

RESEARCH ARTICLE



Scientific literature on neglected tropical diseases: a bibliometric analysis

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ABSTRACT

Neglected tropical diseases (NTDs) are a group of diseases mainly affecting people in low- and middle-income Countries. The aim of this study was to perform a bibliometric analysis of the scientific literature on NTDs. Using the MeSH database, we quantified the number of publications on MEDLINE targeting each NTD, which were published from 1 January 1999 to 31 January 2019. In order to weight the number of publications targeting a given NTD according to the total number of publications/year, we calculated a Yearly Publication Index (YPI) for each NTD/year. Linear regression was used to determine if there was a significant increase or decrease of YPI over time. In order to weight the number of publications according to disease burden (expressed in Disability-adjusted life years – DALYs) we calculated a DALYs-weighted Publication Index (DWPI) for each NTD. The highest absolute number of publications focused on leishmaniasis, dengue and Chagas disease; the lowest on tungiasis, dracunculiasis, chromoblastomycosis and yaws. The number of publications significantly increased for chikungunya, chromoblastomycosis, dengue, leishmaniasis, snakebite envenoming, and yaws. It significantly decreased for ascariasis, cysticercosis, echinococcosis, leprosy, lymphatic filariasis, mycetoma, onchocerciasis. Leprosy had the highest DWPI (i.e. the highest number of publications considering the burden of disease), followed by Chagas disease; lymphatic filariasis had the lowest, followed by onchocerciasis. Overall, lymphatic filariasis, onchocerciasis and ascariasis presented the worst scenario, with both very few publications compared with their disease burden and a decreasing number of publications.

KEYWORDS

Neglected diseases; research and development; scientific publications; bibliometric analysis; low- and middle-income countries

1. Introduction

Neglected tropical diseases (NTDs) are a group of 20 conditions mainly affecting people in low- and middle-income Countries [1]. They concern more than a billion people and represent a major public health challenge, in terms of both morbidity and mortality [2,3]. NTDs include some very different pathologies, caused by a variety of pathogens. However, these diseases have been classified in the overarching group of NTDs because of some shared features. First, NTDs are diseases of poverty; they are mainly prevalent among the populations who have poor access to health care systems in low- and middle-income countries, and, they exacerbate poverty through a vicious circle including physical and mental disability, social stigma, gender inequality, impaired childhood development and socio-economic marginalization. Second, NTDs are still marginal in the global health agenda, and they receive largely insufficient financing [2–5].

International stakeholders (particularly the World Health Organization – WHO – and non-governmental development organizations), are devoting increasing efforts to mitigate the burden of NTDs. These diseases are targeted in the Sustainable Development Goal (SDG) 3 and their mitigation may contribute to

achieving numerous other SDGs [6]. However, less than 1% of the official health development assistance is allocated for programmes tackling NTDs [3].

Another cardinal feature of NTDs is that they remain marginal in the global research and development (R&D) agenda, with few new drug candidates in the pipeline. This is a noteworthy difference with HIV/AIDS, malaria and tuberculosis, whose drug pipelines include hundreds of products at different stages of development [5]. However, among NTDs, some seem to represent a more interesting target for R&D than others. As described by Addisu et al. [5], in 2019 there were in total around 50 drugs in the pipeline for Chagas diseases, Schistosomiasis and Leishmaniasis, whereas for 12/20 (57%) of others NTDs there was no new drugs under investigation.

A related aspect is how much the different NTDs are targeted in the academic scientific literature. Some NTDs seem to be the topic of scientific studies more frequently than others [7,8]. Although this aspect may be crucial to influence decision making at global, national and local levels, it has not been investigated in detail. Moreover, there are few data on time trends concerning academic publications on NTDs.

Bibliometrics is a research field focusing on quantitative evaluation of citation and content analysis of scientific journals and other type of publications; it can be applied also to researchers and research institutions [9]. Bibliometric analysis can be used for several aims, including the analysis of research trends in a given field of investigation [9–11], or quantification of research activity from a given country or geographical area [12]. To give a few examples, through a bibliometric analysis Ellis et al. showed that malaria and leishmaniasis have been the most studied human parasitic infections in the last 30 years [11], whereas Uthman et al. described the profile and determinants of health research productivity in Africa [12].

The aim of this study was to perform a bibliometric analysis of the scientific literature focusing on NTDs and to describe its evolution over time and according to disease burden.

