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 Initiative
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 Countries
MDA - Mass Drug Administration
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 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, trematodiasis, human African trypanosomiasis (HAT), leishamaniais, leprosy, lymphatic filariasis, mycetoma, onchocerciasis, rabies, scabies, schistosomiasis, soil-transmitted helminthos (STH), snakebite envenomimg, 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 invisible 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 diseases 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).
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**

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

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

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”.

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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

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

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

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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.

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

<table>
<thead>
<tr>
<th>Neglected Tropical Diseases (PCT/IDM)</th>
<th>Number of countries</th>
<th>Disease burden</th>
<th>Interventions</th>
<th>Effectiveness of current interventions</th>
<th>Granted patent families/all patent families</th>
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<tr>
<td></td>
<td>Incidence</td>
<td>Prevalence</td>
<td>DALYs</td>
<td>Prevention</td>
<td>Treatment</td>
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<tr>
<td>Buruli ulcer (IDM)</td>
<td>33</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>There are currently no primary preventive measures that can be applied. The mode of transmission is not known and there is no vaccine.</td>
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<td>Rifampicin and clarithromycin</td>
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<tr>
<td>Chagas disease (IDM)</td>
<td>21</td>
<td>8404</td>
<td>6,653,578</td>
<td>236,100</td>
<td>Vector control is the most effective method of prevention. Blood screening is necessary to prevent infection through transfusion and organ transplantation.</td>
</tr>
<tr>
<td>Dengue</td>
<td>&gt; 100</td>
<td>86,257,710</td>
<td>4,729,962</td>
<td>1,892,200</td>
<td>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.</td>
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<tr>
<td>Dracunculiasis (PCT)</td>
<td>3</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>There is no vaccine to prevent. Prevention is possible through complex preventive strategies.</td>
</tr>
<tr>
<td>Echinococcosis</td>
<td>Very few countries are completely free of these parasites</td>
<td>313,264</td>
<td>1,382,975</td>
<td>600,000</td>
<td>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.</td>
</tr>
<tr>
<td>Food-borne trematodiases</td>
<td>75</td>
<td>No data</td>
<td>71,095,424</td>
<td>168,500</td>
<td>Veterinary public health measures and food safety practices and education are recommended to reduce the risk of infection. Triclabendazole/Praziquantel through MDA programs.</td>
</tr>
<tr>
<td>Neglected Tropical Diseases (PCT/IDM)</td>
<td>Number of countries</td>
<td>Disease burden</td>
<td>Preventive Chemotherapy/ Intensified disease management</td>
<td>Effectiveness of current interventions</td>
<td>Total granted/ patent families</td>
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<tr>
<td>Human African trypanosomiasis (IDM)</td>
<td>13</td>
<td>7,013,10,687,202,400</td>
<td>Vector control and effective disease surveillance. Pentamidine and Suramin (First stage treatment)</td>
<td>Yes (87) No Low High</td>
<td>41/198</td>
</tr>
<tr>
<td>Leishmaniasis (IDM)</td>
<td>10</td>
<td>1,051,824,3,859,307,3,859,307</td>
<td>Vector control and effective disease surveillance. Social mobilization and strengthening partnerships. Amphotericin B, Miltefosine, fluconazole, itraconazole</td>
<td>Yes (88) No Low High/Low</td>
<td>140/2652</td>
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<tr>
<td>Leprosy (PCT)</td>
<td>136</td>
<td>57,405,514,203,31,000</td>
<td>BCG Vaccination Multidrug therapy</td>
<td>Yes (89) No Low High</td>
<td>522/2206</td>
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<tr>
<td>Lymphatic filariasis (PCT)</td>
<td>73</td>
<td>No data, 38,464,150,2,075,000</td>
<td>Albendazole through MDA programs. Mosquito control is a supplemental strategy supported by WHO. Albendazole with either ivermectin or diethylcarbamazine</td>
<td>Yes (90) Yes High High</td>
<td>69/287</td>
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<td>Onchocerciasis (PCT)</td>
<td>31</td>
<td>No data, 15,531,530,1,135,700</td>
<td>Ivermectin through MDA programs. Vector control. Ivermectin</td>
<td>Yes (91) Yes High High</td>
<td>88/313</td>
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<tr>
<td>Rabies</td>
<td>150</td>
<td>18,312,704,931,600</td>
<td>Integrated bite case management, Preventive immunization (vaccination) Post-exposure prophylaxis, Integrated bite case management</td>
<td>No No High High</td>
<td>569/2694</td>
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<tr>
<td>Schistosomiasis (PCT)</td>
<td>78</td>
<td>No data, 252,339,520,2,613,300</td>
<td>Praziquantel through MDA programs. Additionally, access to safe water, improved sanitation, hygiene education, and snail control. Praziquantel</td>
<td>Yes (92) Yes High High</td>
<td>321/1722</td>
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<tr>
<td>Soil-transmitted helminthes (PCT)</td>
<td>118</td>
<td>No data, 761,893,771,3,378,300</td>
<td>Albendazole/Mebendazole through MDA programs. Health education and improvement in personal hygiene are essential components of prevention. Albendazole/ Mebendazole</td>
<td>Probably (93) No High High</td>
<td>83/584</td>
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</table>
Table 4c: Global data of countries affected by NTDs, drugs donated, burden of each disease, and number of patent families.

