A novel representation of terms related to infectious disease epidemiology for epidemic modeling

The Apollo Structured Vocabulary and pre-existing representations

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***Abstract*—The Apollo Structured Vocabulary (Apollo-SV) is a Web Ontology Language 2 (OWL 2) representation of terms related to epidemic simulation. We are developing Apollo-SV by ontological analysis of the information used and created by epidemic simulators and the entities this information is about.**

A key finding of our analysis is that the input of an epidemic simulator is properly understood as (1) a representation of an ecosystem at simulator time zero, (2) information about infectious diseases of interest in the ecosystem, and (3) information about plans to control the diseases. This insight is reflected in the scope of Apollo-SV, which includes terms from the domains of both infectious disease epidemiology and population biology.

We also found that some definitions in the Infectious Disease Ontology (IDO), including 'infection', 'infection acquisition', 'infectious disease', 'pathogen', and 'host', were not compatible with the meanings of the terms as used in epidemic simulation; thus, we created new definitions of these terms.

Our analysis of epidemic simulators—which are mathematical models of phenomena studied by infectious disease epidemiology—afforded several advantages that likely explain why we discovered limitations of IDO. As a result, we recommend that development of biomedical ontologies intended for reuse consider the perspective of the overlapping biological science(s) involved.

Apollo-SV is freely available at: http://purl.obolibrary.org/obo/apollo_sv.owl.

Keywords—disease transmission models, epidemic simulators, biomedical ontology, infectious disease epidemiology

I. INTRODUCTION

The science and practice of infectious disease epidemiology, like climate science, is increasingly reliant on computational simulation. The simulators—known as epidemic simulators or more generally disease transmission models (DTMs)[1]—require machine-interpretable information about pathogens, rates of infection transmission, populations of hosts, interventions, and the outcomes of infections. Using this *input* information—which we refer to as an *infectious disease scenario*—a simulator's algorithm computes the progression of one or more infections in one or more populations over time, under zero or more interventions. The result of this computation—the *output* of the simulator—is information on which decision makers can base policy or decisions about disease control.

At present, each simulator uses its own representation of its input and output information. For example, the FRED simulator, version 2.0.1 [1] refers to the duration of school closure[2] as 'school_closure_period', whereas FluTE version 1.15 [2] refers to it as 'schoolclosuredays'. The differences make it difficult to compare simulators and re-use machine readable information. For example, Halloran et al. spent 6 months creating a comparative study of three simulators [3].

To address this problem, we are developing machine-interpretable representations for the input and outputs of DTMs and promulgating their adoption as de facto standards. The key goal of the standards is to enable an analyst to specify the same infectious disease scenario exactly once, and run the scenario on multiple simulators with no additional effort.

In this paper, we describe one element of our proposed standards—the Apollo Structured Vocabulary (Apollo-SV). Apollo-SV is an OWL 2 representation of terms related to epidemic simulation. The other two elements are an XML Schema Document (XSD), which defines the syntax for simulator input, and a database schema that defines the representation of simulator output. Apollo-SV defines the terminology used in the XSD and database schema. These elements are described in Wagner et al. [4]

[1] DTMs also model endemic infections such as malaria.

[2] Closing schools is one infectious disease control strategy that simulators study for the control of influenza epidemics. The duration of the closure is the length of time during which schools are closed.

II. METHODS

We developed Apollo-SV for use in a set of Web services designed to improve access to epidemic simulators. We begin this section with an overview of these services, then detail our methods to develop Apollo-SV, including conformance to OBO Foundry Principles, methods to ensure validity for its intended use, and multi-disciplinary development.

The Apollo Web Services: Briefly, the Apollo Web Services are a set of Web services designed to allow a publicly available, Web-based, end-user application to access multiple epidemic simulators through requests to a single Broker service (Fig. 1).

