Ontology-based Representation and Analysis of Vaccination Informed Consent

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***Abstract* —** Although signing a vaccination (or immunization) informed consent form is not a federal requirement in the US and Canada, such a practice is required by many states and pharmacies. The content and structures of these informed consent forms vary, which make it hard to compare and analyze without standardization. To facilitate vaccination informed consent data standardization and integration, it is important to examine various vaccination informed consent forms, patient answers, and consent results. We have previously developed two related ontologies: Informed Consent Ontology (ICO) for representing general informed consent entities; Vaccine Ontology (VO) for representing vaccines, vaccine formulations, and vaccination details. Both ICO and VO are aligned with the Basic Formal Ontology (BFO) and developed by following OBO Foundry principles. In this study, we report a Vaccination Informed Consent Ontology (VICO) that integrates and extends ICO and VO to vaccination informed consent domain. Current VICO includes over 570 terms. VICO ontologically represent vaccination informed consent forms from the Walgreens and Costco pharmacies and the government of Manitoba, Canada. VICO extends ICO by adding questionnaire and question terms. The usages of VICO in combination with Semnatics Web technologies were demonstrated in two use cases using both Description Language (DL)-Query and SPARQL queries. The first use case was to compare informed consent forms from different sources. The second one was to identify vaccination contraindications based on patients' answers to determine who cannot be vaccinated by some vaccines. Our use cases validate that VICO is able to represent various vaccination informed consent forms, guide the report of instance consent data, support cross-source data queries. The VICO ontology is available at https://github.com/vico-ontology/VICO.

I. INTRODUCTION

Different countries and organizations have various regulations in terms of the requirement of informed consent to vaccination before vaccinating a patient. The US Federal legislation establishing the 1976 swine flu immunization program included requirements that recipients of the swine flu vaccine be fully informed of the risks and benefits of immunization and that written consent forms be used (42 U.S.C.A.§247b(j) (1) (F) (Supp.1977) [1]. The USA National Childhood Vaccine Injury Act of 1986 (NCVIA - 42 U.S.C. § 300aa-26) requires that the Vaccine Information Statements (VISs) (http://www.cdc.gov/vaccines/hcp/vis/) must be provided by all public and private vaccination providers to the patient (or parent or legal representative) prior to every dose of specific vaccines. Although there is no US federal requirement for informed consent to all vaccinations, the documentation of consent is recommended or required by certains states, local health authorities, school authorities, or pharmacies. For example, new laws in Texas were passed in 2013 to allow pregnant minors and minor parents to consent to their own vaccination [2]. The Manitoba Province in Canada provides vaccination informed consent guidlines for routine immunization in accordance with The Public Health Act (C.C.S.M. c. P210) [3]. Many pharmacies' immunization protocols require the signatures of recipients or legal representatives on specific vaccination informed consent forms before vaccination in accordance with local state's legislation.

Due to different policies and vaccination informed consent forms offered by authorities and pharmacies, it is difficult to compare and mange vaccination informed consent procedures and data from different resources. Ontologies, sets of terms and relations that represent entities in a domain and how they relate to each other, support data integration and computer-assisted processing. Developing a vaccination informed consent ontology to integrate data from different resources may advance the researchs in informed consent and vaccine policy. Therefore, more efficient patient safty management maybe achieved .

To ontologically represent vaccination informed consents, two existing ontologies could be re-utilized. One is the community-based Informed Consent Ontology (ICO) [4]. ICO represents the informed consent forms and informed consent processes. ICO was developed to support informed consent data integration and reasoning in the clinical research space. Another related ontology is the Vaccine Ontology (VO) [5, 6]. VO represents vaccines that are licensed, in clinical trials, or have been experimentally verified in research laboratories. In addition, many other vaccine-related information including vaccine components, vaccine licenses, vaccine manufacture, vaccination, and vaccination doses are also represented in VO. Both ICO and VO are aligned with the upper level Basic Formal Ontology (BFO) [7] and developed by following the OBO Foundry ontology development principles [8]. Built on the same upper ontology, ICO and VO can be seamlessly integrated for representing vaccination informed consent.

