THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

Title

Investigating and Analysing Research, Patent and Funding Landscapes of Rare Diseases in the European Union and Beyond

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ABBREVIATIONS

AMR – Antimicrobial Resistance

CDC – Center for Disease Control and Prevention

DNDi – Drugs for Neglected Diseases Initiaite

FP – Framework Program

GAP – Global Action Plan

HAT – Human African Trypanosomiasis

HIC – High Income Countries

IDM - Innovative and Intensified Disease Management

IPC – International Patent Classification

LMIC – Low- Middle- Income Contries

MDA - Mass Drug Administraion

MDGs – Millenium Development Goals

NGOs – Non-Governmental Organizations

NTDs – Neglected Tropical Diseases

PCT - Preventive Chemotherapy and Transmission Control

R&D – Research and Development

SDGs – Sustainable Development Goals

STH – Soil-Transmitted Helminthes

UHC – Universal Health Coverage

UN – United Nations

WHO – World Health Organization

CHAPTER ONE

1.1 BACKGROUND

The demand for health services is both growing and changing in nature globally, yet resources are limited to respond to the scale and scope of need. Thus, organizations such as United States Centre for Disease Control and Prevention (CDC), World Health Organization (WHO) and the United Nations (UN) are under increasing pressure to facilitate equitable and affordable health care (1). In spite of substantial contribution of knowledge and technology to health improvements, there are still noticeable disparities in life expectancy and disease burden between low- and middle-income countries (LMIC), and high-income countries (HIC) (1).

"Health for all" is a WHO priority by ensuring universal health coverage (UHC) without impoverishment (2). WHO implements UHC by supporting national health authorities' efforts in strengthening all the building blocks of health systems and to enact policies aimed at ensuring health care is equitable and affordable for all (2). The UN General Assembly adopted 17 Sustainable Development Goals (SDGs) in September 2015, otherwise known as the "Global Goals", as a universal call to end poverty, protect the planet and ensure that all people enjoy peace and prosperity (3). These goals were developed based on the successes of the Millennium Development Goals (MDGs) which focused on a narrow set of disease-specific health targets for 2015. SDGs are broader by including new areas such as climate change, economic inequality, innovation, sustainable consumption, peace and justice, among other priorities (3, 4). The SDGs work in the spirit of partnership and pragmatism to make the right choices to improve lives in a sustainable way. The 17 SDGs provide clear guidelines and targets for countries to adopt in accordance with their own priorities and the environmental challenges of the world at large (3). Goal 3 of the SDGs is to "Ensure healthy lives and promote well-being for all at all ages."

More so, a value- and evidence- based health policy framework for health and well-being among the people of the WHO European Region was adopted and called “Health 2020”. The key aim of the “Health 2020” is to provide understanding and inspiration to everyone across the European region aimed at improving the health and well-being of present and future generations (5). “Health 2020” identifies new systems of collaborative leadership to encourage innovative approaches to social mobilization for equitable, sustainable and accountable health development. It also details a variety of innovative and effective ways to address today’s complex public health challenges, by outlining a variety of strategies and interventions to address major health challenges across lifespan, related to both non-communicable and infectious diseases (5). “Health 2020” strategic objectives are to improve health for all and reducing health inequalities; and to improve leadership and participatory governance for health (5, 6). One of the priority areas of “Health 2020” for policy action is “Investing in health through a life-course approach and empowering people.” European Union (EU) Framework Programme for Research & Innovation was also initiated called “Horizon 2020.” It is the biggest EU research and innovation programme ever, which has made available almost €80 billion of funding over 7 years (2014 to 2020) with a budget of €449.4 million on health programs (7).

In recent decades, considerable attention has been focused on efforts to stimulate research, development and marketing of medicinal products for rare diseases worldwide (8). Global spending on research and development (R&D) has reached a record high of almost US$ 1.7 trillion. About 10 countries account for 80% of spending. As part of the SDGs, countries have pledged to substantially increase public and private R&D spending as well as the number of researchers by 2030 (9). For quite a number of years, rare diseases were hardly addressed by research, and inadequate investment in R&D needed to address specific health problems is a vital contributing factor (10).

CHAPTER TWO

2.1 LITERATURE REVIEW

Innovations in health care have cured diseases, reduced harm and risk in surgical procedures, prolonged the average life expectancy and consequently increased demand for additional care with corresponding costs (11). In many countries, policy makers and management believe that innovation is a major contribution to improve efficiency in health care (11).

A rare disease or 'orphan' disease is defined as one that affects a restricted number of people. In the USA, the Orphan Drug Act (1983) defines orphan disease as a disease or condition which affects less than 200,000 people in the USA or has a prevalence of 7.5 per 10,000 Americans (12). The definition for orphan disease agreed by the European Committee for Orphan Medicinal Products (COMP) (12) is a life-threatening or very serious disease affecting as much a as 5 per 10,000 Europeans. More than 6,800 different conditions qualify as rare diseases, and 6-8% of the world's population is affected (13). Rare diseases are sets of genetic and chronic conditions that afflict various organ systems, with wide ranging prognoses. Patients with rare diseases also tend to be underserved both clinically and scientifically (13, 14). For many rare diseases, basic knowledge such as the cause of the disease, pathophysiology, natural course of the disease and epidemiological data is limited or not available. These pose significant challenges that impact patients care, the clinicians who care for them, and probably the investigators who study their conditions (15).

There is a small market size for rare diseases due to their low prevalence, making it commercially unattractive for pharmaceutical firms and other medical suppliers to invest in developing new products (14). The public funders cannot fulfil the role of the private funders due to the lack of institutions and knowledge in the public sectors. For example, the cost of developing a new prescription medicine that gains marketing approval is estimated to cost **$2.6 billion** according to a recent study by Tufts Centre for the Study of Drug Development (16, 17). Certain rare diseases with available funds and therapeutics manufacturers, such as Gaucher

disease and Hodgkin lymphoma, have well developed research background, however, most diseases suffer from methodological and data constraints limiting the ability to generate research evidence and/or evidence on patient health outcomes (13). Relatively, little is known about the clinical course of many rare diseases and few treatment options exist (14).

Neglected tropical diseases (NTDs) are categorized under "rare diseases" in Europe (although they affect more than 1 billion people in endemic countries) but they are judged separately from the international perspective. The status of their specific treatment is often referred to as orphan drugs, which allows them gain profit incentives by the law in Europe (18).

NTDs have been defined as a group of infections strongly associated with poverty in tropical and subtropical environments. They are diverse in biological and transmission characteristics, and predominantly infect populations in LMIC with limited access to health (19). NTDs kill, impair or permanently disable, often resulting in life-long physical pain and social stigmatisation (20). Approximately one billion people have now or are at risk of getting an NTD and yet less than 5% of research funds are focused on providing treatments and prevention of these highly debilitating and deadly conditions (21). The categorization of these diseases as "neglected" was established by Peter Hotez, Alan Fenwick and Alan Fairlamb in the aftermath of the establishment of the MDGs (2000) (22).

WHO has acknowledged twenty NTDs and these include buruli ulcer, Chagas disease, dengue, dracunculiasis, echinococcosis, trematodiais, human African trypanosomiasis (HAT), leishamaniasis, leprosy, lymphatic filariasis, mycetoma, onchocerciasis, rabies, scabies, schistosomiasis, soil-transmitted helminthes (STH), snakebite envenoming, taeniasis, trachoma, and yaws (23, 24). Over the past 15 years, there has been unprecedented political and financial commitment to tackle NTDs, including the forging of new global alliances, non-profit public–private partnerships (e.g. the Medicines for Malaria Venture and the Drugs for Neglected Diseases initiative (DNDi)), and massive scale-up of interventions enabled by multimillion dollar investments by philanthropic institutions (e.g. the Bill & Melinda Gates

Foundation) and development and cooperation agencies (e.g. the UK Department for International Development) (25). In spite of interventions to address NTDs, only 0.6% of official development assistance for health is provided. This underinvestment reflects a persistent and continuing inequity in global health financing (19).

Rare diseases and NTDs tend to share a quite number of similarities; low profit potential for drug manufacturers, lack of perceived disease "sexiness," and a fund-raising importance for non-governmental organizations (NGOs). These categories of diseases tend to differ, in that, rare diseases focus on trying to attract funds that will induce and enable scientists to find a cure, while for many NTDs, scientists have already found the cure and prevention methods. Some of the rare diseases attract more funds, unlike NTDs, in which funds are available not to fund the science, but rather to enable people gain access to the often cheap and effective cures and prevention that they need. In a purview of these diseases, it seems that "rare diseases" are more likely to be neglected than the so-called "neglected tropical diseases," in that, in terms of NTDs, it is not the diseases but the "affected people" that are neglected (26).

NTDs are often misdiagnosed and treatments are less available. Unlike rare diseases, inaccessibility to treatment due to excessive financial burden, distance from specialists, lack of availability, or limited data on the conditions resulting to disability, loss of income and even discrimination for those affected. While rare diseases and NTDs generally take up different spaces in the health sphere, both experience a lack of awareness and research-based funding as they continue to afflict countless people globally.

2.2 RESEARCH RATIONALE

2.2.1 Rationale for Research into Rare Diseases

The EU aims to improve rare disease patients' access to prevention, diagnosis and treatment throughout the member states by establishing strategies that meet the disease challenges. One of the pillars of the EU strategy is to accelerate R&D in the field of rare diseases and orphan drugs (27).

Research activities have been a priority as indicated in the EU's Research and Innovation Framework Program for 2007-2013 (FP7) and in the current framework program (Horizon 2020). Since 2007, the EU has invested over €620 million in collaborative research on rare diseases, funding almost 120 projects (28). However, the research landscape for rare diseases has become complex in recent years (29) due to the fragmentation of research centers and the small number of patients affected by a specific rare disease, but the complexity has been diffused partly by the EU research support and the presence of quite a number of diverse funders.

The most obvious challenge in rare diseases research is the small number of eligible patients for a given study. Geographic dispersion of patients, lack of knowledge about the clinical course of disease, and lack of appropriate comparator treatments further hinder the generation of evidence (13, 30). Although, rare diseases may present unique clinical problems and methodological challenges to studying health outcomes, developed innovative epidemiological and clinical trial methods will enhance more efficient and effective research (13).

According to a widely used classification, research funding of rare diseases comes from three major sources: public sector funding, non-profit, and for-profit funding of the private sector (31). Public sector funding uses money raised through taxation (32) which includes bodies operating at either international or national level, such as government departments, local authorities and non-departmental public bodies, such as academic research institutes (29). The

impact of non-profit private funding from philanthropists, crowd-funding, non-profit foundations and professional organizations is also highly significant (33).

Research progress can be observed for specific rare diseases through a systematic database that underlines the research trends and gaps. Interestingly, rare diseases are rarely represented in international classifications, and therefore invisble in health information systems, contributing to their invisibility in society at large. Most countries hospital information systems use the WHO's International Classification of Diseases (ICD) in its 10th version. Only around 500 rare diseases are listed in ICD-10, and only half of these diseases have their own specific code . The lack of specific codes for most rare diseases in ICD is so unfortunate now that technology allows for the integration of multiple sources of information (34, 35). The availability of open-access clinical and research databases in the field of rare diseases is likely to boost research and innovations, especially given that rare diseases are disease models that help to understand the physiopathology of diseases for direct patient benefit (35). More so, recent qualitative studies have found that, rare disease patients and caregivers are not only the drivers of institutional research, they invent a myriad of valuable solutions to improve their personal medical situations. Patients and caregivers who develop solutions to address some of their disease related problems can potentially give valuable contributions to the body of knowledge about their diseases and ways to cope with them (14).

Data collection of granted research projects by funders is required for a comprehensive purview of research landscape. Funders interested in rare disease research are not willing to make substantial investment decisions in the absence of effective and accurate data (36). A systematic specific disease data collection in the EU requires significant effort due to lack of uniform reporting system and diversity of languages used in research funding administration (36). Although, there are voluntary data collections of research studies and trials for rare disesases in the EU, such as the ORPHANET (36), but such collections often overlook significant amount of data. In order to increase the volume of available and accessible

information on rare diseases, emphasis on data collection of research projects need to intensified.

2.2.2 Rationale for Research into Neglected Tropical Diseases

In the last two decades, over two billion of the world's poorest people have been affected by NTDs. NTDs are mainly grouped into parasitic, viral and bacterial infections in Africa, Asia and America (22, 37). The emergence of NTDs necessitates global response owing to its widespread and often catastrophic consequences. WHO has identified twenty NTDs (23, 24). Out of these, 11 are considered as major NTDs (38). The 11 major NTDs are Chagas disease, food-borne trematodiasis, HAT, leishmaniasis, leprosy, lymphatic filariasis, schistosomiasis, STH, taeniasis, onchocerciasis, and trachoma.

EU's FP has supported research on NTDs since the 4th FP (FP4, 1994-1998). NTD research was identified as a specific priority for the 7th EU FP (FP7, 2007-2013) (39). WHO launched its first report on NTDs in 2010, which defined the strategic approaches for reducing the burden of these diseases (40) and provided a "roadmap" revealing the targets for eradication, elimination and intensified control of identified NTDs set for 2015 and 2020 (22). The Bill and Melinda Gates Foundation and Wellcome Trust were the largest philanthropic investors, having a total contribution of US$ 660 million on R&D on NTDs in 2014 (41). The London Declaration ensured the donation of drugs for NTDs but diagnostics is critically needed for monitoring progress towards elimination and assessing the impact of special intervention (42). More so, another "road map" was also defined in 2013 by WHO that includes five key interventions to help countries reach the goals set for 2020. These interventions are: (i) preventive chemotherapy based on large-scale use of safe, single-dose medicines at regular intervals; (ii) innovative and intense case management; (iii) vector ecology and management; (iv) improvements in water, sanitation and hygiene in NTD-endemic areas; and (v) veterinary interventions to protect and improve health (42, 43). Two primary methods of interventions for NTDs are "preventive chemotherapy and transmission control" (PCT) which covers "mass

drug administration" (MDA), and "innovative and intensified disease management" (IDM) (22). Global strategies and applicable tools are readily available for PCT (22). IDM focuses more on NTDs for which simple tools and treatments are not yet available and wide scale prevention cannot be applied (22, 44). According to WHO, an estimate of 1.7 billion people in 185 countries needed mass and/or individual treatment and care for NTDs in 2014 (41). In recent times, tremendous steps have been taken to curtail NTDs by Global Network and public-private partnership. In 2011, there was a 37% average coverage of PCT for NTDs but with the involvement of strong partnerships, the average coverage of PCT increased to 63% by 2016 (45). Several pharmaceutical companies, such as Merck & Co., Pfizer, GlaxoSmith etc. have been donating key drugs to address NTDs since the mid-1980s. In the case of Merck & Co., there is a program to donate ivermectin (Mectizan) indefinitely to support the fight against onchoceriasis (46).

From a recent WHO report on "Unprecedented progress against NTDs", one billion people have been treated for at least one NTD in 2015 alone (47). However, progress has been uneven, leaving many people without access to the benefits of the advances made so far. According to Hotez, WHO has discovered that less than two-thirds of the global population that needs treatment for NTDs are covered, and treatment for trachoma and schistosomiasis is quite not impressive (24).

PCT involves three main activities: (1) access to effective essential medicines (mostly donated), (2) decision of governments/other agencies to commit human and financial resources, and (3) delivery of those medicines to those who require treatment (48). It has been discovered that PCT covering MDA programs appears to be less effective compared to the original framework. There is a need for the MDA programs to be continued for a much longer period, in spite of the development of drug resistance due to long and continuous usage that remains undesirable (49). More so, diagnostics needed to guide chemotherapy and surveillance has not been improved due to the perceived lack of a commercially viable market for NTD (19, 42). A

lack of precise diagnostics strategy has resulted in limited surveillance data, with countries often using only disease burden as a proxy for countrywide data (42). Solomon et al., suggested that country programs for control and elimination of NTDs demand improved diagnostic tools in order to "guide decisions on the required intensity, frequency, and duration of intervention and to conduct surveillance for re-emergence of infection after elimination" (42, 50). Various types of diagnostics are needed to inform policy decisions at different stages of control for NTDs for which MDA is the main control strategy (42, 51). After multiple rounds for MDA, highly sensitive and specific diagnostics are needed to locate "hot spots" of residual infection. For schistosomiasis, the intensity of transmission decreases with decreasing prevalence of infection (42). Table 1 shows an overview of major NTDs, their causal agents, and drugs (donated and not donated drugs).

Table 1 Major NTDS with donated drugs and their causal agents

	NTDs	**Causal agents**	**Drugs**
Bacterial infections	Trachoma (PCT - MDA)	*Chlamydia trachomatis*	Azithromycin (donated)
	Leprosy (PCT - MDA)	*Mycobacterium leprae*	Rifampicin, clofazimine, and dapsone (donated - MDT)
Helminth infections	Food-borne trematodiasis	*Fasciola hepatica, Fasciola gigantica*	Praziquantel
	Lymphatic filariasis (PCT - MDA)	*Wuchereria bancrofti*	Albendazole (donated)
			Ivermectin (donated)
	Schistosomiasis (PCT - MDA)	*Schistosoma spp.*	Praziquantel (donated)
	Soil transmitted helminthiasis (PCT - MDA)	*Ascaris lumbricoides*	Mebendazole (donated)
	Taeniasis	*Taenia solium*	Praziquantel
	Onchocerciasis (PCT - MDA)	*Onchocerca volvulus*	Ivermectin (donated)
Protozoan infections	Chagas disease (IDM)	*Trypanosoma cruzi*	Nifutimox (donated)
	Leishmaniasis (IDM)	*Leishmania*	Amphotericin B
	Human African trypanosomiasis (IDM)	*Trypanosoma brucei gambiense and Trypanosoma brucei rhodesiense*	Eflornithine Melarsoprol Pentamidine Suramin

PCT = Preventive Chemotherapy and Transmission Control
MDA = Mass Drug Administration
IDM = Innovative and Intensified Disease Management
MDT = Multi-Drug Therapy
Sources: The NTDs drugs used (Preventive Chemotherapy and Transmission; and Innovative Disease Management) and their causal agents were obtained from WHO fact sheets (43, 52).

2.3 RESEARCH AIM AND OBJECTIVES

The overall **aim** of this thesis is to analyse the research landscape and financing of NTDs and rare diseases in European Union and beyond.

The **specific objectives** of this study are to map out research activities of rare diseases and NTDs through;

1) Creating a database for Rett syndrome research projects carried out in the EU, and provide a landscape analysis by showing the magnitude of financial support from public and private organizations, by presenting trends in research funding through identifying funded research topics, and evaluating the role of different funding sectors.
2) Determining the trends of R&D on NTDs by performing a patent landscape analysis addressing the patenting trends, current legal status of patents, priority countries by earliest priority years and their assignee types, technological fields of patent documents over time, and lastly, original and current patent assignees in the last 30 (1985 – 2015) years, and
3) Identifying the trends of drug resistance for 11 major NTDs and 20 drugs over a specific period by analyzing: the study type, socio-demographic factors, resistance, study settings, and countries of studies.

2.4 RESEARCH JUSTIFICATION

2.4.1 Rett syndrome Database

Rett syndrome was selected as our case study for rare disease because there has been a significant effort by several research groups worldwide to better understand the nature of this disorder and to discover its treatment.

Rett syndrome with OMIM Entry 312750 (53) is a severe neuro-developmental rare disease that affects approximately 1 in 10,000 live female births. It is often caused by mutations in Methyl-CpG-binding protein 2 (MECP2) (54). It is characterized by arrested development between 6 and 18 months of age, regression of acquired skills, mental retardation, stereotypic movements (classically of the hands), microcephaly, seizures, and loss of speech. Rarely, classically affected males with somatic mosaicism or an extra X chromosome have been described (53, 55). Unfortunately, there are currently no specific treatments for the disease. The management of the disease is mainly symptomatic and individualized, aiming to optimise each patient's symptom resolution and relief (56). Pharmacological approaches to managing problems associated with Rett syndrome include melatonin for sleep disturbances, several agents for the control of breathing disturbances, seizures and stereotypic movements, and L-carnitine for general well-being. Rett syndrome patients have an increased risk of life threatening arrhythmias, and so avoidance of a number of drugs is recommended, including prokinetic agents (e.g. cisapride), antipsychotics (eg, thioridazine), tricyclic antidepressants (e.g. imipramine), antiarrhythmics (e.g. quinidine, sotolol, and amiodarone), anaesthetic agents (e.g. thiopental and succinylcholine), and antibiotics (e.g. erythromycin and ketoconazole). In addition, careful evaluation for evidence of central autonomic function using noninvasive methods may be of value in identifying specific patterns of disturbance, and may ultimately lead to specific therapies for this sometimes very distressing set of clinical problems (56).

2.4.2 Patent Analysis of NTDs

Intellectual protection is mainly via patents, and it is essential to effectively commercialize an innovation and in the absence of such protection, companies are unlikely to invest in the development of diagnostic tests or treatments (57). The impact of patents can be observed at a research stage, at a point of commercialization, and also when used in diagnostic tests. Understanding patent landscape is essential in the process of translational research and the development of innovations for clinical use (58).

Historically, patents encourage research by giving monopoly to inventors over invention for 20 years and disclosing these inventions for public use after this period of time. To obtain a patent, an inventor must file a patent application. Performing a patent landscape analysis is an established method for understanding R&D trends in the biomedical field because innovations stemming from biomedical research possess a great potential for developments which are often subjected to patent filings (59). Additionally, due to novel, user friendly data visualization technologies and publicly accessible patent databases, patent landscape analysis has become a widely used method by researchers and stakeholders to investigate emerging areas and also to identify white spots (60). In the recent years, visualization methods, artificial intelligence, machine and deep learning are available for intellectual protection management and patent system use. Today, unlike a traditional state-of-the-art search which provides relevant information in text format, patent landscape analysis provides graphics and charts that demonstrate patenting trends, leading patent assignees, collaboration partners, white space analysis, and technology evaluations (61). By using network based and big-data analysis, important patents information owner, inventor, attorney, patent examiner or technology can be determined instantly. Presently, patent portfolios can be unlocked and democratized due to access to patent analysis. Moreover, in the near future, automated patent landscaping will generate high-quality patent landscapes with minimal effort by leveraging human domain expertise, heuristics based on patent metadata, and machine learning thereby increasing the

access to conducting patent landscape analysis (62). Although, there are millions of published patents and patent application references available for public review but the collection of such information can only be made useful by identifying the critical, relevant references in a given technology and thereafter analyse those references in a manner that provides information for actionable decision making. Patent landscape analysis provides insight into the innovations that underlie technology and products. A completed patent landscape analysis project consists of a set of technical references and accompanying analytics from which important legal, business, and technology information can be extracted. This information enables large corporations, startups, universities, research institutions, and investors to understand and make informed decisions prior to investing time and money into new technology and product development opportunities (63).

2.4.3 Antimicrobial Resistance of NTDs

Antimicrobials are drugs that destroy disease-causing microbes, also called pathogens, such as certain bacteria, viruses, parasites, and fungi. Antimicrobial resistance (AMR) occurs when pathogens undergo adaptive evolutionary changes that enable them to withstand antimicrobials (64, 65). AMR is a global public health threat, and its impacts have the potential to kill millions of people. Also, it is a fundamental commercial challenge for private sector companies because, developing new antimicrobials is often expensive and it requires a long-term proposition (41). In recent times, AMR has increasingly become a problem because of a tremendous increase of antimicrobials use which has caused the rate at which resistance is developing and spreading to increase (65). Unfortunately, there are no adequate new drugs to address this situation (65). According to projections, if AMR is not controlled or reversed, drug-resistant viruses, bacteria, parasites and fungi could cause 10 million deaths per year by 2050, and cost the global economy at least US$ 100 trillion (65). In the last two years, there has been a global political momentum addressing AMR. At the 68th World Health Assembly in May 2015, governments adopted a Global Action Plan (GAP) which identifies a set of strategic objectives (66). In January 2016, the United Nations General Assembly held their first high-level meeting on AMR where a declaration was adopted with representatives of the pharmaceutical, biotechnology and diagnostics industries present (41, 66). WHO has taken leadership on AMR with its Global Action Plan on Antimicrobial Resistance (GAP-AMR) by combining new medicine discovery, development and stewardship (41, 67). Following the London declaration on NTDs in 2012 focusing on drug development (45), WHO and Drugs for Neglected Diseases initiative in May 2016 launched a global R&D partnership in order to develop new antibiotics and promote their responsible use (41, 64, 68).

CHAPTER THREE

3.0 METHODOLOGY

The following methods were used to map out the research activities of rare diseases and NTDs:

3.1 Developing a database for Rett Syndrome research performed in the European Union: A research for researchers and stakeholders.

Three major steps were taken into consideration in order to develop a database for Rett syndrome research in the EU, and they are:

i) Identification of research projects from public and non-profit funders' databases,

ii) Data extraction from projects and budget analysis, and

iii) Making extracted dataset available online.

3.1.1 Identification of projects

Two approaches were applied in determining public and non-profit funders' databases:

1) Funders defined in Rett syndrome articles acknowledgments were searched for in the Web of Science (WoS) in 2013/2014 with the terms; "Rett" OR "mecp2" OR "methyl CpG binding protein". These keywords were selected because they have the same meaning irrespective of the project country's language, bearing in mind that there are 24 official languages in the EU. Projects' time frame of the project was not a limiting criteria in the search.
2) National public research funders were identified through Science Europe (https://www.scienceeurope.org/), an umbrella organization for national research funding institutions (69). This list was complemented by the European Commission as a prominent research funder of rare diseases (70).

Results of the search were refined based on EU member states information on Rett syndrome projects funding. The number of records with information on the funding source was 1025 out of 1585 records found. Based on the 500 most relevant funding sources which were reported in the funding acknowledgement data of WoS records (71), 363 research funders' website were

found through web search. The process of identifying research databases, funders and projects of Rett syndrome is presented in Figure 1.

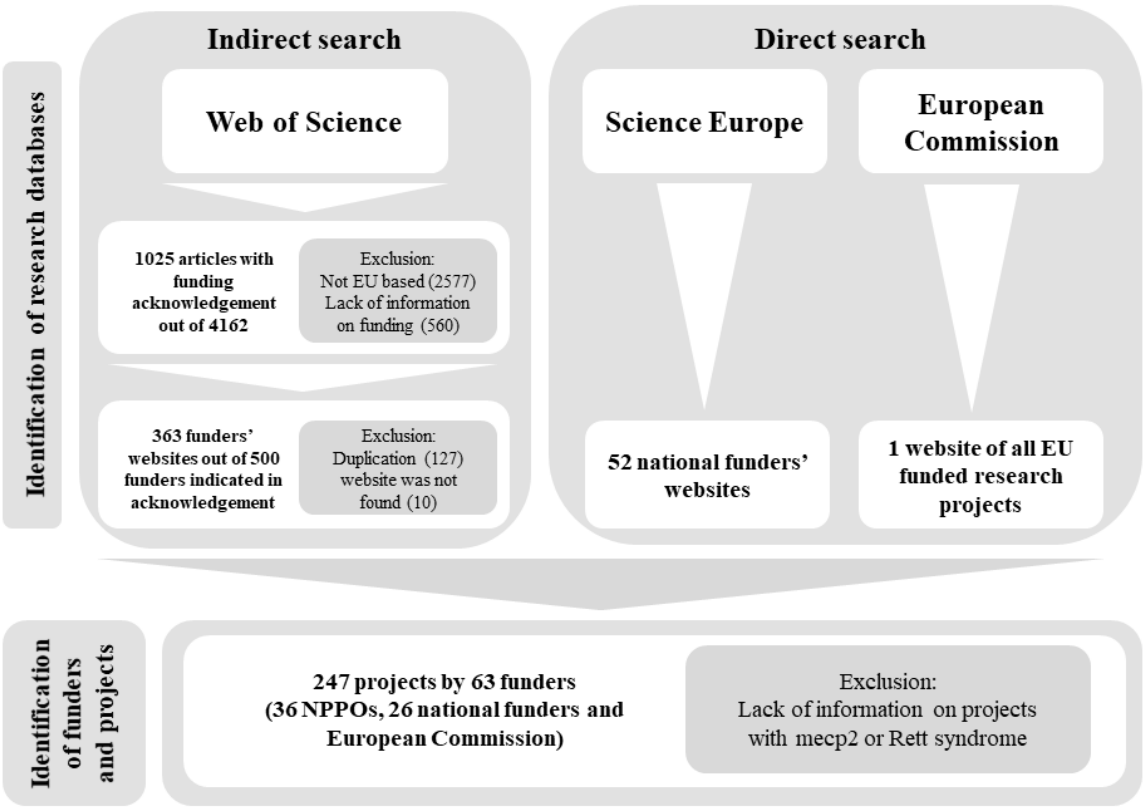

Figure 1 Flowchart of Rett syndrome projects identification

Projects were identified from funding acknowledgements in scientific articles indirectly (based on exclusion) and directly through national and European Commission research databases.

3.1.2 Data extraction

Identified projects were managed in an Excel table (Microsoft Office Excel 2010). The information extracted from each identified research project were identity code, title, abstract, first and final year of the project, amount of funding, country of execution, name and type of the funding organization. A project's title and its country of execution is a mandatory inclusion criteria. In case a project was performed in more than one country, all the countries involved were included in the analysis. Projects carried out over several years were considered by their annual funding in the analysis.

In order to characterize the identified project topics, the title and abstract of each project were reviewed and categorized according to the ORPHANET classification system which comprises of 19 categories (36) (72). These 19 categories were classified into three main research groups; clinical, translational and basic research according to NIH Research Portfolio Online Reporting Tools (73).

Clinical research includes diagnostic tool/protocol development, epidemiological study, health sociology study, human physiopathology study, medical device/instrumentation development, genotype-phenotype correlation, observational clinical study and public health/health services study. Translational research includes health economics study, pre-clinical cell therapy, pre-clinical drug development/drug delivery, pre-clinical gene therapy and pre-clinical vaccine development, and the basic research includes animal model creation/study, biomarker development, gene expression profile, gene search, in vitro functional study and mutations (10).

3.1.3 Creating an online database

An online database (www.retts.unideb.hu) was set up which provides an open access to data on research projects (74). All the projects identified were represented with a unique name. These records were converted into a MySQL database and for the data representation using CMS Word Press. The website was implemented in PHP and MySQL, and stored on a webserver running an Apache HTTP. The operating system's server is Linux. Creating an online database

3.2 Patent landscape of neglected tropical diseases: an analysis of worldwide patent families.

Patent documents were extracted from the Patseer (http://patseer.com/) which is an international database of patents from over 100 patent issuing authorities worldwide (75). Evaluation of the patent documents were carried out using the combination of different search terms related to each identified NTD. The final set of keywords is presented in Appendix 1a-c.

Keywords of each identified NTD (their synonyms and truncation to cover different endings, singular/plural etc) were obtained from Medical Subject Headings (MeSH) database of the National Library of Medicine, in which vocabulary thesaurus is used for indexing articles for PubMed, fact sheets relating to NTDs produced by the WHO, and Google Scholar.

PatBase software (76) was also used as an additional database to visualize R&D trends of NTDs. Patent documents retrieved from Patseer were uploaded and analyzed in PatBase.

Technology domains and International Patent Codes (IPC) were adopted for topic identification for each identified NTD. Technology domains are comprehensive allocations of patented inventions. The first 4 digits of IPC codes are linked with the thirty-five fields of technology, in which categorization has been revised by the World Intellectual Property Organization (77). The IPC categorizes similar inventions, thus, provides a single source to browse through all inventions related to a specific NTD using the titles, abstracts and claims of patent families accessed.

The analysis was based on simple patent families (a group of one or more patent applications which represent the same invention) since patent applications are often filed in more than one country. Duplicates were removed by creating simple families which represent the family members of a particular patent record with same priority dates.

Legal status information is an important component of patent information as it determines whether examination of a patent application is still pending, or the application was withdrawn or rejected, or a patent has been granted and is still valid or a granted patent has expired, lapsed

or been revoked due to an opposition. In PatSeer, setting “one member per family” deduplication mode for an entered query, the displayed record is represented by the legal status of its family members. For example, if any one of the family members has legal status as granted, the record displayed will be marked as granted.

3.3 Drug resistances and neglected tropical diseases: A systematic review

3.3.1 Protocol registration

This study was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement recommendations (78). The study protocol was determined prior to commencement, and it was registered in the PROSPERO-International prospective register of systematic review with the identification number CRD42016050563 available at: https://www.crd.york.ac.uk/prospero/#recordDetails.

3.3.2 Eligibility criteria

Studies that assessed the resistance of drugs with identified WHO NTDs were included in this review. All relevant studies were included irrespective of study type, study design, and countries of study. The included studies are limited to studies performed on human subjects. Decisions on eligibility were made by two independent reviewers; all discrepancies and disagreements with respect to study and report eligibility were resolved.

3.3.3 Search strategy

Studies analyzed in this review were identified by searching electronic public databases including: PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and Scopus (http://www.scopus.com/). The searches were performed in August 2016 with no limit set for dates of publications. After the removal of duplications, publications before year 2000 were also removed due to inaccessibility and lack of full text availability. As a result, this study analyzed publications from year 2000–2016. A full description of search terms and search strategy is provided in Appendix 2a-c. Efforts were made to download the full text of included articles, and when not available, authors of such articles were contacted. For unresponsive authors, reminders were sent to allow for a time duration of two weeks, before such studies were excluded and classified as “full text not available”.

3.3.4 Study selection

Initial eligibility assessments on the retrieved titles and abstracts were performed by two independent reviewers. Full texts of eligible articles were retrieved and reviewed for inclusion in the systematic review. The inclusion or exclusion of a study considered conclusive, controversial or ambiguous by either of the reviewers was resolved through deliberations between the reviewers. When necessary, disagreements and discrepancies were resolved by consensus with a third reviewer. Care was taken to identify more than one article reporting a single study. When such was encountered, the overlap was identified and resolved.

3.3.5 Assessment of the methodological quality

Based on recommendations from a number of authors (79-82), the Quality Assessment Tool for Quantitative studies (developed by the Effective Public Health Project) (81), has been adapted for evaluating observational and experimental studies. The Assessment Tool contains 19 items in 8 key domains for evaluating study quality. The 8 domains are study design, blinding, selection bias, withdraws/drop outs, confounders, data collection, data analysis, and reporting.

Using a range of 1 (low risk-of-bias; high methodological quality) to 3 (high risk-of-bias; low methodological quality), an overall rating for each study was determined based on the component rating for each study. Strong was attributed to those with no weak ratings, and at least five strong ratings, moderate was assigned to those with one weak rating or fewer than five strong ratings, and weak was attributed to those with two or more weak ratings.

CHAPTER FOUR

4.0 RESULTS

Most rare diseases and NTDs are significantly under-resourced and lack sufficient information on funding landscape which are obstacles in making effective decisions on research.

4.1 Developing a database for Rett Syndrome research performed in the European Union: A research for researchers and stakeholders.

A total of 63 research funding organizations were identified, they are European Commission (EC), national public funders (n = 26) and non-profit private organizations (NPPOs) (n = 36). In the time frame of 1997-2018, a total of 247 projects (including closed and on-going projects) related to Rett syndrome were funded in the member states of the EU. The 247 projects were performed in 13 different EU countries. A total number of 63 grantors of projects were identified. Out of the 63 grantors, 60 were located in the EU and 3 located outside the EU (2 grantors in the US and 1 grantor in Australia). Grantors located in the EU funded 237 projects out of 247. Within the time frame of this study, a total of €69,172,585 was allocated to fund 237 Rett syndrome projects by grantors in the EU, with grants ranging from €1,200 - €12,500,500, for a time frame of 1 year to 8 years. The research expenditures by national public funders had its peaks in 2008, in 2010 for the EU, and in 2011 for the NPPOs.

Table 2 shows an overall summary of the contribution of the EU based funders. Assessing the magnitude of support, EC contributed the highest amount of money (€32,292,653) and the public national funders the least (€15,234,221).

