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# THOMSON REUTERS GLOBAL RESEARCH REPORT NEGLECTED TROPICAL DISEASES

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#### FOREWORD

Professor David Molyneux is an author of recent papers on health policy and neglected tropical diseases (NTDs) published in leading journals including *The Lancet*, the *British Medical Journal*, the *New England Journal of Medicine* and *PLoS Medicine*. He is recognized as one of the scientific community's key advocates in raising the profile of NTDs to the extent that they are now a priority of the World Health Organization (WHO). He currently serves as a member of the WHO Expert Panel on Parasitic Diseases and is a member the WHO Strategic and Technical Advisory Group on the Neglected Tropical Disease Programme (2007-2009). He recently chaired the WHO/TDR Disease Reference Group on Zoonotic Diseases and is a member of two International Commissions.

Professor Molyneux is also Senior Professorial Fellow in the Liverpool School of Tropical Medicine and in the Centre for Neglected Tropical Diseases supported by UK Department for International Development (DFID) and GlaxoSmithKline (GSK), and Emeritus Professor in the University of Liverpool. Previously, he was Director of the Liverpool School of Tropical Medicine (1991-2000) and Professor of Tropical Health Sciences of the University of Liverpool. He has published over 300 papers, written over 20 reviews and contributed to books as well as a textbook on trypanosomes and leishmania. In recognition of his scientific contributions, he was awarded a Doctor of Science degree honoris causa of Georgetown University and an honorary fellowship (Liverpool John Moores University). In 2007, he received the Donald Mackay Medal of the American Society of Tropical Medicine and Hygiene. Molyneux recently delivered the David Livingstone Lecture of the Royal College of Physicians and Surgeons of Glasgow.

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## THOMSON REUTERS GLOBAL RESEARCH REPORT NEGLECTED TROPICAL DISEASES

### FOREWORD

I am pleased to contribute to this timely and welcome analysis of the research environment around Neglected Tropical Diseases (NTDs).

Since the publication of the World Health Organization's 2010 Global Report on "Working to overcome the global impact of neglected tropical diseases" there has been much progress, culminating in a meeting on 30th January 2012 in London. Agencies representing the governments of affected and developed countries, CEOs of major pharmaceutical companies, the Director General of WHO and Bill Gates gathered to announce new drug donations and significantly enhanced research funding, and endorsed the London Declaration on Neglected Tropical Diseases.

The possible eradication of one NTD (guinea-worm infection) was a product of the meeting, with new funds committed from the UK, the United Arab Emirates, and the Gates Foundation. For the core 17 NTDs, partners signed up to the WHO "road map": a template for action to 2020. The meeting also saw the launch of the UK Coalition against NTDs, an umbrella forum representing and coordinating the most active UK organizations in NTD research. The aims of the Coalition are to raise policy awareness and influence policy decisions towards sustainable control of NTDs, to expand the support for NTD control, and to foster and facilitate communication amongst agencies working in NTD control and elimination.

This Thomson Reuters Global Research Report emphasizes an increasing interest in research and control of NTDs. Clinicians, biomedical scientists and health researchers have long been attracted by the complex biology and life cycles of the organisms which cause these diseases, their epidemiology, the clinical conditions which the infections impose on individuals, and the challenges of control in the diverse health systems of NTD-endemic countries. But only within the last decade has the NTD brand identity emerged as an enabling factor to crystallize that interest in policy and programs.

The UN's Millennium Development Goals (MDGs) subsumed NTDs among "other diseases." This categorization denigrated and disenfranchised at least a billion sufferers among the world's poorest, whilst donors focused on HIV/AIDS, malaria and TB. NTD advocates need a strong platform to assert their demands for increased attention and resources, and their voice is strengthened by the new availability of donated drugs and the demonstrably low cost of delivery. But, beyond this comparative argument, there is a broader social and economic rationale. Resources used to deliver efficacious products not only have a direct impact on NTD transmission and elimination. Delivery through communities and schools also ensures more equitable access to health resources, allays downstream costs to patients, and contributes to strengthening national health systems.

There has been a view that NTD control is a vertical approach, one that impedes health-system development

by diverting limited national resources at the local level. Such a criticism could be levelled at any intervention including the HIV/AIDS programs or malaria bed-net distribution. Against this, NTD advocates point to powerful social, economic, and development benefits. NTD programs focus on the basic needs of the poorest, address equity, provide hope of freedom from offensive clinical conditions that stigmatize, disable, and impose costs and social detriment on family and community. Better treatment and greater control would enable more rapid achievement of other UN goals, including reduced hunger and poverty (MDG 1), improved child survival (MDG 4), and lower maternal mortality (MDG 5).

