

Fostering Canadian drug research and development for neglected tropical diseases

PATRICIA GABRIEL, REBECCA GOULDING,
CECILY MORGAN-JONKER, SHANNON TURVEY,
JASON NICKERSON

Patricia Gabriel, MD, is a family medicine resident at St. Paul's Hospital, Vancouver, BC, Canada. **Rebecca Goulding**, PhD, is a postdoctoral fellow at the ISIS Research Centre, Sauder School of Business, University of British Columbia, Vancouver. **Cecily Morgan-Jonker**, BSc, is a medical student at the University of British Columbia. **Shannon Turvey**, MSc, is a medical student at the University of British Columbia. **Jason Nickerson**, MA, RRT, is a PhD candidate at the Centre for Global Health, Institute of Population Health, at the University of Ottawa, Ottawa, Ont.

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Correspondence: Rebecca Goulding, ISIS Research Centre, Sauder School of Business, University of British Columbia, 2053 Main Mall, Vancouver, BC, Canada V6T 1Z2; regoulding@gmail.com

NEGLECTED DISEASES ARE AILMENTS THAT CAUSE significant morbidity or mortality but for which treatments are unavailable, ineffective or toxic. These conditions, which include HIV/AIDS, tuberculosis, malaria, and an assemblage of "neglected tropical diseases" (NTDs) comprised of various helminthic, protozoan, viral and bacterial infections, primarily affect impoverished people in low- and middle-income countries.^{1,2} The fact that most people who are affected by NTDs cannot afford expensive treatments has inhibited investment in research and development (R&D) in this area. However, roughly a billion people worldwide are infected with one or more NTD,³ leading to 530 000 deaths annually and a global burden of disease (GBD) of 57 million disability adjusted life years (DALYs).⁴ This is a significant GBD when compared with the global burden of 84.5, 46.5 and 34.7 million DALYs attributed to HIV/AIDS, malaria and tuberculosis, respectively.⁴ DALYs are thought to systematically underestimate the

burden of NTDs.⁴ The calculation of DALYs does not take into account the long-term nature of NTDs or the subclinical morbidities associated with them.^{4,5} A number of studies have demonstrated that NTDs are, relative to their global burden, the most neglected of the world's diseases.^{4,6} A study on the funding of ND research found that 30 NDs (including NTDs) received only 0.016% of the US\$160 billion allocated to health research globally in 2007.⁶ Of the 1556 new drugs marketed between 1975 and 2004, only 21 were indicated for neglected diseases (including malaria and tuberculosis, but not HIV), and a mere 10 were directed at NTDs.⁷

Many people have advocated an increase in drug R&D for NTDs, along with other medical, social and economic interventions, since effective treatments are predicted to have a positive impact on both the health status and the economic well-being of affected populations.^{8,9} Recently, the World Health Organization (WHO) Intergovernmental Working Group on Public Health, Innovation and Intellectual Property has emphasized the need for new R&D incentive mechanisms (e.g., prize funds that reward the development of innovative medical interventions), intellectual property strategies such as patent pools, and an increase in contributions to global R&D from all countries, proportional to their relative wealth.¹⁰ In this commentary we analyze how Canada has responded to the NTD R&D crisis within both governmental and academic institutions. On the basis of this analysis, we comment on the potential for Canada to mitigate the suffering of the world's poorest and most vulnerable people.

The role of the Canadian federal government

The Canadian Institutes for Health Research (CIHR) is Canada's largest federal funding agency for research in the health sciences. In 2002, CIHR identified Global Health Research as one of its 5 major strategic initiatives¹¹ and reaffirmed its commitment to helping Canada work toward the Millennium Development Goals,¹¹ one of which is to address neglected diseases. We conducted a search to identify the proportion of publicly awarded research funds directed toward the 13 most prevalent NTDs⁴ (see Table 1) and found that, from 1999 to 2009, Canadian researchers were awarded CIHR grants and fellowships in the amount of C\$29.8 million to study NTDs, out of a total of C\$6.36 billion (Fig. 1). The greatest proportion of funding (C\$21 million, 70%) was allocated to leishmaniasis research (Fig. 2). Total research into NTDs represented 0.46% of the total CIHR research budget from 1999 to 2009, as compared with 3.99% for HIV, 0.22% for malaria and 0.56% for tuberculosis

research during the same period. When we consider the global disease burden as measured by the percentage of total DALYs attributed to these diseases,¹² the discrepancy in funding becomes even more clear (Fig. 3). It is possible, however, that the low proportion of NTD-related CIHR awards may reflect a lack of competitive NTD research proposals, as opposed to a bias against this type of research.