<table>
<thead>
<tr>
<th>Neglected Tropical Diseases (PCT/IDM)</th>
<th>Number of countries</th>
<th>Disease burden</th>
<th>Preventive Chemotherapy/Intensified disease management</th>
<th>Effectiveness of current interventions</th>
<th>Total granted/patent families</th>
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<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Taeniasis</td>
<td>&gt;75</td>
<td>No data</td>
<td>No data</td>
<td>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.</td>
<td>Yes (94)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trachoma (PCT)</td>
<td>42</td>
<td>No data</td>
<td>3,557,122</td>
<td>Azithromycin through MDA programs SAFE strategy</td>
<td>Yes (95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>279,200</td>
<td>Azithromycin, Tetracycline</td>
<td></td>
</tr>
<tr>
<td>Yaws (IDM)</td>
<td>13</td>
<td>No data</td>
<td>No data</td>
<td>Azithromycin through MDA programs. Health education and improvement in personal hygiene are essential components of prevention.</td>
<td>Probably (96)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Azithromycin Benzathine Penicillin</td>
<td></td>
</tr>
</tbody>
</table>

PCT = Preventive Chemotherapy and Transmission Control  
IDM = Innovative and Intensified Disease Management  
MDA = Mass drug administration  
N/A = Not applicable  
SAFE = Surgery for advanced disease, Antibiotics to clear Chlamydia trachomatis infection, Facial cleanliness, and Environmental 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 categories. 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.

![Graph showing patenting trend](image)

**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 continuous 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).

![Pie chart showing current legal status of patent families of NTDs]

**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 University 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 assignees. 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

- **PUBMED**
  - (n = 1550)

- **SCOPUS**
  - (n = 1746)

- **Number of duplicates removed**
  - (n = 380)

- **Records after duplicates removed**
  - (n = 2916)

- **Titles and abstracts screening**
  - (n = 2916)

- **Exclusion based on title and abstract**
  - (n = 2101)
    - Not within the search period (2000-2016) = 1451
    - No abstract = 141
    - Animal/Plant studies = 216
    - Out of topic = 255
    - Multidrug = 38

- **Records screened**
  - (n = 815)

- **Further exclusion**
  - (n = 707)
    - No full-text available = 146
    - Review papers/letters = 135
    - Animal/Plant studies = 64
    - Out of topic = 284
    - Data not extractable = 75
    - Text not in English = 3

- **Studies included in qualitative analysis**
  - (n = 108)
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.