2. Materials and methods

2.1. Quantification of publications targeting NTDs

We identified the list of NTDs, as defined by WHO [1] (Table 1).

The first step of our study was to quantify the number of scientific publications targeting each NTD.

We considered publications indexed on MEDLINE. We searched the Medical Subject Headings (MeSH) database using as search term the official WHO denomination of each NTD. Some NTDs (i.e. foodborne

trematodiasis, soil-transmitted helminthiasis, deep mycoses and ectoparasitoses) are caused by several pathogens. In these cases, we selected those having the major epidemiological relevance and having a corresponding MeSH term (Table 1).

For each NTD we selected all related MESH items (except ‘Supplementary concepts’) and we combined them by the PubMed search builder, using ‘OR’ as Boolean operator. Finally, we searched PubMed, including studies published from 1 January 1999 to 31 December 2019. The MeSH term for Buruli ulcer was introduced in 2008 and that for tungiasis in 2011. All the others already existed in 1999.

The searches were performed in November 2021.

2.2. Definition of yearly publication index

Since the number of publications indexed on MEDLINE is constantly increasing over time [13], the second step of our study was to weight the number of indexed publications targeting a given NTD, according to the total number of publications/year indexed on MEDLINE.

For this purpose we defined a Yearly Publication Index (YPI), taking into account the number of indexed publications targeting a given NTD in a given calendar year and the number of total publications indexed on MEDLINE in that calendar year (Figure 1). The latter information derived from the MEDLINE Citation Counts by Year of Publication (as of January 2021) [13].

Table 1. Number of publications for each studied neglected tropical disease and variation over time of Yearly publication Index.

Disease	Total number of publications from 1999 to 2019	Variation of Yearly Publication Index over time (p value)
African trypanosomiasis	2856	NS
Ascariasis	1400	Decrease (<.0001)
Buruli ulcer	597	NS
Chagas disease	11858	NS
Chikungunya	3216	Increase (<.0001)
Chromoblastomycosis	423	Increase (0,0461)
Cysticercosis	3476	Decrease (<.001)
Dengue	14372	Increase (<.0001)
Dracunculiasis	296	NS
Echiococcosis	8353	Decrease (.0004)
Fascioliasis	2026	NS
Hookworm infections	1282	NS
Leishmaniasis	15625	Increase (<.0001)
Leprosy	6438	Decrease (<.0001)
Lymphatic filariasis	1755	Decrease (.01)
Mycetoma	962	Decrease (.001)
Onchocerciasis	1436	Decrease (.002)
Rabies	5739	NS
Scabies	1713	NS
Schistosomiasis	9745	NS
Snakebite envenoming	2605	Increase (0,0009)
Trachoma	1240	NS
Trichuriasis	846	NS
Tungiasis	107	NS
Yaws	423	Increase (<.0001)

NS: not significant.

1) Yearly Publication Index (YPI) = $\frac{\text{Indexed publications targeting a given NTD in a given calendar year}}{\text{Total publications indexed on MEDLINE in that calendar year}} \times 1000$	
<i>Examples</i>	
Leprosy YPI for 2001 = $\frac{\text{Indexed publications targeting leprosy in 2001}}{\text{Total publications indexed on MEDLINE in 2001}} \times 1000 = \frac{283}{505.770} \times 1000 = 0.56$	
Leprosy YPI for 2019 = $\frac{\text{Indexed publications targeting leprosy in 2019}}{\text{Total publications indexed on MEDLINE in 2019}} \times 1000 = \frac{305}{898.145} \times 1000 = 0.34$	
2) DALYs-weighted Publication Index (DWPI) = $\frac{\text{Indexed publications targeting a given NTD from 2015 to 2019}}{\text{DALYs of that NTD in 2019 according to WHO}}$	
<i>Examples</i>	
Leprosy DWPI = $\frac{\text{Indexed publications targeting leprosy from 2015 to 2019}}{\text{DALYs of leprosy in 2019 according to WHO}} = \frac{1527}{36} = 42.42$	
Rabies DWPI = $\frac{\text{Indexed publications targeting rabies from 2015 to 2019}}{\text{DALYs of rabies in 2019 according to WHO}} = \frac{1671}{2653} = 0.63$	

NTD: neglected tropical disease; DALY: Disability-adjusted life year

Figure 1. Methos. Note: NTD: neglected tropical disease; DALY: Disability-adjustedlife year

The YPI was then calculated for each NTD/year from 1999 to 2019 and linear regression was used to determine if there was a significant increase or decrease of YPI over time.

