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Scientific literature on neglected tropical diseases: a bibliometric analysis

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1 **TITLE**

2 **Scientific literature on neglected tropical diseases: a bibliometric analysis**

3

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16

17 **ABSTRACT**

18 Neglected tropical diseases (NTDs) are a group of diseases mainly affecting people in low- and
19 middle-income Countries. The aim of this study was to perform a bibliometric analysis of the
20 scientific literature on NTDs. Using the MeSH database, we quantified the number of publications
21 on MEDLINE targeting each NTD, which were published from 01/01/1999 to 31/01/2019. In order
22 to weight the number of publications targeting a given NTD according to the total number of
23 publications/year, we calculated a Yearly Publication Index (YPI) for each NTD/year. Linear
24 regression was used to determine if there was a significant increase or decrease of YPI over time. In
25 order to weight the number of publications according to disease burden (expressed in Disability-
26 adjusted life years - DALYs) we calculated a DALYs-weighted Publication Index (DWPI) for each
27 NTD.

28 The highest absolute number of publications focused on leishmaniasis, dengue and Chagas disease;
29 the lowest on tungiasis, dracunculiasis, chromoblastomycosis and yaws. The number of
30 publications significantly increased for chikungunya, chromoblastomycosis, dengue, leishmaniasis,
31 snakebite envenoming, and yaws. It significantly decreased for ascariasis, cysticercosis,
32 echinococcosis, leprosy, lymphatic filariasis, mycetoma, onchocerciasis. Leprosy had the highest
33 DWPI (i.e. the highest number of publication considering the burden of disease), followed by
34 Chagas disease; lymphatic filariasis had the lowest, followed by onchocerciasis.

35 Overall, lymphatic filariasis, onchocerciasis and ascariasis presented the worst scenario, with both
36 very few publications compared with their disease burden and a decreasing number of publications.

37

38 **Keywords:** Neglected diseases; research and development; scientific publications; bibliometric
39 analysis; low- and middle-income countries

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42

43 Word count: 2328

44

45 *1. Introduction*

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

56 International stakeholders (particularly the World Health Organization – WHO - and non-
57 governmental development organisations), are devoting increasing efforts to mitigate the burden of
58 NTDs. These diseases are targeted in the Sustainable Development Goal (SDG) 3 and their mitigation
59 may contribute to achieving numerous other SDGs(6). However, less than 1% of the official health
60 development assistance is allocated for programmes tackling NTDs(3).

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

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

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

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

83

84

85 **2. Materials and methods**

86 **2.1 *Quantification of publications targeting NTDs***

87 We identified the list of NDTs, as defined by WHO (1) (Table 1).

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

89 We considered publications indexed on MEDLINE. We searched the Medical Subject Headings
90 (MeSH) database using as search term the official WHO denomination of each NTD. Some NTDs
91 (i.e. foodborne trematodiasis, soil-transmitted helminthiasis, deep mycoses and ectoparasitoses) are
92 caused by several pathogens. In these cases, we selected those having the major epidemiological
93 relevance and having a corresponding MeSH term (Table 1).

94 For each NTD we selected all related MESH items (except “Supplementary concepts”) and we
95 combined them by the PubMed search builder, using “OR” as Boolean operator. Finally, we searched
96 PubMed, including studies published from 01/01/1999 to 31/12/2019. The MeSH term for Buruli
97 ulcer was introduced in 2008 and that for tungiasis in 2011. All the others already existed in 1999.
98 The searches were performed in November 2021.

99

100 *2.2 Definition of Yearly Publication Index*

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

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

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

110

111 *2.3 Definition of DALY-weighted Publication Index*

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

114 For this purpose we defined a Disability-adjusted life year (DALY)-weighted Publication Index
115 (DWPI), taking into account the number of indexed publications targeting a given NTD from 2015
116 to 2019 and the disease burden of that NTD in 2019 (Figure 1). Disease burden was quantified in
117 DALYs, according to the Global Burden of Disease 2019 (14,15). In accordance with median value
118 and interquartile range [IQR] of DWPI, each NTD was then categorised as: low DWPI (lowest
119 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 14792529, according to the MEDLINE Citation Counts by Year of Publication. Overall, among these, we identified 98789 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, snakebite 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 13704 DALYs. Considering the 2000-2019 period, 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

146 tripanosomiasis, and leishmaniasis. Four NTDs were in the low DWPI category, with lymphatic
147 filariasis having the lowest DWPI, followed by onchocerciasis, hookworm infections, and ascariasis.
148 The DWPI of leprosy was 140 times higher than DWPI of lymphatic filariasis (Table 2).

