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<th>Description</th>
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<tbody>
<tr>
<td>ADP</td>
<td>Access and Delivery Partnership</td>
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<tr>
<td>aDSM</td>
<td>Anti-TB drugs active drug safety monitoring</td>
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<tr>
<td>AFR</td>
<td>WHO Africa Region</td>
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<tr>
<td>AFRO</td>
<td>WHO Regional Office for Africa</td>
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<tr>
<td>AMR</td>
<td>Antimicrobials resistance</td>
</tr>
<tr>
<td>AMR</td>
<td>WHO Americas Region</td>
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<tr>
<td>AMRO</td>
<td>WHO Regional Office for the Americas</td>
</tr>
<tr>
<td>ASEAN NDI</td>
<td>ASEAN Network for Drugs, Diagnostics, Vaccines and Traditional Medicine Innovation</td>
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<tr>
<td>ASEAN</td>
<td>Association of Southeast Asian Nations</td>
</tr>
<tr>
<td>CARN-TB</td>
<td>Central African Regional Network for TB Control</td>
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<tr>
<td>CDTI</td>
<td>Community-directed treatment with ivermectin</td>
</tr>
<tr>
<td>CSIR</td>
<td>Council for Scientific and Industrial Research, Ghana</td>
</tr>
<tr>
<td>DFID</td>
<td>Department for International Development, United Kingdom</td>
</tr>
<tr>
<td>EDCTP</td>
<td>European and Developing Countries Clinical Trials Partnership</td>
</tr>
<tr>
<td>ESPEN</td>
<td>Expanded Special Project for Elimination of NTDs</td>
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<tr>
<td>EUR</td>
<td>WHO Europe Region</td>
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<tr>
<td>EWARS</td>
<td>Early Warning and Response System</td>
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<tr>
<td>GFTAM</td>
<td>Global Fund to Fight AIDS, Tuberculosis and Malaria</td>
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<tr>
<td>GTB</td>
<td>WHO Global TB Programme</td>
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<tr>
<td>IDDO</td>
<td>Infectious Diseases Data Observatory</td>
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<tr>
<td>IDRC</td>
<td>International Development Research Centre, Canada</td>
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<tr>
<td>IIR</td>
<td>Intervention and Implementation Research</td>
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<td>IIR</td>
<td>Intervention and Implementation Research Unit</td>
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<tr>
<td>IRS</td>
<td>Indoor residual spraying</td>
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<tr>
<td>JCB</td>
<td>TDR Joint Coordinating Board</td>
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<tr>
<td>LMIC</td>
<td>Low- and middle-income country</td>
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<tr>
<td>LSHTM</td>
<td>London School of Hygiene and Tropical Medicine</td>
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<tr>
<td>M&amp;E</td>
<td>Monitoring and evaluation</td>
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<tr>
<td>MDA</td>
<td>Mass drug administration</td>
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<tr>
<td>MDGH</td>
<td>Medicines Development for Global health</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<td>---------</td>
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<tr>
<td>MDR-TB</td>
<td>Multidrug resistant tuberculosis</td>
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<td>MoH</td>
<td>Ministry of Health</td>
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<tr>
<td>NMP</td>
<td>National malaria programme</td>
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<tr>
<td>NTD</td>
<td>Neglected tropical disease</td>
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<tr>
<td>NTP</td>
<td>National Tuberculosis Programme</td>
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<tr>
<td>OR/IR</td>
<td>Operational and implementation research</td>
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<tr>
<td>PAHO</td>
<td>Pan-American Health Organization</td>
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<tr>
<td>PCT</td>
<td>Preventive chemotherapy treatment</td>
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<tr>
<td>PI</td>
<td>Project investigator</td>
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<tr>
<td>RTC</td>
<td>Regional Training Centre</td>
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<td>SDG</td>
<td>Sustainable Development Goal</td>
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<tr>
<td>SEAR</td>
<td>WHO South-East Asia Region</td>
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<tr>
<td>SMC</td>
<td>Seasonal malaria chemoprevention</td>
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<tr>
<td>SORT IT</td>
<td>Structured Operational Research and Training Initiative</td>
</tr>
<tr>
<td>STH</td>
<td>Soil-transmitted helminth</td>
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<tr>
<td>SWG</td>
<td>Scientific Working Group</td>
</tr>
<tr>
<td>TDR</td>
<td>UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases</td>
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<tr>
<td>The Union</td>
<td>International Union Against Tuberculosis and Lung Disease</td>
</tr>
<tr>
<td>UHC</td>
<td>Universal health coverage</td>
</tr>
<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
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<tr>
<td>US-FDA</td>
<td>United States of America Food and Drug Administration</td>
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<tr>
<td>WAHO</td>
<td>West African Health Organization</td>
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<tr>
<td>WARN-TB</td>
<td>West African Regional Network for TB control</td>
</tr>
<tr>
<td>WHO/HQ</td>
<td>World Health Organization headquarters in Geneva, Switzerland</td>
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<tr>
<td>WPR</td>
<td>WHO Western Pacific Region</td>
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Introduction

Research to identify new interventions suitable for incorporation into guidelines and policies and research for more effective implementation of policy interventions is essential for health systems in low- and middle-income countries (LMICs) to deliver better health to the people. This research is consequently a key element of the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) strategy.

The Intervention and Implementation Research (IIR) unit addresses some of the critical obstacles to achieving the Sustainable Development Goals (SDGs) for health. To better respond to the needs for improved disease control, elimination and response to emerging threats – as set out in TDR’s 2018-2023 strategy – IIR will focus on research for the development of policies and guidelines and their effective implementation in public health programmes.

As further detailed in figure 1, the workplan provides supporting research to determine and evaluate:

- **WHAT** tools (medicinal products, diagnostics, interventions, approaches and strategies) that have been developed are suitable for introduction into guidelines and policies
- **HOW** guidelines and policies can be implemented (scaled up) in public health programmes to maximize their impact
- How to assess the **IMPACT** of their implementation
- The directional perspectives on **INNOVATION** that will inform R&D, addressing insufficient as well as yet unattended health needs.

Figure 1. IIR – From Tools to Impact
This report summarises the IIR workplan, achievements and future plans with respect to four main questions:

1. What new tools are critically needed to improve disease control and possibly achieve elimination? This covers how to provide a directional perspective to new developments so that they generate the health solutions that disease-endemic countries need; and how TDR, through its convening power and its special positioning and close links with both research and disease control, can promote innovation to generate more adapted health solutions. These requirements have been abundantly made clear through the recent succession of outbreaks.

2. How can the utility of current medicines be protected? Available effective interventions are few, and some diseases rely on a single drug for control, prevention and treatment. Antimicrobial resistance is now a general concern worldwide, at all levels of country development.

3. How can informed recommendations and policy decisions best be made on the use of available health interventions? The evidence base for a number of recommendations is weak due to a combination of insufficient research, insufficient standardization of research methodologies, and insufficient level of analysis of research results. Correcting these shortcomings is of paramount importance and is expected to translate into a more efficient use of resources and more informed directions for both research and disease control. TDR’s recognized convening power is applied to broker agreements across a range of stakeholders towards optimizing the use of available data for sharing and analysis.

4. How can proven interventions be effectively deployed and adapted to achieve disease control and elimination objectives, while building sustainable in-country capacity? A number of approaches are used, such as supporting defined programme objectives (e.g. the elimination of visceral leishmaniasis (VL), also known as kala-azar in the Indian subcontinent; subregional initiatives to achieve the objectives of WHO’s End TB Strategy; outbreak preparedness for dengue and other arboviruses); and creating in-country capacity for operational and implementation research.

Objectives

The IIR workplan has been reorganized into three main areas of activity:

1. **RESEARCH FOR POLICIES**: to understand and produce evidence on large-scale performance, acceptability, feasibility, implementation needs and potential impact of available tools as a basis for determining WHAT tools are suitable for guidelines and policies.

2. **RESEARCH FOR IMPLEMENTATION**: to understand and address barriers to effective, quality and equitable implementation of health interventions, strategies, guidelines and policies to provide the evidence as to HOW these can best be implemented for maximum IMPACT.

3. **RESEARCH FOR INNOVATION**: to provide directions for the development of improved and adapted new tools and strategies needed, and to promote their development and use.

The above-mentioned objectives are being implemented through seven expected results that have been developed in coordination with TDR’s Scientific Working Group (SWG) (see figure 2).
Key achievements in 2018

Moxidectin for treatment of onchocerciasis

- On 13 June 2018, the United States Food and Drug Administration (US-FDA) approved moxidectin for treatment of onchocerciasis in patients 12 years and older. The pivotal efficacy and safety had been acquired in TDR-managed and financed studies between 2006 and 2012 in Ghana, Liberia and the Democratic Republic of the Congo. The new drug application (NDA) to the US-FDA was prepared and submitted by the not-for-profit organization Medicines Development for Global Health (MDGH) to which WHO had licensed all data at its disposal after TDR’s pharmaceutical company partner had discontinued the collaboration. The registration in the United States is a critical milestone towards availability of moxidectin for onchocerciasis control and elimination programmes in Africa.

Preparedness for early identification and response to dengue outbreaks

- Significant progress has been made to support countries in building capacity for early detection and response to dengue outbreaks, including:
  - the publication of the updated version of the “Operational Guide: Early Warning and Response System (EWARS) for dengue outbreaks” and the translation into Spanish by PAHO (in progress);
  - further technical developments of the EWARS tool with a Dashboard 1 for the national level (Ministry of Health) and Dashboard 2 for the district level;
EWARS training included regional workshops for the South-East Asia and Western Pacific regions (eight countries) and country support in Latin America and Asia through teleconferences;
- confirmation in Colombia that EWARS is also useful for chikungunya outbreak prediction and most likely for Zika as well;
- ongoing work to automate the calibration of alarm signals to increase user-friendliness; and
- expansion of EWARS support to cover a wider spectrum of countries and collect information from users about their experience.

**Visceral leishmaniasis (VL) elimination in the Indian subcontinent**
- Implementation research studies provide evidence of efficacy of integrated case detection of VL and other febrile illnesses combined with vector control. It also provided evidence for the efficacy of innovative tools (e.g. wall painting, wall lining) and of combined tools (e.g. bed net impregnation plus insecticide residual spraying) as well as of vector susceptibility of commonly used insecticides in the context of vector and transmission control. TDR has been actively present on the international scene: i) an extensive analysis and account of TDR contributions towards countries in the Indian subcontinent reaching the kala-azar elimination target has been published; ii) five papers published in peer reviewed open-access journals; and iii) several stakeholder meetings mainly in India about current and future research activities to support the VL elimination initiative.

**Enhanced country research capacity to support WHO’s End TB strategy**
- The regional model launched in West Africa in 2015, through the West African Regional Network for TB control (WARN-TB), has successfully mobilized contributions by a range of partners (such as WHO’s Global Task Force on digital health for TB (WHO/GTB), the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFTAM), USAID, the West African Health Organization (WAHO) and the Damien Foundation) to enhance country research capacities in this region, which has translated to approximately US$ 8.6 million leveraged in 2018 for regional activities. Some implementation research project results already changed in-country policies. Results were also shared within the network and adopted by other national TB programmes (NTPs) in the region to be piloted in their country next year. Based on successful experience in West Africa, the Central Africa Regional Network for TB Control (CARN-TB) was established. It will replicate and build on the WARN-TB model for a step-wise approach to strengthen TB control through country-led research.

**Safety first**
- TDR brings safety to the fore as an essential element of evidence-based decision-making. There is growing awareness and buy-in by countries of the two initiatives launched in 2016 to share safety data on drug exposures during pregnancy, in collaboration with WHO/HIV, and on novel treatments for multidrug-resistant tuberculosis (MDR-TB), in collaboration with WHO’s Global TB Programme. New data sharing agreements were signed this year and the first analysis of the two main databases took place. The databases will generate evidence of drug safety in routine use that is needed to support treatment guidelines.
Increased operational research (OR) capacity in LMICS orienting towards the SDGs, universal health coverage (UHC) and gender equity

- The well-established Structured Operational Research and Training Initiative (SORT IT) programme coordinated by TDR and implemented with partners was scaled up to 90 project countries with alumni being the leaders of 11 of 12 courses offered in 2018. Following advice from the SWG, franchising and reorientation are still in progress. Franchising is being fostered through the development of the following: new tools including standard operating procedures to facilitate independent organization of SORT IT courses, on-line resources (rosters, video lectures, real-time updates of the TDR website); databases and frameworks for ensuring quality and accountability; increased collaboration (with academic institutions, NGOs and WHO departments); and promoting country-level funding (Global Fund in Pakistan, Accelerating Progress Toward HIV/AIDS Epidemic Control (PEPFAR) in Ukraine and the MoHs in Kenya and China). In Pakistan, Kenya and Colombia, SORT IT alumni secured independent funds including from the Global Fund. These may serve as examples for expansion to other countries. SORT IT is also progressively re-orienting towards the SDGs by embracing thematic areas (disease-specific and health systems) such as key populations, neglected tropical diseases (NTDs), migrants and refugees, water and sanitation, adolescent male circumcision, and the effects of Ebola on health systems recovery. In 2018, an “e-SORT IT” and more complex study designs, including mixed methods and qualitative research, were completed. Importantly, a three-year grant of almost US$ 10 million was secured to build sustainable operational research capacity that will generate and use evidence on the emergence, spread and health impact within the Americas region to limit this serious health problem. High outputs were maintained. By October 2018, 534 papers were submitted, 432 (81 per cent) published in 42 journals (impact factor 0.4–19), in five languages with 68 per cent reporting an effect on policy and practice. In 2018, individuals from LMICs constituted 98 per cent of first authors, 48 per cent of publications had a woman as first author and 81 per cent of last authors were from LMICs.