In Figure 1, the Simple End User Application (SEUA) creates an infectious disease scenario for simulation, encoded in an XML document that conforms to the Apollo XSD, which uses terminology defined by Apollo-SV. The SEUA invokes the *runSimulation()* method of the Broker service with the infectious disease scenario. The Broker service invokes the Translator service, which translates the infectious disease scenario into the native terminology and syntax of the requested simulator(s).

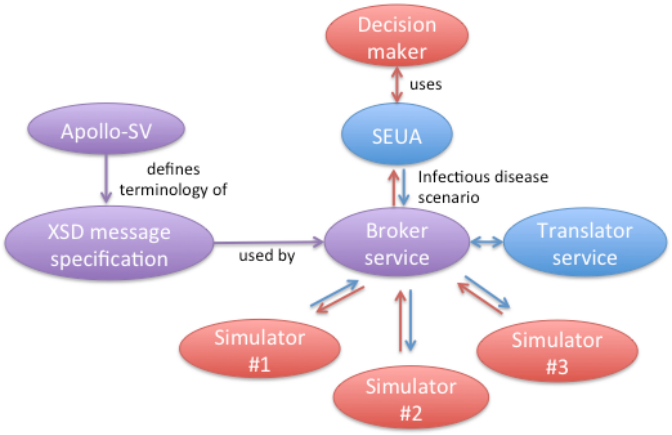

Fig. 1. The relationships of Apollo components and epidemic simulators. Apollo-SV defines the terminology used in Apollo XSD, which specifies the message syntax for the Web services [1]. The SEUA calls the Broker service to configure simulators (messages passed along blue arrows) and to access simulator output (messages passed along red arrows). The Translator service translates Apollo messages to/from native simulator input/output. The SEUA is available at http://research.rods.pitt.edu; the XSD is available at: http://research.rods.pitt.edu/apollo-types_2.0.2.xsd. Purple ovals represent Apollo standards; blue ovals represent Apollo-developed software that use the Apollo Web services; and red ovals represent entities interacting with Apollo.

Upper ontology: We import Basic Formal Ontology (http://www.ifomis.org/bfo/1.1) into Apollo-SV as its upper ontology [5].

Conformance with OBO Foundry principles: We followed the principles of the OBO Foundry in implementing Apollo-SV [6, 7]. Thus we release it in a common format, OWL 2 [8].

In accordance with Foundry principles, we write a textual definition for every term that we create. Because formal ontological textual definitions often use the technical language of ontologists, we created an elucidation annotation for classes in Apollo-SV. The elucidation restates the definition in language more familiar to subject matter experts. We also axiomatize Apollo-SV terms wherever possible (e.g., Fig. 2-5).

In accordance with the Foundry principle of orthogonality, which stipulates that a given term is defined only once across all ontologies, we search for and import pre-existing ontological representations into Apollo-SV. Besides importing entire ontologies, we import selected classes, individuals, and properties using the Minimum Information to Reference an External Ontology Term (MIREOT) [9] Protégé plugin that we developed [10].

We also adhere to Foundry naming conventions [11]. We edit our terms to (1) avoid connectives ('and', 'or'), (2) prefer singular nouns, (3) avoid the use of negations, and (4) avoid catch-all terms such as "Unknown x".

To help link the OWL file with the XSD, we create a Unique Apollo Label (UAL) for classes in Apollo-SV. The UAL is the exact XSD type or attribute name to which the class in Apollo-SV corresponds, for example, InfectiousDisease and basicReproductionNumber.

Analysis of simulators' input and output files, and documentation: We analyzed the input and output files of four epidemic simulators. We also analyzed documentation, such as user guides and published papers. We reviewed terms that we extracted from these resources with the developers of the simulators to identify relevant but missing terms, to discover synonymy among terms, and to detect and resolve ambiguity.

Validation by representation in XSD message syntax: We further refine our OWL DL representations by using the terms in the XSD representation as it progressively expands to be able to represent the input of four simulators.

Validation by automatic translation: The process of developing the mappings from the XSD and Apollo-SV terms to the native language of the simulators identifies additional issues with Apollo-SV that we feed back into our analysis.