149

150

151 **4. Discussion**

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

154 NTDs have been defined as diseases of inequity(5). They share some common features, which are
155 inter-dependent and may be defined as dimensions of neglect, such as: i) they affect poor people and
156 exacerbate poverty; ii) they receive little financing; iii) they represent a low priority in the global
157 health agenda; iv) they represent a marginal market for pharmaceutical business; v) and they receive
158 insufficient attention in terms of R&D(2,5,16,17). Our study focused on this last aspect.

159 Some previous bibliometric analysis focused on single NTDs and, sometimes, specific geographical
160 areas; however, each study applied a different bibliographic methodology, making comparisons
161 difficult. For examples, Ellis et al. showed that leishmaniasis (after malaria) has been the most studied
162 parasitic infection in the last 3 decades(11); Mota et al. showed the increase of publications over time
163 about dengue (18) and Hassan et al. about trypanosomiasis(19); Schoonbaert et al. showed the
164 declining trend in publication about leprosy(20). Other studies are available for other NTDs(21–23).
165 Recently Fontecha et al. performed a more comprehensive bibliometric analysis on 19 NTDs and
166 calculated that dengue and leishmaniasis were the most commonly studied NTDs (in Latin America
167 and the Caribbean), in terms of absolute number of publications(7).

168 However, despite the relative abundance of publications in this context, we believe that our work
169 provides some new insights on this relevant topic. First, it encompassed all NTDs, which were studied
170 with the same bibliometric methodology and without geographical limitations, providing a way to
171 make comparisons among them. Moreover, former bibliometric analysis usually reported absolute

172 numbers of publications, not taking into account neither the total number of publication/year indexed
173 on MEDLINE (which is dramatically increasing over time), nor the burden of disease of each NTD
174 in terms of DALYs, when available(14,15). In order to contextualise the absolute number of
175 publications in accordance with these two factors, we introduced two bibliometric indexes, YPI and
176 DWPI (Figure 1).

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

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

188 Overall, we found the worst scenario for lymphatic filariasis, onchocerciasis and ascariasis (Table 1
189 and 2): these diseases share both a very low DWPI (thus, there are few publications considering their
190 disease burden) and a decreasing YPI (thus, there are relative decreasing number of publications over
191 time). These data about these relevant diseases raise a warning, and they are in contrast with the
192 increasing financing for NTDs recorded in the last years(24), as well as with the increasing number
193 of programmes addressing NTDs(3). A few years ago, the WHO (together with other institutional
194 stakeholders) released a detailed report for research in the field of infectious diseases of poverty,
195 which provided many pathways to revert this scenario of progressive scientific neglect on some very
196 relevant pathologies(17). More recently, the Global Report on NTDs and the WHO Road Map for

197 NTDs underlined the need for more research effort, including R&D for diagnostics, essential
198 technologies and treatments, as well as operational and field research(25,26).

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

212 Moreover, the burden of NTDs has evolved in the 2000-2019 period(14,15), as synthesised in Table
213 2. For some of the NTDs, it is stable over time, whereas fortunately it decreased for some others, even
214 considerably (e.g. African trypanosomiasis and lymphatic filariasis). Dengue is an exception in this
215 encouraging panorama(29). The evolution of the burden of disease can probably influence in a
216 variable way how much a disease is central in the scientific debate: in the case of dengue, it is
217 understandable that it attracts growing interest, due to the menacing spread of this disease in many
218 countries. To the contrary, we can presume that a decreasing burden of disease may be accompanied
219 by (and perhaps promoted by) rich scientific production, but also with a declining interest.

220 The evolution of incidence and prevalence of NTDs may also influence how much they are present
221 in the scientific literature. Although a detailed review of the changing epidemiology of each NTD is
222 beyond the purpose of this study, chikungunya is a good example: the incidence and the geographical

223 spread of chikungunya increased dramatically in the last two decades(30); our study registered a
224 remarkable increase of scientific publication in the same period.

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

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

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

255

256

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