Summary progress description

TDR project support often spans several years, and in some cases, covers different diseases. Table 1 provides an overview of this work, followed by a narrative. SORT IT activities that were in the previous biennium under ER 1.2.4 are now incorporated under ER 1.1.7 Maximized utilization of data for public health decision-making. The finalization of the work done in the last biennium under ER 1.2.3 “Research in support of control programmes: Improved management of febrile illnesses” has now been included under ER 1.1.4.
Table 1. IIR workplan overall progress

<table>
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<tr>
<th>Ongoing expected results by outcome</th>
<th>Indicators and progress against targets</th>
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<td><strong>Research for policy</strong></td>
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</table>
| **1.1.4. Country resilience to the threat of drug-resistant infections**: i) Operational and implementation research (OR/IR) strategies for countries to build effective systems for monitoring and responding to emerging drug resistance of all relevant infectious agents; ii) evaluation of practical approaches to improve targeted treatment and reduce drug misuse and risk of resistance; iii) strategies for monitoring and responding to potential emergence of drug resistance in helminths; and iv) strategies for monitoring potential emergence of resistance during seasonal malaria chemoprevention (SMC). | By 2019: i) initial set of approaches to support countries selected for piloting; ii) strategy related to helminths proposed to WHO/NTD Department/ESPEN for discussion with stakeholders; iii) potential strategy for monitoring potential malaria resistance during SMC evaluated.  
- On track |
| **1.1.1. Country preparedness for disease outbreaks**: i) Training and “train the trainers” curricula; ii) consensus agreement of major stakeholders on critical elements of policies and guidelines for arbovirus surveillance; and iii) consensus agreement of major stakeholders on critical elements of policy and guidelines for arbovirus outbreak response. | By 2018: Training curricula was made available on TDR website and shared with TDR Regional Training Centres and other interested stakeholders.  
- Completed, curricula available online and have been shared with interested stakeholders, as well as TDR Regional Training Centres (RTCs)  
By 2019: i) critical elements for policy and guidelines for arbovirus surveillance; ii) and response; and iii) identified for further development.  
- On track |
| **Research for implementation**     |                                        |
| **1.1.7. Maximized utilization of data for public health decision-making**: i) capacity built for effective collection and analysis of data; ii) effective policies and outputs in countries to stimulate use of data; iii) support for interoperable data platforms; and iv) evidence-informed policy. | By 2018: i) training curriculum for data managers developed; and ii) at least four self-sustained SORT IT programmes established at country and subregional levels.  
- On track: Eleven planned training modules were developed. One additional module focusing on the use of new applications for data collection is at a drafting stage  
- Completed  
By 2019, (iii) support provided to at least three platforms.  
- On track |
<table>
<thead>
<tr>
<th>Ongoing expected results by outcome</th>
<th>Indicators and progress against targets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.1.8. Maximized utilization of safety information for public health decision-making:</strong> i) capacity for safety monitoring of new drugs built in target countries; ii) improved evidence of drug safety in vulnerable patient groups; and iii) piloting of innovative approaches for safety monitoring that facilitate and improve normative guidance.</td>
<td>By 2018: i) first part of the Access and Delivery Partnership (ADP) completed; ii) at least two databases related to drug exposure obtained and analysed, in collaboration with control programmes and other WHO Departments; and iii) utility of one innovative approach for monitoring safety in mass drug administration (MDA) assessed.</td>
</tr>
<tr>
<td></td>
<td>- Completed. The first phase of ADP was completed by March 2018</td>
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<td></td>
<td>- Completed: aDSM database analysed mid 2018; pregnancy exposure central registry analysed mid-December 2018</td>
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<td>- Completed: Use of mobile phones for safety monitoring evaluated and found to improve reporting rate in Ghana and Tanzania</td>
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<td><strong>1.2.1. Strategies to achieve and sustain disease elimination:</strong> i) evidence on sustainable strategies for the elimination of VL in the Indian subcontinent; ii) improved basis for monitoring progress of preventive chemotherapy-based elimination programmes towards elimination and for decisions to stop interventions; and iii) approaches to facilitate malaria elimination in target countries.</td>
<td>By 2019: i) sustainable strategies for maintaining VL elimination in the Indian subcontinent proposed to countries; and ii) proposed improved basis discussed with stakeholders</td>
</tr>
<tr>
<td></td>
<td>- On track</td>
</tr>
<tr>
<td><strong>1.2.6. Optimized approaches for effective delivery and impact assessment of public health interventions:</strong> i) strengthened regional network of WARN-TB capable of identifying research priorities, and designing and conducting OR/IR to generate the evidence base for policy decisions to achieve the goals of the End TB strategy; ii) expanded WARN-TB approach to other geographical areas and/or other diseases; and iii) approaches to optimized delivery of preventive chemotherapy-based helminth control strategies evaluated.</td>
<td>By 2019: i) report on the strengthened regional network WARN-TB provided to SWG and stakeholders at country, regional and global level; and ii) feasibility of expanding approach to other areas (e.g. Central Africa assessed.</td>
</tr>
<tr>
<td></td>
<td>- Completed. CARN-TB was established in March 2018 with planned activities similar to the one conducted with the WARN-TB.</td>
</tr>
<tr>
<td>Research for innovation</td>
<td></td>
</tr>
<tr>
<td><strong>1.1.5. Directions for development and accelerated access to new tools and strategies:</strong> i) evidence and advice to provide directional perspective for R&amp;D for new tools as well as new ways of implementing tools; ii) optimized methodologies to assess response to case- and population-based interventions; and iii) strategy development, implementation and monitoring.</td>
<td>By 2019: i) involvement in at least two initiatives; and ii) optimized methodologies to measure effects of interventions for at least two diseases developed.</td>
</tr>
<tr>
<td></td>
<td>- On track, Involved in three initiatives</td>
</tr>
<tr>
<td></td>
<td>- On track, for VL, CL, schistosomiasis</td>
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</tbody>
</table>
Progress description and plans for 2019–2021

- Research for policies

This area of work aims to understand and produce evidence on large-scale performance, acceptability, feasibility, implementation needs and potential impact of available tools as a basis for determining WHAT tools are suitable for guidelines and policies.

There are two expected results for this area of work, which are both continuing or evolving work from the last biennium.

ER 1.1.1: Country preparedness for disease outbreaks

_TDR is working with country control programmes and researchers to identify signals that can alert country control programmes to an impending dengue outbreak. This has led to a model contingency plan and an Early Warning and Response System (EWARS) for arbovirus outbreaks. Countries can test and potentially customize this to apply to other arboviral diseases like Zika, chikungunya, yellow fever and others._

Dengue and other _Aedes_-borne arboviruses like Zika and chikungunya can cause outbreaks which generate enormous health, social and economic burden across all continents, and are not restricted to tropical areas. Country response usually starts late and is of limited efficacy, as documented by earlier reports of this project.

TDR coordinates research across a number of dengue-endemic countries in Latin America, Asia and now Africa on how to improve dengue surveillance, outbreak preparedness, detection and response. This has already led to an evidence-based model contingency plan adaptable to country needs, providing countries with practical solutions to respond to dengue outbreaks and to the EWARS. TDR has worked closely with the WHO/NTD Department, the Infectious Hazard Management (IHM) team and other major stakeholders, such as national control programmes of dengue-endemic countries in Asia and Latin America, WHO regional offices, research institutions and international organizations (International Red Cross and Red Crescent Movement, and others) in order to translate research findings into policy and practice. The project, originally centred on dengue, has evolved to cover arboviruses more broadly, like Zika and chikungunya, that are transmitted by the same mosquito species, _Aedes_.

Progress in 2018

TDR-supported research has produced research outputs that can contribute to policy and practice. Based on the analysis of the retrospective study on alarm signals for dengue outbreaks in five countries (Brazil, Dominican Republic, Malaysia, Mexico and Viet Nam). The recommendations from EWARS users in the prospective study led to the development of a user-friendly tool and reliable software, a workbook for users which has been field tested in 30 health districts in Brazil, Malaysia and Mexico. The recommendations were also incorporated into the second-generation EWARS-R, using the free “R-software”. New calculations with the updated tool, as well as recent surveillance data and signal combinations, resulted in higher sensitivities and positive predictive values of alarm signals compared to the first generation EWARS (Hussain-Alkhaateb et al., 2018).

The open access “R-software” has been transferred to a Dashboard 1 and Dashboard 2 with the help of Umeå University, Sweden and the Microsoft team in Zurich and the user-friendliness of the EWARS system has been improved. Password-protected Dashboard 1 is designed for the centralized national level in each country (usually the MoH) and allows the calibration of different alarm indicators in order to identify those with the highest sensitivity and positive predictive values (PPVs).
Dashboard 2 is designed for the decentralized, district level where threshold levels and alarm indicators are fixed and the district officer needs only to input weekly data on cases and alarm indicators (climatic, entomological and serological information) in order to view the level of outbreak warning (none, initial, early, late alarm). Dashboard 1 also allows access to all district-level Dashboards 2 for monitoring and evaluation purposes. The adoption by countries is facilitated by the web publication of the updated version of the training handbook. The first presentation of the updated EWARS tool was given at a bi-regional training workshop in Sri Lanka for the South-East Asia and Western Pacific regions with the participation of eight countries, with representatives from WHO/HQ, SEARO and WHO Representatives from India and Sri Lanka. The follow-up is being done by teleconference and later on by country visits. The EWARS tool was then successfully tested for predicting chikungunya outbreaks in Colombia.

In addition to the development of EWARS, work has been done on improved response activities, mainly vector management. TDR-supported research has shown the prolonged protective efficacy of house screening against dengue vectors (Che-Mendoza et al., 2018) and a further step was initiated with the design of a large-cluster randomized trial to test the protective efficacy, cost and feasibility of insecticidal paint for *Aedes* control (in progress).

The process was accompanied by close consultations with national control programmes, WHO/NTD and regional offices, academics and international experts and was reinforced at an expert meeting in November 2018 at which the progress, further software development timelines and dissemination activities were discussed. Dissemination will be facilitated by:

1. a publication which summarizes the process of dengue-related TDR-supported research and translational activities from research to policy and practice (Olliaro et al., 2018);
2. a publication on development and implementation of the EWARS tool (Hussain et al., 2018); and
3. dissemination of success stories, such as the Mexico example, where EWARS was integrated into the national surveillance platform.

New partners have shown interest in a close collaboration with TDR in relation to EWARS, particularly UNICEF, the Inter-American Development Bank and academia. The WHO/NTD Department invited TDR to collaborate on the second edition of the Global Dengue Guidelines, in particular the chapters on surveillance and outbreak detection and response.

In addition, IIR worked with TDR/VES to provide country support for arboviral disease outbreak preparedness in the Africa region. Further to an original request by Burkina Faso, TDR organized a regional meeting in West Africa to map the issues, knowledge and capacity gaps for vector control, surveillance and outbreak response. A plan was also developed for building regional capacity through OR/IR to generate evidence-based interventions. This activity was strengthened by WHO/NTD and by including African representatives in the annual evaluation and planning meetings.

**Results dissemination and uptake**

Mexico has integrated the EWARS tool into its national surveillance system and made the dashboards available to endemic municipalities. Brazil is starting to do the same in some states as a model for others. Other countries are implementing the tool but have yet to learn how to get weekly access to climate data (which are important outbreak predictors).
Remaining challenges

- Further refining of the EWARS tool is needed. The growing datasets are being re-analysed in order to stabilize correlations between alarm and outbreak indicators. New analyses are being undertaken on additional indicators.
- Testing an arbovirus alert tool that will include both qualitative and quantitative risk indicators for dengue, Zika and chikungunya outbreaks is planned.
- The new version of the EWARS tool needs to be disseminated through further regional training courses, country support and supervision. Close collaboration with WHO regional offices is required. Furthermore, scientific publications, communication, and information included in WHO dengue guidelines and policy briefs needs increased uptake at regional and country levels.
- Further verification of applicability of identified approaches is needed in a broader range of countries.
- Developing the EWARS response element is needed, including a testing framework, to increase the efficiency of outbreak response (improved surge capacity), and strengthen country capacity to conduct clinical and operational research during outbreaks.

Plans for 2019–2021

EWARS:
- Develop the EWARS tool further by automatization of the calibration process which is currently done “by hand” in order to provide maximum sensitivity and PPV for outbreak prediction;
- Build in-country capacity and disseminate the second generation of the EWARS tool through regional training workshops and country visits in the South-East Asia and Western Pacific regions. This will include ongoing activities in the Americas, in collaboration with AMRO; and
- Update, validate and adapt the signals used in a number of dengue-endemic countries.

Country support for arboviral disease surveillance and vector control in the WHO African region.

