University of New Hampshire School of Law

International Technology Transfer Institute

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Patent Landscape of Helminth Vaccines and Related Technologies

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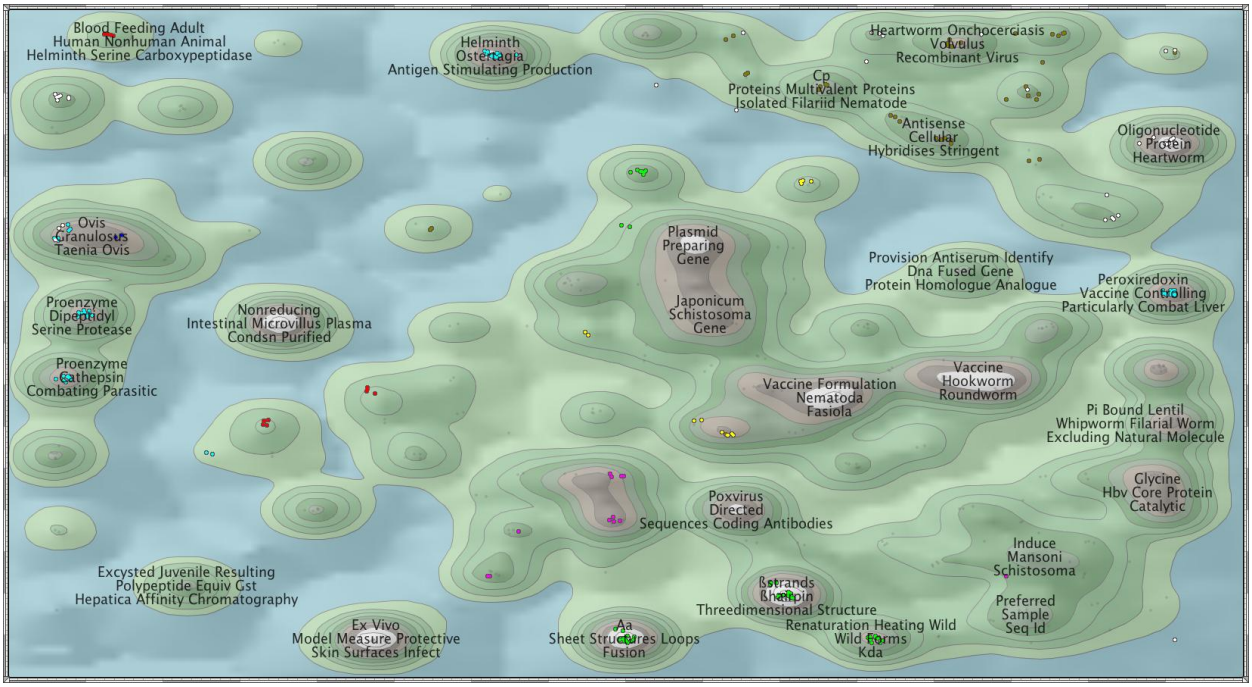
Introduction

Executive Summary

This report focuses on patent landscape analysis of technologies related to vaccines targeting parasitic worms, also known as helminths. These technologies include methods of formulating vaccines, methods of producing of subunits, the composition of complete vaccines, and other technologies that have the potential to aid in a global response to this pathogen. The purpose of this patent landscape study was to search, identify, and categorize patent documents that are relevant to the development of vaccines that can efficiently promote the development of protective immunity against helminths.

The search strategy used keywords which the team felt would be general enough to capture (or "recall") the majority of patent documents which were directed toward vaccines against helminths. After extensive searching of patent literature databases, approximately 2847 publications were identified and collapsed to about 446 INPADOC families. Relevant patent families, almost half of the total relevant families (210 being total number of relevant families), were then identified and sorted into the categories of tremetodes, cestodes, nematodes or non-specific helminth. The 210 patent families that were divided into these four major categories were then further divided into sub categories relating to common fields of technology (e.g. DNA vaccine, vaccine formulations, methods to produce subunits) This sorting process increased the precision of the result set.

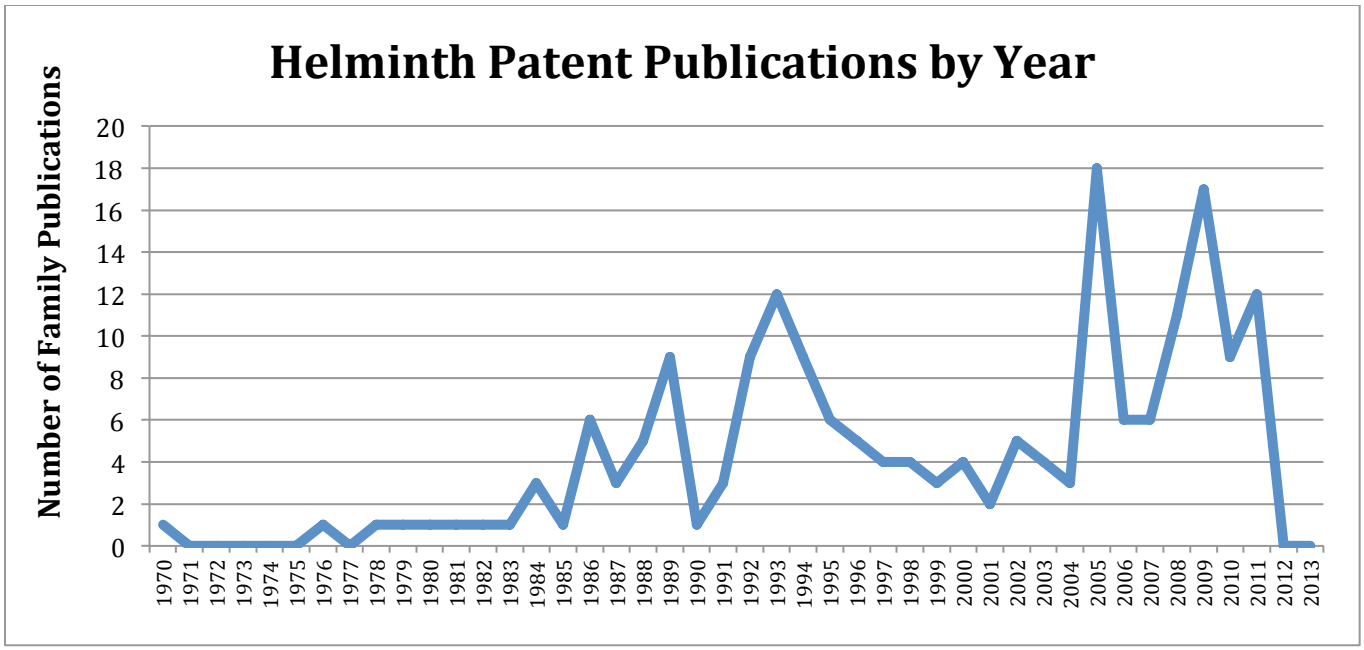
The four major categories (cestodes, nematodes, trematodes, and non specific applications) as well as the overall data set of the 210 relevant family members were subjected to a range of analytics in order to extract as much information as possible from the dataset. First, patent landscape maps were generated to assess the accuracy of the sorting procedure and to reveal the relationships between the various technologies that are involved in creating an effective vaccine. Then, filings trends are analyzed for the overall dataset of the 210 relevant families as well as by the categories of trematodes, cestodes, and nematodes. The country of origin each member of the 210 relevant families was determined, and the range of distribution to other jurisdictions was assessed. Filings were also analyzed by year, by assignee. Finally, the various patent classification systems were mapped to find which particular classes tend to hold helminth vaccine-related technologies. Besides the keywords developed during the searches and the landscape map generation, the classifications represent an alternate way for further researchers to identify emerging helminth vaccine technologies.



ThemeScape map of terms from helminth vaccine patent documents. This category contained approximately 210 INPADOC patent families (analysis presented here is based on documents expanded from the 210 family members, only 751 documents were accepted by the Themespace program). See Figure 21.

The analysis included creation of a map of keywords describing the relationship of the various technologies involved in the development of helminth vaccines. The map has regions corresponding to plasmids and other gene based technologies used in DNA vaccines for Japonicum Schistosoma. Important technologies listed on the map include the use of reverse genetics to create reassorted viruses targeted for the use in veterinary applications. Additionally, the map suggests that numerous subunits exist for use in vaccines targeting cestodes, trematodes, and nematodes.

Another major finding was that the number of patent documents related to helminths being published has been steadily increasing in the last decade, as shown in the figure below. Until the early-1990s, there were only a few helminth vaccine related patent documents being published each year. The number of publications increased noticeably when TRIPS took effect, resulting in publication of patent applications. However, since 2006 the number of vaccine publications has exploded. In the years 2011 and 2012, about 23 references disclosing parasitic worm vaccine technologies were published each year. Thus, interest in developing new and more efficacious helminth vaccines has been growing in recent years.

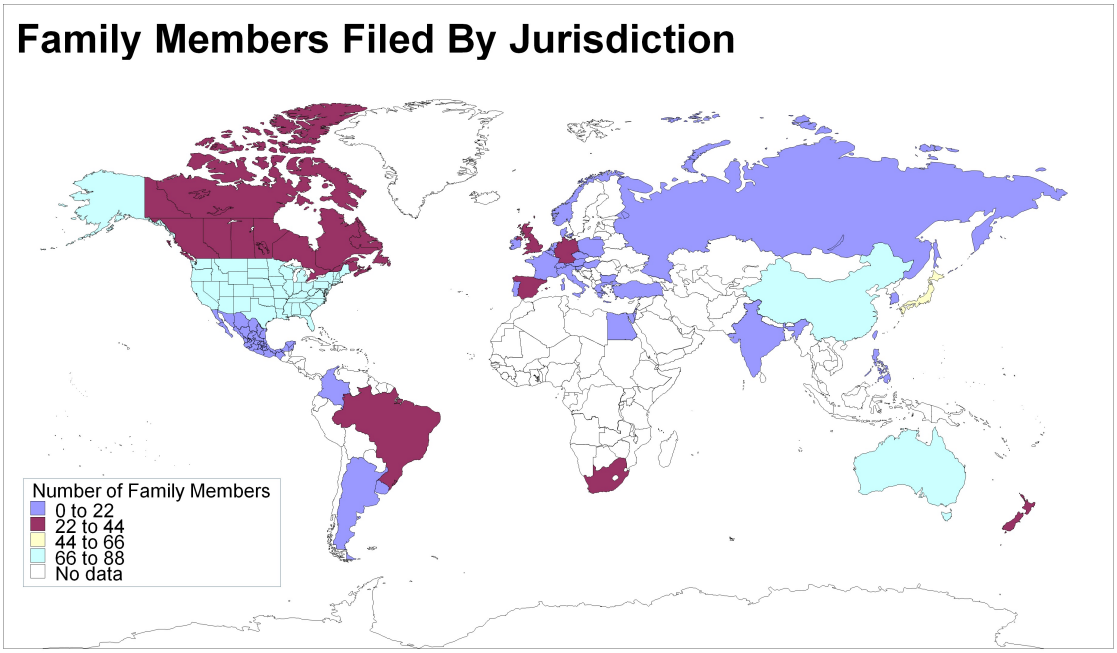


Publication trends for helminth vaccine documents. Publications increased in the 1990s when patent applications began to be published. See Figure 26

The origin of the vaccine-related inventions was also analyzed. The team determined the country in which the priority application was filed, which was taken as an indication of the country where the invention was made or where the inventors intended to practice the invention. By far, most of the relevant families originated with patent applications filed in the United States and China. Other prominent priority countries were the United Kingdom, Japan, Brazil, Australia and France. Countries with the most filings were also analyzed. Countries that were heavily targeted for patent filings included the United States, Australia, Canada, and New Zealand.

Top assignees for these families were mostly large pharmaceutical companies, with the majority of patent families coming from Heska, followed by Merck & Co., Institut Pasteur, AusBiotech Biotechnology, and Biological Sciences Research Council.

Lastly, the jurisdictions were inventors have sought protection for their vaccine technologies were determined, and the number of patent families filing in a given country is plotted on the



Jurisdictions for filing applications and issuing patents related to helminth vaccines. Filings in multi-jurisdictional agencies, such as ARIPO, the Gulf Cooperation Council, WIPO and the European Patent Office, are not shown. The number of patent families is out of 210 total families. See Figure 25 for a more detailed description.

world map shown (Fig. 25). The United States, Canada, Australia, Japan, New Zealand and France have the highest level of filings, followed by Germany, Brazil, India, United Kingdom and Spain. However, although there are a significant number of filings in Brazil, the remainder of Central and South America has only sparse filings. Of concern, with the exception of South Africa, few other African nations have a significant number of filings.

In summary, the goal of this report is to provide a knowledge resource for making informed policy decisions and for creating strategic plans concerning the assembly of vaccines targeting highly prevalent helminth infections. The ITTI team has defined the current state of the art of technologies involved in the manufacture of helminth vaccines, and the important assignees, inventors, and countries have been identified. This document should aid in evaluating the current state of vaccines technologies targeting helminths and the potential outgrows of these technological fields. Furthermore, as this report illustrates, the steady increase in helminth patenting, expanded diversity of assignees and greater global filings, indicates that intellectual property protection does not inhibit the development of crucial innovations for this class of neglected diseases, but, on the contrary, appears to be a driver of accelerated research and development.

Acknowledgements

We would like to thank those who provided invaluable assistance in the completion of this project.

We are thankful to the University of New Hampshire School of Law Dean John Broderick, and Associate Dean Jordan Budd, as well as to the faculty of the Franklin Pierce Center for Intellectual Property, for supporting this project.

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We are thankful to Mr. Mark Bauer and Thomson-Reuters for graciously facilitating access to Thomson-Innovation, for providing invaluable guidance, and training on other aspects of patent database mining and research. We also thank LexisNexis and GenomeQuest for providing access to their platforms.

Disclaimer

This educational report is neither inclusive nor comprehensive. Rather, it is an informational resource intended to facilitate a better understanding of the international patent literature landscape regarding vaccines against helminths.

This report is not a list of all potentially relevant patents. Importantly, it is not a Freedom to Operate (FTO) opinion, but instead constitutes an educational analysis of potentially relevant material. While the search platforms utilized in this project were extensive, none were comprehensive, and some countries and jurisdictions were underrepresented in the databases, either in the time frame covered, the availability of translated documents, and the completeness of the records. Further, it is likely that the International Technology Transfer Institute (ITTI) team did not obtain the entire spectrum of relevant patents utilizing the various search strategies and methods articulated herein. Therefore, the ITTI team does not guarantee that all relevant patents were discovered during the creation of this report.

As the ITTI team members are not experts in the field of helminth related vaccines and related technologies, it is likely that the categorization of the patents found and coded are incomplete. Further, many patent documents contain material relevant to multiple categories; the documents were placed in the category that the team, in its judgment, felt best represented the overall focus of the document. The ITTI team cannot guarantee that the patents discovered were evaluated at the level of expert scientific sophistication.

The limited time frame, competing academic demands, and the general press of business dictated the number of patents evaluated. As such, additional patents may have been available that were not considered due to time constraints.

Many names are capitalized and may or may not be trademarked and/or otherwise protected intellectual property. The team apologizes for any errors or mistaken omissions.

Abbreviations and Definitions

Below is a list of abbreviations and definitions for terms and keywords used throughout the ITTI Fall 2012 report and the reported results.

Adjuvants – defined herein as a substance sometimes included in a vaccine formulation to enhance or modify the immune-stimulating properties of a vaccine.[1]

Antibody – defined herein as an infection-fighting protein molecule in blood or secretory fluids that tags, neutralizes, and helps destroy pathogenic microorganisms (e.g., bacteria, viruses) or toxins. Antibodies, known generally as immunoglobulins, are made and secreted by B-lymphocytes in response to stimulation by antigens. Each specific antibody binds only to the specific antigen that stimulated its production.[2]

Antibody-mediated immunity – defined herein as the immunity that results from the activity of antibodies in blood and lymphoid tissue (also called humoral immunity).[3]

Antigens - (immunogens; substances capable of provoking an immune response) – defined herein as foreign substances in the body that are capable of causing disease. The presence of antigens in the body triggers an immune response, usually the production of antibodies. Antigens may be soluble substances, such as toxins and foreign proteins, or particulate, such as bacteria and tissue cells; however only the portion of the protein of polysaccharide molecule known as the antigenic determinant combines with antibody or a specific receptor on a lymphocyte.[4]

Anti-idiotype - herein defined as a manufactured antibody (Ab2) that can recognize the idiotype of another antibody (Ab1). Theoretically, the anti-idiotype antibody mimics the structure of the antigen recognized by Ab1. When Ab2 is injected into the host, the host develops immunological memory comprising antibodies (Ab3) which have similar specificities as Ab1.[5]

B cells – defined herein as small white blood cells that help the body defend itself against infection. These cells are produced in bone marrow and develop into plasma cells that produce antibodies. These cells are also known as B-lymphocytes.[6]

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[1] American Heritage Dictionary definition: http://education.yahoo.com/reference/dictionary/entry/adjuvant.
[2] http://medical-dictionary.thefreedictionary.com/antibody.
[3] http://medical-dictionary.thefreedictionary.com/humoral+immunity.
[4] http://medical-dictionary.thefreedictionary.com/antigen.
[5] http://en.wikipedia.org/wiki/Anti-idiotypic_vaccine.
[6] http://en.wikipedia.org/wiki/B_cell.

BLAST – defined herein as the acronym for Basic Local Alignment Search Tool. This program compares nucleotide or protein sequences to sequence databases and calculates the statistical significance of matches.

Booster – defined herein as a second or later vaccine dose given after the primary dose(s) to increase the immune response to the original vaccine antigen(s). The vaccine given as the booster dose may or may not be the same as the primary vaccine.[7]

Cestode- defined herein as a member of the phyla Platyhelminths. Commonly known as a tapeworm. Also a member of the group called helminths.[8]

Delivery Systems – defined herein as a method or system by which a vaccine is delivered to the host body.[9]

DNA (deoxyribonucleic acid) - defined herein as the double-stranded, helical molecular chain found within the nucleus of each cell. DNA carries the genetic information that encodes proteins and enables cells to reproduce and perform their functions.[10]

DNA vaccine (nucleic acid vaccine) - defined herein as direct injection of a gene(s) coding for a specific antigenic protein(s), resulting in direct production of such antigen(s) within the vaccine recipient in order to trigger an appropriate immune response.[11]

DWPI – defined herein as Derwent World Patent Index, which is the world's most comprehensive database of patent documents. DWPI includes over 20 million patent document families, which covers over 42.5 million patent documents. The DWPI database includes coverage from over 44 worldwide patent authorities.[12]

Efficacy - defined herein in vaccine research, the ability of a vaccine to produce a desired clinical effect, such as protection against a specific infection or disease, at the optimal dosage and schedule in a given population. A vaccine may be tested for efficacy in Phase 3 clinical trials if it appears to be safe in Phase 1 trials and has shown efficacy at certain dosages in Phase 2 trials.[13]

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[7] http://en.wikipedia.org/wiki/Booster_dose.
[8] http://en.wikipedia.org/wiki/Cestoda
[9] Crystal Chan, et. al., *Advancing Adjuvants and Vaccine Delivery Systems for Better Vaccination Strategies*, BioPharm Int'l Supplements, Jan. 2, 2010.
[10] http://education.yahoo.com/reference/dictionary/entry/DNA.
[11] http://www.who.int/biologicals/areas/vaccines/dna/en/index.html. *See also* http://www.dnavaccine.com/.
[12] http://thomsonreuters.com/products_services/legal/legal_products/a-z/derwent_world_patents_index/.
[13] http://en.wikipedia.org/wiki/Vaccine_efficacy.

Epitope - defined herein as a specific site on an antigen that stimulates specific immune responses, such as the production of antibodies or activation of immune cells.[14]

Expression system - defined herein as in genetic engineering, the cells into which a gene has been inserted into a host cell in order to manufacture desired proteins.[15]

Functional antibody - defined herein as an antibody that binds to an antigen and has an effect that can be demonstrated in laboratory tests.[16]

Gene – defined herein as a unit of genetic material (DNA); a segment of DNA encoding a protein molecule; a segment of DNA that contains the information for a specific function.[17]

Helminth- defined herein as a parasitic worm belonging to phylum nematoda or phylum platyhelminthies.[18]

Host - defined herein as a plant or animal harboring another organism or a pharmaceutical composition.[19]

Immune system - defined herein as the complex system (network of specialized cells and organs) in the host body responsible for fighting and responding to disease (immune response). Its primary function is to identify foreign substances (antigens of bacteria, viruses, fungi, or parasites) in the body and develop a defense against them. It involves production of proteins called antibodies to eliminate these foreign organisms that have invaded the host, and the generation of cytotoxic activity to eliminate infected cells.[20]

Immunity - defined herein as a natural or acquired resistance provided by the immune system to a specific disease. Immunity may be partial or complete, specific or nonspecific, long lasting or temporary. Immunity is indicated by the presence of antibodies and antigen-reactive cells in the blood and can usually be determined with a laboratory test.[21]

Immunization - defined herein as the process by which a person or animal becomes protected against a disease; the process of inducing immunity by administering an antigen (vaccine) to

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[14] http://medical-dictionary.thefreedictionary.com/epitope.
[15] http://www.news-medical.net/health/Gene-Expression-System.aspx.
[16] http://en.wikipedia.org/wiki/Antibody.
[17] http://en.wikipedia.org/wiki/Gene.
[18] http://www.who.int/topics/helminthiasis/en/; see also, http://www.phsource.us/PH/PARA/Chapter_4.htm
[19] http://en.wikipedia.org/wiki/Host_%28biology%29.
[20] http://en.wikipedia.org/wiki/Immune_system.
[21] http://medical-dictionary.thefreedictionary.com/immunity.

allow the immune system to prevent infection or illness when it subsequently encounters the infectious agent. This term is often used interchangeably with vaccination or inoculation.[22]

INPADOC (International Patent Document Center) – defined herein as a patent database maintained by the European Patent Office (EPO).[23]

ITTI – defined herein as International Technology Transfer Institute, an intellectual property clinic at the University of New Hampshire School of Law.[24]

NCBI – defined herein as the acronym for National Center for Biotechnology Information. NCBI provides access to biomedical and genomic resources, such as BLAST.[25]

Nematode- defined herein as a member of the phylum nematoda, common specimens of nematodes include roundworms, whipworms, and threadworms.[26]

Parasitic Worm- defined herein as a member of the phyla Nematoda or plathyhelminthies. Also known as a helminth.

Passive immunization – defined herein as the introduction of antibodies or antiserum into a host to treat an infection, wherein such treatment does not result in immunological memory and long-lasting immunity in the host.[27]

Patent document count – defined herein as an expanded patent family which includes all issued patents and patent applications that fall within that family.

Patent family – defined herein as a group of patent documents having a commonality such as priority document (INPADOC) or claimed invention (DWPI). The patent documents can be from any jurisdiction.

PCT – defined herein as the Patent Cooperation Treaty, which is an international treaty whose goal is to provide a unified procedure for filing patent applications in the contracting states. A contracting state is a country which has signed onto the treaty. A patent application filed under the PCT is commonly referred to as an international application, or PCT application.[28]

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[22] http://www.who.int/topics/immunization/en/.
[23] http://www.epo.org/searching/essentials/patent-families/inpadoc.html.
[24] http://law.unh.edu/franklin-pierce-ip-center/international-technology-transfer-institute.
[25] http://www.ncbi.nlm.nih.gov/.
[26] http://en.wikipedia.org/wiki/Nematode
[27] http://en.wikipedia.org/wiki/Passive_immunity.
[28] http://www.wipo.int/pct/en/texts/articles/atoc.htm.

Pharmaceutical Compositions – defined herein as the combination of distinct parts or elements to form a whole relating to pharmacy, drugs, or medicine. This can include anything from vitamins, antibodies, antigens, medicaments, and adjuvants.

Trematoda- defined herein as a subphyla of phylum platyhelminthies. This phylum contains one of the most commonly known helminth, liver flukes.[29]

Vaccine - defined herein as a preparation that stimulates an immune response that can prevent an infection or create resistance to an infection based upon an antibody response to an antigen.[30]

Veterinary Vaccines- herein defined as vaccines targeting helminths for the specific use in non-human animals. Target animals include fowl (chicken, ducks, geese, etc.), pigs, horses, and dogs.[31]

[29] http://en.wikipedia.org/wiki/Trematode
[30] http://en.wikipedia.org/wiki/Vaccine.
[31] http://www.ott.nih.gov/Technologies/abstractDetails.aspx?RefNo=1731.

Background of the Technology

Parasitic worms, also known as helminths are worm-like organisms that live in and feed on living hosts. These parasitic worms are multicellular organisms that are generally visible to the naked eye in their adult stages.[32] Parasitic worms general fall into three different phyla: plathyhelminthies or flatworms, acanthocephia or thorny headed worms, and nematoda or roundworms.[33] This report focuses on parasitic worms that are from the phyla nematoda and platyhelminths and not those from the phyla acanthocephia.

The phylum plathyhelminths, also known as flatworms, is a diverse phylum that contains cestodes (tapeworms), trematodes (flukes) and tubellaria. The class tubellaria will not be included in this report as they do not infect humans. The term cestode is derived from the Latin word *cestus*, which means "tape". The adult forms of all 3,400 species of cestodes are internal parasites in the organs of vertebrates, including fish, cats, dogs and humans.[34] Cestodes have no mouths as their syncitial skin absorbs nutrients from their host. This syncitium also disguises these nutrients chemically chemically to avoid attacks by the host's immune system.[35]

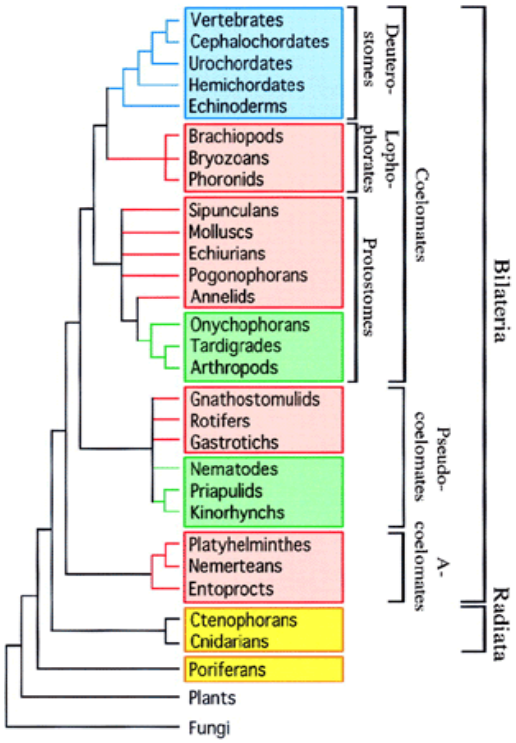

Figure 1. An image depicting phyla nematoda and platyhelminthies relationship to other phyla.

