

Report of the WHO Strategic and Technical Advisory Group for Neglected Tropical Diseases

Salle B, WHO headquarters, Geneva, Switzerland 8–9 April 2014

The seventh meeting of the Strategic and Technical Advisory Group for Neglected Tropical Diseases (STAG-NTD) was held at the headquarters of the World Health Organization (WHO) in Geneva, Switzerland, on 8–9 April 2014. The list of participating members, observers and secretariat is attached as **Annex 1**.

Day 1

The Chairman, Professor Peter Holmes, welcomed the members of STAG and led members in observing a minute's silence in memory of Professor Pierre-Ambroise Thomas, a former STAG member who passed away recently.

Welcome and introduction

Dr Hiroki Nakatani, WHO's Assistant Director-General for HIV/AIDS, Tuberculosis, Malaria and Neglected Tropical Diseases, opened the meeting by identifying three main areas for STAG to consider: (i) changes in the landscape of NTD control; (ii) specific issues relating to NTDs; and (iii) strategic questions. He reminded STAG that the NTD landscape within the scientific community, the donor organizations and the Member countries has changed over the years. Much of the population requiring preventive chemotherapy (PC) interventions are no longermostly in low-income countries but are now among the poor in low middle-income countries. Discussion of the post-MDG 2015 agenda is currently very active, and NTD issues must be communicated to the diplomats who are working on it. Disease-specific issues include dracunculiasis eradication, which is in the last mile; human African trypanosomiasis (HAT), which needs to move from control to elimination; and yaws eradication, which will require greater commitment. Finally, Dr Nakatani posed some strategic questions to STAG: How can we ensure that NTDs are high on the post-MDG agenda? How can we get buy-in for NTD control from middle-income countries like Brazil? How can we support Member States where overseas development assistance is not available (e.g. middle-income countries)?

Dr Nakatani ended by noting that this is Dr Savioli's last STAG meeting as Director of the Department of Control of Neglected Tropical Diseases (WHO/NTD), and thanked him for his outstanding service to WHO.

1. Report from the Director on status, progress and challenges with NTD control

Dr Lorenzo Savioli (outgoing Director, WHO Department of Control of Neglected Tropical Diseases) noted the ongoing transition to a new leadership within the Department, and welcomed Dr Dirk Engels as the new Director. Dr Savioli summarized the highlights of 2013–2014. These included:

• Issues arising from resolution WHA66.12 on NTDs adopted by the World Health Assembly in 2013, such as country ownership of control programmes; expansion of interventions;

advocacy for long-term financing of control activities and capacity strengthening; integration of control programmes into primary health-care services; and universal access to interventions to achieve the targets of the WHO roadmap on NTDs.

- Roadmap targets towards 2020: eradication of dracunculiasis and yaws; global elimination targets; regional elimination targets; control targets and milestones for 2015 and 2020. There is a need to identify targets for 2030, especially given the MDG post-2015 agenda.
- Universal health coverage for NTDs; the impact of shifting of critical Member States from low to lower middle-income status; and the out-of-pocket spending that is required for case management of visceral Leishmaniasis, Buruli ulcer, dengue and other NTDs.
- Eradication of dracunculiasis and yaws: only 148 cases of guinea-worm disease were reported in 2013, the lowest number ever reported, but challenges remain; a consultation on yaws was held in March 2014 to review ongoing pilot implementation of the Morges Strategy; there is a possibility of Pfizer donating azithromycin free of charge for yaws.
- Global elimination of NTDs: a new medical officer has been appointed as the focal point for trachoma in the NTD Department; there is a lot of interest among partner organizations (especially the Gates Foundation) in working towards elimination of HAT; the annual number of new cases of leprosy reported has remained virtually unchanged and progress towards elimination needs to improve; a lot of documentation has been published regarding implementation of lymphatic filariasis (LF) elimination.
- Regional elimination of NTDs: Onchocerciasis in Latin America has made good progress and guidelines for verification of elimination will be completed by September 2014; proof of concept for control of rabies in dogs has been demonstrated; a major increase in qualityassured praziquantel is anticipated by 2016, but schistosomiasis control programmes in countries need to be scaled up; non-vectorial transmission of Chagas disease and expansion in geographical distribution beyond Latin America have been clearly demonstrated; but there has been good progress towards elimination of visceral Leishmaniasis in Bangladesh, India and Nepal.
- Intensified control of NTDs: there has been good progress from surgical treatment of Buruli ulcer to early diagnosis and pharmacological treatment; there have been problems with serious outbreaks of cutaneous Leishmaniasis in the Middle East (especially the Syrian Arab Republic) with increasing political instability; early diagnosis and treatment standard operating procedures (SOPs) for echinococcosis are being developed for adaptation in local settings; the donation of triclabendazole from Novartis has made an important contribution towards control of fascioliasis but serious adverse events resulting from distribution of medicines by nongovernmental organizations needs attention; coverage of anthelminthics among school-aged children has increased, but coverage for preschool-aged children has declined and scaling up of interventions is anticipated; dengue was a major topic of discussion at World Health Day celebrations this year and Europe is also starting to take dengue transmission seriously; a meeting of the Vector Control Advisory Group was held and the WHO Pesticide Evaluation Scheme, which includes insecticides and molluscicides, is being expanded.

Dr Dirk Engels (incoming Director, Department of Control of NTDs) summarized the future work and the anticipated challenges for the Department. He highlighted the marked gap between the current trajectory in the scale-up of PC and the required trajectory to meet 2020 targets. The main reason for slow progress has been slow implementation of LF control in India, Mozambique and Myanmar. Problems are less with onchocerciasis; PC coverage for STH and schistosomiasis has increased markedly; coverage for trachoma has also increased. Merck will increase its donation of praziquantel as promised, but implementation of control programmes at country level needs to be stepped up. Challenges include year-on-year consistent implementation of LF interventions; extra resource mobilization for implementation; and national and district capacity to implement control. Capacity strengthening is very important for PC as well as other NTD interventions. Good progress has been made by the Working Group on Capacity Strengthening, which has held two meetings since the last STAG meeting. Learning modules for national training have been finalized; establishment of a laboratory network has started; the NTD toolbox has been finalized; school-based educational materials have been developed; and new editions of older bench aids have been published. The current focus is on strengthening national capacity in management of NTD programmes, with development of a course for district-level managers; ongoing development of an e-learning platform for in-service training; and strengthening laboratory capacity in support of NTD implementation.

Dr Engels also presented the response of the Department to the points identified by STAG in 2013 for follow-up action by WHO. Implementation of Guidelines for verification of elimination of human onchocerciasis was identified as particularly important as an example for other NTDs.

The issues to be considered by STAG in 2014 include:

- Defining principles and processes of verification, validation and certification
- Positioning of NTDs in the post-MDG 2015 agenda
- Mobilizing resources for yaws eradication
- Accelerating work to control neglected zoonotic diseases and vector-borne diseases
- Responding to the dengue epidemic, especially in Africa

STAG agreed to send a statement to Richard Horton, Editor of the *Lancet*, for a statement editorial regarding the recent Paris meeting, on the inclusion of NTDs in the post MDG 2015 agenda. The statement published in the *Lancet* is attached as **Annex 2**.

2. Report of the meeting on Investment for Impact in the control of NTDs

Dr Deborah MacFarland and Christopher Fitzpatrick made a joint presentation on the Report on Investment for Impact in the Control of NTDs. An informal meeting was held on 16–17 December 2013 with representatives from Ministries of Health and Finance in six endemic countries as well as international experts on economics and impact of NTD interventions. The report of this meeting is attached as **Annex 3**. The objectives of the meeting were to inform the forthcoming third WHO report on NTDs and to develop a proposal for the establishment of a WHO Working Group on Investment for Impact. Common themes and endemic country wisdom that emerged at the meeting were highlighted. WHO resources for this effort were identified.

The proposed Mission for a new Working Group on NTD Control Investment for Impact would be "Generating evidence for investment and impact in the prevention, control, elimination and eradication of neglected tropical diseases"; its objectives would be to optimize the level of investment in NTD control by endemic countries or regions and their partners in development, better leveraging the resources already available, and diversifying or increasing them as necessary; and to demonstrate the impact of those investments beyond epidemiological impact and across development sectors.

The activities of the proposed Working Group would be to identify gaps in the evidence; provide support to countries; improve collaboration among partners; flag emerging issues of strategic importance; and assess and synthesize evidence.

The membership would be broad, but time-bound. STAG will biennially nominate a Working Group Chairperson to act for a two-year term, and nominations will be submitted to WHO for presentation to the STAG. The Working Group would consist of participants, invited experts, observers and

networks, and be supported by existing WHO staff, but participants would be responsible for meeting their own expenses. Several participants have already offered to advocate for fund-raising.

The third WHO report on NTDs will focus on 'Investment for Impact'. It will include a chapter on investment, including preparation for the post-2015 development agenda; develop investment benchmarks for universal coverage (including investment in health systems); and explore innovative funding opportunities. The proposed outline of the chapter on investment was presented.

STAG endorsed the terms of reference for the Working Group on Investment for Impact, and the proposed outline and process for development of the sections on investment in the third NTD report.

3. Control, elimination and eradication: concepts and terminology

Professor Peter Holmes made a brief presentation on concepts and terminology in relation to control, elimination and eradication of NTDs. He emphasized the need to distinguish between these three terms. The proposed principles and processes in relation to control, elimination as a public health problem (which would require a process of validation), elimination (which would require a process termed verification) and eradication (which requires formal certification) were described. The processes involved in validation, verification and certification were discussed in some detail. STAG members noted that every target achieved on the Roadmap needs recognition in some way.

STAG endorsed the proposed terminology and processes and recommended that WHO publishes a booklet that clearly sets out these definitions and processes (generic SOPs and disease-specific).

4. Report from the Working Group on Capacity Strengthening for NTDs (WG-CS)

Professor David Molyneux presented the second report from the WG-CS, which last met on 9–10 January 2014 (see meeting report attached as **Annex 4**), the objectives of the WG-CS, the 2012 STAG recommendations and challenges experienced in implementing these recommendations. The four key achievements and outcomes in 2013 include:

- (i) Convening a meeting on development and roll-out of a standardized district-level management NTD training course in July 2013
- (ii) Developing a simplified protocol for training needs assessments
- (iii) Strengthening the laboratory network for NTDs
- (iv) Releasing the beta version of the NTD toolbox

A sample of results from needs assessment among national and state-level NTD programme managers was presented. In February 2014, a training of state-level NTD programme managers took place in Nigeria. A scoping survey to strengthen laboratory networks for NTDs has been carried out. 162 laboratories outside Africa were identified, but only 22 responded (13%). The beta-version of the NTD toolbox has been developed. Other highlights include several ongoing NTD-CS and training activities in other units (IDM, NZD, VEM, WHO Integrated Management of Adult Illness, training initiatives by NTD partners). There has been significant input from WHO/TDR and there is much potential for collaboration. Regional and country NTD–CS priorities have been identified, but human resources are constrained.

WG-CS has worked on compiling a comprehensive inventory of existing NTD training courses and resources for all NTDs; promoting eLearning platforms and tools; and harmonizing field-guides, job

aides and training materials in use. All of the above are directly dependent on effective mobilization of sufficient resources for capacity strengthening for NTD programmes. Finally, the beta-version of the NTD toolbox was presented to STAG.

Recommendation for endorsement by STAG

WG-CS calls on WHO for sufficient mobilization of human and financial resources for capacity strengthening for NTD programmes

- I. Acknowledge the vast scope and scale of capacity strengthening activities that need to be implemented in order to achieve the NTD roadmap goals
- II. Provide dedicated NTD staff and required financial resources to empower WHO's coordination and leadership role in capacity strengthening activities at;
 - WHO/NTD department, HQ
 - WHO regional offices
 - WHO country offices particularly for the high-burden priority countries
- III. Draft a comprehensive strategy for capacity strengthening in support of NTD roadmap goals, and beyond;
 - CS resource mapping by all NTD stakeholders
 - Scheduling of CS activities by type, in support of national NTD programmes
 - Include CS evaluation plan against NTD roadmap timelines
 - Proactive engagement of the academic sector for longer term capacities

STAG noted the contents of the report.

5. Report from the Working Group on Access to Quality-Assured Essential Medicines (WGA)

Professor Nilanthi de Silva presented the report on the 6th meeting of WGA, which was held by teleconference on 20 March 2014 (report in **Annex 5**).

The Secretariat met with key partners on 21 January 2014 to discuss the global forecast and joint supply of the NTD medicines praziquantel, albendazole and mebendazole, all of which have issues relating to quantity and quality of supply. Those represented at the meeting included USAID, DFID, GSK, J&J, Merck KGaA, RTI, CWW and World Vision (a new partner). The 2014 global forecast for joint supply includes 262 million tablets of praziquantel to 39 countries; 188 million tablets of albendazole to 33 countries; and 135 million tablets of mebendazole to 13 countries.

WHO has solicited bids for prequalification of NTD medicines that have problems relating to supply of quality-assured tablets (DEC, praziquantel, albendazole and mebendazole), but the response has been poor. Only DEC has been approved for prequalification so far. Expert Review Panels have been used for review of 2 dossiers for albendazole and 13 for praziquantel.

WGA expressed particular concern over new regulations brought into effect within EU countries and the USA that require reporting of all adverse events (and not only serious adverse events), which could pose a major deterrent in implementation of control programmes.

There are many significant problems relating to the supply and quality of medicines for treatment of the Leishmaniases and Chagas disease.

Recommendations to STAG

- 1. Continue to support joint forecasting and sharing of information among interested parties.
- 2. Assist countries in developing plans of action and capacity to distribute available donated NTD medicines and expand coverage.

- 3. WHO/NTD, with input from the WHO Prequalification Programme (PQP), to seek technical support from the United States Pharmacopeia to produce the necessary data that would permit to ascertain whether bioequivalence study requirements could be waived for praziquantel without compromising its quality.
- 4. WHO/NTD, with input from PQP, to arrange a meeting with generic manufacturers to encourage them to submit applications for praziquantel.
- 5. Urge concerned national drug regulatory authorities to address the quality issues identified by the survey conducted in East Africa and South-East Asia.
- 6. WHO and donation partners to finalize the adverse event reporting form that is currently under final editing and revision.
- 7. WHO, national NTD control programmes and other concerned parties to develop a document outlining the peculiarities of preventive chemotherapy that can be used to raise the matter with the European Medicines Agency and seek a different set of reporting requirements for preventive chemotherapy interventions.
- 8. WHO, national NTD control programmes and other concerned parties to prepare for intensifying training on drug safety monitoring in national PC interventions.
- 9. To support the sustainable production of antileishmanial medicines and ensure adherence to international Good Manufacturing Practice standards, particularly for quality-assured sodium stibogluconate and paromomycin, in collaboration with PQP and other international partners.
- 10. To continue encouraging manufacturers of generic liposomal amphotericin B to undergo prequalification process and strengthen monitoring of treatment outcomes.
- 11. To continue studies on pharmacology, safety and efficacy of benznidazole and nifurtimox, taking into account the geographical differences on Chagas disease and responses to antiparasitic treatment.
- 12. To implement a network of sentinel centres to collect data and produce reports in a standardized format.

STAG noted the contents of the report.

6. Report from the Expanded Working Group on Monitoring and Evaluation of Preventive Chemotherapy Interventions (WG M&E)

Dr Sam Zaramba and Dr Mahmoun Homeida presented the reports from the merged working groups, which met on 18–20 February 2014.

Dr Zaramba presented the report on behalf of the M&E subgroup, which focuses on PC (see **Annex 6** for report). The Joint Application Package (JAP) is an integrated planning tool for countries that is now in use by all countries seeking support from WHO. In 2014, 50 countries requested medicines using JAP. Improving timeliness, completeness and triangulation of data has been pursued by HQ, WHO regions and countries. A data quality assessment tool has been developed and field tested in Cameroon, Nicaragua and Uganda with good results. To strengthen end-stage strategies and surveillance methods, a handbook of practical entomology for LF elimination has been finalized and published; a new strip test for diagnosis of LF has been field-tested. Country progress with the Global Programme to Eliminate Lymphatic Filariasis (GPELF) programme steps (mapping, MDA and surveillance) was presented. New tools for STH control and elimination are being developed at

present. PC data updates and data sharing have been done through regular publications. The global status of PC in 2012 indicates that progress is not very good except with regard to onchocerciasis. Ten major constraints and areas for strengthening M&E of national NTD programmes have been identified. M&E disease-specific indicators are under development for schistosomiasis, STH, trachoma, onchocerciasis, LF and Loa loa as well as a multiplex platform.

Professor Mamoun Homeida presented the report of the subgroup with focus on drug efficacy (see **Annex 7**). He focussed on progress in 2013 with regard to ivermectin for onchocerciasis and LF, benzimidazoles, praziquantel and flubendazole, as well as planned work in relation to each of these medicines.

Recommendations to STAG

- 1. Establish a Working Group on Investment for Impact to which Expanded WG M&E will provide regular epidemiological data and input.
- 2. Convene a technical consultation to develop a body of evidence around the global distribution of *Strongyloides* and its importance, and potentially develop public health recommendations.
- 3. Allow interim processes needed to acknowledge the achievements of countries that have achieved the LF elimination goals. In the absence of definitive global guidance, expanded Regional Programme Review Groups should be permitted to provide this recognition to countries for their achievement of LF elimination goals.
- 4. Prioritize programme evaluations and ensure these are conducted on a periodic basis in order to further improve the management and effectiveness of national NTD programmes.
- 5. Develop a systematic process to evaluate new diagnostic tools for NTDs (especially for surveillance of LF elimination), to review their utility for programmes and to develop recommendations for programmes on their use.

STAG noted the contents of the report.

7. Report from the Vector Control Advisory Group (VCAG)

Dr Marc Coosemans presented the work of VCAG, which was jointly established by the Global Malaria Programme and WHO/NTD to provide strategic advice to the WHO Malaria Policy Advisory Committee (MPAC) and STAG on the public health value of new forms of vector control. VCAG reviews and assesses the public health value of new paradigms of vector control (new tools, new technologies and new approaches) within the context of integrated vector management in multi-disease settings. The assessment will be based on evidence derived from practical tests demonstrating the candidate intervention's effect, in entomological and epidemiological terms; the intervention must therefore be something that can be defined in these terms. Submissions to VCAG can be made by any interested parties (manufacturers, academia, donors, innovators, etc.) with the relevant body of evidence on the public health value of such tool, technology or approach.