Potential new activities:
- After successfully testing a more comprehensive alert and response tool (EWARS plus) for chikungunya outbreaks, this will now also be done for Zika and potentially other diseases like influenza, malaria and cholera (to be developed and discussed with other WHO units and then with partner countries). The development of risk maps adaptable to country needs is intended. These will be incorporated into the EWARS dashboards
- Discussions will be held with other WHO units and partner countries about the potential for application to other diseases like influenza, malaria and cholera
- New partners for the dissemination of the EWARS tool, such as UNICEF, and Banco Interamericano de Desarrollo (BID), have been contacted and informed but further negotiations are needed to come to a formal collaboration.
Partnerships and collaborations

The programme facilitated a strong partnership with WHO Regions (AMRO, WPRO, SEARO) and with ministries of health (Brazil, Colombia, Dominican Republic, Malaysia, Mexico, and Sri Lanka). Close academic partners contributing to the further development of EWARS are: University of Gothenburg (Global Public Health) and Umeå University (Centre for Global Health Research), Sweden, and Freiburg University (Centre for Medicine and Society: Global Health), Germany. The project also collaborated with the WHO Emergency Department/Zika team to build country capacity to respond to arbovirus epidemics.

Leverage created by this project

This project is funded through a combination of TDR core funds (about 60 per cent) and considerable co-financing (about 40 per cent corresponding to US$ 56 000 of workshops and visits to study districts by ministries of health in the participating countries. Umeå University and Banco Interamericano de Desarrollo (BID) funds also contributed to the financing of workshops, technical meetings for the development of EWARS and dissemination activities in various countries.

Gender aspects and vulnerable populations

Amongst the public health institutions currently collaborating with IIR, those in Nigeria, Thailand, Singapore, Peru, Ecuador, and Brazil have female representatives. When calculating gender specific incidence rates, we found that females are over-represented for Zika and chikungunya but not for dengue. The biological and social factors will be analysed in more detail.

Training

- D. Benitez (PhD completed in August 2018)
- J. Quintero (PhD), Tatiana Garcia-Betancourt (MSc completed in February 2018)

Strengthened institutions or networks

In all partner countries, the institutions involved in the development and application of the EWARS tool and the internal cooperation among surveillance and response units have improved their awareness of the need for a robust surveillance system (see Hussain-Alkhateeb et al., 2018). Likewise, the teleconferencing network in the Americas, the South-East Asia and Western Pacific regions has strengthened the bond between countries.

Publications


Related news

ER 1.1.4: Country resilience to the threat of drug-resistant infections

Tropical disease control and elimination programmes based on preventive chemotherapy, as well as health care for individual patients, are vulnerable to the emergence of resistance to the drugs used, especially when only a single drug or drug combination is available. For the programmes to have the data needed to plan for and implement appropriate strategies in response to emerging resistance, further research is needed on:

- The probability and expected timeframe of resistance emerging and spreading within and across geographical areas;
- The impact of emerging resistance on control/elimination objectives;
- Options for reducing the probability of emergence of resistance;
- Tools and strategies to detect emerging resistance; and
- Strategies for mitigating the impact of emerging resistance, including both currently available and potential new tools and strategies.

The number of drugs, tools for detecting resistance, probability of resistance emerging, or strategies to reduce the probability of emerging resistance and mitigating its impact, differ between diseases, driven by a number of factors ranging from parasite biology to control strategies. The TDR portfolio reflects these differences.

1. STRATEGIES FOR MONITORING AND RESPONDING TO POTENTIAL EMERGENCE OF DRUG RESISTANCE

Identification of genetic markers of suboptimal response (SOR) of *O. volvulus* to ivermectin as a basis for field suitable tool to monitor SOR prevalence. The current methodology for identifying SOR is not suitable for monitoring of SOR prevalence by control programmes. These are serial skin snipping of individuals before and after ivermectin treatment and evaluation of the number of microfilariae at different time points or nodulectomies with histopathological analysis or embryograms of the microfilariae. The objective of this project is to identify genetic markers of response of *O. volvulus* to ivermectin, the drug used to control *O. volvulus* morbidity and transmission. This is needed as a basis for an assay or tool that can be used by local laboratories to determine the prevalence of parasites with suboptimal response to ivermectin using parasites collected either through catching vectors or present in skin snips.

**Progress in 2018**

Completion of the genotyping of samples obtained in TDR-funded field studies to validate the utility of previously identified single nucleotide polymorphisms (SNPs) for characterizing ivermectin response in Ghana has not progressed as planned due to malfunctioning equipment in the collaborating laboratory in Ghana. Of 400 adult female worms collected during the TDR-funded field study on suboptimal response conducted by the team in Cameroon, 96 were genotyped. Two-hundred and fifty SNPs with strong association to the phenotype were identified with 35 per cent overlapping with SNPs identified as associated with response to ivermectin in analysis of worms from Cameroon (Doyle et al., 2017) and Ghana (see also section on ER 1.2.1, Onchocerciasis elimination in Africa).
Remaining challenges

Validation of genetic markers and development of an assay format is needed that can allow laboratories within onchocerciasis-endemic countries to run the assay. This would require development of a laboratory-based assay that does not need specialized equipment or (ideally) identification of a manufacturer for an “off-the-shelf” assay that does not require any molecular biology laboratory capacity.

Plans for 2019–2021

• Complete sample analyses planned for 2018 (see above) in Ghana and related biostatistical analyses for validation of previously identified markers in Australia.

• Analyse microfilariae from different onchocerciasis endemic areas for presence of suboptimal response markers.

• Evaluate feasibility of a laboratory assay not requiring the specialized equipment.

• Continuation of discussion with organizations specialized in development of diagnostic assays to evaluate the potential of an 'off the shelf' assay which does not require molecular biology laboratory capacity and of a manufacturer of such assay with very little or no profit potential.

Partnerships and collaborations

La Trobe University, Australia; Council for Scientific and Industrial Research (CSIR) Ghana; the Research Foundation in Tropical Diseases and Environment (REFOTDE), Cameroon

Leverage created by this project

The laboratory in Australia has leveraged the project for grants for PhD students from Nigeria.

Gender aspects and vulnerable populations

Both project implementers are males. No female scientist responded to the call proposals.

Training

M. Awobifa (woman from Nigeria) in an Australian laboratory

Strengthened institutions or networks

Completed before 2018 (MDSC/APOC laboratory in Ouagadougou, CSIR in Ghana, REFOTDE in Cameroon)
2. EVALUATION OF PRACTICAL APPROACHES TO IMPROVE TARGETED TREATMENT AND REDUCE DRUG MISUSE AND RISK OF RESISTANCE

(1) Evaluation of C-reactive protein (CRP) as a biomarker for bacterial infection or marker of severity in dengue; and (2) Identification of microbiological causes of invasive infection in young infants

Febrile illnesses lacking proper diagnosis are leading to suboptimal case management and unnecessary overuse of antimicrobials, raising the risk of antimicrobials resistance (AMR). There is therefore a need to obtain better evidence on causal agents of fever and assess effectiveness and feasibility of point-of-care marker that would guide use of antibiotics and medical management in general at field level.

Progress in 2018

**CRP as a biomarker of bacterial infection in febrile patients in Africa:** Data analysis on stored samples from a cohort of febrile patients in Africa was finalized and published. It shows that CRP is moderately sensitive for bacterial zoonoses and highly sensitive for identifying bloodstream infections. Based on these results, operational studies would be interesting to assess the safety and clinical utility of CRP for the management of non-malaria febrile illness at first-level health facilities in sub-Saharan Africa.

**CRP as a biomarker of severity in dengue:** In areas of dengue transmission, yearly seasonal epidemics occur and can very quickly overwhelm health facilities. As the vast majority of symptomatic infections will result in a benign disease course, the ability to identify patients at high risk of progression now appears as a priority. Even though CRP was suggested as a marker of severity, results from small studies have produced inconsistent findings; data derived from a larger cohort is in progress and analysis pending.

**Microbiological causes of invasive infection in young infants in rural Africa:** Data on the pathogens causing infection in babies born at home are scarce, particularly for infections in the first weeks and months of life. These data are necessary to provide insights on the antibiotic regimens that can be used in case management for serious infections in young infants in outpatient or home settings in developing countries. The data are particularly valuable in areas of high neonatal mortality in order to analyse explicitly defined criteria for community-acquired infections. The prospective study in Burkina Faso was completed at the beginning of 2018, and analysis of samples collected was completed by end of 2018 for the two prospective sites in Tanzania and Burkina Faso and a retrospective study in Kenya. Statistical analysis is ongoing.

Remaining challenges

Analysis of samples by polymerase chain reaction (TaqMan Array Cards) took longer than expected due the lengthy lab process and number of samples. Evaluation of CRP in cohorts of febrile patients requires good data on the etiological causes of fever in cohort patients. For those cohorts where samples were available, the evaluation of the etiology of fever is usually limited, and hence it is difficult to obtain a full picture of the potential of CRP as a biomarker.

Results dissemination and uptake

- CRP in febrile patients: poster presented at the American Society of Tropical Medicine and Hygiene Conference; peer review publication submitted
- CRP in Dengue: publication to be prepared in 2019
- Study on infections in neonates: paper to be published in 2019
Plans for 2019–2021

- Finalize analysis of results from evaluation of CRP in Dengue. Based on results, decision to be made on progress into further study/evaluation of CRP as a biomarker in Africa
- Study report and publication of research on microbiological causes of invasive infections in young African infants

Partnerships and collaborations

- TaqMan tests have been provided by the University of Virginia
- Samples for the evaluation of CRP in febrile patients were provided by Duke University
- Samples for evaluation of CRP in dengue were provided by the Oxford University Clinical Research Unit, Viet Nam

Leverage created by this project

The total figure leveraged under this project is US$ 300 000. It includes the cost of the TaqMan test, estimated to be US$ 100 000, and the cost of sample collection for evaluation of CRP as a biomarker which is estimated to be US$ 100 000.

Gender aspects and vulnerable populations

Among the PIs for those studies, two are women and three are men.

Strengthened institutions or networks

Capacity building for use of TaqMan in Burkina Faso and Kenya.

Publications

Submission: M. Rubach et al., Sensitivity of C-reactive protein for the identification of patients with laboratory confirmed bacterial infections in northern Tanzania

3. STRATEGIES FOR MONITORING POTENTIAL EMERGENCE OF RESISTANCE DURING SEASONAL MALARIA CHEMOPREVENTION (SMC)

This project supports countries to define and implement the most cost-effective drug resistance surveillance strategies in the context of mass drug administration (MDA).

In 2016, some 18 million children received preventive treatment for malaria during the rainy season in Central and West Africa. This means there is a vast pool of parasites at risk of drug resistance to amodiaquine and sulphadoxine/pyrimethamine (AQ-SP) now and in the future. The research project aims at informing the national malaria programmes of affected countries on how best to detect the emergence of this drug resistance in the context of mass drug administration.

Following a 2012 WHO recommendation, 13 sub-Saharan Africa countries with high seasonal malaria transmission have adopted and integrated SMC into their policy documents and strategic plans. However, little is known concerning the risk of drug-resistant parasites being spreading while implementing SMC at a large scale, and which cost-effective strategy options can be made available to national malaria programmes (NMPs) to monitor drug sensitivity.

This project, conducted in partnership with NMPs and the London School of Hygiene and Tropical Medicine (LSHTM), compared two surveillance strategies: i) drug resistance surveys in the general population before and after SMC campaigns; and ii) monitoring of drug resistance at 32 outpatient
sentinel sites. The rationale is, that while the latter might suffer from a selection bias (only malaria cases coming to a clinic are investigated), the proportional change in parasite susceptibility and genetic profiles might generate signals to pinpoint drug resistance early and more cheaply than cross-sectional survey sampling across the general population. Though this provides a less biased estimation of the prevalence of drug resistance indicators in the general population, it is burdened with complex and costly logistics.

**Progress in 2018**

In 2015, a study protocol was developed by the NMP of Senegal, with TDR and LSHTM support. Ethical approval was obtained from the Senegalese National Ethical Committee and the WHO Ethics Review Committee (ERC). Pre- and post-SMC surveys were conducted in 2016 and data from the sentinel sites were collected. Samples were sent to LSHTM for molecular testing to identify resistance markers to sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ). Data analysis was completed, and the paper is ready for submission.

**Plans for 2019–2021**

Study results will be published in Q1 2019 and the results shared within the SMC workgroup. The results will also be shared at a policy revision meeting that will be organized by the WHO Global Malaria Programme Q1 2019.

**Partnerships and collaborations**

Université Cheick Anta Diop (UCAD), Senegal and the London School of Hygiene and Tropical Medicine (LSHTM)

**Leverage created by this project**

An estimated US$ 100 000 was leveraged from the LSHTM as part of a Unitaid-funded project for performing molecular tests.

**Strengthened institutions or networks**

This project strengthened capacities of the UCAD team.

**Publications**

Research results will be published in a scientific paper that will be finalized and submitted in Q1 2019. The study results will also be presented at the next SMC working group meeting (March 2019).

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1 Unitaid is a global health initiative that is working with partners to end the world’s tuberculosis, HIV/AIDS, malaria and hepatitis C epidemics; see their website https://unitaid.org/#en.
4. INTERRUPTION OF MASS DRUG ADMINISTRATION (MDA) FOR SOIL-TRANSMITTED HELMINTHS (STHS) IN THE CONTEXT OF STH ELIMINATION

STHs are controlled through the mass drug administration (MDA) of preventive chemotherapy treatment (PCT). However, as countries progress towards elimination, questions arise as to when to stop PCT and what should happen after it stops. After years of deworming, parts of Bolivia have reached the low STH endemicity level at which the WHO recommends halting PCT. This new project offers a unique opportunity to test measures to be taken when PCT is stopped in order to prevent STHs returning. This pilot project will evaluate possible follow-up and the role of water and sanitation programmes in the post-MDA phase.

Progress in 2018

The Bolivian study is still in progress. The first evaluation has taken place and the data are currently being entered into a database for subsequent analysis.

