

RRR for NNN—a rapid research response for the Neglected Tropical Disease NGDO Network: a novel framework to challenges faced by the global programs targeting neglected tropical diseases

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While global programs targeting the control or elimination of five of the neglected tropical diseases (NTDs)—lymphatic filariasis, onchocerciasis, soil-transmitted helminthiasis, schistosomiasis and trachoma—are well underway, they still face many operational challenges. Because of the urgency of 2020 program targets, the Bill & Melinda Gates Foundation and the U.S. Agency for International Development devised a novel rapid research response (RRR) framework to engage national programs, researchers, implementers and WHO in a Coalition for Operational Research on NTDs. After 2 years, this effort has succeeded as an important basis for the research response to programmatic challenges facing NTD programs.

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Global support for the control and elimination of neglected tropical diseases (NTDs) increased dramatically after international partners made expanded resource commitments following the 2012 London Declaration.¹ This declaration pledged to control or eliminate 10 NTDs by 2020—a goal that was established in support of the earlier WHO *Roadmap for NTDs*,² itself a plan detailing specific goals for each of the targeted diseases.

For five of those NTDs—lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminthiasis and trachoma—preventive chemotherapy (PC) is the tool of choice for disease control or elimination, and the principal strategy for delivering the PC is mass drug administration (MDA).³ Whole populations or whole segments of populations identified as living in areas endemic for one or more NTDs are offered the appropriate NTD medications (usually given once-yearly) without having the need for specific diagnoses made for each individual.

This MDA approach has the advantage of treating not only those with easily recognized infections but also those whose infections may be ‘sub-clinical’ yet still transmissible and able later to develop into overt disease. Such an MDA strategy is feasible and particularly appropriate when the disease is widespread and when the medicines used have few or no side effects, bring health benefits to most of those receiving them and are available at little or no cost to the populations in need, as is the case for the drugs used in the five PC-NTD MDA programs: i.e., albendazole (donated by GlaxoSmithKline for lymphatic filariasis and soil transmitted helminthiasis); azithromycin (donated as Zithromax

by Pfizer for trachoma); diethylcarbamazine (donated by Eisai for lymphatic filariasis); ivermectin (donated as Mectizan by Merck & Co, Inc. for onchocerciasis and lymphatic filariasis), mebendazole (donated by Johnson & Johnson for soil transmitted helminthiasis) and praziquantel (donated by Merck Serono for schistosomiasis).

The scope of the current global programs to eliminate these NTDs is unprecedented, targeting more than a billion people for MDA in more than 100 countries worldwide.⁴ Because of the enormous scope, complexity and relative newness of MDA as a public health strategy, the international community is still learning how to implement current WHO guidelines most effectively and how to adapt approaches using new tools and science to reach elimination targets. As a result, NTD programs are faced with a daunting and evolving array of challenging questions that must be resolved for program success. For example, How do we establish baselines for disease prevalence (‘mapping’) across all regions? How do we know which persons to sample and test in a population for best prevalence estimates? Which tools should be used to evaluate impact? How do we ensure that medicines reach the entire populations at-risk? How do we verify when a disease is gone and MDA can be stopped? How do we ensure that program successes are sustained? How do we achieve multi-disease outcomes through integrated service delivery platforms?

For many of these and similar questions few answers are available in large part because until recently the NTDs were, as their name would imply, ‘neglected’ and with limited research to guide program implementation.⁵ However, because the ‘scaling-up’

of these massive programs is already well underway, and because the targeted end-dates are close, traditional investigator-initiated approaches to research may not be sufficient to meet the challenges of these NTD programs in real time. Rather, a new research-support mechanism is required—one that is tailored to target programmatic problems as they arise, is rapidly responsive, has flexibility in its agenda and processes, engages and coordinates many different programs and investigators around the world, and whose successes are defined by programmatic solutions and improved WHO guidelines rather than by academic metrics.

