Scientific literature on neglected tropical diseases: a bibliometric analysis

TITLE

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 01/01/1999 to 31/01/2019. 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 publication 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

Word count: 2328

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 marginalisation. 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 organisations), 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 NDTs, 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 trematodiases, soil-transmitted helminthiases, 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 01/01/1999 to 31/12/2019. 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).

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 categorised 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 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

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 contextualise 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 (Table 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 dew 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 synthesised 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 travellers, 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 contextualise our findings. First, this was a bibliometric evaluation, thus no information has been collected and analysed 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 grey 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 recognised system of categorisation 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 minimise 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.

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263 REFERENCES

264 1. Neglected tropical diseases. World Health Organization (WHO). [Internet]. [cited 2023 Jan 8].
265 Available from: https://www.who.int/health-topics/neglected-tropical-diseases

266 2. World Health Organization. Neglected tropical diseases [Internet]. [cited 2023 Jan 4]. Available
267 from: https://www.who.int/news-room/questions-and-answers/item/neglected-tropical-diseases

268 3. Molyneux DH, Savioli L, Engels D. Neglected tropical diseases: progress towards addressing the
269 chronic pandemic. Lancet Lond Engl. 2017 Jan 21;389(10066):312–25.

270 4. Liese B, Rosenberg M, Schratz A. Programmes, partnerships, and governance for elimination
271 and control of neglected tropical diseases. Lancet Lond Engl. 2010 Jan 2;375(9708):67–76.

272 5. Addisu A, Adriaensen W, Balew A, Asfaw M, Diro E, Garba Djirmay A, et al. Neglected
273 tropical diseases and the sustainable development goals: an urgent call for action from the front
274 line. BMJ Glob Health. 2019;4(1):e001334.

275 6. United Nations. Sustainable Development Goals [Internet]. [cited 2023 Jan 4]. Available from:
276 https://sdgs.un.org/

277 7. Fontecha G, Sánchez A, Ortiz B. Publication Trends in Neglected Tropical Diseases of Latin
278 America and the Caribbean: A Bibliometric Analysis. Pathog Basel Switz. 2021 Mar
279 17;10(3):356.

280 8. Bai J, Li W, Huang YM, Guo Y. Bibliometric study of research and development for neglected
281 diseases in the BRICS. Infect Dis Poverty. 2016 Sep 6;5(1):89.

282 9. Donthu N, Kumar S, Mukherjee D, Pandey N, Lim WM. How to conduct a bibliometric analysis:
283 An overview and guidelines. J Bus Res. 2021 Sep 1;133:285–96.

284 10. Ramos JM, González-Alcaide G, Bolaños-Pizarro M. Bibliometric analysis of leishmaniasis
285 research in Medline (1945-2010). Parasit Vectors. 2013 Mar 7;6:55.

286 11. Ellis JT, Ellis B, Velez-Estevez A, Reichel MP, Cobo MJ. 30 years of parasitology research
287 analysed by text mining. Parasitology. 2020 Dec;147(14):1643–57.

288 12. Uthman OA, Wiysonge CS, Ota MO, Nicol M, Hussey GD, Ndumbe PM, et al. Increasing
289 the value of health research in the WHO African Region beyond 2015--reflecting on the past,
290 celebrating the present and building the future: a bibliometric analysis. BMJ Open. 2015 Mar
291 13;5(3):e006340.

292 13. MEDLINE® Citation Counts by Year of Publication (as of January 2022)* [Internet]. U.S.
293 National Library of Medicine; [cited 2023 Feb 5]. Available from:
294 https://www.nlm.nih.gov/bsd/medline_cit_counts_yr_pub.html

295 14. The Lancet: Global Burden of Disease [Internet]. [cited 2023 Jan 9]. Available from:
296 https://www.thelancet.com/gbd

297 15. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries
298 in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of
299 Disease Study 2019. Lancet Lond Engl. 2020 Oct 17;396(10258):1204–22.