Plans for 2019–2021

The study is in progress and analysis of the first-year data continues. Final data from the study are not expected before end of 2021 (four-year study).

Partnerships and collaborations

University of Firenze, control programme in the Chaco Boliviano.

Leverage created by this project

An estimated US$ 150 000 was leveraged from Cooperazione Sanitaria Internazionale, University of Firenze, Italy; and from a “Convenio de Salud” for the conduct of the main study that serves as the basis for the Bolivian project.

Strengthened institutions or networks

National control programme in Bolivia

- Research for implementation

This area of work aims to understand and address barriers to effective, quality and equitable implementation of health interventions, strategies, guidelines and policies to provide the evidence as to HOW these can best be implemented for maximum IMPACT. There are four expected results for this area of work which are all continuing or evolving work from the last biennium.

ER 1.1.7: Maximized utilization of data for public health decision-making

*TDR promotes, supports and contributes to databases from both research and control programmes to strengthen the evidence base for better-informed treatment policy decisions, and to identify research gaps. Through its convening power and networks, TDR plays a role as honest broker and guarantor of process integrity, at the crossroads between research, control and policy.*

This expected result includes work done to support data-sharing activities and optimal use of data, and SORT IT work.
1. DATA PLATFORMS

1. TB-PACTS data-sharing platform

The TB-Platform for Aggregation of Clinical TB Studies (TB-PACTS) is a partnership among the institutions providing the data – TDR, the TB Alliance, and St. George’s, University of London, with the platform developed by the Critical Path Institute (C-Path). The platform contains fully anonymised, patient-level data from the REMoxTB, RIFAQUIN, and OFLOTUB clinical trials which can be accessed and analysed in aggregate or filtered and viewed as individual records. Types of data available include demographic, concomitant medications and dose/concentration information, outcome data, and relevant covariates of interest. The platform is equipped to host data from additional studies in the future.

Researchers applying for access must agree to the Terms and Conditions for Use of the TB-PACTS data platform and submit an online application form to request access to the data platform (for more information, see http://c-path.org/programs/tb-pacts/).

Progress in 2018

By September 2018, a total of 38 requests were received, 28 of which were approved by the Steering Committee within an average of 20 days. A Steering Committee meeting was held to discuss how to communicate more broadly around this initiative. A common paper will be drafted. Various key stakeholders (such as publishers, and funders, etc.) will be approached to discuss long-term financing of this platform.

2. Helminths data-sharing platform

In the context of the ER 1.1.4 project, a systematic review has been conducted in collaboration with Infectious Diseases Data Observatory (IDDO) on the availability of individual patient data to assess the variability of response of soil-transmitted helminths (Ascaris lumbricoides (roundworm), Trichuris trichiura (whipworm) and hookworm species (Halder et al, 2017)). This complements a similar analysis published in 2016 on schistosomiasis (Julé et al., 2016). The estimated potential of the database is predicted to contain:

- **Schistosomiasis**: 90 studies, ~20,000 participants, 26 countries (Julé et al., *PLoS NTD* 2016); and
- **Soil-transmitted helminths**: 129 studies, ~35,000 participants, 39 countries (Halder et al., *ECTMIH 3510, 2017 and PLoS NTD, 2017*).

The current database includes – Schistosomiasis = 9,494 (~48 per cent of target); and STH = 5,564 (~16 per cent of target). For the time being, these are closed databases, where data have been shared for the purpose of specific analyses, and all contributors are authors in the eventual publication.

In addition, the database is temporarily hosted at the Luxembourg Institute of Health (LIH) with a view to being transferred to IDDO – which has received Wellcome Trust funding for the development of a data-sharing and analysis platform for NTDs (leveraged with the funds TDR provided for and collaboration established through ER 1.1.4).

Progress in 2018

Data contributors have shared further individual patient data for treatments for schistosomiasis and STHs. These data are currently stored at the LIH with TDR funding but a new repository at IDDO, funded independently by Wellcome Trust, has been identified. Discussions are being held both with IDDO and the data providers regarding the transfer of data and the nature and governance of the new platform. This will take place in close collaboration with Global Engagement and will also include visceral leishmaniasis in collaboration with Drugs for Neglected Diseases initiative (DNDi).
3. Relationship between Loa loa microfilaremia, clinical symptoms of filariasis and treatment regimens: Analysis of historical data of Loa loa in Gabon

Loiasis (aka African eye worm) is a filariasis caused by the worm *Loa loa*. Clinically, it can manifest as eye and skin disease (Calabar swelling) which requires treatment, though most infections remain asymptomatic. Adult worms, however, can live in humans for several years and keep generating thousands of microfiliariae every day. Loiasis is a concern because subjects infected with both Loa loa and Onchocerca could experience serious and even life-threatening adverse events when treated with ivermectin – which is why preventive chemotherapy treatment (PCT) cannot be implemented in areas of co-endemicity. However, patients with symptomatic loiasis also need treatment, but no comprehensive data exist on long-term treatment efficacy and safety. For this reason, TDR, in collaboration with the Institut de la Recherche pour le Développement, France, and the Luxembourg Institute of Health, is supporting the Department of Parasitology and Mycology at the University of Health Sciences in Gabon to strengthen country capacity to collect and analyse *Loa loa* data in order to understand the relationship between microfilaraemia, symptoms and treatment outcome. The local institute has 45,000 patient files in its possession – the largest known database on loiasis.

**Progress in 2018**

After delay of data acquisition due to difficulties with Internet connectivity and civil unrest, data entry into an electronic database has been completed. Quality control continues.

**Remaining challenges**

- Helminth platform: Governance strategy for new data platform
- TB-PACTS: Funding for the next phase if current hosting organization cannot secure this
- *Loa loa*: Evaluate quality and consistency of database before analysis

**Results dissemination and uptake**

No specific details for 2018. The TB-PACTS initiative has a webpage.

**Plans for 2019–2021**

**TB-PACTS**

- Communicate on approach and outcomes (lessons learned paper)
- Further expand data set
- Continue to monitor the use of this platform

**Helminth platform**

- Plans 2019 - work towards the establishment of an appropriate governance and fair data sharing practices that meet the needs of public health and data providers.
- In the future, work on database governance will be covered by TDR Global Engagement team.

**Loa loa database**

Analysis once quality control is completed. Further data entry in country to keep the database as an up-to-date database.

**Leverage created by this project**

- Helminth platform: funds to Infectious Diseases Data Observatory (IDDO)
- TB-PACTS: funds leveraged for the full functioning of the platform

**Strengthened institutions or networks**

Department of Parasitology and Mycology, the University of Health Sciences in Gabon
2. MAXIMIZED UTILIZATION OF DATA FOR PUBLIC HEALTH DECISION-MAKING: STRUCTURED OPERATIONAL RESEARCH AND TRAINING INITIATIVE (SORT IT)

TDR is helping governments and institutions in low- and middle-income countries to develop operational research capacity in line with the SDGs and to generate evidence-informed decisions for improving public health.

As the Minister for Health of Fiji commented some years ago “our country is data rich but information poor” implying that much data is generated at country level but the full potential to use these data to inform improvements in public health is rarely achieved.

The Structured Operational Research and Training Initiative (SORT IT) seeks to make countries “data rich, information rich and action rich”. SORT IT is a global partnership initiative coordinated by TDR and implemented with partners since 2012. It builds on pre-existing work started by Médecins Sans Frontières (MSF) and the International Union Against Tuberculosis and Lung Disease (the Union) in 2009. The aim of SORT IT is to support countries and institutions to: conduct operational research around their priorities; build sustainable operational research capacity; and make evidence-informed decisions for improving public health.

SORT IT has proven to be adaptable, output-oriented, gender balanced and having built-in metrics for quality control and accountability. It is also well recognized having been promoted by a DFID independent evaluation as a model which “sets a bench-mark in operational research capacity building” and by ESSENCE good practice guidelines. Several WHO documents including the World Health Report 2013, the Global action framework for TB research and the WHO European Action plan to strengthen the use of evidence for policy-making have advocated its use. The institutions which have adopted the SORT IT model include: Partners in Health; the Damien Foundation; the National Institute for Virology, Nigeria; the National Institute of Cancer Prevention and Research, India; MSF; the Union; and a number of MoHs and other academic institutions in the North and South.

About two years ago, the SWG advised to franchise and reorient SORT IT in order to maintain relevance and cope with growing expansion. Efforts in 2018 were thus focused on (see figure 3):

- Developing new tools, online resources and databases to enhance franchising while ensuring quality;
- Continuing geographic scale-up but re-orienting towards the SDGs, UHC and increasing gender equity;
- Piloting innovative ways of delivery;
- Enhancing sustainable leadership capacity and expanding partnerships; and
- Securing designated funds for reorienting SORT IT to SDG themes with a major focus on AMR.
Progress in 2018

There has been continued geographic scale-up with outputs including gender equity and LMIC authorship. To date, SORT IT has been scaled up to 90 project countries and has enrolled 746 participants (46 per cent women).

By 31 December 2018, 54 courses had been completed with 589 participants; 88% completed all milestones, 527 papers were submitted and 446 (78%) have been published (83 were published in 2018). Of the 320 papers systematically assessed 18 months after course completion, 69% self-reported having had an effect on policy and practice. In 2018, individuals from LMICs constituted 98% of first authors, 48% of publications had a woman as first author and 92% of last authors were from LMICs (up from 61% in 2017). Alumni were leaders in 14 of 16 courses initiated in 2018. Alumni led two regional SORT IT courses in Africa and Asia, and national workshops were held in Armenia, China, India (4), Ethiopia, Myanmar, Pakistan, South Africa, Uganda, Ukraine and Zimbabwe.

1. Re-orienting towards the SDGs and UHC with a major focus on AMR

In 2018, SORT IT began orienting towards the SDGs and UHC by embracing new thematic areas (disease-specific and health systems) including key populations, NTDs, migrants and refugees, water and sanitation, adolescent male circumcision, cancer and the longer-term effect of Ebola on health systems. Importantly, close to US$ 10 million was secured to build sustainable operational research capacity that can generate and use evidence on the emergence, spread and health impact of AMR to limit this serious public health problem. The project targets six LMICs, with a focus on Fleming Fund supported countries. These include: Colombia (not a Fleming Fund country), Ghana, Myanmar, Nepal, Uganda and Sierra Leone.
2. Enhancing franchising while ensuring TDR quality standards

Franchising to allow the expansion of training beyond the limits of TDR direct facilitation is being fostered through the development of new tools including standard operating procedures to facilitate independent organization of SORT IT courses such as:

- on-line resources (rosters, video lectures, real-time updates on the TDR-website);
- databases and frameworks for standardized metrics and monitoring quality;
- increased collaboration with academic institutions, NGOs, and WHO departments; and
- promoting country-level funding (Global Fund in Pakistan, PEPFAR in Ukraine, and the MoHs in Kenya and China).

Academic institutions working in the South such as the Kirby Institute in New South Wales, Public Health England, University of Bergen, Norway and the Institute of Tropical Medicine, Belgium, have also sourced funding that is being used to implement SORT IT in Africa and Asia. These initiatives may serve as examples for expansion to other countries.

3. Innovative and methodological adaptation

Armenia has completed a pioneering SORT IT using educational technology (e-SORT IT with online video lectures) thereby cutting on facilitator and participant travel costs by 75%. The same team is now developing a 100% certified distance-learning SORT IT course supported by TDR. This will serve as a complimentary option for promising candidates who do not manage to get selected to highly competitive SORT IT courses. Two complex study designs (mixed methods and qualitative research) were completed.

4. Sustainable operational research leadership

There is evidence that research capacity built through SORT IT is being used subsequently in an independent manner. Of the first 25 completed courses, which assessed 265 cohorts (of a total of 269) 18 months after completion of their final workshop module, 49% had independently completed new research projects, 37% had published papers and 32% served as facilitators at further research workshops.

For example, in 2018, alumni from Kenya in collaboration with the University of Nairobi and the MoH successfully completed a national SORT IT course and published 13 papers. This initiative was unique in that it focused entirely on the district level in Kenya. Being decentralized, it was 100% run by Kenyan SORT IT alumni highlighting national capacity. Data were sourced from a mobile web-based platform with integrated mechanisms for data validation. This use of digital technology allowed spring-boarding, resulting in successful course completion within a short five-month time frame.

Through collaboration with the Kenyan MoH, the master’s programme for medical graduates at the University of Nairobi also integrated the SORT IT model for thesis projects. The latter will utilize under-exploited programme data from disease control programmes. This is an effective manner of introducing operational research to future programme staff.

In Armenia and Ukraine, alumni led pioneering SORT IT courses focused on key and vulnerable populations. These courses were adapted by EURO which intends to use SORT IT alumni to initiate a regional SORT IT course, bringing together six countries. This is an example of collaboration leading to a “community of practice” that strengthens regional efforts to use operational research to improve public health.

A SORT IT fellowship programme also exists and currently includes 19 operational research fellows leading research activities at country level. Since 2009, these fellows have been involved with over
1600 research projects and 1030 publications. Eight of these research fellows completed PhDs (Benin, India (three), Malawi, the Sudan, Viet Nam and Zimbabwe), and four others are finalizing their PhDs in Egypt, Lebanon and Myanmar (two).

5. Accountability and quality control

SORT IT has global metrics of enrolled participants and their outputs, gender balance and LMIC authorship. Impact monitoring is systematically done 18 months after course completion. This allows quarterly reporting at global level. In 2018, a tool kit for independent impact evaluation was developed in collaboration with the Kirby Institute, University of New South Wales and will be put to use.