VCAG has a wide range of expertise, and its first meeting was held in July 2013 in order to standardize the operational procedures and submission dossier. The second VCAG meeting reviewed the first batch of submissions from innovators in February 2014. Eight items relating to five different paradigms were reviewed. The five paradigms are:

- a) Combination nets for use in areas of pyrethroid resistance (2)
- b) Microbial control of human pathogens in adult vectors (1)
- c) Spatial repellent (1)

- d) Lethal house lure (1)
- e) vector traps for disease management (3).

None of the above paradigms have reached the final stage for the consideration of STAG/MPAC. One product (combination net) has met the product claim but the exact criteria for its assessment will be developed by a VCAG subgroup in order to address the needs of higher efficacy in wild, resistant mosquitoes. Three other items are in the second step of the evaluation process, while the remaining products are at early stage of notification.

STAG noted the contents of the report.

Day 2

The day began with Professor Holmes summarizing the most important points from the presentations and discussions that took place on Day 1.

8. Progress towards dengue control

Dr Ron Rosenberg presented an update on WHO's Global Strategy for dengue prevention and control, 2012–2020. He also highlighted the recent invasion of chikungunya into the Western hemisphere. It is estimated that 4 billion people are at risk of dengue in 128 countries, with 390 million infections, 2.1 million severe cases and 21 000 deaths each year. Chikungunya and a newly emergent virus, Zika, are transmitted by the same vectors – *Aedes aegypti* and *Aedes albopictus* – that transmit dengue. Therefore, vector control strategies aimed at preventing dengue will also largely prevent these two emerging viruses. The rationale for a new global strategy for control of dengue and significant changes in the last 17 years were summarized. These include the likelihood for commercially available vaccines and several innovative methods for vector control. The specific objectives of the Global Strategy and the technical elements necessary for achievement of the objectives were reviewed, especially the need to understand how vaccines and vector control can be implemented together to reduce or eliminate transmission.

Dr Raman Velayudhan spoke on the recent activities relating to key technical elements for diagnosis and case management of dengue, integrated surveillance and outbreak preparedness, sustainable vector control, future vaccine implementation, basic operations and implementation research. He highlighted the enabling factors: advocacy and resource mobilization; partnership, coordination and collaboration; monitoring and evaluation; capacity strengthening, especially at country level; and communication for behavioural impact. The challenges for dengue control were summarized.

The following issues were presented for consideration by STAG:

- 1. Progress continues to be made by the international dengue community towards fulfilling the goals of the Global Strategy, which has been generally well received.
- 2. In particular, the date for the goal of estimating the true burden of dengue is 2015. A WHO-sponsored ad hoc advisory group is currently mapping progress towards this goal.
- 3. Several STAG members and regional representatives strongly supported the establishment of a technical working group or equivalent as necessary to enable the programme to lead the global effort, advise on the implementation of the global strategy, avoid duplication of and synergize global efforts.

STAG recognized the importance of the rising epidemic of dengue fever and endorsed these recommendations.

9. Challenges in eradication of yaws and update on HAT elimination programme

Dr Kingsley Asiedu updated STAG on progress towards eradication of yaws. He summarized key historical aspects of the disease, the current WHO strategy for eradication of yaws, and the outcomes of the third consultative meeting held on 24–25 March 2014. Results of the pilot implementation of the Morges Strategy were presented, along with the results of evaluation of the rapid diagnostic test for yaws (DPP Syphilis Screen), and studies on the molecular detection of azithromycin resistance markers. Progress in prevalence surveys in Benin, the Philippines and the Solomon Islands were summarized. The update from India suggests that transmission has been interrupted there. The conclusions of the 2014 meeting were summarized. STAG noted that donation of azithromycin could make a crucial difference in progress towards the goal of eradication.

Dr Jose Ramon Franco Minguell presented an update on progress in the HAT elimination programme. The indicators used to measure progress towards elimination were described, along with presentation of the number of cases reported each year from 2004 to 2013 in comparison with the required trajectory towards elimination, the geographical extent of diagnosed cases of *Trypanosoma gambiense* and the geographical areas at different levels of risk of HAT. Although the total population at risk has increased somewhat, this is all in areas of low risk, due to natural growth in population. The facilities that provide diagnosis and treatment for gambiense HAT have been mapped. Key events since the last STAG meeting include a meeting of the WHO Expert Committee on Control and Surveillance of HAT (December 2013), and the first WHO stakeholders meeting on gambiense HAT elimination (March 2014). STAG noted good progress towards the agreed targets.

10. Intensified control of neglected zoonotic diseases

Dr Bernadette Abela-Ridder reported on progress made by the working group on neglected zoonotic diseases (NZDs) that will focus on rabies, neurocysticercosis, echinococcosis and foodborne trematodes. The working group has realigned itself with the WHO roadmap on NTDs to focus on key affected countries and have their participation in the WG, as well as to allow a more flexible membership with project leads on priority areas of work that allow participation from the wider stakeholders and networks, and with representation from FAO and OIE. Rabies-related activities include using the proof of concept for rabies control and lessons learnt; elaborating the investment case; facilitating access to canine and human vaccines possibly via vaccine banks. A special effort to collate data and presenting on WHO Global Health Observatory will be made. For neurocysticercosis, an informal consultation for building a framework for control/progressive elimination is planned for June 2014. For echinococcosis, the control handbook is planned for completion in September 2014.

The recommendations to STAG included:

- Identify bridging points to other NTDs and sectors
- Increase critical mass.

Dr Malika Kachani also spoke on control of NZDs as a route to poverty alleviation among livestock-keeping communities and progress made in building advocacy in cross-sectoral partnerships.

11. Conclusions and main recommendations

The following were identified as the main issues of concern for STAG in 2014:

- Support for countries to increase coverage with integrated interventions
- Establishing principles and processes of verification, validation and certification
- Positioning NTDs in the post-MDGs 2015

- Mobilizing resources for yaws eradication
- Accelerating the work to control NZDs
- Responding to the dengue epidemic

The afternoon session of the second day was open to partners in NTD control and other invited stakeholders.

12. Summary of STAG deliberations

Professor Holmes presented a short summary of main issues discussed by STAG at the current meeting. Dr Savioli spoke on progress towards Roadmap targets in relation to diseases slated for eradication, global elimination and regional elimination. Dr Engels spoke on progress regarding scale up of PC and projections to reach 2020 targets. Professor Holmes spoke on the proposed principles and processes of verification, validation and certification to be adopted by WHO.

Short presentations were made regarding the activities of the expanded WG-M&E, WG-CS, WGA, WG-NZD; challenges for dengue control and prevention; and the work on Investment for Impact in NTD Control.

13. Open discussion with partners

STAG received a statement from Dr Chris Lewis (UK Department for International Development) regarding the inclusion of NTDs in the post-MDG 2015 agenda, especially in relation to universal health coverage; a presentation from Adriano Casulli of the European Union Reference Laboratory for Parasites regarding the HERACLES project on cystic echinococcosis; and a presentation from Professor Ahamed Hassan Fahal of the Mycetoma Consortium regarding mycetoma.

14. Points for follow-up action

Inclusion of NTD in the United Nations Sustainable Development Goals post-2015 and Universal Health Coverage agenda

 Action points: A group of key individuals from the NTD and sustainable development communities to be coordinated to jointly advocate for the inclusion of NTDs in the post-2015 development goals (L. Savioli to lead). WHO/NTD to initiate in-house discussions for inclusion of NTDs in Universal Health Coverage.

Eradication of dracunculiasis

STAG noted the significant progress made towards dracunculiasis eradication, with the lowest number of 148 cases being reported in 2013. However, it noted with concern the unusual epidemiology of dracunculiasis in Chad where dogs have been found to be infected, possibly posing the risk that a significant non-human reservoir exists. STAG recommends that WHO/NTD, CDC Atlanta and The Carter Center carry out a detailed epidemiological assessment of dracunculiasis transmission in Chad and recommend interventions to ensure that transmission is interrupted by 2015 as indicated in the WHO roadmap on NTDs, a prerequisite for eradication.

Other general points for follow-up

- Include a presentation by Director-APOC/PENDA at the next STAG meeting regarding changes in the Onchocerciasis Control Programme
- Include a presentation on quality of antileishmanial medicines at the next STAG meeting
- Revise the terms of reference for Regional Programme Review Groups
- Do not restrict dengue to a Working Group but provide a much stronger solution, such as a dengue unit in WHO with epidemiological expertise for surveillance, virological expertise to prepare for vaccine use and vector control expertise.
- If the 2015 and 2020 targets are to be met, there is an urgency to scale up capacity strengthening activities for national programmes.
- Review the remit of Working Groups and include executive summaries for reporting to STAG.
- Celebrate achievements over 10 years of NTD control after the meeting in Berlin, April 2005.

Professor Holmes thanked the partners for joining the STAG meeting, STAG members, members of the WHO NTD Department and Dr Savioli for his charismatic leadership in NTD control.

The STAG 2014 meeting was closed by Dr Hiroki Nakatani, who thanked all the STAG members and partners in NTD control for their unswerving commitment.

This meeting of the STAG was facilitated by the excellent administrative work of Ms Linda Aimé-McDonald and Ms Corinne Suchet, to whom warm thanks are extended.

STAG is most grateful to Professor Nilanthi de Silva and Dr Denis Daumerie for their prompt and accurate provision of this report.

- Annex 1. List of participants
- Annex 2. Neglected tropical diseases: becoming less neglected. *Lancet*, 2014, 383(9925):1269.
- Annex 3. Report of the WHO Informal Meeting on Investment for Impact in the Control of Neglected Tropical Diseases
- Annex 4. Report of the Global Working Group Meeting on Capacity Strengthening for Control of Neglected Tropical Diseases
- Annex 5. Report of the Working Group on Access to Quality Assured Medicines for Neglected Tropical Diseases
- Annex 6. Report of the 5th NTD-STAG Global Working Group meeting on Monitoring and Evaluation of Preventive Chemotherapy
- Annex 7. Report of the 5th meeting of the Working Group on Monitoring of Neglected Tropical Diseases Drug Efficacy



SEVENTH STRATEGIC AND TECHNICAL ADVISORY GROUP FOR NEGLECTED TROPICAL DISEASES 8-9 April 2014 WHO/HQ, Salle B

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Chair of Informal Working Group Meeting on Investment for Impact in the Control of Neglected Tropical Diseases *Professor Deborah McFarland* Emory University, Rollins School of Public Health, Atlanta, USA

Neglected tropical diseases: becoming less neglected

Neglected tropical diseases (NTDs) cover a wide range of infections that predominantly affect the poorest and most vulnerable individuals. Neglected, but not unknown, these diseases are preventable and treatable. They threaten the lives of more than 1 billion people worldwide, including half a billion children. To take the "neglected" out of NTDs, public and private partnersincluding drug companies, donors, and governmentscommitted to what is now referred to as the 2012 London Declaration to control, eliminate, or eradicate by 2020 ten NTDs (lymphatic filariasis, trachoma, soil-transmitted helminths, onchocerciasis, schistosomiaisis, leprosy, quinea worm, visceral leishmaniasis, Chagas disease, and human African trypanosomiasis). The promises made were to ensure the supply of drugs, to advance research and development, to enhance collaboration and coordination at national and international levels, to enable adequate funding, and to monitor programmes.

Honouring their pledge to provide regular updates, on April 2, 2014, global health leaders gathered at the Institut Pasteur in Paris for the release of Uniting to Combat NTDs: Delivering on Promises and Driving Progress, a report assessing gains and setbacks towards reaching the 2020 NTD goals. With about 1.35 billion treatments donated in 2013, a 35% increase since 2011, pharmaceutical companies met 100% of requests for drugs. The number of countries requesting and receiving NTD drug donations increased from 37 in 2011 to 55 in 2012. Clinical trials are underway for a new oral drug for human African trypanosomiasis, and a paediatric formulation of praziguantel for schistosomiasis is also under development. Drug companies have supported these goals by opening their compound libraries, and the Drugs for Neglected Disease initiative is screening more than 7000 compounds. More than 70 countries have now developed national NTD plans. Brazil, with the largest NTD burden in the Americas, included NTD programmes in its Without Extreme Poverty plan and launched a school-based strategy combining deworming and leprosy screening. Colombia became the first country in the world to eliminate onchocerciasis.

Despite impressive progress, the fight is far from over. Only 36% of people in need of NTD drugs worldwide received what they needed. Several indicators are not yet on target to achieve the 2020 goal to control NTDs. Worryingly, coverage is low for schistosomiasis; in 2012, only 31 of 52 endemic countries implemented treatment programmes. Conflicts in countries such as South Sudan are also affecting programme performance. Partnerships with the pharmaceutical industry have been and remain crucial. But drugs are only effective when they reach the people who need them, so more effort is needed to increase scale-up and timely delivery in many countries. Other key challenges identified in the report that must be addressed include financial resources to support programme implementation from public, private, and domestic sources; and increased collaboration across key health sectors-sanitation, education, and nutrition. We emphasise two additional challenges. One is highlighted in the report-namely "there has been no systematic effort to support these goals with quantitative modeling to ensure that the various strategies being implemented can be expected to achieve them". A new NTD modelling consortium has been created and its future role will be crucial. Also, the Stakeholders Working Group includes representatives of organisations that signed the London Declaration-that is, the group is not independent. The accountability arrangements to monitor and review NTD programme progress need to be made more robust.

Looking ahead the focus must be on long-term sustainability and continued equity in NTD control, including expansion of NTDs tackled beyond the selected ten. Putting in place coherent and sustainable health and social protection systems is also key. This can only be achieved by countries committing to universal health coverage and anchoring NTDs in the post-2015 sustainable development goals (SDGs). Access to NTD control interventions and increasing their impact on reducing chronic disability must top the agenda. If NTDs are to be an SDG sub-goal, which targets and indicators will be needed? For such a disparate group of diseases, can a single indicator be agreed upon, especially one that goes beyond mortality and captures the burden of disability caused by NTDs? Unfortunately, there was too little time for discussions in Paris last week to refine targets and indicators to assess access and impact of NTD control as part of any future SDGs. To be sure, political and financial commitments need to be strengthened much more if the London Declaration and the WHO Roadmap are to be fulfilled. The Lancet



For the **2012 London Declaration** see http://unitingtocombatntds. org/resource/london-declaration

For the **report Uniting to Combat NTDs: Delivering on Promises and Driving Progress** see http:// unitingtocombatntds.org/ resource/delivering-promisesand-driving-progress-secondprogress-report

WHO informal meeting on investment for impact in the control of Neglected Tropical Diseases

Geneva, Switzerland 16–17 December 2013

Note for the record

Summary

WHO's informal meeting on investment for impact in the control of Neglected Tropical Diseases (NTD) was the first meeting of its kind for the NTD Department, bringing together Ministries of Health (NTD programmes), Ministries of Finance, and international experts in the economics and impact of NTD control interventions.

The objectives of the meeting were:

- 1. To inform the forthcoming WHO report on "Investing to overcome the global impact of neglected tropical diseases", to be published end 2014;
- 2. To develop a proposal for the establishment of a WHO working group on "investment for impact", to be presented to the WHO NTD Strategic and Technical Advisory Group (STAG) in April 2014.

The outcomes included:

- 1. Recommendations for content for the WHO report which, it was agreed, should feed also into the forthcoming update to Disease Control Priorities Project.
- 2. Commitments from participants to contribute to this work in 2014 during writing and peer review and, beyond 2014, to increase coordination and collaboration across the growing number of projects being funded in the area of NTD economics.
- 3. Draft terms of reference for a working group to continue this work at the countrylevel beyond 2014; these will be presented to the STAG for their consideration and endorsement in April 2014.

See also "Minutes of the meeting" and "Decisions and action points", below.

Participants

The final list of participants is available <u>here</u>. If there are corrections to be made to contact details, they may be "commented" in the file by opening it in Google Docs.

Agenda

The final agenda is available <u>here</u>.

Background documents

Background documents are available <u>here</u>. Please note that some of these documents were revised in light of the discussions of the group, most notably the proposed terms

of reference for the Working Group (please see Decisions and action points below or the revised version <u>here</u>).

Presentations

Presentations, listed by the presenter's last name, are available <u>here</u>.

Minutes of the meeting

Detailed minutes of the meeting are available courtesy of Ms Alexander, <u>here</u>. If there is anything that you would like to add or revise, you may comment the file by opening it in Google Docs.

Decisions and action points

Day 1: Strategic and technical consultation on investment for impact in the control of NTDs

Participants from endemic countries made presentations about investment and impact from the perspective of national programmes.

- *Decision*: The group considers it useful to develop case studies of integrated NTD plans within broader development / poverty reduction plans, and of how this has led to investment and impact.
 - Action: With support from the group, participants from Brazil and Uganda will contribute to the WHO NTD Report with a short description from their countries (e.g. how Brazil successfully integrated NTDs within Brazil Without Poverty).
- *Decision*: The group considers it important to summarize also the evidence on health systems cost and catastrophic health expenditure due to NTDs, especially given the relatively little focus thus far on case management NTDs (i.e. the IDM diseases).
 - Action: With support from the group, participants from Nepal and Philippines will provide a short description of action taken by their countries to protect against catastrophic expenditure (e.g. conditional cash transfers for kala-azar in Nepal).
- *Decision*: The group considers it instructive to consider the (at least) two very distinct pathways toward investment and impact: priority setting by economic rationale and priority-setting by champions.
 - Action: Bangladesh can contribute to the WHO NTD Report with an example of how economic rationale (e.g. the relative cost-effectiveness of dog vaccination versus case management) can prevail.
 - Action: Yemen can contribute with an example of how with a good story and political will, resources can be found, and impact relatively quickly achieved.
- *Decision*: The group considers that domestic funding within endemic countries is critical to the success of NTD control, but so is the continuation of drug donations.
 - *Action*: The group should demonstrate how government investments in NTD control can leverage billions in drug donations.

The draft outline for the next WHO NTD Report was discussed, the working title of which is "Investing to overcome the global impact of neglected tropical diseases".

- *Decision*: The group broadly agrees with the proposed outline and commits to supporting the development of content for the WHO NTD Report.
 - *Action*: In particular, the group will work towards filling some of the gaps in the evidence, such as:
 - evidence of the contribution of control of case management, veterinary public health and vector control interventions to the Millennium Development Goals (retrospective)
 - forecasts of socioeconomic/equity impact of NTD control (prospective)
- *Decision*: The group considers that Universal Health Coverage would be a useful framework for post-2015 investment benchmarks and that we should look at innovative financing mechanisms
 - Action: WHO will work with the World Bank in developing content for the WHO NTD report.

The group then discussed a presentation from the Task Force on EMPaCT.

- *Decision*: The group welcomes the establishment of a platform for research projects in response to country requests and considers that it is important to include the other NTDs in this effort, while recognizing that the demonstration of long-term impact (experimental designs) may require different mechanism and funding.
 - *Action*: The group will review the concept notes and different analytical frameworks.
 - *Action*: Countries are invited to volunteer to pilot test the platform (Christy Hanson is to follow up directly with country participants)
 - *Action*: Academic institutions are invited to express interest in having their students participate.

