluates the *redundancy*, *ambivalence*, *circularity*, and *deficiency* anomalies that possibly occur between the knowledge-base and the rule-base (see **Figure 5.6**). There are six anomaly types that may occur in a knowledge-base containing a rule-

base: *unsatisfiable condition*, *duplicate rules*, *unusable consequent*, *contradictory rules*, *circular rules*, and *unused inputs*.

The definition of each anomaly type is given below,

1. *Unsatisfiable condition* occurs if an IDR rule contains an individual (in its antecedent) that is not match with an individual in the IDR disease-specific ontology.
2. *Duplicate rules* are flagged when there are more than one rules contain the same risk quantifications (in their consequents) for the same antecedents.
3. *Unusable consequent* is indicated when an IDR rule contains an individual (in its consequent) that is not match with an individual in the IDR disease-specific ontology.
4. *Contradictory rules* occur when there are more than one IDR rules contain the different risk quantifications (in their consequents) for the same antecedents.
5. *Circular rules* are identified when there is a circular chain of rules referring from consequents to antecedents.
6. *Unused inputs* happen if the IDR rules contain an individual that is declared in the IDR disease-specific ontology, but it is unused.

These anomalies are screened at the knowledge-encoding time, after the epidemiologists selecting the relevant ontology objects from the IDR generic ontology to construct the IDR disease-specific ontology. Thereafter, the epidemiologists bind the risk factors with their risk ratios from the case-control studies using semantic-web rules; in this stage, these anomalies are identified.

5.5.2 IDR Evaluation Cases

From the criteria, several infectious diseases are match with the *second* criterion (prevalent in several countries) based on WHO [31] are: cholera, diphtheria, anthrax, leprosy, meningococcal (meningitis), pertussis, tetanus, tuberculosis, typhoid fever, measles, mumps, smallpox, yellow fever, malaria. Whereas, dengue fever is chosen because it is prevalent in Indonesia, as the country where the author lives.

To find whether those diseases can match for the *first* criterion, the mentioned infectious diseases from previous paragraph are categorized by the reservoir type, transmission modes, and risk factor categories as presented in **Table 5.4**. These two selection criteria were intended to select sufficient evaluation cases that cover all reservoirs and transmission modes, thus, the selected evaluation cases are representative.

Table 5.4: Selection of infectious diseases for evaluation

	Infectious Diseases
Reservoir Types	
Human	cholera, diphtheria, leprosy, meningococcal, pertussis, tetanus, tuberculosis, typhoid fever, measles, mumps, yellow fever, malaria, (dengue fever)
Animal	cholera, diphtheria, anthrax, leprosy, yellow fever, malaria, (dengue fever)
Inanimate	anthrax, leprosy, cholera, tetanus
Unknown	smallpox
Transmission Modes	
Direct contact	diphtheria, meningococcal, pertussis, measles, smallpox
Fecal-oral	cholera
Blood-borne	tetanus, malaria
Food-borne	cholera, diphtheria, anthrax
Water-borne	cholera
Vehicle	anthrax, tetanus, typhoid fever, meningococcal, smallpox
Vector	cholera, typhoid fever, yellow fever, malaria, (dengue fever)
Air/droplet	anthrax, leprosy, tuberculosis, measles, smallpox
Person	cholera, diphtheria, anthrax, meningococcal, pertussis, tetanus, tuberculosis, typhoid fever, mumps, smallpox, yellow fever, malaria, (dengue fever)
Climate	cholera, anthrax, tuberculosis, typhoid fever, yellow fever, malaria, (dengue fever)
Location	cholera, anthrax, meningococcal, pertussis, tuberculosis, mumps, yellow fever, malaria, (dengue fever)
Miscellaneous	-

From **Table 5.4**, the infectious diseases are chosen as representative for each reservoir type, transmission mode, and the categories of the risk factor: at least one infectious disease per item. Therefore, 5 infectious diseases are chosen: tuberculosis, meningitis, dengue fever, cholera, malaria.

Articles that publish the risk factors of those infectious diseases along with their risk ratios in around 4 or 5 countries are gathered; 22 case-control articles can be found and thus they are used. The profile of each infectious disease is presented in **Table 5.5**. Since the risk factors for the chosen infectious diseases are all different and all countries have different prevalence values, thus one IDR knowledge-base is created per infectious

disease-country context. So, there are 22 knowledge-bases that are used as evaluation cases. The profile of each evaluation case is presented in **Table 5.6**. These evaluation cases are used for assessing the *usefulness* and *completeness* of the IDR rule types and the IDR generic ontology, also for identifying *anomalies* in the IDR rule-base.

Table 5.5: The coverage of the infectious diseases selected for the evaluation based on the reservoir types, transmission modes and the risk factor categories.

Criteria	Coverage of the selected infectious diseases				
	Tuberculosis	Meningitis	Dengue Fever	Cholera	Malaria
Reservoir Types					
Human	☒	☒	☒	☒	☒
Animal	☐	☐	☒	☒	☒
Inanimate	☐	☐	☐	☒	☐
Unknown	☐	☐	☐	☐	☐
Transmission Modes					
Direct contact	☐	☒	☐	☐	☐
Fecal-oral	☐	☐	☐	☒	☐
Blood-borne	☐	☐	☐	☐	☒
Food-borne	☐	☐	☐	☒	☐
Water-borne	☐	☐	☐	☒	☐
Vehicle	☐	☒	☐	☐	☐
Vector	☐	☐	☒	☐	☒
Air/droplet	☒	☒	☐	☐	☐
Context-dependent predictors					
Person	☒	☒	☒	☒	☒
Climate	☒	☒	☒	☒	☒
Location	☒	☒	☒	☒	☒
Miscellaneous	☐	☐	☐	☐	☐
Prevalent in	Indonesia, Africa, Croatia, China	Chile, South Korea, United States, Gaza Strip	Indonesia, Singapore, Sudan, Rep. Dominican, Brazil, Nepal	India, Papua New Guinea, Zimbabwe, Rep. Dominican	Mali, Malaysia, Ethiopia, Colombia

Table 5.6: Descriptions of the case-control studies used for evaluation

Sources	**IDR label**	**Year of subjects were obtained**	**Location of the subjects**	**Number of case/control subjects**	**Specific criteria of the subjects**
Tuberculosis					
[132]	TB^{INS}	2007	Indonesia	1,582	Adults
[21]	TB^{AF}	1996-1998	Africa	247	Adults (>14 years old)
[6]	TB^{CRT}	2006-2008	Croatia	300 / 300	Adults (>14 years old)

[136]	TB^{CHN}	2015-2016	North China	461	Spinal Tuberculosis cases in Adults (>16 years old)
Meningitis					
[8]	MEN^{CHL}	2012-2013	Chile	76 / 337	Children (<5 years old)
[168]	MEN^{KOR}	2013-2014	South Korea	24 / 554	Comorbidity with Herpes Zoster
[169]	MEN^{US}	1998-1999	US	82 /50	Adults (18 to 23 years old)
[170]	MEN^{GZ}	2009	Gaza strip	1,853	Hospitalized children
Dengue Fever					
[148]	DF^{INS}	2014	Indonesia	3,194	Children (<19 years old)
[49]	DF^{SGP}	2005-2013	Singapore	395 / 1,308	Adults (21 to 40 years old)
[149][230]	DF^{SDN}	2012	Sudan	491	Adults (16 to 60 years old)
[171]	DF^{DOM}	2011-2012	Dominican Republic	796	Children (<16 years old)
[41]	DF^{BRZ}	2003-2005	Brazil	170 / 1,175	Comorbidity with Diabetes
[7]	DF^{NPL}	2011-2012	Nepal	834	Per household
Cholera					
[172]	$Chol^{IND}$	2009-2011	India	7,661	Registered to selected hospitals
[147]	$Chol^{PAP}$	2010	Papua New Guinea	54 / 122	Adults (>20 years old)
[173]	$Chol^{ZIM}$	2009	Zimbabwe	55 / 110	Not toddler (>5 years old)
[146]	$Chol^{DOM}$	2012	Dominican Republic	363	Haitian and Dominicans only
Malaria					
[231]	Mal^{MALI}	1999	Bamako, Mali	130 / 260	Children (±2 years)
[232]	Mal^{MAS}	2012-2015	Sabah, Malaysia	320 / 953	Dwellers around agricultural area
[233]	Mal^{ETHI}	2001-2003	Southeastern Colombia	290 / 977	Above 1 year
[234]	Mal^{COL}	2016	Dembia, Colombia	185 / 185	Adults (±26 years)

5.5.3 Evaluation Results: IDR Rule Types

IDR rule types are available at the IDR generic ontology. During the knowledge-building time, the epidemiologists create the IDR rules by instantiating them from IDR rule types. The usefulness and completeness of the IDR rule types are assessed by identifying how many of them are used for 22 evaluation cases.

Usefulness

Usefulness of the IDR rule types is defined by to what extent the five IDR rule types are used to bind the risk factors with their risk quantifications (e.g. odds ratios, prevalence

rate). For example, to encode $Chol^{IND}$ risk knowledge, we need four IDR rule types. The usefulness of the IDR rule types for each evaluation is available in **Table 5.7**.

Table 5.7 shows the use of five IDR rule types in encoding risk quantifications for each evaluation case. From five IDR rule types, two rule types (the *real prevalence* and the *real direct risk ratios*) are used for all 22 IDR knowledge-bases; 1 of 22 cases, MEN^{KOR}, uses three rule types (with addition of the *vague risk ratios*); 2 of 22 cases, TB^{CHN} and $CHOL^{IND}$, use four rule types (with addition of the *real indirect risk ratios*); and one case, DF^{NPL}, uses all rule types.

Table 5.7: The IDR rule types usefulness

IDR Label	The IDR rule types					Total of IDR rule types
	Real Prevalence	Vague Pathogen Status	Real Direct Risk Ratios	Real Indirect Risk Ratios	Vague Risk Ratios	
TB^{INS}	√		√			2
TB^{AF}	√		√			2
TB^{CRT}	√		√			2
TB^{CHN}	√		√	√	√	4
$Chol^{IND}$	√		√	√	√	4
$Chol^{PAP}$	√		√			2
$Chol^{ZIM}$	√		√			2
$Chol^{DOM}$	√		√			2
DF^{INS}	√		√			2
DF^{SGP}	√		√			2
DF^{SDN}	√		√			2
DF^{DOM}	√		√			2
DF^{BRZ}	√		√			2
DF^{NPL}	√	√	√	√	√	5
MEN^{CHL}	√		√			2
MEN^{KOR}	√		√		√	3
MEN^{US}	√		√		√	2
MEN^{GZ}	√		√		√	2
Mal^{MALI}	√		√			2
Mal^{MAS}	√		√			2
Mal^{ETHI}	√		√			2
Mal^{COL}	√		√			2
	22	1	22	3	6	54

From the 22 evaluation cases, the most useful rule types are the *real prevalence* and *real direct risk ratio*. This is because the main results of the case-control studies are the odds ratios, and they are used to calculate the infectious disease risk prediction using the Bayes chain rule. However, few of them also gives the risk quantifications as ordinal values and in addition or reduction in percentages, therefore, the *vague risk ratio* and *real indirect risk ratio* rule types are utilized. Only one article explains the pathogen status; this knowledge is encoded using *vague pathogen status* rule type. To sum up, since there is no unused IDR rule type, thus, all IDR rule types are 100% useful.

Completeness

Completeness of the IDR rule types is determined by to what extent the five IDR rule types can encode risk quantifications in the evaluation cases. During IDR instantiation process, all risk ratios and prevalence rates can be encoded using the five provided IDR rule types. This suggests that all needed IDR rule types are provided in this research. Thus, make these five IDR rule types complete.

5.5.4 Evaluation Results: IDR Rules

The number of rules used to encode each of the evaluation studies is given in **Table 5.8**.

Table 5.8: Summary of the number of IDR rules for each knowledge-base.

IDR Label	Total of IDR rules
TB^{INS}	5
TB^{AF}	40
TB^{CRT}	26
TB^{CHN}	22
$Chol^{IND}$	15
$Chol^{PAP}$	10
$Chol^{ZIM}$	6
$Chol^{DOM}$	14
DF^{INS}	17
DF^{SGP}	30
DF^{SDN}	9
DF^{DOM}	5
DF^{BRZ}	12
DF^{NPL}	15
MEN^{CHL}	34
MEN^{KOR}	6
MEN^{US}	15
MEN^{GZ}	13

Mal^{MALI}	13
Mal^{MAS}	13
Mal^{ETHI}	10
Mal^{COL}	16

Anomalies

This section discusses the possibility and the incidence of the rule anomaly types listed in section 5.5.1 in the knowledge-bases of the 22 evaluation cases.

The *circular rule* anomaly type cannot happen in IDR rule-bases since the antecedent and consequent parts of the IDR rules always refer to individuals in different classes. The antecedent refers to individuals in either person or environment risk factor class, whereas, the consequent refers to an individual in infectious disease class (i.e. name of the infectious disease whose being predicted).

The *unused input* anomaly type does not happen in the IDR rule-bases for this moment because all risk factors in the IDR disease-specific ontology were selected from IDR generic with a purpose to bind them with their risk quantifications. However, this anomaly type is possible when an epidemiologist decides to unbind risk quantification from an individual, as the knowledge develops. This may result that there is an unused individual in the IDR disease-specific ontology without having any risk quantifications specified in any IDR rules.

The *unsatisfiable condition* and *unusable consequent* anomaly types are possible when the used knowledge management system has no integrity checking. For example, if an individual is renamed in the IDR disease-specific ontology after it is defined and used in an IDR rule. Since both risk factor classes and infectious disease class can be renamed anytime when needed, then inconsistencies may occur in both antecedent and consequent.

The *contradictory rules* anomaly type can happen when more than one epidemiologist or more than one case-control study binds the different risk ratios for the same risk factors in one knowledge-base. However, since each 22 knowledge-bases is created based on one case-control study, therefore, this anomaly type does not occur in the IDR knowledge-bases for the evaluation cases.

One small solution has been prepared to resolve this conflict: prioritization. Before submitting the IDR rules, epidemiologists will be asked to specify their confidence level regarding the risk quantifications with a value between 0 and 1. Where there are two conflicting rules with the same risk ratios, then the knowledge manager resolves the conflict by assigning different priority to the duplicating rules, the rule with the highest priority level is included to populate the CPT.

Duplicate rule anomaly types can occur when different rule types are used to express the same risk ratios for the same risk factor in one knowledge-base. For example, to encode the declarative knowledge: *a person who does not consume vitamin D will have tuberculosis risk 2.85 times higher than a person who consumes vitamin D regularly*. This knowledge can be encoded by using *real indirect risk ratios* rule type with 285% as the quantification or using *real direct risk ratios* type with risk ratio 2.85. Even though this case is possible, but the *real indirect risk ratio* is an alternative to encode risk quantifications when they are not presented as odds ratios or relevance risks. So, if this case ever happened, the knowledge manager should assign higher priority for the *direct risk ratio* instead of the *indirect* one.

One preventive solution in the user interfaces for experts in the system has been prepared; a feature is designed (as a table) to inform experts about similar pre-defined risk factors for a knowledge-base. However, this feature is not able to diminish all the duplicate rules perfectly, but this should eliminate duplicate rule entries. See the design of the user interfaces at Appendix 2.

5.5.5 Evaluation Results: IDR Generic Ontology

The IDR generic ontology is designed by collating all mentioned risk factors in the AHID, CDC, WHO factsheets because these knowledge sources cover all human infectious diseases that exists in the world, not specific to particular infectious diseases. Therefore, some risk factors in the IDR generic ontology might not be used in the IDR disease-specific ontology during knowledge-encoding time for the 22 evaluation cases. However, the aim of this thesis is to provide an IDR generic ontology that helps the epidemiologists to encode their knowledge, so the higher the *usefulness* and *completeness* the better.

Usefulness

The *usefulness* of the IDR generic ontology is determined by how many ontology objects (individuals and sub-classes) in the IDR generic ontology are used to encode the risk quantifications. If some ontology objects are never used for encoding knowledge in evaluation cases, then, they might nonetheless be useful. **Table 5.9** shows the summary of the used ontology objects for all 22 case-control studies. The objects that are used more than once are counted only once. The percentage is obtained by dividing the number of used ontology objects with the total ontology objects provided by the IDR generic ontology per predictor category. For example, to obtain how useful individuals in the person category is, 151 is divided to 221 (68.33). The bold numbers show the most useful category during knowledge encoding of 22 evaluation knowledge-bases.

Table 5.9: The used individuals in IDR generic ontology

Predictor categories	Total of objects provided in the IDR generic ontology		Percentage of used IDR generic ontology objects (%)	
	individuals	sub-classes	individuals	sub-classes
Person	221	126	151 (68.33)	76 (60.32)
Climate	7	21	5 (**71.43**)	18 (**85.71**)
Location	18	46	10 (55.55)	27 (58.7)
Overall	246	207	166 (67.48)	121 (58.45)

Table 5.9 shows that the *climate* is the most used category (the percentage of both individuals and sub-classes are the highest). This number shows that the climate factors found in AHID [13] to predict infection risks are consistent with climate factors found in 22 case-control studies. To sum up the degree of usefulness of the initial version of the IDR generic ontology is 68.33% for individuals and 60.32% for classes. To sum up, more than 64.32% (mid-point of 68.33% and 60.32%) ontology objects of the IDR generic ontology is used.

The *climate* category is highly useful since there are not much differences between the climate details that formalized as ontology objects and the details given in the cross-sectional studies. This is also because the climate terminology doesn't vary much from across countries or in most continents.

The *person* category is useful even though it has hundreds of ontology individuals and objects, around 68.33% of them are used to encode the knowledge. Also, all 22 evaluation cases (i.e. IDR knowledge-bases) use the person risk factors. Thus, the person category is a crucial in the IDR generic ontology.

The *location* category has the least usefulness compared to other two risk factors. However, the average of usefulness in the *location* category is more than half of ontology objects; to be precise, it is 57.13% (mid-point of 55.55% and 58.7%). This is because *location feature* sub-classes under *location* category collated from AHID, WHO, and CDC which then formalized as the IDR generic ontology objects are sometimes different than in case-control studies which then formalized as the IDR disease-specific ontology; the case-control studies focus on one or two specific region(s) in one country.

During the knowledge-encoding time, the unused ontology objects are due to some reasons, (1) the risk factors are not specific enough, so, epidemiologists need to encode the knowledge precisely to minimize the ambiguity across epidemiologists, (2) the encoded risk factors do not represent the elaborated knowledge in the case-control studies. The following evaluation will assess the gap between the risk knowledge in the case-control studies and the mentioned risk factors in the AHID, CDC, and WHO factsheets.

Completeness

Completeness of the IDR generic ontology is defined by to what extent the initial version of the IDR generic ontology contains objects that represent the infection risk factors in the 22 evaluation cases. Each evaluation case uses one case-control study that contains several contextual risk factors to be encoded by selecting relevant objects from IDR generic ontology to become IDR disease-specific ontology. During this knowledge-encoding time, risk factors that are not found in the IDR generic ontology should be added as new individuals or sub-classes.

To assess the *completeness* of the IDR generic ontology, for each evaluation case, an investigation of how many risk factors per predictor are found in the IDR generic ontology is conducted. For example, in order to encode only MEN^{CHL} risk factors and their quantifications, 29 individuals and 14 sub-classes of *person* category are needed: 22

of 29 individuals were found in the IDR generic ontology; 11 of 29 individuals are new. Also, 13 of 14 sub-classes were found in the IDR generic ontology; only 1 is new. **Table 5.10** provides average of found ontology objects from all 22 IDR knowledge-bases per category, per ontology object (individual or sub-class). Also, for each category, how many IDR knowledge-bases that containing each category.

Table 5.10: The summary of the completeness evaluation

Predictor category	Percentage of objects that are found in the IDR generic ontology		
	Individuals (%)	Sub-classes (%)	Found in (out of 22)
Person	47	85	22
Climate	71	90	3
Location	77	94	22
Overall	65	89.67	

Table 5.10 exhibits that all IDR disease-specific ontologies contain *person* and *location* categories, but only three of them contain risk knowledge for *climate* category. Therefore, 71% individuals and 90% sub-classes of the IDR disease-specific ontologies that are found under *climate* class of IDR generic ontology are only calculated from three ontologies that encode climate risk factors. Whereas 47% individuals and 85% sub-classes of the IDR disease-specific ontologies that are found under *person* class of the IDR generic ontology are calculated from all 22 evaluation cases. Also, in all 22 evaluation cases, 77% individuals and 94% sub-classes of IDR disease-specific ontologies are found under *location* class of the IDR generic ontology.

From all 22 IDR disease-specific ontologies, more than half (65%) of the required individuals were contained in the IDR generic ontology. However, the new individuals (35%) can be added in the IDR sub-classes; 89.67% of the needed sub-classes are found in the IDR generic ontology. This suggests that the IDR generic ontology is a good start for an initial design of infectious disease risk knowledge representation.

5.6 Conclusion

This chapter described the design of a form of knowledge representation which is required to encode the infectious disease risk knowledge. Started from the state-of-the-art influences to understand what and how knowledge to be represented, the IDR generic

ontology containing three main categories (*person, climate, location*) and the IDR rule-types are designed. The *usefulness* and *completeness* of the designed knowledge representation is then evaluated.

Several infectious diseases were selected carefully with aim to choose the most representative infectious diseases based on their reservoir types, transmission modes, their risk factor categories, and their prevalence. So, in order to test the *usefulness* and *completeness* of the designed knowledge representation, it is not necessary to test all of the collated 234 infectious diseases.

Five infectious diseases prevalent in total 20 countries described in the 22 case-control studies were encoded as 22 IDR knowledge-bases (i.e. evaluation cases). Through the evaluation process, all rule types were found 100% useful. Minimum two IDR rule types were used per evaluation case. For all 22 evaluation cases, there was no need to add new IDR rule types to bind risk factors with their risk quantifications. This suggests that the IDR rule types are 100% complete for binding risk factors with their risk quantifications, for all evaluation cases.

An investigation of how much of the IDR generic ontology is reusable to build the evaluation cases was carried out. Roughly more than 77% of ontology objects (mid-point of 65% and 89.67%) of the IDR generic ontology were used to encode infection risk factors (see **Table 5.9**). Completeness evaluation on the IDR generic ontology showed that the initial version is a good start for representing infectious disease risk factors needed in the 22 evaluation cases. To evaluate the usefulness of the IDR generic ontology, how many individuals and sub-classes are used during knowledge encoding of the 22 evaluation cases is observed. As results, 62.97% ontology objects (mid-point of 67.48% and 58.45%) of the IDR generic ontology are used.

To sum up, two types of ontology are created to encode knowledge about infectious disease relevant to risk prediction. The ontologies are *IDR generic ontology,* and the disease-specific ontologies as a result from instantiation of the IDR generic ontology. Further, *five IDR rule types* are developed to bind the infectious disease risk factors with their quantifications. From the evaluation, the IDR generic ontology and the rule types are proven to be complete and useful.

6. DESIGN AND TEST OF THE BN-BUILDER ALGORITHM

6.1 Introduction

In chapter 4, the coverage of this thesis was outlined in the context of the personalized infectious disease risk prediction (PROSPECT-IDR) system. The thesis covers the knowledge representation for infectious disease risk (IDR), and the BN-Builder algorithm that keeps knowledge consistency between the knowledge-base and prediction model. The previous chapter has described the design and test of the IDR knowledge-base, so this chapter explains the design and test of the BN-Builder algorithm. The BN-Builder aims to generate a BN from the IDR disease-specific ontology structure, as well as populate the CPT of the generated BN from the IDR semantic-web rules. The early version of the BN-Builder algorithm had been published in an article, attached as Appendix 5.

6.2 Influences from the State of the Art

Section 3.3 discussed the approaches that allow knowledge representation and yield a prediction as probability from the encoded knowledge. Based on the state-of-the-art gathered from section 3.3, this section describes what influences inspired the design of the BN-Builder algorithm.

BayesOWL (see section 3.3.5), in its way of generating a BN structure, uses a conversion table that specifies *what inputs (ontology objects) become what outputs (BN objects)*. This table is then reused every time the *BayesOWL* generates the BN. This table can be updated if there is new formalization on the ontology structure that is considered to have impact on the BN structure.

BNTab plugin (see section 3.3.5) shows how a semantic query (e.g. SPARQL) can be used to select appropriate ontology and semantic-web rule objects to be later converted to nodes, states, and a conditional probability table of a BN. Besides showing the way SPARQL can be used to select the ontology and semantic-web objects, an automatic program that converts ontology and semantic-web rules to a BN is an inspiration for this research. However, the generated CPT is only limited to binary states only; this limitation makes the BNTab plugin unsuitable for this thesis and thus, the features need to be

expanded. To be more specific, the features that fit to the characteristics of the (infectious) disease risk knowledge.

A reduction of the iterations needed to populate the conditional probability table can be achieved by grouping the likelihood of events occurrence. Then, *a weight-sum algorithm* is used to calculate the prediction (see section 3.2.3).

6.3 The Design of BN-Builder Algorithm

The BN-Builder algorithm is designed to make sure that the encoded knowledge in the IDR knowledge-base is consistent with the prediction results of the BN. From chapter 5, it is known that the IDR knowledge-base consists of the IDR disease-specific ontology and IDR semantic-web rules; each IDR knowledge-base encodes one infectious disease prevalent in one country. The IDR disease-specific ontology represents the risk factors as sub-classes and individuals. The IDR semantic-web rules encode the risk ratio for each represented risk factor. To be more precise, the BN-Builder aims to generate a BN from the IDR disease-specific ontology structure, as well as populate the CPT of the generated BN from the IDR semantic-web rules.

The BN-Builder algorithm is needed every time the domain experts input or update the content of the knowledge-base or the knowledge manager finish managing the conflicting or redundant knowledge at the knowledge-encoding time. The BN-Builder algorithm aims to produce a Bayesian network that is *fully-functioning* and *consistent* with the encoded knowledge. Fully-functioning means that the generated BN not only contain nodes and states, but also contains conditional probabilities for the basis of predictive reasoning, Conditional Probability Table (CPT), as a placeholder for all combinations of all states in the all nodes. Consistency means that the generated BN structure matches the ontology structure and the populated CPT contains the same ratio between the encoded risk ratios and the generated results. In order to optimize the performance of the BN-Builder to populate the CPT, some impossible combinations are not included in the CPT population process. For example, a `<child>` who works as a `<nurse>`.

To sum up, the BN-Builder algorithm aims to (1) *construct* a Bayesian network structure based on the associated IDR knowledge-base, (2) populate the CPT *correctly* from

various categorical node attributes that appear on the infectious disease risk knowledge, and (3) optimize the algorithm by *deducing the impossibility* of an event. Evaluations of the BN-Builder algorithm are conducted based on its first and second purposes, whereas for the third purpose, the algorithm will be evaluated whether it can recognize the impossible events correctly or not. The evaluation results will be presented in section 6.4.

6.3.1 Translation from Ontology to Bayesian Network

A Bayesian Networks (BN) consists of a *network* and a *Conditional Probability Table* (CPT). The network contains nodes (including states) and links. A basic network has two types of nodes: *parent* and *child* nodes which are connected by links. In this system, the risk factors become the parent nodes and the disease whose risk is being predicted becomes the child node. The network links are used to define a causal relationship between the predictors (parent nodes) and the predicted infectious disease risk (child node). Each BN is generated from an associated IDR knowledge-base which contains an infectious disease risk knowledge for an infectious disease prevalent in a country, thus, the BN scope is one infectious disease-country context.

The network (nodes and links) is built from the structure of IDR disease-specific ontology. Both ontology and BNs have the same hierarchical structure [33], [91], [221], therefore, conversion from an ontological knowledge-base to a BN is straightforward. Once the network is generated, a CPT has to be added. The CPT is populated from the IDR semantic-web rules that encode risk quantifications for each risk factors. The CPT population uses the Bayes chain rule as the basic formula for calculation of conditional probabilities.

A BN node is a condition which contains more than one discrete attribute (i.e. state) which can be nominal, ordinal, or binary. When using nodes to represent risk factors, the states are the possible values for the risk factor. For example, the risk of contracting dengue fever is determined by the *gender* of the person. So, *gender* is the node, while *male* and *female* are the condition values (i.e. states) of the *gender* node.

To represent an actual condition at a time, in the prediction phase, only one state is selectable per node [235]. Therefore, as mentioned in section 5.3, the IDR ontologies

(both generic and disease-specific) is designed so that mutually exclusive values are represented as one risk factor (e.g. *infant* / *elderly* are individuals of *development stage* ontology sub-class), becoming one node in the BN; whereas values that can co-occur, such as *weather* conditions *cloudy* and *cold*, need to be represented in different sub-classes, and become separate nodes in the generated BN. Then, the individuals of the *cloudy* and *cold* can be *yes* or *no*, and *low*, *medium*, *high*, respectively.

To facilitate the explained situation, the BN-Builder algorithm is designed to convert ontology sub-classes to BN nodes and ontology individuals to BN states. The *network construction* procedure of the BN Builder algorithm handles the construction of the network from the IDR ontology, addressing the first aim of the algorithm.

As mentioned in section 3.2.3, a CPT is a table that contains probabilities, either marginal or conditional, for combinations of states in a BN. The second aim of the algorithm is to populate the main CPT. The main CPT for the parent nodes, infectious disease risk factors, contain states and their probabilities. An addition of one parent node causes an addition of exponential set of conditional probabilities in the main CPT which could affect the tractability of runtime calculation.

The other type of CPT needs marginal probability values (e.g. the probability of a person being a child); an example of the marginal probability table can be seen in **Figure 3.17**. These values can be loaded from UNSD API, but if no values are available or provided, probabilities in parent nodes are distributed uniformly by default.

The CPT for the child node (see **Figure 3.17** for the child node), predicted infectious disease risk, consists of all parent states' combinations and their conditional probabilities (e.g. the conditional probability of a *female infant* contracting *dengue fever*). The contents of this CPT are populated by *CPT population* procedure of the BN-Builder algorithm, based on the risk ratios in the IDR rules.

The third aim of the BN builder algorithm is to optimize the BN-Builder algorithm by reducing the number of iterations for impossible combinations. This function is facilitated by a library that contains pairs of items that cannot appear together. For example, a child who works as a nurse, the library will consist of `<child> <nurse>`. Thereafter, the

algorithm scans whether the pairs appear in this library, and if so, the algorithm excludes the event from CPT population iteration.

By achieving these aims, an IDR knowledge-base that contains ontology and semantic web-rules can be converted into a Bayesian Network. Since the BN-Builder algorithm is not designed as part of the knowledge-base management system (Protégé) unlike BNTab, then, the ontology and semantic-web rules for each IDR knowledge-base are exported as RDF and treated as an XML file by the BN Builder algorithm. A query language that is commonly used in XML technology, XPath, is used to retrieve ontology objects and convert them into BN objects.

6.3.2 Intermediate Representation of Network and Rule Structure

Two procedures are designed in the BN-Builder algorithm with aim to convert the IDR knowledge-base (ontology and semantic web-rules) to the BN: *Network Structure*, and *CPT Population*. Both procedures need their own intermediate representation (abstract data type) that can be reused several times to achieve the outputs.

Network Structure

In the network structure procedure, the BN-Builder needs information about the classes, individuals, and rules to construct the network structure and to populate the CPT. The information is obtained from the knowledge-base export representation, RDF (**Figure 6.1**) using XPath to locate their paths. The bold tags show sections needed to build a BN. The information about nodes and states to construct a BN are stored in `<Classes>` and `<Individuals>` tags, while resources about OR, prevalence, and other information needed to populate child node's CPT are stored in `<Rules>` tags; handling of `<Rules>` element will be discussed in the next sub-section.

```
<Object Properties>
<Data Properties>
<Classes>
<Individuals>
<Rules>
      <body>
            <args>
      <body>
            <args>
```

Figure 6.1: RDF Structure

In the conversion from ontology to BN structure, there is a problem related to similar attribute names. Basically, the Protégé does not allow two or more individuals to have the same literal. But, in the Bayesian Network, states can have the same name, as long as the states are contained in the different nodes. Duplicated names of individuals occur quite commonly. For example, *smoking* and *eating* habit sub-classes might both have an individual named *unknown* (see **Figure 6.2** for the illustration). Ontology classes and individuals in **Figure 6.2** are illustrated by rectangles and ellipses, respectively. Whereas, the labels of the lines illustrate the ontology object properties. To facilitate this in the ontology modelling within Protégé, the *unknown* individual is shared between *smoking* and *eating* habit sub-classes. When converting to network structure, these shared individuals need to become separate states in each of the separated nodes (e.g. an *unknown* state in the *smoking habit* node and *unknown* state in the *eating habit* node). Therefore, as an identification about which *unknown* state belongs to which node, the state name is concatenated with the node name in the back-end system (including in the intermediate representation).

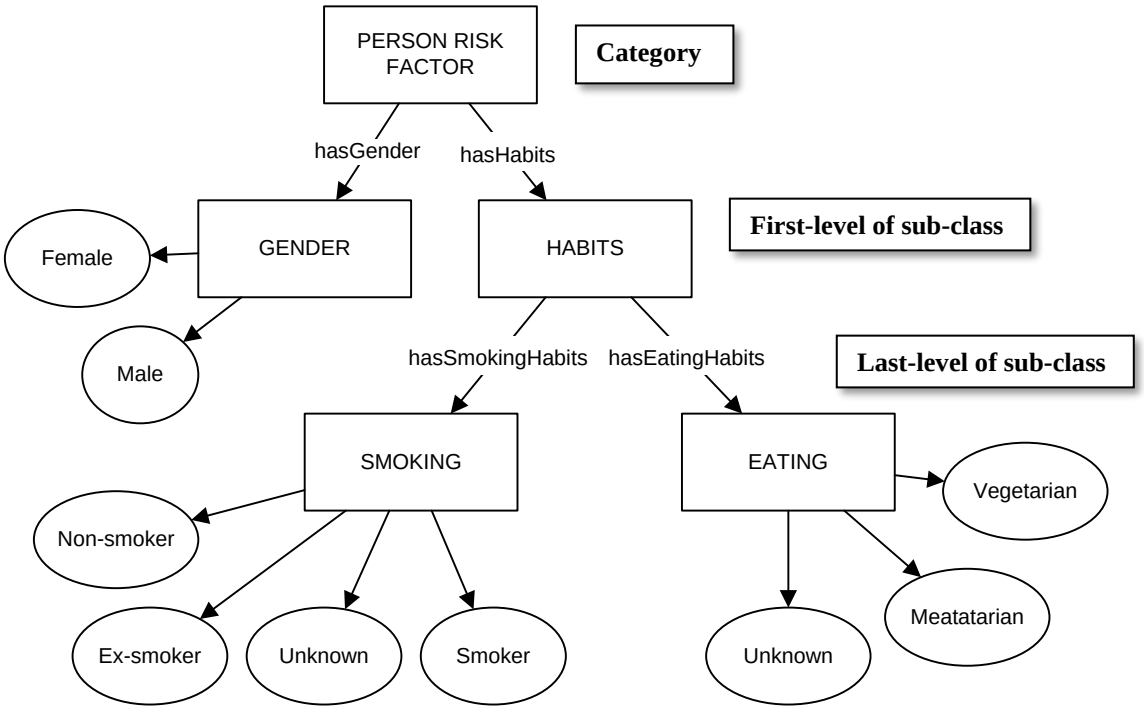

Figure 6.2: A sample of person risk factor multiple hierarchy

The intermediate representation for the ontology network in **Figure 6.2** can be either as in **Table 6.1** or **Table 6.2**. The first approach (**Table 6.1**) concatenates the first-level sub-class, *habits*, directly to the individuals. This approach does not solve the problem, since it is still not clear whether the *unknown* state belongs to *smoking* or *eating* habits; both are *HabitsUnknown*.

Table 6.1: First option of the network intermediate representation

Node names (generated from ontology sub-class)	State names (generated from ontology individuals)	
	Back-end version	Front-end version
Gender	GenderMale	Male
	GenderFemale	Female
Habits	HabitsSmoker	Smoker
	HabitsNonSmoker	NonSmoker
	HabitsExSmoker	ExSmoker
	HabitsUnknown	Unknown
Habits	HabitsVegetarian	Vegetarian
	HabitsMeatatarian	Meatatarian
	HabitsUnknown	Unknown

The second approach (**Table 6.2**) concatenates the last-level sub-class, *smoking* or *eating*, to the individuals. This approach is feasible and clear enough to point which individual to which sub-classes. BN-Builder uses this second approach to generate the network structure. By using this, it suggests no matter how long the hierarchy represented in the IDR disease-specific ontology instance of an IDR knowledge-base, only the last-level sub-classes and the individuals that are converted to the BN.

Table 6.2: Second option of the network intermediate representation

Node names (generated from ontology sub-class)	State names (generated from ontology individuals)	
	Back-end version	Front-end version
1	**2**	**3**
Gender	GenderMale	Male
	GenderFemale	Female
Smoking	SmokingSmoker	Smoker
	SmokingNonSmoker	NonSmoker
	SmokingExSmoker	ExSmoker
	SmokingUnknown	Unknown
Eating	EatingVegetarian	Vegetarian
	EatingMeatatarian	Meatatarian
	EatingUnknown	Unknown

```
<owl:NamedIndividual rdf:about="[IDR URL]#Male">
        <rdf:type rdf:resource="[IDR URL]#Gender"/>
    </owl:NamedIndividual>
<owl:NamedIndividual rdf:about="[IDR URL]#Female">
        <rdf:type rdf:resource="[IDR URL]#Gender"/>
    </owl:NamedIndividual>
<owl:NamedIndividual rdf:about="[IDR URL]#Smoker">
        <rdf:type rdf:resource="[IDR URL]#Smoking"/>
    </owl:NamedIndividual>
<owl:NamedIndividual rdf:about="[IDR URL]#NonSmoker">
        <rdf:type rdf:resource="[IDR URL]#Smoking"/>
    </owl:NamedIndividual>
……
```

Figure 6.3: An RDF representation of some class and individual of the example given in **Figure 6.2**

As mentioned above, XPath queries are used to obtain all nodes and states from the RDF file, including the `<Individuals>` tags. In **Figure 6.4**, the *nodesQuery* and *statesQuery* are intended for retrieve node and the associated state names, respectively.

```
nodesQuery = "/rdf:RDF/owl:NamedIndividual/rdf:type/@rdf:resource";
statesQuery = "/rdf:RDF/owl:NamedIndividual/@rdf:about";
```

Figure 6.4: XPath queries for retrieving node and state names from RDF

Intermediate representation for rule structure

The semantic-web rules are designed to encode the risk quantification for each risk factor in the scope of one IDR knowledge-base. All rules in the IDR knowledge-base are parsed into an intermediate representation for storing their important items to be reused during BN-Builder algorithm execution, specifically for calculating each conditional probability (i.e. CPT population). Recall that there are five IDR rule types designed for this thesis: real prevalence, real direct risk ratio, real indirect risk ratio, vague risk ratio, and vague pathogen status (refer to **Table 5.3**). Examples of rule types are shown in **Figure 6.5**,

```
            CategoryClass(?x) ^ objectProperties(?x, Individual) ->
        ruleProperties(InfectiousDiseaseIndividual, riskQuantification)

PersonRiskFactor(?all) ^ hasSmokingHabits(?all, Smoker) -> alterRisk(TB, 1.4)
PersonRiskFactor(?all) ^ hasSmokingHabits(?all, NonSmoker) -> alterRisk(TB,
0.7)
PersonRiskFactor(?all) ^ hasGender(?all, Male) -> estimateRisk(TB, High)
PersonRiskFactor(?all) ^ hasSmokingHabits(?all, Smoker) ^ hasGender(?all,
Male)-> alterRisk(TB, 13)
```

Figure 6.5: Rule examples and their design

The centered rule at the top of the box is the basic structure of the semantic-web rule in an IDR knowledge-base. For each rule, atoms that need to be kept in an intermediate representation are the risk quantifications (e.g. risk ratios), the individuals (i.e. values of risk factor – *male*), object property (e.g. hasGender), and the data properties which refer to a particular rule type (e.g. alterRisk – *realDirectRiskRatio*). These atoms are required to calculate the correct conditional probabilities.

Furthermore, to handle rule anomalies using the rule priority system, the priority level and the rule identifier (i.e. unique number of rule – *S1*) are needed. The priority level and the rule identifier can be seen in **Figure 5.5**. Since, in the current implementation of the PROSPECT-IDR, each IDR knowledge-base is scoped to one infectious disease only, the inclusion of the disease name has no impact yet on the generated CPT.

The upper part of **Figure 6.6** shows a rule relating to the impact of smoking on TB risk. The risk factor is *Smoker*, an individual of *PersonRiskFactor* class whose object property is *hasSmokingHabits*. The rule type is determined from the *alterRisk* (see **Table 5.3** to know which rule types have which rule property), and the *1.4* (risk ratio) is the risk quantification of the rule. All are needed for computing conditional probabilities.

The rule name, *S1*, is generated automatically as a unique name by SWRL add-ins of Protégé. The rule status, *Part*, is generated automatically by the BN-Builder algorithm; this rule is used to identify whether a rule encodes dependent or independent risk factor(s). The mechanism will be further explained (section 6.3.4). Since this rule status is automatically generated, it does not appear in **Figure 6.5**.

The rule priority, *1*, is entered in the comment field by the epidemiologist to represent his confidence in the rule. The lower part of **Figure 6.6** is the row example for the rule intermediate interpretation. The complete intermediate representation of **Figure 6.5** is presented in **Table 6.3**.

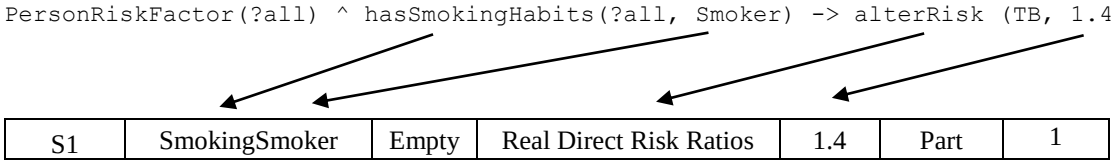

Figure 6.6: Rule splitting illustration

Table 6.3: Sample components of intermediate representation of the sample rules in **Figure 6.5**

Rule ID	Mandatory Risk Factors	Optional Risk Factors	Rule Types	Risk Quant./ Prevalence	Rule Status	Priority
1	**2**	**3**	**4**	**5**	**6**	**7**
S1	SmokingSmoker	Empty	Real Direct Risk Ratios	1.4	Part	1
S2	SmokingNonSmoker	Empty	Real Direct Risk Ratios	0.7	Solo	1
S3	GenderMale	Empty	Vague Risk Ratios	High [1.59]	Part	0.8
S10	SmokingSmoker	GenderMale	Real Direct Risk Ratios	13	Multiple	1
S4	CountryUS	Empty	Real Prevalence	0.12	Solo	1

The RDF representation of S1 (**Figure 6.3**) is given in **Figure 6.7**. The bold letters show the location of the items required for the intermediate representation (as in **Table 6.3**). XPath queries are applied to the RDF representation of the SWRL rule to extract the necessary items and format them as a multimap. The following paragraphs describe this process in detail.

```
<rdf:Description>
    ...
    <rdfs:comment rdf:datatype="XMLSchema#string">1</rdfs:comment>
    <rdfs:label rdf:datatype="XMLSchema#string">S1</rdfs:label>
    ...
       <swrl:body>
       ...
        <rdf:type rdf:resource="swrl#ClassAtom"/>
        <swrl:classPredicate rdf:resource="[IDR URL]#Person"/>
        <swrl:argument1 rdf:resource="[IDR URL]#all"/>
    ...
            <rdf:type rdf:resource="swrl#IndividualPropertyAtom"/>
            <swrl:propertyPredicate rdf:resource="[IDR URL]#hasSmokingHabits"/>
            <swrl:argument1 rdf:resource="[IDR URL]#all"/>
            <swrl:argument2 rdf:resource="[IDR URL]#Smoker"/>
    </swrl:body>
    <swrl:head>
       ...
        <rdf:type rdf:resource="swrl#DatavaluedPropertyAtom"/>
        <swrl:propertyPredicate rdf:resource="[IDR URL]#alterRisk"/>
        <swrl:argument1 rdf:resource="[IDR URL]#Tuberculosis"/>
        <swrl:argument2 rdf:datatype="XMLSchema#float">1.4</swrl:argument2>
       ...
    </swrl:head>
</rdf:Description>
```

Figure 6.7: The SWRL rule RDF representation of the S1 in Figure 6.6
(some unimportant URL was truncated)

In the rule description, the *rule priority* (column #7 in **Table 6.3**) and *rule ID* (column #1 in **Table 6.3**) are located in `<rdfs:comment>` and `<rdfs:label>`. There are two segments of the rule in the RDF: `<swrl:body>` that specifies all items before '`->`' (antecedent), and `<swrl:head>` that specifies all items after '`->`' (consequent). In the

<swrl:body>, the individual and its last-level sub-class are located in <swrl:argument2> and <swrl:propertyPredicate>, respectively. In the <swrl:head>, the rule type and its risk quantification are located in <swrl:propertyPredicate> and <swrl:argument2>, respectively.

The XPath queries that are used to extract those items from the tags are given in **Figure 6.8**. The order of the XPath queries below is to fill the *rule ID, mandatory risk factor, rule types, risk quantification,* and *priority* in **Table 6.3**.

```
ruleName = "/rdf:RDF/rdf:Description/rdfs:label";
ruleRF = "/rdf:RDF/rdf:Description/swrl:body/.//swrl:argument2/@rdf:resource";
ruleType =
"/rdf:RDF/rdf:Description/swrl:head/.//swrl:propertyPredicate/@rdf:resource";
ruleRQ = "/rdf:RDF/rdf:Description/swrl:head/.//swrl:argument2";
rulePriority = "/rdf-RDF/rdf-Description/rdfs-comment";
```

Figure 6.8: XPath queries for retrieving items in the rule intermediate representation from RDF

In the RDF representation, the *optional risk factor* appears as a nested tag inside the *mandatory risk factor*, therefore, the XPath query for extracting the optional risk factor is slightly different to *ruleRF* in **Figure 6.9**.

```
ruleRF2 = "/rdf:RDF/rdf:Description/swrl:body/.//rdf-first/rdf-
Description/swrl-argument2/@rdf-resource"";
```

Figure 6.9: XPath query for retrieving item in the optional risk factor from RDF

Dependency correlation between risk factors is encoded as odds ratio. This odds ratio is shown as *optional risk factor* (column #3 in **Table 6.3**). The dependent risk factors are encoded as *optional risk factor* which can be flexibly extended in the multimap. From case-control studies gathered in section 3.1 the maximum number of risk factors in a "dependent" rule is two. So, the current implementation handles only two risk factors, one *mandatory risk factor* and one *optional risk factor* (see an example in **Table 6.3**). If an intermediate rule representation only contains one *mandatory risk factor* and no *optional risk factor*, it means that the associated rule is an *independent* rule. If a rule contains both *mandatory* and *optional*, then it means that the rule is a *dependent* rule.

There are four regulations that should be obeyed when converting rules to the CPT:

(1) If there are risk factors that appear in both dependent and independent rules, then, the dependent rules have to be processed before independent rules. For example, consider the

condition of *a male adult who is regularly tobacco smoking* in a knowledge-base for TB risk. From **Table 6.3**, the rules that apply to the given condition are S1 (independent), S3 (independent), and S10 (dependent). The correct conditional probability for this combination is given by rule S10, not S1 and S3. The OR for such condition is 13 instead of (1.4 x 1.59).

(2) The risk quantification of the *real indirect risk ratio* rule type is given as addition or reduction with certain percentage. The percentages are translated into odd ratios, eqs. 2 and 3 (see section 3.1.2) which appear in Pseudocode 1 as lines 2b and 2c.

(3) The risk quantifications specified in the *vague rule types* (vague pathogen status and vague risk ratios) have to be converted to a numerical risk ratio (since a CPT by definition contains numbers). Consider rule S3 in **Table 6.3**, which represents a rule that needs a risk ratio generated using random distribution. The original rule's quantification is "High"; this is converted into 1.59. This random system can yield odd ratio estimation; the impact is the generated odd ratio changes every time the BN-Builder algorithm is executed. Pseudocode 1 at line 3 and 4 show the main flow of the algorithm of how to get OR from Uniform and Gaussian distribution parameters.

To facilitate the modifications that may come, a *central tendency* and *dispersion* of the Gaussian distribution or *minimum* and *maximum* of the Uniform distribution are modifiable by the domain experts. In the real code implementation, these parameters of the statistical distributions are coded in variables, so, by putting them in variables, it can facilitate the experts to modify the value (if needed). Associated user interfaces can be designed to help epidemiologists.

Pseudocode 1: GetOR Calculation

```
1.  Get the risk quantification of the rule (RQ)
2.  IF the rule type is real indirect risk ratio
     a. Get the rule property
     b. IF the rule property is reduceRisk
            OR = 1-(RQ/100);
     c. ELSE
            OR = 1+(RQ/100);
3.  IF the rule type is vague risk ratio
     a. IF RQ is Low
            OR is a pseudorandom (Uniformly distributed) number between 0.25
            and 0.5;
     b. ELSE IF RQ is Medium
            OR is a pseudorandom (Uniformly distributed) number between 0.75
            and 1.25;
     c. ELSE IF RQ is High
            OR is a pseudorandom (Uniformly distributed) number between 1.5 and
            1.75;
```

```
     d. ELSE IF RQ is n-ish
            OR is a pseudorandom (Uniformly distributed) number between (n-
            0.25) and (n+0.25);
4.  IF the rule type is vague pathogen status
     a. IF RQ is Inactive
            OR is a pseudorandom (Gaussian distributed) number with mean 0.25
            and SD 0.25;
     b. ELSE IF RQ is LessActive
            OR is a pseudorandom (Gaussian distributed) number with mean 1 and
            SD 0.25;
     c. ELSE IF RQ is Active
            OR is a pseudorandom (Gaussian distributed) number with mean 1.25
            and SD 0.25;
     d. ELSE IF RQ is MoreActive
            OR is a pseudorandom (Gaussian distributed) number with mean 1.5
            and SD 0.25;
5.  Return the OR
6.  end
```

(4) *Conflicting* and *duplicate* rules need to be addressed appropriately using the prioritization system (see definition of conflicting and duplicate rules in section 5.5.4). The prioritization system can be identified by priority value (real number between 0-1) that is specified in the comment label for each semantic-web rule. In **Table 6.3**, the priority is given in the right-most column.

The impact on the BN-Builder of the first regulation is the *rule status* (in **Table 6.3**, the rule status is shown in column #6). The need for these, their impact on the CPT, will be explained in section 6.3.4. There are three rule status values: *part*, *solo*, and *multiple* which are generated automatically by the BN-Builder. Assume that in a rule-base, there are only four rules like those in **Table 6.3**. *Solo* status means that the *mandatory risk factor* of a rule is not contained in either *mandatory risk factor* or *optional risk factor* of other rules. *Part* status means that the *mandatory risk factor* of a rule is contained in other rules. *Multiple* status means that the rules contain both *mandatory* and *optional* risk factor.

For example, the *NonSmoker* individual in the *mandatory risk factor* of rule S2 is not contained in other rules, thus, the BN-Builder generate the *solo* status for S2. The *smoker* and *male* individuals in rule S1 and S3, respectively, are found in S10. Therefore, the S1 and S3 have *part* status from the BN-Builder. Since S10 has mandatory and optional risk factors, then the BN-Builder generates *multiple* status for S10.

To sum up, this section explained the needed intermediate representations to generate the BN. There is one intermediate representation for the network, and one for the IDR rules.

The procedure for converting these to the BN network and CPTs are described in sections 6.3.3 and 6.3.4, respectively.

6.3.3 Network Construction procedure

Now that the intermediate representation for Bayesian network construction has been presented in the previous section, this section describes how the Bayesian network structure is constructed from it. From the discussion of advantage and drawbacks of two choices in preceding section, the relevant intermediate representation for this section is presented by **Table 6.2**.

Referring to the column #1 of **Table 6.2**, the node names for parent nodes in the network are *gender*, *smoking*, *eating habit*, while the items in column #3 for the associated row are node states. The disease name (e.g. *tuberculosis*) becomes the child node name (see the explanation of parent and child nodes in section 3.3).

In order to construct the network, the BN Builder closely follows the Netica-J procedure in **Pseudocode 2** (Norsys, 1995-2017). The bold items represent the automation this research presents.

Pseudocode 2: Network Construction

```
1. Create and set the Netica environment
2. Declaration and assignment of a child node
3. Declaration of parent nodes
4. Loading resources from intermediate representations
5. foreach node do
   a. Assign each parent node using three input parameters: node name,
      stateString (result from Statenames Concatenation – Pseudocode 2),
      Netica environment
   b. Construct the marginal probability of each parent node using two input
      parameters: node name, MarginalProb array (result from MarginalProb
      Concatenation – Pseudocode 3)
   c. Save the order of parent node into nodequeue
   d. Connect parent with child node
6. Construct the conditional probability of the child node using nodequeue.
7. Write the network into Netica readable file (.dne file)
```

Pseudocode 3: Statenames Concatenation

```
1. Create a stateString
2. foreach state in a parent node do
   a. Append the the state name to stateString, followed by a comma.
3. end
```

Pseudocode 4: MarginalProb Concatenation

```
1. Create a MarginalProb array
2. foreach state in a parent node do
    a. Append the MarginalProb array with related marginal probability.
3. end
```

Line 2 of the **Pseudocode 2** shows the declaration and assignment of a child node. To declare and assign the child node, it needs the infectious disease name whose risk is being predicted and states of this node. The infectious disease name is *tuberculosis*, and by default there are only two states: *AtRisk*, *NotAtRisk*. The *AtRisk* state contains the final result of conditional probability for a person's risk of contracting tuberculosis given several conditions. Since the total of percentage of all states must be 100%, then, the *NotAtRisk* value is the probability of the person not contracting the tuberculosis, thus, 100% - *AtRisk*.

This percentage characteristic has been taken on the risk quantifications, including the prevalence values. The prevalence values are usually presented in 10,000 or 100,000 units depending on the disease. In order to match with the Netica-J percentage requirement, the data range for real prevalence rule type is %.

The automation of **Pseudocode 2** begins with parent node assignment (line 3 and 5). The Netica-J built-in function to assign a node is given as follows:

```
Node temporary = new Node (String nodename, String statenames, net);
```

The declaration of a temporary node starts in line 3 and it is initialized with null value. In line 5a of **Pseudocode 2**, the temporary node will be assigned with real nodes and states taken from the intermediate representation. The assignment of this node is called for as many nodes as are found in **Table 6.2**; for this simple example, this node is called only three times (for *gender*, *smoking*, *eating* risk factors).

Marginal probabilities, for example the ratio of *male* to *female* in a specific region, are provided by the 'package for collecting personal and environmental facts' (see **Figure 4.2**). In this prototype PROSPECT-IDR system, the assignment of the marginal probability is by default using uniform distribution. By using uniform distribution, it means that the ratio of male to female is 1:1 or in marginal probability it means 50% for male and 50% for female. However, if the marginal probability is provided, the statement below can be used to use the provided data,

```
parentNode.setCPTable(MarginalProb[]);
```

Once the nodes and their states are defined, the order of parent nodes must be saved (line 5c in **Pseudocode 2**) before connecting the parents with child node (line 5d in **Pseudocode 2**). The order will be used by the *CPT Population* algorithm. Line 6 in **Pseudocode 2** handles the CPT population for the child node. The details of the CPT population algorithm are explained in the next section. The result of the network construction procedure is given in **Figure 6.10**.

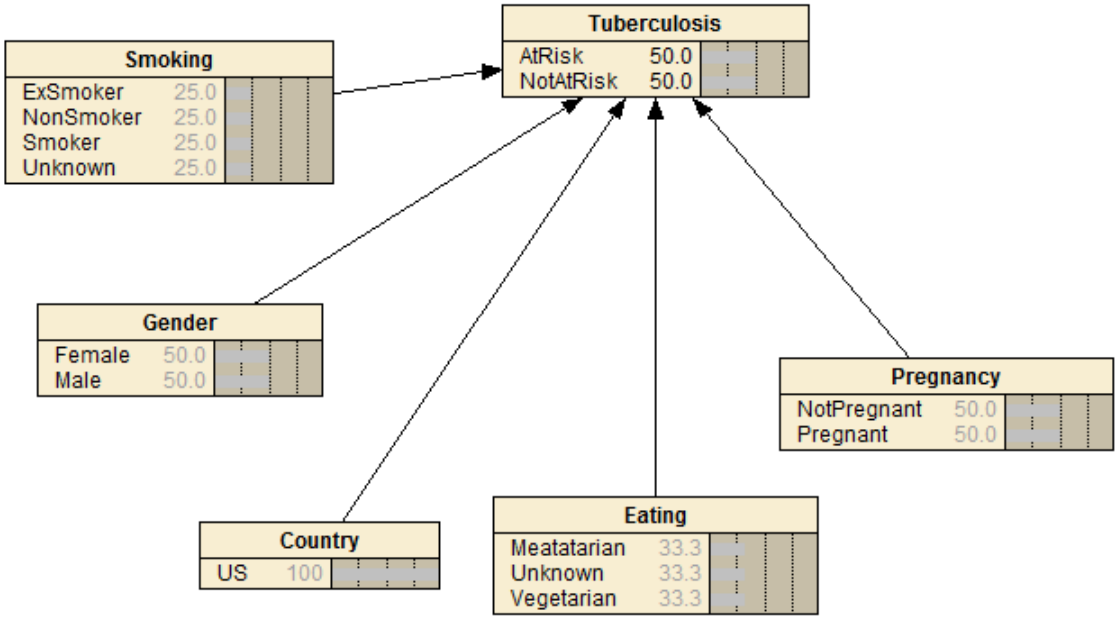

Figure 6.10: The generated sample Tuberculosis BN

6.3.4 CPT Population procedure

After the Bayesian network structure is created, the next step is populating the CPT for the child node (i.e. tuberculosis). The CPT population procedure avails of the rule intermediate representation described in section 6.3.2 and shown in **Table 6.3**.

The CPT population procedure follows the *Bayes chain rule* (explained in section 4.4) which was intentionally rewritten to fit the coding of algorithm (see eq. 6). Thus, this *Bayes chain rule* will be implemented in the BN-Builder algorithm to populate the conditional probability table of the generated BN. By using the eq. 6, the BN is able to manage categorical (mixed binary, ordinal, and nominal) data type as the main character of the (infectious) disease risk knowledge. This procedure involves generating all

combinations of the relevant states and then computing the conditional probability for each combination. See **Figure 6.11** for an example of CPT for tuberculosis.