In this paper, we report our development of the Vaccination Inform Consent Ontology (VICO) by extending and integrating ICO and VO. The goal of VICO is to organize vaccination informed consent-related entities and to establish relations between those entities so that the knowledge maybe captured explicitly. The current delevelopment focus is to represent different vaccination informed consent forms, so that VICO will support consistent representation of immunization screening questionnaires, thus enable systematic form comparions and patients' informed consent data query and analysis. We hypothesized that VICO would significantly enhance standard data representation, integration and query of informed consent related to various vaccine immunization procedures. To validate the hypothesis, we implemented two uses cases to demonstrate the advantages of utilizingVICO for knowledge acquisition, and supporting decision making, for example, detecting patient who may not be suitable for certain

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vaccine immunization due to his/her allergic history or health condition.

II. METHODS

A. Collection of vaccination informed consent forms

Example vaccination informed consent forms were collected from three resources: Costco Pharmacy (http://www2.costco.com/Images/Content/misc/PDF/Immunization_consent_form_v2-2012.pdf), Walgreens Pharmacy (https://www.walgreens.com/images/pdfs/IN-2225/WAG_VAR_Form_EDIT_10172013_v1.pdf), and Manitoba government Public Health division (http://www.gov.mb.ca/health/publichealth/cdc/div/docs/7707.pdf). The information in these forms were modeled and represented in VICO.

B. VICO ontology development

VICO was formatted in the Web Ontology Language (OWL2) [9]. Vaccination-related informed consent terms were manually selected and extracted from ICO using the OntoFox tool [10]. After obtained a list of licensed vaccines in USA and Canada retrieved from the VO RDF triple store using Ontobee SPARQL Protocol and RDF Query Language (SPARQL) program (http://www.ontobee.org/sparql) [11], a portion of VO that contains the vaccines in the list, their related terms (classes and relations) and annotations were extracted using OntoFox. The extracted portion of ICO and VO were then imported into the VICO as the backbone for further VICO development. The HermiT reasoner (http://hermit-reasoner.com/) tool was employed to perform the reasoning over VICO to detect inconsistencies or conflicts due to the integration of VO and ICO. VICO specific terms were added and edited using the Protégé OWL Editor [12].

C. VICO evaluation by use cases

At the current stage of development, we focused on representing informed consent questionnaire in VICO. Description Logic (DL) or SPARQL queries were performed to evaluate and demonstrate the potential application of VICO in vaccination informed consent data integration and analysis. Two use cases were designed and implemented. One is to query the questions shared by different vaccination informed consent forms, and the other is to detect the patients who are not qualified for a certain vaccination based on their answers to the screening questionnaires.

D. Ontology source access and license

The source of VICO is freely available at the URL: https://github.com/vico-ontology/VICO. VICO is released under a Creative Commons 3.0 License.

III. RESULT

A. VICO ontology design and top level structure

VICO is an ontology that crosses both ICO and VO domains, therefore, we built VICO based on both ICO and VO. Specifically, we first imported informed consent-related terms from ICO and licensed vaccine-related terms from VO into VICO (Fig. 1). We then added VICO-specific terms to represent vaccination informed consent forms and processes. For example, we generate VICO-specific terms to present those vaccination informed consent forms from different pharmacies such as Costco, Walgreens, and states such as Manitoba in Canada (Fig. 1). Each of these forms contains a screening questionnaire form, which includes a list of questions for vaccine recipients or their legal representatives to answer before a vaccination procedure is conducted. VICO defines these questions in a structured logical manner.

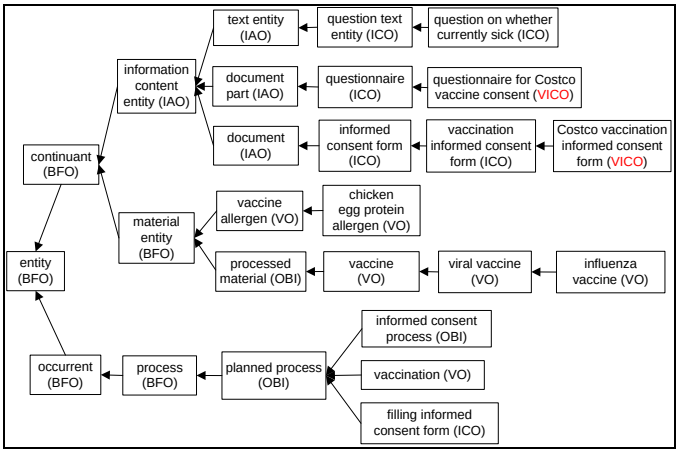


Fig. 1. Top level terms and hierarchical structure of VICO. VICO imports many top level terms from VO and ICO. Two terms highlighted in red (*e.g.*, Costco vaccination informed consent form) are included as representatives of VICO-specific terms.