Validation by implementation in a user application: The SEUA exposes Apollo-SV definitions and elucidations in tool tips that appear when the mouse hovers over a term. This view identifies problems with elucidations by placing them into the context of an end-user configuring a simulator, and wanting to understand what is meant by a term.

Public release: To encourage adoption of Apollo-SV and to allow external scientific review, comments, and requests for additions, we make Apollo-SV publicly available at http://purl.obolibrary.org/obo/apollo_sv.owl, a permanent URL (PURL). We also ensure that Apollo-SV is easily accessible for browsing and download at the Web-based Ontobee portal: http://www.ontobee.org/browser/index.php?o=APOLLO_SV. The issue tracker and under-development version of Apollo-SV are located at our Google Code site. The PURL to the development version of Apollo-SV is http://purl.obolibrary.org/obo/apollo_sv/dev/apollo_sv.owl.

Multi-disciplinary development: The team developing Apollo-SV comprises personnel with backgrounds in simulator development, disease surveillance, medicine, biomedical informatics, medical terminologies, ontological engineering, artificial intelligence, and formal logic. All these individuals, including a simulator developer (author SB), have been

actively engaged in review of Apollo-SV, and their feedback guides design decisions.

III. RESULTS

Overall, Apollo-SV has 594 classes: 287 that we created new in Apollo-SV and 307 that we imported: 57 via MIREOT (Table I) and 250 from entire ontologies. The number of imported classes is artificially high because the import of entire ontologies brings classes into Apollo-SV we do not require.

TABLE I. RE-USE OF CLASSES AND OBJECT PROPERTIES FROM PRE-EXISTING ONTOLOGIES IN APOLLO-SV VIA MIREOT.

Ontology (by OBO Foundry namespace)	*Classes*	*Object Properties*	**Total**
UBERON	7	1	8
OMRSE	26	7	33
GO	1	0	1
OGMS	11	0	11
OBI	9	5	14
IDO	3	7	10
Totals	57	20	77

The core classes in Apollo-SV represent key entities of interest to infectious disease epidemiology and population biology (Table II). Throughout the course of developing the Apollo standard, we reached the conclusion that the input to an epidemic simulator is properly understood as a representation of an ecosystem at simulator time zero, with additional information about infectious diseases and planned or ongoing interventions to control them. This conclusion motivates the inclusion in Apollo-SV of terms from population biology. In turn, the ecosystem viewpoint heavily influenced our definitions of key terms in infectious disease epidemiology.

At present, Apollo-SV and the XSD enable configuration of three epidemic simulators with the same infectious disease scenario in the SEUA. We are piloting a fourth simulator. They are (1) a compartmental model developed by authors MMW, NEM, and JDL (disease agnostic); (2) the FRED model developed by the University of Pittsburgh Public Health Dynamics Laboratory in collaboration with the Pittsburgh Supercomputing Center and the School of Computer Science at Carnegie Mellon University, University of Pittsburgh and Imperial College (influenza A in humans); and (3) the FluTE model developed by the University of Washington and Fred Hutchinson Cancer Research Center in Seattle and the Los Alamos National Laboratories (influenza A in humans).

With respect to Foundry orthogonality, we attempted to reuse IDO's definitions of 'infection', 'pathogen', 'host', but had to create new definitions (and thus new representations) for them in Apollo-SV as discussed in the following sections.

A. Infection

IDO defines *infection* as a *material entity* that is:

A part of an extended organism that itself has as part a population of one or more infectious agents and that is (1) clinically abnormal in virtue of the presence of this infectious agent population, or (2) has a disposition to bring clinical abnormality to immunocompetent organisms of the same Species as the host (the organism corresponding to the extended organism) through transmission of a member or offspring of a member of the infectious agent population.