![Bar chart showing the number of publications by continent and year](chart.png)

**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**

<table>
<thead>
<tr>
<th>Study type</th>
<th>Average number of people</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case control</td>
<td>1964</td>
</tr>
<tr>
<td>Case report</td>
<td>1.000</td>
</tr>
<tr>
<td>Cohort study</td>
<td>1468</td>
</tr>
<tr>
<td>Cross sectional study</td>
<td>998</td>
</tr>
<tr>
<td>Non-random experimental</td>
<td>3234</td>
</tr>
<tr>
<td>Random experimental</td>
<td>1016</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1110</strong></td>
</tr>
</tbody>
</table>

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, Côte 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

<table>
<thead>
<tr>
<th>DATA</th>
<th>NEGLECTED TROPICAL DISEASES (NTDs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Human African trypanosomiasis (Studied drugs)</td>
</tr>
<tr>
<td></td>
<td>Eflornithine</td>
</tr>
<tr>
<td>TYPE OF STUDY</td>
<td>Case control</td>
</tr>
<tr>
<td></td>
<td>Case reports</td>
</tr>
<tr>
<td></td>
<td>Cohort study</td>
</tr>
<tr>
<td></td>
<td>Cross sectional study</td>
</tr>
<tr>
<td></td>
<td>Non-random experimental study</td>
</tr>
<tr>
<td></td>
<td>Random experimental</td>
</tr>
<tr>
<td>STUDY DESIGN</td>
<td>Experimental</td>
</tr>
<tr>
<td></td>
<td>Observational</td>
</tr>
<tr>
<td>CLINICAL SETTINGS</td>
<td>Emergency unit</td>
</tr>
<tr>
<td></td>
<td>Hospital ward</td>
</tr>
<tr>
<td></td>
<td>Intensive care unit</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>Outpatient</td>
</tr>
<tr>
<td>STUDY SETTINGS</td>
<td>Not specified</td>
</tr>
<tr>
<td></td>
<td>Rural</td>
</tr>
<tr>
<td></td>
<td>Urban</td>
</tr>
<tr>
<td>GENDER</td>
<td>Both</td>
</tr>
<tr>
<td></td>
<td>Female only</td>
</tr>
<tr>
<td></td>
<td>Male only</td>
</tr>
<tr>
<td>SPECIMEN</td>
<td>CSF and blood</td>
</tr>
<tr>
<td></td>
<td>Blood and Organ tissue</td>
</tr>
<tr>
<td></td>
<td>Blood and Skin</td>
</tr>
<tr>
<td></td>
<td>Stool</td>
</tr>
<tr>
<td></td>
<td>NA</td>
</tr>
</tbody>
</table>
Table 6b Characteristics of reviewed NTDs and their treatments

<table>
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<tr>
<th>DATA</th>
<th>NEGLECTED TROPICAL DISEASES (NTDs)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Human African trypanosomiasis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Studied drugs)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leishmaniasis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Studied drug)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Onchocerciasis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Studied drug)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Schistosomiasis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Studied drug)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Soil-transmitted helminthes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Studied drugs)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trachoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Studied drug)</td>
<td></td>
</tr>
<tr>
<td>EFFLORNITHINE</td>
<td>Melarsoprol</td>
<td>Pentamidine</td>
</tr>
<tr>
<td>Adults</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Both</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Children</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>USAGE</td>
<td>Individual</td>
<td>Mass</td>
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<tr>
<td>AGE RANGE</td>
<td>Adults</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>0</td>
</tr>
<tr>
<td>DDD</td>
<td>Maximum</td>
<td>Minimum</td>
</tr>
<tr>
<td>RESISTANCE</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>CLINICAL</td>
<td>RESISTANCE</td>
<td>Yes</td>
</tr>
<tr>
<td>EXPOSURE</td>
<td>VARIABLE</td>
<td>Defined daily dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical manifestations</td>
</tr>
<tr>
<td>COUNTRIES OF STUDY</td>
<td>Angola, Cote d’Ivoire, Democratic Republic of Congo, Germany, South Sudan, Uganda and Western Australia</td>
<td>Angola, Cote d’Ivoire, Central Africa Republic (CAR) Democratic Republic of Congo, Equatorial Guinea, Kenya, South Sudan, Tanzania, and Uganda</td>
</tr>
<tr>
<td>DDD: Defined daily dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA: Not applicable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 universities 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 is 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 universities 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

