Published in final edited form as:
J Med Entomol. 2013 January ; 50(1): 1–14.

Ontology for Vector Surveillance and Management

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Abstract

Ontologies, which are made up by standardized and defined controlled vocabulary terms and their interrelationships, are comprehensive and readily searchable repositories for knowledge in a given domain. The Open Biomedical Ontologies (OBO) Foundry was initiated in 2001 with the aims of becoming an "umbrella" for life-science ontologies and promoting the use of ontology development best practices. A software application (OBO-Edit; *.obo file format) was developed to facilitate ontology development and editing. The OBO Foundry now comprises over 100 ontologies and candidate ontologies, including the NCBI organismal classification ontology (NCBITaxon), the Mosquito Insecticide Resistance Ontology (MIRO), the Infectious Disease Ontology (IDO), the IDOMAL malaria ontology, and ontologies for mosquito gross anatomy and tick gross anatomy. We previously developed a disease data management system for dengue and malaria control programs, which incorporated a set of information trees built upon ontological principles, including a "term tree" to promote the use of standardized terms. In the course of doing so, we realized that there were substantial gaps in existing ontologies with regards to concepts, processes, and, especially, physical entities (e.g., vector species, pathogen species, and vector surveillance and management equipment) in the domain of surveillance and management of vectors and vector-borne pathogens. We therefore produced an ontology for vector surveillance and management, focusing on arthropod vectors and vector-borne pathogens with relevance to humans or domestic animals, and with special emphasis on content to support operational activities through inclusion in databases, data management systems, or decision support systems. The Vector Surveillance and Management Ontology (VSMO) includes >2,200 unique terms, of which the vast majority (>80%) were newly generated during the development of this ontology. One core feature of the VSMO is the linkage, through the has_vector relation, of arthropod species to the pathogenic microorganisms for which they serve as biological vectors. We also recognized and addressed a potential roadblock for use of the VSMO by the vector-borne disease community: the difficulty in extracting information from OBO-Edit ontology files (*.obo files) and exporting the information to other file formats. A novel ontology explorer tool was developed to facilitate extraction and export of information from the VSMO *.obo file into lists of terms and their associated unique IDs in *.txt or *.csv file formats. These lists can then be imported into a database or data management system for use as select lists with predefined terms. This is an

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important step to ensure that the knowledge contained in our ontology can be put into practical use.

Keywords

ontology; vector; pathogen; surveillance; management

Background

Tremendous amounts of information relating to arthropod vectors and their associated pathogens are generated each year through research and operational public health activities. However, lack of standardization in terminology presents a stumbling block to maximize the value potentially gained from these data, for example by 1) conducting meta-analyses drawing on and integrating data from multiple sources, or 2) simply comparing the results of similar studies from different geographic areas or time periods (Topalis et al. 2008a, Dialynas et al. 2009, Lawson et al. 2009, Megy et al. 2012). Lack of standardization in terminology can result from multiple names being in use for the same process, concept (information artifact), or physical entity. This is familiar to medical entomologists, who are accustomed to taxonomic name changes for both vectors (e.g., the tick *Boophilus microplus* (Canestrini) being reassigned to *Rhipicephalus microplus*(Canestrini)) and agents of vector-borne diseases (e.g., the causative agent of human granulocytic anaplasmosis, previously known as human granulocytic ehrlichiosis, being reassigned from *Ehrlichia phagocytophila* to *Anaplasma phagocytophilum*). Important vector species commonly have numerous synonyms and in some instances the use of multiple names for the same species is acceptable in scientific journals, such as is currently the case for the arbovirus vector *Aedes aegypti* (L.) or *Stegomyia aegypti* (L.). At present, the Journal of Medical Entomology encourages authors dealing with aedine mosquitoes to maintain usage of traditional names (e.g., *Aedes aegypti*) (Editor-in-Chief and Subject Editors of JME 2005) but allows authors who are so inclined to use the revised nomenclature (in this case *Stegomyia aegypti*) suggested by Reinert (2000) and Reinert et al. (2004).

Another important issue is the lack of comprehensive resources for standardized terminology across the broad range of topics relating to the biology and ecology of vectors and vector-borne pathogens, and their surveillance and management. The difficulty in tracking down clearly defined and referenced terminology, which in many cases requires access to high-end library resources, promotes unclear and inaccurate use of terms and can prevent data integration exercises. This issue is not specific to the domain of vectors and vector-borne pathogens but rather a universal problem in biology and medicine, especially in the explosive domain of molecular biology where the Gene Ontology was developed to provide a single source for standardized terminology relating to genes and their products (Ashburner et al. 2000).

An ontology is made up by standardized and defined controlled vocabulary terms and their interrelationships (Smith et al. 2005). One foundational relationship used in ontologies is the is_a relationship, for example *Aedes aegypti* is_a *Aedes* and *Aedes* is_a Culicidae. This relationship allows for the development of hierarchical structures within the ontology for a variety of topics, including the taxonomy of arthropods or microorganisms. The ontology can then be augmented by the inclusion of additional relationships, such as has_vector (dengue virus has_vector *Aedesaegypti*) or has_role (dengue virus has_role viral mosquito-borne pathogen of human), to add knowledge content through linkages between terms based on specific relationships.

After the early success of the Gene Ontology, the Open Biomedical Ontologies (OBO) Foundry was initiated in 2001 with the aims of becoming an “umbrella” for life-science ontologies (Smith et al. 2007) and promoting the use of ontology development best practices. OBO applies the key principles that ontologies be 1) open in the sense that they, and the bodies of data described in their terms, should be available for use without any constraint or license and so be applicable to new purposes without restriction; 2) receptive to modification as a result of community debate; 3) orthogonal to ensure additivity of annotations and to bring the benefits of modular development; 4) instantiated in a well-specified syntax to support algorithmic processing; and 5) designed to share a common system of identifiers to enable interoperability and backward compatibility with legacy annotations (Ashburner et al. 2003, Smith et al. 2007). This was facilitated by the development of a software application for ontology development and editing, OBO-Edit, along with the *.obo file format (Day-Richter et al. 2007). The OBO ontology format is supported by the National Institutes of Health’s National Center for Biomedical Ontology through its BioPortal, a web portal that provides access via web services and web browsers to a library of biomedical ontologies (Noy et al. 2009, Whetzel et al. 2011). It also is compatible with other similar web access services for ontologies, such as the BioGateway (Antezana et al. 2009) and the Ontology Lookup Service (Cote et al. 2006). In addition, a standardized set of publically accessible scripts were developed to allow for automatic conversion of ontologies from *.obo format to a representation in the Web Ontology Language (http://www.w3.org/TR/owl2-overview/).