Fortunately, the Bill & Melinda Gates Foundation (BMGF), the U.S. Agency for International Development (USAID) and the U.K. Department for International Development—all working with WHO—in recognition of this challenge have had the foresight to create a strategy to meet this need for a rapid research response (RRR) mechanism. In 2013, BMGF, in consultation and subsequent collaboration with USAID, laid the foundation for a Coalition for Operational Research on the NTDs (COR-NTD) managed by the Neglected Tropical Diseases Support Center (NTD-SC) at the Task Force for Global Health.⁶

The grant funds from these donors have facilitated collaborations between national NTD programs who (along with their NGDO implementing partners) generate the questions, and expert scientists who work with these programs towards solutions through a series of steps that:

- identify the most important and researchable needs for each of the disease-specific, global NTD programs;
- identify the gaps in available research support for the needed studies;
- initiate collaborative operational research studies (usually at multiple locations) whose outcomes are targeted to improve program effectiveness; and
- assemble, through close collaboration with WHO, the evidence-base for improved international WHO guidelines and recognized best practices.

In its first 2 years, this RRR framework has already helped support a diverse portfolio of nearly 100 operational research projects⁷ involving 88 partners and 37 ministries of health. In addition to these individual operational research studies, this mechanism

has been particularly effective in supporting a major initiative with WHO's Africa Regional Office (AFRO) for rapid completion of the mapping of PC-NTDs. Piloting some of the newest diagnostic tools, the AFRO Mapping Initiative will have filled the remaining gaps in defining PC-NTD endemicity in the region by 2016, while at the same time testing these tools for further application to other program needs.

Essential to the success of COR-NTD is communication both with and within the broader NTD community. Through an annual meeting, COR-NTD convenes international researchers, program implementers, donors and WHO with the goal of engaging this broad community to address knowledge gaps in a coordinated (not competitive) way and to find the solutions needed to overcome the obstacles facing global NTD programs.

Not only does the COR-NTD help set the agenda for research projects and facilitate communication across partners, but, through its secretariat, it has established the Operational Research Inventory,⁸ an online database that allows all researchers to input their own operational research projects and, thereby, create a high-level dashboard of the research being conducted around the world on NTDs. The inventory also allows countries to share their programs' top research priorities. By providing a picture of what is being done and where, the developing inventory signals to both donors and other researchers where the gaps in program success might lie and what kind of projects might require a RRR to help country programs and their NGDO partners fill them.

The practical value of this novel RRR mechanism for facilitating global NTD programs can be seen clearly both from the number and the range of operational research projects supported during its first 2 years and the number of global guidelines and agreed best-practices already modified as a result (Box 1). Indeed, thanks to the RRR framework that takes advantage of the insight and direct engagement of a broad range of partners to develop strategies that address program needs, donors are able to continually re-shape their support as part of the effort to push the targeted diseases ever closer to elimination.

As programs progress, their needs change and research must evolve rapidly along with them. This coordinated RRR effort is meant to be accessible to all,^{7,8} to speed progress towards the goals laid out in the London Declaration, and to provide both efficiency and innovation in undertaking the challenges of 'the last mile' in the NTD programs' race to meet 2020 targets.

Box 1. Working with partners to translate rapid research responses (RRR) into practice

RRR collaborative research targets	Successes: policy recommendations
Validation of filariasis test strip (FTS)	Endorsed by WHO Scientific and Technical Advisory Committee (STAG) in 2015
Lymphatic filariasis 'confirmation mapping' protocol developed and validated	Endorsed by WHO Monitoring & Evaluation (M&E) Working Group in 2015
Coverage survey designs simplified	WHO M&E Working Group endorsement anticipated in 2016
Validation of Circulating Cathodic Antigen (CCA) diagnostic for schistosomiasis and incorporation into Africa Regional Office (AFRO) mapping	Endorsed by WHO STAG in 2015
Introduction of Ov16 rapid diagnostic antibody test for use in African onchocerciasis programs	Endorsed by WHO Guidelines Review Group in 2015

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