The number of combinations for child node's CPT is $\prod_{i=1}^{n} s_i$ where s_i is number of states in node i, and n is number of parent nodes. For example, since 2, 3, 4 are the numbers of state, thus, the full combination is 2 x 3 x 4 or 24. To calculate a conditional probability (`condProb`), for a state combination, we apply **Pseudocode 5** using the rule intermediate representation as in **Table 6.3**.

Pregnancy	Eating	Country	Gender	Smoking	AtRisk	NotAtRisk
NotPregnant	Vegetarian	US	Male	NonSmoker	0.084	99.916
NotPregnant	Vegetarian	US	Male	Smoker	1.56	98.44
NotPregnant	Vegetarian	US	Male	Unknown	0.12	99.88
Pregnant	Meatatarian	US	Female	ExSmoker	0.12	99.88
Pregnant	Meatatarian	US	Female	NonSmoker	0.084	99.916
Pregnant	Meatatarian	US	Female	Smoker	0.168	99.832
Pregnant	Meatatarian	US	Female	Unknown	0.12	99.88
Pregnant	Meatatarian	US	Male	ExSmoker	0	100
Pregnant	Meatatarian	US	Male	NonSmoker	0	100
Pregnant	Meatatarian	US	Male	Smoker	0	100
Pregnant	Meatatarian	US	Male	Unknown	0	100
Pregnant	Unknown	US	Female	ExSmoker	0.12	99.88
Pregnant	Unknown	US	Female	NonSmoker	0.084	99.916
Pregnant	Unknown	US	Female	Smoker	0.168	99.832
Pregnant	Unknown	US	Female	Unknown	0.12	99.88
Pregnant	Unknown	US	Male	ExSmoker	0	100
Pregnant	Unknown	US	Male	NonSmoker	0	100
Pregnant	Unknown	US	Male	Smoker	0	100
Pregnant	Unknown	US	Male	Unknown	0	100
Pregnant	Vegetarian	US	Female	ExSmoker	0.12	99.88
Pregnant	Vegetarian	US	Female	NonSmoker	0.084	99.916
Pregnant	Vegetarian	US	Female	Smoker	0.168	99.832
Pregnant	Vegetarian	US	Female	Unknown	0.12	99.88
Pregnant	Vegetarian	US	Male	ExSmoker	0	100
Pregnant	Vegetarian	US	Male	NonSmoker	0	100
Pregnant	Vegetarian	US	Male	Smoker	0	100
Pregnant	Vegetarian	US	Male	Unknown	0	100

Figure 6.11: Sample extract of Tuberculosis CPT

Pseudocode 5: CondProb Calculation

```
1. Initialize condProb to 1
2. IF the combination is impossible
    a. Set the condProb to 0
3. ELSE IF there is a matching risk factor in a real prevalence rule type with
   the highest priority
    a. Set the condProb to that value (prevalence)
4. For each matching risk factor in real indirect risk ratios, vague pathogen
   status, vague risk ratios rule type with the highest priority
    a. obtain the OR using getOR function
    b. condProb = condProb * OR
```

```
5.  For each matching risk factor from real direct risk ratios with the highest
    priority
     a. condProb = condProb * OR
6.  Return condProb
7.  end
```

For each line, the algorithm checks whether the `stateString` is an impossible condition or not, for example, `<male> <pregnant>`. The checking of impossible condition(s) is necessary because the algorithm generates all possible combinations which may include impossible combination(s). The `stateString` is the combination of states from all nodes. In **Figure 6.11**, the stateString begins with `<NotPregnant> <Vegetarian> <US> <Male> <NonSmoker>`. If this stateString contains an impossible combination, then, its `condProb` will be 0 (line 2 in **Pseudocode 5**). To deduce whether a combination is an impossible combination, a specific resource to document known impossible combinations is needed. A sample extract of such a resource is given in **Figure 6.12**.

By filtering these conditions upfront, only possible combinations that need calculation of conditional probabilities are left. **Figure 6.11** shows the impossible combinations for `<male> <pregnant>` were identified and hence, zero probabilities.

Since the order of the parent nodes is unknown until the CPT is generated, thus, the resource is made with aim to catch the impossible combinations in any possible order. Another option is a special function to catch the impossible combinations in any possible order with loose input parameters. But since the later approach consumes more computation, and more memory, then the first approach is used.

```
{"Male", "Pregnant"},
{"Pregnant", "Male"},

{"Children", "Nurse"},
{"Children", "Soldier"},
{"Nurse", "Children"},
{"Soldier", "Children"},

{"Female", "Children", "Pregnant"},
{"Female", "Pregnant", "Children"},
{"Children", "Female", "Pregnant"},
{"Children", "Pregnant", "Female"},
{"Pregnant", "Children", "Female"},
{"Pregnant", "Female", "Children"},
```

Figure 6.12: A resource to specify impossible combination

If the combination is possible, the next step is to find the prevalence value based on the location context (e.g. country). This is performed in Line 3 of **Pseudocode 5**. Thereafter, the rule types are distinguished as follows: the rule type that provides direct risk ratio (e.g. *real direct risk ratios*), or the rule types that need an additional procedure to retrieve the numerical risk ratio from an ordinal value (e.g. *real indirect risk ratios, vague risk ratios, vague pathogen status*). The rule types that need additional procedure call the getOR procedure to get the numerical OR (see **Pseudocode 1** in section 6.3.2).

After the OR is obtained, for each rule type, if the attribute value is contained in the state combination, the rule is considered "a match". For example, the first stateString: `"Female, Vegetarian, Smoker"`, only `Smoker` is considered as "match" with S1 rule. Then, the conditional probability is calculated by multiplying the OR of S1 (e.g. 1.4) with the existing `condProb` (line 5a). Another example for *dependent* rule type: `"Male, Meatatarian, Smoker"`, both `Male` and `Smoker` is considered as "match" with S10 rule. Then the conditional probability is calculated by multiplying the OR of S10 (e.g. 13) with the existing `condProb`. The logic flow of the **Pseudocode 5** follows the rewritten Bayes chain rule (eq. 6) explained in section 4.4.

6.3.5 Summary

This section explains how an IDR knowledge-base which consists of the IDR disease-specific ontology and a set of IDR rules is converted into a *fully functioning* and *consistent* Bayesian network using the BN-Builder algorithm. The ontology subclasses and individuals are transformed into the BN nodes and states. The rules which encode the risk quantifications (odds ratios, percentages, prevalence value) are used to populate the CPT of the generated BN. To convert the ontology and rules, two types of intermediate representation (i.e. multimap) are used to facilitate the resource reusability (e.g. risk quantifications, prevalence values) during the transformation process from an ontology to a BN. Two procedures that make use these intermediate representations are then designed and implemented as part of BN-Builder algorithm: *network construction*, and *CPT population*.

6.4 BN-Builder Testing

This section explains the BN-Builder algorithm testing. The procedures of creating the Bayesian network structure and populating the CPT for the child node were explained in section 6.3.3 and 6.3.4. As explained in section 6.3, the aim of the BN-Builder algorithm testing is to ensure that the encoded knowledge in the IDR knowledge-base is consistent with the generated Bayesian Network. To be more detailed, the BN-Builder is expected to be able to accommodate the variations that appear on the IDR knowledge-base. The variation of the IDR knowledge-base here means the mixed categories of the ontology individuals, not only one type of category (binary only, ordinal only). Since the aim of the BN-Builder is not only creating BN structure, but also populating the CPT of the child node, thus, the variation on the data types of each rule type described in section 5.3.3 are also accommodated.

6.4.1 Testing Plan and Testing Cases

Test Plan

There are two procedures in the BN-Builder: *network construction*, and *CPT population* that covered by this thesis. The *network construction* procedure is aimed to generate the IDR disease-specific ontology to become a BN. To test whether the *network construction* procedure is correct, the structure of the generated BN is compared to the structure of the ontology instance. So, if all sub-classes and individuals in the ontology are all correctly converted to BN nodes and states, the *network construction* procedure is correct.

The *CPT population* procedure calculates all combinations of the generated BN conditions to populate the CPT. Thus, to evaluate the *CPT population* procedure, the generated CPT is compared with the manual calculation of the conditional probabilities using the Bayes chain rule. Two measurements are used to justify whether the CPT is calculated correctly: (1) *distance* between the generated conditional probability and the manually calculated conditional probability. To measure how minimum that the distance can be accepted statistically, a chi-square test is used. (2) *ratio* between the observed attributes. The first measurement is intended for checking whether the Bayes chain rule is correctly implemented in the BN-Builder algorithm. Whereas the second measurement

is aimed to make sure whether the BN-Builder algorithm picks the correct IDR rules for the correct condition and dependency. This can be observed by comparing the baseline of the risk factor with the other risk factors.

Test Cases

To test the features of the BN-Builder algorithm, test cases (as a form of IDR knowledge-base) need to be prepared carefully using these criteria:

For the rule-base specification, the test cases should contain (1) all five IDR rule types, (2) risk quantifications that are covered by all rule types, (3) both dependent and independent types, (4) conflicting and duplicate rules with different priority values.

To test whether the BN-Builder algorithm are capable of generating a *fully-functioning* and *consistent* BN from a knowledge-base, the test cases are prepared (5) to prevalent in two locations that have different prevalence values, (6) to have impossible combinations, (7) to contain multi-level sub-classes, (8) to have a similar individual name for different nodes, and (9) to have mixed categorical attributes.

Admittedly, IDR knowledge-bases that contain all these criteria might not exist. Therefore, the closest IDR knowledge-bases are chosen from the 22 IDR knowledge-bases used for ontology evaluation in section 5.5. Two of those, intrathoracic tuberculosis in Indonesia (TB^{INS}) and spinal tuberculosis in China (TB^{CHN}), cover almost all the criteria, and no other knowledge-base adds to the covered criteria. Therefore, *dummy* rules are added to the chosen two to meet the missing criteria (the validity of the test knowledge-bases is irrelevant for this evaluation).

The left-most column in **Table 6.4** shows that all criteria are allocated either in the TB^{INS}, or in the TB^{CHN} case, or both. This table makes sure that all designed functions of the BN-Builder are implemented and tested accordingly in at least one IDR knowledge-base.

Table 6.4: Coverage of test cases

Test Coverage	Context of the IDR Knowledge-base	
	Tuberculosis in Indonesia TB^{INS}	Tuberculosis in China TB^{CHN}
Rule Types and Data Types		
Real Prevalence	√	√
Vague Pathogen Status		
Inactive		√
LessActive	√	
Active		√
MoreActive	√	√
Real Direct Risk Ratios	√	√
Real Indirect Risk Ratios		√
reduceRisk		√
addRisk		√
Vague Risk Ratios		
Low	√	
Medium	√	
High	√	
n-fold	√	
Dependency Types		
Independent	√	√
Dependent	√	
Anomaly Types		
Duplicate Rules	√	
Conflicting Rules	√	
Other criteria		
Impossible combination (e.g. child who works as nurse)		√
Multi-level sub-classes	√	√
Similar individual name	√	
Mix categorical variable	√	√

For both test cases, the tuberculosis risk quantifications may not be entirely true. Some of the encoded knowledge is modified in order to fit the coverage of the test cases. Such modifications do not affect the testing of the algorithm. The declarative knowledge in **Table 6.5** shows the tuberculosis risk knowledge in Indonesia (for intrathoracic tuberculosis), and in China (for spinal tuberculosis).

Table 6.5: The declarative risk knowledge encoded in TB^{INS} and TB^{CHN}

The declarative Tuberculosis risk knowledge taken from literature	The encoded risk factors	
	TB^{INS}	**TB^{CHN}**
"The laboratory studies demonstrate that **males** show more susceptibility to infections than **females**; this difference has been linked with the influence of steroid hormones on immune function." [21]	Gender: Male > Female	
"The tuberculosis cases have been reported to be different by gender in the studies conducted in Cameroon and Mongolia, the number of notified cases was higher for male than that of female. This has been attributed to their often more extroverted activities which include high social interaction (often in overcrowded environments), drinking and **smoking**; all activities which enhance the spread of tuberculosis." [21]	Habits: Smoking	
"The risk of developing tuberculosis (TB) is estimated to be between 16-27 times greater in people living **with HIV** than among those without HIV infection." [138]	Pre-existing Illness: HIV positive > HIV negative	
"Generally, man spends more time indoors in cold than in **warm** season, which coincides with the scientific fact that overcrowding, increased humidity, and low airflow provide a suitable environment for Mycobacterium tuberculosis to survive. Additionally, transmission is more likely during **winter** months due to diminished amounts of natural ultraviolet light. In summer season, the absorption of natural ultraviolet light is higher and can kill Mycobacterium tuberculosis within a short time, while it can survive in darker conditions for a longer period. These properties of Mycobacterium tuberculosis support the suggestion that most disease transmissions occur **indoor**." [137]	Season: Warm < Cold (two-season country)	Season: Warm < Cold (four-season country) Living Habit: Indoor > Outdoor
"Register-based data from Hunan Province in China showed that the prevalence of tuberculosis was more than twice as high in those **aged 65 years** and older than in younger adults (aged 15–64)." [236]		Age or Development Stage: Elderly > Adult > Children
"However, majority of the study participants (58.5%) gave a self-report of at least once weekly intake of vitamin D fortified **milk** and fish which are both rich in vitamin D. Consumption of more than 100gram fortified milk per day reduce 33.8% TB risk because of hypovitaminosis." [136]		Habits: Drinking: Milk
"**Nurses** employed in hospitals (particularly in emergency departments, pulmonary departments, and HIV units), long term care facilities, outpatient clinics and prisons are at risk for contracting tuberculosis." [237]		Occupation: Nurse

Based on the declarative knowledge in **Table 6.5**, in TB^{INS} there are four tuberculosis risk factors: *smoking habits* (personal), *gender* (personal), *pre-existing illness* (personal), *season* (environmental). The same individual name for different classes is presented (*unknown* for smoking status, *unknown* for HIV status). Mixed categorical attributes occur in the TB^{INS}, for example the *gender* and *season* classes are the binary attributes; the *smoking* habit class is an ordinal attribute; *HIV* class is a nominal attribute. These risk factors are formalized as IDR ontology structure in **Figure 6.13**.

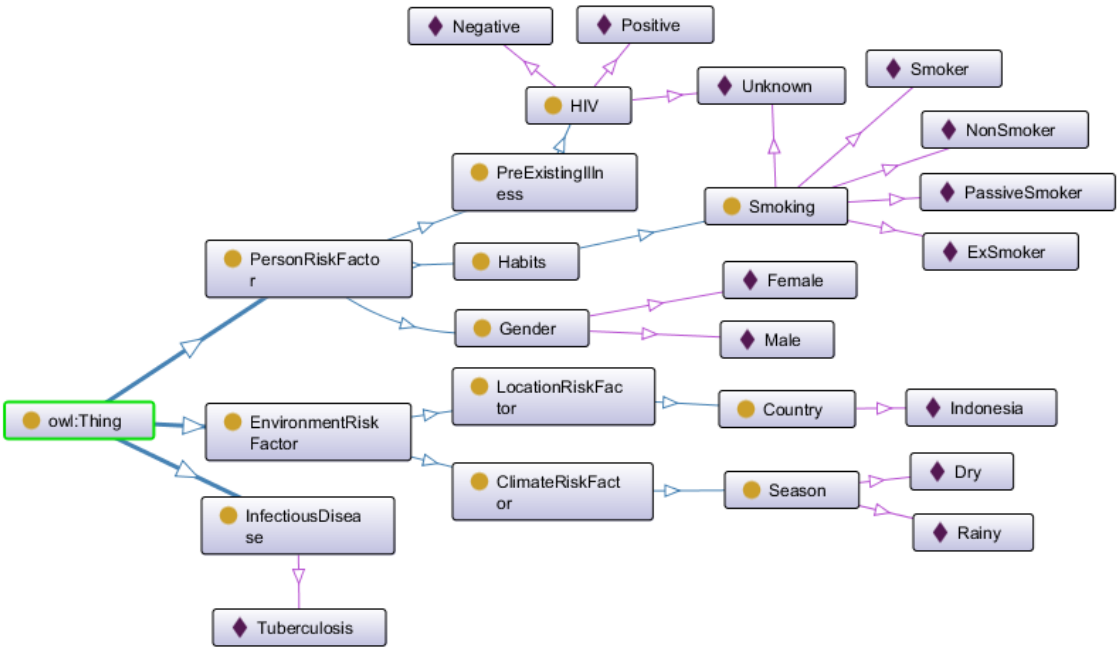

Figure 6.13: The IDR ontology structure for the tuberculosis in Indonesia

To address the test scope given in **Table 6.4**, the TB^{INS} IDR rules are shown in **Figure 6.14**. The *contradictory* (S7 and S10) and *duplicating* (S3 and S6) rules are inserted in the rule base to test the whether the priority in the *comment* column is working properly for defining the certainty degree. A dependent rule between *gender* (male) and *pre-existing illness* (HIV) is included.

Name	Rule	Comment
S1	PersonRiskFactor(?all) ^ hasGender(?all, Male) -> alterRisk(Tuberculosis, 2.37)	Priority: 1
S10	PersonRiskFactor(?all) ^ hasHIV(?all, Positive) -> alterRisk(Tuberculosis, 0.75)	Priority: 0.9
S11	EnvironmentRiskFactor(?all) ^ hasSeason(?all, Rainy) -> setPathogen(Tuberculosis, "MoreActive")	Priority: 1
S12	EnvironmentRiskFactor(?all) ^ hasSeason(?all, Dry) -> setPathogen(Tuberculosis, "LessActive")	Priority: 1
S13	PersonRiskFactor(?all) ^ hasSmokingHabits(?all, ExSmoker) -> estimateRisk(Tuberculosis, "Medium")	Priority: 1
S2	PersonRiskFactor(?all) ^ hasSmokingHabits(?all, Smoker) -> estimateRisk(Tuberculosis, "2-ish")	Priority: 1
S3	PersonRiskFactor(?all) ^ hasSmokingHabits(?all, PassiveSmoker) -> estimateRisk(Tuberculosis, "High")	Priority: 0.8
S4	EnvironmentRiskFactor(?all) ^ hasCountry(?all, Indonesia) -> setRisk(Tuberculosis, 0.395)	Priority: 1
S5	PersonRiskFactor(?all) ^ hasSmokingHabits(?all, Unknown) -> estimateRisk(Tuberculosis, "Low")	Priority: 1
S6	PersonRiskFactor(?all) ^ hasSmokingHabits(?all, PassiveSmoker) -> alterRisk(Tuberculosis, 1.53)	Priority: 1
S7	PersonRiskFactor(?all) ^ hasHIV(?all, Positive) -> alterRisk(Tuberculosis, 4.79)	Priority: 1
S8	PersonRiskFactor(?all) ^ hasHIV(?all, Unknown) -> alterRisk(Tuberculosis, 1.15)	Priority: 1
S9	PersonRiskFactor(?all) ^ hasGender(?all, Male) ^ hasHIV(?all, Positive) -> alterRisk(Tuberculosis, 6.5)	Priority: 1

Figure 6.14: The IDR rules for the tuberculosis in Indonesia

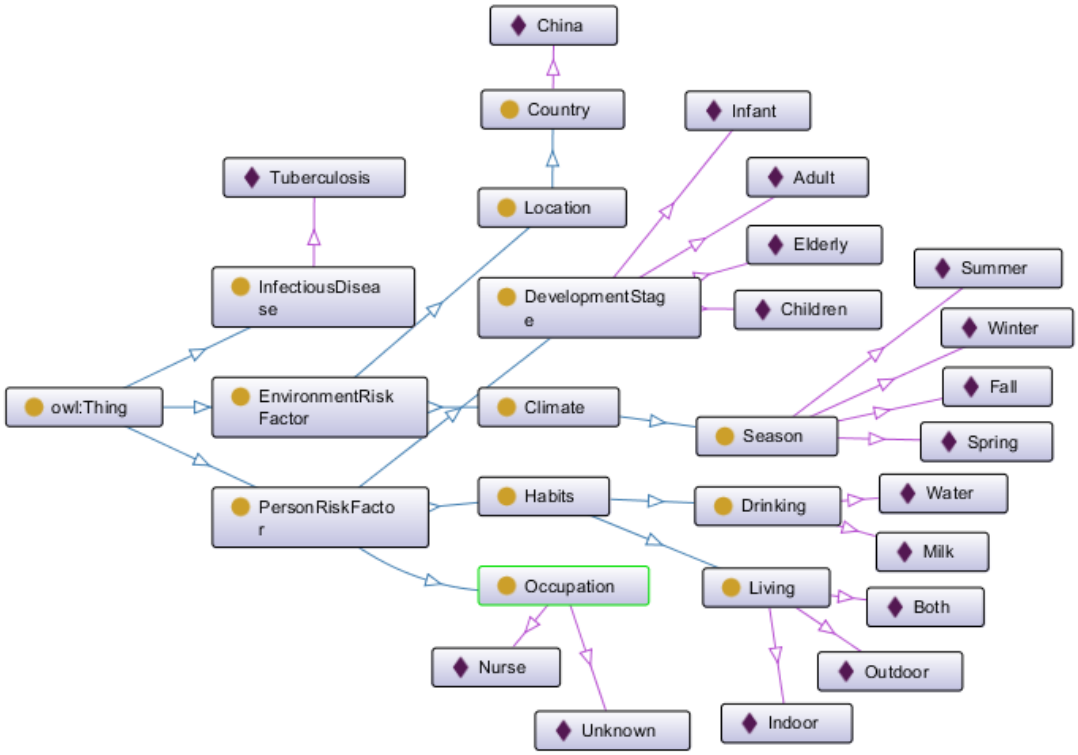

Figure 6.15: The IDR ontology structure for the tuberculosis in China

Based on declarative knowledge for spinal tuberculosis given in **Table 6.5**, TB^{CHN} has also four tuberculosis risk factors: *living habit* (personal), *development stage* (personal), *drinking habit* (personal), *occupation* (personal), and *season* (environment). In TB^{CHN}, the binary attributes are shown by *drinking habit* class. The ordinal attributes are encoded by *development stage* class. Whereas the nominal attributes are presented by *occupation*, *season* and *living habit* classes. The TB^{CHN} IDR ontology structure and rules are shown in **Figure 6.15** and **Figure 6.16**, respectively.

Name	Rule	Comment
S1	EnvironmentRiskFactor(?all) ^ hasSeason(?all, Winter) -> setPathogen(Tuberculosis, "InActive")	Priority: 1
S10	PersonRiskFactor(?all) ^ hasDevelopmentStage(?all, Adult) -> estimateRisk(Tuberculosis, "High")	Priority: 1
S11	PersonRiskFactor(?all) ^ hasDevelopmentStage(?all, Elderly) -> alterRisk(Tuberculosis, 1.85)	Priority: 1
S12	PersonRiskFactor(?all) ^ hasLivingHabits(?all, Both) -> estimateRisk(Tuberculosis, "Medium")	Priority: 1
S2	EnvironmentRiskFactor(?all) ^ hasSeason(?all, Spring) -> setPathogen(Tuberculosis, "Active")	Priority: 1
S3	EnvironmentRiskFactor(?all) ^ hasSeason(?all, Fall) -> setPathogen(Tuberculosis, "Active")	Priority: 1
S4	EnvironmentRiskFactor(?all) ^ hasSeason(?all, Summer) -> setPathogen(Tuberculosis, "MoreActive")	Priority: 1
S5	EnvironmentRiskFactor(?all) ^ hasCountry(?all, China) -> setRisk(Tuberculosis, 0.403)	Priority: 1
S6	PersonRiskFactor(?all) ^ hasLivingHabits(?all, Indoor) -> addRisk(Tuberculosis, "28%")	Priority: 1
S7	PersonRiskFactor(?all) ^ hasDrinkingHabits(?all, Milk) -> reduceRisk(Tuberculosis, "42%")	Priority: 1
S8	PersonRiskFactor(?all) ^ hasOccupation(?all, Nurse) -> alterRisk(Tuberculosis, 2.44)	Priority: 1
S9	PersonRiskFactor(?all) ^ hasDevelopmentStage(?all, Children) -> alterRisk(Tuberculosis, 1.2)	Priority: 1

Figure 6.16: The IDR rules of tuberculosis in China

Table 6.6 shows that all the test coverage has been allocated to at least one of the test case. Test coverage for rule types, data, dependency, and anomaly types are implemented as IDR rule-base which encodes the risk factors and their risk quantifications. The other criteria (last 4 rows) are implemented as IDR disease-specific ontology.

Table 6.6: The coverage of each test case

Test Coverage	Context of the IDR Knowledge-base	
	Tuberculosis in Indonesia TB^{INS}	Tuberculosis in China TB^{CHN}
Rule Types and Data Types		
Real Prevalence	S4	S5
Vague Pathogen Status		
Inactive		S1
LessActive	S12	
Active		S2
MoreActive	S11	S4
Real Direct Risk Ratios	S1, S8	S8 – S12
Real Indirect Risk Ratios		
reduceRisk		S7
addRisk		S6
Vague Risk Ratios		
Low	S5	
Medium	S13	
High	S3	
n-ish	S2	
Dependency Types		
Independent	Other than S9	All independent
Dependent	S9	
Anomaly Types		
Duplicate Rules	S7, S10	
Conflicting Rules	S3, S6	

Other criteria		
Impossible combination (e.g. child who works as nurse)		Development stage and occupation
Multi-level sub-classes	Habits > Smoking	Habits > Drinking Habits > Living
Similar individual name	Unknown at HIV and Smoking	
Mix categorical variable	Binary in season, ordinal in smoking, mixed binary and nominal in HIV	Nominal in occupation, ordinal in development stage, binary in drinking

This section described the test cases built for testing the BN-Builder algorithm. The test cases are then used by the BN-Builder to generate BNs and populate their CPT. The test results are analyzed based on the completeness of the ontology objects in the generated network and the correctness of the populated conditional probabilities. These results will be explained in the following section.

6.4.2 Test Results: BN structure

Each IDR knowledge-base that was presented in the previous section (TB^{INS} and TB^{CHN}) are then transformed into a Bayesian Network using BN-Builder algorithm. The transformation is performed by executing the BN-Builder algorithm. The resulting Bayesian Networks not only have the simple BN structure (one child and multiple parent nodes), but the CPT is also populated. The generated BN structure is evaluated through the isomorphism with the ontology instance in the IDR knowledge-bases.

Before measuring whether the generated BN structure is isomorphic with the ontology instance for each TB^{INS} and TB^{CHN} knowledge-base, all of the ontology objects that matters to the test are first retrieved.

To obtain all individuals in all sub-classes of TB^{INS} ontology instance, this SPARQL query is executed in Protégé.

```
SELECT * WHERE {?individual rdf:type ?subclass . OPTIONAL
{?subclass rdfs:subClassOf ?class}} ORDER BY ?subclass
```

The result of the SPARQL query above is given in **Figure 6.17**. All individuals and subclasses appear as states and nodes in the BN (see **Figure 6.18**), respectively, except the *infectious disease* class. This is because other classes than the infectious disease (*tuberculosis*) are risk factors, but, the *infectious disease* class contains the name of disease whose being predicted. Therefore, even though the *tuberculosis* is an individual in the ontology, in the BN – it becomes a node name instead of state name. Furthermore, the tuberculosis node is being referred by other nodes, and always has two fixed attributes (*AtRisk, NotAtRisk*). These two attributes are not formalized in the ontology.

individual	subclass	class
Indonesia	Country	LocationRiskFactor
Male	Gender	PersonRiskFactor
Female	Gender	PersonRiskFactor
Positive	HIV	PreExistingIllness
Negative	HIV	PreExistingIllness
Unknown	HIV	PreExistingIllness
Tuberculosis	InfectiousDisease	
Rainy	Season	ClimateRiskFactor
Dry	Season	ClimateRiskFactor
NonSmoker	Smoking	Habits
Unknown	Smoking	Habits
ExSmoker	Smoking	Habits
Smoker	Smoking	Habits
PassiveSmoker	Smoking	Habits

Figure 6.17: SPARQL query result for TB^{INS}

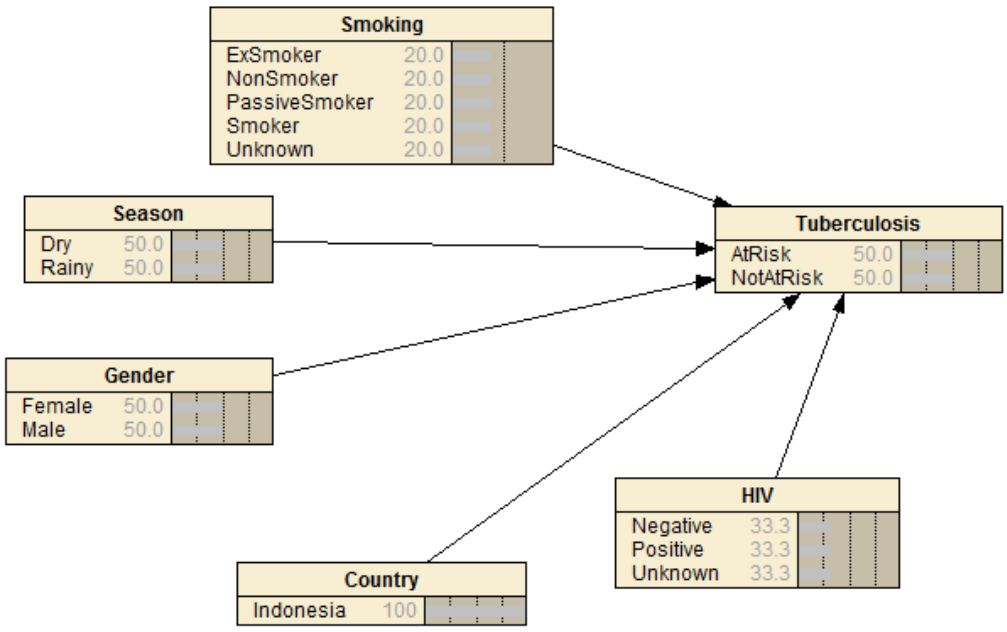

Figure 6.18: The generated BN for TB^{INS}

From **Figure 6.18**, it can be seen that the BN-Builder is able to handle the same name ontology individual, the *unknown* individual appears in both HIV and Smoking nodes. Also, the BN-Builder can generate the mixed categorical individuals as presented by *gender*, *smoking*, and *HIV*. As can be seen in **Figure 6.19**, the designed procedure to concatenate state name with the node name in the backend succeeds to generate the *unknown* individual to different node. Also, in the CPT population, the concatenation can distinguish which *unknown* is for which node.

```
GenderMale S1 EmptyEmpty alterRisk Tuberculosis
SmokingSmoker S2 EmptyEmpty alterRisk Tuberculo
SmokingPassiveSmoker S3 EmptyEmpty alterRisk Tul
CountryIndonesia S4 EmptyEmpty setRisk Tubercul
SmokingUnknown S5 EmptyEmpty alterRisk Tubercul
SmokingPassiveSmoker S6 EmptyEmpty alterRisk Tul
HIVPositive S7 EmptyEmpty alterRisk Tuberculosi
HIVUnknown S8 EmptyEmpty alterRisk Tuberculosis
GenderMale S9 HIVPositive alterRisk Tuberculosi
HIVPositive S10 EmptyEmpty alterRisk Tuberculos
SeasonRainy S11 EmptyEmpty alterRisk Tuberculos
SeasonDry S12 EmptyEmpty alterRisk Tuberculosis
SmokingExSmoker S13 EmptyEmpty alterRisk Tuberc
```

Figure 6.19: The backend encoding of unknown individual that is shared between smoking and HIV sub-classes

The same SPARQL query is executed for TB^{CHN}, the result can be seen in **Figure 6.20**. The BN-Builder convert all individuals and subclasses into states and nodes, respectively (**Figure 6.21**).

individual	subclass	class
China	Country	Location
Infant	DevelopmentStage	PersonRiskFactor
Elderly	DevelopmentStage	PersonRiskFactor
Adult	DevelopmentStage	PersonRiskFactor
Children	DevelopmentStage	PersonRiskFactor
Water	Drinking	Habits
Milk	Drinking	Habits
Tuberculosis	InfectiousDisease	
Outdoor	Living	Habits
Indoor	Living	Habits
Both	Living	Habits
Unknown	Occupation	PersonRiskFactor
Nurse	Occupation	PersonRiskFactor
Fall	Season	Climate
Spring	Season	Climate
Winter	Season	Climate
Summer	Season	Climate

Figure 6.20: SPARQL query result for TB^{CHN}

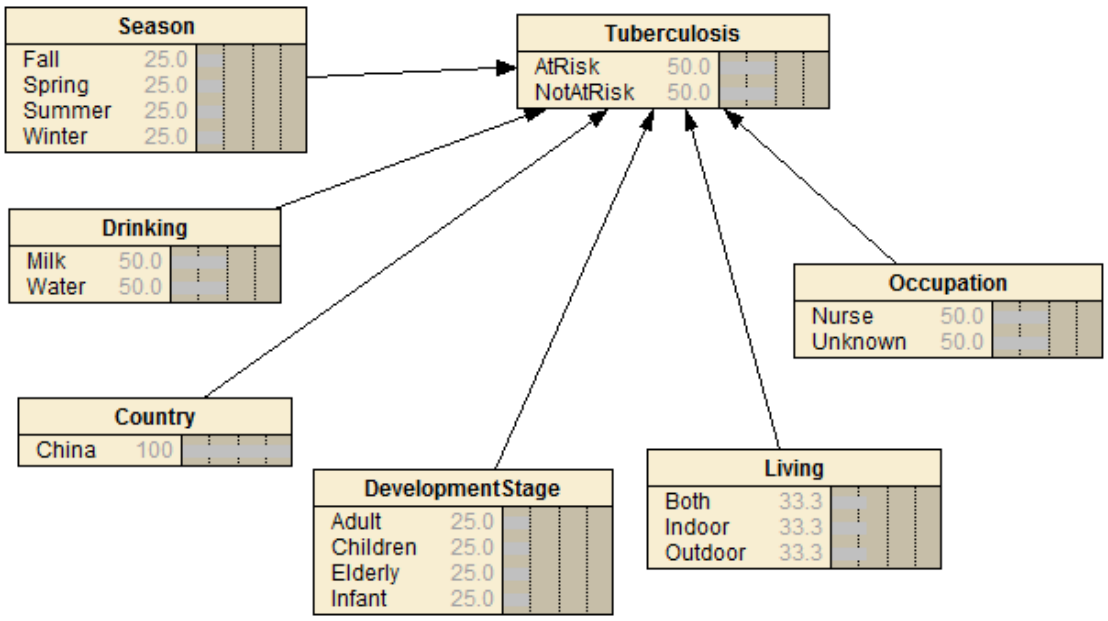

Figure 6.21: The generated BN for TB^{CHN}

As the multi-level sub-classes appear on the ontology design, the generated BN has unique node names which are obtained from the lowest-level of the sub-class. For example, in the ontology, there is a *habits* class that has two sub-classes: *drinking* and *living*. *Drinking habit* sub-class has two individuals: *water*, and *milk*. *Living habit* sub-class has three individuals: *outdoor*, *indoor*, and *both*. In the generated BN, *drinking habit* and *living habit* are generated to *drinking* and *living* nodes.

From the generated BNs (TB^{CHN} and TB^{INS}), it can be seen that all ontology sub-classes and individuals were generated to BN states and nodes. The BN-Builder is able to handle similar name of individual that are shared between classes. Furthermore, mixed categorical attributes that appear on each knowledge-base are able to be transformed become the BN states.

6.4.3 Test Results: CPT

As described in the evaluation plan (section 6.4.1), the correctness of the CPT population procedure is measured by comparing the result of the conditional probabilities with the manual calculation of the eq. 6.

First, the coverage of the evaluation cases is addressed. **Table 6.4** above listed the situations to be covered and indicated which ones were covered by each of the two test cases. **Table 6.7** below shows in detail how the ticks in **Table 6.4** for the TB^{INS} column were arrived at. The (generated) rule status (column #7 in **Table 6.7**) tells us which rules are identified as having dependent risk factors (those with *multiple* rule status) or not (those with *solo* or *part* status)

All rule types started by 'vague' have to generate their risk quantification based on the Gaussian or Uniform distributions. For rules that are instantiations of *vague risk ratio* or *vague pathogen status*, the generated risk ratio is given in column #7.

Table 6.7: Explanation Table of IDR rules in TB^{INS}

#Rule	Rule Type	Rule Dependency	Rule Anomaly	(Generated) Rule Status	Data Type	(Generated) Risk Ratio
1	**2**	**3**	**4**	**5**	**6**	**7**
S1	Real Direct Risk Ratio	Independent		Part of S9	OR	2.37
S2	Vague Risk Ratio	Independent		Solo	Around 2	1.89
S3	Vague Risk Ratio	Independent	Duplicate with S6	Solo	High	1.627
S4	Real Prevalence	Independent		Solo	Prevalence in %	0.395
S5	Vague Risk Ratio	Independent		Solo	Low	0.3
S6	Real Direct Risk Ratio	Independent		Solo	OR	1.53
S7	Real Direct Risk Ratio	Independent		Part of S9	OR	4.79
S8	Real Direct Risk Ratio	Independent		Solo	OR	1.15
S9	Real Direct Risk Ratio	Dependent		Multiple	OR	6.5
S10	Real Direct Risk Ratio	Independent	Conflicting with S7	Part of S9	OR	0.75
S11	Vague Pathogen Status	Independent		Solo	MoreActive	1.434
S12	Vague Pathogen Status	Independent		Solo	LessActive	1.029
S13	Vague Risk Ratio	Independent		Solo	Medium	0.959

Table 6.8 shows the correctness test of the populated CPT based on the risk quantifications in the TB^{INS} IDR rules (**Table 6.7**).

Table 6.8: The correctness test of the TB^{INS}

Risk factors	Risk ratios encoded on the rules (#rule)	The conditions	The result if calculated manually	The generated result	The distance between calculated manually and the generated result	The ratio between the encoded knowledge and the generated results
1	**2**	**3**	**4**	**5**	**6**	**7**
Independent Rule						
Gender	Male = 2.37 x Female (S1)	TB risk in rainy season for a ***female*** passive smoker with negative HIV	1x1.53x1x(1.434) x0.395 = **0.866638**	**0.866760**	0.00012	2.37:2.369
		TB risk in rainy season for a ***male*** passive smoker with negative HIV	2.37x1.53x1x(1.434) x0.395 = **2.053932**	**2.054221**	0.00029	
Smoking Habit	Smoker = around 2 x NonSmoker (S2)	TB risk in rainy season for a female ***non-smoker*** with negative HIV	1x1x1x(1.434)x 0.395 = **0.56643**	**0.56651**	0.00008	(2-ish) 1.89:1.888
		TB risk in rainy season for a female ***smoker*** with negative HIV	1x(1.889)x1x(1.434) x0.395 = **1.069986**	**1.070481**	0.00049	
	PassiveSmoker is high risk (S6)	TB risk in rainy season for a female ***passive smoker*** with negative HIV	1x(1.53)x1x(1.434) x0.395 = **0.866638**	**0.866760**	0.000032	High > Medium > Low 1.53 > 0.959 > 0.395
	ExSmoker is medium risk (S13)	TB risk in rainy season for a female ***ex-smoker*** with negative HIV	1x(0.959)x1x(1.434) x0.395 = **0.543206**	**0.543319**	0.000112	
	UnknownSmoker is low risk (S5)	TB risk in rainy season for a female ***unknown*** status of ***smoking*** with negative HIV	1x(0.301)x1x(1.434) x0.395 = **0.170495**	**0.170420**	0.000075	
HIV	PositiveHIV = 4.79 x NegativeHIV (S7)	TB risk in rainy season for a female passive smoker with ***positive HIV***	1x1.53x4.79x(1.434) x0.395 = **4.151195**	**4.151781**	0.000585	4.79:4.79
		TB risk in rainy season for a female passive smoker with ***negative HIV***	1x1.53x1x(1.434) x0.395 = **0.866638**	**0.866760**	0.000032	
	UnknownHIV = 1.15 x NegativeHIV (S8)	TB risk in rainy season for a female passive smoker with ***unknown*** status of ***HIV***	1x1.53x1.15x(1.434) x0.395 = **0.996633**	**0.996774**	0.00014	1.15:1.15

Season	TB pathogen is more active in Rainy than Dry (S11, S12)	TB risk in ***rainy*** season for a female passive smoker with negative HIV	1x1.53x1x(1.434) x0.395 = **0.866638**	**0.866760**	0.000032	N/A
		TB risk in ***dry*** season for a female passive smoker with negative HIV	1x1.53x1x(1.029) x0.395 = **0.621876**	**0.622335**	0.00046	N/A
Dependent Rule						
Gender and HIV	The OR of male with positive HIV is 6.5 (S9)	TB risk in rainy season for a ***male*** non-smoker with ***positive HIV***	6.5x1x(1.434) x0.395 = **3.681795**	**3.682314**	0.00052	N/A
		TB risk in rainy season for a ***male*** non-smoker with ***negative HIV***	2.37x1x1x(1.434) x0.395 = **1.342439**	**1.342628**	0.00019	N/A
		TB risk in rainy season for a ***female*** non-smoker with ***positive HIV***	1x1x4.79x(1.434)x 0.395 = **2.7132**	**2.713582**	0.00038	N/A

The minimum distance shows that the Bayes chain rule was implemented correctly in the BN-Builder algorithm, including the capability of detecting impossible conditions. The consistent ratio shows whether the BN-Builder picks the correct rules for every condition, for independent and dependent risk factors, and for conflicting and duplicating rules. The comparison between ratios are given in column #6 in **Table 6.8**. Column #6 is distance between column #5 and column #4.

Column #7 is given to test whether the ratio between observed conditions reflects the encoded risk ratio. To obtain column #7, the generated result for non-baseline is divided by baseline. The indicator whether a condition is baseline or not can be seen in the underlined risk factor in column #2. For example, the encoded risk ratio for *male* of contracting of tuberculosis is 2.37. To check whether the ratio of the generated probabilities is consistent or not, the value in column #5 for male (2.054) is divided by column #5 for female (0.866). The result of division (2.369) is then compared with the encoded risk ratio for gender (2.37). The comparison can be seen in column #7. For some rows, the ratio is not available (N/A), this because there is no baseline of the condition.

Using chi-square test, the distance between manually calculated risk (column #4) and the generated risk result (column #5) are tested. All 60 conditional probabilities are included in the chi-square test with aim to prove that the result between the generated risk and manually calculated are not different to each other. The p-value result is 0.9999 which means that the manually calculated risk probability is same with the generated ones. In other word, the BN-Builder generate the conditional probability correctly based on Bayes chain rule.

From **Table 6.8**, it can be seen that all distances and ratios are minimum, thus, the CPT is populated correctly by the BN-Builder algorithm.

Since there are no dependent rules in the TB^{CHN}, therefore all rules are independent and have ‘solo’ status. Also, there is no rule anomaly in this knowledge-base. **Table 6.9** aims to address every tick of **Table 6.4** for TB^{CHN}.

Table 6.9: Explanation Table of IDR rules in TB^{CHN}

#Rule	Rule Type	Data Type	(Generated) Risk Ratio
S1	Vague Pathogen Status	MoreActive	2.38
S2	Vague Pathogen Status	Active	1.805
S3	Vague Pathogen Status	LessActive	0.963
S4	Vague Pathogen Status	InActive	0.044
S5	Real Prevalence	Prevalence in %	0.403
S6	Real Indirect Risk Ratio	Reduction in %	1.28
S7	Real Indirect Risk Ratio	Addition in %	0.58
S8	Real Direct Risk Ratio	OR	2.44
S9	Real Direct Risk Ratio	OR	1.2
S10	Vague Risk Ratio	High	1.637
S11	Real Direct Risk Ratio	OR	1.85
S12	Vague Risk Ratio	Medium	0.999

Impossible combination is shown in this IDR^{CHN} knowledge-base. The BN-Builder generates all possible combinations, including the combination that represent *a child who works as nurse* which is the impossible to happen in the real world. The BN-Builder is expected to yield zero when populating the CPT for this combination.

Same approach for calculating the distance and ratio with TB^{INS} are also applied for TB^{CHN}, but, in the TB^{CHN} knowledge-base, several impossible combinations have zero conditional probabilities. The distance and ratio might not be applicable for these impossible conditions. **Figure 6.22** show the generated console message to identify how many lines of CPT have been written, how many lines are possible and impossible combinations. From this figure, 48 impossible combinations were found as result from an infant or children who works as a nurse.

```
Finish writing 192 lines of CPT
Contain 144 lines of possible combinations and 48 impossible combinations
That took 446 milliseconds
Network and CPT have been created!!
```

Figure 6.22: Capture from the BN-Builder algorithm console showing the number of impossible combinations

Inside the populated CPT, the impossible conditions are generated and filled with zeros by the BN-Builder algorithm. Some of the impossible (8 out of 48) conditions are presented in **Figure 6.23**.

Occupation	Living	DevelopmentStage	Country	Drinking	Season	AtRisk	NotAtRisk
Nurse	Both	Adult	China	Water	Spring	2.351	97.649
Nurse	Both	Adult	China	Water	Summer	2.13	97.87
Nurse	Both	Adult	China	Water	Winter	0.412	99.588
Nurse	Both	Children	China	Milk	Fall	0	100
Nurse	Both	Children	China	Milk	Spring	0	100
Nurse	Both	Children	China	Milk	Summer	0	100
Nurse	Both	Children	China	Milk	Winter	0	100
Nurse	Both	Children	China	Water	Fall	0	100
Nurse	Both	Children	China	Water	Spring	0	100
Nurse	Both	Children	China	Water	Summer	0	100
Nurse	Both	Children	China	Water	Winter	0	100
Nurse	Both	Elderly	China	Milk	Fall	1.318	98.682
Nurse	Both	Elderly	China	Milk	Spring	1.451	98.549
Nurse	Both	Elderly	China	Milk	Summer	1.314	98.686

Figure 6.23: 8 of 24 impossible combinations inside the TB^{CHN} CPT

Using chi-square test, the distance between manually calculated risk (column #4 of **Table 6.10**) and the generated risk result (column #5) are tested. 144 conditional probabilities (including 48 impossible combinations) are included in the chi-square test. The p-value result is 0.9999 which means that the manually calculated risk probability is perfectly same with the generated ones. In other word, the BN-Builder correctly generate the conditional probability based on the Bayes chain rule including the identification of the impossible combinations.

From the generated BNs above, the BN-Builder algorithm is able to populate the CPT from (1) mixed categorical (binary, nominal, and ordinal) parent nodes, (2) multi-level sub-classes, (3) similar individual names. Also, the number of iterations can be optimized by excluding impossible combinations.

Table 6.10: The correctness test of the TB^{CHN}

Risk factors	Risk ratios encoded on the rules (#rule)	The conditions	The manually calculated result	The generated result	The distance between calculated manually and the generated result	The ratio between the encoded knowledge and the generated results
1	**2**	**3**	**4**	**5**	**6**	**7**
Possible						
Season	Tuberculosis is inactive in Winter (S1)	TB risk in ***Winter*** for an adult nurse who spent most her time indoor	1.637x2.44x1.28x 2.38x0.403 = **4.904**	**4.9055**	0.0015	N/A
	Tuberculosis is active in Spring and Fall (S2 and S3)	TB risk in ***Spring*** for an adult nurse who spent most her time indoor	1.637x2.44x1.28x 1.805x0.403 = **3.719**	**3.72158**	0.00258	N/A
		TB risk in ***Fall*** for an adult nurse who spent most her time indoor	1.637x2.44x1.28x 0.963x0.403 = **1.984**	**1.98522**	0.00122	N/A
	Tuberculosis is more active in Summer (S4)	TB risk in ***Summer*** for an adult nurse who spent most her time indoor	1.637x2.44x1.28x 0.044x0.403 = **0.0906**	**0.0915**	0.0009	N/A
Living Habits	Spending time indoor adding 28% of TB risk (S6)	TB risk in Spring for an adult nurse who spent most her time ***indoor***	1.637x2.44x1.28x 1.805x0.403 = **3.719**	**3.72158**	0.00258	1.28:1.279
		TB risk in Spring for an adult nurse who spent most her time ***outdoor***	1.637x2.44x1x 1.805x0.403 = **2.905**	**2.90748**	0.00248	
Drinking Habits	Drinking milk reducing 42% of TB risk than drinking water (S7)	TB risk in Spring for an adult nurse who likes ***drinking milk***	1.637x2.44x1x 0.58x1.805x0.403 = **1.685**	**1.68634**	0.00134	0.58:0.579
		TB risk in Spring for an adult nurse who likes ***drinking water***	1.637x2.44x1x 1.805x0.403 = **2.905**	**2.90748**	0.00248	

Occupation	Nurse = 2.44 x Unknown (S8)	TB risk in Spring for an adult ***nurse*** who spent most her time indoor	1.637x2.44x1.28x 1.805x0.403 = **3.719**	**3.72158**	0.00258	2.44:2.439
		TB risk in Spring for an adult with ***unknown occupation*** who spent most her time indoor	1.637x1x1.28x 1.805x0.403 = **1.524**	**1.52523**	0.00123	
Development Stage	Children = 1.2 x Infant (S9)	TB risk in Spring for a ***child*** with unknown occupation who spent most her time indoor	1.2x1x1.28x 1.805x0.403 = **1.117**	**1.1178**	0.0008	1.2:1.2
	Adult = 1.637 x Infant (S10)	TB risk in Spring for an ***adult*** with unknown occupation who spent most her time indoor	1.637x1x1.28x 1.805x0.403 = **1.524**	**1.52524**	0.00124	1.637:1.6374
		TB risk in Spring for an ***infant*** with unknown occupation who spent most her time indoor	1x1x1.28x1.805x 0.403 = **0.93109**	**0.93149**	0.0004	
	Elderly has high TB risk (S11)	TB risk in Spring for an ***elderly*** with unknown occupation who spent most her time indoor	1.85x1x1.28x 1.805x0.403 = **1.7225**	**1.72327**	0.00077	N/A
Impossible						
Development Stage and Occupation		TB risk in Spring for a ***child nurse*** who spent most her time indoor	**0.0000**	**0.0000**	0.0000	N/A

6.5 Conclusion

The BN-Builder algorithm is designed to generate the BN structure from the ontology structure and populate the CPT of the BN from the IDR rules. From testing results, the BN-Builder algorithm can generate the BN structure from ontology nodes and states correctly. By implementing the Bayes chain rule, the BN-Builder is able to populate CPT from mixed binary, ordinal and nominal nodes. These results suggest that the BN-Builder algorithm can surpass the existing algorithms for populating the CPT (e.g. Noisy-OR, Noisy-AND, weight-sum) or existing approaches (e.g. BayesOWL, BNTab).

However, the Bayes chain rule is limited to (infectious) disease risk calculation only since it makes use of risk ratios and prevalence value. For general purposes, it will require different version of the Bayes chain rule.

The testing has shown that the BN-Builder algorithm can handle shared individual names in the ontology correctly, as demonstrated by the *unknown* status for person's *smoking habit* and *HIV pre-existing illness*. This suggests that BN-Builder algorithm can facilitate shared individuals in an ontology sub-class each becoming a separate state in a different node. Besides that, the testing has also demonstrated that the BN-Builder algorithm can manage hierarchical relationships (i.e. multi-level sub-classes). For example, a person's *habits* have specialization: *smoking* habit or *drinking* habit. The BN-Builder is able to pick the lowest level to preserve the uniqueness of the node names.

All *distances* and *ratios* between the generated CPT and the manually calculated probabilities are measured. Chi-square test statistics prove that there is no significant difference between the generated and manual calculation of conditional probabilities ($p > 0.05$). From this testing, it can be concluded that the BN-Builder algorithm can *correctly* populate the CPT based on the Bayes chain rule.

For the ordinal risk ratios, the BN-Builder can generate a risk ratio based on the encoded ordinal values (e.g. low, medium, high). The comparisons between the conditional probability results and the ordinal values are consistent. Besides the ordinal risk ratios, the conditions that involve the pathogen activation status (e.g. inactive, less active, active, more active) that are also presented as ordinal values are correctly populated.

Another form of risk ratios, addition or reduction with certain percentage, is included in the test knowledge-base (TB^{CHN}). The results are observed and consistent with the encoded percentage values.

Some conditions which are considered as impossible are identified by putting resources in a library. The BN-Builder algorithm is able handle them correctly. For example, *a child who works as a nurse*, as a result from auto-combination result between development stage (infant, child, adult, elderly) and occupation (nurse, unknown). The conditional probability for these impossible combinations are proven to be zeros.

To sum up, the BN-Builder algorithm has been designed to be able to deal with the special characteristics of infectious disease risk knowledge which have mixed categorical, similar individuals, and hierarchy that was encoded in the IDR knowledge-bases. It is also able to handle the risk quantifications relevant to infectious disease risk knowledge: *risk ratios* (in ratio, percentage, and ordinal), and *prevalence value*. From the testing, it can be concluded that the BN-Builder algorithm can generate BN and populate the CPT correctly, thus, it demonstrates that the generated BN is *fully functioning* and *consistent*.

7. CONCLUSIONS

7.1 Overview

This thesis has presented the knowledge representation (chapter 5) that is able to encode the declarative infectious disease risk knowledge published in the Atlas of Human Infectious Diseases (AHID), WHO, CDC factsheets, and other journals related to epidemiology for infectious diseases. The related algorithm, the BN-Builder, which aims to convert the instantiation of the knowledge representation (i.e. knowledge-base) into an equivalent risk prediction model, is also presented (chapter 6). The contextual system architecture in which these knowledge representation and algorithm will be expected to work is also presented (chapter 4).

This chapter discusses the objectives of the thesis and how they are answered. Also, the contribution this work has made to the state of the art of infectious disease risk knowledge representation and in particular the BN-generation algorithm is stated.

7.2 Objectives and Achievements

The research question in this thesis was 'can a *useful* knowledge representation be designed to encode infectious disease risk knowledge and can this the encoded knowledge be *correctly* availed of to yield personalized infectious disease risk prediction?'. To answer this research question, three objectives were posed.

The first objective of the research described in this thesis was to understand the knowledge of epidemiology for infectious disease risk in general, and how to estimate disease risk in a person using a prediction model.

This objective was achieved through comprehending the concepts of human *infection flow, chain of infection*, and all *affecting environmental risk factors* for human infectious diseases from established knowledge sources. From the *infection flow in a person*, four compartments that are used to estimate a person's infectious disease risk in epidemiology are: Susceptible (S) – Exposed (E) – Infected (I) – Recovered (R). Factors that contribute to the S and E compartments need to be modelled and quantified in a relevant way to calculate the personalized infectious disease risk. Most person risk factors were identified

from this knowledge. For example, common person attributes that are relevant to a person's susceptibility level are development stage, nutrition intake, habits. From the *chain of infection*, pathogen life requirements, reservoirs, transmission modes, and susceptible hosts were learned. From this knowledge, the general implication of the person and environment attributes to the infectious disease risk were investigated. For example, *Mycobacterium Tuberculosis* does not exist during Summer due to ultraviolet light that prevents these bacteria thriving and multiplying. More detailed atmospheric attributes of weather and season are also known to have direct contribution to infectious disease risks.

To estimate a person's risk of contracting human infectious diseases, the obtained personal and environmental infectious disease risk factors need to be quantified. Relevant formulae that are used to calculate a personalized infectious disease risk from several risk quantifications were investigated. Some limitations that appear in these formulae, such as, binary or multivalued attributes were overcome using the Bayes chain rule for infectious disease risk prediction.

The second objective of the research was to design a knowledge representation that is able to encode the declarative infectious disease risk knowledge that allows automatic generation of a prediction model.

This objective could be accomplished through utilizing an ontology for encoding the infectious disease risk factors and availing of semantic-web rules for encoding risk quantifications that are needed by the Bayes chain rule. *The IDR generic ontology* was built to model the structure of the infectious disease risk factors. The IDR generic ontology consists of the main classes that are always inherited by the IDR knowledge-bases: person risk factor, environment risk factor, infectious disease. The IDR generic ontology is expected to be representative and evolution-proof for all human infectious diseases, including new ones. *The IDR disease-specific ontology* was built from using the ontology objects (individuals, sub-classes) of the IDR generic ontology. The IDR ontology was developed to accommodate all mentioned personal and environmental risk factors for all human infectious diseases from AHID, WHO, and CDC factsheets. Thereafter, all types of (infectious) disease risk quantifications were investigated and *five IDR rule types* were established to accommodate all the kinds of risk quantifications. The

IDR generic ontology and five IDR rule types are designed to help epidemiologists to instantiate a contextual knowledge-base that encodes an infectious disease risk knowledge prevalent in a particular country.

An algorithm, BN-Builder, was then designed for converting the encoded infectious disease risk prediction in the knowledge-base into the risk prediction model (Bayesian Network). The BN-Builder converts the knowledge-base into an equivalent Bayesian Network. Some reasoning ability is included in the BN-Builder to allow it to: manage similar ontology individual(s) in generating the BN and populating the CPT; infer impossible conditions; and generate numerical risk ratios from the encoded ordinal values in the IDR rules using statistical distributions.

The third objective of the research was to evaluate the resulting knowledge representation, and the generated prediction model. The resulting knowledge representations in this thesis are the *IDR generic ontology, IDR disease-specific ontology*, and *IDR rule types*; the generated prediction model is the Bayesian Network that models one infectious disease risk knowledge prevalent in one country. For the knowledge representation, the evaluations were performed by assessing whether kinds of changes that may occur in the future can affect the structure of the designed generic ontology. For testing whether the IDR ontology and IDR rule types are complete and useful enough for encoding the declarative infectious disease risk knowledge, 22 epidemiological studies that present risk quantifications for a particular infectious disease prevalent in a country were retrieved. For each such study, a knowledge-base, that consists of an ontology and semantic-web rules, was built.

To assess the *completeness* and *usefulness* of the IDR ontology and IDR rule types, the same 22 evaluation knowledge-bases were used. Both *stable* and *temporary* infectious disease risk knowledge were encoded in each IDR knowledge-base. Since the sources used for IDR ontology building (AHID, WHO, CDC) are different from the evaluation knowledge-bases, some disease risk factors mentioned in the 22 articles may not be included in the initial version of the IDR ontology. From this deviation, the degree of completeness is calculated. To measure how useful the IDR ontology and IDR rule types are, the portion of the ontology objects for each IDR knowledge-base that is reused from

IDR ontology and IDR rule types are counted. The results are used to estimate the degree of usefulness of the IDR ontology and IDR rule types.

Several anomaly types that are common in rule-base systems are investigated. Some anomaly types are irrelevant to IDR rules. Two rule anomaly types are addressed. The *conflicting* rule anomaly type is addressed with a facility to associate a certainty level to rules. Users are helped to avoid *duplicate* rules through a user interface feature.