Class trematoda, individuals of this class known as trematodes, contains the organism known as flukes, one of the most well known and most prevalent helminths to infect humans.[36] The term trematoda refers to the cavities in their holdfasts, which resemble a sucker of leech, and anchors them within their host.[37] The skin of all trematodes is composed of a syncitium, a layer of cells that shares a single external membrane. The class trematoda contains more than 11,000 unique species, making it one of the most prevalent types of parasitic worms on earth.

The last phyla of interest is nematoda, members of this phylum are also known as roundworms. Phylum nematoda is one of the largest groups of animals as over two thousand eight hundred species are contained in this phylum[38] Species from phylum nematoda inhabit

[32] Maizels RM, Yazdanbakhsh M, "Immune regulation by helminth parasites: cellular and molecular mechanisms". *Nat. Rev. Immunol.* 3 (9): 733–44. (2003)
[33] Ibid
[34] Ruppert, E.E., Fox, R.S., and Barnes, R.D. (2004).*Invertebrate Zoology* (7 ed.). Brooks / Cole. pp. 226–269.
[35]Ibid
[36] Ibid.
[37] Ibid.
[38] Hugot J-P, Baujard P, Morand S (2001). "Biodiversity in helminths and nematodes as a field of study: an overview". *Nematology* 3 (3): 199–208

almost every ecosystem known to man.[39] Nematodes vary greatly in size as some may be as long as 5cm while others may be microscopic in size.[40] Unlike the group platyhelminthies, nematodes outer covering may be either a syncitum or a thick nonliving cuticle layer.[41]

Helminth Life Cycles, Diseases, and Epidemiology

Approximately one billion people in the poor, developing regions of sub-Saharan Africa, Asia, and the Americas are infected with one or more parasitic helminth. [42] The most common helminth diseases are caused by an infection from soil-transmitted nematodes (e.g. the roundworm), filarial worms, flukes, or tapeworms (See Table 1). Many of the people living in poor rural villages in the tropics and subtropics are often chronically infected with several different species of parasitic worm, commonly referred to as "polyparasitized".[43] Note that the above table is from 2008 and that the prevalence for some helminths have decreased and increased remarkably. More accurate statistics will be further reflected in the report.

The major human helminthiases and their global prevalence and distribution

Disease	Major etiologic agent	Global prevalence	Regions of highest prevalence
Soil-transmitted nematodes			
Ascariasis	*Ascariasis lumbricoides* (roundworm)	807 million	Developing regions of Asia, Africa, and Latin America
Trichuriasis	*Trichuris trichiura* (whipworm)	604 million	Developing regions of Asia, Africa, and Latin America
Hookworm	*Necator americanus*; *Ancylostoma duodenale*	576 million	Developing regions of Asia, Africa, and Latin America (especially areas of rural poverty)
Strongyloidiasis	*Strongyloides stercoralis* (thread worm)	30–100 million	Developing regions of Asia, Africa, and Latin America (especially areas of rural poverty)
Filarial nematodes			
LF	*Wuchereria bancrofti*; *Brugia malayi*	120 million	Developing regions of India, Southeast Asia, and sub-Saharan Africa
Onchocerciasis (river blindness)	*Onchocerca volvulus*	37 million	Sub-Saharan Africa
Loiasis	*Loa loa*	13 million	Sub-Saharan Africa
Dracunculiasis (guinea worm)	*Dracunculus medinensis*	0.01 million	Sub-Saharan Africa
Platyhelminth flukes			
Schistosomiasis	*Schistosoma haematobium*;	207 million	Sub-Saharan Africa
	Schistosoma mansoni;		Sub-Saharan Africa and Eastern Brazil
	Schistosoma japonicum (blood flukes)		China and Southeast Asia
Food-borne trematodiases	*Clonorchis sinensis* (liver fluke);	>40 million	Developing regions of East Asia
	Opisthorchis viverinni (liver fluke);		
	Paragonimus spp. (lung flukes);		
	Fasciolopsis buski (intestinal fluke);		
	Fasciola hepatica (intestinal fluke)		
Platyhelminth tapeworms			
Cysticercosis	*Taenia solium* (pork tapeworm)	0.4 million (Latin America only)	Developing regions of Asia, Latin America, and sub-Saharan Africa

Figure 2. Major human helminthiases and their global prevalence and distribution[44]

[39] Borgonie G, García-Moyano A, Litthauer D, Bert W, Bester A, van Heerden E, Möller C, Erasmus M, Onstott TC (June 2011). "Nematoda from the terrestrial deep subsurface of South Africa". *Nature* 474 (7349): 79–82.
[40] Ruppert EE, Fox RS, Barnes RD (2004). *Invertebrate Zoology* (7th ed.). Brooks/Cole.
[41] Ibid.
[42] Hotez, Peter, Paul Brindley, Jeffrey Bethony, Charles King, Edward Pearce, and Julie Jacobson. "Helminth infections: the great neglected tropical diseases." *The Journal of Clinical Investigation* 118, no. 4 (2008): 1311.
[43] Ibid.
[44] Ibid. at 1312.

There are four primary modes of helminth transmission: soil-borne, foodborne, water-borne, and insect-borne. Most of the diseases WHO determined neglected tropical diseases are soil-borne.[45] Environmental factors, such as warm, moist climates and poor sanitation and hygiene, make tropical areas the perfect habitat for soil-borne helminths, however, many species may survive in temperate climes, as well, especially during the summer. In Latin America and the Caribbean, soil-transmitted helminths are present in all countries with an estimated 26.3 million school-age children at risk of infection. In 13 of the 14 countries in this region, many areas have infection prevalence higher than 20%. Globally, approximately 300 million people suffer from severe morbidity that results in 10,000–135,000 deaths annually. However, their greatest impact is through the impairment of physical and mental development in children, which ultimately retards educational advancement and economic productivity. [46]

A study of detailed description of the global limits for *Ascaris lumbricoides*, *Trichuris trichiura*, and the hookworms *Ancylostoma duodenale* and *Necator americanus* using surveys of infection prevalence derived from the Global Atlas of Helminth Infection.[47] Figure 1 shows the transition stability of soil-transmitted helminths (excluding some countries on the basis of socioeconomic status).

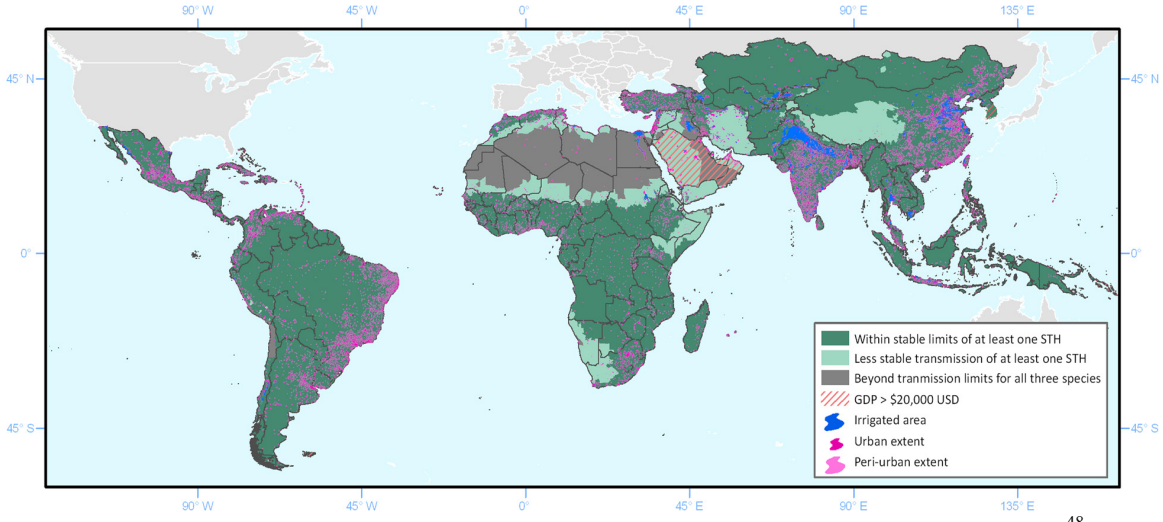

Figure 3. Distribution of soil-transmitted helminth indicating areas at stable risk of transmission in 2010[48]

Based on factors such as climatic and socio-demographic indicators, human population density and settlement patterns, it was estimated that "5.08 billion people (1.0 billion of school-going age) live in areas of stable hookworm transmission worldwide, 22% located in Africa and

[45] World Health Organization. "Neglected Tropical Diseases." WHO Programmes and Projects. www.who.int/neglected_diseases/diseases/en/ (accessed February 25, 2013).
[46] Ibid.
[47] Pullan, Rachel, and Simon Brooker. "The global limits and population at risk of soil-transmitted helminth infections in 2010." *Parasites and Vectors* 5, no. 81 (2012): 2.
[48] *Ibid.* at 11.

the Middle East, 69% in Asia and 9% in Latin America and the Caribbean".[49]

Generally, soil-borne worm eggs or juveniles contaminate soil via animal and human defecation or the use of feces containing such eggs or juveniles as fertilizer for produce. The eggs are ingested via contaminated produce or by placing fingers or other objects that have come into contact with contaminated soil into one's mouth. Usually there is no vector which the egg or juvenile must pass through and mature in before infecting the terminal host.

Because most soil-borne worms primarily infect the small and large intestine, individuals parasitized by different species of these worms often present with a similar set of gastrointestinal symptoms.

Ascaris lumbricoides is one of the most prevalent of the prevalent, accounting for a large percentage of the global parasitic worm burden.[50] The CDC estimates that 807-1,221 million people worldwide are infected by this species. The ascarid lifecycle is unique from other soil-borne worms in that the larvae must mature in the lungs. Eggs are ingested and hatch in the gastrointestinal tract from which they burrow through the mucosa to the portal veins leading to alveoli and pulmonary vascular capillary beds.[51] The larvae cause lung irritation which results in the host coughing the larvae up into the oral cavity where they are swallowed back down into the GI tract.[52]The female can release 200,000 eggs each day. Adults live for a year or two.

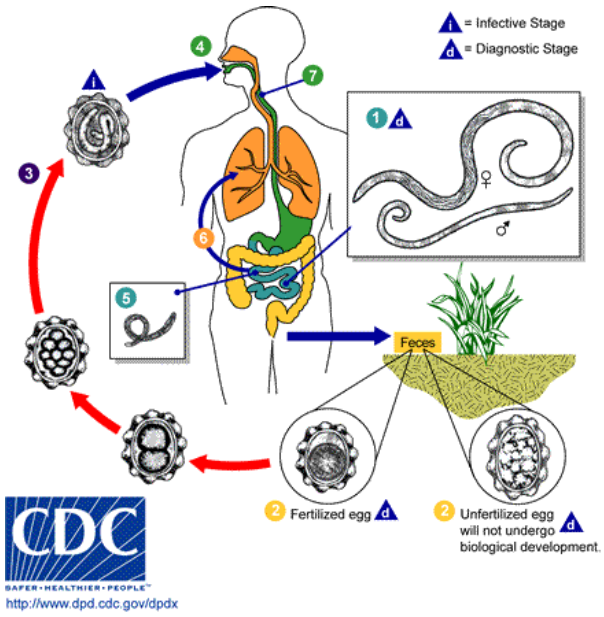

Figure 4. Lifecycle of *A. Lumbricoides*

Ascariasis is more burdensome for children, and can be transmitted to a fetus transplacentally. Annually, there are 8-100,000, most of which are children with obstructed or perforated bowels. Along with the GI symptoms common to all intestinal worms, ascariasis can also present with wheezing, intestinal blockage, tingling throat, appendicitis, pancreatitis, and impaired growth in children.[53]

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[49] Pullan, Rachel, and Simon Brooker. "The global limits and population at risk of soil-transmitted helminth infections in 2010." *Parasites and Vectors* 5, no. 81 (2012): 10.
[50] Centers for Disease Control and Prevention. "CDC - Ascariasis." Centers for Disease Control and Prevention. http://www.cdc.gov/parasites/ascariasis/index.html (accessed May 9, 2013).
[51] Medscape Reference. "Ascaris Lumbricoides." Drugs, Diseases, & Procedures. emedicine.medscape.com/article/788398-overview (accessed May 9, 2013).
[52] Centers for Disease Control and Prevention. "CDC - Ascariasis." Centers for Disease Control and Prevention. http://www.cdc.gov/parasites/ascariasis/index.html (accessed May 9, 2013).
[53] Medscape Reference. "Ascaris Lumbricoides." Drugs, Diseases, & Procedures. emedicine.medscape.com/article/788398-overview (accessed May 9, 2013).

Hookworms are estimated to infect between 760 million-1.3 billion people worldwide.[54] Two main species, *Anclostoma duodenale* and Necator americanus, are responsible for the global worm burden. Hookworm infection is widespread throughout the tropics and subtropics. *N. americanus* is the most prevalent hookworm, being found throughout sub-Saharan Africa, tropical regions of the Americas, south China, and Southeast Asia while *A. duodenale* is spreading in parts of India, China, Africa, and parts of the Americas.[55]

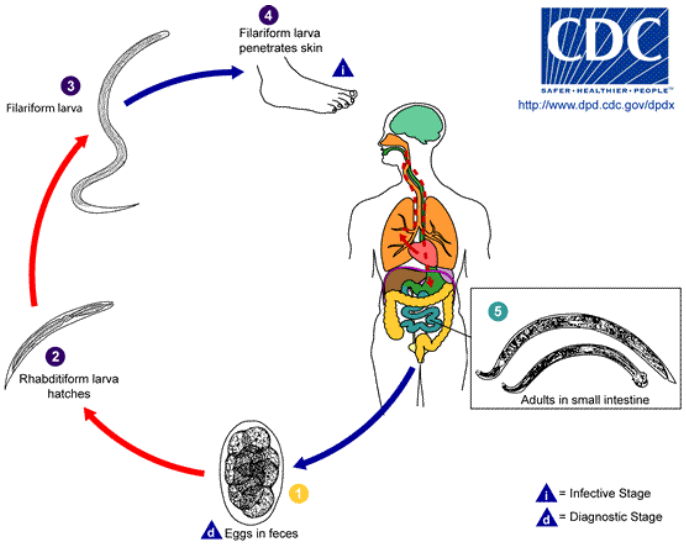

Figure 5. Lifecycle of the hookworm

The eggs of these species are not infectious. The eggs are released into the soil in feces, where they mature into larvae. Unlike other soil-borne helminths, an individual becomes infected when a larva penetrates one's bare feet. *A. duodenale* larvae are infectious if ingested, while this is not the case for *N. americanus*.

Ancylostomiasis is often symptomless if the parasite burden is low. A higher burden presents with anemia and fatigue, along with GI symptoms. Because children and women of reproductive age have reduced iron reserves, both are at particular risk. In children, anemia and protein malnutrition resulting from chronic intestinal parasitism can cause impairment in physical, intellectual, and cognitive development. In pregnant women, severe iron deficiency anemia arising from hookworm disease can result in additional health risks for the mother and fetus or newborn. [56]

[54] Lustigman, Sara, Roger Prichard, Andrea Gazzinelli, Warwick Grant, Boakye Boatin, James McCarthy, and Maria Basanez. "A Research Agenda for Helminth Diseases of Humans: The Problem of Helminthiases." *PLoS neglected tropical diseases* 6, no. 4 (2012): 4.
[55] Ibid.
[56] Ibid at 283.

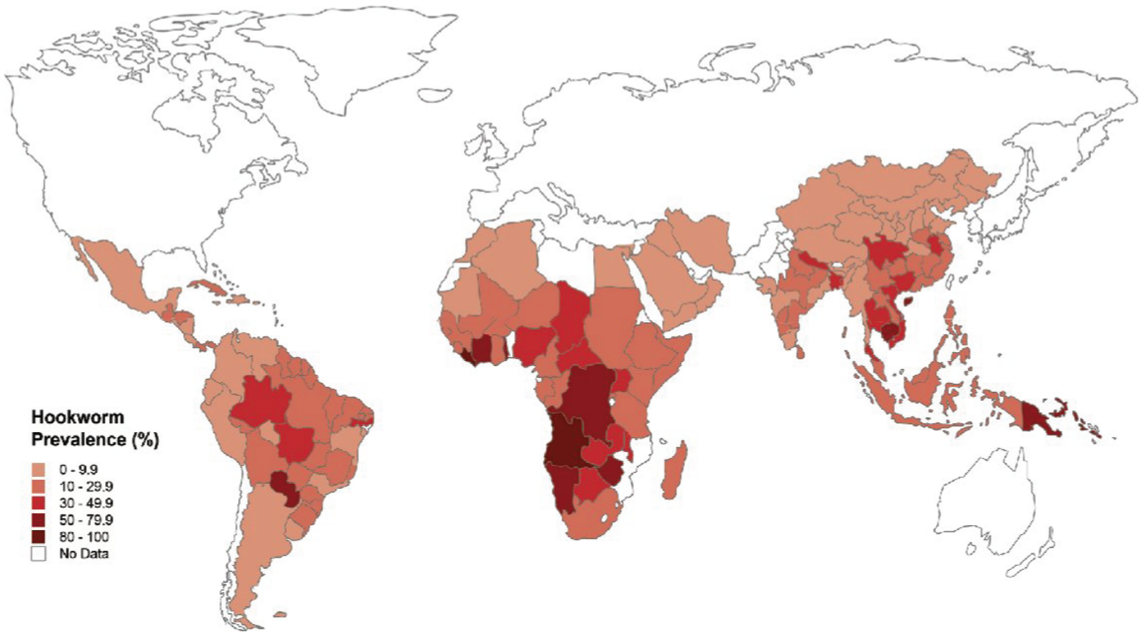

Figure 6. Prevalence of hookworm infection worldwide [57]

Food-borne helminths are transmitted through ingestion of undercooked meat (including fish, mammals, and mollusks), raw aquatic plants, and raw vegetables contaminated by fecal matter. Poor hygiene, unsanitary food preparation and undercooking are the leading factors of transmission. Diseases caused by foodborne helminths have common symptoms: abdominal pain, diarrhea, muscle pain, cough, lesions, malnutrition, weight loss, and neurological deficiencies.[58]

Trichinella spiralis is a nematode that requires two intermediate hosts. The worm initially infects a rodent, which is then eaten by a pig or another carnivore. A human ingests undercooked pork containing encysted larvae. Encysting allows the larvae to remain dormant for years while waiting

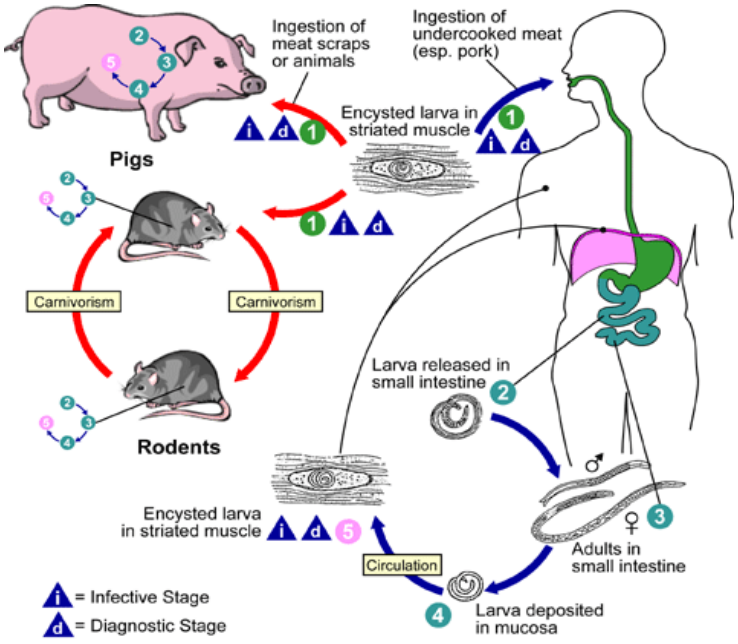

Figure 7. Lifecycle of *T. spiralis*

[57] Ibid. at 284.
[58] "CDC - Parasites - Food." Centers for Disease Control and Prevention. http://www.cdc.gov/parasites/food.html (accessed May 9, 2013).

to be transmitted to a terminal host. Gastric acid and pepsin in the host stomach degrade the cyst and allow the release of the larva. The larvae mature in the small intestine, where they live for about 4 months.[59]

Trichinella can be found in almost every corner of the world. Other species of Trichinella infect different hosts and may also infect humans. T. pseudospirals infects mammals and birds, however, it does not encyst in the striated muscle *like T. spiralis*. *T. native* infects arctic bears. *T. nelson* infects African predators and scavengers. *T. brivovi* infects European and Asian carivores.[60]

The severity of the symptoms of trichinellosis (or trichinosis) is correlated to the worm burden of the afflicted host. If the burden is low, the host may be asymptomatic or presenting with mild gastric symptoms like nausea and diarrhea. Mild cases tend to mirror the flu and clear up on their own within a few months. Severe infection can result in difficulty coordinating movements, cardiac and pulmonary problems, and even death.[61]

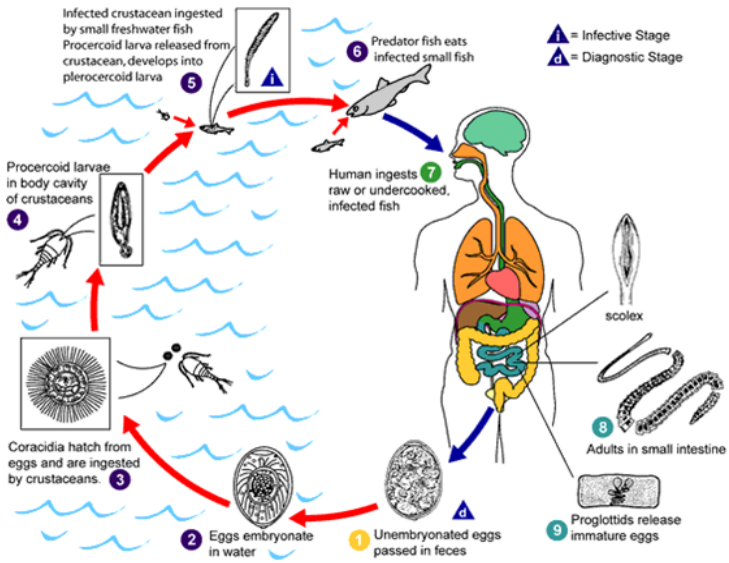

Figure 8. Lifecycle of Diphyllobothrium

Diphyllobothrium is transmitted through fish and is found in Europe, Asia, Russia, North America, Uganda, and Chile. This tapeworm has become an increasingly global problem as infected fish are sold on the world market. Luckily, this tapeworm is killed by properly cooking or freezing the infected fish. Fish become infected after eating an infected copepod. The mature adults live in the small intestine of humans. A female has over 3, 000 gravid proglottids-where each proglottid is capable of releasing huge numbers of eggs-resulting in around a million eggs released per worm each day. There are several species of *Diphyllobothrium. D. latum* is the largest and can grow up to 30 feet in length.[62]

Diphyllobothriasis is usually asymptomatic and can go years without detection. In severe cases, the host may suffer intestinal obstruction, gall bladder disease caused by migrating proglottids, the common GI symptoms noted above. Severe vitamin B12 deficiency may occur

[59] "CDC - Trichinellosis." Centers for Disease Control and Prevention. http://www.cdc.gov/parasites/trichinellosis/ (accessed May 9, 2013).
[60] Ibid.
[61] Ibid.
[62] "CDC - Diphyllobothrium." Centers for Disease Control and Prevention. http://www.cdc.gov/parasites/diphyllobothrium/ (accessed May 9, 2013).

after years of infection, as the parasite absorbs approximately 80% of the hosts B12. Subacute degeneration of the spinal cord also occurs in more severe cases.[63]

Taenia sp. are cestodes found in Latin America, Asia, and Africa.[64] Some of the prevalence of this parasite in developed countries is because of immigration from and tourism. [65]Humans are their only terminal host. Cows are the vectors for *T. saginata*. Pigs are the vectors for *T. solium*. Poor sanitation and improper food preparation lead to human infection when humans eat undercooked contaminated pork or beef. Gravid proglottids containing eggs are released in feces and remain infective for months in moist environments. Cattle and pigs are infected after eating contaminated vegetation. Oncospheres hatch from the eggs in the vector's

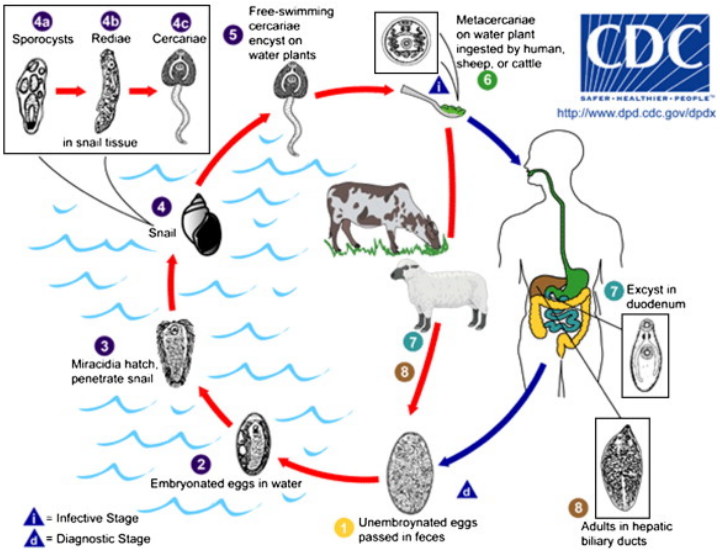

Figure 9. Lifecycle of *Taenia*

intestine. The oncospheres invade the intestinal wall and migrate to the striated muscle where they encyst as cysticerci, which can survive dormant for years. A human eats this undercooked meat. Adults attach to the small intestine. Six gravid proglottids are released in feces each day, with each proglottid containing hundreds of thousands of eggs.[66]

Taeniasis can be asymptomatic when acute. *T. saginata* tends to be more symptomatic than *T. solium.* In more serious infections the host experiences abdominal pain, appetite loss, weight loss, upset stomach. Proglottids may get stuck in appendix, or in the biliary or pancreatic ducts. *T. solium* can cause cysticercosis, an infection of the brain, muscle and other tissues by cystircerci. Symptoms include seizures, muscle and eye damage. [67]

Flukes are a type of trematode that infect 56 million people in 70 countries. All members of this group have similar life cycles, with the exception of schistosomes, which will be covered in waterborne worms below.