The OBO Foundry now comprises over 100 ontologies and candidate ontologies (http://www.obofoundry.org/), including the NCBI organismal classification ontology—NCBITaxon (http://www.obofoundry.org/wiki/index.php/NCBITaxon:Main_Page), the chemical entities of biological interest ontology—ChEBI (Degtyarenko et al. 2008), the Mosquito Insecticide Resistance Ontology—MIRO (Dialynas et al. 2009, Topalis et al. 2011), the Infectious Disease Ontology— IDO (Cowell and Smith 2010), the IDOMAL malaria ontology (Topalis et al. 2010, 2011), and ontologies for mosquito gross anatomy and tick gross anatomy (Topalis et al. 2008b). These ontologies include well defined and referenced terms, and therefore can be used as repositories for standardized terminology. However, based on the relationship structures within the ontologies, they also can be used for other purposes, such as reasoning to enable practical querying (Bodenreider 2008, Blonde et al. 2011) or knowledge modeling (Lin and Sakamoto 2009, Bertaud-Gounot et al. 2012). After the explosion of ontology development in the last decade, one critical issue is how to ensure that biomedical ontologies are put to real world use (Smith and Brochhausen 2010). This requires an ontology to not only include high-quality content but also be structured in such a way that the information that can be extracted from it is of practical use.

We recently developed a disease data management system for dengue and malaria control programs, which incorporated a set of information trees built upon ontological principles, including a “term tree” to promote the use of standardized terms (Eisen et al. 2011, Lozano-Fuentes et al. 2011). In the course of doing so, we realized that, with the notable exceptions of the specific topics of mosquito insecticide resistance and surveillance and control of malaria vectors and malaria (Dialynas et al. 2009, Topalis et al. 2010), there was a gap in existing ontologies with regards to concepts, processes, and, especially, physical entities (e.g., vector species, pathogen species, and vector surveillance and management equipment) in the domain of surveillance and management of vectors and vector-borne pathogens.

The primary aim of this work, therefore, was to produce an ontology for vector surveillance and management—the Vector Surveillance and Management Ontology (VSMO)—with special emphasis on content to support operational activities through inclusion in databases, data management systems, or decision support systems. This included arthropod vectors and vector-borne pathogens with relevance to humans as well as domestic animals. A secondary aim was to produce a novel ontology explorer tool to make it easier to search and to extract and export information contained in the VSMO *.obo file to a *.txt file or *.csv file for downstream inclusion, for example as select lists with defined terms, in a database, data management systems, or decision support system.

Developing the VSMO

Technical Aspects of the Ontology Development

The Vector Surveillance and Management Ontology (VSMO) was developed using OBO-Edit version 2.2 (http://www.oboedit.org/). OBO-Edit is an open source ontology editor, written in Java, developed by the Berkeley Bioinformatics and Open Source Projects through funding from the Gene Ontology Consortium (Day-Richter et al. 2007). The VSMO follows the rules set out by the OBO Foundry consortium (Smith et al. 2007), and its high-level structure is based on the Basic Formal Ontology (http://www.ifomis.org/bfo) and the Infectious Disease Ontology (http://infectiousdiseaseontology.org/page/Main_Page). The VSMO includes five relationships. Four of these (is_a, has_quality, has_role, part_of) already were defined in the Relationship Ontology (Smith et al. 2005). The remaining one (has_vector) was generated, in consultation with the developers of the Infectious Disease Ontology, for the VSMO, and also will be useful in other ontologies dealing with vector-borne pathogens such as IDOMAL.

The new relationship has_vector is formally defined within the Infectious Disease Ontology to mean that a microorganism of a given type can be transmitted to a new host via a transmission process in which an organism of a given type serves as a vector, for example dengue virus has_vector *Aedes aegypti.* In the VSMO, we assert the has_vector relation between pathogens and their biological arthropod vectors. That is, we assert has_vector when evidence supports that a given arthropod species is capable of acquiring a given pathogen while feeding, maintaining it for some period of time, and then transmitting it during a subsequent bloodmeal. We have not asserted has_vector between pathogens and mechanical vectors, such as where blood remaining on an arthropod’s mouthparts and containing viable pathogenic microorganisms is the source of infection.

In the vast majority of cases, the use of the relationship has_vector in the VSMO was based on experimental demonstration that a given arthropod species can acquire, maintain, and transmit the pathogenic microorganism in question. Ideally, such a demonstration involves evidence of pathogen transmission to a susceptible host after a bloodmeal by an infected arthropod. This is not always practically possible, however, and so we also accepted demonstration of the presence of infectious microorganisms (i.e., virus, bacteria, or the infectious life stages of protozoans or round worms) in the arthropod’s saliva, salivary glands, or head. Assertion of the has_vector relation in VSMO does not imply that the arthropod species in question is a “natural vector” of the pathogenic microorganism, only that it is capable of experimental transmission. There are some instances where experimental confirmation of vector status is still lacking for arthropod species suspected to be vectors of a given pathogen based on commonly detected infection in field collected specimens. In such cases, the has_vector relation was not asserted, but we noted as a comment for the term representing the arthropod species in question that it is a suspected vector of a given pathogen.

The VSMO ontology will be submitted to the OBO Foundry and to the National Center for Biomedical Ontology for viewing and browsing through their Bio-Portal (http://bioportal.bioontology.org/). The most current version of the VSMO also is accessible from http://code.google.com/p/vector-surveillance-and-management-ontology/downloads/list.

Knowledge Content of the Ontology

The knowledge content of the VSMO was assembled from a variety of sources, including 1) the related ontologies NCBITaxon, ChEBI, MIRO, IDO, and IDOMAL; 2) domain relevant textbooks and manuals (Oldroyd 1957; WHO 1975, 1990, 1997, 2003, 2006, 2010; Sonenshine 1991, 1993; Service 1993, 2001; Sonenshine and Mather 1994; Kettle 1995; Gubler and Kuno 1997; Gratz 1999; Last 2001; Gray et al. 2002; Warrell and Gilles 2002; Eldridge and Edman 2004; Goodman et al. 2005; Marquardt et al. 2005; Taylor et al. 2007; Silver 2008; Mahy 2009; Mullen and Durden 2009); 3) domain relevant review articles (e.g., Pollitzer 1960; Traub and Wisseman 1974; Lent and Wygodzinsky 1979; Naumov et al. 1980; Ryckman 1984, 1986; Russell 1998; Mellor et al. 2000; Horak et al. 2002; Weaver et al. 2004; Turell et al. 2005, 2006; Pattnaik 2006; Barrett and Higgs 2007; Jansen et al. 2008; Sharma and Singh 2008; Eisen et al. 2009; Van den Hurk et al. 2009; Manguin et al. 2010; Sinka et al. 2010a, b; 2011); and 4) domain relevant online resources (Adler and Crosskey 2009; Kolonin 2009; Borkent 2011; Centers for Disease Control and Prevention Arbovirus catalog 2012; *Culicoides*. NET 2012; ECLAT 2012; ITIS 2012; Nomina Insecta Nearctica 2012; Walter Reed Biosystematics Unit 2012a, 2012b).