It is instructive to measure the Canadian government's involvement in solving the NTD R&D crisis against that of other countries. The first Global Funding of Innovation for Neglected Diseases Report (G-FINDER)⁶ examined national contributions to neglected disease

research (including HIV/AIDS, tuberculosis, malaria and NTDs). Canada ranked eighth in the world, contributing a total of US\$19 million in public funding for R&D in neglected diseases in 2007. These contributions were from CIHR, the Canadian International Development Agency, and the Public Health Agency of Canada, representing 0.001% of the national GDP (Table 2). Meanwhile, the US government contributed nearly three-quarters of global public spending with an investment of US\$1.25 billion in 2007, which corresponded to 0.009% of GDP: 9 times the Canadian equivalent. The European Union accounted for US\$384.9 million (0.003% GDP), primarily from the United Kingdom, the Netherlands, the Re-

public of Ireland, and Sweden. At a G8 meeting in 2008, government officials from the United Kingdom announced that they would contribute GB£50 million over 5 years toward the control and elimination of NTDs, and the US government pledged US\$350 million over a 5-year period toward global NTD control efforts.¹³ Unfortunately, Canada has made no such commitment to NTD research.

The Canadian government's investment in research for neglected diseases generally, and NTDs specifically, leaves plenty of room for improvement. For example, the CIHR could make a specific call for NTD research, offer NTD-specific funding, and target researchers in NTDs and other biomedical fields to raise awareness. Recent initiatives, such as the co-funding of an NTD Research Chair,¹⁴ should be continued and broadened. Canada could also contribute indirectly through external NTD R&D initiatives, such as the not-for-profit Drugs for Neglected Diseases initiative (www.dndi.org). Additionally, to further support NTD research, we recommend that federal research funding agencies formally report all basic science and drug R&D spending on NTDs.

We welcome the recent launch of Grand Challenges Canada (GCC) (<http://www.grandchallenges.ca/>), which has a mission to identify five health-related global grand challenges and to fund Canadian and international researchers to

Table 1: List of terms used to search the CIHR online "funding decisions" database for neglected tropical disease research from 1999 to 2009

Neglected tropical disease	Search terms*	Total funding
Leishmaniasis	leishmaniasis†	8 329 697
	leishmania	20 604 805
Human African typanosomiasis	human African typanosomiasis	149 081
Chagas disease	Chagas disease	1 685 721
Trachoma	trachoma	3 511 227
Leprosy	leprosy	1 952 349
	<i>Mycobacterium leprae</i>	–
Buruli ulcer	Buruli ulcer	–
Hookworm	hookworm	344 300
	intestinal worms	–
Ascariasis	ascariasis	–
Trichuriasis	trichuriasis	–
Lymphatic filariasis	lymphatic filariasis	275 940
Onchocerciasis	onchocerciasis	75 530
Guinea worm	guinea worm	–
	dracunculiasis	–
Schistosomiasis	schistosoma	–
	schistosomes	–
	schistosomiasis	487 579
	swimmer's itch	–
	bilharzia	–
	trematodes	–
Total		29 086 532

Database website: http://webapps.cihr-irsc.gc.ca/cfdd/db_search?p_language=E

* Search terms were for the 13 most prevalent neglected tropical diseases.⁴

† All projects found using the search term "leishmaniasis" were also found using the term "leishmania."