Table 2 Funding by type of Funders

Type of Funders	Total number of projects	Number of projects with information on funding	Projects number, % of Total	Resources	Resources, % of Total
National	**103**	**44**	**26.19%**	**€15,234,221**	**22.02%**
EC	**14**	**12**	**7.14%**	**€32,292,653**	**46.68%**
NPPOs	**130**	**112**	**66.67%**	**€21,645,711**	**31.29%**
TOTAL	**247**	**168**	**100%**	**€69,172,585**	**100%**

The final dataset contains information on the overall number of projects awarded and the types of funders. This represents a total sum of €69 M for 168 projects funded. Only projects with financial details are included in the table. Around 32% of the total funding was provided by European Commission (EC) -based non-profit private organizations (NPPOs) over the analysed period.

The number of projects on Rett syndrome per funder was assessed in order to determine the magnitude of support of each funder. Out of the 63 organizations, 11 organizations funded at least two projects, while the other 52 organizations funded only one project each. Most projects received support from Italy through AIRETT, National Research Council and Telethon which funded 26, 22 and 19 projects respectively.

More than half of the funded projects fell within the broad category of basic research, while less grants were allocated to clinical and translational research. In basic research category, gene expression (18%), animal model creation/study (14%) and in-vitro functional (10%) received more funding than others within the investigated period. In clinical research, human physiopathology studies (10%), genotype-phenotype correlation (10%) and observational clinical study (7%) were funded, while in translational research, pre-clinical drug development/drug delivered (5%), pre-clinical cell therapy (2%) and pre-clinical gene therapy (1%) were funded as well. (See Figure. 2). All the funders favour basic research topics, national funders and NPPOs support a wider range of projects. Projects falling in the ORPHANET research categories funded by the European Commission, national funders, and NPPOs were

7, 15 and 13 respectively. The composition of research topics of NPPOs and public funders were similar (See Figure. 2).

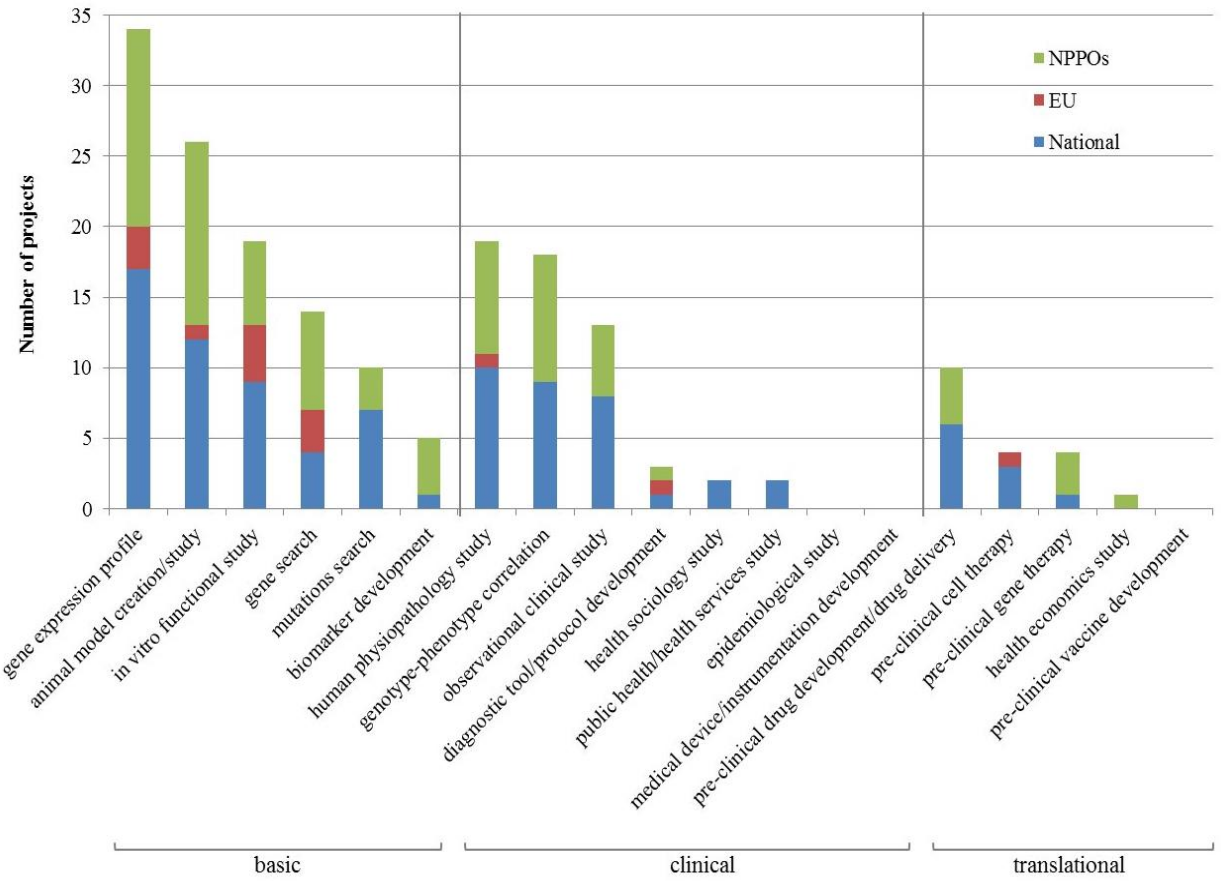

Figure 2 Research topics based on ORPHANET research categories

Projects with abstract (n = 132) were analyzed for research topics. Each project can fall into more than one ORPHANET research categories, thus a total of 184 research projects were presented in this figure. Gene expression profile has the highest percentage followed by the animal model creation/study. Simplified categorization shows that research topic of most funded projects fell within the broad category of basic research (58.7%), less grants were allocated to clinical (31%) and translational research (10.3%). The three colors in each ORPHANET research category column indicate the funder types (as described by the label in the upper-right corner of the diagram). Projects were funded in 13 out of 19 ORPHANET categories by non-profit private organizations (NPPOs), 15 out of 19 by national funders (national), and 7 out of 19 by the European Commission (EC).

The trend analysis of research topics showed a slight shift towards clinical/translational research projects. Trends in Rett syndrome research were assessed by frequency of research topics between the following time frames: before 1999, 2000 - 2004, 2005 - 2009, 2010 - 2014 and after 2015. Gene expression profile projects were highly funded in all the time frames, while animal model creation/study increased slightly over the years. Animal model

creation/study was observed to be prominent within the time frame of 1997-2018. However, after 2000, pre-clinical cell/gene therapy and biomarker development projects were significantly included in the research profile (See Figure 3).

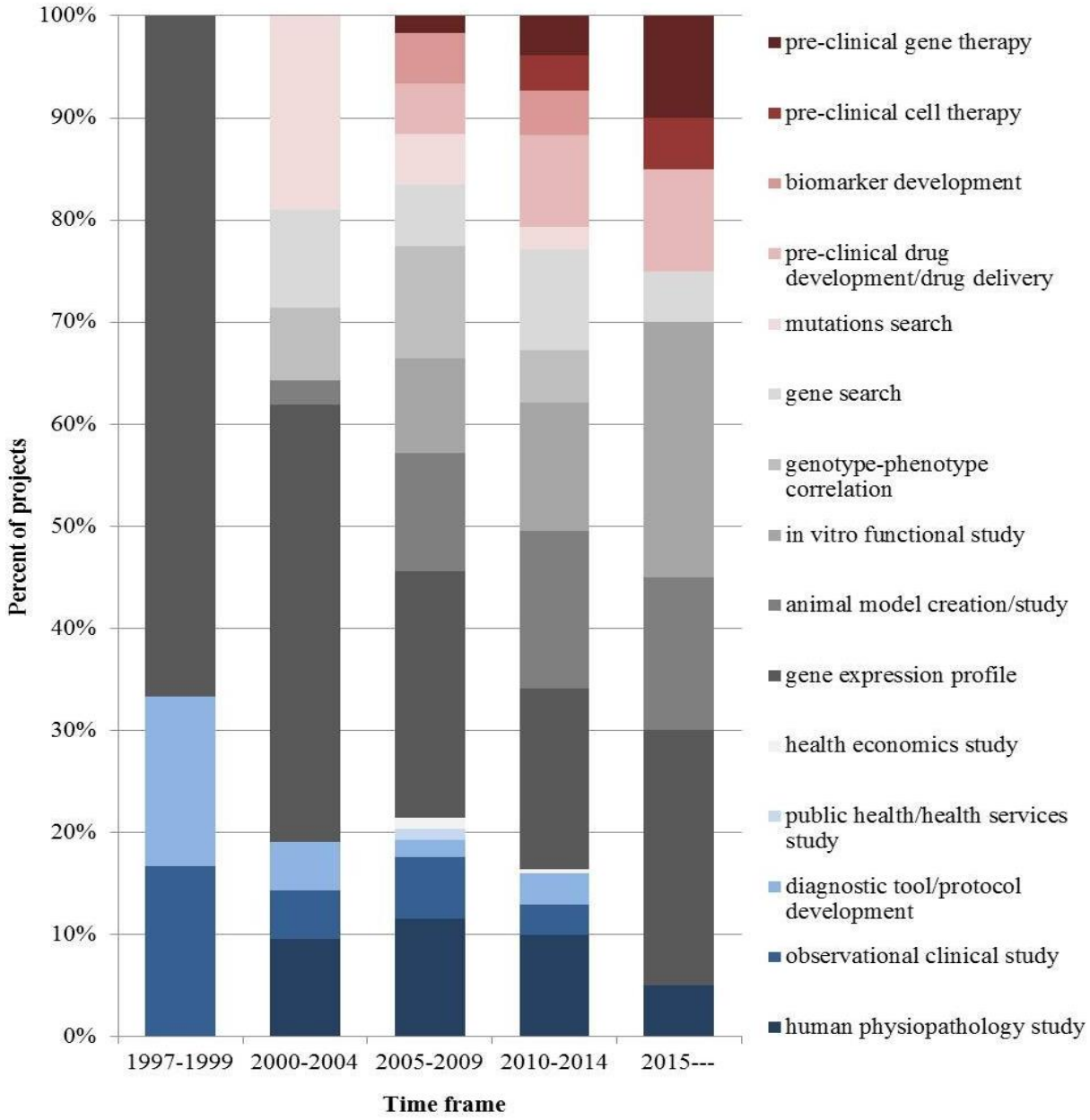

Figure 3 Number of projects according to ORPHANET research categories with time frame

Projects with abstract and information on time period of research conducted were analyzed (n = 98) for research topics. Each project can fall into more than one ORPHANET research categories, thus a total of 175 research projects were presented in this figure. Independently of the investigated time period, research projects including research on gene expression profile and animal model creation/study dominated the funded projects. No projects were categorized to health sociology study, medical device/instrumentation development, epidemiological study and pre-clinical vaccine development.

The geographical location, time pattern of funding and topics of funded projects were assessed in order to understand the role of funders in Rett syndrome research. The geographical distribution of projects was found to be uneven among the member states (see Table 3a-b). Research hotspots were observed to be Italy and UK, where 8 and 5 NPPOs respectively have granted one third of all projects, 69 in Italy and 34 projects in the UK. NPPOs seem to collaborate solely with national research institutions; cross border research funding has not been developed.

The national public funders initiated the funding of projects on Rett syndrome in 1997, followed by NPPOs (1998) and the EC (1999). With respect to the number of project-funders, national public funders have their peak in 2008, EU in 2010 and NPPOs in 2012 (see Table 3a-b).

Table 3 Total number of projects funded by different sources for the EU member states 1997-2018

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Austria								E1	E1	E1	N1 E1 P1	N1 E1 P1	N1 E1 P1	N1 E2 P1	N1 E1 P1	N1 E1	E1 P1	E1 P1	E1 P1				**N1 E2 P3**
Belgium													E1	E1	E1	E1	E1						**N0 E1 P0**
Cyprus													E1	E1	E1	E1							**N0 E1 P0**
Czech Republic							N1	N1	N1	N1			E1	E1	E1	E1							**N1 E1 P0**
Estonia									N1	N1	N1	N1	E1	E1	N1 E1	N2 E1	N2	N2	N1				**N3 E1 P0**
Denmark														P2	P2	P2	P2	P2					**N0 E0 P2**
France						P1		E1	N1 E1	N6 E1 P1	N6 E1 P1	N9 E2	N6 E3	N4 E5	N3 E3	N3 E3 P5	N2 E3 P7	N2 E1 P7	N2 E1 P2				**N12 E5 P9**
Germany	N1	N1	N1	N1	N2	N2	N3	N4 E1 P1	N3 E1 P1	N4 E1	N2 E1	N4 E2	N5 E2	N2 E4 P1	N2 E3 P2	N2 E3 P3	N1 E4 P2	E2	E2				**N13 E6 P4**
Greece													E1	E1	E1	E1	E1						**N0 E1 P0**
Hungary												N1	N1	N1	N1	N1	N1	N1					**N2 E0 P0**
Ireland														E1	E1	E1							**N0 E1 P0**
Italy			P1	P1	P3	P6	N1 P7	N2 E1 P9	N2 E1 P7	N3 E1 P4	N4 E1 P5	N3 E2 P20	E4 P21	N5 E4 P33	N5 E2 P22	N4 E2 P24	N3 E1 P13	N1 P4	P3	P1			**N13 E4 P68**
Lithuania													E1	E1	E1	E1							**N0 E1 P0**

Table 3b: Total number of projects funded by different sources for the EU member states 1997-2018

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Netherlands								N1 E1	N1 E1	N1 E1	N1 E1	N2 E1	N2 E1	N1 E3	N2 E2	N2 E2	N1 E2	N1 E1	N1 E1	N1			**N3** **E3** **P0**
Poland													E1	E1	E1	E1							**N0** **E1** **P0**
Portugal					N1										N1 P1		N1	N1	N1	N1	N1	N1	**N3** **E0** **P1**
Spain							E2	E2	E2 P1	E1 P1	E1	E2 P1	E3 P3	N2 E5 P2	N2 E3 P2	N1 E3 P2	N1 E3 P1	N1 E1	E1				**N2** **E6** **P5**
Sweden			E1	E1	E1	N1 E1	N1	E1	E1	E1	E1	E1	E1	E2	E1	E1	E1						**N1** **E3** **P0**
United Kingdom		P1	N1 E1 P1	N1 E1 P2	N1 E1 P3	N1 E1 P4	N1 P4	N1 E1 P8	N1 E1 P10	N1 E1 P10	E1 P8	N3 E2 P9	N3 E3 P11	N3 E5 P9	N2 E3 P14	N2 E3 P15	N3 E3 P13	N2 E1 P7	N2 E1 P4	N2 P1			**N8** **E6** **P33**

The table indicates the number of overlapping projects by years and countries of execution, and also funding sources located in the EU. For each cell, "N" represents the national funded projects, "E" represents the European Commission funded projects, "P" stands for non-profit private organizations (NPPOs) funded projects while the number after the letters is the number of projects awarded in the given year by the given funder. The last column indicates the actual number of projects carried out in each country in the same manner. Only projects with information on the years of execution (n = 199) are included into the table. Each project could be performed in more than one country thus a total of 230 research projects were presented in this figure.

4.2 Patent landscape of neglected tropical diseases: an analysis of worldwide patent families.

The total number of patent families reviewed in this study was 12,350, and 3179 out of these studies were granted patent families. There is a dissimilarity between research activities for each NTD. Among the NTDs, leishmaniasis, dengue, and rabies have the highest number of families, while taeniasis and dracunciliasis have the least. The number of granted patent families and total patent families for each NTD is presented in Table 4a-c. The overall patenting trend for NTDs is often characterized by the total number of simple families and granted patent families (by year when it was granted). As presented in Figure 4 and with background data in Appendix 3, there is a substantial increase in patenting activities between 1985 and 2014 both in the total numbers of patent families including applications and in granted patent families. Although, total patenting activity became fluctuant between 2003 and 2008 and followed by a 6-year stagnation due mainly to the the decreasing number of applications. The increase in the granted families is continuous albeitt slow.

Table 4 Global data of countries affected by NTDs, drugs donated, burden of each disease, and number of patent families.

Neglected Tropical Diseases (PCT/IDM)	Number of countries	Disease burden			Interventions				Effectiveness of current interventions		Granted patent families/ all patent families
		Incidence	Prevalence	DALYs	Prevention	Treatment	Drug Resistance	Drug Donated	Prevention	Treatment	
Buruli ulcer (IDM)	33	No data	No data	No data	There are currently no primary preventive measures that can be applied. The mode of transmission is not known and there is no vaccine.	Rifampicin and streptomycin	Yes (83)	No	N/A	High	103/322
						Rifampicin and clarithromycin	Yes (83)	No		High	
Chagas disease (IDM)	21	8404	6,653,578	236,100	Vector control is the most effective method of prevention. Blood screening is necessary to prevent infection through transfusion and organ transplantation.	Benznidazole and Nifurtimox	Yes (84)	No	Low	High	449/1658
Dengue	> 100	86,257,710	4,729,962	1,892,200	The main method of prevention is to combat vector mosquitoes. The first dengue vaccine, Dengvaxia (CYD-TDV) by Sanofi Pasteur, was registered in several countries.	No specific drug to treat	No	No	Low	N/A	829/2879
Dracunculiasis (PCT)	3	No data	No data	No data	There is no vaccine to prevent. Prevention is possible through complex preventive strategies.	No specific drug to treat	No	No	High	N/A	15/63
Echinococcosis	Very few countries are completely free of these parasites	313,264	1,382,975	600,000	Prevention programs focus on deworming of dogs and sheep. In the case of cystic echinococcosis, control measures also include improved food inspection, slaughterhouse hygiene, and public education campaigns.	Percutaneous treatment of the hydatid cysts with PAIR (Puncture, Aspiration, Injection, Re-aspiration) technique	Yes (85)	No	High	Low	96/535
Food-borne trematodiases	75	No data	71,095,424	168,500	Veterinary public health measures and food safety practices and education are recommended to reduce the risk of infection. Triclabendazole/ Praziquantel through MDA programs.	Triclabendazole/ Praziquantel	Yes (86)	Yes	High	High	59/269

Table 4b Global data of countries affected by NTDs, drugs donated, burden of each disease, and number of patent families.

Neglected Tropical Diseases (PCT/IDM)	Number of countries	Disease burden			Preventive Chemotherapy/ Intensified disease management				Effectiveness of current interventions		Total granted/ patent families
		Incidence	Prevalence	DALYS	Prevention	Treatment	Resistance	Donated	Prevention	Treatment	
Human African trypanosomiasis (IDM)	13	7,013	10,687	202,400	Vector control and effective disease surveillance.	Pentamidine and Suramin (First stage treatment)	Yes (87)	No	Low	High	41/198
Leishmaniasis (IDM)	10	1,051,824	3,859,307	3,859,307	Vector control and effective disease surveillance. Social mobilization and strengthening partnerships.	Amphotericin B, Miltefosine, fluconazole, itraconazole	Yes (88)	No	Low	High/Low	740/2652
Leprosy(PCT)	136	57,405	514,203	31,000	BCG Vaccination	Multidrug therapy	Yes (89)	No	Low	High	522/2206
Lymphatic filariasis (PCT)	73	No data	38,464,150	2,075,000	Albendazole through MDA programs. Mosquito control is a supplemental strategy supported by WHO.	Albendazole with either ivemectin or diethylcarbamazine	Yes (90)	Yes	High	High	69/287
Onchocerciasis (PCT)	31	No data	15,531,530	1,135,700	Ivermectin through MDA programs. Vector control.	Ivermectin	Yes (91)	Yes	High	High	88/313
Rabies	150	18,312	704	931,600	Integrated bite case management, Preventive immunization (vaccination)	Post-exposure prophylaxis, Integrated bite case management	No	No	High	High	569/2694
Schistosomiasis (PCT)	78	No data	252,339,520	2,613,300	Praziquantel through MDA programs. Additionally, access to safe water, improved sanitation, hygiene education, and snail control.	Praziquantel	Yes (92)	Yes	High	High	321/1722
Soil-transmitted helminthes (PCT)	118	No data	761,893,771	3,378,300	Albendazole/Mebendazole through MDA programs. Health education and improvement in personal hygiene are essential components of prevention.	Albendazole/ Mebendazole	Probably (93)	No	High	High	83/584

Table 4c: Global data of countries affected by NTDs, drugs donated, burden of each disease, and number of patent families.

Neglected Tropical Diseases (PCT/IDM)	Number of countries	Disease burden			Preventive Chemotherapy/ Intensified disease management				Effectiveness of current interventions		Total granted/ patent families
		Incidence	Prevalence	DALYS	Prevention	Treatment	Resistance	Donated	Prevention	Treatment	
Taeniasis	>75	No data	No data	503,000	Praziquantel/ Niclosamide through MDA, identification and treatment of cases, health education including hygiene and food safety, improved sanitation, improved pig husbandry, anthelmintic treatment of pigs, vaccination of pigs, Improved meat inspection and processing of meat products.	Praziquantel/ Niclosamide	Yes (94)	Yes	High	High	48/231
Trachoma (PCT)	42	No data	3,557,122	279,200	Azithromycin through MDA programs SAFE strategy	Azithromycin, Tetracycline	Yes (95)	Yes	High	High	514/2094
Yaws (IDM)	13	No data	No data	No data	Azithromycin through MDA programs. Health education and improvement in personal hygiene are essential components of prevention.	Azithromycin Benzathine Penicillin	Probably (96)	No	High	High	203/880

PCT = Preventive Chemotherapy and Transmission Control
IDM = Innovative and Intensified Disease Management
MDA=Mass drug administration
N/A = Not applicable
SAFE = **S**urgery for advanced disease, **A**ntibiotics to clear *Chlamydia trachomatis* infection, **F**acial cleanliness, and **E**nvironmental improvement to reduce transmission.
Sources: 1) The disease burden disability adjusted life years (DALYS) (the sum of years lost due to premature death (YLLs) and years lived with disability (YLDs)), Incidence (the total number of cases of a given disease in a specified population at a designated time), and Prevalence (the number of new cases of a given disease during a given period in a specified population), values -2015 were obtained from Global Health Data Exchange (97) and (98), 2) The number of countries and drugs used (Preventive Chemotherapy and Transmission Control; and Innovative and Intensified Disease Management) were obtained from WHO fact sheets (99), 3) Data on number of patent families was retrieved from Patseer database, 4) Efficacy/effectiveness/efficiency notes were obtained from the Third WHO Report on Neglected Tropical Diseases (100).

The variable trends in NTDs patenting can be classified into three distinguished catergories. The first category shows an increasing trend in the number of granted patents based on patent families (buruli ulcer, Chagas disease, dengue, onchocerciasis); the second category is mostly characterized by stagnation (echinococcosis, leishmaniosis, leprosy, rabies, schistosomiasis, trachoma, yaws); while the third category lacks a clear trend due to the low number of filings (dracunculiasis, food-borne trematodiasis, HAT, lymphatic filariasis, soil-transmitted helminthes, taeniasis). There was no significant increase in the number of granted patent families for any of the NTDs in the last ten years. The figures of annual patenting trends for each NTD are presented in Appendix 4a-f.

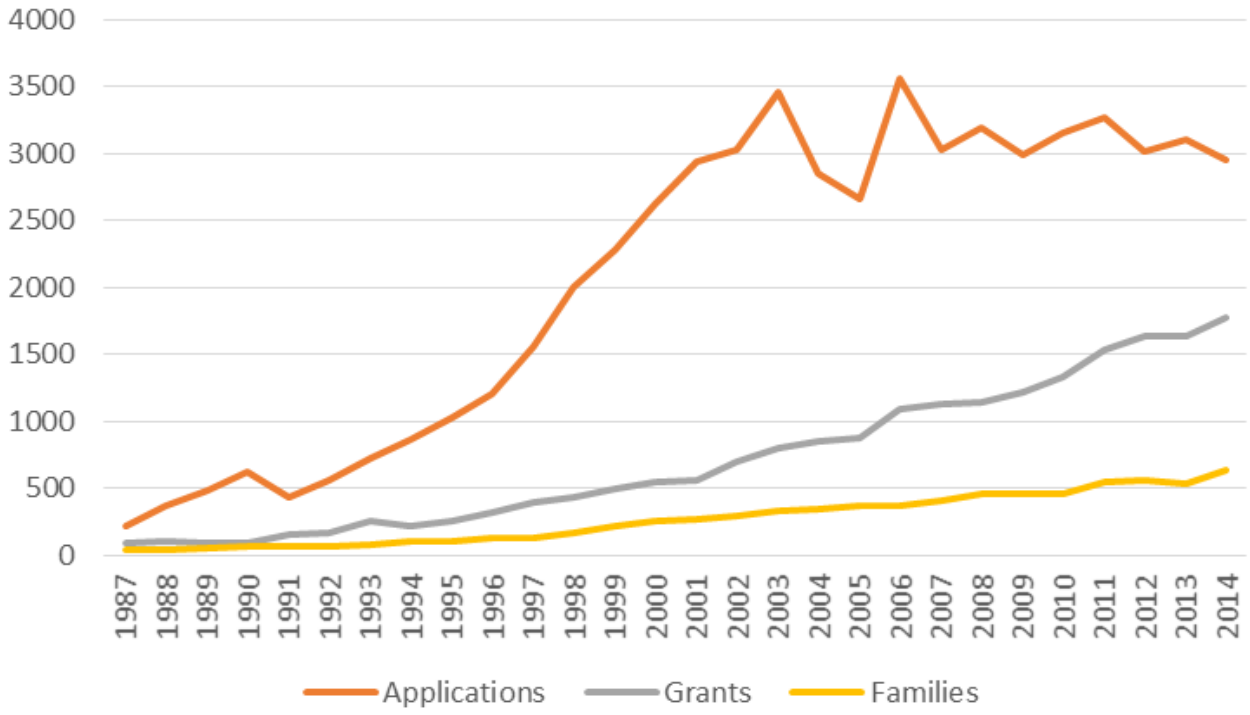

Figure 4 Patenting trend

The overall filing trend in the last 30 years for NTDs reveals an increasing trend between 1985 and 2014. Following the intense growing period between 1985 and 2008, there is no steady increase in the number of total patent families, but there is a slow but continous growth in the number of granted patent families. Patent applications are not published until after 18 months, this explains why no data is presented after 2014.

One may wonder whether there is a difference in patenting trends of IDM and PCT group of diseases. While the biphasic appearance of the trends (growing followed by stagnation/moderate decline) is similar, comparing the patenting trends of the two groups a slight but clear difference can be observed: the IDM group showed a more intense growing period and stagnation (no decline) after 2008 (see Appendix 4, Figures B).

Patent applications are not published until after 18 months, so information after 2014 is not presented in Figure 4. Patents expire after 20 years. Legal status is important for information on commercial exploitability of patents. Analysis of current legal status of the patent families of NTDs, presented in Figure 5, reveals that approximately 50% of the patents are non-active. This fact suggests that investing in NTDs has a low commercial value. Among the 17 NTDs identified, the prevalence of non-active patents is noticeably high in leprosy, schistosomiasis, trachoma and trematodiasis (see Appendix 4, Figures D).

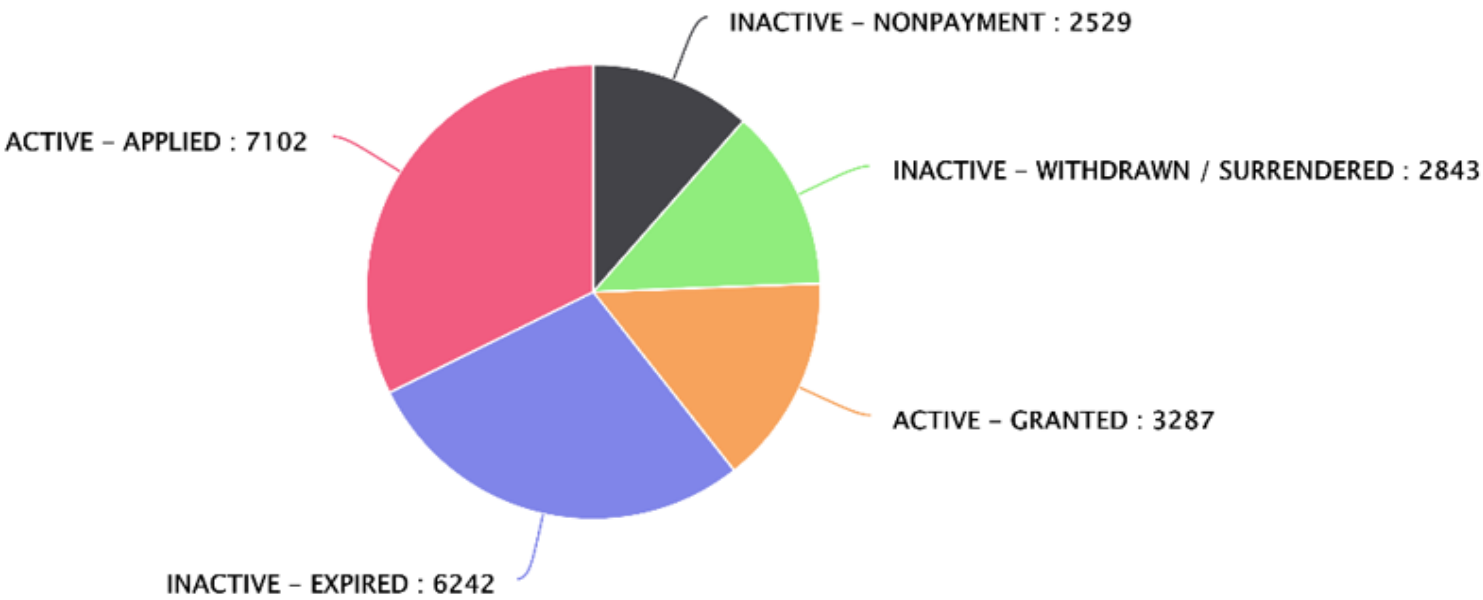

Figure 5 Current legal status of patent families of NTDs

Almost 50% of the patents are not active. Record numbers refer to the number of patent families.

Analyzing the top priority countries (countries where initial patent filing was submitted) for the granted patent families, it was observed that the main priority countries are the United States (US), European Union (EP), Korea (KR), Japan (JP) and Great Britian (GB) in the last 30 years as presented in Figure 6a. However, by focusing on the trend of the total number of patent families, the leading countries are the US, China (CN), JP, EP, and GB. The gap between the first two priority countries is high, the US and China are with 6154 and 2423 patent families respectively. Different patenting activity level of US and China can be assessed by the ratio of applications for patent families and granted patent families: 1898/3302 (10:17) and 87/1525 (1:18) respectively. With respect to NTDs, China appears as an emerging priority country compared with the US since 2010 as presented in Figure 6b. This trend is observed particularly for echinococcosis, rabies, schistosomiasis, and soil-transmitted helminthes. For example, China has a set priority for the soil-transmitted helminthiasis since 2010. Nonetheless, US has kept its leading role in intensive research on NTDs, such as leprosy, leishmaniasis and dengue. An interesting exception is observed for trematodiasis, which has Russia as its important priority country.

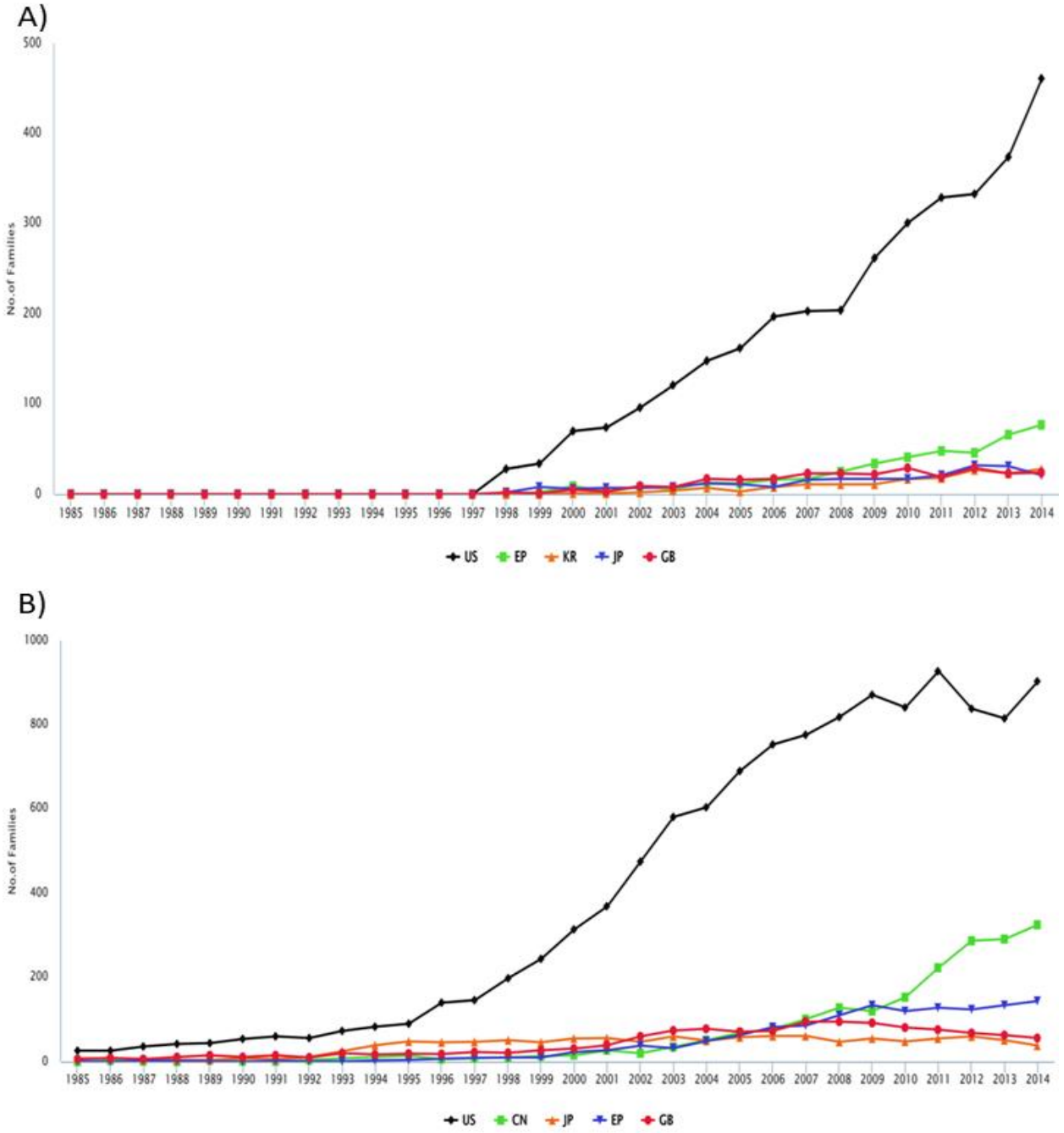

Figure 6 Priority countries by early priority years

A: Main countries with source of inventions are the United States and the European Union-European Patent Office. Record numbers refer to the number of granted patent families. Priority countries are: US (United States), EP (European Union-European Patent Office), KR (Korea), JP (Japan), GB (Great Britain).
B: Main countries with source of inventions are the United States and China. Record numbers refer to the number of patent families. Priority countries are: US (United States), CN (China), JP (Japan), EP (European Union-European Patent Office), GB (Great Britain).

In the US, firms hold a large percentage of patent families in comparison to other interest groups such as individuals, universities, governments, and institutes as presented in Figure 7a. In China, France, Korea, and Russia, more than 50% of patents and applications were assigned to entities other than firms. By focusing on the assignee types of granted patent families, the role of firms is dominant, except for France, Korea and Russia as presented in Figure 7b. In Korea especially the universities, and in Russia not specified assignees are the major patent holders.