The basic VICO ontology design pattern is shown in Fig. 2. Specifically, before a vaccination process, a vaccination informed consent form is provided for a vaccine recipient or his/her legal representative to answer a list of questions about the recipient. Contents of these questions often cover different topics such as the patient's current health status, current treatment, and allergic reaction history. The intended human vaccine (recipient) has different qualities such as age and gender (female or male). The status of these qualities may affect the decision of choosing vaccine types and route for administration. The vaccine itself also has different features such as its quality of being live or inactived and its targeted pathogen (*e.g.*, influenza virus). The vaccination route is unfolded in the vaccination process (Fig. 2). More details about ontological modeling of vaccine/vaccination and informed consent can be found in our previous VO and ICO papers [4-6]. Overall, VICO provides a platform to link intended human vaccinee, vaccine, vaccination and informed consent.

Currently, VICO contains 574 terms, including 452 classes, 74 object properties, and 48 annotation properties. VICO includes 11 VICO-specific classes and properties with the "VICO_" prefix. In our VICO development, we also identified over 50 terms that were more generic than vaccination informed consent domain, which maybe useful for other domain-specific studies (*e.g.*, biospecimen collections) as well. After submiting those terms to ICO, we then reuse those terms in VICO. In addition to ICO and VO, VICO also reused terms from approximately 18 other OBO Foundry ontologies including IAO and OBI, which mainly indirectly imported due to imports of ICO and VO. The detailed statistics of VICO can be found

on the Ontobee: http://www.ontobee.org/ontostat.php?ontology=VICO.

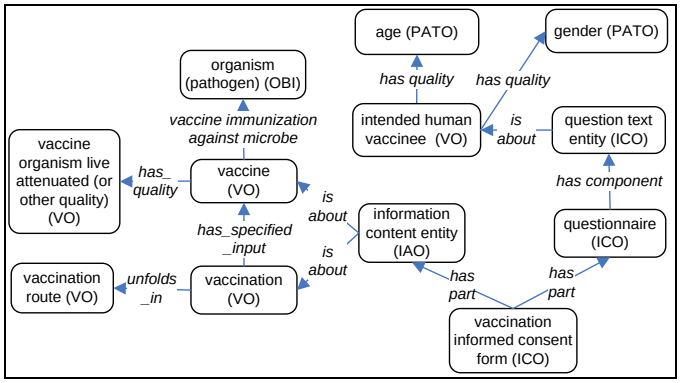


Fig. 2. Basic VICO design pattern.

VICO has been deposited in the Ontobee RDF triple store [11] and can be visualized and queried on the Ontobee website: http://www.ontobee.org/browser/index.php?o=VICO. VICO is also available on the NCBO BioPortal: http://bioportal.bioontology.org/ontologies/VICO.

B. VICO modeling of vaccination informed consent form

It is mandatory that all vaccine providers, public or private, must give an appropriate VIS to a patient (or parent or legal representative) prior to every dose of a specific vaccine (National Vaccine Childhood Injury Act (NCVIA - 42 U.S.C. § 300aa-26). Therefore, it is essential for VICO to provide correct vaccine information, such as vaccine ingredients. The vaccine-related terms in VICO were imported from VO. Fig. 3 shows an example of VO's representation of a vaccine, Afluria.