TABLE II. CLASSES IN APOLLO-SV BY SUBDOMAIN

Domain	**Classes in Apollo-SV**	
Infectious disease epidemiology	Infection	Infection acquisition
	Pathogen	Host
	Latent period	Infectious period
	Contaminated thing	Contamination acquisition
	Contamination	
	Infectious disease scenario	Basic reproduction number
	Transmission coefficient	Transmission probability
	Disease transmission model	Infectious disease control strategy
	Susceptible population	Exposed population
	Infectious population	Resistant population
Population biology	Ecosystem	Biotic ecosystem
	Abiotic ecosystem	Community
	Population	Population census
	Population infection and immunity census	Abiotic ecosystem census

However, epidemic simulators represent infection as a process, because that is how 'infection' is defined in infectious disease epidemiology. For example, [13, 14] define 'infection' as the invasion of a host organism's tissue by pathogens, the multiplication of those pathogens, and the reaction of the host's tissue(s) to the pathogens and the toxins they produce.

Also, the IDO definition requires that an infection cause clinical abnormality in an individual of a particular species. However, infectious disease epidemiology recognizes the existence of species that do not experience clinical abnormalities when infected with a particular pathogen. The importance in epidemic simulation is that members of species that can experience clinical abnormalities when infected can acquire infection with the pathogen from a 'carrier' species.

Apollo-SV defines 'infection' as: *A reproduction of a pathogen in (a part of) the tissue of an organism from another species* (Fig. 2).

This biologically-grounded definition recognizes that two species are interacting and—from the pathogen species point of view—infection is a process of reproduction. The definition only requires reproduction of one species within the tissues of an individual (organism) from another species.

B. Infection Acquisition (reformulation of Transmission Process)

IDO imports two definitions of 'transmission process' from the Transmission Ontology:

1. *A process that is the means during which the pathogen is transmitted directly or indirectly from its natural reservoir, a susceptible host or source to a new host.*

2. *Suggested definition: A process by which a pathogen passes from one host organism to a second host organism of the same Species.*

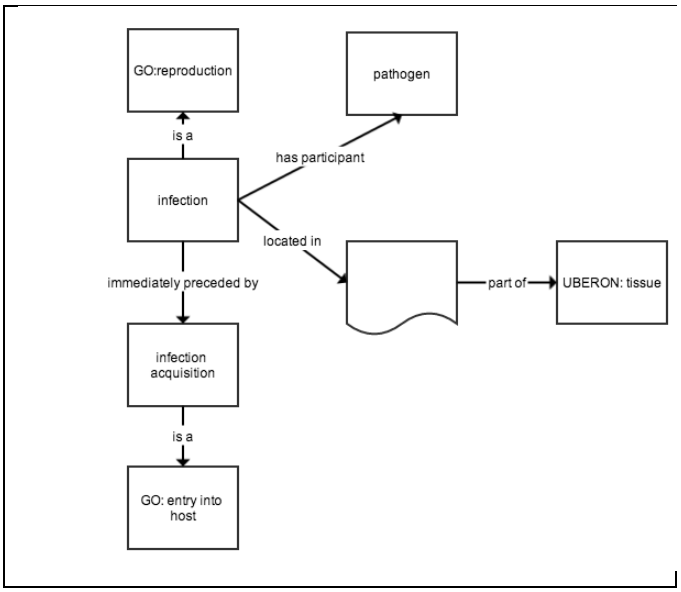

Fig. 2. Representation of the equivalent class axiom for 'infection' in Apollo-SV. Boxes represent named classes, boxes with curved bases represent anonymous classes, arrows represent object properties. In the boxes is the rdfs:label and the namespace of the source ontology, if different from Apollo-SV. Each arrow is labeled with the rdfs:label of the property it represents.

The second, "suggested definition" erroneously restricts transmission to occur only between two hosts of the same species. It is thus not usable in infectious disease epidemiology or any other science that deals with cross-species transmission.

The first definition of 'transmission process' has two major problems. The first problem is that it is circular, defining 'transmission process' in terms of a pathogen being transmitted, with no definition of 'transmitted.'