Moving on to evaluation of the BN-Builder algorithm, the algorithm is designed to correctly generate the BN structure and populate the CPT. The generated BN structure and CPT are then evaluated.

An infectious disease, tuberculosis, prevalent in two countries, Indonesia and China, is encoded as two test cases (i.e. knowledge-bases). This aims to encode the difference of tuberculosis prevalence in two countries, Indonesia and China, and also the differences of the risk ratios and their quantifications. These evaluation knowledge-bases are managed by the BN-Builder algorithm to handle similar individual names, multi-level sub-classes, and all data types of all IDR rule types (e.g. low, medium, high).

Through the design, development, and evaluation in this system, it can be concluded that the research meets the objectives listed in chapter 1. However, there are some limitations to this research which will be explained in section 7.4.

7.3 Contribution to the State of the Art

As stated in section 1.5, the format of knowledge representation that allows domain experts to encode infectious disease risk knowledge, and the BN generation algorithm that helps to convert the knowledge representation into a risk prediction model that predicts the personalized infectious disease risk, is the primary contribution of this thesis. Section 3.3 reviewed the existing knowledge representation related to (infectious) disease. From the reviews, there is no existing knowledge representation that meets the requirements that are explained below.

Firstly, the IDR ontology is made with the aim to be able to encode the declarative infectious disease risk knowledge given in the literature and to allow the domain experts to modify or renew the knowledge. Therefore, the IDR ontology is made through the combination of three epidemiology concepts for human infectious diseases. This is because there is no single concept that can be used to explain the risk factors that affect a person's risk of contracting infectious diseases. The combined concepts are (1) the explanation of *four infection stages* in a person, (2) *the chain for infection* that describe pathogen, reservoir, transmission modes, and hosts, and (3) the correlation between *environment (location and weather)* to infectious disease risks.

Secondly, the IDR ontology encodes personal and environmental risk factors for human infectious diseases that are not encoded yet in the existing ontologies. The established ontologies that are related to infectious diseases and risk factors are categorized into (1) the ontologies that encode personal risk factors for non-infectious diseases (e.g. CARRE, OBESTTD), (2) the ontologies that describe the knowledge of infectious diseases but not specific to their risk factors (e.g. IDO).

A minor contribution of this thesis is the design of a personalized infectious disease risk prediction system architecture which allows (1) the PROSPECT-IDR system aims to facilitate continuously encoding of infectious disease risk knowledge by the domain experts (epidemiologists), (2) and to keep the knowledge consistent with the prediction model (Bayesian Network).

The existing systems are (1) data-driven systems (i.e. machine learning) that yield the risk quantifications from *who got what diseases* and *when and where the disease occurred* data, (2) the SEIR mathematical model which does not allow continuously encoding of infectious disease risk knowledge, (3) knowledge-driven systems that utilizes prediction models (e.g. BN, FCM) but do not facilitate the domain experts to update and manage the disease risk knowledge continuously, (4) systems that combine the knowledge representation and the prediction models as a single method. The last type facilitates the domain experts to continuously encode and make sure that the prediction model contains the same information with the encoded knowledge. However, this kind of system is for general use, not specific for disease risk prediction. Thus, the used quantification (e.g. joint distributions) needs to be adjusted to be more relevant for disease risk quantifications

(e.g. risk ratios and disease prevalence). The general use of the system only allows *binary* or *multivalued* state generation only for one BN. To generate only binary state BN and populate its CPT, Noisy-OR algorithm and its generalizations is used. To generate only multivalued state BN and populate its CPT, combination between Noisy-OR and weight-sum algorithm is utilized. To model only continuous state generation, FCM is used. Whereas, the *nominal* BN cannot be automatically generated using those existing algorithms.

To encode infectious disease risk knowledge, the BN may need to contain the combination of *binary* (e.g. male and female for gender), *multivalued* (e.g. less than one pack/day, one pack/day, more than one pack/day for tobacco smoking), *nominal* (e.g. vegetarian, meatatarian, low carbo diet for eating habit).

The designed system of this thesis utilizes an algorithm, *BN-Builder*, that is different from the existing conversion algorithms (e.g. Noisy-OR, weight-sum). The BN-Builder is not limited to *binary* nodes only (e.g. Noisy-OR, BayesOWL), or to *multivalued* nodes only (e.g. Noisy-OR, weight-sum algorithm). Moreover, the BN-Builder is able to handle *mixed categorical* nodes which none of the existing algorithms has addressed before. However, the BN-Builder could not handle the continuous states, and this will be further explained in the limitation section.

7.4 Limitations

There are two scopes of limitations in this thesis: limitations of the research, and limitations of the proposed solutions (IDR generic ontology, five IDR rule types, BN-Builder algorithm). The former is discussed in section 7.4.1, the latter in section 7.4.2.

7.4.1 Limitations of the research

This section discusses the limitation of the research, scoped from the knowledge of the case-control studies that are encoded as knowledge-bases. The knowledge-bases were built to evaluate the form of knowledge representation. Another limitation of this research is also at the used technology (i.e. semantic-web rules, Bayesian networks).

The evaluation knowledge-bases

The knowledge-bases that were used for evaluating how much the cases covered a limited set of conditions (i.e. 22 contextual IDR knowledge-bases). The twenty-two IDR knowledge-bases were developed to evaluate the IDR generic ontology and five rule types. However, they do not cover *unknown* reservoir type (e.g. Trichomoniasis), *sexually*-transmitted infection (STI) (e.g. HIV/AIDS), *unknown* transmission mode (e.g. Burkholderia), and *miscellaneous* predictor. This is because (1) the case-control studies for these criteria are limited, (2) even if some infectious diseases listed in *miscellaneous* predictor are common (e.g. Tuberculosis, Cholera), the existing studies do not discuss the natural disaster that is included in *miscellaneous* predictor, (3) there are difficulties to validate the metric-based evaluation results if the transmission mode or reservoir is *unknown*, (4) the STI risk is affected by *person* category only.

The following explanations are the limitations of the solutions proposed in this thesis. These limitations are technology for ontological encoding and for the semantic-web rules, and in the structure of the generated BN that is used to predict the personalized infectious disease risks.

Limitation of the SWRL

Since the semantic-web rules in this PROSPECT-IDR are implemented using SWRL in order to be compatible with OWL ontology, thus, the limitation of SWRL are inherited: unable to encode *negation* and *or* logical operator. Therefore, the infectious disease risk knowledge that needs *negation* and *or* encoding will require more rules. This is because the *or* logical operator is represented by different lines of semantic-web rules. Whereas the negation logic statement can be solved by incorporating the *inactive* data range in the consequent part of the IDR rule types.

The intermediate nodes

The BN-Builder developed for this thesis does not generate intermediate node(s) between parent nodes and the child node like the Probabilistic Knowledge-base does. Even if the user puts intermediate node(s) in the IDR ontology as multi-level sub-classes, the generated BN only contains the lowest-level sub-class.

To some extent, the intermediate nodes can clarify the assumptions between domain experts. For example, Dengue Fever risk factors are gender, pregnancy status, development stage, and blood group. However, the original source mentions that the true risk factor that affects a person's Dengue Fever risk is CO_2 emission from skin pore which attract the vector of Dengue Fever (e.g. Aedes Aegypti) to land. The CO_2 emission can be deduced from the *gender, pregnancy status, development stage,* and *blood group* of a person. Thus, these personal risk factors do not directly affect a person's Dengue Fever risk, but the CO_2 emission does.

Since the generated BN does not contain intermediate nodes, it only generates the parent (i.e. risk factors) and child nodes (i.e. infectious disease). This can drive the misunderstanding that the infectious disease whose risk is being predicted is affected by the risk factors.

7.4.2 Limitations of the proposed solution

This section explains the limitations of the thesis solution. The limitations lie in the rule types or the inability of the designed rule type to encode a characteristic of the infectious disease risk knowledge.

More than one rules that are have the same priority level

Duplicating and conflicting rules are aimed to be minimized by some features of the user interfaces. The user interfaces allow the domain experts to associate a level of certainty with the rules; however, there is a chance to have equal certainty for duplicating or conflicting rules. For example, one epidemiologist says that male's TB risk is higher than female. Another epidemiologist opines that female's TB risk is higher than male. When both epidemiologists put the same certainty degree, this knowledge will result in two rules that are conflicting to each other and equally certain.

```
PersonRiskFactor(?all) ^ hasGender(?all, Male) ->
alterRisk(Tuberculosis, 2.12)                          - Priority: 1

PersonRiskFactor(?all) ^ hasGender(?all, Female) ->
alterRisk(Tuberculosis, 1.56)                          - Priority: 1
```

This kind of situation is not solved yet in the conflict resolution strategy of PROSPECT-IDR. Therefore, as mentioned above, one of the knowledge manager's jobs is to manage this kind of conflict.

Unable to handle continuous knowledge in the BN

In section 3.1, it was apparent that the infectious disease risk knowledge contains binary, multivalued, nominal, and continuous knowledge. Even though the *continuous* risk factors are not found in the 22 evaluation knowledge-bases, this kind of knowledge is revealed on a source [100]. When this kind of knowledge appear, the information obtained from regression formula could not be facilitated by the designed five rule types. The kind of continuous knowledge is like every 1^{o}C increase in temperature, it will cause 1% increase in mumps case.

7.5 Discussion

This section elaborates the long-term vision of the continuation of this research. As mentioned in motivation of chapter 1, this thesis is initial research of a vision. The ultimate vision of this research is to support users to prevent themselves from infectious disease risks. This thesis provides a form of knowledge representation and BN-Builder algorithm to convert the encoded infectious disease risk knowledge into a BN that is ready to calculate the personalized infectious disease risk.

Besides that, as the research in the pathogen detection developed, the status of pathogen activity can be connected to this system via *vague pathogen status* rule type. Therefore, the pathogen status in a region can be more precise and no longer vague. However, this needs other studies that describe pathogen role to infectious disease risk to get the odds ratios of risk factors related to pathogen activity. Research in air pollution can also be plugged in to this system as API data provider. Air pollution plays a significant role in air-borne infection transmission.

From the resulting risk prediction, the personalized actions to prevent the predicted infectious diseases are advised. The envisaged recommendations are for example, *the precipitation level was recorded to be increasing in the last 4 weeks, the malaria case is predicted to increase in this week (4-week lag). Since you have a sensitive skin, then, to*

prevent mosquito bites, a mosquito repellant will not be advised for you to apply. Alternatively, a mosquito net can reduce the malaria risk, by applying mosquito net every day starting from today, your malaria risk will decrease by 50%.

With this kind of personalized suggestion, the users will be expected to take the preventable actions, so, the number of incidences like presented in **Table 1.2** might be reduced. Or at least, the users are acknowledged about their infection risks based on their personal attributes and current geo-position.

7.6 Future Work

This section describes the possible research that could be extended from this thesis for achieving the long-term vision explained in the previous section.

Creating the case-base for personalized advice reasoning

Research into the personalization of infectious disease risk prevention is a continuation of this research. To generate relevant advice for preventing the predicted infectious diseases risk, person and other attributes need to be modelled. Extensive dialogs with the epidemiologists will then be required to create cases as the basis of advice reasoning.

The cases will make use of the outputs of this thesis: meningitis risk is predicted to be high for a particular person. The person is a female, age 20-30 years, A blood-type, living in humid and windy region. To generate the automatic advice relevant to the person model and the predicted meningitis risk, the actionable preventions for meningitis risk are searched. Then, the discovered preventions are matched with the person model. If needed, some additional information is required (e.g. allergy information). For example, a person who is allergic to nuts will need another source of protein (e.g. egg, milk, fish) to prevent them from the meningitis risk that is predicted to be increasing in the following weeks because of the weather conditions. This leads to a need for research to find the relevant advice which is based on the person model, the predicted infectious disease risks, and environment conditions (climate and location).

Importing the odds ratios automatically from documents

There are two possible knowledge sources for this thesis: (1) risk factors and quantifications from the case-control studies and (2) directly from the epidemiologists before they are published in an article. The latter knowledge source is envisaged for the future. In order to source knowledge automatically as it is published, a group of keywords could be set to a journal repository to identify relevant journal articles in the public health and infectious disease domains. Then the tabulated data in these articles, the risk factors, odds ratios and number of case-control subjects could be captured. Then, the risk factors and their odds ratios could be harvested using a text-mining technique. The harvesting process could be done automatically without waiting for an expert user to encode them into the PROSPECT-IDR system. However, the precision of the gleaned risk knowledge should be validated by a human to make sure that they were harvested correctly.

Auto-detect the anomalies

The author envisages that the PROSPECT-IDR system will help epidemiologists all over the world to encode their infectious disease risk knowledge in the IDR knowledge-base. This may cause an abundance of IDR rules in an IDR knowledge-base. Besides the abundance of rules, the knowledge manager is also expected to work with the IDR knowledge-base continuously, as the knowledge develops. To help the work of the knowledge manager, a computer program could be built with the aim to detect anomalies automatically. Then this program could list the IDR rules involved in the conflicts. The knowledge manager will observe the IDR rules from the list to decide which IDR rules that have higher priority over the other ones.

Addition of multiple case-control studies

Multiple case-control studies which specify the same infectious disease in one location context can be used to generate one knowledge-base. Two approaches can be used to facilitate the case-control studies addition: (1) recalculate the odd ratios (pooled odd ratios), and (2) machine learning. The resulting knowledge of both pooled odd ratios and machine learning need validation from experts. Both approaches make the addition of case-control studies less automated than current approach.

Data-driven approaches to deep learn Bayesian Networks

Besides encoding the risk factors and the related odds ratios, there is another way to get the knowledge: deep learning for BNs. By deep learning the BNs, the changes of data or pattern can be recognized quickly. Also, the resulting knowledge is up-to-date because represents the current health data. However, this demands data which is often confidential in nature and cannot be openly shared with researchers.

REFERENCES

[1] World Health Organization, "Disease burden and mortality estimates," World Health Organization, 2018.

[2] World Health Organization, "Disease incidence, prevalence and disability."

[3] I. Albert, E. Grenier, J. Denis, and J. Rousseau, "Quantitative Risk Assessment from Farm to Fork and Beyond : A Global Bayesian Approach Concerning Food-Borne Diseases," *Risk Anal.*, vol. 28, no. 2, pp. 557–571, 2008.

[4] T.-Y. Lee, C.-B. Wang, T.-T. Chen, K. N. Kuo, M.-S. Wu, J.-T. Lin, and C.-Y. Wu, "A Tool to Predict Risk for Gastric Cancer in Patients with Peptic Ulcer Disease, Based on a Nationwide Cohort.," *Clin. Gastroenterol. Hepatol.*, vol. 13, pp. 287–293, 2015.

[5] H. Cao, L. Zhang, L. Li, and S. Lo, "Risk Factors for Acute Endophthalmitis following Cataract Surgery : A Systematic Review and Meta- Analysis," *PLoS One*, vol. 8, no. 8, pp. 1–18, 2013.

[6] A. Jurcev-Savicevic, R. Mulic, B. Ban, K. Kozul, L. Bacun-Ivcek, J. Valic, G. Popijac-Cesar, S. Marinovic-Dunatov, M. Gotovac, and A. Simunovic, "Risk factors for pulmonary tuberculosis in Croatia: a matched case-control study," *BMC Public Health*, vol. 13, p. 991, 2013.

[7] M. Dhimal, I. Gautam, H. D. Joshi, R. B. O'Hara, B. Ahrens, and U. Kuch, "Risk Factors for the Presence of Chikungunya and Dengue Vectors (Aedes aegypti and Aedes albopictus), Their Altitudinal Distribution and Climatic Determinants of Their Abundance in Central Nepal," *PLoS Negl. Trop. Dis.*, vol. 9, no. 3, pp. 1–20, 2015.

[8] A. Olea, I. Matute, C. González, I. Delgado, L. Poffald, E. Pedroni, T. Alfaro, M. Hirmas, M. Nájera, A. Gormaz, D. López, S. Loayza, C. Ferreccio, D. Gallegos, R. Fuentes, P. Vial, and X. Aguilera, "Case − Control Study of Risk Factors for Meningococcal Disease in Chile," *Emerg. Infect. Dis.*, vol. 23, no. 7, pp. 1070–1078, 2017.

[9] D. Raja, "Artificial Intelligence in Medical Epidemiology - AIME." .

[10] M. Woolhouse, "How to make predictions about future infectious disease risks," *Philos. Trans. R. Soc. B Biol. Sci.*, vol. 366, no. 1573, pp. 2045–2054, 2011.

[11] P. R. O. Payne, "Chapter 1: Biomedical Knowledge Integration," *PLoS Comput. Biol.*, vol. 8, no. 12, 2012.

[12] CDC, "Principles of Epidemiology | Lesson 1 - Section 1." .

[13] H. F. L. Wertheim, P. Horby, and J. P. Woodall, *Atlas of Human Infectious Diseases*. Wiley-Blackwell, 2012.

[14] M. A. Al-Mozaini and M. K. Mansour, “Personalized medicine Is it time for infectious diseases?,” *www.smj.org.sa Saudi Med J*, vol. 37, no. 12. 2016.

[15] S. Y. Yang and C. L. Hsu, “A location-based services and Google maps-based information master system for tour guiding,” *Comput. Electr. Eng.*, vol. 000, pp. 1–19, 2015.

[16] R. Chinnachodteeranun, N. D. Hung, K. Honda, A. V. M. Ines, and E. Han, “Designing implementing weather generators as web services,” *Futur. Internet*, vol. 8, no. 4, 2016.

[17] R. Lowe, C. Barcellos, C. A. S. Coelho, T. C. Bailey, G. E. Coelho, R. Graham, T. Jupp, W. M. Ramalho, M. S. Carvalho, D. B. Stephenson, and X. Rodó, “Dengue outlook for the World Cup in Brazil: an early warning model framework driven by real-time seasonal climate forecasts,” *Lancet Infect. Dis.*, vol. 14, no. 7, pp. 619–626, Jul. 2014.

[18] M. Chilvers and J. Willbur, “Sporecaster: New white mold risk prediction smartphone app now live | MSU Extension,” 2018. .

[19] United Nations, “WHO morbidity report in UN Data.” .

[20] L. K. Alexander, B. Lopes, K. Ricchetti-Masterson, and K. B. Yeatts, “Cross-sectional Studies,” 2015.

[21] P. Gustafson, V. F. Gomes, C. S. Vieira, P. Rabna, R. Seng, P. Johansson, A. Sandström, R. Norberg, I. Lisse, B. Samb, P. Aaby, and A. Nauclér, “Tuberculosis in Bissau : incidence and risk factors in an urban community in sub-Saharan Africa,” *Int. J. Epidemiol.*, vol. 33, no. 1, pp. 163–172, 2018.

[22] L. G. Cowell and B. Smith, “Infectious disease ontology,” *Infect. Dis. Informatics*, pp. 373–395, 2010.

[23] Y. Lin, Z. Xiang, and Y. He, “Brucellosis Ontology (IDOBRU) as an extension of the Infectious Disease Ontology,” *J. Biomed. Semantics*, vol. 9, no. 2, pp. 1–18, 2011.

[24] G. Camara, S. Despres, R. Djedidi, and M. Lo, “Design of Schistosomiasis Ontology (IDOSCHISTO) Extending the Infectious Disease,” in *Medical Informatics*, 2013, no. 1, pp. 466–470.

[25] Y. Zhao, F. Parvinzamir, H. Wei, E. Liu, Z. Deng, F. Dong, A. Third, V. Marozas, E. Kaldoudi, and G. Clapworthy, “The CARRE Project,” 2013.

[26] Ö. Kafalı, M. Sindlar, T. Van Der Weide, and K. Stathis, “ORC: an Ontology Reasoning Component for Diabetes.”

[27] A. Khan, A. Sadia, S. Ahmed, H. Tabassum, and M. S. Khan, “HEPO: The hepatitis ontology for abductive medical diagnostic systems,” in *2017 International Conference on Communication, Computing and Digital Systems (C-CODE)*, 2017, pp. 271–275.

[28] D. Vrajitoru, “Knowledge Representation.” .

[29] S. Colton, “Knowledge Representation.” .

[30] CDC, “Infectious Diseases | 2018 National Notifiable Conditions.” .

[31] WHO, “WHO | Infectious diseases,” *WHO*, 2016. .

[32] M. Szumilas, “Explaining odds ratios.,” *J. Can. Acad. Child Adolesc. Psychiatry*, vol. 19, no. 3, pp. 227–9, Aug. 2010.

[33] P. C. G. Da Costa, K. B. Laskey, and K. J. Laskey, “PR-OWL: A bayesian ontology language for the Semantic Web,” *Lect. Notes Comput. Sci. (including Subser. Lect. Notes Artif. Intell. Lect. Notes Bioinformatics)*, vol. 5327 LNAI, pp. 88–107, 2008.

[34] Z. Ding, Y. Peng, and R. Pan, “BayesOWL : Uncertainty Modeling in Semantic Web Ontologies,” *StudFuzz*, vol. 204, pp. 3–29, 2006.

[35] R. Pan, Z. Ding, Y. Yu, and Y. Peng, “A Bayesian Network Approach to Ontology Mapping,” in *International Semantic Web Conference*, 2005, pp. 1–16.

[36] D. Settas, A. Cerone, and S. Fenz, “Expert Systems with Applications Enhancing

ontology-based antipattern detection using Bayesian networks," *Expert Syst. Appl.*, vol. 39, no. 10, pp. 9041–9053, 2012.

[37] P. J. Giabbanelli, T. Torsney-Weir, and V. K. Mago, "A fuzzy cognitive map of the psychosocial determinants of obesity," *Appl. Soft Comput. J.*, vol. 12, no. 12, pp. 3711–3724, 2012.

[38] N. Douali, H. Csaba, J. De Roo, E. I. Papageorgiou, and M. C. Jaulent, "Diagnosis Support System based on clinical guidelines: Comparison between case-based fuzzy cognitive maps and bayesian networks," *Comput. Methods Programs Biomed.*, vol. 113, no. 1, pp. 133–143, 2014.

[39] P. Dawson, R. Gailis, and A. Meehan, "Detecting disease outbreaks using a combined Bayesian network and particle filter approach," *J. Theor. Biol.*, vol. 370, pp. 171–183, 2015.

[40] Q. Jiang, J. T. Zhou, Z. B. Jiang, and B. Xu, "Identifying risk factors of avian infectious diseases at household level in Poyang Lake region, China," *Prev. Vet. Med.*, vol. 116, no. 1–2, pp. 151–160, 2014.

[41] M. A. A. Figueiredo, L. C. Rodrigues, M. L. Barreto, J. W. O. Lima, M. C. N. Costa, V. Morato, R. Blanton, P. F. C. Vasconcelos, M. R. T. Nunes, and M. G. Teixeira, "Allergies and diabetes as risk factors for dengue hemorrhagic fever: Results of a case control study," *PLoS Negl. Trop. Dis.*, vol. 4, no. 6, 2010.

[42] C. M. Lewis, S. C. L. Whitwell, A. Forbes, J. Sanderson, and C. G. Mathew, "Estimating risks of common complex diseases across genetic and environmental factors: the example of Crohn disease," pp. 689–694, 2007.

[43] A. N. Freedman, D. Seminara, M. H. Gail, P. Hartge, G. A. Colditz, R. Ballard-barbash, and R. M. Pfeiffer, "Cancer Risk Prediction Models : A Workshop on Development, Evaluation, and Application," *J. Natl. Cancer Inst.*, vol. 97, no. 10, 2005.

[44] Merriam-Webster, "Predicting | Definition of Predicting by Merriam-Webster," 1828. .

[45] I. Ahmed, T. P. Debray, K. G. Moons, and R. D. Riley, "Developing and validating risk prediction models in an individual participant data meta-analysis," *BMC Med. Res. Methodol.*, vol. 14, no. 1, p. 3, Dec. 2014.

[46] M. Menk, L. Giebelhäuser, G. Vorderwülbecke, M. Gassner, J. A. Graw, B. Weiss, M. Zimmermann, K.-D. Wernecke, and S. Weber-Carstens, "Nucleated red blood cells as predictors of mortality in patients with acute respiratory distress syndrome (ARDS): an observational study," *Ann. Intensive Care*, vol. 8, no. 1, p. 42, Dec. 2018.

[47] C. Toma, A. D. Shaw, R. J. N. Allcock, A. Heath, K. D. Pierce, P. B. Mitchell, P. R. Schofield, and J. M. Fullerton, "An examination of multiple classes of rare variants in extended families with bipolar disorder," *Transl. Psychiatry*, vol. 8, no. 1, p. 65, Dec. 2018.

[48] C. Wright and T. Dent, *Quality standards in risk prediction: A summary of an expert meeting*. Cambridge: PHG Foundation, 2011.

[49] C. F. Yung, S. P. Chan, T. L. Thein, S. C. Chai, and Y. S. Leo, "Epidemiological risk factors for adult dengue in Singapore : an 8-year nested test negative case control study," *BMC Infect. Dis.*, pp. 1–9, 2016.

[50] M. J. Pencina, R. B. D. A. Sr, M. G. Larson, J. M. Massaro, and R. S. Vasan, "Predicting the Thirty-Year Risk of Cardiovascular Disease: The Framingham Heart Study," *Circulation*, vol. 119, no. 24, pp. 3078–3084, 2009.

[51] T.-C. Li, C.-I. Li, C.-S. Liu, W.-Y. Lin, C.-H. Lin, S.-Y. Yang, J.-H. Chiang, and C.-C. Lin, "Development and validation of prediction models for the risks of diabetes-related hospitalization and in-hospital mortality in patients with type 2 diabetes," *Metabolism*, vol. 85, pp. 38–47, Aug. 2018.

[52] R. Landy, L. C. Cheung, M. Schiffman, J. C. Gage, N. Hyun, N. Wentzensen, W. K. Kinney, P. E. Castle, B. Fetterman, N. E. Poitras, T. Lorey, P. D. Sasieni, and H. A. Katki, "Challenges in risk estimation using routinely collected clinical data: The example of estimating cervical cancer risks from electronic health-records," *Prev. Med. (Baltim).*, vol. 111, pp. 429–435, Jun. 2018.

[53] K. Y. Clement, W. J. Wouter Botzen, R. Brouwer, and J. C. J. H. Aerts, "A global review of the impact of basis risk on the functioning of and demand for index insurance," *Int. J. Disaster Risk Reduct.*, vol. 28, pp. 845–853, Jun. 2018.

[54] C. Policiano, A. Fonseca, J. M. Mendes, N. Clode, and L. M. Graça, "Small-for-gestational-age babies of low-risk term pregnancies: does antenatal detection matter?," *J. Matern. Neonatal Med.*, vol. 31, no. 11, pp. 1426–1430, Jun. 2018.

[55] C.-H. Chan, H.-K. Wong, and P. S.-F. Yip, "Exploring the use of telephone helpline pertaining to older adult suicide prevention: A Hong Kong experience," *J. Affect. Disord.*, vol. 236, pp. 75–79, Aug. 2018.

[56] Merriam-Webster, "Personalize | Definition of Personalize by Merriam-Webster." .

[57] National Cancer Institute at the National Institutes of Health, "Definition of personalized medicine - NCI Dictionary of Cancer Terms - National Cancer Institute." .

[58] W. K. Redekop, "The Faces of Personalized Medicine: A Framework for Understanding Its Meaning and Scope," *Value Heal.*, vol. 16, pp. 1–6, 2013.

[59] D. Becker, W. van Breda, B. Funk, M. Hoogendoorn, J. Ruwaard, and H. Riper, "Predictive modeling in e-mental health: A common language framework," *Internet Interv.*, vol. 12, pp. 57–67, Jun. 2018.

[60] G. Colella, F. Fazioli, M. Gallo, A. De Chiara, G. Apice, C. Ruosi, A. Cimmino, and F. de Nigris, "Sarcoma Spheroids and Organoids—Promising Tools in the Era of Personalized Medicine," *Int. J. Mol. Sci.*, vol. 19, no. 2, p. 615, Feb. 2018.

[61] P. S. Pratiwi and D. Tjondronegoro, "Towards personalisation of physical activity e-coach using stage-matched behaviour change and motivational interviewing strategies," in *2017 IEEE Life Sciences Conference (LSC)*, 2017, pp. 5–8.

[62] K. Selby, G. Bartlett-Esquilant, and J. Cornuz, "Personalized cancer screening: helping primary care rise to the challenge.," *Public Health Rev.*, vol. 39, p. 4, 2018.

[63] C. Butts, S. Kamel-Reid, G. Batist, S. Chia, C. Blanke, M. Moore, M. B. Sawyer, C. Desjardins, A. Dubois, J. Pun, K. Bonter, and F. D. Ashbury, "Benefits, issues, and recommendations for personalized medicine in oncology in Canada.," *Curr. Oncol.*, vol. 20, no. 5, pp. e475-83, Oct. 2013.

[64] National Cancer Institute (NCI), "Value of Personalized Medicine." PhRMA, 2015.

[65] C. L. Ratcliff, K. A. Kaphingst, and J. D. Jensen, "When Personal Feels Invasive: Foreseeing Challenges in Precision Medicine Communication," *J. Health Commun.*, vol. 23, no. 2, pp. 144–152, Feb. 2018.

[66] S. O. Jensen and S. J. van Hal, "Personalized Medicine and Infectious Disease Management," *Trends Microbiol.*, vol. 25, no. 11, pp. 875–876, Nov. 2017.

[67] CDC, "Principles of Epidemiology | Lesson 1 - Section 10," 2012. .

[68] B. Pam and F. Gorder, "Computational Epidemiology," *Comput. Sci. Eng.*, 2010.

[69] CDC, "Public Health 101 Series Introduction to Public Health Informatics Instructor name Course Topics Introduction to Public Health Informatics," 2009.

[70] American Medical Informatics Association (AMIA), "Public Health Informatics." .

[71] Public Health Informatics Institute (PHII), "Defining Public Health Informatics." .

[72] D. Zeng, H. Chen, C. Lynch, and M. Eidson, "Chapter 13 INFECTIOUS DISEASE INFORMATICS AND OUTBREAK DETECTION," in *Medical Informatics*, 2005, pp.

359–395.

[73] M. Salathe, L. Bengtsson, T. J. Bodnar, D. D. Brewer, J. S. Brownstein, C. Buckee, E. M. Campbell, C. Cattuto, S. Khandelwal, P. L. Mabry, and A. Vespignani, "Digital epidemiology," *PLoS Comput. Biol.*, vol. 8, no. 7, pp. 1–5, 2012.

[74] Z. Huang, A. Das, Y. Qiu, and A. J. Tatem, "Web-based GIS: the vector-borne disease airline importation risk (VBD-AIR) tool.," *Int. J. Health Geogr.*, vol. 11, p. 33, 2012.

[75] R. Nelson, "HealthMap: the future of infectious diseases surveillance?," *Lancet Infect. Dis.*, vol. 8, no. 10, p. 596, 2008.

[76] C. C. Freifeld, K. D. Mandl, B. Y. Reis, and J. S. Brownstein, "HealthMap : Global Infectious Disease Monitoring through," *J. Am. Med. Informatics Assoc.*, vol. 15, no. 2, pp. 150–157, 2014.

[77] S. Sindi, E. Calov, J. Fokkens, T. Ngandu, H. Soininen, J. Tuomilehto, and M. Kivipelto, "The CAIDE Dementia Risk Score App: The development of an evidence-based mobile application to predict the risk of dementia," *Alzheimer's Dement. Diagnosis, Assess. Dis. Monit.*, vol. 1, no. 3, pp. 328–333, 2015.

[78] E. B. Postnikov and D. V Tatarenkov, "Prediction of flu epidemic activity with dynamical model based on weather forecast," *Ecol. Complex.*, vol. 15, pp. 109–113, 2013.

[79] G. M. Hwang, P. J. Mahoney, J. H. James, G. C. Lin, A. D. Berro, M. A. Keybl, D. M. Goedecke, J. J. Mathieu, and T. Wilson, "A model-based tool to predict the propagation of infectious disease via airports," *Travel Med. Infect. Dis.*, vol. 10, no. 1, pp. 32–42, 2012.

[80] P. Diaz, P. Constantine, K. Kalmbach, E. Jones, and S. Pankavich, "A modified SEIR model for the spread of Ebola in Western Africa and metrics for resource allocation," *Appl. Math. Comput.*, vol. 324, pp. 141–155, May 2018.

[81] S. Side, Y. M. Rangkuti, D. G. Pane, and M. S. Sinaga, "Stability Analysis Susceptible, Exposed, Infected, Recovered (SEIR) Model for Spread Model for Spread of Dengue Fever in Medan," *J. Phys. Conf. Ser.*, vol. 954, p. 012018, Jan. 2018.

[82] T. Iskandar, N. A. Chaniago, S. Munzir, V. Halfiani, and M. Ramli, "Mathematical model of tuberculosis epidemic with recovery time delay," in *AIP*, 2017, p. 020021.

[83] X. Wang, S. Panchanathan, and G. Chowell, "A Data-Driven Mathematical Model of CA-MRSA Transmission among Age Groups: Evaluating the Effect of Control Interventions," *PLoS Comput. Biol.*, vol. 9, no. 11, 2013.

[84] B. S. Glicksberg, L. Li, M. A. Badgeley, K. Shameer, R. Kosoy, N. D. Beckmann, N. Pho, J. Hakenberg, M. Ma, K. L. Ayers, G. E. Hoffman, S. D. Li, E. E. Schadt, C. J. Patel, R. Chen, and J. T. Dudley, "Comparative analyses of population-scale phenomic data in electronic medical records reveal race-specific disease networks," *Bioinformatics*, vol. 32, no. 12, pp. i101–i110, 2016.

[85] R. Villamarín, G. Cooper, M. Wagner, F. C. Tsui, and J. U. Espino, "A method for estimating from thermometer sales the incidence of diseases that are symptomatically similar to influenza," *J. Biomed. Inform.*, vol. 46, no. 3, pp. 444–457, 2013.

[86] R. G. C. Scholte, L. Gosoniu, J. B. Malone, F. Chammartin, J. Utzinger, and P. Vounatsou, "Predictive risk mapping of schistosomiasis in brazil using bayesian geostatistical models," *Acta Trop.*, vol. 132, no. 1, pp. 57–63, 2014.

[87] M. J. Vilar, S. Virtanen, R. Laukkanen-Ninios, and H. Korkeala, "Bayesian modelling to identify the risk factors for Yersinia enterocolitica contamination of pork carcasses and pluck sets in slaughterhouses," *Int. J. Food Microbiol.*, vol. 197, pp. 53–57, 2015.

[88] X. L. Zhang, X. J. Shao, J. Wang, and W. L. Guo, "Temporal characteristics of respiratory syncytial virus infection in children and its correlation with climatic factors at a public pediatric hospital in Suzhou," *J. Clin. Virol.*, vol. 58, no. 4, pp. 666–670, 2013.

[89] L. Getoor, N. Friedman, D. Koller, A. Pfeffer, and B. Taskar, "Probabilistic Relational

Models," in *Introduction to Statistical Relational Learning*, 2007, pp. 129–174.

[90] J. Lenfestey, T. Temple, and E. Howe, "Intro to Probabilistic Relational Models." .

[91] B. Borghetti, "Bayesian Knowledge Bases." .

[92] E. Santos, E. S. Santos, and S. Eyal, "Implicitly preserving semantics during incremental knowledge base acquisition under uncertainty," *Int. J. Approx. Reason.*, vol. 33, pp. 71–94, 2003.

[93] L. Ngo and P. Haddawy, "Answering queries from context-sensitive probabilistic knowledge bases," *Theor. Comput. Sci.*, vol. 171, no. 1–2, pp. 147–177, 1997.

[94] P. Haddawy, "Generating Bayesian Networks from Probablity Logic Knowledge Bases," pp. 262–269, 1994.

[95] L. L. Santos, R. N. Carvalho, M. Ladeira, and W. Li, "A New Algorithm for Generating Situation-Specific Bayesian Networks Using Bayes-Ball Method," *Uncertain. Reason. Semant. Web*, 2016.

[96] Z. Ding, Y. Peng, and R. Pan, "BayesOWL : Uncertainty Modelling in Semantic Web Ontologies," *Soft Comput. Ontol. Semant. Web*, vol. 29, pp. 3–29, 2006.

[97] N. C. Stenseth, N. I. Samia, H. Viljugrein, K. L. Kausrud, M. Begon, S. Davis, H. Leirs, V. M. Dubyanskiy, J. Esper, V. S. Ageyev, N. L. Klassovskiy, S. B. Pole, and K.-S. Chan, "Plague dynamics are driven by climate variation," *Proc. Natl. Acad. Sci.*, vol. 103, no. 35, pp. 13110–13115, 2006.

[98] H. Khiabanian, A. B. Holmes, B. J. Kelly, M. Gururaj, G. Hripcsak, and R. Rabadan, "Signs of the 2009 influenza pandemic in the New York-Presbyterian hospital electronic health records," *PLoS One*, vol. 5, no. 9, pp. 1–8, 2010.

[99] S. M. Upadhyayula, S. Rao Mutheneni, H. K. Nayanoori, A. Natarajan, and P. Goswami, "Impact of weather variables on mosquitoes infected with Japanese encephalitis virus in Kurnool district, Andhra Pradesh.," *Asian Pac. J. Trop. Med.*, vol. 5, no. 5, pp. 337–41, 2012.

[100] D. Onozuka and M. Hashizume, "Effect of weather variability on the incidence of mumps in children: a time-series analysis.," *Epidemiol. Infect.*, vol. 139, no. 11, pp. 1692–700, 2011.

[101] C. Imai, B. Armstrong, Z. Chalabi, P. Mangtani, and M. Hashizume, "Time series regression model for infectious disease and weather.," *Environ. Res.*, vol. 142, pp. 319–327, 2015.

[102] M. Reyes, M. Eriksson, R. Bennet, K.-O. Hedlund, and A. Ehrnst, "Regular pattern of respiratory syncytial virus and rotavirus infections and relation to weather in Stockholm, 1984-1993," *Clin. Microbiol. Infect.*, vol. 3, no. 6, pp. 640–646, Dec. 1997.

[103] T. S. Chang, R. E. Gangnon, C. David Page, W. R. Buckingham, A. Tandias, K. J. Cowan, C. D. Tomasallo, B. G. Arndt, L. P. Hanrahan, and T. W. Guilbert, "Sparse modeling of spatial environmental variables associated with asthma," *J. Biomed. Inform.*, vol. 53, pp. 320–329, 2015.

[104] Y. Nakamura, H. Kawanohara, and M. Kamei, "Proposition of real-time precise prediction model of infectious disease patients from Prescription Surveillance using the National Database of Electronic Medical Claims," *J. Infect. Chemother.*, vol. 21, no. 11, pp. 776–782, 2015.

[105] R. K. Meentemeyer, M. A. Dorning, J. B. Vogler, D. Schmidt, and M. Garbelotto, "Citizen science helps predict risk of emerging infectious disease," 2015.

[106] R. D. Melamed, H. Khiabanian, and R. Rabadan, "Data-driven discovery of seasonally linked diseases from an Electronic Health Records system.," *BMC Bioinformatics*, vol. 15 Suppl 6, no. Suppl 6, p. S3, 2014.

[107] A. B. Holmes, A. Hawson, F. Liu, C. Friedman, H. Khiabanian, and R. Rabadan, “Discovering disease associations by integrating electronic clinical data and medical literature,” *PLoS One*, vol. 6, no. 6, 2011.

[108] T. W. Guilbert, B. Arndt, J. Temte, A. Adams, W. Buckingham, A. Tandias, C. Tomasallo, H. a Anderson, and L. P. Hanrahan, “The theory and application of UW ehealth-PHINEX, a clinical electronic health record-public health information exchange.,” *Wis. Med. J.*, vol. 111, no. 3, pp. 124–133, 2012.

[109] H. Nesse, “SEIR Model.” .

[110] T. Jombart, A. Cori, X. Didelot, S. Cauchemez, C. Fraser, and N. Ferguson, “Bayesian Reconstruction of Disease Outbreaks by Combining Epidemiologic and Genomic Data,” *PLoS Comput. Biol.*, vol. 10, no. 1, 2014.

[111] A. Huppert, O. Barnea, G. Katriel, R. Yaari, U. Roll, and L. Stone, “Modeling and statistical analysis of the spatio-temporal patterns of seasonal influenza in Israel.,” *PLoS One*, vol. 7, no. 10, p. e45107, 2012.

[112] S. Side, Irwan, U. Mulbar, and W. Sanusi, “SEIR model simulation for Hepatitis B,” 2017, p. 020198.

[113] P. Kostkova, M. Szomszor, and C. St. Luis, “#Swineflu: The Use of Twitter as an EarlyWarning and Risk Communication,” *ACM Trans. Manag. Inf. Syst.*, vol. 5, no. 2, pp. 1–25, 2014.

[114] E. J. Tomayko, B. A. Weinert, L. Godfrey, A. K. Adams, and L. P. Hanrahan, “Using Electronic Health Records to Examine Disease Risk in Small Populations: Obesity Among American Indian Children, Wisconsin, 2007-2012.,” *Prev. Chronic Dis.*, vol. 13, no. E29, pp. 1–9, 2016.

[115] L. Faisandier, V. Bonneterre, R. De Gaudemaris, and D. J. Bicout, “Occupational exposome: A network-based approach for characterizing Occupational Health Problems,” *J. Biomed. Inform.*, vol. 44, no. 4, pp. 545–552, 2011.

[116] Healthians, “India’s largest Blood Test & Health Test @ Home Service | Healthians.” .

[117] P. Tiwari, A. Jaiswal, N. Vishwakarma, and P. Patel, “Smart Health Care (an Android app to predict disease on the basis of symptoms),” *Int. Res. J. Eng. Technol.*, pp. 2395–56, 2017.

[118] MdCalc, “Framingham Coronary Heart Disease Risk Score - MDCalc.” .

[119] “Infectious Disease Advisor App.” .

[120] J. Huan, “Smartphone app to detect risk for Ebola exposure.” .

[121] M. A. Ali, Z. Ahsan, M. Amin, S. Latif, A. Ayyaz, and M. N. Ayyaz, “ID-Viewer: a visual analytics architecture for infectious diseases surveillance and response management in Pakistan,” *Public Health*, vol. 134, pp. 72–85, 2016.

[122] H. Rahman, “Monitoring , Surveillance and Forecasting of Infectious Animal Diseases in India,” vol. 16, pp. 177–181, 2015.

[123] I. M. Blake, P. Chenoweth, H. Okayasu, C. A. Donnelly, R. B. Aylward, and N. C. Grassly, “Faster detection of poliomyelitis outbreaks to support polio eradication,” *Emerg. Infect. Dis.*, vol. 22, no. 3, pp. 449–456, 2016.

[124] W. K. Wong, a. Moore, G. Cooper, and M. Wagner, “Bayesian network anomaly pattern detection for disease outbreaks,” *Mach. Learn. Work. Then Conf.*, vol. 20, no. 2, p. 808, 2003.

[125] W.-K. Wong, A. Moore, G. Cooper, and M. Wagner, “WSARE: What’s Strange About Recent Events?,” *J. Urban Health*, vol. 80, no. 2 Suppl 1, pp. i66-75, 2003.

[126] M. L. Barreto, M. Glo, and E. H. Carmo, “Infectious diseases epidemiology,” *J.*

Epidemiol. Community Heal., vol. 60, pp. 192–195, 2006.

[127] X. Wu, Y. Lu, S. Zhou, L. Chen, and B. Xu, "Impact of climate change on human infectious diseases: Empirical evidence and human adaptation," *Environ. Int.*, vol. 86, pp. 14–23, 2016.

[128] A. Kilianski, P. Carcel, S. Yao, P. Roth, J. Schulte, G. B. Donarum, E. T. Fochler, J. M. Hill, A. T. Liem, M. R. Wiley, J. T. Ladner, B. P. Pfeffer, O. Elliot, A. Petrosov, D. D. Jima, T. G. Vallard, M. C. Melendrez, E. Skowronski, P. L. Quan, W. I. Lipkin, H. S. Gibbons, D. L. Hirschberg, G. F. Palacios, and C. N. Rosenzweig, "Pathosphere.org: Pathogen detection and characterization through a web-based, open source informatics platform," *BMC Bioinformatics*, vol. 16, no. 1, pp. 1–13, 2015.

[129] S. Altizer, A. Dobson, P. Hosseini, P. Hudson, M. Pascual, and P. Rohani, "Seasonality and the dynamics of infectious diseases," *Ecol. Lett.*, vol. 9, pp. 467–484, 2006.

[130] K. Yeatts, P. Sly, S. Shore, S. Weiss, F. Martinez, A. Geller, P. Bromberg, P. Enright, H. Koren, D. Weissman, and M. Selgrade, "A brief targeted review of susceptibility factors, environmental exposures, asthma incidence, and recommendations for future asthma incidence research.," *Environ. Health Perspect.*, vol. 114, no. 4, pp. 634–40, Apr. 2006.

[131] S. D. Gale, L. D. Erickson, A. Berrett, B. L. Brown, and D. W. Hedges, "Infectious disease burden and cognitive function in young to middle-aged adults," *Brain. Behav. Immun.*, 2015.

[132] P. F. D. Scheelbeek, A. J. G. Wirix, M. Hatta, R. Usman, and M. I. Bakker, "Risk factors for poor tuberculosis treatment outcomes in Makassar, Indonesia," *Southeast Asian J. Trop. Med. Public Health*, vol. 45, no. 4, pp. 853–858, 2014.

[133] S. J. Chapman and A. V. S. Hill, "Human genetic susceptibility to infectious disease," vol. 13, no. March, 2012.

[134] G. G. R. Murray, M. E. J. Woolhouse, M. Tapio, M. N. Mbole-Kariuki, T. S. Sonstegard, S. M. Thumbi, A. E. Jennings, I. C. Van Wyk, M. Chase-Topping, H. Kiara, P. Toye, K. Coetzer, B. M. Dec Bronsvoort, and O. Hanotte, "Genetic susceptibility to infectious disease in East African Shorthorn Zebu: A genome-wide analysis of the effect of heterozygosity and exotic introgression," *BMC Evol. Biol.*, vol. 13, no. 1, 2013.

[135] H. Yi, B. R. Devkota, J. Yu, K. Oh, J. Kim, and H.-J. Kim, "Effects of global warming on mosquitoes & mosquito-borne diseases and the new strategies for mosquito control," *Entomol. Res.*, vol. 44, no. 6, pp. 215–235, 2014.

[136] Q. Wang, Y. Liu, Y. Ma, L. Han, M. Dou, Y. Zou, L. Sun, H. Tian, T. Li, G. Jiang, B. Du, T. Kou, and J. Song, "Severe hypovitaminosis D in active tuberculosis patients and its predictors," *Clin. Nutr.*, 2017.

[137] A. Fares, "Seasonality of tuberculosis.," *J. Glob. Infect. Dis.*, vol. 3, no. 1, pp. 46–55, Jan. 2011.

[138] "WHO | Tuberculosis and HIV," *WHO*, 2018.

[139] D. M. Pigott, R. E. Howes, A. Wiebe, K. E. Battle, N. Golding, P. W. Gething, S. F. Dowell, T. H. Farag, A. J. Garcia, A. M. Kimball, L. K. Krause, C. H. Smith, S. J. Brooker, H. H. Kyu, T. Vos, C. J. L. Murray, C. L. Moyes, and S. I. Hay, "Prioritising infectious disease mapping," *PLoS Negl. Trop. Dis.*, vol. 9, no. 6, pp. 1–21, 2015.

[140] J. Casqueiro, J. Casqueiro, and C. Alves, "Infections in patients with diabetes mellitus : A review of pathogenesis," *Indian J. Endocrinol. Metab.*, vol. 16, pp. 27–36, 2018.

[141] T. N. A. of Sciences, *Critical Aspects of EPA's IRIS Assessment of Inorganic Arsenic*. Washington, D.C.: National Academies Press, 2014.

[142] R. K. Smith and D. J. Maron, "Epidemiology, risk factors, and prevention," *Semin. Colon Rectal Surg.*, vol. 27, no. 4, pp. 176–180, 2016.

[143] O. Shirai, T. Tsuda, S. Kitagawa, K. Naitoh, T. Seki, K. Kamimura, and M. Morohashi,

"Alcohol ingestion stimulates mosquito attraction.," *J. Am. Mosq. Control Assoc.*, vol. 18, no. 2, pp. 91–6, Jun. 2002.

[144] K. Lönnroth, B. G. Williams, S. Stadlin, E. Jaramillo, and C. Dye, "Alcohol use as a risk factor for tuberculosis - A systematic review," *BMC Public Health*, vol. 8, no. May 2014, 2008.

[145] R. Mukherjee, D. Halder, S. Saha, R. Shyamali, R. Ramakrishnan, M. V Murhekar, and Y. J. Hutin, "Five Pond-centred Outbreaks of Cholera in Villages of West Bengal , India : Evidence for Focused Interventions," *J. Heal. Popul. Nutr.*, vol. 29, no. 5, pp. 421–428, 2011.

[146] A. J. Lund, H. M. Keys, S. Leventhal, J. W. Foster, and M. C. Freeman, "Prevalence of cholera risk factors between migrant Haitians and Dominicans in the Dominican Republic," *Pan Am. J. Public Heal.*, vol. 37, no. 3, pp. 125–132, 2015.

[147] A. Rosewell, B. Addy, L. Komnapi, F. Makanda, B. Ropa, E. Posanai, S. Dutta, G. Mola, W. Y. N. Man, A. Zwi, and C. R. Macintyre, "Cholera risk factors , Papua New Guinea , 2010," *BMC Infect. Dis.*, vol. 12, pp. 287–293, 2012.

[148] A. Prayitno, A. Taurel, J. Nealon, H. I. Satari, R. Karyanti, R. Sekartini, S. Soedjatmiko, H. Gunardi, E. Medise, R. T. Sasmono, J. M. Simmerman, A. Bouckenooghe, and S. R. Hadinegoro, "Dengue seroprevalence and force of primary infection in a representative population of urban dwelling Indonesian children," *PLoS Negl. Trop. Dis.*, vol. 11, no. 6, pp. 1–16, 2017.

[149] M. A. Soghaier, S. F. Mahmood, O. Pasha, S. I. Azam, M. M. Karsani, M. M. Elmangory, B. A. Elmagboul, S. I. Okoued, S. M. Shareef, H. S. Khogali, and E. Eltigai, "Factors associated with dengue fever IgG sero-prevalence in South Kordofan State , Sudan , in 2012 : Reporting prevalence ratios," *J. Infect. Public Health*, vol. 7, no. 1, pp. 54–61, 2014.

[150] Centers for Disease Control and Prevention (CDC), "Cryptosporidiosis outbreak at a summer camp--North Carolina, 2009.," *MMWR. Morb. Mortal. Wkly. Rep.*, vol. 60, no. 27, pp. 918–22, Jul. 2011.

[151] CDC, "Principles of Epidemiology | Lesson 3 - Section 2." .

[152] M. Lappenschaar, A. Hommersom, P. J. F. Lucas, J. Lagro, and S. Visscher, "Multilevel Bayesian networks for the analysis of hierarchical health care data," *Artif. Intell. Med.*, vol. 57, no. 3, pp. 171–183, 2013.

[153] M. Blangiardo, F. Finazzi, and M. Cameletti, "Two-stage Bayesian model to evaluate the effect of air pollution on chronic respiratory diseases using drug prescriptions," *Spat. Spatiotemporal. Epidemiol.*, 2016.

[154] C. Lau, P. Weinstein, and D. Slaney, "Imported cases of Ross River virus disease in New Zealand - a travel medicine perspective.," *Travel Med. Infect. Dis.*, vol. 10, no. 3, pp. 129–134, 2012.

[155] P. D. Loprinzi and A. Nooe, "Health characteristics and predicted 10-year risk for a first atherosclerotic cardiovascular disease (ASCVD) event using the Pooled Cohort Risk Equations among US adults who are free of cardiovascular disease," *Physiol. Behav.*, vol. 151, pp. 591–595, 2015.

[156] L. M. Artigao-Rodenas, J. A. Carbayo-Herencia, J. A. Divisón-Garrote, V. F. Gil-Guillén, J. Massó-Orozco, M. Simarro-Rueda, F. Molina-Escribano, C. Sanchis, L. Carrión-Valero, E. López de Coca, D. Caldevilla, J. López-Abril, C. Carratalá-Munuera, and A. Lopez-Pineda, "Framingham Risk Score for Prediction of Cardiovascular Diseases: A Population-Based Study from Southern Europe," *PLoS One*, vol. 8, no. 9, pp. 1–10, 2013.

[157] S. Kalayanarooj, R. V. Gibbons, D. Vaughn, S. Green, A. Nisalak, R. G. Jarman, M. P. Mammen, Jr., and G. Perng, "Blood Group AB Is Associated with Increased Risk for Severe Dengue Disease in Secondary Infections," *J. Infect. Dis.*, vol. 195, no. 7, pp. 1014–

1017, 2007.

[158] A. L. Greer, S. J. Drews, and D. N. Fisman, “Why ‘Winter’ vomiting disease? seasonality, hydrology, and norovirus epidemiology in Toronto, Canada,” *Ecohealth*, vol. 6, no. 2, pp. 192–199, 2009.

[159] I. Stephenson and M. Zambon, “The epidemiology of influenza,” *Occup. Med. (Chic. Ill).*, vol. 52, no. 5, pp. 241–247, 2002.

[160] S. Subak, “Effects of climate on variability in Lyme disease incidence in the northeastern United States,” *Am. J. Epidemiol.*, vol. 157, no. 6, pp. 531–538, 2003.

[161] K. Kleinman, R. Lazarus, and R. Platt, “A generalized linear mixed models approach for detecting incident clusters of disease in small areas, with an application to biological terrorism,” *Am. J. Epidemiol.*, vol. 159, no. 3, pp. 217–224, 2004.

[162] G. M. Liumbruno and M. Franchini, “Beyond immunohaematology: the role of the ABO blood group in human diseases,” *Blood Transfus*, vol. 11, pp. 491–499, 2013.

[163] K. Kengkla, N. Charoensuk, M. Chaichana, S. Puangjan, T. Rattanapornsompong, J. Choorassamee, P. Wilairat, and S. Saokaew, “Clinical risk scoring system for predicting extended-spectrum β-lactamase-producing Escherichia coli infection in hospitalized patients.,” *J. Hosp. Infect.*, vol. 93, no. 1, pp. 49–56, 2016.

[164] A. Ascherio and M. A. Schwarzschild, “The epidemiology of Parkinson’s disease: risk factors and prevention,” *Lancet Neurol.*, vol. 15, no. 12, pp. 1257–1272, 2016.

[165] S. A. J. Schmidt, M. Vestergaard, L. M. Baggesen, L. Pedersen, H. C. Schønheyder, and H. T. Sørensen, “Prevaccination epidemiology of herpes zoster in Denmark : Quantification of occurrence and risk factors,” *Vaccine*, vol. 35, no. 42, pp. 5589–5596, 2017.

[166] H. Zhang, T. Yang, M. Wu, and F. Shen, “Intrahepatic cholangiocarcinoma: Epidemiology, risk factors, diagnosis and surgical management,” *Cancer Lett.*, vol. 379, no. 2, pp. 198–205, 2016.

[167] C. A. Rostad, K. Wehrheim, J. K. Kirklin, D. Naftel, E. Pruitt, T. M. Hoffman, T. L’Ecuyer, K. Berkowitz, W. T. Mahle, and J. N. Scheel, “Bacterial infections after pediatric heart transplantation: Epidemiology, risk factors and outcomes,” *J. Hear. Lung Transplant.*, vol. 36, no. 9, pp. 996–1003, 2017.

[168] S. H. Kim, S. M. Choi, B. C. Kim, K. H. Choi, T. S. Nam, J. T. Kim, S. H. Lee, M. S. Park, and S. J. Kim, “Risk factors for aseptic meningitis in herpes zoster patients,” *Ann. Dermatol.*, vol. 29, no. 3, pp. 283–287, 2017.

[169] Bruce MG; Rosenstein NE; Capparella JM; Shutt KA; Perkins B; Collins M, “Risk Factors for Meningococcal Disease in College Students.,” *J. Am. Med. Assoc.*, vol. 286, no. 6, pp. 688–693, 2001.

[170] A. Moat, A. Jarousha, and A. Al Afifi, “Epidemiology and Risk Factors Associated with Developing Bac- terial Meningitis among Children in Gaza Strip,” *Iran. J. Public Health*, vol. 43, no. 9, pp. 1176–1183, 2014.

[171] A. J. M. Lora, J. Fernandez, A. Morales, Y. Soto, J. Feris-iglesias, and M. O. Brito, “Disease Severity and Mortality Caused by Dengue in a Dominican Pediatric Population,” *Am. J. Trop. Med. Hyg.*, vol. 90, no. 1, pp. 169–172, 2014.

[172] V. Kumar, S. Devika, S. George, and L. Jeyaseelan, “ScienceDirect Spatial mapping of acute diarrheal disease using GIS and estimation of relative risk using empirical Bayes approach,” *Clin. Epidemiol. Glob. Heal.*, vol. 5, no. 2, pp. 87–96, 2017.

[173] D. Morof, S. T. Cookson, S. Laver, D. Chirundu, S. Desai, P. Mathenge, D. Shambare, L. Charimari, S. Midzi, C. Blanton, and T. Handzel, “Community Mortality from Cholera : Urban and Rural Districts in Zimbabwe,” *Am. J. Trop. Med. Hyg.*, vol. 88, no. 4, pp. 645–650, 2013.

[174] C. O. Schmidt and T. Kohlmann, “When to use the odds ratio or the relative risk?,” *Int. J. Public Health*, vol. 53, pp. 165–167, 2008.

[175] M. S. Hossain, I. B. Habib, and K. Andersson, “A belief rule based expert system to diagnose dengue fever under uncertainty,” in *2017 Computing Conference*, 2017, pp. 179–186.

[176] I. Ramalhosa, P. Mateus, V. Alves, H. Vicente, F. Ferraz, J. Neves, and J. Neves, “Diagnosis of Alzheimer Disease Through an Artificial Neural Network Based System,” Springer, Cham, 2018, pp. 162–174.

[177] M. H. F. Zarandi and M. Abdolkarimzadeh, “Fuzzy Rule Based Expert System to Diagnose Chronic Kidney Disease,” Springer, Cham, 2018, pp. 323–328.

[178] C. Zhao, J. Jiang, Z. Xu, and Y. Guan, “A study of EMR-based medical knowledge network and its applications,” *Comput. Methods Programs Biomed.*, vol. 143, pp. 13–23, May 2017.

[179] M. Krishnamurthy, P. Marcinek, K. M. Malik, and M. Afzal, “Representing Social Network Patient Data as Evidence-Based Knowledge to Support Decision Making in Disease Progression for Comorbidities,” *IEEE Access*, vol. 6, pp. 12951–12965, 2018.