Table 2: Spending on neglected disease research in relation to GDP, 2007

Country/region	Total GDP, US\$ billion (2007 estimates)	Spending on neglected disease research, US\$ billion (2007)*	% of GDP spent on neglected disease research
United States	13 840	1.251	0.009
Canada	1 432	0.019	0.001
European Union	14 960	0.385	0.003

*As reported in Moran et al 2009⁶

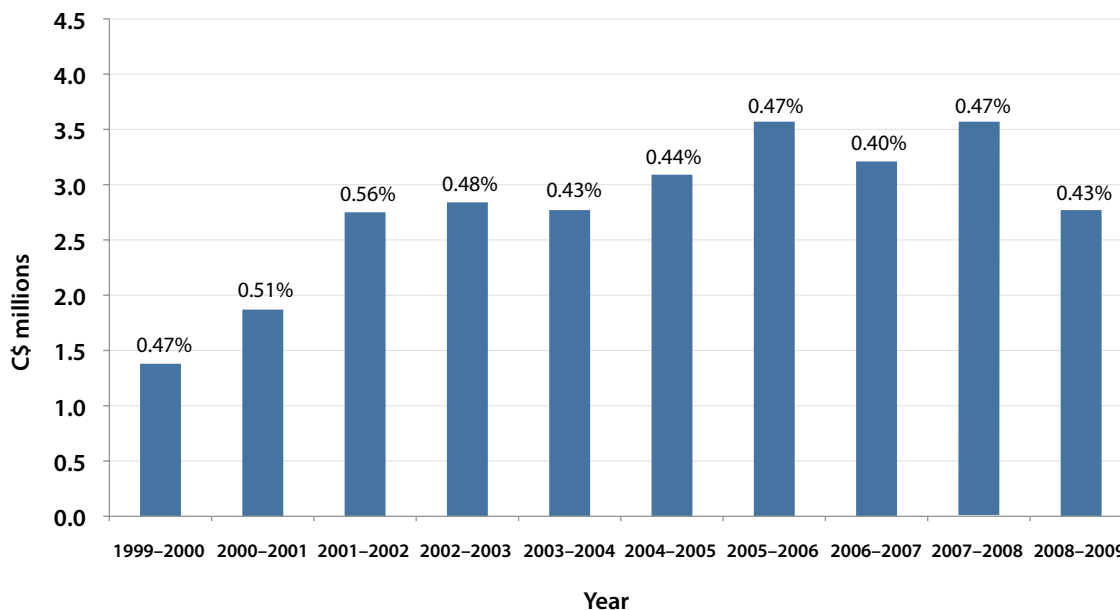


Figure 1: CIHR funding for research on neglected tropical diseases (NTDs), 1999-2009. Figures above columns show the percentage of total funding for a given year that was awarded for NTD research. The total funding for the 10-year period was C\$6.36 billion, of which 0.46% was awarded for NTD research.

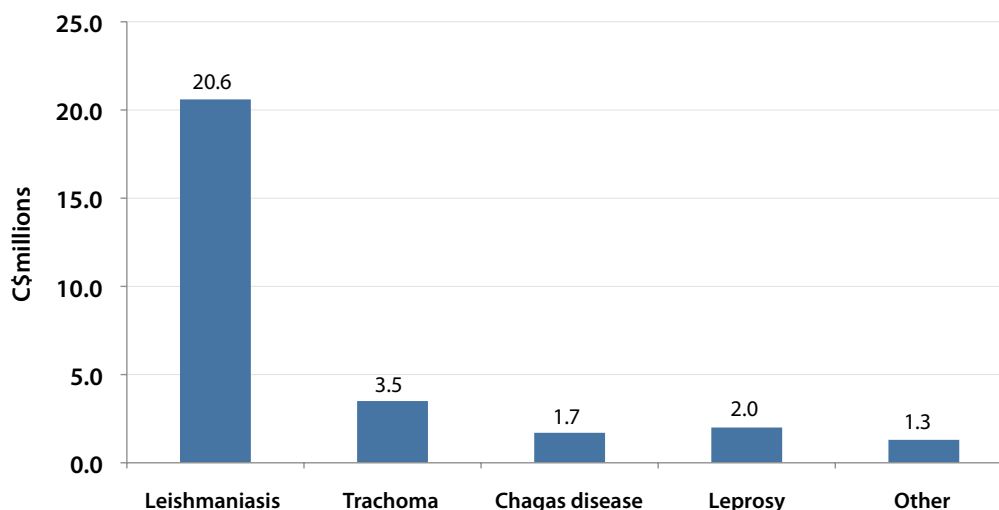


Figure 2: CIHR funding for research on neglected tropical diseases (NTDs), 1999-2009, by specific disease. The “other” category includes human African trypanosomiasis, lymphatic filariasis, schistosomiasis and hookworm.

address these challenges and to support implementation and commercialization of emergent solutions. C\$225 million over 5 years has been allocated to GCC through the Development Innovation Fund announced in 2008 by the Canadian government. While not targeted specifically at NTDs, this fund represents a great opportunity for NTD R&D. The first grand challenge announced by the GCC is related to the creation, development and implementation of new point-of-care diagnostics (<http://www.grandchallenges.ca/html/programs/programs.shtml>).