Clonorchis sinensis is a liver fluke found primarily in Asia. It infects does and fish eating carnivores. Eggs are released with feces. They require freshwater to develop into cercaria. The

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[63] "CDC - Diphyllobothrium." Centers for Disease Control and Prevention. http://www.cdc.gov/parasites/diphyllobothrium/ (accessed May 9, 2013).
[64] [64] "CDC - Taeniasis." Centers for Disease Control and Prevention. http://www.cdc.gov/parasites/taeniasis/ (accessed May 9, 2013).

[65]Lustigman, Sara, Roger Prichard, Andrea Gazzinelli, Warwick Grant, Boakye Boatin, James McCarthy, and Maria Basanez. "A Research Agenda for Helminth Diseases of Humans: The Problem of Helminthiases." *PLoS neglected tropical diseases* 6, no. 4 (2012): 4.
[66] "CDC - Taeniasis." Centers for Disease Control and Prevention. http://www.cdc.gov/parasites/taeniasis/ (accessed May 9, 2013).
[67] Ibid.

cercaria is eaten by a snail, where it matures into a metacercaria. The metacercaria leaves the snail and penetrates a fish, encysting in the subcutaneous tissue. That fish is eaten by a carnivore. The metacercaria is released from the cyst in the host's intestine, whence it migrates to the bile ducts.[68]

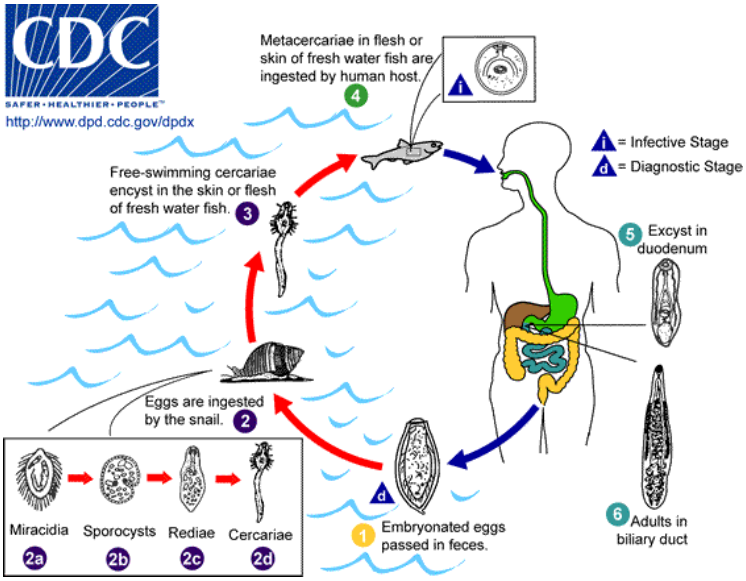

Figure10 . Lifecycle of the Fluke.

Clonorchiasis affects 12.5 million people in China alone. An acute infection may be asymptomatic. More severe infections cause fever, pain in the upper right quadrant, colon pain, gall bladder obstruction. Chronic infection destroys the liver parenchyma and causes inflammation of the walls of the bile ducts, resulting in fibrosis. Fibrosis of the bile ducts puts the host at risk for cholangiocarinoma, which is severe and often fatal bile duct cancer.[69]

Fasciola hepatica and *Fasciola gigantica* are local to Europe, the Americas, Oceania and especially the South American highlands. Greater incidences of infection are found along trade routes of the host plants, watercress and water mint. Other hotspots for infection include the Nile valley, Caspian Sea basin, as well as East and Southeast Asia. 2.4 million People are infected in over 70 countries. The worms contaminate a freshwater source when an infected animal defecates in or near that source. Cercariae hatch from the eggs and penetrate snails. The cercariae mature into metacercariae and leave the snail. The metacercariae affix themselves to an aquatic plant and form metacercarial cysts. Humans are infected either by eating the plant or an animal that has eaten the plant, or by imbibing water with free floating metacercarial cysts. In the human host, metacercariae penetrate the intestinal wall and peritoneum to get to the liver, which they burrow through on their way to the bile ducts. Metacercariae mature into adults in the bile ducts and then release eggs into the bile which flows to the intestine and out with feces.[70]

Fascioliasis is asymptomatic in the acute phase. After two to four months, the host suffers internal bleeding (due to migration of the metacercaria), fever, nausea, swollen liver, skin rashes, and severe abdominal pain. Once the metacercariae reach the bile ducts the host suffers

[68] "CDC - Clonorchis - Biology." Centers for Disease Control and Prevention. http://www.cdc.gov/parasites/clonorchis/biology.html (accessed May 9, 2013).
[69] World Health Organization. "Clonorchiasis." Foodborne Trematode Infection. www.who.int/foodborne_trematode_infections/clonorchiasis/en/ (accessed February 25, 2013).
[70] World Health Organization. "Fascioliasis." Foodborne Trematode Infection. www.who.int/foodborne_trematode_infections/clonorchiasis/en/ (accessed February 25, 2013).

intermittent pain, jaundice, anemia, pancreatitis, gallstones, and liver fibrosis due to prolonged inflammation. Secondary infection often occurs.[71]

Waterborne helminths are transmitted through contact with water either via imbibition or physical contact.[72]

Drancunculus medinensis, or the Guinea worm, is transmitted to humans when a human drinks water containing infected copepods. The copepods die in the GI tract and release larvae. The larvae penetrate the host's stomach or intestinal wall and migrate to the abdominal cavity and retroperitoneal space, where they mature into adults. After copulating the male dies and the female migrates to the subcutaneous tissue of a lower extremity. After a year of living in the subcutaneous tissue, a blister forms around the worm. When the blister ruptures, the female emerges and releases larvae upon contact with water. Those larvae are eaten by copepod, in which they molt twice before becoming infective to humans.[73]

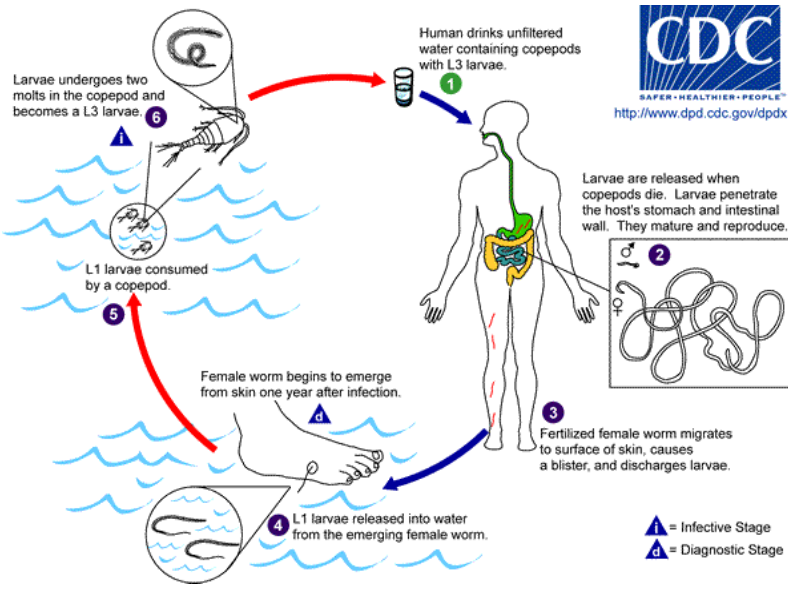

Figure 11. Lifecycle of the Guinea Worm

A human with dracunculiasis, or Guinea worm disease, remains asymptomatic for approximately a year while the worm is maturing, mating, and migrating.[74]Once the worm is ready to release larvae, the host may suffer from blisters, ulcers and edema which cause a burning pain that the host tries to alleviate by dipping the lesion in cool water.[75] These symptoms are accompanied by itchy rashes, fever, nausea, vomiting, diarrhea, and dizziness.[76] It is common for the host to suffer secondary infection due to exposure of lesion. In that case, the host may suffer cellulitis (redness and swelling of the skin), abscesses, sepsis, septic arthritis-infections of the joints that may lead to deformation of the joints, and tetanus. The disease is treated by wrapping the worm around a rod and turning that rod a little bit every day to remove the worm without breaking it. Breaking the worm causes inflammation and painful cellulitis where the

[71] Ibid
[72] "CDC - Parasites - Water." Centers for Disease Control and Prevention. http://www.cdc.gov/parasites/water.html (accessed May 9, 2013).
[73] "CDC - Guinea Worm." Centers for Disease Control and Prevention. http://www.cdc.gov/parasites/guineaworm/ (accessed May 9, 2013).
[74] Ibid
[75] World Health Organization. "About Guinea Worm Disease." Dracunculiasis. www.who.int/dracunculiasis/disease/en/ (accessed February 25, 2013).
[76] "CDC - Guinea Worm." Centers for Disease Control and Prevention. http://www.cdc.gov/parasites/guineaworm/ (accessed May 9, 2013).

worm degrades. This disease causes lack of mobility for 2 months or more and can cause permanent disability in children.[77]

The number of new cases of dracunculiasis occurring worldwide each year has decreased from an estimated 3.5 million to 1,058 since the 1986 World Health Assembly, the decision-making body of the World Health Organization, declared global elimination as a goal.[78] The number of dracunculiasis cases reported worldwide in 2011 declined by 41%, compared with 2010, and by 51% from January–June 2011 to January–June 2012. Transmission remains endemic in four countries, with just one, South Sudan, accounting for 99% of all reported cases during January–June 2012.[79]

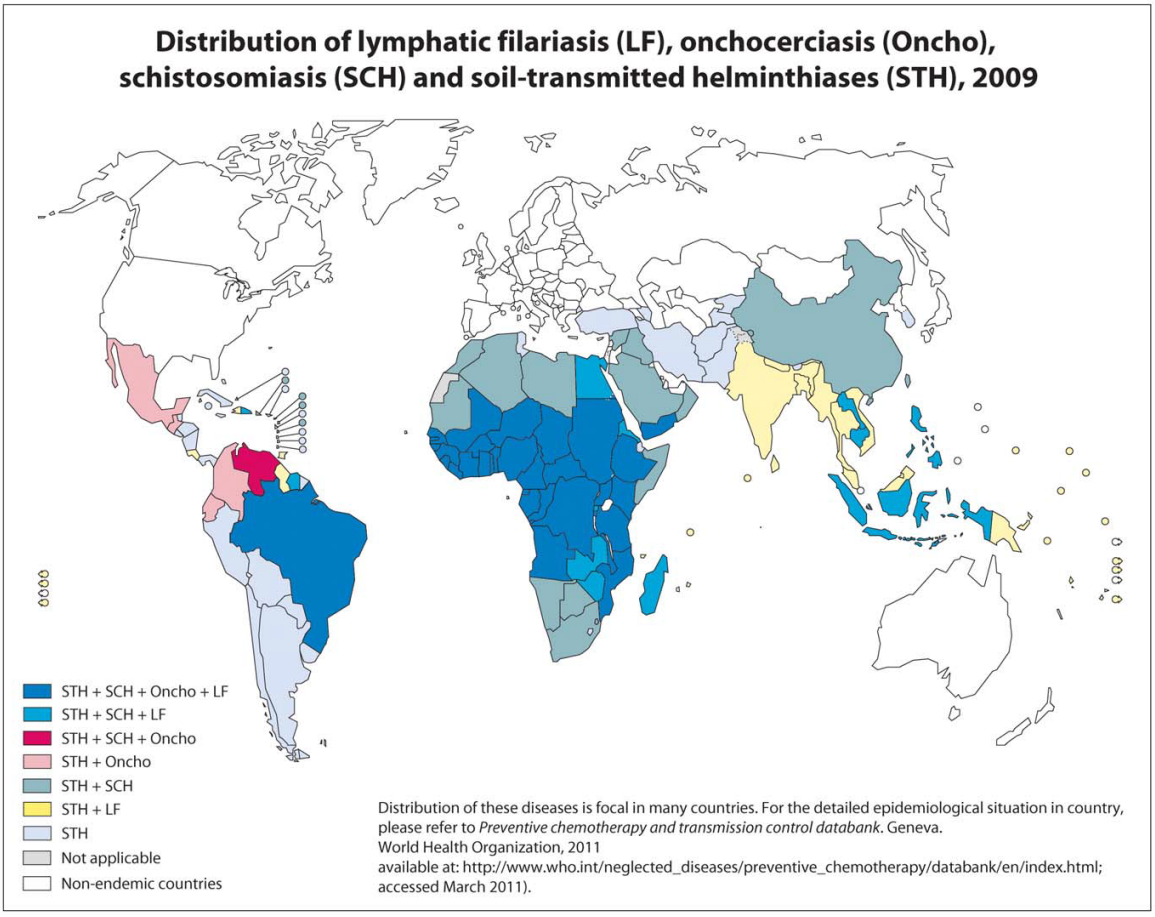

Figure 12. Geographical distribution of co-infections with helminth infections. Infections include: lymphatic filariasis (LF), onchocerciasis (Oncho), schistosomiasis (SCH), and soil-transmitted helminthiases (STH). [80]

[77] Ibid
[78] Centers for Disease Control and Prevention. "Newborn Screening for Critical Congenital Heart Disease: Potential Roles of Birth Defects Surveillance Programs — United States, 2010–2011." *Morbidity and Mortality Weekly Report*, October 26, 2012.
[79] Ibid.
[80] Lustigman, Sara, Roger Prichard, Andrea Gazzinelli, Warwick Grant, Boakye Boatin, James McCarthy, and Maria Basanez. "A Research Agenda for Helminth Diseases of Humans: The Problem of Helminthiases." *PLoS Neglected Tropical Diseases* 6, no. 4 (2012): 5.

Schistosomes are known as the blood flukes.[81] This trematode is the cause of widespread infection in 76 countries and territories. *Schistosoma mansoni* is endemic in 54 countries and *S. haematobium* in 55. Infection by *S. japonicum* remains an important public health burden in the Philippines, China, and parts of Indonesia, despite the program controls taking place. Almost 800 million individuals are at risk across the globe; about 200 million people are infected. Of the 200 million people infected with *Schistosoma spp.* in the world, 160 live in SSA, where approximately 110 million are infected with *S. haematobium*. Schistosomiasis causes "15,000–280,000 deaths annually in SSA alone and severe disability in approximately 20 million people".[82]

Schistosome eggs are passed in feces or urine and hatch in water. The larvae penetrate a snail in which they mature into an infective stage larvae. These infective larvae are released back into the water, where they can survive for up to two days while waiting to encounter a host. When a human steps into the contaminated water the schistosome larva penetrates the skin on the individual's foot. From the foot the larva migrates through the tissues to the veins.[83] Adults live in the mesenteric venules emptying into the unrinary tract, intestine and abdominal cavity. Eggs often get trapped in the body causing tissue damage.[84]

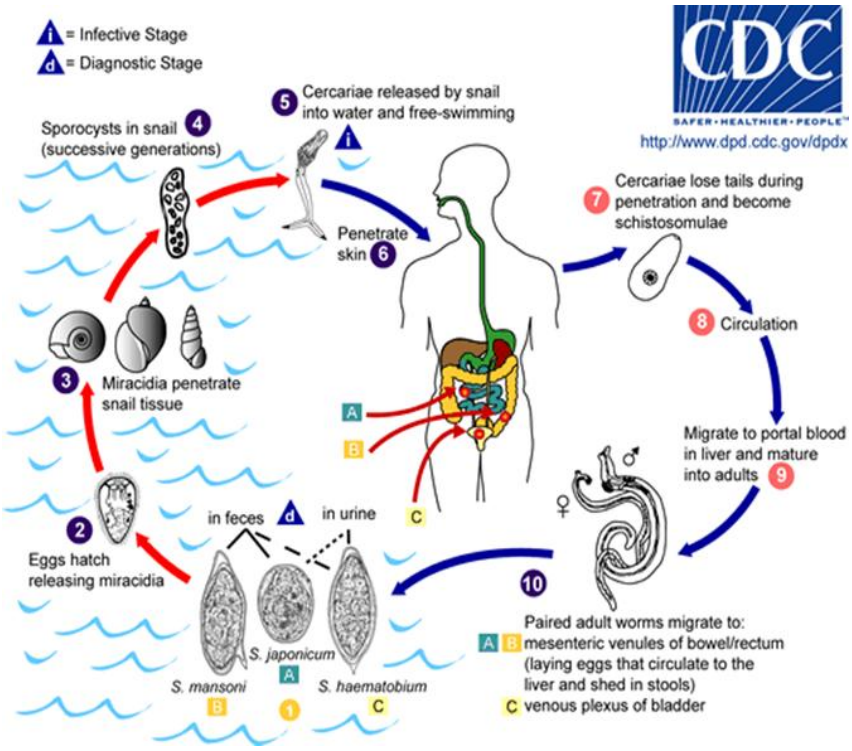

Figure 13. Lifecycle of a Schistosome

Schistosomiasis is known in some parts of the world as bilharzia. The host is initially asymptomatic. A few days after infection the host develops an itchy rash. After a month or two fever, chills, cough and muscle ache set in. Years of infection causes damage to the liver, intestine, spleen, lungs and bladder. 200,000 cases a year result in death in sub-Saharan Africa. There are two types of schistosomiasis: intestinal and urogenital. Intestinal schistosomiasis causes

[81] World Health Organization. "Schistosomiasis." Programmes and Projects. www.who.int/schistosomiasis/en/index.html (accessed February 25, 2013).
[82] *Ibid.* at 5.
[83] Ibid
[84] World Health Organization. "Schistosomiasis." Programmes and Projects. www.who.int/schistosomiasis/en/index.html (accessed February 25, 2013).

abdominal pain, enlarged liver, bloody stool, diarrhea and enlarged spleen. Urogential schistosomiasis causes difficulty urinating, heightened risk of bladder cancer, bloody urine, infertility and bladder and ureteral fibrosis. Urogenital schistosomiasis can cause infertility in both men and women. Women may suffer from lesions on the cervix or vagina, vaginal bleeding, nodules on the vulva, and pain during intercourse. Men may suffer damage to the seminal vesicles and prostate. Eggs released by schistosomes that inadvertently migrate to the brain or spinal cord cause seizures, paralysis and inflammation of the spinal cord. Children are especially susceptible to anemia, malnutrition and learning disabilities. Different species are correlated with certain types of cancer and fibrosis.[85]

Insect-borne are transmitted to humans when the insect-vector bites a human. *Onchocerca volvulus* is prevalent in fertile riverside areas where Simulium blackflies live. An infected fly bites a human, passing the larvae to the subcutaneous tissue. The larva creates a nodule, where it matures into an adult. The female releases around 1,000 juveniles a day. The juveniles migrate to the subepidermal tissue so that they may be transmitted to a fly when the human is bitten.[86]

Onchocerciasis, also known as River Blindness, has rendered around half a million people blind and is the leading cause of blindness in west and central Africa. The disease is also prevalent in 6 Latin American countries. Presently, it is estimated that 37 million people carry *O. volvulus*, with 90 million at risk in Africa. Morbidity at present is estimated at 987,000 disability-adjusted life-years and there are 46,000 new cases of blindness annually.[87] See Figure 13.

Onchocerciasis causes skin rashes and lesions, intense itching and depigmentation, as well as optical symptoms. The eye may be inflicted with bleeding, lesions and inflammation. Every part of the eye is subject to infection, except the lens, however the lens may still become inflamed. These symptoms cause blindness.[88]

[85] "CDC - Schistosomiasis." Centers for Disease Control and Prevention. http://www.cdc.gov/parasites/schistosomiasis/ (accessed May 9, 2013).
[86] "World Health Organization, "Prevention of Blindness and Visual Impairment: Onchocerciasis." Programmes and Projects. www.who.int/blindness/causes/priority/en/index3.html (accessed May 9, 2013).
[87] Ibid.
[88] Ibid

Figure 14. World distribution of onchocerciasis[89]

Wucheria bancrofti is transmitted through mosquito bites. The larva migrate to lymphatic vessels after transmission and mature into adults.[90] The resulting disease is lymphatic filariasis, which is endemic in 83 countries and territories. It is estimated that 1.3 billion people are at risk for developing the disease, with some 120 million people being infected. Over 40 million people are seriously incapacitated and disfigured by the disease. Of these, 95% are infected with *Wuchereria bancrofti*, and the remainder with *Brugia malayi* or *Brugia timori*. The infection, usually acquired in early childhood, causes considerable morbidity and social stigma because of the deformities it produces.[91]. Lymphedema, or pooling of lymphatic fluid in the extremities, occurs in the early stages of this disease. Late stage lymphatic filariasis results in elephantiasis.[92]

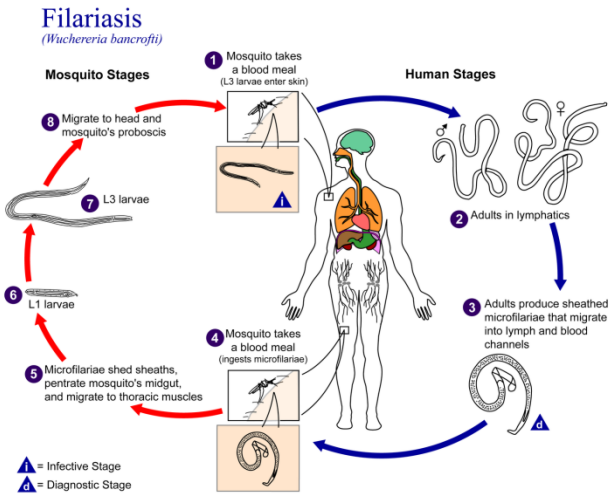

Figure 15. Lifecycle of *W. bancrofti*

[89] Ibid. at 1381.
[90] World Health Organization. "Lymphatic Filariasis." Programmes and Projects. www.who.int/lymphatic_filariasis/en/ (accessed February 25, 2013).
[91] Lustigman, Sara, Roger Prichard, Andrea Gazzinelli, Warwick Grant, Boakye Boatin, James McCarthy, and Maria Basanez. "A Research Agenda for Helminth Diseases of Humans: The Problem of Helminthiases." *PLoS neglected tropical diseases* 6, no. 4 (2012): 3.
[92] World Health Organization. "Lymphatic Filariasis." Programmes and Projects. www.who.int/lymphatic_filariasis/en/ (accessed February 25, 2013).

Types of Vaccines

The types of vaccines encountered are divided into protein subunit vaccines and DNA vaccines. Protein vaccines formed by introducing a fragment of microorganism to the immune system to create an immune response.[93] Examples include the subunit vaccine against Hepatitis B virus that is composed of only the surface proteins of the virus.[94]

DNA vaccines employ modified DNA that is injected into the cells of the body, where the "inner machinery" of the host cells "reads" the DNA and uses it to synthesize the pathogen's proteins.[95] Because these proteins are recognized as foreign, when they are processed by the host cells and displayed on their surface, the immune system is alerted, which then triggers a range of immune responses.[96]

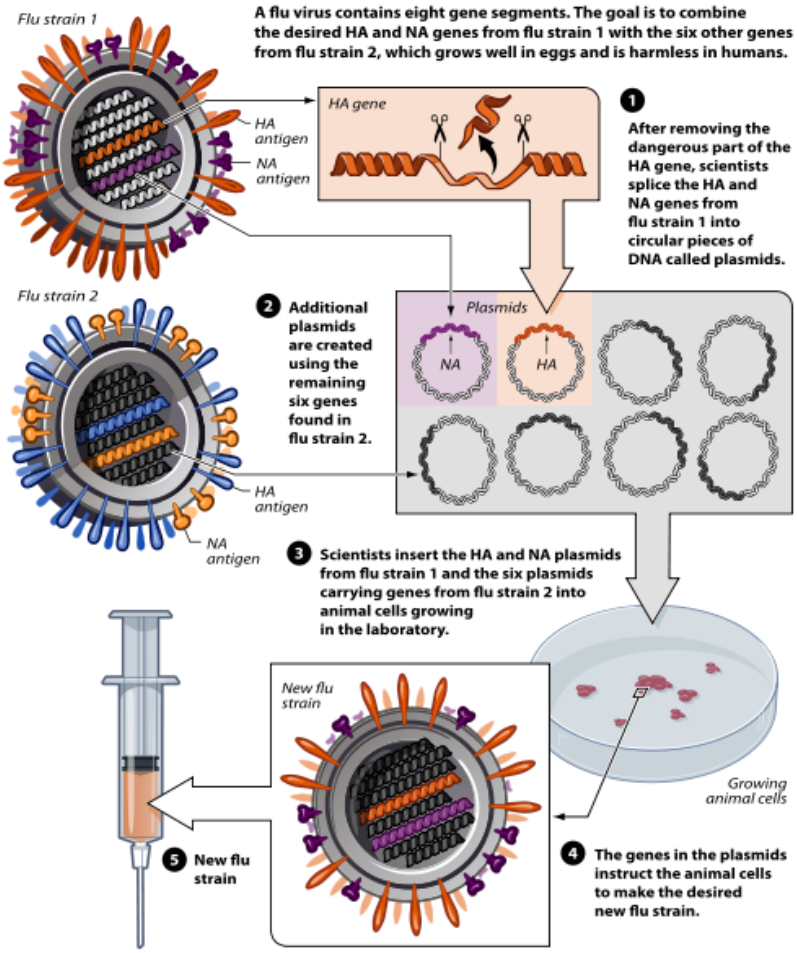

Figure 16. Production of recombinant viruses in cell lines (this image is used to fundamental principles of recombinant DNA molecular biology)

[93] http://www.niaid.nih.gov/topics/vaccines/understanding/pages/typesvaccines.aspx.
[94] *Id.*
[95] http://www.niaid.nih.gov/topics/vaccines/understanding/pages/typesvaccines.aspx.
[96] *Id.*

Advances in Helminth Vaccines

The emergence of drug resistant parasites and the limited sustainability of drug administration programs in endemic areas have provided great incentive for the development of molecular vaccines for helminth infections.[97] Vaccines targeting particular proteases produced by helminths represent an area of which the most success in helminth vaccinology has been achieved. [98]

Additionally, endeavors into vaccines targeting infective helminth larvae are increasingly common as the adult stage of many problematic helminths are not only drug resistant but also less susceptible to type II immune responses.[99]

Potential Advantages of Vaccination.