The group then discussed a presentation from the WHO health financing team, on Universal Health Coverage (UHC).

- *Decision*: The group considers that the NTD community can probably best inform UHC decisions (e.g. about what interventions are to be covered) during the priority setting process.
 - Action: The group should explore further the usefulness of extended costeffectiveness (i.e. cost-effectiveness that accounts explicitly for equity) or multicriteria decision analysis in making the investment case for inclusion of NTDs in UHC packages.

The group then discussed presentations from the WHO team looking at costs, effectiveness, expenditure and priority-setting across the Organization.

- *Decision*: The group considers that WHO-CHOICE and the OneHealth Tool may help prioritize and integrate NTDs within health sector plans and budgets.
 - *Action*: WHO will seek to mobilize resources for the inclusion of NTDs in these tools, and provide technical guidance to their development.

- *Action*: Country participants are asked to consult with people at home whether there would be interest in piloting a OneHealth Tool NTD module.
- *Decision*: The group acknowledges that health accounting is the WHO recommended method of monitoring NTD expenditures in a way that is comparable with other diseases and hopefully least onerous for NTD programme staff.
 - *Action*: The group is invited to review the "guidance document" for health accounting, available for review, edits and contributions <u>here</u>.
 - *Action*: countries are invited to "pilot test" NTD resource tracking during their next health accounting exercise.

The group then discussed presentations from WHO technical focal points for water and sanitation and the social determinants.

- *Decision*: Given the importance of WASH and the social determinants more generally to NTD control, the group considers it important to "monitor the monitoring" of investment and impact in these sectors, assessing whether they are being made to maximize NTD impact.
 - Action: The proposed working group should invite experts from WASH, education, transportation to identify opportunities for joint action on common barriers to financial risk protection and effective service coverage.
 - Action: The proposed working should engage with relevant partners, including the M&E working group, to examine possibilities for gender/income/education and other disaggregation of routine data to capture barriers to coverage.

The group then discussed a verbal intervention from a representative of the World Bank.

- Decision: The group considers that new and innovative sources of financing will play an increasingly important role in NTD control.
 - Action: WHO and the WB will document for the WHO NTD Report case studies of IDA loans and Results-based financing for NTD control, including regional pooling of funding to deal with transborder issues.
 - Action: The proposed working group will consider providing guidance/assistance to countries in the development of proposals for other innovative financing instruments and countries should test appetite for them within MoH and MoF

Day 2: Consultation on the establishment of a Working Group (WG) on Investment for Impact in the control of NTDs

Terms of reference for the working group were revised on the basis of the discussions of the group. The latest version is available <u>here</u>. It may be further "commented" by opening it in Google Docs.

These terms of reference and a results framework (logframe) will be presented to the STAG in April 2014 and, after endorsement by STAG, a call for nominations will be issued. WHO counts on the meeting participants to help disseminate the call and enlist a diversified and qualified group of members.

REPORT OF THE GLOBAL WORKING GROUP MEETING ON CAPACITY STRENGTHENING FOR CONTROL OF NEGLECTED TROPICAL DISEASES

World Health Organization, Geneva, Switzerland 9-10 January 2014, Salle M505

Chairman: Prof. David Molyneux Rapporteurs: Ms Kimberly Won, Dr Marco Albonico

Introduction

A meeting of the Working Group on Capacity Strengthening for Control of Neglected Tropical Diseases (WG-CS) was held at the headquarters of the World Health Organization (WHO) in Geneva, Switzerland, on 9-10 January 2014. The agenda (Annex 1) and list of participants (Annex 2) are included in this report.

Dr. Savioli opened the meeting and drew attention to the World Health Assembly resolution (WHA66.12) on Neglected Tropical Diseases (NTD) that was adopted in May 2013¹. Although this resolution summarizes clear directives for the global NTD community, it also exposes potential challenges that will be faced. There is a critical need to rapidly scale-up programs in the next two years (2014-2015) in order to ensure NTD Roadmap to 2015 and 2020 goals are met. In WHA 66.12, capacity strengthening (CS) is included as a major priority to accelerate implementation of NTD programs. WHO is committed to ensuring NTD goals are met.

Summary report on recommendations from WG CS 2012

Professor Molyneux called attention to the increased global recognition of NTDs. In the recent report *A New Global Partnership: Eradicate Poverty and Transform Economies through Sustainable Development* to the UN Secretary General, NTDs were specifically stated in goal #4: Ensure Healthy Lives. Additionally, in a report by Seddoh et al (2013)², the unit costs for NTD programs were confirmed and an annual funding shortfall of \$200 million was reported. This budget shortfall can potentially be found within national health expenditure budgets; for example India, Nigeria, Brazil and the Philippines could likely treat all citizens at risk of NTD infection by dedicating less than 10% of incremental new health funding to their national NTD programmes³. Professor Molyneux reminded the group of the WG-CS recommendations made to the Strategic and Technical Advisory Group for NTDs (STAG-NTD) after the first WG-CS meeting held in December 2012.

¹ SIXTY-SIXTH WORLD HEALTH ASSEMBLY WHA66.12, Agenda item 16.2 (27 May 2013), Neglected tropical diseases, http://www.who.int/neglected_diseases/mediacentre/WHA_66.12_Eng.pdf

² Anthony Seddoh, Adiele Onyeze, John Owusu Gyapong, Janet Holt, Donald Bundy, LANCET COMMISSION ON INVESTING IN HEALTH WORKING PAPER: Towards an Investment Case for Neglected Tropical Diseases, 2013 ³ Confronting neglected tropical diseases: will highly endemic countries buy in? URL http://dalberg.com/blog/?p=2372, accessed 17 March 2014

There were 8 recommendations made, of which the 3 key recommendations were to:

- Focus on strengthening capacity to scale up NTD programs in five identified highly populous countries (Democratic Republic of the Congo, Ethiopia, Nigeria, Tanzania and Indonesia) targeted for NTD control or elimination interventions
- To develop an NTD toolbox and determine appropriate content to support national programme managers.
- To harness Institutional capacity that exists for laboratory strengthening and beyond; build capacity of local national/regional Institutions and develop regional network of training Institutes to deliver training packages, improve diagnostic tools for mapping and monitoring etc.

The details of the recommendations can be found in the report from the December 2012 meeting.

Dr. Rio presented a summary of progress of implementation and follow-up on the nine recommendations made to the STAG-NTD in 2013. Significant progress has been made on the following recommendations:

- A generic 'job description' has been developed for NTD teams
- An NTD toolbox and its contents has been developed, a β-version of which will be released April 2014.
- A training needs assessment (TNA) was completed by State level NTD programme managers in Nigeria and a training needs survey was completed by national programme managers in the African region. (AFRO)
- An inventory to assess laboratory capacity to support NTD programs was initiated and completed in 5 of the 6 WHO regions
- The Kenya Medical Research Institute (KEMRI) and The Noguchi Memorial Institute for Medical Research (NOGUCHI) are two centers in the African region that were identified to serve as sites for the first Training of Trainers for the Program Managers' and other NTD workshops to be conducted in AFRO.

Details of main outcomes WG CS Workplan 2013 activities

1) Meeting on development and roll-out of a standardized district level management NTD training The above meeting was held 17-18 July 2013 at WHO HQ to

- develop a focused strategy and propose tools for capacity strengthening especially in highburden WHO regions;
- Identify specific capacity strengthening needs at the district level in order to accelerate scale-up of coverage in the most highly populous countries in AFRO and SEARO.

Dr. Kabatereine, chair of the July 2013 meeting, presented the major outcomes and recommendations to the WG-CS. During the July meeting the significant achievements in NTD control were highlighted. However, it was also recognized that the current trajectory of NTD interventions was not adequate for reaching 2020 goals. The ability to reach these goals will require rapid scaling up of NTD interventions especially in the five most populous countries (DRC, Ethiopia, Nigeria, Tanzania and Indonesia). A district level managers training course curriculum following the EPI model was proposed as the main action point from the meeting. Through presentations from WHO regional offices and partners, it was found that many resource manuals already exist. However, there was a felt need to harmonize all of the materials into a single standardized training course based on the following 10 modules:

	Block (Sub-sections of the block are referred to as units)	Lead developer	Additional team members
1.	Introduction (including basic knowledge of PCT NTDs: epidemiology and prevention measures; basic mgmt. and coordination principles)	WHO	
2.	District coordination and program management	NOGUCHI	WHO
3.	Program planning, budgeting, resource mobilization (including identifying target population)	RTI	SCF, DtW, CWW, ITI
4.	Advocacy, sensitization and social mobilization	RTI	HKI, ITI
5.	Program operations and logistics (for MDA)	WHO	SCF, DtW, CWW, ITI
6.	Morbidity management	RTI	HKI, ITI WHO
7.	Training for service delivery (health workers/teachers/Community volunteers)	KEMRI	DtW, SCF, ITI
8.	Other preventative measures and related sectors	CWW	DtW, RTI (Vector
	-	(WASH)	mgmt)
			WHO
9.	Laboratory and Diagnostics (as extra module if needed)	CNTD	WHO
10.	Monitoring, Evaluation and surveillance	WHO	RTI,CNTD

The proposed district level managers training modules will follow the same 'Sunflower' concept used for the National Programme Managers' training course but will be simplified and adapted to be relevant for sub-national level NTD programme management.

A working group has coordinated the development of draft modules, but significant revision is still required. A pilot training was scheduled for the first quarter of 2014, but will be delayed in order to complete the revision. Additionally, a similar activity to develop a field guide for implementation of Mass Drug Administration activities is being undertaken by AFRO. There needs to be a concerted effort to coordinate and harmonize the WHO/HQ and AFRO activities.

2) NTD toolbox

PAHO worked closely with WHO HQ to identify an experienced company to participate in the development of an NTD toolbox. Significant progress has been made to develop an electronic platform for the application. Dr. Saboya informed the WG-CS that the recruitment process and contract with a private company based in Colombia were finalized in November 2013. The NTD toolbox is a virtual repository of operational guidelines, documents, videos and photographs that allows easy, fast and userfriendly searching of information resources needed to support the work on Neglected Tropical Diseases. The content of the application has been organized in the same 'Sunflower' framework as the National Program Managers training course. Users will be able to search for relevant documents by topic or disease. The main concepts and information will be available in English, French, Spanish and Portuguese. Currently, approximately 450 documents have been added to the repository, but several key documents still need to be included -notably including those from NTD partners. The included documents are intended to be operational in nature and not a collection of research reports. The content of the NTD toolbox will be updated every six months. When completed the toolbox will be available on Android, iOS and Windows platforms (including a multimedia version available in DVD) and will be easily accessible from several different types of devices, including computers, tablets and smartphones. This will allow for greater accessibility to resource information across NTD programs. It is envisaged that the Beta-version of the NTD toolbox will be ready by April 2014.

3) Laboratory strengthening

It has been recognized that a lack of effective laboratory capacity is a critical bottleneck in progress toward NTD Roadmap goals. Regional Reference Laboratories (RRLs) are essential as laboratory hubs for NTD diagnoses, monitoring and surveillance. However, knowledge of RRLs working on NTDs is fragmented and not well coordinated across WHO regions. Professor Bates presented preliminary results from a WHO commissioned RRL scoping survey conducted from October 2013 – January 2014. This inventory was undertaken as an initial step to identify the existing network of strategically located, international standard NTD RRLs. The objectives of this survey were to:

- Map the geographical distribution of NTD laboratories in five WHO regions (excluding AFRO)
- Describe their roles, capacities and needs
- Identify any NTD RRL networks

An RRL was defined as a laboratory that offered technical and scientific support for at least one NTD and 1) provided training; 2) were technically competent and quality assured (QA); and 3) interacted with other institutions.

An electronic survey was distributed to laboratory managers of 162 identified laboratories. As of mid-December 2013, only 13% (n=22/162) had responded to the survey. Preliminary analysis of the initial responses indicated that 55% of the laboratories were government laboratories and most were in an academic institution. Approximately 50% of the laboratories employ fewer than 10 staff. More than 70% employ scientists and researchers and nearly one-third of the laboratories lack key human resources. Each of the 17 NTDs was covered by at least one laboratory and the majority (77%) covered two or more NTDs. However, only three laboratories (14%) fulfilled all three RRL criteria (training, QA and external interactions). It was discovered that a low proportion of the laboratories adhered to quality standards.

A similar inventory is being conducted in AFRO. The activity in AFRO will be coordinated with the survey led by Liverpool School of Tropical Medicine. An effort will be made to use the same definitions to provide the ability to merge results to create a comprehensive global landscape of the available laboratory capacity. Moving forward, decisions need to be made on how to select and invest in RRLs for future development in order to plan for rapid scale-up of NTD laboratory support systems.

Capacity Strengthening activities by WHO region: priorities, progress, challenges and needs

Reports were given by Drs. Saboya (AMRO), Ben-Ismail (EMRO) and Dayanghirang (WPRO). Drs. Onyeze (AFRO) and Kusriastuti (SEARO) were unable to attend the WG-CS meeting but were able to make their presentations via teleconference. Dr. Ejov, also unable to attend the meeting, provided an update to Dr. Mbabazi, who presented on behalf of EURO. Major priorities and progress as well as challenges and needs in each of the regions are summarized in Table 1 below.

Region	Priorities and Progress	Challenges and Needs
AFRO	 -Regional NTD strategic plan developed -Coordinated MDA and community directed treatment for NTDs -Mapping will be complete by mid-2015 (Gates funding) -Elimination targets set for LF, SCH and TRA for 'quick win' countries by 2015 	 -High burden of NTDs in region -Short term needs: MDA targeted CS including field guides for district level managers and community distributors -Long term needs: Program and institutional CS -Increased advocacy and funding
AMRO	 -Integrated national plans of action for neglected infectious diseases (NIDs) -Integrated modules for monitoring programs -Development of training courses that can be adapted and shared with other regions. 	 -Development and adaptation of tools to support integrated plans of action (e.g. TIPAC) -Integration of NID control and elimination efforts with interprogrammatic and intersectoral efforts (e.g. toolbox for STH) -Monitoring progress toward control and elimination of NIDs (e.g. survey support and training) -Seed funding for program implementation; funding to retain technical support at the regional level and support travel of external facilitators.
EMRO	-LF: 2 of 3 countries in post-MDA stage; training workshops held -SCH: very low endemic (near elimination) in 12/15 countries; high political commitment in Yemen; MDA started in Sudan (2013) ONCHO: active programs in Yemen and Sudan -Strong laboratory networks exist (but generally not for NTDs)	 -Complex emergency situations and political instability may limit ability to reach 2020 goals. -Sensitive diagnostic tools needed to verify elimination of SCH -Fundraising and capacity strengthening needed, especially for Sudan.

Table 1. Capacity Strengthening Activities by WHO Region: Priorities, Progress Challenges and Needs

EURO	-STH is only PC NTD in the region; mapping to be completed in 2014; highest burden in central Asia - Draft of the Strategic Framework on control and prevention of STH has been discussed and agreed during regional consultations on STH in 2012 and 2013 -Laboratory capacity available in the region	 -Develop and publish a regional resource manual on control and prevention of STH in EURO. -Develop and publish regional training curriculum for STH control -Assistance to countries to develop national strategies and plans of action for STH control
SEARO	 -Integrated NTD control and elimination in the region; Regional Strategic plan -LF, STH, SCH, TRA, Yaws MDAs being conducted -LF programs scaling down in 5 of 9 endemic countries -Program evaluation for LF and STH (Thailand, Myanmar, Timor Leste) 	 -Scaling up LF program in Indonesia; 181 out of 300 districts still need to start MDA Need for NTD human resources at regional level Need to improve data management practices and data quality. -Funding (e.g. cost of scaling down LF in India) -Strengthening morbidity management for LF
WPRO	-Regional Action Plan addresses all 13 NTDs in region -LF elimination on course for 2020; SCH declining in all four endemic countries; STH starting to scale up -Plans to update national NTD plans of action	 Curb high turnover of NTD program managers, especially at regional level and need for dedicated national NTD programme managers Logistical challenges in reaching Pacific Islands Special dedicated effort needed following destruction of infrastructure after natural disasters (Typhoon) Need laboratory capacity strengthening Need assistance on coverage validation surveys Implementation of pharmacovigilance Need guidance on LF post-MDA surveillance foster intersectoral collaborations. respond to formal requests for training from countries, e.g Fiji for training of NTD programme managers.

The priorities of the WG-CS during the first year were mainly focused on preventive chemotherapy (PC) efforts. Although scaling up PC interventions will remain a priority for the upcoming year, efforts will be extended to include CS for intensified disease management (IDM), neglected zoonotic diseases (NZD) and Vector Ecology and Management (VEM).

Capacity strengthening for Intensified Disease Management

Dr. Jannin presented an overview of the six IDM NTDs slated for eradication (Yaws), elimination (Human African Trypanosomiasis, Visceral leishmaniasis and Chagas disease) and control (Cutaneous leishmaniasis and Buruli Ulcer). The IDM strategy to reach the Roadmap to 2020 targets is based on the completion of seven main strategic components and guiding principles of which CS is one. Given the nature of the IDM approach, there is a requirement for thorough training at all levels (i.e. subnational, national and regional). IDM capacity strengthening prioritizes training for:

- Treatment monitoring and drug resistance surveillance
- Proper drug administration and surveillance
- Evaluation and use of diagnostic tests

Systematic training is critical to ensure proper implementation of IDM strategies. Because of the emphasis on CS pre-service and in-service training, disease-specific educational materials and training courses have been developed for use at all levels in each of the WHO regions where IDM NTDs are endemic.

Capacity strengthening for Neglected Zoonotic Diseases

Neglected zoonotic diseases require intensified control, but the presence of animal reservoirs makes it difficult to target these diseases for elimination. Currently, only rabies is scheduled for regional elimination. The complexity of the control efforts requires intersectoral collaboration and capacity across different disciplines. Dr. Abela-Ridder presented the strategy for strengthening capacity for NZDs. Capacity is required at individual, organizational and systems levels and CS efforts are focused on each of these levels. Dr. Abela-Ridder explained the close collaboration at the human-animal-ecosystems interface. Training in each of these sectors includes topics of interest across all of the disciplines in an effort to create a harmonized control approach. Because of the importance of coordination, training courses are carefully designed to employ adult learning theories and are focused on ensuring the appropriate personnel are being trained. Non-traditional, e-learning strategies are often used and there is a concerted effort to evaluate the trainings to gauge knowledge uptake and translation.