2.3. Definition of DALY-weighted publication index

Since each NTD accounts for a different burden of disease, the third step of our study was to weight the number of indexed publications targeting a given NTD, according to disease burden.

For this purpose we defined a Disability-adjusted life year (DALY)-weighted Publication Index (DWPI), taking into account the number of indexed publications targeting a given NTD from 2015 to 2019 and the disease burden of that NTD in 2019 (Figure 1). Disease burden was quantified in DALYs, according to the Global Burden of Disease 2019 [14,15]. In accordance with median value and interquartile range [IQR] of DWPI, each NTD was then categorized as: low DWPI (lowest quartile); intermediate DWPI (second and third quartile); high DWPI (last quartile).

3. Results

3.1. Publications targeting NTDs (Table 1)

Twenty-five diseases were included in the analysis (Table 1).

The total number of publications indexed on MEDLINE between 1999 and 2019 was 14,792,529, according to the MEDLINE Citation Counts by Year of Publication. Overall, among these, we identified 98,789 publications targeting NTDs (0.67%).

The highest absolute number of indexed publications in the study period focused on leishmaniasis (15625 publications), dengue (14372) and Chagas disease (11858); the lowest, tungiasis (107), dracunculiasis (296), chromoblastomycosis and yaws (423 both) (Table 1).

3.2. Yearly publication index and its evolution over time (Table 1 and Figure 2)

Taking into account the variations over time by YPI, the number of indexed publications was significantly increasing in the 1999–2019 period for chikungunya, chromoblastomycosis, dengue, leishmaniasis, snake-bite envenoming, and yaws; it was significantly decreasing for ascariasis, cysticercosis, echinococcosis, leprosy, lymphatic filariasis, mycetoma, onchocerciasis; it remained stable for the other NTDs (Table 1 and Figure 2).

3.3. DALYs-weighted publication index (Table 2)

DALYs were available for 15/25 NTDs included in the analysis. According to the Global Burden of Diseases [14,15], overall these NTDs accounted in 2019 for 13,704 DALYs. Considering the 2000–2019 period,

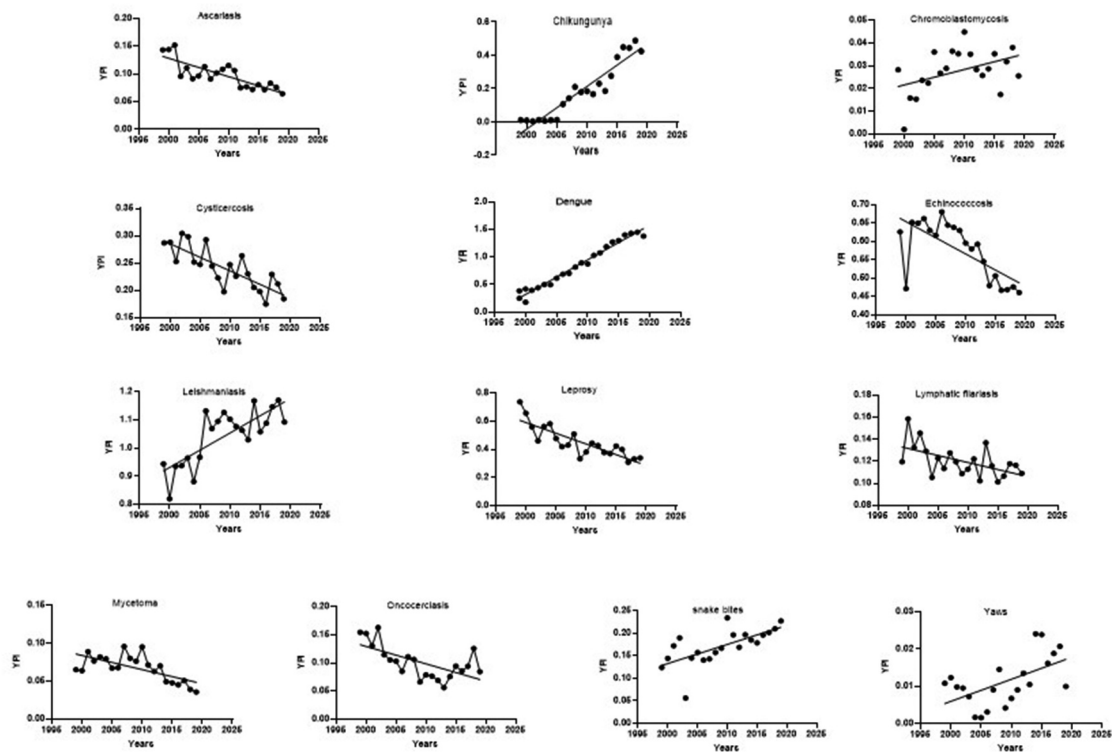


Figure 2. Statistically significant changes of Yearly publication Index over time.

