Analysis of Vaccine-related Networks using Semantic MEDLINE and the Vaccine Ontology

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ABSTRACT

A major challenge in the vaccine research has been to identify important vaccine-related networks and logically explain the results. In this paper, we showed that networkbased analysis of vaccine-related networks can discover the underlying structure information consistent with that captured by the Vaccine Ontology and propose new hypotheses for vaccine disease or gene associations. First, a vaccine-vaccine network was inferred using a bipartite network projection strategy on the vaccine-disease network extracted from the Semantic MEDLINE database. In total, 76 vaccines and 573 relationships were identified to construct the vaccine network. The shortest paths between all pairs of vaccines were calculated within the vaccine network. The correlation between the shortest paths of vaccine pairs and their semantic similarities in the Vaccine Ontology was then investigated. Second, a vaccinegene network was also constructed, in which several important vaccine-related genes were identified. This study demonstrated that a combinatorial analysis using literature knowledgebase, semantic technology, and ontology is able to reveal unidentified important knowledge critical to biomedical research and public health and generate testable hypotheses for future experimental verification.

1 INTRODUCTION

Vaccines have been one of the most successful public health interventions to date with most vaccine-preventable diseases having declined in the United States by at least 95-99% (1994). However, vaccine development is getting more difficult as more complex organisms become vaccine targets. In recent years, drug repositioning has been growing in last few years and achieved a number of successes for existing drugs such as Viagra (Goldstein, Lue et al. 1998) and thalidomide (Singhal, Mehta et al. 1999). By definition, drug repositioning is the "process of finding new users outside the scope of the original medical indications for existing drugs or compounds" (Chong and Sullivan 2007). In 2009, more than 30% of the 51 new medicines and vaccines were developed based on previous marketed products. This suggested that drug repositioning has drawn great attention from the both industry and academic institutes (Graul, Sorbera et al. 2010). However, many of these drug repositioning have been serendipitous discoveries (Ashburn and Thor 2004) or on observable clinical phenotypes, which are lack of systematic ways to identify new targets. Recent research has shown that bioinformatics-based approaches can aid to reposition drugs based on the complex relationships among drugs, diseases and genes (Liu, Fang et al. 2013). Such approaches can also be applied in the future vaccine development.

In recent years, high-throughput biological data and computational systems biology approaches has provided an unprecedented opportunity to understand the disease etiology and its underlying cellular subsystems. Biological knowledge such as drug-disease networks, and biomedical ontologies have accelerated the development of network-based approaches to understanding disease etiology (Ideker and Sharan 2008; Barabasi, Gulbahce et al. 2011) and drug action (network pharmacology) (Berger and Iyengar 2009; Mathur and Dinakarpandian 2011). Such approaches could also be applied in the vaccine research, aiming to investigate the vaccine-related associations derived from public knowledgebase such as PUBMED literature abstracts. For example, a Vaccine Ontology (VO)-based literature mining research was reported last year to study all gene interactions associated with fever alone or both fever and vaccine (Hur, Ozgur et al. 2012). This study focused on the retrieval of gene-gene associations based on their direct interactions in the context of fever and vaccine. The centrality-based network approach (Ozgur, Vu et al. 2008) evaluated the level of importance for each gene in extracted gene interaction network. Novel gene interactions were identified to be essential in fever- or vaccine-related networks that could not be found before. A similar VO and centrality-based literature mining approach was also used to analyse vaccine-associated IFN- γ gene interaction network (Ozgur, Xiang et al. 2011). Ball et al. compiled a network consisting of 6,428 nodes (74 vaccines and 6,354 adverse events) and more than 1.4 million interlinkages, derived from

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Vaccine Adverse Event Reporting System (VAERS) (Ball and Botsis 2011). This network demonstrated a scale-free property, in which certain vaccines and adverse events act as "hubs". Such network analysis approaches complement current statistical techniques by offering a novel way to visualize and evaluate vaccine adverse event data. However, the relationships among different vaccines in the context of vaccine-vaccine and vaccine-gene networks have not been well studied yet. A systematic level investigation of such relationships will help us understand better how vaccines are related to each other and whether such information can complement the existing knowledge such as VO.