6. Expanding partnerships

The SORT IT partnerships include:

- Institute of Tropical Medicine, Belgium
- Makarere University, Uganda
- National Institute of Virology, Nigeria
- Royal National Tuberculosis Foundation
- University of Antioquia, Colombia
- University of Bergen, Norway
- University of Nairobi, Kenya
- University of Toronto, Canada
- WHO country and regional offices
- WHO’s Evidence-informed Policy Network
- Center for Disease Control, the United States
- Department for International Development, the United Kingdom
- Ministries of health
- Agency for International Development, the United States
- Damien Foundation
- Dignitas International, Switzerland
- Médecins sans Frontières
- The Union
- Vital Strategies & Partners in Health

Remaining challenges

- Creating a sustainable funding environment at country level through streamlining operational research within national strategic plans, in global fund and other donor applications. This is vital to embed operational research and capacity building in a sustainable manner within public health programmes and academic institutions.
- Cost of open access publications is exorbitant and finding ways forward are needed.

Results dissemination and uptake

All SORT IT publications are available in an open access manner on the TDR website. Of 269 papers systematically assessed 18 months after course completion, 68% self-reported having had an effect on policy and/or practice.

Plans for 2019–2021

- While ensuring SORT IT standards, IIR will continue to expand collaboration and partnerships for franchising SORT IT through national leadership on themes related to the SDGs and UHC.
- Ebola and health systems will be assessed to determine the long-term legacy of Ebola on health systems recovery in Sierra Leone.
- A pioneering SORT IT on NTDs will be completed in collaboration with the Institute of Tropical Medicine, Belgium and the University of Gondar, Ethiopia.
Main focus – antimicrobial resistance

- Garner engagement and ensure the ground work for effective implementation of regional and national SORT IT programmes on AMR in Asia, Africa and Latin America.
- Use the AMR project to evolve SORT IT into a broader, more comprehensive effort to use data and research to improve public health. Upstream improvements in data collection will be coupled with downstream efforts to enhance dissemination and improved use of evidence for decision-making (“data rich, information rich, action rich”).
- Use new SORT IT initiatives to enhance TDR visibility and catalytic funding.

Partnerships and collaborations

In 2018, the following institutions became TDR partners: Public Health England; the Kirby Institute; the University of New South Wales, the University of Gondar, Ethiopia; The National Institute of Cancer Research, India; the Narotam Sekhsaria Foundation, India; the Alliance for Public Health, and China.

Leverage created by this project

Approximately US$ 10 million was leveraged (US$ 8 million from the Department of Health, United Kingdom for a SORT IT on AMR. US$ 1.5 million on eight courses was financed by other partners, open access publications and specific grants received by NGOs. US$ 70,000 was leveraged as contributions from the Institute of Tropical Medicine, Belgium, and the WHO/HIV Department.

Gender aspects and vulnerable populations

Cumulatively, 46% of trainees are women. The aim is to reach 50% or more. In 2018, TDR supported SORT IT courses focused on vulnerable and key populations (Ukraine and Armenia) and neglected tropical diseases (Ethiopia).

Training

The core focus of SORT IT is research implementation coupled with capacity building. In 2018, TDR supported five SORT IT workshops enrolling 50 participants. These courses were run in Ukraine (key populations), Armenia (one course on TB and another on key populations), Uganda (TB), and Ethiopia (NTDs).

Number of advanced degrees under way due to this project: There are 19 operational research fellows leading research activities at country level and based in MoHs, NGOs (the Union, MSF) and Departments of Medical Research (Myanmar). Eight PhDs have been completed (India (three), Malawi, Sudan, Zimbabwe, Benin and Viet Nam) and four are pursing PhDs in Myanmar (two), Lebanon and Egypt.

Strengthened institutions or networks

The SORT IT partnership now includes over 25 implementing partners (see above for names of institutions) and a network of almost 696 alumni and 190 mentors. Partners include disease control programmes, academia, NGOs and the corporate sector.

Publications

- In 2018, there were 83 publications with individuals from LMICs constituting 92% of first authors and 73% of last authors.
- Cumulatively since 2009, there have been 446 publications issued by the SORT IT partnership in 42 journals (impact factor 0.4–19) and in five languages (English, Russian, Spanish, Portuguese and French).

Related news

- Building the capacity of public health programmes to become data rich, information rich and action rich. Public Health Action, 2018; 8(2): 34-6. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6012955/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6012955/)
ER 1.1.8: Maximized utilization of safety information for public health decision-making

TDR actively promotes safety evaluation, working with countries to improve systems to monitor and effectively use drug safety data to strengthen evidence informing treatment guidelines and improve patient outcomes.

A major limitation of current efforts to ramp up access to medicines is the lack of monitoring programmes of similar scale to evaluate potential safety issues. In many disease-endemic countries, safety monitoring systems are still weak, and under-reporting is a persistent problem. New approaches need to be identified in order to provide countries and programmes with more efficient and reliable systems. This is especially true for preventive MDA programmes where drugs are administered at the community level and/or through non-medical personnel.

At the same time, it is also important to optimize the use of safety data collected by different partners; sharing and pooling data is promoted to improve our understanding of risks related to medications. TDR works with other WHO programmes to that effect, and in collaboration with WHO/HIVAIDS, a pregnancy drug safety database was developed which pools country data issued from national or local pregnancy exposure registries to document risks to mothers and their babies following drug exposures during pregnancy. On a similar project, TDR works with the WHO/GTB to develop a global database to pool and consolidate safety information on medications used to treat MDR-TB in different countries, called the global aDSM database. More recently TDR also collaborated with WHO/HIV to set up a new database for antiretroviral (ARV) toxicity monitoring.

This expected result has been only slightly evolving over time, but remains a key, distinctive area of work for TDR. This expected result had four main area of works in 2018:

- The central databases for safety data (central database for pregnancy exposure registries, global aDSM database for TB drugs, and central ARV database);
- Innovative strategies to improve safety monitoring at community level;
- Capacity building for safety monitoring in scope of the ADP project focusing on building capacity to facilitate access and delivery of new health technologies for tuberculosis, malaria and NTDs; and
- Optimize acquisition and analysis of safety data.

This work is funded by core funding and designated funds from the UNDP for the Access and Delivery Partnership projects.

Progress in 2018

1. Central databases for safety data

Central database for pregnancy exposure registries: Advocacy and work continues to formalize data transfer agreements and proceed to data transfer. The networking with countries was strengthened, and the University of Liverpool was added as new data contributor (signature of the data sharing agreement). Data transfer, however, has not yet been fully formalized for some of the projects despite obtaining a data-sharing agreement. The initiative gained further interest from stakeholders in the scope of the introduction of new antiretrovirals for which there is a dire lack of evidence on safety for use in pregnancy. The initiative was presented at two major international events: AIDS 2018, Amsterdam 2018; and the International Society of Pharmacovigilance Annual Conference, Geneva, held November 2018.
Global aDSM database for TB drugs: Two data sharing agreements were signed, including one covering large data collected through WHO’s End TB project. TDR provided support to several countries willing to implement aDSM national databases and it is expected that data collection will increase in the coming year. The first data analysis was done mid-2018 to provide further data to WHO/HTB in advance of their review of the treatment guidelines for MDR-TB.

Central database for the safety monitoring of dolutegravir and antiretrovirals in the general population: Upon request from WHO/HIV, TDR is working with them to develop a new central database to collect information on serious adverse events (SAE) and adverse events (AE) of specific interest following dolutegravir exposure. The database should provide further data and evidence to support treatment guidelines. A data sharing agreement in Brazil was signed, and mapping of the data is in progress.

2. Innovative approaches for safety monitoring at community level

Innovative approaches for safety monitoring are being tested in the context of MDA. Two studies in Ghana and Tanzania to evaluate the use of m-Health tools to improve efficiency of safety monitoring in the context of MDA for NTD were completed and their publications are in preparation. The analysis shows that m-Health tools can greatly improve adverse event reporting. A meeting planned to bring together the PIs of three studies on safety monitoring at community level undertaken in 2017 and 2018 was postponed to 2019. The meeting will review challenges and lessons learned across the three different studies focusing on tools used and evidence generated in the studies to identify best practices for future implementation.

3. Capacity building for safety monitoring (UNDP Access and Delivery Partnership project)

Different capacity-building activities were organized or funded under the scope of the Access and Delivery Partnership (ADP) project in Ghana and Tanzania responding to national workplans and related to strengthening safety monitoring capacity. In March 2018, three new countries were included (India, Malawi and Senegal) and initial activities have started in those countries.

- **Tanzania:** Remaining capacity strengthening activities of the workplan were conducted: Additional training sessions and support for capacity strengthening of key staff at the Tanzania Food and Drug Authority. Evaluation of the reporting rate at the end of the project shows an increase in the country after implementation of the training activities.

- **Ghana:** A second wave of training sessions to support the implementation of the newly developed electronic system for Individual Case Safety Reports took place. The new system helps the country to deal more efficiently with safety reports issued including those issued for new health technologies. This will find a direct application within the pilot programmatic introduction of the new malaria vaccine, which requires close safety monitoring. TDR also provided support for the development of an application that allows reporting from mobile phones (health care provider and/or customer) and related advocacy and training activities.

- **An inception meeting took place in Ghana, Malawi and India to introduce the project to national stakeholders, define priorities and prepare workplans.**

- **Senegal and WARN-TB:** Leveraging on the WARN-TB project included a workshop which was organized with co-funding from the ADP project and WARN-TB to help Senegal and other countries within the WARN-TB network to prepare proposals for implementation research to address the problem of MDR-TB in countries.

The current funding is up to March 2018, but discussions are continuing as regards the extension of the project for another four additional years.

4. Optimize acquisition and analysis of safety data

Loa loa: See ER 1.1.7 above.
Remaining challenges

Though data sharing is an accepted principle, agreements and formalization of this take considerable time. Activities of the ADP project in new target countries were slow to start due to delays in organizing a project inception meeting with national stakeholders.

Results dissemination and uptake

- National dissemination
- Presentation at international events (pregnancy exposure registry – see above)
- Publications (see above)
- Web page covering the different initiatives on data sharing
- Data from central database taken in consideration by relevant WHO departments (in particular for the aDSM database for WHO/GTB – see above)

Plans for 2019–2021

- Databases: Continuation of data sharing efforts, acquisition of additional data and analysis of data, to take place toward Q4–2019.
- Organization of a meeting to discuss lessons learned from innovative approaches with m-Health tools to improve safety monitoring at community levels (delayed from 2017 due to lack of time to organize the meeting).
- ADP: In collaboration with WARN-TB a workshop will be organized around MDR-TB in West African countries. Training on aDSM will be discussed.
- ADP: Support for capacity strengthening in ADP target countries will continue, including expansion to new countries (workplan to be developed Q1-2019). It is expected that pharmacovigilance capacity strengthening activities in Tanzania will be put on hold as the country is receiving separate support from other projects in the same area of work (Pavia and Proforma projects funded by EDCTP).
- Loa loa: Final analysis of the data.

Partnerships and collaborations

- Countries involved in safety data collection who are contributing data to the central databases.
- UNDP, WHO (strengthening regulatory capacity) and PATH are partners of the ADP projects.

Leverage created by this project

Estimated to be:

- US$ 50 000 representing time from experts involved in the project and collection work; and
- US$ 400 000 (in-kind from countries and other collaborators participating to projects, in particular for data collection).

Gender aspects and vulnerable populations

- Of the two PIs on the study of pharmacovigilance in MDA: one is a woman and one is a man.
- The project on pregnancy exposure registry specifically targets needs and gaps in knowledge with reference to women’s health.
Strengthened institutions or networks

Institutions within the MoHs in target countries were supported with capacity for safety monitoring through the ADP project.

Publications


ER 1.2.1: Strategies to achieve and sustain disease elimination

Elimination programmes generally evolve along a similar path, including an “attack”, a “consolidation” and a “maintenance” phase. The characteristics of tools and delivery systems required for each of those phases differ significantly.

Research for tools and strategies to initiate control/elimination campaigns is important. Additionally, the research for strategies and tools needed for the “last mile” phase is also crucial, as it is at this point that the per-unit cost of prevention and treatment increases with decreasing prevalence/incidence of infection. Failure to get the right tools and strategies in place for the “last mile” phase compromises all previous achievements and investments and has economic, societal and political costs.

The IIR SWG identified “the science of elimination” as one of the big-ticket items for TDR. Currently, TDR focuses mainly on the elimination of two diseases:

- Elimination of Visceral leishmaniasis (VL) as a public health problem in the Indian subcontinent—aka KEP (kala-azar elimination programme) – see ER 1.2.1
- Elimination of *O. volvulus* transmission in Africa – see ER 1.2.1 and ER 1.1.4.

For both diseases, long-term TDR investments resulted in the development of tools and strategies that enabled the current control/elimination campaigns: e.g. single-agent and combination treatments; diagnostics and elimination strategies for VL; safety of ivermectin during MDA; community-directed ivermectin distribution strategies; rapid mapping of onchocerciasis and loiasis endemicity; and clinical development of moxidectin treatment for onchocerciasis.

TDR is now focusing on these “last-mile” challenges and looking ahead to identify obstacles and establish sustainable solutions. These two elimination programmes present some common features but each has a distinctive approach driven by the disease-specific and transmission characteristics. The research supporting these elimination programmes is reflected below.
1. VISCERAL LEISHMANIASIS (VL) IN THE INDIAN SUBCONTINENT

This is a country-led, long-term project that aims to generate an evidence base for approaches and interventions to be deployed throughout the different phases of VL elimination programmes, and ensures policy uptake and rollout.