<table>
<thead>
<tr>
<th>Neglected Tropical Diseases</th>
<th>Search Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buruli</td>
<td>(Mycobacterium ulcerans) OR (M. ulcerans) OR (Buruli Ulcer) OR (non-tubercul* mycobacter*)</td>
</tr>
<tr>
<td>Chagas</td>
<td>(Chagas disease) OR (trypanosomias*) OR (Trypanosoma cruzi) OR (T. cruzi)</td>
</tr>
<tr>
<td>Dengue</td>
<td>(Dengue w5 virus*) OR (Dengue disease*) OR (Dengue w5 fever) OR (Breakbone fever) OR (Chikungunya w5 fever) OR (Chikungunya w5 virus*)</td>
</tr>
<tr>
<td>Dracunculiasis</td>
<td>(Dracunculiasis) OR (Guinea Worm) OR (Guinea-worm disease) OR (Dracunculus medinensis)</td>
</tr>
<tr>
<td>Echinococcosis</td>
<td>(Echinococcos*) OR (hydatid disease) OR (hydatidosis) OR (echinococcal disease) OR (Echinococcus) OR (cystic echinococcosis) OR (alveolar echinococcosis) OR (polycystic echinococcosis) OR (unicycstic echinococcosis)</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>Leishmanias* OR leishmania OR leishmaniosis</td>
</tr>
<tr>
<td>Leprosy</td>
<td>(Leprosy) OR (Hansen's disease) OR (Mycobacterium leprae) OR (Mycobacterium lepromatosis) OR (nontubercul* mycobacter*) NOT (Mycobacterium ulcerans) NOT (Mycobacterium tuberculosis*)</td>
</tr>
<tr>
<td>Lymphatic Filariasis</td>
<td>(WUCHERERIA BANCROFTI) OR (BRUGIA MALAYI) OR (lymphatic filariasis) OR (Elephantias*) OR (Brugia timori)</td>
</tr>
<tr>
<td>Onchocerciasis</td>
<td>Onchocercias* OR (Onchocerca volvulus) OR (river w5 blindness) NOT (trachoma)</td>
</tr>
<tr>
<td>Rabies</td>
<td>(rabies w5 virus) OR (lyssa*) OR (rabies w5 infection*) OR (rabies w5 disease)</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>(Schistosomiasis) OR (snail fever) OR (bilharzia) OR (Katayama fever) OR (Schistosomiasis haematobia) OR (Schistosomiasis japonica) OR (Schistosomiasis mansoni) OR (Schistosoma) OR (blood-flukes)</td>
</tr>
<tr>
<td>Soil-transmitted helminthias</td>
<td>(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 (Ancylostoma duodenale) OR (Trichuris trichiura) OR (Trichurias*)</td>
</tr>
<tr>
<td>Taeniasis</td>
<td>(taeniasis) OR (Taenia solium) OR (pork tapeworm) OR (Taenia saginata) OR (beef tapeworm) OR (Taenia asiatica) OR (Taenia w5 Infection*)</td>
</tr>
<tr>
<td>Thymosis</td>
<td>(Treponema pallidum) OR (Yaws disease*) OR (Thymosis) OR (framboesia) OR (Frambesia) OR (Treponema pertenue)</td>
</tr>
</tbody>
</table>
## Appendix 1b: Final search terms