Capacity strengthening for vector control

The Vector Ecology and Management (VEM) department at WHO promotes strategies for integrated vector management (IVM) and there are cross-cutting roles within NTDs and other WHO departments. Dr. Velayudhan presented current IVM initiatives to the WG-CS. Some current VEM responsibilities include providing technical guidance to regions and countries, global coordination of dengue control and vector control at points of entry. Dr. Velayudhan emphasized the need for entomological surveillance and monitoring for insecticide resistance. Capacity strengthening to address these needs include:

• Long-term training courses – diploma in applied parasitology and entomology (Malaysia); master's degree programs (Benin, Pakistan, Sudan, India, UK)

- Short-term courses IVM workshops; dengue workshops (Cuba, Singapore)
- Area-specific courses management of public health pesticides (e.g. Cape Town University)

Although these courses exist, there is a need for course material and curricula to be streamlined. Capacity strengthening processes can be improved by building linkages within Ministries of Health to develop career pathways for public health entomologists. Additionally, regional networks should be encouraged to enhance IVM efforts.

The strategies used by IDM, NZD and VEM necessitate cross-sector coordination and collaboration. It was suggested that PC programs should incorporate some of the effective approaches to CS from these non-PC programs.

Capacity strengthening activities by NTD partners: 2013

IMAI-IMCI

The WHO Integrated Management of Adult Illness (IMAI) District Clinician Manual (DCM) was published in 2012. The IMAI DCM was developed to be used as a reference resource for doctors and clinical officers at district hospitals in resource limited countries. Volume 2 of the DCM includes a syndromic approach by main symptoms for the management of adult illness and includes differential diagnosis tables which include NTDs. Dr. Gove presented progress made on the process required to adapt the DCM for national and/or regional use. A workshop held in Uganda highlighted the strength of using an integrated approach for case management, and the Ugandan adaptation of the DCM included all 17 NTDs. The adapted manual will be distributed in hard copy to district hospitals. It will also be available in soft copy on smartphones and tablets. The WG-CS recognized that the role of clinicians is often neglected in implementing NTD programs and clinical guidelines are needed for caregivers. Surveillance requires good recognition of disease and a well-adapted, integrated DCM can support both pre-service and in-service medical training to improve clinical care. Neglected tropical diseases modules could be added to case management training, and it was suggested that DCMs modules be added to the NTD toolbox.

Laboratory network for monitoring drug efficacy

Current PC NTD programs depend on the use of few drugs and there is minimal effort to identify new drugs to use for program implementation. Therefore, monitoring the efficacy of the current drugs is critical for program success. Dr. Vercruysse presented the rationale for the need to establish laboratory networks to monitor drug efficacy. It was suggested such a network could comprise:

- **Reference laboratories** 1-5 per continent; experienced laboratory technicians responsible for oversight of guidelines, reporting and training.
- **Partner laboratories** 1-5 per country; experienced laboratory technicians responsible for monitoring, reporting and training

Dr. Vercruysse also described several new and innovative diagnostic tools and methods with potential use in NTD programs. However, many of these tools are still considered research applications and are not yet available for routine programmatic use. There was discussion on the need to identify ways to accelerate the process of translating research tools into programmatic tools.

The WG-CS discussed the need to assess the current status of laboratories and their competencies for stool diagnosis. This inventory would not only identify the location of laboratories but would also assess expertise within the facilities and identify needs.

NTD Envision/RTI International

Dr. Doherty provided an update on the activities supported by Envison/RTI in 2013. In collaboration with WHO and the global NTD community, RTI supported the following:

- **Course development** RTI has worked with partners to contribute to the development of NTD related training courses including involvement in the current initiative to develop the District Level Manager's course.
- Workshop implementation workshops covered topics such as Tool for Integrated Planning and Costing (TIPAC), Transmission Assessment Survey, M&E, media training, grants management, Zithromax MDA training, Global Trachoma Mapping Project (GTMP) and cascaded training for MDA.
- Technical assistance provided in 25 countries
- **Tools** collaborated in the development of Data Quality Assessment tutorial, TIPAC demonstration, Trachoma best practices manual, electronic data collection and NTD database template
- **Resources** RTI provided human and financial resources for several training workshops
- Job aides production of a Health Worker Pocket NTD Manual

In continued commitment to NTD control and elimination efforts, RTI will again support workshops and training courses in 2014. These will include the following:

- NTD Program Managers Training Course
- Data management courses
- 5th AFRO M&E workshop
- National Database template training for Power Users; Training of Trainers
- Grants management training
- Media training
- TIPAC regional training workshops

To address the need for rapid scaling up of NTD interventions in the highly populous countries, RTI in collaboration with Sightsavers will conduct the NTD Program Manager's Training workshop in Abuja, Nigeria (3-8 February 2014). Key personnel from all 36 states will participate in the training. In addition to the training in Nigeria, RTI is in a position to support two additional Program Manager's Training courses and invited suggestions from the group on possible sites for the training.

Sightsavers

In alignment with the Sightsavers' mission to eliminate avoidable blindness and promote equality of opportunity for disabled people, Sightsavers has a strong commitment to reaching the Roadmap targets set for onchocerciasis and trachoma. Mr. Bush provided an overview of Sightsavers activities to the WG-CS. Sightsavers was responsible for providing 73 million treatments for onchocerciasis and trachoma in 2013 and utilized a network of 300,000 community drug distributors and 20,000 health care workers. Sightsavers has had an integral role in the Global Trachoma Mapping Project (GTMP) and to date 730 districts have been mapped. The project has used a core team of trainers and local mapping

teams. Standardized training materials and an electronic (mHealth) data collection system have facilitated the effort.

In 2014-15, using funding committed by the UK government, Sightsavers will continue NTD activities primarily in Africa. One project on which Sightsavers will focus will be integrated NTDs in Nigeria. With anticipation of program activities to be handed over to the Ministry of Health after the first three years, a strong emphasis is being placed on CS. The program will be embedded within existing service delivery platforms which will strengthen national ownership and capacity. The four focus areas for CS activities have been identified as:

- Providing technical assistance in drug supply chain management
- Providing technical assistance to support coordination, strategy and policy development of NTD activities
- Providing technical assistance and support to the state MOH in targeted states in implementing the integrated NTD program
- Providing a CS plan to enable delivery of full health systems planning and management with implementation of the CS plan

Capacity strengthening for highly populous countries (HPC)

It is recognized that the current trajectory of NTD interventions will not be adequate to reach established targets by 2020, and there is a need to rapidly scale up NTD programs. In order to address this significant need, the focus has been on identifying ways to quickly scale up programs in the most populous countries targeted for NTD control and elimination. Based on country reports received in July 2013, Dr. Mbabazi presented key accomplishments, current CS initiatives, priorities and needs from six HPC (DRC, Ethiopia, Nigeria, Tanzania, Bangladesh and Indonesia). Across all the countries five key issues were expressed:

- •Advocacy and sensitization a need for appropriate and effective information, education and communication (IEC) strategies
- •**Training** for mapping, scale-up, morbidity management, M&E, medicines safety, logistics and program management; especially at district and peripheral levels
- •**Technical tools** a need for simple, practical field guides; available in local languages
- •Finances national master NTD plan funding gaps, including for training and M&E activities
- •Human resources high staff turnover at regional level and at national level
- **Context-specific strategies for hard-to-reach populations** large distances, difficult terrain, humanitarian and complex emergencies

The approaches to address these issues were categorized into short-term and long term actions:

- Short term capacity building targeted capacity building training/re-fresher training activities (1 -2 days) implemented in the immediate period leading up to field activities to support scaleup and effective delivery of interventions (e.g. field guides for district managers, health facilities and community distributors).
- **Longer-term capacity strengthening** to initiate and sustain CS gains e.g. national NTD manager's training courses, institutional CS, working with NTD centers of excellence etc.

A summary of individual country accomplishments, current CS initiatives, priorities and needs are presented in Table 2.

Current CS activities or Country Key accomplishments CS and training needs and resources available priorities 2.4.1 Nigeria • NTD Master Plan recently • Over 15.000 health workers and • M&E launched Plan adapted by states 150.000 CDDs trained or • Integrated data management, retrained in 2012 including at state and LGA level • Ongoing mapping and MDA • Completing planning and costing • MDA training training (TIPAC) at national activities • Re-orientation training needed for level integration to discourage vertical approach Ongoing field testing of the • A well-structured health facility • Integrated MDA at various levels manual in some States level and implementers training • Advocacy for state policy makers manual/ guide developed as to address low NTD commitment approved by NTD Steering • TIPAC Training at State Level. committee. 2.4.2 Tanzania • Program carrying out many • Clear list of job duties by level • TIPAC training coordinated and integrated • Training manual for district-• Mapping MDA activities level health workers • Data management • Well-defined cascaded training • Training manual for CDDs • Data analysis and manuscript structure, operating procedures • Package w/ check list, dose preparations and job descriptions poles, forms, registers, timetable, • Impact surveys to determine • Well-developed training agenda, drugs MDA scale-down materials and resources across • Pre- and post-training tests • Program management cascaded levels • Standard operating procedure – • Medicine safety, logistics and on how district and regions supply chain should conduct their MDAs • Advocacy and communication • M&E framework • Policy document development • Need advocacy and sensitization • Need behavior communication strategy / IEC strategy 2.4.3 DR • Training for national, regional • Good onchocerciasis mapping • More than 8,000 Health Workers Congo coverage and 100,000 CDDs trained and provincial/intermediate level • Additional mapping ongoing • Onchocerciasis program using • District/health zone cascaded training, but needs • Cascaded training underway for implementation training training materials; Hoping to use onchocerciasis control • Cascaded training for CDDs onchocerciasis training • Working to build the capacity of • Generally increase motivated, a newer program experience to inform other PCT skilled human resources for NTD NTD trainings programs • Cascaded mapping training • Further CS gaps are being • Training methods and content of determined with partners training vary by level and responsibility of trainees 2.4.4 • Training for MDA throughout • Integrated LF & STH approach • M&E Bangladesh cascading chain, including to • Solid government infrastructure • Turnover/staff and expertise village and school level for and Gov't-NGO collaboration retention teachers • Collaboration across ministries • Cascaded training, including of and departments Training of "Little Doctors," 83.000 school teachers child-to-child educators to • Good reported coverage • Health worker CS, including inform fellow school-aged around morbidity management children, including those out of and disability prevention IEC school materials • Advocacy materials • Reaching out-of-school children and non-permanent populations

Table 2: CS priorities for PC NTDS in HPC

Country	Key accomplishments	Current CS activities or	CS and training needs and
2.4.5 Indonesia	 National program focusing on 3 of the 5 PCT NTDs (STH, Schisto, and LF) Coordination between national and district levels to reach districts in remote areas 	Ongoing CS and training activities at the national and district levels	 General scale-up of NTD CS activities M&E CS of health workers in rural areas WASH scale-up CS activity delivery through strengthened integration with other sectors and programs (education, religion, public work, agriculture, NGOs, private sector)
2.4.6 Ethiopia	 Recently launched National NTD Master Plan Health Extension Program (HEP) with strong reach into remote rural communities, with both government and community ownership, which can be built upon for NTD program scale-up Mapping efforts ongoing Inter-sectoral collaboration 	 Trainings for health extension worker (HEWs) Training of Health development army (HAD) by HEWs 	 Additional NTD-specific training needs for health extension workers and health development army Regional level NTD plans

Region-specific proposals: Brazil

With approximately 200 million inhabitants, Brazil is the fifth most populous country in the world. Although a high proportion of the population uses improved drinking water and sanitation facilities, approximately 16 million (8.5%) people live in extreme poverty. Dr. Saboya presented an overview of Brazil's plan to reduce extreme poverty, which includes plans to target the five PC diseases and leprosy. In this plan, 796 municipalities are targeted for control or elimination of Neglected Infectious Diseases (NIDs). In 2013, as part of an integrated campaign for NIDs, school-age children (SAC) were targeted for STH, leprosy, and trachoma interventions. Approximately 3 million SAC received albendazole. Nearly 2.5 million SAC performed self-checks for leprosy of whom 230,000 were referred to local health facilities and approximately 290 new cases of leprosy were confirmed in children under 15 years old.. Just over 1,800 SAC were found to have active trachoma. All of the identified children were treated with azithromycin and an additional 1,100 close contacts received treatment as well.

Plans for 2014-15 include the following:

- **STH** –expand deworming program to increase more SAC, reinforce monitoring and evaluation of the national integrated campaign; deworming would be expanded to pre-school age children using existing platform (e.g. Vitamin A, EPI, programmes for child health of catholic church/pastoral da Crianca)
- Trachoma screening expanded to other areas; maintain integration with leprosy and STH
- Schistosomiasis MDA, snail control, health education, technical cooperation for verification of elimination
- Lymphatic filariasis Transmission Assessment Survey (TAS) workshop; TAS in Recife
- **Onchocerciasis** binational agreement with Venezuela to reinforce actions in the last remaining focus in AMRO

• **TIPAC training workshop** – conducted for several states; 24-28 March 2014

Brazil has committed resources for control and elimination of NIDs in Latin American countries and is expected to continue this support in 2014-2015.

The WG-CS recognized Brazil's commitment to NIDs as demonstrated through program implementation and provision of the necessary financial resources to support implementation of national programme activities. It was stated that if other middle-income countries were to similarly commit resources to their respective NTD programmes, a large proportion of the current global funding gap would be reduced.

WHO TDR

TDR was established in 1974 to develop tools for the control of tropical diseases and to strengthen the research capability. TDR's overall objective is to develop a sustainable health research environment in support to public health activities and to harmonize global research efforts aiming at an enhanced leadership of disease endemic countries in health research. Dr. Launois presented an overview of TDR's Research Capacity Strengthening (RCS) objective, which strives to provide leadership development and project related capacity building in low and middle income countries.

Through networks and partnerships, the RCS strategy aims to align research priorities with the need for evidence-based results to inform disease control programs and has thus shifted from a basic science and clinical trial focus to implementation and operational research.

TDR CS activities include the following:

- **Individual targeted academic research training** degree training (MSc, PhD) with preference given to local and regional training in priority areas of public health
- **IMPACT grant** output driven, short-term training, mentorship or methodology development aimed to improve disease control
- **Implementation research toolkit** module based tutorial covering topics such as protocol development, planning and executing research, analyzing research data, monitoring and evaluating projects and communicating results
- Career development fellowships and clinical R&D initial six month placements in pharmaceutical companies; development of projects at home institution
- Small grants \$10,000-\$15,000 awards for implementation research on regional priorities
- **Regional training centers (RTC)** four centers identified in AMRO (Columbia), SEARO (Indonesia), EURO (Kazakhstan) and WPRO (Philippines); centers in AFRO and EMRO will be identified in 2014-15

TDR RTCs have the potential to serve as regional hubs for identifying training needs within each region, and there may be effective ways for NTD control programs to partner with TDR. Additionally, many training materials have been developed by TDR, and an inventory of available resources will be shared with the WG-CS.

Examples of potential collaboration between TDR and national NTD control programmes could include introduction of good health research practices to strengthen capacities in national reference laboratories and peripheral laboratories (to detect antimicrobial resistant strains, and monitor drugs safety and efficacy of the target populations), and integrated case management for vector borne diseases including improved case detection and management, and provision of bed-nets.

Meeting Recommendations & Outcomes

WG CS acknowledged the various contributions that are being made by the various entities responding to felt needs expressed by national NTD programmes. These efforts can contribute to a common work plan and priorities for CS in 2014 as follows:

- 1. **CS framework**: There is a need to develop a common CS framework to encompass the diverse group of actors who support a variety of CS initiatives (for PCT, IDM, VEM, NZD) in a number of different countries. A consultative process should be undertaken to compile a comprehensive inventory of ongoing CS initiatives for NTDs. A common capacity strengthening framework for NTD programmes should be developed in order to provide criteria and indicators for monitoring and evaluating capacity strengthening for NTDs.
- 2. In order to maximize efficiencies, on-going work of WG CS should be divided into 3 main areas of work for 2014, namely;
 - i. **Training courses and workshops:** Several training courses have been developed by WHO in collaboration with NTD partners. These should be implemented in accordance to the requirements of WHO regions and countries as identified through training needs assessments, with a particular focus on highly populous countries (HPC). The Programme managers course should be implemented with priorities in HPC, and regional adaptation of the Programme managers curricula should be completed for AFRO, AMRO and EURO. The development of the district level NTD managers training course should finalized and pilot-tested as soon as possible in 2014. Additionally, further technical and financial support should be provided to facilitate country specific adaptations of IMAI guidelines and NTD training courses in high-burden countries. NTD partners should coordinate their training schedules and resources to improve efficiencies and effectiveness of the limited capacity strengthening resources available, particularly in countries that account for the highest implementation deficits.
 - ii. **Training centers**: The NTD training centers network should be extended to include centers of excellence from other WHO Regions and the WHO/TDR capacity strengthening network. Additionally, more non-Anglophone centers should be included among the training centers.
 - iii. NTD laboratory strengthening: Phase 1 of the NTD laboratory scoping study should be completed by implementing the same tool in the AFRO region. Phase II for establishing the NTD laboratory network should be implemented in 2014 through the strategic selection of a few NTD laboratories in each of the WHO regions and supporting them to reach internationally-recognized standards for reference laboratories, including ensuring that they are externally quality assured through links with international centres of excellence. Thereafter, in phase 3 these regional NTD laboratories will establish a network of national and sub-national NTD specialist laboratories and strengthen the capacity of these laboratories to meet international standards appropriate for their level of operation
 - 3. **eLearning platforms and tools**: Development of the NTD toolbox should be finalized and the β-version released during the NTD STAG in April 2014. NTD partners and who have not been yet provided their operational guidelines are encouraged to share these with WHO for inclusion in the NTD toolbox. The inventory of documents should be updated every 6 months and made accessible via the WHO website. Efforts to develop an eLearning platform for NTD training should continue to be supported and prototypes presented at the next WG CS.
- 4. **Harmonization of field guides and job aides**: Ongoing efforts to develop practical field guides to support sub-national level health workers should be coordinated. In particular WHO/HQ should work with AFRO and APOC to harmonize the content and publication of field guides for implementation of preventive chemotherapy (Field guide for Mass Drug Administration). WHO and NTD partners should similarly coordinate the development of other practical field guides and simplified "job aides" to provide in-service technical support to health workers at sub-national and peripheral levels. Such field guides and job aides are required for NTD related WASH, health education, health promotion, morbidity management, posters etc. which should also be provided in locally appropriate languages.
- 5. Resource mobilization: The absence of dedicated NTD programme personnel in most WHO regional offices and high-burden WHO Country offices is continuing to impede follow-up and implementation of activities at field level. There is a need to mobilize resources among NTD stakeholders to support the strategic long-term placement of personnel required to provide technical assistance for programme activities, particularly during the current phase of accelerating scale-up of coverage. National NTD programmes need to be provided with financial resources to support in-country distribution of donated medicines. WHO Country offices need to be allocated specified financial resources to facilitate their role of conducting coordination meetings and follow-up at country level.