Table 2. Dalys-weighted publication Index. Only neglected tropical diseases for whom DALYs are available are included in the table.

Disease	DALYs (000s) in 2000 according to WHO	DALYs (000s) in 2019 according to WHO	DALYs (000s) trend in 2000–2019 period	DALYs-weighted Publication Index – Value	DALYs-weighted Publication Index – Category
African trypanosomiasis	1586	102	↓↓↓	7.18	High
Ascariasis	1604	749	↓↓	.44	Low
Chagas disease	275	217	↔	15.54	High
Cysticercosis	1558	988	↔	.88	Intermediate
Dengue	1566	1952	↔	3.11	Intermediate
Echinococcosis	906	461	↓↓	4.5	Intermediate
Hookworm infections	2099	962	↓↓	.36	Low
Leishmaniasis	942	722	↔	6.70	High
Leprosy	49	36	↓↓	42.42	High
Lymphatic filariasis	5046	1616	↓↓	.30	Low
Onchocerciasis	1134	1210	↔	.35	Low
Rabies	5394	2635	↓↓	.63	Intermediate
Schistosomiasis	2220	1628	↓	1.66	Intermediate
Trachoma	271	194	↔	1.96	Intermediate
Trichuriasis	532	232	↓↓	1.07	Intermediate

↔ : variation less than 25%.

↓ : decrease > 25% and < 50%.

↓↓ : decrease > 50% and < 75%.

↓↓↓ : decrease > 75%.

DALYs decreased remarkably, even more than 50% for 6 of the NTDs. DALYs remained substantially stable for 4 NTDs (<25% variation) and increased only for dengue.

The median and interquartile range [IQR] of DWPI were 1.66 [0.54–5.6]. Four NTDs were in the high DWPI category, with leprosy having the highest DWPI, followed by Chagas disease, African trypanosomiasis, and leishmaniasis. Four NTDs were in the low DWPI category, with lymphatic filariasis having the lowest DWPI, followed by onchocerciasis, hookworm infections, and ascariasis.

The DWPI of leprosy was 140 times higher than DWPI of lymphatic filariasis (Table 2).

4. Discussion

In this study, we performed a bibliometric evaluation of the scientific literature indexed on MEDLINE focusing on NTDs, in the last two decades (1999–2019).

NTDs have been defined as diseases of inequity [5]. They share some common features, which are

inter-dependent and may be defined as dimensions of neglect, such as: i) they affect poor people and exacerbate poverty; ii) they receive little financing; iii) they represent a low priority in the global health agenda; iv) they represent a marginal market for pharmaceutical business; v) and they receive insufficient attention in terms of R&D [2,5,16,17]. Our study focused on this last aspect.

Some previous bibliometric analysis focused on single NTDs and, sometimes, specific geographical areas; however, each study applied a different bibliographic methodology, making comparisons difficult. For examples, Ellis et al. showed that leishmaniasis (after malaria) has been the most studied parasitic infection in the last 3 decades [11]; Mota et al. showed the increase of publications over time about dengue [18] and Hassan et al. about trypanosomiasis [19]; Schoonbaert et al. showed the declining trend in publication about leprosy [20]. Other studies are available for other NTDs [21–23].

Recently Fontecha et al. performed a more comprehensive bibliometric analysis on 19 NTDs and calculated that dengue and leishmaniasis were the most commonly studied NTDs (in Latin America and the Caribbean), in terms of absolute number of publications [7].

However, despite the relative abundance of publications in this context, we believe that our work provides some new insights on this relevant topic. First, it encompassed all NTDs, which were studied with the same bibliometric methodology and without geographical limitations, providing a way to make comparisons among them. Moreover, former bibliometric analysis usually reported absolute numbers of publications, not taking into account neither the total number of publication/year indexed on MEDLINE (which is dramatically increasing over time), nor the burden of disease of each NTD in terms of DALYs, when available [14,15]. In order to contextualize the absolute number of publications in accordance with these two factors, we introduced two bibliometric indexes, YPI and DWPI (Figure 1).