To analyse the possible common protective immunity or adverse event mechanisms among different vaccines, it is critical to study all possible vaccine-vaccine and vaccine-gene associations using network analysis approaches. The hypotheses behind this are: (1) if two vaccines have coupling relationship with common disease(s)/gene(s), they are linked in the vaccine network; (2) the closer two vaccines are in the vaccine network, the more similar they are in the context of literature knowledgebase, such as Semantic MEDLINE (Rindflesch, Kilicoglu et al. 2011). In this paper, we proposed a network-based approach to investigate the underlying relationships among vaccines in the context of the vaccine-related network derived from Semantic MEDLINE. The distances of the vaccines were further compared with their semantic similarities in the VO. The results demonstrated that the structure information of vaccine network is consistent with that captured by VO. Such network-based analysis can serve as an independent data resource to construct and evaluate biomedical ontologies. In addition, the vaccine-gene network was also constructed based on Semantic MEDLINE information, in which important vaccine-related genes were identified and further investigated by VO and related independent resources.

The rest of the paper is organized as follows. Section 2 introduces the data resources and the proposed network-based framework. Section 3 illustrates the results generated from each step in the proposed computational framework. Section 4 provides a thorough discussion of the results and concludes the paper.

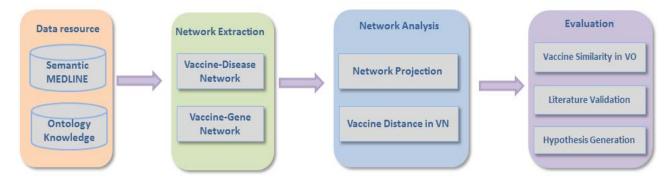


Fig. 1. Overview of the proposed framework. The proposed method consists of three steps: 1) Extraction of vaccine-related associations from Semantic MEDLINE using ontology based terms; 2) Network based analyses to identify vaccine-vaccine associations and vaccine-gene associations; 3) Evaluation of inferred vaccine-vaccine and vaccine-gene relationships using vaccine ontology hierarchical structure and literature validation.

2 MATERIALS AND METHODS

In this section, we describe the data resources and preprocessing method in this work. We then introduce our proposed network-based approach for investigating vaccinerelated associations derived from PubMed literature abstracts. The evaluation of the discovered vaccine-vaccine and vaccine-gene relationships is conducted based on the VO hierarchy and logical definitions. Fig. 1 illustrates the steps of the proposed approach.

2.1 Data Resources and preprocessing

2.1.1. Data Resources

In this study, we use Semantic MEDLINE as the data resource to build the networks. Semantic MEDLINE (Rindflesch, Kilicoglu et al. 2011) is a National Library of

Medicine (NLM) initiated project which provides a public available database that contains comprehensive resources with structured annotations for information extracted from more than 19 million MEDLINE abstracts. Since the Semantic MEDLINE is a comprehensive resource that contains heterogeneous data with different features extracted, our previous research has reorganized this data source and optimized it for informatics analysis (Tao, Zhang et al. 2012). Using the Unified Medical language System (UMLS) semantic types and groups (2012), we extracted unique associations among diseases, genes, and drugs, and represented them in six Resource Description Framework (RDF) graphs. In this paper, we used our optimized Semantic MEDLINE RDF data as the data source to perform network analysis for vaccine-related networks. Our RDF-based Semantic MEDLINE resource currently contains 843k disease-disease, 111k disease-gene, 1277k disease-drug, 248k drug-gene, 1900k drug-drug, and 49k gene-gene associations. Since this resource contains high-level terms (e.g., gene, protein, disease) that are not useful for network analysis, we further manually filtered out these terms using the following strategy. For disease terms, we only included those terms that are included in ICD9. For gene terms, we only include those terms that have an Entrez gene ID.