Additional literature searches for the combinations of 1) a pathogen name AND the term vector, or 2) a pathogen name AND the common name of the group of arthropods transmitting it (e.g., mosquito or tick) were conducted using the Web of Science (http://thomsonreuters.com/products_services/science/science_products/a-z/web_of_science/), PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), and the Armed Forces Pest Management Board's Literature Retrieval System (http://www.afpmb.org/content/welcome-literature-retrieval-system). Individual pieces of information obtained from single publications in scientific journals, and not included in any of the other sources outlined above, were referenced as VSMO:Authors.

Each of the terms included in the ontology has a name, a unique ID, a definition, and one or several references for the definition. When applicable, we also added a comment, synonyms, and cross-references to other ontologies, such as NCBITaxon or MIRO. The taxonomy for aedine mosquitoes is based on traditional names. This is consistent with MIRO but differs from the systematic catalog of Culicidae from the Walter Reed Biosystematics Unit (2012a) and NCBITaxon, which, for example, use *Ochlerotatus* as a genus rather than a subgenus of *Aedes* and, for NCBITaxon, lists the traditional names (e.g., *Aedes communis* (de Geer)) as synonyms of the revised ones (*Ochlerotatus communis* (de Geer)). Because of minor differences in the content of the definitions for arthropod species or microorganisms, compared with NCBITaxon, MIRO, or IDOMAL, we generated unique VSMO IDs but added cross-references to the corresponding IDs in the other ontologies. The most complete organismal classification ontology, NCBITaxon, was found to contain 90% of the microorganisms included in the VSMO but only 58% of the arthropod species.

Developing a Novel Ontology Explorer Tool to Extract and Export Information Contained in the VSMO *.obo file to a *.txt file or *.csv file

To facilitate the exploration of content in the VSMO *.obo file, we developed a tool—the VSMO-Explorer—that is aware of some of the semantics and relationships used in the VSMO, and therefore can perform a series of specific core searches that we expect will be used repeatedly (e.g., which pathogens are transmitted by a given arthropod species or which arthropod species transmits a given pathogen). The tool also has generic functionality to extract information from an *.obo file, which makes it useful beyond the VSMO. This includes extracting text information related to a term (e.g., name, VSMO ID, definition, comment, references for the definition, cross-references to other ontology terms, and synonyms) and the ability to generically query linkages for parent or child terms based on a defined relationship (e.g., show all children terms linked to parent term A with an is_a relationship). In addition, web links to GoPubMed (http://www.gopubmed.org/web/gopubmed/) are provided for the term in question and related terms. The VSMO-Explorer is entirely written in Java (http://www.java.com/en/). It is designed in such a way that it can be extended with minimal effort to incorporate new semantics of the VSMO and to support new VSMO-specific queries. The VSMO-Explorer uses OBO-Edit's parser for parsing *.obo files.

Freely available downloads include the VSMO-Explorer tool (http://sourceforge.net/projects/vsmoexp/files/latest/download), the source code for the VSMO-Explorer tool (http://svn.code.sf.net/p/vsmoexp/code/trunk), and the manual for the VSMO-Explorer (http://sourceforge.net/p/vsmoexp/wiki/Home).

Overview of the VSMO Content Introductory Comments

The VSMO includes >2,200 unique terms, of which the vast majority (>80%) were newly generated during the development of this ontology. The remaining terms originated from other ontologies, including the Basic Formal Ontology (BFO) (the six upper-class terms of object, object aggregate, process, quality, role, and temporal region; fig. 1A), the Mosquito Insecticide Resistance Ontology (MIRO) (>250 terms for chemical compounds with relevance to vector control, which also are cross-referenced to the ontology for chemical entities of biological interest (ChEBI), the IDOMAL malaria ontology (life stages of malaria parasites), and the Infectious Disease Ontology (IDO) (general terms relating broadly to infectious diseases). The most extensive upper class is object (>1,750 unique terms), which includes species of arthropod vectors ($n = 786$), pathogenic microorganisms ($n = 237$), chemical compounds of relevance to insecticide resistance, and equipment used to collect or control arthropod vectors. The other upper classes include smaller numbers of unique terms, in the range of 100–200 terms for process, quality, and role, and 15–20 terms for object aggregate and temporal region.

Some individual terms are shown in more than a single place in the ontology tree viewer. For example, in the upper class of object, a given pathogenic microorganism is shown once with an is_a relationship in the taxonomic hierarchy for microorganisms (e.g., see *Anaplasma phagocytophilum* in fig. 1A) but may be shown on several other occasions linked to vector species with the has_vector relationship in the taxonomic hierarchy for arthropods (e.g., see linkages for *Anaplasma phagocytophilum* with *Ixodes pacificus* Cooley& Kohls and *Ixodes scapularis* Say in fig. 1B). Further, a pathogenic microorganism also may be shown under the upper class of role, with a has_role relationship (e.g., see inclusion of *Anaplasma phagocytophilum* as a bacterial hard tick-borne pathogen of humans in fig. 1C).

Each of the VSMO terms in the *.obo file has a name, a unique ID, a definition, and one or several references (Dbxrefs) for the definition (see example for *Ixodes scapularis* in fig. 2). When applicable, we also have added a comment, cross-references (Xrefs) to other ontologies, and synonyms for the term (fig. 2). The full reference can be viewed by opening a given reference in the Dbxrefs panel in the *.obo file, and can be exported through the VSMO-Explorer tool described in section, *Overview of the VSMO-Explorer Tool's Functionalities.*

VSMO Upper Class of Object

This is the most extensive upper class, dealing with abiotic and biotic objects. Abiotic objects are subcategorized as chemical compounds or equipment. Chemical compounds include an exhaustive list of terms for chemical pesticide active substances, originating from

MIRO and with cross-references to ChEBI. The equipment section includes terms for equipment used to collect or control vectors (e.g., tick drag, CDC light trap, long-lasting insecticidal net, autocidal oviposition trap, and side-carried compression sprayer) or vertebrate pathogen hosts (e.g., 4-poster deer self-treatment device and pesticide-treated oral bait).

The section for equipment for the collection of arthropods comprises a large number of terms for various traps and other types of equipment used to collect arthropods, with the majority of terms originating from Service's books on field sampling methods for mosquitoes (Service 1993, Silver 2008). The section is structured based on whether the targeted arthropods are in the egg stage (equipment for collection of arthropod eggs), aquatic immature stages (equipment for collection of aquatic arthropod immatures), ground-based immature or adult stages (equipment for collection of ground-based arthropods), or adult flying stage (equipment for collection of adult flying arthropods) (fig. 3). Equipment for collection of arthropod eggs includes dippers, collection nets for eggs, soil sample egg extractors, and various gravid or oviposition traps. Collection of aquatic arthropod immatures can be achieved with a wide range of different types of equipment, including pipettes, dippers, collection nets for immatures, and various types of pumps or area samplers. Equipment for collection of ground-based arthropods includes a smaller number of terms, such as Berlese funnel, burrow swab, carbon dioxide-baited ground trap, tick drag, and tick flag. finally, the equipment for collection of adult flying arthropods is an extensive section that includes aspirators, collecting tubes, collection nets for adults, and traps. Different trap types are so numerous that we subdivided this section based on the activity of the targeted organism (resting, general flight, emergence, host-seeking, or flight of gravid female seeking an oviposition site) (fig. 3). The section for vector management equipment includes terms for different tools used to kill vectors or prevent contact with humans, such as aircraft-mounted cold fogger, backpack-carried powered duster, shoulder-sling granule applicator, and repellent-treated clothing.