<table>
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<tr>
<th>Neglected Tropical Diseases</th>
<th>Search Terms</th>
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<tbody>
<tr>
<td>Trachoma</td>
<td>(Trachoma) OR (Egyptian Ophthalmia) OR (Chlamydia trachomatis) OR (granular conjunctivitis)</td>
</tr>
<tr>
<td>Rabies</td>
<td>(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)</td>
</tr>
<tr>
<td>Trypanosomiasis</td>
<td>(African Trypanosomias*) OR (sleeping sickness) OR (nagana) OR (African Trypanosomias*) OR (Trypanosoma brucei gambiense) OR (Trypanosoma brucei rhodesiense) NOT (Chagas OR Plasmodium)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Search Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>(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 (Postpericardiomyopathy Syndrome) OR (Pulmonary Heart Disease) OR (Rheumatic Heart Disease) OR (Ventricular Dysfunction) OR (Ventricular Outflow Obstruction) OR (cardiovascular 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))</td>
</tr>
<tr>
<td>Cancer</td>
<td>(Cancer OR (Anti<em>cancer) OR Chemotherap</em> OR Oncol* OR Carcinog* OR Neoplas* OR Tumor OR Metastat* OR Malignan*)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>(pulmonary cancer) OR (lung cancer) OR (lung neoplasm) OR (carcinoma OR cancer OR metastasis OR neoplasm OR tumor) AND (lung OR Trachea OR bronchus)</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>(HIV OR (Human Immunodeficiency Virus)) OR (AIDS OR (acquired immune deficiency syndrome))</td>
</tr>
<tr>
<td>Malaria</td>
<td>Malaria OR plasmodium</td>
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</table>

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

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>DRUGS</th>
<th>SEARCH TERMS</th>
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<th>NUMBER OF DOCUMENTS FOUND</th>
<th>NUMBER DOWNLOADED</th>
<th>SAVED TO ENDNOTE FOLDER</th>
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<tbody>
<tr>
<td>Chagas Disease</td>
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### Appendix 2b: A full description of NTDs search terms and search strategy

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

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Appendix 3: Figures of annual patenting trends NTDs

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Appendix 4a: Figures of annual patenting trends for each NTD (Buruli ulcer and Chagas disease)
Appendix 4b: Figures of annual patenting trends for each NTD (Dengue and 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)
Appendix 4f: Figures of annual patenting trends for each NTD (Onchocerciasis and Rabies)
Appendix 4g: Figures of annual patenting trends for each NTD (Schistosomiasis and STH)
Appendix 4f: Figures of annual patenting trends for each NTD (Taeniasis and 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

Records after duplicates removed (n = 2916)

Titles and abstracts screening (n = 2916)

Exclusion based on title and abstract (n = 2101)
- Not within the search period (2000-2016) = 1451
- No abstract = 141
- Animal/Plant studies = 216
- Out of topic = 255
- Multidrug = 38

Records screened (n = 815)

Further exclusion (n = 707)
- No full-text available = 146
- Review papers/letters = 135
- Animal/Plant studies = 64
- Out of topic = 284
- Data not extractable = 75
- Text not in English = 3

Studies included in qualitative analysis (n = 108)
DISEASE: Chagas disease  
DRUG: Nifurtimox

PUBMED  
(n = 36)  

SCOPUS  
(n = 46)  

Number of duplicates removed  
(n = 13)  

Records after duplicates removed  
(n = 69)  

Titles and abstracts screening  
(n = 69)  

Exclusion based on title and abstract  
(n = 51)  
- Not within the search period (2000-2016) = 31  
- No abstract = 3  
- Animal/Plant studies = 7  
- Out of topic = 7  
- Multidrug = 3

Records screened  
(n = 18)  

Further exclusions  
(n = 18)  
- No full-text available = 4  
- Review papers/letters = 2  
- Animal/Plant studies = 4  
- Out of topic = 8

Studies included in qualitative analysis  
(n = 0)
DISEASE: Human African Trypanosomiasis
DRUG: Suramin

PUBMED
(n = 157)

SCOPUS
(n = 34)

Number of duplicates removed
(n = 15)

Records after duplicates removed
(n = 176)

Titles and abstracts screening
(n = 176)

Exclusion based on title and abstract (n = 117)
- Not within the search period (2000-2016) = 101
- No abstract = 3
- Animal/Plant studies = 6
- Out of topic = 5
- Multidrug = 2