2.1.2. Data extraction

We identified those associations relevant to vaccines only. Specifically, vaccine terms were identified based on SNOMED CT (<u>http://www.ihtsdo.org/snomed-ct</u>). All the terms under the SNOMED CT term *Vaccine* (CUI: C0042210) were first extracted. A manual review by 3 experts further removed those common terms (e.g., bacteria vaccine) or animal vaccine terms.

2.2 Network analysis of Vaccine Network

2.2.1. Projection of bipartite vaccine-disease network

In graph theory, a bipartite network is composed of two non-overlapping sets of nodes and links that connect one node in the first node set with one node in the second node set. The properties of bipartite networks are often investigated by considering the one-mode projection of the bipartite network. The one-mode projection network can be created by connecting two nodes in the same node set if they have at least one common neighboring node in the other node set. For instance, the vaccine-disease association network is one bipartite network: vaccines and diseases constitute two node sets, and links are generated between vaccine and disease if they are associated in the Semantic MEDLINE. Therefore, the vaccine-vaccine network can be investigated by projecting vaccine-disease associations to vaccine-vaccine associations, in which two vaccines are connected if they are associated with at least one same disease. In this work, all links were generated based on the associations extracted from Semantic MEDLINE as described in Section 2.1. A vaccine-vaccine network was generated consisting of all the links identified in vaccine-disease associations.

2.2.2. Network distance between vaccines

The distance between any two vaccines in the vaccine network was calculated as the length of the shortest path between them (Fekete, Vattay et al. 2009). The hierarchical clustering analysis was performed on the distance matrix of all vaccines (Guess and Wilson 2002). A heat map was generated based on the clustering analysis results.

2.2.3. Analysis of vaccine-gene network

The vaccine-gene network was constructed by vaccinegene associations extracted from the drug-gene associations in our RDF-based data resource. The important vaccine-related genes were identified by their significant higher node degree compared to other vaccine/gene in the same network. The Cytoscape tool (Smoot, Ono et al. 2011) was selected to visualize the network. Cytoscape is an open-source platform for integration, visualization and analysis of biological networks. Its functionalities can be extended through Cytoscape plugins. Scientists from different research fields have contributed over 160 useful plugins so far. These comprehensive features allow us to perform thorough network level analyses and visualization of our association tables, and integration with other biological networks in the future.

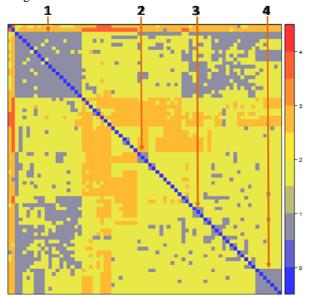


Fig. 2. The heat map of vaccine-vaccine associations. The shortest path matrix of all vaccine pairs was used to generate the heat map. Each row (column) represents a vaccine term. The color scale represents the shortest path between any vaccine pair.

2.3 Analysis of vaccine groups using VO

The community-based Vaccine Ontology (VO) has included over 4,000 vaccine-specific terms, including all licensed human and veterinary vaccines currently used in the USA. Logical axioms have been defined in VO to represent the relations among vaccine terms (Ozgur, Xiang et al. 2011). The Semantic MEDLINE analysis uses SNOMED terms to represent various vaccines. VO has established automatic mapping between SNOMED vaccine terms and VO terms. Based on the mapping, we first extracted all vaccine terms from the Semantic MEDLINE and mapped to VO. The ontology term retrieval tool OntoFox (Xiang, Courtot et al. 2010) was then applied to obtain the hierarchies of the total vaccines or subgroups of the vaccines identified in this study.