Beyond CIHR’s support of NTD research, the Canadian government has an opportunity to become a leader in health diplomacy on the global stage. Canada could begin by encouraging the formation of patent pools, or by setting up an international or Canadian prize fund for NTD drug development.¹⁵ Canada could also foster an increase in NTD drug R&D in biotech and biopharmaceutical industries by means of tax incentives, regulatory exclusivity (similar to orphan drug development in the United States¹⁶), and review vouchers

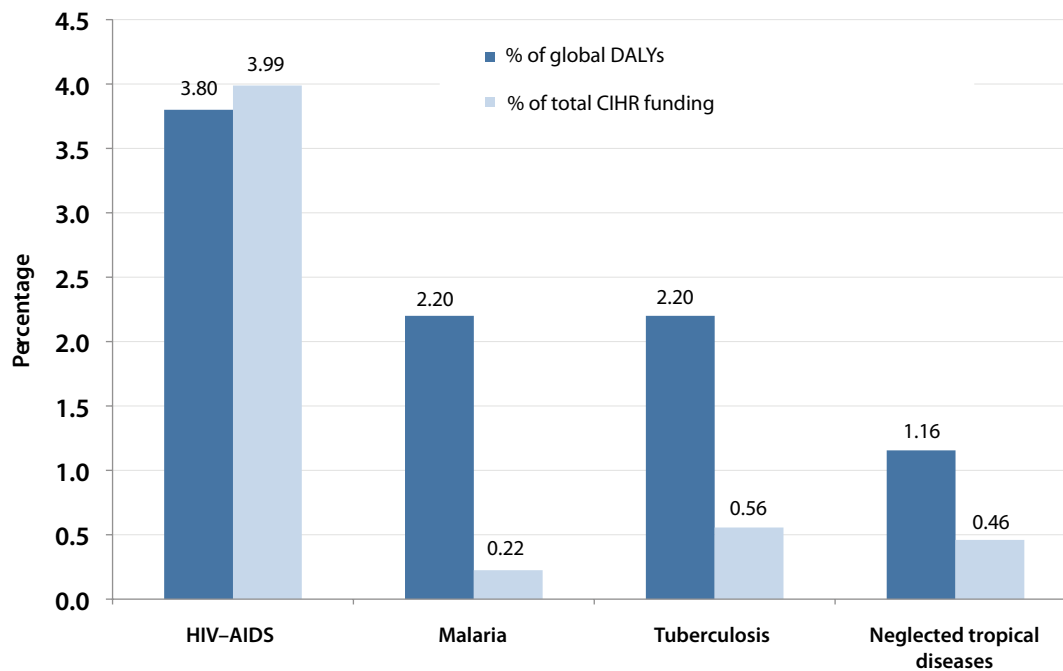


Figure 3: CIHR funding for research on NTDs in comparison with proportion of global burden of disease, 1999-2009. The light blue columns represent the percentage of total CIHR spending on NTD research; the dark blue columns represent the percentage of total global DALYs accounted for by those same diseases (based on WHO data for 2004).¹² Note that percentages shown for NTD DALYs are likely to be an underestimate.^{4,5}

(comparable to the US FDA vouchers for NTD-targeted drugs¹⁷).