Much continued research is needed. First, new products must be developed to meet specific target product profiles, capable of being administered orally with minimal medical supervision, at an affordable price! If any vaccine should be developed, it needs to be capable of incorporation into existing immunization platforms. Countries that spend less than US\$ 10 per capita per year on health need that research to be subsidized and products to be donated. Second, new diagnostic tools are needed but they too are constrained by affordability and deployment. Third, support must be given to large-scale programs of control and elimination with research. Of particular importance are alternative therapeutic approaches to overcome loss of efficacy and resistance to existing drugs. Beyond this we need improved monitoring and surveillance to ensure impact against epidemiological targets. We need better health-systems research to ensure lessons are embedded. And we need social and economic research to address access, coverage, and compliance.

We must maintain current interest in NTDs amongst a diversity of partners in a variety of alliances. Each party has specific interests but we should seek to expand the interested constituencies, articulate the rationale for further investment, and appreciate that NTDs represent the low-hanging fruit in many challenging health environments. WHO has reported that mass drug administration interventions now reach some 800 million people each year. That is certainly a great achievement but it must continue and expand.

Some 13 major pharmaceutical companies donate products at an estimated annual value around US\$ 2 billion. The cost of delivering preventive chemotherapy is perhaps as little as US\$ 0.40-.50 per person per year. Independent assessment of the value in health terms makes this a best-buy for global public health. If we cannot even deliver free drugs with massive benefits to the poorest billions at trivial unit costs, is it likely that we will achieve health goals that demand more complex solutions?

Professor David Molyneux

#### BACKGROUND

The Global Research Report series informs policymakers about the changing landscape of the global research base. This report focuses on the growth of the literature in a policy and research area of global relevance that historically has been significantly underdeveloped.

What is a Neglected Tropical Disease? David Molyneux, in his Foreword, sets out our scope and explains why the term "neglected" must be applied to a group of diseases that impact daily life for a huge part of the world's population. Our data sadly confirm the significance of the term.

The list of Neglected Tropical Diseases used here is that described by the World Health Organization on its website (see APPENDIX). This does not include well-known diseases such as cholera or malaria. Nor does it include cancer, diabetes and cardiovascular disease although these affect many in the tropics. Instead, it focuses on diseases specific to the tropics and some other parts of developing nations of the South, understudied in research, underserved by public health services, and only partly addressed by contemporary biomedical research-focused drug development, vaccines, or diagnostics.

#### **A BRIEF HISTORY**

Diseases that predominantly, but not exclusively, burden those in tropical and rural locations have captured a new degree of attention over the last decade — from scientists, public health officials, national leaders, non-governmental organizations, and research and public health funders. These diseases are generally not well recognized by the public. Research and treatment is significantly less well funded than HIV/AIDS, malaria, and tuberculosis. They nonetheless have similar catastrophic impact when measured by disabilityadjusted life years (DALYs), a standard index of health that combines morbidity and mortality.<sup>12</sup>

More than 1 billion and perhaps more than 2 billion people are chronically infected with one or more Neglected Tropical Diseases (NTDs) and more than half a million people die every year from their infections.<sup>3</sup> By comparison, devastating diseases such HIV infect some 40 million globally. However, the NTDs collectively received just 0.6% of international development assistance for health while 42% of that aid and a total of 80% of health R&D spending in developing countries was devoted to HIV/AIDS, malaria, and tuberculosis.<sup>4 5</sup> The victims of NTDs are among the poorest people of the world, living on less than US\$ 2 per day. Infected adults lose their capacity to work, exacerbating poverty. Young victims are stunted physically and cognitively, and their education suffers. Environmental conditions make vulnerable people particularly prone. Costly or unavailable treatment means that disease keeps them in poverty.<sup>6</sup> There is incalculable social and psychological devastation: sufferers are shamed by their condition and shunned by their

communities.<sup>7</sup> In fact, these diseases create a hitherto unrecognized burden of mental illness not only for sufferers but also for caregivers.

For the developed world, out of sight appears to have been out of mind. But recently, through a variety of efforts, these diseases have begun to receive greater attention and are consequently becoming less neglected.

A turning point came in 2000 — ironically, through omission. Neglected tropical diseases were not mentioned when the United Nations announced its eight Millennium Development Goals.<sup>8</sup> The UN's sixth goal was to "combat HIV/AIDS, malaria, and other diseases." The omission served as a call to action for a group of concerned scientists who had been working in the field and in the laboratory on specific neglected tropical diseases. Among these were David Molyneux (focusing on lymphatic filariasis and onchocerciasis), Peter J. Hotez (on hookworm) and Alan Fenwick (on schistosomiasis).

At the same time, the Bill & Melinda Gates Foundation stepped up funding for research and public health projects related to global health, including the NTDs.<sup>9</sup> A notable milestone, encouraged by financial support from the Gates Foundation, was the 2006 founding of the Global Network for Neglected Tropical Diseases. This brought together independent and disease-specific organizations for the purpose of coordinating their efforts in disease intervention and in developing a new generation of improved control tools.<sup>10</sup> Some of the partner members of the Global Network include the Liverpool School of Tropical Medicine, the Schistosomiasis Control Initiative, and the International Trachoma Initiative.