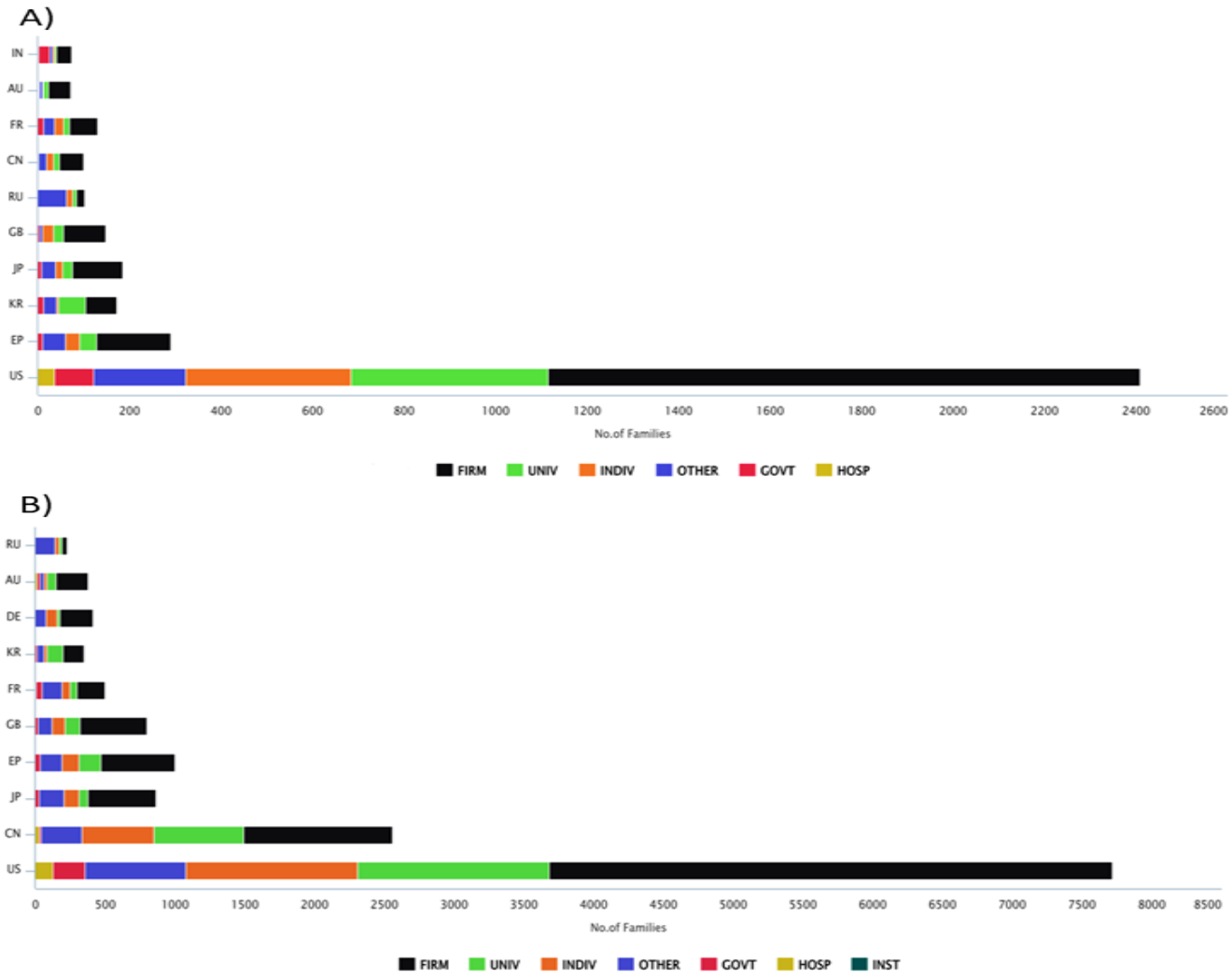

Figure 7 Priority countries by assignee types

A: Firm (firms), indiv (individuals), univ (universities), inst (non-profit institutions), govt (governments) and hosp (hospitals) are assignee types. "Others" classify the assignee names or company names which do not fall under these categories (university, government, non-profit institution, hospital, individuals). Record numbers referring to the number of granted patent families. Priority countries are: US (United States), EP (European Union-European Patent Office), KR (Korea), JP (Japan), GB (Great Britain), RU (Russia), CN (China), FR (France), AU (Australia), IN (India).

B: Firm (firms), indiv (individuals), univ (universities), inst (non-profit institutions), govt (governments) and hosp (hospitals) are assignee types. "Others" classify all the assignee names or company names which do not fall under these categories (university, government, non-profit institution, hospital, individuals). Record numbers refer to the number of patent families. Priority countries are: US (United States), CN (China), JP (Japan), EP (European Union-European Patent Office), GB (Great Britain), FR (France), KR (Korea), DE (Germany), AU (Australia), RU (Russia).

Figure 8a-b provides an overview of the identified NTDs patent landscape in the form of technological fields. The main technological subdomains are pharmaceuticals, biotechnology, organic fine chemistry, analysis of biological materials, basic materials chemistry and medical technology. According to the NTDs trends, pharmaceuticals and biotechnology accounted for most patent families filed in the last 30 years. These two fields have shown substantial growth since 1985 (Fig 8). Filings in organic fine chemistry have dropped in the last ten years (Fig 8). The analysis of biological materials seems to be a popular field of innovation. Patent families for basic materials chemistry and medical technology have also shown substantial growth, in the overall analysis, however, they account for a small portion of the filings. By focusing on the granted patent families the stagnation/decline of the fields of pharmaceuticals, biotechnology, organic fine chemistry is not yet present. The percentage of technical subdomains (pharmaceuticals, biotechnology, organic fine chemistry, analysis of biological materials, basic materials chemistry and medical technology) for alive versus non-alive patent families were similar (Fig 8). The highest proportions were observed in the pharmaceutical field, and the growing proportion of the pharmaceutical patents among dead patent families is caused by the declination in patent applications as presented in Figure 8b. Additionally, by comparing the technical subdomains of the IDM and PCT groups, the same subdomains with the same ranking order was found. However, while the hierarchy among subdomains of IDM is rather constant, there are changes in the positions of the subdomains of PCT. A very important observation is the clear decline in the number of patent families for pharmaceuticals and organic fine chemistry in the group of PCT.

The IPC classification of NTDs patents showed that class A61 is the most prominent class in which NTDs research patents are being categorised. In respect of this categorisation, A61K39/00 (medicinal preparations containing antigens or antibodies) is the most dominant

IPC subgroup within the A61 class. A detailed research focus of each disease is presented by IPC subgroups in Appendix 4, Figures C.

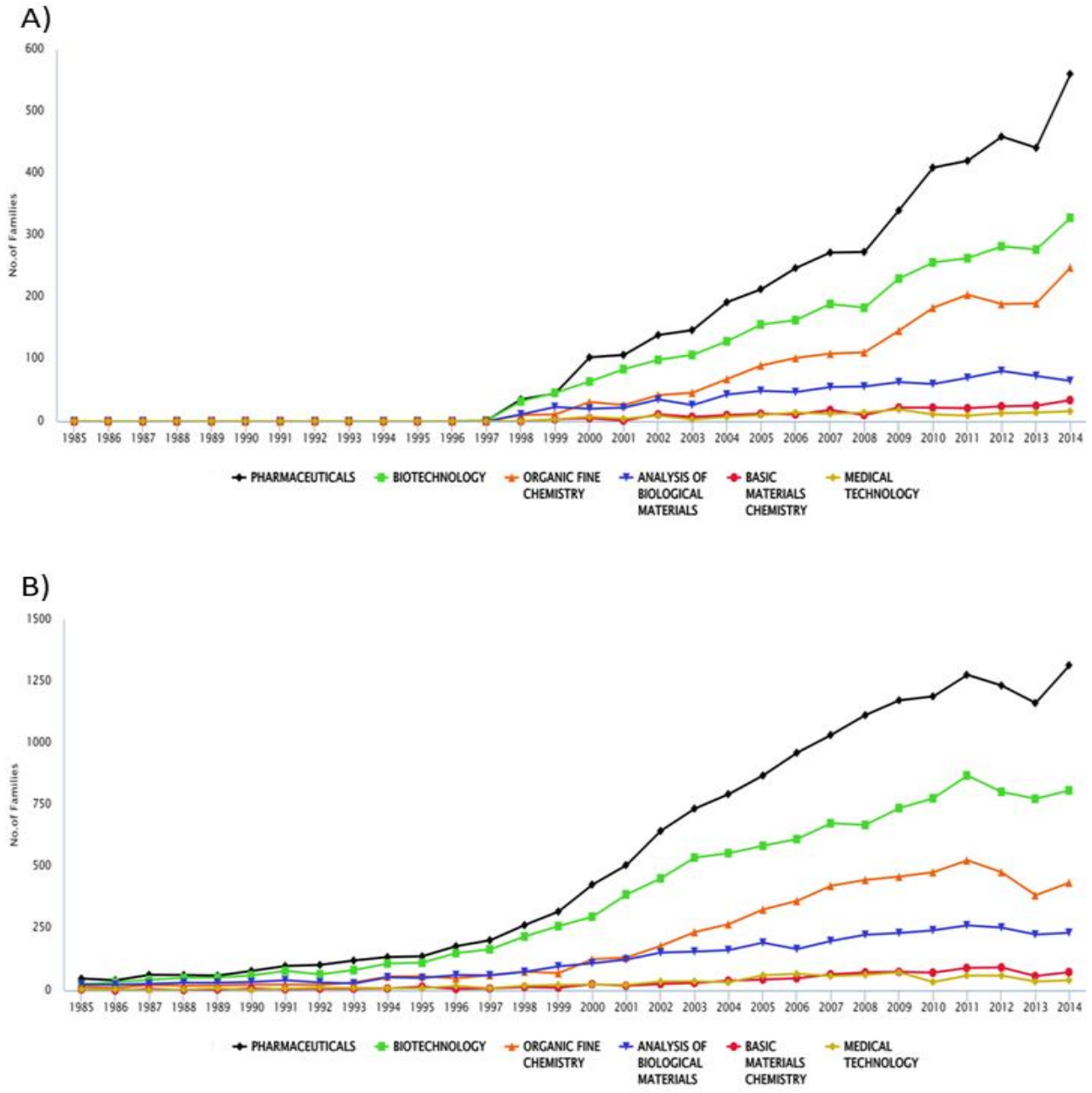

Figure 8 Technological fields of patent families over time

A: The main technological subdomains are pharmaceuticals, biotechnology, organic fine chemistry, analysis of biological materials, basic materials chemistry and medical technology. Continuous growth can be observed especially in the field of pharmaceuticals, biotechnology, organic fine chemistry. Record numbers refer to the number of granted patent families.
B: The main technological subdomains are pharmaceuticals, biotechnology, organic fine chemistry, analysis of biological materials, basic materials chemistry and medical technology. Continuous growth can be observed especially in the field of pharmaceuticals, biotechnology, organic fine chemistry between 1985 and 2011 followed by stagnations/slight decline. Record numbers referring to the number of patent families.

For a patent landscape analysis, analyzing the distribution of active patent applicants in a research field is important. With respect to NTDs research, a lack of dominant assignees (more than 33% of patents) was observed (Figure 9). The main original assignees for NTDs research are governmental institutions and universities, such as Univeristy of California (US) or Pasteur Institute (FR). Among current assignees, firms such as Merck, Vertex Pharma Inc tend to take more financial risks on NTDs research.

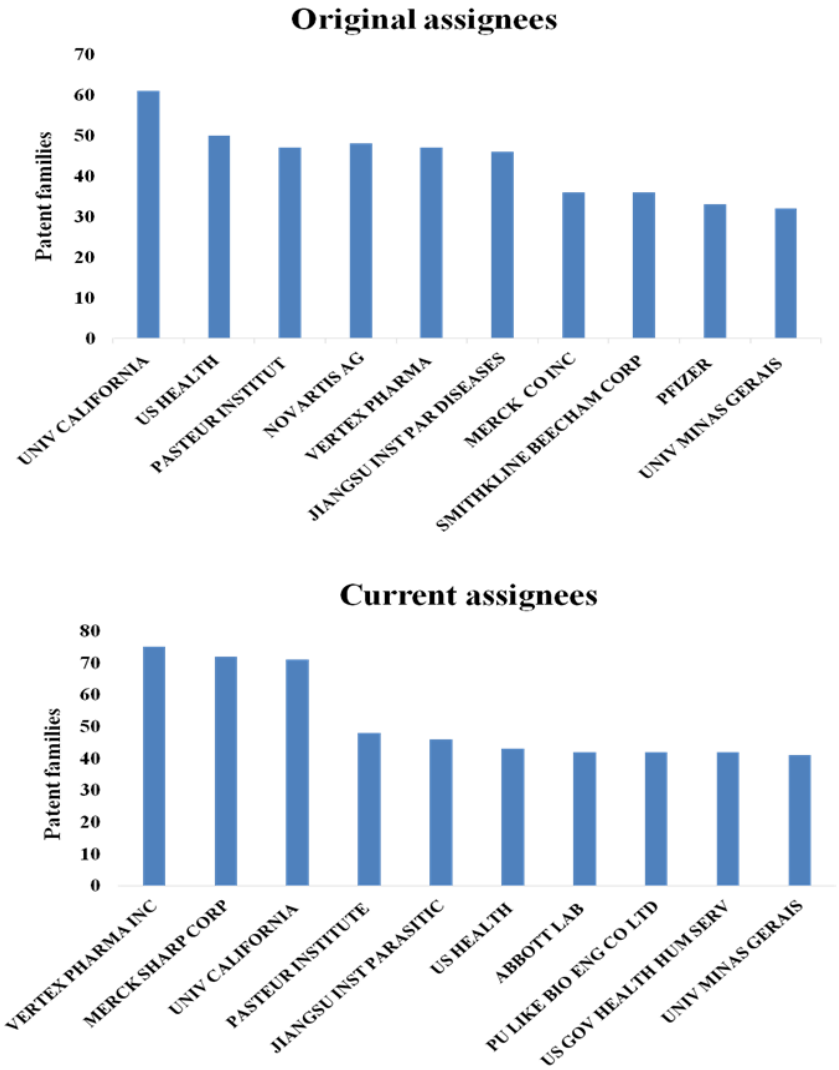

Figure 9 Original and current patent assignees

For patent families of all NTDs, University of California and US Health are the major original assignees, and Vertex Pharmaceuticals, Merck Sharp Incorporation are the main current assigness. Record numbers refer to the number of patent families.

4.3 Drug resistances and neglected tropical diseases: A systematic review.

The development of AMR is a major concern due to the fact that alternative drugs for NTDs-PCT are not able to respond to drug resistance should it occur.

Using the search terms for each identified major NTD, 2916 articles were screened based on title and abstract, and 815 studies were included for full text reading. The two reviewers agreed on 145 decisions, and 37 discrepancies were resolved by discussion and consensus. A total of 108 studies were included in the final review (see Figure 10). The flowcharts of each reviewed NTDs and the corresponding drugs for treatment are provided in Appendix 5.

Out of 11 NTDs, six NTDs have information on drug resistance, namely HAT, leishmaniasis, onchocerciasis, schistosomiasis, soil-transmitted helminthiasis, and trachoma. 3 out the 6 NTDs have old publications that provide information on drug resistance, and most recent articles are from 2012.

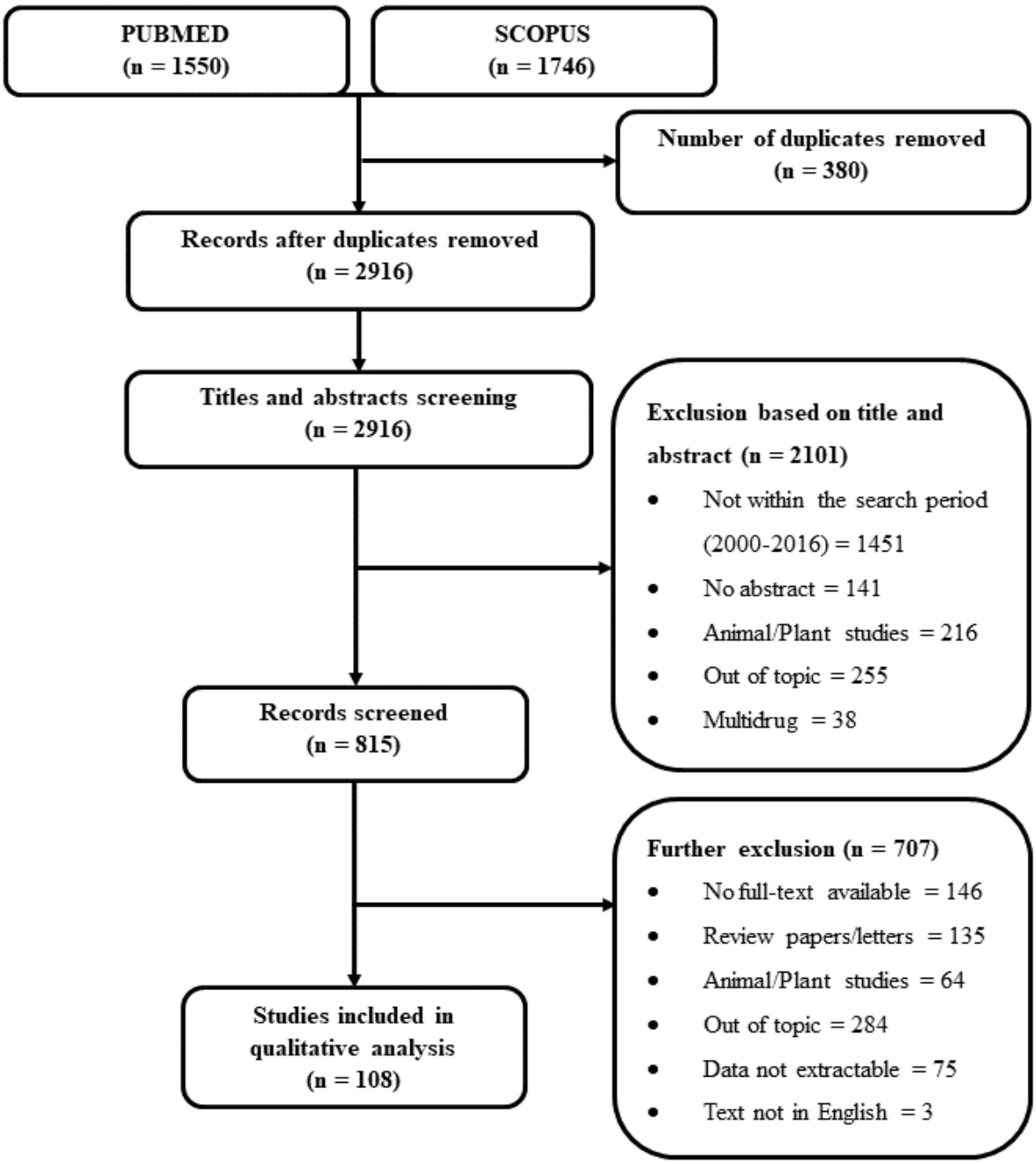

Figure 10 PRISMA flow chart

As presented in Figure 11, there were more publications between 2000-2005 and 2006-2010 in Africa. In Asia, it was observed that the number of publications were steady in 2000-2005 and 2006-2010, with an increase in 2011-2016.

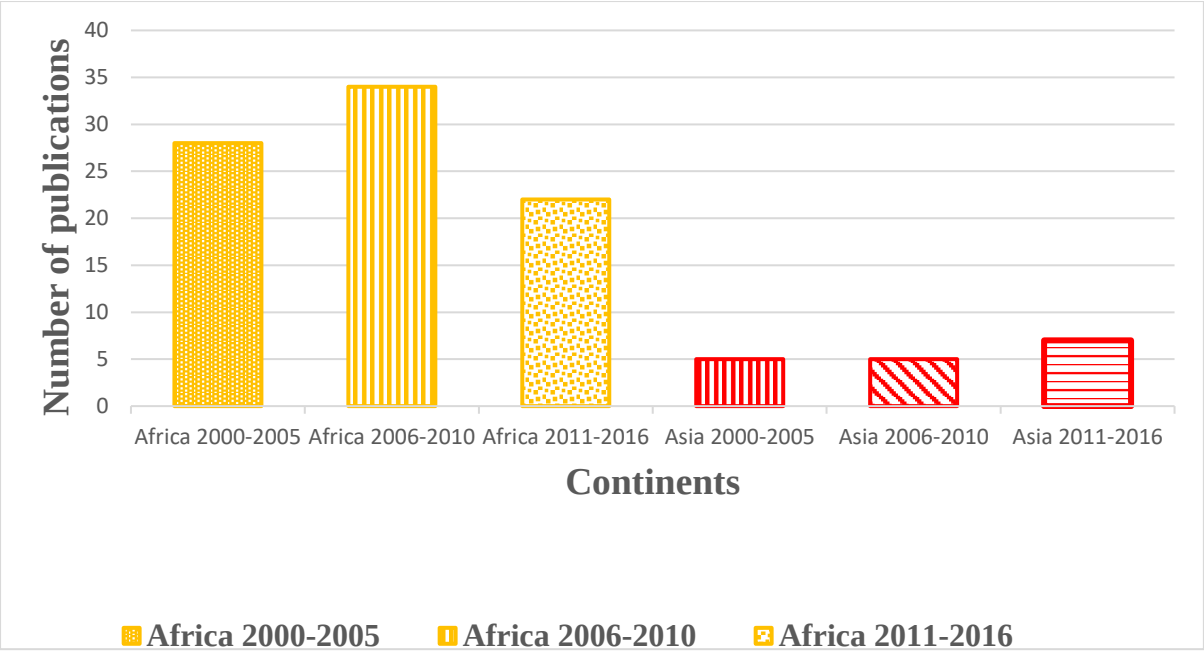

Figure 11 Publication year of studies with continents

Studies in Africa have highest publications in 2006-2010. Studies from other continents are marginal.

Out of a total of 108 studies, 79 were observational studies (26 cohort studies, 28 cross-sectional studies, 16 case reports and 9 case control studies), and 29 articles were experimental studies (21 random experimental studies, and 8 non-random experimental studies). The most studied NTDs are the HAT and schistosomiasis. HAT has the highest number of cross-sectional studies while schistosomiasis has the highest number of cohort study. The study type with respect to the studied NTDs is presented in Figure 12.

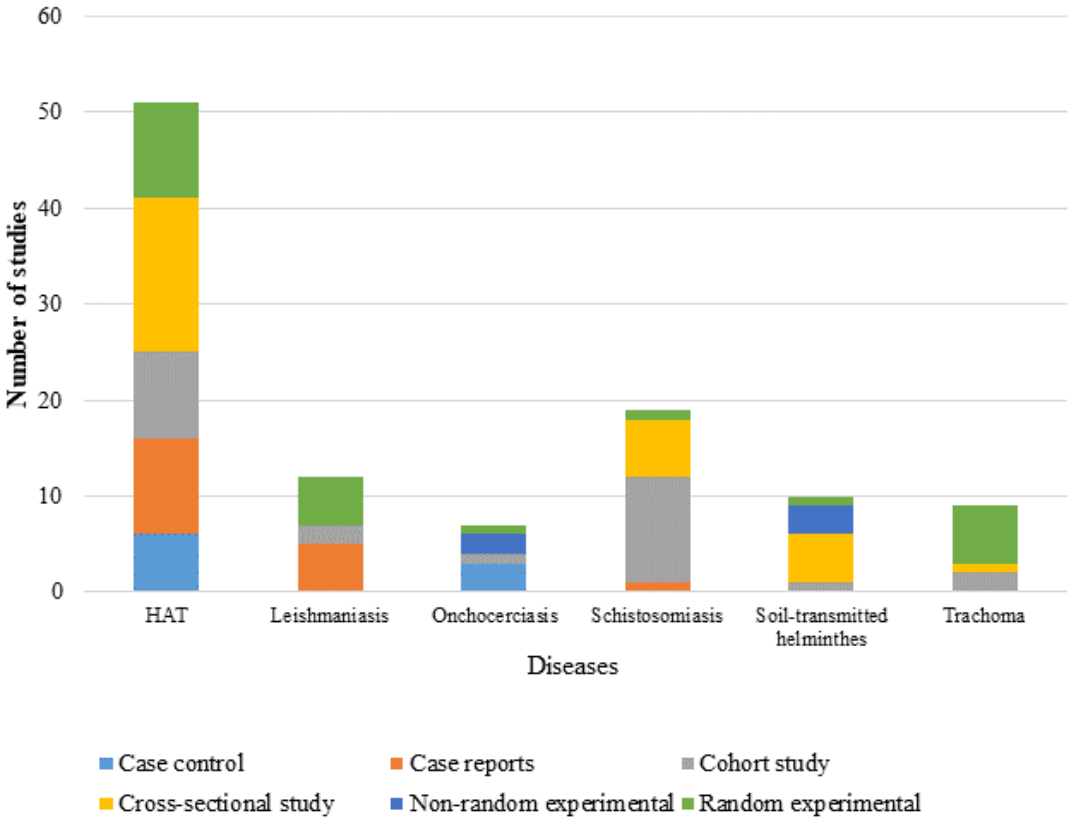

Figure 12 Prevalence of study type of diseases

HAT studies have 31% of cross-sectional studies and 20% case reports. Schistosomiasis studies have 58% cohort studies and 32% cross-sectional studies.

There is a large diversity in the study population. Table 5 presents the average of the study population in the reviewed studies based on study type.

Table 5 Study type and average number of people in each study

Study type	**Average number of people**
Case control	1964
Case report	1.000
Cohort study	1468
Cross sectional study	998
Non-random experimental	3234
Random experimental	1016
Total	**1110**

Studies involving both genders were observed in 84 reviewed articles. Studies on male only were observed in 19 reviewed articles and 5 studies were for female only. Reviewing the age range of the studies, 45 articles were studies conducted on both adults and children, 31 studies were on only adults, and 24 studies involved only children.

With respect to resistance of the reviewed studies, 92% of the articles indicated the confirmation of resistance by test, and 8.0% did not provide enough information on resistance confirmation. 42% of the studies indicated clinical resistance, while the remaining 58% indicated the absence of clinical resistance.

Considering the clinical settings of the reviewed studies, 63 of the studies were conducted outside hospital settings, 36 studies were conducted within hospital settings (34 studies in the hospital wards, 1 study in the intensive care unit and 1 study in the emergency room), and while the remaining 9 studies were conducted on outpatients.

Out of the 108 included studies, 70 were performed in the rural settings, 22 were in the urban settings and 16 did not specify their study settings. Based on the population of subjects studied, 99 studies recorded resistance by test and 45 recorded clinical resistance. Out of the 28 countries of study, it was observed that more studies were performed in South Sudan, Tanzania,

Kenya, Cameroon, Uganda, Cote d'Ivoire, Democratic Republic of Congo (DRC), Angola and India.

78% of the included studies were performed in Africa, 15% in Asia and 1% in Australia.

Of the 84 studies conducted in Africa, 55% were on HAT, 20% on schistosomiasis, 8.3% on both onchoceriasis and trachoma, and 6.0% and 2.4% on soil-transmitted helminths and leishmaniasis respectively. For Asia, 17 studies were conducted, 47% on leishmaniasis, 18% on trachoma and soil-transmitted helminths, 12% on schistosomiasis, and 5.9% on HAT.

Detailed characteristics of the 108 studies included in this systematic review are summarized in Table 6a-b.

Table 6 Characteristics of reviewed NTDs and their treatments

DATA		NEGLECTED TROPICAL DISEASES (NTDs)									
		Human African trypanosomiasis (Studied drugs)				Leishmaniasis (Studied drug)	Onchocerciasis (Studied drug)	Schistosomiasis (Studied drug)	Soil-transmitted helminthes (Studied drugs)		Trachoma (Studied drug)
		Eflornithine	Melarsoprol	Pentamidine	Suramin	Amphotericin B	Ivermectin	Praziquantel	Albendazole	Mebendazole	Azithromycin
YEAR OF PUBLICATION	First	2000	2001	2003	2004	2003	2002	2000	2009	2002	2002
	Last	2014	2012	2014	2012	2014	2012	2014	2013	2012	2015
TYPE OF STUDY	Case control	0	2	4	0	0	3	0	0	0	0
	Case reports	2	1	1	6	5	0	1	0	0	0
	Cohort study	3	1	5	0	2	1	11	0	0	3
	Cross sectional study	3	10	2	1	0	0	6	3	2	1
	Non-random experimental	0	0	0	0	0	2	0	1	0	0
	Random experimental	2	6	1	1	5	1	1	1	2	6
STUDY DESIGN	Experimental	2	6	1	1	5	3	1	2	2	6
	Observational	8	14	12	7	7	4	18	3	2	4
CLINICAL SETTINGS	Emergency unit	0	0	1	0	0	0	0	0	0	0
	Hospital ward	5	13	4	4	8	0	0	0	0	0
	Intensive care unit	0	0	0	0	0	0	1	0	0	0
	Other	2	3	6	4	4	7	18	5	4	10
	Outpatient	3	4	2	0	0	0	0	0	0	0
STUDY SETTINGS	Not specified	4	3	3	2	0	0	1	2	0	1
	Rural	4	17	6	5	2	7	13	3	4	9
	Urban	2	0	4	1	10	0	5	0	0	0
GENDER	Both	7	18	12	3	7	4	14	5	4	10
	Female only	1	0	0	0	1	0	3	0	0	0
	Male only	2	2	1	5	4	3	2	0	0	0
SPECIMEN		CSF and blood	CSF and blood	CSF and blood	Blood	Blood and Organ tissue	Blood and Skin	Blood, Stool and Urine	Stool	Stool	NA

Table 6b Characteristics of reviewed NTDs and their treatments

DATA		NEGLECTED TROPICAL DISEASES (NTDs)									
		Human African trypanosomiasis (Studied drugs)				Leishmaniasis (Studied drug)	Onchocerciasis (Studied drug)	Schistosomiasis (Studied drug)	Soil-transmitted helminthes (Studied drugs)		Trachoma (Studied drug)
		Eflornithine	Melarsoprol	Pentamidine	Suramin	Amphotericin B	Ivermectin	Praziquantel	Albendazole	Mebendazole	Azithromycin
AGE RANGE	Adults	6	8	3	5	5	4	6	0	0	0
	Both	4	12	9	2	6	3	6	0	1	2
	Children	0	0	1	1	1	0	7	5	3	8
USAGE	Individual	9	16	7	7	8	5	16	4	4	3
	Mass	1	2	6	0	4	2	3	1	0	7
	Other	0	2	0	1	0	0	0	0	0	0
DDD	Maximum	400 mg	100 mg	300 mg	100 mg	48 mg	150 mg	40 mg	400 mg	500 mg	20 mg
	Minimum	100 mg	2.2 mg	4 mg	10 mg	3 mg	0.15 mg	NA	NA	NA	NA
RESISTANCE BY TESTS	Yes	9	18	13	8	9	6	18	5	4	9
	No	1	2	0	0	3	1	1	0	0	1
CLINICAL RESISTANCE	Yes	6	6	7	7	10	0	4	1	0	4
	No	4	14	6	1	2	7	15	4	4	6
EXPOSURE VARIABLE	Defined daily dose	10	17	13	8	12	6	19	4	4	9
	Clinical manifestations	0	3	0	0	0	0	0	0	0	0
	Genetic manifestations	0	0	0	0	0	1	0	1	0	1
COUNTRIES OF STUDY		Angola, Cote d'Ivoire, Democratic Republic of Congo, Germany, South Sudan, Uganda and Western Australia.	Angola, Cameroon, Cote d'Ivoire, Central Africa Republic (CAR), Democratic Republic of Congo, Equatorial Guinea, Kenya, South Sudan, Tanzania, and Uganda	Angola, Central African Republic (CAR) Cote d'Ivoire, Democratic Republic of Congo, Equatorial Guinea, South Sudan, and Uganda	Belgium, Cameroon, Democratic Republic of Congo, India, London, Malawi and Tanzania	Brazil, China, Ethiopia, India, Sudan, and Kenya	Cameroon, Ghana and South Sudan	China, Cote d'Ivoire, Egypt, Kenya, South Sudan, Tanzania, Uganda, and Zambia	Brazil, Cambodia, Cameroon, Ethiopia, Haiti, India, Indonesia, Kenya, Panama, Tanzania and Vietnam	Indonesia and Tanzania	Ethiopia, Nepal, and Tanzania

CSF: Cerebrospinal fluid
DDD: Defined daily dose
NA: Not applicable

Also, this review has tried to establish a link between the countries of studies and disease burden. DRC, Angola, Uganda and South Sudan have more HAT studies. HAT is highly prevalent in DRC (5,324), Central Africa Republic (CAR) (567), and Gabon (264) as shown in Figure 13. It was also observed that HAT studies were conducted on both adults and children. Most of the reviewed studies were performed in the rural communities of the countries of investigation.

The highest number of studies on leishmaniasis was observed to have been performed in India. Other countries of study were Brazil, China, and Ethiopia. Leishmaniasis is highly prevalent in Afghanistan (2,718,088), Yemen (563,129), and Pakistan (468,699) as shown in Figure 14.

Studies on soil-transmitted helminthes were carried out mainly in Brazil, Cambodia, Cameroon, and Ethiopia. The highest number of studies was observed in the Republic of Tanzania. Soil-transmitted helminthes is highly prevalent in China (110,467,322), India (222,188,768) and Nigeria (47,675,898) as shown in Figure 15. Approximately 90% of the studies reviewed were conducted on children in the rural communities.

Studies on schistosomiasis were mostly conducted in Africa. The highest numbers of studies were observed in Egypt, Cote d'Ivoire and Kenya. Schistosomiasis is highly prevalent in the following countries; Nigeria (35,206,218), DRC (22,147,801), and Ethiopia (21,988,940) as shown in Figure 16.

Studies on trachoma were conducted in Africa and Asia. It was observed that trachoma studies were only conducted in Tanzania, Ethiopia and Nepal. Trachoma is highly prevalent in India (1,758,651), China (320,309) and Egypt (175,849) as shown in Figure 17.

Studies on onchocerciasis were only conducted in Cameroon, Ghana, and South Sudan. The prevalence of onchocerciasis is high in DRC (7,498,418), Nigeria (2,277,404) and South Sudan (1,343,869) as shown in Figure 18.

Source: The maps and prevalence of the studied NTDs were created and retrieved from Global Health Data Exchange (101).

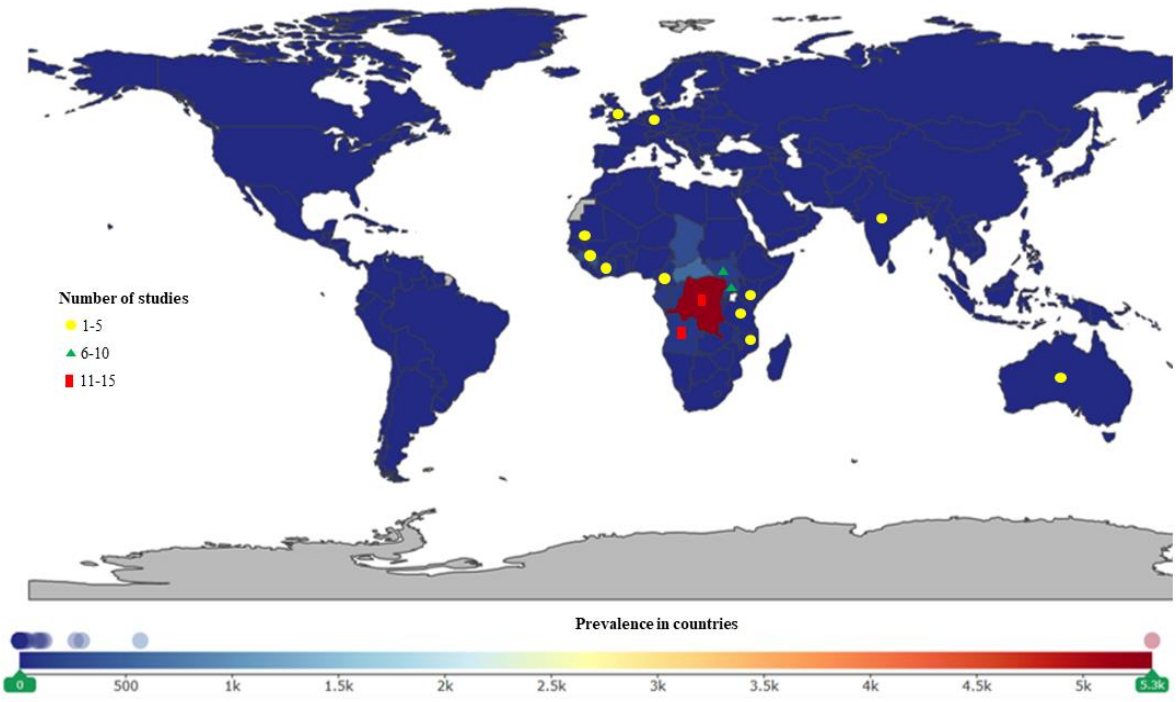

Figure 13 Geographic overlap and distribution of HAT

HAT studies were conducted in Africa, Asia, Australia and Europe. More studies were conducted in DRC, Angola, South Sudan and Uganda. DRC, CAR and Gabon have the highest number of prevalence.