Records screened
(n = 59)

Further exclusion (n = 51)
- No full-text available = 6
- Review papers/letters = 13
- Animal/Plant studies = 4
- Out of topic = 28

Studies included in qualitative analysis
(n = 8)
DISEASE: Human African Trypanosomiasis
DRUG: Eflornithine

PUBMED
(n = 174)

SCOPUS
(n = 41)

Number of duplicates removed
(n = 13)

Records after duplicates removed
(n = 202)

Titles and abstracts screening
(n = 202)

Exclusion based on title and abstract (n = 108)
- Not within the search period (2000-2016) = 86
- No abstract = 17
- Animal/Plant studies = 4
- Out of topic = 1

Records screened
(n = 94)

Further exclusion (n = 84)
- No full-text available = 6
- Review papers/letters = 24
- Animal/Plant studies = 6
- Out of topic = 38
- Data not extractable = 10

Studies included in qualitative analysis
(n = 10)
DISEASE: Human African Trypanosomiasis
DRUG: Melarsoprol

PUBMED (n = 262)

SCOPUS (n = 123)

Records after duplicates removed (n = 358)

Exclusion based on title and abstract (n = 277)
- Not within the search period (2000-2016) = 155
- No abstract = 14
- Animal/Plant studies = 21
- Out of topic = 87

Titles and abstracts screening (n = 358)

Further exclusion (n = 61)
- No full-text available = 14
- Review papers/letters = 13
- Animal/Plant studies = 3
- Out of topic = 27
- Data not extractable = 4

Records screened (n = 81)

Studies included in qualitative analysis (n = 20)
DISEASE: Human African Trypanosomiasis
DRUG: Pentamidine

- **PUBMED** (n = 158)
- **SCOPUS** (n = 43)

**Records after duplicates removed** (n = 179)

**Titles and abstracts screening** (n = 179)

**Exclusion based on title and abstract** (n = 89)
- Not within the search period (2000-2016) = 58
- No abstract = 13
- Animal/Plant studies = 8
- Out of topic = 7
- Multidrug = 3

**Records screened** (n = 90)

**Further exclusion** (n = 77)
- No full-text available = 8
- Review papers/letters = 21
- Animal/Plant studies = 8
- Out of topic = 36
- Data not extractable = 4

**Studies included in qualitative analysis** (n = 13)
DISEASE: Leishmaniasis
DRUG: Amphotericin B

PUBMED
(n = 60)

SCOPUS
(n = 223)

Number of duplicates removed
(n = 39)

Records after duplicates removed
(n = 244)

Titles and abstracts screening
(n = 244)

Exclusion based on title and abstract (n = 168)
- Not within the search period (2000-2016) = 52
- No abstract = 14
- Animal/Plant studies = 24
- Out of topic = 60
- Multidrug = 18

Records screened
(n = 76)

Further exclusion (n = 64)
- No full-text available = 13
- Review papers/letters = 7
- Animal/Plant studies = 7
- Out of topic = 25
- Data not extractable = 11
- Text not in English = 1

Studies included in qualitative analysis
(n = 12)
DISEASE: Leprosy
DRUG: Rifampicin

PUBMED
(n = 123)

SCOPUS
(n = 269)

Number of duplicates removed
(n = 61)

Records after duplicates removed
(n = 331)

Titles and abstracts screening
(n = 331)

Exclusion based on title and abstract (n = 267)
- Not within the search period (2000-2016) = 235
- No abstract = 8
- Animal/Plant studies = 16
- Out of topic = 7
- Multidrug = 1

Records screened
(n = 64)

Further exclusion (n = 64)
- No full-text available = 30
- Review papers/letters = 5
- Animal/Plant studies = 1
- Out of topic = 18
- Data not extractable = 10

Studies included in qualitative analysis
(n = 0)
DISEASE: Leprosy
DRUG: Clofazimine

PUBMED
(n = 18)

SCOPUS
(n = 179)

Number of duplicates removed
(n = 11)