On January 30<sup>th</sup> 2012 new and unprecedented support was announced. At a meeting at the Royal College of Physicians in London, 13 pharmaceutical companies, the governments of the United States, the United Kingdom, and the United Arab Emirates, the World Bank, the Bill & Melinda Gates Foundation and other organizations pledged more than US\$ 785 million to accelerate research and development of new drugs for NTDs and to expand effective drug distribution.<sup>11 12</sup> The partners also endorsed the "London Declaration on Neglected Tropical Diseases."13 Simultaneously, WHO published Accelerating Work to Overcome the Global Impact of Neglected Tropical Diseases: a Roadmap for Implementation, its plans for the control, elimination or eradication of specific diseases and its targets from 2012 through 2020.14

#### LITERATURE ON NEGLECTED TROPICAL DISEASES

Research relevant to tropical hygiene and medicine is spread across a very wide range of journals, topics, and field categories. Earlier bibliometric studies dealing with the tropical disease literature provide background to the present document. Some three dozen such studies published over the last four decades were identified, but three recent papers warrant particular attention. Dieter Vanderelst and Niko Speybroeck quantified the relative lack of scientific interest in NTDs in a 2010 study that compared the publication output of specific neglected diseases against other diseases with a similar DALY score. They took the premise that two illnesses with similar burdens ought to receive similar research attention that would be revealed in volume of publication. "Our analysis shows that NTDs are less researched than the matched conditions with comparable DALYs," the authors state. "Moreover, the gap has widened in recent years."<sup>15</sup> Data in this report (below) confirm this gap.

Jennifer Keiser and Jürg Utzinger looked at 50year trends in the literature on tropical medicine in a 2005 study. They found that while international collaboration had increased, the percentage of authors from countries most affected by these diseases actually declined. They noted the practical challenges to engagement that are faced by the researchers located where effort is most relevant.<sup>16</sup>

A 2009 paper, from Carlos Morel of the Rio de Janeiro Institute for Science and Technology on Innovation on Neglected Diseases and colleagues elsewhere in Brazil, is both retrospective and prospective. A social network analysis of coauthorship on Brazilian publications focusing on seven NTDs targeted by the nation's Ministry of Health identified authors and institutions playing major roles. This information was applied to strategic planning, implementation, and monitoring of the Ministry's program. In this way, analysis of the literature "afforded a more proactive role of the funding agencies in relation to public health and equity goals ... and a more consistent engagement of institutions and authors from endemic regions."<sup>17</sup> It is to be hoped that this approach can be employed more widely.

The data and analyses in this report will confirm the historical lack of global R&D investment. We are able, however, to highlight the impact of the research that has emerged and the growth of research in Brazil and other emerging economies. This establishes a new geography for NTD research with much benefit to affected populations.

#### DATA FOR THIS REPORT

Publication data were drawn from *Web of Science*<sup>SM</sup> databases which annually index the contents of 11,500 journals covering over 1.1 million research articles and reviews.

We surveyed these research papers for the two decades from 1992-2011. First, we drew out all the papers that used the term "neglected tropical disease(s)" anywhere in their title, abstract, or keywords (Figure 1).

The data show that the use of the term "neglected tropical diseases" has risen rapidly in the last decade and particularly since 2005. This does not represent growth in research activity as much as the "rebranding," noted by David Molyneux, by tropical medicine researchers bringing separate diseases

FIGURE 1: INCREASING OCCURRENCE OF PHRASE "NEGLECTED TROPICAL DISEASE(S)" IN SCHOLARLY PAPERS



Source: Thomson Reuters Web of Knowledge<sup>™</sup>

together under one rubric in order to call greater attention to them.<sup>18</sup>

To explore the literature fully we need to focus on specific diseases and targeted research papers. For this more comprehensive analysis, we drew out every paper that made reference to at least one of the diseases on the WHO list (see APPENDIX).

For the 20-year period to 2011, there were 73,212 papers that identified at least one of the NTDs in the WHO list. Most of these papers (about 67,000) focused on just a single disease but there were 5,412 that referenced two diseases in their title, abstract, or keywords, 788 that referenced three diseases, and 181 that referenced four or more. Just two papers covered 10 NTDs, so most of the literature is fairly specific in its focus.

Web of Science uses 254 categories to group journals that publish material in related fields. We can look at the way the papers discussing specific NTDs are published across journals allotted to these categories. Not surprisingly, the greatest numbers of NTD-specific papers are found in the categories for Parasitology and Tropical Medicine. However, the diversity of relevant methods and results is wider than that. There are 10 or more papers published in journals from 140 different categories.