Biotic objects are subcategorized as Arthropoda, which in the VSMO includes arthropod species capable of serving as biological vectors of pathogens affecting humans or domestic animals, and microorganisms, which in the VSMO includes viruses, bacteria, and eucaryotic protozoans (apicomplexans and kin- etoplasts) or parasitic round worms (nematodes) transmitted by arthropod vectors and causing disease in humans or domestic animals. The structures of these sections follow taxonomic hierarchies (figs. 1A–B). Searching for a given vector or pathogen species can be achieved through OBO-Edit's search panel functionality or by directly navigating the ontology tree viewer (or alternatively via the VSMO-Explorer tool). To make the taxonomic hierarchies for Arthropoda and microorganisms easy to navigate in the ontology tree viewer, we avoided the use of nonessential taxonomic ranks, such as subgenera for mosquitoes, which can make it unnecessarily difficult to navigate the taxonomic hierarchy to find a given species.

The definition and comment fields for a given arthropod species collectively include common name(s), when applicable, and its broad geographic distribution (e.g., North America or Americas), as well as a list of the pathogenic microorganisms for which it serves as a biological vector (fig. 2). Pathogenic microorganisms for which the arthropod species in question is suspected, but not experimentally demonstrated, to be a vector are included in the comment, but it is clearly noted that vector status is only suspected. Arthropod species are cross-referenced to NCBITaxon and MIRO, and synonyms for species names also are provided. The definition and comment fields for a given microorganism collectively include a broad categorization of its vectors (e.g., mosquitoes, hard ticks, or fleas), the name of the disease it is causing (e.g., dengue, Lyme disease, or bovine babe-siosis), the affected hosts (e.g., humans, cattle, or cats), and its broad geographic distribution. Microorganisms are cross-referenced to NCBITaxon and IDOMAL.

One core feature of the VSMO is the linkage of arthropod species to the pathogenic microorganisms for which they serve as biological vectors. This is accomplished not only through information contained in the definition and comment for the arthropod species terms but also through the use of the has_vector relationship (fig. 1B). The use of a formally defined relationship enables use of the information by query and reasoning software. The pathogens transmitted by a given arthropod species can be viewed directly in OBO-Edit's ontology tree editor (fig. 1B) and the reverse option of viewing the arthropod species serving as vectors of a given pathogen of interest can be visualized through the graph editor (fig. 4). A novel tool to extract this type of information from the VSMO *.obo file to a *.txt or *.csv file is described in the section, *Overview of the VSMO-Explorer Tool's Functionalities.*

VSMO Upper Class of Object Aggregate

The upper class of object aggregate contains only a small number of terms dealing with aggregates of arthropods or microorganisms. Examples of included terms are genetic arthropod population and bacteremia.

VSMO Upper Class of Process

The upper class of process includes terms dealing with various processes relating to 1) the life course of arthropods or microorganisms; 2) the surveillance of vectors, pathogens, or vertebrates; 3) the management of vectors or vertebrate pathogen reservoirs; or 4) pesticide delivery. Examples of terms are insect pupal stage, mark-release-recapture, mosquito age-grading (with descendant terms representing specific age-grading techniques, such as determination of cuticular hydrocarbons), estimation of daily arthropod survival rate, pathogen detection (with descendant terms representing specific detection methods, such as morphological taxonomic identification), and indoor residual spraying.

VSMO Upper Class of Quality

The upper class of quality includes terms that relate to some quality of a physical entity or a group of entities. This includes, for example, the sex of an arthropod (female or male), the parity status of a female insect (nulliparous or parous, with the subclassifications for parous of uniparous or multiparous), and the infection status of an arthropod or vertebrate (infected, with the subclassification of infectious). Also included are terms relating to infection in aggregates of arthropods or vertebrates (e.g., infection prevalence and intensity of infection) or to pathogen transmission by arthropods or vertebrates (e.g., vector competence and entomological inoculation rate). Other terms refer to qualities of vector management materials, such as the shapes of mosquito nets or the formulations of a pesticide, including different subtypes of dry or wet pesticide formulations (e.g., pesticide granule or pesticide aerosol spray). finally, provisionally included under quality are terms that define measures or indices to estimate the abundance or density of an aggregate of arthropods (e.g., Bailey's triple catch estimate, Breteau index, and specific flea index). These can be viewed as information artifacts and may downstream be moved to another upper class, yet to be added to the VSMO, where they are a better fit.

VSMO Upper Class of Role

The upper class of role includes a variety of terms dealing with the roles of different physical entities; for example, surveillance or management tools for arthropods or vertebrates (e.g., sentinel animal and bacterial control agent), or trap enhancing entities (e.g., animal bait and optical trap enhancing entity). It also includes a section for pathogen role broken down by type of microorganism (bacterial pathogen, parasitic round worm pathogen, protozoan pathogen, and viral pathogen), whether they impact domestic animals humans, or both, and which type of arthropod vector they are transmitted by (fig. 1C).

VSMO Upper Class of Temporal Region

The upper class of temporal region contains a small number of terms that relate to time periods (i.e., continuous temporal intervals) and are subdivided into 1) temporal region of pathogen in arthropod (e.g., extrinsic incu- bation period), 2) temporal region of pathogen in vertebrate (e.g., intrinsic incubation period), and 3) temporal region of arthropod (e.g., peak diel activity period of host-seeking arthropod and seasonal period of peak activity of arthropod).

Overview of the VSMO-Explorer Tool's Functionalities

To make it easier to extract and export information contained in the VSMO *.obo file, we developed a novel ontology explorer tool: the VSMO-Explorer. The VSMO-Explorer is comprised of a relationship explorer and a term explorer. The relationship explorer is based on five queries, of which the first four are VSMO-specific: 1) Which pathogens are transmitted by a given vector species? 2) Which vector species transmit a given pathogen? 3) Which pathogens have a given role? 4) What are the roles of a given pathogen? (fig. 5). Choosing one of these queries produces a list of relevant terms to select from (fig. 5). The fifth query—Query any arbitrary relationship—allows the user to ask two different types of generic questions: 1) Which are the parent terms of a given child with respect to a given relationship? and 2) Which are the children terms of a given parent with respect to a given relationship? This requires the user to first define a relationship type and then a specific parent or child term (fig. 6). When the user selects a relationship type, the parent list is populated with all the terms that are parents of any relationship of the selected type, and the children list is populated with all the terms that are children for any relationship of the selected type.