Records after duplicates removed
(n = 186)

Titles and abstracts screening
(n = 186)

Exclusion based on title and abstract (n = 156)
- Not within the search period (2000-2016) = 141
- No abstract = 4
- Animal/Plant studies = 4
- Out of topic = 6
- Multidrug = 1

Records screened
(n = 30)

Further exclusion (n = 30)
- No full-text available = 8
- Review papers/letters = 1
- Out of topic = 20
- Text not in English = 1

Studies included in qualitative analysis
(n = 0)
DISEASE: Leprosy
DRUG: Dapsone

PUBMED (n = 262)

SCOPUS (n = 383)

Number of duplicates removed (n = 129)

Records after duplicates removed (n = 516)

Titles and abstracts screening (n = 516)

Exclusion based on title and abstract (n = 462)
- Not within the search period (2000-2016) = 434
- No abstract = 12
- Animal/Plant studies = 2
- Out of topic = 10
- Multidrug = 4

Records screened (n = 54)

Further exclusion (n = 54)
- No full-text available = 18
- Review papers/letters = 2
- Animal/Plant studies = 2
- Out of topic = 25
- Data not extractable = 7

Studies included in qualitative analysis (n = 0)
DISEASE: Trachoma
DRUG: Azithromycin

PUBMED
(n = 13)

SCOPUS
(n = 25)

Number of duplicates removed
(n = 3)

Records after duplicates removed
(n = 35)

Titles and abstracts screening
(n = 35)

Exclusion based on title and abstract (n = 17)
- Not within the search period (2000-2016) = 8
- No abstract = 3
- Out of topic = 6

Records screened
(n = 18)

Further exclusion (n = 8)
- Review papers/letters = 2
- Out of topic = 4
- Data not extractable = 2

Studies included in qualitative analysis
(n = 10)
DISEASE: Taeniasis
DRUG: Praziquantel

PUBMED (n = 3)

SCOPUS (n = 6)

Records after duplicates removed (n = 9)

Records screened (n = 2)

Studies included in qualitative analysis (n = 0)

Number of duplicates removed (n = 0)

Exclusion based on title and abstract (n = 7)
  • Not within the search period (2000-2016) = 7

Further exclusion (n = 2)
  • Out of topic = 1
  • Data not extractable = 1

Records screened (n = 2)

Titles and abstracts screening (n = 9)
DISEASE: Taeniasis
DRUG: Niclosamide

PUBMED (n = 1)

SCOPUS (n = 3)

Number of duplicates removed (n = 0)

Records after duplicates removed (n = 4)

Titles and abstracts screening (n = 4)

Exclusion based on title and abstract (n = 2)
- Not within the search period (2000-2016) = 2

Records screened (n = 2)

Further exclusion (n = 2)
- No full-text available = 1
- Data not extractable = 1

Studies included in qualitative analysis (n = 0)
DISEASE: Trematodiasis
DRUG: Triclabendazole

**PUBMED**
(n = 37)

**SCOPUS**
(n = 12)

Number of duplicates removed
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Records after duplicates removed
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Titles and abstracts screening
(n = 49)

Exclusion based on title and abstract (n = 36)
- Not within the search period (2000-2016) = 5
- No abstract = 9
- Animal/Plant studies = 19
- Out of topic = 3

Records screened
(n = 13)

Further exclusion (n = 13)
- No full-text available = 6
- Review papers/letters = 5
- Out of topic = 1
- Data not extractable = 1

Studies included in qualitative analysis
(n = 0)
DISEASE: Lymphatic filariasis
DRUG: Albendazole

PUBMED

(n = 3)

SCOPUS

(n = 18)

Number of duplicates removed

(n = 1)

Records after duplicates removed

(n = 20)

Titles and abstracts screening

(n = 20)

Exclusion based on title and abstract (n = 2)
- No abstract = 2

Records screened

(n = 18)

Further exclusion (n = 18)
- No full-text available = 3
- Review papers/letters = 6
- Animal/Plant studies = 1
- Out of topic = 5
- Data not extractable = 3