The current method of mass treatment for helminth infections is through a deworming campaign where the worm is either physically removed or removed by providing the infected with medication.[100] The cost of mass deworm is little, roughly estimated at $0.25USD per child under WHO's current treatment plan.[101] While cost of removing helminths by medication is low, this style of treatment needs to be performed twice to three times yearly in areas with medium or high prevalence of infection.[102] Additionally, deworming by medication does little to prevent rapid reinfection of a parasite.[103] It is for this reason that a vaccine targeting helminths may be a more desirable form of treatment as a vaccine would likely prevent reinfection and require far fewer deworming campaigns as the immunity would likely stay with the inoculated for a much longer period of time.

Scope of the Project

The ITTI team began this project by setting the goal for the team to produce a patent landscape report surveying the technologies necessary to produce a vaccine targeted parasitic worms that infect humans. The ITTI team then needed to limit the scope of the project in both the types of technologies to be surveys and the types of organizes to be surveyed. The ITTI team set the

[97] Loukas, A. and Bethony, J.M. (2008). New drugs for an ancient parasite. Nat. Med. 14, 365–367.
[98] Pearson et al. (2010) Blunting the knife: development of vaccines targeting digestive proteases of blood-feeding helminth parasites Biol. Chem., Vol. 391, pp. 901–911

[99] Harris, N. (2011) Advances in helminth immunology: optimism for future vaccine design. Trends in Parasitology June Vol. 27, No. 7
[100] Hall, N (2008) The Costs and Cost-Effectiveness of Mass Treatment for Intestinal Nematode Worm Infections Using Different Treatment Thresholds. PLOS Neglected Tropical Disease.
[101] *Id.*
[102] *Id.*
[103] Tie Wu Jia. Soil-Transmitted Helminth Reinfection after Drug Treatment: A Systematic Review and Meta-Analysis. PLOS Neglected Tropical Disease.

scope of the project to include the following: all types of complete vaccines, veterinary vaccines, methods of vaccine production and formulation, methods of producing subunits useful for vaccines, and general platforms related to parasitic worm vaccines. In addition, the ITTI team decided the scope of the project would include all species of parasitic worms that fall under the phyla nematoda or platyhelminthies as the members of these phyla generally have the potential to infect humans.

The ITTI team decided that complete vaccines are relevant to the subject and thus fall within the scope of the project. Although the ITTI team did not know all of the types of vaccines patents a landscape analysis would discover, the ITTI team subdivided the vaccine category into subunit vaccines and DNA vaccines.

In reviewing the patents related to vaccines, the ITTI team recognized the need to address the issue of when the claims of a patent were directed to vaccines mainly used in animals. Given that a parasitic worms can use an animal as an intermediary (also known as a vector) before infecting humans and that there is a need to vaccinate livestock against parasitic worms, vaccines directed solely to the use in animals were included as relevant documents and given a separate category in veterinary vaccines.[104] In some cases, patent documents may have claims directed to a vaccine useful against all nematodes but the specification of patent would be directed towards a vaccine useful against parasitic worms that mainly infect livestock.[105] In such cases the patent would be included in the relevant vaccine category and not the veterinary category. In other cases if the claims were directed specifically to nematodes that infect mainly animals and not human the patent was sorted into the veterinary vaccine category.[106]

One of the most important decisions made was how to deal with adjuvants. The main problem with adjuvants is that an adjuvant patent often claims use in vaccines for parasitic worms in a large Markush group, along with hundreds of other diseases. On the other hand, an adjuvant could be limited to just parasitic worms. Faced with these two issues, adjuvants were divided into two groups, general adjuvants, defined as an adjuvant that listed parasitic worms in a large Markush group, would be excluded from the report[107] and related adjuvants, defined as adjuvants used just for parasitic worms would be considered relevant.

[104] See CA2153494C
[105] See US20100255037A1
[106] See US20030129204A1

[107] See US8211861B2

Patent Search Methodology

> *Guess, compute the consequences to see what that guess would imply, and compare directly with observation to see if it works. If it disagrees with the experiment, it's wrong. It's that simple. It doesn't matter how beautiful your guess is, how smart you are, or what your name is. Looking at the universe, the great power of science, there's no such thing as authority of nature. If it doesn't agree with the experiment, then it's wrong.*
>
> - *Richard Feynman*

Iterative Process

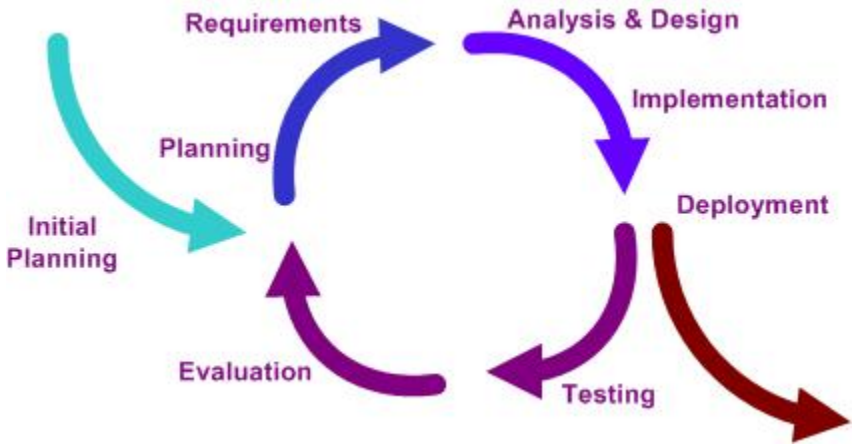

Figure 17. Iterative development model. Taken from Wikipedia.

The iterative process is defined as the act of repeating a process with the aim of approaching a desired goal, target, or result. Each repetition of the process is called an iteration, and the results of one iteration are used as the starting point for the next iteration. In the field of patent searching, the iterative process is a searching methodology wherein at the end of a search cycle, the search is evaluated, and its shortcoming assessed. The shortcomings are then addressed in the next cycle of searches in order to capture the documents. The next search can be either wider in scope or could be a narrower search depending on the results gained from the previous search.

In this study, keyword searching identified relevant documents, from which were extracted further keywords as well as classification codes. The classification codes were used to locate additional documents. Keywords were adjusted and used for another round of searching.

Precision and Recall[108]

The number of patent documents worldwide, including patents (issued, re-issued, and re-examined) and applications, is over 60 million[109]. Selecting relevant documents from such a huge dataset can be difficult, and this type of document retrieval is governed by the mathematical theory of Precision and Recall. Precision is the percentage of retrieved documents that are relevant and is calculated as the number of retrieved relevant documents divided by the total number of retrieved documents. Recall is the fraction of relevant documents retrieved and is calculated as the number of retrieved relevant documents divided by the total number of existing relevant documents. These concepts are illustrated in Figure 7[110] below.

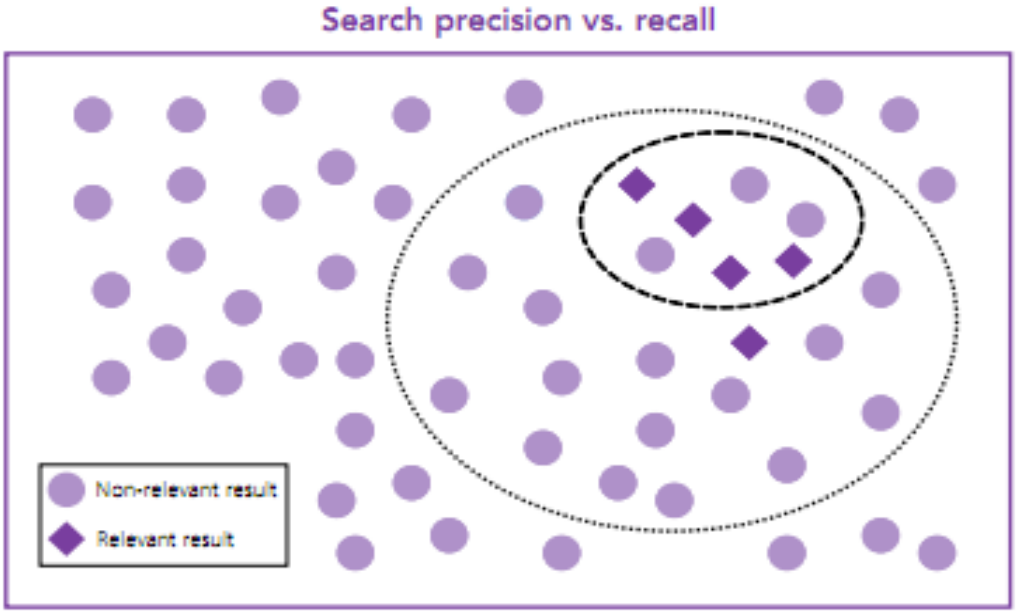

Figure 18. Increasing precision of a search means some relevant results are excluded.

Thus, any set of retrieved of documents will always include a certain fraction of irrelevant documents, also termed false positives. As a search attempts to capture an ever higher fraction of relevant documents, the sensitivity of the search will decrease because the proportion of false positives will increase. In the extreme, every relevant document can only be captured if every irrelevant document is also captured, as depicted in Figure 8[111].

[108] *See also* J. Davis and M. Goadrich, The relationship between precision-recall and ROC curves, Proceedings of the 23rd International Conference on Machine Learning, Pittsburgh, PA, 2006.
[109] Based on data from 2007. http://www.taeus.com/article.php?id=66.
[110] http://www.wipo.int/freepublications/en/patents/434/wipo_pub_l434_03.pdf
[111] Precision Recall Graph, Mirrored ROC Curve, www-csli.stanford.edu.

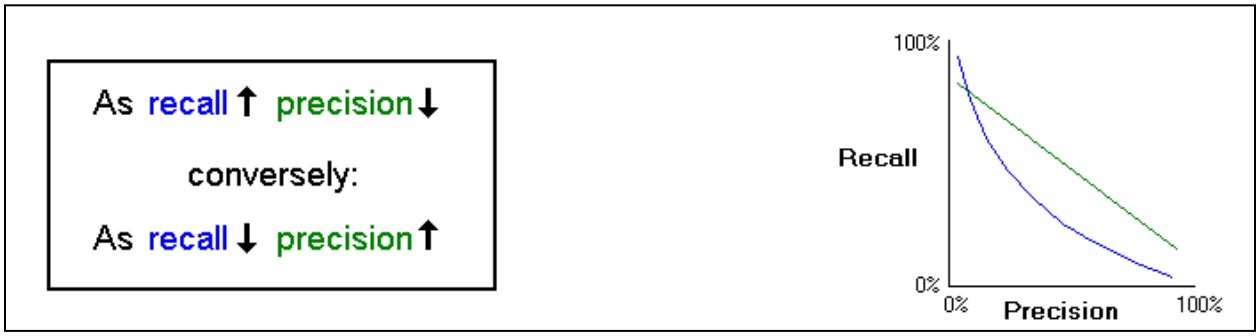

Figure 19. Inverse relationship between recall and precision.

Stated another way, a high **recall** means you haven't missed anything but you may have a lot of useless results to sift through (which would imply low **precision**). High **precision** means that everything returned was a relevant result, but you might not have found all the relevant items (which would imply low **recall**).[112]

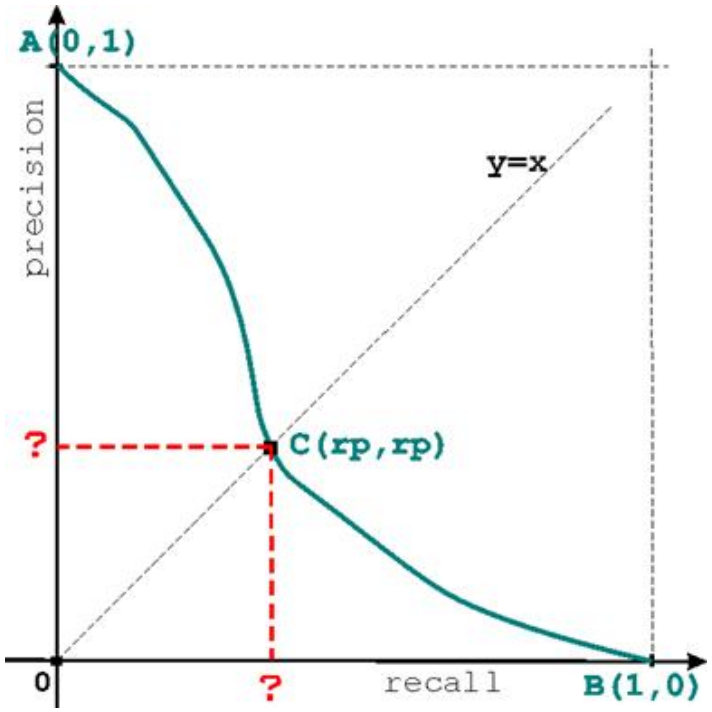

Figure 20. An optimal balance can be achieved which is neither 100% precise nor contains 100% recall.

An optimal balance, point C in Figure 9[113], must therefore be achieved between precision (degree of relevance of all retrieved documents) and recall (fraction of relevant documents retrieved). In terms of patent searching, and in particular searching for relevant vaccine patents within the parasitic worm vaccine landscape, one deciding on that balance point must have experience in

[112] Wikipedia, the free encyclopedia, http://en.wikipedia.org/wiki/Precision_and_recall.
[113] http://www.ccs.neu.edu/home/jaa/CSG339.06F/Homeworks/hw.01.html.

patent searching in general, knowledge concerning the technology involved, and an understanding of the goal of the search. The purpose of the methodology described in the previous report and refined in this update is to provide a framework for such a decision-making process.

A search method example that resulted in high levels of recall and low levels of precision is semantic searching. In this search method, recall was high but precision was low. The reason semantic searching may have been less than effective is that the boundaries that create accuracy in a search, the keywords, were computer generated. Although it is difficult to judge the precision levels of semantic searching based on our limited attempts, this results seem to indicate that the keywords generated by a computer do not result in high levels of precision.

Other databases were more successful for obtaining high levels of precision. For example, when the search string was controlled and the database being searched was efficient, the results that were obtained were an optimal balance between precision and recall. For example, Derwent is a pre-screened database, where language and classifications are carefully standardized. Therefore, precision is increased due to accuracy and efficiency of searching.

Platform Services

U.S. Patent and Trademark Office[114]

ITTI utilized the USPTO database for classification searching, a patent search platform created by the United States Patent and Trademark Office, which provides function to search for patents within any of the USPTO's classifications. The USPTO database also allows for non-classification searching.

Thomson Innovation[115]

ITTI utilized Thomson Innovation, a patent search platform that integrates the best of the suite of Thomson tools, Aureka, Delphion and MicroPatent. Thomson Innovation is a single, integrated tool that combines intellectual property, scientific literature, business data and news with analytic, collaboration, and altering tools in a robust platform.

TotalPatent[116]

ITTI also utilized TotalPatent, a LexisNexis platform, to search patents and patent applications world-wide. TotalPatent provides several additional countries that are not included in other platforms. Also, TotalPatent offers useful tools such as semantic searches, the ability to search for subsidiary companies and corporate structure, and analytics.

[114] http://www.uspto.gov/.
[115] http://info.thomsoninnovation.com/.
[116] http://www.lexisnexis.com/en-us/products/total-patent.page.

Deduplication Process and Collapsing into Families

The search results from ITTI's secondary patent searches were combined to form a single list of patent documents. The combined search results were placed into Microsoft Excel as publication numbers and deduplicated. The number of duplicates was taken as an indication of the level of recall. For example, a high percentage of duplicates would mean that most of the relevant results had been identified. However, publications numbers with different file extensions, such as PCT extensions A1, A2, and A3, would be recognized as different even though the numbers corresponded to the same application.

A further method of deduplication employed Thompson Innovation. A publication number search was performed and all related INPADOC family members were returned in the result set. The data was saved as a work file. The same procedure was performed with a different team member's search results. One work file could be subtracted from the other, and the size of the subtracted file would indicate the level of overlap and thus the level of recall being achieved. The work files could also be merged, and Innovation would automatically remove duplicates in the merged work file.

Once a compiled list of all search results was deduplicated, the results were then collapsed by INPADOC family to reduce the initial search results into representative patent family documents. ITTI gave preference to US documents because these documents were easier for the team to analyze and they tended to contain the most complete bibliographic information available. The collapsed list was a much more manageable number of documents which the team could efficiently code into categories. The team recognizes that the representative family member could be a divisional application and thus would not claim the full limit of the invention. Although this could result in an error, either towards inclusion or exclusion, time constraints prohibited coding of every publication individually.

Results

Relevant/Irrelevant Determination

A master of list of parasitic worm-related documents was assembled following three complete rounds of searching by each of the three team members.[117] On the second round of searching, about 90% of nearly 2800 documents were repeated among the different members' results. The third round of searching generated 4 new INPADOC families and 20 new patent documents. This increased the percent of repeated documents to nearly 99% Thus, the team was confident that at least 96% of the helminth-related documents had been captured.

[117] The keywords used in patent searching are located in Appendix L.

The results were compiled and a publication number search was performed using Innovation to expand the families. Approximately 2847 total documents were identified, and these results were collapsed into almost 447 INPADOC patent families.[118] Representative family members were then subjected to a coding process. Publications that were irrelevant to vaccines directed towards helminths or were outside the scope of this project were excluded. Documents were also excluded if there was too little information in the record to support a coding decision, such as some documents having only a title.

Documents were considered relevant if they specifically claimed a member of either phylum platyhelminthies or phylum nematoda. Coding was done on the claims of the representative family members, or, if no claims were available, coding was done using other family members. INPADOC family members were given preference, but DWPI family members were used alternatively. Family members were selected in the following order, as available: a U.S. application (assumed to have the broadest claims), U.S. patent, a PCT application, and finally a document having claims in English, such as a document from Great Britain or Australia. If no family members had claims in English, foreign language claims were translated into English using either a translation provided by Thomson Innovation, Lexis Total Patent, or Google Translate.[119] If there were no family members having claims in their records, the family was coded using a DWPI summary of the claims, or if absolutely necessary, on the abstract alone. In the final case, the coding was done very conservatively and the document was excluded unless it obviously related to a vaccine targeting parasitic worms.

In this manner, over 98% of the results were either assigned to one of the coding categories given below or were excluded as outside the scope of this report. Many documents were relevant to multiple categories, but each representative family was placed in only one category, that category being the best fit for the overall focus of the document. For example, a document claiming both a complete vaccine and the components to be assembled into that vaccine was placed into one of the vaccine categories. Alternatively, if the document focused on the process of making the vaccine, the document was coded to one of the method categories. In general, there were four major categories for coding documents: vaccines, supporting technologies, general platforms, and excluded documents. The first two categories were divided into subcategories. The definitions and criteria for each category are given below. The Master Coding Document can be found in Appendix A.

[118] Results are given in approximations because new family members were continually being identified and publications were added to existing families. Thus, the actual numbers changed each week with total documents increasing and the number of families decreasing.
[119] http://translate.google.com/.

Coding Categorization of Patent Documents

General platforms.
A document had to specifically claim a type of parasitic worm or parasitic worms in general to be considered relevant. The technology described in such documents could be useful in constructing a vaccine directed towards helminths, but could just as easily serve as a platform for vaccines against a wide range of pathogens. These documents were considered to have a low level of relevance. While these documents are captured and reported in Appendix A, they are not included in any of the analysis below.

Vaccines.
Vaccines were divided into two subcategories: subunit vaccines, and DNA vaccines. Subunit vaccines contain individual helminth antigens or a mixture of a limited number of antigens. The antigens could either be a portion of a helminth[120], a purified surface antigen of a helminth[121] or a chemical a helminth excretes.[122] The subunits could be also be expressed by viruses, bacteria, or other organisms that act as a carrier for a helminth antigen.

DNA vaccines are nucleic acid constructs which, when injected into an animal, cause expression of an helminth antigen by host cells that take up the nucleic acid constructs These nucleic acid constructs could be either linear pieces of DNA or RNA, which are short-lived in the host, or DNA plasmids, which can persist for a period of time.[123]

To be considered a vaccine-related publication, the representative document must have claimed compositions of matter having all aspects of a true vaccine: antigen(s), adjuvant (if necessary), carriers/diluents, and a means or route of delivery. If the claims do not meet these aspects, or were solely method claims, the family was placed in one of the supporting technology categories. Merely terming a composition was not sufficient; the claims must have had enough detail to describe an actual vaccine. Some allowance was made for foreign language documents in that a broader range of terminology was accepted as a description of a vaccine.

Supporting Technologies.
Some documents claimed parasitic worms in the independent claims yet did not sufficiently claim a vaccine composition for use in humans. These documents describe the antigenic components of a vaccine, but lack detail of carriers, adjuvants, and route of administration. Thus, these documents were coded as one of the supporting technologies which are important for the construction or manufacture of vaccines. Included in the supporting technologies

[120] See US4756908A
[121] *Id.*
[122] See AU2003294191B2
[123] See US5021342A; see also, CN100528240C

subcategories is novel subunit constructs useful in vaccines. As such, these two subcategories were focused on compositions of matter.

Two other subcategories of the supporting technologies were focused more on methods utilized in vaccine manufacture. The first such subcategory contains documents describing methods of making vaccines. The other subcategory contained documents describing methods of producing subunits useful for vaccines. These method including nucleic acid constructs which could be used to produce recombinant viruses,[124] or cell lines which could be used to produce subunits[125] While the former subcategory was mostly for method patent documents, the latter subcategory contained a mixture of method and composition of matter claims.

A final subcategory under the heading of supporting technologies was for veterinary vaccines. While the documents in this subcategory described complete vaccines, those vaccines were not for use in humans, although it is possible some may have been able to be adapted for human use. These vaccines were targeted towards pigs, horses, dogs, and other domesticated animals. Such vaccines may be useful not only veterinary purposes but also to prevent transmission of parasitic worms to humans. Veterinary vaccines were included in the relevant dataset for analysis as the line between purely veterinary vaccine, veterinary vaccines with human applications, and vaccines with veterinary applications was generally too close to make an absolute call on whether to include or exclude veterinary related documents.

The heading of supporting technologies thus contains a broad spectrum of patent documents covering a variety of different technologies. However, all of these documents are relevant to the production of helminth vaccines and the prophylactic treatment of human populations. The entire list of these documents is presented in Appendix A.

Note on the order of placement

As mentioned above, relevant documents may fit in multiple categories, but these documents were placed in the category which was the most relevant to the overall focus of the document. The order of placement was:

1. Subunit vaccines
2. DNA vaccines
3. Subunits useful for vaccines
4. Methods of making vaccines
5. Methods of producing subunits
6. Veterinary vaccines

[124] See CN102277373A
[125] See IN200705429P4

Documents were placed in the highest category in which the claims from that document fit. However, if no claims were available in the record of that document or any of its family members, the document were conservatively coded, mostly in the lower categories. If the available record mentioned multiple pathogens, the document without claims was often placed in the platform category.

Excluded irrelevant documents

Approximately half of the documents were excluded as irrelevant or as having insufficient information to allow coding. The full list of these documents can be found on the Master Coding Sheet in Appendix A, but it is useful to detail the reasons for exclusions here, to clarify the scope of the project.

1. Therapeutic interventions, such as small molecule medicines.
2. Means of detecting the presence of a parasitic worm.
3. Diagnostic methods.
4. Passive immunization.
5. Antibodies directed against helminths. These could be used in any of the above categories. A few patent document mentioned using anti-helminth antibodies to stimulate anti-idiotype responses, but few of those documents disclosed an anti-idiotype monoclonal antibody that could be used to immunize humans.
6. Adjuvants, when a parasitic worm is not specifically claimed.
7. Use of helminths in autoimmune therapy.
8. Use of helminths for agricultural purposes
9. Delivery systems for vaccines.
10. Immunization schedules, when a particular vaccine formulation is not disclosed.
11. Documents actually related to *Plasmodium*, a protozoa responsible for malaria. Searches for the helminths often returned this pathogen as well.
12. Documents which were not related to helminths.

Distribution of coding categories

The relative distribution of the results into the various categories is given in Table I. Almost half of the search results were considered relevant as either a vaccine document or a document describing one of the supporting technologies. Analytics was performed on these patent documents. The remainder of the results are reported in the appendix but were not included in the analysis.

Table I. Distribution of results (210 families) into coding categories.

Cestode	**12.9%**
Vaccines	6.7%
Subunit vaccines	6.2%

DNA vaccines	0.5%
Supporting Technologies	6.2%
Novel subunits useful in vaccines	4%
Method of making vaccines	1.5%
Veterinary vaccines	0.7%
Nematodes	30.5%
Vaccines	12.9%
Subunit vaccines	12%
DNA vaccines	.9%
Supporting Technologies	17.6%
Novel subunits useful in vaccines	5.2%
Method of making vaccines	1.9%
Veterinary vaccines	10.5%
Trematodes	49%
Vaccines	23.3%
Subunit vaccines	16.2%
DNA vaccines	7.1%
Supporting Technologies	26.2
Novel subunits useful in vaccines	21.4
Method of making vaccines	4%
Method of producing subunits	.5%
Veterinary vaccines	.5%
Non-Distinguished	8.1%
Vaccines	3.33%
Subunit vaccines	3.33%
DNA vaccines	0.0%
Supporting Technologies	4.8%
Novel subunits useful in vaccines	.95%
Method of making vaccines	2.4%
Veterinary vaccines	.95%
Platform technologies	2.0%
Excluded as irrelevant	50.1%

Relevant Helminth Vaccine and Vaccine Technology Documents

Searching was done for helminth-related patent documents which were then categorized based on their relationship to vaccines for parasitic worms. Not all documents were specific as to whether the technology could be used towards helminths that infect predominately human; helminths that infect predominately animals; or both. The team decided to err on the side of inclusion, so that a document was considered relevant if it mentioned a vaccine that targeted

helminths generally, a helminths that can infect humans. Documents representing each family are presenting in Table II. Full information on those documents can be found in Appendices B and C.