[180] B. MacKellar and C. Schweikert, “Conflict Discovery and Analysis for Clinical Trials,” in *Proceedings of the 2017 International Conference on Digital Health - DH ’17*, 2017, pp. 72–76.

[181] M. A. Kadhim, M. A. Alam, and H. Kaur, “A Multi-Intelligent Agent for Knowledge Discovery in Database (MIAKDD): Cooperative Approach with Domain Expert for Rules Extraction,” Springer, Cham, 2014, pp. 602–614.

[182] W. Chen, A. Fang, and W. Wang, “Traditional Chinese Medicine Syndrome Knowledge Representation Model of Gastric Precancerous Lesion and Risk Assessment Based on Extenics,” Springer, Berlin, Heidelberg, 2011, pp. 585–590.

[183] J. Vilhena, M. Rosário Martins, H. Vicente, J. M. Grañeda, F. Caldeira, R. Gusmão, J. Neves, and J. Neves, “An Integrated Soft Computing Approach to Hughes Syndrome Risk Assessment,” *J. Med. Syst.*, vol. 41, no. 3, p. 40, Mar. 2017.

[184] M. Rajabi, A. Mansourian, P. Pilesjo, F. Hedefalk, R. Groth, and A. Bazmani, “Comparing Knowledge - Driven and Data - Driven Modeling methods for susceptibility mapping in spatial epidemiology : a case study in Visceral Leishmaniasis,” in *Proceedings of AGILE 2014 International Conference on Geographic Information Science*, 2014, pp. 1–5.

[185] J. Wiens, J. Guttag, and E. Horvitz, “Patient Risk Stratification with Time-Varying Parameters: A Multitask Learning Approach,” *J. Mach. Learn. Res.*, vol. 17, pp. 1–23, 2016.

[186] J. F. Sowa, *Knowledge representation : logical, philosophical, and computational foundations*. Brooks/Cole, 2000.

[187] M. Negnevitsky, *Artificial intelligence : a guide to intelligent systems*. Addison Wesley, 2002.

[188] P. Q. Rashid, “Semantic Network and Frame Knowledge Representation Formalisms in Artificial Intelligence.”

[189] A. Onisko, P. Lucas, and M. J. Druzdzel, “Comparison of Rule-Based and Bayesian Network Approaches in Medical Diagnostic Systems,” *Artif. Intell. Med. 8th Conf. Artif. Intell. Med. Eur. AIME 2001, Cascais, Port. July 1-4, 2001 Proc.*, vol. 2101, p. 283, 2001.

[190] J. Prentzas and I. Hatzilygeroudis, “Integrations of Rule-Based and Case-Based Reasoning,” *Proc. Int. Conf. Comput. Commun. Control Technol.*, vol. 4, pp. 81–85, 2003.

[191] P. Smets, “Jeffrey’s rule of conditioning generalized to belief functions,” *Uncertain. Artif. Intell.*, 1993.

[192] National Center for Biomedical Ontology, “Welcome to the NCBO BioPortal | NCBO BioPortal,” 2018. .

[193] OBO, “The OBO Foundry,” 2018. .

[194] Google, “Google Code Archive - Long-term storage for Google Code Project Hosting.” .

[195] C. Pesquita, J. D. Ferreira, F. M. Couto, and M. J. Silva, “The epidemiology ontology : an ontology for the semantic annotation of epidemiological resources,” pp. 1–7, 2014.

[196] University of Michigan Medical School, “VIOLIN: Vaccine Investigation and Online Information Network.” .

[197] L. M. Schriml, C. Arze, S. Nadendla, Y. W. W. Chang, M. Mazaitis, V. Felix, G. Feng, and W. A. Kibbe, “Disease ontology: A backbone for disease semantic integration,” *Nucleic Acids Res.*, vol. 40, no. D1, pp. 939–946, 2012.

[198] S. El-Sappagh and F. Ali, “DDO: a diabetes mellitus diagnosis ontology,” *Appl. Informatics*, vol. 3, no. 1, p. 5, Dec. 2016.

[199] C. L. Gordon, S. Pouch, L. G. Cowell, M. R. Boland, H. L. Platt, A. Goldfain, and C. Weng, “Design and evaluation of a bacterial clinical infectious diseases ontology.,” *AMIA ... Annu. Symp. proceedings. AMIA Symp.*, vol. 2013, pp. 502–11, 2013.

[200] E. Younesi, S. Ansari, M. Guendel, S. Ahmadi, C. Coggins, J. Hoeng, M. Hofmann-Apitius, and M. C. Peitsch, “CSEO - the Cigarette Smoke Exposure Ontology.,” *J. Biomed. Semantics*, vol. 5, p. 31, 2014.

[201] W. R. Hogan, M. M. Wagner, M. Brochhausen, J. Levander, S. T. Brown, N. Millett, J. Depasse, and J. Hanna, “The Apollo Structured Vocabulary : an OWL2 ontology of phenomena in infectious disease epidemiology and population biology for use in epidemic simulation,” *J. Biomed. Semantics*, pp. 1–12, 2016.

[202] C. X. Hong, Z. Y. Feng, C. X. Rong, L. Tian, W. Y. Wei, and M. Li, “The ontology-based knowledge representation modeling of the traditional-Chinese-medicine symptom,” in *2017 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)*, 2017, pp. 1345–1349.

[203] A. Al-Rumkhani, M. Al-Razgan, and A. Al-Faris, “TibbOnto: Knowledge Representation of Prophet Medicine (Tibb Al-Nabawi),” *Procedia Comput. Sci.*, vol. 82, pp. 138–142, Jan. 2016.

[204] M. Richard, X. Aimé, M.-O. Krebs, and J. Charlet, “Enrich classifications in psychiatry with textual data: an ontology for psychiatry including social concepts.,” *Stud. Health Technol. Inform.*, vol. 210, pp. 221–3, 2015.

[205] A. Assawamakin, “A Development of Knowledge Representation for Thalassemia Prevention and Control Program Ontological Knowledge Base of Southeast Asian Thalassemia.”

[206] M. A. Elhefny, M. Elmogy, and A. A. Elfetouh, “Building OWL ontology for obesity related cancer,” in *2014 9th International Conference on Computer Engineering & Systems (ICCES)*, 2014, pp. 177–183.

[207] V. Rawte and B. Roy, “OBESTDD: Ontology Based Expert System for Thyroid Disease Diagnosis,” in *2015 International Conference on Nascent Technologies in the Engineering Field (ICNTE)*, 2015, pp. 1–6.

[208] A. Ruttenberg, “Basic Formal Ontology (BFO) | Home.” .

[209] E. I. Papageorgiou, “Learning Algorithms for Fuzzy Cognitive Maps - A Review Study,” *IEEE Trans. Syst. Man, Cybern. Part ASystems Humans*, vol. 42, no. 2, pp. 150–163, 2012.

[210] R. H. Lathrop, “Bayesian Networks.”

[211] D. N. Barton, S. Kuikka, O. Varis, L. Uusitalo, H. J. Henriksen, M. Borsuk, A. D. La Hera, R. Farmani, S. Johnson, and J. D. C. Linnell, “Bayesian networks in environmental and

resource management," *Integr. Environ. Assess. Manag.*, vol. 8, no. 3, pp. 418–429, 2012.

[212] B. Das, "Generating Conditional Probabilities for Bayesian Networks: Easing the Knowledge Acquisition Problem," *CoRR*, pp. 1–24, 2004.

[213] J. Pearl and Judea, *Probabilistic reasoning in intelligent systems : networks of plausible inference*. Morgan Kaufmann Publishers, 1988.

[214] M. Henrion, *Practical issues in constructing a Bayes' belief network*. Virginia: North-Holland, 1987.

[215] L. Perreault, S. Strasser, M. Thornton, and J. W. Sheppard, "A Noisy-OR Model for Continuous Time Bayesian Networks," *Proc. Twenty-Ninth Int. Florida Artif. Intell. Res. Soc. Conf.*, pp. 668–673, 2016.

[216] G. Cheng, Q. Du, and H. Ma, "The Design and Implementation of Ontology and Rules Based Knowledge Base for Transportation," *2008 Int. Conf. Comput. Sci. Softw. Eng.*, pp. 1035–1038, 2008.

[217] Shortliffe, *Computer-Based Medical Consultation. MYCIN*. New York: Elsevier, 1976.

[218] M. O 'connor, "The Semantic Web Rule Language."

[219] L. Getoor, N. Friedman, D. Koller, and A. Pfeffer, "Learning Probabilistic Relational Models," in *Relational Data Mining*, Berlin, Heidelberg: Springer Berlin Heidelberg, 2001, pp. 307–335.

[220] J. and E. S. S. Eugene. Santos, "A Framework for Building Knowledge-Base Under Uncertainty," *J. Exp. Theor. Artif. Intell.*, vol. 11, no. 2, pp. 265–286, 1999.

[221] K. B. Laskey, "MEBN: A language for first-order Bayesian knowledge bases," *Artif. Intell.*, vol. 172, no. 2–3, pp. 140–178, 2008.

[222] P. C. G. Costa and K. B. Laskey, "Multi-Entity Bayesian Networks Without Multi-Tears," pp. 1–20, 2006.

[223] L. G. Cowell, B. Smith, L. G. Cowell, and B. Smith, "Infectious Disease Ontology," *Infect. Dis. Informatics*, pp. 373–395, 2010.

[224] A. Third, E. Kaldoudi, G. Gkotsis, S. Roumeliotis, K. Pafili, J. Domingue, and M. Keynes, "Capturing Scientific Knowledge on Medical Risk Factors," 2010.

[225] M. C. Thomson, F. J. Doblas-Reyes, S. J. Mason, R. Hagedorn, S. J. Connor, T. Phindela, A. P. Morse, and T. N. Palmer, "Malaria early warnings based on seasonal climate forecasts from multi-model ensembles," *Nature*, vol. 439, no. 7076, pp. 576–579, 2006.

[226] S. Falconer, "OntoGraf - Protege Wiki." .

[227] WHO, "WHO | Disease burden and mortality estimates," *WHO*, 2018. .

[228] S. Tartir, I. Arpinar, M. Moore, a Sheth, and B. Aleman-Meza, "OntoQA: Metric-Based Ontology Quality Analysis," *IEEE Work. Knowl. Acquis. from Distrib. Auton. Semant. Heterog. Data Knowl. Sources*, pp. 45–53, 2005.

[229] A. D. Preece and R. Shinghal, "Foundation and application of knowledge base verification," *Int. J. Intell. Syst.*, vol. 9, no. 8, pp. 683–701, 1994.

[230] M. A. Soghaier, S. Himatt, K. E. Osman, S. I. Okoued, O. E. Seidahmed, M. E. Beatty, K. Elmusharaf, J. Khogali, N. H. Shingrai, and M. M. Elmangory, "Cross-sectional community-based study of the socio-demographic factors associated with the prevalence of dengue in the eastern part of Sudan in 2011," *BMC Public Health*, pp. 1–6, 2015.

[231] I. Safeukui-Noubissi, S. Ranque, B. Poudiougou, M. Keita, A. Traoré, D. Traoré, M. Diakité, M. B. Cissé, M. M. Keita, A. Dessein, and O. K. Doumbo, "Risk factors for severe malaria in Bamako, Mali: A matched case-control study," *Microbes Infect.*, vol. 6, no. 6, pp. 572–578, 2004.

[232] M. J. Grigg, J. Cox, T. William, J. Jelip, K. M. Fornace, P. M. Brock, L. von Seidlein, B. E. Barber, N. M. Anstey, T. W. Yeo, and C. J. Drakeley, "Individual-level factors

associated with the risk of acquiring human Plasmodium knowlesi malaria in Malaysia: a case-control study," *Lancet Planet. Heal.*, vol. 1, no. 3, pp. e97–e104, 2017.

[233] F. Agegnehu, A. Shimeka, F. Berihun, and M. Tamir, "Determinants of malaria infection in Dembia district, Northwest Ethiopia: A case-control study," *BMC Public Health*, vol. 18, no. 1, pp. 1–8, 2018.

[234] N. Alexander, M. Rodriguez, L. Perez, and J. Caicedo, "Case-control Study of Mosquito Nets Against Malaria in the Amazon Region of Colombia," *Am. J. Trop. Med. Hyg.*, vol. 73, no. 1, pp. 140–148, 2005.

[235] Norsys Software Corp., "Norsys Software Corp. - Bayes Net Software." .

[236] J. Negin, S. Abimbola, and B. J. Marais, "Tuberculosis among older adults – time to take notice," *Int. J. Infect. Dis.*, vol. 32, pp. 135–137, Mar. 2015.

[237] Institute of Medicine (US) Committee on Enhancing Environmental Health Content in Nursing Practice, *Nursing Health, & Environment: Strengthening the Relationship to Improve the Public's Health*. Washington (DC): National Academies Press (US), 1995.

[238] R. A. Vinarti and L. Hederman, "Introduction of a Bayesian Network Builder Algorithm - Personalized Infectious Disease Risk Prediction," *Proc. 11th Int. Jt. Conf. Biomed. Eng. Syst. Technol.*, vol. 5, no. Biostec, pp. 115–126, 2018.

[239] R. A. Vinarti and L. Hederman, "Personalization of Infectious Disease Risk Prediction: Towards Automatic Generation of a Bayesian Network," in *Proceedings - IEEE Symposium on Computer-Based Medical Systems*, 2017, vol. 2017–June.

[240] H. M. Nemati, A. Sant'Anna, and S. Nowaczyk, "Bayesian Network representation of meaningful patterns in electricity distribution grids," *2016 IEEE Int. Energy Conf. ENERGYCON 2016*, 2016.

[241] E. Kaldoudi, J. Domingue, and E. Liu, "Personalized Patient Empowerment and Shared Decision Support for Cardiorenal Disease and Comorbidities - The Carre Project," pp. 1–152, 2014.

[242] S. E. Keith R.Bisset, "HIGH PERFORMANCE INFORMATICS FOR PANDEMIC PREPAREDNESS Keith," *Proc. 2012 Winter Simul. Conf.*, vol. 1, pp. 804–815, 2012.

[243] R. J. Hoekstra, "Ontology Representation: design patterns and ontologies that make sense," 2009.

[244] R. J. Brachman, *On the Epistemological Status of Semantic Networks*. New York: Academic Press, 1979.

[245] R. Hartley and J. Barnden, "Semantic Networks: Visualizations of Knowledge."

[246] T. Azuma, N. Nakada, N. Yamashita, and H. Tanaka, "Prediction, risk and control of anti-influenza drugs in the Yodo River Basin, Japan during seasonal and pandemic influenza using the transmission model for infectious disease," *Sci. Total Environ.*, vol. 521–522, pp. 68–74, 2015.

[247] V. L. Yu and S. C. Edberg, "Global Infectious Diseases and Epidemiology Network (GIDEON): A World Wide Web-Based Program for Diagnosis and Informatics in Infectious Diseases," *Clin. Infect. Dis.*, vol. 40, no. 1, pp. 123–126, 2005.

[248] R. A. Vinarti, "Appendix (44 articles)," 2018. .

[249] R. A. Vinarti, "IDR Ontologies." Open Science Framework, 2018.

[250] M. Horridge, M. E. Aranguren, J. Mortensen, M. Musen, and N. F. Noy, "Ontology Design Pattern Language Expressivity Requirements."

APPENDICES

Appendix 1 – Articles used in Knowledge Representation Design

List of authors, title, and year published of 188 articles that are contained in **Table 3.4**.

No	Authors	Title	Year
1	Roldán-García M.D.M., Uskudarli S., Marvasti N.B., Acar B., Aldana-Montes J.F.	Towards an ontology-driven clinical experience sharing ecosystem: Demonstration with liver cases	2018
2	Kamišalić A., Riaño D., Welzer T.	Formalization and acquisition of temporal knowledge for decision support in medical processes	2018
3	Krishnamurthy M., Marcinek P., Malik K.M., Afzal M.	Representing social network patient data as evidence-based knowledge to support decision making in disease progression for comorbidities	2018
4	Hossain M.S., Habib I.B., Andersson K.	A belief rule based expert system to diagnose dengue fever under uncertainty	2018
5	Ramalhosa I., Mateus P., Alves V., Vicente H., Ferraz F., Neves J., Neves J.	Diagnosis of Alzheimer disease through an artificial neural network-based system	2018
6	Guo S., Xu K., Zhao R., Gotz D., Zha H., Cao N.	EventThread: Visual Summarization and Stage Analysis of Event Sequence Data	2018
7	Zhao C., Jiang J., Guan Y., Guo X., He B.	EMR-based medical knowledge representation and inference via Markov random fields and distributed representation learning	2018
8	Zarandi M.H.F., Abdolkarimzadeh M.	Fuzzy rule based expert system to diagnose chronic kidney disease	2018
9	Porebski S., Straszecka E.	Diagnostic rule extraction using the Dempster-Shafer theory extended for fuzzy focal elements	2018
10	Pooja M.R., Pushpalatha M.P.	An empirical analysis of machine learning classifiers for clinical decision making in Asthma	2018
11	Garcia-Gathright J.I., Matiasz N.J., Adame C., Sarma K.V., Sauer L., Smedley N.F., Spiegel M.L., Strunck J., Garon E.B., Taira R.K., Aberle D.R., Bui A.A.T.	Evaluating Casama: Contextualized semantic maps for summarization of lung cancer studies	2018
12	Guo Y., Liu T., Guo X., Yang Y.	Research on key technology in traditional Chinese medicine (TCM) smart service system	2018
13	Martins B., Rei J., Braga M., Abelha A., Vicente H., Neves J., Neves J.	Kidney care—a personal assistant assessment	2018
14	Neves J., Vicente H., Ferraz F., Leite A.C., Rodrigues A.R., Cruz M., Machado J., Neves J., Sampaio L.	A Deep Learning Approach to Case Based Reasoning to the Evaluation and Diagnosis of Cervical Carcinoma	2018
15	Oyelade O.N., Obiniyi A.A., Junaidu S.B., Adewuyi S.A.	ST-ONCODIAG: A semantic rule-base approach to diagnosing breast cancer base on Wisconsin datasets	2018
16	Hong C.X., Feng Z.Y., Rong C.X., Tian L., Wei W.Y., Li M.	The ontology-based knowledge representation modeling of the traditional-Chinese-medicine symptom	2017

No	Authors	Title	Year
17	Lossio-Ventura J.A., Hogan W., Modave F., Guo Y., He Z., Hicks A., Bian J.	OC-2-KB: A software pipeline to build an evidence-based obesity and cancer knowledge base	2017
18	Agustina E., Pratomo I., Wibawa A.D., Rahayu S.	Expert system for diagnosis pests and diseases of the rice plant using forward chaining and certainty factor method	2017
19	Kalet A.M., Doctor J.N., Gennari J.H., Phillips M.H.	Developing Bayesian networks from a dependency-layered ontology: A proof-of-concept in radiation oncology	2017
20	MacKellar B., Schweikert C.	Conflict discovery and analysis for clinical trials	2017
21	Yingying L., Xiaoyan Z., Xiaodong Z., Shibin L., Na Z., Min S.	Knowledge expression and reasoning model for tomato disease diagnosis	2017
22	Coelho A., Marques P., Magalhães R., Sousa N., Neves J., Alves V.	A knowledge representation and reasoning system for multimodal neuroimaging studies	2017
23	Khan A., Sadia A., Ahmed S., Tabassum H., Khan M.S.	HEPO: The hepatitis ontology for abductive medical diagnostic systems	2017
24	Zhao C., Jiang J., Xu Z., Guan Y.	A study of EMR-based medical knowledge network and its applications	2017
25	Anselma L., Piovesan L., Terenziani P.	Temporal reasoning techniques for the analysis of interactions in the treatment of comorbid patients	2017
26	Vilhena J., Rosário Martins M., Vicente H., Grañeda J.M., Caldeira F., Gusmão R., Neves J., Neves J.	An Integrated Soft Computing Approach to Hughes Syndrome Risk Assessment	2017
27	Cahan A., Cimino J.J.	A learning health care system using computer-aided diagnosis	2017
28	Minutolo A., Esposito M., De Pietro G.	A hybrid reasoning system for mobile and intelligent health services	2017
29	Anselma L., Piovesan L., Terenziani P.	Temporal detection and analysis of guideline interactions	2017
30	Ojeme B., Mbogho A., Meyer T.	Probabilistic expert systems for reasoning in clinical depressive disorders	2017
31	Lossio-Ventura J.A., Hogan W., Modave F., Hicks A., Hanna J., Guo Y., He Z., Bian J.	Towards an obesity-cancer knowledge base: Biomedical entity identification and relation detection	2017
32	Karim R., Andersson K., Hossain M.S., Uddin M.J., Meah M.P.	A belief rule based expert system to assess clinical bronchopneumonia suspicion	2017
33	Tawil S.F.M., Ismail R., Wahid F.A., Norwawi N.M., Mazlan A.A.	Application of OASys approaches for dates ontology	2017
34	Faria R., Alves V., Ferraz F., Neves J., Vicente H., Neves J.	A case base approach to cardiovascular diseases using chest X-ray image analysis	2017
35	Jeddi F.R., Arabfard M., Kermany Z.A.	Intelligent Diagnostic Assistant for complicated skin diseases through C5's algorithm	2017
36	Riaño D., Fernández-Pérez A.	Simulation-based episodes of care data synthetization for chronic disease patients	2017
37	Elhefny M.A., Elmogy M., Elfetouh A.A., Badria F.A.	Developing a fuzzy OWL ontology for obesity related cancer domain	2017
38	Merhej E., Schockaert S., McKelvey T.G., De Cock M.	Generating conflict-free treatments for patients with comorbidity using answer set programming	2017
39	Tahar K., Xu J., Herre H.	Expert2OWL: A methodology for pattern-based ontology development	2017
40	Doulaverakis C., Koutkias V., Antoniou G., Kompatsiaris I.	Applying SPARQL-based inference and ontologies for modelling and execution of clinical	2017

No	Authors	Title	Year
		practice guidelines: A case study on hypertension management	
41	Kobrinskii B.A.	Approaches to the construction of cognitive linguistic–image models of knowledge representation for medical intelligent systems	2016
42	Diriba C., Meshesha M., Tesfaye D.	Developing a knowledge-based system for diagnosis and treatment of malaria	2016
43	Soualmia L.F., Charlet J.	Efficient Results in Semantic Interoperability for Health Care. Findings from the Section on Knowledge Representation and Management	2016
44	Chen Z., Marple K., Salazar E., Gupta G., Tamil L.	A Physician Advisory System for Chronic Heart Failure management based on knowledge patterns	2016
45	Vilhena J., Vicente H., Martins M.R., Grañeda J.M., Caldeira F., Gusmão R., Neves J., Neves J.	A case-based reasoning view of thrombophilia risk	2016
46	Kahn C.E.	Transitive closure of subsumption and causal relations in a large ontology of radiological diagnosis	2016
47	Yu T., Li J., Gao H., Yu Q., Cui M.	Ontology-based modeling of clinical reasoning in traditional Chinese medicine	2016
48	Basso-Blandin A., Fontana W., Harmer R.	A knowledge representation meta-model for rule-based modelling of signalling networks	2016
49	Nusai C., Chankeaw W., Sangkaew B.	Dairy cow-vet: A mobile expert system for disease diagnosis of dairy cow	2016
50	Brugués A., Bromuri S., Barry M., del Toro Ó.J., Mazurkiewicz M.R., Kardas P., Pegueroles J., Schumacher M.	Processing Diabetes Mellitus Composite Events in MAGPIE	2016
51	Al-Rumkhani A., Al-Razgan M., Al-Faris A.	TibbOnto: Knowledge Representation of Prophet Medicine (Tibb Al-Nabawi)	2016
52	Neves J., Gonçalves N., Oliveira R., Gomes S., Neves J., Macedo J., Abelha A., Analide C., Machado J., Santos M.F., Vicente H.	Screening a case base for stroke disease detection	2016
53	Vilhena J., Vicente H., Rosário Martins M., Grañeda J.M., Caldeira F., Gusmão R., Neves J., Neves J.	Antiphospholipid syndrome risk evaluation	2016
54	Uma V., Aghila G.	Mining frequent arrangements and sequencing of events for diseases prognosis using reference event-based temporal relations	2016
55	Halpern Y., Horng S., Choi Y., Sontag D.	Electronic medical record phenotyping using the anchor and learn framework	2016
56	Dias S.B., Hadjileontiadou S.J., Diniz J.A., Barroso J., Hadjileontiadis L.J.	On modeling the quality of nutrition for healthy ageing using fuzzy cognitive maps	2016
57	Zamborlini V., Hoekstra R., Da Silveira M., Pruski C., Ten Teije A., Van Harmelen F.	Inferring recommendation interactions in clinical guidelines	2016
58	Putman T.E., Burgstaller-Muehlbacher S., Waagmeester A., Wu C., Su A.I., Good B.M.	Centralizing content and distributing labor: A community model for curating the very long tail of microbial genomes	2016
59	Naydanov C., Palchunov D., Sazonova P.	Development of automated methods for the critical condition risk prevention, based on the	2015

No	Authors	Title	Year
		analysis of the knowledge obtained from patient medical records	
60	Kostek B., Kupryjanow A., Czyżewski A.	Knowledge representation of motor activity of patients with Parkinson's disease	2015
61	Neves J., Martins M.R., Vilhena J., Neves J., Gomes S., Abelha A., Machado J., Vicente H.	A Soft Computing Approach to Kidney Diseases Evaluation	2015
62	Rahimi A., Parameswaran N., Ray P.K., Taggart J., Yu H., Liaw S.-T.	Development of a methodological approach for data quality ontology in diabetes management	2015
63	Fernandes F., Vicente H., Abelha A., Machado J., Novais P., Neves J.	Artificial neural networks in diabetes control	2015
64	Zhang Q.	Dynamic uncertain causality graph for knowledge representation and probabilistic reasoning: Directed cyclic graph and joint probability distribution	2015
65	Vybornova O., Fonteyne P.-A., Gala J.-L.	Ontology-based knowledge representation and information management in a biological light fieldable laboratory	2015
66	Minelli L., D'Ornellas M.C., Winck A.T.	Knowledge representation for lung cancer patients' prognosis	2015
67	Kharadkar R., Justus S.	Designing knowledge representation framework for ICD-10	2015
68	Rovetto R.J., Mizoguchi R.	Causality and the ontology of disease	2015
69	Neves J., Cunha A., Almeida A., Carvalho A., Neves J., Abelha A., Machado J., Vicente H.	Artificial neural networks in diagnosis of liver diseases	2015
70	Davis J., Sucar L.E., Orihuela-Espina F.	Treatment of disease: The role of knowledge representation for treatment selection	2015
71	Binder J., Boue S., Di Fabio A., Fields R.B., Hayes W., Hoeng J., Park J.S., Peitsch M.C.	Reputation-based collaborative network biology	2015
72	Neves J., Guimarães T., Gomes S., Vicente H., Santos M., Neves J., Machado J., Novais P.	Logic programming and artificial neural networks in breast cancer detection	2015
73	Nusai C., Cheechang S., Chaiphech S., Thanimkan G.	Swine-vet: A web-based expert system of swine disease diagnosis	2015
74	Rawte V., Roy B.	OBESTDD: Ontology based expert system for thyroid disease diagnosis	2015
75	Billis A.S., Papageorgiou E.I., Frantzidis C.A., Tsatali M.S., Tsolaki A.C., Bamidis P.D.	A decision-support framework for promoting independent living and ageing well	2015
76	Minutolo A., Esposito M., De Pietro G.	Design and validation of a light-weight reasoning system to support remote health monitoring applications	2015
77	Racoceanu D., Capron F.	Towards semantic-driven high-content image analysis: An operational instantiation for mitosis detection in digital histopathology	2015
78	Cardoso Coelho K., Barcellos Almeida M.	Representation of Biomedical Expertise in Ontologies: A Case Study about Knowledge Acquisition on HTLV viruses and their clinical manifestations	2015
79	Richard M., Aimé X., Krebs M.-O., Charlet J.	Enrich classifications in psychiatry with textual data: An ontology for psychiatry including social concepts	2015

No	Authors	Title	Year
80	Heß M., Kaczmarek M., Frank U., Podleska L.-E., Taeger G.	Towards a pathway-based clinical cancer registration in hospital information systems	2015
81	Melgar S H.A., Guillén D.S., Maceda J.G.	Ontology based inferences engine for veterinary diagnosis	2015
82	Ahmed I.M., Alfonse M., Aref M., Salem A.-B.M.	Reasoning Techniques for Diabetics Expert Systems	2015
83	Rodrigues P.P., Santos D.F., Leite L.	Obstructive sleep apnea diagnosis: the bayesian network model revisited	2015
84	Hema N., Justus S.	Conceptual graph representation framework for ICD-10	2015
85	Douali N., De Roo J., Sweetman P., Papageorgiou E.I., Dollon J., Jaulent M.-C.	Personalized decision support system based on clinical practice guidelines	2015
86	Dogmus Z., Erdem E., Patoglu V.	REHABROBO-ONTO: Design, development and maintenance of a rehabilitation robotics ontology on the cloud	2015
87	Economou G.-P.K., Sourla E., Stamatopoulou K.-M., Syrimpeis V., Sioutas S., Tsakalidis A., Tzimas G.	Exploiting expert systems in cardiology: A comparative study	2015
88	Sanchez E., Peng W., Toro C., Sanin C., Graña M., Szczerbicki E., Carrasco E., Guijarro F., Brualla L.	Decisional DNA for modeling and reuse of experiential clinical assessments in breast cancer diagnosis and treatment	2014
89	Younesi E., Ansari S., Guendel M., Ahmadi S., Coggins C., Hoeng J., Hofmann-Apitius M., Peitsch M.C.	CSEO - the cigarette smoke exposure ontology	2014
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121	Kamsu-Foguem B., Diallo G., Foguem C.	Conceptual graph-based knowledge representation for supporting reasoning in African traditional medicine	2013
122	Gordon C.L., Pouch S., Cowell L.G., Boland M.R., Platt H.L., Goldfain A., Weng C.	Design and evaluation of a bacterial clinical infectious diseases ontology.	2013

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126	Amin I.I., Kassim S.K., Hassanien A.E., Hefny H.A.	Formal concept analysis for mining hypermethylated genes in breast cancer tumor subtypes	2012
127	Moawad N., Liu K., El-Helly M.	Knowledge elicitation and representation in a normative approach-a case study in diagnosis of plant diseases in Egypt	2012
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153	Townsend C., Huang J., Dou D., Dalvi S., Hayes P.J., He L., Lin W.-C., Liu H., Rudnick R., Shah H., Sun H., Wang X., Tan M.	OMIT: Domain ontology and knowledge acquisition in microRNA target prediction (short paper)	2010
154	Möller M., Sintek M., Biedert R., Ernst P., Dengel A., Sonntag D.	Representing the international classification of diseases version 10 in OWL	2010
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156	Papageorgiou E.I., Froelich W.	Forecasting the state of pulmonary infection by the application of fuzzy cognitive maps	2010
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162	Taboada M., Meizoso M., Riaño D., Alonso A., Martínez D.	From natural language descriptions in clinical guidelines to relationships in an ontology	2010
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164	Haddad B., Awwad A.	Representing uncertainty in medical knowledge: An interval-based approach for binary fuzzy relations	2010
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175	Abidi S.R.	A conceptual framework for ontology-based automating and merging of clinical pathways of comorbidities	2009
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No	Authors	Title	Year
182	Lin Y., Sakamoto N.	Ontology driven modeling for the knowledge of genetic susceptibility to disease	2008
183	Rhaman M.K., Endo T.	Recurrent neural network classifier for three-layer conceptual network and performance evaluation	2008
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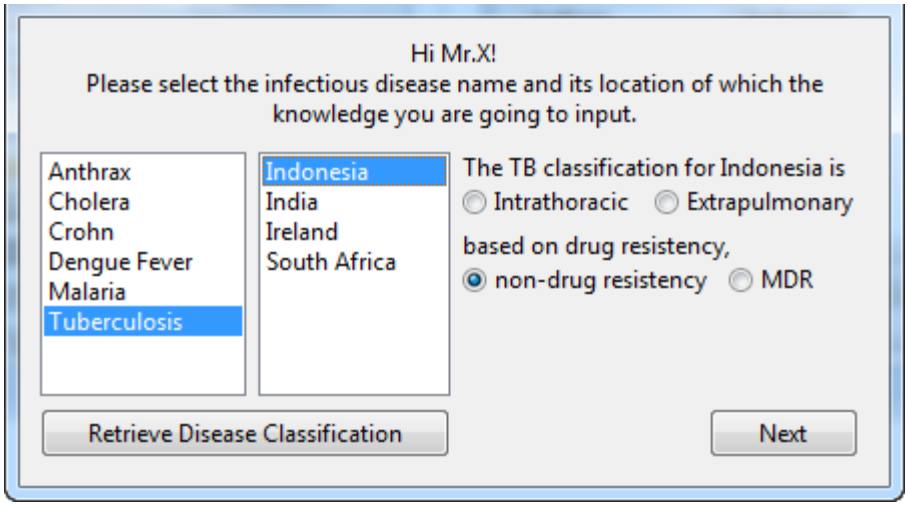
187	Scherer K.P.	Knowledge representations of constraints for patient specific IOL-destination	2008
188	Gudivada R.C., Qu X.A., Chen J., Jegga A.G., Neumann E.K., Aronow B.J.	Identifying disease-causal genes using Semantic Web-based representation of integrated genomic and phenomic knowledge	2008

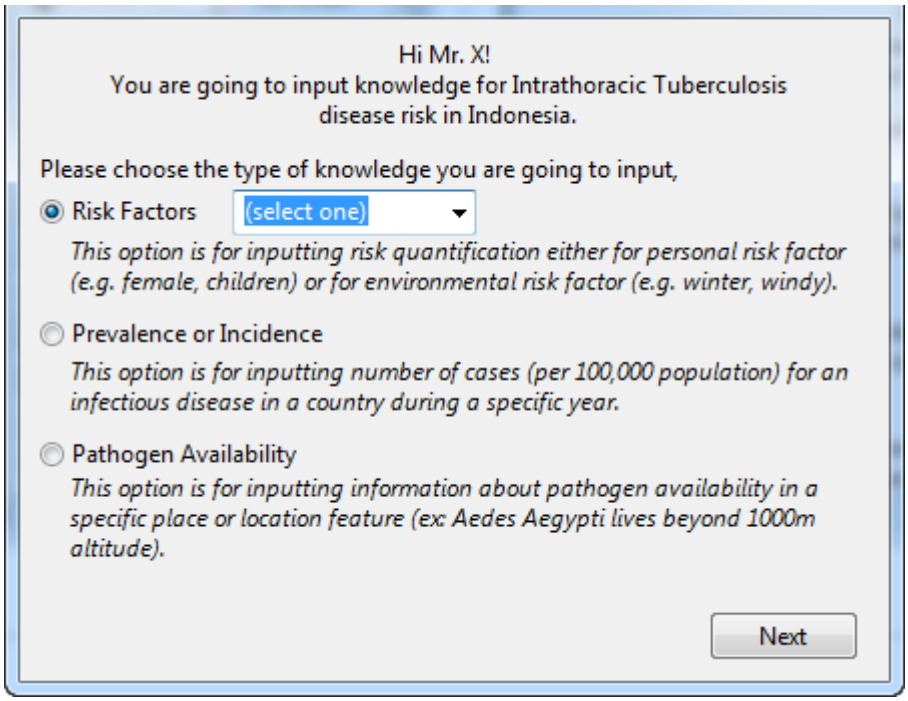
Appendix 2 – Design of the User Interfaces for Knowledge Encoding

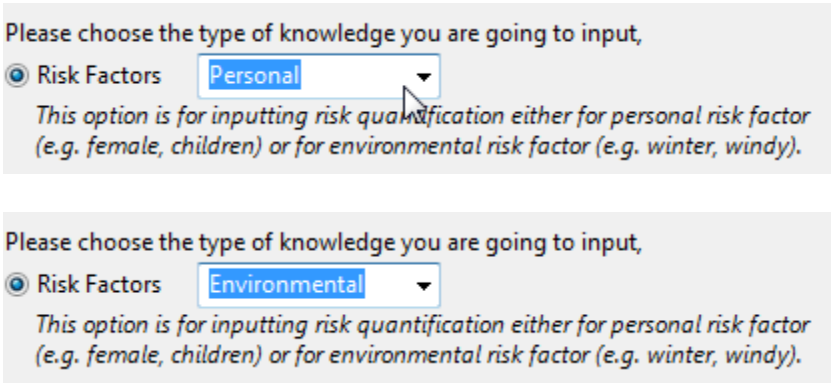
Design of the user interfaces for epidemiologists to encode their knowledge.

1. The opening user interface is designed to ask epidemiologists about the name of infectious disease (specific to the strain) and the country to which the knowledge to be entered applies.

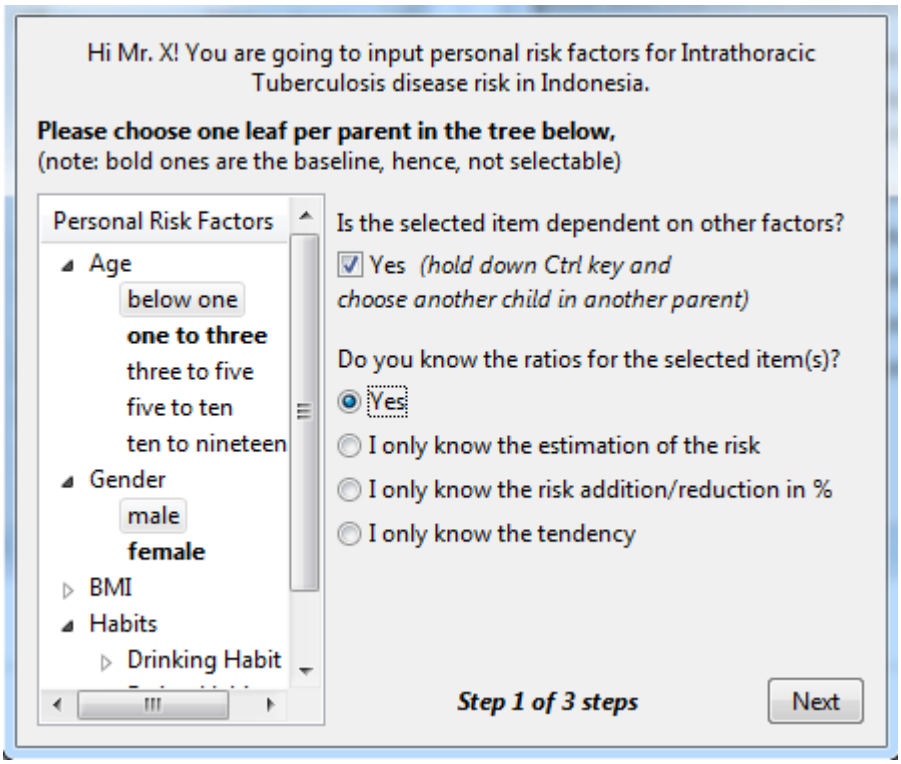


2. After selecting the infectious disease name and the country, the epidemiologist is asked whether the risk factors are related to *person* or *environment*.





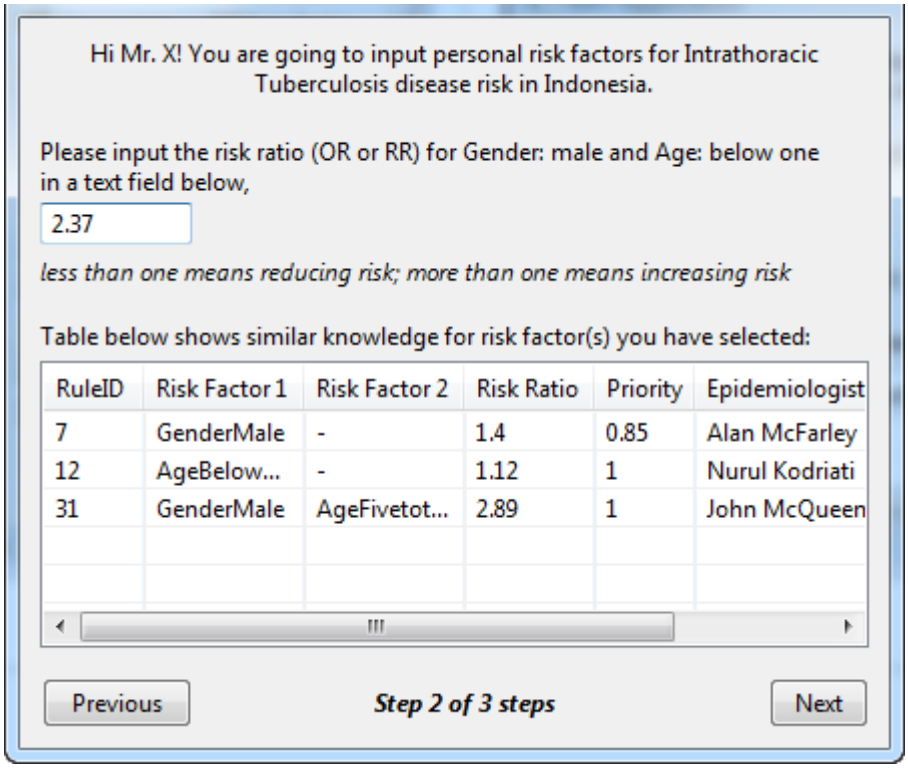
3. The user interface below shows the interface about *personal risk factors* and the type of the odds ratios they are going to encode (step 1). The tree on the left-side is the personal risk factors and their values. The epidemiologist is expected to choose from the non-bold ones to enter the risk ratios from them; the bold ones are the baseline whose risk ratios are always 1.



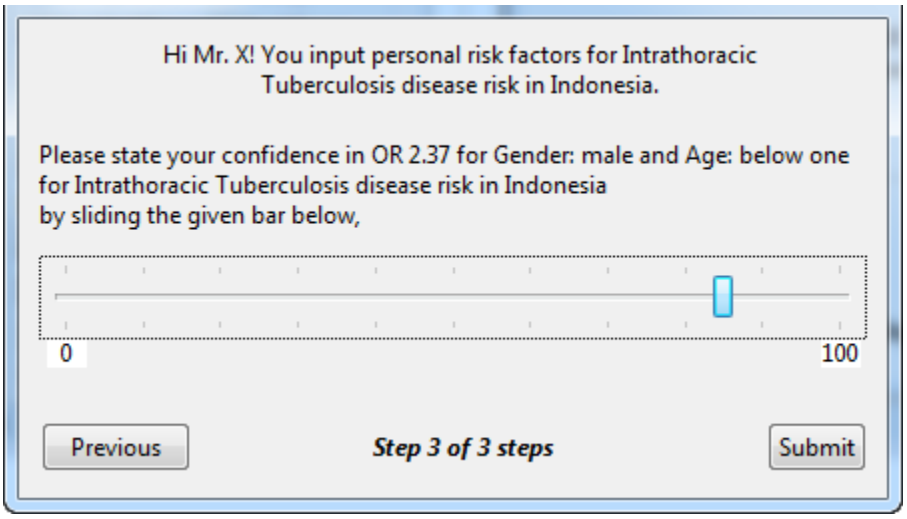
In the user interface above, there are four options provided to the epidemiologists. **Yes** option means the epidemiologists is ready to input the odds ratios of the chosen personal risk factors. This option will use the *real direct risk ratio* rule type to bind the OR with the chosen risk factors (e.g. male). **I only know the estimation of the risk** option means that the epidemiologist only knows the estimation of the risk (e.g. around 2 or around

1.5). This option will use the *vague risk ratio* rule type. **I only know the risk addition/reduction in %** option means that the epidemiologist will give either addition or reduction in percentage. This option will use the *real indirect risk ratio* rule type and convert the percentages into odds ratios. **I only know the tendency** option means that the epidemiologist will input the 'high', 'medium', 'low'. This option will use the *vague risk ratio* rule type. (Refer to section 5.4 for detail on IDR rule types)

4. After the epidemiologist chooses **Yes** option in the preceding dialog; an associated risk ratio (OR or RR) for the selected risk factors is then asked. In the same user interface, a table shows the available similar knowledge for the stored risk factors that have been selected in prior dialog.



5. Thereafter, the confidence level of the inputted knowledge is required from the epidemiologist. This ranges between 0 to 100; it will become the priority level of each rule. The priority level is assigned for every IDR rule to resolve the conflict (contradict and duplicate) between rules.


Hi Mr. X! You input personal risk factors for Intrathoracic Tuberculosis disease risk in Indonesia.
Please state your confidence in OR 2.37 for Gender: male and Age: below one for Intrathoracic Tuberculosis disease risk in Indonesia by sliding the given bar below,
0
100
Previous
Step 3 of 3 steps
Submit

Appendix 3 – CBMS Proceeding Publication

An article published in the Proceedings of 30th IEEE Computer-based Medical Systems (CBMS) International Conference. Thessaloniki, Greece, 22-24 June 2017. DOI: 10.1109/CBMS.2017.24

Personalization of Infectious Disease Risk Prediction:
Towards automatic generation of a Bayesian Network

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***Abstract*— Infectious diseases are a major cause of human morbidity, but most are avoidable. An accurate and personalized risk prediction is expected to alert people to the risk of getting exposed to infectious diseases. However, as data and knowledge in the epidemiology and infectious diseases field becomes available, an updateable risk prediction model is needed. The objectives of this article are (1) to describe the mechanisms for generating a Bayesian Network (BN), as risk prediction model, from a knowledge-base, and (2) to examine the accuracy of the prediction result. The research in this paper started by encoding declarative knowledge from the Atlas of Human Infectious Diseases into an Infectious Disease Risk Ontology. Automatic generation of a BN from this knowledge uses two tools (1) a Rule Converter generates a BN structure from the ontology (2) a Joint & Marginal Probability Supplier tool populates the BN with probabilities. These tools allow the BN to be recreated automatically whenever knowledge and data changes. In a runtime phase, a third tool, the Context Collector, captures facts given by the client and consequent environmental context. This paper introduces these tools and evaluates the effectiveness of the resulting BN for a single infectious disease, Anthrax. We have compared conditional probabilities predicted by our BN against incidence estimated from real patient visit records. Experiments explored the role of different context data in prediction accuracy. The results suggest that building a BN from an ontology is feasible. The experiments also show that more context results in better risk prediction.**

Keywords; Bayesian Network, Risk, Personalised Prediction, Infectious diseases

I. Introduction

Infectious disease is listed as a major cause of human morbidity [1]. However, many infectious diseases are avoidable. There is a need for accurate prediction related to infection risk [2] so that those at risk can take appropriate avoidance precautions. Infectious disease risk is the result of interaction between a person, pathogenic agent[15] and environment [3], The purpose of this research is to provide people with personalised information about their risk of being infected by a disease. The research faces several challenges such as (1) the continuous update of knowledge of predictors of risk, (2) the limited sources of experimental and observational data which are costly to retrieve in full, (3) the need for data, contexts and knowledge to describe a complex situation that resembles the real world about risk of getting an infectious disease, (4) establishing relevant contextual data from a user's details and location.

There has been extensive research in algorithms and techniques for risk prediction, such as fuzzy logic [4,5], Bayesian network [6,7], logistic regression [8-10] or combinations between them [11,12]. In general, a Bayesian network offers flexibility to incorporate dependencies between variables by defining probabilistic relationships [13], works under incomplete data [14] and its results are highly accurate compared to other prediction methods [5].

For this research, using a Bayesian Network approach, knowledge is represented as a network during the knowledge building phase. In this phase, person, season, weather and location risk factors are identified from declarative knowledge sources. Each factor is filled by a parameter value provided by a United Nations Data (UN) API. Then, predictors are transformed into BN nodes and states. After the network is created, the risk is calculated during the runtime phase. In this phase, person-related facts are given by the user. Weather and environment details are also retrieved based on user's location from OpenWeather API and GoogleMaps API. All the retrieved facts are used to yield the personalized infectious disease risk prediction.

A recent innovation of Bayesian Networks to model relationships between variables is Dynamic Bayesian Networks (DBN) [15]. A DBN approach has been used in

[15] Agent is a microorganism (e.g. fungus, bacteria, virus, prion, parasite or mix) that cause illness.

prediction [16-18] and diagnosing various problems [15] [19] in medical, supply chain and banking cases. Most of the temporal statements in a DBN are the result of machine learning [16-18] while a few of them use manual acquisition from domain experts [15]. A DBN is built by adding temporal dependencies to a static BN [19]. Machine learning approach works well when there is plentiful training data to construct stronger [17] and simpler static BN [18].

In this paper, we adopt the dynamicity concept of a DBN by designing tools that allow refining a BN based on newest information stored in a knowledge-base. However, for infectious disease risk prediction, we have well-established knowledge, encoded in sources such as the Atlas of Human Infectious Diseases [20], Centres of Disease Control and Prevention [21], Health Protection Surveillance Centre [22] and the Infectious Disease Ontology (Ruttenberg, Goldfain, Diehl, Smith, & Peters, 2016). Also, we use probability data summarised in the United Nations Statistical Division (UNSD) for demographic parameters and World Health Organization (WHO) for prevalence rates. Thus, machine learning is not appropriate. Instead we seek to directly convert these sources into a BN.

Rules are versatile and have been widely used in health systems [24]. In terms of knowledge-base, rules are usually built on the predefined knowledge structure (e.g. Ontology). This research started by gathering knowledge from various forms of knowledge sources to build an Infectious Disease Risk ontology as base of rules. Thereafter, a knowledge engineer adds disease-centred rules which explain about personal and environmental contribution to the specific infection risk. A tool to auto-create a BN based on the newest rules is then executed. This paper also presents mechanisms and evaluation of the BN by measuring the accuracy of the risk prediction. The risk prediction results are compared to ground truth taken from patient records collected by hospitals in a county in US during a specific time.

The rest of the paper is organized as follows. Section 2 explains an infectious disease risk prediction service where the BN is the key of the service; this is the grand design of the whole research. Section 3 describes the design of tools that are needed to build the system defined in Section 2. The tools are Rule Converter, Joint and Marginal Probability Supplier (JMP) and Context Collector. The Rule Converter and part of the JMP has been created and explained in another related-article [25]. Section 4 presents a process to prepare "ground truth" data used to measure the risk prediction result. Section 5 explains the method to examine prediction accuracy and presents the results. Section 6 reviews conclusions and suggests possible future work.

II. The Personalized Infectious Disease Risk Prediction Service

The infectious disease risk prediction web service is designed to serve client applications which advise users when and how to protect themselves from infections. The service computes a person's risk of being infected by a specified disease in a specific time frame (may differ for different infections), given their demographic details and location. The service uses the location to find weather, season and environmental features (e.g. swamp, forest, river). This process works at a runtime using the latest version of BN model.

This section explains the components of the service that are needed during knowledge building phase: (1) an ontology that describes Infectious Disease risk; (2) rules to represent the relationships between risk predictors and infectious diseases; the rules are taken from declarative knowledge in Atlas of Human Infectious Diseases (AHID) and represented in the Semantic Web Rule Language (SWRL); finally, (3) a BN representing the newest knowledge is constructed. The prediction accuracy of this BN is what is evaluated in the third section.

A. Overview of Ontology and Rule Structure

An Infectious Disease Risk (IDR) Ontology (shown in Figure 1) was developed to describe the interaction between human and environment in the context of infectious disease risk. Existing ontologies related to this subject have been studied and reused (Ruttenberg, Goldfain, Diehl, Smith, & Peters, 2016). Infectious Disease Ontology and Epidemiology Ontology were used as references. Since their focus are not on the *risk prediction* task, the IDR was created.

The relevant concepts were established by studying the AHID, identifying and organising all predictors which might be useful in determining a person's risk[16]. A knowledge-engineer then translated all predictors into classes and sub-classes in the IDR ontology, and rules defined over that ontology. Rules are used to describe predictors' contribution to a disease risk.

In the IDR, Environment is defined by three classes: Location, Climate and Feature details. These explain a person's surroundings, for example the weather and season at the access time, also the location and its feature details (e.g. near woods, river) at a given geocode. The Climate (e.g. weather, season) is retrieved from OpenWeatherMap API while the Feature details of a person's specific location is retrieved from GoogleMaps API.

A person is represented by his demographic details and his surroundings (exact position, nearest features and climate at the access time). In the IDR ontology, this is illustrated by three arrows pointing out of the Person class. An infectious disease risk is mostly determined by the disease prevalence in a specific location, its feature details and the climate condition. Some weather or season may boost or limit certain pathogens [26-30]. In figure 1, this is

[16] The result of the AHID study is stored in an online spreadsheet https://is.gd/IDcompletelist

illustrated by three arrows pointing in to the Infectious Diseases class. Then, a person's risk of being infected by a specified disease today, given their demographic details and environment is illustrated by a line pointing into Person class which is labelled 'risk of'.

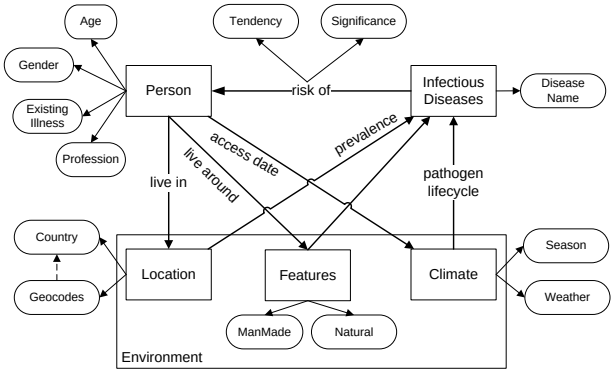

Figure 0.1 The infectious disease Risk (IDR) Ontology

Rules facilitate statements in first-order logic about how predictors impact infection risks. The common composition of rules is antecedent/predictor (A), consequent or infectious disease (B) and denoted as (A → B). An antecedent can be formed by individuals (in classes or sub-classes) and object/data properties with AND (^). The narrative knowledge written in AHID determines the individuals and their impact on a disease. The impact includes odds ratios and tendency. A knowledge engineer creates rules to represent all knowledge written in declarative source [20-22]. Table 1 shows sample rules encoding various tendency levels given by certain predictors of Anthrax risk (e.g. high, zero, x, y). For example, `increaseRisk(Anthrax, 200)` would mean the risk of Anthrax is doubled in Summer.

B. Overview of BN

The Bayesian Network is the core risk prediction model for the service. The BN is generated using Rule Converter that takes the newest knowledge in the IDR ontology and turns it into nodes, states and Conditional Probability Tables (CPTs) through several procedures. In figure 2, nodes are represented by a table, whereas states and CPTs are listed each node.

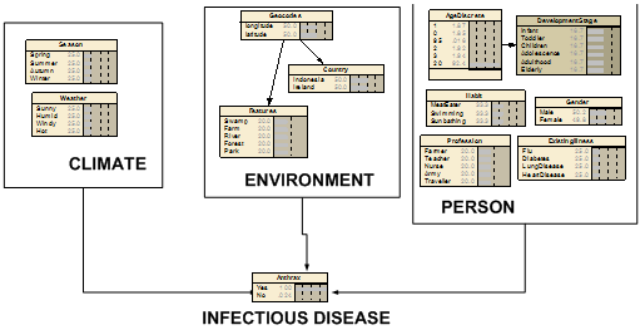

Figure 0.2. Structure of the Bayesian Network corresponding to Figure 1

To improve accuracy of prediction and as the knowledge develops, more predictors may need to be taken into consideration. In the example, to predict Anthrax risk, the major predictors like Age and Gender need to be taken into the initial risk prediction model. Then, as data and information become more available, more predictors like Profession, Habit, refine the initial model and make the Anthrax risk prediction become more accurate.

The BN consists of predictors (upper blocks), in three node groups: Person, Climate, and Environment, which contribute to determine the infectious disease(s) risk in a lower block. Nodes are taken from sub-classes, whereas states are taken from individuals in each of the sub-classes. Links between predictors within a group are taken from object or data properties, while links between predictor and infectious disease are taken from SWRL rules. Figure 2 depicts the generated BN from IDR in figure 1.

III. Design of Tools

The Rule Converter tool is used to translate the SWRL rules (Table 1) and IDR ontology (Figure 1) into a BN (Figure 2). Netica-J [31], a Java API for Bayesian Network modeller, is used to calculate the Infectious Disease risks.

TABLE 0.1 SAMPLE RULE ENCODING FOR ANTHRAX RISK

Declarative Knowledge	SWRLs
Farmers or people who live close to livestock farms are at high risk. Non-vegetarians are at medium risk.	`Person(?allpeople) ^ hasProfession(?allpeople, Farmers) -> hasRiskOf(Anthrax, high)`
	`Person(?allpeople) ^ liveAround(?allpeople, Farms) -> hasRiskOf(Anthrax, high)`
	`Person(?allpeople) ^ hasHabits(?allpeople, EatingMeats) -> hasRiskOf(Anthrax, medium)`
Anthrax pathogens are dormant during winter and the bacteria are naturally found in soil or grass in US.	`Person(?allpeople) ^ liveIn(?allpeople, US) ^ accessDuring(?allpeople, Summer) -> increaseRisk(Anthrax,x)`
	`Person(?allpeople) ^ liveIn(?allpeople, US) ^ accessDuring(?allpeople, Winter) -> setRisk(Anthrax,0)`

They are easily spread by the wind.	`Person(?allpeople) ^ liveIn(?allpeople, US) ^ accessDuring(?allpeople, Windy) ^ accessDuring(?allpeople, Summer) -> increaseRisk(Anthrax,y)`

Netica-J allows a developer to create, modify and connect the package with other APIs. By using this API, the web service will be flexible and easy to be maintained in the future. First, node and states labels are identified by querying sub-class and individuals for each sub-class in the generated RDF17. Then, object and data properties are queried to define links between predictor nodes. All properties related to rules are then retrieved to define links between predictors and associated infectious disease. These steps are used to define network properties and are executed using SPARQL18.

After knowing the network properties, several Netica built-in functions (presented in Script 1 and 2) are used to auto-create the BN structure.

```
Node  age = new Node ("Age", "Children, Working, Elderly", net);
Node  influenza = new Node ("Flu", "None, Low, High, Decline", net);
Node  location = new Node ("Region", "North, South, Central, East, West", net);
Node  anthrax = new Node ("Anthrax", "AtRisk, NotAtRisk", net);
```

Script 1 Code Example to generate BN nodes and states from IDR

```
anthrax.addLink(age);
anthrax.addLink(influenza);
anthrax.addLink(location);
```

Script 2 Code Example to generate BN link from IDR

The joint and marginal probabilities are the core of the risk prediction values which will be delivered to the clients. These probabilities are aimed to be populated in each CPT using a Joint and Marginal Probability Supplier (JMP).