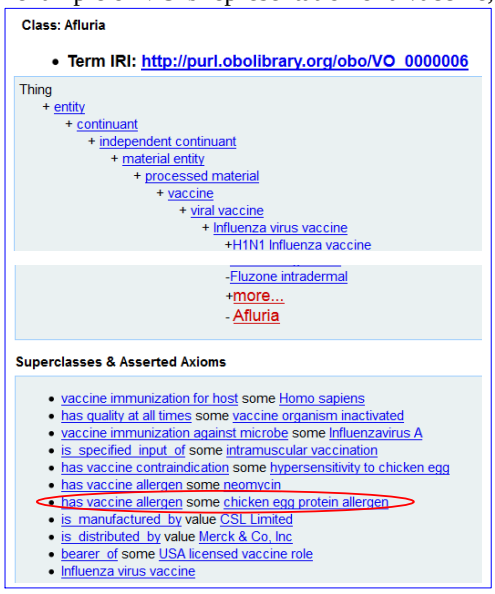
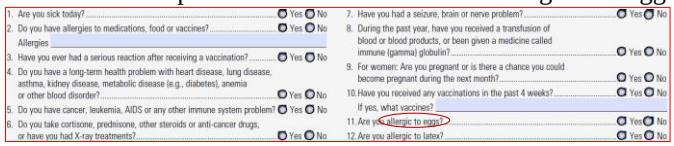


Fig. 3. The ontology hierarchy and associated axioms of the Afluria influenza vaccine. The contents are defined in VO and imported to VICO. The figure is a screenshot from Ontobee [11]. The highlighted egg allergen axiom is used for a use case demo detailed later in this paper.

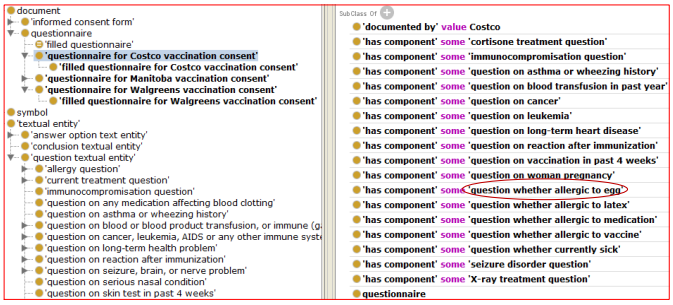
Afluria is a human influenza viral vaccine licensed for use in the USA. It is an inactivated vaccine against Influenzavirus A. It is manufactured by the CSL Limited, and distributed by Merck & Co, Inc. Various characteristics of Afluria were represented using logical axioms. For example, the axiom: *'has vaccine allergen' some 'chicken egg protein allergen'* encodes that the Afluria vaccine contains a trace of chicken egg protein which is able to induce allergic reaction in certain population. Therefore, the hypersensitivity to chicken egg becomes a contraindication to this vaccine. Another vaccine allergen associated with this vaccine is neomycin. This vaccine is administered via an intramuscular route.

All the vaccination informed consent forms contain a form of screening questionnaire asking intended vaccinee's health condition, allergic history and medical treatments. Answers to these questions allow health providers to identify potential contraindications, so that the potential severe adverse events caused by a vaccine, or so-called 'vaccine injuries', will be avoided. For example, if a patient is allergic to egg, the health provider would not recommend an administration of the vaccine that contains egg product allergen (*e.g.*, Afluria).

Fig. 4A shows the full list of screening questionnaire consisting 12 questions in the Costco informed consent form. Fig. 4B demonstrates how VICO represents these questions. Basically, a questionnaire 'has component' (RO_0002180) some questions, for example, 'question on whether allergic to egg', which asks a patient whether he/she is allergic to egg.



(A) Questionnaire of Costco informed consent form



(B) Representation of part of the questionnaire of Cosco informed consent form

Fig. 4. Questionnaire in Costco vaccination informed consent form and its representation in VICO. (A) All the questions shown in the in Costco informed consent form. (B) VICO representation of the questions in the Costco form questionnaire.

The answer to such a question is "Yes" or "No". VICO represents the answer to a question using 'yes (or no) answer text entity'. For example, we can represent a filled questionnaire that has a question textual entity which:

'has component' some 'yes (or no) answer text entity'

In this case, a questionee can provide a yes or no answer to a question.

Different agents may provide different questions although many components are the common. In addition to Costco (Fig. 4), all the questions listed in the Walgreens and Manitoba vaccination informed consent forms were represented in VICO.

C. VICO Use Cases and Evaluations

Two use cases are provided to evaluate and demonstrate the usages of VICO:

Use case 1. Comparison of different informed consent forms

As discussed above, the details of different vaccination informed consent forms are represented consistently in VICO, therefore, the forms from different sources can be compared by querying VICO knowledge base.