Since 2005, TDR has been working with both research institutions and control programmes in the Indian subcontinent to conduct research that informs policy and practice for the elimination target of one case of VL per 10,000 inhabitants. One of the longest and most successful implementation research programmes at TDR, these efforts have contributed to a sharp reduction of cases. One of the reasons for this success is that the research has been planned and executed by country control programme managers and researchers, ensuring the pertinence of research and facilitating result uptake into policy and practice. In the past few years, support has been concentrated in Bangladesh and Nepal for increased efficiency. Nepal is now filing for certification of elimination, and Bangladesh reached the target in 2017.

However, further investments and new approaches are required to ensure elimination is sustained, and to prevent resurgence of the disease and the consequent waste of the current efforts to control the spread of the disease. To address this, work is underway at the level of i) active case detection; ii) vector control and reduction of transmission; and iii) research policy interface.

Progress in 2018

• A previous study in Bangladesh and Nepal showed the efficacy of sand fly control in and around houses of a recently detected VL case using durable wall lining and insecticide-treated bed nets and — for an even longer duration — applying insecticide-treated paint. Based on these findings, two new studies were conducted testing the rapid response to newly detected VL cases (index cases) in villages which apply the pilot-tested extended fever-camp approach. This includes the search for VL/PKDL (Post-kala-azar dermal leishmaniasis), malaria, tuberculosis and leprosy, and conducting vector control. Per camp, 0.5 new cases were detected. Vector control with insecticidal paint in Nepal and wall lining in Bangladesh had the most pronounced effect in reducing vector densities for up to 12 months and even longer. This approach seems to be promising for the maintenance phase of VL elimination when indoor residual spraying (IRS) is abandoned.

• A study on the performance and efficacy of IRS in Bangladesh using the M&E tool kit which was developed by TDR/IIR showed the need for continuous monitoring of spraying activities by national programmes in order to achieve the expected results.

• The analysis of insecticide resistance in field-collected P. argentipes sandflies in Bangladesh and Nepal showed their continued susceptibility to pyrethroids and recommended the annual evaluation of resistance levels by national programmes.

• Two field studies in Nepal were conducted showing 1) that Female Community Volunteers can cope with their current workload only because of the support provided by their husbands and other family members and that their potential role in active case detection can only be accomplished if communication with the district health office is improved and 2) that housing conditions (such as old bamboo walls or use of animal charcoal for plastering walls) are a risk factor for vector breeding and VL transmission.

• Participants at the October 2018 VL expert meeting in Freiburg, Germany included national VL control programme managers, researchers from the target countries and international experts. Conclusions of the meeting showed that in the post-elimination phase, speedy detection of new cases in low-endemicity areas (“non-programme areas”) should be a focus, and that the search for secondary cases and vector control can be done by the community. The research programme has already been designed and will start in early 2019 in Nepal and
Bangladesh. It includes the community-based surveillance of infected VL vectors, active case search by village health workers and community-based vector control.

- A study to evaluate the use of the rK39 diagnostic test in febrile populations presenting in secondary-level health centres in Bangladesh and India is in progress and should provide insights on the best diagnostic tool for the elimination phase.

Results dissemination and uptake

- Presentation of findings were undertaken at the American Society of Tropical Medicine and at stakeholder meetings in India (SPEAK India meeting; SPEAK India health systems consultative workshop, April 2018; and at the International Conference on Innovations for the Elimination and Control of Visceral Leishmaniasis (IEC-VL) November 2018).
- Advocacy continued for investments in research, surveillance and policy briefs.
- The results of research regarding combined fever camps for active case detection, as well as the findings on improved vector management, have been taken up by national control programmes and incorporated into their guidelines.
- The company producing the insecticidal paint identified a local business partner in Bangladesh which would organize the local production and distribution of the paint to public health services – making them independent of imported goods. However, the wide utilization of the paint has yet to be decided by the government, despite the fact that IRS continues to be the main vector control tool.
- Joint meetings with other stakeholders contributing to the VL elimination initiative (e.g. SPEAK India, KalaCORE India and CARE India) have also been instrumental in disseminating TDR-supported research findings and making them available to a wide range of public and private institutions.

Remaining challenges

- Knowledge gaps: Clarifying the significance of the elimination target (<1 case per 10,000 population) vis-à-vis zero transmission to achieve “real” elimination.
- Programmatic issues: Identifying the best, most sustainable, multi-disease and inter-sectoral approaches that can eventually lead to zero VL transmission.
- Beyond science and programmes: Elimination is as much a political as a scientific challenge, requiring the mobilization of human resources and financial capital to ensure success. Additionally, the identification of sustainable approaches to prevent interrupted transmission from starting again is needed.

Plans for 2019–2021

- A major research initiative will begin in Bangladesh and Nepal to test for the post-elimination phase for the most suitable interventions in low VL/PKDL-endemicity areas. This will be aimed at detection of secondary cases after an index case has been diagnosed in a local hospital; vector surveillance (detecting infected vectors in new foci); vector control with community managed tools; and social mobilization.
- An annual meeting will be held with national programme managers and academics for reviewing achievements and defining research needs.
- Current studies will continue, and study reports and related publications will be completed.
**Partnerships and collaborations**

A strong multi-institutional partnership has evolved through close collaboration between academic institutions: The International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR-B); the Rajendra Memorial Research Institute of Medical Sciences (RMRI), India; the Public Health and Infectious Disease Research Center (PHIDRC) in Nepal. This is further supported by national programme managers in the three countries, TDR staff, and other collaborators from WHO/HQ and SEARO.

**Leverage created by this project**

In-kind contributions and direct investments into research in the three countries are difficult to assess in monetary terms. There has been direct financial support from meeting participants (about 30% of the meeting budgets).

**Gender aspects and vulnerable populations**

A sub-project on information systems in Nepal and a feasibility study in Bangladesh were carried out by women researchers. The Nepalese field staff includes three women. In Bangladesh, due to the remote areas where the project takes place, no women could be included.

The work on VL elimination has highlighted the substantial role of female community volunteers. In particular, two field studies in Nepal were conducted showing that female community volunteers can cope with their current workload only because of support provided by their husbands and other family members. It was further noted that their potential role in active case detection can only be accomplished if communication with the district health office is improved.

**Training**

Dajull Lim (PhD; completed in February 2018)

**Strengthened institutions or networks**

All partner institutions are sharing lessons learned and contributing to research designs. This is further linked to the successful translation of findings into policy and practice.

**Publications**


2. ONCHOECRIASIS ELIMINATION IN AFRICA

Elimination of transmission of *O. volvulus* by 2020 is now targeted in some African countries and in 80 per cent of African endemic countries by 2025. The principal onchocerciasis control strategy is community-directed treatment with ivermectin (CDTI), in most areas annually. The elimination target was set when country and the WHO African Programme for Onchocerciasis Control (APOC) evaluations (in areas under long-term CDTI) showed prevalence levels that suggested parasite transmission had already been or would be eliminated after a few additional years of CDTI (see figure 4).

A number of funders are investing heavily into supporting country activities for onchocerciasis elimination. The TDR portfolio addresses issues not addressed by others, notably:

- The *2016 Guidelines for stopping mass drug administration and verifying elimination of human onchocerciasis* provides criteria for stopping CDTI but does not address how areas where CDTI can be stopped are to be delineated to minimize the risk of re-introduction of infection from neighbouring areas with continuing transmission via infective vectors or infected individuals.
- In some areas with long-term CDTI, concerns have been raised that “suboptimal response” (SOR) to ivermectin will prevent transmission elimination. Identification of SOR is based on counting the parasites in skin snips taken before and at several times after treatment with ivermectin - a laborious, time- and resource-consuming method that is not suitable for routine surveillance.

Figure 4. Relevance of TDR human onchocerciasis projects during Phase 1-3

Notes: ATP: annual transmission potential, M&E: Monitoring and evaluation, PES: post elimination surveillance, PTS: post treatment surveillance

• While two different transmission models have been used to support onchocerciasis elimination programme decisions, none of these models includes modules that take into account genetically determined variability of response to ivermectin or is able to model transmission across areas with different levels of infection prevalence with “parasite migration” between them (via infected humans or infective vectors) and thus estimate the risks associated with stopping interventions in one area when a “neighbouring area” does not meet stopping criteria.

• Notwithstanding the success of CDTI which has allowed to target elimination, the last document APOC issued before its closure stressed the need for “alternative treatment strategies” to achieve elimination in areas posing particular challenges for elimination. One such strategy is mass drug administration with more effective drugs, including moxidectin.

Table 2 below provides an overview of the key issues that the TDR portfolio addresses and relates them to the different stages in the conceptual framework for elimination of human onchocerciasis, as presented in the 2016 WHO guidelines.

Table 2. Key issues addressed by TDR portfolio on research for onchocerciasis elimination in Africa

<table>
<thead>
<tr>
<th>Project outcome</th>
<th>Key issues addressed and positioning within the conceptual framework of onchocerciasis elimination in Africa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Tool to delineate <em>O. volvulus</em> transmission zones</td>
<td>Support decisions to stop treatment: Decision (transition from Phase 1 to Phase 2) is taken only when criteria are met across the whole transmission zone (TZ) or (in conjunction with Phase 5) risk of continuing low-level transmission in one area is considered acceptable.</td>
</tr>
<tr>
<td>2. Tool for monitoring the decline in the number of reproductively active female parasites</td>
<td>M&amp;E for progress towards elimination: Monitoring of the adult worm population.</td>
</tr>
<tr>
<td>3. Tool for monitoring prevalence of <em>O. volvulus</em> with low susceptibility to IVM*</td>
<td>M&amp;E for progress towards and probability of achieving elimination: Monitoring the prevalence of <em>O. volvulus</em> with low susceptibility to ivermectin, informing need for alternative treatment strategies [Boussinesq et al., 2018].</td>
</tr>
<tr>
<td>4. Variability of pre-MDA parasite response to anthelminthic drugs**</td>
<td>M&amp;E for progress towards elimination: Reference for conclusions about changes in drug susceptibility during long term CDTI.</td>
</tr>
<tr>
<td>5. Transmission models to estimate the impact of migration of infected humans or infective vectors (with any or a specific genotype, e.g. low susceptibility) on <em>O. volvulus</em> prevalence and transmission (with any or a specific genotype)</td>
<td>M&amp;E for progress towards elimination: Estimate increase in prevalence of parasites with suboptimal response to ivermectin and impact on achieving elimination with the current and alternative treatment strategies. Support decisions to stop treatment: Estimate risk of resurgence of transmission due to ‘import’ of parasites from areas with ongoing transmission into areas where interventions were stopped. Support decisions on the frequency of post-treatment and post-elimination surveillance: Estimate risk of resurgence of transmission due to ‘import’ of parasites from areas with ongoing transmission into areas where interventions were stopped.</td>
</tr>
<tr>
<td>6. Data supporting WHO guidelines and country policies on moxidectin use for onchocerciasis elimination ***</td>
<td>Reduce time to elimination: Acceleration of the decrease in ATP and adult worm population through a more effective drug.</td>
</tr>
</tbody>
</table>

Notes: * currently part of ER 1.1.4 but will be transitioned to ER 1.2.1 because of significant synergy between work on outcomes 1, 2 and 3. ** No further TDR involvement since the investigators funded in the last biennium managed to leverage the work done with TDR funding for a significant grant (see 2017 annual report). *** With the US-FDA approval achieved, moxidectin moves into “Research for Policy”. To avoid fragmentation of the portfolio, work on moxidectin will be part of ER 1.2.1.
Progress in 2018

New data from genotyping microfilariae from the Republic of the Congo and two regions of the Democratic Republic of the Congo extend the broad conclusion that transmission zones defined by population genetics are large. Inclusion of sequence data from the literature, covering a greater geographic range, showed a strong “isolation-by-distance” correlation between genetic differentiation and geographical separation. This further strengthens the conclusion that transmission zones are likely best described as a series of overlapping zones, each of which extends over hundreds of kilometres and will span river basins and national boundaries. These data also support the design of a “pan-African” panel of geographically informative genetic markers.

The microfilariae mitochondrial data used for population structure analysis from the Republic of the Congo and the Democratic Republic of the Congo was also analysed from the perspective of estimating the number of reproductively active females amongst the individuals from which the microfilariae were obtained. These data suggest that: i) the three transmission zones sampled have different intensities of infection (lowest in Brazzaville; highest in the north-east of the Democratic Republic of the Congo); and ii) there is a strong correlation between the number of active females and a person’s age, but [surprisingly] there is also no correlation between the skin microfilarial density and the number of reproductively active females which contributed to these skin microfilariae.

Preliminary trials of whole genome sequencing from single microfilariae that were preserved in alcohol (rather than dried on glass slides) showed that recovery of entire mitochondrial genomes at high depth is feasible and that low-depth nuclear genome coverage is also feasible. This will expedite the further investigation of markers for demarcation of transmission zone boundaries (as well as suspected ivermectin suboptimal response).

Lymphatic Filariasis programmes are already facing problems of infections being detected in areas where MDA was stopped. Consequently, the methodology developed for onchocerciasis is utilized to determine that new infections detected in American Samoa after MDA was stopped and originates from a single source.