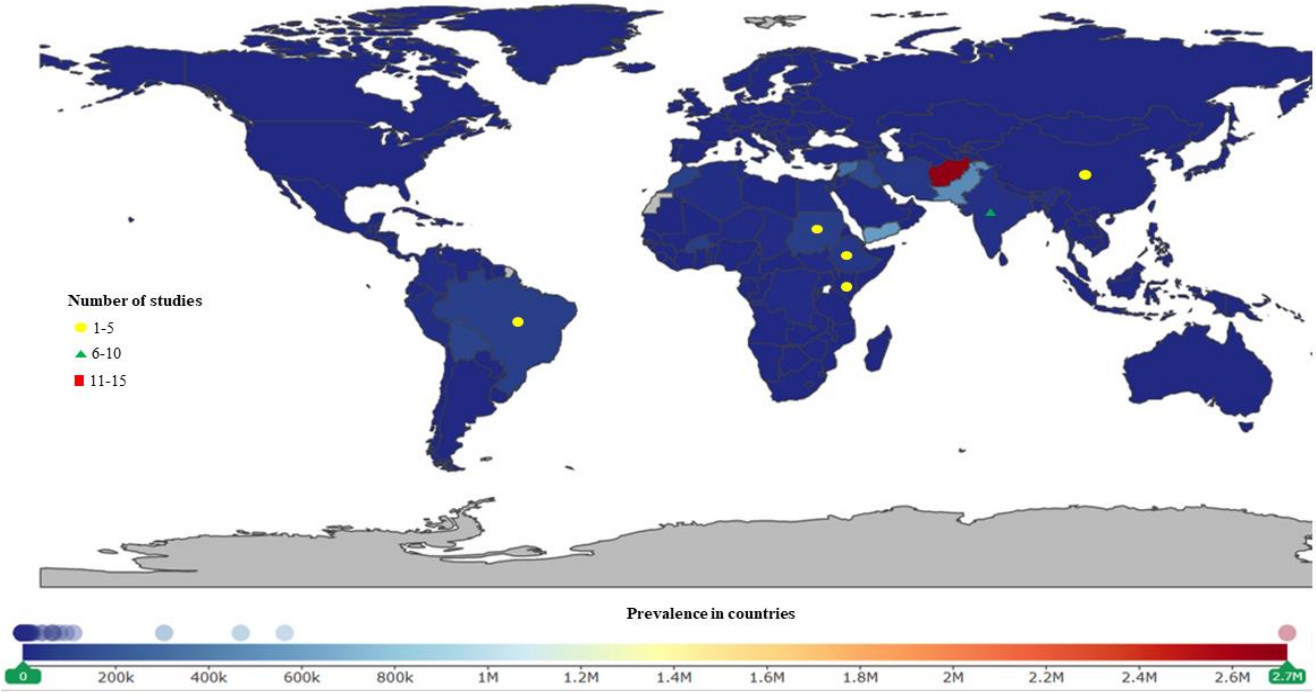

Figure 14 Geographic overlap and distribution of leishmaniasis

Leishmaniasis studies were conducted more in Asia. India has the highest of studies. Afghanistan, Yemen and Pakistan have the highest number of prevalence.

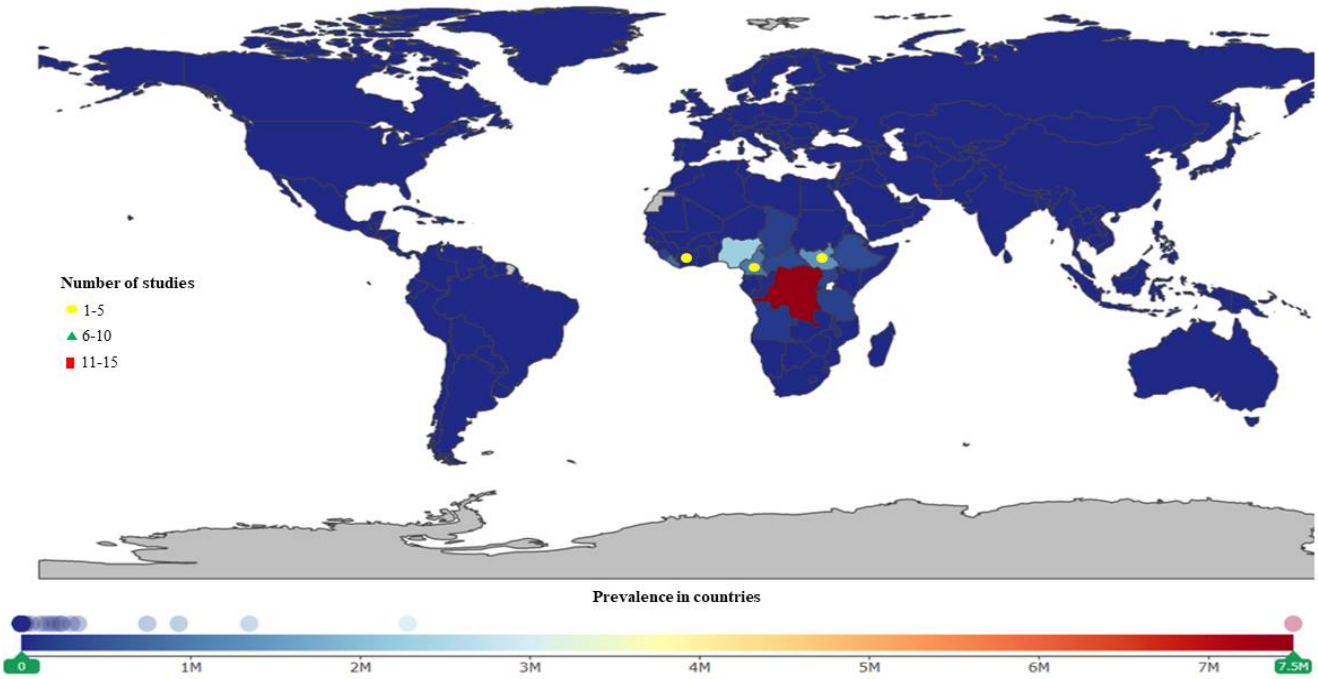

Figure 15 Geographic overlap and distribution of onchocerciasis
Onchocerciasis studies were conducted only in Africa (Cameroon, Ghana and South Sudan). Onchocerciasis is highly prevalent in DRC, Nigeria and South Sudan.

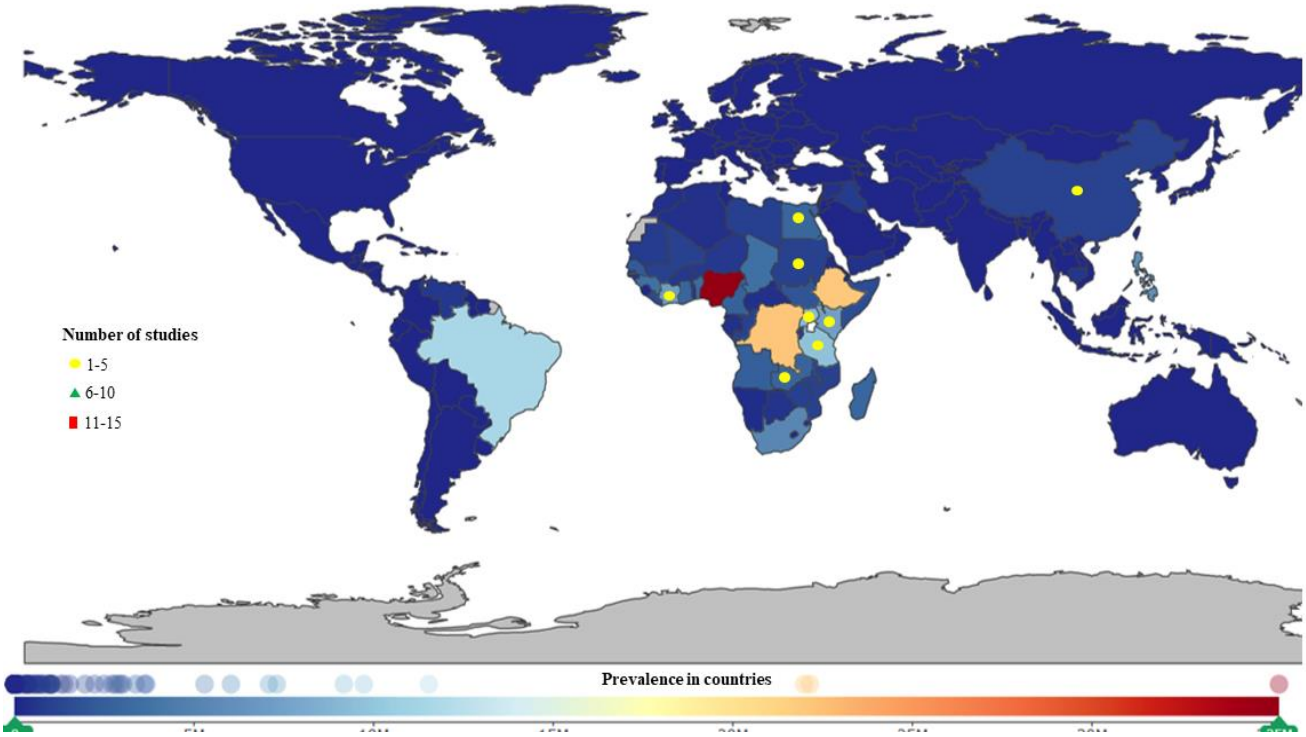

Figure 16 Geographic overlap and distribution of schistosomiasis
Schistosomiasis studies were mostly conducted in Africa. Egypt and Cote d'Ivoire have the highest number of studies. Nigeria, DRC and Ethiopia have the highest number of prevalence.

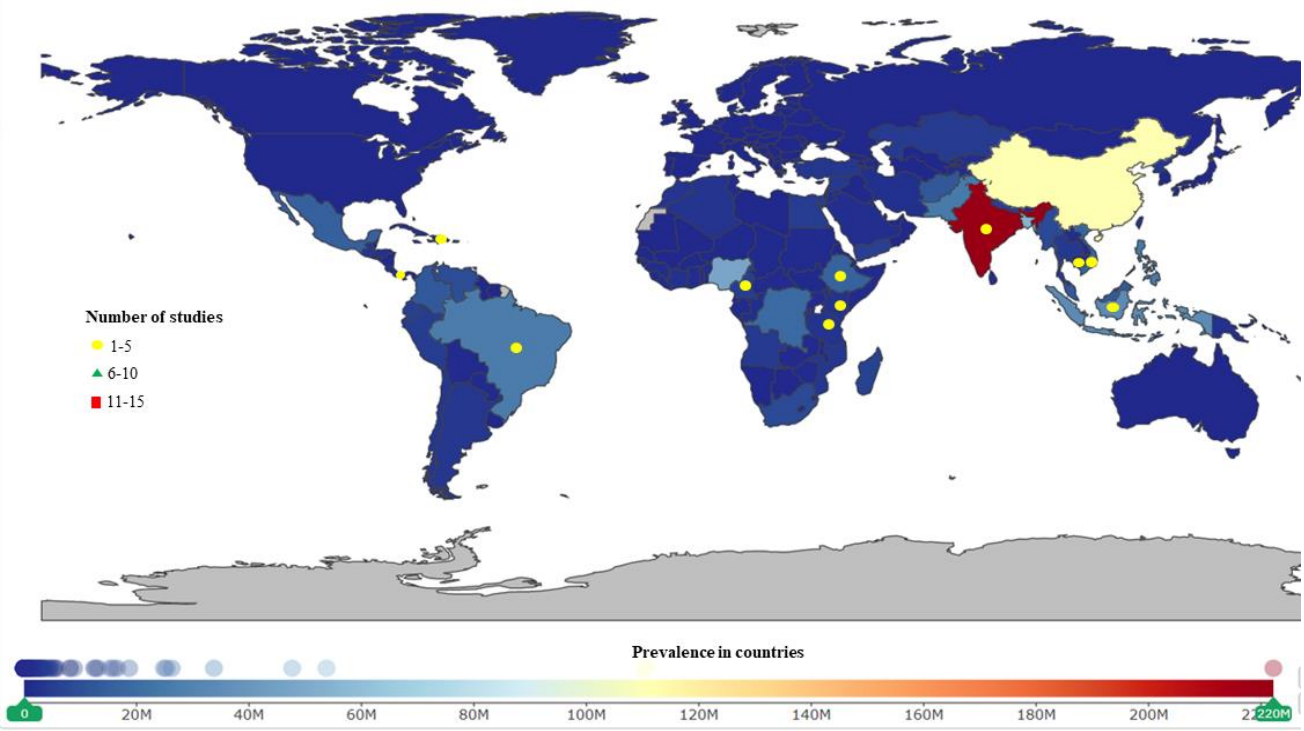

Figure 17 Geographic overlap and distribution of soil-transmitted helminths
Soil-transmitted helminthes studies were conducted more in Africa. China, India and Nigeria have the highest number of prevalence.

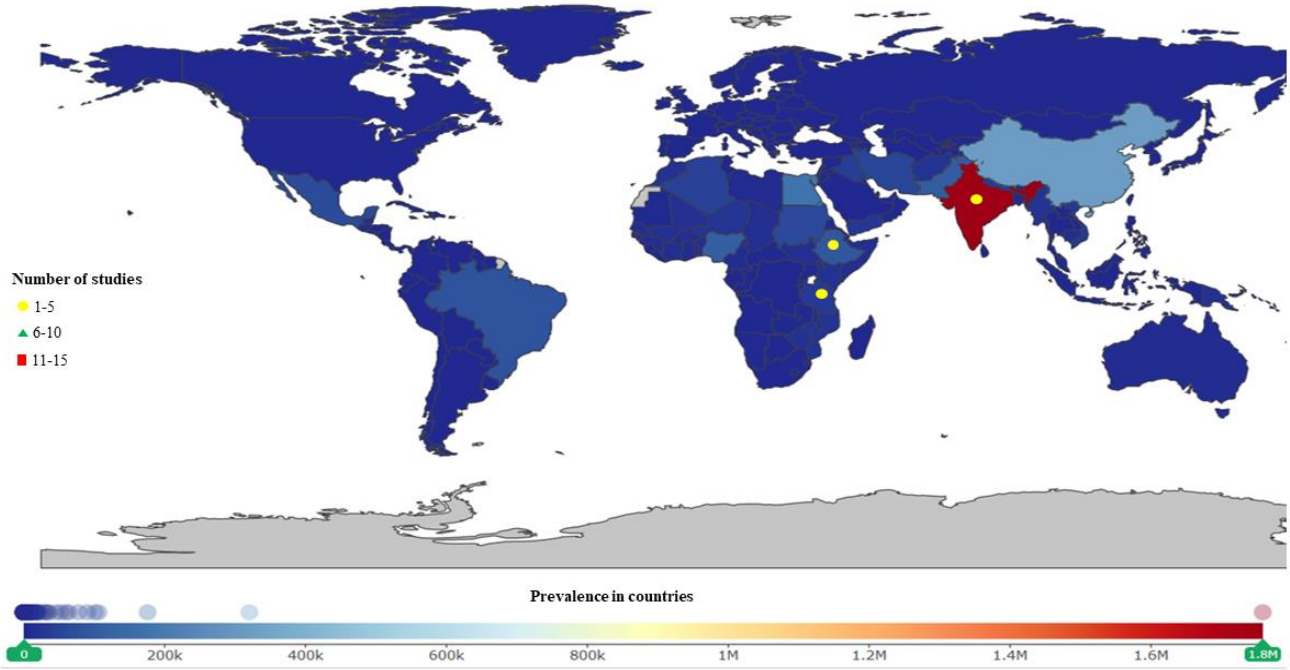

Figure 18 Geographic overlap and distribution of trachoma
Trachoma studies were conducted more in Africa and Asia. Tanzania, Ethiopia and Nepal have the highest number of studies. Trachoma is highly prevalent in India, China and Egypt.

Methodological quality assessment

In the overall assessment, the methodological quality of 6 reviewed studies was rated as strong, 23 and 79 articles were rated as moderate and weak respectively (full details of the quality assessment are provided in Appendix 6a-c). 20 reviewed studies were rated as weak for data collection because the authors did not provide sufficient information on the validity or reliability of their measure of collection, 40 rated moderate and 42 articles rated strong. With respect to confounders, thirty-seven articles were rated as weak, and eighteen and fifty-two articles were rated as moderate and strong respectively. Based on data analysis involved in each reviewed studies, 63.3% of the reviewed articles were rated as strong, while 14.3% and 22.4% were rated as moderate and weak respectively. The reporting quality of the reviewed articles was also analyzed. Out of the 108 articles included, 59.3% were rated as strong, 28.7% and 12.0% were rated as moderate and weak respectively.

CHAPTER FIVE

5.0 DISCUSSION

R&D is an important contributor to improving health and thus an essential component of investments in health (102). R&D landscape areas include initial discovery, proof of principle, risks and benefits, delivery, and evaluation of impact. With such a wide range of possible contributions from so many ongoing R&D initiatives globally, it is exceedingly difficult to predict which innovations and discoveries in fundamental science will lead to a translational breakthrough. In recent times, R&D spectrum has been threatened by economic austerity. It is important to note that for every decade without continuing investments in R&D (development of new and better technology for diagnostics, drugs, vaccines, and strategies to implement them, with improved or wider potential impacts on health), there will be a decade set back (103).

5.1 Rett syndrome Research Landscape

Understanding how funders contributed to different research directions is a pillar of research landscape analysis. Conventionally, R&D has been generally covered by private funding and basic research by public sector funding (104). An appropriate and strategic structure of funders is a principal significance in the formulation of research policy (105). The significance of such structure has been recognized by the EC in the Lisbon agenda (Barcelona targets) which states that, "the appropriate split for R&D is 1/3 financed by public funds and 2/3 by private industrial funds" (106, 107). From the study, R&D split for Rett syndrome research does not align with the Lisbon agenda. Approximately 70% of Rett syndrome research is financed by public funds (20% by governments, 50% by the EU) and 30% by NPPOs. A landscape analysis of Rett syndrome research funding which was published in 2008 by the International Rett Syndrome Foundation (IRSF) reported similar split for research funding. Public agencies contributed 77% of all funds (72% from the NIH alone that gives an 88% funding from the US for Rett syndrome

research) while private grant contribution was 23% (55% of which originated at the IRSF, representing 12.7% of the total funding) (17).

From the study, the total expenditures on Rett syndrome research was almost €70 million, with a peak between 2008 and 2011. National public research expenditure decrease in EC while NPPOs research contribution increased after 2008. It can be deduced that the economic crisis in 2008, which affected the EC had an impact on national research budget (108) than NPPOs. Also, one can elucidate that reversibility of symptoms discovered in the field of Rett syndrome boosted the NPPOs research funding (16). From Table 2 and Figure 2, the information showed that NPPOs supported most of the projects but EC provided the largest amount of funds for Rett syndrome research.

With respect to the research topics, a massive dominance of basic research topics was observed to be in consonance with the results of IRSF report on Rett syndrome landscape analysis, which although, had a slightly different research topic categorization (17). The IRSF study reported that 82% was for etiological research, and 0.5% for treatment development. The distribution of the funding allocation reflects the genetic nature of the disease and the lack of treatment (109). Additionally, the evolution of profile research projects is influenced by the development and accessibility of novel technologies, such as genome/exome sequencing. Further explanations may exist for marginal funding in human and social sciences, including the fact that health care systems vary largely in different European countries. The lack of strong interconnections between researchers and health care givers may be a source of difficulty for the European research projects.

The landscape study indicates that funders' research activity is not homogeneously distributed among European member states. Most projects were performed in Italy and UK. The public in UK and Italy has a long history of shaping global research culture of promoting excellent research and researchers, and they have been actively involved in charities. Notably, Adrian

Bird's team discovered the ground breaking (and Rett UK Fund) reversal of Rett syndrome in mice in 2007. This piece of research has become the basis of many further studies into the MECP2 gene and its role in Rett syndrome. An overlap was identified in the research density of NPPOs commitment to research activities. NPPOs supported mostly national research groups and their involvement in national research financing was crucial because of their regular funding. This inclination is important because commitment from these funders may help to consolidate scientific communities (110). Although, the role of NPPOs is very important for research funding, it should not be considered as a single pillar of sustainability, since private non-profit organizations also fund research via the calls for projects and not always provide recurrent funding.

5.2 NTD Research Landscape

Patent landscape analysis provides insight into the innovations that underlie technology and products. A completed patent landscape analysis project consists of a set of technical references and accompanying analytics from which important legal, business, and technology information can be extracted. This information enables large corporations, startups, universities, research institutions, and investors to understand and make informed decisions prior to investing time and money into new technology and product development opportunities (63). Patent landscape reports (PLRs) provide a snapshot of the patent situation of a specific technology, either within a given country or region, or globally. They can inform policy discussions, strategic research planning or technology transfer. They may also be used to analyze the validity of patents based on data about their legal status (111).

This research addresses the patenting trends, current legal status of patents, priority countries by earliest priority years and their assignee types, technological fields of patent documents over time, and lastly, original and current patent assignees of NTDs.

This study shows a long term trend with a continuous growth in the number of patent families of NTDs with a slight decrease after 2008. This continuous growth in trends is not uniform for all the NTDs because a significant decline in trachoma and leprosy research were observed. Focusing on the granted patent families, a stagnation was observed after 2008, not a decline. Additionally, previously marginalized diseases such as dracunculiasis were successful in attracting research interest in the last ten years. However, global patenting trend is in sharp contrast with our findings on NTDs. In the last 20 years, the total number of global patenting applications has tripled (112), but NTD patent application has not increased.

In order to demonstrate the proportions of patenting activity effectively, the number of patent families, corrected for normalized DALY (2015), were compared with a few other selected similarly robust social, health and economic impact diseases such as HIV/AIDS, malaria, cardiovascular diseases, cancers, and lung cancer (98). The gap between patenting NTDs and cardiovascular diseases/cancers is conspicuous; the number of filed patents for cardiovascular diseases or cancer is at least 200 times larger than NTDs. Individual NTDs lag behind lung cancer, malaria or HIV/AIDS in patenting activities. In a study by Anthony and Quentin (103), it was discovered that, in a survey of R&D projects focused on neglected diseases, BioVentures for Global Health found 218 R&D projects on AIDS, tuberculosis and malaria which is over four times the number of projects on diarrheal diseases and pneumococcal disease (103). R&D interests among NTDs is very uneven. Leishmaniasis, dengue, schistosomiasis and rabies accounted for most of the growth in patenting activities. An obvious link between disease burden or availability of treatment (eg. PCT or IDM category) and patenting activity could not be identified in this study. This study finding shows that there is a limited attractiveness in this field, and this is consistent with previous articles on novel drug and vaccine landscape of NTDs by showing decrease as a tendency. Cohen *et al*., found 32 new chemical entities between 1975 and 1999, while between 2000 and 2009, there was only 26 newly approved drugs and vaccines

for NTDs (113). Pedrique *et al*., reported that most progress towards reducing the burden of NTDs focuses on repurposing or reformulating existing drugs (114). The Bill and Melinda Gates Foundation which has funded Policy Cures Research to conduct the last nine annual G-FINDER surveys also found stagnation in terms of new chemical entities of NTDs (115).

The analysis of this study also showed that the US is losing its position as a major priority country. This is consistent with the fact that China now drives global patent applications beginning with a new record achieved in 2015 (77). For the first time, more than 3 million patent applications were filed worldwide in a single year, with a 8.3% increase from 2015. Such a strong growth was driven by an exceptional number of filings in China, which received about 236,600 or 98% of additional filings while the next largest contributor was the US with around 16,200 additional filings (116). Diversity between original and current assignees such as US Health vs Merck & Co.; Pasteur vs Vertex Pharma Institute have been found in the patent database. This is a clear sign of emerging new interested parties. However, a high number of non-firm assignees indicates the limited level of industrial maturity in this field. A higher percentage of firms are assignees resident in the US in the field of NTDs compared to China. However, in China, there is a high proportion of patent families linked to univeristies or individuals which indicates high research activity.

Most patent applications do not become patents, and many patents do not survive to the end of their terms. Every day, patents are becoming dead for failure to pay maintenance fees or other deficiencies (117), which is an additional concern for the high proportion of expired NTDs patents. Expired patents have limited strategic value to their assignees. This is because others cannot be excluded from using the invention(s) disclosed in the patent. Under the current Patent Act, patents last a maximum of 20 years from the date of filing. There ise also ‘Old Act’ in which patents expiry is 20 years later from the date of filing or 17 years from the date of issue (117). However, information from expired patents may be relevant in the mitigation of NTDs,

and can be used by NGOs or private-public partnerships who are key players to curbing the spread of NTDs (118).

The overall description of information contained in patent families was through technology fields. The main technology subdomains with emerging trends are pharmaceuticals and biotechnology. Many of the patents retrieved have strong focus towards medicinal preparations containing antigens or antibodies.

Based on the method of patent landscape analysis, patent families of each NTD were identified, merged and analysed to get overall insights regarding the trends, topics, and stakeholders in this field. This research could be a robust basis for future research in order to plan, monitor or justify decisions for R&D policies. From this study, it is important to intensify R&D efforts in NTDs through the development of new innovations. R&D does not provide answers for several observed problems within the NTDs. It is imperative to pay attention to the broad social factors affecting NTDs; parallel improvements in hygiene, sanitation and access to medical care. Finding effective ways for development seems possible through public-private partnerships or new innovative alliances, established on case by case basis. Ways of addressing social challenges of NTDs may be found by taking good examples from HIV/AIDS management (119). Finally, R&D analysis alone cannot show trends and future scencarios of research fields. Patent landscape analyses are quite simple, yet an effective way of planning and/or monitoring R&D of NTDs.

5.3 NTD Drug Resistance

In addition, the study identified the trends of drug resistance for 11 major NTDs and 20 drugs over a specific period by analyzing: the study type, socio-demographic factors, resistance, study settings, geographical locations, and countries of studies. AMR threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi. AMR is an increasingly serious threat to global public health that requires

action across all government sectors and society (120). Loss of drug-effectiveness because of antimicrobial resistance (AMR) is increasing in both developing and developed countries. If this trend continues unchecked, the world will confront a reality where many infectious diseases have “no cure and no vaccine” (121).

This study reviewed 11 out of 20 NTDs identified by WHO as the most important NTDs (38), and have specific drugs for treatment, and they are Chagas disease, food-borne trematodiasis, HAT, leishmaniasis, leprosy, lymphatic filariasis, schistosomiasis, soil-transmitted helminthiasis, taeniasis, onchocerciasis, and trachoma.

One of the major findings of this study is that only six NTDs have information on drug resistance, namely HAT, leishmaniasis, onchocerciasis, schistosomiasis, soil-transmitted helminthiasis, and trachoma, while there was lack of data to determine the magnitude and scope of AMR in the other reviewed NTDs. It can be inferred that the missing data were from countries without surveillance or as a result of under-reporting in some countries. WHO is committed to developing a global consensus approach to AMR monitoring, with predefined measures of impact and outcome consistent with GAP (122). WHO is supporting Member States to develop national action plans on antimicrobial resistance, based on the GAP. One of the main objectives of GAP-AMR is to ensure that there is successful treatment and prevention of infectious diseases with effective and safe medicines that are quality-assured, and accessible to people at risk (123, 124). Global AMR surveillance (GLASS) is the cornerstone to assessing the spread of AMR, by informing and monitoring the impact of local, national, and global strategies (123). WHO is providing technical assistance to help countries develop their national action plans, and strengthen their health and surveillance systems so that they can prevent and manage antimicrobial resistance. It is collaborating with partners to strengthen the evidence base and develop new responses to this global threat (120). However, there is no harmonized system in place to standardize the collection of AMR data that can present a comprehensive

purview of the global occurrence of AMR (122, 123). Even though PCT-MDA programs are currently effective in mitigating the morbidity of NTDs and improving life quality in the most affected countries (125), there is insufficient information on programs monitoring the effects of PCT-MDA. For an effective monitoring of AMR, collection of surveillance is paramount to inform and estimate AMR burden of NTDs. The integrated NTD database developed by WHO to improve evidence-based planning and management of NTD programs at the national and sub-national levels following a recommendation by the Working Group on Monitoring and Evaluation of the Strategic and Technical Advisory Group for NTDs does not contain information on AMR (126). Immersed efforts are required to ensure that treatments are implemented efficiently and that monitoring and surveillance tools are improved (127). Inefficient monitoring and surveillance tools, coupled with reporting systems will hinder progress towards the 2020 roadmap targets for NTDs. The health systems in countries where NTDs are endemic are often constrained by insufficient funding, limited human resources, insufficient management and poor governance which has impact on the NTD volunteers in those regions (128).

This study also showed inadequate research efforts on AMR due to limited number of NTDs studies reviewed. AMR being one of the greatest public health challenge, there is need to identify the current research gaps and fund innovation (129). The limited efforts on research were also observed in the last year of publication of reviewed NTDs. The most recent publications of NTDs such as HAT, onchocerciasis and soil-transmitted helminthes studies were published in 2012.

This study finding showed that there is a high prevalence of resistance by tests, approximately 90% in each of the studied NTDs. Although, less than half of the reviewed studies indicated clinical resistance. This indicates that observing people is not enough, there is an urgent need for accessible diagnostic technologies for AMR (42). It has been observed that PCT suboptimal

effect is weak, and this maybe as a result of increased drug pressure due to the mechanism of drug resistance. Drug efficacy monitoring is important for control programs based on PCT in order to support the correct use of antimicrobial (dosage, frequency, combinations), by ensuring the implementation of successful mitigation strategies (130, 131). According to a survey by experts (132), the survey respondents were of the opinion that a major challenge for elimination of the NTDs is drug resistance. This is as a result of global health community's previous experience with malaria, in which resistance was found to have emerged after the mass distribution of medicated salts (133). AMR has been recorded in malaria treatment, due to inappropriate, badly executed, or poorly accepted MDA. However, effective MDA with good adherence can prevent the emergence of AMR (134). This study also showed that there was more information on the individual usage of the drugs compared to MDA. PCT-MDA NTDs like onchocerciasis, schistosomiasis, and soil-transmitted helminthes studies had less information on their MDA programs. The issue of low coverage of MDA program is not a surprise, it is a recognized challenge as the 2020 deadline for most NTDs approaches.

This analysis discovered that some of the reviewed studies were conducted in countries where NTDs are prevalent and with less information on their AMR. Moreover, there are countries with high prevalence of NTDs, for example, leishmaniasis is highly prevalent in Afghanistan, Yemen, Pakistan; onchocerciasis in DRC, and Nigeria but there were no studies in this review performed in these countries. This might be as a consequence of inefficient monitoring and surveillance tools or the political instability in some of these countries (135).

The overall description of the study settings of this review shows that most studies were conducted in the rural areas. Ponte-Sucre et al., highlighted that poor socioeconomic conditions is one of the fundamental contributory factors of AMR (125), which as well resonates with the fact that these diseases are prevalent amongst poorest populations of the world, putting an estimated 2.7 billion people at risk (136). NTDs have a great relevance for achieving

Sustainable Development Goal 3, which states, “ensure healthy lives and promote well-being for all at all ages” (127, 137). The burden of NTDs can be taken up by long-term capacity building and health system–wide reforms, of which, a large part of the response will depend on health systems stepping up to meet the demands for services as part of their transition towards UHC. Therefore, there is much that NTD programs have to share with national health systems as they strive towards UHC (127).

5.4 Study limitations

One of the main limitations of creating database for Rett syndrome research projects is that our study focused on public sector and NPPO fundings only. This is due to the limited contribution of pharmaceutical companies to Rett syndrome research and information on investments of for-profit private sector is often not made public. Methodologically, there were specific limitations due to features of the Web of Science which addresses the funding source only from 2008. This makes it difficult to retrieve funding information before 2008. Remarkably, almost all EC projects information were made available for transparency but some information were often missing for national funding organizations and NPPOs projects.

The use of patent data as an indicator of technological development was limited. This is primarily because not all inventions meet patentability standards, and inventors tend to rely on secrecy or other appropriate means to protect their inventions. Although, the developed search criteria facilitated the retrieval of patents of each NTD but the absolute scope of a patent search was limited which implies that some patents might have not been included in the dataset intentionally. This is, however, a general limitation of all patent landscape analyses. Additionally, there is usually a time lag of at least 18 months between the first patent filing and the patent publication; and even longer time is used for granting.

In identifying the trends of drug resistance through a systematic review, data extraction and compilation are prone to bias, as a result, efforts were made to identify and screen published

literature with a specific search query. More also, some relevant studies might have been excluded due to the search criteria narrowing publication dates from 2000 – 2016 due to inaccessibility and lack of full text availability. Also, all studies with incomplete information were excluded. This review has relied completely on published literature where grey literature and studies with minimal or negative results may not have been included resulting in publication bias.

CHAPTER SIX

6.1 RECOMMENDATIONS

6.1.1 Rett syndrome Research Landscape

In order to intensify R&D on rare diseases, a strong interconnections between researchers and health care givers is crucial to be established.

Effective and accurate data for rare disease research should be made available or generated for interested funders, patients and researchers in order to facilitate substantial investment

6.1.2 NTD Research Landscape

Patent landscape analysis is a reliable method for providing feedback on overall research progress and impacts of research policy. Performing patent landscape analysis is highly recommended for researchers and stakeholders in order to strengthening the health systems, political and global health efforts.

6.1.3 NTD Drug Resistance

It is vital to foster national surveillance systems and harmonize global standards that estimate the extent of AMR globally. It is highly recommended to design data monitoring and national surveillance systems so that information from such systems will nurture research directions and policies for rare diseases.

6.2 CONCLUSION

It is crucial to intensify R&D efforts into rare diseases. Involving new players, such as more NGOs may help to mitigate and reduce the burden of these diseases. Strengthening the health systems, political and global health efforts will be of immense benefits to facilitate R&D of these diseases. More also, international organizations with broader mandates need to be involved and international health policies need to be developed for rare diseases in order to assist policymakers, funding agencies, and the research community in setting priorities. Effective and efficient monitoring and international surveillance systems of rare diseases should be developed and maintained to mitigate the privation of private organizations impact.

SUMMARY

The demand for health services is both growing and changing in nature globally. In spite of substantial contribution of knowledge and technology to health improvements, there are still noticeable disparities in life expectancy and disease burden. For quite a number of years, rare diseases and NTDs were hardly addressed by research, and inadequate investment in R&D needed to address specific health problems is a vital contributing factor.

A rare disease or 'orphan' disease is defined as one that affects a restricted number of people. Rare diseases are sets of genetic and chronic conditions. NTDs have been defined as a group of infections strongly associated with poverty in tropical and subtropical environments.

The goal of this study are to map out research activities of rare diseases and NTDs through a landscape analysis of Rett syndrome showing the magnitude of financial support from public and private organizations the EU, determining the trends of R&D on NTDs by performing a patent landscape analysis and identifying the trends of drug resistance for 11 major NTDs and 20 drugs.