The second problem is an ontological one. It attributes to one process the property of being the means by which something else happens. For example, assume droplet spread of infection from one host to another by a sneeze. This definition equates the sneeze with the transmission process. That is, it says that only the sneeze exists, but it also has the property of "having transmitted the pathogen". However, equating the sneeze to the transmission process is nonsensical because for transmission to be complete, the second host must have an infection. But this infection will not begin for minutes to hours after the sneeze is over. The sneeze cannot somehow extend itself in time until an infection is established, but conversely not extend in time when no infection results. There exist two distinct processes: the sneeze and the transmission.

We also had the insight that it is only the second host who acquires the infection that undergoes a change during the process. Therefore, we chose to rename it 'infection acquisition'. We recognize that we are diverging from standard terminology in the field, but anyone wishing to add an alternative label to the infection acquisition class in Apollo-SV could do so without changing the meaning of the class.

Apollo-SV defines 'infection acquisition' as: *The biological process of pathogen organism(s) entering (the body of) a host organism from a contagious host or a contaminated thing and reproducing using host resources*.

As with our definition of 'infection', this definition is biologically grounded and recognizes that from the pathogen species' point of view, infection acquisition is the entry into a host and the beginning of reproduction there. Note that Apollo-SV's definition of 'contaminated thing' is general and includes natural reservoirs, vector organisms that are not infected (a.k.a. mechanical vectors), and fomites like contaminated pencils.

C. Host

IDO defines 'host' as: *An organism bearing a host role*

This definition is not sufficient in and of itself to understand what IDO refers to by 'host'. It is also necessary to review its definitions of 'host role' and 'extended organism':

1. 'Host role': A *role borne by an organism in virtue of the fact that its extended organism contains a material entity other than the organism*.
2. 'Extended organism': *An object aggregate consisting of an organism and all material entities located within the organism, overlapping the organism, or occupying sites formed in part by the organism*.

Under these definitions, any organism that has an artificial joint, a penny in its gut, or an arrow through its chest is a host. The fact that a person with a prosthetic knee is a "host" is counterintuitive. This definition is too admissive for our use cases (and for clinical medicine, too): any foreign material entity inside the organism's body renders the organism a host.

In addition, from the ontological perspective, we doubt there is any such entity as host role. First, according to BFO, a role is manifested or realized in one or more processes. However, because there is no representation of the infection process in IDO, infection cannot be the realization. No other process in IDO suffices, either. If there is no process that realizes a role, then by definition of 'role', there is no role.

Apollo-SV defines host as: *An organism that has as part some tissue that is the location of an infection* (Fig. 3).

We therefore distinguish pathogen and host based on which one is reproducing inside tissue (pathogen) and which one is the location of the reproduction (host).

D. Pathogen

IDO defines 'pathogen' as: *A material entity with a pathogenic disposition.*

Again, this definition requires the definitions of other terms to understand its meaning:

1. 'Pathogenic disposition': *A disposition to initiate processes that result in a disorder.*
2. 'Disorder': *A material entity which is clinically abnormal and part of an extended organism. Disorders are the physical basis of disease.*

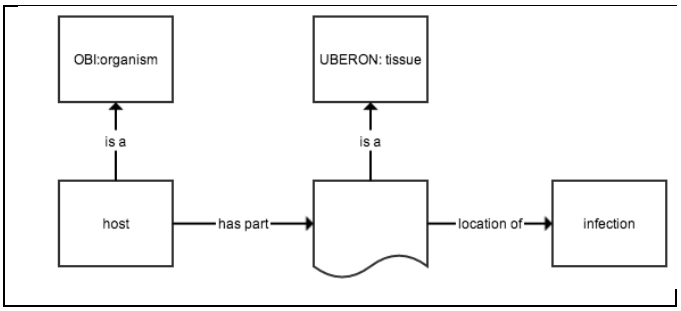

Fig. 3. Representation of the equivalent class axiom for "host" in Apollo-SV. The graphical representation is analogous to Fig. 1.