Remaining challenges

- Identification of additional financial resources to support the development of M&E tools for country programmes.
- Identify sources of parasites from a wide range of endemic areas and establish collaboration with relevant control programmes and investigators.

Plans for 2019–2021

- Validate transmission zone markers identified to date against samples from other endemic areas in Africa, explore extension to vectors for the development of an M&E tool when no infective/infected vectors are caught.
- Refinement of methodology to identify the number of reproductively active male and female parasites contributing to the sample of microfilariae or infective larvae.
- Establish collaboration with control programmes in American Samoa to continue investigation into the source of new Lymphatic Filariasis infections detected after stopping MDA and investigate the sources of continuing transmission.
- Finalization of protocols for moxidectin studies in the Democratic Republic of the Congo and Cameroon, and regulatory and ethics approvals for study initiations.
Partnerships and collaborations

Moxidectin: NTD researchers; NTD control programme managers; NTD M&E advisory group; AFRO/ESPEN onchocerciasis focal point (D. Bakajika who was one of the PIs on the pivotal study for the US-FDA registration); NTD HQ onchocerciasis focal point; and the Comité d'experts independent pour l'élimination de l'onchocercose in the Democratic Republic of the Congo.

Tool to delineate transmission zones, monitor decline of adult worm population and SOR: Council for Scientific and Industrial Research (CSIR) Ghana; Research Foundation in Tropical Diseases and Environment, Cameroon; ESPEN laboratory in Ouagadougou (formerly APOC, MDSC laboratory); Division Provinciale de la Santé de l'Itrui du Ministère de la Santé Publique, Democratic Republic of the Congo; Communauté Evangélique au Centre de l'Afrique, Democratic Republic of the Congo; and the University of Antwerp, Belgium.

Accelerate ATP and adult worm population decrease (moxidectin): Division Provinciale de la Santé de l'Itrui du Ministère de la Santé Publique, Democratic Republic of the Congo; Communauté Evangélique au Centre de l'Afrique, Democratic Republic of the Congo; University of Antwerp, Belgium; Medicines Development for Global Health, Australia, Luxembourg Institute of Health, University of Health and Allied Sciences, Ghana; Erasmus University Medical Center, the Netherlands, the Royal Veterinary College, the United Kingdom; the Imperial College of Science, Technology and Medicine, the United Kingdom; and EDCTP (funder).

Leverage created by this project

The TDR-funded work on moxidectin, TDR staff input into the grant application to EDCTP, and the Agence Nationale de la Recherche Française resulted in grants of Euro4.7 million and Euro0.36 million committed for studies on data that contribute to WHO guidelines and country policies on moxidectin use for onchocerciasis elimination (see ER 1.1.5).

The laboratory in Australia has leveraged the project for grants for PhD students from Ghana and Mexico.

Gender aspects and vulnerable populations

All PIs of TDR funded activities are male (no woman submitted a proposal). See below for trainees.

Training

E. Gyan (one man from Ghana) and P. Zendajas (a woman from Mexico) working in an Australian laboratory

Publications

Guidelines for stopping mass drug administration and verifying elimination of human onchocerciasis.

ER 1.2.6: Optimized approaches for effective delivery and impact assessment of public health interventions

Collaborative models to create a regional dynamic, synergize all partner efforts and enhance the conduct of operational and implementation research addressing national and regional research priorities.

In order to improve the delivery of interventions, OR/IR needs to be embedded within country control programme activities as a key driver for i) assessing the quality and effectiveness of a control programme intervention; ii) understanding the barriers to achieving a fully effective intervention; iii) developing new strategies to improve effectiveness and cost-effectiveness; and iv) piloting and implementing at-scale successful strategies.

In WHO’s End TB Strategy, endorsed by the World Health Assembly in May 2014, the role of research is distinctly recognized and is the third pillar of the strategy. Tuberculosis was the first worldwide infectious killer, despite the availability of effective treatments. More OR/IR TB research is needed in countries to identify better and more efficient ways of using existing tools for
controlling TB. Supporting NTPs to improve the delivery of interventions has therefore been included in the IIR strategic plan since 2015.

While TB is the initial focus, it is also seen as the entry point for the long-term plan of bridging OR/IR and health systems. In parallel with the activities described below, foundations for working with other control programmes – such as malaria (seasonal malaria chemoprevention, SMC delivery)\(^2\), arboviral disease control (arboviral disease surveillance and vector control interventions\(^3\)), HIV/AIDS and non-communicable diseases (diabetes) – have been established.

As recommended by the WHO’s Global TB Programme, and as part of the End TB Strategy endorsed by the World Health Assembly in May 2014, more cost-effective use of existing diagnostic tests and treatments could help decrease the burden of tuberculosis. More OR/IR TB research is needed in countries to identify better ways of controlling TB epidemics. To this end, a regional, collaborative, multipronged, and STEPwise approach\(^4\) to support the West African countries was adopted. The following phases were defined for enhancing TB research at national and regional levels:

- **Phase 1**: Creating an enabling environment at regional and national level
- **Phase 2**: Helping countries for the development of their TB research plan
- **Phase 3**: Facilitating countries’ implementation of their TB research plan
- **Phase 4**: Sharing the lessons learned

This project also aims at combining the efforts of all major partners and funders involved in TB control and TB research in West Africa by bringing them together in this regional initiative. From 2016–2017, phases 1 to 3 were conducted in West Africa, in particular:

The **West African Regional Network for TB control (WARN-TB)**, composed of the national TB programmes of 16 West African countries, was established with TDR support in June 2015 and regional funding was secured for its functioning for 2018–2019 (WAHO and Global Fund funding).

All 16 countries established a **multidisciplinary national TB committee (TB taskforces)** for the development of their national TB research plan as per Global TB framework guidance and the monitoring of its implementation. TDR provided seed funding for the establishment of these committees. Their functioning for 2018–2020 will be funded through the countries’ Global Fund grant.

The country **TB surveillance system** capacity of WARN-TB countries was strengthened for improving the quality of NTP data and allowed its reliable use for defining TB control research priorities. Two workshops were organized to strengthen the capacities of the NTPs for the analysis of the key TB indicators at national and subnational level.

All 16 countries defined their national TB research priorities and capacity strengthening needs. Eight countries out of 16 developed a national TB research agenda and have integrated it into their NTPs.

Three of the four modules of the OR/IR training programme were developed with WARN-TB and address training needs relevant to WARN-TB. Module 1 covers research basics. Module 2 provides training on protocol development and project management. Module 3 covers data management and data analysis. Through this learning-by-doing training, participants from the 16 countries developed OR/IR projects that addressed one research priority defined in their NTP. TDR provided small grants for the conduct of these research projects and funding for conducting some of the other research priorities was linked to country Global Fund Concept Note (2018–2020).

\(^2\) This is one of the key interventions supported by the Global Malaria Programme for reducing childhood malaria mortality rate.

\(^3\) Arboviral disease outbreaks of dengue, chikungunya and Zika are a major threat in West and Central Africa.

\(^4\) For more information on WHO’s STEPwise approach, see [https://www.who.int/ncds/surveillance/steps/en/](https://www.who.int/ncds/surveillance/steps/en/).
Progress in 2018

1. The West African Regional Network for TB control (WARN-TB)

The last training module, Module 4 on oral and written communication of study results, was developed. The results of all research were shared and discussed; some were also presented at the World TB Conference held at The Hague, October 2018. All country teams started the drafting of scientific papers to be published in 2019. The following are some highlights of research results and work in 2018:

- The results of the RAFAscreen projects (the cost-effectiveness of TB screening strategies for HIV and diabetic patients) were discussed within the WARN-TB. The NTPs of Burkina Faso, Ghana, Guinea Bissau, Mali, Nigeria and Togo began development of an IR project for increasing TB diagnosis in HIV patients based on RAFAscreen results. TDR provided technical assistance for submitting the project to Expertise France for funding (results of the application are pending).
- The Burkina Faso NTP used the protocol and experience of Niger to design a research project for investigating patient and health system factors associated with TB treatment defaulting.
- Based on successful feasibility results of integrating TB screening into other programme activities (SMC activities), the NTPs of Mali and Senegal started development of an IR project to integrate door-to-door TB screening within nutritional programme activities. Côte d’Ivoire started development of a project to integrate TB screening into vaccination programme activities and looking into the feasibility and cost-effectiveness of these screening strategies.
- The Benin NTP shared its results for screening TB in pregnant women (not a cost-effective intervention even if pregnant women are more at risk of TB. The Benin NTP task force also plans to explore the feasibility of screening for TB in post-partum women, as they come in later for their new-born vaccinations. Senegal will join this IR project.
- The NTPs of Niger and Mali conducted OR projects for understanding the causes of treatment defaulting (patients and health system factors. These two countries have already used their study results to improve treatment management.
- The Nigeria NTP used research results to inform policy for public-private partnerships.

A regional meeting was organized in collaboration with the Global Fund in March 2018 to discuss strategies for improving TB case finding. Based on discussions, all 16 WARN-TB countries have defined new strategies for intensifying TB case finding to be piloted and scaled up.

In October 2018, TDR organized a protocol writing workshop to support the countries in the development of new research projects. All country teams are currently finalizing their research protocol. Small grants will be given to the countries who will not be in position to use Global Fund grants or other funding schemes.

2. The Central African Regional Network for TB control (CARN-TB)

A meeting between NTP managers of the WARN-TB and CARN-TB networks was organized in March 2018 to share experiences. It was decided to replicate WARN-TB experience within the NTPs of the Central African Region. See figure 5 for a mapping of the WARN-TB and CARN-TB countries.

CARN-TB was established in March 2018. Its board is comprised of NTP managers from the eleven countries in the Central African region (Angola, Burundi, Cameroon, Chad, Central Africa Republic, Republic of the Congo, Democratic Republic of the Congo, Equatorial Guinea, Gabon, Rwanda, Sao Tome and Principe). There are three co-chairs: francophone Africa – Cameroon; a Lusophone country – Angola; and one from civil society – Pont Santé Afrique, Democratic Republic of the Congo.
A regional workshop was organized in collaboration with WHO’s Global TB Programme for strengthening the capacities of the TB surveillance system of the 11 countries. Programmatic data was safeguarded in the DHIS2-TB module developed by WHO/GTB. Two NTP staff per country were trained on TB data analysis, defining TB control gaps and TB research priorities.

The training programme on OR/IR started in November 2018 with the conduct of Module 1 on basic research aspects. All participants began development of a protocol for a research project addressing a country priority. A team of facilitators and mentors was established with expertise in epidemiology, research methodology, statistics, health economics, and qualitative research) to support participants in the finalization of their research protocol.

3. Other TB-related activities

The RAFAscreen project aims at defining the most appropriate TB screening strategies for diabetic and HIV patients (who are also at high risk of having TB) and piloting these screening strategies through implementation at all levels of the health-care system. This is a TDR/Expertise France co-funded project. Around 9,000 diabetic or HIV patients were screened for TB. The results concerning the most cost-effective algorithms for screening these patients in Benin, Guinea and Senegal were presented at the World TB Conference at The Hague, October 2018 (a publication is in preparation).

Figure 5. WARN-TB and CARN-TB countries
The Diagnosis of Multidrug-resistant tuberculosis in Africa (DIAMA) project was launched in June 2017. The project is led by the Benin NTP. Collaborators are: TDR; the Institute of Tropical Medicine (ITM), Belgium; and the NTPs of seven African countries (Cameroon, the Democratic Republic of the Congo, Ethiopia, Mali, Nigeria, Rwanda, and Senegal). The project explores the feasibility and accuracy of diagnosing TB resistance to first- and second-line drugs through novel molecular multiplex assays developed by GenoScreen. The project is also developing and setting up alternative culture-free approaches for the monitoring of patient response to rifampicin-resistant treatment. The DIAMA project will also evaluate the impact of implementing an e-connectivity system for real-time monitoring of molecular test results on treatment outcome. The project is funded by the EDCTP for five years.

Results dissemination and uptake

Through the WARN-TB and CARN-TB networks, results of research aiming to improve TB case finding or TB treatment outcome are shared and inform decisions of NTPs, either to implement solutions in their own countries, or to pilot similar strategies in other NTPs.

Remaining challenges

- NTP staff need more training on health economics and social sciences, which are key but complex topics.
- Sustainability of WARN-TB and CARN-TB is being addressed prospectively by involving various stakeholders to establish a favourable environment that will sustain in-country TB research.

Plans for 2019–2021

For the CARN-TB:
- Modules 2 and 3 of the OR/IR training are planned for Q1–2019 and Q4–2019.
- Technical and financial support for the conduct of OR/IR projects in 2019.

For the WARN-TB:
- Support for finalizing written communication of the results of the studies conducted in 2017–2018.

For both networks:
- Strengthened collaboration with the GFTAM, WHO’s Global TB Programme and Stop TB. In particular, organization of a one-week training on Implementation Research for 50 National Project Officers of the WHO for the Africa region (co-organized with AFRO) for improving support to the NTPs for conducting OR/IR projects in Africa.
- Strengthened collaboration with International Organization for Migration (IOM) for the conduct of OR/IR aiming at improving TB diagnosis and care in Nomadic population (a priority issue for the NTPs of Chad, Mali, Niger and Mauritania).
- Resource mobilization for the conduct of WARN-TB and CARN-TB activities.