Rett syndrome with OMIM Entry 312750 is a severe neuro-developmental rare disease that affects approximately 1 in 10,000 live female births. In Rett syndrome study, it was discovered that funders' research activity was not homogeneously distributed among member states. Most projects were performed in Italy and UK. The landscape study indicates that funders' research activity is not homogeneously distributed among European member states.

Patent landscape analysis provides insight into the innovations that underlie technology and products. This study shows a long term trend with a continuous growth in the number of patent families of NTDs. This continuous growth in trends is not uniform for all the NTDs. However, global patenting trend is in sharp contrast with our findings on NTDs. In the last 20 years, the total number of global patenting applications has tripled, but NTD patent application has not increased.

The analysis of this study also showed that the US is losing its position as a major priority country. This is consistent with the fact that China now drives global patent applications beginning with a new record achieved in 2015. A higher percentage of firms are assignees resident in the US in the field of NTDs compared to China. However, in China, there is a high proportion of patent families linked to univeristies or individuals which indicates high research activity. R&D does not provide answers for several observed problems within the NTDs. It is imperative to pay attention to the broad social factors affecting NTDs; parallel improvements in hygiene, sanitation and access to medical care.

Antimicrobial resistance is a global public health threat, and its impacts have the potential to kill millions of people. From identifying drug resistance trends in NTDs, it was discovered that only six NTDs have information on drug resistance. There was lack of data to determine the magnitude and scope of AMR in the other reviewed NTDs. It is crucial to foster national surveillance systems and harmonize global standards that estimate the extent of AMR globally. Understanding research trends and how funders contributed to different research directions is a pillar of research policy making. It is crucial to intensify R&D efforts into rare diseases. Involving new players, such as more NGOs may help to mitigate and reduce the burden of these diseases. Strengthening the health systems, political and global health efforts will be of immense benefits to facilitate R&D of these diseases.

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APPENDIX

Appendix 1a: Final search terms

Neglected Tropical Diseases	Search Terms
Buruli	(Mycobacterium ulcerans) OR (M. ulcerans) OR (Buruli Ulcer) OR (non-tubercul* mycobacter*)
Chagas	(Chagas disease) OR (trypanosomias*) OR (Trypanosoma cruzi) OR (T. cruzi)
Dengue	(Dengue w5 virus*) OR (Dengue disease*) OR (Dengue w5 fever) OR (Breakbone fever) OR (Chikungunya w5 fever) OR (Chikungunya w5 virus*)
Dracunculiasis	(Dracunculiasis) OR (Guinea Worm) OR (Guinea-worm disease) OR (Dracunculus medinensis)
Echinococcosis	(Echinococcos*) OR (hydatid disease) OR (hydatidosis) OR (echinococcal disease) OR Echinococcus OR (cystic echinococcosis) OR (alveolar echinococcosis) OR (polycystic echinococcosis) OR (unicystic echinococcosis)
Leishmaniasis	Leishmanias* OR leishmania OR leishmaniosis
Leprosy	(Leprosy) OR (Hansen's disease) OR (Mycobacterium leprae) OR (Mycobacterium lepromatosis) OR (nontubercul* mycobacter*) NOT (Mycobacterium ulcerans) NOT (Mycobacterium tuberculos*)
Lymphatic Filariasis (Elephantiasis)	(WUCHERERIA BANCROFTI) OR (BRUGIA MALAYI) OR (lymphatic filariasis) OR (Elephantias*) OR (Brugia timori)
Onchocerciasis	Onchocercias* OR (Onchocerca volvulus) OR (river w5 blindness) NOT (trachoma)
Rabies	(rabies w5 virus) OR (lyssa*) OR (rabies w5 infection*) OR (rabies w5 disease)
Schistosomiasis	(Schistosomiasis) OR (snail fever) OR (bilharzia) OR (Katayama fever) OR (Schistosomiasis haematobia) OR (Schistosomiasis japonica) OR (Schistosomiasis mansoni) OR (Schistosoma) OR (blood-flukes)
Soil-transmitted helminthiasis	(Soil transmitted w5 helminthias*) OR (soil transmitted w5 helminths)OR (ascarias*) OR (hookworm infection*) OR (hookworm disease*) OR (ancylostomias*) OR (necatorias*) OR (whipworm infection*) OR (Ascaris lumbricoides) OR (Necator americanus) OR (Ancyclostoma duodenale) OR (Trichuris trichiura) OR (Trichurias*)
Taeniasis	(taeniasis) OR (Taenia solium) OR (pork tapeworm) OR (Taenia saginata) OR (beef tapeworm) OR (Taenia asiatica) OR (Taenia w5 Infection*)
Thymosis	(Treponema pallidum) OR (Yaws disease*) OR (Thymosis) OR (framboesia) OR (Frambesia) OR (Treponema pertenue)

Appendix 1b: Final search terms

Neglected Tropical Diseases	Search Terms
Trachoma	(Trachoma) OR (Egyptian Ophthalmia) OR (Chlamydia trachomatis) OR (granular conjunctivit*)
Rabies	(Food-borne Trematodias*) OR (Clonorchiasis OR Opisthorchiasis OR Fascioliasis OR Paragonimiasis) OR (Chinese liver fluke) OR (Clonorchis sinensis) OR (Opisthorchis viverrini) OR (Opisthorchis felineus) OR (fascioliasis OR fasciolasis OR distomatosis) OR (liver rot) OR (Fasciola hepatica) OR (Fasciola gigantica) OR (Paragonimus westermani) NOT (ruminant OR animals OR cattle OR Schistosomiasis OR schistosoma)
Trypanosomiasis	(African Trypanosomias*) OR (sleeping sickness) OR (nagana) OR (African Trypanosomias*) OR (Trypanosoma brucei gambiense) OR (Trypanosoma brucei rhodesiense) NOT (Chagas OR Plasmodium)

Keywords and terms were searched in any of the Title, Abstract or Claims fields. W5 symbol: two words that may appear side by side or separated by up to five words. * Wildcard: symbol that broadens a search by finding words that start with the same letters.

Appendix 1c: Final search terms of some selected diseases

Cardiovascular disease	(Arrhythmias OR Cardiac OR (Carcinoid Heart Disease) OR (Cardiac Output) OR (High Cardiac Output) OR (Low Cardiac) OR Tamponade OR Cardiomegaly OR Cardiomyopathies OR Endocarditis OR (Heart Aneurysm) OR (Heart Arrest) OR (Heart Defects) OR (Congenital Heart) OR (Heart Rupture) OR (Heart Valve Diseases) OR (Myocardial Ischemia) OR (Myocardial Stunning) OR (Pericardial Effusion) OR Pericarditis OR Pneumopericardium OR (Postpericardiotomy Syndrome) OR (Pulmonary Heart Disease) OR (Rheumatic Heart Disease) OR (Ventricular Dysfunction) OR (Ventricular Outflow Obstruction)) OR (cariovascular OR (heart disease) OR angina OR (heart failure) OR (heart attack)) OR (Aneurysm OR Angiodysplasia OR Angioedema OR Angiomatosis OR (Aortic Diseases) OR (Arterial Occlusive Diseases) OR (Arteriovenous Malformations) OR (Capillary Leak Syndrome) OR (Cerebrovascular Disorders) OR (Ischemic Compartment Syndrome) OR (Diabetic Angiopathies) OR (Embolism) OR (Thrombosis) OR (Hand-Arm Vibration Syndrome) OR (Hemorrhoids) OR (Hemostatic Disorders) OR (Hepatic Veno-Occlusive Disease) OR Hyperemia OR Hypertension OR Hypotension OR (Mesenteric Ischemia) OR (Optic Neuropathy) OR (Ischemic Peripheral Vascular Disease) OR Prehypertension OR (Pulmonary Veno-Occlusive Disease) OR (Reperfusion Injury) OR (Retinal Vein Occlusion) OR (Scimitar Syndrome) OR (Spinal Cord Vascular Diseases) OR (Splenic Infarction) OR (Stenosis Pulmonary Vein) OR (Superior Vena Cava Syndrome) OR Telangiectasis OR (Thoracic Outlet Syndrome) OR Varicocele OR Varicose OR Veins OR (Vascular Fistula) OR (Vascular Neoplasms) OR (Vascular System Injuries) OR Vasculitis OR Vasoplegia OR (Venous Insufficiency)))
Cancer	(Cancer OR (Anti*cancer) OR Chemotherap* OR Oncol* OR Carcinog* OR Neoplas* OR Tumor OR Metastat* OR Malignan*)
Lung cancer	(pulmonary cancer) OR (lung cancer) OR (lung neoplasm) OR (carcinoma OR cancer OR metastasis OR neoplasm OR tumor) AND (lung OR Trachea OR bronchus))
HIV/AIDS	(HIV OR (Human Immunodeficiency Virus)) OR (AIDS OR (acquired immune deficiency syndrome)
Malaria	Malaria OR plasmodium

Keywords and terms were searched in any of the Title, Abstract or Claims fields. W5 symbol: two words that may appear side by side or separated by up to five words. * Wildcard: symbol that broadens a search by finding words that start with the same letters.

Appendix 2a: A full description of NTDs search terms and search strategy

DISEASE	DRUGS	SEARCH TERMS	WEBSITE	NUMBER OF DOCUMENTS FOUND	NUMBER DOWNLOADED	SAVED TO ENDNOTE FOLDER
Chagas Disease	Nifurtimox	Chagas disease AND Drug Resistance AND nifurtimox	Pubmed and Scopus	69	69	Nifurtimox
Human African Trypanosomiasis	Suramin	Human African Trypanosomiasis AND Drug Resistance AND Suramin	Pubmed and Scopus	178	178	Suramin
	Eflornithine	Human African Trypanosomiasis AND Drug Resistance AND Eflornithine	Pubmed and Scopus	203	203	Eflornithine
	Melarsopol	Human African Trypanosomiasis AND Drug Resistance AND Melarsopol	Pubmed and Scopus	262	262	Melarsopol
	Pentamidine	Human African Trypanosomiasis AND Drug Resistance AND Pentamidine	Pubmed and Scopus	181	181	Pentamidine
Leishmaniasis	Amphotericin B	"Leishmaniasis" (MeSH) AND "Drug Resistance (MeSH)" AND "Amphotericin B (MeSH)"	Pubmed and Scopus	251	251	Amphotericin B
Leprosy	Rifampicin	"Leprosy (MeSH)" AND "Drug Resistance (MeSH)" AND "Rifampicin (MeSH)"	Pubmed and Scopus	332	332	Rifampicin
	Clofazimine	"Leprosy (MeSH)" AND "Drug Resistance (MeSH)" AND "Clofazimine (MeSH)"	Pubmed and Scopus	186	186	Clofazimine
	Daposne	"Leprosy (MeSH)" AND "Drug Resistance (MeSH)" AND "Daposne (MeSH)"	Pubmed and Scopus	516	516	Dapsone

Appendix 2b: A full description of NTDs search terms and search strategy

DISEASE	DRUGS	SEARCH TERMS	WEBSITE	NUMBER OF DOCUMENTS FOUND	NUMBER DOWNLOADED	SAVED TO ENDNOTE FOLDER
Trachoma	Azithromycin	"Trachoma (Major)" AND "Drug Resistance" (MeSH) AND "Azithromycin (MeSH)"	Pubmed and Scopus	35	35	Azithromycin
Taeniasis	Praziquantel	"Taeniasis (Major)" AND "Drug Resistance (MeSH)" AND "Praziquantel (MeSH)"	Pubmed and Scopus	6	6	Praziquantel
	Niclosamide	"Taeniasis (Major)" AND "Drug Resistance (MeSH)" AND "Niclosamide (MeSH)"	Pubmed and Scopus	4	4	Niclosamide
Trematodiasis	Triclabendazole	"Trematodiasis (Major)" AND "Drug Resistance (MeSH)" AND "Triclabendazole (MeSH)"	Pubmed and Scopus	37	37	Triclabendazole
Lymphatic filariasis	Albendazole	"Elephantiasis, Filarial (Major)" AND "Drug Resistance (MeSH)" AND "Albendazole(MeSH)"	Pubmed and Scopus	20	20	Albendazole
	Ivermectin	"Elephantiasis, Filarial (Major)" AND "Drug Resistance (MeSH)" AND "Ivermection(Major)"	Pubmed and Scopus	17	17	Ivermectin
	Diethylcarbamazine (DEC)	"Elephantiasis, Filarial (Major)" AND "Drug Resistance (MeSH)" AND "Diethylcarbamazine (MeSH)"	Pubmed and Scopus	21	21	Diethylcarbamazine

Appendix 2c: A full description of NTDs search terms and search strategy

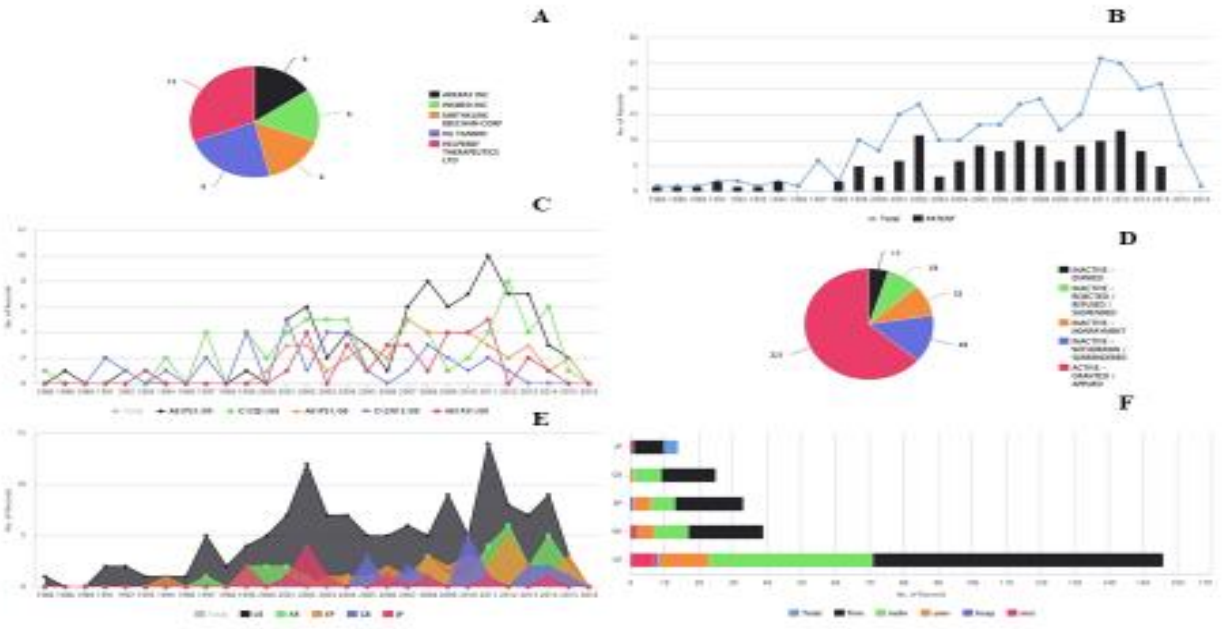
DISEASE	DRUGS	SEARCH TERMS	WEBSITE	NUMBER OF DOCUMENTS FOUND	NUMBER DOWNLOADED	SAVED TO ENDNOTE FOLDER
Schistosomiasis	Praziquantel	"Schistosomiasis (MeSH)" AND "Drug Resistance (MeSH)" AND "Praziquantel (MeSH)"	Pubmed and Scopus	267	267	Praziquantel
Soil-transmitted helminthes	Mebendazole	"Helminthiasis (Major)" AND "Drug Resistance (MeSH)" AND "Mebendazole (MeSH)"	Pubmed and Scopus	30	30	Mebendazole
	Albendazole	"Helminthiasis (Major)" AND "Drug Resistance (MeSH)" AND "Albendazole (MeSH)"	Pubmed and Scopus	102	129	Albendazole

Appendix 3: Figures of annual patenting trends NTDs

Year	Applications	Grants	Families
1987	221	92	39
1988	362	96	33
1989	480	93	50
1990	627	95	64
1991	425	156	59
1992	559	169	64
1993	718	260	75
1994	858	219	108
1995	1024	260	104
1996	1205	314	121
1997	1554	387	133
1998	2002	434	171
1999	2277	490	218
2000	2623	539	252
2001	2941	562	270
2002	3023	694	289
2003	3460	800	326
2004	2846	852	346
2005	2653	877	368
2006	3555	1093	373
2007	3023	1122	412
2008	3195	1137	452
2009	2994	1213	456
2010	3156	1325	454
2011	3272	1529	540
2012	3013	1630	563
2013	3105	1637	529
2014	2951	1770	631

Appendix 4a: Figures of annual patenting trends for each NTD (Buruli ulcer and Chagas disease)

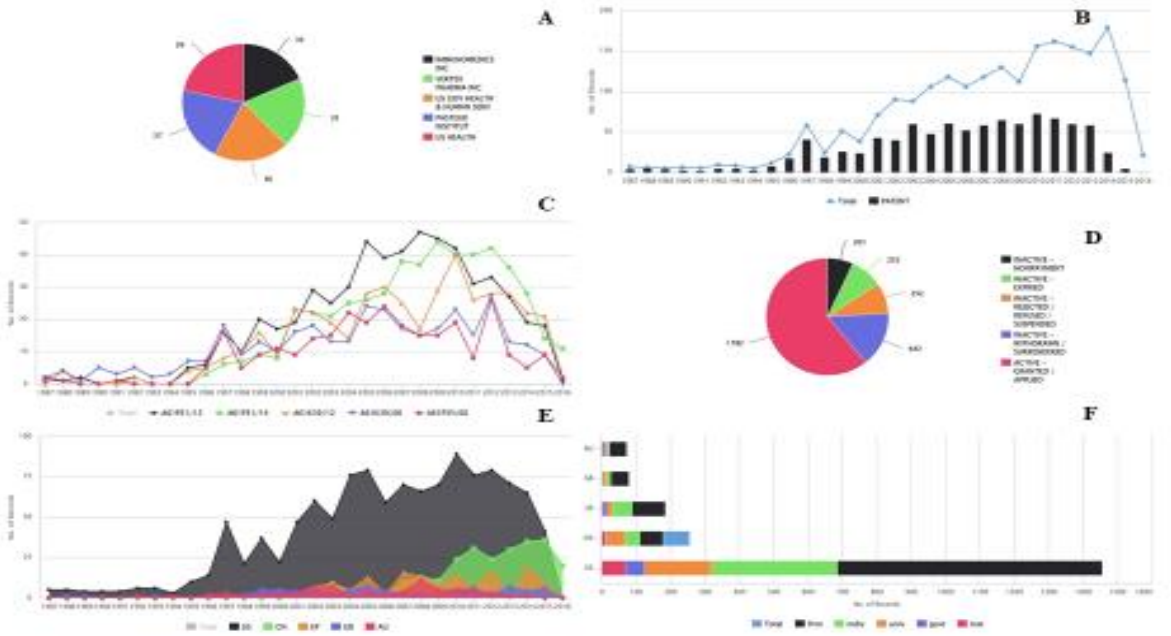
Buruli ulcer



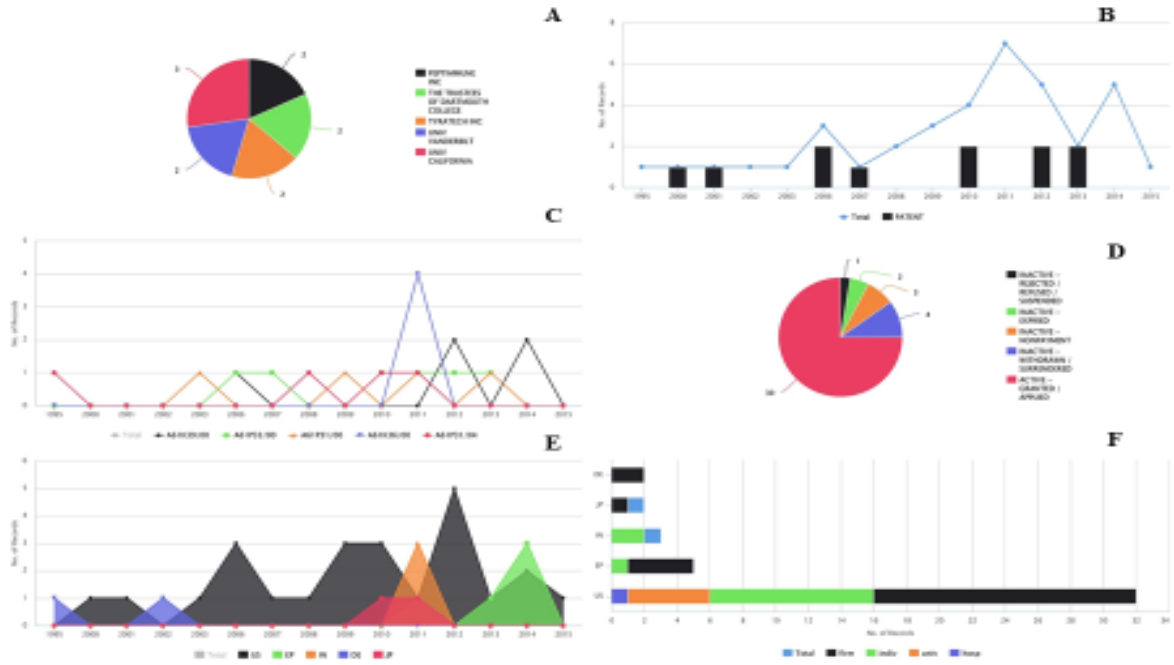
Chagas disease

Appendix 4b: Figures of annual patenting trends for each NTD (Dengue and Dracunculiasis)

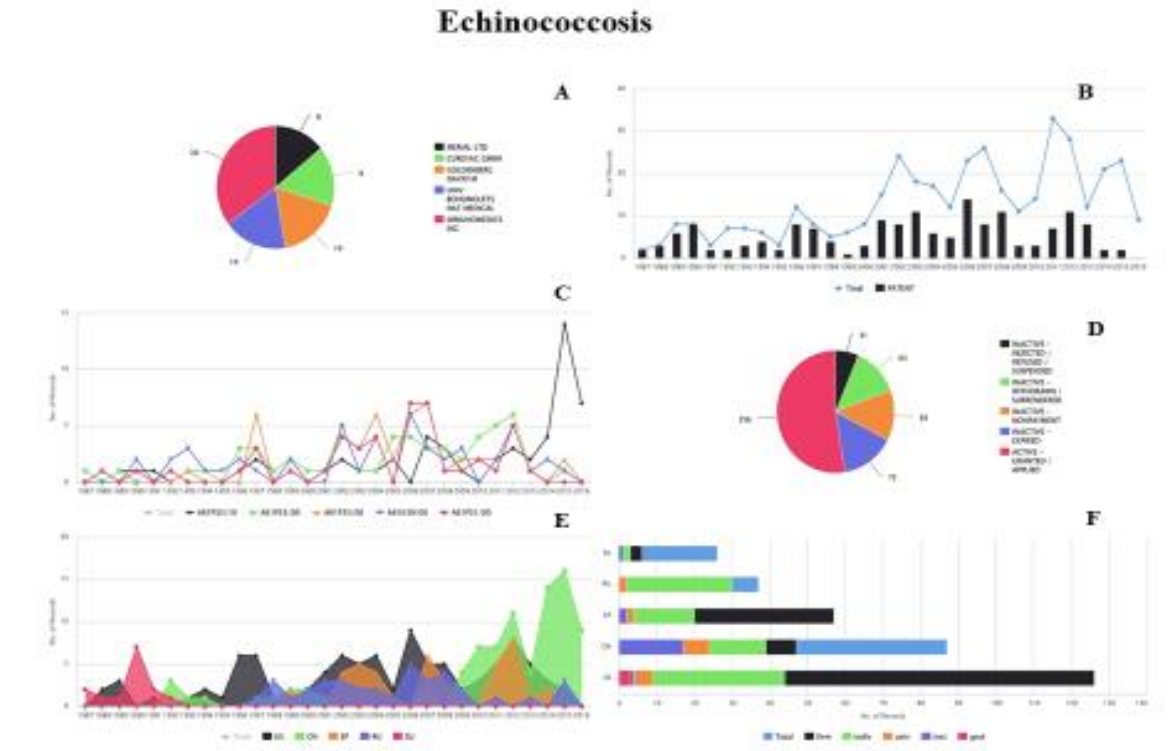
Dengue

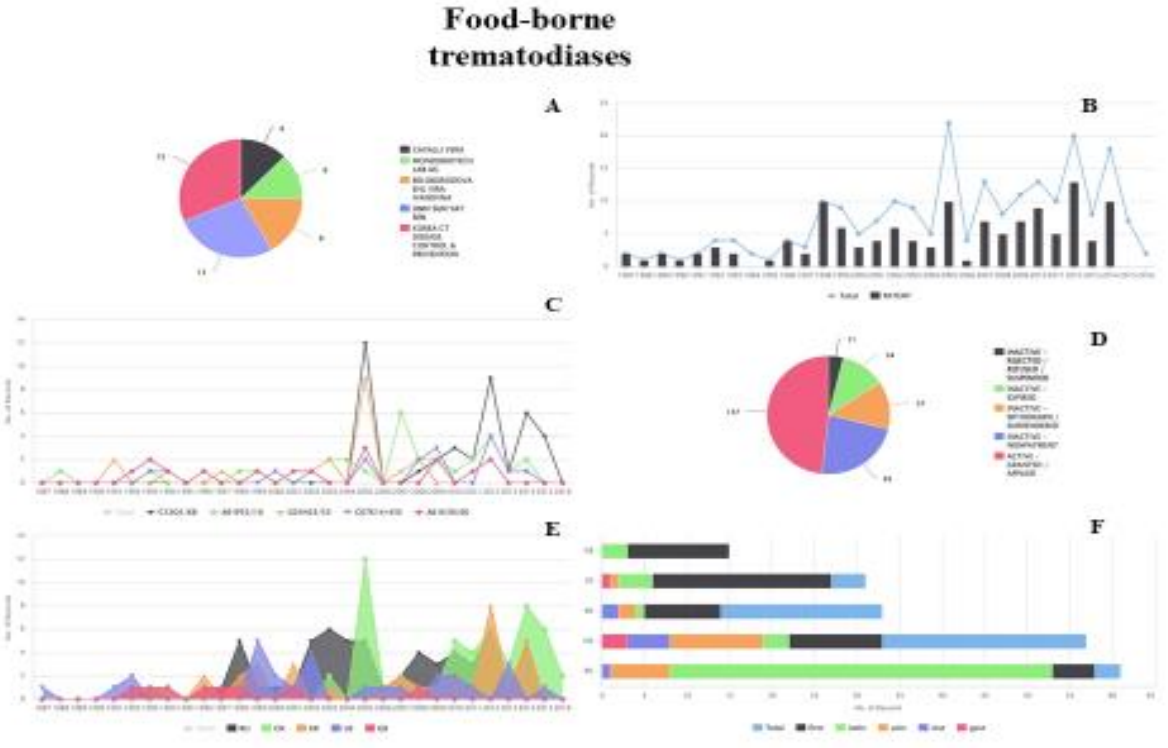


Dracunculiasis

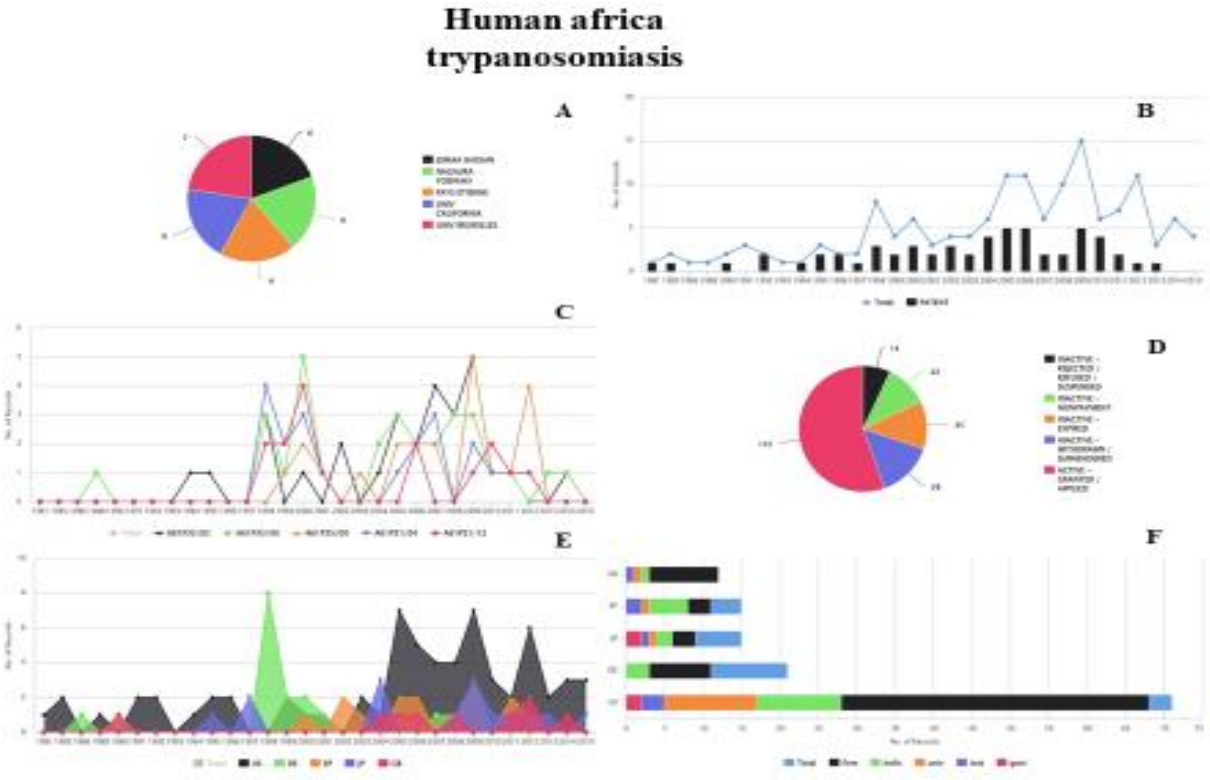


Appendix 4c: Figures of annual patenting trends for each NTD (Echinococcosis and Food-borne trematodiases)



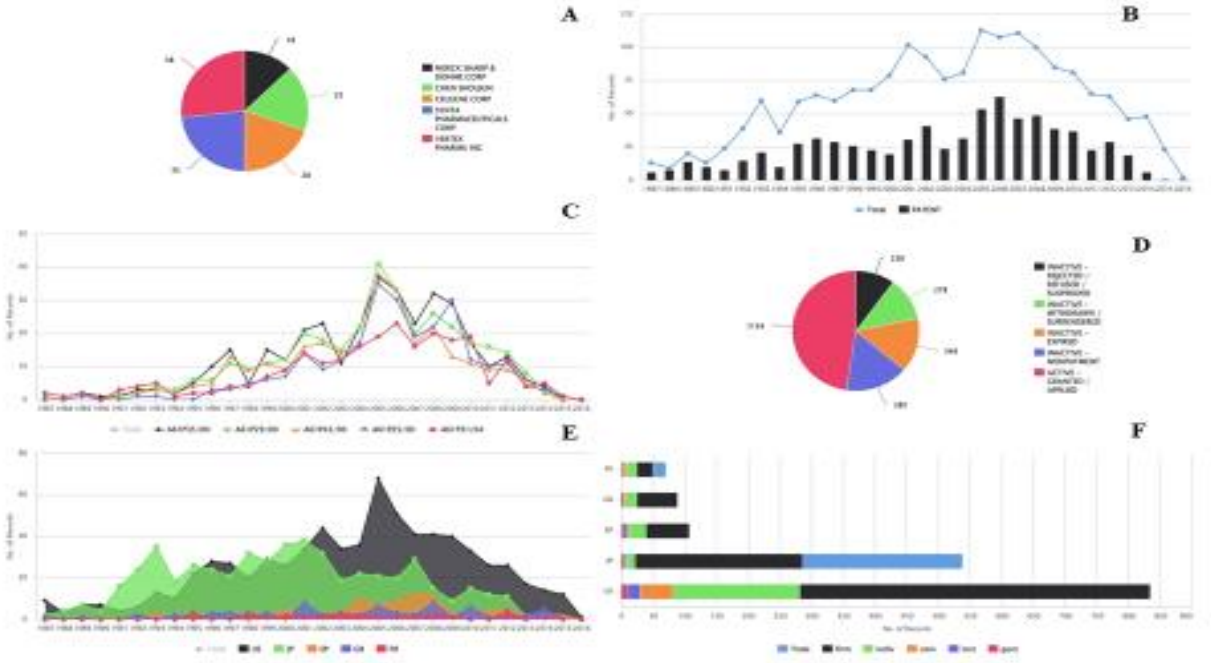


Appendix 4d: Figures of annual patenting trends for each NTD (HAT and Leishmaniasis)

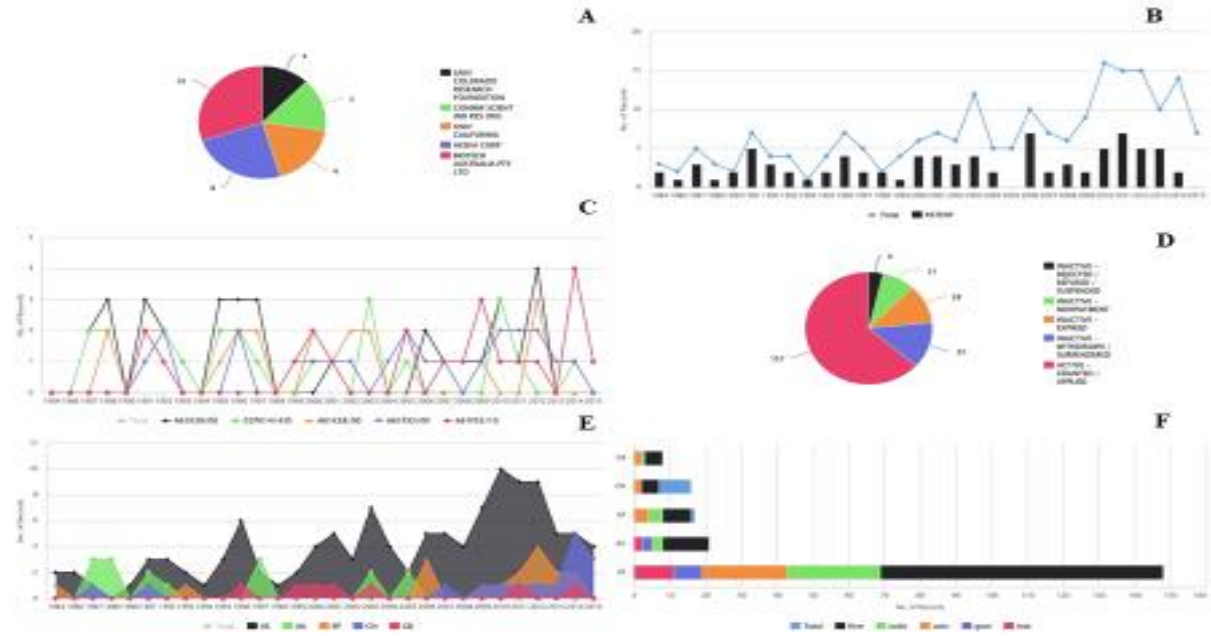


Appendix 4e: Figures of annual patenting trends for each NTD (Leprosy and Lymphatic filariasis)