This disciplinary diversity is not exceptional for a dataset on an important topic and it reflects the interdisciplinary research that underpins most fields of endeavor. For example, in this instance, papers appear in zoology and ecology journals (the biology of the disease vectors) and a wide range of medical and engineering journals (environmental and healthcare solutions). The high placing of "public, environmental and occupational health" in Table 1 is a signal of the emergence of a focus on healthcare protocols that can be as significant as new treatments and drugs.

#### TABLE 1: DISTRIBUTION OF PAPERS ACROSS JOURNAL CATEGORIES

JOURNAL CATEGORY	COUNT OF PAPERS	SHARE (%) OF NTD DATASET
Parasitology	17,237	23.54
Tropical Medicine	11,761	16.06
Immunology	9,820	13.41
Public, Environmental & Occupational Health	7,298	9.97
Biochemistry & Molecular Biology	7,065	9.65
Veterinary Sciences	6,115	8.35
Infectious Diseases	5,794	7.91
Microbiology	5,412	7.39
Entomology	3,016	4.12
Virology	2,903	3.97
Pharmacology & Pharmacy	2,559	3.50

Source: Thomson Reuters Web of Knowledge<sup>™</sup>

Distribution of papers on Neglected Tropical Diseases across journal categories in *Web of Science*. The categories with 2,500 papers or more for the period 1992-2011 are shown. Some journals are assigned to several cognate categories, and totals can add up to more than 100% of a dataset. The publication analysis in the report uses a deduplicated dataset.

### ANALYSIS

#### PUBLICATION VOLUME

The number of papers in our dataset on NTDs has risen over the 20 years, broadly doubling from around 2,500 papers in 1992 to well over 5,000 papers in 2011. The growth profile in the overall data is mirrored in the most frequent journal categories (Parasitology and Tropical Medicine).

As a share of world research output, the papers on these diseases accounted for around 0.4% of total global articles and reviews for much of the period, but that share began to rise in 2005, around the time that the general term for this disease group also started to come into use (Figure 1). By 2011, world share had risen to nearly 0.5%. This rise may seem marginal but it should be noted that world publication output had itself doubled, so NTDs are taking a bigger slice of a growing global portfolio of papers.

Citation impact is not a critical factor in our analysis since we are more interested in the spread of research activity. Nonetheless, it is heartening to note that the NTD dataset is cited more frequently in every year than papers generally for either Parasitology or Tropical Medicine. Ten years after publication, papers in those journal categories typically plateau at an average of around 15 citations. The NTD data are cited more frequently and average around 20 citations per paper after 10 years, continuing to accumulate citations to an average over 25 citations per paper for the papers published in the early 1990s. Thus, while NTD research may receive less than its due global investment, the *Web of Science* data indicate that the quality of that research is well above average and that the scientists involved gain significant and lasting peer recognition.

#### PUBLISHING COUNTRIES

Web of Science indexes author addresses in all instances when these are listed in the published paper, and we can use this information to determine where the authors are located.

Not surprisingly, most papers carry an author from one of the research-rich economies in the G7. What is remarkable about this dataset, however, is the powerful presence of Brazil and India. There are more papers on NTDs in 2011 that have an author or co-author from Brazil than from the UK. India is more productive in this field than either France or Germany.

The general trend in output for the established economies is of a gradual upwards trajectory. India's trajectory is steeper and it has grown past other countries while Brazil's output has grown even more steeply. That rate of increase is typical of most other countries in which these diseases have a direct economic and social impact.

The distribution of NTD research by country is far from typical of the usual global pattern (Figure 2). In most research fields, the USA produces about three times as many papers as the UK, which itself produces slightly more papers than Germany or France. However, in the NTD research area, the UK is relatively more productive. It produces around half the output of the USA and more than half as much again as its major European neighbors. This is almost certainly a consequence of its global history, its continuing links with the Commonwealth, and the funding activities of The Wellcome Trust, which has long supported research in tropical medicine. France is also markedly more productive in NTD research than Germany and that too may be a consequence of a colonial legacy.

The major producers of papers on neglected tropical diseases outside the established economies are shown in Figure 3. Note that China — growing very rapidly — and Argentina publish about the same number of papers as Japan, Spain, Switzerland, and Australia.

Other countries active in NTD research are Iran, Thailand and Turkey, where the rise of output is remarkable and impressive. For Kenya, an early research leader among African nations, the profile is rather static.

NTD research is often a significant part of the research base for developing and emergent economies because of its obvious economic and social relevance. Brazil is evidently a global research leader, with a substantial volume of NTD papers in its portfolio. Its neighbors in Bolivia and Paraguay have much smaller overall research profiles but they have focused even more strongly on NTD targets including Chagas disease.