Partnerships and collaborations

<table>
<thead>
<tr>
<th>WHO Global TB programme</th>
<th>Agency for International Development (USAID)</th>
<th>Université de Reims, Faculté de Médecine, France</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFRO</td>
<td>London School of Hygiene and Tropical Medicine</td>
<td>Université Abomey Calavi, Benin</td>
</tr>
<tr>
<td>WHO Department for West and Central Africa</td>
<td>Liverpool School of Tropical Medicine</td>
<td>Université Cheikh Anta Diop, Senegal</td>
</tr>
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<td>WHO Health Information Systems</td>
<td>MacGill University</td>
<td>Centre Muraz, Burkina Faso</td>
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<tr>
<td>GFTAM</td>
<td>Action contre la Faim, France</td>
<td>Université Gamal Abdel Nasse, Conakry</td>
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<tr>
<td>The Union</td>
<td>Institut de Recherche pour le Développement, France</td>
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<td>Damien foundation</td>
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<tr>
<td>West African Health Organization (WAHO)</td>
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<td></td>
</tr>
<tr>
<td>Expertise France</td>
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</table>
Leverage created by this project

The DIAMA project leveraged €2.4 million. Since 2016, WARN-TB activities leveraged US$ 8.6 million.

- US$ 1.3 million from the French government for conducting the RAFAScreen project, for which TDR contributed 18% of the total amount
- US$ 300 000 from the Global Fund for strengthening the national TB surveillance systems of WARN-TB countries in order to use reliable data for defining OR/IR priorities
- US$ 50 000 from WAHO for organizing the annual WARN-TB meeting in 2016
- US$ 50 000 from the Damien Foundation to participate in the training and financial support for projects conducted in Guinea Conakry, as part of the WARN-TB activities
- US$ 600 000 from USAID for 2017–2018 WARN-TB activities (intensification of TB case finding)
- US$ 100 000 from WHO/GTB for the coordination of the conduct of TB epidemiological reviews in West Africa and associated capacity-building activities
- US$ 100 000 from the Global Fund for the organization of the regional workshop “Intensifying TB case finding”
- US$ 100 000 from the Global Fund (through country grant) for organizing a West and Central Africa workshop of TB cost surveys.
- US$ 6 million for the WARN-TB from the Global Fund to support the Supra National Laboratory of Benin for strengthening the National Reference Laboratory of the WARN-TB and CARN-TB countries (with funding for operational research strengthening activities).

Gender aspects and vulnerable populations

The WARN-TB is co-chaired by one woman and one man. Among the 16 NTP coordinators, seven are women, and among the 41 M&E and research focal persons trained, eight were women.

One of the three co-chairs of the CARN-TB is a woman. Among the 11 NTP coordinators, none are women, and among the 22 M&E and research focal persons trained, four are women.

Training

Two Masters and two PhDs are linked to the DIAMA project.

Strengthened institutions or networks

Through this project, two networks were established (WARN-TB and CARN-TB) and all activities that were conducted, or which are planned, are aimed at strengthening these networks and the NTPs in the 27 countries represented in these networks.

Publications

Three papers are at a drafting stage.

Oral communications on WARN-TB activities: presentations were given at the African Union Congress, Accra, July 2017 and at the European Congress on Tropical Medicine and International Health, Antwerp, October 2017. The RAFAScreen and DIAMA project presentations were given at the African Union Congress, Accra, July 2017 and the World TB conference, The Hague, October 2018.

Related news

- Regional Workshop on TB cost surveys: https://youtu.be/Tczb5BEaO9k
Research for innovation

There is one expected result for this area of work which is continuing from the last biennium.

ER 1.1.5: Directions for development and accelerated access to new tools and strategies

Through TDR’s convening power and expertise, it provides a directional perspective and adapted methodologies for the development and assessment of new interventions and tools to achieve programme objectives for poverty-related diseases. This includes technical advice to external organizations as well as to other WHO programmes and departments.

1. TECHNICAL ADVICE TO ORGANIZATIONS OUTSIDE WHO

Progress in 2018

Moxidectin for onchocerciasis control and elimination (collaboration with Medicines Development for Global Health (MDGH) and the IRD): The US-FDA approved moxidectin on 13 June 2018. IIR staff provided technical advice to MDGH to respond to EDCTP questions on the grant for collection of further data to support country decisions on integration of moxidectin into their onchocerciasis control and elimination programmes. Furthermore, TDR provided technical advice to the IRD for the design of a study to obtain initial data on the safety and efficacy of moxidectin in Loa loa infected individuals. The MDGH and IRD grant applications were funded.

With the US-FDA approval of moxidectin, TDR activities from June 2018 fall within “Research for Policy” and “Research for Implementation” and are reported within ER 1.2.1.

Drug development for onchocerciasis (Drugs for Neglected Diseases initiative, DNDi): TDR staff is providing its expertise in support of the DNDi activities as and when requested, and furthermore, TDR staff contributed to the first Onchocerciasis Research Network meeting.

Contributions to committees of partner institutions committees, e.g. SPEAK India, EDCTP (selection committees for various calls).

Results dissemination and uptake

Moxidectin US-FDA approval and further study plans.

Plans for 2019–2021

Continue to respond to requests from within and outside WHO.

Partnerships and collaborations

Medicines Development for Global Health (MDGH) and IRD

Leverage created by this project

The funded grant applications for moxidectin studies resulted in the submitting consortia receiving 4.7 and 0.36 Million Euros, respectively.

Gender aspects and vulnerable populations

O. volvulus infection affects both genders from a health as well as socio-economic perspective. Both women and men were enrolled in the moxidectin studies resulting in US-FDA regulatory approval and will be enrolled in the studies supporting country policy and implementation decisions.

Onchocerciasis is a disease that primarily affects very poor populations.
Publications


Related news
Moxidectin:

2. SUPPORT TO OTHER WHO PROGRAMMES AND DEPARTMENTS
Progress in 2018
WHO/NTD: Revision of dengue guidelines.

WHO/GTB in assessing methods and products: i) WHO/GTB: 8th Meeting of WHO Task Force on the Development of Policies for Introduction of New TB Drugs and Treatment Regimens; ii) TB-ReFLECT Steering Committee; iii) WHO Task Force on pharmacokinetics-pharmacodynamics of tuberculosis medicines; and iv) Expert Committee on delamanid.

WHO/HTB: Membership in and/or contribution to i) steering committee for the guidelines on treatment of multidrug- and rifampicin-resistant TB; ii) interim delamanid assessment and WHO position statement on short-term regimens (WHO/CDS/TB/2018.1); and iii) initiative on advances in clinical trial design for development of new TB treatments.

WHO/EML (essential medicines list): Contribution to a new established list of essential diagnostics.

Other WHO departments: WHO/HIS Health Information Systems and WHO/HEP, Health Emergencies Programme on R&D Blueprint for Crimean Congo Haemorrhagic Fever (CCHF) and Lassa fever.

Plans for 2019–2021
Continue to respond to requests from within and outside WHO.
3. OPTIMIZED METHODOLOGIES TO ASSESS RESPONSE TO CASE-BASED AND POPULATION-BASED INTERVENTIONS

See linked project under ER 1.1.7 database platforms, in particular the work on the STH platform and database for Loa loa.

4. ADDITIONAL PROJECTS

Clinical Research During Outbreaks (CREDO) training curriculum: Generating clinical evidence during outbreaks in LMICs

This is a training curriculum to help clinicians and researchers in LMICs generate clinical evidence during outbreaks of infectious diseases.

Patients are at the heart of every outbreak and patient-centred research is essential to generate evidence to improve patient care and to guide the public health response. The conduct of clinical research during epidemics poses special challenges and historically has been inadequate. To address this gap, the CREDO training curriculum was designed to support investigators to generate clinical evidence during outbreaks of infectious diseases in LMICs. The idea of a training curriculum approach to guiding decisions about epidemic research was recommended by a group of experts attending the meeting “Generating Evidence for Infectious Diseases with Epidemic Potential”. The CREDO training initiative is aligned with the WHO R&D Blueprint for Action to Prevent Epidemics.

The training curriculum encompasses the full spectrum of activities that generate clinical evidence, from gathering descriptive clinical data through to conducting clinical trials of experimental therapeutic interventions.

Progress in 2018

A training workshop took place in Kinshasa, DRC from 21 to 25 October 2018 to provide support to the Institut Nationale de Recherche Biomedicale (INRB) to conduct clinical research during a major epidemic in response to the ongoing Ebola Virus Disease (EVD) outbreak in Eastern DRC.

The goal of the workshop was to strengthen the capacity of INRB to implement Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI) protocols. The workshop involved field staff who are currently implementing the protocols, to increase their knowledge and understanding of best practice in the conduct of clinical research, e.g. Good Clinical Practice, ethics and consent, data management and adverse events reporting. MEURI is being used pending implementation of a formal clinical trial. A clinical trial protocol is being developed by INRB with support from WHO and other partners. This training will lay the early foundations of clinical trials capacities at INRB.

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5 This meeting was jointly organized by WHO, the Wellcome Trust, the University of Oxford, and TDR, London, 20 October 2015. The meeting report is available at: http://www.who.int/medicines/ebola-treatment/meetings/Mee%20MeetingReport_GEIDEP.pdf.

6 For more information on the WHO R&D Blueprint for Action to Prevent Epidemics Initiative, see: http://www.who.int/blueprint/en/.

7 For more information on CREDO training, see https://globalhealthtrainingcentre.tghn.org/credo-study-design/.
Progress on past expected results

Table 3. Progress on past expected results

<table>
<thead>
<tr>
<th>Past expected results</th>
<th>Progress on outcomes</th>
</tr>
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<tbody>
<tr>
<td>Past ER. Development of rectal artesunate</td>
<td>Rectal artesunate suppository (RAS) was pre-qualified by WHO. This will expand access in LMICs to RAS.</td>
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<tr>
<td></td>
<td>TDR had managed RAS development including all clinical studies and preparation of the initial dossier for regulatory approval. These studies had shown the value of pre-referral RAS treatment for reducing morbidity in young children with suspected severe malaria and informed WHO guidelines.</td>
</tr>
</tbody>
</table>
## Budget and financial implementation

Table 1: Approved Programme Budget 2018–2019 and 2018 funds utilized (preliminary results)

<table>
<thead>
<tr>
<th>Expected result</th>
<th>Research for Implementation (IRI)</th>
<th>$40m budget scenario</th>
<th>Funds utilized as at 31 December 2018</th>
<th>Implementation rate</th>
<th>Revised planned costs at January 2019</th>
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<td>Research for policy</td>
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Table 2: Proposed programme budget and workplan 2020-2021

In line with the 2018-2023 strategy, financial figures are now shown under the heading of Research for Implementation.

<table>
<thead>
<tr>
<th>Expected result</th>
<th>Research for policy</th>
<th>$40m scenario</th>
<th>$50m scenario</th>
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<td>Strategies to promote gender-responsive health interventions on prevention and control of infectious diseases of poverty</td>
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<td>Directions for development and accelerated access to new tools and strategies</td>
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<td>Urban health interventions for vector-borne and other infectious diseases of poverty</td>
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<tr>
<td>Testing of innovative strategies for vector control</td>
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<td>100 000</td>
<td>800 000</td>
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<td>Multisectoral approach for malaria and emerging arboviral diseases</td>
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<td>Total</td>
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## Funding by project

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<th>Project ID</th>
<th>Principal Investigator</th>
<th>PI Gender</th>
<th>Supplier Name (Institution)</th>
<th>Project title</th>
<th>Funding in US$</th>
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<td>2018/863744</td>
<td>Youssoupha Ndiaye</td>
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<td>Direction de la Planification de la Recherche Et Des Statistiques (DPRS)</td>
<td>The costs of a 2-day stakeholder consultation meeting.</td>
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<td>Access and Delivery</td>
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<td>Samuel Wanji</td>
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<td>Research Foundation in Tropical Diseases and Environment</td>
<td>Research for Genetic Markers of O. Volvulus Response to Ivermectin and Development of an Onchocerciasis Control Programme Surveillance Tool</td>
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<td>Michel Vaillant</td>
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<td>LIH - Luxembourg Institute of Health</td>
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<td>University of Freiburg</td>
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<td>University of Freiburg</td>
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<td>24 825</td>
<td>Arboviruses</td>
<td>Germany</td>
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<td>B70073</td>
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<td>M</td>
<td>Convenio de Salud</td>
<td>Support to Intensive health education program for primary schools of rural communities of the Bolivian Chaco</td>
<td>34 153</td>
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<td>Rhona Mijumbi-Deve</td>
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<td>Makerere University College of Health Sciences</td>
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<td>Improved VL Surveillance, Case Detection and Vector Control for the Support of the VL Elimination Initiative in Bangladesh and Nepal with Emphasis on the Consolidation and Maintenance Phase</td>
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<td>Payment for Publication</td>
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<td>PI Gender</td>
<td>Supplier Name (Institution)</td>
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<td>Funding in US$</td>
<td>Disease or research topic</td>
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<td>Foundation for Innovative New Diagnostics (Find)</td>
<td>Reimbursement of air ticket for Piero’s duty travel to India</td>
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<td>Visceral Leishmaniasis</td>
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TDR funding in 2018

<table>
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<tr>
<th>CONTRIBUTOR</th>
<th>Amount (US$)</th>
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<td><strong>Core contributors</strong></td>
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<td>Sweden</td>
<td>5,037,631</td>
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<td>United Kingdom of Great Britain and Northern Ireland (UK)</td>
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<td>Other</td>
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<td><strong>TOTAL CONTRIBUTIONS</strong></td>
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The contribution from the Government of Sweden reflects the 2018 portion of their 2018-2019 funding agreement.