Leprosy

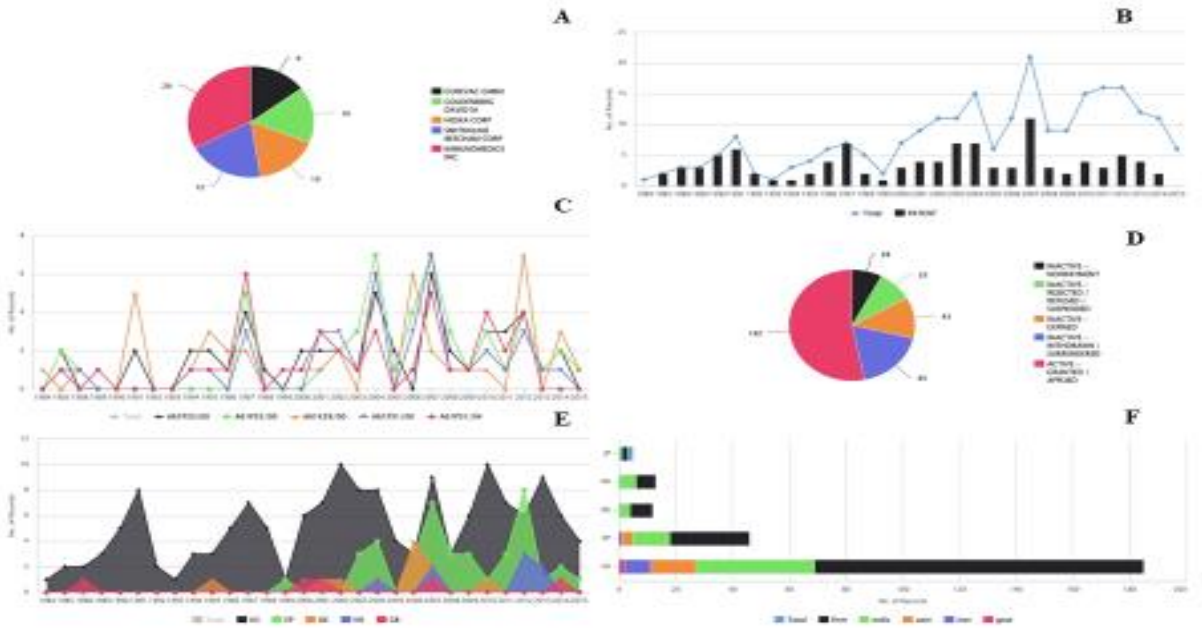


Lymphatic filariasis



Appendix 4f: Figures of annual patenting trends for each NTD (Onchocerciasis and Rabies)

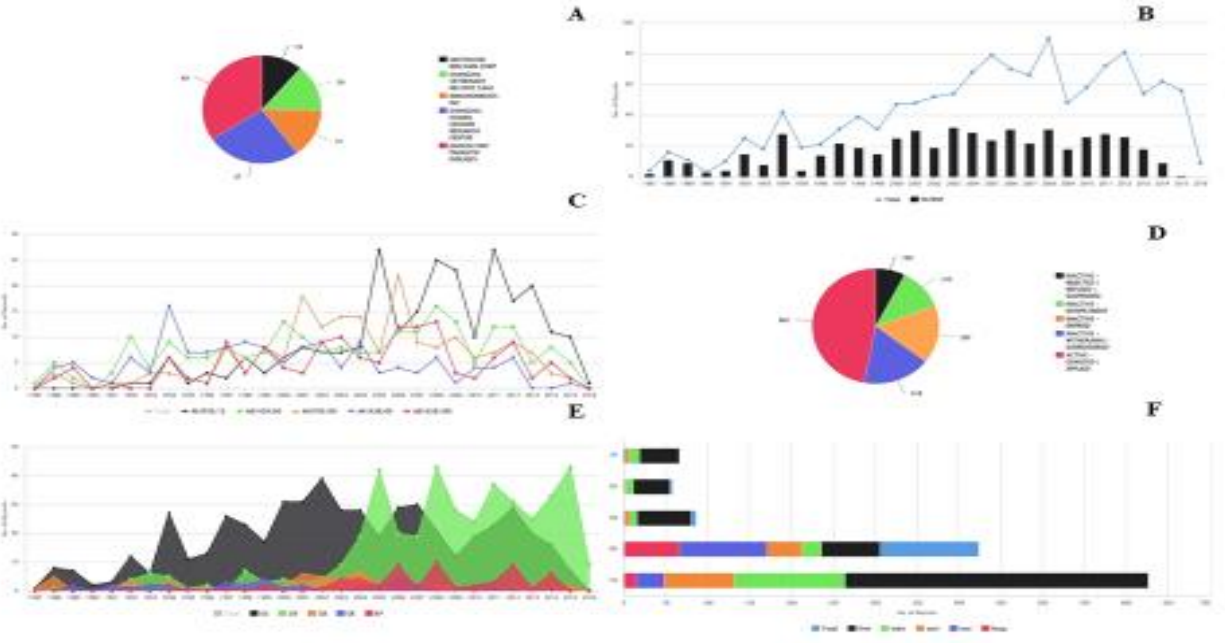
Onchocerciasis



Rabies

Appendix 4g: Figures of annual patenting trends for each NTD (Schistosomiasis and STH)

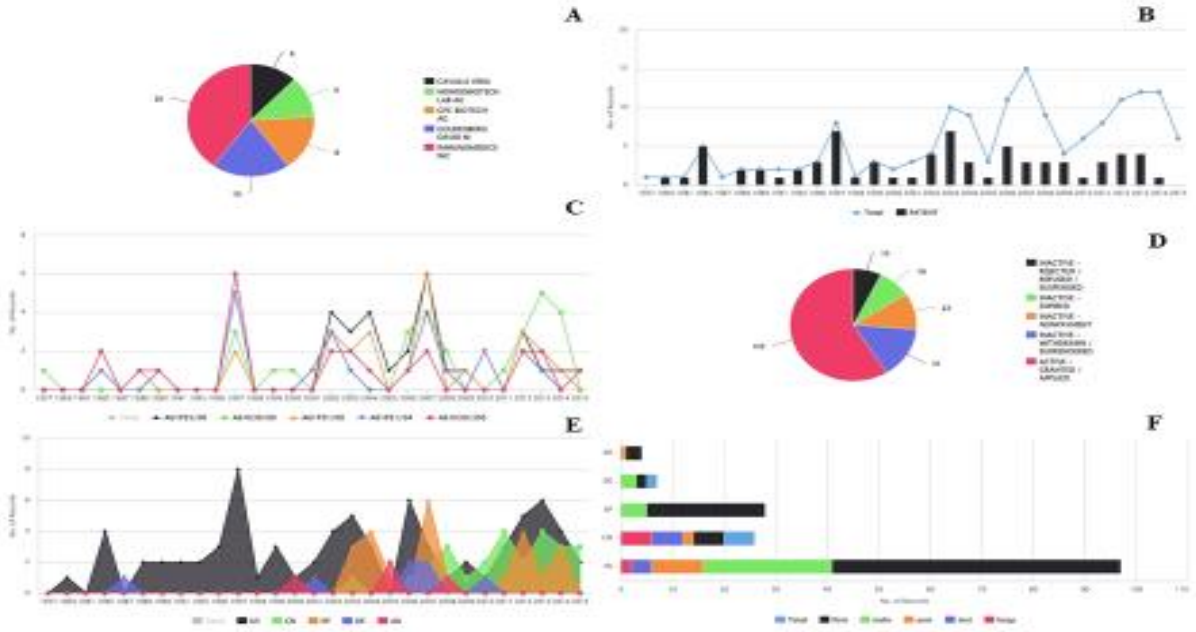
Schistosomiasis



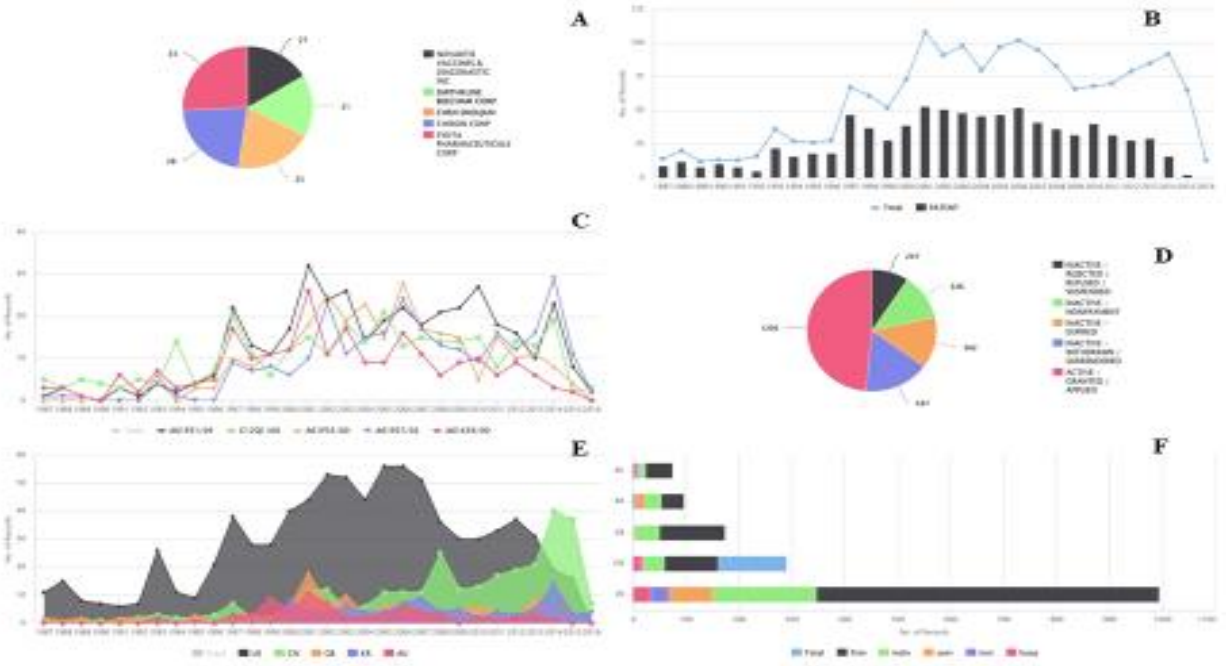
Soil transmitted helminthes

Appendix 4f: Figures of annual patenting trends for each NTD (Taeniasis and Trachoma)

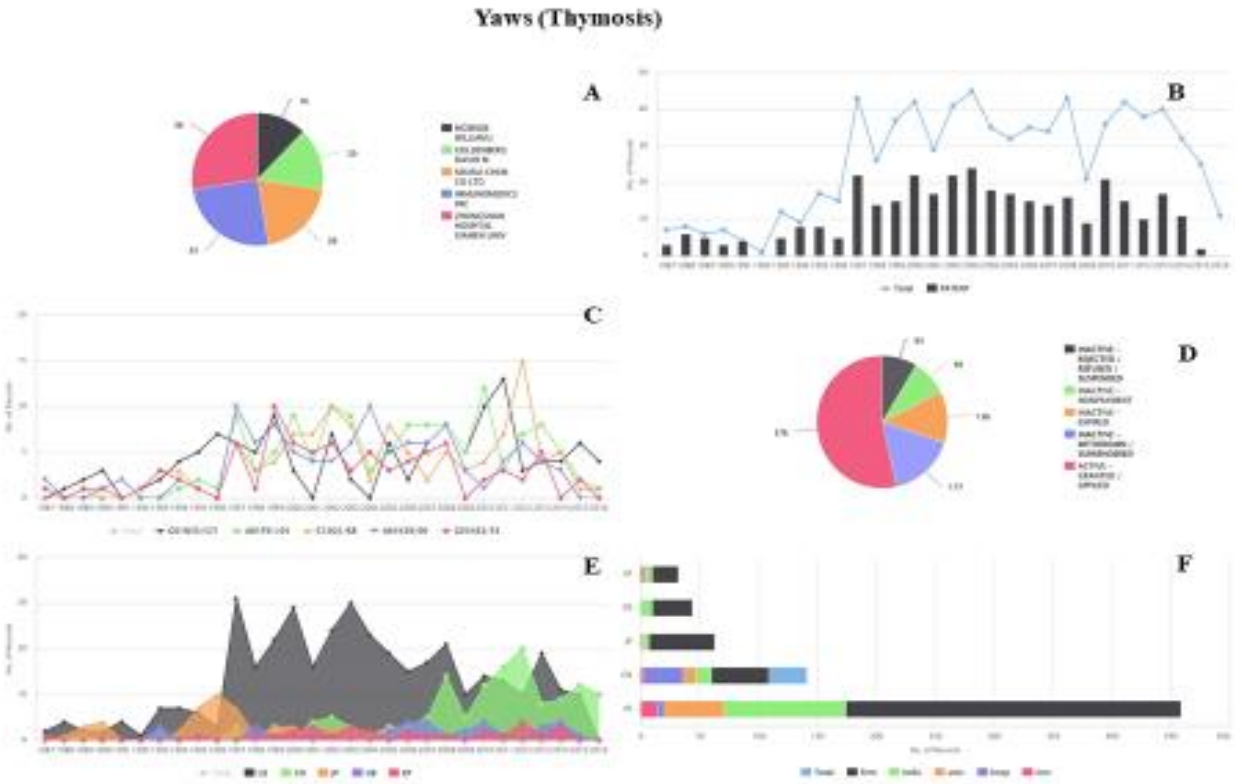
Taeniasis



Trachoma



Appendix 4f: Figures of annual patenting trends for each NTD (Yaws)



A - Major assignees

B – Filing trend by earliest priority year

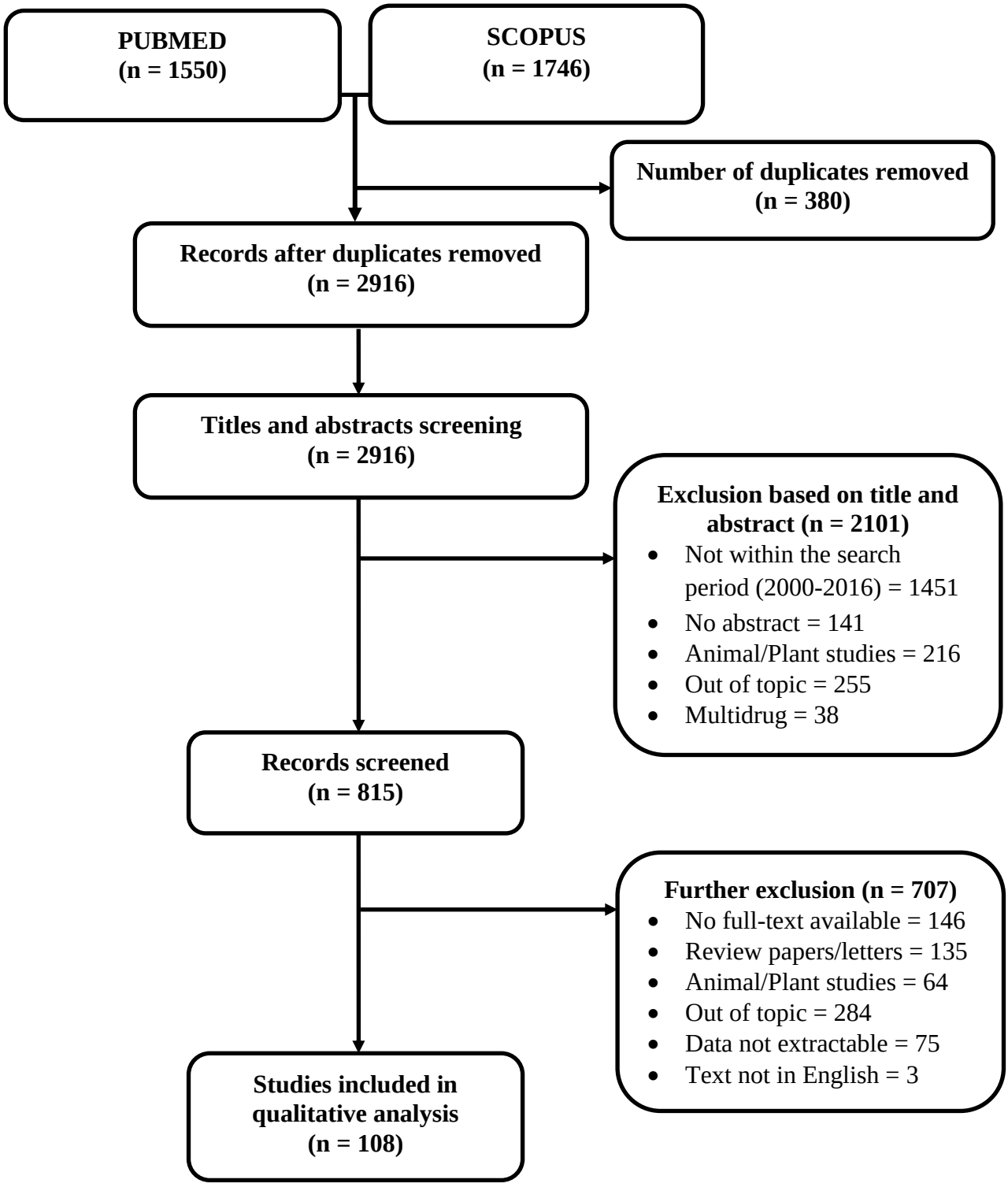
C – International Patent Classification (IPC) system

D – Current legal status of patent applications

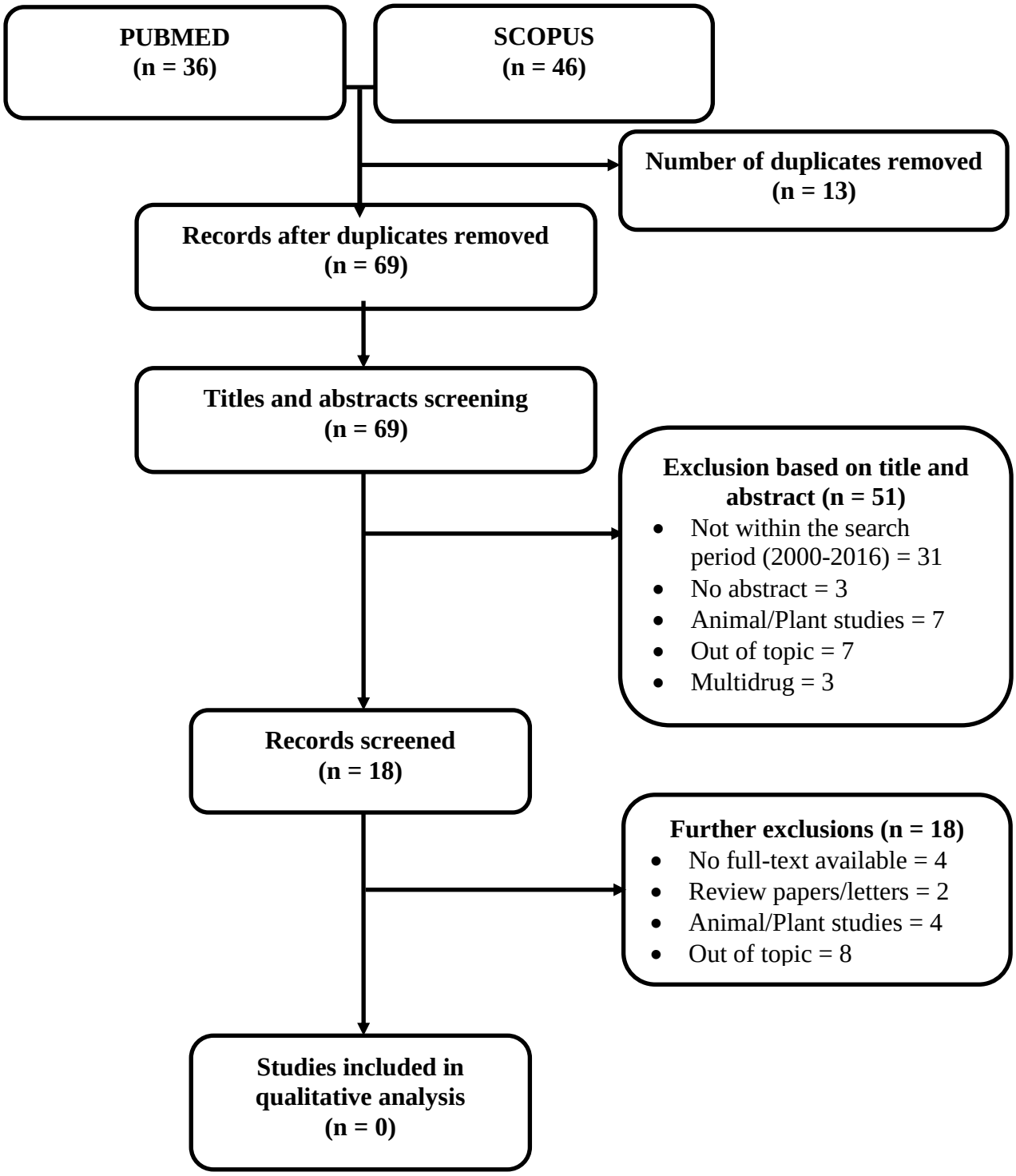
E – Major country

F – Priority countries by assignee types

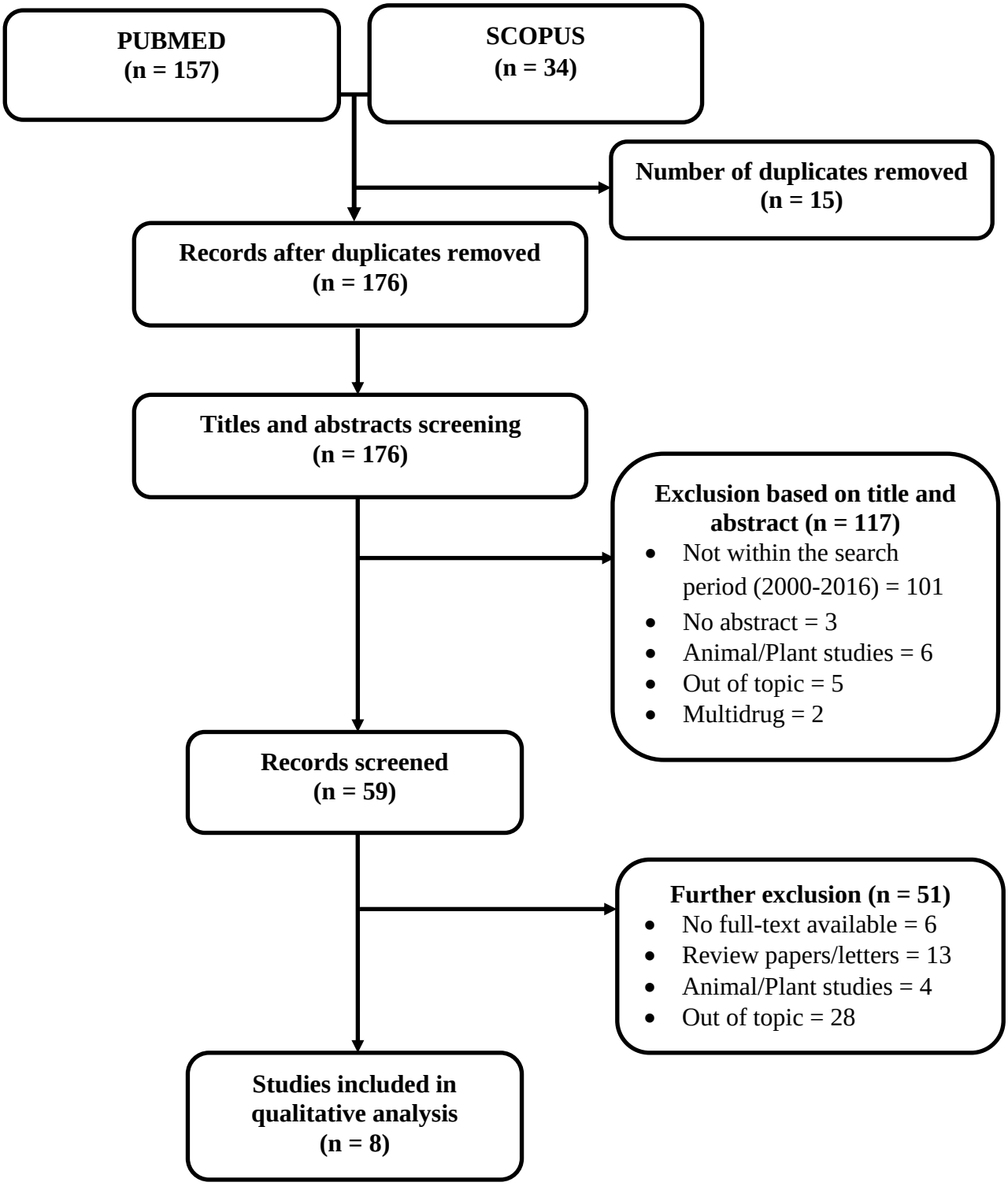
Appendix 5: The flowcharts of each reviewed NTDs and their corresponding drugs for treatment



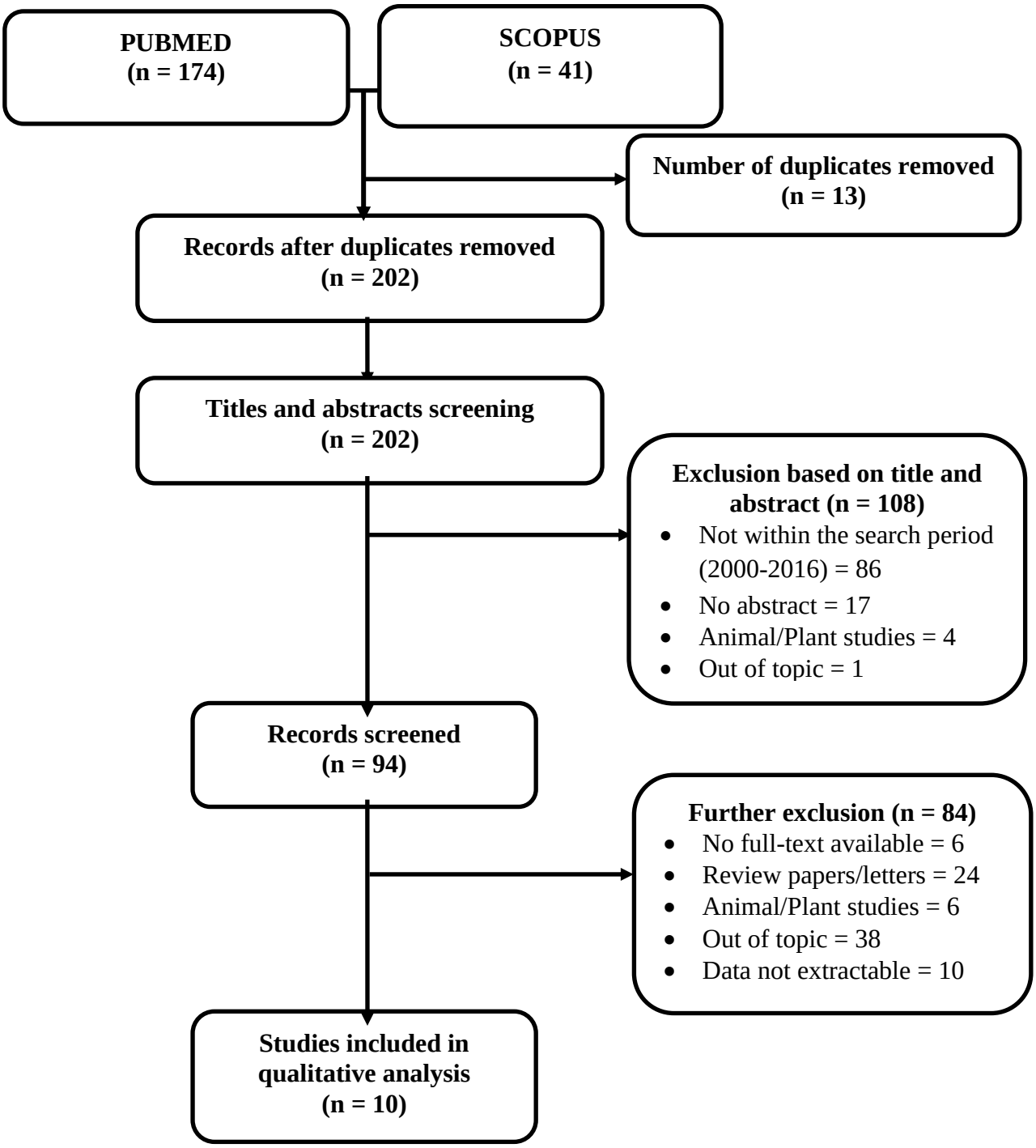
DISEASE: Chagas disease
DRUG: Nifurtimox



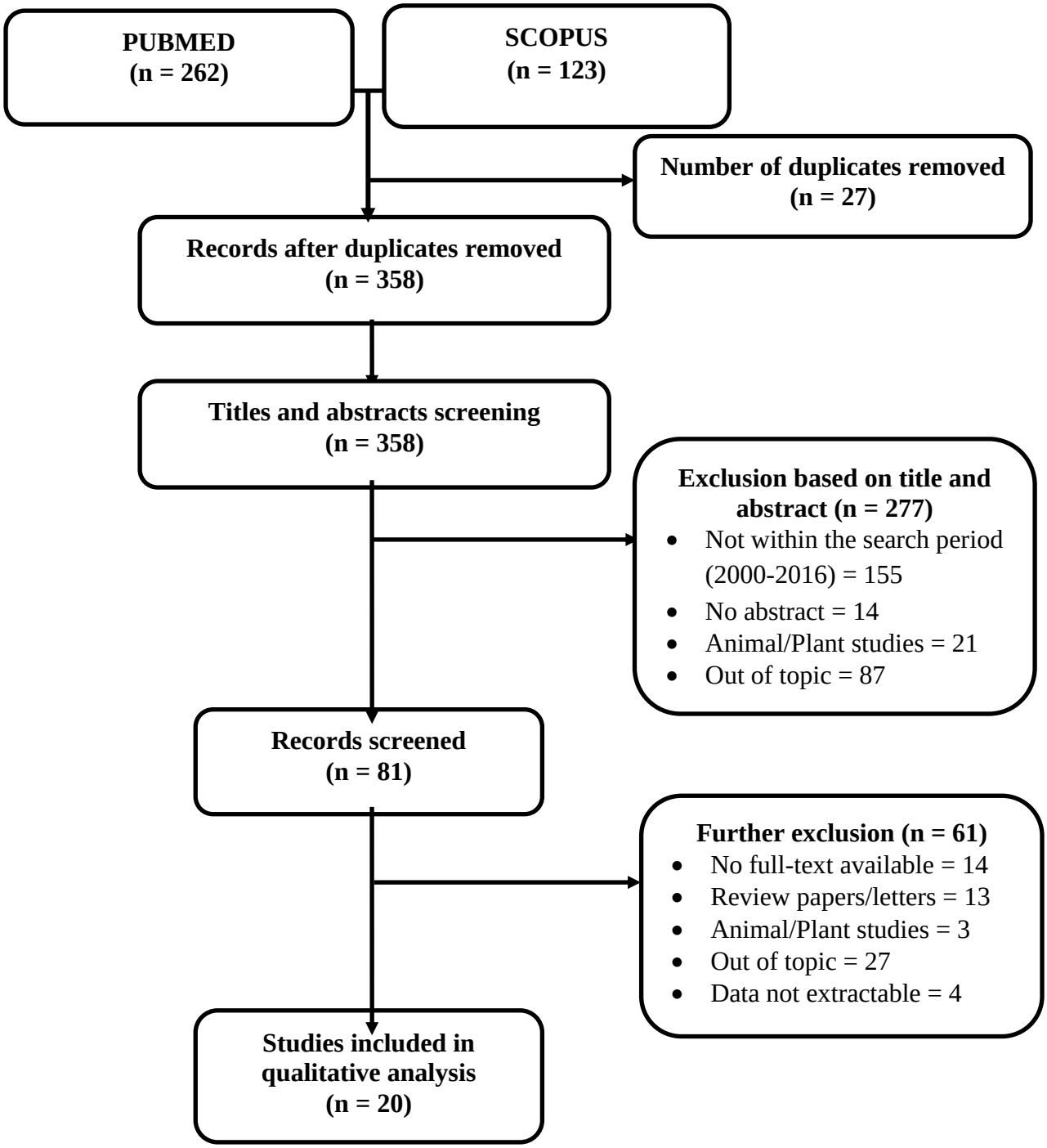
DISEASE: Human African Trypanosomiasis
DRUG: Suramin



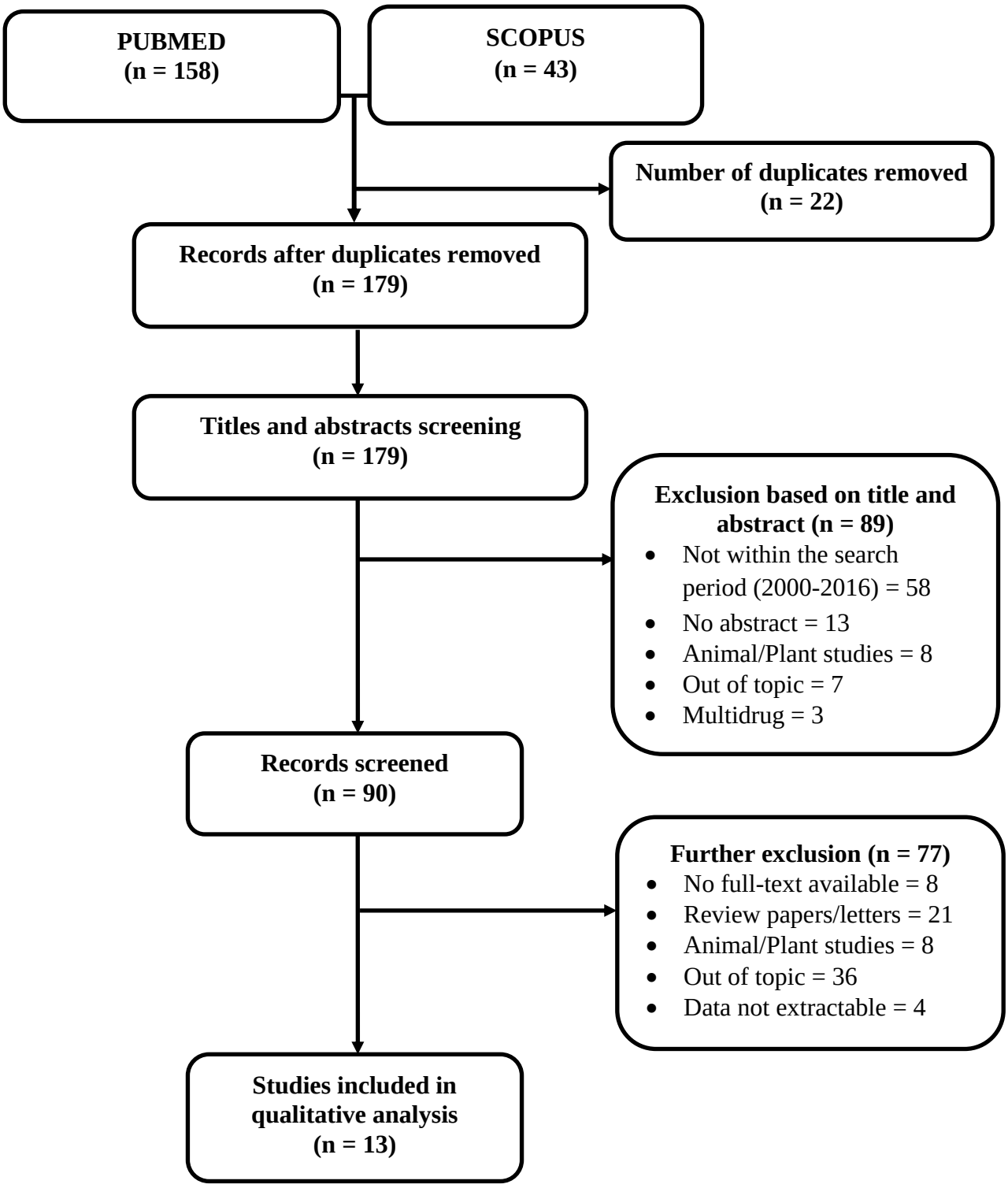
DISEASE: Human African Trypanosomiasis
DRUG: Eflornithine