To fill in the parent nodes' CPTs, data is downloaded from the United Nations Data web service in the form of SDMX[19]. Then the values are placed in each associated state in a node. Whereas, the child node's CPT is filled by taking numerical arguments and property predicates from the SWRL rules. The probability of a person with their demographic details for the risk of contracting Anthrax (e.g. 0.2, 0.25, 0.35) is assigned in each line in Script 3.

```
anthrax.setCPTable("Children, Low, North", 0.004, 0.996);
anthrax.setCPTable("Working, High, West", 0.0001, 0.9999);
anthrax.setCPTable("Elderly, None, South", 0.0008, 0.9992);
```

Script 3 Code Example to populate CPT

While the Rule Converter and JMP are used for preparing the BN using the newest knowledge, the Context Collector performs the personalization part of the service at runtime. The Context Collector collects facts given by the clients related to demographic and location details.

The collection of clients' facts (e.g. gender, age and current location) are taken as beliefs in the risk calculation process. The collections of a client's facts are exemplified as follows: 3-year old females located at (82.1673907, -168.9778799) are looking for the risk of Anthrax on that day (4th of July 2015). The current weather, season and country name will be automatically retrieved based on access date and time. Then, all the retrieved contexts will be used to calculate the Anthrax risk using Script 4.

```
location.finding().enterState (locationstr);
gender.finding().enterState(keyhumid);
age.finding().enterState(agestr);
double beliefA = anthrax.getBelief ("AtRisk");
```

Script 4 Code Example to enter the known facts into BN

IV. Validation

In order to prove the concept of using a knowledge-base to construct an associated BN, a validation step has been carried out. This research uses patient data to provide the conditional probabilities, whereas the predicted probabilities are generated from the BN. By measuring the distance between conditional probabilities taken from patient visit records and prediction probabilities, the accuracy of the prediction can be observed.

We used two datasets: patients' visit records (whose metadata is given in Table 2) and Anthrax outbreak dates[20] [27,28]. The patient data was taken from Emergency Department of health care units located in Allegheny County, Pittsburgh, US., The datasets present the visit records from January 2002 until December 2003 with 38,596 in total. The datasets contain demographic details, visit time, and the reported symptoms. These visit records might contain any possible diseases other than Anthrax, thus, another dataset is needed to help identify Anthrax cases within the dataset. The Anthrax outbreak detection project, WSARE[21], supplies this need by giving the estimation of Anthrax occurrences (date). Knowledge taken from an interview with a GP was also needed to determine the Anthrax key symptom (e.g. Rash).

TABLE 0.2 PATIENT METADATA

[17] RDF (Resource Description Framework) is a model for encoding semantic relationships between items of data so that these relationships can be interpreted computationally.

[18] SPARQL (Simple Protocol and RDF Query Language) is a standard query language to retrieve and manipulate data stored in RDF format.

[19] SDMX (Statistical Data and Metadata eXchange) is a standard designed to describe statistical data and normalise their exchange.

[20] Both datasets were downloaded from https://www.autonlab.org/autonweb/15959.html?branch=1&language=2 [Accessed 21/05/2015] but now the web is under construction.

[21] WSARE (What's Strange About Recent Events) is a project to early detection of disease outbreaks by searching a database of emergency department cases for anomalous patterns.

Contexts	Field Names	Data Types
Person	Age	child, adult, senior
	Gender	male, female
	Flu	none, low, high
Climate	Weather	hot, cold
	Season	winter, spring, summer, fall
	Date	mmm-dd-yyyy
Location	Region	N, W, C, E, S
Inf. Disease	Reported_symptom	none, respiratory, nausea, rash

Thus, conditional probabilities are estimated from the patient visit records by following these steps: (1) take the Anthrax outbreak data (date) and add the incubation (7 days) and prodromal periods (46 days), (2) select the patients who present to ER within that period (18,527 records), (3) select patients who have 'Rash' as reported symptom (3,112 records), (4) count Anthrax patients for each demographic combination (e.g. elderly females living in South Allegheny County) (5) divide the counts by the corresponding proportion of total population of the region. These probabilities are taken as "ground truth".

The BN for predicting Anthrax risk for this study was built from knowledge in AHID, medical journals, and an interview with a GP. Some marginal probability values (e.g. the probability of female children in a given location) were obtained from WHO and UNSD. To fill the CPTs, a state's value in each node must be acquired (see Figure 1). The Age CPT values were filled by summarizing age structure information from UNSD. Since Influenza was the only illness reported as occurring in conjunction with Anthrax - the risk of Anthrax increases when patients have Influenza – the Existing Illness node only handles Influenza. The basic knowledge about Anthrax risk and Influenza occurrence is acquired using a probability table of reported_symptoms [35-37] and interview with GP. Seasons are represented by Northern Meteorological term (e.g. Winter begins on 1 Dec). Interestingly, the ground truth data used astronomical seasons. To obtain Location context, a deeper investigation of location-related factors needed to be carried out. The marginal probability for the Location at which a Person lives (e.g. N, W, E, S) is obtained by summarizing the population distribution from Allegheny County Information Portal [29]. Another Location factor is the regional distribution of Anthrax (e.g. farms). The marginal probability was obtained by summarizing the number of farms per region and dividing by total farms in Allegheny. This information was manually obtained from Allegheny County Farm Land website [38]. The regional contributions to Anthrax environmental risks are estimated as North (30%), West (13%), South (26%), East (15%), Central (13%).

Infectious disease node (Anthrax) is a child node. Consequently, the child node contains all combinations of states from its parent nodes. Therefore, other information needed to build the Anthrax CPT includes:

a. Children are susceptible to Influenza more than Anthrax, while for a working Adult it is vice versa.
b. Influenza occurs in all seasons, while Anthrax is dormant in Winter and peaks in Summer.

By encoding these rules in the BN, the probability of a person, with his details and contexts, being infected by Anthrax in a specific given time and place, can be estimated.

IV. Evaluation Method and Results

To measure the performance of the BN prediction result, Root Mean Square Error (RMSE) is a common measurement used to assess the prediction accuracy [39]. The lower the errors the better the prediction. In this case, the BN prediction result will be compared against the "ground truth" derived from ED patient visit records (i.e. actual).

$$RMSE = \sqrt{\frac{\sum(prediction - actual)^2}{n}}$$

The RMSEs are categorised by each context in Table 3 below. Thus, n is the number of attribute value combinations.

TABLE 0.3 PREDICTION ACCURACY GROUPED BY CONTEXTS

Contexts	Context Details	RMSE	Norm RMSE	n
One-context Combination				
Person	Age	0.006006	0.698444	3
	Flu	0.000736	**0.287605**	4
	Age, Flu	0.004341	0.359710	12
Climate	Season	0.000910	0.386974	4
Location	Region	0.007810	0.458550	5
Two-context Combination				
Person – Climate	Age – Season	0.003114	0.314958	12
	Flu – Season	0.001610	0.331685	9
	Age, Flu – Season	0.004270	0.303918	27
Person – Location	Age – Region	0.024840	0.337633	15
	Flu – Region	0.007460	0.316629	20
	Age, Flu – Region	0.018278	**0.196407**	60
Climate – Location	Season – Region	0.004783	0.283449	20
Three-context Combination				
Person – Climate – Location	Age – Season – Region	0.015134	0.243600	60
	Flu – Season – Region	0.066149	0.197595	45
	Age, Flu – Season – Region	0.035340	**0.174622**	135

The RMSEs show that each context detail has good accuracy. But, to conclude which contexts give the best accuracy, the RMSE needs to be compared equally based on each of the context details' range. Range in each context details is not same, for instance, (Age, Flu) ranged from [0.0003, 0.01] and (Age, Flu - Season - Region) ranged from [0, 0.2023]. Thus, RMSE in each context detail (i) needs to be rescaled into the range 0-1 with a formula below.

$$NormRMSE_i = \frac{RMSE_i}{(MAX_i - MIN_i)}$$

By having all RMSEs normalized, context details that give best prediction in each context combination can be identified (written in bold in Table 3). For all context combinations, the inclusion of Influenza yields the best accuracy. Also, the Norm RMSEs show that inclusion of more contexts (the bottom of the Table 3) gives better predictions.

V. Conclusion

In this paper, we have introduced an ontology and several disease risk oriented rules: Infectious Disease Risk (IDR) Ontology and described tools which generate a BN from knowledge represented as SWRL rules and using the IDR ontology. We believe that such tools are necessary to allow epidemiologists to refine the prediction model as new data and knowledge of infectious diseases becomes available. As is confirmed by the experiments presented in Table 3, the more factors (contexts) that are taken into consideration, the better the Anthrax risk prediction.

Also in this paper, we have evaluated the accuracy of a BN for personalised Anthrax risk that encodes current knowledge. We compared conditional probabilities taken from patient visit records with BN predictions. We tested different combinations of context details, each of which came out with good accuracy. This suggests that building CPTs from knowledge as rules is a feasible option.

The infectious disease risk prediction system described here will be offered as a web service which advises users when and how to protect themselves from infections. The web service will be linked to several live APIs for supplying the current environmental data to compute a person's risk of being infected by a specified disease in a specific time frame given their demographic details and location.

The further work of this research covers: developing BNs for prediction of risk for other infectious diseases and measuring their accuracy; and prioritizing rules to deal with opposing, partially completed or out-of-date rules. Providing a tool to facilitate the system to auto-extract knowledge and convert it into IDR and rules is also a potential future work.

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References

[1] A. E. Aiello, A. M. Simanek, M. C. Eisenberg and A. R. Walsh, "Design and methods of a social network isolation study for reducing respiratory infection transmission: The eX-FLU cluster randomized trial," vol. 15, 2016.

[2] E. Fukuda, S. Kokubo and J. Tanimoto, "Risk assessment for infectious disease and its impact on voluntary vaccination behavior in social networks.," *Chaos, Solitons & Fractals,* vol. 68, pp. 1-9, 2014.

[3] L. J. Carpenito, Nursing Diagnosis: Application to Clinical Practice, Philadelphia: Wolters Kluwer Health, 2007.

[4] P. J. Giabbanelli, T. Torsney-Weir and V. K. Mago, "A fuzzy cognitive map of the psychosocial determinants of obesity," vol. 12, no. 12, 2012.

[5] N. Douali, H. Csaba, J. D. Roo, E. I. Papageorgiou and M.-C. Jaulent, "Diagnosis Support System based on clinical guidelines: Comparison between case-based fuzzy cognitive maps and bayesian networks," vol. 113, no. 1, 2014.

[6] H. M. Semakula, G. Song, S. P. Achuu and S. Zhang, "A Bayesian belief network modelling of household factors influencing the risk of malaria: A study of parasitaemia in children under five years of age in sub-Saharan Africa," vol. 75, 2016.

[7] M. Lappenschaar, A. Hommersom, P. J. F. Lucas, J. Lagro and S. Visscher, "Multilevel Bayesian networks for the analysis of hierarchical health care data," vol. 57, no. 3, 2013.

[8] K. Kengkla, N. Charoensuka, M. Chaichana and S. Puangjan, "Clinical risk scoring system for predicting extended-spectrum β-lactamase-producing Escherichia coli infection in hospitalized patients.," *The Journal of hospital infection,* pp. 49-56, 2016.

[9] E. J. Tomayko, B. A. Weinert, L. Godfrey, A. K. Adams and L. P. Hanrahan, "Using Electronic Health Records to Examine Disease Risk in Small Populations: Obesity Among American Indian Children, Wisconsin, 2007-2012.," vol. 13, no. 29, 2016.

[10] Q. Jiang, J. Zhou, Z. Jiang and B. Xu, "Identifying risk factors of avian infectious diseases at household level in Poyang Lake region, China," *Preventive Veterinary Medicine,* pp. 151-160, 2014.

[11] A. S. Fialho, S. M. Vieira, U. Kaymak and R. J. Almeida, "Mortality prediction of septic shock patients using probabilistic fuzzy systems," *Applied Soft Computing,* pp. 194-203, 2016.

[12] G. Koop, C. A. Collar, N. Toft, M. Nielen and T. v. Werven, "Risk factors for subclinical intramammary infection in dairy goats in two longitudinal field studies evaluated by Bayesian logistic regression," vol. 108, no. 4, 2013.

[13] D. Beaudequin, F. Harden, A. Roiko, H. Stratton and C. Lemckert, "Beyond QMRA: Modelling microbial health risk as a complex system using Bayesian networks," vol. 80, 2015.

[14] P. A. Aguilera, A. Fernandez, R. Fernandez, R. Rumi and A. Salmeron, "Environmental Modelling & Software Bayesian networks in environmental modelling," *Environmental Modelling and Software,* vol. 26, no. 12, pp. 1376-1388, 2011.

[15] T. Charitos, L. C. van der Gaag, S. Visscher and K. A. M. Schurink, "A dynamic Bayesian network for diagnosing ventilator-associated pneumonia in ICU patients," *Expert Systems with Applications,* vol. 36, no. 2, pp. 1249-1258, 2009.

[16] P. Panayiotis, H. X. Simon, A. Denise and B. A. T. Alex, "Prediction of lung cancer incidence on the low-dose computed tomography arm of the National Lung Screening Trial: A dynamic Bayesian network," *Artificial Intelligence in Medicine,* vol. 72, pp. 42-55, 2016.

[17] Q. Xiao, L. Xing and G. Song, "Time series prediction using optimal theorem and dynamic," *Optics,* vol. 127, p. 11063–11069, 2016.

[18] J. J. Dabrowski, C. Beyers and J. P. de Villiers, "Systemic banking crisis early warning systems using dynamic Bayesian," *Expert Systems with Applications,* vol. 62, pp. 225-242, 2016.

[19] H.-Y. Kao, C.-H. Huang and H.-L. Li, "Supply chain diagnostics with dynamic Bayesian networks," *Computers & Industrial Engineering,* vol. 49, pp. 339-347, 2005.

[20] H. F. L. Wertheim, P. Horby and J. P. Woodall, Atlas of Human Infectious Diseases, Oxford: Wiley-Blackwell, 2012.

[21] CDC, "Lesson 1: Introduction to Epidemiology," 18 May 2012. [Online]. Available: http://www.cdc.gov/ophss/csels/dsepd/ss1978/lesson1/section10.html.

[22] HSPC, "Health Protection Surveillance Centre," 2016. Available: http://www.hpsc.ie/NotifiableDiseases/NotifyingInfectiousDiseases/

[23] A. Ruttenberg, A. Goldfain, A. Diehl, B. Smith and B. Peters, "Infectious Disease Ontology," The National Center for Biomedical Ontology, 5 July 2016. [Online]. Available: http://purl.obolibrary.org/obo/ido.owl.

[24] A. Onisko, P. Lucas and M. J. Druzdzel, "Comparison of Rule-Based and Bayesian Network Approaches in Medical Diagnostic Systems," in *8th Conference on Artificial Intelligence in Medicine*, Portugal, 2001.

[25] R. A. Vinarti and L. M. Hederman, "A Performance Analysis of an Algorithm to Auto-create a Bayesian Network," in *Database and Expert System Applications*, Lyon, 2017.

[26] W. H. O. WHO, "Climate Change and Human Health - Risks and Responses Summary," World Health Organization, Geneva, 2003.

[27] X. Wu, Y. Lu, S. Zhou, L. Chen and B. Xu, "Impact of climate change on human infectious diseases: Empirical evidence and human adaptation," vol. 86, 2016.

[28] D. N. Fisman, "Seasonality of viral infections: Mechanisms and unknowns," *American Journal of Preventive Medicine,* vol. 18, no. 10, pp. 946-954, 2008.

[29] T. P. Monath and P. F. C. Vasconcelos, "Yellow fever," *Journal of Clinical Virology,* vol. 64, pp. 160-173, 2015.

[30] H. Yi, B. R. Devkota and J.-s. Yu, "Effects of global warming on mosquitoes & mosquito-borne diseases and the new strategies for mosquito control," *Entomological Research,* vol. 44, no. 6, pp. 215-235, 2014.

[31] Norsys, "Examples," Norsys Software Corporation, 1995-2017. [Online]. Available: https://www.norsys.com/netica-j/examples/SimulateCases.html.

[32] W.-K. Wong, A. Moore, G. Cooper and M. Wagner, "Bayesian network anomaly pattern detection for disease outbreaks," in *Twentieth International Conference on Machine Learning*, Washington, D.C., 2003.

[33] W.-K. Wong, A. Moore, G. Cooper and M. Wagner, "Rule-based anomaly pattern detection for detecting disease outbreaks," in *Eighteenth National Conference on AI*, Alberta, 2002.

[34] A. C. I. Portal, "Allegheny County Information Portal," Pittsburgh, Pennsylvania, US, [Online]. http://www.alleghenycounty.us/.

[35] F. Carrat, A. Tachet, C. Rouzioux and B. Housset, "Evaluation of clinical case definitions of Influenza: detailed investigation of patients during 1995 - 1996 epidemic in France," *Clinical Infectious Diseases,* vol. 28, pp. 283-290, 1999.

[36] A. S. Monto, S. Gravenstein, M. Colopy and J. Scweinle, "Clinical signs and symptoms predicting influenza infection," *Arch International Medicine,* vol. 160, pp. 3243-3247, 2000.

[37] D. N. Kyriacou, A. C. Stein, P. R. Yarnold and D. M. Courtney, "Clinical predictors of bioterrorism-related inhalational anthrax," *The Lancet,* vol. 364, pp. 449-452, 2004.

[38] A. Farmland, "Allegheny County Farmland Preservation Program," [Online]. Available: http://www.alleghenyfarmland.com/.

[39] E. W. Steyerberg, A. J. Vickers, N. R. Cook and T. Gerds, "Assessing the performance of prediction models: a framework," *Epidemiology,* vol. 21, no. 1, pp. 128-138, 2010.

Appendix 4 – MIE Book Section Publication

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A Knowledge-base for a Personalized Infectious Disease Risk Prediction System

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Abstract. We present a knowledge-base to represent collated infectious disease risk (IDR) knowledge. The knowledge is about personal and contextual risk of contracting an infectious disease obtained from declarative sources (e.g. Atlas of Human Infectious Diseases). Automated prediction requires encoding this knowledge in a form that can produce risk probabilities (e.g. Bayesian Network – BN). The knowledge-base presented in this paper feeds an algorithm that can auto-generate the BN. The knowledge from 234 infectious diseases was compiled. From this compilation, we designed an ontology and five rule types for modelling IDR knowledge in general. The evaluation aims to assess whether the knowledge-base structure, and its application to three disease-country contexts, meets the needs of personalized IDR prediction system. From the evaluation results, the knowledge-base conforms to the system's purpose: personalization of infectious disease risk.

Keywords. knowledge-base, rules, ontology, infectious disease, risk.

Introduction

We envisage a service which predicts a person's risk of contracting an infectious disease (ID) based on their personal attributes (age, diet) and their location (weather, geographical features). This service will supply risk predictions to advisor applications designed to help users take risk-reducing actions (e.g. wear a mask to avoid influenza during a windy week in autumn).

Knowledge about personal and contextual risk of contracting an ID is largely communicated in declarative form; general, stable knowledge is documented in the Atlas of Human Infectious Diseases (AHID) and similar books [1-3]; more specific and up to date knowledge is conveyed in epidemiology journals. Automated prediction requires encoding this knowledge in a form that can produce risk probabilities, such as in a Bayesian Network (BN). In previous work (Vinarti & Hederman, Personalization of Infectious Disease Risk Prediction Towards automatic generation of a Bayesian Network, 2017) we showed that we can yield accurate predictions by manually encoding the IDR knowledge in a BN. But this approach is not scalable to all IDs, regions and risk factors, nor maintainable to model new knowledge.

Rather than hardcoding current general knowledge for all IDs as a BN, we seek to facilitate the ongoing encoding by epidemiologists of up to date and region-specific ID risk. The knowledge is manually represented by experts as ID risk rules (e.g. a rule that says smoking can double Tuberculosis (TB) risk) defined over a special purpose ontology of ID risk. The knowledge-base (an ontology and collection of ID risk rules) is then automatically converted to a BN, using the BN builder algorithm described in [5]. This paper describes the design and evaluation of the knowledge-base.

Knowledge-base Design

This section describes the methodology used to design the knowledge-base. First, the ID literature was summarized to identify risk elements and quantitative forms of risk. From this summary, the 'backbone' of the

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IDR ontology: *person*, *infectious disease* and *environment* was created. Then, five IDR rule types were designed for representing quantitative forms of how risk factors affect an ID risk, defined over the ontology.

The role of the infectious disease risk (IDR) ontology is to capture and organize general IDR knowledge, for both the experts and the BN builder algorithm. An infectious disease is an illness caused by a specific pathogen that results from transmission from infected person, animal or its reservoir to a susceptible human host [9]. From this definition, three entities are involved: (1) pathogen's availability [10-14], (2) transmission method, and (3) susceptible host [15-17]. The compiled summary[23] consists of 234 unique IDs listed in these declarative sources [1-3]; it was clear that *demography*, *behavior* and *environment* are risk elements. Only a few IDs have a *genetic* risk element.

Three main ontology classes were created to the represent IDR 'backbone' specified in this collation: *Infectious disease* class represents an infectious disease name whose risk is being predicted. The *person* class accommodates the personal risk groups for the disease named in the *infectious disease* class. Risk groups describe susceptibility level of host by defining their *demographic* and *behavioral* risk elements. The e*nvironment* class explains the transmission method, pathogen reservoir and availability of the specified disease. This structure (Fig.1) represents a basic semantic structure for general IDs. By default, the ontology instantiated for each ID will contain this structure.

Knowledge about how these risk factors impact risk of a person contracting an ID is encoded as IDR rules over the IDR ontology. The IDR rules are designed to be easy for domain experts to use, while allowing automatic population to a BN's base reasoning. The ID risk knowledge is divided into: (1) *risk ratios* for each risk factor, (2) *prevalence values* for specified regions, (3) *pathogen activity* information during particular climate or location features (e.g. Aedes Aeqypti mosquitoes live at altitudes below 1000m). The IDR rules allow three quantitative forms of knowledge: risk ratios as numerical values, risk tendency as ordinal values, and risk addition or reduction as percentages. The IDR rule types to represent these forms are shown in Table 1, with some declarative examples.

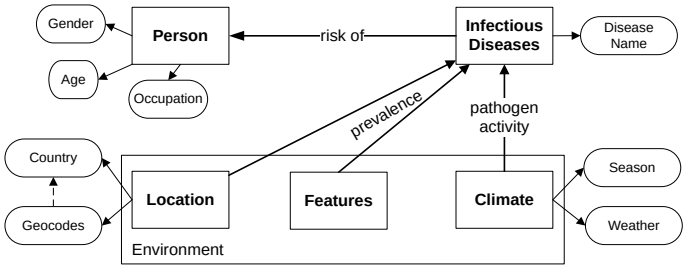

Figure 1. The IDR ontology basic structure with some samples of sub-classes (ellipses)

Table 1. The IDR rule types that encode quantitative knowledge forms over the IDR ontology, with examples.

Rule Types	Ontology *class* to encode	Value in data forms	Examples of declarative knowledge to encode
Real Direct Risk Ratios	{risk factors} in *person* or *environment*	Risk ratio in $0 < \mathbb{R} < \infty$	Males have 2.37 times more TB risk than females [19]
`Rule: Person(?all) ^ hasGender(?all, Male) -> alterRisk(TB, 2.37)`			
Real Indirect Risk Ratios	{risk factors} in *person* or *environment*	Risk ratio in %	Fish intake can reduce the TB risk by 50% [20]
`Rule: Person(?all) ^ hasEatingHabits(?all, fish) -> reduceRisk(TB, 50%)`			
Vague Pathogen Status	{location features and climate} in *environment*	Pathogen Activity in Inactive, LessActive, MoreActive	*Mycobacterium tuberculosis* is more active during humid condition [20]
`Rule: Environment(?all) ^ during(?all, humid) -> setPathogen(TB, MoreActive)`			

[23] The summary is available at http://is.gd/IDcompilation

Vague Risk Ratios	{risk factors} in *person* or *environment*	Risk ratio in High, Low, Medium, n-fold	People who have low body mass index are at a high risk [20]
`Rule: Person(?all) ^ hasBMI(?all, low) -> estimateRisk(TB, high)`			
Real Prevalence	{location and specific features} in *environment*	Prevalence rate in %K or %	TB prevalence in Africa is 395 per 100,000 population.
`Rule: Environment(?all) ^ hasCountryName(?all, Indonesia) -> setRisk(TB, 0.395)`			

Evaluation

Evaluation of the knowledge-base aims to assess whether the ontology and rules meet the requirement of the personalization system. Current approaches are evolution-based, logical-based, and metric-based [21]. This evaluation was based on the ontology and rule types described above being instantiated for three disease-country contexts: TB-Africa (34 rules), Dengue-Indonesia (23 rules) and Cholera-India (18 rules) representing air-borne, vector-borne and food/water-borne ID, respectively [18, 26, 27].

An evolution-based approach evaluates the ontology based on the changes that may happen. A good ontology is able to accommodate changes without reconstructing the basic ontology structure [21, 22]. In the IDR ontology, changes in domain happen when new risk factors are found which the knowledge engineer needs to represent in the ontology. Changes in conceptualization happen as result of different perspectives between experts. Informally, a GP and an epidemiologist were asked to advise on the IDR ontology: the changes were specific to risk details. Both kinds of changes occurred, but the ontology basic structure remains the same. Changes in the explicit specification occur when an ontology is translated from other knowledge representation forms. Since the IDR ontology was built from ID literature, these changes do not occur.

The logical-based approach evaluates IDR rules based on rule anomalies that usually occur in rule-bases. We used anomalies defined by COVER [23, 24]: unused inputs, unsatisfiable condition, unusable consequent, duplicate, circular and contradictory rules. All subclasses are created for the purpose of describing ID risk; therefore, the unused inputs anomaly cannot happen. All antecedents and consequents of IDR rules refer to different classes, thus, there are no circular rules. For the three disease-country contexts implemented, there are no unsatisfiable condition and unusable consequent anomalies. However, these may happen when the knowledge-base management system has no integrity checking (e.g. renaming the instances after defining rules). Contradictory rules happen when using more than one source to describe the IDR knowledge (e.g. one source says, males have higher TB risk than females, another says males have lower risk). In this case, the epidemiologist is asked to specify a priority [0-1]; the rules with the highest priority are used for BN building. Duplicate rules happen when the same risk ratio is expressed using different rule types (e.g. increase risk by 285% using Real Indirect Risk Ratios, and risk ratio 2.85 using Real Direct Risk Ratios type). A user interface with grouping feature will be designed to inform experts about similar pre-defined rules at the same disease-country context in the IDR knowledge-base; this should eliminate entry of duplicate rules.

The metric-based approach evaluates the ontology using OntoQA metrics [25]: class richness, class importance and relationship richness. The metrics evaluate the placement of instances within the ontology and the knowledge-base effectiveness. The class richness shows the percentage of unused sub-classes; the lower the percentage, the more effective the class. The class importance infers the importance based on the dispersion of number of instances. The relationship richness shows: (1) for the infectious disease class, how many rule types are utilized; (2) for the person and environment class, how many relations are used. Looking at class richness in Table 2, TB is affected by personal (no subclasses unused), rather than environmental risk factors (50% unused). The class importance confirms this finding as person class for TB is the highest (81.8%); and environment class for Cholera has the highest value (54.84%). With regard to relationship richness, the person and infectious disease class have higher percentage (66.67% and 80%) than environment class. This shows that the IDR is capable of personalized decisions; and four of five rule types are used to express IDR knowledge.

Table 2. Results of each OntoQA metric for each main class of the IDR[24]

Metrics	**Class**	**Results** (in %)

[24] Details of the TB-IDR, Dengue-IDR and Cholera-IDR can be found in https://is.gd/IDRforMIE

		Tuberculosis	Dengue	Cholera
Class Richness	Person	0/7 = 0	0/9 = 0	0/4 = 0
	Environment	2/4 = 50	0/8 = 0	0/7 = 0
	Infectious Disease	0/1 = 0	0/1 = 0	0/1 = 0
Class Importance	Person	27/33 = **81.8**	24/46 = 52.17	13/31 = 41.93
	Environment	5/33 = 12.15	21/46 = 45.65	17/31 = **54.84**
	Infectious Disease	1/33 = 3.03	1/46 = 2.17	1/31 = 3.22
Relationship Richness	Person	6/9 = **66.67**	9/17 = 52.9	5/11 = 45.45
	Environment	3/9 = 33.33	8/17 = 47.06	6/11 = **54.54**
	Infectious Disease	2/5 = 40	4/5 = **80**	4/5 = **80**

Conclusion and Further Works

This paper has presented a knowledge-base for encoding infectious disease risk knowledge which is used in a personalized IDR prediction system. The basic structure of the knowledge-base consists of an ontology and five rule types that represent IDR knowledge for all IDs. Three approaches to knowledge-base evaluation have been applied. Changes are unavoidable in the ontology evolution; however, none of the changes have impact on the ontology basic structure. Four out of six anomaly types are possible in the IDR knowledge-base, however, only one of them is caused by overuse of IDR rule types. Based on three tested cases, the metric-based approach shows that (1) most classes are effective, (2) the ontology is centralized at person and environment classes; both are equally important for modelling IDR knowledge, (3) high utilization in person and infectious disease classes confirm the system's purpose: personalization of ID risk prediction.

References

[1] H. F. L. Wertheim, P. Horby, Atlas of Human Infectious Diseases, Oxford: Wiley-Blackwell, 2012.

[2] CDC, "Emerging Infectious Diseases," Centers for Disease Control, 2017. https://wwwnc.cdc.gov/eid.

[3] WHO, "Infectious Diseases," WHO, 2017.http://www.who.int/topics/infectious_diseases/factsheets/en/.

[4] R. A. Vinarti and L. M. Hederman, "Personalization of ID Risk Prediction towards automatic generation of a Bayesian Network," in *IEEE Computer-based Medical Systems*, Thessaloniki, Greece, 2017.

[5] R. A. Vinarti and L. M. Hederman, "Introduction of a BN Builder Algorithm: Personalized Infectious Disease Risk Prediction," in *11th International Health Informatics, ACM*, Funchal, Madeira, 2018.

[6] J. Ralyte, X. Franch and S. Brinkkemper, "Advanced Information Systems Engineering," in *24th International Conference, CAiSE 2012*, Gdansk, Poland, 2012.

[7] A. Ruttenberg, A. Goldfain, A. Diehl, "Infectious Disease Ontology," The National Center for Biomedical Ontology. http://purl.obolibrary.org/obo/ido.owl.

[8] A. Third, "BioPortal: CARRE Ontology," 2014. https://bioportal.bioontology.org/ontologies/CARRE.

[9] M. L. Barreto, M. G. Teixeira and E. H. Carmo, "Infectious diseases epidemiology," *Journal of Epidemiology in Community Health,* vol. 60, pp. 192-195, 2006.

[10] N. C. Stenseth, N. I. Samia, "Plague dynamics are driven by climate variation.," vol. 103, no. 35, 2006.

[11] S. M. Upadhyayula, S. R. Mutheheni and H. K. Nayanoori, "Impact of weather variables on mosquitoes infected with Japanese encephalitis virus in Kurnool district, Andhra Pradesh.," vol. 5, no. 5, 2012.

[12] D. Onozuka and M. Hashizume, "Effect of weather variability on the incidence of mumps in children: a time-series analysis.," vol. 139, no. 11, 2011.

[13] W. F. Petersen, "Tuberculosis Weather and Resistance *," 1942.

[14] C. Lau, P. Weinstein and D. Slaney, "Imported cases of Ross River virus disease in New Zealand - a travel medicine perspective.," vol. 10, no. 3, 2012.

[15] A. Fares, "Seasonality of TB *of Global Infectious Diseases,* vol. 3, no. 1, pp. 46-55, 2011.

[16] H. W. Hethcote, "The Mathematics of Infectious Diseases*," vol. 42, no. 4, 2000.

[17] T. Ditsuwan, T. Liabsuetrakul and V. Chongsuvivatwong, "Assessing the Spreading Patterns of Dengue Infection and Chikungunya Fever Outbreaks in Thailand Using a GIS," vol. 21, no. 4, 2011.

[18] P. Gustafson, V. F. Gomes, C. S. Vieira, "TB in Bissau: incidence and risk factors in an urban community in sub-Saharan Africa," *International Journal of Epidemiology,* vol. 33, pp. 163-172, 2004.

[19] D. Guwatudde, M. Nakakeeto, E. C. Jones-Lopez, "TB in Household Contacts of Infectious Cases in Kampala, Uganda," *American Journal of Epidemiology,* vol. 158, no. 9, pp. 887-898, 2003.

[20] Q. Wang, Y. Liu, Y. Ma and L. Han, "Severe hypovitaminosis D in active TB patients and its predictors," *Clinical Nutrition,* pp. 1-7, 2017.

[21] S. Tartir, I. B. Arpinar and A. P. Sheth, "Ontological Evaluation and Validation," in *Theory and Applications of Ontology: Computer Applications*, Dordrecht, Springer, 2010, pp. 115-130.

[22] N. F. Noy and M. A. Musen, "The PROMPT Suite: Interactive Tools For Ontology Merging And Mapping," *International Journal of Human-Computer Studies,* vol. 59, no. 6, pp. 983-1024, 2003.

[23] A. Preece, "Evaluating verification and validation methods in knowledge engineering," 2001.

[24] A. Preece and R. Shinghal, "Foundation and application of knowledge base verification," *International Journal of Intelligent Systems,* vol. 9, no. 8, pp. 683-701, 1994.

[25] S. Tartir, I. B. Arpinar, M. Moore and A. P. Sheth, "OntoQA: Metric-based Ontology Quality Analysis," in *IEEE ICDM 2005 Workshop on Knowledge Acquisition.* Houston, Texas, 2005.

[26] A. Prayitno, A.-F. Taurel, J. Nealon, "Dengue seroprevalence and force of primary infection in urban Indonesian children population," *PLoS: Neglected Tropical Diseases,* vol. 11, no. 6, pp. 1-16, 2017.

[27] V. S. Kumar, S. Devika, S. George and L. Jeyaseelan, "Spatial mapping of acute diarrheal disease using GIS and estimation of relative risk using empirical Bayes approach," vol. 5, 2017.

Appendix 5 – HealthInf Proceeding Publication

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Introduction of a Bayesian Network Builder Algorithm

Personalized Infectious Disease Risk Prediction

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Abstract: We introduce an algorithm for auto-generating a Bayesian Network (BN) structure from a knowledge-base represented as an ontology with rules. The ontology and rules represent the assumptions of infectious disease risk in the epidemiology domain. The resulting BN will be the computational model for an infectious disease risk prediction service. The BN structure consists of one child node, to represent the chosen infectious disease, with multiple parent nodes to represent the contexts which affect infection risk. Thus, this BN generation algorithm is constrained to a relatively simple structure. The algorithm generates a BN using the API of BN modeler software, Netica-J. We evaluate two aspects of the generated BN: the network structure and the conditional probability tables (CPTs). The validation result shows that the algorithm generates an isomorphic BN compared with the ontology and the CPTs are populated with consistent ratios from epidemiological rules. Furthermore, the generated BN has resulted in a personalized infectious disease risk prediction based on the personal attributes and their environments.

1. Introduction

Risk prediction is an estimation of the chance of a person having an *adverse event*. Infectious disease risk prediction is considered as adverse event in this article since it is a major cause of deaths worldwide (Aiello, et al., 2016). Conventionally, infectious disease risk prediction deals with whether a new infectious disease outbreak is likely to happen (1), how fast an infection is likely to spread and the specific location affected (2), and how likely it is that certain measures will change the course of an epidemic if certain measures are taken (3). The system, for which this paper develops the algorithm, takes a different approach by calculating a personal risk of getting infected based on certain personal and environmental attributes (Rev2, 2017). Adding person properties to the prediction model allows it to account for human susceptibility to certain diseases, which differs from person to person (Shirai, et al., 2004) (Shirai, et al., 2002).

Besides personalization, environment also plays an important part in determining infection risk. The environment is represented by the user location and climate, including weather and season. Both environment and climate have been proven to have specific roles in boosting or limiting certain pathogens (Fisman, 2008) (Monath & Vasconcelos, 2015) (WHO, 2003) (Wu, et al., 2016) (Yi, et al., 2014). For example, children below five years old or male adolescents or soldiers who live in Indonesia or any countries between 30°N and 30°S are at twice the risk for Tuberculosis in summertime than others (Wertheim, et al., 2012). These predictors (*person*, *location*, *weather* and *season*) will be represented as knowledge to predict infectious disease risk in a person at a place and time.

As epidemiological knowledge develops, more predictors may need to be taken into consideration in order to improve accuracy of prediction. In the previous example, to predict Tuberculosis risk, the person predictors, demographic risk factors (e.g. *age*, *occupation* and *gender*), are included in an initial risk prediction model. While Tuberculosis risk is now well understood, knowledge of newer predictor, behavioural risk factor (e.g. *habit*), is discovered. Therefore, an infectious disease risk prediction

system that can be renewed to take account of new diseases, new predictors and new data is required.
Knowledge about infectious disease predictors is available from authorized health agencies (e.g. WHO, CDC) in the Atlas of Human Infectious Diseases (AHID) and epidemiological journals in declarative form. Ontologies are used to represent this knowledge (Ruttenberg, Goldfain, Diehl, Smith, & Peters, 2016) (Third, 2014). Meanwhile, the predicted risk values need to be presented in numerical form. So, both ontology and rules need to be converted into a quantitative model that calculates the risk prediction.

In this paper, we implement knowledge-driven model generation which focuses on Bayesian Networks (BN) as the generated model. We start by building a knowledge-base that becomes the main source of BN generation, Infectious Disease Risk Ontology (IDR), by accumulating the declarative knowledge manually. The IDR consists of general infectious disease risk knowledge structure and epidemiological rules. We introduce and validate an algorithm that allows the automatic generation of a BN, including populating the Conditional Probability Tables (CPTs), directly from the knowledge-base.

The structure of the paper is as follows. Section 2 discusses related work. Section 3 presents the main components of the Infectious Disease Risk Prediction service including the BN generation algorithm. Section 4 describes the evaluation of the generated BN. Section 5 presents the evaluation results. Section 6 discusses the limitations and the advantages of using this algorithm to generate a BN. Section 7 summarizes the contributions of the current work and outlines future plans.

2. Related Work

Knowledge-driven model generation has several advantages in the context of continuously growing knowledge rather than the former approach, data-driven model generation. The knowledge-driven system facilitates experts to contribute their best knowledge without ruling out data and the given contexts (Baumeister & Striffler, 2015). The knowledge-driven modelling approach relies mainly on the given domain knowledge (Fan, et al., 2015). Domain knowledge for this research (i.e. infectious disease risk) is available from various knowledge sources and structures. Although some basic knowledge structure is provided by BioPortal in Ontology form (e.g. Epidemiology Ontology – EPO, Infectious Disease Ontology – IDO and ClinicAl Risk factoRs, Evidence and observables – CARRE) (Ruttenberg, Goldfain, Diehl, Smith, & Peters, 2016) (Third, 2014), a significant body of relevant knowledge is gathered from the Atlas of Human Infectious Diseases in declarative form (Wertheim, et al., 2012).

Some quantitative models, in the public health risk prediction domain, allow this knowledge incorporation, such as Rule-based prediction model, Logistic Regression, Fuzzy Cognitive Map and Bayesian Networks (BN) (Lopman, et al., 2009) (Blake, et al., 2016) (Jiang, et al., 2014) (Semakula, et al., 2016) (Onisko, et al., 2001) (Jombart, et al., 2014) (Austin & Onisko, 2015) (Douali, et al., 2014) (Kunjunninair, 2012). BNs are able to incorporate personal factors as nodes and connect to other nodes without difficulties (e.g. data training, model fitting). Also, BNs have been used in both personalization and risk prediction research (Gao, et al., 2010).

Our previous work looked out at whether BNs that built from declarative knowledge gathered from AHID, CDC, and WHO fact sheets had a promising risk prediction result (Vinarti & Hederman, Personalization of Infectious Disease Risk Prediction Towards automatic generation of a Bayesian Network, 2017). The paper predicted risk prediction result in Anthrax disease compared with real patient data records. The Anthrax BN was built manually, neither learnt from historical datasets nor generated automatically by a specific mechanism – which this paper now presents.

```
Rule1: The type of neighbourhood someone
lives in influences whether their house will
be burglarized.
IF: Neighbourhood(x): {bad, average, good}
THEN: Burglary(x): {true, false}
Matrix: (6 entries)

Rule2: Both a burglary and an earthquake can
cause someone's alarm to go off.
IF: Burglary(x): {true, false} AND
EarthQuake: {tremor, moderate, severe}
THEN: Alarm(x): {true, false}
Matrix: (12 entries)

Rule2: An earthquake is often reported on the
radio.
IF: EarthQuake: {tremor, moderate, severe}
THEN: Radio: {true, false}
Matrix: (6 entries)

.....
```

Figure 1. Probability Logic Knowledge-base. (Haddawy, 1994)

Generating a Bayesian Network from a probabilistic knowledge-base was pioneered by Peter Haddawy

(Haddawy, 1994). He used Horn clauses to form a probabilistic knowledge-base (Figure 1). The knowledge-base used rules to define predictors, and matrix to define conditional probability tables. By using these clauses, he generated an isomorphic Bayesian Network automatically. Whereas Haddawy used random values in order to generate the BN, this article seeks to populate these tables with appropriate conditional probability values.

3. The Personalized Infectious Disease Risk Prediction

The infectious disease risk prediction web service is designed to serve client applications which advise users when and how to protect themselves from infections. The service computes a person's risk of being infected by a specified disease today (or this week or season depending on the disease), given their demographic details and location. The service uses geocodes to find weather, season and location features (e.g. swamp, forest, river). For example, a 3-year old female located at (40.440625, -79.995886) is looking for their risk of Anthrax on the day (04/07/2017, 07:55:45).

This section explains the components of the service that are needed for predicting infectious disease risk: (1) an ontology and rules that describes the main elements of infectious disease risk to represent the relationships between risk predictors and a disease; (2) a main engine to predict the risk, a quantitative prediction model (BN), which represents the newest knowledge for each infectious disease; (3) packages that support the BN to predict accurately (weather, location APIs, health surveillance APIs and simple functions to accommodate inputs/outputs). The service will contain multiple independent BNs, one per infection.

When epidemiologists find new knowledge or new predictors about infectious disease risk, new objects will be added to the ontology and rules, and the BN model needs to be renewed. The renew process makes use of the algorithm proposed in this article to auto-generate the BN so that the prediction model is isomorphic with the knowledge-base that stores newest information. In this system, the generated BN is isomorphic if all individuals and sub-classes in the IDR Ontology have been transformed. The individuals become the states and their sub-classes become their nodes in the BN.

At runtime, the Live APIs tier collects current contexts of the environment based on user's location and sends the retrieved values to the Context Collector in the Logic tier. The BN model, also in the Logic tier, takes the person's demographics and values from the Context Collector as inputs (i.e. beliefs). Thereafter, the BN uses the CPT to yield the risk prediction which is passed to the client through the Presentation layer. In Figure 2, the separation between runtime (left-side) and BN build time (right-side) is illustrated by a dashed line.

The BN used at runtime is initially generated, and further rebuilt every time there is something new added to the knowledge-base (ontology and rules). In order to generate a BN, nodes and states need to be extracted from the ontology. Also, the child node's CPT needs to be populated by computing numerical values from the rules. This is the main role of the BN Builder package. For parent nodes, marginal probability data is retrieved from sources such as the United Nations (UN) Data API by MarginalProb Supplier. Then, they are loaded to form parent nodes' CPTs.

3.1. Structure of the Knowledge Base and the Generated Bayesian Network

An ontology is used to represent the relationship between predictors and infectious disease risk. Existing ontologies related to this subject and some declarative knowledge sources have been studied and reused to create the Infectious Disease Risk (IDR) ontology (Figure 3). The main classes (e.g. Person, Infectious Disease, Environment) are denoted by rectangles. Sub-classes represent the risk factors of an infectious disease for each class (e.g. *age, gender* in a *person*); they are denoted by ellipses. Individuals are the instances of the sub-classes (e.g. *female* and *male* in *gender*).

Some individuals are different for each disease, for example, *age* in Tuberculosis will have different categorization with *age* in Anthrax. But, some other individuals are same (e.g. *female* and *male* as instances of *gender*). The individuals are not illustrated in Figure 3. The IDR ontology is used to support epidemiological rules in Semantic Web Rule Language (SWRL). The SWRL rules refer to the IDR classes, sub-classes and individuals.

Rules are used to define statements about the factors of a person, and their environment, that affect whether they get infected by a disease. These rules are manually encoded from declarative knowledge sources: Atlas of Human Infectious Disease (AHID), Centres of Disease Control and Prevention (CDC).

They are written in SWRL form by a knowledge engineer using numerical inputs (x1, x2, y, z in Table 1) from Health Surveillance Reports and journals related to epidemiology of infectious diseases.

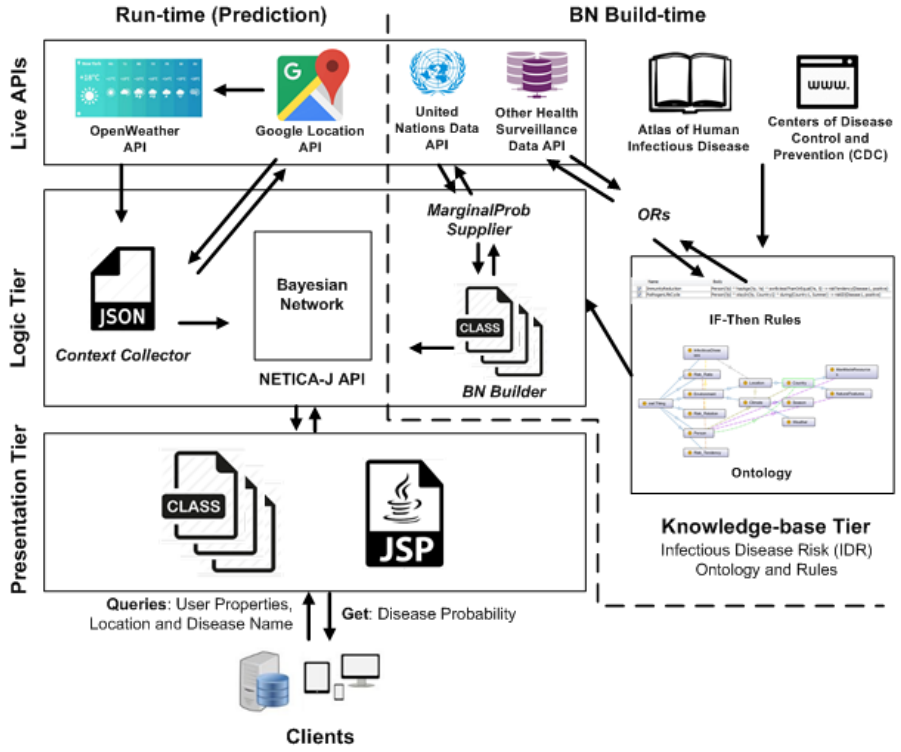

Figure 2. The Infectious Disease Risk Prediction Service Architecture.

The common composition of rules is antecedent (A), consequent (B) and denoted as (A → B). The antecedent covers the predictors and the consequent covers the disease. CARRE project and its related publications introduce the clinical risk model to describe a disease risk in a person (Third, 2014). They involved risk quantification as risk ratio (i.e. Odds Ratio – OR or Relative Risk – RR) for each risk factor. Therefore, for the algorithm introduced in this research, each antecedent load personal attribute(s) as risk factor (e.g. *vegan*, *farmers*, or *adult* in Table 1). Whereas its consequent has two components: the disease name and the numerical value that shows the significance of the risk factor to the infectious disease risk. The numerical value is either an OR/RR or a prevalence rate or zero (in the case of pathogen dormancy).

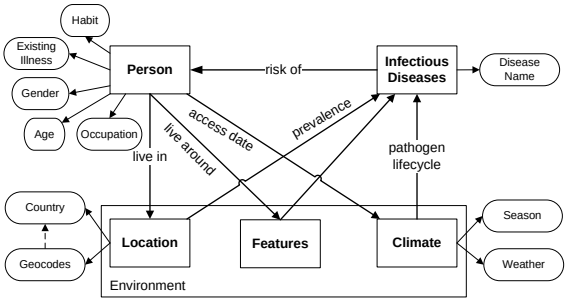

Figure 3. The Generic Infectious Disease Risk Ontology (IDR).

For Anthrax, these numerical values are expressed in %K units (K=0.001), which show the risk of a disease per 100,000 population in a particular location. Other diseases may use different units. These values will be inputted by the epidemiologist by identifying them from the declarative knowledge sources. Later, the CPT will be populated from these values by following several procedures and computations. The

computation is embedded in the BN generation algorithm.

There are three types of rule for representing infectious disease risk: the first, stores OR values for each state, the second type stores prevalence or incidence rate for each disease, and the third type describes the pathogen availability in specific conditions (e.g. location, weather, season). The key difference between OR and prevalence-type rules is the predicate at the consequent part. An OR-type rule has alterRisk while the prevalence-type rule has setRisk predicate (bold letters in Table 1). Therefore, one disease ontology has multiple OR-type rules and at least one prevalence-type rule.

In this version of algorithm, the pathogen-type rule uses the same predicate as prevalence-type rule (setRisk), but the numerical value of the pathogen-type rule is zero. This follows the assumption that the pathogen is always considered as active unless there is a declaration of inactivity (dormancy).

Table 0.4: Sample SWRL Rule Encoding for Anthrax Risk.

Simplified Declarative Knowledge	Rules	Rule Type
Anthrax prevalence in the US is 12 per 100,000 population per year.	`Person(?all) ^ liveIn(?all, US) -> setRisk(Anthrax, 1.12)`	Prevalence
An analysis of seven studies estimated a pooled odds ratio for Anthrax risk in non-vegan compared with vegan is doubled.	`Person(?all) ^ hasHabits(?all, vegan) -> **alterRisk**(Anthrax,x1)` `Person(?all) ^ hasHabits(?all, carnivore) -> **alterRisk**(Anthrax,x2)`	OR
Farmers are at the highest risk.	`Person(?all) ^ hasOccupation(?all, farmers) -> **alterRisk**(Anthrax,y)`	OR
Children are at less risk of Anthrax compared to Adult or Elderly	`Person(?all) ^ hasDevelopmentStage(?all, Children) -> **alterRisk**(Anthrax,z)`	OR
Anthrax pathogens are dormant during winter.	`Person(?all) ^ accessDuring(?all, Winter) -> **setRisk**(Anthrax,0)`	Pathogen

The numerical values which are stored in the rules bring important epidemiological parameters to populate the child node's CPT. Meanwhile, these rules depend on the ontology structure (classes, sub-classes and individuals). So, both ontology and SWRL rules inside the knowledge-base tier need to be transformed carefully into a prediction model (Bayesian Network).

3.2 The BN Builder Package

A basic BN consists of *parent* and *child* nodes. In this system, the predictors become parent nodes and the disease whose risk is being predicted becomes the child node. Each node contains a CPT which consists of states and probabilities. Parent nodes' CPTs need marginal probability values (e.g. the probability of a person being a child). These values are loaded from UN Data API. The child node's CPT stores all parent's states combinations and their conditional probabilities (e.g. the probability of a female child getting Anthrax).

The BN Builder package aims to generate code to call Netica-J built-in functions that generate an isomorphic BN from the knowledge-base. The BN Builder has two tasks: (1) create the network structure, and (2) fill in the parent and child nodes' CPTs. To fulfil these objectives, two algorithms are introduced in this article: Network Construction and CPT Population algorithm. The Network Construction algorithm is used to create the BN structure while the CPT Population algorithm is used to transform rules into child node's CPT. Both algorithms use intermediate representations (Table 2 and Table 3 in the next sub-section).

It is also useful for the algorithm to have a specification of impossible combinations of parent nodes' states as done by (Das, 2004). For example, (e.g. *pregnant – male*, *male – pregnant*). By having this, some unnecessary work can be reduced in the later stage (CPT Population).

Software for managing the knowledge-base, Protégé, is used to create the IDR and write the SWRL rules. In general, there are two ways of using an ontology in the context of knowledge-driven model generation: exporting it to RDF representation and using XML technology to query the RDF, or directly by querying the knowledge-base using SPARQL. This research uses XPath to retrieve items in the knowledge-base then store them into intermediate representations.

3.2.1 Intermediate Representation of Network Structure and Rules

The creation of a network structure needs some information needed to create a BN structure. The information is obtained from the knowledge-base representation, RDF (Figure 4). XPath queries are then used to select the items by locating their paths in the RDF.

```
<Object Properties>
<Data Properties>
<Classes>
<Individuals>
<Rules>
        <body>
                <args>
        <head>
                <args>
```

Figure 4. RDF Structure.

The bold tags show the sections needed to build a BN. The information about nodes and states to construct a BN are stored in <Individuals> tags, while resources about OR, prevalence and other information needed to populate child node's CPT are stored in <Rules> tags. An example of a line in <Individuals> expressing a state named *female* belonging to a node named *gender* is given below.

```
IDR:Female rdf:type owl:NamedIndividual ,
IDR:Gender .
```

XPath queries are used to obtain all nodes and states from the <Individuals> tags (given below). The results of these queries are then stored in the intermediate representation in a fixed order as presented in Table 2.

```
nodesQuery = "/rdf:RDF/owl:NamedIndividual/
rdf:type/@rdf:resource";
statesQuery = "/rdf:RDF/owl:NamedIndividual/
@rdf:about";
```

Table 2: Sample Content of the Nodes and States.

Order	Nodes	States
1	Age	Child Adult Elderly
2	Gender	Female Male
3	Occupation	Farmers Soldiers

For the rules, the intermediate representation uses five components: name, disease, attribute value, predicate and the numerical value (Table 3). Since our rules each only refer to one attribute, this representation is sufficient.

Table 3: Sample of the Rule Components.

name	disease	attribute value	predicate	num. values
AntLoc1	Anthrax	US	set	1.12
AntEnv3	Anthrax	Winter	set	0
AntPrson2	Anthrax	Children	alter	0.85

Table 3 shows examples of Prevalence, Pathogen and OR-type rules, respectively. Each numerical value represents OR, prevalence rate or pathogen dormancy depending on the rule type. To fill Table 3, antecedent and consequent of a rule is identified by swrl:body and swrl:head tags, respectively. The queries are given below Table 3.

```
ruleName = "/rdf:RDF/rdf:Description/
rdfs:label";
ruleDisease = "/rdf:RDF/rdf:Description/
swrl:head/.//swrl:argument1/@rdf:resource";
ruleAtt = "/rdf:RDF/rdf:Description/
swrl:body/.//swrl:argument2/@rdf:resource";
rulePredicate = "/rdf:RDF/rdf:Description/
swrl:head/.//swrl:propertyPredicate/@rdf:res
ource";
ruleNum = "/rdf:RDF/rdf:Description/
swrl:head/.//swrl:argument2";
```

These intermediate representations are used to construct the Network and populate the child node's CPT as explained in the following sub-sections.

3.2.2 Constructing the Network

A BN structure consists of *nodes* and *states*. Referring to the Table 2 as example, *age*, *gender*, *occupation*, and *Anthrax* are nodes, while the items on the right-side column are their states. These details are obtained from the intermediate representation (Table 2). For the disease prediction BN, the predictors (*age*,

gender, *occupation*) form the parent nodes, and the disease (e.g. *Anthrax*) is the child node.

In order to construct the network, the BN Builder closely follows the Netica-J procedure in Pseudocode 1 (Norsys, 1995-2017). The bold items represent the automation this paper presents.

Pseudocode 6: Network Construction

```
1.  Create and set the Netica environment
2.  Declaration and assignment of a child
    node
3.  Declaration of parent nodes
4.  Loading resources from intermediate
    representations
5.  foreach node do
    a. Assign each parent node using three
       input parameters: node name,
       stateString (result from Statenames
       Concatenation), Netica environment
    b. Construct the marginal probability
       of each parent node using two input
       parameters: node name, MarginalProb
       array (result from MarginalProb
       Concatenation)
    c. Save the order of parent node into
       nodequeue
    d. Connect parent with child node
6.  Construct the conditional probability
    of the child node using nodequeue.
7.  Write the network into Netica readable
    file (.dne file)
```

The automation of Pseudocode 1 begins with parent node assignment (line 3 and 5). The Netica-J built-in function to assign a node is given as follows:

```
Node temporary = new Node (String nodename,
String statenames, net);
```

The declaration of a temporary node starts in line 3 and it is initialized with null value. In line 5a, the temporary node will be assigned with real nodes and states taken from the intermediate representation. The assignment of this node is called for as many nodes as found in the Table 2.

Pseudocode 7: Statenames Concatenation

```
1.  Create a stateString
2.  foreach state in a parent node do
    a. Append the the state name to
       stateString, followed by a comma.
3.  end
```

Pseudocode 8: MarginalProb Concatenation

```
1.  Create a MarginalProb array
2.  foreach state in a parent node do
    a. Append the MarginalProb array with
       related marginal probability.
3.  end
```

Marginal probabilities, for example the ratio of Male to Female in a specific region, are provided by the MarginalProb Supplier package (see Figure 2). Information to fill MarginalProb is usually found in UN Data API. In Netica, the assignment of the marginal probability to a node uses a statement:

```
parentNode.setCPTable(MarginalProb[]);
```

However, if no marginal probability data is provided, Netica-J, by default, assigns equal fractions based on number of states in the node. For instance, the default MarginalProb of a two-state node is <0.5, 0.5>.

Once the nodes and their states are defined, the order of parent nodes must be saved (line 5c) before connecting the parents with child node (line 5d). The order will be used by CPT Population algorithm. Line 6 in Pseudocode 1 handles the CPT population for the child node. The details are explained in the next sub-section.

3.2.3 Populating the CPT

The child node's CPT is calculated from the numerical parameters in the intermediate representation of rule (Table 3). This involves first, generating all combinations of the relevant states and then computing the conditional probability for each combination. See Figure 9 for sample extract of the CPT for Anthrax in Netica.

To illustrate, the needed state combinations are presented in Figure 5. The number of combinations is $\prod_{i=1}^{n} s_i$ where s_i is number of states in node i, and n is number of nodes.

```
Age, Gender, Occupation
Children, Male, Farmers
Children, Male, Soldiers
Children, Female, Farmers
Children, Female, Soldiers
Adult, Male, Farmers
...
```

Figure 5 Sample of the StateCombination.

To calculate a conditional probability (`condProb`), for a state combination, we apply Pseudocode 4 using the intermediate representation for rules as in Table 3. The algorithm can distinguish rule types as follows: pathogen-type rules are those where the predicate is `setRisk` and the value is 0; prevalence-type rules are those whose predicate is `setRisk` and the value is non-zero; OR-type rules are those with predicate

`alterRisk`. Then, the numerical values of each rule type are used in different part in the process of populating the CPT.