The role of universities

Collectively, Canadian universities account for 36% of research conducted in Canada, worth an estimated C\$10.4 billion annually.¹⁸ The vision statements of these public institutions include performing research for the benefit of the public good, both locally and globally.^{19,20} Given their mandate to serve the public good, and the relative lack of attention to NTDs by commercial enterprise, universities are well positioned to assume an important role in fostering biomedical research and drug discovery for these diseases.²¹

Universities can also help to effect change by raising awareness and supporting education about NTDs and their contribution to global health inequities. They can encourage new graduates to pursue NTD research through postgraduate scholarships and postdoctoral fellowships. They can also form initiatives that foster the growth of an NTD scientific community. In line with this, universities can coordinate efforts by stakeholders in NTD R&D by hosting conferences and workshops. To address funding challenges directly, money could be directed from endowment funds toward NTD drug research, or new endowments could be established for this purpose. In addition, universities can help to ensure

equitable access to emerging treatments and technologies by strategically patenting and licensing therapeutic and preventive innovations in the field of NTDs. In 2007 the University of British Columbia (UBC) used global access principles (www.uilo.ubc.ca/about/initiatives/global.html) when licensing a new oral formulation of amphotericin B (non-oral formulations are associated with high levels of infusion-related toxicity) that has the potential to treat both fungal infections in HIV patients (which represents a large developed world market for the formulation) and patients with leishmaniasis (occurring mostly in developing countries). The presence of a developed world market for the formulation garnered interest from the Vancouver-based biotechnology company iCo Therapeutics to develop the product for use in developed countries. In an attempt to improve global access, UBC included terms in the exclusive license with iCo Therapeutics to ensure at-cost prices for the formulation in the developing world.²²

Within each of these efforts, Canadian universities should partner with universities in countries where NTDs are endemic, through North-South initiatives for curriculum development, research collaborations, the creation of online communities, or direct financial aid for travel to conferences or research programs. It is encouraging that university-based research institutes are beginning to place greater emphasis on NTDs. For

example, at McGill University, the Institute of Parasitology is conducting research on at least 4 NTDs.²³ UBC launched a Neglected Global Diseases Initiative in January 2010, which as a research-based institution aims to bring together multiple disciplines including bench science, biotechnology, pharmaceutical and health research, business, social policy, and law to investigate successful pathways of neglected disease drug development and delivery (www.ngdi-ubc.com). In addition, a development of great interest at UBC is the Centre for Drug Research and Development (www.cdrd.ca), which represents a new model for preclinical drug research and could theoretically be harnessed in the future for NTD research purposes.

Conclusion

Efforts to address the NTD R&D crisis within Canada are occurring at the governmental as well as institutional level, yet are insufficient relative to the global burden of these infectious diseases. Although many challenges are associated with fostering NTD drug R&D in high-income countries, potential solutions do exist (Textbox 1).

Textbox 1: Summary of recommendations

Government

- Increase total funding to CIHR and/or prioritize NTD funding
- Formally report all basic science and drug R&D spending on NTDs
- Foster regulatory incentives for NTD drug R&D
- Establish a prize fund for NTD drug R&D
- Support the establishment of public-private partnerships for NTD drug R&D
- Encourage formation of patent pools for NTD drug R&D

Universities

- Include NTD content in relevant undergraduate and graduate curricula in diverse fields
- Create scholarships for postgraduate and post-doctoral positions in NTD research
- Create NTD research communities and initiatives
- Collaborate with developing world partners
- Provide funds for NTD biomedical research and drug discovery research through university endowment funds
- Strategically patent and license NTD technologies to ensure access for developing countries

In addition, these proposed solutions could be extended to other areas of neglected disease research in general, such as malaria, HIV/AIDS, tuberculosis, diarrhoeal illness, nutritional health, maternal health, and treatment of chronic diseases in resource-poor settings. By uniting the efforts of government, universities, industry and non-governmental organizations, Canada can act as a world leader in solving the NTD R&D crisis. Over one billion people in the world deserve a better life free from NTDs. As a country with the resources to respond, Canada has the responsibility to increase its attention

toward the heavy burden of NTDs. Whether we will find the political will to do so remains to be seen.

Contributors: Patrica Gabriel conceptualized the initial study design. Subsequently all of the authors contributed to the concept and study design. All authors carried out some preliminary data extraction. Rebecca Goulding carried out the final data extraction for the study, did the large majority of the analysis and with the help of Patricia Gabriel interpreted the results. Patricia Gabriel also carried out some data analysis. All of the authors contributed to writing the first draft of the manuscript. All of the authors critically reviewed the manuscript and approved the final version submitted for publication. Rebecca Goulding is the corresponding author and guarantor for the research.

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