Table II. Documents representing the 210 relevant patent families referencing helminth vaccine and related technologies.

Publication Number	Title - DWPI	Assignee/Applicant
AU2010241253B2	Constructing peptides based on three-dimensional structure of homologs, useful as vaccines for protecting against helminth infections and for diagnosis	FUNDACAO OSWALDO CRUZ
US8211438B2	Vaccine composition useful for vaccinating a patient against hookworm infection, comprises hookworm antigens Na-APR-1 and Na-GST	The George Washington University,Washington,DC,US
BRPI9808251B1	Protective protein derived from parasite protease, e.g. Fasciola hepatica may be detected using ex vivo animal model, useful for, e.g. vaccinating mammals against parasite	
ES2376874T3	Novel Schistosoma mansoni recombinant protein of specific molecular weight, useful as protecting antigen against Schistosoma and Fasciola infection affecting humans and animals	FUNDACAO OSWALDO CRUZ
US7303752B2	Composition useful for vaccinating or eliciting immune response against hookworm in mammal, comprises copy of recombinant or synthetic antigen or their fragments derived from hookworm, and carrier	The George Washington University,Washington,DC,US
US20070079388A1	Composition for producing immune response, comprises human hookworm, in carrier, and human hookworm is produced by administering non-adapted human hookworm to non-human primate, obtaining fecal material, isolating human hookworm	The Secretary of State for Defence

US7144878B2	Preventing and treating roundworm infestations in animals, comprises orally administering parasiticidal formulation comprising non-aqueous liquid, thickening agent and different agents effective against nematodes to animals	IVX Animal Health Inc.,St. Joseph,MO,US
CA2153494C	New parasitic helminth proteins, pref. from Dirofilaria immitis used to protect animals from helminth infection, pref. heartworm	COLORADO STATE UNIVERSITY RESEARCH FOUNDATION,FORT COLINS,CO,US | HESKA CORPORATION,FORT COLLINS,CO,US
US6790630B1	New Dirofilaria immitis parasite protein exhibiting antigenic cross-reactivity with human Onchocerca volvulus filarial parasite protein and immune-reactivity with sera having heartworm infection, for diagnosis of heartworm infection	New England Biolabs Inc.,Beverly,MA
US6756043B2	Composition containing polypeptides from adult Taenia solium, useful for detecting taeniasis, particularly differentiation between infection by adults and larvae	The United States of America as represented by the Department of Health and Human Services Centers for Disease Control and Prevention,Washington,DC
CA2403985C	Inducing angiogenesis in a tissue using the Ov-ASP protein isolated from the nematode Onchocera volvulus is useful to treat circulatory or vascular disease such as ischemia	NEW YORK BLOOD CENTER INC.,NEW YORK,NY,US | CASE WESTERN RESERVE UNIVERSITY,CLEVELAND,OH,US | THE UAB RESEARCH FOUNDATION,BIRMINGHAM,AL,US
DE69737691T2	Vaccine for controlling infection by helminth parasites containing new peroxiredoxin or beta-tubulin, particularly used to combat liver fluke	Dalton John Pius Blackrock Dublin IE
US6673345B2	Novel isolated protein useful for identify a compound capable of inhibiting astacin metalloproteinase activity of a parasite	Heska Corporation,Fort Collins,CO

US20050208063A1	Thiol proteases with Cathepsin L-type activity useful in vaccine formulations against helminth parasites	John P. Dalton,Dublin,IE
US6489448B1	Nucleic acid encoding thiol-specific antioxidant protein of helminth larvae useful for treatment or prevention of helminth infection, specifically heartworm	Heska Corporation,Ft. Collins,CO
US6455039B2	Isolated parasitic helminth macrophage migratory inhibitory factor and related nucleic acid, useful for protecting animals from heartworm or onchocerciasis.	Heska Corporation,Ft. Collins,CO
US6414115B1	New isolated parasitic nematode transglutaminase genes used to develop products for the detection, prevention and treatment of infections by parasitic nematodes	Heska Corporation,Fort Collins,CO | Board of Regents The University of Texas System,Austin,TX
US6413521B1	A helminth parasite antigen with aminopeptidase like activity for use in vacuums to stimulate an immune response against helminth parasites pref. gastric nematodes of the gastro-intestinal tracts of mammals	The Barbraham Institute,Cambridge,GB
US6392017B1	A new parasitic helminth Antigen-2 protein, designated DiAg2, from Dirofilaria immitis reacts with sera from immune dogs and is useful to prevent and treat parasitic helminth infection, particularly heartworm in dogs	Heska Corporation,Fort Collins,CO
US6365569B1	New ankyrin proteins encoded by nucleic acids which hybridize to nucleic acids from Dirofilaria and Brugia are useful to immunize against platyhelminth parasites which cause disease such as heartworm, elephantitis and hydrocele	Heska Corporation,Fort Collins,CO

US6352836B1	New isolated thioredoxin peroxidase type-2 nucleic acid obtained from a Dirofilaria and Brugia, used to develop products for protection against parasite helminth disease such as heartworm disease	Heska Corporation and Colorado State University Research Foundation,Fort Collins,CO
BR199815440A	Homogeneous population of parasite cells for long term in vitro culture particularly derived from nematodes, suitable for use in vaccines, also related antibodies and anti-idiotypic antibodies for diagnosis of infestation and treatment	UNIV MISSISSIPPI
US5948644A	Excretory-secretory antigens from parasitic nematode(s) confer immunity to responsive hosts to parasitic nematode stages	Biotechnology Australia Pty Ltd.,Roseville,AU | Commonwealth Scientific & Industrial Research Org.,Campbell,AU
US5942413A	Vaccines comprise antigens derived from parasitic nematodes useful for passive immunisation against roundworm, whipworm, filarial worm, threadworm and hookworm.	Biotech Australia PTY Limited,Roseville,AU | Commonwealth Scientific and Industrial Research Organization,Campbell,AU
DK703789T3		ANDREWS STUART JOHN | DALTON JOHN PIUS
US5871738A	Antigens derived from parasitic nematodes used in vaccines against hookworm, roundworm, whipworm, filarialworm, or threadworm	Biotech Australia Pty. Limited,Roseville,AU | Commonwealth Scientific and Industrial Research Organization,Campbell,AU
CA1340301C	Protein derived from parasitic nematode species used to provide protective immunity against nematode parasites of man and domestic animals	COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANIZATION,CAMPBELL,AU | BIOTECHNOLOGY AUSTRALIA PTY. LTD.,AU
EP836481A4		HESKA CORP

US20030091591A1	Use of packaging defective alpha-virus expression vectors for prodn. of protective cpds. for protecting animals from disease, partic. toxoplasmosis	HESKA CORPORATION
US5753236A	New epitope contg. fragments of Schistosoma mansoni 28 kD protein prepd. by digestion with V8 protease, useful as vaccine components	Institut Pasteur de Lille,Lille,FR | Institut Pasteur,Paris Cedex,FR
JP03103592B2	Protein complex parasitic nematode useful as an immunogen and anthelmintic agent in vaccine	MUNN E A
DE4419264B4	Sm14 from Schistosoma mansoni binds fatty acids and confers up to 100 percent helminth infection protection; useful in vaccinations against helminth diseases.	Fundação Oswaldo Cruz (Fiocruz) Rio de Janeiro BR
CA2215529C	Vaccine which protects animal from Trichinella infection comprises beta-tyvelose-contg. compsn. or mimetope, which is beta-tyvelose or beta-tyvelose joined through glycosidic linkage to mono:saccharide to form oligosaccharide, and excipient	COLORADO STATE UNIVERSITY RESEARCH FOUNDATION,FORT COLINS,CO,US
US5618542A	Antigenic polypeptide(s) of Taenia ovis used in vaccines to protect ruminants against infection by cestode parasites and to develop identifying probes	Coopers Animal Health NZ Limited,Upper Hutt,NZ | University of Melbourne,Victoria,AU | Ministry of Agriculture & Fisheries,Wellington,NZ
DK173779B1	New protein contg. epitopes of P28 Schistomonas antigen corresp. DNA sequences and transformed cells and viruses, useful in vaccines and diagnosis	TRANSGENE SA
US5541078A	New immunogenic peptide sequence from Echinococcus granulosus for in vitro diagnosis of hydatidosis by ELISA and radioimmunological methods, also as vaccine against	Institut Pasteur de Lille,Lille Cedex,FR | Institut National de la Sante et de la Recherche Medicale (Inserm),Paris Cedex,FR | Institut Pasteur,Paris Cedex,FR

	hydatidosis	
US5492695A	Vaccine for susceptible hosts against non-adapted parasites e.g. dirofilaria immitis esp. used to protect cats against heart-worm	Colorado State University Research Foundation,Fort Collins,CO,US
US5422263A	DNA encoding sequence homologous to trichinella spiralis sequence of 53 kilodalton excretory-secretory antigen used in diagnosis and as vaccine for trichinellosis	The United States of America as represented by the Secretary of Agriculture,Washington,DC,US
JP02759652B2	Membrane associated proteins from nematodes used in the prodn. of vaccines against haemonchosis, ostertagiasis and other nematode infections	BABURAHAMU INST
US5219566A	New cDNA encoding polypeptide of Schistosoma mansoni includes protein epitope(s) present on Schistosomula surface, used in vaccines against bilharziasis	The Johns Hopkins University,Baltimore,MD,US
US5021560A	Glyco:protein cpds. from mollusc haemo:cyanine and glycan epitope(s) with same antigenicity as shistosoma mansoni surface antigen, useful for making anti-bilharzia vaccines and protective sera	Institut Pasteur,Paris,FR | Institut Pasteur de Lille,Lille,FR | Institut National de la Sante et de la Recherche Medicale (INSERM),Paris,FR
US5021342A	DNA encoding onchocerca/volvulos volvulos antigen used to express recombinant antigen for vaccine against onchocerciasis or river blindness	University Hospitals of Cleveland,Cleveland,OH,US
USN7366844N	DNA encoding sequence homologous to trichinella spiralis sequence of 53 kilodalton excretory-secretory antigen used in diagnosis and as vaccine for trichinellosis	

US4795633A	Vaccine for swine Trichinosis comprising inert new:born larvae of Trichinella spiralis emulsified with an adjuvant	The United States of America as represented by the Secretary of Agriculture,Washington,DC,US
IE59292B1		BRITISH TECH GROUP
USN7068499N	Vaccine for swine Trichinosis comprising inert new:born larvae of Trichinella spiralis emulsified with an adjuvant	
US4656033A	Vaccine against Schistosoma mansoni contg. soluble antigen from larvae or adults, administered with BCG adjuvant	The United States of America as represented by the Department of Health and Human Services,Washington,DC,US
US4396600B1	Antigenic prepn. obtd. by saline extn. of schistosome worms useful in vaccines against schistosome infections	
US4314992A	Fascioliasis vaccine prodn. by gamma irradiation of meta:cercaria(e) obtd. by infecting Lymnaea natalensis snails with Fasciola gigantica miracidia	BITAKARAMIRE PETER K
US3676547A	Ascaris suum vaccine for pig immunization obtd from second and third stage larvae	Eli Lilly and Company,Indianapolis,IN,US
US3395218A	Anti-nematodal vaccines	ALLEN & HANBURYS LTD

US20130064853A1	New antigens from the fourth stage larvae of non-blood feeding parasitic nematodes, useful for raising an immune response and for treating, preventing or reducing symptoms of diseases such as Bovine ostertagiasis	Smith William David,Penicuik,GB | Newlands George Fredrick James,Penicuik,GB | Smith Stuart,Penicuik,GB | Halliday Aileen,Penicuik,GB
EP2531210A1	New isolated antigen useful in e.g. vaccine for protecting a mammal against Strongyloides stercoralis infection, comprising Strongyloides stercoralis immunoreactive antigen protein	The United States Of America As Represented By The Office of Technology Transfer National Institutes Of Health,Bethesda, Maryland 20892-7660,US,101263691 | Thomas Jefferson University,Philadelphia, PA 19107,US,101093759
US20120128721A1	Large scale production of a full length Schistosomal paramyosin coiled coil dimmer composition comprises contacting a composition comprising recombinant paramyosin with a strand separation agent	
JP2012519496A	Recombinant Bacillus Calmette-Guerin auxotrophic Pasteur strain used for controlling human infections caused by parasites e.g Schistosoma mansoni, and for controlling tumors, is supplemented for amino acid leucine	
US20110200640A1	Multivalent anti-helminthic vaccine comprises recombinant hookworm antigens and recombinant schistosome antigens, useful for vaccinating an individual against hookworm infection and schistosomiasis	
US20110158998A1	Novel isolated protein comprising immunogenic, extracellular fragment of schistosome tegument protein tetraspanin-1 TSP-1, TSP-2 or 7TM, useful for preparing immunotherapeutic composition for immunizing against schistosomiasis	THE COUNCIL OF THE QUEENSLAND INSTITUTE OF MEDICAL RESEARCH,Queensland,AU
EP2264057A4		UNIV GRANADA

EP2485725A2	Composition, useful e.g. for the prevention or control of parasitic infection (Helminthiasis and Fasciola species) in warm-blooded animal e.g. sheep, comprises oil adjuvant, macrocyclic lactone e.g. milbemycin, and immunogenic polypeptide	PAH W LLC,New York NY 10017-5755,US,101347569
CN102596226A	Vaccine composition useful for preventing schistosomiasis comprises a full length cDNA of the large subunit of Schistosoma mansoni calpain cloned into a vector	UNIV TEXAS TECH SYSTEM,US
US20100255037A1	New isolated Haemonchus contortus polynucleotide and polypeptide, useful for manufacturing immunogenic composition for preventing or treating H. contortus infection in an animal, and for identifying analogous proteins from other helminths	
US20030176382A1	New vaccine composition for the treatment of hookworm infection comprises aspartyl proteinase from Necator americanus	
US20030129204A1	Protective helminth parasite antigen used in vaccine directed against parasitic nematodes of mammalian gastro-intestinal tract e.g. Haemonchus contortus	Moredun Scientific Limited,GB
EP992582A3		University of Wales Bangor,Bangor, Gwynedd LL57 2DG,GB,02522642
AU2003294191B2	New polypeptide produced in a genetically modified microorganism containing the amino-acid sequence of the liver fluke cysteine protease fused to the sequence of hepatitis B virus core protein, for use as a vaccine against liver fluke	INST PARAZYTOLOGII PAN | INST BIOTECHNOLOGII ANTYBIOTYKOW

AU2003295293B2	New chimeric protein containing cysteine protease of the liver fluke fused to hepatitis B core protein or ubiquitin, useful in treating liver fluke infection and in inducing immunicity	INST OF BIOORG CHEMISTRY | INST OF PARASITOLOGY POLISH AC | INST OF BIOTECHNOLOGY ANTIBIOT
RU2145876C1	Use of anti-helminth vaccines to control disease associated with loss of natural immunity esp. for control of periparturient rise of Haemonchus in sheep and of type II ostertagiasis	MALLINKRODT VETERINARI INK
EP2328610A2	Immunogenic formulation useful for protecting and/or treating an animal against a parasitic nematode, and for vaccinating a susceptible animal against infection from the parasitic nematode	Moredun Research Institute,Bush Loan, Penicuik EH16 0PZ,GB,101167975
CN101563103A	Identifying anthelmintic agents comprises contacting an agent with a helminth protein having dipeptidyl peptidase IV activity and resulting in an increase in blood clotting time	MOREDUN RES INST,GB
JP2000500474A	Isolated nematode antigens useful for diagnosis, prevention and therapy of nematode infections prepared by culturing L4-stage nematode larvae in vitro in which antigens immunoreact with protective antiserum raised against L3 to L4 stage	
EP707597A4		MALLINCKRODT VETERINARY LTD | UNIV MELBOURNE | PASTORAL AGRIC RES INST NZ LTD
EP694043A4		MALLINCKRODT VETERINARY LTD | UNIV MELBOURNE | PASTORAL AGRIC RES INST NZ LTD

EP772679A1	New Schistosoma, partic. S. haematobium proteins for use as pharmaceuticals, partic. as vaccines, blood processing agents and as anticoagulants	IMPERIAL COLLEGE OF SCIENCE TECHNOLOGY & MEDICINE,London SW7 2BB,GB,00633556
BR199404004A	Isolated polypeptide from Fasciola species useful as vaccines against e.g. spread of infection of liver fluke	DARATECH PTY LTD
JP8503935A	Monoclonal antibodies specific for nematode beta-tubulin and vaccines contg. a nematode antigen used to immunise against parasitic infection, pref. filariasis.	
EP554064A1	Vaccine against schistosomiasis comprising recombinant Schistosoma mansoni integral membrane protein or its derivs.	YEDA RESEARCH AND DEVELOPMENT CO. LTD.,Rehovot 76100,IL,00268945
AU638728B2	Vaccine composition for gastro-intestinal nematode infections comprises antigenic component of e.g. Ostertagia circumcinta extract	DARATECH PTY LTD
EP434909A3	Protein from Haemonchus contortus and other nematodes used as therapeutic and prophylactic agent to protect plants, animals or humans from parasitic nematode infection	SYNERGEN INC
AU634754B2	Vaccine against liver fluke infection in ruminants. esp. sheep comprises glutathione-S-transferase extracted from adult fasciola hepatica worms	DARATECH PTY LTD
AU198826483A	Monoclonal antibody binds to 68 KD antigen of schistosoma mansoni to give immunity	UNIV CLEVELAND HOSPITALS

PT84788B		INST NAT SANTE RECH MED | PASTEUR INSTITUT
NZ214215A		BIOTECH AUSTRALIA PTY LTD
AU198426739A	Helminth parasitosis e.g bilharziasis vaccine-medicament is derived from e.g. ecdysterone, pref. coupled with a macromolecule esp. protein(s) e.g. serum albumin	IMMUNOTECH SA
KR2012110430A	New protein useful for diagnosing and treating liver fluke infection, comprises specific amino acid sequences	CHUNG-ANG UNIVERSITY INDUSTRY-ACADEMY COOPERATION FOUNDATION
WO2012145355A1	Composition useful for e.g. producing immune response in subject and immunizing subject against Schistosoma infection, comprises slurry matrix, and antigens	UNIVERSITY OF GEORGIA RESEARCH FOUNDATION INC.,US | HARN Donald A.,US | QUEIROZ Rafaella,US | MCEWEN Lisa,US
WO2012104837A1	Composition useful as antinematodal composition for treating nematode e.g. Trichuris muris infection in subject e.g. human and animal, comprises non-insect cell or viral particle expressing exogenous nematode fusogenic protein	TECHNION RESEARCH AND DEVELOPMENT FOUNDATION LTD.,IL | UNIVERSITY OF VIRGINIA PATENT FOUNDATION,US | PODBILEWICZ Benjamin,IL | AVINOAM Ori,IL | WHITE Judith M.,US
WO2012067866A3	New multivalent vaccine comprising isolated antigens from filarial nematodes, useful for preventing or controlling filariasis in humans and animals	THE BOARD OF TRUSTEES OF THE UNIVERSITY OF ILLINOIS,US | KALYANASUNDARAM Ramaswamy,US
BRPI1005855A2		FUNDACAO OSWALDO CRUZ | ALVOS CONSULTORIA DESENVOLVIMENTO E COM IZACAO DE PRODUTOS BIOTECNOLOGICOS S A

AR76555A1		VERENIGING VOOR CHRISTELIJK HOGER ONDERWIJS | STICHTING TECH WETENSCHAPP
FR2898276B1		CENTRE NAT RECH SCIENT | UNIV CLAUDE BERNARD LYON | ECOLE NATIONALE VETERINAIRE | CAMBRIDGE ENTERPRISEA | UNIV DE LA REPUBLICA | ISNTITUT AGRONOMIQUE ET VETERI
BR200413944A	New isolated nucleic acid molecule encoding a Schistosoma mansoni protein, useful for as a vaccine or for preventing, diagnosing, or treating Schistosoma mansoni infection	FUNDACAO DE AMPARO A PESQUISA
CO5210982A1		NOVARTIS AG | AGRICULTURE VICTORIA SERV PTY
AU199720786A	Vaccine for schistosomiasis comprising a non-integrating DNA sequence encoding Schistosoma mansoni glutathione S-transferase	UNIV SOUTH ALABAMA
AU199655380A	New vaccines for filarial parasite infection(s) comprising C-terminal beta-tubulin amino acid sequence from a parasite	UPJOHN CO | UNIV MCGILL
AU199535747A	Vaccines against helminth parasites contain haemo-protein derived from e.g. flukes such as Fasciola hepatica for treating cattle	MALLINCKRODT VETERINARY INC
ZA199408729A	Protective helminth parasite antigen is used in the stimulation of an immune response against helminth parasites in mammals	BIOTECH & BIOLOG SCIEN RES

FR2656626B1		PASTEUR INSTITUT
WO1990002563A1	Vaccine against Schistosoma mansoni comprising antigens present in surface membrane of adult worm	MEDICAL RESEARCH COUNCIL | SIMPSON Andrew John George | SMITHERS Sidney Ronald
AU198778719A	New recombinant DNA coding for helminth parasite antigen and derived polypeptide(s), useful for making vaccines and diagnostic antibodies	UNIV AUSTRALIAN
DE2936061C2	Vaccine for birds consists of avian blood contg. immune factors against viruses, bacteria, protozoa, nematodes, trematodes and/or fungi	Schmidt Werner Dr.,DE | Wessjohann Berthold,DE
FR2573983B1		LEW KENNETH
GB1580539A	Orally administrable antiparasitic vaccine for immuno-prophylaxis of trichostrongylosis, strongylosis etc. opt. administered with adjuvants such as tetramisole and levamisole	INST NAT SANTE RECH MED
DE1160139A1	Non-living vaccines contng. antigens stimulating production in the host of antibodies and which give protection when injected against diseases caused by nematod	
CH370526A		UNIV GLASGOW

FR2689906B1		INST NAT SANTE RECH MED | PASTEUR INSTITUT
FR2688008B1		INST NAT SANTE RECH MED | PASTEUR INSTITUT
JP02672712B2		
JP1457233C		
JP05055522B2	Novel EMY162 polypeptide specifically inducing antibodies specific to Echinococcus multilocularis, useful as vaccine against Echinococcus multilocularis infectious disease, or as marker for diagnosing Echinococcus infection	UNIV HOKKAIDO,JP | HOKKAIDO PREFECTURE,JP
JP03692396B2	New DNA encoding a 14 kDa antigen of Ascaris suum infective larvae, for producing the antigen protein which is used in a systemic and mucosa-inductive type vaccine	DOKURITSU GYOSEI HOJIN NOGYO SEIBUTSU SH
JP03613577B2	Novel DNA having biological activity of 16kDa antigen protein of the pig roundworm, useful as vaccine for pig roundworm infection	DOKURITSU GYOSEI HOJIN NOGYO SEIBUTSU SH
CN102558306A	New epitope comprising specified amino acid sequence, useful for preventing and/or treating nematode disease, such as Trichinella disease or infection	Capital University of Medical Sciences,CN

CN102392031A	New Schistosoma japonicum gene which is thioredoxin glutathione reductase gene having specific amino acid sequence, used in vaccine for preventing or treating bilharziasis	Shanghai Veterinary Research Institute CAAS,CN
CN102337265A	New Taenia solium microsomal RNA (microRNA), useful for preparing Taenia solium vaccine or composition for restraining growth and development of Taenia solium	Institute for Parasitic Disease Chinese Center for Disease Control and Preventi,CN
CN102329798A	New Taenia saginata microRNA, useful for preparing T. saginata vaccine or composition for inhibiting growth and development of T. saginata	Institute for Parasitic Disease Chinese Center for Disease Control and Preventi,CN
CN102329385A	New Schistosoma japonicum anti-apoptosis protein, useful for preparing medicine for preventing and treating Japanese schistosomiasis	Shanghai Veterinary Research Institute CAAS,CN
CN102277373A	Salmonella expression vector secreting attenuated Schistosoma japonicum vaccine useful for preparing Schistosoma japonicum vaccine, comprises bacterial promoter regulating Salmonella secretion effector protein and secretion signal	NANJING UNIVERSITY,CN
CN102168100A	New Echinococcus granulosus glutathione transferase gene, useful for preparing a vaccine for cystic echinococcosis	Institute for Parasitic Disease Chinese Center for Disease Control and Preventi,CN
CN102168089A	New calcium reticulated protein gene of Echinococcus granulosus, useful for preparing vaccine for immunization against Echinococcus granulosus disease, and for preparing diagnostic reagent for diagnosing cystic echinococcosis	Institute for Parasitic Disease Chinese Center for Disease Control and Preventi,CN

CN102167735A	New recombinant antigen protein of Schistosoma japonicum SjTollip useful in preparing vaccine for preventing and treating Schistosoma japonicum	Huazhong Normal University,CN | Institute for Parasitic Disease Chinese Center for Disease Control and Preventi,CN
CN102040658B	New Schistosoma japonicum polypeptide with immunogenicity is useful for preparing vaccine for preventing schistosomiasis or drug for treating schistosomiasis, and for preparing product for diagnosing the schistosomiasis	Shanghai Veterinary Research Institute CAAS,CN
CN102079783A	New Schistosoma japonicum protein, useful for preparing vaccine for preventing or treating schistosomiasis and preparing a product for diagnosing schistosomiasis	Shanghai Veterinary Research Institute CAAS,CN
CN102070710A	New Clonorchis sinensis specificity GRA2a antigenic protein, useful for preparing a medicament for treating, diagnosing or preventing infection caused by C. sinensis	Institute for Parasitic Disease Chinese Center for Disease Control and Preventi,CN
CN102010863A	New microRNA of Ascaris suum having difference in sex expression useful for preparing Ascaris suum vaccine or Ascaris lumbricoides vaccine	South China Agricultural University,CN
CN101985468A	New SJ16 recombinant protein, useful for preparing a bilharziasis diagnostic reagent, a bilharziasis vaccine and a medicine for treating bilharziasis, and as an immunosuppressive agent	SUN YAT-SEN UNIVERSITY,CN
CN101948836A	New Schistosoma japonicum zinc finger protein coding gene useful for preparing genetically engineered vaccine for preventing Schistosoma japonicum infection	Shanghai Veterinary Research Institute CAAS,CN
CN101935659A	New microRNA isolated from female adult Ascaris suum useful for preparing ascarid vaccine, preferably Ascaris suum vaccine or human ascarid vaccine	South China Agricultural University,CN