In order to find out the similarities and differences between Walgreens and Costco vaccination informed consent form, we performed SPAQL queries against the VICO. SPARQL is an Resource Description Framework (RDF) query language able to retrieve data stored in the RDF format [13]. Table 1 shows the comparison of questions listed in Walgreens and Costco vaccination informed consents.

Table 1. Comparison of questions listed in Walgreens and Costco vaccination informed consents

	Question	Walgreens / Costco
1	question on vaccination in past 4 weeks	Walgreens; Costco
2	question on blood transfusion in past year	Walgreens; Costco
3	question whether allergic to vaccine	Walgreens; Costco
4	question on asthma or wheezing history	Walgreens; Costco
5	question on leukemia	Walgreens; Costco
6	question whether allergic to medication	Walgreens; Costco
7	seizure disorder question	Walgreens; Costco
8	question on cancer	Walgreens; Costco
9	question whether allergic to egg	Walgreens; Costco
10	X-ray treatment question	Walgreens; Costco
11	question whether allergic to latex	Walgreens; Costco
12	question on woman pregnancy	Walgreens; Costco
13	question whether currently sick	Costco
14	question on long-term heart disease	Costco
15	cortisone treatment question	Costco
16	immunocompromisation question	Costco
17	question on reaction after immunization	Costco
18	question on whether fainted or felt dizzy after immunization	Walgreens
19	question on skin test in past 4 weeks	Walgreens
20	question whether currently sick with a moderate to high fever, vomiting/diarrhea	Walgreens
21	question on serious nasal condition	Walgreens
22	question on high-dose steroid therapy for longer than 2 weeks	Walgreens
23	question on thymus disease	Walgreens
24	question on current aspirin therapy	Walgreens
25	question on current antibiotics usage	Walgreens

In total, there are 12 questions in common. Question 13 to 17 are Costco unique questions; and question 18 to 25 are questions used in Walgreens only. There are more questions listed in the Walgreens vaccination consent form than Costco's. Note that question 18 (question on whether fainted or felt dizzy after immunization) is the subclass of question 17 (question on reaction after immunization) in VICO. This reveals that although both Costco and Walgreens ask the adverse event after vaccination, but Walgreens asks only more specific and narrower question than Costco. Similarly, question 13 used by Costco is mother term of question 20 used by Walgreens. The question 23 (question on current aspirin therapy) and 24 (question on current antibiotics usage) are both Walgreens' questions, and question 24 is a subclass of question 23. The same type of questions used in a same questionnaire is because that Walgreens asks more specific questions with regard to a specific vaccine. For example, question 23 is asked specifically for FluMist Quadrivalent, whereas question 24 is for oral typhoid vaccine. This comparison revealed that Walgreens' vaccination informed consent asks more specific questions than Costco. This example demonstrates how VICO can be used to compare different informed consent forms developed by different pharmacies.

Use case 2. Identification of vaccination contraindications and patients who cannot be vaccinated

A contraindication to vaccination is a rare condition in a recipient that increases the risk for a serious adverse reaction. Ignoring contraindications can lead to avoidable vaccine reactions. Contraindications can be permanent, such as known allergies to a vaccine component, or temporary, such as an acute febrile illness. For example, influenza vaccination of egg-allergic patients with allergic reactions to egg is currently not recommended [14]. In this section, we will demonstrate how VICO and OWL-based technologies can be used to identify whether a patient is allergic to egg and thus cannot be vaccinated with a vaccine containing a trace of egg protein. Basically, this use case contains two-steps:

Step 1: Find if a vaccine contains egg allergen.

Step 2: Find if a patient is allergic to egg.

If the answers to both questions are positive, this patient cannot be administered with the vaccine found in step 1.

Below we provide a sandbox demonstration to show how these two steps can be implemented:

Step 1: Find if a vaccine contains egg allergen

Fig. 5 shows a query to identify vaccines that have restriction on egg allergic reaction. As a result, eight licensed vaccines were identified as vaccines containing chicken egg protein allergen.

