

SHORT 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**

By

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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. 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).

“Health for all” is a WHO priority by ensuring universal health coverage (UHC) without impoverishment. 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. 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. Goal 3 of the SDGs is to “Ensure healthy lives and promote well-being for all at all ages.”

In recent decades, considerable attention has been focused on efforts to stimulate research, development and marketing of medicinal products for rare diseases worldwide. 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. 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.

1.2. LITERATURE REVIEW

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 that afflict various organ systems, with wide ranging prognoses. Patients with rare diseases also tend to be underserved both clinically and scientifically. For many rare diseases, basic knowledge such as the cause of the disease, pathophysiology, natural cause of the disease and epidemiological data is limited or not available.

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. NTDs kill, impair or permanently disable, often resulting in life-long physical pain and social stigmatisation. 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.

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.

1.3. RESEARCH RATIONALE

1.3.1. Rationale for Research into Rare Diseases

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. 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.

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. 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. Although, there are voluntary data collections of research studies and trials for rare diseases in the EU, such as the ORPHANET, 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.

1.3.2. 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. The emergence of NTDs necessitates global response owing to its widespread and often catastrophic consequences. WHO has identified twenty NTDs. Out of these, 11 are considered as major NTDs.

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). WHO launched its first report on NTDs in 2010, which defined the strategic approaches for reducing the burden

of these diseases and provided a “roadmap” revealing the targets for eradication, elimination and intensified control of identified NTDs set for 2015 and 2020. 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. 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. 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.

2. 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.

2.1. RESEARCH JUSTIFICATION

2.1.1. 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 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). 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. 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.

2.1.2. 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. 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.

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. 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.

2.1.3. 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. 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. 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. Unfortunately, there are no adequate new drugs to address this situation. WHO has taken leadership on AMR with its Global Action Plan on Antimicrobial Resistance by combining new medicine discovery, development and stewardship. Following the London declaration on NTDs in 2012 focusing on drug development, 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.

3. 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.

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".
- 2) National public research funders were identified through Science Europe, an umbrella organization for national research funding institutions. This list was complemented by the European Commission as a prominent research funder of rare diseases.

Results of the search were refined by EU member states. The number of records with information on the funding source was 1025 out of 1585 records found.

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. These 19 categories were classified into three main research groups; clinical, translational and basic research according to NIH Research Portfolio Online Reporting Tools.

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. All the projects identified were represented with a unique name.

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

Patent documents were extracted from the Patseer (<http://patseer.com/>) which is an international database of patents from over 100 patent issuing authorities worldwide. Evaluation of the patent documents were carried out using the combination of different search terms related to each identified NTD.

Keywords of each identified NTD (their synonyms and truncation to cover different endings, singular/plural) 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 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.

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.

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. 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.

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.

4. 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). 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 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. All the funders favour basic research topics, national funders and NPPOs support a wider range of projects. 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. 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. Research hotspots were observed to be Italy and 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.

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

The total number of patent families reviewed was 12,350, and 3179 out of these 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 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). 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.

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 reveals that approximately 50% of the patents are non-active. This fact suggests that investing in NTDs has a low commercial value.

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) and European Union (EP) in the last 30 years. However, by focusing on the trend of the total number of patent families, the leading countries are the US and China (CN). 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.

In China, France, Korea, and Russia, more than 50% of patents and applications were assigned to entities other than firms.

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.

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. A total of 108 studies were included in the final review.

Out of 11 NTDs, six NTDs have information on drug resistance, namely HAT, leishmaniasis, onchocerciasis, schistosomiasis, soil-transmitted helminthiasis, and trachoma.

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.

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.

Out of the 108 included studies, 70 were performed in the rural settings, 22 were in the urban settings and 16 did not specify their study settings. Based on the population of subjects studied, 99 studies recorded resistance by test and 45 recorded clinical resistance. Out of the 28 countries of study, it was observed that more studies were performed in South Sudan, Tanzania, Kenya, Cameroon, Uganda, Cote d'Ivoire, Democratic Republic of Congo (DRC), Angola and India. 78% of the included studies were performed in Africa, 15% in Asia and 1% in Australia. 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. 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.

5. DISCUSSION

R&D is an important contributor to improving health and thus an essential component of investments in health. 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.

5.1. Rett syndrome Research Landscape

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).

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 than NPPOs. Also, one can elucidate that reversibility of symptoms discovered in the field of Rett syndrome boosted the NPPOs research funding.

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. The distribution of the funding allocation reflects the genetic nature of the disease and the lack of treatment. 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. 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 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, 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. 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. 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. 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.

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. 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.

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.

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. 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”.

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. 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.

This study finding showed that there is a high prevalence of resistance by tests 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. 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. However, effective MDA with good adherence can prevent the emergence of AMR. 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.

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, 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. 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”.

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.

6. RECOMMENDATIONS

6.1. 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

6.2. 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.

6.3. 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.

7. 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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2. **Akinsolu, F. T.**, De Paiva, V. N., Souza, S. S., Varga, O.: Patent Landscape of Neglected Tropical Diseases: An analysis of worldwide patent families.
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