This focus is because the impacts on national health costs and the productivity of the workforce are enormous. Figures 4 and 5 show a broad global analysis, summarizing the total publication output of the last 20 years. This output is illustrated here in two ways: in Figure 4, in terms of relative output compared to world total research activity on NTDs; in Figure 5, in terms of NTD research relative to national total research output. The contrast between the two pictures is evident.

#### PUBLICATIONS BY DISEASE

The overall growth pattern discussed earlier shows a general trend for NTD research, with more than a doubling of output between 1992 and 2011. Another way of indexing growth would be to describe this as an increase of 1.6-fold between the first and second decade. To reveal some of the specific focuses, we can disaggregate that pattern by individual disease (Table 2).

#### FIGURE 2: OUTPUT FROM WORLD'S MOST RESEARCH-ACTIVE ECONOMIES



Source: Thomson Reuters Web of Knowledge<sup>™</sup>

Annual counts of papers from the most research-active economies publishing in Neglected Tropical Diseases. A paper counts towards a country's tally if one or more author addresses include that country. USA and Brazil (dotted lines) are plotted on the right-hand axis.

#### FIGURE 3: OUTPUT FROM WORLD'S LEADING EMERGING ECONOMIES



Source: Thomson Reuters Web of Knowledge<sup>™</sup>

Annual counts of papers from leading emerging economies publishing on Neglected Tropical Diseases. Note that Brazil and India are covered in Figure 2 as their current research output on NTDs is greater than the countries shown here. A paper counts towards a country's tally if one or more author addresses include that country. FIGURE 4: SHARE OF TOTAL WORLD OUTPUT ON NEGLECTED TROPICAL DISEASES RESEARCH



Source: Thomson Reuters Web of Knowledge<sup>™</sup>

Total publication output naming one or more of the Neglected Tropical Diseases listed by WHO. Color intensity scale reflects share of world output of 73,000 articles and reviews between 1992-2011. Productivity is greatest relative to the rest of the world for the USA, Brazil, UK and India.



#### FIGURE 5: NEGLECTED TROPICAL DISEASES RESEARCH RELATIVE TO NATION'S TOTAL RESEARCH OUTPUT

Source: Thomson Reuters Web of Knowledge<sup>sm</sup>

Relative publication output naming one or more of the Neglected Tropical Diseases listed by WHO. Color intensity scale reflects NTD as percent of total national articles and reviews between 1992-2011. There is a focus for emerging research economies across the tropics, notably in the status in Latin America of Paraguay and Bolivia; in Africa of Angola, Mali, and Sudan; and in Asia of Cambodia, Laos, and Nepal. These are not rich countries but their research targets these diseases.

#### TABLE 2: OUTPUT ON SPECIFIC DISEASES COMPARED OVER TWO DECADES

	DISEASE	PAPERS 1992-2001	PAPERS 2002-2011	RATIO
Helminth infections	Soil transmitted helminthiasis	3,789	6,981	1.8
	Schistosomiasis	4,147	4,768	1.1
	Lymphatic filariasis	667	1,191	1.8
	Cysticercosis	905	1,331	1.5
	Onchocerciasis	1,270	1,186	0.9
	Fascioliasis	1,052	1,495	1.4
	Dracunculiasis	97	48	0.5
	Echinococcosis	1,886	2,792	1.5
Protozoan infections	Leishmaniasis	3,923	6,519	1.7
	Chagas disease	3,851	6,501	1.7
	Human African trypanosomiasis	1,833	2,813	1.5
Bacterial infections	Trachoma	270	556	2.1
	Leprosy	2,601	2,458	0.9
	Buruli ulcer	98	379	3.9
	Yaws	78	80	1.0
Viral infections	Dengue	2,818	8,052	2.9
	Rabies	1,832	2,674	1.5

Source: Thomson Reuters Web of Knowledge<sup>™</sup>

Count of papers by specific Neglected Tropical Disease for the two 10-year periods 1991-2000 and 2001-2010. The ratio between the two periods indicates the relative growth of research activity and is a 1.6-fold increase for the total dataset. Thus, whereas the already substantial volume of research on Dengue has almost trebled, output on most diseases has not quite doubled and some areas have grown much less or even declined in output.

As shown in Figure 6, The growth of research on dengue is exceptional but this is a disease associated with the growing numbers of urban poor in the third world, epidemics in Southeast Asia and Brazil, and the increase in efforts to develop a vaccine.