Table 3 below presents the proposed timelines for implementation of the NTD Capacity Strengthening activities in 2014.

Recommendation		Activities	Deadline
1.	Capacity Strengthening framework	WHO work in concert with key stakeholders develop an operational CS framework	April 2014
2.	Dividing WG-CS into sub-working groups to address 1) training curricula (including programme managers training and District level management training) 2) laboratory strengthening 3) NTD toolkit; e-learning This sub-division will not result in more meetings nor in more expense, but would be a way to maximize efficiency of the available human and technical resources of the present WG.	Identify subgroup coordinators and allocate people to each group, in order to define a work plan with specific activities to be implemented	April 2014
3.	eLearning platforms and toolsa. Completion of NTD toolkitb. eLearning platformc. Evaluate eLearning toolkit	Make available on the web the first version of NTD toolkit Develop prototypes Ongoing	April 2014 October 2014
4.	Coordination/harmonization among WHO HQ, WHO regions, countries and partners: a. Development of practical field guides b. Job aides and tools	Seek to coordinate training courses and harmonize/adapt training curriculum among WHO regions, countries, key partners	July 2014 Dec 2014
5.	Resource mobilization:a. Human resources for WHO Regionsb. Human resources for High-burden countriesc. Financial resources	NTD focal points in ROs NTD NPOs Effective fundraising; commitment from middle- income countries	Oct 2014 Oct 2014 Oct 2014
Specif	ic tasks		
6.	Completion and piloting of District level manager's training course	Develop training modules and pilot the course in an endemic country	June 2014
7.	Implementation of NTD PM training targeting high populous countries as a priority	Carry out NTD PM training in three big countries (Nigeria, Ethiopia and Congo DRC /Tanzania)	December 2014
8. Identif	Laboratory capacity strengthening: a. Completion of scoping study b. Publication of Phase I results fication of RRL and implementation of Phase II.	Identify RRL and improve the capacity of potential laboratories. Finalize the list of RRL from the African Region	May 2014 Oct 2014 Dec 2104

Table 3: Proposed timelines for NTD Capacity Strengthening activities in 2014.

ANNEX 1: Agenda



NTD STAG Global Working Group Meeting on Capacity Strengthening for Control of Neglected Tropical Diseases (WG-CS), Geneva, Switzerland 9 – 10 January 2014, Room M 505.

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT			
AGENDA			
Day I	Item	Name	
09:00-09:20	Welcoming remarks, meeting objectives and introductions	L. SAVIOLI D. MOLYNEUX	
		D. ENGELS	
09:20-09:45	Summary report on recommendations from WG CS 2012	F. RIO	
09:45-10:20	District Level Managers training course	N. KABATEREINE	
10:20 - 10:40	APW/NTD Toolkit	M. SABOYA	
10.40 - 11.00	Coffee break		
11.00 - 12.30	Capacity Strengthening activities by WHO regions: priorities, progress, challenges and needs for NTD programmes, with discussions: AFRO	A. ONYEZE*	
	APW/Laboratory Strengthening	I. BATES	
	Capacity Strengthening activities by WHO regions: priorities, progress, challenges and needs for NTD programmes, with discussions: SEARO	R. KUSRIASTUTI*	
12:30 - 14:00	Lunch break		
	Capacity Strengthening activities by WHO regions: priorities, progress, challenges and needs for NTD programmes, with discussions:		
14:00 - 14:25	 AMRO 	M. SABOYA	
14:25 - 15:00	■ EMRO	R. BEN-ISMAIL	
15:00 - 15:20	• EURO	M. EJOV*	
15:20 - 15:45	• WPRO	N. DAYANGHIRANG	
15:45 - 16:00	Coffee break		
16:00 - 16:25	Capacity Strengthening for Intensified disease management	R. VELAYUDHAN	
16:25 - 16:50	Capacity Strengthening for Neglected Zoonotic Diseases	J. JANNIN	
16:50 - 17:25	Capacity Strengthening for Vector Control	B. ABELA-RIDDER	
17:25 – 18:15	Capacity Strengthening activities by NTD partners: 2013 activities, opportunities and future plans.		
	IMAI-IMCI Alliance	S. GOVE	
	General discussion	D MOLYNFUX	
18.15	Conclusion of Day 1	CHAIR	
10.15			

*Unable to attend in person. Presentations made via teleconference



NTD STAG Global Working Group Meeting on Capacity Strengthening for Control of Neglected Tropical Diseases (WG-CS), Geneva, Switzerland

9 – 10 January	2014.	Room	M 505.
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	AGENDA	
Day II:	Item	Name
08:45 - 09:00	Re-cap of Day 1	Rapporteurs
09:00 - 09:15 09:15 - 09:30 09:30 - 09:45 09:45 - 10:00	 Capacity Strengthening activities by NTD partners: 2013 activities, opportunities and future plans, with discussions Laboratory network for monitoring drug efficacy NTD ENVISION/RTI International Sight Savers Discussion 	J. VERCRUYSSE A. DOHERTY S. BUSH ALL
10:00 - 10:15	Capacity Strengthening for highly populous countries: updates and proposals for 2014 – 2015 Region-specific proposals: AMRO - Brazil	(P. MBABAZI*)
10:15 - 10:40	WHO/TDR: Planned Capacity Building activities, and opportunities for collaboration with NTD programmes	P. LAUNOIS
10.40 - 11.00	Coffee break	
11:00 - 12:30	 Capacity Strengthening work plan for 2014 – 2015 and beyond Priority tasks, task allocation & task coordination Capacity Strengthening technical meetings for 2014 	GENERAL DISCUSSION
	 Capacity Suchgiteling technical incernigs for 2014 Timelines: Work plan for 3, 6, 12, 24 months Resources: Financial resources, technical resources, inventories of training materials, expert groups, facilitators, financial facilitation and support etc. 	
12:20 – 12:50 12:50 – 13:00	 Capacity Suchgitering technical meetings for 2014 Timelines: Work plan for 3, 6, 12, 24 months Resources: Financial resources, technical resources, inventories of training materials, expert groups, facilitators, financial facilitation and support etc. World Health Day 2014 (WHD2014) General remarks 	R. VELAYUDHAN D. MOLYNEUX
12:20 - 12:50 12:50 - 13:00 13: 00 - 14:00	 Capacity Suchgitering technical meetings for 2014 Timelines: Work plan for 3, 6, 12, 24 months Resources: Financial resources, technical resources, inventories of training materials, expert groups, facilitators, financial facilitation and support etc. World Health Day 2014 (WHD2014) General remarks 	R. VELAYUDHAN D. MOLYNEUX
12:20 - 12:50 $12:50 - 13:00$ $13:00 - 14:00$ $14:00 - 15:20$	 Capacity Suchgitering technical meetings for 2014 Timelines: Work plan for 3, 6, 12, 24 months Resources: Financial resources, technical resources, inventories of training materials, expert groups, facilitators, financial facilitation and support etc. World Health Day 2014 (WHD2014) General remarks Lunch break WG CS Recommendations and Report to STAG 2014 	R. VELAYUDHAN D. MOLYNEUX ALL
12:20 - 12:50 $12:50 - 13:00$ $13:00 - 14:00$ $14:00 - 15:20$ $15:20 - 15:30$	 Capacity Suchgitering technical meetings for 2014 Timelines: Work plan for 3, 6, 12, 24 months Resources: Financial resources, technical resources, inventories of training materials, expert groups, facilitators, financial facilitation and support etc. World Health Day 2014 (WHD2014) General remarks Lunch break WG CS Recommendations and Report to STAG 2014 Closing	R. VELAYUDHAN D. MOLYNEUX ALL D.ENGELS and F.RIO
12:20 - 12:50 $12:50 - 13:00$ $13:00 - 14:00$ $14:00 - 15:20$ $15:20 - 15:30$ $15:45 - 16:15$	 Capacity Suchgitering technical meetings for 2014 Timelines: Work plan for 3, 6, 12, 24 months Resources: Financial resources, technical resources, inventories of training materials, expert groups, facilitators, financial facilitation and support etc. World Health Day 2014 (WHD2014) General remarks Lunch break WG CS Recommendations and Report to STAG 2014 Closing Coffee break	R. VELAYUDHAN D. MOLYNEUX ALL D.ENGELS and F.RIO

*Tabulated summary hand-out provided.

<u> ANNEX II – List of Participants</u>

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WGA Teleconference, 20 March 2014

Summary minutes¹ and Recommendations to the STAG

Agenda

Introduction	Chair, Nilanthi De Silva
1. Joint forecast for albendazole, mebendazole and praziquantel	Denis Daumerie
 Ways to address shortage of quality-assured NTD medicines: Experience with Prequalification and Expert Review Panel 	Valerio Reggi
 An update on the quality survey concerning albendazole and mebendazole 	Valerio Reggi
4. Management of serious adverse events	Denis Daumerie
5. Overview of issues affecting availability and quality of selected	
NTD medicines:	
a. Leishmaniases	Daniel Argaw Dagne
b. Chagas disease	Pedro Albajar
Conclusion	Chair, Nilanthi De Silva

List of attendees²

Members

ASAOLU, Samuel BARRETT, Mike BLAYNEY, Benedict DEN BOER, Margriet DE SILVA, Nilanthi (Chair) GARRISON, Kama ROSENBERG, Mark VESSOTSKIE, Janet

Secretariat

ALBAJAR, Pedro DAGNE, Daniel Argaw DAUMERIE, Denis JANNIN, Jean MONTRESOR, Antonio PARK, Munjoo REGGI, Valerio SUCHET, Corinne

 $^{^{\}rm 1}$ To be read in conjunction with the attached 'Notes for discussion' – Annex 1

² List of members and WHO secretariat in Annex 2

1. Joint forecast for albendazole (ALB), mebendazole (MEB) and praziquantel (PZQ)

Denis Daumerie reported on the outcome of the meeting of 21 January 2014 and progress concerning ALB, MEB, PZQ supply. The discussion led to the following <u>Action points /</u> <u>recommendations to the WHO Strategic and Technical Advisory Group for Neglected Tropical</u> <u>Diseases (STAG, NTD)</u>:

- To continue to support joint forecast and sharing of information among interested parties
- To assist countries in developing plans of action and capacity to distribute available donated NTD medicines and expand coverage

2. Ways to address shortage of quality-assured NTD medicines: Experience with Prequalification (PQ) and Expert Review Panel (ERP)

Valerio Reggi reported on the above. The meeting agreed that shortage of availability should not lead to accepting lower quality requirements. The discussion led to the following <u>Action points / recommendations to the STAG</u>:

- WHO-NTD, with input from WHO-Pre-Qualification Programme (PQP), to seek technical support from US Pharmacopeia to produce the necessary data that would permit to ascertain whether bioequivalence study requirements could be waived for PZQ without compromising quality.
- NTD, with input from PQP, to arrange a meeting with generic manufacturers to encourage them to submit applications for PZQ.

3. An update on the quality survey concerning albendazole and mebendazole

Valerio Reggi reported on this for information of WGA. The discussion led to the following <u>Action</u> <u>points/recommendations to the STAG</u>:

• Urge concerned national drug regulatory authorities to address the quality issues identified by the survey conducted in East Africa and South-East Asia.

4. Management of serious adverse events

The meeting agreed that training of NTD programme managers and other national programme staff should be intensified to ensure that proper reporting is implemented. However, it was pointed out that the new EU requirements (Regulation (EU) No 1235/2010 and Directive 2010/84/EU) impose reporting all kinds of Adverse Events (AEs) and not just serious AEs. This may discourage NTD managers and delay expansion of coverage. The discussion led to the following <u>Action points / recommendations to the STAG</u>:

- WHO and donation partners to finalize adverse event reporting form that is currently under final editing/revision.
- WHO, national NTD control programmes and other concerned parties to develop a document that outlines the peculiarities of preventive chemotherapy and can be used to raise the matter with the European Medicines Agency and seek a different set of reporting requirements for preventive chemotherapy interventions.

• WHO, national NTD control programmes and other concerned parties to prepare for intensifying training on drug safety monitoring in national Preventive Chemotherapy (PC) interventions.

5. Overview of issues affecting availability and quality of NTD medicines for Chagas disease and leishmaniasis

The meeting was briefed about the mechanisms for quality assurance and monitoring regarding drugs for Chagas disease, human African trypanosomiasis and the leishmaniases. Surveillance for those diseases is linked to a monitoring system for treatment and drug resistance. Management of SAEs of donated drugs is based on the memorandum of understanding between WHO and the donating companies. Specific issues on drugs for leishmaniasis and Chagas disease were presented and details can be found in Annex 1.

Action points / recommendations to the STAG with regard to

Antileishmanial medicines

- To support the sustainable production of antileishmanial medicines and ensure adherence to international Good Manufacturing Practice standards, particularly for quality-assured sodium stibo-gluconate and paromomycin, in collaboration with the WHO prequalification program and other international partners;
- To continue encouraging generic liposomal amphotericin B manufacturers to undergo prequalification process and strengthen treatment outcome monitoring.

Drugs for Chagas disease

- To continue studies on pharmacology, drug safety and efficacy of benznidazole and nifurtimox, taking into account the geographical differences on Chagas disease and response to antiparasitic treatment
- To implement a network of sentinel centres to collect data and produce reports in a standardized format.

WGA Teleconference Notes for discussion (updated 18 March 2014)

These notes are aimed at facilitating discussion among WGA members. It is envisaged that discussion will take place in two ways:

- after receiving the notes all members may send written comments back to <u>daumeried@who.int</u> and <u>suchetc@who.int</u>; comments may address topics already included in the notes or propose additional topics for discussion; received comments will be consolidated and shared with all members (unless senders requested otherwise) at the end of every week until one week before the teleconference;
- b) notes (including a report to the STAG) will be finalized after the discussion taking place at the teleconference.

At this stage, the topics proposed for discussion are five:

- 1. Joint forecast for albendazole, mebendazole and praziquantel
- 2. Ways to address shortage of quality-assured NTD medicines: Experience with Prequalification and Expert Review Panel
- 3. An update on the quality survey concerning albendazole and mebendazole
- 4. Management of serious adverse events
- 5. Overview of issues affecting availability and quality of NTD medicines for Chagas disease and Leishmaniases

1 – Joint forecast

On 21 January 2014, a meeting, "Provision of quality-assured albendazole, mebendazole and praziquantel for the control of neglected tropical diseases through preventive chemotherapy", has permitted to share forecast information among WHO, USAID, DFID, GSK, J&J, Merck KGaA, RTI, CWW, and World Vision. The meeting report is available, on request, from WHO's NTD Department. A most notable sign of progress this year has been the participation of World Vision and their decision to share information and to make use of WHO's Expert Review Panel in their NTD medicines procurement process.

Action proposed: continue to support joint forecast and sharing of information among interested parties.

2 - Ways to address shortage of quality-assured NTD medicines: Experience with Prequalification and Expert Review Panel

Over the last few years, WHO has intensified its activities aimed at ensuring that medicines used in PC are of the required quality. At the same time, many endemic countries have strengthened their drug regulatory systems. This has revealed that there were gaps in the ways in which quality was assured in some supply systems and that there is a shortage of quality-assured medicines (i.e. quality assured on the basis of the criteria used by most OECD countries or the WHO Prequalification Programme - PQP). To contribute to address this shortage, NTD has intensified its collaboration with the PQP, is encouraging manufacturers to submit applications to the PQP, and assisting manufacturers to prepare for the PQP process.

A recent meeting held at WHO addressed the collaboration established between WHO's Prequalification Programme (PQP) and the NTD department. PQP now accepts submissions for tablets and APIs of four NTD medicines: albendazole, DEC, mebendazole, and praziquantel. Applications have been received only for DEC tablets and mebendazole API. One DEC tablet product has been prequalified, the other two applications are under assessment and awaiting feedback from the applicants. The Expert Review Panel (ERP) is a procedure that has been established by WHO's PQP (in collaboration with The Global Fund) to assess dossiers of products that have not yet been prequalified by WHO or a stringent drug regulatory authority. The process is simpler and faster than full PQ and provides a time-limited indication of possible quality risks concerning the products assessed. Three rounds of ERP assessments have been carried out so far: one for albendazole and two for praziquantel. A presentation of the activities conducted by WHO's PQP in relation to NTD medicines and APIs is available, on request, from WHO's NTD Department.. Two most notable issues were discussed, among others, at the meeting: a) the need to support manufacturers who may need limited assistance to meet PQP requirements, and b) the need to produce data that may permit to waive PQP's requirement for bioequivalence (BE) studies under certain circumstances.

Having regard to the first point, it was pointed out that activities to support manufacturers are envisaged and/or actually being carried out by USAID (through USP and MSH), PQP, and more recently NTD. It was agreed that it was useful to exchange information and contacts to see how such activities could be coordinated and synergies sought.

<u>Action proposed</u>: NTD to proactively seek opportunities to establish/improve coordination among these concerned parties.

Regarding the second point it was recognized that BE studies are costly and may represent an insurmountable hurdle for generic manufacturers of NTD medicines because of the relatively limited profit that can be anticipated. Subsidizing such studies is not a straightforward operation for donors because it would entail generating the required policy decision, creating a specific fund and establishing criteria and procedures for its use. On the other hand, it was pointed out that, in the case of praziquantel, the lack of data on permeability (the speed at which the active substance travels through the gut wall) is the main reason for requiring BE studies.

<u>Action proposed</u>: NTD, with input from PQP, to identify a suitable institution and assess the feasibility and cost of producing the necessary data.

3 - An update on the quality survey concerning albendazole and mebendazole

As reported at the 5th WGA meeting in 2013, a large proportion of samples failed quality testing this is cause of concern and calls for effective action. The countries involved in the survey are members of established regional networks of drug regulatory authorities, namely the East African Community and ASEAN's ACCSQ-PPWG. It was considered that the quality problems identified by the survey are likely to be equally present in most countries of the same network. It was therefore decided to discuss the results of the survey at a regional meeting of all the regulators of the respective networks. In the interest of time and resources, it was proposed that these discussions take place as an additional agenda item of one of the regular network's meetings. The PPWG has now accepted to include this item in their next meeting of 16-19 June 2014 in Kuala Lumpur. A date and venue for the East African Community meeting is not yet decided.