3 RESULTS

3.1 The overall network view

In total, 76 vaccines, annotated by the SNOMED CT term *Vaccine* (CUI: C0042210), were used to extract related vaccine-disease and vaccine-gene associations from the drug-disease and drug-gene association tables respective-ly. In the vaccine-disease network, there were 1127 nodes (178 vaccines and 949 diseases) and 1741 vaccine-disease associations. In the vaccine-gene network, there were 170 nodes (85 vaccines and 85 genes) and 94 vaccine-gene associations. One vaccine network was generated by the projection of the vaccine-disease bipartite network, consisting of 76 vaccines and 573 associations. This vaccine network was then used to analyze the vaccine relationships. The derived vaccine-gene network was also investigated by the VO knowledge.

3.2 Analysis of vaccine network

Fig. 2 showed a heat map of hierarchical analysis results, providing a direct visualization of potential vaccine-vaccine associations. Here we selected four relatively big vaccine-vaccine association groups on the diagonal from Fig. 2 and explain them in detail:

1) This group contains 18 very widely-studied vaccines. Many interesting results are obtained from the analysis of this group of vaccine-disease-vaccine associations. For example, the results from this group show that influenza vaccines and Rabies vaccines have been associated with the induction of a severe adverse event Guillain-Barré syndrome (GBS) (Hemachudha, Griffin et al. 1988; Hartung, Keller-Stanislawski et al. 2012). GBS is a rare disorder in which a person's own immune system damages their nerve cells, causing muscle weakness and sometimes paralysis. This group also includes five other vaccines associating with nervous system disorder, including Pertussis Vaccine (Wardlaw 1988), Diphtheria-Tetanus-Pertussis Vaccine (Corkins, Grose et al. 1991), Hepatitis B Vaccines (Comenge and Girard 2006), Chickenpox Vaccine (Bozzola, Tozzi et al. 2012), and Poliovirus Vaccine (Friedrich 1998; Korsun, Kojouharova et al. 2009). As shown by a VO hierarchical structure layout (Fig. 3), these seven vaccines belong to different bacterial or viral vaccines. The Diphtheria-Tetanus-Pertussis vaccine (DTP) is a combination vaccine that contains three individual vaccine components, including a Pertussis vaccine. DTP is asserted in VO as a subclass of "Diphtheria-Tetanus vaccine". Different from SNOMED, VO logically defines vaccines based on their relation to the pathogen organisms defined in the NCBI Taxon ontology. Since multiple inheritances are not used in VO, an inference

using an ontology reasoner was used to infer that the DTP is also *Bordetella pertussis* vaccine (*i.e.*, Pertussis vaccine) (Fig. 3). It is likely that the association of the combination vaccine DTP with neurological disorder is at least partially due to the Pertussis vaccine component.

Our study also identified many other diseases associating with different vaccines. For example, five vaccines (*e.g.*, pertussis vaccine) were found to be associated with various types of antimicrobial susceptibility, and eight vaccines (*e.g.*, influenza vaccine) have been co-studied with patients having the asthma condition. Due to the relative poor annotation of the vaccine data in the Semantic MEDLINE system, the vaccines identified in the semantic analysis were poorly classified. The incorporation of VO in the study clearly classifies these vaccines, leading to better understanding of the result of the Semantic MEDLINE analysis.

2) This group of vaccines, including Q fever vaccine, Parvovirus vaccine, and Tick-borne encephalitis vaccine, is associated with the common disease "Delayed Hypersensitivity". Delayed type reactions may occur at days after vaccination and often raise serious safety concerns. Delayed hypersensitivity is not antibody-mediated but rather is a type of cell-mediated response. The study of common vaccines and related gene and pathway features related to the delayed reaction will help to reveal the cause of DTR and eventually prevent it. While these vaccines are developed against different bacterial or viral diseases, there may be similarities among these vaccines, such as common vaccine ingredients (e.g., adjuvant) and a shared target to some common biological pathway in humans. An identification of these common features may indicate a common cause of the DTR.