CN101935658A	New microRNA specifically expressed in Ascaris suum male adult, used for preparing ascarid vaccine for affecting human ascarid physiological function or sexual development and differential function for preventing ascariasis	South China Agricultural University,CN
CN101921787A	New adenosine deaminase gene isolated from Schistosoma japonicum, useful for useful for preparing medicine and schistosome-resisting antibody, screening drugs, and in serology diagnosis process and gene therapy	Shanghai Human Gene Team Research Centre,CN
CN101921783A	New Schistosoma japonicum L-lactic dehydrogenase gene useful in serodiagnosis, screening medicines and in preparing Schistosoma antibody	Shanghai Human Gene Team Research Centre,CN
CN101921768A	New 14-3-3 protein gene useful for preparing medicine and schistosome-resisting antibody, screening drugs, and in serology diagnosis process and gene therapy	Shanghai Human Gene Team Research Centre,CN
CN101921767A	New Schistosoma japonicum MF3 gene useful for preparing schistosome vaccine and schistosome-resisting antibody, screening drugs, and in serology diagnosis process and gene therapy process	Shanghai Human Gene Team Research Centre,CN
CN101838639A	New Schistosoma japonicum proteasome alpha 5 subunit (SjPSM A5) recombinant antigen, useful for preparing preventative vaccines for schistosomiasis japonica	Shanghai Veterinary Research Institute CAAS,CN
CN101748139A	New Schistosoma japonicum enolase gene, useful for gene therapy, and for preparing Schistosoma vaccine, selecting medicines, preparing Schistosoma antibody, and serological diagnosis	Shanghai Human Gene Team Research Centre,Shanghai 201203,CN

CN101748138A	New Schistosoma japonicum superoxide dismutase gene, useful for gene therapy, and for preparing Schistosoma vaccine, for selecting medicines, for preparing Schistosoma antibody, and for serological diagnosis	Shanghai Human Gene Team Research Centre,Shanghai 201203,CN
CN101748128A	New Schistosoma japonicum titin gene, useful for gene therapy and for preparing schistosome vaccine, selecting drugs, preparing anti-schistosome antibody, and serodiagnosis	Shanghai Human Gene Team Research Centre,Shanghai 201203,CN
CN101748127A	New Schistosoma japonicum actin gene, useful for gene therapy and for preparing schistosome vaccine, selecting drugs, preparing anti-schistosome antibody, and serodiagnosis	Shanghai Human Gene Team Research Centre,Shanghai 201203,CN
CN101747422A	New fatty acid binding protein of Schistosoma japonicum, useful for preparing schistosoma vaccine and anti-schistosoma antibody, for selecting a medicament, and in serodiagnosis and gene therapy	Shanghai Human Gene Team Research Centre,Shanghai 201203,CN
CN101690806A	New dendrimer-DNA vaccine, useful for preventing infection caused by Schistosomiasis japonica	Southeast University,Wuxi, Jiangsu 214064,CN | Jiangsu Institute for Bilharziasis Prevention and Control
CN101671690B	New recombinant expression carrier comprises Schistosoma japonicum gene, useful for preparing vaccine for preventing or treating schistosomiasis and for diagnosing schistosomiasis	Shanghai Veterinary Research Institute CAAS,CN
CN101671689A	New recombinant expression carrier with Schistosoma japonicum gene, useful for preparing vaccine for preventing or treating schistosomiasis, and for preparing product for diagnosing schistosomiasis	Shanghai Veterinary Research Institute CAAS,Shanghai 200241,CN

CN101624422B	New recombinant poly-epitope antigen of Japanese schistosome, useful for preparing immunoprophylaxis vaccine of schistosomiasis japonica	Shanghai Veterinary Research Institute CAAS,CN
CN101555483B	New polynucleotide encoding Echinococcus granulosus fatty acid binding protein (EgFABP)-Eg95 polypeptide, useful for treating echinococcosis	SUN YAT-SEN UNIVERSITY,CN | Institute for Parasitic Disease Chinese Center for Disease Control and Preventi,CN
CN101524547A	DNA vaccine useful for preventing and/or treating Cysticercus cellulosae infection, comprises eukaryotic expression vector and Cysticercus cellulosae antigen, e.g. Cysticercus cellulosae annexin gene	PLA Second Military Medical University,Shanghai 200433,CN
CN101434962B	Eastern schistosomiasis tyrosine kinase conserved gene useful in preparing recombinant protein vaccine and DNA vaccine for preventing and controlling schistosomiasis	Institute for Parasitic Disease Chinese Center for Disease Control and Preventi,CN
CN101475938A	New echinococcosis egG1Y162 antigen gene obtained from Echinococcus granulosus, useful for preparing vaccine or diagnostic reagent for preventing and treating human or livestock echinococcosis	Xinjiang Medical Univ.,Urumqi, Xinjiang 830054,CN
CN101444622A	New Japanese blood fluke gene recombinant live vaccine comprises a protective antigen gene of Japanese blood fluke and porcine pseudorabies virus, useful for inducing immune protection against Japanese blood fluke	Military Veterinary Institute of Academy of Military Medical Sciences of Chinese People's Liberation Army,Changchun, Jilin 130062,CN
CN101397558A	Producing Schistosoma japonicum integral membrane tetraspanin 2 (TSP2) fusion protein useful in preparing vaccine for schistosomiasis, by cloning and expressing Schistosoma japonicum TSP2 gene in Escherichia coli	Chinese Academy of Agricultural Sciences Shanghai Institute of Veterinary,Shanghai 200232,CN

CN101270361B	New extracellular cycle 2 gene encoding thrombospondins (TSPs) protein, useful for preparing a vaccine against Schistosoma japonicum	SICHUAN UNIVERSITY,CN
CN101050235A	New Japanese schistosomiasis natural molecular vaccine candidate antigen comprises immature insect egg soluble antigen 66-68kDa molecule of Japanese blood fluke, used for reducing propagation of blood fluke egg	WANG Shi-ping,Changsha, Hunan 410078,CN
CN100553683C	Peptide-DNA bi-vaccine for anti-inflection of schistosoma japonicum based on T-cell epitope	UNIV NANJING MEDICAL
CN1986797A	Schistosoma japonicum tegument antigen gene, its encoding protein and its application	Parasite Prevention Control Office China Disease Prevention Control Center | Shanghai Human Gene Group Research Center,Shanghai 201203,CN
CN100394984C	Bivalent DNA vaccine for Japanese blood fluke and preparation process thereof	Huazhong University of Science and Technology
CN100497627C	Cloning of Japanese blood fluke vaccine antigen gene and its expression and application	TIONAL INST PARASITIC DISEASES CHINESE CENT D | SHANGHAI HUMAN GENOME RES CENT
CN1904053B	Fusion gene of Japan schistosome antigen gene and constituted DNA vaccin and preparing process	Huazhong University of Science & Technology,CN
CN100528240C	Preparation method and medicinal uses of Trichinella eelworm vaccine	ZHANG X

CN100398155C	DNA vaccine for preventing Haemonchus contortus disease of ruminant	Nanjing Agricultural University
CN100393357C	Young schistosomiasis cell style vaccine for preventing from schistosomiasis disease	UNIV CENT SOUTH,CN
CN100335636C	Thioredoxin gene of Schistosoma japonicum (Chinese Mainland Strain), useful in preparation of DNA vaccine for preventing and treating Schistosomiasis japonica	China Disease Prevent and Cure Control Center Verminosis Prevent and Cure Control Office
CN1749395A	Cloning and expression of Japanese blood flukes SJCXSWL gene and DNA vaccine	LU ZHIYUE
CN1749394A	Cloning and expression of HGPRT gene of Japanese blood fluke for preparation of DNA vaccine	WANG SHIPING
CN100374559C	New protease subunit C3 of Clonorchis sinensis, and genes encoding it, for use in a diagnosis reagent kit, and for use in a vaccine	UNIV ZHONGSHAN,CN
CN100360665C	New type I aldehyde dehydrogenase of clonorchis sinensis, for use in a diagnosis reagent kit and for use in a vaccine	UNIV SUN YET-SEN,CN
CN1670206A	New protease subunit C7-I of Clonorchis sinensis for use in a diagnosis reagent kit, vaccine and pharmaceutical composition	UNIV SUN YAT SEN

CN1670202A	New microsome glutathione S-transferase-1 of Clonorchis sinensis for use in a diagnosis reagent kit, vaccine and pharmaceutical composition	UNIV SUN YAT SEN
CN1670201A	New fumaric reductase Ip subunit of liver fluke and polynucleotide encoding it, for use in a diagnosis reagent kit, and for use in a vaccine	UNIV SUN YAT SEN
CN1670200A	New lactate dehydrogenase of clonorchis sinensis for use in a diagnosis reagent kit, vaccine and pharmaceutical composition	UNIV SUN YAT SEN
CN1670198A	New thermostable type cytoplasm malic dehydrogenase of clonorchis sinensis for use in a diagnosis kit, and vaccine	UNIV SUN YAT SEN
CN1670197A	New arginase of Japanese blood fluke, for use in a diagnosis reagent, vaccine and in a pharmaceutical composition	UNIV SUN YAT SEN
CN100389831C	Gene engineering vaccine used for preventing pig cysticercosis and its preparation method	China PLA Logistic PLA Nanjing Military Medicine Institute
CN1272435C	Gene of Chinese Mainland SJPP gene stock of japanese blood fluke, clone, expression and application	Of Animal XUE Experiment | Shanghai Animal Biological Technology Research Centre | China Academy of Science Shanghai Livestock Verminosis Research Institute
CN1511588A	Japanese nucleic acid vaccine for blood fluke, comprises a eukaryotic expression vector and blood fluke antigen genes	TONGJI MEDICAL COLLEGE CENTRAL

CN1249232C	Schistosomiasis japonica (Chinese Continental strain) MFS4 gene clone, expression amd DNA vacine	Shanghai Animal Biological Technology Research Centre,CN | Of Animal XUE Experiment,CN | China Academy of Science Shanghai Livestock Verminosis Research Institute,CN
CN1100788C	Peptide for vaccine of schistosomiasis	UNIV BEIJING,CN
CN1100787C	Peptide for vaccine of schistosomiasis	UNIV BEIJING,CN
CN1100881C	Nucleic acid vaccine for cysticercosis co-contracted by human and pig	Second Military Medical University of PLA
CN1052011C		Beijing Medical University,CN
CN1061991C	Schistosome vaccine peptide No.3	UNIV BEIJING MEDICAL,CN
CN1068334C	Schistosome vaccine peptide No.2	UNIV BEIJING MEDICAL,CN
CN1061990C	Schistosome vaccine peptide No.1	UNIV BEIJING MEDICAL,CN

CN1020797C		Beijing Solar Energy Institute
IN201110079P1	Vaccine composition useful for preventing schistosomiasis comprises a full length cDNA of the large subunit of Schistosoma mansoni calpain cloned into a vector	
ZA201102008A	Immunogenic formulation useful for protecting and/or treating an animal against a parasitic nematode, and for vaccinating a susceptible animal against infection from the parasitic nematode	
IN248555B	New compositions comprising recombinant or synthetic antigens derived from hookworm, useful as a vaccine against hookworm infection, or for reducing hookworm size or reducing hookworm burden in a patient infected with hookworm	
IN201101367I4	Peptide immunogens of lymphatic filarial abundant larval transcript and lymphatic filarial vaccine composition comprising same	
IN201101366I4	Dominant T epitope of filarial transglutaminase and chimeric peptide vaccines for lymphatic filariasis	
IN241402B	Constructing peptides based on three-dimensional structure of homologs, useful as vaccines for protecting against helminth infections and for diagnosis	
IN200806261P4	New membrane protein Sm29, useful as vaccines for generating a protective immunity against infections caused by helminths, including Schistosoma and Fasciola, and for treating allergic diseases	

IN200705429P4	Constructing peptides based on three-dimensional structure of homologs, useful as vaccines for protecting against helminth infections and for diagnosis	
IN200402472P4	Constructing peptides based on three-dimensional structure of homologs, useful as vaccines for protecting against helminth infections and for diagnosis	
IN200401050P1	New compositions comprising recombinant or synthetic antigens derived from hookworm, useful as a vaccine against hookworm infection, or for reducing hookworm size or reducing hookworm burden in a patient infected with hookworm	
UY28972A1		CARMONA CARLOS
AU2002335061A8	New compositions comprising recombinant or synthetic antigens derived from hookworm, useful as a vaccine against hookworm infection, or for reducing hookworm size or reducing hookworm burden in a patient infected with hookworm	
IN200101455P4	Novel isolated cyst wall cysteine proteinase derived from Taenia solium useful as vaccine for treating cysticercosis or neurocysticercosis	
RU2205875C2	New Echinococcus granulosus poly:peptide antigen used to prepare vaccines for preventing infection by Echinococcus or Taeniid parasites	UT LTD | UNIV OF MEL BURN | N JU ZILAND PASTEHREHL EHGRIKA

AU2002334119A1	New vaccines comprising a 64p protein, useful against infectious diseases borne by blood-sucking ectoparasites, e.g. malaria, dengue fever, yellow fever, arboviral encephalitides, lymphatic filariasis, plague or Lyme disease	
AU731026B2	Thiol proteases with Cathepsin L-type activity useful in vaccine formulations against helminth parasites	JOHN P DALTON
AU200020764A	Novel vaccine comprising helminth larvae and antihelmintic for providing non-pathogenic productive immunity against parasites in ruminants	NEW ZEALAND MEAT RESEARCH & DE
MX199810276A	Vaccine for controlling infection by helminth parasites containing new peroxiredoxin or beta-tubulin, particularly used to combat liver fluke	
MX190278B	Use of anti-helminth vaccines to control disease associated with loss of natural immunity esp. for control of periparturient rise of Haemonchus in sheep and of type II ostertagiasis	
NZ264575A	Providing non-pathogenic immunity against parasites in ruminants by admin. of vaccine contg. helminth larvae followed by admin. of anthelmintic after 5-21 days	NEW ZEALAND MEAT RESEARCH & DE
RU2095082C1	Safe, effective anthelmintic vaccine contains conjugate of immuno-stimulating carrier and protective protein antigen	ATAULLAKHANOV RAVSHAN I | NEKRASOV ARKADIJ V | PUCHKOVA NATALYA G | PETROV REM V | KHAITOV RAKHIM M
ZA199402410A	Taenia ovis antigenic polypeptide used to develop vaccines to protect against infection by a cestode parasite, partic. in ruminants.	PITMAN MOORE NEW ZEALAND LIMIT | PASTORAL AGRIC RES INST NZ LTD | UNIV MELBOURNE

EG19342A		NAT RESEARCH CENTER
NZ245236A	Protein complex parasitic nematode useful as an immunogen and anthelmintic agent in vaccine	
CS274305B1		LUKES STEPAN
CS274304B1		LUKES STEPAN
CS273807B1		LUKES STEPAN
IL62142A	Vaccine against Schistosomiasis prepd. by sonicating Schistosomiasis parasites	YEDA RES & DEV
NL255469B	Non-living vaccines contng. antigens stimulating production in the host of antibodies and which give protection when injected against diseases caused by nematod	

Analysis

Categories of Analysis

Analysis is presented for the overall dataset (210 relevant families) as well as the four major relevant categories, Cestodes, Nematodes, Trematodes and nonspecific helminths. The subcategories under each of these major headings were pooled together and analyzed as a group in order to present a large enough dataset for generating meaningful results. In most instances the data within the four groups was pooled together and analyzed as a group in order to present a large enough dataset for generating meaningful results. Platform technologies were not analyzed.

ThemeScape Map of Derwent Data

A graphical representation of the results was generated using ThemeScape, a tool within the Aureka platform initially developed by Aurigin Systems, Inc., and now available through Innovation.[126] ThemeScape creates a virtual "map" of patent data by extracting keywords from the documents and plotting those topics in relation to one another. "Islands" are formed by closely related topics and "mountains" are formed when a large number of documents all contain the same or similar keywords. Gaps between distantly related topics represent an "ocean." ThemeScape is a powerful tool which can reveal relationships within a large dataset that are not otherwise apparent.

ThemeScape provides options for the sources of keywords within each document. The maps presented below were derived from the DWPI title, DWPI abstract, and claims in English from one representative of each INPADOC family. Extracting data only from representative documents prevents large patent families from skewing the results and gives equal weight to each invention. Not all references had this DWPI data in their records, so the maps represent a subset of the entire datasets.

The map in Figure 20 shows the topic found within the overall dataset of relevant documents. Many of the topics agree with the coding criteria. At the center left of the map is a series of mountains labeled with "Taenia Ovis, Serine Protease and Proenzyme" which represents the subunit vaccines category for the subgroup "Cestode". This isolated grouping concurs with the patent documents analyzed as taenia document tended to refer only to taenia and not other types of helminths.[127]

[126] http://www.intellogist.com/wiki/Report:Thomson_Innovation/Viewing_Results/Analyzing_Results/ThemeScape.
[127] See US5618542A

At the center top and extending to the top right of the map contains a series of islands containing mountains labeled “Helminth, Ostergitae, Heartworm Onchocerciasis and Proteins Multivalent Proteins. This chain of mountains represents two unique categories, the first being the coding category of veterinary vaccines under the category of nematodes. Additionally this chain of mountains also represents subunit vaccines in regard to both veterinary vaccine for nematodes and also for vaccines to nematodes in general.

The largest chain of islands extending from the center of the map to the bottom right represents both nematode vaccines as well as trematode vaccines as the labels “Nematode, Fasciola, Hookworm and Schistosoma” are present. This chain of islands is related to both DNA vaccine technology and subunit vaccine technology. These different types of technology also related to both trematodes and nematodes.

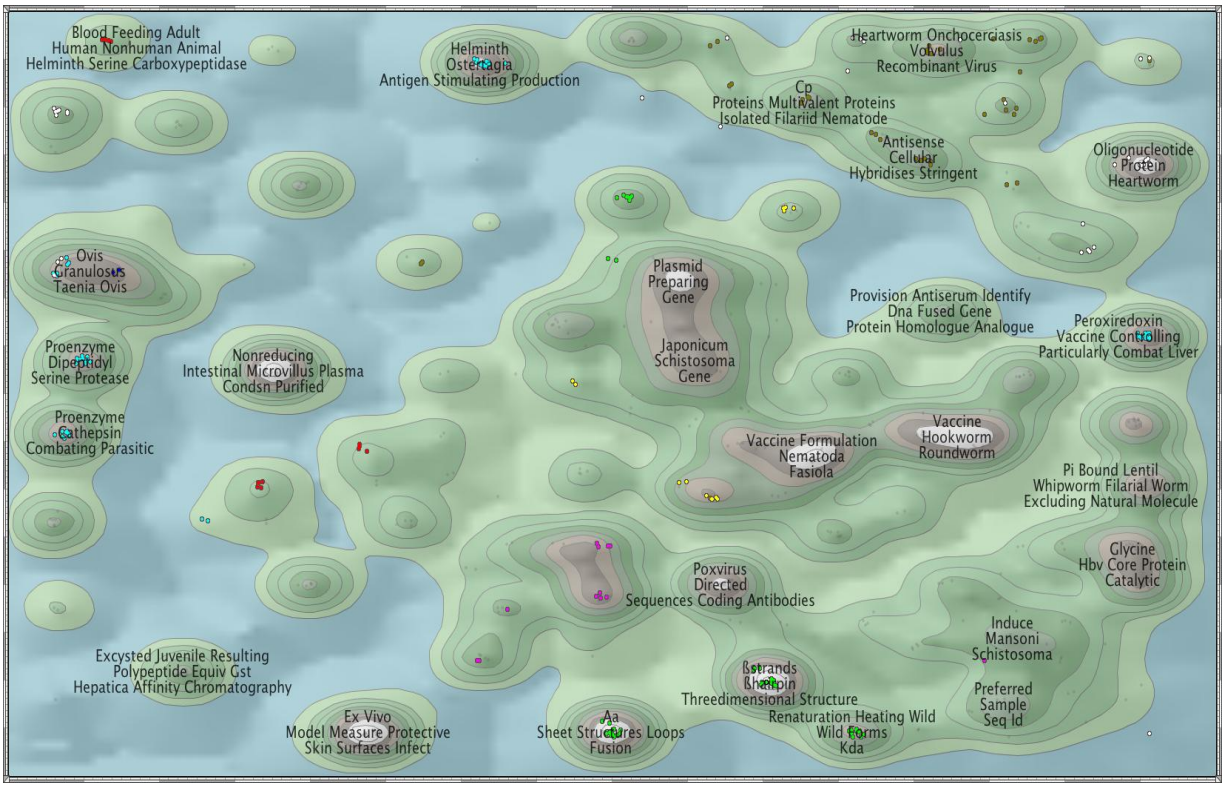

Figure 21. ThemeScape map of the representative documents from 752 helminth vaccine and related technology documents. These documents collapsed to 207 family members out of the 210 documents. The dots on the map are assignees according to the legend below.

Color	Assignee
	Moredun
	Pasteur
	Mallinckrodt and Merck
	Fundacao Oswaldo Cruz
	Colorado state
	Heska
	U Melbourne

The Themescape map also indicates the involvement of different assignee in the various fields of technology. The distribution and clustering of the assignees into distinct islands and distinct mountains suggests that these top seven assignees are generally working in separate technological fields.

In summary, the Themescape map illustrates the coding of the documents successfully placed the majority of the documents into correct subcategories as the labels on the peaks also correspond to the subcategories. These maps not only reveal the relationships between the different technologies in each group but they also validate the document coding protocol which is the basis for the further analytics presented below. Additionally, the map suggests that each of the top seven assignees provided are involved in distinct areas of helminth vaccine and vaccine related technology.

Priority Country v. Document Count

Important questions to ask in the analysis of patent data is "where does the technology come from?" and "where is the technology being used?" The first question can be answered by analyzing the priority country, which is the country in which the priority patent document is filed. Further data can be gleaned from the country in which the top assignees are based, which is presented below. The second question can be answered by analyzing the multi-jurisdictional filings, which also follows below.

Although information regarding the priority country is useful, it does not necessarily indicate the source of the technology. For example, publications HK1154041A0 and HK1156969A0 are assigned to Medicago, Inc., a Canadian company. However, Medicago[128] tends to file applications first in the U.S., and the priority documents for both of these references are U.S. applications. Also, IN200503876P1 is assigned to a group of French entities - CNRS, the Pasteur Institute, and the University of Paris - but the priority document is a Canadian application. Thus, some assignees file first in other jurisdictions, perhaps to take advantage of that country's patent laws or because the patent will be practiced primarily in that country. For example, Medicago has a manufacturing plant in the U.S., although its research facility is apparently in Canada.

Most documents have priority data recoded in the Innovation database, but a few do not. In the majority of cases, priority data can be found through patent family members. When possible, priority information was added to the data. Highlighted cells in the files presented in Appendices C and D indicate such manually corrected data.

[128] http://www.medicago.com/.

The priority country information for vaccine patent documents is presented in Figures 12 and 13. China is by far the largest source of priority documents. The United States and Great Britain are secondary sources, followed by Russia, Brazil, Australia and New Zealand.

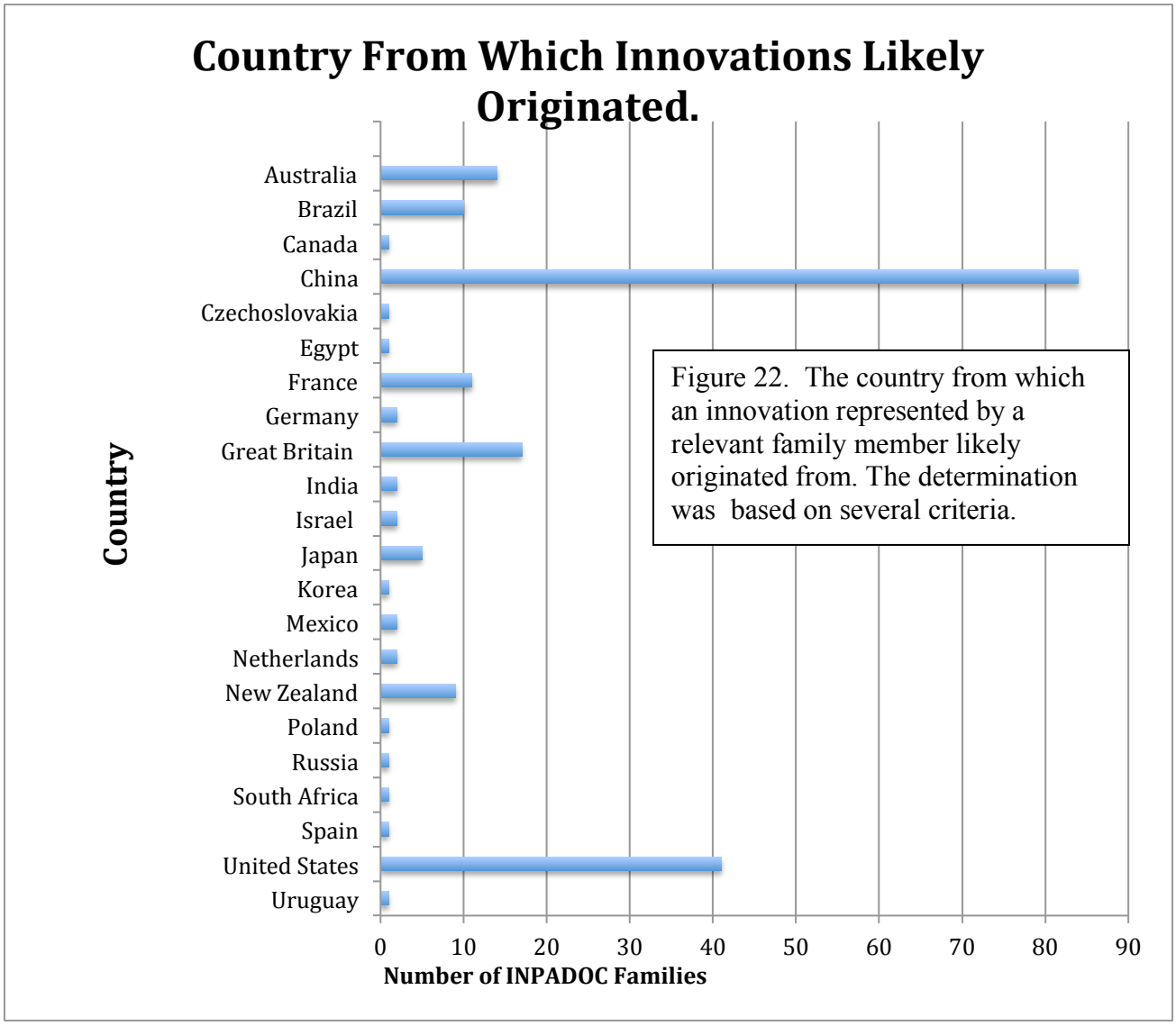

Figure 22. The country from which an innovation represented by a relevant family member likely originated from. The determination was based on several criteria.