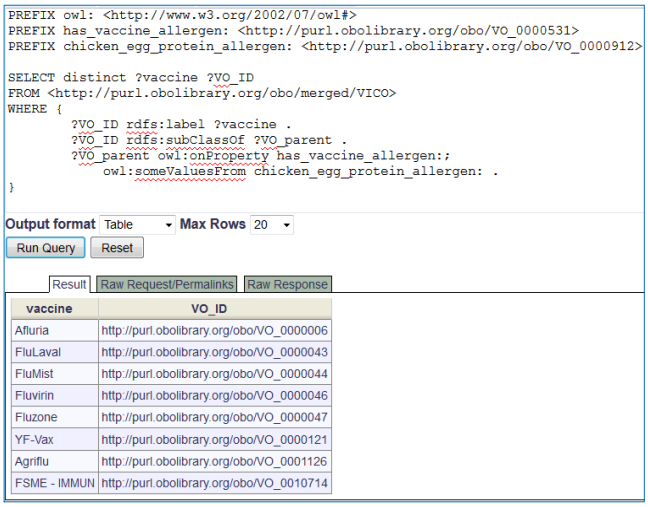


Fig. 5. SPARQL query of vaccines that have egg protein allergen. This query was performed using both the Protégé 5.0.0 SPARQL Query plug-in and the Ontobee SPARQL query website (http://www.ontobee.org/sparql/). The SPARQL query codes are available in the Github repository.This figure is a screenshot of the query execuation and results using the Protégé SPARQL program.

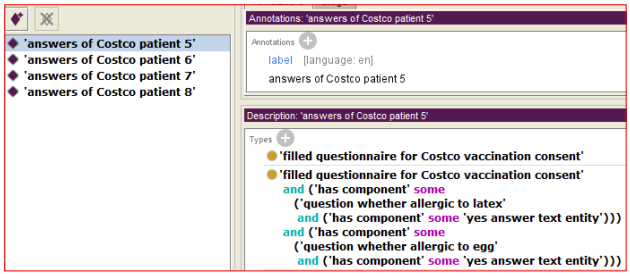
Step 2: Find if a patient is allergic to egg

After Step 1, we would ask another question: Can a patient(s) be administrated with the vaccine indentified in step 1?

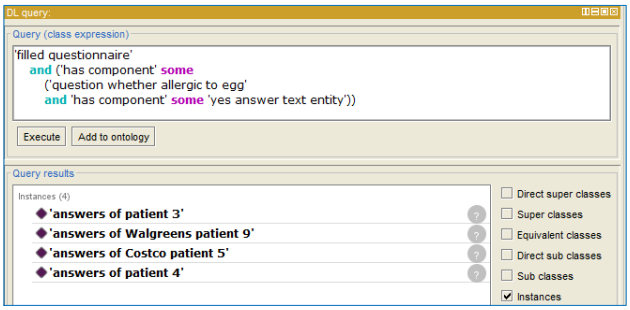
To address this question, first we need to ontologically represent a patient' answers to the questions in an filled informed consent form. As we mentioned before, in VICO, a patient's answers to questions can be represented as a component of a filled questionnaire instance (Fig. 7). For example, in a Costco vaccination informed consent form, a patient's 'No' answer to the question 'whether the patient is allegic to egg or not' is represented as:

'filled questionnaire for Costco vaccination consent'
and ('has component' some ('question whether allergic to egg' and ('has component' some 'no answer text entity')))

After the patients' answers to the informed consent questions are represented using VICO, we can perform queries to answer the question of who would not be allowed to get vaccinated with a specific vaccine, *e.g.*, Afluria. In Fig. 6, we demonstrate how a DL query was constructed in the DL Query Tab in the Protégé OWL editor to perform such a query. The query is generated using the Manchester OWL syntax, a user-friendly syntax for OWL DL [15]. In this sandbox use case study, in total there are twelve patients answered the questions from the Costco vaccination informed consent form, the Walgreens vaccination informed consent form, and the Manitoba informed consent form. Out of these twelve patients's answers, we identified four patients (one Costco patient, one Walgreens patient, and two Manitoba patients) who answered that they were allergic to egg proteins. Therefore, these patients may not be recommended for vaccination with those vaccines containing egg allergen (Fig. 6).