3) This group of vaccines is associated with the common disease "Mumps". The vaccines in this group include Mumps Vaccine, "measles, mumps, rubella, varicella vaccine", and "diphtheria-tetanus-pertussis-haemophilus b conjugate vaccine" (DTP-Hib). The first two vaccines protect against Mumps. DTP-Hib was compared with a Mumps vaccine in a study (Henderson, Oates et al. 2004).

4) This vaccine group consists of seven vaccines (e.g., *Brucella abortus* vaccine and bovine rhinotracheitis vaccine) with direct associations between them. They are all associated with the common term "calve" in the literature abstracts. Since "calve disease" has a synonym "Scheuermann's Disease", these vaccines have all been linked to "Scheuermann's Disease". This is due to the ambiguity of the Nature Language Processing (NLP) process. This can be improved by future improvement of the disambiguity capacity of NLP tools.

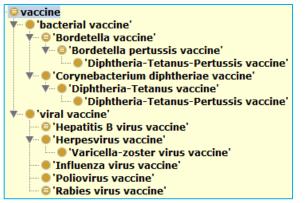


Fig. 3. The VO hierarchical structure of the seven vaccines associating with neurological disorder. A reasoning process assigned the Diphtheria-Tetanus-Pertussis vaccine under *Bordetella pertussis* vaccine. The Protégé-OWL editor 4.2 was used for the figure generation.

3.3 Vaccine-gene network

In the vaccine-gene network, many genes were found to interact with different vaccines. For example, our study identified that CD40LG (CD40 ligand) is closely associated with five vaccines: Diphtheria toxoid vaccine, Cholera vaccine, Tetanus vaccine, Chickenpox vaccine, and inactivated poliovirus vaccine (Fig. 4). CD40LG plays an important role in antigen presentation and stimulation of cytotoxic T lymphocytes (Kornbluth 2000). CD40LG can also be used in rational vaccine adjuvant design (Kornbluth and Stone 2006). Our finding confirms the important role of CD40LG and provides specific details on how this immune factor interacts with various bacterial and viral vaccines.

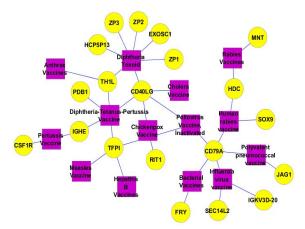


Fig. 4. A vaccine-gene subnetwork. The associations between vaccines and related genes were visualized by the Cytoscape tool (Smoot, Ono et al. 2011). Purple rectangular node represents vaccine, and yellow circle node represents gene.

4 DISCUSSIONS AND FUTURE WORK

In this paper, we proposed a novel network-based approach to investigate the vaccine relationships in the con-

text of vaccine network extracted from PubMed literature abstracts. The investigations of vaccine-vaccine, vaccinedisease, and vaccine-gene networks demonstrate that such literature-based associations can be better analyzed using VO and such a combinatorial analysis is able to reveal the association patterns and identify new knowledge. The identified vaccine-vaccine associations based on vaccinedisease distance analysis are consistent with their VO categories and often lead to the generation of new hypotheses. Our studies discovered some novel vaccinevaccine relationships by discovering a group of vaccines associated with some common diseases as demonstrated in the heat map analysis in the Results section. Due to the incompleteness of such information existing in the literature abstracts, such vaccine-vaccine associations need further validation in independent databases or through future experimental studies. For example, while our analysis reveals associations between a group of vaccines and neurological adverse events, it is noted that the evidences of these associations, although reported by some PubMed abstracts, are not necessarily commonly acknowledged (Sarntivijai, Xiang et al. 2012). More analysis may be required for clarification.

Future extensions of this work include: (1) integration of more comprehensive vaccine-disease association databases (e.g., VAERS system) to construct more complete vaccine-related networks; (2) generation of vaccinerelated gene network by extending the neighbour genes of vaccine-associated genes; (3) network-based investigation of the relationships among vaccines and other drugs using vaccine-drug associations; (4) investigation on possible ways to improve the network by assigning weights or confident rates to different types of associations or associations from different sources.

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