16. Centers for disease control and prevention (CDC). Neglected Tropical Diseases [Internet]. 2022 [cited 2023 Jan 30]. Available from: https://www.cdc.gov/globalhealth/ntd/diseases/index.html

17. World Health Organization, UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. Global report for research on infectious diseases of poverty 2012. 168 P [Internet]. 2012 [cited 2023 Feb 2]; Available from: https://apps.who.int/iris/handle/10665/44850

18. Mota FB, Fonseca B de PFE, Galina AC, Silva RM da. Mapping the dengue scientific landscape worldwide: a bibliometric and network analysis. Mem Inst Oswaldo Cruz. 2017 May;112(5):354–63.

19. Hassan MD, Castanha RCG, Wolfram D. Scientometric analysis of global trypanosomiasis research: 1988-2017. J Infect Public Health. 2020 Apr;13(4):514–20.

20. Schoonbaert D, Demedts V. Analysis of the leprosy literature indexed in Medline (1950-2007). Lepr Rev. 2008 Dec;79(4):387–400.

21. Gonzalez-Alcaide G, Sosa N, Shevy L, Belinchon-Romero I, Ramos-Rincon JM. Global research on cysticercosis and neurocysticercosis: A bibliometric analysis. Front Vet Sci. 2023;10:1156834.

22. Vera-Polania F, Muñoz-Urbano M, Bañol-Giraldo AM, Jimenez-Rincón M, Granados-Álvarez S, Rodriguez-Morales AJ. Bibliometric assessment of scientific production of literature on chikungunya. J Infect Public Health. 2015;8(4):386–8.

23. Ahmad T, Haroon, Khan M, Murad MA, Baig M, Murtaza BN, et al. Research trends in rabies vaccine in the last three decades: a bibliometric analysis of global perspective. Hum Vaccines Immunother. 2021;17(9):3169.

24. Jan 28 P, 2020. The U.S. Government and Global Neglected Tropical Disease Efforts [Internet]. KFF. 2020 [cited 2023 Feb 2]. Available from: https://www.kff.org/global-health-policy/fact-sheet/the-u-s-government-and-global-neglected-tropical-diseases/

25. Global report on neglected tropical diseases 2023 [Internet]. [cited 2023 Feb 3]. Available from: https://www.who.int/teams/control-of-neglected-tropical-diseases/global-report-on-neglected-tropical-diseases-2023

26. Ending NTDs: together towards 2030 [Internet]. [cited 2023 Feb 3]. Available from: https://www.who.int/teams/control-of-neglected-tropical-diseases/ending-ntds-together-towards-2030

27. Ferreira AF, Heukelbach J, Costa CHN, Souza EA de, Maciel AMS, Correia D, et al. Scientometric review of research on Neglected Tropical Diseases: a 31-year perspective from the Journal of the Brazilian Society of Tropical Medicine. Rev Soc Bras Med Trop. 2023;56:e0403-2022, S0037-86822023000100300.

28. Okorie PN, Bockarie MJ, Molyneux DH, Kelly-Hope LA. Neglected tropical diseases: a systematic evaluation of research capacity in Nigeria. PLoS Negl Trop Dis. 2014 Aug;8(8):e3078.

29. Stanaway JD, Shepard DS, Undurraga EA, Halasa YA, Coffeng LE, Brady OJ, et al. The global burden of dengue: an analysis from the Global Burden of Disease Study 2013. Lancet Infect Dis [Internet]. 2016 Feb [cited 2016 May 24]; Available from: http://linkinghub.elsevier.com/retrieve/pii/S1473309916000268

30. Vairo F, Haider N, Kock R, Ntoumi F, Ippolito G, Zumla A. Chikungunya: Epidemiology, Pathogenesis, Clinical Features, Management, and Prevention. Infect Dis Clin North Am. 2019 Dec;33(4):1003–25.

31. Ready PD. Leishmaniasis emergence in Europe. Euro Surveill Bull Eur Sur Mal Transm Eur Commun Dis Bull. 2010 Mar 11;15(10):19505.

32. Leung AKC, Lam JM, Leong KF. Scabies: A Neglected Global Disease. Curr Pediatr Rev. 2020;16(1):33–42.

33. Kraemer MUG, Reiner RC, Brady OJ, Messina JP, Gilbert M, Pigott DM, et al. Past and future spread of the arbovirus vectors Aedes aegypti and Aedes albopictus. Nat Microbiol. 2019 May;4(5):854–63.