The fall in publication output on dracunculiasis (guinea-worm disease) is likely due not only to the success story in eradication but also because there are no laboratory models for the disease and hence the only studies published are related to field work. Dracunculiasis and trachoma provide examples of diseases that can be reduced through improved sanitation, hygiene, and vigilance. The guinea worm is transmitted when humans swallow water containing copepods. Inside the body, larvae in the copepods mature to worms. In 1986, it was estimated that there were more than 3 million cases of guinea-worm infection. Only 25 years later, there were just over 1,000 reported. The eradication of guinea-worm disease has been hastened by the advocacy of former US President Jimmy Carter, the Carter Center, the U.S. Centers for Disease Control and Prevention (CDC), UNICEF, and WHO.<sup>19</sup> The key has been the increased provision of safe water (protected wells and bore holes), filters to remove

#### FIGURE 6: FIVE DISEASES MOST FREQUENTLY SPECIFIED IN RESEARCH PAPERS



Source: Thomson Reuters Web of Knowledge<sup>sh</sup>

copepods from contaminated drinking water, treatment of infected water sources with temephos, and containment of cases to prevent contamination as well as integrated educational efforts. The research that supported this implementation is captured in earlier literature not covered here: an example of success signaled by a shift into application beyond the academic literature.

The growth in the volume of research on dengue is very clear and there are now in excess of 1,000 papers per year. The soil-transmitted helminthiases, which affect perhaps as many as an estimated 2 billion individuals globally, are also receiving significantly more attention than in the past but output has not increased at the same rate nor to the same level as dengue although prevalence is much higher. The volume of research on Chagas disease is also notable given that it would not normally be considered amongst the most prevalent diseases. By contrast to the others in Figure 6, the volume of research on schistosomiasis has barely changed from 500 papers per year over 20 years although it affects 200 million people. One research paper per 400,000 victims per year would seem a poor disease response in any developed economy.

The less intensively researched diseases fall into three groups by volume (Figure 7). There are four diseases with around 300-400 papers per year currently, four with 100-200 papers per year, and four with fewer than 100 papers per year.

For trachoma, a bacterial infection that can cause blindness, successful treatment has included a large environmental intervention component. SAFE is an effective control and prevention strategy for trachoma, standing for Surgery, Antibiotics, Face washing, and Environmental control.<sup>20</sup> Improved hygiene and sanitation greatly reduces trachoma and, in 2006, Morocco successfully used SAFE to eliminate trachoma as a public health problem.

The two now least-frequent research areas, yaws and dracunculiasis, have responded well to recent treatment regimes and are both much rarer than they have been: the potential for early eradication exists. However, the low and static research outputs in other instances are less readily explained.

#### RESEARCH OUTPUT AND DISEASE PREVALENCE

How do the numbers of papers published on NTDs compare with research output relevant to other diseases? At the beginning of this report we noted the balance of funding on research for different diseases, and this is inevitably reflected in the output of academic papers. The following summary figures are minimum estimates made from a relatively simple keyword search on these terms in *Web of Science*.

- 16,000 papers per year on HIV/AIDS
- 15,000 papers per year on coronary heart disease
- 5,000 papers per year on tuberculosis
- 3,500 papers per year on malaria
- In excess of 85,000 papers per year on cancer, in multiple forms

#### FIGURE 7: TWELVE LESS-INTENSIVELY RESEARCHED DISEASES



Source: Thomson Reuters Web of Knowledge<sup>SM</sup>

For each disease the data reveal a rising, sometimes steeply rising, trajectory. The research output specifically on the NTDs covered in this report is a total of no more than 6,000 papers per year, and even with other publications relevant to supporting research, that would come to well under 10,000 papers. There is no doubt at all that these other diseases have huge impact and that they are rightly the target of some of the best biomedical research in Europe and North America, but it is also evident that the term "neglected" is only too appropriate for the diseases WHO highlights.

What about the match between prevalence and relative research activity among the NTDs? The data summarized in Figure 8 suggest a broad correlation with some challenging outliers. For example, there is more research on soil-transmitted helminthiasis than fascioliasis but the former disease affects a much larger population. By contrast, there are some departures from any general relationship between impact and effort: for example, Chagas disease and leishmaniasis are protozoan diseases receiving a relatively high level of research attention but affecting fewer people than lymphatic filariasis and onchocerciasis. The protozoan diseases may represent a more tractable challenge than the helminths and, while it is difficult to explain the difference in activity, it is possibly related to what are reported to be limited animal models for the latter diseases on the one hand and the opportunity for vaccine development for Chagas and leismaniasis and their endemicity in Brazil (Chagas) and India and Brazil (leishmaniasis). Such models are an important part of developing a successful research and exploratory treatment program



Sources: Thomson Reuters Web of Knowledge<sup>SM</sup>, World Health Organization

A comparison of the prevalence and research output for the Neglected Tropical Diseases. Prevalence is shown on a log scale (6 is the marker for one million and 9 is the marker for one billion) because it is so high in some instances. Helminth diseases are shown in shades of blue; protozoan diseases in orange; bacterial diseases in grey; and viral diseases in green. The position of each bubble is determined by prevalence on the horizontal axis (from Hotez, 2008) and research output (2002-2011) on the vertical axis. The size of the bubble reflects the relative growth in research output between the earlier (1992-2001) and later decades in the analysis: bigger bubbles (e.g. dengue) indicate relatively more growth.