Thus per IDO any material that causes injury is a pathogen, including the endotoxin of *Clostridium difficile* or an overdose of acetaminophen. IDO does have an infectious agent class as a subtype to pathogen that refers specifically to organisms that enter into a host cause injury. But this definition is not how infectious disease epidemiology uses the term 'pathogen'.

IDO also asserts pathogens must typically cause disease. However, attenuated poliovirus used in oral polio vaccines infects the gut mucosa of humans and thus is a pathogen (or infectious agent per IDO), but it causes disease in only one per 2.7 million first doses of vaccine.

Apollo-SV defines 'pathogen' as: *A material entity that is the bearer of a disposition that, when realized, is realized as an infection* (Fig. 4).

E. *Infectious disease*

IDO defines 'infectious disease' as:

A disease whose physical basis is an infectious disorder.

Per IDO, infectious disorder is a subytpe of infection. However, we require a representation of infectious disease that is consistent with our definition of 'infection' as a process. But because IDO defines 'infection' and thus by inheritance 'infectious disorder' as a material entity, we could not reuse this definition of 'infectious disease'.

Apollo-SV defines 'infectious disease' as: *A disease that inheres in a host and, when realized, is realized as a disease course that is causally preceded by an infection* (Fig. 5). This definition is compatible with the OBO Foundry definition of disease, which is in the Ontology of General Medical Science (OGMS) [15]. We thus were able to reuse the OGMS definition of disease, in keeping with the Foundry principle of orthogonality.

Note that the disease inheres only in the host. From the pathogen's perspective, there is no clinical abnormality (which is a necessary condition to meet the definition of disease in OGMS). For the pathogen, infection is perfectly normal.

IV. DISCUSSION

Apollo-SV version 2.0.1 is an ontology for use in representing DTM input and output. It includes core terms from infectious disease epidemiology and population biology. Apollo-SV currently supports the representation of infectious disease scenarios that can be run on three epidemic simulators and the results of the simulations.

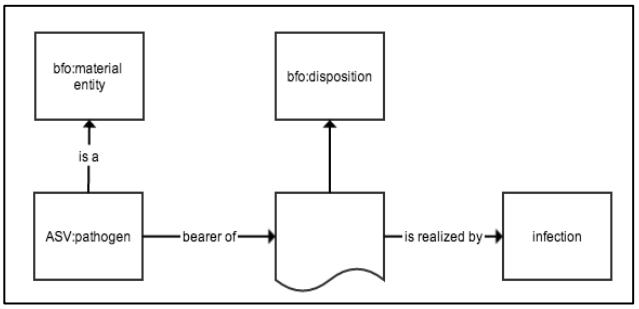

Fig. 4. Representation of the equivalent class axiom for "pathogen" in Apollo-SV. The graphical representation is analogous to Fig. 1.

We set a high priority on implementing Apollo-SV in a Web service for three reasons. First, we wanted to demonstrate the capability to initialize multiple simulators with one infectious disease scenario to motivate the adoption of Apollo. In addition, we wanted to lower barriers to adoption by making available a reference implementation. Lastly, implementation is the basis of our iterative development and refinement process that ensures Apollo is production ready and flexible, which also lowers the barriers to adoption.

A key insight from our iterative development of Apollo-SV and XSD is that a simulator configuration is properly understood as a representation of an ecosystem at a particular time. This insight led us to include in Apollo-SV key terms from population biology, such as 'ecosystem' and 'census'. Furthermore, it led us to our redefinition of 'infection', which was central to redefining other IDO terms.