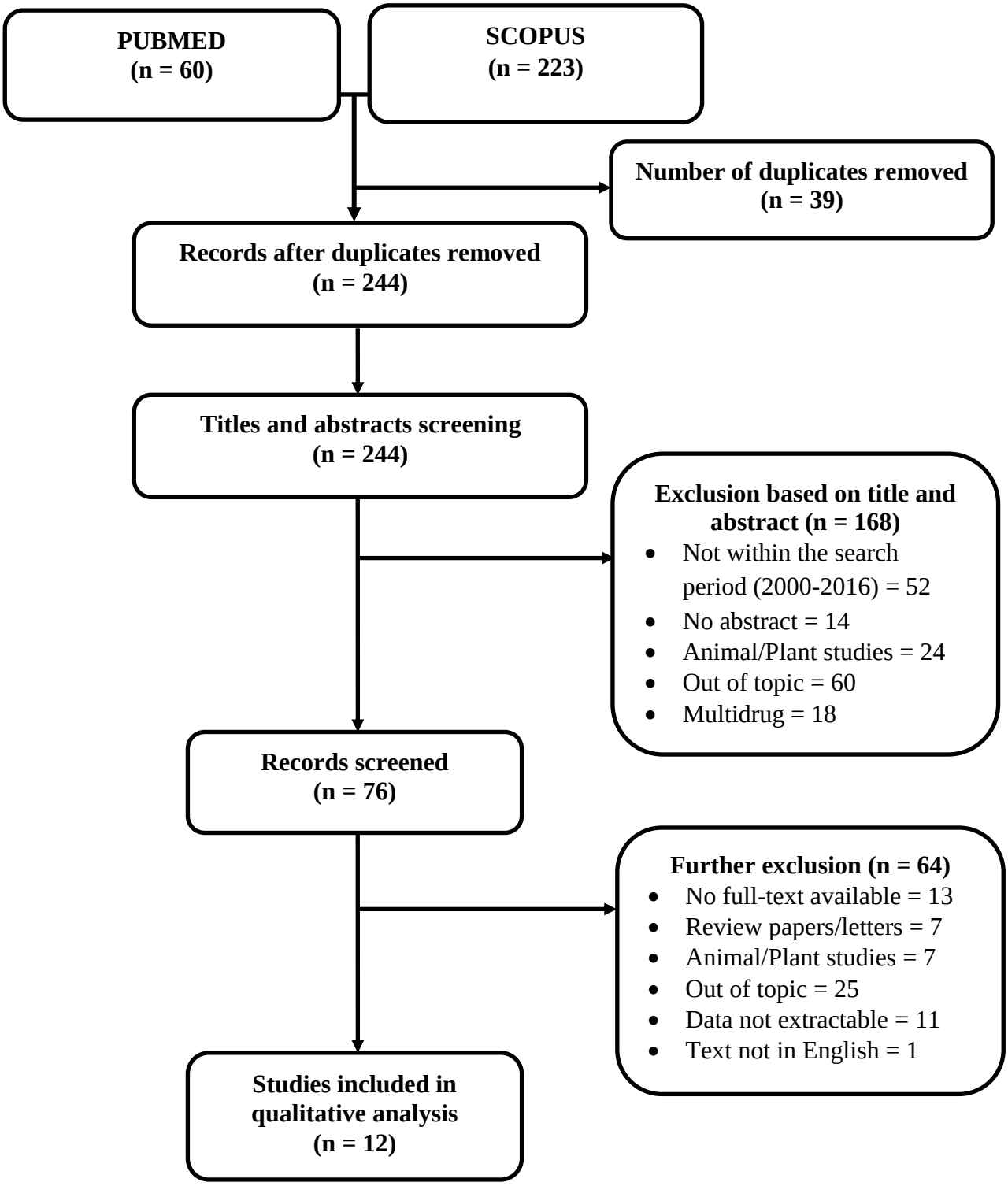
DISEASE: Human African Trypanosomiasis
DRUG: Melarsoprol



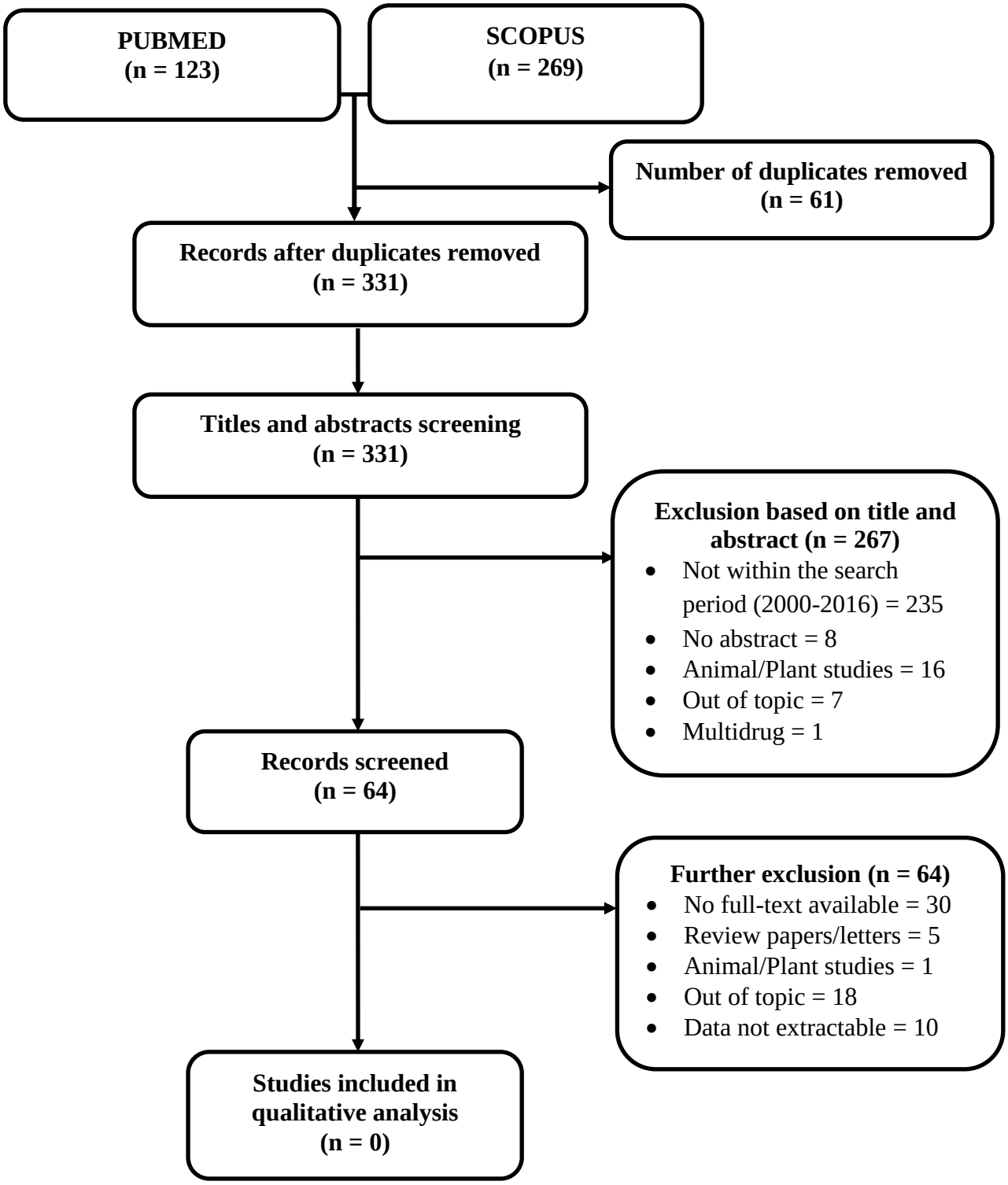
DISEASE: Human African Trypanosomiasis
DRUG: Pentamidine



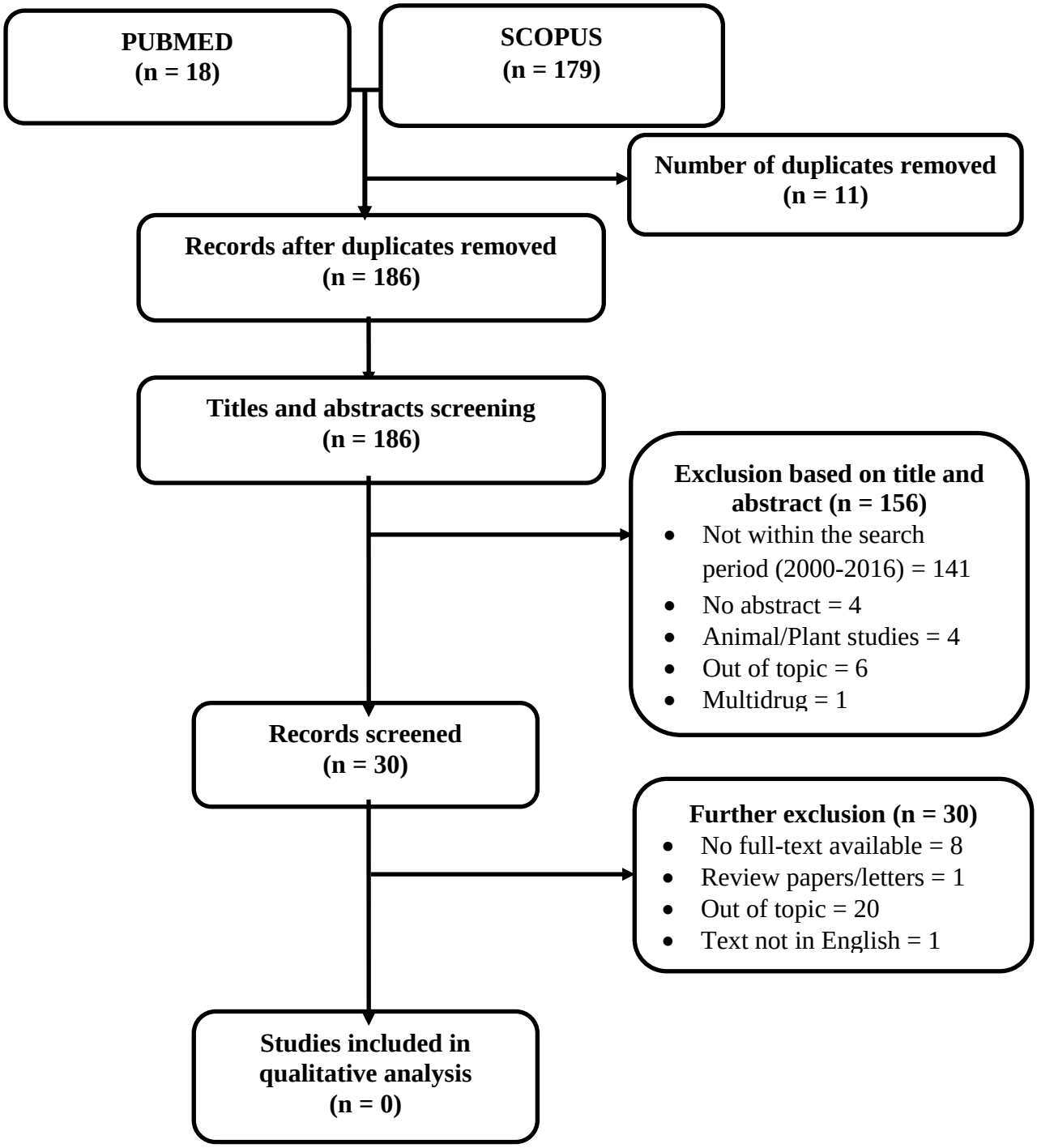
DISEASE: Leishmaniasis
DRUG: Amphotericin B



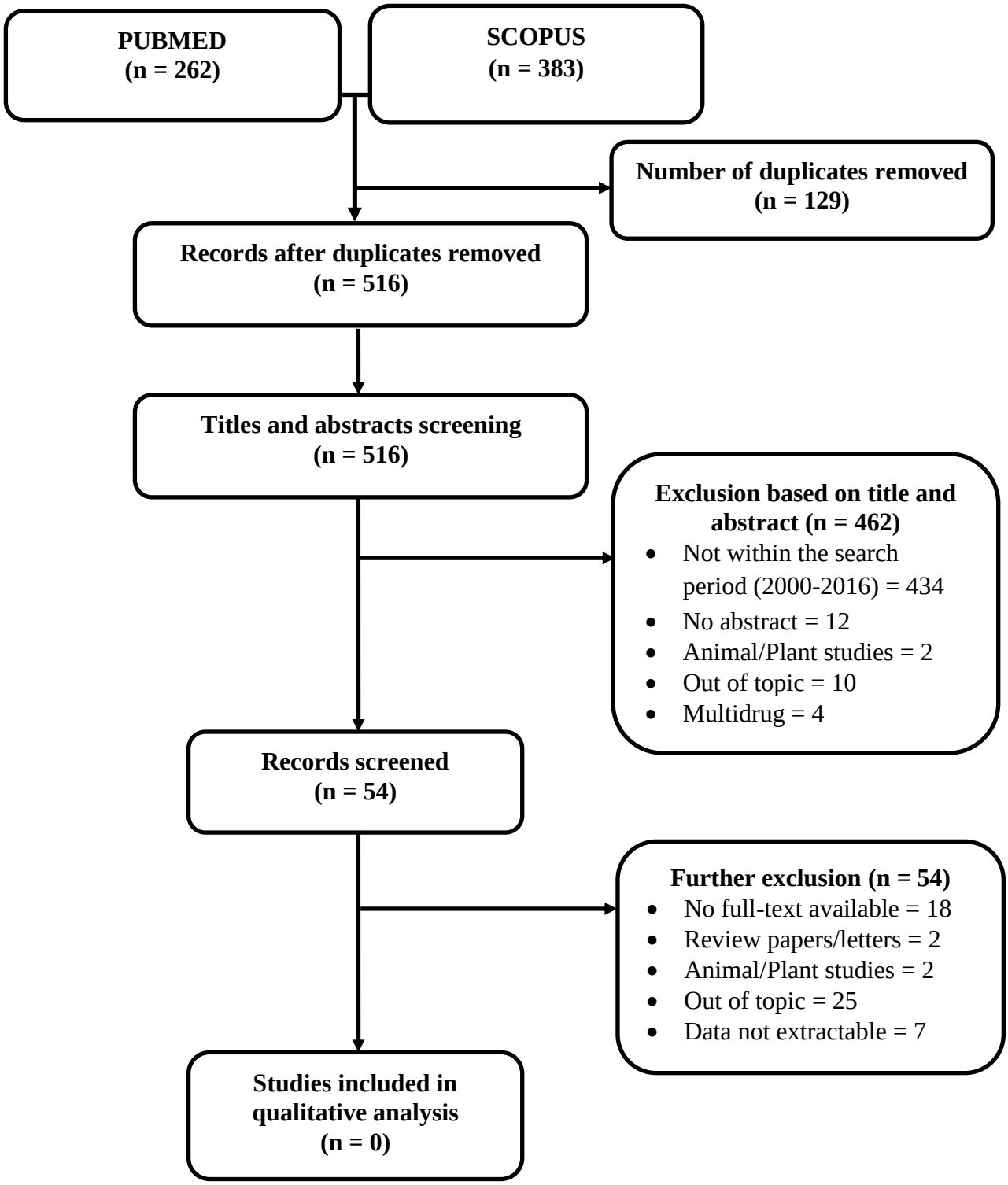
DISEASE: Leprosy
DRUG: Rifampicin



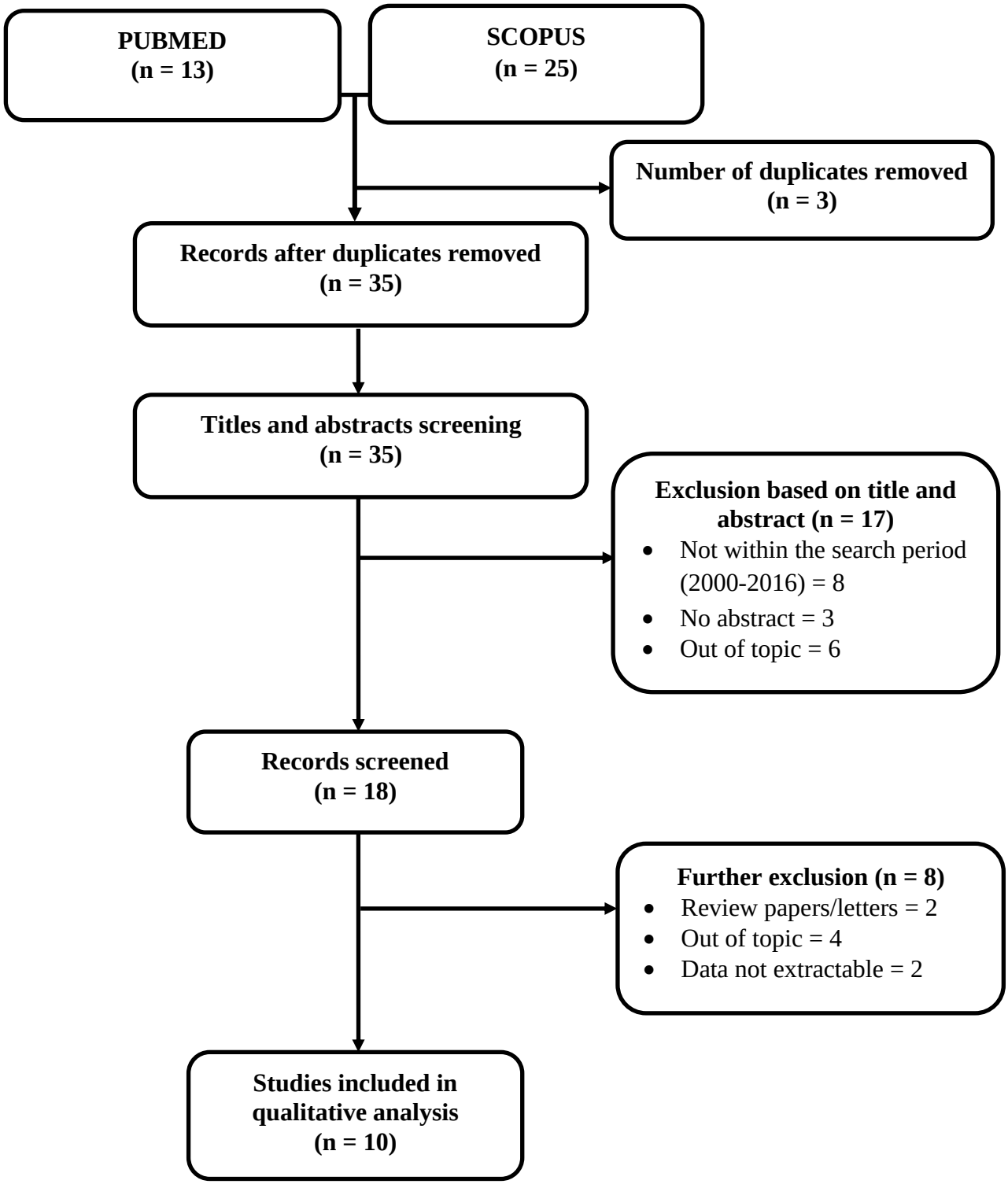
DISEASE: Leprosy
DRUG: Clofazimine



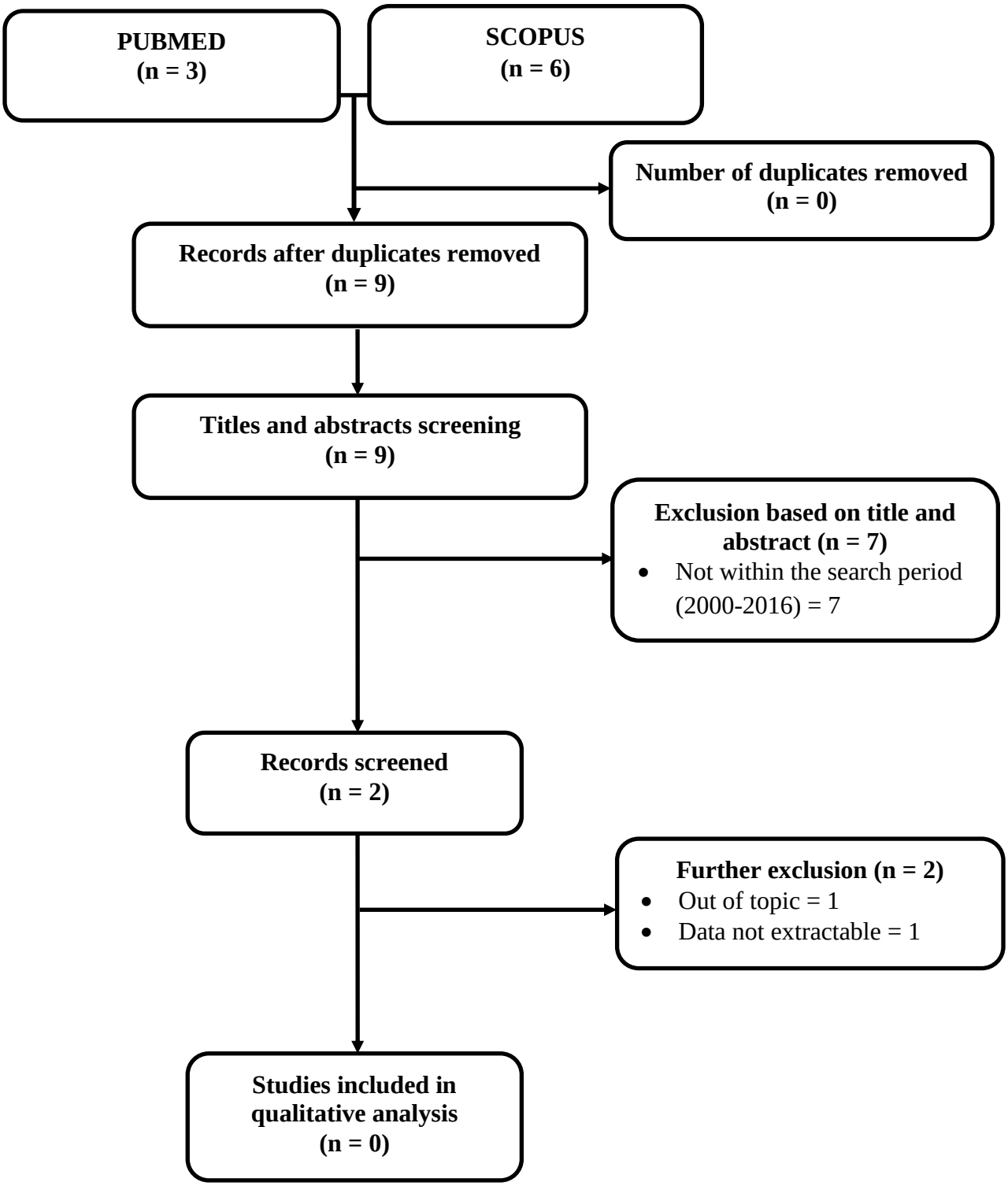
DISEASE: Leprosy
DRUG: Dapsone



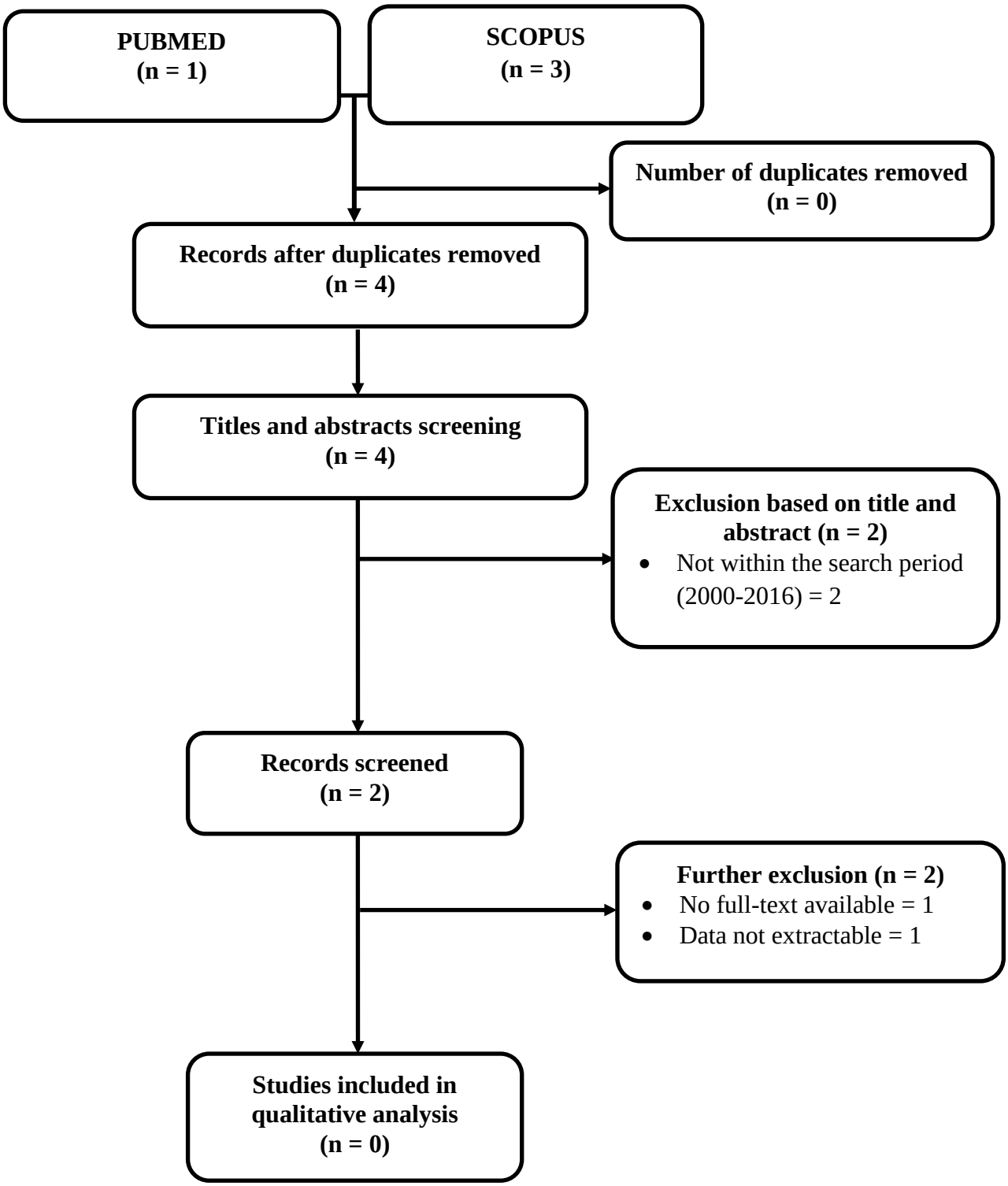
DISEASE: Trachoma
DRUG: Azithromycin



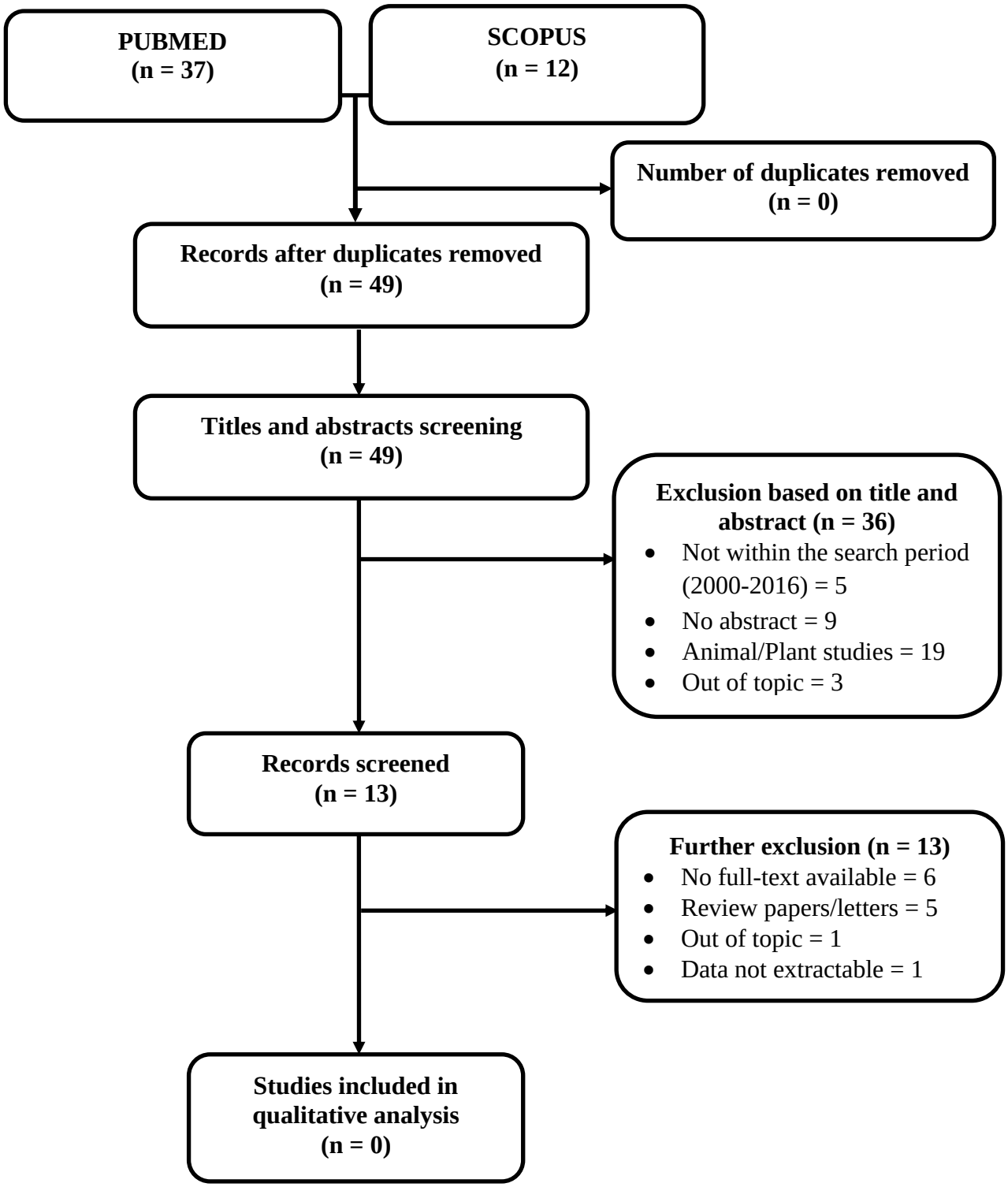
DISEASE: Taeniasis
DRUG: Praziquantel



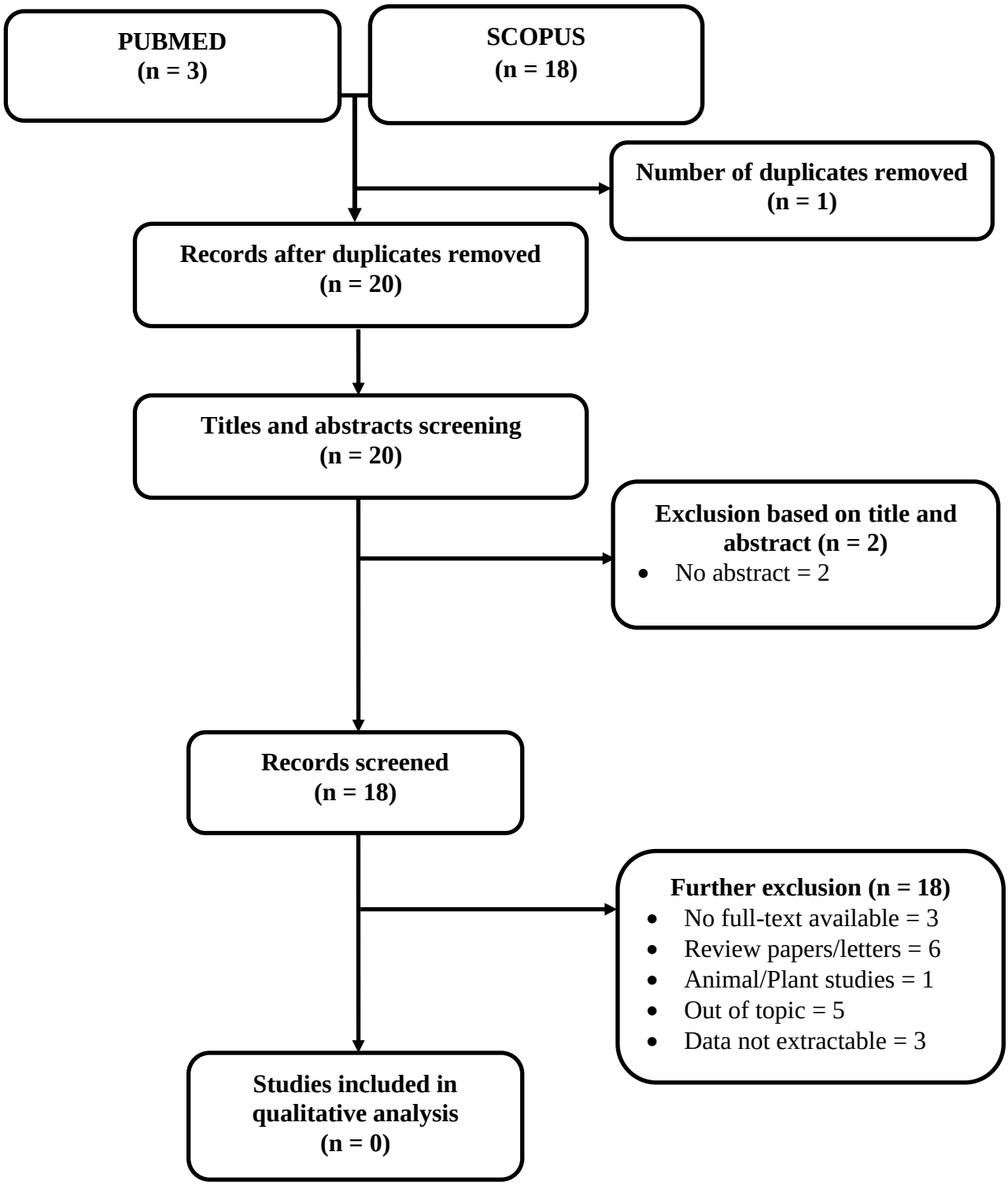
DISEASE: Taeniasis
DRUG: Niclosamide



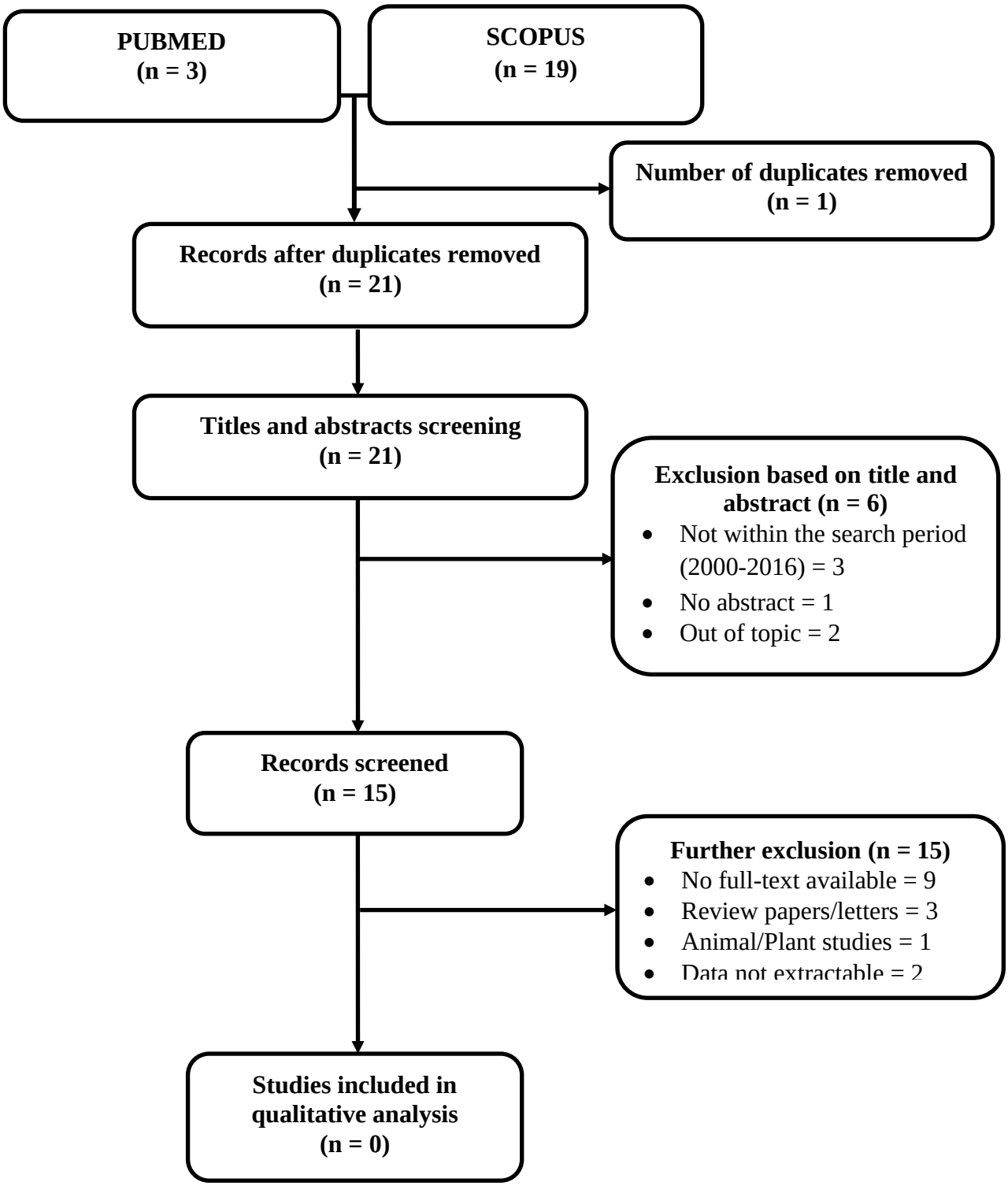
DISEASE: Trematodiasis
DRUG: Triclabendazole