4 - Management of serious adverse events

New pharmacovigilance legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU) has come into force in the EU. This has an impact on adverse drug reaction reporting requirements for products authorised for marketing in the EU which are also marketed outside the EU (which includes donation programmes). The main changes in the requirements include, *inter alia*, the following:

- Submission of consumer reports in addition to health professional reports.
- Submission of non-serious drug-related spontaneous reports within 90 days.
- Reporting overdose and medication error reports that result in ADRs.

This is a major change in reporting affecting donation programmes involving products marketed in the EU (GSK and Merck KGaA being the most obviously concerned). These matters were discussed at the last PDCI meeting and the following key issues were identified:

- Adequate planning and preparation of MDAs, involving DRAs whenever feasible;
- Intensified training of staff involved in implementation of donation programmes on management of ADRs;
- Ensuring involvement/strengthening/setting up of national pharmacovigilance centres as locally meaningful.

USAID has collected information from the countries they supporting and has provided information on available tools such as the manual developed by the WGA

(http://whqlibdoc.who.int/publications/2011/9789241502191 eng.pdf).

Partners' efforts may nonetheless be unable to achieve the level of reporting as required by the new EU legislation, especially regarding non-serious adverse events.

<u>Action proposed</u>: WHO and other concerned parties to develop a document that outlines the peculiarities of preventive chemotherapy and can be used to raise the matter with the European Medicines Agency and seek a different set of reporting requirements for this type of public health interventions.

5 - Overview of issues affecting availability and quality of NTD medicines for Chagas disease and Leishmaniases

Introduction on Chagas disease drugs

At present two drugs are available for the antiparasitic treatment: benznidazole (first-line treatment in most countries) and also nifurtimox.

Both medicines are almost 100% effective in curing the disease if given soon after infection at the onset of the acute phase. However, the efficacy of both diminishes the longer a person has been infected. Treatment is also indicated for those in whom the infection has been reactivated (for example due to immunosuppression), for infants with congenital infection and for patients during the early chronic phase. Infected adults, especially those with no symptoms, should be offered treatment. The potential benefits of medication in preventing or delaying the development of Chagas disease should be weighed against the long duration of treatment (up to 2 months) and possible adverse reactions.

During the antiparasitic treatment, adverse reactions with benznidazole and nifurtimox are described in 20-40% of cases and they are less frequent at younger age. The first-option medication has to be chosen according to the clinical background of the patient, due to the different adverse reactions and contraindications.

Benznidazole and nifurtimox should not be taken by pregnant women or by people with kidney or liver failure. Nevertheless, recent studies done in Argentina showed that neither nifurtimox nor benznidazole should be contraindicated during breast feeding. Nifurtimox is also contraindicated for people with a background of neurological or psychiatric disorders.

Another recent study in Spain showed that nifurtimox as second line therapy in patients who discontinued benznidazole specifically due to hypersensitivity reactions appears to be safe and does not seem to be associated with a higher incidence of adverse reactions, what supports present protocols.

Additionally, specific treatment for cardiac, digestive or neurological manifestations, together with other treatment for other chronic infectious or non-infectious conditions may be required, but there are no evidence-based studies on drug interactions (with medicines used for other infectious and non-communicable diseases), just observational studies with limited series of patients.

Recent studies on antiparasitic treatment with other drugs, alone (posaconazole, ravuconazole/E1224), did not provide any superiority to benznidazole, so we expect to wait several years, yet, until getting any new drug/drug combination.

In 2014, among others, DNDi is going to focus on the following issues: a) knowledge increase (drug metabolization) and new possible posologies for benznidazole and nifurtimox; b) possibility of reducing the APW price and consequent benznidazole price; c) initiation of the study of fexinidazole for Chagas disease; d) help Laboratorio Elea/Chemo to register benznidazole in the FDA.

Quantities used and reports of resistance

With the support of subregional intergovernmental initiatives of Chagas disease control in the Americas, countries increased case detection and antiparasitic treatment was broadened, from fewer than 50 treatments with nifurtimox in 2005 to more than 1,500 in 2010 and >6,000 people treated with benznidazole at the beginning of 2011. From 2007 to 2011 benznidazole and/or nifurtimox was distributed in 18 countries of Latin America and 15 in the rest of the world. However, the world shortage of benznidazole since August 2011 dramatically slowed treatment and even detection worldwide. Between 2011 and 2012 doubled the second-line treatment (nifurtimox) use, but benznidazole could not practically be used.

Especially since the beginning of 2013, a progressive increase in detection and antiparasitic treatment with both benznidazole and nifurtimox has been detected in disease endemic and non-endemic countries, reaching almost 10,000 treated patients.

There were no reported cases of drug resistance that exceeded the expected treatment failure rate. Nevertheless, monitoring and evaluation activities have been very incipient and incomplete. A project of a network of sentinel centres has been discussed and its implementation depends on resources.

As part of the strengthening treatment measures, healthcare protocols continue to be harmonized at country level, and systems for treatment monitoring have been implemented in few countries since 2011. Last three two years, in the annual meetings of the Intergovernmental Initiatives, national programmes of control of Chagas disease and those administering drugs were encouraged to report efficacy and adverse events.

Drug manufacturing and distribution of benznidazole and nifurtimox

In 2010 Mundo Sano Foundation (<u>www.mundosano.org</u>), from Argentina, asked Laboratorio Elea (<u>http://www.elea.com</u>), one of the companies that support the Foundation, about the possibility to produce benznidazole. In 2011 Laboratorio Elea started the production of benznidazole and in January 2012, as Abarax[™], it has got the registration by the national agency of drugs of Argentina: Agencia Nacional de Medicamentos, Alimentos y Tecnología Médica - ANMAT (<u>http://www.anmat.gov.ar/principal.asp</u>). After the world benznidazole shortage (from August 2011), in November 2012 Abarax[™] reached full worldwide distribution.

The benznidazole Active Pharmaceutical Ingredient (API) and drug transportation are done by different companies of the same pharmaceutical group. The companies and drug has got all quality certificates and is produced and distributed according to a no-cost/no-profit strategy.

Two benznidazole presentations are produced: bottles containing 100 tablets of 100 mg and 50 mg each. In Latin America prices are USD 60 and USD 40, respectively. In Europe prices are EUR 60 and EUR 30, respectively, including transport and importation taxes. Both presentation tablets are slotted twice and disintegrate in water, covering both adult and paediatric administration needs.

Laboratorio Elea has started a production of a new presentation of 12.5 mg that will be available in the second semester of 2014.

Since the beginning of 2012 Laboratório Farmacêutico do Estado do Pará - LAFEPE (<u>www.lafepe.pe.gov.br</u>), in Recife, Brasil, has restarted the production of boxes of 100 tablets of 100 mg (slotted) and 12.5 mg each, with the API manufactured by Nortec Quimica (<u>http://www.nortecquimica.com.br/</u>), in Rio de Janeiro, Brazil. The problem has been the lack of the Good Manufacturing Practices (GMP) certificate (the last one expired at the beginning of 2010 and it has not been renewed, yet, by the national agency of sanitary surveillance of Brazil: Agência Nacional de Vigilância Sanitária – ANVISA (<u>http://portal.anvisa.gov.br/wps/portal/anvisa/home</u>).

Additionally, the Secretary of Science, Technology and Strategic Products at the Brazilian Ministry of Health requested an alternative production of benznidazole to the Laboratorio Farmacêutico da Marinha do Brasil (<u>https://www.mar.mil.br/lfm/</u>), in Rio de Janeiro, using the same API of Nortec Química.

Nothing is known, yet, about a series of remaining challenges: a) destination of the benznidazole tablets produced since February 2010 without GMP certificate; b) future system of distribution outside Brazil and the PAHO revolving found and WHO Department of Control of Neglected Tropical Diseases.

Through a renewed WHO and Bayer agreement, from the beginning of this year the available amount of donated nifurtimox per year has doubled (one million tablets) and access to free quality nifurtimox (second-line treatment) is ensured until 2017.

The production, again, of a new paediatric formulation of 30mg has started and it will be available in the second semester of 2014.

In April 2013 the WHO List of Essential Medicines for Children was updated with two new presentations: the 12.5 and 50 mg presentations. A 30 mg presentation of nifurtimox was already included.

Drug distribution linked to rational use and epidemiological surveillance

Drug distribution linked to rational use and epidemiological surveillance has been a WHO strategy already discussed and agreed with Laboratorio Elea, Bayer and national agencies. In fact, drug distribution is an instrument to collect information on Chagas disease cases and active transmission routes and specific Request Form for benznidazole & nifurtimox (attached) is used for this purpose. The underdiagnosis index and the illegal status of thousands of affected people in disease non-endemic countries are main limitations of the collected information.

The "rational use" component should include pharmacovigilance and pharmacoepidemiology. As mentioned before, drug distribution is done promoting standard pharmacovigilance procedures and Lyell's syndrome (toxic epidermal necrolysis)/Stevens-Johnson syndrome has been the two most frequent life-threatening condition reported (1/000 approximately). In the case of Chagas disease, nevertheless, it has been showed that early detection and care of drug adverse reactions can reduce morbidity and totally avoid mortality.

Last year the proposal of a network of sentinel centres for Chagas disease has been presented, including its inclusion/exclusion criteria and common protocols to guarantee the comparability. Its main objectives are to collect information on drug efficacy, possible resistance appearance and assessment geographical differences. It should be implemented through a world network (national reference centres with the components of diagnosis, treatment and follow-up). Main challenges are: Chagas disease diversity (due to *T. cruzi* variety and diversity of host, life styles and environments); diverse treatment response due to infection duration (parallelism with age...); limited tools to assess therapy response (cure markers).

Final points

This year remain as relevant the following recommendations:

- As new protocols/drugs/combinations become available WHO should take the lead in establishment of pro-active reporting on efficacy and safety. Stake holders should be invited to contribute to agreed procedures.

- Assess candidates for surrogate end-point markers for "cure" is an issue for Chagas disease. And it is important to establish markers/assays to distinguish "resistance" and "inefficacy".

- WHO should continue the efforts to have a policy of facilitating drug donation or financing drugs.

- It is essential to empower countries to have the right mechanism in place to manage the monitoring of drug (distribution, safety - adverse events/reactions, efficacy)...

- It is of key importance to continue to implement a network to collect data from sentinel sites (clinics) and have report efficacy and adverse events in a standard format.

Additional related needs for the Programme on Control of Chagas disease in future:

- Better epidemiology of the geographical distribution of different *T. cruzi*, with assessment of geographical differences.

Improve the report of pharmaco-epidemiology at country level.

- Updating treatment guidelines according to the evidence-based knowledge (taking into account the geographical differences).

Key Issues regarding antileishmanial medicines

- 1. <u>Sodium stibogluconate (SSG)</u>
 - The first line of therapy for VL in East Africa in combination with Paromomycin
 - The manufacturer of SSG, Albert David Ltd, India has somehow respected the stability of the cost of the medicine around USD 6.42/vial of 30ml. The WHO procurement unit is in the process to sign a Long Term Agreement to keep the cost.
 - Quality concerns- The leishmaniasis programme supported the re- inspection of the manufacturing site and it was found to be WHO/GMP compliant as the company addressed most of the deficiencies identified during the first visit.
 - However, as there are still some structural deficiencies the WHO prequalification unit has recommended a shorter interval inspection than the routine 3 years.
 - This implies cost and it seems there is no organization or programme to cover inspection cost on regular basis
- 2. <u>Miltefosine</u>
 - With the increasing shift to the use of Liposomal AmBisome as first line therapy in South East Asia, the demand for Miltefosine is dwindling which is affecting access to availability.
 - Better forecasting of the needed quantity and coordination or pooling of procurement have been suggested by different partners and the company, however, due to the different policies in the procuring agencies and governments, the feasibility of these solutions seems less likely.
 - Currently WHO and partners have planned to continue discussion with the manufacturer including the implication of the recent sale of the company to another company, knight phramaceuticals.
 - Regarding the cost, the WHO agreed price is for large quantities and the company seems not interested to reduce or offer a preferential price for small quantities in the face of declining demand.

<u>Meglusan</u>

This product has been circulating in Iran, Afghanistan and Pakistan. Recently WHO has stopped transfer of this medicine from Iran to Afghanistan thru WHO offices. Both WHO offices have been informed about the quality concerns and validation status of the drug.

3. Generic liposomal Amphotericin B

Potential companies have been informed that they can apply and participate in the 10th WHO prequalification unit Expression of Interest (EOI) invitation. Nevertheless, no company has responded to the invitation until recently as far as we know.

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Fifth NTD-STAG Global Working Group Meeting on Monitoring and Evaluation of Preventive Chemotherapy

Department of Control of Neglected Tropical Diseases Geneva, 19-20 February 2014

Chair: Dr. Sam Zaramba Rapporteurs: Ms. Katie Zoerhoff, Dr. Reda Ramzy



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1 Executive Summary

The fifth NTD-STAG Global Working Group Meeting on M&E of Preventive Chemotherapy was held in Geneva, Switzerland, on 19-20 February 2014 (WG M&E 2014). The objective of the meeting was to review progress made in 2013, identify work plan priorities for 2014 and prepare a report for the NTD Strategic Technical Advisory Group.

Recommendations from the fourth WG M&E 2013 were reviewed to note areas where progress had been made and where additional work is required with regard to improving data sharing, data utilization by national programs, strengthening country ownership of data and programme evaluation. Subgroup 1 reported on **Monitoring and Evaluation of National NTD programs** highlighting the resource implications and need to focus on evaluations in order to better assess coverage, measure impact through disease-specific evaluations, and determine appropriate interventions to address programme challenges. Representatives from various WHO regions & APOC presented achievements, and highlighted the major constraints to effective M&E at the regional and country levels. Subgroup 2 reported on progress with regard to **Monitoring of Disease-Specific Indicators** using transmission assessment survey (TAS), country readiness for conducting disease-specific assessments, use and availability of new diagnostic tools, new tools for new tools to guide STH control and elimination activities, and the role of RPRGs in support to making decisions at programme transition points. Potential avenues to more productive engagement of the WG M&E with the operations research grant funded by the Bill and Melinda Gates Foundation were discussed.

Update on specific M&E issues presented and discussed included the joint mechanism for medicines request and PC data reporting, data quality assessment (DQA) tool and accompanying, a template for the National NTD database, and an update on monitoring and management of SAEs that may result from preventive chemotherapy interventions. Expert committees presented updates related to 2013 and 2014 planned activities. Mectizan Donation Program reported on the ivermectin supply chain, monitoring drug efficacy, SAEs and challenges associated with implementation of PC in Loa loa co-edemic areas. Children Without Worms highlighted progress made, and the major shift being experienced by the STH community as it returns towards its roots by promoting the implementation of a comprehensive strategy of disease control with PC, safe drinking water, basic sanitation, health promotion, and education. Deworm the World Initiative (DtW) summarized key program inputs taking place which include monitoring quality and success of program processes, determining coverage of deworming in different groups, measuring epidemiological, validation of coverage, and use of M&E to improve program processes and reach. Use of the ICOSA grant for process monitoring, performance monitoring (including reported and surveyed treatment coverage), impact monitoring using parasitological and morbidity indicators using cohorts and cross-sectional studies was presented. Additionally, Centre for Neglected Tropical Diseases (CNTD) reported its work on improving data timeliness and analysis, strengthening laboratories in Africa, supporting the roll-out of new tools and capacity strengthening workshops, and providing technical assistance to countries facing challenges such as mapping in low transmission areas, interpreting mapping results in the context of multiple interventions, urban transmission, and changing scenarios.

The outcomes and recommendations of the **Working Groups** on Economics & Impact of NTD interventions, (WG E&I) Monitoring Drug Efficacy for preventive chemotherapy (WG MDE), and Capacity Strengthening for NTD programmes (WG CS) shared progress made in 2013, highlights for 2014, and areas for potential collaboration with the WG M&E.

The meeting concluded with discussion and identification of 12 recommendations related to supporting the Working Group on Economics and Impact; supporting countries to strengthen activities for ensuring data quality and facilitating use of data for decision-making; enhance the capacity of expanded RPRGs to review country readiness to conduct TAS and other disease-specific assessments; standardizing practices and processes for data sharing between all NTD stakeholders; a process for recognition of countries for their achievement of LF elimination goals; systematization of processes to evaluate new diagnostic tools for NTDs and review their utility for programmes; development of a global strategic plan to guide the implementation and allocation of resources for M&E; a technical consultation to develop a body of evidence around the global distribution of Strongyloides and its importance; response mechanisms and strengthening of capacity for SAE management; placement of dedicated NTD personnel at regional levels and in key priority countries with a high implementation deficit; a standardized methodology for joint evaluations of integrated NTD control programmes; and development of a common framework of mHealth applications in which a shared language and technological approach is provided to guide the use in national NTD programmes.

The fifth NTD-STAG Global Working Group Meeting was well attended, with representation relevant experts and focal persons from all WHO regions (except EURO), APOC, international donor agencies and several NTD implementing partners whose valuable contributions to this meeting are gratefully acknowledged.

2 Introduction

Dr. Zaramba opened the meeting by noting that good progress has been achieved since the meeting of last year. He acknowledged efforts of the Chairs of the two Sub-groups and the WHO secretariat. Finally, he congratulated Dr. Dirk Engels (Coordinator, NTD/PCT) for taking over the position as Director, NTD, WHO, HQ.

In his welcoming remarks, Dr. Engels recalled the recommendation to merge Working Group on Monitoring and Evaluation of Preventive Chemotherapy with the Working Group on Monitoring Drug Efficacy which was effected last year. Dr. Mbabazi then reviewed the outcomes and recommendations from last year's meeting. The NTD-STAG 2013 endorsed 3 recommendations out of the 7 recommendations of last year. These include:

- (1) Monitoring scale-up of treatment coverage: Progress has been made with regard to monitoring use of donated drugs; improving timeliness, completeness and triangulation of PC data; and improving data quality. However, other issues still need to move forward, including the use of mHealth to improve data transmission, and mobilizing resources to support the finalization and implementation of integrated national M&E plans. Additionally, data collection and M&E of morbidity management and disability prevention (MMDP) activities have not been scaled-up as planned.
- (2) Intensify efforts for integrated monitoring: Progress has been made on the co-implementation of LF, STH, and schistosomiasis transmission assessments; discussions on harmonization of LF and onchocerciasis frameworks is ongoing; and discussions with regard to improving access and affordable diagnostic tests for use by national NTD programmes are ongoing.
- (3) Strengthen end-stage strategies and surveillance methods: The handbook of practical entomology for lymphatic filariasis elimination was finalized and published. Work to define cost-effective surveillance strategies for scale-down is still ongoing and further work on xenomonitoring for vector-borne diseases is still ongoing.