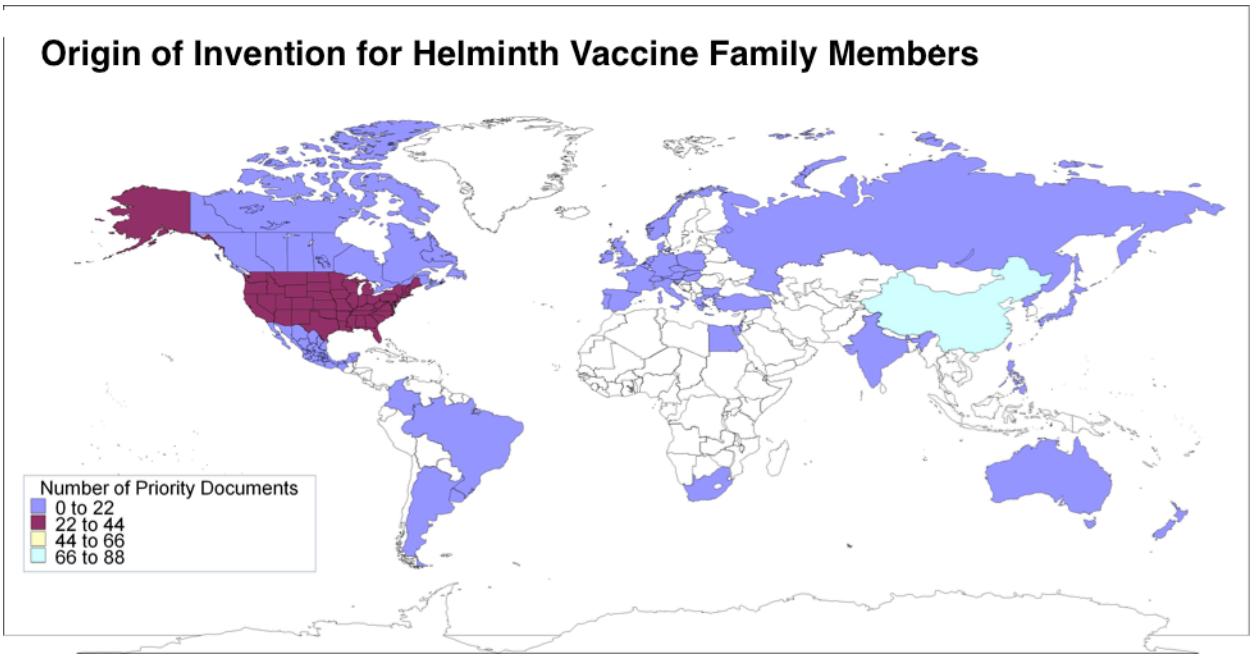

Figure 23. Counties from which an invention related to helminth vaccine technology originated. Countries shown in white have are not the origin of any Helminth vaccine technology amongst the 210 families. Multijurisdictional agencies, such as WIPO and the EPO, are not indicated.

Top Vaccine Families for Multi-Jurisdictional Filings

Vaccine technologies that have been transferred to the most other countries were calculated by first determining the size of each INPADOC family within the vaccine document dataset. This data may be slightly skewed because applications filed in certain jurisdictions are not recorded as being members of INPADOC families.[129] These jurisdictions include Hong Kong, India, Mexico, the Philippines, Portugal, Taiwan, and Viet Nam. For this reason, the TotalPatent Extended Family was also retrieved for each of the largest INPADOC families to try to capture family members from these jurisdictions. It is still possible these jurisdictions remain under-represented in the dataset. The extended family was not retrieved for all documents because the export functions of TotalPatent do not allow this data to be captured in a convenient manner. The number of jurisdictional filings was determined by combining the INPADOC, DWPI, and TotalPatent families for each representative document.

Twelve representative family members had INPADOC families with 10 or more members. The top family was represented by RU2145876C1, an older document whose family already contains 16 members. The INPADOC family represented by RU2145876C1 has also been filed in 32 different jurisdictions, which is the most of this group. Two families are assigned to Merck and two to Biotech Australia . No other assignee is represented multiple times. The top ten families

[129] See also Notes on Patent Families in Appendix M.

according to filings in different jurisdictions are shown in Table III, and the details of each family can be found in Appendix E.

Table III. Top Multi-Jurisdictional Filings per INPADOC Family.

Publication Number	**Assignee/Applicant**	Filing Jurisdictions	Total number of jurisdictions
US5942413A	Biotech Australia PTY Limited,Roseville,AU | Commonwealth Scientific and Industrial Research Organization,Campbell,AU	AT, AU, CA, DE, DK, EP, ES, GR, JP, NZ, US, WO	12
US5871738A	Biotech Australia Pty. Limited,Roseville,AU | Commonwealth Scientific and Industrial Research Organization,Campbell,AU	AT, AU, CA, DE, DK, EP, ES, GR, JP, NZ, US, WO,	12
US20050208063A1	John P. Dalton,Dublin,IE	AT, AU, CA, DE, DK, EP, ES, GB, JP, NZ, PT, US	12
DE69737691T2	Dalton John Pius Blackrock Dublin IE	AT, AU, BR, CA, CN, DE, EP, ES, GB, MX, NZ, US, WO	13
JP03103592B2	MUNN E A	AT, AU, CA, DE, DK, EP, ES, GB, HK, IN, JP, NZ, US, WO, ZA	15

BRPI9808251 B1		AT, AU, BR, CA, DE, EP, JP, NZ, TR, US, WO	11
RU2205875C2	UT LTD | N JU ZILAND PASTEHREHL EHGRIKA | UNIV OF MEL BURN	AT,AU,BG,CA,CZ,DE,EP,ES,GB,HU,JP, MX,NO,NZ,WO,ZA	16
DK173779B1	TRANSGENE SA	AT, AU, CA, CN, DE, DK, ES, EP, FR, JP, PH, US,	12
DK703789T3	DALTON JOHN PIUS | ANDREWS STUART JOHN	AT, AU, DE, DK, EP, ES, GB, GR, HU, JP, NZ, SI, US, WO ,ZA	15
MX190278B		AU, BR, DE, EP, ES, JP, MX, NO, NZ, RU, US, WO, ZA	13

Global Filing Trends for Helminth Vaccines

The previous section assessed filing trends for individual family trends. The relevant dataset was analyzed to determine the jurisdictions in which the entire vaccine population was filed. The INPADOC and DWPI patent families were combined for each reference document, and each jurisdiction was counted only once per family. For example, if a representative document had three European Patent Office applications, the EPO was counted once for that family. The TotalPatent families were not incorporated into this dataset, due to the difficulties with exporting such data. Thus, certain jurisdictions such as India, Taiwan and the Philippines may be under-represented.

Of over 230 possible different jurisdictions in which patent applications could potentially be filed, helminth vaccine families were filed in a total of 45 jurisdictions. As shown in Figure 14, North America and Europe are popular locations for assignees to seek protection for inventions directed towards parasitic worms. Of Asian countries, China, India, Japan, and Hong Kong were targets for filing. Australia and New Zealand also were targeted jurisdictions for filing.

However, Central and South America, other than Brazil, were poorly represented, and no filings were done in any African country other than South Africa. Countries are only shown in Figure 14 if at least one filing occurred in that country.

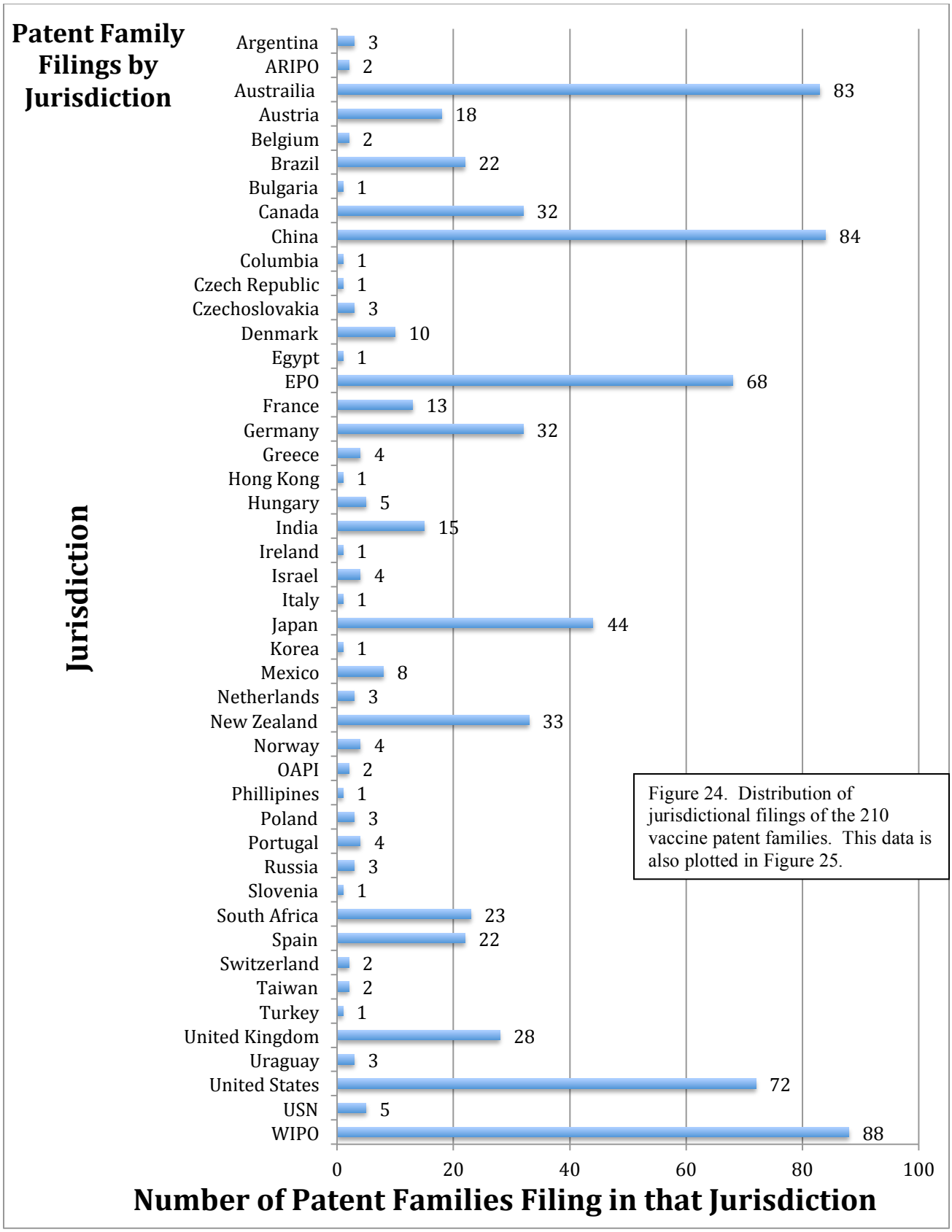

Figure 24. Distribution of jurisdictional filings of the 210 vaccine patent families. This data is also plotted in Figure 25.

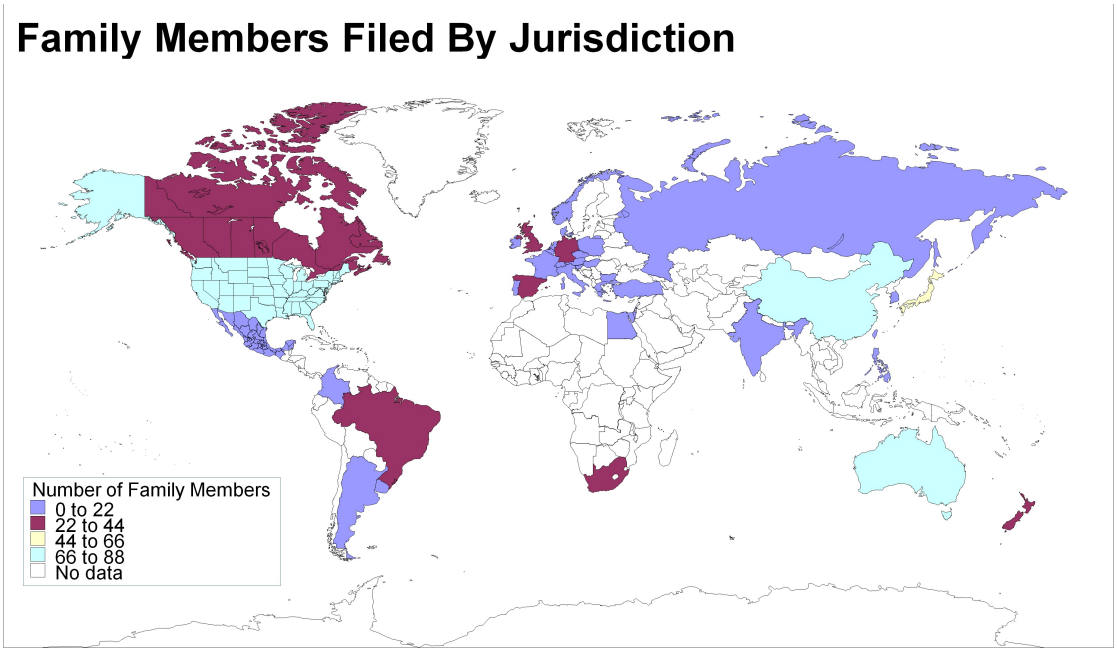

Figure 25. Global filing trends by country. The number of patent families that have sought protection in a given country are indicated by colors. Countries shown in white have no identified filings among the 210 family members. Multijurisdictional agencies, such as WIPO and the EPO, are not indicated.

The jurisdictions where each patent family chose to seek patent protect was also plotted on a world map (see Fig. 15, above). Each jurisdiction is indicated once per family. For example, if a given patent family filed three U.S. applications, the United States was counted once for that family. Greenland was considered part of Denmark for this analysis. Also, the former Yugoslavia was indicated under Serbia and Montenegro, the former Czechoslovakia under the Czech Republic, and the former Soviet Union under Russia. Multijurisdictional agencies were not plotted. Nearly 70% of patent families had filed PCT applications with WIPO, so excluding PCT filings probably did not skew the results, as each country was affected equally. Also, since the map only indicates countries where PCT applications entered the national phase, the map gives a more accurate portrayal of the jurisdictions in which assignees are most interested. However, exclusion of filings at the European Patent Office (EPO), probably does leave some European countries slightly underrepresented on the map. Other multijurisdictional agencies not

indicated on the map are the Eurasian Patent Office (EAPO)[130] which consists of countries belonging to the former Soviet Union and in which 20 patent families filed, the African Regional Intellectual Property Organization (ARIPO)[131] which currently represents 18 nations and in which seven patent families filed, and the Cooperation Council for the Arab States of the Gulf (GCC)[132] which represents six nations on the Arabian peninsula and in which two patent families filed.

The map demonstrates that the majority of patent families file in just a few countries. The top nations for filings, indicated in red, are Australia, Canada, China, Japan, the Republic of Korea (South Korea), and the United States. Secondary target nations, indicated in purple, are Brazil, Germany, India, Mexico, and New Zealand, followed by a group (in blue) that includes Austria, Norway, Russia, Spain, and South Africa. A final group (in green) includes the Philippines, Vietnam, and several European nations. No other nation had more than 20 patent family filings. Filings were particularly sparse in South America and Africa.

Top Assignees by Patent Document Count

Assignee data for patent documents is often inaccurate. The patent rights could be sold to another assignee, who does not record the assignee. Also, a company holding the rights changes its name or is sold *in toto* and new assignments are not recorded. Some companies do not record an assignment until a patent is allowed, so published applications that are later abandoned or rejected do not have assignment data. Outside of the U.S., university faculty members retain rights in their inventions so the name of the university is not given on the patent document. None of the patent databases maintain accurate updates for such changes or account for such missing data.

Correction of patent assignee information must be performed manually. While this represents a burden on clinic members' time, such information would is invaluable to the use of the clinic report. Accurate assignee information is essential in order for the report data to be updated, and so the correct owners of the technologies can be contacted for licensing inquiries.

The main protocol for correcting assignee names is to use Google, searching for the company website or new releases about the company. Business Week[133] is a great source of information, as are technology-specific business reporters such as Fierce Biotech[134]. These sources reveal the current accurate name of the company listed as the assignee or whether the company is now a wholly-owned subsidiary of a larger company.

[130] http://www.eapo.org/en/.
[131] http://www.aripo.org/.
[132] http://www.gcc-sg.org/eng/.
[133] http://www.businessweek.com/.
[134] http://www.fiercebiotech.com/.

If no information was readily obtainable, the assignee was searched using Innovation, restricting the date field to after the publishing date of the known document. The Derwent Assignee field may have another assignee commonly listed with the company being researched. A Google search of the two names together sometimes revealed a link between the two, such as a name change or an acquisition. The Derwent assignee code[135] is another source of assignee information. Other companies may be linked to the same code, such as ASTR being used for both AstraZeneca and its acquired company MedImmune.

If the only information available is the inventor name(s), then the document was located on Google Patent[136]. This website has hyperlinks to other patent documents by the same inventor which may have assignee data recorded. The name of the inventor was also searched on Google to find an association between the inventor and a particular company. To make the search more accurate, the search includes both the inventor's name and some keywords from the patent document. LinkedIn[137] and other networking websites are another source of information, and can be especially useful if an inventor is associated with multiple companies. Typically the date of the application can be associated with a date range for when the inventor was working for one company rather than another. Since patent applications can be filed months if not years after the date of the invention, this latter method was used with caution.

Using the above methodology, the assignee information for each relevant document in the vaccine and supporting technologies categories was manually corrected as accurately as possible. The results were then sorted on assignee names to reveal the number of patent families associated with each assignee. The two categories were analyzed together so a single list of assignees was generated, which is presented in Table IV.

Table IV. Assignees with the Most INPADOC Patent (210 Families).

Standardized Assignee	Number of families	Home Country
Heska	12	U.S.A.
Merck & Co.	9	U.S.A.
Institut Pasteur	7	France
AusBiotech	5	Australia
Biotechnology and Biological Sciences Research Council	5	U.K.

[135] http://ip-science.thomsonreuters.com/support/patents/dwpiref/reftools/companycodes/lookup/.
[136] www.google.com/patents.
[137] http://www.linkedin.com.

Publication Year v. Patent Document Count

Trends in publication of patent documents were analyzed for the entire dataset as well as for the three major categories, Cestodes Nematodes, and Trematodes. Non-distinguished patent documents were not charted due to the extremely low number of documents. Publication date was chosen as the parameter for analysis, which indicates publication of applications generally 18 months after filing and publication of patents after allowance. In the few cases in which the publication date was not recorded, the year of publication could usually be found in DWPI data such as the DWPI update information. Additionally, the earliest published family member of an INPADOC family was used in this analysis as it would correlate with filing date of each families priority document.

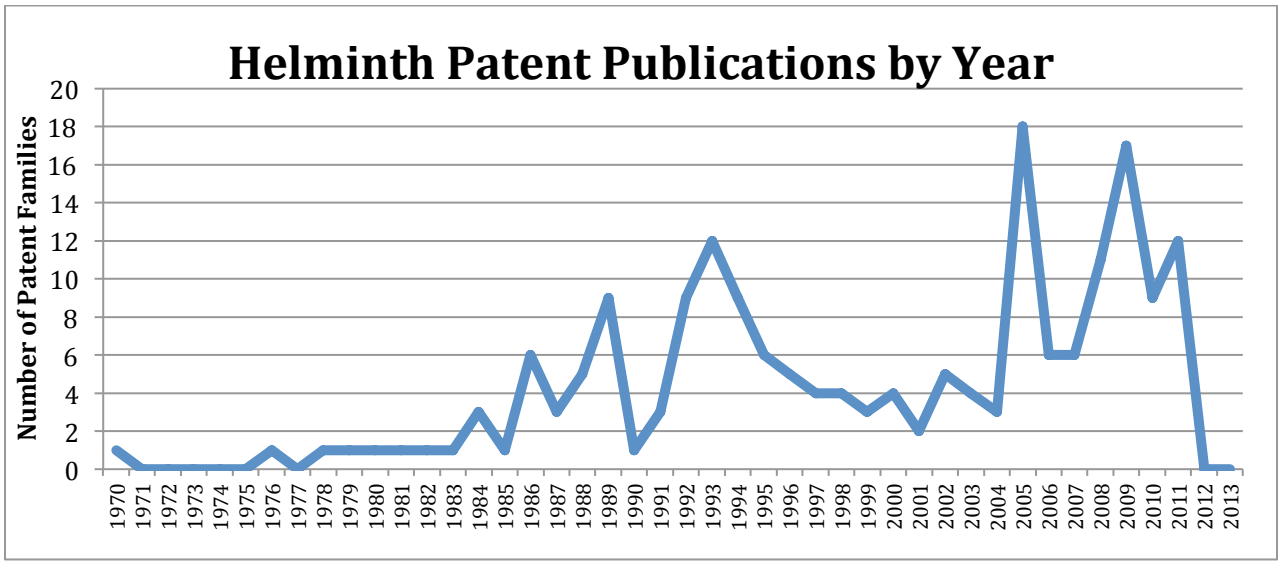

Figure 26. Publication trends for patent families for the entire data set. The year of publication of each representative document of the 210 families is shown.

The earliest representative family member was a U.S. patent issued in 1972, as shown in Figure 16. The second place document was published 8 years later in 1980. From the early 1970's until 1980s it appears only two patents. After 1980, the rate of patent publications directed towards helminth vaccines increased from 1 ever 8 years to 1 to 2 documents ever year. In the early 1990's the average number of publications leapt to roughly 5 publications a year, possibly because the TRIPS Agreement took effect in 1996 and patent applications began to be published 18 months after filing. The average number of filings per year remained around 5 until 2000 and onwards where the rate of publications began to steadily climb, up to 24 in 2012. The number of publications in 2013 was approximately equal to 3. Considering this report includes a thorough search of patents only up to early March 2013, the search did not cover the entire 2013 calendar year.

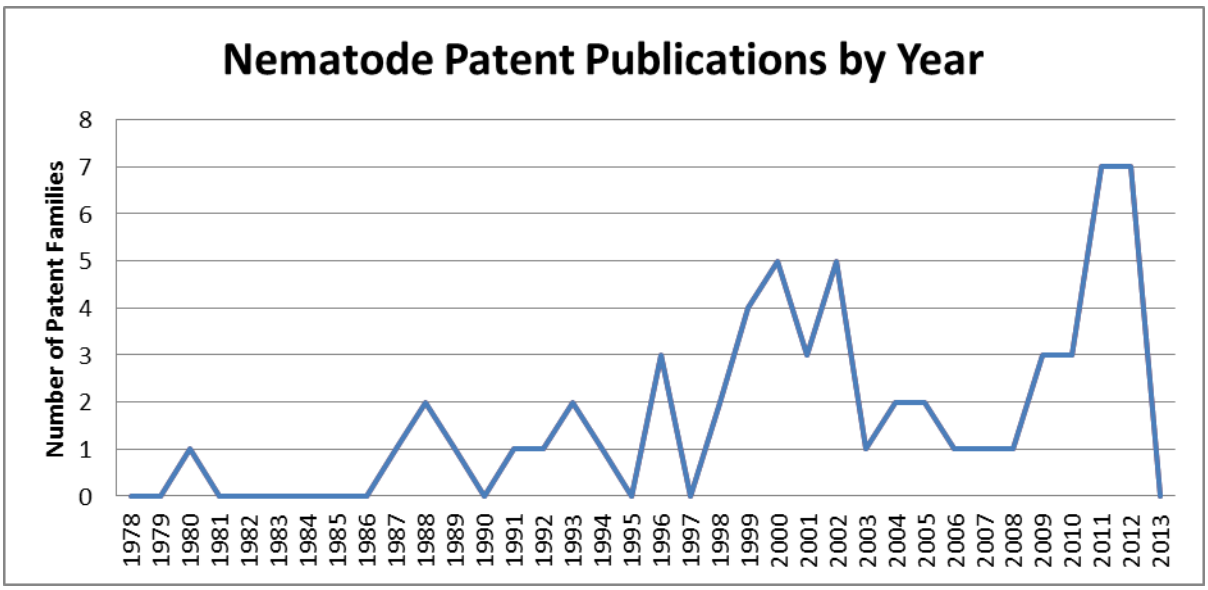

Figure 27. Publication trends for patent families grouped into the category of Nematodes

The earliest representative family member was a foreign patent issued in 1980. The second place document was published seven years later in 1987. Patent publication spiked in the late 1990's-early 2000's and again starting around 2010. Seven patent family representatives were published in both 2011 and 2012. There has been nothing published for 2013.