The algorithm checks for conditions that result in zero disease risk (line 2 in Pseudocode 4): either there is matching a pathogen-type rule attribute or there is an impossible combination. By filtering these conditions upfront, only combinations that need calculation of conditional probabilities is left.

After the prevalence rate is obtained and set as the `condProb` (line 3a), for each OR-type rule, if the attribute value is contained in the state combination, the rule is considered "a match". For example, each of 'Adult', 'Male', 'Farmers' in the 'Children, Male, Farmers' combinations, only `Farmers` is considered as "match" with AntPerson1 rule. Then, the conditional probability is calculated by multiplying the ORs of the matched rule by the existing `condProb` (line 4a).

Pseudocode 9: CondProb Calculation

```
1.  Initialize condProb to 1
2.  IF there is a matching pathogen-type
    rule attribute or IF the combination is
    impossible
     a. Set the condProb to 0
3.  ELSE IF there is a matching prevalence-
    type rule attribute,
     a. Set the condProb to that value
        (Prevalence)
4.  ELSE for each matching OR-type rule
    attribute
     a. condProb = condProb * OR
5.  end
```

4 Evaluations

The algorithm's main functions are converting the IDR into an isomorphic BN, and populating its CPT based on the inputted OR and prevalence values. Therefore, the evaluation of the algorithm's correctness will consider the BN result and the child node's CPT values.

The BN generation algorithm described above was tested on two diseases along with their risk factors as predictors: Anthrax and Tuberculosis. The Anthrax BN has 13 parent nodes, 36 states in total, and 248,832 state combinations, of which only 96,768 combinations are possible. The Tuberculosis has 12 parent nodes, 34 states in total and 138,240 state combinations, and all are possible combinations.

An OntoGraf, a common layout for organizing an ontology structure in Protégé, is used to present the created IDR (Figure 6). The class and subclasses are marked with circle symbol, while, individuals are symbolized by diamonds. The example of Weather's individuals (Humid, Windy, Sunny, Cold) are given in the right-hand side of Figure 6. The solid and dashed lines represent direct and indirect relationship in a class, respectively.

In Figure 7, SWRL rules for Anthrax are presented. For OR-type rules, the numerical values less than one show a decreased risk (AntPerson2), and those of more than one show an increased risk of the disease (AntEnv1). These rules use the alterRisk predicate. Meanwhile, the setRisk rules can have two options: zero and non-zero.

For AntEnv3, the zero value means the pathogen is inactive, thus, it represents a pathogen-type rule. The non-zero values mean prevalence or incidence rates of the disease in the certain location (e.g. AntLoc1), thus, it represents prevalence-type rules.

Figure 8 shows the generated BN for Anthrax; the number of states per node varies and all states are successfully added to its node. Also, the parent nodes are all connected to the child node, as expected from the algorithm. The marginal probabilities for all parent nodes are set to default. This happens because for this test we did not provide exact values for the marginal probabilities but let the program use the default uniform distribution setting.

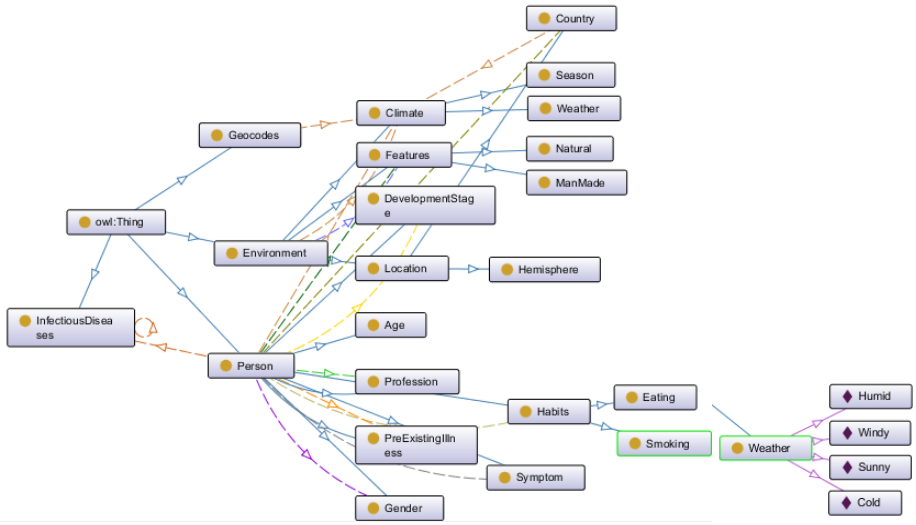

Figure 6. OntoGraf of the IDR.

Name	Rule
AntEnv1	Environment(?all) ^ accessDuring(?all, Summer) -> alterRisk(Anthrax, 2.05)
AntEnv2	Environment(?all) ^ accessDuring(?all, Windy) -> alterRisk(Anthrax, 1.55)
AntEnv3	Environment(?all) ^ accessDuring(?all, Winter) -> setRisk(Anthrax, 0)
AntEnv4	Person(?all) ^ liveAround(?all, Farms) -> alterRisk(Anthrax, 3.16)
AntLoc1	Person(?all) ^ liveIn(?all, US) -> setRisk(Anthrax, 1.12)
AntPerson1	Person(?all) ^ hasProfession(?all, Farmers) -> alterRisk(Anthrax, 1.83)
AntPerson2	Person(?all) ^ hasDevelopmentStage(?all, Children) -> alterRisk(Anthrax, 0.85)
AntPerson3	Person(?all) ^ hasHabits(?all, Omnivore) -> alterRisk(Anthrax, 1.73)
AntPerson4	Person(?all) ^ hasHabits(?all, Carnivore) -> alterRisk(Anthrax, 1.93)

Figure 7. SWRL rules for Anthrax used to populate CPT.

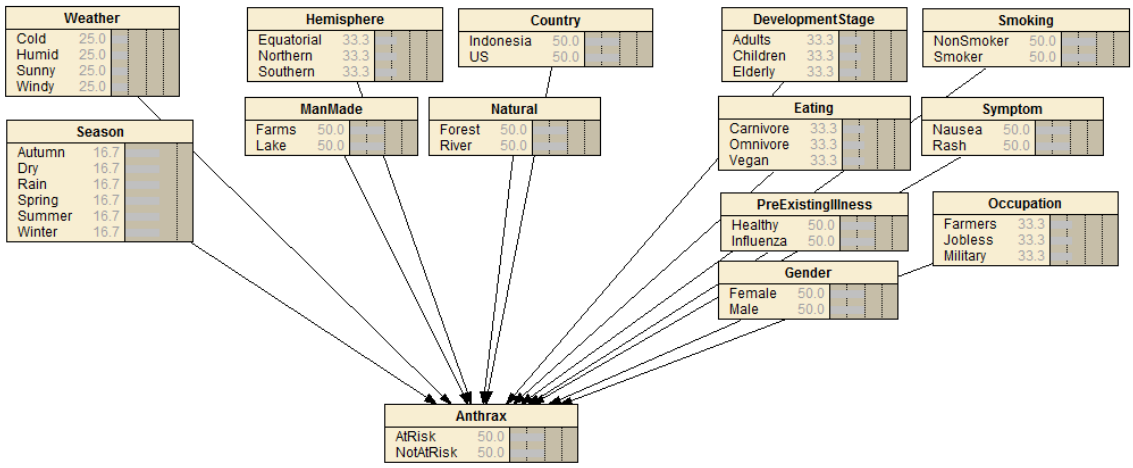

Figure 8. The generated isomorphic BN.

Figure 9 shows a small extract of the generated CPT for the child node. It consists of state combinations (left-side of the table) which are generated by StateCombination Generation and a conditional probability value for each child node's state (i.e. AtRisk) (right-side of the table) which are calculated by CondProb Calculation.

The last two rows in Figure 9 shows that a function to check impossible permutations is working for <<Indonesia> <Autumn>> – they have AtRisk

values of 0. The middle four rows show that the pathogen-type rule works properly on all state combinations that contain "Winter" – they have AtRisk values of 0.

A computer with specification Intel Core i3 CPU 1.7GHz with 4GB of memory was used to generate the BNs and populate the CPTs. It took 17 to 19 minutes approximately. The generation of state combinations accounts for most of the time.

5. Evaluation Results

Results of the validation will be justified by the correctness of the algorithm. The algorithm is correct when it generates an isomorphic BN and populates the CPT as given odds ratios.

5.1 Evaluation on the Generated BN

Not all classes or sub-classes in the IDR will be transformed into nodes in the BN; only classes that have at least one individual are converted. To compare the generated BN with the IDR, a mechanism to retrieve all the individuals with their corresponding classes and sub-classes directly from the Protégé is needed. A SPARQL query is used in the Protégé environment to execute the required mechanism.

```
SELECT *
WHERE {?individual rdf:type ?type .
OPTIONAL {?type rdfs:subClassOf ?class}}
ORDER BY ?type
```

Thereafter, the results of this query were compared with the generated BN (Figure 8). It can be seen from Fig. 6 that all sub-classes are transformed into nodes and all individuals are transformed into states. Furthermore, the node-state arrangements in the BN follow exactly the sub-classes and individuals' arrangements in the ontology. Other cases have been checked, for example, having empty sub-classes or non-referenced data or object properties in the IDR. Those conditions have no impact on the generated BN. Thus, it has been shown that the generated BN is isomorphic with the IDR.

5.2 Evaluation of the Populated CPT

To show that the algorithm correctly represents the SWRL rules presented in Figure 7 in the child node's CPT, an evaluation of the CPT is carried out.

The numerical values stored in the SWRL rules reveal the behaviour (e.g. inclination or declination) of the disease risk. The CPT population algorithm makes use of these numerical values to produce the conditional probabilities. Thus, all rules are taken as inputs and the related conditional probabilities are taken as outputs of this evaluation.

Then, the correctness of the CPT population algorithm is analysed by observing the outputs in two aspects: (1) the behaviour of the conditional probabilities has a consistent ratio with the given numerical values in the rules, and (2) the generated probabilities have different values for different personal and environmental conditions.

Table 4 shows validation for all Anthrax rules shown in Figure 7. Two countries are involved in this evaluation: US and Indonesia. All results for correspondent country are given for each OR-type and pathogen-type rules. The aggregated ratio for each state is given in the Result column. Then, to observe the ratio of prevalence between two countries, all ratios for OR-type rules are aggregated and placed on the Ratio column (e.g. 1.12043 for the AntLoc1 rule). From this process, the algorithm populates the child node's CPT automatically from the SWRL rules as presented in Figure 7. Also, they produce the comparable ratios with the given numerical values in the SWRL rules.

Furthermore, the resulting conditional probabilities show that these conditions result in different prediction results as stated on the rules.

(a) different personal attributes (e.g. Age, Gender) which are taken as different person
(b) the same person living in a country during different season (e.g. Winter, Spring)
(c) or the same person moving to different location features (e.g. Lake, Farms) within a country

Thus, we see that the populated CPT yield a personalized infectious disease risk prediction based on the personal and environmental attributes.

6. Discussion

The algorithm describes about a mechanism to convert a knowledge-base (ontology and rules)

representing an infectious disease to a risk prediction model (BN and its CPT). Since this paper introduces a BN generation algorithm, the comparative evaluation is of the functional requirements of the standard BNs. The requirements are generating BN structure (1), and populating the CPT (2). However, the algorithm makes some assumptions which lead to some limitations that are discussed in this section.

Eating	Hemisphere	Gender	Natural	Weather	Occupation	PreExistingIllness	ManMade	DevelopmentStage	Country	Season	Symptom	Smoking	AtRisk
Carnivore	Equatorial	Female	River	Cold	Farmers	Influenza	Farms	Elderly	US	Summer	Rash	NonSmoker	25.625
Carnivore	Equatorial	Female	River	Cold	Farmers	Influenza	Farms	Elderly	US	Summer	Rash	Smoker	25.625
Carnivore	Equatorial	Female	River	Cold	Farmers	Influenza	Farms	Elderly	US	Winter	Nausea	NonSmoker	0
Carnivore	Equatorial	Female	River	Cold	Farmers	Influenza	Farms	Elderly	US	Winter	Nausea	Smoker	0
Carnivore	Equatorial	Female	River	Cold	Farmers	Influenza	Farms	Elderly	US	Winter	Rash	NonSmoker	0
Carnivore	Equatorial	Female	River	Cold	Farmers	Influenza	Farms	Elderly	US	Winter	Rash	Smoker	0
Carnivore	Equatorial	Female	River	Cold	Farmers	Influenza	Lake	Adults	Indonesia	Autumn	Nausea	NonSmoker	0
Carnivore	Equatorial	Female	River	Cold	Farmers	Influenza	Lake	Adults	Indonesia	Autumn	Nausea	Smoker	0

Figure 9. Extract of the child node's CPT.

Table 4: Evaluation of generated model.

DESIGN				RESULT		
Rule Names	**Type of attribute**	**Numerical Values given on the Rules**	**Rule Type**	**Generated conditional probability values**		**Ratio**
Context: People living in the US and Indonesia during rainy season seek for Anthrax risk disease						
AntLoc1	Country	US = 1.12, Indonesia = 1	Prevalence	US	Indonesia	1.12043
AntPerson1	Personal	Farmers = 1.83 x Military or Jobless	OR	Farmers = 0.06476 Military = 0.03539 Jobless = 0.03539	Farmers = 0.05782 Military = 0.03159 Jobless = 0.03159	1.83005
AntPerson2	Personal	Children = 0.85 x Adult or Elderly	OR	Adult = 0.03539 Children = 0.03008 Elderly = 0.03539	Adult = 0.03159 Children = 0.02686 Elderly = 0.03159	0.85005
AntPerson3	Personal	Omnivore = 1.73 x Vegan	OR	Vegan = 0.03539 Omnivore = 0.06128	Vegan = 0.03159 Omnivore = 0.05466	1.7309
AntPerson4	Personal	Carnivore = 1.93 x Vegan	OR	Carnivore = 0.06831	Carnivore = 0.06098	1.93025
AntEnv4	Feature of Location	Farms = 3.16 x Lake	OR	Farms = 0.03539 Lake = 0.0112	Farms = 0.03159 Lake = 0.00999	3.16095
AntEnv1	Season	Summer = 2.05	OR	Winter = 0, Spring = 0.03539 Summer = 0.0725 Autumn = 0.03539	Rain = 0.03159 Dry = 0.03159	2.0486
AntEnv3	Climate	Winter = 0	Pathogen			-

States in a node are assumed to be unique and discrete. Some possibilities that makes a node become non-unique are (1) continuous states, and (2) non-unique individual names across classes. Netica-BN allows continuous numerical forms as states but later any continuous nodes taking part in an equation must first have been discretized (Norsys, 1995-2017). However, no need for continuous nodes for modelling infectious disease risk prediction. In addition, continuous numerical forms of predictor rarely use a BN as the prediction model. A Logistic Regression or Bayesian Logistic Regression is more suitable for this kind of forms (Koop, et al., 2013).

Rules in the IDR are assumed to have one attribute per rule. For most diseases, the OR usually represents one risk factor (e.g. *male*) which is independent of the disease risk. However, other diseases may have two or more risk factors for one OR (e.g. *male*, *adult*) or dependent risk factors. This condition is not equal with multiplying OR for *male* and *adult*. The current version of the algorithm cannot handle more than one attribute in one rule.

Another limitation of this algorithm is on handling non-unique individual names. For example, an individual *none* belong to *vaccinated* and *symptoms* sub-classes. For now, if this situation happens, the knowledge engineer should concatenate the names with attribute values (e.g. *notVaccinated*).

The underlying assumption of the generated BN is no intermediate nodes between parent and child nodes, and all predictors are assumed to be independent of each other. Most interdisciplinary

research takes this assumption to simplify the network and prediction model (Fenton, et al., 2016).

The current system only allows for pathogen to be active and inactive (set risk to 0). A support for more complex pathogen model (Kilianski, et al., 2015) (Huang, et al., 2012) would be beneficial.

Finally, for the requirements to predict a personalized infectious disease risk, some critical features are already facilitated in initial version in this paper. Further development related to detailed specification can be accommodated without significant changes to either the knowledge-base or the generation algorithm.

7 Conclusions and Future Works

This paper has described an algorithm for generating a Bayesian Network from the declarative infectious disease knowledge stored in an Ontology and SWRL rules. This algorithm allows additions or modifications to the ontology and will generate an isomorphic Bayesian Network and populate its child node's CPT automatically. However, the algorithm is a preliminary result with several limitations.

This paper uses the IDR, an Infectious Disease Risk Ontology and SWRL rules, as main reference of BN generation. This IDR will have numerous individuals for each disease as the knowledge becomes available in the future. Three types of rules have been introduced in this paper: OR, prevalence, pathogen-type rules. In this algorithm version, the pathogen availability is considered as always active, unless there is a declaration of pathogen inactivity. Another progressing work is ready to be published in a separated article.

The algorithm introduced in this paper only covers one possible source of OR and prevalence values – explicitly provided by experts within rules. There is another source that is possible to access: WHO data sources in UN Data or Health Surveillance API. By opting in these sources, there will be an automated process that aims to put the numerical values in the rule. This leads to some possibilities that are not covered by this algorithm for now, such as contradicting the established rules. A procedure to manage the rules might be a substantial improvement in the future.

Some other further works be (1) modifying the intermediate representation and the XPath queries for accommodating more than one dependent attribute in one rule, (2) observing relevant time period for predicting various infectious disease risks; this will impact on the conditional probabilities given to a client and thus will slightly modify the CPT Population algorithm.

To sum up, from the evaluation section, it can be concluded that the Network Creation algorithm has successfully generated an isomorphic BN from the Ontology structure. In addition, the CPT Population algorithm has auto-populated the child node's CPT and the ratio of the conditional probability results are consistent with the inputted OR. Furthermore, the BN Builder package has resulted in a personalized infectious disease risk prediction based on the personal attributes and their environments.

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References

Aiello, A. E., Simanek, A. M., Eisenberg, M. C. & Walsh, A. R., 2016. Design and methods of a social network isolation study for reducing respiratory infection transmission. Vol. 15.

Aliferis, C. F., Tsamardinos, I., Statnikov, A. R. & Brown, L. E., 2005. *A Causal Probabilistic Network Learning Toolkit for Biomedical Discovery.* Las Vegas, Nevada, Mathematics and Engineering Techniques in Medicine and Biological Sciences.

Austin, R. M. & Onisko, A., 2015. Increased cervical cancer risk associated with extended screening intervals after negative human papillomavirus test results 1(1).

Baumeister, J. & Striffler, A., 2015. Knowledge-driven systems for episodic decision support. *Knowledge-based systems,* Volume 88, pp. 45-56.

Blake, I. M., Chenoweth, P., Okayasu, H., 2016. Detection of poliomyelitis outbreaks to support polio eradication. *Emerging Infectious Diseases,* 22(3), pp. 449-456.

Chang, T. S., Gangnon, R. E., Page, D., 2015. Sparse modeling of spatial environments associated with asthma. Volume 53.

Das, B., 2004. Generating Conditional Probabilities for Bayesian Networks: Easing the Knowledge Acquisition Problem. *CoRR,* pp. 1-24.

Douali, N. et al., 2014. Comparison between case-based fuzzy cognitive maps and bayesian networks. 113(1).

Fan, X.-R.et al., 2015. A knowledge-and-data-driven modeling approach for simulating plant growth: A

case study on tomato growth. *Ecological Modelling,* Vol 312, pp. 363-373.
Fenton, N., Neil, M. & Lagnado, D., 2016. How to model mutually exclusive events based on independent causal pathways in Bayesian network models. Volume 113.
Fisman, D. N., 2008. Seasonality of viral infections: Mechanisms and unknowns. *American Journal of Preventive Medicine,* 18(10), pp. 946-954.
Gao, M., Liu, K. & Wu, Z., 2010. Personalisation in web computing and informatics. *Information Systems Frontiers,* 12(5), pp. 607-629.
Giabbanelli, P. J., Torsney-Weir, T. & Mago, V. K., 2012. A fuzzy cognitive map of the psychosocial determinants of obesity. 12(12).
Haddawy, P., 1994. *Generating Bayesian Networks from Probability Logic Knowledge Bases.* Seattle, Morgan Kaufmann Publishers Inc. San Francisco, CA, USA.
Huang, Z., Das, A., Qiu, Y., 2012. The vector-borne disease airline import. risk (VBD-AIR) tool. Vol. 11.
Jiang, Q., Zhou, J. T., Jiang, Z. B. & Xu, B., 2014. Identifying risk factors of avian infectious diseases at household level in Poyang Lake region, China. *Preventive Veterinary Medicine,* 116(2), pp. 151-160.
Jombart, T., Aanensen, D. M., Baguelin, M., 2014. A platform for disease outbreak using the R. Vol. 7.
Kahn Jr., C. E., Roberts, L. M., Shaffer, K. A. & Haddawy, P., 1997. Construction of a BN for mammographic diagnosis of breast cancer. *Computers in Biology and Medicine,* 27(1), pp. 19-29.
Kilianski, A., Carcel, P., Yao, S. & Roth, P., 2015. Pathosphere.org: pathogen detection and characterization through a web-based. *BMC Bioinformatics,* 416(16), pp. 1-12.
Koop, G. et al., 2013. Risk factors for subclinical intramammary infection in dairy goats in two longitudinal field studies evaluated by Bayesian logistic regression. 108(4).
Kunjunninair, A. P., 2012. Clinical decision support system: risk level prediction of heart disease using weighted fuzzy rules and decision tree rules. *Central European Journal of Computer Science,* 2(1).
Laskey, K. B. & Mahoney, S. M., 2000. Network Engineering for Agile Belief Network Models. *IEEE Transactions on Knowledge and Data Engineering,* 12(4), pp. 487-499.
Lopman, B., Armstrong, B., Atchison, C., 2009. Host, weather and virological factors drive norovirus epid. *PLoS One,* 4(8).
Monath, T. P. & Vasconcelos, P. F. C., 2015. Yellow fever. *Journal of Clin. Viro.,* Volume 64, pp. 160-173.
Ngo, L. & Haddawy, P., 1995. Probabilistic logic programming and Bayesian networks. *Lecture Notes in Computer Science,* Volume 1023, pp. 286-300.
Norsys, 1995-2017. https://www.norsys.com/netica-j/examples/SimulateCases.html.
Onisko, A., Lucas, P. & Druzdzel, M. J., 2001. *Comparison of Rule-Based and Bayesian Network Approaches in Medical Diagnostic Systems.* Portugal.
Rev2, 2017. *HealthInformatics Conference: Reviewer comment #2.* Unknown: Primoris.
Ruttenberg, A. et al., 2016. *Infectious Disease Ontology.* http://purl.obolibrary.org/obo/ido.owl.
Semakula, H. M., Song, G., Achuu, S. P., 2016. A Bayesian belief network modelling of household factors influencing the risk of malaria. Vol 75.
Shirai, O., Tsuda, T. & Kitagawa, S., 2002. Alcohol stimulates mosquito. *Journal of the American Mosquito Control Association,* 18(2), pp. 91-96.
Shirai, Y., Funada, H. & Seki, T., 2004. Landing preference of Aedes albopictus on human skin among ABO blood groups, secretors or nonsecretors. *Journal of Medical Entomology,* 41(4), pp. 796-799.
Third, A., 2014. *BioPortal: CARRE Risk Factor Ontology.* https://bioportal.bioontology.org/ontologies/CARRE.
Vinarti, R. A. & Hederman, L. M., 2017. *Personalization of Infectious Disease Risk Prediction Towards automatic generation of a Bayesian Network.* Thessaloniki, Greece.
Wertheim, H. F. L., Horby, P. & Woodall, J. P., 2012. *Atlas of Human Infectious Diseases.* Oxford: Wiley-Blackwell.
WHO, 2003. *Climate Change and Human Health - Risks and Responses Summary,* Geneva: WHO.
Wu, X. et al., 2016. Impact of climate change on human infectious diseases. Vol. 86.
Yi, H., Devkota, B. R. & Yu, J.-s., 2014. Effects of global warming on mosquitoes & mosquito-borne diseases and the new strategies for mosquito control. *Entomological Research,* 44(6), pp. 215-235.

Appendix 6 – ESWA Journal Submission

An article submitted to the International Journal of Expert Systems with Applications (20th of March, 2018).

A Personalized Infectious Disease Risk Prediction System

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Abstract

This article presents a system for predicting a human's risk of contracting infectious diseases based on their personal attributes and environments (region, specific location features and climate contexts). This system is also intended to help human experts in the domain (i.e. epidemiologists) to represent their knowledge and ease their jobs related to personalized infectious disease risk prediction. The system consists of a knowledge representation to encode epidemiological knowledge about infectious disease risk, and an algorithm that auto-converts the encoded knowledge into a model that predicts the risk as a probability. The knowledge representation, Infectious Disease Risk (IDR), consists of an ontology and rules to represent the knowledge structure and its quantification in a way that allows auto-generation to a prediction model, Bayesian Network (BN). The algorithm, BN-Builder, converts the IDR knowledge-base to an infectious disease risk BN, including populating the basis of predictive reasoning from the IDR rules. A user interface facilitates encoding of epidemiological knowledge into the IDR knowledge-base. The system's output, personalized infectious disease risk prediction, is validated for three disease-country contexts: Dengue Fever and Tuberculosis in Indonesia, and Cholera in India. The personalized infectious disease risks are reliable (p values > 0.05) for each population parameter. The personalized infectious disease risk probability can be reliably predicted using this system. Inclusion of more granularity on contexts in this domain will be considered in further development of this system.

Keywords: infectious disease, risk prediction, Bayesian Network, ontology, rule.

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I. INTRODUCTION

We aim to create a system to predict a person's risk of being infected by a specific infectious disease today (or this week or season depending on the disease), given their demographic details (e.g. age, gender) and their surrounding environment conditions (e.g. location, weather, nearby terrain features). In addition, the system facilitates human experts (e.g. epidemiologists) to encode up-to-date and location-specific infectious disease (ID) risks. In order to achieve these aims, the system contains a knowledge representation, an algorithm that allows generation of a prediction model from the knowledge representation, and a user interface.

The structure of the knowledge-base, Infectious Disease Risk (IDR), is designed from a collation of all human IDs which is mostly documented in declarative forms. The contents of the IDR knowledge-base are risk factors (both personal and environmental risk factors) and the extent to which different value of those factors impact on ID risk. An example of the collated knowledge is *Aedes aegypti mosquito that causes Dengue Fever (DF) can only live below 1000m altitude where usually have warm climate (above 20^{o}C); children have four-times more risk than toddlers; pregnant mothers are at high risk*. This kind of knowledge for all IDs was collated manually from (Wertheim, Horby, & Woodall, 2012) (WHO, Fact Sheets: Infectious Diseases, 2017) (CDC, Emerging Infectious Diseases, 2017). But only a small subset has been encoded to date; we facilitate further encoding by epidemiologists with a user interface whose design is presented in this paper.

An algorithm, BN-Builder, was developed to auto-generate a prediction model, Bayesian Network (BN), to yield personalized ID risk probability based on personal and location attributes. For example, *a 6-year old female living in [-7.2759, 112.8083] is asking for DF risk at 13:55 on 4th of July 2017*. To respond to this request, the system (1) translates the given geocode into a location (e.g. Surabaya, Indonesia) using Google Reverse Geocoding API, (2) retrieves the altitude of the given geocode from Google Elevation API, (3) retrieves the temperature of Surabaya in Indonesia on 04/07/2017 at 13:55 from Open Weather API, (4) retrieves the DF prevalence in Indonesia from WHO section of UNSD[25] API, (5) retrieves the proportion of children in Indonesia and proportion of females in Indonesia from UNSD API, (6) categorizes the client into children age category, and (7) deduces a non-pregnant status from this age category even though the client is a female. Then, based on these facts, the generated BN computes DF risk probability using a general Bayesian theorem.

The structure of the paper is as follows. Section 2 discusses related work. Section 3 presents the research methodology. Section 4 gives the results of each step of the research methodology. Section 5 shows the system architecture. Section 6 presents the personalized ID risk reliability results at population-level. Section 7 discusses the

[25] United Nations Statistical Division (UNSD) compiles and disseminates global statistical information for major divisions in UN such as WHO, ILO, OECD, UNHCR, World Bank, etc.

limitations of this system. Section 8 summarizes the contributions of the current work and outlines future plans.

II. RELATED WORK

Several projects have been published in the infectious disease and epidemiology areas. Map-based web services (e.g. HealthMap (Nelson, 2008), VBD-AIR (Huang, Das, Qiu, & Tatem, 2012), SickWeather (SickWeather, 2011-2017)) provide information about ID outbreaks based on location and online case reports. Those projects use data sources from Centers for Disease Control and Prevention (CDC), WHO, and Google APIs to visualize their maps. However, they only present current location of ID outbreaks; they do not have reasoners to predict the disease risk for an individual.

Other relevant health projects use an ontology as a knowledge representation: EPidemiology Ontology (Pesquita, 2017), Infectious Disease Ontology (Cowell, 2016) and CARdioRENal ontology (Third, 2014). EPO is designed to support semantic annotation of epidemiology resources. In EPO, *region* and *specific location features* are infection risk factors. IDO established eight instances per disease (e.g. HIV, Malaria) that contains a set of biomedical and clinical aspects, such as body mass index, and vaccination. The CARRE ontology represents a concept of human susceptibility to cardiorenal diseases by providing personal risk factors (e.g. *demographic*, *biomedical* and *behavioral* risk factors). Each factor is quantified by *risk ratios*.

To model the risk of a person contracting an ID, two aspects are involved: (1) the spreading of ID in three contexts: *epidemiological*, *individual* and *biological*, and (2) human immune system (Camara, Despres, Djedidi, & Lo, 2013). From IDO, we reused standardized vocabularies of the *biological* aspect of ID in general, including the pathogens, hosts, and vectors. From EPO, we reused the *epidemiological* aspect at population scale, vector distributions across regions and the transmission modes of IDs in general. From CARRE, we reused only *personal* risk factor types relevant to infection. However, none of the above ontologies represent the role weather plays in both spreading of, and immunity to, IDs, though the connection between weather and IDs is well documented (Division, 2001).

Disease risk prediction projects have specific requirements that lead to particular prediction models. The requirements are the ability to encode human-readable knowledge, and to yield accurate predictions. The prediction models are suitable for these needs: Logistic Regressions, Fuzzy Cognitive Maps, and Bayesian Networks (BN) (Panayiotis, Simon, Denise, & Alex, 2016). BN is selected as the risk prediction model in this system because there are general-purpose algorithms that allow BN generation from other knowledge representations (e.g. probability logic knowledge-bases) (Haddawy, 1994) (Zagorecki & Druzdzel, 2013) and BNs do not require training data to build the basis of predictive reasoning. However, for disease risk purpose, the BN generation algorithm must be redeveloped to fit the mathematical relationship between disease risk factors and their quantifications.

III. RESEARCH METHODOLOGY

The process of developing the personalized ID risk system is explained in this section (see Fig. 1). The corresponding results for each sub-section are presented in the next section.

A. Seek sources for human infectious diseases

Basic information about IDs and epidemiology was found in the Atlas of Human Infectious Diseases (Wertheim, Horby, & Woodall, 2012). For each ID the personal and environmental risk factors (e.g. location and weather) were extracted. Detailed explanations about risk factors were obtained from CDC (CDC, Emerging Infectious Diseases, 2017), WHO (WHO, Fact Sheets: Infectious Diseases, 2017). During this process, the conclusion that ID risks are related to location and climate (as well as human susceptibility) was confirmed.

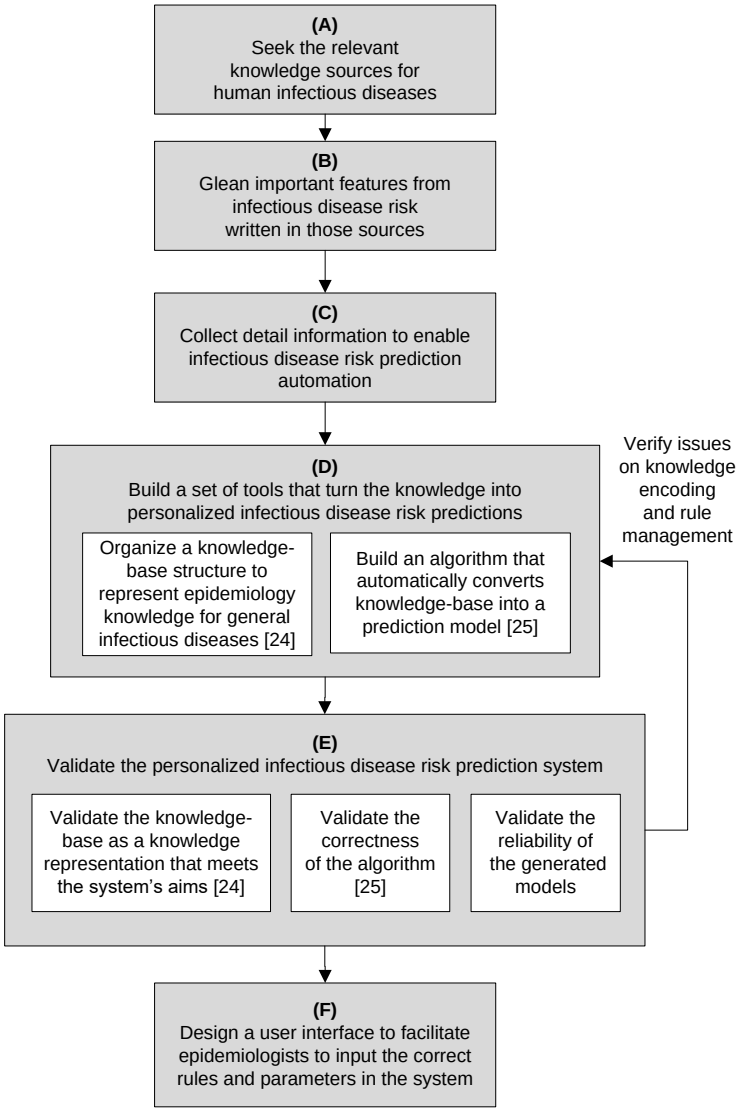

Fig. 1. The research methodology of the personalized ID risk system

B. Glean important features of infectious diseases

The factors that correlate between IDs and environmental risk factors were obtained from epidemiology books and detailed ID risk articles (CDC, Lesson 1: Introduction to Epidemiology, 2012) (Fares, 2011) (Hu, Tong, Mengersen, & Oldenburg, 2006). The correlation is caused by ID features: (1) pathogen availability in certain region, location features and climate conditions (e.g. *Aedes aegypti* mosquito dwell in regions between 35^{o}N and 35^{o}S latitudes), (2) transmission method that is influenced by specific weather (e.g. temperature is no colder than 10^{o}C), and (3) climate influences on human susceptibility (e.g. the absence of sunlight weakens human immune system). These features are taken into consideration in the process of designing the knowledge representation structure (i.e. ontology) in step D.

C. Collect detailed information to enable infectious disease risk prediction automation

Various ways to present information about disease risks factors are obtained from clinical journals (Kumar, Devika, George, & Jeyaseelan, 2017) (Cao, Zhang, Li, & Lo, 2013) (Schmidt, Vestergaard, Baggesen, & Pedersen, 2017) (Greer, Drews, & Fisman, 2009) (Gustafson, Gomes, Vieira, & Rabna, 2004) (Guwatudde, Nakakeeto, Jones-Lopez, & Maganda, 2003) (Prayitno, Taurel, Nealon, & Satari, 2017). The definite numerical forms like *risk ratios* and *prevalence* are commonly used. Other vague representations like adding or reducing risks by percentages or presented as ordinal values (e.g. high, medium, low) also appear. In addition, a mathematical expression that yields disease risk prediction (Lewis, Whitwell, Forbes, & Sanderson, 2007) (Freedman, Seminara, Gail, & Hartge, 2005) from disease risk factors and their quantification forms is identified and adapted in this step.

D. Build a knowledge representation and an algorithm to convert knowledge into a prediction model

The knowledge representation in this system aims to capture and organize concepts of the ID risk knowledge, and to enable auto-generation of the BN. The collation of ID risk knowledge from steps A-C, and some of entities from the existing ontologies (EPO, IDO, CARRE) are reused to design a basic structure that applies for all IDs (i.e. IDR ontology). This structure is instantiated for each ID-country context[26].

In order to bind the ID risk knowledge with its quantification forms, either in numerical or ordinal forms, a logical representation is used (i.e. rules). Thus, an *instantiation* covers specifying sub-classes and their individuals in the IDR ontology (registering risk factors to an ID risk), then assigning their quantifications as IDR rules. An instantiated IDR

[26] Besides country, other location scopes can be used as context, for example, ID-region, ID-continent, ID-province.

knowledge-base consists of one IDR ontology and a set of IDR rules specific for one ID-country context (e.g. Cholera-India) (Vinarti & Hederman, A knowledge-base for a Personalized Infectious Disease Risk Prediction System, 2018).

Our BN-Builder algorithm (Vinarti & Hederman, Introduction of A Bayesian Network Builder Algorithm: Personalized Infectious Disease Risk Prediction, 2018), is then used to generate a BN from the IDR knowledge-base. This BN-Builder, has three aims: (1) it generates an isomorphic BN structure, (2) it populates a correct basis of predictive reasoning in BN (i.e. Conditional Probability Table), and (3) it deduces the personal facts (6-year female has zero possibility to get pregnant).

E. Validate the personalized ID risk prediction system

Three key aspects of the system were evaluated, as follows:

1. Validate the IDR knowledge-base (Vinarti & Hederman, A knowledge-base for a Personalized Infectious Disease Risk Prediction System, 2018)

The IDR knowledge-base consists of two representations: IDR ontology to represent the structure of knowledge, and IDR rules to represent quantifications over the IDR ontology. So, we used ontological (Tartir, Arpinar, & Sheth, 2010) and rule-based system (Preece, 2001) approaches for evaluating the IDR ontology and the IDR rules, respectively.

2. Validate the BN-Builder algorithm (Vinarti & Hederman, Introduction of A Bayesian Network Builder Algorithm: Personalized Infectious Disease Risk Prediction, 2018)

The BN-Builder's main function is generating an equivalent BN for each instantiated knowledge-base. The equivalency was measured by (1) the isomorphisms of the generated BN from the instantiated IDR ontology structure, (2) and the correctness of the populated BN's CPT. (3) Several boundary conditions of the personal facts were tested to deduce their possibility.

3. Validate the personalized ID risk probability

Existing disease risk assessments were studied (Freedman, Seminara, Gail, & Hartge, 2005). In our previous work (Vinarti & Hederman, Personalization of Infectious Disease Risk Prediction: Towards automatic generation of a Bayesian Network, 2017), the *accuracy* was used to assess risk for Anthrax with a hand-crafted CPT. The accuracy was measured using real hospital visit records in the US. The result is satisfying but since the Anthrax is not a notifiable ID nor regularly reported by WHO, the risk is relatively small and not scalable to validate the risk prediction in this system. Therefore, *calibration* or *reliability* (Freedman, Seminara, Gail, & Hartge, 2005), at population scale, was selected to validate the reliability of the risk probabilities.

B. Design a user interface

The user interface is designed with two aims, (1) to facilitate epidemiologists to encode their knowledge in IDR knowledge-base; results from step A to C are used to design the interface to capture typical experts' knowledge; (2) to provide solutions for rule anomalies that became apparent in step D (Vinarti & Hederman, A knowledge-base for a Personalized Infectious Disease Risk Prediction System, 2018).

IV. RESULTS

This section presents the results of each step of the research methodology presented in the previous section.

A. Seek sources for human infectious diseases

From 234 distinct infectious diseases that were gathered from (Wertheim, Horby, & Woodall, 2012) (WHO, Fact Sheets: Infectious Diseases, 2017) (CDC, Emerging Infectious Diseases, 2017), 215 (91.89%) have personal risk factors, 86 (36.75%) are climate-dependent (happen during certain seasons or weather) and 175 (74.7%) are spread only in specific locations (e.g. country, region, farms, certain altitudes). These percentages conform that ID risks are related to weather besides personal risk factors as explained at (Division, 2001) (Wu, Lu, Zhou, Chen, & Xu, 2016).

B. Glean important features of infectious diseases

Pathogen availability, transmission methods, and human susceptibility to diseases that partly related to climate (CDC, Lesson 1: Introduction to Epidemiology, 2012) are represented as entities in the existing ontologies: *region* and *specific location features* in IDO (Cowell, 2016) and EPO (Pesquita, 2017). Also, the concepts of a *person* susceptibility are captured in CARRE ontology as personal risk factors (Third, 2014). These entities are reused in the IDR. New environmental risk factor which is confirmed in step A, *climate* and its derivations, is added to IDR.

C. Collect detail information to enable infectious disease risk prediction automation

In clinical and epidemiology journals, *risk ratios*, represented as odds ratios (OR) or relative risks (RR), are used to quantify risk factors. Both OR and RR have similar meaning: OR<1 means reducing risk, OR>1 means increasing risk, OR=1 means that more evidence is needed to correlate the risk factor with the disease risk (Szumilas, 2010). For example, the OR for *males* in TB risk is 2.37; this means that *males* tend to have TB risk 2.37 times more than *females*. OR and RR can be used interchangeably with some considerations (Zhang & Yu, 1998). Besides using risk ratios, other representations such as addition/reduction of risks by certain percentages, are also considered. For example, eating one egg per day can reduce TB risk by 34%.

The second most common representation of risk factor quantification is ordinal values (e.g. low, medium, high) instead of numerical forms. For example, the risks of Influenza are *high* during *Fall* and *Winter* seasons. Ordinal representations are also common for defining pathogen availability.

Besides risk factors, a probability of someone contracting an ID is also affected by the commonness of the ID morbidity in a specific region (*prevalence* or *incidence*[27]) (CDC, Lesson 1: Introduction to Epidemiology, 2012). Both measurements are usually for a year and projected as per 10,000 or 100,000 population. For example, the prevalence of TB in Africa in 2015 is 395 per 100,000 population.

D. Build a knowledge representation and an algorithm to convert knowledge into a prediction model

From step B, *region*, *specific location features*, and *person* entities are reused from existing ontologies, while *climate* is added to design the IDR ontology. These entities become IDR ontology classes; and their derivations become sub-classes of the corresponding classes. The values of an entity become *individuals* of the corresponding sub-classes or classes. For example, the derivations of the *climate* entity are *weather* and *season*, thus, they become sub-classes of *climate* class. *Winter* is the value of the *season*, then *winter* is an individual of the *season* sub-class (see Fig. 2) (Vinarti & Hederman, A knowledge-base for a Personalized Infectious Disease Risk Prediction System, 2018). By default, the ontology instantiated for each ID will contain this structure. However, this arrangement can result in less representativeness.

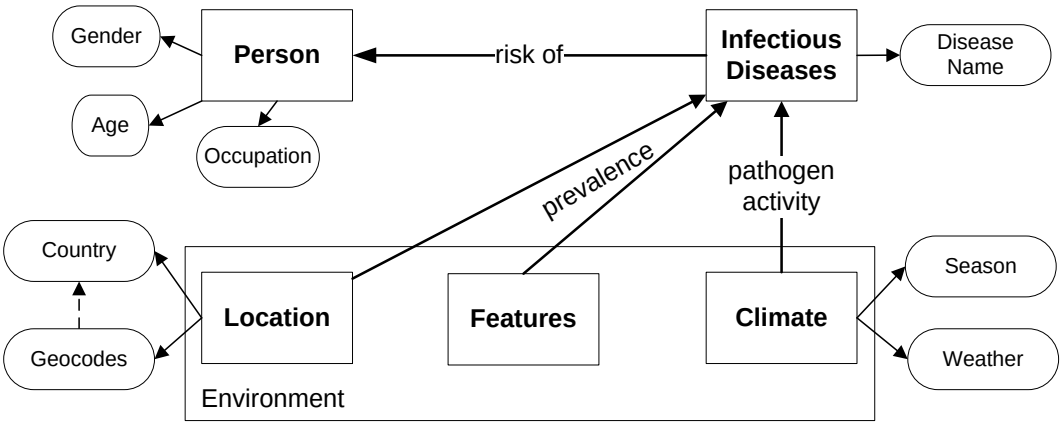

Fig. 2. The IDR ontology basic structure with some samples of sub-classes (presented as ellipses) (Vinarti & Hederman, A knowledge-base for a Personalized Infectious Disease Risk Prediction System, 2018).

[27] Prevalence is a measurement of **all** individuals affected by the disease at a particular time. Incidence is a measurement of the number of **new** individuals who contract a disease during a particular time, usually used for short-term diseases (i.e. Influenza).

IDR rules are used to represent risk quantifications in both numerical and ordinal forms as explained in step C. Five rule types were designed to cover all forms of risk quantifications. Table 1 shows all rule types with their examples. For numerical forms of risk ratios given as OR the IDR rule type is *real direct risk ratios*; where risk ratios are calculated from addition/reduction by percentages the rule type is *real indirect risk ratios*. The IDR rule types that encode ordinal values for pathogen availability status, and risk factors are named as *vague pathogen status* and *vague risk ratios*, respectively. The ordinal values are converted into numerical values using Gaussian or Uniform distribution by the BN-Builder algorithm. The final IDR rule type is *real prevalence* for encoding prevalence or incidence value of a disease in certain region during a particular time. The prevalence is usually provided per 10,000 or 100,000 population depending on the disease, however, the number should be converted to percent to match the CPT units in BN API. See the last row of Table II for an example.

The BN-Builder algorithm, first described in (Vinarti & Hederman, Introduction of A Bayesian Network Builder Algorithm: Personalized Infectious Disease Risk Prediction, 2018), converts the IDR ontology and rules into an equivalent BN. This conversion includes populating CPT (in the BN) with conditional probabilities which are calculated from risk ratios and prevalence. A formula was adopted from disease risk prediction articles (Lewis, Whitwell, Forbes, & Sanderson, 2007) (Freedman, Seminara, Gail, & Hartge, 2005) and rewritten to become eq. (1). Essentially, the BN-Builder implements this formula to populate the BN's CPT (Vinarti & Hederman, Introduction of A Bayesian Network Builder Algorithm: Personalized Infectious Disease Risk Prediction, 2018).

$$p\left(D\middle|y_1^{s_1}, y_2^{s_2}, \ldots, y_n^{s_n}\right) = prev(D).\prod_{i=1;\ j=1}^{n} OR^{y_i^{s_j}} \quad (1)$$

where $p\left(D\middle|y_1^{s_1}, y_2^{s_1}\right)$ is risk probability for disease D given the conditions $y_1^{s_1}, y_2^{s_1}$; $prev(D)$ is the prevalence of the disease D in a specific region during a particular time; $OR^{y_i^{s_j}}$ is a risk ratio for an attribute ($y_i^{s_j}$) of a condition (y_i). For example, TB risk for females living in a sunny day in Indonesia is $(TB - Indonesia\middle|gender^{female}, weather^{sunny})$. To obtain this conditional probability, the following information is needed: (1) prevalence of TB in Indonesia during a year $prev(TB - Indonesia)$, (2) risk ratios for Indonesian female to contract TB ($OR^{gender^{female}}$), (3) risk quantification obtained from tendency of TB risk during sunny day ($OR^{weather^{sunny}}$).

In the context of the TB risk example, the risk probabilities result in different prediction if (1) someone has different personal attributes (e.g. male), (2) the same person living in the same country (Indonesia) during different weather (e.g. muggy, cloudy), or (3) the same person moves to a different country that has different TB prevalence (e.g. Africa).

E. Validate the personalized ID risk prediction system

To evaluate the personalized ID risk prediction system, all components of the system is validated: IDR knowledge-base, the BN-Builder algorithm, and the ID risk probability.

1. Validate the IDR knowledge-base

The IDR knowledge-base is able to encode the IDR knowledge and conform the system's purpose: personalization of ID risk prediction (Vinarti & Hederman, A knowledge-base for a Personalized Infectious Disease Risk Prediction System, 2018). However, validation using the rule-based system approach showed that two rule anomaly types can occur in IDR rules: *duplicate rules*, and *conflicting rules*. Duplicate rules mean two or more rules have the same risk factor(s) with the same risk ratios. For example, rule #12 and #34 say that *males* have 2.37 higher Tuberculosis (TB) risk than *females*. Conflicting rules mean multiple rules have different risk ratios for the same risk factor(s). For example, rule #9 say that *females* have 1.24 higher TB risk than *males*, thus, rule #9 is conflicting with rule #12. The user interface described in section F addresses these anomalies to some extent.

TABLE I

IDR RULE TYPES THAT ENCODE DECLARATIVE KNOWLEDGE OVER IDR ONTOLOGY WITH EXAMPLES

Rule Types	Rule Properties	Ontology class to encode	Value in data forms	Examples of declarative knowledge to encode
Real Direct Risk Ratios	alterRisk	{risk factors} in *person* or *environment*	Risk ratio in $0 < \mathbb{R} < \infty$	Males have 2.37 times more TB risk than females (Gustafson, Gomes, Vieira, & Rabna, 2004)
Rule: Person(?all) ^ hasGender(?all, Male) -> alterRisk(TB, 2.37)				
Real Indirect Risk Ratios	addRisk, reduceRisk	{risk factors} in *person* or *environment*	Risk ratio in %	Fish intake can reduce the TB risk by 50% (Wang, Liu, Ma, & Han, 2017)
Rule: Person(?all) ^ hasEatingHabits(?all, fish) -> reduceRisk(TB, 50%)				
Vague Pathogen Status	setPathogen	{climate} in *environment*	Pathogen Activity in Inactive, LessActive, MoreActive	*Mycobacterium tuberculosis* is more active during humid condition (Wang, Liu, Ma, & Han, 2017)
Rule: Environment(?all) ^ during(?all, humid) -> setPathogen(TB, MoreActive)				
Vague Risk Ratios	estimateRisk	{risk factors} in *person* or *environment*	Risk ratio in High, Low, Medium, n-fold	People who have low body mass index are at a high risk (Wang, Liu, Ma, & Han, 2017)
Rule: Person(?all) ^ hasBMI(?all, low) -> estimateRisk(TB, high)				
Real Prevalence	setRisk	{location and specific features} in *environment*	Prevalence rate in %	TB prevalence in Indonesia is 391 per 100,000 population (WHO, Global Health Estimates 2015: Disease burden by Cause, Age, Sex, by Country and by Region, 2000-2015, 2016)
Rule: Environment(?all) ^ hasCountryName(?all, Indonesia) -> setRisk(TB, 0.395)				

2. Validate the BN-Builder algorithm (Vinarti & Hederman, Introduction of A Bayesian Network Builder Algorithm: Personalized Infectious Disease Risk Prediction, 2018)

To ensure the validity of the generated BN (including the CPT), this algorithm was evaluated. The generated BN is isomorphic and its CPT is correct (Vinarti & Hederman, Introduction of A Bayesian Network Builder Algorithm: Personalized Infectious Disease Risk Prediction, 2018). The BN-Builder generates the equivalent BN and is able to deduce probability of the personal facts that are unlikely to happen (Vinarti & Hederman, Introduction of A Bayesian Network Builder Algorithm: Personalized Infectious Disease Risk Prediction, 2018).

3. Validate the personalized ID risk probability

There are three risk assessments (calibration, discrimination and accuracy) common in disease risk prediction research (e.g. cancer risks) (Freedman, Seminara, Gail, & Hartge, 2005). Calibration (i.e. reliability) is selected to evaluate the output of this system. Reliability of risk predictions is measured using chi-square statistics (i.e. goodness-of-fit) by comparing *observed* and *expected* number of events (for each generated condition in the CPT). The *expected* numbers of events are gathered from country-level health ministry for each context, while the *observed* number of events is the personalized ID risk probability output of this system. The evaluation results are presented in section VI.

A. Design a user interface

The user interface retrieves a list of IDR ontology classes, sub-classes and individuals and lets the user choose the suitable item(s) (step 1 in Fig. 3).

To provide solutions for *duplicate rule anomaly*, the user interface displays the existing relevant knowledge (step 2 in Fig. 3). This feature is expected to prevent users inputting the same value for the same risk factor(s) which may lead to duplicate rule. For the *conflicting rules anomaly*, the user interface seeks the users' confidence in the new rule (step 3 in Fig. 3). The rules with the highest confidence are used to populate the BN's base reasoning by the BN-Builder algorithm. This solution, admittedly, cannot clear up conflicting rules in the IDR rule-base but aims to minimize and keep the users aware of the similar IDR rules.

V. THE SYSTEM ARCHITECTURE

The architecture of personalized ID risk system consists of: (1) the instantiated IDR knowledge-base; (2) the BN-Builder algorithm to generate BN from the IDR knowledge-base; (3) APIs that support the BN by providing the up-to-date data to predict reliable personalized ID risks (see Fig. 4).

The process of building the knowledge representation is denoted *BN-Build time* (right). Once the BN is generated, it is ready to process requests from clients; this phase is denoted *run-time* (left). When the epidemiologists input new knowledge or new risk factors of an ID, new objects will be added to the ontology and rules, and the BN model needs to be renewed.

The renew process uses the BN-Builder algorithm to convert the updated knowledge-base into an equivalent BN. Activities of the renew process are (1) retrieving population-level parameters, such as the proportion of males and females in a country, (2) retrieving the corresponding ID prevalence (if available from WHO API), (3) replacing the old BN by generating a new one.

At runtime, the *live APIs* tier collects current facts of the environment and demography based on users' geocodes and sends the retrieved values to the *context collector* in the *logic* tier. The BN, in the *logic* tier, takes the personal attributes (e.g. age, gender) from the *context collector* as inputs (i.e. beliefs). Thereafter, the BN uses its CPT to select the most suitable conditions that represent client's inputs. The final result is then passed to the client through the *presentation* layer.

VI. RESULTS OF PREDICTION RELIABILITY EVALUATION

After the BN-Builder generates the equivalent BN, the CPT consists of all combinations of registered risk factors (i.e. conditions and its values). The personalized ID risk probability is calculated from the most suitable combination in the CPT.

To measure the reliability of the risk probabilities, data of the *expected* values for each context are taken. For example, data about DF and TB in Indonesia are taken from InfoDatin (Indonesian Health, 2013) and WHO (WHO, Dengue fever in Indonesia, 2017) (WHO, Tuberculosis (TB), 2017), while data for Cholera in India is taken from WHO (WHO, Cholera in India: an analysis of reports, 2006). We evaluate whether the personalized ID risk prediction results (*observed* values) have no significant differences with the *expected* values using the chi-square test.

To validate the reliability of the inputted risk quantifications, only *possible* combinations are included (see Table II). *Impossible* combinations are deduced by the BN-Builder. The total number of combinations is the product of number of values for all conditions. The number of *possible* combinations is obtained by subtracting the number of *impossible* combinations from the total combinations.

P values for chi-square test results are shown in Table II. These *p values* mean that there is not enough evidence to show that there are significant differences between predicted and real number of events in subgroup of country-level population since all *p values* are >0.05. Thus, as a personalized ID risk prediction, the risk probabilities for each context are reliable to 95% confidence level.

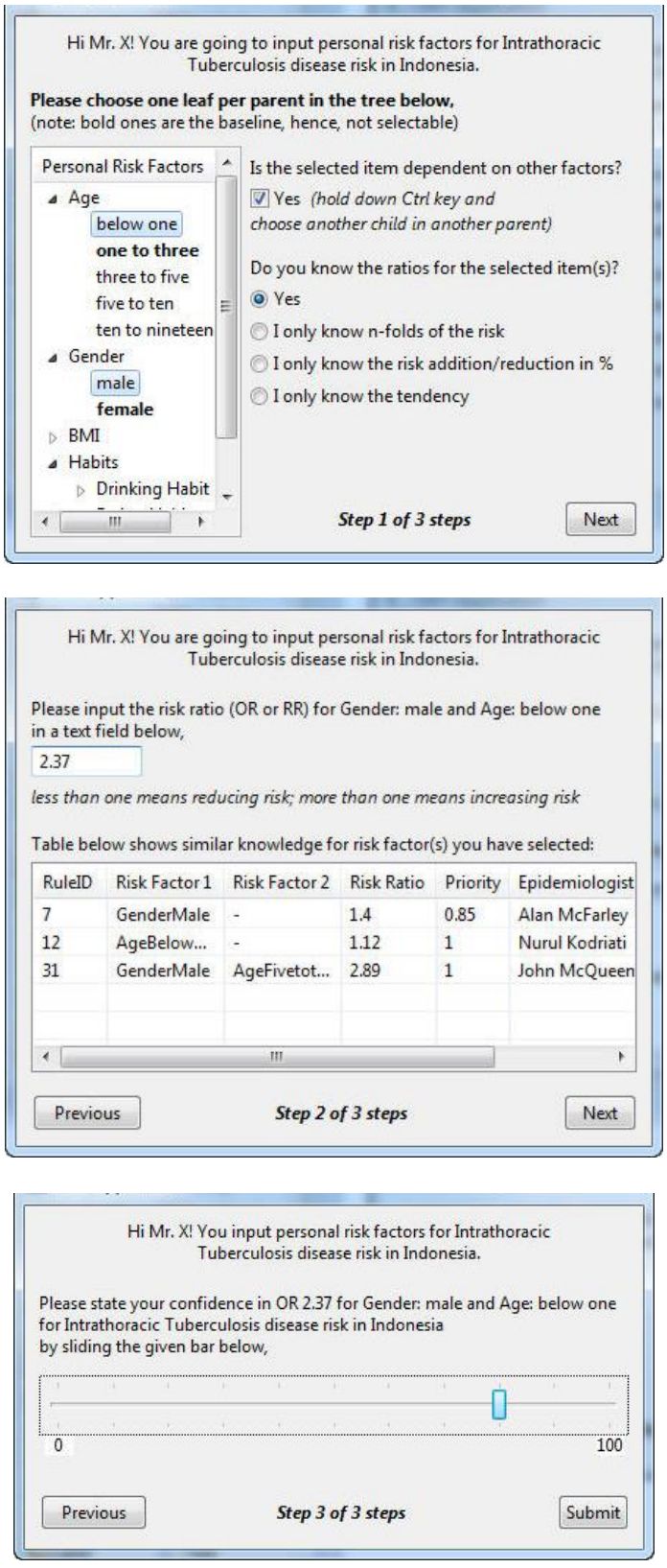

Fig. 3. The user interface for choosing the risk factors (step 1); previewing the registered knowledge (step 2); inputting the user's confidence (step 3).