Studies included in qualitative analysis

(n = 0)
DISEASE: Lymphatic filariasis
DRUG: Diethycarbamazine (DEC)

PUBMED
(n = 3)

SCOPUS
(n = 19)

Number of duplicates removed
(n = 1)

Records after duplicates removed
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Titles and abstracts screening
(n = 21)

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- Not within the search period (2000-2016) = 3
- No abstract = 1
- Out of topic = 2

Records screened
(n = 15)

Further exclusion (n = 15)
- No full-text available = 9
- Review papers/letters = 3
- Animal/Plant studies = 1
- Data not extractable = 2

Studies included in qualitative analysis
(n = 0)
DISEASE: Lymphatic filariasis  
DRUG: Ivermectin

PUBMED  
(n = 1)  

SCOPUS  
(n = 16)  

Number of duplicates removed  
(n = 0)  

Records after duplicates removed  
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Records Excluded not within the search period (2000-2016)  
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Titles and abstracts screening  
(n = 17)  

Exclusion based on title and abstract (n = 3)  
- No abstract = 1  
- Out of topic = 2  

Records screened  
(n = 14)  

Further exclusion (n = 14)  
- No full-text available = 2  
- Review papers/letters = 4  
- Animal/Plant studies = 1  
- Out of topic = 6  
- Data not extractable = 1  

Studies included in qualitative analysis  
(n = 0)
DISEASE: Onchocerciasis
DRUG: Ivermectin

PUBMED (n = 22)

SCOPUS (n = 58)

Number of duplicates removed (n = 6)

Records after duplicates removed (n = 74)

Titles and abstracts screening (n = 74)

Exclusion based on title and abstract (n = 37)
- Not within the search period (2000-2016) = 15
- No abstract = 7
- Animal/Plant studies = 4
- Out of topic = 11

Records screened (n = 37)

Further exclusion (n = 30)
- No full-text available = 3
- Review papers/letters = 6
- Out of topic = 11
- Data not extractable = 10

Studies included in qualitative analysis (n = 7)
DISEASE: Schistosomiasis
DRUG: Praziquantel

PUBMED
(n = 85)

SCOPUS
(n = 218)

Number of duplicates removed
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Records after duplicates removed
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Titles and abstracts screening
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Exclusion based on title and abstract (n = 172)
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- No abstract = 23
- Animal/Plant studies = 54
- Out of topic = 30
- Multidrug = 6

Records screened
(n = 95)

Further exclusion (n = 76)
- No full-text available = 9
- Review papers/letters = 14
- Animal/Plant studies = 22
- Out of topic = 23
- Data not extractable = 8

Studies included in qualitative analysis
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DISEASE: Soil-transmitted helminthes
DRUG: Mebendazole

PUBMED
(n = 30)

SCOPUS
(n = 1)

Records after duplicates removed
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Number of duplicates removed
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Titles and abstracts screening
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- Animal/Plant studies = 4

Records screened
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Further exclusion (n = 3)
- No full-text available = 2
- Out of topic = 1

Studies included in qualitative analysis
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DISEASE: Soil-transmitted helminthes
DRUG: Albendazole

PUBMED
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SCOPUS
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Records after duplicates removed
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Exclusion based on title and abstract (n = 101)
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- Animal/Plant studies = 43
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Titles and abstracts screening
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Records screened
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Further exclusion (n = 23)
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- Review papers/letters = 7
- Animal/Plant studies = 4
- Out of topic = 7
- Text not in English = 1

Studies included in qualitative analysis
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## Appendix 6a: Full details of the quality assessment

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List of publications related to the dissertation

   Child Care Health Dev. 44 (5), 794-800, 2018.
   DOI: http://dx.doi.org/10.1111/cch.12595
   IF: 1.699 (2017)

   IF: 3.031

Total IF of journals (all publications): 4.73
Total IF of journals (publications related to the dissertation): 4.73

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11 December, 2018