After selecting the term of interest and defining whether to view the result as text or in a tree format (figs. 5–6), the user can execute the query and view the output (figs. 6–7). The text option produces a flat list of resulting terms (fig. 7A), whereas the tree option shows how the terms fit into the hierarchy in which they exist in the VSMO (fig. 7B). Query results can be saved as either flat lists of terms (*.txt file or *.csv file) or with the tree structure for the terms (*.csv file). To facilitate use of the terms in other databases data management systems, or decision support systems, the term names are accompanied by their unique term IDs.

The term explorer provides generic capability to extract the text-based information related to a selected term, including the term's name, definition, VSMO ID, comment, references for the definition, cross-references to other ontology terms, and synonyms. In addition, web links to GoPubMed (http://www.gopubmed.org/web/gopubmed/) are provided for the term in question and related terms. The search returns a set of terms related to the selected term and links to GoPubMed pages that list related publications. To facilitate the term selection process, terms are shown in alphabetical order under three groupings: vectors, pathogens, and others (i.e., terms not classified as either vector or pathogen). Query results can be saved as *.txt file or *.csv file.

Practical Use of the VSMO: Opportunities and Challenges

Among other uses, ontologies are comprehensive and readily searchable repositories for knowledge in a given domain. Users can navigate directly to a specific term of interest through a search functionality and then explore the ontology from that starting point using the ontology tree editor or the graph editor. Alternatively, they can browse the ontology tree to more broadly explore the hierarchically structured content under the upper class terms. In addition, we describe a novel ontology explorer tool— the VSMO-Explorer—to facilitate the extraction and export of information contained in the VSMO *.obo file to *.txt file or *.csv file formats for downstream use in databases, data management systems, or decision support systems. Collectively, this provides powerful tools to explore the domain knowledge contained in the VSMO.

A key benefit of an ontology is the compilation of defined and referenced terms. Data are accumulated for arthropod vectors and their associated pathogens by a plethora of researchers and public health personnel across the world, and standardization of terminology is critical to facilitate integration of data originating from these varied sources. Ontologies provide one possible solution to this problem by providing sets of defined terms that can be referenced by their unique IDs and further constrained by their definitions/comments and relationships. One example of this being put into practical use is the development of the Mosquito Insecticide Resistance Ontology and the use of terms defined therein to annotate data populating the IRbase dedicated database for insecticide resistance in mosquitoes (Dialynas et al. 2009).

Another practical use for defined terms contained within an ontology is to use them to populate drop-down or select lists in databases, data management systems, or decision support systems. In this manner, data are annotated using defined terms as they are added to the database or system. We made use of this in a recently developed data management system for malaria and dengue control programs, where a “term tree” based on ontological principles and containing terms that can be tagged with specific IDs, such as the unique ID for a term in an ontology, are used extensively to populate pop-up select lists as well as column headers and rows in data entry tables (Eisen et al. 2011, Lozano-Fuentes et al. 2011). In an ideal scenario, the content of an ontology, or sections thereof, can be envisioned to be imported directly into various databases or systems addressing the same domain but developed by different groups, and thus instantly providing capacity for data integration across these databases and systems.

The development of an ontology is not a trivial task, and all ontologies should be viewed as works in progress. A solid understanding of the domain the ontology addresses is needed both for the selection of terms to include, among all possible terms to include, and to ensure that definitions, comments, and references are as accurate as possible. One main challenge for the development of the VSMO, which aims to cover vectors of pathogens affecting both humans and domestic animals, was to synthesize the available information for a wide range of disease-causing organisms (viruses, bacteria, and eucaryotic protozoans [apicomplexans and kinetoplasts] or parasitic round worms [nematodes]) and the arthropods that serve as biological vectors of these pathogens (ticks, mites, and a wide range of insects). This proved to be a very time-consuming task that was accomplished by first using information from key domain-relevant textbooks (Sonenshine 1993, Kettle 1995, Service 2001, Warrell and Gilles 2002, Eldridge and Edman 2004, Goodman et al. 2005, Marquardt et al. 2005, Taylor et al. 2007, Mullen and Durden 2009) and then complementing this with additional information from online resources or papers published in scientific journals. This included literature searches for each of the pathogens included in the VSMO. Nevertheless, one unavoidable problem with the content of an ontology is that it needs to be regularly updated for the content to be up-to-date; for example, by addition of vectors for a given pathogen as they are determined to be capable of biological transmission and this information is made available in the published literature. As a case in point, the June 2012 issue of the American Journal of Tropical Medicine and Hygiene included an article providing experimental evidence for *Culex neavei* Theo-bald being a biological vector of Usutu virus (Nikolay et al. 2012), which represented the first indisputable evidence of mosquito transmission of Usutu virus and therefore prompted us to add this virus to the VSMO.

One potential improvement to the VSMO in the future is to add detailed descriptions of arthropod species and microorganisms based on their morphological or immunogenic characteristics and molecular genetic data. This would improve the current definitions for arthropod species and microorganisms, but represents a large and complex undertaking that falls outside of the current scope of the VSMO. The taxonomy of arthropods and pathogens can be challenging because taxonomic changes occur with some regularity, for example by species being moved from one genus to another genus, or by a subgenus being raised to genus status. In instances where the recent literature appears to have reached consensus for a given change, this is reflcted in the VSMO with the previous name listed as a synonym. Examples of this include the tick *Carios rudis* (Karsch) (previously known as *Ornithodoros rudis*) and the protozoan *Theileria equi* (previously known as *Babesiaequi*). However, in some cases there is still vigorous debate regarding a proposed change, and in such instances we are conservatively using the traditional nomenclature. One example of this is our continued use of genus *Aedes* for the subgenera of *Ochlerotatus* and *Stegomyia,* for which the proposal to raise these subgenera to the status of genera has met with considerable resistance (Reinert 2000; Reinert et al. 2004, 2009; Savage and Strickman 2004; Editor-in-Chief and Subject Editors of JME 2005). For example, in the VSMO we use the name *Aedes aegypti* but have included *Stegomyia aegypti* as a synonym for that term.

Another challenge is to produce an ontology where the use of relationships to link the terms are compliant with their use within the OBO Foundry, while at the same time presenting an ontological structure that is easily understandable for the viewer. This can present some difficulties in the initial stages of ontology development (Topalis et al. 2011). To ensure the correct use of the new has_vector relationship, we consulted with the working group developing the Infectious Disease Ontology.

A final issue is the difficulty in assigning terms to the correct upper class defined in the Basic Formal Ontology. In the case of the VSMO, this relates primarily to terms asserted under quality. For example, additional discussion within the OBO Foundry community is needed to decide under which upper class terms referring to abundance estimates or indices should be asserted. The structure of the VMSO therefore may need revision in the future to stay current (i.e., by terms being moved from one upper class to another one).