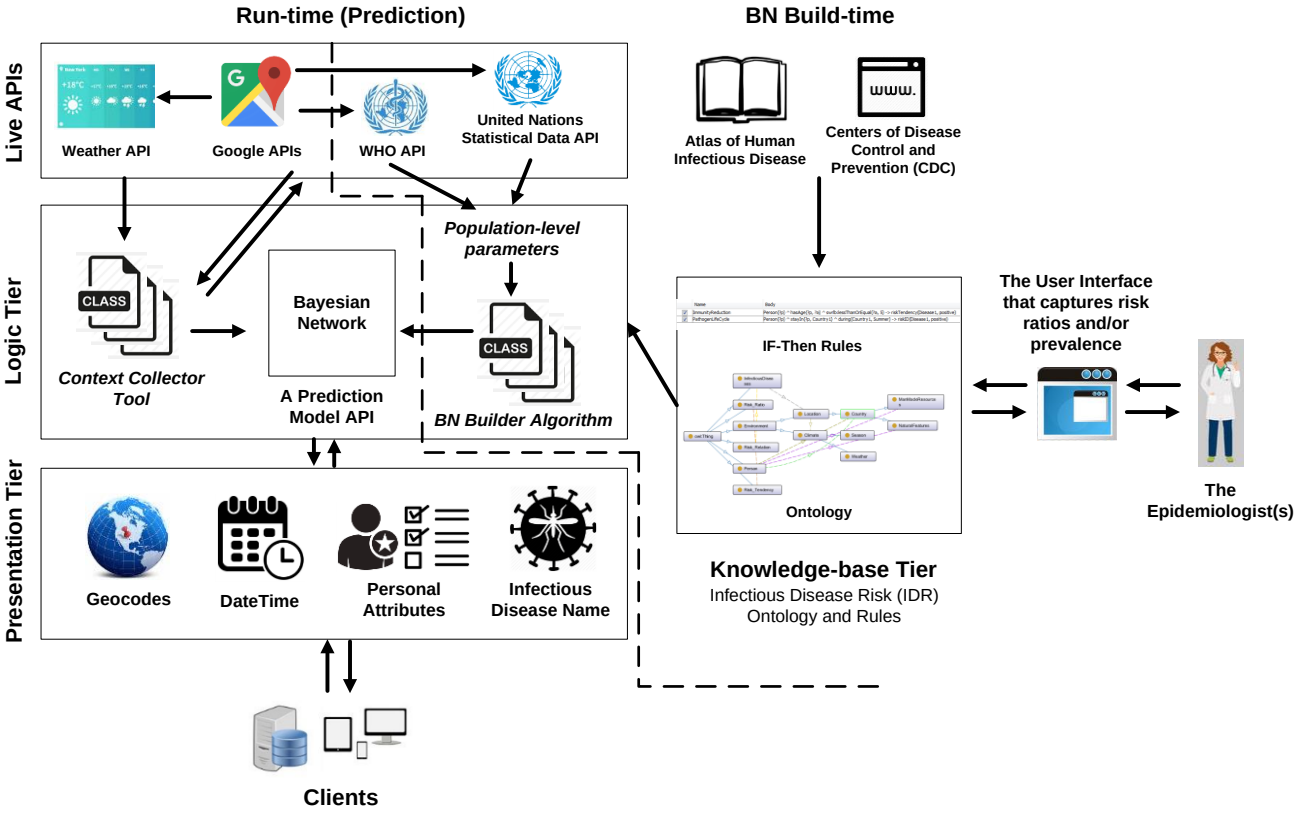

Fig. 4. The system architecture

TABLE II

DETAILS FOR EACH TESTED CONTEXT

Context[28]	Num. of: IDR Rules | *possible* of *total* combinations	Conditions [values]	*P values* of chi-square test[29]
DF in Indonesia	9 rules | 72 of 96 combinations	Gender [Male, Female]; Age [1-4, 5-9, 10-14, 15-18]; House-crowding Level [1-3, 4-5, >5]; Parents Education Level [Primary, Secondary, University]	0.3755
TB in Indonesia	10 rules | 172 of 224 combinations	Gender [Male, Female]; Age [1-5, 6-14, 15-24, 25-34, 35-44, 45-54, >55]; Smoking [Smoker, NonSmoker]; Vaccination [BCG, None]; Education Level [Illiterate, Primary, Secondary, University]	0.495
Cholera in India	12 rules | 80 of 80 combinations	Gender [Male, Female]; Age [0-4, 5-9, 10-19, 20-29, 30-39, 40-49, 50-59, >60]; Season [Jan-Mar, Apr-Jun, Jul-Sep, Oct-Dec, all year]	0.998

[28] Detail IDR knowledge-base and the generated BN for each disease-country context is available at https://is.gd/DetailExpforESWA

[29] Detail conditions and calculation for each disease-country context are available at https://is.gd/calculationsforESWA

VII. DISCUSSION

This personalized ID risk prediction system consists of the IDR knowledge representation, the BN-Builder algorithm, and the user interface to facilitate ongoing ID risk knowledge encoding by epidemiologists. The IDR knowledge-base was validated using ontological and rule-based system approaches; the result is the IDR knowledge-base is generic enough to encode parameters for the disease risk prediction formula for all IDs through time. However, some information like the number of samples and the confidence interval for each risk ratio are not represented in the IDR knowledge-base. Although this information is important for epidemiologists before encoding their knowledge using the user interface, it is not used to calculate risk probabilities. Also, the current design of the IDR ontology structure leads to a minor problem in the generated BN. The conditions that may occur at the same time (e.g. *windy* and *cloudy*) should not be represented as *individuals* but better as *sub-classes*. This is because BN-Builder converts *individuals* in the IDR ontology to become *states* in the BN which can only be selected one at a time.

In the reliability evaluation (section VI), the p-values show that the risk probabilities for each context are reliable to 95% confidence level. However, there are some other possibilities that contribute to the p-values: availability of data that is used to compare the results, and number of samples for each disease-context. The more the samples, the higher the difference tolerance which may cause the model to be overfitted (Freedman, Seminara, Gail, & Hartge, 2005). Recalibration will be needed if one of those cases happen. On the other hand, more samples are preferable to model variability in the real-world cases. Trade-off between the number of samples and the expected p-value is a common issue in the risk probability prediction research.

Admittedly, the feature for solving *duplicate rule* anomaly is a preventive solution. This solution might not be strong enough to reject or clear up the duplicating rules as there might be different confidence for the new rule and the epidemiologist wants to keep both rules as records.

VIII. CONCLUSION AND FURTHER RESEARCH

This paper has described contributions in the context of a personalized infectious disease risk prediction system: (1) IDR knowledge-base, (2) BN-Builder algorithm and (3) the user interface to facilitate the ongoing IDR knowledge encoding. This paper is the continuation of our work in (Vinarti & Hederman, A knowledge-base for a Personalized Infectious Disease Risk Prediction System, 2018) (Vinarti & Hederman, Introduction of A Bayesian Network Builder Algorithm: Personalized Infectious Disease Risk Prediction, 2018) (Vinarti & Hederman, Personalization of Infectious Disease Risk Prediction: Towards automatic generation of a Bayesian Network, 2017) which explain and evaluate

the structure of IDR knowledge-base and BN-Builder algorithm pseudocode. Specifically, this paper presents reliability evaluation for personalized ID risk assessment at population-level. From the evaluation results in three disease-country contexts, the personalized ID risk prediction is reliable.

To inform the epidemiologists about essential circumstances (e.g. specific strain of the ID, number of samples, confidence interval of the risk ratios) before inputting a knowledge using the designed user interface, annotations on the IDR knowledge-base may be used and previewed in the user interface.

An IDR knowledge base guide will be written to help knowledge engineers encode new infectious disease risk knowledge. The guide will include advice on avoiding rule anomalies and on correctly representing overlapping conditions (such as windy and cloudy, as described above).

VIII. REFERENCE

Camara, G., Despres, S., Djedidi, R., & Lo, M. (2013). Design of Schistosomiasis Ontology (IDOSCHISTO) Extending the Infectious Disease. *Medical Informatics.* Washington, D.C.

Cao, H., Zhang, L., Li, L., & Lo, S. (2013). Risk Factors for Acute Endophthalmitis following Cataract Surgery: A Systematic Review and Meta-Analysis. *PLoS ONE, 8*(8), 1-18.

CDC. (2012, May 18). *Lesson 1: Introduction to Epidemiology.* Retrieved August 15, 2016, from Centers for Disease Control and Prevention: http://www.cdc.gov/ophss/csels/dsepd/ss1978/lesson1/section10.html

CDC. (2017). *Emerging Infectious Diseases*. (CDC: Centers for Disease Control and Prevention) Retrieved October 26, 2017, from https://wwwnc.cdc.gov/eid

Cowell, L. (2016, July 5). *Infectious Disease Ontology.* Retrieved December 10, 2016, from BioPortal: http://purl.obolibrary.org/obo/ido.owl

Division, N. R. (2001). *Under the weather : climate, ecosystems, and infectious disease.* Washington, D. C.: National Academy Press.

Fares, A. (2011). Seasonality of Tuberculosis. *Journal of Global Infectious Diseases, 3*(1), 46-55.

Freedman, A. N., Seminara, D., Gail, M. H., & Hartge, P. (2005). Cancer Risk Prediction Models: A Workshop on Development, Evaluation, and Application. *Journal of the National Cancer Institute, 97*(10), 715-723.

Greer, A. L., Drews, S. J., & Fisman, D. N. (2009). Why "Winter" vomiting disease? seasonality, hydrology, and norovirus epidemiology in Toronto, Canada. *EcoHealth, 6*(2), 192-199.

Gustafson, P., Gomes, V. F., Vieira, C. S., & Rabna, P. (2004). Tuberculosis in Bissau: incidence and risk factors in an urban community in sub-Saharan Africa. *International Journal of Epidemiology, 33,* 163-172.

Guwatudde, D., Nakakeeto, M., Jones-Lopez, E. C., & Maganda, A. (2003). Tuberculosis in Household Contacts of Infectious Cases in Kampala, Uganda. *American Journal of Epidemiology, 158*(9), 887-898.

Haddawy, P. (1994). Generating Bayesian Networks from Probability Logic Knowledge Bases. Seattle: Morgan Kaufmann Publishers Inc. San Francisco, CA, USA.

Hu, W., Tong, S., Mengersen, K., & Oldenburg, B. (2006). Rainfall, mosquito density and the transmission of Ross River virus: A time-series forecasting model. *196*(3-4).

Huang, Z., Das, A., Qiu, Y., & Tatem, A. J. (2012). Web-based GIS: the vector-borne disease airline importation risk (VBD-AIR) tool. *11*.

Indonesian Health, M. (2013). *Kementrian Kesehatan Republik Indonesia*. (KemenkesRI) Retrieved 2017, from http://www.depkes.go.id/folder/view/01/structure-publikasi-pusdatin-info-datin.html

Kumar, V. S., Devika, S., George, S., & Jeyaseelan, L. (2017). Spatial mapping of acute diarrheal disease using GIS and estimation of relative risk using empirical Bayes approach. *5*.

Lewis, C. M., Whitwell, S. C., Forbes, A., & Sanderson, J. (2007). Estimating risks of common complex diseases across genetic and environmental factors: the example of Crohn disease. *Journal of Medical Genetics, 44*(11), 689-694.

Nelson, R. (2008). HealthMap: the future of infectious diseases surveillance? *TheLancet, 8*(10).

Panayiotis, P., Simon, H. X., Denise, A., & Alex, B. A. (2016). Prediction of lung cancer incidence on the low-dose computed tomography arm of the National Lung Screening Trial: A dynamic Bayesian network. *Artificial Intelligence in Medicine, 72*, 42-55.

Pesquita, C. (2017). *Epidemiology Ontology*. (The OBO Foundry) Retrieved 2017, from https://www.ebi.ac.uk/ols/ontologies/epo

Prayitno, A., Taurel, A.-F., Nealon, J., & Satari, H. I. (2017). Dengue seroprevalence and force of primary infection in a representative population of urban dwelling Indonesian children. *PLoS: Neglected Tropical Diseases, 11*(6), 1-16.

Preece, A. (2001). Evaluating verification and validation methods in knowledge engineering.

Schmidt, S. A., Vestergaard, M., Baggesen, L. M., & Pedersen, L. (2017). Prevaccination epidemiology of herpes zoster in Denmark: Quantification of occurrence and risk factors. *Vaccine*, 1-8.

SickWeather. (2011-2017). *SickWeather*. (SickWeather Inc.) Retrieved December 12, 2017, from http://www.sickweather.com/

Szumilas, M. (2010, August). Explaining Odds Ratios. *Information Management for the Busy Practitioner*, pp. 227-229.

Tartir, S., Arpinar, I. B., & Sheth, A. P. (2010). Ontological Evaluation and Validation. In *Theory and Applications of Ontology: Computer Applications* (pp. 115-130). Dordrecht: Springer.

Third, A. (2014). *BioPortal: CARRE Risk Factor Ontology*. Retrieved October 18, 2017, from https://bioportal.bioontology.org/ontologies/CARRE

Vinarti, R. A., & Hederman, L. M. (2017). Personalization of Infectious Disease Risk Prediction: Towards automatic generation of a Bayesian Network. *IEEE Computer-based Medical Systems (CBMS).* Thessaloniki, Greece: IEEE.

Vinarti, R. A., & Hederman, L. M. (2018). A knowledge-base for a Personalized Infectious Disease Risk Prediction System. *Medical Informatics Europe (MIE) 2018.* Gothenburg, Sweden.

Vinarti, R. A., & Hederman, L. M. (2018). Introduction of A Bayesian Network Builder Algorithm: Personalized Infectious Disease Risk Prediction. *11th International Health Informatics Conference: ACM Conference Series.* Funchal, Madeira.

Wang, Q., Liu, Y., Ma, Y., & Han, L. (2017). Severe hypovitaminosis D in active TB patients and its predictors. *Clinical Nutrition*, 1-7.

Wertheim, H. F., Horby, P., & Woodall, J. P. (2012). *Atlas of Human Infectious Diseases.* Oxford: Wiley-Blackwell.

WHO. (2006). *Cholera in India: an analysis of reports.* Retrieved 2017, from http://www.who.int/bulletin/volumes/88/3/09-073460/en/

WHO. (2016). *Global Health Estimates 2015: Disease burden by Cause, Age, Sex, by Country and by Region, 2000-2015*. (Geneva, World Health Organization) Retrieved May 30, 2017, from http://www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html

WHO. (2017). *Dengue fever in Indonesia.* Retrieved 2017, from http://www.who.int/csr/don/2004_05_11a/en/

WHO. (2017). *Fact Sheets: Infectious Diseases*. (WHO) Retrieved October 26, 2017, from http://www.who.int/topics/infectious_diseases/factsheets/en/

WHO. (2017). *Tuberculosis (TB).* Retrieved 2017, from http://www.who.int/tb/country/data/profiles/en/

Wu, X., Lu, Y., Zhou, S., Chen, L., & Xu, B. (2016). Impact of climate change on human infectious diseases: Empirical evidence and human adaptation. *86*.

Zagorecki, A., & Druzdzel, M. J. (2013). Knowledge engineering for bayesian networks: How common are noisy-MAX distributions in practice? *IEEE Transactions on Systems, Man, and Cybernetics Part A:Systems and Humans, 43*(1), 186-195.

Zhang, J., & Yu, K. F. (1998). What's the Relative Risk? A Method of Correcting the Odds Ratio in Cohort Studies of Common Outcomes. *JAMA: The Journal of the American Medical Association, 280*(19), 1690-1691.

Appendix 7 – BMC Journal Submission

An article submitted to the BMC – Journal of Biomedical Semantics (10th of July 2018).

Infectious Disease Risk knowledge representation for use in a personalized IDR prediction system

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Abstract

Background: We are developing a personalized infectious disease risk (IDR) prediction system that uses a Bayesian Network as a risk prediction model. The BN is auto-generated from a continuously updateable knowledge-base that encodes declarative infectious disease risk knowledge and risk quantifications that are relevant to calculate the personalized risk prediction. No existing knowledge representations met this need. Therefore, the aim of this paper is to present a development of knowledge-base and other representations that meet the system requirements, and help epidemiologists in future knowledge encoding activities.

Results: We establish and evaluate three elements: an IDR core ontology, five IDR rule types, and an IDR catalog. The IDR core ontology contains three classes to categorize relevant risk factors for human infection (*person, climate, location*) and one *infectious disease* class. The IDR rule types are used to bind infection risk factors with their risk quantifications (e.g. odds ratios, morbidity frequency). The IDR catalog that inherits the IDR core structure consists of 212 classes, 246 individuals that encode all distinct risk factors for all existing 234 human infectious diseases listed in Atlas of Human Infectious Diseases (AHID), Centre for Disease Control and Prevention (CDC), and World Health Organization (WHO) factsheets.

Conclusion: Through 18 cases used in the evaluation, we establish that the categorization of IDR core ontology classes reflects the human infection risk in the epidemiology theory. All risk quantifications to predict disease risk can be encoded by five rule types. Form the evaluation, all needed rule types are provided to bind risk quantifications to represent the infection risk knowledge. The sub-classes and individuals of the IDR catalog are useful (more than 60% are used) and sufficient (more than 75% of the risk factors needed for the 18 evaluation cases), however, the epidemiologists will still need to add some of individuals in the IDR catalog to encode the risk factors when needed. The current version of the IDR catalog will be evolving as the infection risk knowledge develops. The current version of the IDR catalog is freely available at http://dx.doi.org/10.17605/OSF.IO/P6QV8.

Keywords: infectious disease, risk prediction, knowledge representation, ontology, rules.

List of abbreviations: Infectious Disease Risk (IDR), Bayesian Network (BN), Atlas of Human Infectious Diseases (AHID), World Health Organization (WHO), Center for Disease Control and Prevention (CDC), Ontology Quality Analysis (OntoQA), Odds Ratios (OR), Relative Risks (RR), Tuberculosis (TB), Meningitis (MEN), Dengue Fever (DF), Semantic-Web Rule Language (SWRL), sexually-transmitted infections (STI).

Background

We are developing a system that aims to predict a person's risk of contracting (specific) infectious disease based on the personal attributes, current weather and surrounding terrain (including land-use). This system consists of two major phases: *knowledge-gleaning* and *run-time*. In the *knowledge-gleaning* phase, epidemiologists are expected to create a knowledge-base representing epidemiology knowledge for one infectious disease prevalent in one location-context (e.g. country). The context-specific knowledge-base is formed of two knowledge representations: ontology and rules. After the knowledge-base is created, an algorithm, Bayesian Network-Builder, converts it to an equivalent BN [238]. Whenever the epidemiologists update the knowledge-base, the BN-Builder keeps the BN updated as well. In the *run-time* phase, the system retrieves the current weather and surrounding terrain conditions of the user from live APIs based on his geocodes. The retrieved facts are then processed to calculate the personalized infectious disease risk probability using the generated BN from the *knowledge-gleaning* phase. In the long-run, we will provide user interfaces to support epidemiologists to encode their infection risk in the knowledge-base. In our pilot project, the correctness of the risk predictions resulted from a hand-crafted BN for an infectious disease in a country context is satisfying enough (more than 80% accurate) [239].

In the *knowledge-gleaning* phase, stable epidemiology knowledge about infections was obtained from the Atlas of Human Infectious Diseases (AHID) [13], World Health Organization (WHO) [31], Center for Disease Control and Prevention (CDC) [30], and clinical and epidemiologic journal articles. This aims to (1) understand the chain of infection and epidemiology knowledge for infectious diseases, and (2) capture infection risk factors and their quantifications. The results of the first and second aims are a core ontology and collated risk factors (i.e. catalog), respectively. The collated risk factors are represented in an ontology; whereas their quantifications are encoded as rules.

Existing knowledge representations (ontologies) in epidemiology, infectious diseases, risk factors domains, such as Human Disease Ontology [197], Infectious Disease Ontology [22], Epidemiology Ontology [195], Apollo [201], Ontology for human risk factors for Cardiorenal disease [25], have been investigated. No single ontology was intentionally built for encoding the infection risk factors relevant to personalized infectious disease risk predictions. Although the use of rules to support additional information for ontologies has been proven in [96], [240]–[242], no rules in previous research were used to encode risk quantifications used for infection risk predictions.

This paper aims to describe the development of an infectious disease risk (IDR) core ontology, rule types and a catalog. Also, we assess the used methodology by evaluating the IDR core ontology representativeness, and the usefulness and completeness of IDR rule types and IDR catalog using context-specific knowledge-bases (i.e. evaluation cases). These evaluations are inspired by metric-based ontology quality analysis (OntoQA) [228]. An instantiation process is needed to build an IDR knowledge-base from IDR rule types and IDR catalog. An IDR knowledge-base consists of an ontology and set of rules that was created by using relevant sub-classes and individuals in the IDR catalog, and encoding risk quantifications using IDR rule types, respectively. The IDR knowledge-bases will be used to generate an equivalent BN by the BN-Builder algorithm.

The structure of the paper is as follows. Section 2 presents the outcomes: IDR core ontology, IDR rule types and IDR catalog. Section 3 explains the evaluation results for each product. Section 4 discusses the evaluation results, the assumptions, the limitations and the possible future research. Section 5 outlines the conclusions made through the evaluations and

discussions. Section 6 describes the research methodology to develop the IDR core ontology, IDR rule types, IDR catalog, an instantiation process to make the IDR knowledge-base, and evaluation plans.

Results of IDR Ontology and Rule Type Design

This section presents the IDR core ontology that was constructed from the summary of infection drivers, the IDR rule types that facilitate risk quantification encoding over the IDR ontology, and the IDR catalog that was developed from distinct risk factors for all human infectious diseases.

From the *chain of infection risk* definition [12], infectious disease is an ailment caused by a *pathogen*[30] which is transmitted from an infected person, animal or reservoir[31] to a susceptible human using a *vector*[32] or *vehicle*[33] [126]. When a pathogen enters the human, whether the infectious disease will develop or not depends on the human immunity level. Some personal attributes, such as age, genetics, gender, and behaviors may reduce the immunity level. Certain terrain and atmospheric conditions may affect climate-dependent pathogen and vector. For example, *Colorado Tick Fever infection is seasonal, coinciding with the period of Ixodid wood tick activity in early summer. Human cases can be detected from March to September in the Rocky Mountain region. Most human cases are males, aged 20–29 years, reflecting the frequency of outdoor activity in the mountains* [13].

IDR core ontology

In this section, we construct an *epistemological* knowledge representation of infection risks. The *epistemological* representation consists of concept types (i.e. main classes), conceptual sub-pieces (i.e. sub-classes), inheritance and structuring relations between concepts, using a diagrammatic form [243]–[245].

The construction of the IDR core ontology aims to (1) make the domain knowledge (risk factors that affect a person's risk contracting of infectious disease) explicit, and (2) support the IDR catalog by providing the main classes and object properties; these object properties are used to bind the risk factors with their risk quantifications using the IDR rule types.

To make the domain knowledge explicit, we categorized *risk factors* as *person risk factors*, and *environment risk factors*. These categories, together with *infectious disease*, are represented as main classes of the IDR core ontology. This is because personalization and environment are the focus of the system. We define *person risk factors* as attributes of a person (including habits and activities), and *environment risk factors* are determined by climate and location, that affect certain pathogen or vector of an infectious disease to multiply [7], [42], [86], [103], [129], [246]. Seventeen infection risk drivers listed in AHID [13] were summarized into these main classes (see Appendix 1). The decision whether an object is a sub-class or an individual of these main classes is explained in section 2.3.

[30] *Pathogen* is an infectious agent causing an infectious disease (e.g. bacteria, virus, parasite, prion)

[31] *Reservoir* is a habitat in which the infectious agent able to survive and multiply.

[32] *Vector* is a living being (animal) that disseminates the agents, for example, mosquito, mice, flies.

[33] *Vehicle* is inanimate object that transports the agent from reservoir to host

In the IDR core ontology structure, we show the connectivity between classes of the IDR ontology with the IDR rule types. Fig. 1 show the classes of which risk quantifications are encoded by which rule types. The definition of each IDR rule type is explained in the next section.

IDR rule types

Based on [42], [43], [247], we have two kinds of information: (1) morbidity frequency (*prevalence* or *incidence*), (2) risk ratios (*odds ratios* or *relative risks*). By using the keys and criteria explained in Section 6.2, 44 articles were retrieved (i.e. *risk quantification studies*) [248].

For the first required information, *prevalence* or *incidence*, 25 articles use *prevalence* and 16 articles provide *incidence* to describe morbidity frequency of a disease in a location during a specific time period. Two articles do not give information about morbidity cases. *Prevalence* is the proportion of persons who have a particular disease, both new and pre-existing cases, in a population at a specific time period. Whereas *incidence* is limited to new cases only. Both have same units, per 10,000 or 100,000 population depending on the disease [151].

Second required information is *risk ratios* for risk factors; 36 articles present the risk quantifications in numerical forms; 3 articles present them as descriptive statistics. Interestingly, the numerical risk quantifications are not all presented as *risk ratios* in odds ratios (OR) or relative risks (RR) [32], but also as *addition* and *reduction* in percentages. However, only 7 of 44 articles present the risk quantification for environmental risk factors in ordinal values (e.g. high, moderate, low risk). The same ordinal forms also appeared on [13], [30], [31].

To encode all these risk quantification formats, we establish five rule types. *Real prevalence* rule type is provided for encoding prevalence or incidence of an infectious disease. *Vague pathogen status* is used to present the pathogen activity status of an infectious disease. The other three rule types (the last three rows in Table 1) are provided for encoding different forms of a person's risk quantification that we found in case-control studies, AHID, CDC and WHO factsheets [13], [30], [31]. Fig. 2 shows 8 IDR rule examples that are common in encoding activity.

Table 1. The IDR rule types and their encoding examples

IDR Rule Type Number	IDR Rule Type Names	IDR Rule Properties	IDR ontology class to encode	Value in data forms	Examples of declarative knowledge to encode
1	Real Prevalence	setRisk	location	Prevalence rate in %	Tuberculosis (TB) prevalence in Indonesia is 391 per 100,000 population [227]
	IDR Rule: Environment(?all) ^ hasCountryName(?all, Indonesia) -> setRisk(TB, 0.395)				
2	Vague Pathogen Status	setPathogen	weather, season	Pathogen Activity in Inactive, LessActive, MoreActive	*Mycobacterium tuberculosis* is more active during humid condition [136]
	IDR Rule: Environment(?all) ^ during(?all, humid) -> setPathogen(TB, MoreActive)				

3	Real Direct Risk Ratios	alterRisk	person, weather, season, location	Risk ratio in $0 < \mathbb{R} < \infty$	Males have 2.37 times more TB risk than females [21]
	IDR Rule: Person(?all) ^ hasGender(?all, Male) -> alterRisk(TB, 2.37)				
4	Real Indirect Risk Ratios	addRisk, reduceRisk	person, weather, season, location	Risk ratio in %	Fish intake can reduce the TB risk by 50% [136]
	IDR Rule: Person(?all) ^ hasEatingHabits(?all, fish) -> reduceRisk(TB, 50%)				
5	Vague Risk Ratios	estimateRisk	person, weather, season, location	Risk ratio in High, Low, Medium, n-fold	People who have low body mass index are at a high TB risk [136]
	IDR Rule: Person(?all) ^ hasBMI(?all, low) -> estimateRisk(TB, high)				

Most of the risk quantification studies assume risk factors are *independent*. Independence of risk factor means for example, that the risk probability for *male children* of contracting of an infectious disease is the product of risk ratio for *male* and risk ratio for *children*. However, 3 articles discover *dependent* risk factors [8], [21], [49], meaning that the risk probability for *male children* of contracting of an infectious disease may not be equal to the products of risk *ratio* for *male* and risk ratio for *children* (see the Semantic-web Rule Language [218] implementation of this case as S5 in Fig. 2).

IDR catalog

The IDR catalog (Fig. 3) was constructed by extending the main class of the IDR core ontology (Fig. 1). Distinct risk factors from [13], [30], [31] were identified and classified as sub-classes and individuals of the IDR core ontology predictor classes. This IDR catalog is reused to create each IDR knowledge-base that is used to generate the BN. The auto-generation is facilitated by the BN-Builder algorithm [238].

The BN-Builder algorithm converts individuals to states, and sub-classes to nodes. To represent an actual condition at a time, only one state is selectable per node. Therefore, the design decision whether a risk factor will become sub-class or individual depends on whether the risk factor can occur at the same time. For example, *child* and *elderly* become individuals of a *development stage* sub-class because there is no single human that is declared as a child and elderly at the same time. Meanwhile, *cloudy* and *cold* become different sub-classes even though both represent *weather* sub-class. This is because a day can be *cloudy* and *cold* at the same time, so, when there is a cloudy cold day, a user can select both states because they are generated to different nodes.

The IDR catalog was constructed using Protégé and its graph (Fig. 3) was generated using the OntoGraf plugin [226]. Rectangles represent classes; lines between rectangles represent relations; the polygon shows the main classes. The IDR catalog consists of 212 classes (5 main classes, 207 sub-classes) and 246 individuals [249]. The description logic expressivity of the IDR catalog is ALCH(D). This means that the IDR catalog contains hierarchy, complement and data properties to define semantic relations of infectious disease risk knowledge [250].

Evaluation Results

We aim to evaluate the *representativeness* of the IDR core ontology, and the *usefulness* and *completeness* of the IDR rule types and IDR catalog using metrics that are inspired by OntoQA

[228]. To evaluate, we need to assess whether the encoded knowledge aligns with the epidemiology theory (i.e. representativeness), whether the IDR rule types and catalog can be used to encode real epidemiologic knowledge for human infection risks in specific contexts (i.e. usefulness), and whether the IDR rule types and catalog contain enough resource to encode the risk knowledge (i.e. completeness). Using methods described in Section 6.5, we selected articles and infectious diseases that met the evaluation needs. This resulted in four infectious diseases: Tuberculosis (TB), Meningitis (MEN), Dengue Fever (DF), Cholera. The transmission mode profile of each infectious disease is presented in Table 2; sample descriptions of each case-control study are presented in Table 3 (its details is available in an online appendix [248]). Eighteen case-control studies that met the evaluation criteria were obtained; each article contains risk ratios and morbidity frequency for one infectious disease prevalent in a population of one country.

In order to encode knowledge from case-control studies, the IDR *instantiation* was performed (see Section 6.3). The result is eighteen context-specific IDR knowledge-bases where each of them contains one IDR ontology instance and a set of IDR rules that represents one case-control study [249].

Table 2 The coverage of the infectious diseases selected for the evaluation based on the reservoir types, transmission modes and the predictor classes.

Criteria	Coverage of the selected infectious diseases			
	Tuberculosis	Meningitis	Dengue Fever	Cholera
Reservoir Types				
Human	☒	☒	☒	☒
Animal	☐	☐	☒	☒
Inanimate	☐	☐	☐	☒
Unknown	☐	☐	☐	☐
Transmission Modes				
Direct contact	☐	☒	☐	☐
Fecal-oral	☐	☐	☐	☒
Blood-borne	☐	☐	☐	☐
Food-borne	☐	☐	☐	☒
Water-borne	☐	☐	☐	☒
Vehicle	☐	☒	☐	☐
Vector	☐	☐	☒	☐
Air/droplet	☒	☒	☐	☐
Context-dependent predictors				
Person	☒	☒	☒	☒
Climate	☒	☒	☒	☒
Location	☒	☒	☒	☒
Miscellaneous	☐	☐	☐	☐
Prevalent in	Indonesia, Africa, Croatia, China	Chile, South Korea, United States, Gaza Strip	Indonesia, Singapore, Sudan, Rep. Dominican, Brazil, Nepal	India, Papua New Guinea, Zimbabwe, Rep. Dominican

Table 3 Descriptions of the case-control studies used for IDR ontology evaluation

Sources	IDR label	Year of subjects were obtained	Location of the subjects (abbreviations)	Number of case/control subjects	Specific criteria of the subjects
Tuberculosis					
[132]	TB^{INS}	2007	Indonesia (INS)	1,582	Adults

[21]	TB^{AF}	1996-1998	Africa (AF)	247	Adults (>14 years old)
[6]	TB^{CRT}	2006-2008	Croatia (CRT)	300 / 300	Adults (>14 years old)
[136]	TB^{CHN}	2015-2016	North China (CHN)	461	Spinal Tuberculosis cases in Adults (>16 years old)
Meningitis					
[8]	MEN^{CHL}	2012-2013	Chile (CHL)	76 / 337	Children (<5 years old)
[168]	MEN^{KOR}	2013-2014	South Korea (KOR)	24 / 554	Comorbidity with Herpes Zoster
[169]	MEN^{US}	1998-1999	United States (US)	82 /50	Adults (18 to 23 years old)
[170]	MEN^{GZ}	2009	Gaza (GZ)	1,853	Hospitalized children
Dengue Fever					
[148]	DF^{INS}	2014	Indonesia (INS)	3,194	Children (<19 years old)
[49]	DF^{SGP}	2005-2013	Singapore (SGP)	395 / 1,308	Adults (21 to 40 years old)
[149][230]	DF^{SDN}	2012	Sudan (SDN)	491	Adults (16 to 60 years old)
[171]	DF^{DOM}	2011-2012	Dominican Republic (DOM)	796	Children (<16 years old)
[41]	DF^{BRZ}	2003-2005	Brazil (BRZ)	170 / 1,175	Comorbidity with Diabetes
[7]	DF^{NPL}	2011-2012	Nepal (NPL)	834	Per household
Cholera					
[172]	$Cholera^{IND}$	2009-2011	India (IND)	7,661	Registered to selected hospitals
[147]	$Cholera^{PAP}$	2010	Papua New Guinea (PAP)	54 / 122	Adults (>20 years old)
[173]	$Cholera^{ZIM}$	2009	Zimbabwe (ZIM)	55 / 110	Not toddler (>5 years old)
[146]	$Cholera^{DOM}$	2012	Dominican Republic (DOM)	363	Haitian and Dominicans only

Representativeness evaluation of IDR core ontology

Representativeness of the IDR core ontology in this research is defined as the alignment between the encoded knowledge in IDR knowledge-bases and the transmission modes for infectious diseases in general epidemiology theory. We wished to assess to what extent the IDR predictor classes reflect the epidemiologic knowledge presented in Table 2. The assessment is carried out by comparing the number of classes in each predictor category with the total of classes in the ontology (i.e. *class distribution* metric) for all the 18 instances. With this metric, we evaluate the use of a predictor class and conclude whether it reflects the epidemiologic theory for each infectious disease included in the evaluation cases. Since each sub-class represents a risk factor of an infectious disease prevalent in a country, this metric shows the distribution of risk factors for each case-control study that are encoded as sub-classes.

Table 4 presents the class distribution per IDR knowledge-base. The numerator is the number of classes for each predictor, and the denominator is total classes in each IDR knowledge-base. For example, for TB in Indonesia (TB^{INS}) there are 10 risk factors in total, 4 person, 3 climate, and 3 location risk factors. Table 5 presents the average of evaluation cases per predictor category. For example, for *person* class distribution in TB is obtained by calculating the average of TB^{INS}, TB^{AF}*, TB^{CRT}, and TB^{CHN}.

Table 4 Result of *class distribution* metric

IDR Label	predictor classes		
	person	climate	location
TB^{INS}	4/10	3/10	3/10
TB^{AF}*	7/14	4/14	3/14
TB^{CRT}	15/21	3/21	3/21
TB^{CHN}	13/20	5/20	2/20
$Chol^{IND}$	3/11	4/11	4/11
$Chol^{PAP}$	8/14	3/14	3/14
$Chol^{ZIM}$	6/11	3/11	2/11
$Chol^{DOM}$	7/13	3/13	3/13
DF^{INS}	6/12	3/12	3/12
DF^{SGP}*	13/19	3/19	3/19
DF^{SDN}	7/13	3/13	3/13
DF^{DOM}	6/12	3/12	3/12
DF^{BRZ}	7/12	3/12	2/12
DF^{NPL}	1/13	6/13	6/13
MEN^{CHL}*	14/20	3/20	3/20
MEN^{KOR}	6/12	3/12	3/12
MEN^{US}	14/19	3/19	2/19
MEN^{GZ}	10/15	3/15	2/15

* denotes the case-control study that contains *dependent* risk factors (see section 2.2 for the *independence* definition)

Table 5. Summary of *class distribution* metric

Average per ID	Person	Climate	Location
Tuberculosis	56.6%	24.46%	18.93%
Cholera	48.2%	**27%**	24.76%
Dengue Fever	48%	26.67%	**25.28%**
Meningitis	**65.09%**	18.95%	15.96%

Admittedly, the degree of alignment carried out in this evaluation is an arguable measurement since we compare the quantitative measurements against declarative epidemiologic knowledge. Thus, we cannot evaluate by seeking the class distribution of one infectious disease solely. We need to compare the declarative epidemiology theory for a predictor in one infectious disease against the same predictor in another infectious disease, through discussions. If the summary of class distributions reflects the epidemiology knowledge for each predictor, then the predictor categorization in the IDR core ontology aligns, and the predictor categorization is considered as representative. Section 4.1 discusses the degree of alignment of these distributions with the declarative epidemiologic knowledge.

Usefulness evaluation of the IDR rule types and IDR catalog

Usefulness of the IDR rule types is defined by to what extent the five IDR rule types are used to bind the risk factors with their risk quantifications (e.g. odds ratios, prevalence rate) both for independent and dependent risk factors. For example, to encode $Chol^{IND}$ risk factors and their quantifications, we need four IDR rule types. The usability of the IDR rule types for each evaluation is available in Table 6.

From Table 6, all risk quantifications relevant to personalized infectious disease risk prediction are able to be encoded using all five IDR rule types. From five IDR rule types, two rule types (the *real prevalence* and the *real direct risk ratios*) are always used for all IDR knowledge-bases; 1 of 18 cases, MEN^{KOR}, use three rule types (with addition of the *vague risk ratios*); 2 of 18 cases, TB^{CHN} and $CHOL^{IND}$, use four rule types (with addition of the *real indirect risk ratios*); and one case, DF^{NPL}, uses all rule types.

Table 6. The IDR rule types usability

IDR Label	The IDR rule types*					Total
	1	2	3	4	5	
TB^{INS}	v		v			2
TB^{AF}	v		v			2
TB^{CRT}	v		v			2
TB^{CHN}	v		v	v	v	4
$Chol^{IND}$	v		v	v	v	4
$Chol^{PAP}$	v		v			2
$Chol^{ZIM}$	v		v			2
$Chol^{DOM}$	v		v			2
DF^{INS}	v		v			2
DF^{SGP}	v		v			2
DF^{SDN}	v		v			2
DF^{DOM}	v		v			2
DF^{BRZ}	v		v			2
DF^{NPL}	v	v	v	v	v	5
MEN^{CHL}	v		v			2
MEN^{KOR}	v		v		v	3
MEN^{US}	v				v	2
MEN^{GZ}	v				v	2

* the numerical rule type encoding follows the order given in the Table 1

Table 7. The used individuals in IDR catalog

Predictor category	Total of ontology objects in the IDR catalog		Fraction of used ontology objects (%)	
	individuals	sub-classes	individuals	sub-classes
Person	221	126	149 (67.42)	74 (58.73)
Climate	7	21	5 (**71.43**)	18 (**85.71**)
Location	18	46	8 (44.44)	25 (54.34)
Overall	246	207	162 (65.85)	117 (55.52)

The *usefulness* of the IDR catalog is determined by how many ontology objects (individuals and sub-classes) in the IDR catalog are used to encode the risk quantifications. If (many) ontology objects are never used for encoding knowledge in evaluation case, then, they are not useful. Table 7 shows the summary of the used ontology objects for all 18 case-control factor studies. The objects that are used more than once are counted only once. The fraction is obtained by dividing the number of used ontology objects with the total ontology objects per predictor category.

From Table 7, it is shown that the climate is the most used predictor (the fraction of both individuals and sub-classes are the highest). This number shows that the climate factors found in AHID [13] to predict infection risks are consistent with climate factors found in 18 case-control studies. To sum up the degree of usability of the IDR catalog as a whole, 65.85% individuals and 55.52% classes are used. To sum up, more than 60% (mid-point of 65.85% and 55.52%) ontology objects of the IDR catalog is used.

Completeness evaluation of the IDR rule types and IDR catalog

Completeness of the IDR rule types is determined by to what extent the five IDR rule types can encode risk quantifications in the 18 evaluation cases. During IDR instantiation process, all risk ratios and prevalence rates can be encoded using IDR rule types without adding any single rule type. This means that the IDR rule types are complete for binding risk factors with their risk quantifications, for all evaluation cases.

Completeness of the IDR catalog is defined by to what extent the current version of the IDR catalog contains ontology objects represent the infection risk factors in the 18 evaluation cases. Each evaluation case uses one case-control factor study that contains several contextual risk factors to be encoded using IDR ontology objects. During IDR instantiation, risk factors that are not contained in the IDR catalog should be added as new individuals or sub-classes.

To assess the *completeness* of the IDR catalog, for each evaluation case, we investigated how many risk factors per predictor are found in the IDR catalog. For example, in order to encode only MEN^{CHL} risk factors and their quantifications, we need 29 individuals and 14 sub-classes of *person* category: 18 of 29 individuals were found in the IDR catalog; 11 of 29 individuals are new. Also, 13 of 14 sub-classes were in the IDR catalog; only 1 is new. We do this for all 18 IDR knowledge-bases and summarize per category, per ontology object (Table 8).

Table 8 The summary of the completeness evaluation

Predictor category	Fraction of ontology objects that are found in the IDR catalog	
	Individuals (%)	Sub-classes (%)
Person	49	85
Climate	43	80
Location	41	67
Overall	44.33	77.33

From Table 8, to encode one case-control factor, more than half of the required individuals were not contained in the IDR catalog and need to be added as new individuals. However, the new individuals can be added in the current IDR sub-classes. The IDR sub-classes are a good start since the new sub-classes addition is less than a quarter per evaluation case.

Discussion

This section discusses the evaluation results presented in section 3. Some limitations and taken assumptions of the evaluation are also discussed in this section.

Representativeness of the IDR core ontology

In the representativeness evaluation, we intend to evaluate the *knowledge-gleaning* methodology in this article creating knowledge-bases that align with the epidemiology theory. The degree of alignment is assessed by comparing the distribution of predictor classes of the IDR core ontology against the declarative epidemiology theory.

There are two strains of Tuberculosis included in this evaluation: intrathoracic and spinal (TB^{CHN}). Both strains are caused by the same pathogen, *Mycobacterium tuberculosis*, and have the same transmission mode (droplet). But those two strains have different risk factor predictors; the intrathoracic TB mostly affected by personal risk factors, whereas the spinal TB is also affected by environmental risk factors. From Table 5, this epidemiologic knowledge is confirmed through high percentage in *person* category (56.6%); and we found that the spinal TB contributes to the use of *climate* (24.46%) and location (18.93%) contexts.

Two types of Meningitis are included in this evaluation: aseptic Meningitis (Men^{KOR}) which is caused by a virus, and the common Meningitis caused by *Meningococcal* bacteria or mix with fungi. They have different transmission modes. Aseptic Meningitis usually occurs as a secondary infection; therefore, it only has personal risk factors such as *age, gender, pre-existing illness* and *drug consumptions*. The *Meningococcal* disease is spread by direct contact, droplet and sharing fomites. In the encoded knowledge, person category turned out as the highest proportion (65.09%) amongst other infectious diseases and outweighs the climate (18.95%) and location (15.96%) categories. This percentage confirms the alignment of class distribution of personal risk factors in both aseptic and bacterial Meningitis.

Cholera covers all known reservoir types – human, animal and inanimate (water or food). It is usually transmitted through fecal-oral route, ingesting infected food and water; few cases are reported of Cholera transmission by direct contact with the infected person (i.e. human reservoir). Fecal-oral transmission usually occurs to people living close to unhygienic water sources (river). Food and water transmission mode are affected by eating habits, for example, improperly cooked seafood. The percentages of class distribution metric show that the comparison between personal (48.2%), climate (27%) and location (24.76%) is more balanced in Cholera, than in Tuberculosis and Meningitis. This result reflects the Cholera transmission modes that are affected by not only personal but also environmental risk factors (climate and location).

Dengue Fever is solely caused by *Aedes Aegypti* mosquito bite. Transmission of this disease is highly affected by vector survival in current weather and terrain conditions. Temperature, precipitation and humidity are required for *Aedes Aegypti* to multiply. Terrain (e.g. bushes, dense vegetation) and certain elevation are also needed by this mosquito to thrive. Besides that, there are several personal risk factors that increase mosquito landing preferences, such as *blood group, pregnancy,* and *beer-drinking habits*. Again, this epidemiology theory is reflected through lower gaps between the proportion of personal (48%), climate (26.67%) and location (25.28%) in Dengue Fever than in Tuberculosis and Meningitis diseases in the IDR encoding of the respective case-control studies.

To conclude, the encoded knowledge reflects the declarative epidemiology knowledge for each infectious disease. The IDR core ontology provide a basis for building the IDR catalog and IDR knowledge-bases.

Usefulness of the IDR rule types and IDR catalog

For the 18 test IDR knowledge-bases in this research, all five IDR rule types are useful. We also investigated how much of the IDR catalog is reusable to build the evaluation cases. Roughly more than 60% ontology objects of the IDR catalog were used to encode infection risk factors for all.

Completeness of the IDR rule types and IDR catalog

The completeness evaluation aimed to make sure that the IDR rule types and the IDR catalog contains enough resources to help epidemiologists build their IDR knowledge-bases. Minimum two IDR rule types are used per evaluation case. For all 18 evaluation cases, no need to add new IDR rule type to bind risk factors with their risk quantifications. This concludes that all needed IDR rule types are provided in this research.

In order to encode each of the 18 IDR knowledge-bases, sometimes, the epidemiologists need to add new individuals in the IDR catalog to represent the precise risk factors. In all predictor categories for all eighteen IDR knowledge-bases, 49%, 43%, and 41% of the required items for person, climate and location context, respectively are available in the IDR catalog (see Table 8). In other words, we still need to add new individuals more than 50% for each IDR knowledge-base because the IDR catalog does not have them precisely. Most of the new individuals are values for *age* range, *nationality*, *ethnicity*, *belief system*, *income level*, specific part of the city (*district* name) that are largely different from study to study. However, adding such individuals would not be difficult for an epidemiologist using a user interface of this system.

On the other hand, these individuals are within the existing sub-classes in the IDR catalog. 85%, 80%, 67% of the required items for person, climate and location contexts, respectively, are in the IDR catalog (see Table 8). We only need to add less than a quarter new sub-classes to encode epidemiology knowledge for all case-control study. This means that the concepts of risk factor explained in AHID largely comply with the concepts of risk factors in the taken case-control studies. Examples of new sub-classes that need to be added are *allergy*, *hypertension*, *socio-economic*, and *marital status* concepts.

To conclude, the current version of the IDR catalog that was built from distinct risk factors that appeared in the declarative knowledge sources [13], [30], [31] is a good start to represent risk factors and risk quantifications in the selected eighteen case-control studies [6]–[8], [21], [41], [49], [132], [136], [146]–[149], [168]–[173], [230].

Assumptions made during IDR core constructions

The IDR core ontology was made by classifying the seventeen infection drivers presented in AHID [13]. This resulted in main classes: person, and environment (climate and location). However, this categorization reflects the focus of the targeted system on personalized, and environmental context-specific infectious disease risk prediction. In the existing infection and epidemiology concepts in IDO [223] and EPO [195], climate and location usually belong to *spatio-temporal* context. Some articles refer to these *spatio-temporal* risk factors as *environmental* risk factors [7], [42], [86], [103], [129], [246] which is the term used in this article to refer to both climate and location risk factors.

In the Appendix 1, there are two infection drivers that are unable to be categorized as either personal or environmental risk factors: bird migration status, and natural disaster. We grouped these drivers into a *miscellaneous* and do not present it in Fig. 1. This *miscellaneous* also does not appear at all in the 18 evaluation cases (see Table 2). However, we are aware that there are predictors that may not fit to person or environment, thus, we still include sub-classes and individuals of the *miscellaneous* class in the IDR catalog, in case there is an infectious disease that is affected by this kind of drivers.

Limitation of the evaluations

Coverage in this section is intended to explain how much the evaluation cases (i.e. eighteen contextual IDR knowledge-bases) cover the infection risk epidemiology knowledge in AHID. Admittedly, there are a few infection roles (i.e. reservoir type and transmission mode) that are not covered. Thus, the conclusions made through the evaluations may not apply to contexts of the uncovered roles.

The 18 IDR knowledge-bases were developed to evaluate the IDR core ontology, rule types, and catalog. However, they do not cover *unknown* reservoir type (e.g. Trichomoniasis), *blood-borne* transmission mode (e.g. Leishmaniasis), *sexually*-transmitted infection (STI) (e.g. HIV/AIDS), *unknown* transmission mode (e.g. Burkholderia), and *miscellaneous* predictor. This is because (1) the case-control studies for these diseases are limited, (2) even if some infectious diseases listed in *miscellaneous* predictor are common (e.g. Tuberculosis, Cholera), the existing studies do not discuss the natural disaster that is included in *miscellaneous* predictor, (3) we found difficulties to validate the metric-based evaluation results if the transmission mode or reservoir is *unknown*.

Conclusion

This article presents an IDR core ontology designed to become the backbone of the knowledge-base for use in a personalized infectious disease risk prediction system. The core ontology consists of predictor classes: *person*, *climate*, *location*, and one predicted class, *infectious disease*. Through the discussions of the eighteen evaluation cases, the predictor categorization reflects the infection risk described in the epidemiology theory.

Five IDR rule types to bind risk factors in each predictor class with their quantifications are also established. Both numerical and ordinal forms for risk ratios and morbidity frequency are facilitated by these IDR rule types. From the conducted evaluation, these five rule types are able to represent all risk quantifications posed by the eighteen test studies relevant to calculate personalized infectious disease risk predictions.

Also, in this article, we present an initial version of the IDR catalog that consists of 212 classes, 246 individuals in order to facilitate the epidemiologists to build the knowledge-bases. Through the evaluation, more than half of ontology objects (classes, individuals) of the IDR catalog is used during IDR instantiation. For estimation, the epidemiologists can find (1) two-third of the total ontology objects in the current version of the IDR catalog, (2) all needed IDR rule types are provided to bind odds ratios and prevalence rates to represent the infection risk knowledge.

Methods

First, we sought domain knowledge about infectious diseases in humans. The Atlas of Human Infectious Diseases (AHID) [13] lists all existing human infectious diseases with a brief explanation of the epidemiologic knowledge, clinical findings and its distribution map. Besides that, infectious disease drivers are also described. However, the knowledge presented in the

AHID is general, so, we also used WHO [31], CDC [30] factsheets, and clinical and epidemiology journals as additional references.

We summarized the infectious disease drivers explained in AHID to identify infection risk predictors. The predictors will be used to construct the knowledge structure of the infection risk factors, *IDR core ontology*. Thereafter, by following knowledge of *chain of infection risk* in [12], we collated all risk factors of all existing human infectious diseases from [13], [30], [31] based on these predictors. The collation phase has two outputs: risk factors, and forms of risk quantifications relevant to personalized infectious disease risk prediction. Distinct risk factors from the collation are then used to develop ontology objects (classes, sub-classes and individuals) of an *IDR catalog*. Distinct form of risk quantifications (e.g. risk ratios, risk tendencies, and morbidity frequency) are used to develop *IDR rule types*. Using ontology objects in the IDR catalog, the epidemiologists can encode infection risk knowledge in an *IDR knowledge-base* that is specific to one infectious disease prevalent in one location (country) context.

The evaluation plan for the outputs is also explained in this section. We prepared cases in the form of an IDR knowledge-base to evaluate representativeness of the IDR core ontology, usefulness and completeness of the IDR rule types and IDR catalog. The evaluation metrics are inspired by OntoQA [228].

IDR core ontology construction

Seventeen drivers of infectious disease risks are listed in AHID [13] which we used to construct the IDR core ontology. These drivers explain human attributes and activities across domains that are relevant for infectious disease risks in personal and environmental contexts. We categorized these drivers to become the *predictor* classes of the IDR core ontology to fit our system purposes. The resulting IDR core ontology becomes the backbone of the IDR catalog and IDR knowledge-bases. See Section 2.1 for the result.

IDR rule types design

We intended to find risk quantifications that are used by epidemiologists to describe magnitudes of personal or environmental risk factors, and relevant to predict a personalized infectious disease risk. In order to find this kind of article, we used search terms: “disease risk”, “Bayesian Network”, “infection risk”, “risk prediction”, “estimating risk”, “personal factors”, “environmental factors”.

Bayes theorem that is commonly used to calculate a disease risk probability from risk quantifications found in [42], [43], [247]. These articles reveal two important risk quantifications that are used to calculate personalized disease risk predictions: *risk ratios* (odds ratio, relative risk), and *morbidity frequency* (prevalence, incidence). The risk factors which the magnitude is quantified by the risk ratio, and prevalence rate in a location are encoded as rules.

In order to retrieve forms of the risk ratios and morbidity frequency, we searched in journal repositories using search terms: “human infectious diseases”, “risk ratio”, “odds ratio”, “demographic”. We filtered the search results by identifying whether the articles publish the

risk ratios for an infection prevalent in a country during specific year(s) (see Fig. 1 for an example of the risk ratio table). Articles that contain this kind of table are then collected to make decisions about IDR rule types (see Section 2.2 for the result).

IDR catalog construction

Since we envisage that epidemiologists will use the IDR knowledge-base as their knowledge repositories about infection risks, we intend to provide the IDR catalog that contains ontology objects to create the contextual IDR knowledge-bases. The IDR catalog is a collection of sub-classes and individuals which inherits the structure of the IDR core ontology. To obtain all things relevant to infection risks, we collated all mentioned risk factors for each infectious disease listed on the [13], [30], [31]. Appendix 3 shows samples of the collation table. Distinct risk factors are collected to form the IDR catalog (see Section 2.3 for the result).

IDR instantiation

IDR instantiation is the process of building an infectious disease-country context IDR knowledge-base. The instantiation process covers (1) registration of the infectious disease name and the country context as individuals of associated classes, (2) selection of sub-classes and individuals from the IDR catalog or add new items to adjust to the epidemiology knowledge of the registered infectious disease-country context, and (3) bind the risk quantifications with the selected items using IDR rules by following the five IDR rule types. One of the selected individuals represents the *baseline*. Baseline is the referenced risk factor for each attribute which the risk ratio is always 1. In the Fig. 4, *female* and *age group 15-24* are the baseline of the *gender* and *age*, respectively.

Encoding the epidemiologic knowledge using these three steps, creates an *IDR knowledge-base* that consists of *one IDR ontology instance* and *a set of IDR rules*. Thereafter, the BN-Builder algorithm, that utilizes Bayes risk theorem, converts this IDR knowledge-base into an equivalent BN [238]. The generated BN yields personalized infectious disease risk prediction [239] for one infectious disease and one country.

Evaluation of IDR core ontology, IDR rule types and IDR catalog

We evaluate the *knowledge-gleaning* process (explained in Section 6.1 to 6.3) that result in an IDR knowledge-base by (1) making sure the created IDR core ontology *aligns* with the chain of infection risk in epidemiologic knowledge, (2) assessing the *usability* of IDR rule types and IDR catalog during instantiation process to build IDR knowledge-bases, (3) measuring the *completeness* of the IDR rule types and current version IDR catalog.

For these evaluations, we need to prepare cases that are used for evaluating the IDR ontology, rules and catalog (i.e. evaluation cases). Each evaluation case is an IDR knowledge-base that encodes real risk ratios and morbidity frequency for an infectious disease prevalent in one country context. We obtained the real risk ratios and morbidity frequency from publications describing studies of a disease in human population of a country or a region (i.e. *case-control*

study). To optimize the use of IDR rule types and catalog to create an IDR knowledge-base, the infectious diseases chosen for the evaluation cases (1) cover as much as possible infection *roles* of all existing human infectious diseases, (2) have personal and environmental risk factors, (3) and are prevalent in several countries so the classifications of their risk factors are less subjective. The evaluation cases and the results of IDR knowledge-bases are presented in Section 3.

We measure the *degree of alignment* by comparing the encoded knowledge in the IDR ontology instance in the IDR knowledge-base with epidemiology theory. We are inspired by the OntoQA metrics [228] to calculate the number of sub-classes for each predictor class and divide that by the total classes (i.e. class distribution). To conclude whether the encoded knowledge aligns or not, we compare the class distributions with the declarative epidemiologic knowledge through discussions (see Section 4.1).

We assess the *degree of usability* of the IDR rule types and IDR catalog. The degree of usability of the IDR rule types is investigated by counting how many rule types are used to bind risk factors with their risk quantifications for all evaluation cases. Whereas, the IDR catalog usability is assessed by counting how many ontology objects (individuals and sub-classes) of the IDR catalog are used to encode risk factors for all evaluation cases. If more than half rule types or ontology objects are used to encode the risk factors, then the IDR rule types and the IDR catalog are considered as *useful* tools.

We determine the *degree of completeness* for both IDR rule types and IDR catalog. Sometimes, during IDR instantiation process, the risk factors are too specific and not found in the current version of the IDR catalog, hence they should be added as new ontology objects. To conclude the degree of completeness, we count how many of the required rule types and ontology objects are found in the IDR rule types and the IDR catalog. Then, we divide it with the total of the required ontology objects, for all evaluation cases.

Reference List

[1] World Health Organization, “Disease burden and mortality estimates,” World Health Organization, 2018.

[2] World Health Organization, “Disease incidence, prevalence and disability.”

[3] I. Albert, E. Grenier, J. Denis, and J. Rousseau, “Quantitative Risk Assessment from Farm to Fork and Beyond : A Global Bayesian Approach Concerning Food-Borne Diseases,” *Risk Anal.*, vol. 28, no. 2, pp. 557–571, 2008.

[4] T.-Y. Lee, C.-B. Wang, T.-T. Chen, K. N. Kuo, M.-S. Wu, J.-T. Lin, and C.-Y. Wu, “A Tool to Predict Risk for Gastric Cancer in Patients with Peptic Ulcer Disease, Based on a Nationwide Cohort.,” *Clin. Gastroenterol. Hepatol.*, vol. 13, pp. 287–293, 2015.

[5] H. Cao, L. Zhang, L. Li, and S. Lo, “Risk Factors for Acute Endophthalmitis following Cataract Surgery : A Systematic Review and Meta- Analysis,” *PLoS One*, vol. 8, no. 8, pp. 1–18, 2013.

[6] A. Jurcev-Savicevic, R. Mulic, B. Ban, K. Kozul, L. Bacun-Ivcek, J. Valic, G. Popijac-Cesar, S. Marinovic-Dunatov, M. Gotovac, and A. Simunovic, “Risk factors for pulmonary tuberculosis in Croatia: a matched case-control study,” *BMC Public Health*, vol. 13, p. 991, 2013.