In addition, two specific issues were endorsed by NTD-STAG: (i) provisional strategy of integrated vector management and MDA using ALB monotherapy for LF in areas co-endemic with loa; and (ii) new guidelines for the verification of elimination of onchocerciasis: criteria and procedures; the draft is under revision.

In 2013, WHO improved the previously-developed joint data collection and reporting forms. The PCT databank has been maintained and linked with Global Health Observatory (**GHO**). However, there are still delays in reporting from some regions/countries which consequently affects the NTD global summary. Specific points for improvement include improvement in data sharing, improving country ownership, need to facilitate use of data by national programs at country level and implementation of programme evaluation.

3 Report of WG M&E Subgroup 2: Monitoring and Evaluation at Regional and National levels: Updates for 2012-2013, planned activities for 2014 - 2015

Prof. Gyapong provided an overview of the programs to prevent, eliminate and control the NTDs which are amenable to preventive chemotherapy, and the implications of the various program stages on M&E activities and priorities. Countries are in 3 main activity groups for mapping (18%), under MDAs (64%) and surveillance (18%). There is a need to provide sufficient and well-timed resources to support implementation of M&E activities corresponding to the programme phases (start up, scale up and scale down). Human resources to manage and monitor progress toward end-

stage were noted as upcoming challenge which could be a major impediment to verifying programme end points. There has been progress towards integration of M&E activities across disease programmes, but more still needs to be done at both country and regional levels. There is a need for disease-specific evaluations and national NTD Master Plan programme evaluations leading into planning for the next multi-year phase Master Plans.

Prof. Gyapong noted that next steps include:

- 1) Assessments to stage and quantify the M&E needs for blinding trachoma and onchocerciasis;
- An increased focus on the evaluation aspect of M&E, with particular attention to evaluation of treatment coverage, disease-specific epidemiological evaluations and programme evaluations. A set of indicators for programme evaluation need to be determined and a standardized protocol developed.

Representatives from various WHO regions presented contributions on M&E for NTDs/PC in their respective region, including AFRO by Dr. Tiendrebeogo and Dr. Onyeze; AMRO by Dr. Pascual; EMRO by Dr. Ben-Ismail; SEARO by Dr. Mohamed; and WPRO by Dr. Dayanghirang. Additionally, Dr. Afework presented achievements, challenges and opportunities for APOC.

All presentations gave detailed and very informative accounts on NTDs amenable to PC in their region. These include LF, SCH, STH, ONCHO, and trachoma, and yaws and food-borne trematodes in WPRO. National Integrated Plans of Action have been developed and/or implemented in several countries across the different regions. Regional summaries of treatment data reported up to 2012 and some data for 2013 were presented. Progress reports showed countries are at different stages of disease programme stages (mapping, MDA or post-MDA surveillance). Most of the countries have started mapping; many have completed mapping for all diseases, but there are still some areas that require attention. For LF, many countries have IUs implementing TAS and several others will be eligible for TAS in 2014. Significant progress is being made, but much remains to be done in order to meet the NTD roadmap implementation goals.

Major constraints and areas for strengthening for M&E of national NTD programs were reported as;

- 1. Absence of long-term contract personnel or dedicated teams working exclusively in NTDs at national and/or regional levels.
- 2. Persistent delays with data transmission from peripheral to national and regional level.
- 3. There is a need for improved transparency and uniformity of data, data sharing and dissemination.
- 4. Countries need support for data review and standardized analyses prior to making programmatic decisions. Systematic analysis of data should be carried out at the national level under guidance of Country offices and Regional offices.
- 5. There is a need to build M&E capacity at Country and Regional level, including provision of technical resources for staff and in-service training in the use of standardized tools.
- 6. Countries need to be provided with financial resources to support their coordination role to conduct national inter-sectoral workshops on M&E issues, and thereby strengthen national ownership.
- 7. MDA coverage assessments should be systematized in M&E processes, given that very few countries regularly conduct coverage surveys.
- 8. Sufficient technical and logistical resources need to be mobilized to support processes leading to the stopping of MDA and conducting post-MDA surveillance with sufficiently trained staff, tools, and funds.
- 9. Sustaining political commitment and priority for NTDs is a perquisite for effective surveillance.
- 10. There is an immense and urgent need for establishing LF elimination verification process.

4 Report of WG M&E Subgroup 3: Monitoring of Disease-Specific Indicators - Updates for 2012-2013, planned activities for 2014 - 2015

4.1 TAS update, K. Won, E. Ottesen

3.1.1 Diagnostic tools: The transmission assessment survey (TAS) incorporates a robust sampling strategy so that decisions are made based on critical cut-offs. The ICT diagnostic is instrumental for conducting TAS. However, there have been several challenges with using ICT cards, including being relatively expensive, requires cold chain, results must be read at 10 min and false positives can develop when read at later time points.

To overcome the ICT drawbacks, BMGF provided support to AlereTM to develop a new Filariasis Test Strip based on the same antibody with specific design criteria: no requirement for cold chain, heat stable results, and at a lower cost (volume dependent). Comparison studies of the ICT and Strip Test have shown that laboratory testing indicated equivalent results for 2 test formats, >95% sensitive for Mf positive persons and 100% specificity. The new LF strip test can be used now in mapping. Additional data is still needed on its use in TAS and how the new test may affect transmission assessment cut-off levels. Field validation is underway; more side-by-side evaluations need to be conducted before the test can be recommended and rolled out for more widespread use in national NTD programmes. Production of the current ICT is likely to end in 2014.

3.1.2 *Procurement and logistics solutions*: Countries lack the resources to procure diagnostic tests. There is a need for new donor support for test procurement through WHO. Country requests will be made through the new joint application package, and then tests will be shipped to countries via WHO Country Offices.

3.1.3 TAS *courses*: All WHO Regions organized TAS training workshops in 2012-2013. An increasing number of countries are conducting TAS trainings at the national level. Course materials and reporting forms were officially launched on WHO's website in December 2013.

3.1.4 Country Readiness for Conducting Disease Specific Assessment (DSA): This has presented as a major issue in working group discussions, and has also frequently come up at the country level. When to stop MDA and start post-MDA surveillance is one of the hardest decisions that programs have to make.

National programs require assistance in decision-making regarding when to stop MDA. Such assistance should assess readiness of countries for conducting the surveys to determine whether or not to stop MDA. The decisions need to be technically correct, prompt and authoritative (WHO), and with expertise and clear understanding of the local reality. An anticipated mechanism to accomplish this is through WHO's RPRGs, or specialized sub-groups of RPRGs. Specialized sub-groups have not yet been established, and the need is acute for 2014, as there are hundreds of DSA that have to be carried out for LF and trachoma. The challenge will increase arise as progress is made towards SCH and ONCHO elimination.

A bridging solution was proposed via immediate, time-limited technical support to RPRGs, through WHO's M&E sub-group of NTD-STAG, composed of disease-specific and TAS experts from WHO, regions, technical and implementing partners. This would be a temporary mechanism to provide support to RPRGs. Noting that DSA surveys impose substantial financial investment, there is commitment from donors to create this temporary mechanism to move forward. The temporary support will work with the RPRG to assess country readiness for DSA based on existing eligibility forms (e.g., TAS eligibility form), and to recommend the required course of action to the country

programme. Finally, the technical capacity of the RPRGs should be built to conduct rapid reviews and clear back log by end of 2014.

4.2 New Tools for STH Control and Elimination, A. Montresor

Materials that have developed in 2013 include:

- (i) A Standard protocol for assessment of antihelminthic drug efficacy: This is based on measurement of Feacal Egg Count Reduction (based on arithmetic means) surveys, and that therapeutic efficacy below this level following a single dose of ALB should be viewed with concern in light of potential drug resistance. The manual has been printed and is available on WHO site.
- (ii) The <u>Draft manual for collection of STH data during TAS</u> was developed to guide decisionmaking regarding STH control activities after termination of LF elimination activities. The draft manual is ready, and is being field-tested in 4 countries (Ghana in February 2014, Haiti in February 2014, Indonesia in March 2014, and Philippines in March 2014). Findings will be reported to WG M&E 2015.
- (iii) The <u>Draft manual for treatment of women of child-bearing age</u> intends to provide guidance for the scale-up of treatment of this age group. The draft was developed in collaboration with Melbourne University, Australia, and reviewed by the nutrition unit in WHO-HQ. The guidelines will be finalized in 2014 and submitted for peer review.
- (iv) <u>Video tutorials on laboratory methods</u> are being developed: These will be an update of the 1991 WHO bench-aids.
- (v) <u>A guideline on the use of historical STH data for mapping</u> is also being developed. It should provide an initial assessment of a country's epidemiological system, reduce inconsistencies among mapping sources, and facilitate decision making. The draft version of the manual is in preparation; maps of all Indian states have been developed.
- (vi) <u>A spatiotemporal model</u> that can predict evolution of STH epidemiology following implementation of preventive chemotherapy in each district is being developed.

4.3 Verification Issues

4.3.1 WHO Framework, D. Engels

The definitions of control, elimination, and eradication concepts and terminology were presented. Elimination—and verification of elimination—can be an extremely complex matter. There have been differing opinions about the definition and interpretation of "elimination as a public health problem;" some consider it as an advanced form of control, while others have defended this term as it is mentioned in a number of WHA resolutions and is a noble target to aim for, as long as it can be quantified and can put clear figures/definition of what it means.

The endemicity of an NTD progresses from a pre-existing endemic situation to morbidity control, to elimination as a public health problem (defined by elimination of disease, or very low incidence/prevalence of infection) and then to elimination (defined by interruption of transmission,

zero incidence of infection; or eradication if globally eliminated). In this regard, certain issues are to be considered:

- Is the goal an endpoint in itself, or an intermediate step?
- What is the sustainability of achievement? Is there a risk of reintroduction or recrudescence?
- What will be the programmatic guidance provided about how to get to the endpoint, versus verifying that have reached the endpoint?

The acknowledgement processes vary based on the specific endpoint that is being reached. Acknowledging eradication can be straightforward but needs to be a formal endpoint endorsed by WHO governing bodies, with an independent international certification team and commission. Elimination, on the other hand, is not global, but can be achieved on regional basis or in some country-specific contexts where possible (e.g. geographically isolated islands). A concerted effort (and endorsement by WHO) for verification of elimination would only be worthwhile if there is a low or negligible risk of potential recrudescence or re-introduction (e.g. ONCHO elimination in Americas). These definitions have been applied and are presented in the Second WHO Report on NTDs to determine roadmap endpoints (Annex4).

As a next step, it was suggested that WHO will propose standardized processes across all NTDs for "verification" of elimination and "acknowledgement" of elimination as a public health problem, and what can be granted by WHO as the outcome of such a process. An related question that remains is how formally should WHO endorse the achievement of elimination as a public health problem, particularly since this may be time-limited and reversible.

4.3.2 A Disease-Specific Perspective, P. Lammie

It is important to recognize that the though wording of WHA resolutions refers to elimination as a public health problem, operationally GPELF has aimed for interruption of transmission as a target; this has been emphasized to countries, and adopted by donors. The results of the post-MDA surveillance TAS to date suggest that the current guidelines are probably appropriate for not just eliminating LF as a public health problem, but also for interruption of transmission. However, TAS surveys aren't powered to detect changes in antigen (Ag) prevalence, and Ag is a lagging indicator. A stronger evidence base is needed to prove that absence of antibody (Ab) in children is an adequate indicator of transmission, and that transmission doesn't occur in settings which passed TAS.

What is needed now is clarity for countries under surveillance are the contents for inclusion in verification dossiers (especially what is needed for non-endemic areas), and on the need to continue surveillance. Additionally, it would be valuable to have an interim process for countries which have already prepared their dossiers while WHO completes formulation of the mechanism of reviewing these dossiers. A regional process for verification could be considered.

Discussions noted that if countries are not recognized for having reached set goals (either by certification or verification), GPELF will lose a lot of interest before 2020. The definition and acknowledgement will continue to motivate both implementers and donors to maintain their momentum and focus towards attaining set goals.

4.4 Update on Monitoring Disease-Specific Indicators, P. Lammie

Better tools and methodologies for sampling populations are required as programmes progress towards the verification process (stopping PC, post-MDA surveillance). Over the last few years, some progress has been made with funding from BMGF and USAID that has facilitated moving the process forward. BMGF has provided support for operational research on PC-NTDs for "Filling the Gaps."

There have been several updates in diagnostic tools over the past year:

- (i) <u>STH</u>. It was noted that Kato-Katz can be a challenging test to apply in field. There currently is a study comparing three multi-parasite PCR assays; the best performing test will be incorporated into field studies to address issues of feasibility and treatment thresholds.
- (ii) <u>SCH.</u> The CCA test is a point-of-care test for *S. mansoni* which uses urine, rather than stool. A multi-country evaluation was undertaken through SCORE. More information was needed about performance of test in low-prevalence settings, so the CCA performance was reviewed in Namibia. Results showed that CCA is more sensitive than Kato-Katz in these kinds of settings, results were compared well with Kato-Katz measurement, which indicates the value for using the CCA test in low prevalence settings, in addition to mapping to identify priority areas for intervention. One of the benefits of using the CCA is that the operational cost of mapping is lower than Kato-Katz per child tested, given that less time and fewer people are needed to implement surveys. However, where Kato-Katz is not performed, STH results will not be available. An important operational question that remains to be answered is how do to best combine SCH and STH surveys most costeffectively.
- (iii) <u>Trachoma.</u> It was noted that if the results from TF and PCR are monitored and compared over time, after several rounds of MDA it is apparent that they're dissociated. In several research settings, there is no infection in community, but residual clinical activity in terms of TF is still seen. This presents a challenge with using TF to stop MDA. The option of an antibody assay for trachoma was described; sensitivity was >95% for PCR+ children, and children are Ab negative in areas where transmission is absent or interrupted. In principle, Ab prevalence could be used to look at trachoma end points. An important operational research activity is now underway to define the utility of laboratory assays for stopping MDA decisions, utilizing standard trachoma survey methods, clinical, PCR, and Ab methods.
- (iv) <u>ONCHO</u>. BMGF has provided support to PATH for development of Ov-16 Rapid Test. The prototype is undergoing field-testing.
- (v) <u>LF.</u> Good Brugia assays for Ab have been available for some time, but since only recently is there Wb123-specific Ag for *W. bancrofti*. It was shown in laboratory settings that the Wb123 Rapid Test is capable of detecting Wb123 Ab in a rapid test format. A biplex was also created with Ov-16 and Wb123 on same strip; this tool has the potential to be used in areas of ONCHO and LF overlap, to see if positive for LF Ab, ONCHO Ab, or both. During the validation of the biplex, the specificity and sensitivity of the original tests were retained, and it was noted that the results are stable so that strips can be re-read. The NTD operations research grant is supporting the production of a field-friendly format prototype for field-testing. The potential uses for this tool are integrated assessments of LF and ONCHO to assess geographic overlap, conduct impact assessments, contribute to stopping

decisions for MDA, and to facilitate surveillance. This will be an important step for the harmonization of M&E strategies.

- (vi) <u>Loa loa diagnostics</u>. A BMGF-funded project has helped to identify individuals with high counts of Loa loa so that they can be excluded from treatment. A potential tool, Cellscope, can match with image software to count Mf quickly and automatically in field settings.
- (vii) <u>Multiplex approaches to surveillance.</u> It was noted that Ab responses in children provide a measure of exposure to infectious diseases; these responses can be used to monitor the impact of public health programs. A research goal is to develop an integrated surveillance platform for measuring Ab for multiple NTDs. A survey has been conducted in Cambodia using the multiplex to assess Ab for multiple diseases and therefore impact of PH interventions. The key observations related to integrated serosurveys include:
 - Integrated serosurveys are feasible, will generate useful data, and have the potential to save money and human resources;
 - Surveys in children generate the most valuable information;
 - Efforts to standardize assays are needed to guarantee that data can be compared across time;
 - Can add antigens from other diseases to multiplex;
 - National surveys can give a good indication whether something is prevalent or not.

The concurrent finding of high prevalence for Strongyloides results of more than 80% in some communities/provinces where the multiplex was field-tested raised some important questions for consideration:

- MDA should be implemented in these communities as an ethical obligation. However,
- What is the appropriate threshold to commence preventive chemotherapy?
- Is IVM for Strongyloides treatment available at a public health price?

Additionally, there was discussion on what is necessary and sufficient to introduce new tools to NTD programs. It was noted that validation is required both in the laboratory and in field settings. It will be important to define how much validation is required, and to set up a systematic process that will provide benchmarks through steps of validation and then use. It was proposed that such a standardized process should include side-by-side comparison with a standard test in 5-10 endemic settings with 500-1000 tests per site. This would be followed by a technical review by disease-specific experts, M&E Working Group and STAG to develop program recommendations. It is important to set up this process with the new strip test for LF, as well as the CCA. Furthermore, establishing systematic processes will also benefit the other diagnostic tools which will be available for validation and program use in the near future.

4.5 Filling the Gaps: OR for the NTDs, P. Lammie

The new operations research (OR) grant has been funded by the Bill and Melinda Gates Foundation has two major objectives;

- To engage NTD community to set priorities by establishing a coalition for operational research on NTDs (COR-NTD)
- To work closely with WHO to build evidence base for programmatic decision-making

This grant is based on a collaborative approach to OR, and is intended to be flexible and adaptive, with the agenda evolving as program needs evolve. There will be an annual meeting held in conjunction with ASTMH, to provide updates on NTD OR underway and to gather perspectives.

An inaugural meeting was held in November 2013 with nearly 200 people during which a number of cross-cutting OR themes identified as:

- Improved diagnostics are critically needed to support program decisions OR grant efforts are focused on translating new tools into practice
- Modeling approaches can inform research design and programmatic decision making
- Programs need to make improved use electronic data capture methods

Potential avenues to more productively engage the M&E Working Group to help with work going forward were proposed, including through COR-NTD meeting, WHO representation on Advisory Panel, WHO participation in grant Program Technical Group (PTG) meeting, and/or back-to-back scheduling of PTG and M&E meetings.

5 Updates on Specific M&E Issues

5.1 Joint application package, A. Gabrielli

WHO has developed a set of forms design to facilitate integrated planning, implementation and M&E of PC interventions: the Joint Request for Selected Medicines (JRSM), Joint Reporting Form (JRF), Annual Work Plan, and the PC Epidemiological Data Reporting Form. These were introduced in each WHO region in 2013, and are available in English, French, and Spanish. This package is intended to serve as both a planning tool and an application for medicines donations managed through WHO. Ministries of Health are invited to submit the Joint Application Package to WHO electronically, by 15 August annually; for example, in 2013, MOH would report on 2012 implementation and plan/request drugs for 2014 implementation. Applications are reviewed by independent bodies established in each region and coordinated by WHO regional offices.