Thanks to past research and treatment programs, yaws and dracunculiasis are diseases of diminishing significance as public health problems. The similarly low level of research on trachoma may be because the disease is now relatively well understood and the SAFE protocol, now reported and discussed more in "grey literature" than in academic papers, presents a solution including effective antibiotics. What is needed is effective implementation.

Overall, while some explanation of the patterns in Figure 8 can be attempted, the inescapable conclusion is that there are still serious and inexplicable deficits in the balance of research effort.

The geography of these diseases may change. NTDs remain predominantly tropical in their impact at present but climate change, globalization and social factors are creating an emerging risk in temperate areas. In North America, CDC notes that the potential for the spread of Chagas disease is low at present. Whilst more than a quarter-million people in the US have the infection, proven vector-borne transmission thus far remains rare.<sup>21</sup> The risks of increased transmission of Chagas disease relate more to the likelihood of transfusion transmission than to vector-mediated transmission as has recently occurred in Europe. 22 23 24 In Europe, visceral leishmaniasis and dengue fever are already analyzed as a weighted high risk in terms of potential severity and likelihood of increase with climate change.<sup>25</sup>

## TACKLING TROPICAL DISEASES: MORE ATTENTION, EFFECTIVE THERAPIES, NEW DRUGS

The data analyzed in this report describe a disproportionately low level of global research attention for long-known diseases affecting huge numbers of people in some of the world's most challenged economies. These are undoubtedly Neglected Tropical Diseases. This neglect contrasts with the research efforts paid to diseases that have emerged in more affluent regions.

Our review of global NTD research creates an unusually complex research tapestry. We may be skeptical about the rising frequency of "neglected tropical diseases" in paper titles and keywords (Figure 1) but this branding is a positive signal of policy and political change. Increased awareness of NTD research, and its diversity by disease and by topic, is no bad thing. There is a spread of publications across journal categories (Table 1) not just in core biomedical areas but also in fields relating, for example, to the ecology of the disease vectors and — most critically — the social and health environment in which NTDs are prevalent. This signals a shift towards solutions that move from studying the disease towards comprehensive remedies involving control, eradication, prevention, and treatment. Realizing the effective use of what we already know may be as critical as increasing our knowledge base.

David Molyneux argued in his Foreword that it is not just research that has been neglected but also

research outcomes. People at risk live close to the land in unsanitary conditions that spread infectious agents, so effective control requires environmental intervention.<sup>26</sup> NTD research has sometimes pointed to better treatments that have not then been adopted and implemented. Preventive chemotherapy, through mass drug administration and community and school distribution routes, can treat co-endemic conditions in a single dose at one time.<sup>27</sup> The "rapid impact package" combines four drugs in one dose to address up to seven diseases with a cost per person per year that is less than a dollar, thanks to donations by pharmaceutical companies. Since NTDs are often co-endemic with HIV/AIDS and malaria in sub-Saharan Africa, this could be made even more efficient within programs already addressing other conditions. 28 29 30 31 32

Brazil and India stand out as another kind of signal: the shifting geography of research (Figures 2 and 3). The geographical balance of NTD research activity has been unusual: the UK and France, perhaps because of their colonial history, have a relatively high share amongst developed countries of global research activity. But historically, as noted earlier, the involvement of local scientists in NTD areas has often been marginal, even indirect in the absence of local infrastructure. The emergence of a new research base changes the game: rapidly improving research in Brazil and India links to a network of other tropical countries. This indicates a growth in targeted research capacity remedying an infrastructure deficit within the most affected regions. The expanding scale of regional NTD research networks will create research capacity that is likely to drive much faster solutions and a better and sustained focus for external aid. The emphasis can now be on direct support of leading centers and scientists in target areas, with the EU and North America in a virtuous support cycle rather than leading. Our maps (Figures 4 and 5) do show that most papers are still published with G7 authors but they also indicate the critical role of NTD research for research development across the tropics.

The data confirm the neglected nature of the disease group and show just how great that neglect has been compared to overall health R&D investment. There has been a doubling in research output over 1992-2011 to around 6,000 papers per year, and more than a doubling for specific diseases (Table 2; Figures 6 and 7). The overall volume nonetheless remains low compared to diseases prevalent in G20 economies — for example, 15,000 papers per year on coronary heart disease. This comparison presents a challenge: each country must address the threats to its own population, yet we collectively acknowledge the imperative to act responsibly to enable solutions to problems faced by others.