The ontology editor and viewer OBO-Edit is easy to comprehend, and because it is open source software, can be freely downloaded and used (http://www.oboedit.org/). Nevertheless, the need to download a specific software application to view ontologies may prevent their use, even within the scientific community itself, and diminish their value. To counter this, several groups have developed web-based ontology browsers that allow the user to peruse an ontology without the need for specialized software (Cote et al. 2006, Antezana et al. 2009, Noy et al. 2009, Whetzel et al. 2011). This includes BioPortal (http://bioportal.bioontology.org/), which is provided through the National Center for Biomedical Ontology. We recognized and addressed another potential roadblock for use of the VSMO by the vector-borne disease community: the difficulty in extracting data from OBO-Edit *.obo files and exporting the data to other file formats. The novel ontology explorer tool described herein (VSMO-Explorer) not only includes VSMO-specific queries but also provides capability to extract information contained in an ontology *.obo file and then export this information into lists of terms (and their accompanying unique term IDs) in formats (*.txt or *.csv) that can be readily imported into a database or data management system for use as select lists with predefined terms.

We conclude that ontologies hold great promise as tools to identify knowledge gaps, synthesize knowledge, promote use of standardized terminology, and facilitate integration of data from different sources. One main challenge moving forward is to put ontology-derived information into practical use, for example by vector and disease surveillance and control programs annotating data in their electronic databases by using terms tagged with IDs derived from ontologies.

Acknowledgments

The funding agencies (United States National Institutes of Health/National Institute of Allergy and Infectious Diseases; and the Innovative Vector Control Consortium) had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

We thank Sanika Chitari, Jayameenakshi Ganesan, and David Penhall of Colorado State University; and Marlize Coleman of Colorado State University and Liverpool School of Tropical Medicine, for their contributions to the development of the ontology. The IDO and OBI working groups (in particular Alexander Diehl, Alan Ruttenberg, and Barry Smith of the University at Buffalo; Christopher Mungall of the Lawrence Berkeley National Laboratory; and Bjoern Peters of the La Jolla Institute for Allergy and Immunology) assisted with the new has_vector relationship. Pantelis Topalis and Christos Louis of the University of Crete generously shared their experience with ontology development. The contributions of S.L.-F. and L. E. to this work were supported by the United States National Institutes of Health/National Institute of Allergy and Infectious Diseases (1R03AI083254-01) and the Innovative Vector Control Consortium. L.G.C.'s contributions were supported by the United States National Institutes of Health/National Institute of Allergy and Infectious Diseases (1R03AI083254) and a Burroughs Wellcome Fund Career Award at the Scientific Interface.

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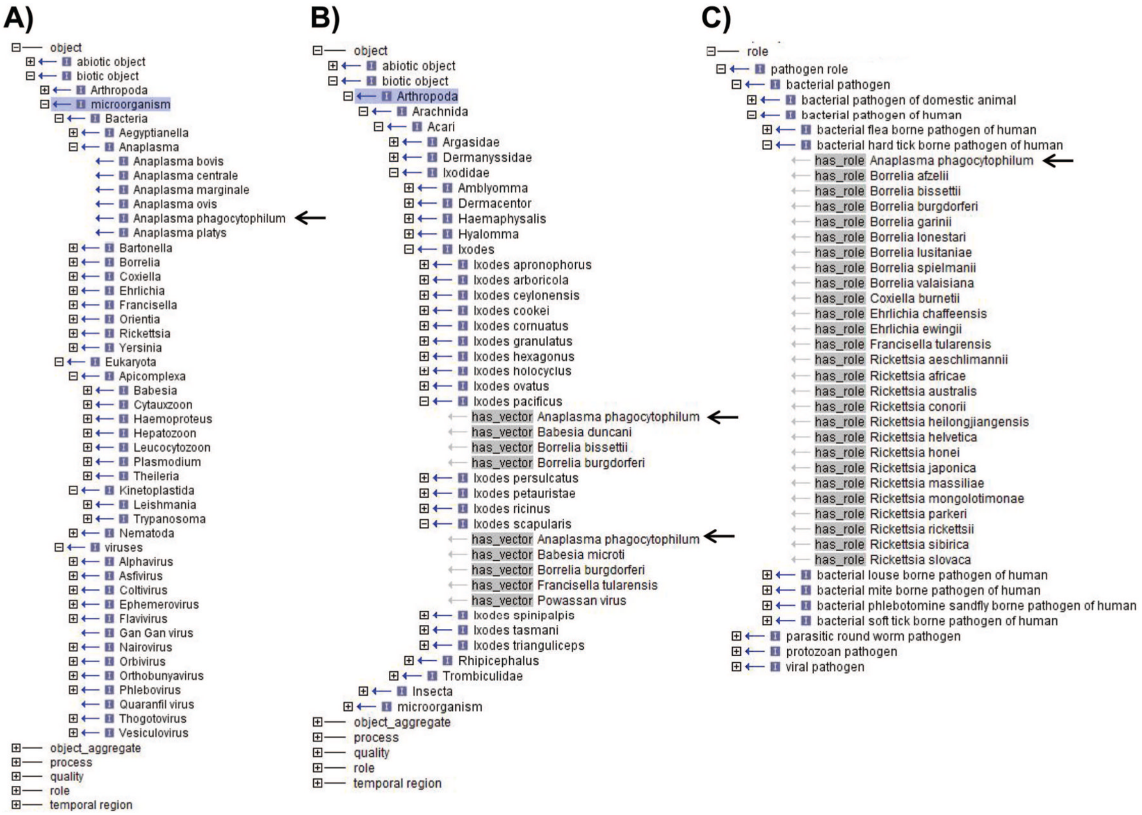
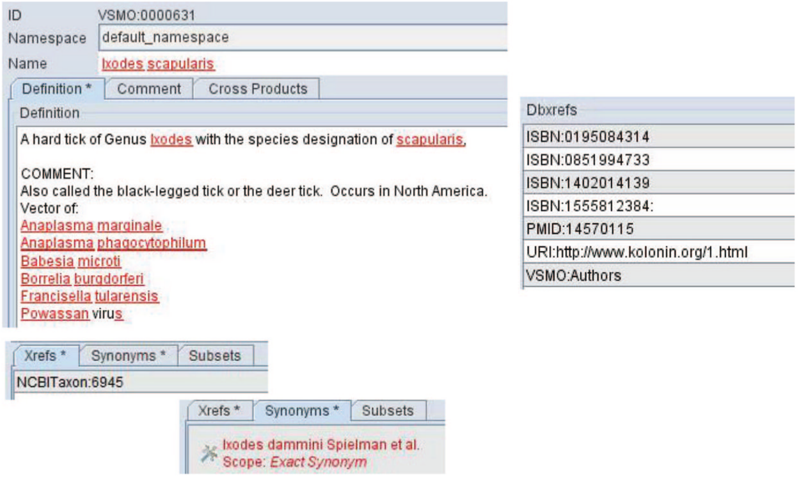


Fig. 1.