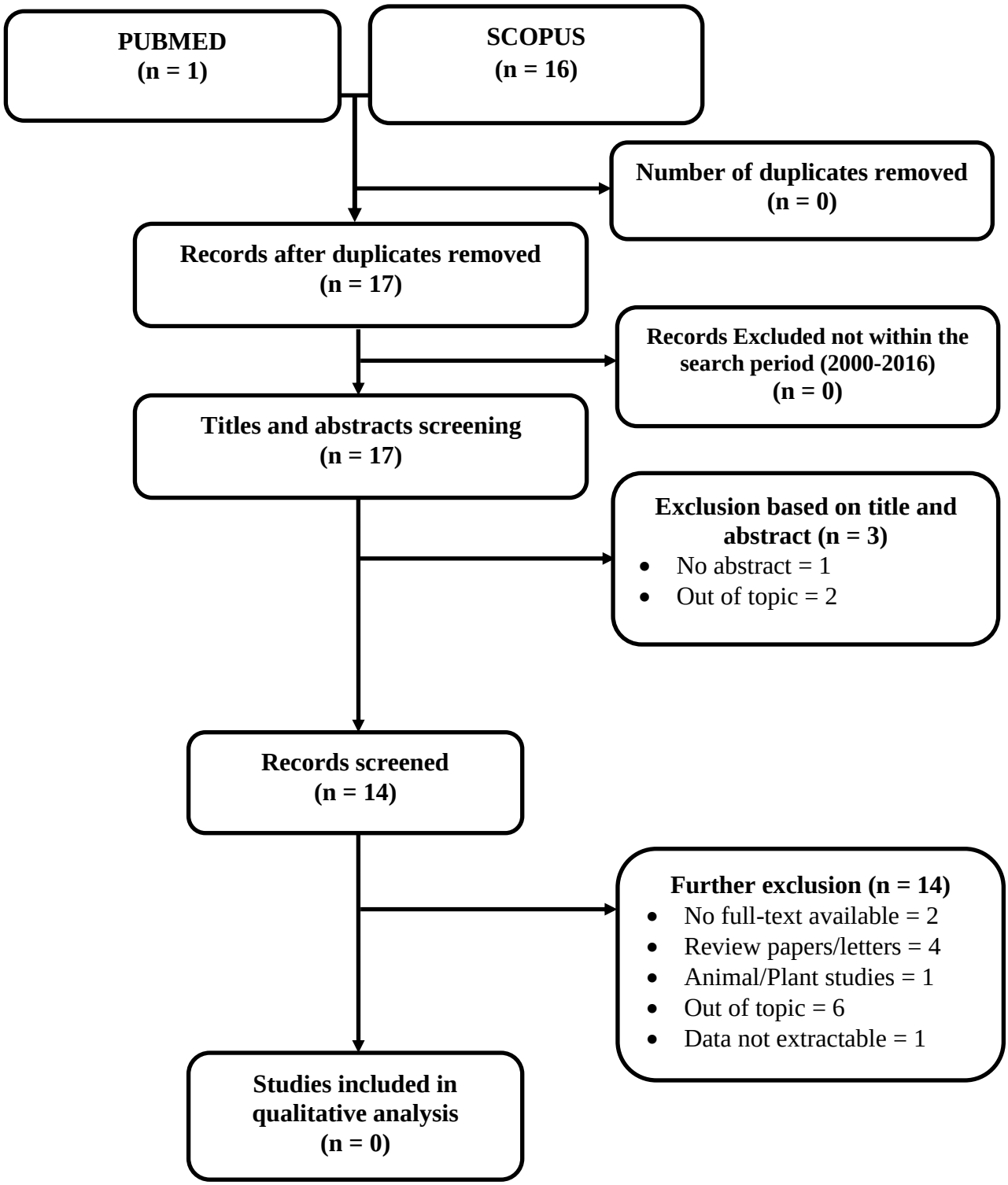
DISEASE: Lymphatic filariasis
DRUG: Albendazole



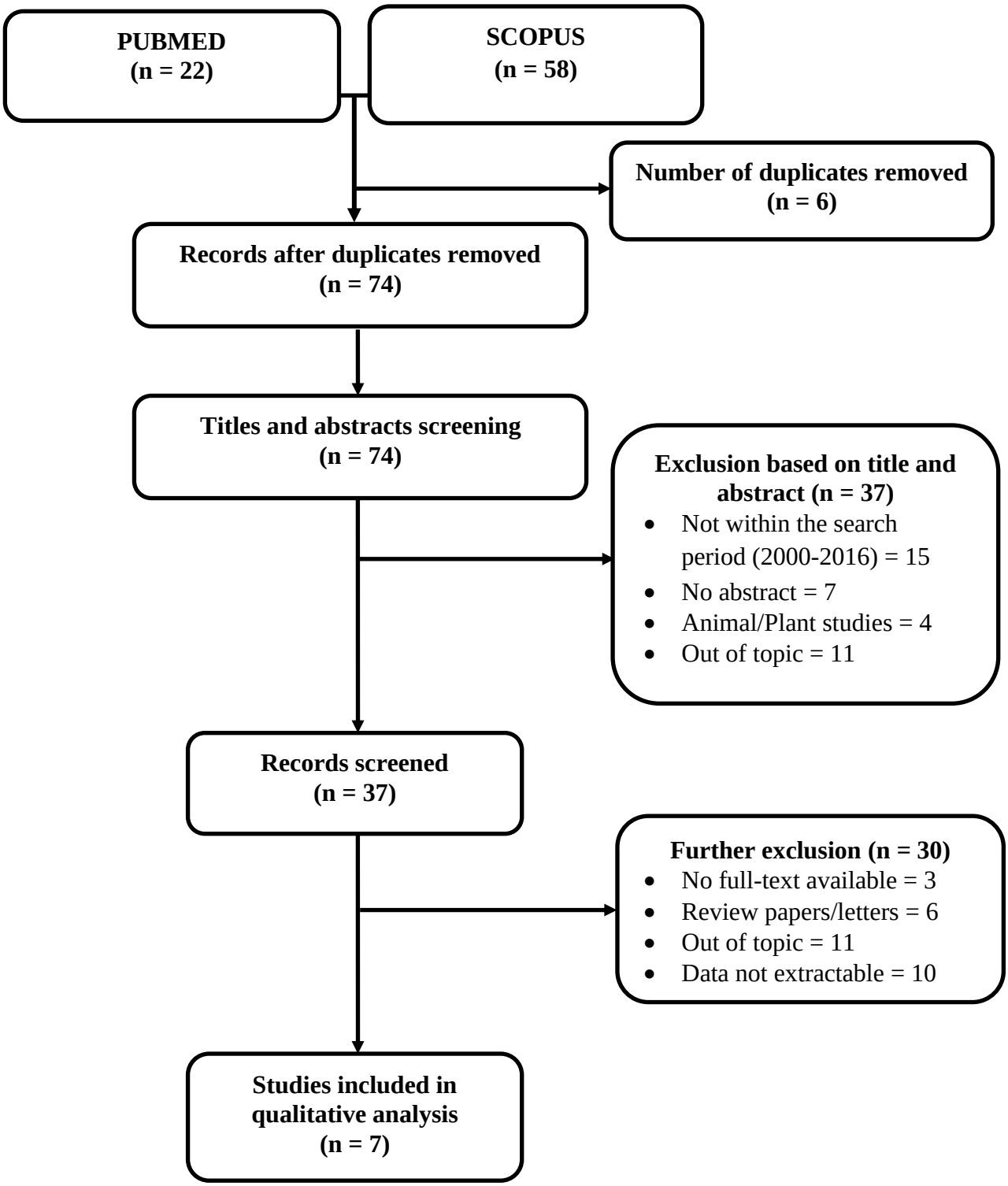
DISEASE: Lymphatic filariasis
DRUG: Diethycarbamazine (DEC)



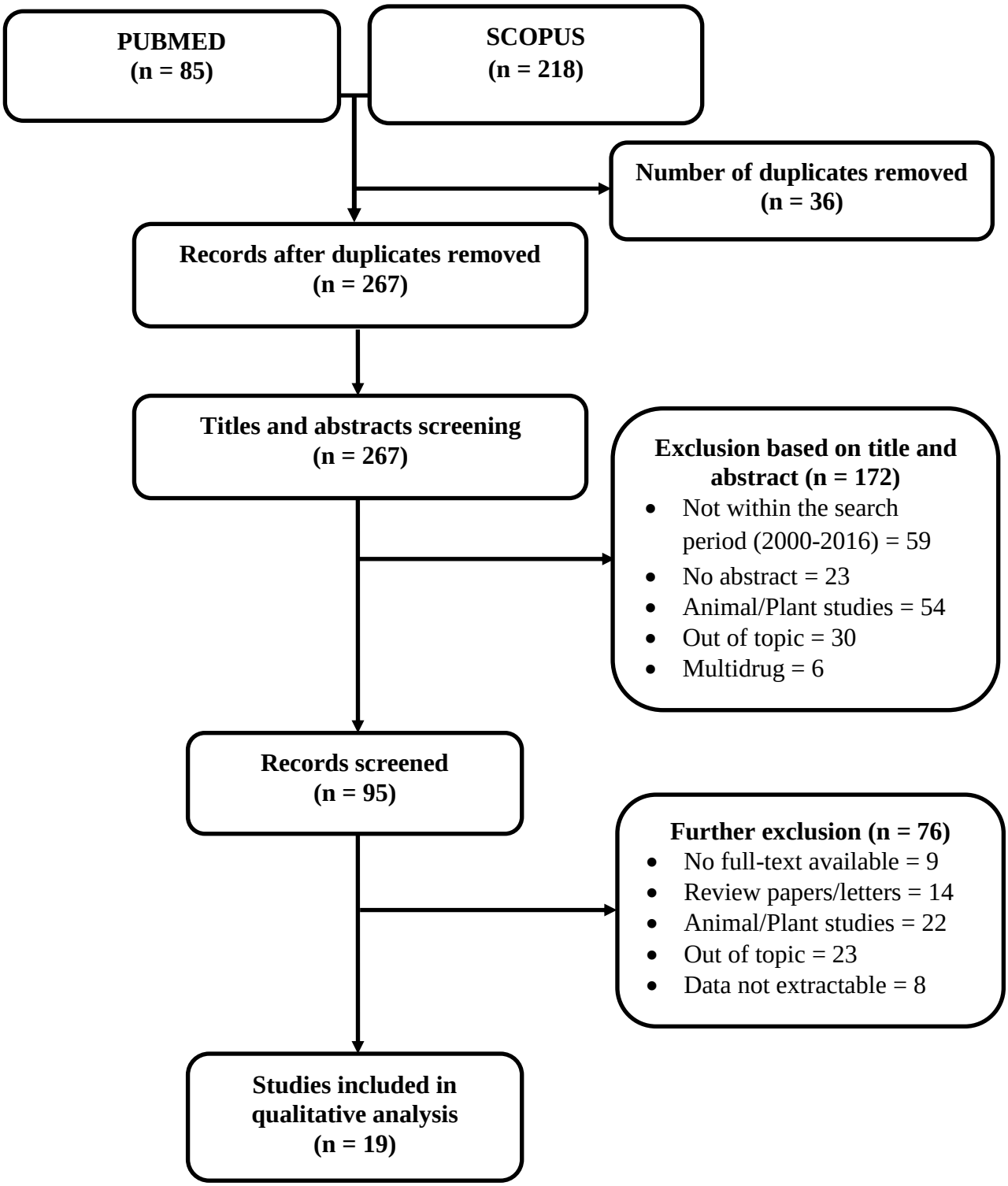
DISEASE: Lymphatic filariasis
DRUG: Ivermectin



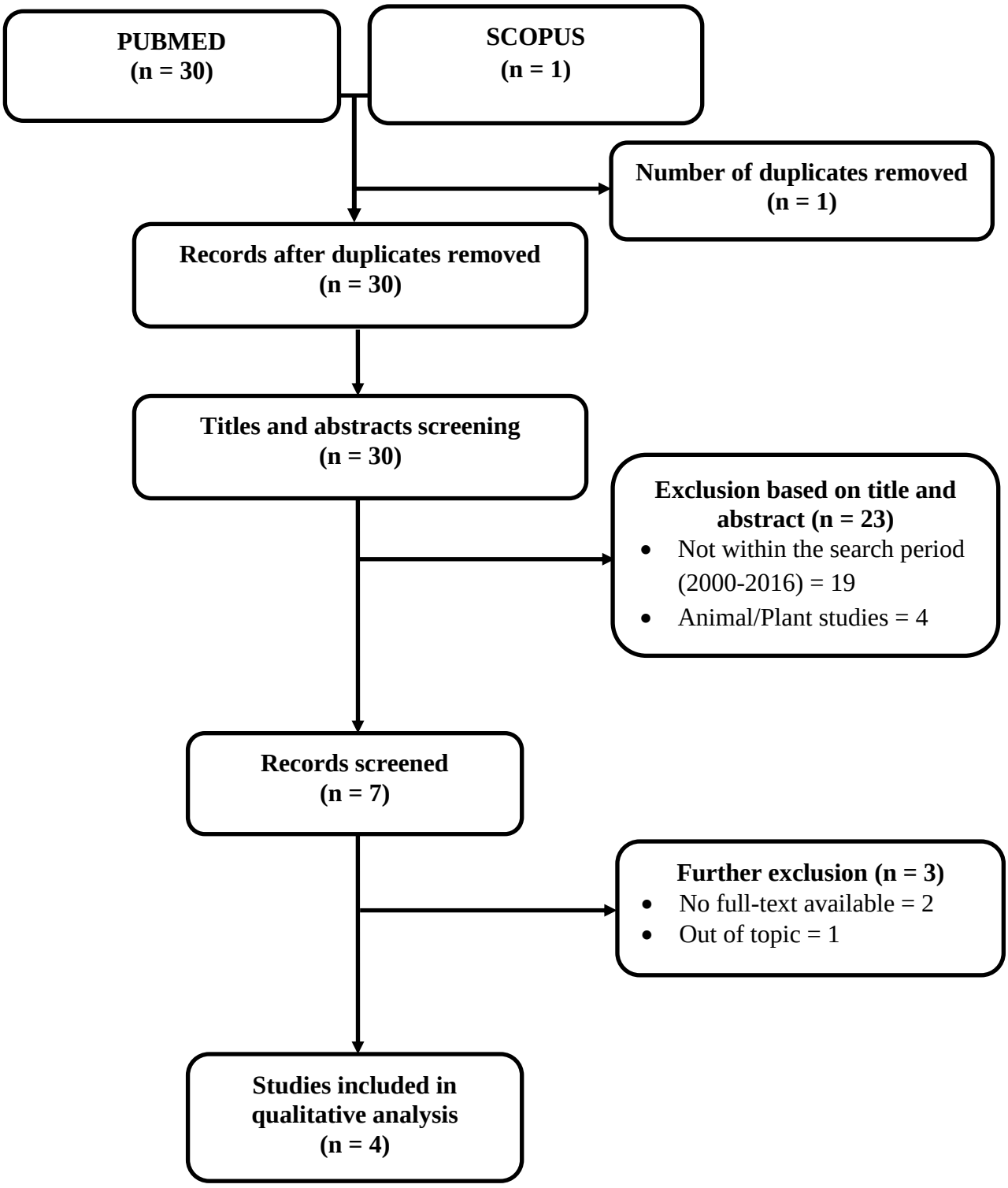
DISEASE: Onchocerciasis
DRUG: Ivermectin



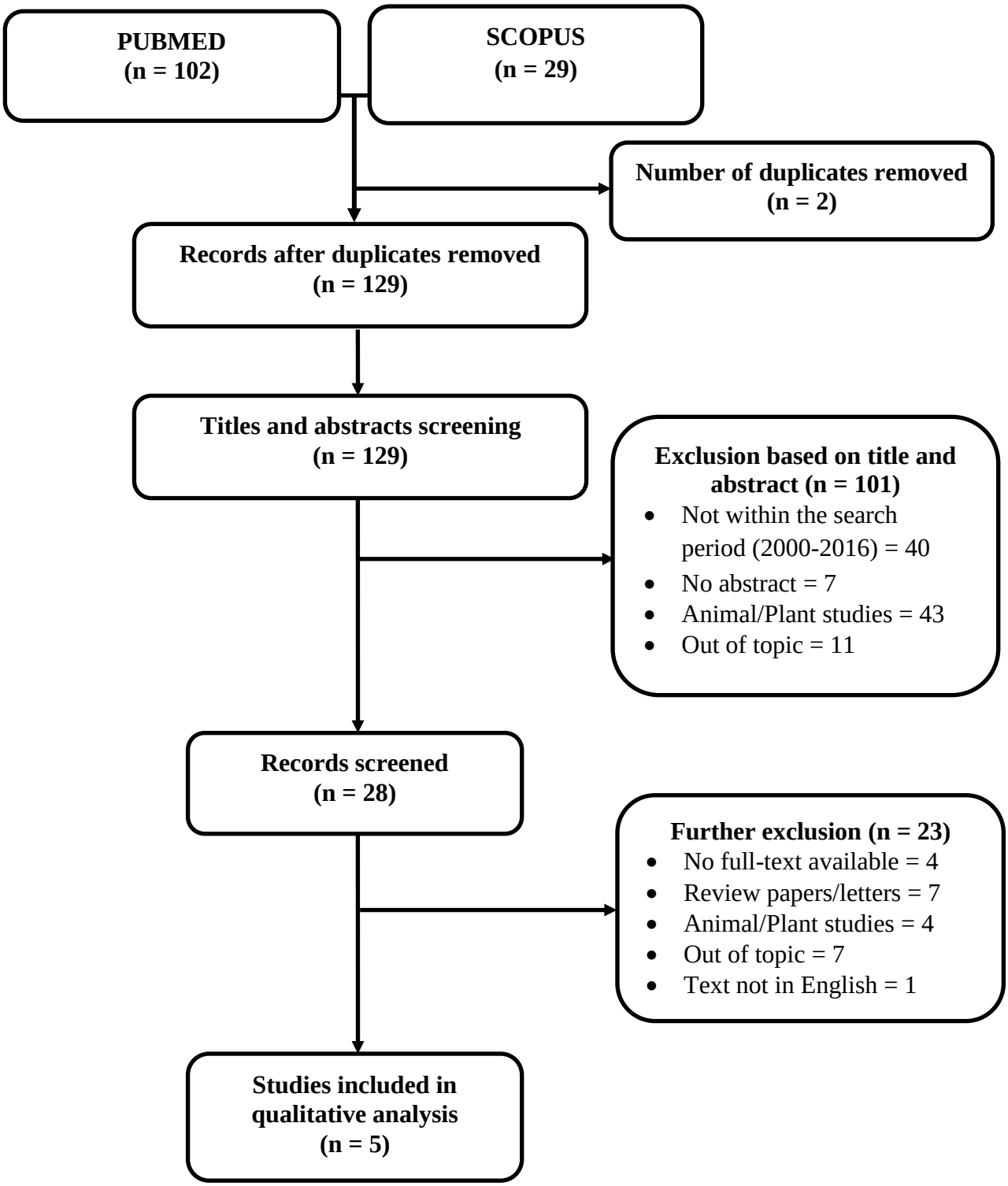
DISEASE: Schistosomiasis
DRUG: Praziquantel



DISEASE: Soil-transmitted helminthes
DRUG: Mebendazole



DISEASE: Soil-transmitted helminthes
DRUG: Albendazole



Appendix 6a: Full details of the quality assessment

AUTHORS	DRUGS	YEAR OF PUBLICATION	STUDY DESIGN	BLINDING	SELECTION BIAS	WITHDRAWALS/ DROP-OUTS	CONFOUNDERS	DATA COLLECTION	DATA ANALYSIS	REPORTING	OVERALL
Kibona et al.	Suramin	2006	strong	weak	no rating	no rating	weak	moderate	weak	strong	weak
Darby et al.	Suramin	2008	weak	weak	no rating	no rating	weak	weak	weak	weak	weak
Ehrhardt et al.	Suramin	2006	weak	weak	no rating	no rating	weak	weak	weak	weak	weak
Leyon et al.	Suramin	2007	moderate	weak	weak	strong	weak	weak	strong	moderate	weak
Croft et al.	Suramin	2006	weak	weak	no rating	no rating	weak	weak	weak	weak	weak
Faust et al.	Suramin	2004	weak	weak	no rating	no rating	weak	weak	weak	weak	weak
Kuepfer et al.	Melarsopol	2012	moderate	weak	weak	strong	weak	weak	moderate	strong	weak
Likeufack et al.	Melarsopol	2006	strong	weak	weak	no rating	weak	weak	moderate	moderate	weak
Simarro et al.	Melarsopol	2006	moderate	weak	weak	strong	weak	moderate	weak	moderate	weak
Brun et al.	Melarsopol	2001	strong	weak	weak	weak	weak	weak	weak	moderate	weak
Pyana et al.	Melarsopol	2011	moderate	weak	moderate	strong	weak	moderate	weak	moderate	weak
Burri et al.	Melarsopol	2007	moderate	weak	weak	strong	weak	moderate	strong	moderate	weak
Bisser et al.	Melarsopol	2007	strong	weak	moderate	strong	strong	weak	strong	moderate	0
Matovu et al.	Melarsopol	2001	strong	moderate	weak	no rating	weak	moderate	weak	moderate	weak
Ruiz et al.	Melarsopol	2002	moderate	weak	strong	strong	weak	moderate	weak	moderate	weak
Eperon et al.	Melarsopol	2007	moderate	weak	strong	strong	strong	strong	strong	moderate	weak
Balasegaram et al.	Melarsopol	2006	moderate	weak	moderate	strong	moderate	moderate	strong	strong	moderate
Lejon et al.	Melarsopol	2008	strong	weak	moderate	moderate	weak	strong	strong	strong	weak
Blum et al.	Melarsopol	2001	moderate	weak	weak	strong	strong	strong	strong	moderate	weak
Kuepfer et al.	Melarsopol	2011	moderate	weak	moderate	strong	strong	strong	strong	strong	moderate
Schmid et al.	Melarsopol	2005	moderate	strong	strong	strong	strong	strong	strong	strong	strong
Kagira et al.	Melarsopol	2011	moderate	weak	weak	strong	strong	strong	strong	strong	moderate
Pepin et al.	Melarsopol	2005	moderate	weak	strong	strong	strong	strong	strong	strong	moderate
Pitto et al.	Eflornithine	2009	strong	moderate	moderate	moderate	strong	strong	strong	strong	strong
Truc et al.	Eflornithine	2012	moderate	weak	weak	strong	moderate	weak	weak	moderate	weak
Truc et al.	Eflornithine	2012	moderate	weak	weak	moderate	moderate	moderate	moderate	moderate	weak
Balasegaran et al.	Eflornithine	2006	moderate	weak	weak	strong	strong	strong	strong	strong	weak
Balasegaran et al.	Eflornithine	2009	moderate	weak	strong	weak	strong	strong	strong	strong	moderate
Chappuis et al.	Eflornithine	2005	moderate	weak	weak	strong	moderate	moderate	moderate	strong	moderate
Priotto et al.	Eflornithine	2008	moderate	weak	moderate	weak	moderate	strong	strong	strong	weak
Wengeer et al.	Eflornithine	2014	weak	weak	no rating	no rating	weak	weak	weak	weak	weak
Balasegaram et al.	Pentamidine	2006	moderate	weak	weak	strong	strong	moderate	strong	strong	weak
Pepin et al.	Pentamidine	2010	moderate	moderate	weak	strong	strong	strong	strong	strong	moderate
Lejon et al.	Pentamidine	2010	strong	weak	weak	strong	strong	strong	strong	strong	moderate
Jamonneau et al.	Pentamidine	2003	moderate	weak	weak	strong	strong	moderate	strong	strong	weak
Paul et al.	Pentamidine	2014	weak	weak	no rating	no rating	strong	weak	moderate	moderate	weak
Ruiz et al.	Pentamidine	2002	moderate	weak	moderate	strong	strong	moderate	strong	strong	weak
Lejon et al.	Pentamidine	2003	strong	weak	weak	moderate	strong	moderate	strong	strong	weak
Simarro et al.	Pentamidine	2006	strong	moderate	weak	moderate	strong	moderate	moderate	moderate	weak

Appendix 6b: Full details of the quality assessment

AUTHORS	DRUGS	YEAR OF PUBLICATION	STUDY DESIGN	BLINDING	SELECTION BIAS	WITHDRAWALS/ DROP-OUTS	CONFOUNDERS	DATA COLLECTION	DATA ANALYSIS	REPORTING	OVERALL
Truc et al.	Pentamidine	2012	moderate	weak	weak	strong	strong	moderate	strong	moderate	weak
Abel et al.	Pentamidine	2004	moderate	weak	weak	strong	moderate	moderate	moderate	moderate	weak
Buguet et al.	Pentamidine	2005	moderate	weak	weak	no rating	strong	moderate	weak	moderate	weak
Chappuis et al.	Pentamidine	2004	moderate	moderate	weak	moderate	moderate	moderate	strong	strong	weak
Eperon et al.	Pentamidine	2007	moderate	moderate	weak	strong	strong	moderate	strong	strong	weak
Clerinx et al.	Suramin	2012	moderate	weak	no rating	no rating	weak	weak	weak	weak	weak
Powar et al.	Suramin	2006	moderate	weak	no rating	no rating	weak	weak	weak	weak	weak
Pepin et al.	Eflornithine	2000	strong	moderate	weak	strong	strong	strong	strong	strong	moderate
Cherian et al.	Eflornithine	2010	moderate	weak	no rating	no rating	weak	weak	weak	weak	weak
Pepin et al.	Melarsopol	2006	strong	weak	weak	weak	strong	moderate	moderate	strong	weak
Sindato et al.	Melarsopol	2008	strong	weak	no rating	no rating	weak	weak	weak	weak	weak
Burri et al.	Melarsopol	2001	moderate	weak	no rating	no rating	weak	weak	weak	weak	weak
Diro et al.	Amphotericin B	2014	moderate	weak	weak	strong	strong	moderate	strong	strong	strong
Srivastava et al.	Amphotericin B	2011	moderate	weak	weak	no rating	weak	moderate	moderate	moderate	weak
Sundar et al.	Amphotericin B	2008	strong	strong	weak	strong	strong	moderate	strong	moderate	moderate
Sundar et al.	Amphotericin B	2003	strong	weak	weak	weak	strong	moderate	strong	strong	weak
Zhao et al.	Amphotericin B	2011	weak	weak	weak	no rating	weak	weak	weak	weak	weak
Sundar et al.	Amphotericin B	2014	strong	weak	weak	strong	strong	moderate	strong	strong	weak
Sundar et al.	Amphotericin B	2008	strong	weak	weak	no rating	strong	moderate	strong	strong	weak
Sinha et al.	Amphotericin B	2006	moderate	weak	weak	weak	weak	weak	weak	moderate	weak
Pimentel et al.	Amphotericin B	2011	weak	moderate	weak	no rating	weak	weak	weak	moderate	weak
Kumar et al.	Amphotericin B	2011	weak	weak	no rating	no rating	strong	weak	weak	moderate	weak
Omollo et al.	Amphotericin B	2011	strong	weak	weak	no rating	no rating	no rating	strong	moderate	weak
Couto et al.	Amphotericin B	2014	weak	weak	no rating	no rating	weak	weak	weak	moderate	weak
Bourguinat et al.	Ivermectin	2008	moderate	weak	moderate	no rating	strong	strong	strong	strong	moderate
Bourguinat et al.	Ivermectin	2007	strong	weak	weak	strong	strong	strong	strong	strong	moderate
Hoeraufet al.	Ivermectin	2008	strong	strong	weak	strong	strong	strong	strong	strong	moderate
Kudzi et al.	Ivermectin	2010	strong	weak	weak	strong	moderate	moderate	strong	moderate	weak
Ali et al.	Ivermectin	2002	moderate	weak	moderate	no rating	weak	moderate	moderate	strong	weak
Nana-Djeunga et al.	Ivermectin	2012	moderate	weak	weak	no rating	moderate	moderate	moderate	strong	weak
Osie-Atweneboana et al.	Ivermectin	2011	moderate	weak	moderate	moderate	strong	strong	strong	moderate	weak
Barakat et al.	Praziquantel	2011	moderate	weak	moderate	strong	moderate	strong	strong	moderate	weak
Botros et al.	Praziquantel	2005	strong	weak	moderate	weak	strong	strong	moderate	moderate	weak
Lawn et al.	Praziquantel	2003	moderate	weak	no rating	no rating	weak	weak	weak	weak	weak
Downs et al.	Praziquantel	2013	moderate	weak	weak	moderate	moderate	moderate	strong	strong	weak
Lelo et al.	Praziquantel	2014	moderate	weak	weak	no rating	moderate	strong	strong	strong	weak
Tweyongyere et al.	Praziquantel	2008	moderate	strong	moderate	weak	strong	strong	strong	strong	moderate
Tweyongyere et al.	Praziquantel	2009	moderate	strong	moderate	moderate	strong	strong	strong	strong	moderate

Appendix 6c: Full details of the quality assessment

AUTHORS	DRUGS	YEAR OF PUBLICATION	STUDY DESIGN	BLINDING	SELECTION BIAS	WITHDRAWALS/ DROP-OUTS	CONFOUNDERS	DATA COLLECTION	DATA ANALYSIS	REPORTING	OVERALL
Utzinger et al.	Praziquantel	2000	moderate	weak	moderate	no rating	strong	strong	moderate	strong	moderate
Yu et al.	Praziquantel	2001	moderate	weak	moderate	strong	strong	strong	strong	strong	moderate
N'Goran et al.	Praziquantel	2003	moderate	weak	weak	weak	moderate	strong	strong	strong	weak
Black et al.	Praziquantel	2009	moderate	weak	no rating	no rating	weak	weak	weak	weak	weak
Guidi et al.	Praziquantel	2010	moderate	weak	weak	moderate	moderate	moderate	strong	strong	weak
Lamberton et al.	Praziquantel	2010	moderate	weak	weak	no rating	moderate	strong	strong	strong	weak
Wang et al.	Praziquantel	2010	moderate	strong	moderate	weak	strong	strong	strong	strong	moderate
Ahmed et al.	Praziquantel	2012	moderate	strong	moderate	moderate	strong	strong	strong	strong	strong
Al-Sherbinyet al.	Praziquantel	2003	moderate	weak	moderate	no rating	strong	strong	moderate	strong	weak
Mwanakasale et al.	Praziquantel	2003	moderate	weak	moderate	strong	strong	strong	strong	strong	moderate
Raso et al.	Praziquantel	2004	moderate	weak	moderate	strong	strong	strong	strong	strong	moderate
Sheir et al.	Praziquantel	2001	moderate	weak	weak	weak	moderate	strong	strong	strong	weak
Vercruysse et al.	Albendazole	2011	strong	weak	strong	strong	strong	strong	strong	strong	moderate
Levecke et al.	Albendazole	2014	moderate	weak	moderate	moderate	weak	strong	strong	strong	weak
Diawara et al.	Albendazole	2009	strong	weak	weak	no rating	weak	weak	weak	moderate	weak
Diawara et al.	Albendazole	2013	moderate	weak	moderate	moderate	strong	strong	strong	strong	moderate
Albonico et al.	Mebendazole	2003	strong	strong	moderate	moderate	moderate	strong	strong	strong	strong
Albonico et al.	Mebendazole	2005	strong	strong	moderate	moderate	moderate	strong	strong	strong	strong
Lubis et al.	Albendazole	2012	moderate	weak	weak	weak	strong	moderate	moderate	strong	weak
Albonico et al.	Mebendazole	2002	moderate	weak	weak	weak	strong	moderate	moderate	strong	weak
Lubis et al.	Mebendazole	2012	moderate	weak	weak	weak	strong	moderate	moderate	strong	weak
Maher et al.	Azithromycin	2012	moderate	moderate	moderate	weak	weak	moderate	strong	strong	weak
Fry et al.	Azithromycin	2002	moderate	weak	moderate	strong	strong	strong	strong	strong	moderate
West et al.	Azithromycin	2014	strong	weak	weak	strong	weak	moderate	moderate	strong	weak
Keenan et al.	Azithromycin	2015	strong	weak	weak	weak	weak	moderate	strong	strong	weak
Haug et al.	Azithromycin	2010	strong	weak	weak	weak	strong	strong	strong	strong	weak
Coles et al.	Azithromycin	2013	moderate	weak	weak	weak	weak	moderate	strong	strong	weak
Batt et al.	Azithromycin	2003	strong	weak	weak	weak	weak	strong	strong	moderate	weak
Gaynor et al.	Azithromycin	2005	strong	weak	weak	weak	weak	moderate	strong	strong	weak
Gaynor et al.	Azithromycin	2003	strong	weak	weak	weak	strong	moderate	weak	strong	weak
Coles et al.	Azithromycin	2013	strong	weak	moderate	weak	strong	strong	strong	strong	weak

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Registry number: DEENK/371/2018.PL
Subject: PhD Publikációs Lista

Candidate: Folahanmi Tomiwa Akinsolu
Neptun ID: HSVVZK
Doctoral School: Doctoral School of Health Sciences

List of publications related to the dissertation

1. **Akinsolu, F. T.**, Balczár, E., Kovács, N., Gáll, T., Harangi, M., Varga, O.: Developing a database for Rett syndrome research performed in the European Union: a resource for researchers and stakeholders.
   Child Care Health Dev. 44 (5), 794-800, 2018.
   DOI: http://dx.doi.org/10.1111/cch.12595
   IF: 1.699 (2017)
2. **Akinsolu, F. T.**, De Paiva, V. N., Souza, S. S., Varga, O.: Patent Landscape of Neglected Tropical Diseases: An analysis of worldwide patent families.
   Globalization and Health. 13 (82), 1-13, 2017.
   IF: 3.031

Total IF of journals (all publications): 4,73
Total IF of journals (publications related to the dissertation): 4,73

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

11 December, 2018

DEBRECENI EGYETEM * Egyetemi és Nemzeti Könyvtár *