Applying these indexes, we demonstrated that some of the NTDs are manifestly more ignored (thus, neglected) in the academic scientific literature, compared with some others. With YPI, we demonstrated that scientific publications have an increasing trend over time for chikungunya, chromoblastomycosis, dengue, leishmaniasis, snakebite envenoming, and yaws, while they have a decreasing trend for ascariasis, cysticercosis, echinococcosis, leprosy, lymphatic filariasis, mycetoma, onchocerciasis (Table 1 and Figure 2).

With DWPI, we showed that some NTDs received relevant attention, relatively to their burden of disease (particularly leprosy, but also Chagas disease, African trypanosomiasis and leishmaniasis), while others were consistently more marginal in the scientific literature (particularly lymphatic filariasis, onchocerciasis, hookworm infections, ascariasis), despite their huge impact in terms of DALYs (Table 2).

Overall, we found the worst scenario for lymphatic filariasis, onchocerciasis and ascariasis (Tables 1 and 2): these diseases share both a very low DWPI (thus, there are few publications considering their disease burden) and a decreasing YPI (thus, there are relative decreasing number of publications over time). These data about these relevant diseases raise a warning, and they are in contrast with the increasing financing for NTDs recorded in the last years [24], as well as with the increasing number of programmes addressing NTDs [3]. A few years ago, the WHO (together with other institutional stakeholders) released a detailed report for research in the field of infectious diseases of poverty, which provided many pathways to revert this scenario of progressive scientific neglect on some very relevant pathologies [17]. More recently, the Global Report on NTDs and the WHO Road Map for NTDs underlined the need for more research effort, including R&D for diagnostics, essential technologies and treatments, as well as operational and field research [25,26].

The dynamics explaining these findings are certainly complex and multifaceted. NTDs are a very heterogeneous group of conditions, with regard to geographic distribution, prevalence and incidence, morbidity and mortality [1,16]. Each of these factors may play a role in explaining our findings. For instance, some diseases (like dengue, leishmaniasis, Chagas disease and leprosy) are prevalent in populous, middle-income countries, like four of the five BRICS countries (i.e. Brasil, India, China, South Africa). In these contexts, there are active academic institutions, close partnerships with high-income countries, and multilevel national and international initiatives for health promotion [7,8,11,27]. Moreover, diseases with such a geographical distribution may represent an interesting pharmaceutical market, encouraging private initiatives for R&D. Chagas disease and leishmaniasis, for example, have several drugs in the research pipeline [5], while many other NTDs do not. To the contrary, many of the NTDs with the lowest DWPI are highly prevalent in low-income countries (mainly in Sub-Saharan Africa), where there may be limited research capability [12], and the pharmaceutical market can be unappealing for private stakeholders [1,7,16,28].

Moreover, the burden of NTDs has evolved in the 2000–2019 period [14,15], as synthesized in Table 2. For some of the NTDs, it is stable over time, whereas fortunately it decreased for some others, even considerably (e.g. African trypanosomiasis and lymphatic filariasis). Dengue is an exception in this encouraging panorama [29]. The evolution of the burden of disease can probably influence in a variable way how much a disease is central in the scientific debate: in the case of dengue, it is understandable that it attracts growing interest, due to the menacing spread of this disease in many countries. To the contrary, we can presume that

a decreasing burden of disease may be accompanied by (and perhaps promoted by) rich scientific production, but also with a declining interest.

The evolution of incidence and prevalence of NTDs may also influence how much they are present in the scientific literature. Although a detailed review of the changing epidemiology of each NTD is beyond the purpose of this study, chikungunya is a good example: the incidence and the geographical spread of chikungunya increased dramatically in the last two decades [30]; our study registered a remarkable increase of scientific publication in the same period.

Lastly, it is worth remarking that some NTDs also represent a public health concern for high-income countries. Some NTDs are endemic in some high-income countries, like leishmaniasis in the Mediterranean region [31] or scabies worldwide [32]; some others are often diagnosed as imported diseases in migrant and travelers, such as chikungunya and dengue [33]. Since it has been shown that high-income countries are still responsible for a relevant amount of papers targeting NTDs [7], this epidemiological feature may represent another factor influencing the amount of publications on different NTDs.