Example of view from the OBO-Edit ontology tree editor. A) Partial view of taxonomic hierarchy for microorganisms under the upper class object. The box with an I denotes the is_a relationship. B) Partial view of taxonomic hierarchy for arthropod species under the upper class object (including links to pathogens with the has_vector relationship). C) Partial view of the section for pathogen role under the upper class role (including the use of the has_role relationship). (Online figure in color.)



ID VSMO:0000631
Namespace default_namespace
Name Ixodes scapularis

Definition
A hard tick of Genus Ixodes with the species designation of scapularis,

COMMENT:
Also called the black-legged tick or the deer tick. Occurs in North America.
Vector of:
Anaplasma marginale
Anaplasma phagocytophilum
Babesia microti
Borrelia burgdorferi
Francisella tularensis
Powassan virus

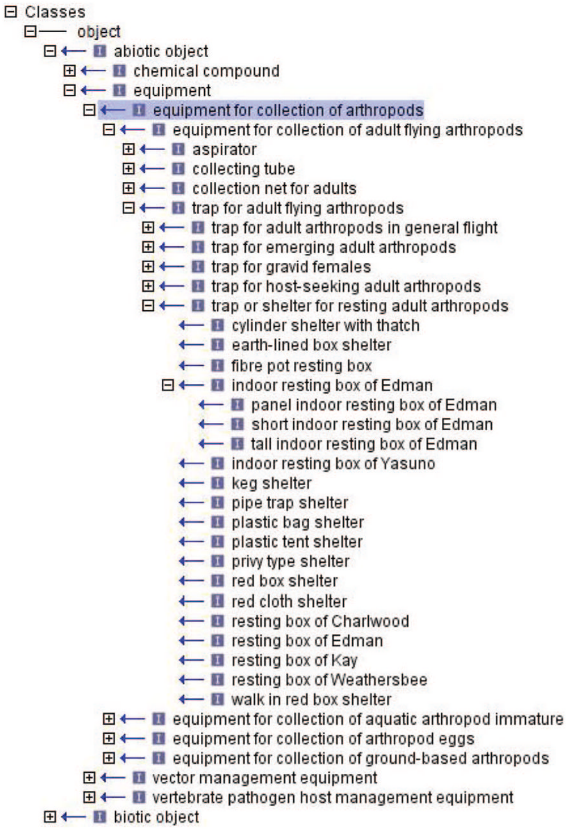
Dbxrefs
ISBN:0195084314
ISBN:0851994733
ISBN:1402014139
ISBN:1555812384:
PMID:14570115
URI:http://www.kolonin.org/1.html
VSMO:Authors

NCBITaxon:6945

Ixodes dammini Spielman et al.
Scope: *Exact Synonym*

Fig. 2.

Example of information for a term (*Ixodes scapularis*) in the OBO-Edit text editor. (Online figure in color.)



- ⊟ Classes
  - ⊟ object
    - ⊟ abiotic object
      - ⊞ chemical compound
      - ⊟ equipment
        - ⊟ equipment for collection of arthropods
          - ⊟ equipment for collection of adult flying arthropods
            - ⊞ aspirator
            - ⊞ collecting tube
            - ⊞ collection net for adults
            - ⊟ trap for adult flying arthropods
              - ⊞ trap for adult arthropods in general flight
              - ⊞ trap for emerging adult arthropods
              - ⊞ trap for gravid females
              - ⊞ trap for host-seeking adult arthropods
              - ⊟ trap or shelter for resting adult arthropods
                - cylinder shelter with thatch
                - earth-lined box shelter
                - fibre pot resting box
                - ⊟ indoor resting box of Edman
                  - panel indoor resting box of Edman
                  - short indoor resting box of Edman
                  - tall indoor resting box of Edman
                - indoor resting box of Yasuno
                - keg shelter
                - pipe trap shelter
                - plastic bag shelter
                - plastic tent shelter
                - privy type shelter
                - red box shelter
                - red cloth shelter
                - resting box of Charlwood
                - resting box of Edman
                - resting box of Kay
                - resting box of Weathersbee
                - walk in red box shelter
          - ⊞ equipment for collection of aquatic arthropod immature
          - ⊞ equipment for collection of arthropod eggs
          - ⊞ equipment for collection of ground-based arthropods
        - ⊞ vector management equipment
        - ⊞ vertebrate pathogen host management equipment
    - ⊞ biotic object

Fig. 3.

Partial view of the upper class object in the OBO-Edit ontology tree editor, relating to equipment for collection of arthropods. The box with an I denotes the is_a relationship. (Online figure in color.)

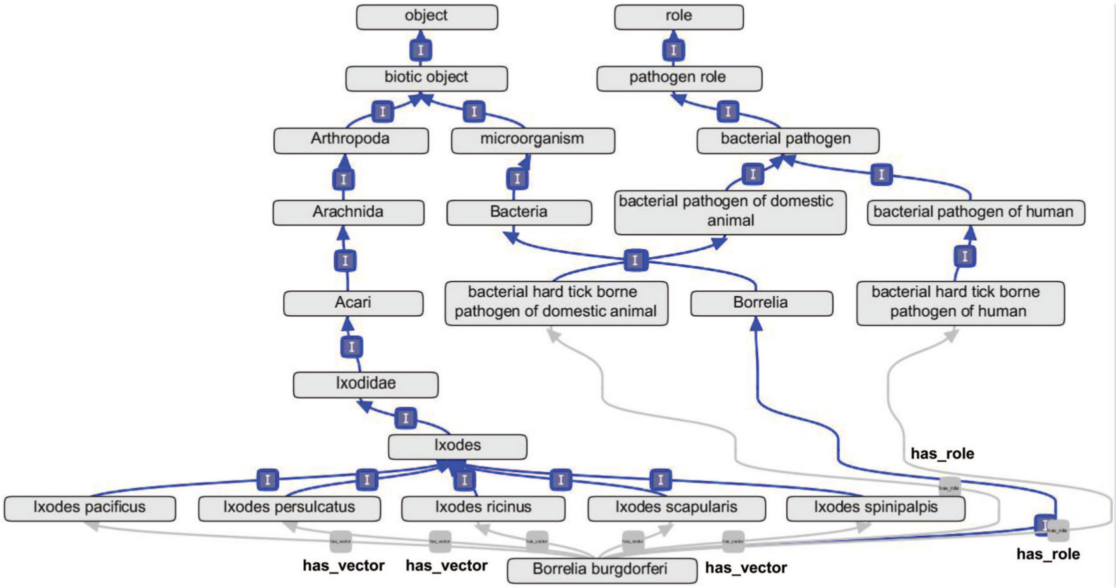


Fig. 4.