(A) Answers of a patient to the Cosco informed consent form questionnaire



(B) A DL Query and the query results

Fig. 6. DL query for patients who are allergic to egg. (A) Example of the answers of a Costco patient's answers to questionnaire. (B) A DL query and its results. The DL query was performed using the Protégé OWL editor.

IV. DISCUSSION

In this paper, we presented our work of developing a Vaccination Informed Consent Ontology (VICO) and validating its usage with different use cases. VICO represents various vaccination informed consent forms and screening questionnaires for vaccination contraindications. VICO and VICO-based instance data were queried using DL Query and SPARQL to compare screening questionnaires in different forms and identifiy the contraindication of a patient for specific vaccinations.

VICO was developed by following the best practice and recommended strategy of ontology reusing [10]. Instead of coding everything from scratch, we imported related terms from both VO and ICO into VICO. The VO includes the information of licensed human vaccines in different countries and related vaccine characteristics. ICO is an ontology representing informed consent that may be applied in broader areas (*e.g.*, clinical trials) than vaccine immunization. By importing related terms from these two BFO-based ontologies, VICO demonstrates a seamless integration of existing ontologies. On top of the imported terms, VICO can then focus on the representation of more specific entities such as vaccination informed consent forms from different pharmacies and authorities. Such a development strategy has been approved successful in our VICO development.

The applications of VICO can be split into class and instance level applications. At the class level, VICO classes and axioms can represent various vaccination informed consent forms. Current article focuses on representating screening questionnaire about the intended human vaccinee. All the information can be queried in an integrative manner. For example, VICO was used to query the similarities and differences of the questionnaires in different forms, which is of great value in informed consent and vaccine policy related research. At the instance level, we demonstrated that based on patients' answers to questions, we can identify the contraindication conditions and hence determine individuals who should not be administrated with a specific vaccine.

Our VICO usage demonstration makes it feasible to develop electronic interoperable vaccination informed consent forms, *e.g.*, by building up a list of questions for generating the questionnaire in the form. Furthmore, it is now possible for vaccine recipients or their legal representatives to sign electronic informed consent forms. With advantage of sharing Electronic Health Record (EHR), software programs can be developed to query the answers across different pharmarcies, individuals vaccination severe reactions and allergic history. Clinic descion making system can help to prevent avoidable contraindications prior to vaccination.

VICO also provides a solution for vaccination informed consent information standardization. For example, some questions have been coded in Logical Observation Identifiers Names and Codes (LOINC), *e.g.*, question 'Are you sick today' has a LOINC code: 66373-2. In Costco's form, the exact text 'Are you sick today' was used. However, the text used in Walgreen's form is 'Are you currently sick with a moderate to high fever, vomiting/diarrhea'. In VICO, ' question whether currently sick' (ICO_0000142) and its subclass 'question whether currently sick with a moderate to high fever, vomiting/diarrhea' (ICO_0000195) were created. We use *oboInOwl#hasDbXref* to reference the exact match ICO_0000142 to LOINC:66373-2 identifier.

VICO-based vaccination informed consent system may be linked to computerized immunization information systems (IIS, or called immunization registries) that are developed to collect and consolidate vaccination data from multi health-care providers, generate automatic notifications, and assess vaccination coverage. Such IIS have been widely established in the US [16]. For example, the KSWebIZ Kansas Immunization Registry is a web-based statewide immunization registry that provides a centralized birth to death database of complete and accurate immunization records for all Kansas residents (http://www.kdheks.gov/immunize/webiz.html). It would be ideal to eventually link electronic informed consent data to IIS directly, and VICO would facilitate such an effort.

In the future, VICO can be expanded to cover the information related to vaccine adverse events. Typically such information is included in the VIS, and the patients need to be notified of the VIS before their consent. Instead of the plain text described in the VIS documents, an Ontology of Vaccine Adverse Event (OVAE) was recently developed to represents various adverse events for each licensed vaccine [17]. OVAE will be imported into VICO, which allows recipients better understanding of possible side effects of vaccinations prior to vaccination, therefore, enhances the informed consent process. We will also develop user-friendly web interfaces for users to compare and query informed consent forms without writing SPARQL or DL queries.

The methods identified in this study can also be applied to represent informed consent forms in other domains of research, for example, biobanking [18].

Acknowledgment

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