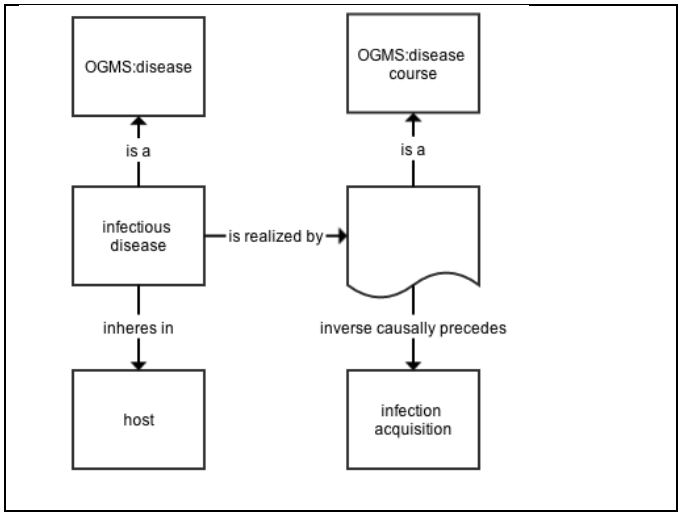

Fig. 5. Representation of the equivalent class axiom for "infectious disease" in Apollo-SV. The graphical representation is analogous to Fig. 1.

A key result of our development of Apollo-SV was that we could not reuse IDO definitions of 'infection', 'host', 'pathogen', and 'infectious disease', and thus we created the definitions presented here. This result was surprising because we had anticipated reuse of IDO at the outset of Apollo-SV development. Given that we did not expect this result, it is worth considering the possible reasons behind it.

A key reason is that our concentration on how terms are used in biological sciences—especially population biology—exposed many issues. This focus differed fundamentally from

IDO's concentration on how the terms are used in clinical medicine. In particular, our focus led us to a requirement to represent the process of infection as opposed to the steady-state, material-entity view of IDO.

So what then led us to the perspective of population biology? We believe the reason we reached this perspective, as well as ontological clarity elsewhere in Apollo-SV, is that working with epidemic simulators quickly brought into view the key phenomena studied (that are also of relevance to epidemic simulation) and their fundamental nature. These simulators are mathematical models in the field of infectious disease epidemiology. They have explicit ontological commitments that have been rigorously vetted through peer review of research using the models (as well as the models themselves). In addition, these ontological commitments comprise the core entities involved in infections and their acquisition, leading us to confront the issues involved in representing them from the outset. It is likely that IDO, by contrast, started with a disease focus and worked from there towards the nature of infection. Finally, because these simulators make a relatively small number of ontological commitments, we had the ability to to devote sufficient time to ontological analysis while still achieving demonstrable progress in implementing the SEUA. Because implementing the SEUA is central to validating Apollo standards, we thus also achieved rapid validation.

We conclude that biomedical ontology developers should incorporate the perspective of the basic sciences that study the phenomena underlying clinical practice, such as medicine and public health practice, when developing ontologies of clinical phenomena. When mathematical models of such phenomena exist, they are potentially useful starting points for analysis.

We also could not reuse prior work on other ontologies that have overlap with Apollo-SV. This work includes the Epidemiology Ontology (EO) [16] and the Ontology for Simulation Modeling of Population Health (SimPHO) [17]. EO (like Apollo-SV) strives to meet Foundry principles [16]. However it, like IDO, also defines 'infection' as a material entity. It erroneously defines infection acquisition as occuring only in humans. It does not axiomatize its classes. Okhmatovskaia et al. do not define for SimPHO [17] any of the terms in Table I. Further comparison is not possible because SimPHO is not publicly available for review/reuse[3].

Note that Apollo-SV is still a significant work in progress. We represented entities sufficient to cover the input and output of just three simulators and did pilot work on a fourth simulator. We have also done preliminary work to represent other types of information in infectious disease epidemiology.

Our future plans include harmonizing Apollo-SV definitions with IDO (we plan to submit the issues described here to the IDO issue tracker) and expanding Apollo-SV to cover additional simulators and types of information used in infectious disease epidemiology. We also plan to study the potential to generate the XSD from the ontology, a successful strategy in other projects [18].

[3] The link provided at http://surveillance.mcgill.ca/trac/star/wiki/StarComponents/Ontology is broken as of this writing.

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