Example of view in the OBO-Edit graph editor of the is_a (darker box with an I) and has_vector or has_role (more light colored solid boxes with text) relationship linkages in the VSMO to a specific microorganism (*Borrelia burgdorferi*). The has_vector relationship links *B. burgdorferi* to five species of *Ixodes* ticks and the has_role relationship links *B. burgdorferi* to bacterial hard tick-borne pathogen of domestic animal and bacterial hard tick-borne pathogen of human. (Online figure in color.)

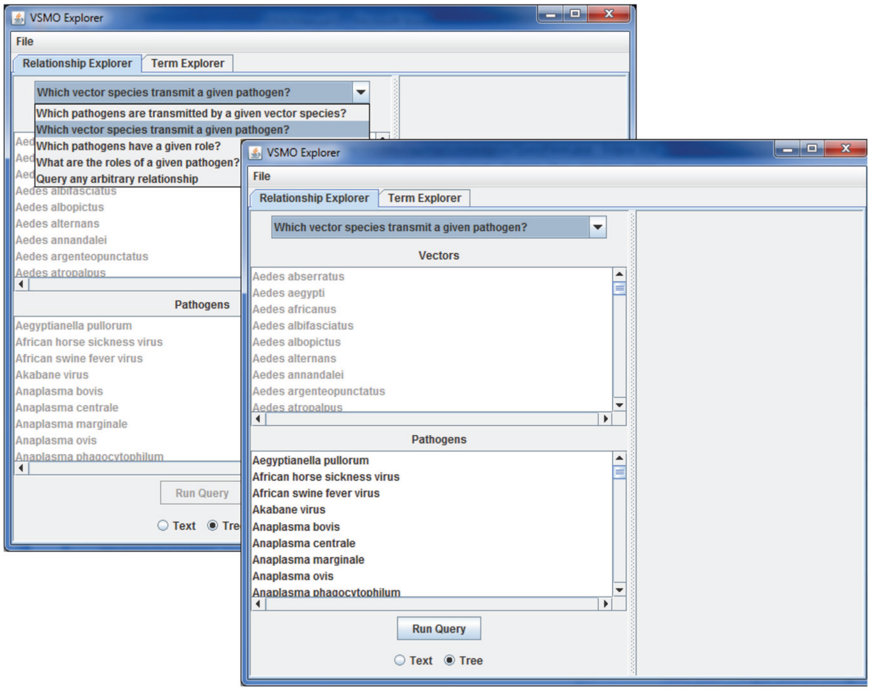
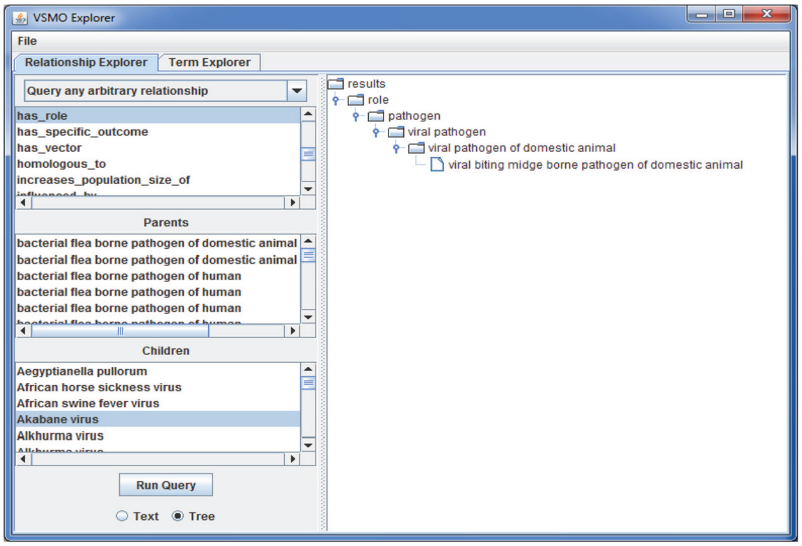


Fig. 5.

Query options in the relationship explorer component of the VSMO-Explorer. Example of query for which vector species that transmit a given pathogen, with the select list for pathogens automatically activated by the choice of query type. (Online figure in color.)



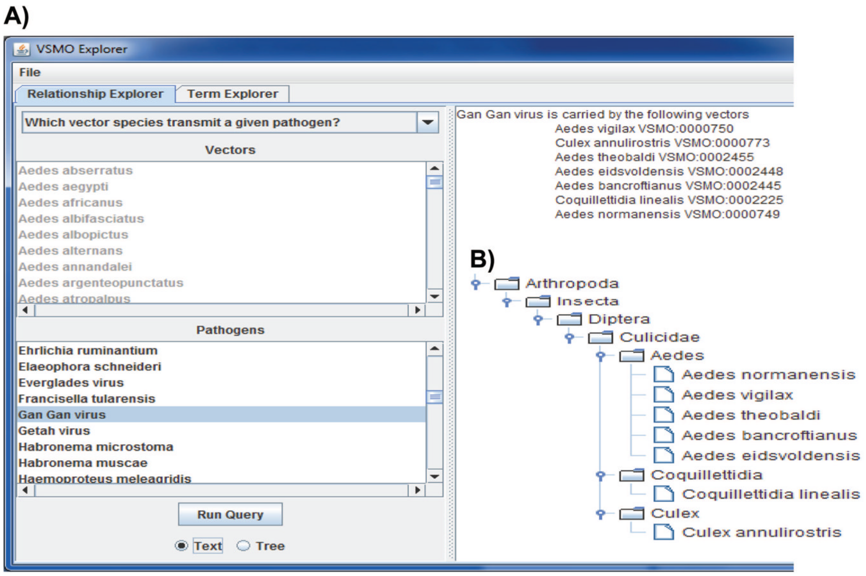
Query any arbitrary relationship

○ Text ● Tree

```
results
  role
    pathogen
      viral pathogen
        viral pathogen of domestic animal
          viral biting midge borne pathogen of domestic animal
```

Fig. 6.

Example of generic query (Query any arbitrary relationship) in the relationship explorer component of the VSMO-Explorer. (Online figure in color.)



```
Gan Gan virus is carried by the following vectors
                    Aedes vigilax VSMO:0000750
                    Culex annulirostris VSMO:0000773
                    Aedes theobaldi VSMO:0002455
                    Aedes eidsvoldensis VSMO:0002448
                    Aedes bancroftianus VSMO:0002445
                    Coquillettidia linealis VSMO:0002225
                    Aedes normanensis VSMO:0000749
```

```
Arthropoda
  Insecta
    Diptera
      Culicidae
        Aedes
          Aedes normanensis
          Aedes vigilax
          Aedes theobaldi
          Aedes bancroftianus
          Aedes eidsvoldensis
        Coquillettidia
          Coquillettidia linealis
        Culex
          Culex annulirostris
```

Fig. 7.

Examples of query results in the relationship explorer component of the VSMO-Explorer. A) Text view. B) Tree view. (Online figure in color.)