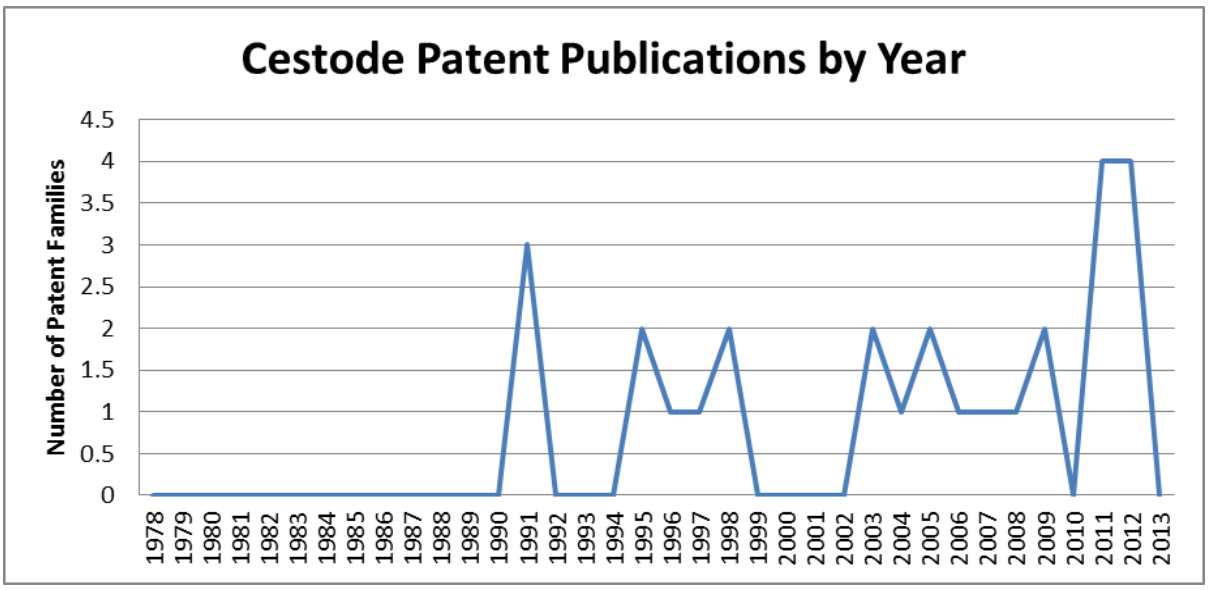

Figure 28. Publication trends for patent families grouped into the category of Cestodes

The earliest representative family members were three patents issued in 1991. The second place documents were published four years later in 1995. There were no patent documents from 1999-2002. From 2003 to 2009 there was a steady trickle of patents published. Publications spiked in

2011 and 2012, with four cestode patent publications issued both years. There has been nothing published for 2013, yet.

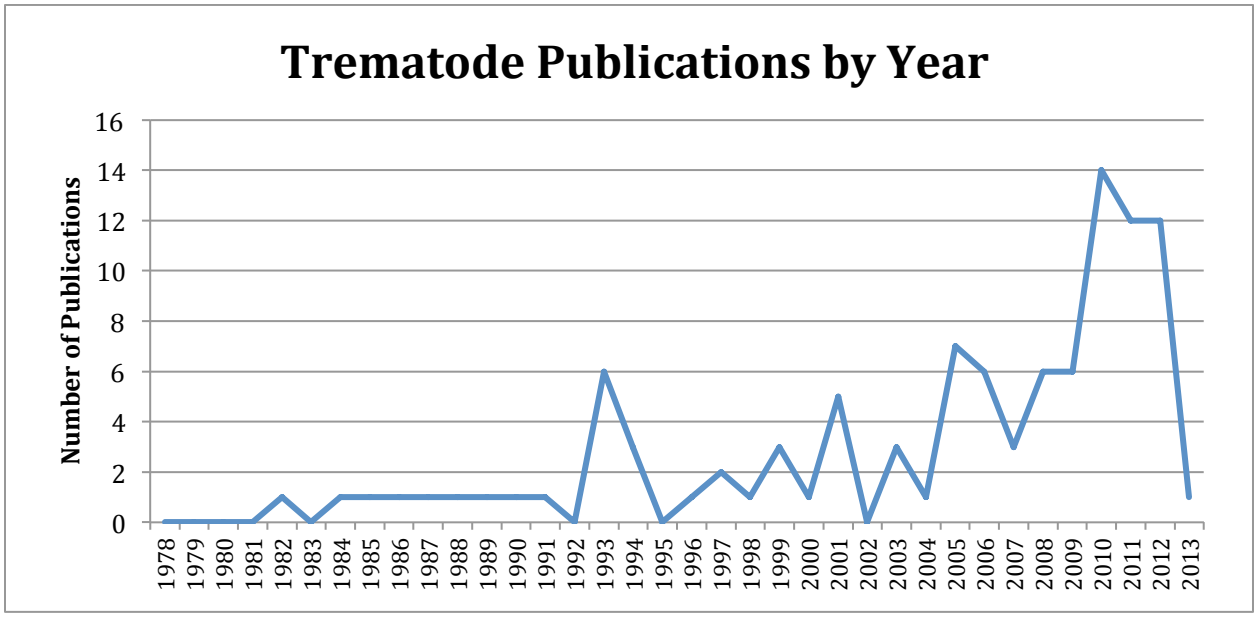

Figure 29. Publication trends for patent families grouped into the category of Trematodes

The earliest representative family member was a foreign patent issued in 1982. The second place document was published two years later in 1984. Patent publication spiked in the early 1990's-early 2000's and again starting around 2010. One-hundred patent family representatives were published in both 2011 and 2012. There has been nothing published for 2013, yet.

Top IPC (Current) Classifications

The International Patent Classification (IPC) system, established in 1971, is administrated by the World Intellectual Property Organization (WIPO). The IPC "provides for a hierarchical system of language independent symbols for the classification of patents and utility models according to the different areas of technology to which they pertain."[138] The IPC contains eight core sections with approximately 70,000 subdivisions, called advanced levels. WIPO continuously revises the IPC, with the core levels being updated every three years and the advance levels being reviewed a few times each year. The current version of the core levels was released in 2012.

The IPC (Current) codes were analyzed for each patent family. Some families had more than one code, and each was counted. For the overall data set 15 codes represented 24 or more

[138] World Intellectual Property Organization, *Preface to the International Patent Classification (IPC)*, WIPO IP SERVICES, http://www.wipo.int/classifications/ipc/en/general/preface.html (last visited Apr. 18, 2012).

families. The top two codes were A61K 39/00 which contains medicinal preparations containing antigens or antibodies and C07K 14/435 which contains organic compounds from humans and from animals.. The definitions for the top 15 IPC families are provided in the table below.

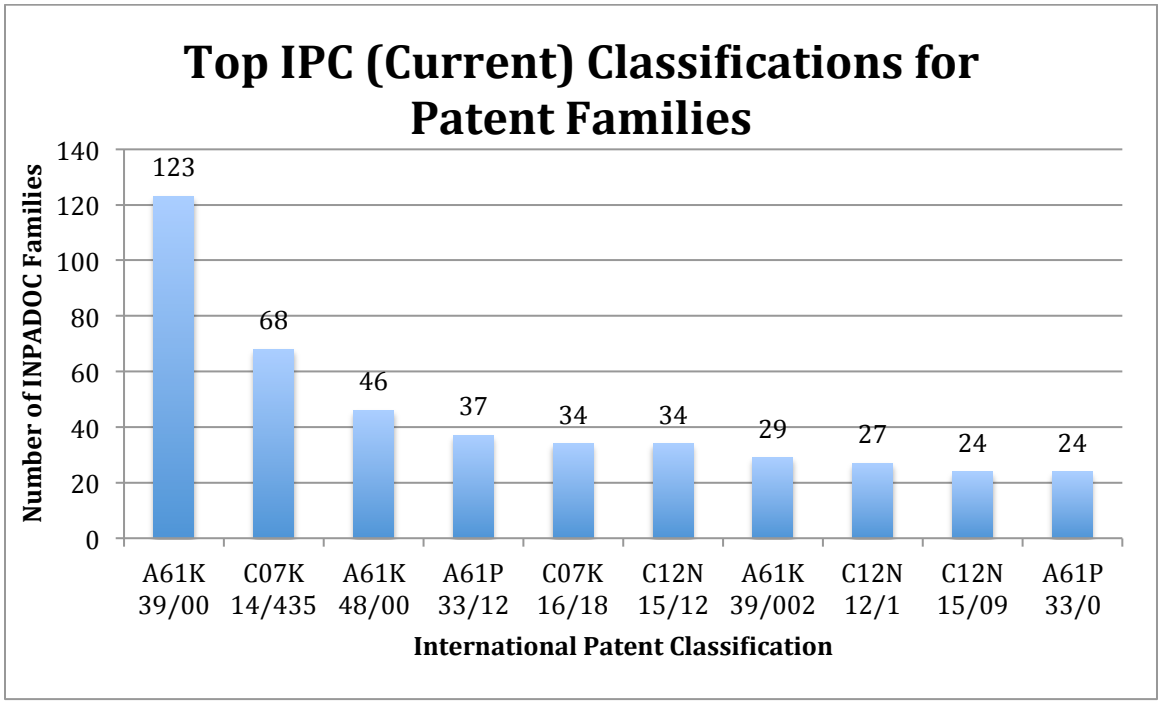

Figure 30. Top IPC (Current) Classification of the entire relevant dataset of 210 relevant families. Each class represented at least 24 different families.

Table IX. Definitions of the Top IPC (Current) Classifications of Vaccine Documents.

A61K 39/00	123	Medicinal preparations containing antigens or antibodies
C07K 14/435	68	Chemistry:Organic Chemisry: From Animals or From Humans
A61K 48/00	46	Medicinal preparations containing genetic material which is inserted into cells of the living body to treat genetic diseases

A61P 33/12	37	Anti-parasitic agent: Schistosomicides
C07K 16/18	34	Immunoglobulins against material from animals or humans
C12N 15/12	34	Mutation or Genetic engineering: Genes encoding animal proteins
A61K 39/002	29	Medicinal Preparations containing Protozoa antigens
C12N 1/21	27	Micro-organism modified by introduction of foreign genetic material
C12N 15/09	24	Mutation or genetic engineering: Recombinant DNA-technology
A61P 33/0	24	Antiparasitic agents

Conclusions

A search of the patent literature for publications containing keywords related to the helminth vaccines returned approximately 2,700 total documents representing almost 447 patent families. After examining the search results 210 of those patent documents related to the prophylactic helminth vaccines or for technologies that are used in the manufacture of vaccines. Of those relevant documents, approximately 13% are specifically related cestodes, 30% were related to nematodes, 49% were related to cestodes with the remainder being non-specific. Thus, vaccine and vaccine related technologies are predominantly focused on nematodes and trematodes. This occurrence is not surprising as trematodes are highly prevalent in South-east Asian and nematodes readily infect both humans as well as livestock.

However, filing of applications related to parasitic worms has been steadily increasing in the last decade, so there are likely many new technological advances that have yet to be fully tested in effectiveness against parasitic worms.

Helminth vaccine technologies appear to originate from a small set of countries, mostly the United States, Great Britain, France, China, Brazil, Australia, and New Zealand. Protection for helminth related intellectual property has been sought worldwide. However, except for Brazil coverage in South America is quite minimal, and except for South Africa protection for these technologies is sparse in Africa.

Top assignees for the relevant families were mostly large pharmaceutical companies, with the majority of patent families coming from Heska, followed by Merck, Institut Pastuer, AusBiotech, and Biotechnology and Biological Sciences Research Council.

Progress is being made towards the development of an effective vaccine against helminthiases, but much work remains to be done, especially testing these novel vaccines under clinical conditions. Additionally, this much-needed technology needs to be distributed to the least-developed nations.

Appendix Materials

APPENDIX A: Master Coding Spreadsheet (electronic version only).

This Excel file contains a series of spreadsheets related to the coding of the representative documents from the 447 INPADOC family members found relevant from our searches. The first sheet contains the 447 family members, the category they were coded into indicated by color, and notes for the family members related to the basis of the coding decisions. The second, third, fourth, and fifth and sixth sheets are divided by categories, cestodes, nematodes, trematodes, nondistinguished and other. Each sheet contains the subcategories for each category and shows the subcategory where each family member was placed.

Table 4. Indicating the color used for coding family members into specific categories

Cestodes		**Nematodes**	
Subunit vaccines		Subunit vaccines	
DNA vaccines		DNA vaccines	
Subunits capable of use in vaccines		Subunits capable of use in vaccines	
Methods of making vaccines (e.g. purification or formulation)		Methods of making vaccines (e.g. purification or formulation)	
Method of producing subunits		Method of producing subunits	
Veterinary vaccines		Veterinary vaccines	
Methods of Vaccination		Methods of vaccination	

Trematodes		Nondistinguished	
Subunit vaccines		Subunit vaccines	
DNA vaccines		DNA vaccines	
Subunits capable of use in vaccines		Subunits capable of use in vaccines	
Methods of making vaccines (e.g. purification or formulation)		Methods of making vaccines (e.g. purification or formulation)	
Method of producing subunits		Method of producing subunits	
Veterinary vaccines		Methods of vaccination	
Methods of vaccination		Veterinary vaccines	

General Platforms	
Excluded	

APPENDIX B: Full Records of Relevant Family Members (electronic version only).

This Excel file contains detailed information of each of the 210 relevant patent family member. The full records, containing all available information extracted from Thomson Innovation, are given for each representative family member. Documents are organized alphabetically by publication number.

APPENDIX C: Full Records of all Relevant Documents (electronic version only).

This Excel file has detailed information of each relevant patent document. The full records, containing all available information extracted from Thomson Innovation, are given for each document. Documents are organized alphabetically by publication number.

APPENDIX D: Top Multi-Jurisdictional Filings Spreadsheet (electronic version only).

This Excel file has representative family members ranked according the size (number of publications) of the INPADOC family each document represents. The top 21 largest families are then analyzed based on the total number of jurisdictions in which each family has been filed. Data is assembled from INPADOC, DWPI and TotalPatent family data.

APPENDIX E: Assignees Analysis Spreadsheet (electronic version only).

Assignee data for each representative family member was manually corrected to reflect changing company names or the acquisition of an assignee by another company. This Excel file details assignee data first by publication number, and then assignees are shown by total number of families believed to be owned by that assignee. All relevant family members were pooled together to generate an assignee list covering all highly relevant documents. The website for each assignee is also given, if possible.

APPENDIX F: Priority Document Spreadsheet (electronic version only).

This Excel file has representative family members marked according to the earliest priority document of each INPADOC family. Data is assembled from INPADOC, DWPI and TotalPatent family data. The determinations is made from a combination of both TI's recommendation as well as by an analysis given by the team member examining the priority document.

Appendix G: PDF Files of Representative Patent Documents (electronic version only).

This folder contains the pdf files for each representative family member, if available. Note that in a few instances a pdf file of the representative family member was not available. Thus these folders do not contain the complete number of representative documents.

Appendix H: PDF Files of Selected Non-Patent Literature (electronic version only).

This folder contains pdf files for selected non-patent literature relevant to helminth vaccines. An extensive search of NPL was not performed; rather the documents included in this folder are mostly review articles which reveal the general state of the art, summarize available technologies, or discuss strategic approaches to immunization.

Appendix I: Keywords Used in Searching.

The following represents the keywords used by the team members in patent database searching. Note that each team member used different combinations of these terms, and only a subset of terms was used for any particular search.

List of parasites and keyword list

Tapeworms

Taenia multiceps
Diphyllobothrium latum
Echinococcus granulosus,
Echinococcus multilocularis,
E. vogeli,
E. oligarthrus
Hymenolepis nana,
Hymenolepis diminuta
Taenia saginata
Taenia solium
Bertiella mucronata,
Bertiella studeri
Spirometra erinaceieuropaei

Flukes

Clonorchis sinensis;
Clonorchis viverrini
Dicrocoelium dendriticum
Fasciola hepatica,
Fasciola gigantica
Fasciolopsis buski
Gnathostoma spinigerum
Gnathostoma hispidum
Metagonimus yokogawai
Opisthorchis viverrini,
Opisthorchis felineus,
Clonorchis sinensis
Paragonimus westermani;
Paragonimus africanus;
Paragonimus caliensis;
Paragonimus kellicotti
;*Paragonimus skrjabini*;
Paragonimus uterobilateralis
Schistosoma sp.
Schistosoma mansoni
Schistosoma haematobium
Schistosoma japonicum
Schistosoma mekongi -
Echinostoma echinatum
Trichobilharzia regenti,
Schistosomatidae

Roundworm
Ancylostoma duodenale
Necator americanus
Angiostrongylus costaricensis
Anisakis
Ascaris sp.
Ascaris lumbricoides
Baylisascaris procyonis
Brugia malayi,
Brugia timori
Dioctophyme renale
Dracunculus medinensis
Enterobius vermicularis,
Enterobius gregorii
Loa loa filaria
Mansonella streptocerca
Onchocerca volvulus,
Onchocerciasis
Strongyloides stercoralis
Toxocara canis,
Toxocara cati
Trichinella spiralis,
Trichinella britovi,
Trichinella nelsoni,
Trichinella nativa
Wuchereria bancrofti
Trichuris trichiura,
Trichuris vulpis

- Parasitic Worm
    - (any genus/species above)
    - Tapeworm
    - Cestoda
    - Ascaris
    - Nematod!
    - Helminth (mess with root extenders with this one)
    - Schistosom*
    - Endoparasit*
- Combination of vaccine and parasitic worms
    - Anthelminthic
    - Anthelmintic
    - Antihelminthic
    - Antihelmintic
    - !helmint!
    - Vermifuge

    - Vermicide
    - vermifugal
    - Anthelminth
    - Dehelminthisation (dehelminthization?)

- Vaccine
    - Immun! (TP) Immun* (TI)
    - Immunologic! Immunologic*
    - Immunostimul! or immuno-stimul!
    - Immunomodul! or immuno-modul!
    - Immunologentic
    - Immunogen! Immunogen*
    - Immuniz! Immuniz
    - Vaccin! (TP) Vaccin* (TI)
    - Virotherap! Virotherap*
    - Prophyl! Prophyl*
    - Antigen! Antigen*
        - Epitope! Epitope*
        - Determinant
    - Antiinfective or anti-infective (sp?)
    - Antiviral or anti-viral or anti viral
    - Viricide or Virucide
    - Prevent! Prevent*
    - Phage
    - **PARASITICIDAL**

Appendix J: Notes on Patent Families.

If there are several applications or publications for an individual invention (in other countries) claiming the same priority or priorities and originating from the same inventors, those documents constitute a "patent family." All of the family members are related to one another by common priority publications with associated priority dates. INPADOC families are organized solely on priority data, whereas DWPI families focus on the inventions such that divisional applications of a single priority document are considered to be in different patent families. Further, Lexis TotalPatent reports "extended families" which are similar to INPADOC families but include more jurisdictions.

The concept of the patent family first emerged through the Paris Convention on the Protection of Intellectual Property in 1883, while automated systems enabling patent family searching became available through the establishment of the IIB in The Hague in 1947and INPADOC in Vienna in 1972. Since then, patent searching has evolved due to exponential improvements in computing and communication technology.

The term patent family can be defined in a number of ways depending on the relationship between a patent document and its priority or priorities within the meaning of the Paris Convention. The differences only become obvious when the structure of a patent application is complex, i.e. when applications are filed in several countries. Such applications may cite various earlier applications as priorities, or the different patent offices involved in the grant process may accept or refuse different patent claims. This results in patents which have different scopes of protection.

An important point when using any database to retrieve information on patent families is that there is never any guarantee that you will find all the corresponding patent documents that exist. Database producers do what they can to ensure completeness, but they can never guarantee it."[139]

The "Extended" (INPADOC) Patent Family

"The biobibliographic and legal status databases form the basis of the EPO's raw data resources (INPADOC). In February 2008 the bibliographic data included about 60 million bibliographic data sets from almost 80 different countries. The legal status database contains a collection of more than 50 million legal events from 48 countries.

From the beginning, the concept was to cover as many countries and as many publication levels as possible. One of the strongest motives for the integration of INPADOC into the EPO was the wish to combine the particular strengths of INPADOC with the EPO's existing in-house bibliographic database, "DOC-DB."

Following integration of the two databases in the 1990s, the raw data behind both databases is now the same. And since esp@cenet draws on the same pool of data as raw data resources (INPADOC) and DOC-DB, it contains the same documentation.

However, the philosophy of the "extended" (INPADOC) patent family is quite different, and so are the results of family searches. Unlike the "also published as" feature in esp@cenet, which only shows "equivalents," i.e. almost identical documents, an INPADOC family search should retrieve all documents relating in any way to the root document.

Features of INPADOC

When using INPADOC via one of the commercial database host services, it bears all the esp@cenet features, plus the following:

[139] EUROPEAN PATENT OFFICE, *Patent Families* (Feb. 29, 2008), http://www.epo.org/patents/patent-information/about/families.html.

- Standardization of applicant and inventor names
- References to abstracts from Chemical Abstracts and Thomson Scientific Abstracts are made within the patent family
- By including the legal status database additional information is available and additional family links can be established
- National application numbers, international application numbers and domestic relations are included in the family search

For both of the EPO's raw data resources (INPADOC) and esp@cenet, even where no priority has been claimed by the patent application, artificial or "intellectual" links are built in systematic way for the complete PCT minimum documentation. The same is done for older documents (pre-1968) for which the priority information is not complete.

Definition of the "extended" (INPADOC) patent family

All the documents directly or indirectly linked via a priority document belong to one patent family. In the case shown below, documents D1 to D5 belong to the same patent family, P1.

FAMILY P1

Document D1	Priority P1		
Document D2	Priority P1	Priority P2	
Document D3	Priority P1	Priority P2	
Document D4		Priority P2	Priority P3
Document D5			Priority P5

As mentioned above, national patent application numbers, international application numbers and domestic relations are included in the family search.

In the "extended" (INPADOC) patent family, it does not matter where a search is started. It can be an application number, a priority application number or a publication number.
If the search starts with a publication number, all application numbers, domestic application numbers, priority numbers and international application numbers are used to retrieve additional documents. For all documents found in this step, step one is repeated. This iteration process ends only when no more new documents can be found.

Raw data resources (INPADOC) also use some additional sophisticated rules for certain countries, for example, if publication numbers are used instead of priority numbers in the original documents. This happened rather frequently for older documents, where the priority claims were not treated as carefully as they are now. The inclusion of legal status information in the patent search also sometimes retrieves additional links, e.g. for divisional applications, continuations, continuations in part or national publications of first filings of PCT (international) applications, where the priority links are often missing.

Limitations of the family search in raw data resources (INPADOC) have to rely on the correctness of the data supplied by the co-operating patent offices and the extent to which it is up to date. In particular, delays in the delivery of bibliographic data can vary significantly depending on the country concerned and the time period covered. Before relying on the completeness of a patent family, users should check where there are gaps or delays in certain areas. This kind of information can be found in the PFS and PRS statistics on the internet, which are updated weekly and contain indications of missing or delayed document series. See raw data resources (INPADOC) useful tables and statistics. To be absolutely sure about the actual status of a patent, users are recommended to contact the appropriate patent issuing authority direct. Particular care has to be taken in the case of European patents which have entered into the national phase. The completeness and accuracy of data can vary significantly from country to country. A good overview of the volume and kind of "post-grant" information available in raw data resources (INPADOC) can be found in the raw data resources (INPADOC) FAQ. For most of the EPO member states, information about the validation, lapse, etc., of European patents is given as part of the legal status information, and as mentioned before is less consistent due to the different quality of data available. Starting from week 50/2007, additional post-grant information is taken from the fee administration system and included in the legal status part of the database.

Thomson Scientific WPI Patent Family (DWPI)

“Patent Families in the Thomson Scientific World Patents Index (WPI) draw together patents covering the same invention. Their relationship is defined by the priority or application details claimed by each document. Thus, in its simplest form, a new document (D1) claiming a unique priority (P1) will be assigned to be the basis of its own, new patent family in Thomson Scientific WPI.

Subsequently, if a second document (D2) also claiming priority P1 is received by Thomson Scientific this will be added (as an ―equivalent‖) to the patent family already containing document D1. Other documents claiming priority P1 will also be added to this family as ―equivalents as they are included in the database. Thus, a patent family may contain anything

from a single document to 10 or more. Each patent family represents a single record in the Thomson Scientific WPI database.

The basic document is the first member of a patent family that appears in Thomson Scientific WPI, so it may not necessarily be the first one published for that invention. Differences in the speed that patenting authorities supply data to Thomson Scientific and in the processing time for documents from different countries may affect which document appears in Thomson Scientific WPI first and becomes basic.

Patents often claim more than a single priority and these must match before any equivalent is added to a family. This means that if a basic document (D3) claims priorities P2, P3 & P4, a subsequent document (D4) claiming priorities P2 & P3 will be added to the family as an equivalent, whereas patent D5 which claims priorities P2, P3 and a unique priority (P5) will form the basis of a new, but related patent family. In cases such as this, the accession number of any related family is included in the cross-reference field of each relevant Thomson Scientific WPI record.

Divisions and continuation patents maintain the same status as the original specification. This means that if GB1 is a basic, and GB2 is divisional to GB1, then GB2 will also be a basic (in its own family). However, if GB1 is equivalent to another document already in the Thomson Scientific WPI database, then GB2 will also join this family as an equivalent. It should be noted that family relationships will be defined by the order in which patents appear in Thomson Scientific WPI.

Thomson Scientific also puts a lot of resources into including patents in families even when no foreign priority is claimed, e.g. when an application has been made beyond the 12 months defined by the Paris Convention. Thomson Scientific identifies these "non-convention" equivalents by the presence of foreign nationals and addresses in the Inventor field in the absence of priority data other than the local filing details. Equivalency is determined through a time-consuming manual check of inventors, subject matter, etc.

In this way Thomson Scientific attempts to make patent families in Thomson Scientific PI as comprehensive as possible. However, because of the incidence of multiple priorities, and patent divisions and continuations (especially continuing applications in US documents), it is important to retrieve all related families through their common priorities in order to have a comprehensive overview of patent family relationships."[140]

[140] *Id*.

Appendix K: PDF Files of This Report (electronic version only).

This folder contains separate pdf files of this report and the cover to the report. The ITTI Clinic wishes for this report to be as widely disseminated as possible, so that all interested parties may have access to the information presented herein. However, anyone is free to base a subsequent report on our work as long as proper attribution is given to ITTI.