This study has some limitations, which deserve to be considered in order to better contextualize our findings. First, this was a bibliometric evaluation, thus no information has been collected and analyzed about study designs (e.g. experimental versus observational studies) or study quality (e.g. low versus high risk of bias). Manifestly, a single, high quality experimental study may play a major role in modifying and improving the management of a given disease or changing healthcare policies; to the contrary many low quality, observational studies may not really increase the body of knowledge about a given topic. However, this exploratory study aimed at overviewing how much a given disease enters the scientific debate worldwide, using the number of publications as quantitative proxy. We searched only MEDLINE, thus we did not screen the gray literature or other databases. We searched for papers through the MeSH database, and we did not perform title-abstract screening or full text analysis. However, this is not a systematic review, it is a bibliometric evaluation of published literature. The MeSH database is an internationally recognized system of categorization of papers, using a systematic approach, consistent over time; it allowed us to screen the literature with a coherent methodology, for each NTD. Finally, the delay in the process of assigning the MeSH terms to each paper may have led to less literature retrieval in more recent years. In order to minimize this potential bias, we decided to include papers until 2019, even if the search was performed in November 2021. However, we cannot be sure that the MeSH term assignment for 2019 was completed at that time.

In conclusion, this bibliometric analysis of scientific literature showed that over the last two decades, NTDs have received inhomogeneous attention in the scientific literature. Some diseases (particularly chikungunya, dengue and leishmaniasis) are receiving increasing attention from scientists, while many others seem to remain neglected from the literature point of view, despite their huge impact on people's health. Further studies are needed in order to better elucidate the different drivers and barriers influencing research about NTDs.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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APPENDIX 1: Search strings

All searches have been performed in November 2021.

Disease	Search string(s)
African trypanosomiasis	"Trypanosomiasis, African"[Mesh]
Ascariasis	"Ascariasis"[Mesh]
Buruli ulcer	"Buruli Ulcer"[Mesh]
Chagas disease	"Chagas Disease"[Mesh] OR "Chagas Cardiomyopathy"[Mesh] OR "Trypanosoma rangeli"[Mesh] OR "Trypanosoma cruzi"[Mesh] OR "5-Amino-3-((5-nitro-2-furyl)vinyl)-1,2,4-oxadiazole"[Mesh]
Chikungunya	"Chikungunya Fever"[Mesh] OR "Chikungunya virus"[Mesh]
Chromoblastomycosis	"Chromoblastomycosis"[Mesh]
Cysticercosis	"Cysticercosis"[Mesh] OR "Neurocysticercosis"[Mesh]
Dengue	"Dengue"[Mesh] OR "Dengue Vaccines"[Mesh] OR "Severe Dengue"[Mesh] OR "Dengue Virus"[Mesh]
Dracunculiasis	"Dracunculiasis"[Mesh]
Echinococcosis	"Echinococcosis"[Mesh]
Fascioliasis	"Fascioliasis"[Mesh]
Hookworm infections	"Hookworm Infections"[Mesh]
Leishmaniasis	"Leishmaniasis Vaccines"[Mesh] OR "Leishmaniasis"[Mesh] OR "Leishmaniasis, Diffuse Cutaneous"[Mesh] OR "Leishmaniasis, Cutaneous"[Mesh] OR "Leishmaniasis, Visceral"[Mesh] OR "Leishmaniasis, Mucocutaneous"[Mesh]
Leprosy	"Leprosy"[Mesh] OR "Leprosy, Multibacillary"[Mesh] OR "Leprosy, Paucibacillary"[Mesh] OR "Leprosy, Tuberculoid"[Mesh] OR "Leprosy, Lepromatous"[Mesh] OR "Leprosy, Borderline"[Mesh]
Lymphatic filariasis	"Elephantiasis, Filarial"[Mesh]
Mycetoma	"Mycetoma"[Mesh]
Onchocerciasis	"Onchocerciasis"[Mesh] OR "Onchocerciasis, Ocular"[Mesh]
Rabies	"Rabies"[Mesh] OR "Rabies virus"[Mesh] OR "Rabies Vaccines"[Mesh]
Scabies	"Scabies"[Mesh]
Schistosomiasis	"Schistosomiasis"[Mesh] OR "Schistosomiasis mansoni"[Mesh] OR "Schistosomiasis japonica"[Mesh] OR "Schistosomiasis haematobia"[Mesh] OR "Neuroschistosomiasis"[Mesh]
Snakebite envenoming	"Snake Bites"[Mesh]
Trachoma	"Trachoma"[Mesh]
Trichuriasis	"Trichuriasis"[Mesh]
Tungiasis	"Tungiasis"[Mesh]
Yaws	"Yaws"[Mesh]