Deconstructing the literature and comparing by disease target, in the bubble diagrams of Figure 8,

reveals more information. The data reveal imbalances between NTDs in relative prevalence and research effort but the balance is far from simple. Research on Chagas disease is boosted by the investments made in Mexico and Brazil. Dengue and leishmaniasis research output are also rising rapidly, above the general trend. Meanwhile the level of research on lymphatic filariasis, onchocerciasis, cysticercosis, and trachoma is far lower although they collectively affect hundreds rather than tens of millions of people.

The analysis points to questions for policymakers, funders, and research leaders. Do these data raise questions about the extent to which a lack of critical mass may have held back the development of basic methodology and models? Do they point to gaps where an escalation of effort might trigger a stepchange in achievement? It is difficult not to think that if a concentrated boost was applied then some of the constraints that make helminth research less tractable might be more rapidly addressed. And are we seeing a rising research focus on some targets because of an emerging threat beyond traditional NTD regions?

Despite these concerns, we can point to very positive outcomes of research over recent decades and to a change in public attention driven by experts and champions. The citation impact of NTD research is greater than comparable activity in the same broad research disciplines. It is cited more frequently and attracts later cross-references over a longer period. That platform of quality fully justifies the increased attention garnered by new advocates such as the Gates Foundation and the governments that have been drawn into a reconsideration of NTD programs. No informed observer denies the substantial and diverse challenges in controlling, eliminating, or eradicating NTDs. But in facing future challenges we can now refer to past successes reflected in the trajectory tracked in our analyses. The near eradication of guinea worm is one, while another is trachoma, eliminated as a public health problem in Morocco, as well as in Iran and Oman. Other gains are summarized by Molyneux and Malecela.<sup>33</sup>

The analysis in this report confirms and quantifies much of what has been described elsewhere. It points to optimism in the emergence of new research economies but raises questions about the balance of research effort both on and amongst NTDs. With greater recognition of the scope of the problem and also of the diversity of information already available, with more resources for public health programs as well as for research grounded in affected areas, and with the collective global commitment to combating Neglected Tropical Diseases demonstrated in London in January 2012, there is reason for optimism about what may be accomplished.

## APPENDIX: MAJOR NEGLECTED TROPICAL DISEASES, GROUPED BY TYPE

	DISEASE NAME	CAUSATIVE AGENT	PREVALENCE	POPULATION AT RISK
Helminth infections	Soil transmitted helminthiasis	Ascaris lumbricoides, Trichuris trichiura, hookworm	ascariasis: 807 million trichuriasis: 604 million hookworm: 576 million	ascariasis: 4.2 billion trichuriasis: 3.2 billion hookworm: 3.2 billion
	Schistosomiasis (Bilharzia, snail fever)	Some Schistosoma spp.	207 million	779 million
	Lymphatic filariasis (elephantiasis)	Wuchereria bancrofti, Brugia malayi, B. timori	120 million	1.3 billion
	Cysticercosis	Taenia solium	50 million	Unknown
	Onchocerciasis (river blindness, Robles' disease)	Onchocerca volvulus	37 million	90 million
	Fascioliasis (Distomatosis)	Fasciola hepatica, F. gigantica	2.4 million	180 million
	Dracunculiasis (Guinea- worm disease)	Dracunculus medinensis	0.01 million	Unknown
	Echinococcosis (Hydatid disease)	Echinococcus granulosus, E. multilocularis, E. vogeli, E. oligarthus	Unknown	Unknown
Protozoan infections	Leishmaniasis	<i>Lutzomyia,</i> sandfly	12 million	350 million
	Chagas disease (Ameri- can trypanosomiasis)	Trypanosoma cruzi	8-9 million	25 million
	Sleeping sickness (Human African tryp anosomiasis)	Glossina, Trypanosoma brucei gambiense and T.b.rhodesiense	0.3 million	60 million
Bacterial infections	Trachoma (granular conjunctivitis, Egyptian ophthalmia)	Chlamydia trachomatis	84 million	590 million
	Leprosy (Hansen's disease)	Mycobacterium leprae	0.4 million	Unknown
	Buruli ulcer	Mycobacterium ulcerans	0.05 million	Unknown
	Yaws (Frambesia tropica)	Treponema pallidum	Unknown	Unknown
Viral infections	Dengue	Aedes aegypti, Aedes spp.	Unknown; as many as 50 million infected annually	Unknown, but increasing numbers at risk
	Rabies		Unknown; 55,000 deaths annually	Unknown

Source: World Health Organization

Diseases listed by the World Health Organization (WHO) as fitting its criteria of a Neglected Tropical Disease (see full background at <a href="http://www.who.int/neglected\_diseases/en/">http://www.who.int/neglected\_diseases/en/</a>). Data on prevalence and 'at risk' from Peter J. Hotez, Forgotten People, Forgotten Diseases: The Neglected Tropical Diseases and Their Impact on Global Health and Development, Washington, D.C.: ASM Press, 2008, Table 1.3.

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