[7] M. Dhimal, I. Gautam, H. D. Joshi, R. B. O’Hara, B. Ahrens, and U. Kuch, “Risk Factors for the Presence of Chikungunya and Dengue Vectors (Aedes aegypti and Aedes albopictus), Their Altitudinal Distribution and Climatic Determinants of Their Abundance in Central Nepal,” *PLoS Negl. Trop. Dis.*, vol. 9, no. 3, pp. 1–20, 2015.

[8] A. Olea, I. Matute, C. González, I. Delgado, L. Poffald, E. Pedroni, T. Alfaro, M. Hirmas, M. Nájera, A. Gormaz, D. López, S. Loayza, C. Ferreccio, D. Gallegos, R. Fuentes, P. Vial, and X. Aguilera, “Case − Control Study of Risk Factors for Meningococcal Disease in Chile,” *Emerg. Infect. Dis.*, vol. 23, no. 7, pp. 1070–1078, 2017.

[9] D. Raja, “Artificial Intelligence in Medical Epidemiology - AIME.” .

[10] M. Woolhouse, “How to make predictions about future infectious disease risks,” *Philos. Trans. R. Soc. B Biol. Sci.*, vol. 366, no. 1573, pp. 2045–2054, 2011.

[11] P. R. O. Payne, “Chapter 1: Biomedical Knowledge Integration,” *PLoS Comput. Biol.*, vol. 8, no. 12, 2012.

[12] CDC, “Principles of Epidemiology | Lesson 1 - Section 1.” .

[13] H. F. L. Wertheim, P. Horby, and J. P. Woodall, *Atlas of Human Infectious Diseases*. Wiley-Blackwell, 2012.

[14] M. A. Al-Mozaini and M. K. Mansour, “Personalized medicine Is it time for infectious diseases?,” *www.smj.org.sa*

Saudi Med J, vol. 37, no. 12. 2016.
[15] S. Y. Yang and C. L. Hsu, "A location-based services and Google maps-based information master system for tour guiding," *Comput. Electr. Eng.*, vol. 000, pp. 1–19, 2015.
[16] R. Chinnachodteeranun, N. D. Hung, K. Honda, A. V. M. Ines, and E. Han, "Designing implementing weather generators as web services," *Futur. Internet*, vol. 8, no. 4, 2016.
[17] R. Lowe, C. Barcellos, C. A. S. Coelho, T. C. Bailey, G. E. Coelho, R. Graham, T. Jupp, W. M. Ramalho, M. S. Carvalho, D. B. Stephenson, and X. Rodó, "Dengue outlook for the World Cup in Brazil: an early warning model framework driven by real-time seasonal climate forecasts," *Lancet Infect. Dis.*, vol. 14, no. 7, pp. 619–626, Jul. 2014.
[18] M. Chilvers and J. Willbur, "Sporecaster: New white mold risk prediction smartphone app now live | MSU Extension," 2018. .
[19] United Nations, "WHO morbidity report in UN Data." .
[20] L. K. Alexander, B. Lopes, K. Ricchetti-Masterson, and K. B. Yeatts, "Cross-sectional Studies," 2015.
[21] P. Gustafson, V. F. Gomes, C. S. Vieira, P. Rabna, R. Seng, P. Johansson, A. Sandström, R. Norberg, I. Lisse, B. Samb, P. Aaby, and A. Nauclér, "Tuberculosis in Bissau : incidence and risk factors in an urban community in sub-Saharan Africa," *Int. J. Epidemiol.*, vol. 33, no. 1, pp. 163–172, 2018.
[22] L. G. Cowell and B. Smith, "Infectious disease ontology," *Infect. Dis. Informatics*, pp. 373–395, 2010.
[23] Y. Lin, Z. Xiang, and Y. He, "Brucellosis Ontology (IDOBRU) as an extension of the Infectious Disease Ontology," *J. Biomed. Semantics*, vol. 9, no. 2, pp. 1–18, 2011.
[24] G. Camara, S. Despres, R. Djedidi, and M. Lo, "Design of Schistosomiasis Ontology (IDOSCHISTO) Extending the Infectious Disease," in *Medical Informatics*, 2013, no. 1, pp. 466–470.
[25] Y. Zhao, F. Parvinzamir, H. Wei, E. Liu, Z. Deng, F. Dong, A. Third, V. Marozas, E. Kaldoudi, and G. Clapworthy, "The CARRE Project," 2013.
[26] Ö. Kafalı, M. Sindlar, T. Van Der Weide, and K. Stathis, "ORC: an Ontology Reasoning Component for Diabetes."
[27] A. Khan, A. Sadia, S. Ahmed, H. Tabassum, and M. S. Khan, "HEPO: The hepatitis ontology for abductive medical diagnostic systems," in *2017 International Conference on Communication, Computing and Digital Systems (C-CODE)*, 2017, pp. 271–275.
[28] D. Vrajitoru, "Knowledge Representation." .
[29] S. Colton, "Knowledge Representation." .
[30] CDC, "Infectious Diseases | 2018 National Notifiable Conditions." .
[31] WHO, "WHO | Infectious diseases," *WHO*, 2016. .
[32] M. Szumilas, "Explaining odds ratios.," *J. Can. Acad. Child Adolesc. Psychiatry*, vol. 19, no. 3, pp. 227–9, Aug. 2010.
[33] P. C. G. Da Costa, K. B. Laskey, and K. J. Laskey, "PR-OWL: A bayesian ontology language for the Semantic Web," *Lect. Notes Comput. Sci. (including Subser. Lect. Notes Artif. Intell. Lect. Notes Bioinformatics)*, vol. 5327 LNAI, pp. 88–107, 2008.
[34] Z. Ding, Y. Peng, and R. Pan, "BayesOWL : Uncertainty Modeling in Semantic Web Ontologies," *StudFuzz*, vol. 204, pp. 3–29, 2006.
[35] R. Pan, Z. Ding, Y. Yu, and Y. Peng, "A Bayesian Network Approach to Ontology Mapping," in *International Semantic Web Conference*, 2005, pp. 1–16.
[36] D. Settas, A. Cerone, and S. Fenz, "Expert Systems with Applications Enhancing ontology-based antipattern detection using Bayesian networks," *Expert Syst. Appl.*, vol. 39, no. 10, pp. 9041–9053, 2012.
[37] P. J. Giabbanelli, T. Torsney-Weir, and V. K. Mago, "A fuzzy cognitive map of the psychosocial determinants of obesity," *Appl. Soft Comput. J.*, vol. 12, no. 12, pp. 3711–3724, 2012.
[38] N. Douali, H. Csaba, J. De Roo, E. I. Papageorgiou, and M. C. Jaulent, "Diagnosis Support System based on clinical guidelines: Comparison between case-based fuzzy cognitive maps and bayesian networks," *Comput. Methods Programs Biomed.*, vol. 113, no. 1, pp. 133–143, 2014.
[39] P. Dawson, R. Gailis, and A. Meehan, "Detecting disease outbreaks using a combined Bayesian network and particle filter approach," *J. Theor. Biol.*, vol. 370, pp. 171–183, 2015.
[40] Q. Jiang, J. T. Zhou, Z. B. Jiang, and B. Xu, "Identifying risk factors of avian infectious diseases at household level in Poyang Lake region, China," *Prev. Vet. Med.*, vol. 116, no. 1–2, pp. 151–160, 2014.
[41] M. A. A. Figueiredo, L. C. Rodrigues, M. L. Barreto, J. W. O. Lima, M. C. N. Costa, V. Morato, R. Blanton, P. F. C. Vasconcelos, M. R. T. Nunes, and M. G. Teixeira, "Allergies and diabetes as risk factors for dengue hemorrhagic fever: Results of a case control study," *PLoS Negl. Trop. Dis.*, vol. 4, no. 6, 2010.
[42] C. M. Lewis, S. C. L. Whitwell, A. Forbes, J. Sanderson, and C. G. Mathew, "Estimating risks of common complex diseases across genetic and environmental factors: the example of Crohn disease," pp. 689–694, 2007.
[43] A. N. Freedman, D. Seminara, M. H. Gail, P. Hartge, G. A. Colditz, R. Ballard-barbash, and R. M. Pfeiffer, "Cancer Risk Prediction Models : A Workshop on Development, Evaluation, and Application," *J. Natl. Cancer Inst.*, vol. 97, no. 10, 2005.
[44] Merriam-Webster, "Predicting | Definition of Predicting by Merriam-Webster," 1828. .
[45] I. Ahmed, T. P. Debray, K. G. Moons, and R. D. Riley, "Developing and validating risk prediction models in an individual participant data meta-analysis," *BMC Med. Res. Methodol.*, vol. 14, no. 1, p. 3, Dec. 2014.
[46] M. Menk, L. Giebelhäuser, G. Vorderwülbecke, M. Gassner, J. A. Graw, B. Weiss, M. Zimmermann, K.-D. Wernecke, and S. Weber-Carstens, "Nucleated red blood cells as predictors of mortality in patients with acute respiratory distress syndrome (ARDS): an observational study," *Ann. Intensive Care*, vol. 8, no. 1, p. 42, Dec. 2018.
[47] C. Toma, A. D. Shaw, R. J. N. Allcock, A. Heath, K. D. Pierce, P. B. Mitchell, P. R. Schofield, and J. M. Fullerton, "An examination of multiple classes of rare variants in extended families with bipolar disorder," *Transl. Psychiatry*,

vol. 8, no. 1, p. 65, Dec. 2018.
[48] C. Wright and T. Dent, *Quality standards in risk prediction: A summary of an expert meeting*. Cambridge: PHG Foundation, 2011.
[49] C. F. Yung, S. P. Chan, T. L. Thein, S. C. Chai, and Y. S. Leo, "Epidemiological risk factors for adult dengue in Singapore : an 8-year nested test negative case control study," *BMC Infect. Dis.*, pp. 1–9, 2016.
[50] M. J. Pencina, R. B. D. A. Sr, M. G. Larson, J. M. Massaro, and R. S. Vasan, "Predicting the Thirty-Year Risk of Cardiovascular Disease: The Framingham Heart Study," *Circulation*, vol. 119, no. 24, pp. 3078–3084, 2009.
[51] T.-C. Li, C.-I. Li, C.-S. Liu, W.-Y. Lin, C.-H. Lin, S.-Y. Yang, J.-H. Chiang, and C.-C. Lin, "Development and validation of prediction models for the risks of diabetes-related hospitalization and in-hospital mortality in patients with type 2 diabetes," *Metabolism*, vol. 85, pp. 38–47, Aug. 2018.
[52] R. Landy, L. C. Cheung, M. Schiffman, J. C. Gage, N. Hyun, N. Wentzensen, W. K. Kinney, P. E. Castle, B. Fetterman, N. E. Poitras, T. Lorey, P. D. Sasieni, and H. A. Katki, "Challenges in risk estimation using routinely collected clinical data: The example of estimating cervical cancer risks from electronic health-records," *Prev. Med. (Baltim).*, vol. 111, pp. 429–435, Jun. 2018.
[53] K. Y. Clement, W. J. Wouter Botzen, R. Brouwer, and J. C. J. H. Aerts, "A global review of the impact of basis risk on the functioning of and demand for index insurance," *Int. J. Disaster Risk Reduct.*, vol. 28, pp. 845–853, Jun. 2018.
[54] C. Policiano, A. Fonseca, J. M. Mendes, N. Clode, and L. M. Graça, "Small-for-gestational-age babies of low-risk term pregnancies: does antenatal detection matter?," *J. Matern. Neonatal Med.*, vol. 31, no. 11, pp. 1426–1430, Jun. 2018.
[55] C.-H. Chan, H.-K. Wong, and P. S.-F. Yip, "Exploring the use of telephone helpline pertaining to older adult suicide prevention: A Hong Kong experience," *J. Affect. Disord.*, vol. 236, pp. 75–79, Aug. 2018.
[56] Merriam-Webster, "Personalize | Definition of Personalize by Merriam-Webster." .
[57] National Cancer Institute at the National Institutes of Health, "Definition of personalized medicine - NCI Dictionary of Cancer Terms - National Cancer Institute." .
[58] W. K. Redekop, "The Faces of Personalized Medicine: A Framework for Understanding Its Meaning and Scope," *Value Heal.*, vol. 16, pp. 1–6, 2013.
[59] D. Becker, W. van Breda, B. Funk, M. Hoogendoorn, J. Ruwaard, and H. Riper, "Predictive modeling in e-mental health: A common language framework," *Internet Interv.*, vol. 12, pp. 57–67, Jun. 2018.
[60] G. Colella, F. Fazioli, M. Gallo, A. De Chiara, G. Apice, C. Ruosi, A. Cimmino, and F. de Nigris, "Sarcoma Spheroids and Organoids—Promising Tools in the Era of Personalized Medicine," *Int. J. Mol. Sci.*, vol. 19, no. 2, p. 615, Feb. 2018.
[61] P. S. Pratiwi and D. Tjondronegoro, "Towards personalisation of physical activity e-coach using stage-matched behaviour change and motivational interviewing strategies," in *2017 IEEE Life Sciences Conference (LSC)*, 2017, pp. 5–8.
[62] K. Selby, G. Bartlett-Esquilant, and J. Cornuz, "Personalized cancer screening: helping primary care rise to the challenge.," *Public Health Rev.*, vol. 39, p. 4, 2018.
[63] C. Butts, S. Kamel-Reid, G. Batist, S. Chia, C. Blanke, M. Moore, M. B. Sawyer, C. Desjardins, A. Dubois, J. Pun, K. Bonter, and F. D. Ashbury, "Benefits, issues, and recommendations for personalized medicine in oncology in Canada.," *Curr. Oncol.*, vol. 20, no. 5, pp. e475-83, Oct. 2013.
[64] National Cancer Institute (NCI), "Value of Personalized Medicine." PhRMA, 2015.
[65] C. L. Ratcliff, K. A. Kaphingst, and J. D. Jensen, "When Personal Feels Invasive: Foreseeing Challenges in Precision Medicine Communication," *J. Health Commun.*, vol. 23, no. 2, pp. 144–152, Feb. 2018.
[66] S. O. Jensen and S. J. van Hal, "Personalized Medicine and Infectious Disease Management," *Trends Microbiol.*, vol. 25, no. 11, pp. 875–876, Nov. 2017.
[67] CDC, "Principles of Epidemiology | Lesson 1 - Section 10," 2012. .
[68] B. Pam and F. Gorder, "Computational Epidemiology," *Comput. Sci. Eng.*, 2010.
[69] CDC, "Public Health 101 Series Introduction to Public Health Informatics Instructor name Course Topics Introduction to Public Health Informatics," 2009.
[70] American Medical Informatics Association (AMIA), "Public Health Informatics." .
[71] Public Health Informatics Institute (PHII), "Defining Public Health Informatics." .
[72] D. Zeng, H. Chen, C. Lynch, and M. Eidson, "Chapter 13 INFECTIOUS DISEASE INFORMATICS AND OUTBREAK DETECTION," in *Medical Informatics*, 2005, pp. 359–395.
[73] M. Salathe, L. Bengtsson, T. J. Bodnar, D. D. Brewer, J. S. Brownstein, C. Buckee, E. M. Campbell, C. Cattuto, S. Khandelwal, P. L. Mabry, and A. Vespignani, "Digital epidemiology," *PLoS Comput. Biol.*, vol. 8, no. 7, pp. 1–5, 2012.
[74] Z. Huang, A. Das, Y. Qiu, and A. J. Tatem, "Web-based GIS: the vector-borne disease airline importation risk (VBD-AIR) tool.," *Int. J. Health Geogr.*, vol. 11, p. 33, 2012.
[75] R. Nelson, "HealthMap: the future of infectious diseases surveillance?," *Lancet Infect. Dis.*, vol. 8, no. 10, p. 596, 2008.
[76] C. C. Freifeld, K. D. Mandl, B. Y. Reis, and J. S. Brownstein, "HealthMap : Global Infectious Disease Monitoring through," *J. Am. Med. Informatics Assoc.*, vol. 15, no. 2, pp. 150–157, 2014.
[77] S. Sindi, E. Calov, J. Fokkens, T. Ngandu, H. Soininen, J. Tuomilehto, and M. Kivipelto, "The CAIDE Dementia Risk Score App: The development of an evidence-based mobile application to predict the risk of dementia," *Alzheimer's Dement. Diagnosis, Assess. Dis. Monit.*, vol. 1, no. 3, pp. 328–333, 2015.
[78] E. B. Postnikov and D. V Tatarenkov, "Prediction of flu epidemic activity with dynamical model based on weather forecast," *Ecol. Complex.*, vol. 15, pp. 109–113, 2013.

[79] G. M. Hwang, P. J. Mahoney, J. H. James, G. C. Lin, A. D. Berro, M. A. Keybl, D. M. Goedecke, J. J. Mathieu, and T. Wilson, “A model-based tool to predict the propagation of infectious disease via airports,” *Travel Med. Infect. Dis.*, vol. 10, no. 1, pp. 32–42, 2012.
[80] P. Diaz, P. Constantine, K. Kalmbach, E. Jones, and S. Pankavich, “A modified SEIR model for the spread of Ebola in Western Africa and metrics for resource allocation,” *Appl. Math. Comput.*, vol. 324, pp. 141–155, May 2018.
[81] S. Side, Y. M. Rangkuti, D. G. Pane, and M. S. Sinaga, “Stability Analysis Susceptible, Exposed, Infected, Recovered (SEIR) Model for Spread Model for Spread of Dengue Fever in Medan,” *J. Phys. Conf. Ser.*, vol. 954, p. 012018, Jan. 2018.
[82] T. Iskandar, N. A. Chaniago, S. Munzir, V. Halfiani, and M. Ramli, “Mathematical model of tuberculosis epidemic with recovery time delay,” in *AIP*, 2017, p. 020021.
[83] X. Wang, S. Panchanathan, and G. Chowell, “A Data-Driven Mathematical Model of CA-MRSA Transmission among Age Groups: Evaluating the Effect of Control Interventions,” *PLoS Comput. Biol.*, vol. 9, no. 11, 2013.
[84] B. S. Glicksberg, L. Li, M. A. Badgeley, K. Shameer, R. Kosoy, N. D. Beckmann, N. Pho, J. Hakenberg, M. Ma, K. L. Ayers, G. E. Hoffman, S. D. Li, E. E. Schadt, C. J. Patel, R. Chen, and J. T. Dudley, “Comparative analyses of population-scale phenomic data in electronic medical records reveal race-specific disease networks,” *Bioinformatics*, vol. 32, no. 12, pp. i101–i110, 2016.
[85] R. Villamarín, G. Cooper, M. Wagner, F. C. Tsui, and J. U. Espino, “A method for estimating from thermometer sales the incidence of diseases that are symptomatically similar to influenza,” *J. Biomed. Inform.*, vol. 46, no. 3, pp. 444–457, 2013.
[86] R. G. C. Scholte, L. Gosoniu, J. B. Malone, F. Chammartin, J. Utzinger, and P. Vounatsou, “Predictive risk mapping of schistosomiasis in brazil using bayesian geostatistical models,” *Acta Trop.*, vol. 132, no. 1, pp. 57–63, 2014.
[87] M. J. Vilar, S. Virtanen, R. Laukkanen-Ninios, and H. Korkeala, “Bayesian modelling to identify the risk factors for Yersinia enterocolitica contamination of pork carcasses and pluck sets in slaughterhouses,” *Int. J. Food Microbiol.*, vol. 197, pp. 53–57, 2015.
[88] X. L. Zhang, X. J. Shao, J. Wang, and W. L. Guo, “Temporal characteristics of respiratory syncytial virus infection in children and its correlation with climatic factors at a public pediatric hospital in Suzhou,” *J. Clin. Virol.*, vol. 58, no. 4, pp. 666–670, 2013.
[89] L. Getoor, N. Friedman, D. Koller, A. Pfeffer, and B. Taskar, “Probabilistic Relational Models,” in *Introduction to Statistical Relational Learning*, 2007, pp. 129–174.
[90] J. Lenfestey, T. Temple, and E. Howe, “Intro to Probabilistic Relational Models.” .
[91] B. Borghetti, “Bayesian Knowledge Bases.” .
[92] E. Santos, E. S. Santos, and S. Eyal, “Implicitly preserving semantics during incremental knowledge base acquisition under uncertainty,” *Int. J. Approx. Reason.*, vol. 33, pp. 71–94, 2003.
[93] L. Ngo and P. Haddawy, “Answering queries from context-sensitive probabilistic knowledge bases,” *Theor. Comput. Sci.*, vol. 171, no. 1–2, pp. 147–177, 1997.
[94] P. Haddawy, “Generating Bayesian Networks from Probablity Logic Knowledge Bases,” pp. 262–269, 1994.
[95] L. L. Santos, R. N. Carvalho, M. Ladeira, and W. Li, “A New Algorithm for Generating Situation-Specific Bayesian Networks Using Bayes-Ball Method,” *Uncertain. Reason. Semant. Web*, 2016.
[96] Z. Ding, Y. Peng, and R. Pan, “BayesOWL : Uncertainty Modelling in Semantic Web Ontologies,” *Soft Comput. Ontol. Semant. Web*, vol. 29, pp. 3–29, 2006.
[97] N. C. Stenseth, N. I. Samia, H. Viljugrein, K. L. Kausrud, M. Begon, S. Davis, H. Leirs, V. M. Dubyanskiy, J. Esper, V. S. Ageyev, N. L. Klassovskiy, S. B. Pole, and K.-S. Chan, “Plague dynamics are driven by climate variation,” *Proc. Natl. Acad. Sci.*, vol. 103, no. 35, pp. 13110–13115, 2006.
[98] H. Khiabanian, A. B. Holmes, B. J. Kelly, M. Gururaj, G. Hripcsak, and R. Rabadan, “Signs of the 2009 influenza pandemic in the New York-Presbyterian hospital electronic health records,” *PLoS One*, vol. 5, no. 9, pp. 1–8, 2010.
[99] S. M. Upadhyayula, S. Rao Mutheneni, H. K. Nayanoori, A. Natarajan, and P. Goswami, “Impact of weather variables on mosquitoes infected with Japanese encephalitis virus in Kurnool district, Andhra Pradesh.,” *Asian Pac. J. Trop. Med.*, vol. 5, no. 5, pp. 337–41, 2012.
[100] D. Onozuka and M. Hashizume, “Effect of weather variability on the incidence of mumps in children: a time-series analysis.,” *Epidemiol. Infect.*, vol. 139, no. 11, pp. 1692–700, 2011.
[101] C. Imai, B. Armstrong, Z. Chalabi, P. Mangtani, and M. Hashizume, “Time series regression model for infectious disease and weather.,” *Environ. Res.*, vol. 142, pp. 319–327, 2015.
[102] M. Reyes, M. Eriksson, R. Bennet, K.-O. Hedlund, and A. Ehrnst, “Regular pattern of respiratory syncytial virus and rotavirus infections and relation to weather in Stockholm, 1984-1993,” *Clin. Microbiol. Infect.*, vol. 3, no. 6, pp. 640–646, Dec. 1997.
[103] T. S. Chang, R. E. Gangnon, C. David Page, W. R. Buckingham, A. Tandias, K. J. Cowan, C. D. Tomasallo, B. G. Arndt, L. P. Hanrahan, and T. W. Guilbert, “Sparse modeling of spatial environmental variables associated with asthma,” *J. Biomed. Inform.*, vol. 53, pp. 320–329, 2015.
[104] Y. Nakamura, H. Kawanohara, and M. Kamei, “Proposition of real-time precise prediction model of infectious disease patients from Prescription Surveillance using the National Database of Electronic Medical Claims,” *J. Infect. Chemother.*, vol. 21, no. 11, pp. 776–782, 2015.
[105] R. K. Meentemeyer, M. A. Dorning, J. B. Vogler, D. Schmidt, and M. Garbelotto, “Citizen science helps predict risk of emerging infectious disease,” 2015.
[106] R. D. Melamed, H. Khiabanian, and R. Rabadan, “Data-driven discovery of seasonally linked diseases from an Electronic Health Records system.,” *BMC Bioinformatics*, vol. 15 Suppl 6, no. Suppl 6, p. S3, 2014.
[107] A. B. Holmes, A. Hawson, F. Liu, C. Friedman, H. Khiabanian, and R. Rabadan, “Discovering disease associations

by integrating electronic clinical data and medical literature," *PLoS One*, vol. 6, no. 6, 2011.
[108] T. W. Guilbert, B. Arndt, J. Temte, A. Adams, W. Buckingham, A. Tandias, C. Tomasallo, H. a Anderson, and L. P. Hanrahan, "The theory and application of UW ehealth-PHINEX, a clinical electronic health record-public health information exchange.," *Wis. Med. J.*, vol. 111, no. 3, pp. 124–133, 2012.
[109] H. Nesse, "SEIR Model." .
[110] T. Jombart, A. Cori, X. Didelot, S. Cauchemez, C. Fraser, and N. Ferguson, "Bayesian Reconstruction of Disease Outbreaks by Combining Epidemiologic and Genomic Data," *PLoS Comput. Biol.*, vol. 10, no. 1, 2014.
[111] A. Huppert, O. Barnea, G. Katriel, R. Yaari, U. Roll, and L. Stone, "Modeling and statistical analysis of the spatio-temporal patterns of seasonal influenza in Israel.," *PLoS One*, vol. 7, no. 10, p. e45107, 2012.
[112] S. Side, Irwan, U. Mulbar, and W. Sanusi, "SEIR model simulation for Hepatitis B," 2017, p. 020198.
[113] P. Kostkova, M. Szomszor, and C. St. Luis, "#Swineflu: The Use of Twitter as an EarlyWarning and Risk Communication," *ACM Trans. Manag. Inf. Syst.*, vol. 5, no. 2, pp. 1–25, 2014.
[114] E. J. Tomayko, B. A. Weinert, L. Godfrey, A. K. Adams, and L. P. Hanrahan, "Using Electronic Health Records to Examine Disease Risk in Small Populations: Obesity Among American Indian Children, Wisconsin, 2007-2012.," *Prev. Chronic Dis.*, vol. 13, no. E29, pp. 1–9, 2016.
[115] L. Faisandier, V. Bonneterre, R. De Gaudemaris, and D. J. Bicout, "Occupational exposome: A network-based approach for characterizing Occupational Health Problems," *J. Biomed. Inform.*, vol. 44, no. 4, pp. 545–552, 2011.
[116] Healthians, "India's largest Blood Test & Health Test @ Home Service | Healthians." .
[117] P. Tiwari, A. Jaiswal, N. Vishwakarma, and P. Patel, "Smart Health Care (an Android app to predict disease on the basis of symptoms)," *Int. Res. J. Eng. Technol.*, pp. 2395–56, 2017.
[118] MdCalc, "Framingham Coronary Heart Disease Risk Score - MDCalc." .
[119] "Infectious Disease Advisor App." .
[120] J. Huan, "Smartphone app to detect risk for Ebola exposure." .
[121] M. A. Ali, Z. Ahsan, M. Amin, S. Latif, A. Ayyaz, and M. N. Ayyaz, "ID-Viewer: a visual analytics architecture for infectious diseases surveillance and response management in Pakistan," *Public Health*, vol. 134, pp. 72–85, 2016.
[122] H. Rahman, "Monitoring , Surveillance and Forecasting of Infectious Animal Diseases in India," vol. 16, pp. 177–181, 2015.
[123] I. M. Blake, P. Chenoweth, H. Okayasu, C. A. Donnelly, R. B. Aylward, and N. C. Grassly, "Faster detection of poliomyelitis outbreaks to support polio eradication," *Emerg. Infect. Dis.*, vol. 22, no. 3, pp. 449–456, 2016.
[124] W. K. Wong, a. Moore, G. Cooper, and M. Wagner, "Bayesian network anomaly pattern detection for disease outbreaks," *Mach. Learn. Work. Then Conf.*, vol. 20, no. 2, p. 808, 2003.
[125] W.-K. Wong, A. Moore, G. Cooper, and M. Wagner, "WSARE: What's Strange About Recent Events?," *J. Urban Health*, vol. 80, no. 2 Suppl 1, pp. i66-75, 2003.
[126] M. L. Barreto, M. Glo, and E. H. Carmo, "Infectious diseases epidemiology," *J. Epidemiol. Community Heal.*, vol. 60, pp. 192–195, 2006.
[127] X. Wu, Y. Lu, S. Zhou, L. Chen, and B. Xu, "Impact of climate change on human infectious diseases: Empirical evidence and human adaptation," *Environ. Int.*, vol. 86, pp. 14–23, 2016.
[128] A. Kilianski, P. Carcel, S. Yao, P. Roth, J. Schulte, G. B. Donarum, E. T. Fochler, J. M. Hill, A. T. Liem, M. R. Wiley, J. T. Ladner, B. P. Pfeffer, O. Elliot, A. Petrosov, D. D. Jima, T. G. Vallard, M. C. Melendrez, E. Skowronski, P. L. Quan, W. I. Lipkin, H. S. Gibbons, D. L. Hirschberg, G. F. Palacios, and C. N. Rosenzweig, "Pathosphere.org: Pathogen detection and characterization through a web-based, open source informatics platform," *BMC Bioinformatics*, vol. 16, no. 1, pp. 1–13, 2015.
[129] S. Altizer, A. Dobson, P. Hosseini, P. Hudson, M. Pascual, and P. Rohani, "Seasonality and the dynamics of infectious diseases," *Ecol. Lett.*, vol. 9, pp. 467–484, 2006.
[130] K. Yeatts, P. Sly, S. Shore, S. Weiss, F. Martinez, A. Geller, P. Bromberg, P. Enright, H. Koren, D. Weissman, and M. Selgrade, "A brief targeted review of susceptibility factors, environmental exposures, asthma incidence, and recommendations for future asthma incidence research.," *Environ. Health Perspect.*, vol. 114, no. 4, pp. 634–40, Apr. 2006.
[131] S. D. Gale, L. D. Erickson, A. Berrett, B. L. Brown, and D. W. Hedges, "Infectious disease burden and cognitive function in young to middle-aged adults," *Brain. Behav. Immun.*, 2015.
[132] P. F. D. Scheelbeek, A. J. G. Wirix, M. Hatta, R. Usman, and M. I. Bakker, "Risk factors for poor tuberculosis treatment outcomes in Makassar, Indonesia," *Southeast Asian J. Trop. Med. Public Health*, vol. 45, no. 4, pp. 853–858, 2014.
[133] S. J. Chapman and A. V. S. Hill, "Human genetic susceptibility to infectious disease," vol. 13, no. March, 2012.
[134] G. G. R. Murray, M. E. J. Woolhouse, M. Tapio, M. N. Mbole-Kariuki, T. S. Sonstegard, S. M. Thumbi, A. E. Jennings, I. C. Van Wyk, M. Chase-Topping, H. Kiara, P. Toye, K. Coetzer, B. M. Dec Bronsvoort, and O. Hanotte, "Genetic susceptibility to infectious disease in East African Shorthorn Zebu: A genome-wide analysis of the effect of heterozygosity and exotic introgression," *BMC Evol. Biol.*, vol. 13, no. 1, 2013.
[135] H. Yi, B. R. Devkota, J. Yu, K. Oh, J. Kim, and H.-J. Kim, "Effects of global warming on mosquitoes & mosquito-borne diseases and the new strategies for mosquito control," *Entomol. Res.*, vol. 44, no. 6, pp. 215–235, 2014.
[136] Q. Wang, Y. Liu, Y. Ma, L. Han, M. Dou, Y. Zou, L. Sun, H. Tian, T. Li, G. Jiang, B. Du, T. Kou, and J. Song, "Severe hypovitaminosis D in active tuberculosis patients and its predictors," *Clin. Nutr.*, 2017.
[137] A. Fares, "Seasonality of tuberculosis.," *J. Glob. Infect. Dis.*, vol. 3, no. 1, pp. 46–55, Jan. 2011.
[138] "WHO | Tuberculosis and HIV," *WHO*, 2018.
[139] D. M. Pigott, R. E. Howes, A. Wiebe, K. E. Battle, N. Golding, P. W. Gething, S. F. Dowell, T. H. Farag, A. J. Garcia,

A. M. Kimball, L. K. Krause, C. H. Smith, S. J. Brooker, H. H. Kyu, T. Vos, C. J. L. Murray, C. L. Moyes, and S. I. Hay, “Prioritising infectious disease mapping,” *PLoS Negl. Trop. Dis.*, vol. 9, no. 6, pp. 1–21, 2015.

[140] J. Casqueiro, J. Casqueiro, and C. Alves, “Infections in patients with diabetes mellitus : A review of pathogenesis,” *Indian J. Endocrinol. Metab.*, vol. 16, pp. 27–36, 2018.

[141] T. N. A. of Sciences, *Critical Aspects of EPA’s IRIS Assessment of Inorganic Arsenic*. Washington, D.C.: National Academies Press, 2014.

[142] R. K. Smith and D. J. Maron, “Epidemiology, risk factors, and prevention,” *Semin. Colon Rectal Surg.*, vol. 27, no. 4, pp. 176–180, 2016.

[143] O. Shirai, T. Tsuda, S. Kitagawa, K. Naitoh, T. Seki, K. Kamimura, and M. Morohashi, “Alcohol ingestion stimulates mosquito attraction.,” *J. Am. Mosq. Control Assoc.*, vol. 18, no. 2, pp. 91–6, Jun. 2002.

[144] K. Lönnroth, B. G. Williams, S. Stadlin, E. Jaramillo, and C. Dye, “Alcohol use as a risk factor for tuberculosis - A systematic review,” *BMC Public Health*, vol. 8, no. May 2014, 2008.

[145] R. Mukherjee, D. Halder, S. Saha, R. Shyamali, R. Ramakrishnan, M. V Murhekar, and Y. J. Hutin, “Five Pond-centred Outbreaks of Cholera in Villages of West Bengal , India : Evidence for Focused Interventions,” *J. Heal. Popul. Nutr.*, vol. 29, no. 5, pp. 421–428, 2011.

[146] A. J. Lund, H. M. Keys, S. Leventhal, J. W. Foster, and M. C. Freeman, “Prevalence of cholera risk factors between migrant Haitians and Dominicans in the Dominican Republic,” *Pan Am. J. Public Heal.*, vol. 37, no. 3, pp. 125–132, 2015.

[147] A. Rosewell, B. Addy, L. Komnapi, F. Makanda, B. Ropa, E. Posanai, S. Dutta, G. Mola, W. Y. N. Man, A. Zwi, and C. R. Macintyre, “Cholera risk factors , Papua New Guinea , 2010,” *BMC Infect. Dis.*, vol. 12, pp. 287–293, 2012.

[148] A. Prayitno, A. Taurel, J. Nealon, H. I. Satari, R. Karyanti, R. Sekartini, S. Soedjatmiko, H. Gunardi, E. Medise, R. T. Sasmono, J. M. Simmerman, A. Bouckenooghe, and S. R. Hadinegoro, “Dengue seroprevalence and force of primary infection in a representative population of urban dwelling Indonesian children,” *PLoS Negl. Trop. Dis.*, vol. 11, no. 6, pp. 1–16, 2017.

[149] M. A. Soghaier, S. F. Mahmood, O. Pasha, S. I. Azam, M. M. Karsani, M. M. Elmangory, B. A. Elmagboul, S. I. Okoued, S. M. Shareef, H. S. Khogali, and E. Eltigai, “Factors associated with dengue fever IgG sero-prevalence in South Kordofan State , Sudan , in 2012 : Reporting prevalence ratios,” *J. Infect. Public Health*, vol. 7, no. 1, pp. 54–61, 2014.

[150] Centers for Disease Control and Prevention (CDC), “Cryptosporidiosis outbreak at a summer camp--North Carolina, 2009.,” *MMWR. Morb. Mortal. Wkly. Rep.*, vol. 60, no. 27, pp. 918–22, Jul. 2011.

[151] CDC, “Principles of Epidemiology | Lesson 3 - Section 2.” .

[152] M. Lappenschaar, A. Hommersom, P. J. F. Lucas, J. Lagro, and S. Visscher, “Multilevel Bayesian networks for the analysis of hierarchical health care data,” *Artif. Intell. Med.*, vol. 57, no. 3, pp. 171–183, 2013.

[153] M. Blangiardo, F. Finazzi, and M. Cameletti, “Two-stage Bayesian model to evaluate the effect of air pollution on chronic respiratory diseases using drug prescriptions,” *Spat. Spatiotemporal. Epidemiol.*, 2016.

[154] C. Lau, P. Weinstein, and D. Slaney, “Imported cases of Ross River virus disease in New Zealand - a travel medicine perspective.,” *Travel Med. Infect. Dis.*, vol. 10, no. 3, pp. 129–134, 2012.

[155] P. D. Loprinzi and A. Nooe, “Health characteristics and predicted 10-year risk for a first atherosclerotic cardiovascular disease (ASCVD) event using the Pooled Cohort Risk Equations among US adults who are free of cardiovascular disease,” *Physiol. Behav.*, vol. 151, pp. 591–595, 2015.

[156] L. M. Artigao-Rodenas, J. A. Carbayo-Herencia, J. A. Divisón-Garrote, V. F. Gil-Guillén, J. Massó-Orozco, M. Simarro-Rueda, F. Molina-Escribano, C. Sanchis, L. Carrión-Valero, E. López de Coca, D. Caldevilla, J. López-Abril, C. Carratalá-Munuera, and A. Lopez-Pineda, “Framingham Risk Score for Prediction of Cardiovascular Diseases: A Population-Based Study from Southern Europe,” *PLoS One*, vol. 8, no. 9, pp. 1–10, 2013.

[157] S. Kalayanarooj, R. V. Gibbons, D. Vaughn, S. Green, A. Nisalak, R. G. Jarman, M. P. Mammen, Jr., and G. Perng, “Blood Group AB Is Associated with Increased Risk for Severe Dengue Disease in Secondary Infections,” *J. Infect. Dis.*, vol. 195, no. 7, pp. 1014–1017, 2007.

[158] A. L. Greer, S. J. Drews, and D. N. Fisman, “Why ‘Winter’ vomiting disease? seasonality, hydrology, and norovirus epidemiology in Toronto, Canada,” *Ecohealth*, vol. 6, no. 2, pp. 192–199, 2009.

[159] I. Stephenson and M. Zambon, “The epidemiology of influenza,” *Occup. Med. (Chic. Ill).*, vol. 52, no. 5, pp. 241–247, 2002.

[160] S. Subak, “Effects of climate on variability in Lyme disease incidence in the northeastern United States,” *Am. J. Epidemiol.*, vol. 157, no. 6, pp. 531–538, 2003.

[161] K. Kleinman, R. Lazarus, and R. Platt, “A generalized linear mixed models approach for detecting incident clusters of disease in small areas, with an application to biological terrorism,” *Am. J. Epidemiol.*, vol. 159, no. 3, pp. 217–224, 2004.

[162] G. M. Liumbruno and M. Franchini, “Beyond immunohaematology: the role of the ABO blood group in human diseases,” *Blood Transfus*, vol. 11, pp. 491–499, 2013.

[163] K. Kengkla, N. Charoensuk, M. Chaichana, S. Puangjan, T. Rattanapornsompong, J. Choorassamee, P. Wilairat, and S. Saokaew, “Clinical risk scoring system for predicting extended-spectrum β-lactamase-producing Escherichia coli infection in hospitalized patients.,” *J. Hosp. Infect.*, vol. 93, no. 1, pp. 49–56, 2016.

[164] A. Ascherio and M. A. Schwarzschild, “The epidemiology of Parkinson’s disease: risk factors and prevention,” *Lancet Neurol.*, vol. 15, no. 12, pp. 1257–1272, 2016.

[165] S. A. J. Schmidt, M. Vestergaard, L. M. Baggesen, L. Pedersen, H. C. Schønheyder, and H. T. Sørensen, “Prevaccination epidemiology of herpes zoster in Denmark : Quantification of occurrence and risk factors,” *Vaccine*, vol. 35, no. 42, pp. 5589–5596, 2017.

[166] H. Zhang, T. Yang, M. Wu, and F. Shen, “Intrahepatic cholangiocarcinoma: Epidemiology, risk factors, diagnosis and surgical management,” *Cancer Lett.*, vol. 379, no. 2, pp. 198–205, 2016.
[167] C. A. Rostad, K. Wehrheim, J. K. Kirklin, D. Naftel, E. Pruitt, T. M. Hoffman, T. L’Ecuyer, K. Berkowitz, W. T. Mahle, and J. N. Scheel, “Bacterial infections after pediatric heart transplantation: Epidemiology, risk factors and outcomes,” *J. Hear. Lung Transplant.*, vol. 36, no. 9, pp. 996–1003, 2017.
[168] S. H. Kim, S. M. Choi, B. C. Kim, K. H. Choi, T. S. Nam, J. T. Kim, S. H. Lee, M. S. Park, and S. J. Kim, “Risk factors for aseptic meningitis in herpes zoster patients,” *Ann. Dermatol.*, vol. 29, no. 3, pp. 283–287, 2017.
[169] Bruce MG; Rosenstein NE; Capparella JM; Shutt KA; Perkins B; Collins M, “Risk Factors for Meningococcal Disease in College Students.,” *J. Am. Med. Assoc.*, vol. 286, no. 6, pp. 688–693, 2001.
[170] A. Moat, A. Jarousha, and A. Al Afifi, “Epidemiology and Risk Factors Associated with Developing Bac- terial Meningitis among Children in Gaza Strip,” *Iran. J. Public Health*, vol. 43, no. 9, pp. 1176–1183, 2014.
[171] A. J. M. Lora, J. Fernandez, A. Morales, Y. Soto, J. Feris-iglesias, and M. O. Brito, “Disease Severity and Mortality Caused by Dengue in a Dominican Pediatric Population,” *Am. J. Trop. Med. Hyg.*, vol. 90, no. 1, pp. 169–172, 2014.
[172] V. Kumar, S. Devika, S. George, and L. Jeyaseelan, “ScienceDirect Spatial mapping of acute diarrheal disease using GIS and estimation of relative risk using empirical Bayes approach,” *Clin. Epidemiol. Glob. Heal.*, vol. 5, no. 2, pp. 87–96, 2017.
[173] D. Morof, S. T. Cookson, S. Laver, D. Chirundu, S. Desai, P. Mathenge, D. Shambare, L. Charimari, S. Midzi, C. Blanton, and T. Handzel, “Community Mortality from Cholera : Urban and Rural Districts in Zimbabwe,” *Am. J. Trop. Med. Hyg.*, vol. 88, no. 4, pp. 645–650, 2013.
[174] C. O. Schmidt and T. Kohlmann, “When to use the odds ratio or the relative risk?,” *Int. J. Public Health*, vol. 53, pp. 165–167, 2008.
[175] M. S. Hossain, I. B. Habib, and K. Andersson, “A belief rule based expert system to diagnose dengue fever under uncertainty,” in *2017 Computing Conference*, 2017, pp. 179–186.
[176] I. Ramalhosa, P. Mateus, V. Alves, H. Vicente, F. Ferraz, J. Neves, and J. Neves, “Diagnosis of Alzheimer Disease Through an Artificial Neural Network Based System,” Springer, Cham, 2018, pp. 162–174.
[177] M. H. F. Zarandi and M. Abdolkarimzadeh, “Fuzzy Rule Based Expert System to Diagnose Chronic Kidney Disease,” Springer, Cham, 2018, pp. 323–328.
[178] C. Zhao, J. Jiang, Z. Xu, and Y. Guan, “A study of EMR-based medical knowledge network and its applications,” *Comput. Methods Programs Biomed.*, vol. 143, pp. 13–23, May 2017.
[179] M. Krishnamurthy, P. Marcinek, K. M. Malik, and M. Afzal, “Representing Social Network Patient Data as Evidence-Based Knowledge to Support Decision Making in Disease Progression for Comorbidities,” *IEEE Access*, vol. 6, pp. 12951–12965, 2018.
[180] B. MacKellar and C. Schweikert, “Conflict Discovery and Analysis for Clinical Trials,” in *Proceedings of the 2017 International Conference on Digital Health - DH ’17*, 2017, pp. 72–76.
[181] M. A. Kadhim, M. A. Alam, and H. Kaur, “A Multi-Intelligent Agent for Knowledge Discovery in Database (MIAKDD): Cooperative Approach with Domain Expert for Rules Extraction,” Springer, Cham, 2014, pp. 602–614.
[182] W. Chen, A. Fang, and W. Wang, “Traditional Chinese Medicine Syndrome Knowledge Representation Model of Gastric Precancerous Lesion and Risk Assessment Based on Extenics,” Springer, Berlin, Heidelberg, 2011, pp. 585–590.
[183] J. Vilhena, M. Rosário Martins, H. Vicente, J. M. Grañeda, F. Caldeira, R. Gusmão, J. Neves, and J. Neves, “An Integrated Soft Computing Approach to Hughes Syndrome Risk Assessment,” *J. Med. Syst.*, vol. 41, no. 3, p. 40, Mar. 2017.
[184] M. Rajabi, A. Mansourian, P. Pilesjo, F. Hedefalk, R. Groth, and A. Bazmani, “Comparing Knowledge - Driven and Data - Driven Modeling methods for susceptibility mapping in spatial epidemiology : a case study in Visceral Leishmaniasis,” in *Proceedings of AGILE 2014 International Conference on Geographic Information Science*, 2014, pp. 1–5.
[185] J. Wiens, J. Guttag, and E. Horvitz, “Patient Risk Stratification with Time-Varying Parameters: A Multitask Learning Approach,” *J. Mach. Learn. Res.*, vol. 17, pp. 1–23, 2016.
[186] J. F. Sowa, *Knowledge representation : logical, philosophical, and computational foundations*. Brooks/Cole, 2000.
[187] M. Negnevitsky, *Artificial intelligence : a guide to intelligent systems*. Addison Wesley, 2002.
[188] P. Q. Rashid, “Semantic Network and Frame Knowledge Representation Formalisms in Artificial Intelligence.”
[189] A. Onisko, P. Lucas, and M. J. Druzdzel, “Comparison of Rule-Based and Bayesian Network Approaches in Medical Diagnostic Systems,” *Artif. Intell. Med. 8th Conf. Artif. Intell. Med. Eur. AIME 2001, Cascais, Port. July 1-4, 2001 Proc.*, vol. 2101, p. 283, 2001.
[190] J. Prentzas and I. Hatzilygeroudis, “Integrations of Rule-Based and Case-Based Reasoning,” *Proc. Int. Conf. Comput. Commun. Control Technol.*, vol. 4, pp. 81–85, 2003.
[191] P. Smets, “Jeffrey’s rule of conditioning generalized to belief functions,” *Uncertain. Artif. Intell.*, 1993.
[192] National Center for Biomedical Ontology, “Welcome to the NCBO BioPortal | NCBO BioPortal,” 2018. .
[193] OBO, “The OBO Foundry,” 2018. .
[194] Google, “Google Code Archive - Long-term storage for Google Code Project Hosting.” .
[195] C. Pesquita, J. D. Ferreira, F. M. Couto, and M. J. Silva, “The epidemiology ontology : an ontology for the semantic annotation of epidemiological resources,” pp. 1–7, 2014.
[196] University of Michigan Medical School, “VIOLIN: Vaccine Investigation and Online Information Network.” .
[197] L. M. Schriml, C. Arze, S. Nadendla, Y. W. W. Chang, M. Mazaitis, V. Felix, G. Feng, and W. A. Kibbe, “Disease ontology: A backbone for disease semantic integration,” *Nucleic Acids Res.*, vol. 40, no. D1, pp. 939–946, 2012.
[198] S. El-Sappagh and F. Ali, “DDO: a diabetes mellitus diagnosis ontology,” *Appl. Informatics*, vol. 3, no. 1, p. 5, Dec.

2016.
[199] C. L. Gordon, S. Pouch, L. G. Cowell, M. R. Boland, H. L. Platt, A. Goldfain, and C. Weng, “Design and evaluation of a bacterial clinical infectious diseases ontology.,” *AMIA ... Annu. Symp. proceedings. AMIA Symp.*, vol. 2013, pp. 502–11, 2013.
[200] E. Younesi, S. Ansari, M. Guendel, S. Ahmadi, C. Coggins, J. Hoeng, M. Hofmann-Apitius, and M. C. Peitsch, “CSEO - the Cigarette Smoke Exposure Ontology.,” *J. Biomed. Semantics*, vol. 5, p. 31, 2014.
[201] W. R. Hogan, M. M. Wagner, M. Brochhausen, J. Levander, S. T. Brown, N. Millett, J. Depasse, and J. Hanna, “The Apollo Structured Vocabulary : an OWL2 ontology of phenomena in infectious disease epidemiology and population biology for use in epidemic simulation,” *J. Biomed. Semantics*, pp. 1–12, 2016.
[202] C. X. Hong, Z. Y. Feng, C. X. Rong, L. Tian, W. Y. Wei, and M. Li, “The ontology-based knowledge representation modeling of the traditional-Chinese-medicine symptom,” in *2017 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)*, 2017, pp. 1345–1349.
[203] A. Al-Rumkhani, M. Al-Razgan, and A. Al-Faris, “TibbOnto: Knowledge Representation of Prophet Medicine (Tibb Al-Nabawi),” *Procedia Comput. Sci.*, vol. 82, pp. 138–142, Jan. 2016.
[204] M. Richard, X. Aimé, M.-O. Krebs, and J. Charlet, “Enrich classifications in psychiatry with textual data: an ontology for psychiatry including social concepts.,” *Stud. Health Technol. Inform.*, vol. 210, pp. 221–3, 2015.
[205] A. Assawamakin, “A Development of Knowledge Representation for Thalassemia Prevention and Control Program Ontological Knowledge Base of Southeast Asian Thalassemia.”
[206] M. A. Elhefny, M. Elmogy, and A. A. Elfetouh, “Building OWL ontology for obesity related cancer,” in *2014 9th International Conference on Computer Engineering & Systems (ICCES)*, 2014, pp. 177–183.
[207] V. Rawte and B. Roy, “OBESTDD: Ontology Based Expert System for Thyroid Disease Diagnosis,” in *2015 International Conference on Nascent Technologies in the Engineering Field (ICNTE)*, 2015, pp. 1–6.
[208] A. Ruttenberg, “Basic Formal Ontology (BFO) | Home.” .
[209] E. I. Papageorgiou, “Learning Algorithms for Fuzzy Cognitive Maps - A Review Study,” *IEEE Trans. Syst. Man, Cybern. Part ASystems Humans*, vol. 42, no. 2, pp. 150–163, 2012.
[210] R. H. Lathrop, “Bayesian Networks.”
[211] D. N. Barton, S. Kuikka, O. Varis, L. Uusitalo, H. J. Henriksen, M. Borsuk, A. D. La Hera, R. Farmani, S. Johnson, and J. D. C. Linnell, “Bayesian networks in environmental and resource management,” *Integr. Environ. Assess. Manag.*, vol. 8, no. 3, pp. 418–429, 2012.
[212] B. Das, “Generating Conditional Probabilities for Bayesian Networks: Easing the Knowledge Acquisition Problem,” *CoRR*, pp. 1–24, 2004.
[213] J. Pearl and Judea, *Probabilistic reasoning in intelligent systems : networks of plausible inference*. Morgan Kaufmann Publishers, 1988.
[214] M. Henrion, *Practical issues in constructing a Bayes’ belief network*. Virginia: North-Holland, 1987.
[215] L. Perreault, S. Strasser, M. Thornton, and J. W. Sheppard, “A Noisy-OR Model for Continuous Time Bayesian Networks,” *Proc. Twenty-Ninth Int. Florida Artif. Intell. Res. Soc. Conf.*, pp. 668–673, 2016.
[216] G. Cheng, Q. Du, and H. Ma, “The Design and Implementation of Ontology and Rules Based Knowledge Base for Transportation,” *2008 Int. Conf. Comput. Sci. Softw. Eng.*, pp. 1035–1038, 2008.
[217] Shortliffe, *Computer-Based Medical Consultation. MYCIN*. New York: Elsevier, 1976.
[218] M. O ’connor, “The Semantic Web Rule Language.”
[219] L. Getoor, N. Friedman, D. Koller, and A. Pfeffer, “Learning Probabilistic Relational Models,” in *Relational Data Mining*, Berlin, Heidelberg: Springer Berlin Heidelberg, 2001, pp. 307–335.
[220] J. and E. S. S. Eugene. Santos, “A Framework for Building Knowledge-Base Under Uncertainty,” *J. Exp. Theor. Artif. Intell.*, vol. 11, no. 2, pp. 265–286, 1999.
[221] K. B. Laskey, “MEBN: A language for first-order Bayesian knowledge bases,” *Artif. Intell.*, vol. 172, no. 2–3, pp. 140–178, 2008.
[222] P. C. G. Costa and K. B. Laskey, “Multi-Entity Bayesian Networks Without Multi-Tears,” pp. 1–20, 2006.
[223] L. G. Cowell, B. Smith, L. G. Cowell, and B. Smith, “Infectious Disease Ontology,” *Infect. Dis. Informatics*, pp. 373–395, 2010.
[224] A. Third, E. Kaldoudi, G. Gkotsis, S. Roumeliotis, K. Pafili, J. Domingue, and M. Keynes, “Capturing Scientific Knowledge on Medical Risk Factors,” 2010.
[225] M. C. Thomson, F. J. Doblas-Reyes, S. J. Mason, R. Hagedorn, S. J. Connor, T. Phindela, A. P. Morse, and T. N. Palmer, “Malaria early warnings based on seasonal climate forecasts from multi-model ensembles,” *Nature*, vol. 439, no. 7076, pp. 576–579, 2006.
[226] S. Falconer, “OntoGraf - Protege Wiki.” .
[227] WHO, “WHO | Disease burden and mortality estimates,” *WHO*, 2018. .
[228] S. Tartir, I. Arpinar, M. Moore, a Sheth, and B. Aleman-Meza, “OntoQA: Metric-Based Ontology Quality Analysis,” *IEEE Work. Knowl. Acquis. from Distrib. Auton. Semant. Heterog. Data Knowl. Sources*, pp. 45–53, 2005.
[229] A. D. Preece and R. Shinghal, “Foundation and application of knowledge base verification,” *Int. J. Intell. Syst.*, vol. 9, no. 8, pp. 683–701, 1994.
[230] M. A. Soghaier, S. Himatt, K. E. Osman, S. I. Okoued, O. E. Seidahmed, M. E. Beatty, K. Elmusharaf, J. Khogali, N. H. Shingrai, and M. M. Elmangory, “Cross-sectional community-based study of the socio-demographic factors associated with the prevalence of dengue in the eastern part of Sudan in 2011,” *BMC Public Health*, pp. 1–6, 2015.
[231] I. Safeukui-Noubissi, S. Ranque, B. Poudiougou, M. Keita, A. Traoré, D. Traoré, M. Diakité, M. B. Cissé, M. M. Keita, A. Dessein, and O. K. Doumbo, “Risk factors for severe malaria in Bamako, Mali: A matched case-control study,” *Microbes Infect.*, vol. 6, no. 6, pp. 572–578, 2004.

[232] M. J. Grigg, J. Cox, T. William, J. Jelip, K. M. Fornace, P. M. Brock, L. von Seidlein, B. E. Barber, N. M. Anstey, T. W. Yeo, and C. J. Drakeley, "Individual-level factors associated with the risk of acquiring human Plasmodium knowlesi malaria in Malaysia: a case-control study," *Lancet Planet. Heal.*, vol. 1, no. 3, pp. e97–e104, 2017.
[233] F. Agegnehu, A. Shimeka, F. Berihun, and M. Tamir, "Determinants of malaria infection in Dembia district, Northwest Ethiopia: A case-control study," *BMC Public Health*, vol. 18, no. 1, pp. 1–8, 2018.
[234] N. Alexander, M. Rodriguez, L. Perez, and J. Caicedo, "Case-control Study of Mosquito Nets Against Malaria in the Amazon Region of Colombia," *Am. J. Trop. Med. Hyg.*, vol. 73, no. 1, pp. 140–148, 2005.
[235] Norsys Software Corp., "Norsys Software Corp. - Bayes Net Software." .
[236] J. Negin, S. Abimbola, and B. J. Marais, "Tuberculosis among older adults – time to take notice," *Int. J. Infect. Dis.*, vol. 32, pp. 135–137, Mar. 2015.
[237] Institute of Medicine (US) Committee on Enhancing Environmental Health Content in Nursing Practice, *Nursing Health, & Environment: Strengthening the Relationship to Improve the Public's Health*. Washington (DC): National Academies Press (US), 1995.
[238] R. A. Vinarti and L. Hederman, "Introduction of a Bayesian Network Builder Algorithm - Personalized Infectious Disease Risk Prediction," *Proc. 11th Int. Jt. Conf. Biomed. Eng. Syst. Technol.*, vol. 5, no. Biostec, pp. 115–126, 2018.
[239] R. A. Vinarti and L. Hederman, "Personalization of Infectious Disease Risk Prediction: Towards Automatic Generation of a Bayesian Network," in *Proceedings - IEEE Symposium on Computer-Based Medical Systems*, 2017, vol. 2017–June.
[240] H. M. Nemati, A. Sant'Anna, and S. Nowaczyk, "Bayesian Network representation of meaningful patterns in electricity distribution grids," *2016 IEEE Int. Energy Conf. ENERGYCON 2016*, 2016.
[241] E. Kaldoudi, J. Domingue, and E. Liu, "Personalized Patient Empowerment and Shared Decision Support for Cardiorenal Disease and Comorbidities - The Carre Project," pp. 1–152, 2014.
[242] S. E. Keith R.Bisset, "HIGH PERFORMANCE INFORMATICS FOR PANDEMIC PREPAREDNESS Keith," *Proc. 2012 Winter Simul. Conf.*, vol. 1, pp. 804–815, 2012.
[243] R. J. Hoekstra, "Ontology Representation: design patterns and ontologies that make sense," 2009.
[244] R. J. Brachman, *On the Epistemological Status of Semantic Networks*. New York: Academic Press, 1979.
[245] R. Hartley and J. Barnden, "Semantic Networks: Visualizations of Knowledge."
[246] T. Azuma, N. Nakada, N. Yamashita, and H. Tanaka, "Prediction, risk and control of anti-influenza drugs in the Yodo River Basin, Japan during seasonal and pandemic influenza using the transmission model for infectious disease," *Sci. Total Environ.*, vol. 521–522, pp. 68–74, 2015.
[247] V. L. Yu and S. C. Edberg, "Global Infectious Diseases and Epidemiology Network (GIDEON): A World Wide Web-Based Program for Diagnosis and Informatics in Infectious Diseases," *Clin. Infect. Dis.*, vol. 40, no. 1, pp. 123–126, 2005.
[248] R. A. Vinarti, "Appendix (44 articles)," 2018. .
[249] R. A. Vinarti, "IDR Ontologies." Open Science Framework, 2018.
[250] M. Horridge, M. E. Aranguren, J. Mortensen, M. Musen, and N. F. Noy, "Ontology Design Pattern Language Expressivity Requirements."

Appendix 8 – A Collation Table