Out of the 122 countries requiring PC and eligible for requesting drugs, 75 provided a 2012 report, of which 61 provided a 2012 report using the JRF. Sixty one countries concurrently applied for 2014 drugs, of which 50 used the JRSM. Twenty three countries submitted a 2014 annual work plan. Meeting participants were requested to provide support to countries to utilize these tools for reporting and planning.

5.2 Data Quality Assessments for National NTD Programmes, P. Mbabazi

Most national programs have been implementing NTD activities for more than 5 years, with little or no action at the country level to validate reported data. Coverage surveys are often not implemented at recommended regularity. Integration has created new ways of working, with new challenges/concerns for data management. However, achieving—and documenting the achievement of—the NTD roadmap milestones requires robust, reliable data.

To assess the quality of NTD data, a data quality assessment (DQA) tool and accompanying guidelines have been developed with funding from USAID, following the recommendation of the 2013 M&E Working Group meeting. The DQA is a process that aims to expose technical implementation data issues to plan and deploy data enrichment strategies for national programs. There are both quantitative and qualitative objectives, to assess the quality of reported data for a given time period through data verification, and to assess the ability of the NTD data management system to collect and report quality data through a systems assessment. The NTD DQA tool and guidelines are available in English, French, and Spanish; additional training resources are being translated, and the entire package will also be translated into Portuguese. To date, the DQA has been field-tested in Uganda, Nicaragua, and Cameroon. The exercise has proven valuable in each

country, highlighting the strengths and weaknesses of the data management system for NTDs. By implementing the DQA with multiple stakeholders engaged, including the MOH, WHO, and partners, the MOH ownership of the data and reporting system is emphasized while also providing an opportunity for accountability and stakeholder buy-in for identified recommendations.

It was noted that the DQA is a valuable M&E tool that should be used to elucidate national NTD information system strengths, and determine country-specific data quality issues to be addressed. Countries and partners are encouraged to implement DQAs at least once every 3-5 years as part of programme and coverage evaluation, using probabilistic sampling, in order to ensure robust, high quality data. The DQA for NTDs should be considered for integration with assessments for other public health programs, as was done in Nicaragua. In addition to the DQA, it was recommended that concordance monitoring/rapid coverage monitoring (RCM) be implemented within one week of preventive chemotherapy as an in-process exercise, in order to take immediate corrective action to treat communities that are missed and thereby raise coverage. Additionally, a data quality self-assessment (DQS) should be implemented at least once a year in each district as part of supportive supervision.

5.3 National NTD Database Template, K. Zoerhoff

Many countries don't have an integrated, national database for NTDs. However, databases are necessary for effective data management and M&E processes to inform national program implementation. As a result of the recommendation from the 2013 M&E Working Group meeting, a national NTD database template has been developed to strengthen the capacity of national NTD programs to store, manage, analyze, and report their data. Building on the work already done by AFRO for its regional database for LF data, the development has been a collaborative process over the past year, including input from several Ministries of Health, WHO/HQ, AFRO, SEARO, WPRO, APOC, CNTD, and RTI, with funding from USAID. Indicators were drawn from established reporting forms and WHO (particularly AFRO), NTD partner databases, collaborating organizations, drug donation programs, an SAE expert, and the core indicators outlined in the draft WHO Indicator Compendium. Intended to be used and owned by national programs, the database promotes effective data storage and analysis at the country level, as well as facilitates reporting by generating standard reports required for submission to WHO and partners.

The database has been introduced in Nigeria in January 2014. A Training of Trainers workshop will be held at KEMRI at the end of February, and it is anticipated that NTD-endemic countries will be introduced to the tool during regional data management workshops and in-country technical assistance, for a period of extended field-testing in 2014. Feedback from countries and stakeholders, including members of the M&E Working Group, is requested, and will be incorporated into an updated version in early 2015.

During the discussion, it was suggested to explore ways in which the database can be linked with mobile data capture efforts, as well as to consider incorporation of financial aspects of program management into the database. Additionally, it was suggested that a module be added that facilitates making decisions from the data based on WHO guidelines , and that features be included that help users identify data quality issues and inconsistencies, to ensure that the quality of data entered is high.

5.4 Monitoring and Management of SAEs, V. Reggi

Adverse reaction/adverse events and serious adverse reaction/adverse events following preventive chemotherapy were defined. SAEs are included in the WHO NTD repository, and the cases reported from 2012-2014 were indicated. There are a number of reasons to intensify work on SAEs in PC, including an ethical obligation, the integrity of PC interventions, and new EU pharmacovigilance legislation that introduces reporting requirements for products authorized in the EU which are also marketed outside the EU.

It was highlighted that adequate planning of MDAs including for adverse drug reactions (ADRs) should be carried out; training of staff involved in PC should be intensified, particularly related to management of ADRs; implementers should ensure the involvement of national medicines regulatory authorities, and strengthen existing or support the set up national pharmacovigilance centres. Additionally, a document outlining the peculiarities of PC should be developed to collate information for the European Medicines Agency in order to develop the appropriate set of reporting requirements for PC. It was noted during discussion that capacity building for clinical management of cases and clarifying response mechanisms during PC should be strengthened. Additionally, APOC/AFRO/HQ should have access to the Loa loa database that is maintained by the Mectizan Donation Program (MDP).

6 Expert Committees: Report on 2013 M&E Activities & 2014 Priorities

6.1 Mectizan Expert Committee/Albendazole Committee, Y. Sodahlon

Dr. Sodahlon's presentation focused on monitoring of SAEs, monitoring drug efficacy, and supply chain management. It was noted that Loa loa is a major impediment for onchocerciasis control/elimination and LFE in Africa, given that ivermection (IVM) is associated with high risk of SAEs in Loa loa endemic areas. This creates difficulty with implementing and expanding MDA for oncho and LF particularly in Central African countries. Details of SAEs reported in 2012 (19 in DRC) and 2013 (27 in DRC, 8 in Cameroon) were presented. As of December 2013, a total of 1335 cases have been reported cumulatively reported since 1989.

MDP convened a meeting on onchocerciasis elimination in Africa to discuss current data available on efficacy of IVM and to determine what procedures program managers should follow to ensure that IVM remains efficacious. The review of the evidence showed that IVM works very efficiently, even in difficult programmatic situations, and with continued use it can break the transmission of onchocerciasis. At present, resistance to IVM doesn't appear to be a major global problem, and programmatic issues remain the major cause of Atypical Response (AR). It was recognized that a rigorous definition of optimal and atypical responses to IVM treatment at individual and community levels is needed, and the most effective use of IVM needs to be considered along with what additional drugs and intervention tools could be used. Tests and protocols should be developed that can confirm the presence of IVM resistance. MDP will work with APOC (TCC) to produce a guide for program managers to use where AR is suspected and inform all programme managers on its availability and use.

The supply chain management process was described, and it was noted that there have been recurrent issues with import tax for IVM in some countries. The advantages of adopting the widespread use of the JRSM and JRF were highlighted, and some issues to address with the forms were identified, including the need to accommodate requests for Loa loa co-endemic areas, ensuring that epidemiological data are also reported and transparency of reported drug inventory management. It was recognized that strong communication remains key to ensure effective

coordination with the medicines that are not donated through WHO. MDP fully endorses the new mechanism, and will contribute to the forms' use, improvement, and assist in training.

6.2 Update from Children Without Worms and STH Advisory Committee, D. Addiss

Dr. Addiss noted that the STH community is experiencing a major shift towards returning to a comprehensive strategy of disease control with PC, safe drinking water, basic sanitation, health promotion, and education. In 2013, CWW worked to expand partnerships and the diversity of its partnerships, including engaging with the WASH community, and provide technical support on STH. Additionally, CWW has worked with WHO to develop guidelines on STH and TAS, publish the results of the NGDO Deworming Inventory, and support implementation of coverage evaluation surveys. CWW has been engaged in various operations research activities, including the feasibility of adding STH to LF TAS, in collaboration with partners, and working with the NTD Support Center on the "Filling the Gaps" grant. The STH Advisory Committee Meetings over the past year recognized that the TOR are shifting, as they are no longer reviewing country requests for mebendazole (MBD), and there is an opportunity for expanding the linkages with Johnson and Johnson, GSK, the NTD Support Center and NTD STAG. The most recent committee meeting noted the need to scale up PC, and recognized WHA54.19 as a guiding tool to implement a comprehensive strategy. Implementation of the STH strategy requires a multi-sector approach, coordinated partnerships, and a wider variety of partners, with operations research and a strong evidence base to guide the global programme. CWW was urged to work with partners to facilitate this work.

The 2014 priorities include:

- Finalization of guidelines on assessing STH with LF TAS
- Longitudinal STH monitoring, including sentinel sites
- Evaluate parasitological impact of PC, including determining the most effective PC frequency, clarifying administrative units, and field-testing of WHO interim guidelines
- Monitoring of drug coverage, including school-based PC and "unprogrammed" deworming
- Monitoring drug efficacy using new WHO guidelines
- Better monitoring and data capture of WASH, so as to incorporate indicators into priority setting and monitoring

6.3 Deworm the World (DtWI): M&E of School-based Deworming Activities, G. Hollister

In 2013, DtWI became part of a new non-profit called Evidence Action. The key objectives of M&E for DtWI include confirming that key program inputs are taking place, monitor quality and success of program processes, determine coverage of deworming in different groups, measure program impact on prevalence and intensity of worms, validate coverage through using a secondary mechanism to confirm preliminary data, and use M&E to improve program processes and reach.

DtWI has 5 core M&E activities:

- Preparatory monitoring: employing telecallers and independent monitors to call a sample of schools, blocks, and districts to monitor preparedness
- Process monitoring: Independent monitors
- Coverage reporting
- Coverage validation
- Prevalence surveys

Recent results from DtWI support in India and Kenya, and key areas of technical assistance were shared. Achievements in India included treatment of 2.4M children dewormed (1.7M
SAC,~678,000 PSAC in anganwadis) in Dehli in September 2013, and 6.7M SAC dewormed (~82% programme coverage) 3.98M PSAC dewormed in anganwadis in Rajasthan in October 2013. In Kenya 5.96M SAC and PSAC were reached in Year 1 of implementation, surpassing the programme target by 18%.

In 2014, DtWI will prioritize ensuring faster return of quality coverage data to facilitate improved program reporting/data sharing, and improving country/state responsibility for and ownership of data. Additional priorities include integrating data collection with existing government forms/ systems where practical and possible, and determining the right-size data collection so that it's useful for program implementation and improvements. Lastly, DtWI will explore potential technological solutions to capture prevalence and program coverage data.

7 Other M&E Updates

7.1 M&E within ICOSA, A. Fenwick

The rationale for M&E to provide empirical evidence about program progress was described. DFID's grant reporting requirements primarily focus is on the number of treatments, value for money, impact, and integration. ICOSA's metrics are related to those areas, and are measured through process monitoring, including costs and costs of treatment; performance monitoring, including reported and surveyed treatment coverage; and impact monitoring using parasitological and morbidity indicators using cohorts and cross-sectional studies. In each country programme where SCI is active, longitudinal cohort studies have been set up to monitor health impact. SCI is also working to evaluate the move towards elimination in Uganda, and examining the outcome in low transmission districts.

7.2 M&E Updates: New solutions for New Challenges, M. Rebollo

Dr. Rebollo highlighted the solutions that CNTD has been implementing to address M&E challenges related to data quality; timeliness; capacity building, particularly related to data analysis; and new challenges. To address the issue of poor laboratory practices and data management capacity, CNTD is supporting laboratories for NTD control across Africa and Asia. Additionally, CNTD will support roll-out of the national NTD database template, and the development of a database to store raw survey data at the individual level. CNTD has contributed to AFRO M&E Training, GIS training, NTD database development and DQA training, and provided technical support to select countries to build capacity in data analysis and coverage surveys. Some of the new challenges experienced by national NTD programs include the challenge of mapping in low transmission areas such as LF in Ethiopia; interpreting DRC mapping results in the context of onchocerciasis treatment and use of Long Lasting Insecticide Nets (LLINs); pattern of urban transmission in some West African countries; and changing scenarios, such as impact of bednet distribution on LF transmission.

8 Working Group Updates

8.1 Working Group on Economics and Impact of NTD Interventions, P. Fitzpatrick

The first informal meeting took place in Geneva, and brought together Ministry of Health (MoH), Ministry of Finance (MoF), academic institutions, NGOs. The objectives of the working group, its activities, structure and membership, and financing were described. Action-points arising from the meeting included developing content for the NTD report, rolling out the EMPaCT platform, linking to the universal health coverage (UHC) policy discussion, getting NTDs on health-sector-wide priority-setting, development of budgeting and expenditure-tracking tools, connecting with WASH, and exploring "innovative" models of financing.

The following was proposed as potential contributions from the M&E Working Group:

- Disseminate call for nomination of members of this working group (coming)
- Tack onto OR projects economic or socio-economic evaluation
- Contribute to monitoring of social determinants/barriers to coverage
 - Sex/income/education disaggregation
 - Collaboration with SDH team at WHO in context of monitoring barriers to UHC

8.2 Monitoring Drug Efficacy for Preventive Chemotherapy (WG MDE), A. Montresor

The progress made in 2013 and planned work were shared for the various PC medicines. Key highlights include:

- (i) <u>IVM for ONCHO</u>: Progress made in 2013 included the identification of putative markers of low response and an epidemiological evaluation. The development of a user-friendly software is planned in order to facilitate follow-up progress towards elimination in countries.
- (ii) <u>IVM for LF:</u> Progress was made in 2013 towards how to test for drug resistance. Modeling exercises to predict changes in prevalence during the implementation of elimination activities are planned.
- (iii) <u>Benzimidazoles</u>: A manual was published on a standardized protocol on drug efficacy, and a mathematical model predicting the changes in STH prevalence is being developed. Various assessments are planned for 2014, as well as the introduction of new technologies and the development of video tutorials of operational procedures.
- (iv) <u>PZQ for SCH</u>: An assessment of the efficacy of PZQ against *Schistosoma spp* was carried out, and possible sources of resistance to PZQ have been identified. The development of a mathematical model to predict epidemiological changes is planned for 2014.
- (v) <u>Flubendazole</u>: The dossier of FLBZ was reviewed, an oral formulation of FLBZ was developed, and FLBZ was toxicologically evaluated. In 2014, planned work includes optimizing of oral formulation and efficacy studies.

The detailed meeting report of the Working Group on Monitoring Drug Efficacy for Preventive Chemotherapy is available as an addendum to this WG M&E 2014 report.

8.3 Capacity Strengthening for NTD Programmes, P. Mbabazi

The M&E Working group in 2012 recommended the development of a working group on capacity strengthening, which was endorsed by the NTD STAG in 2012. It was recognized that the global community is operating in a very supportive policy environment, and the focus should be on the scale-up of preventive chemotherapy given that the required trajectory to reach the control and elimination goals is not being attained.

Having reviewing the responsibilities of a programme manager, the working group developed main thematic areas to create a "sunflower concept." The aim is to put together operational guidelines

related to these thematic areas, as there is a recognized need to improve knowledge management and transfer to country level programme personnel.

In 2013, a WHO meeting was convened on the acceleration of scale-up on PC coverage, particularly in highly populous countries, and needs assessments were conducted to identify regional needs, country-specific priorities, and programme manager opinions. Knowledge transfer management and transfer is being prioritized by implementation of the National Programme Manager Training Course through regional adaptation and country-specific adaptation for mega-countries and specific requests; M&E training workshops, including the 5th AFRO M&E Workshop to be held in Addis in 2014; and the current development of a district-level NTD managers training course.

KEMRI and Noguchi were designated as NTD Training Centres, in order to strengthen specific technical skills to support NTD programs. This includes GIS training, a TOT for the National NTD Database and DQA, and laboratory strengthening. Additionally, TDR training networks are being considered, and meeting participants were requested to suggest other potential training centres. The priorities and recommendations for 2014 were described, and it was noted that the NTD Toolbox should be released within the next month.

9 Meeting Outcomes and Recommendations

WG M&E 2014 acknowledged the various contributions that are being made by the various entities responding to needs expressed by national NTD programmes. These efforts can contribute to a common work plan and priorities for M&E in 2014 as follows;

- Support the work of the interim group on Investment and Impact of NTDs which is developing an investment case for NTD elimination. WG M&E 2014 seconds the proposal to establish a formal Working Group on Economics and Impact, and will work to provide regular technical updates and epidemiological data summaries that will be required by this group.
- 2. All WHO regions reported that lack of human resources continues to impede function and effective follow-up of PC programme activities. This persistent absence of dedicated NTD personnel at regional levels and in priority countries continues needs to be addressed urgently and conclusively.
 - a. Dedicated personnel should be situated in the WHO regional offices, with appropriate contractual arrangements to enable continuity in function.
 - b. National programme officers (NPO) should be situated in WHO Country offices, particularly in high-burden countries where acceleration of scale-up of preventive chemotherapy is essential for meeting the global deficit in PC coverage.
 - c. Relevant in-service training opportunities for NTD programme personnel should be provided.
- 3. Strengthen PC data management at all levels: Data quality, timeliness, analysis, and taking required corrective action is a major priority. WHO HQ, Regional Offices, and NTD partners should support countries to strengthen activities for ensuring data quality and facilitating use of data for decision-making. This should include the finalization and

roll-out of tools developed to date, including the national database template and data quality assessment tool, as well as developing and utilizing mHealth platforms to improve data transmission. The national database template should incorporate features to ensure data quality and facilitate data use and decision-making by countries, such as indicating data inconsistencies, highlighting low coverage, and projecting when impact assessments are due.

- a. It is recognized that we are at a stage in program maturation where it is important to move past simply monitoring treatments, and additionally **focus on assessing coverage** by implementing performance monitoring and **real-time analyses of implementation data**.
- b. There is a need to increase focus on the evaluation component of M&E, **particularly the institutionalization of coverage evaluations, disease-specific epidemiological evaluations and programme evaluations**. The use of the DQA could be incorporated in this process.
- c. We should support countries to ensure that **disease-specific assessments (DSA)** are implemented at the right time, with high quality, and will meet criteria and technical scrutiny.
- d. Countries and NTD stakeholders should **collaborate, coordinate and provide sufficient funds to implement national M&E plans in order** to ensure that activities are implemented as required.
- e. Routine data capture and M&E for Morbidity Management and Disability **Prevention (MMDP)** should be implemented.
- f. Significant progress has been made regarding compilation of performance of national PC programmes. Further efforts should be made to incorporate data on blinding trachoma, loa loa, and drug inventory in national reporting forms. This would require modification of appropriate reporting forms. In the use of these joint tools, it is necessary to recognize that communication remains key to ensure coordination with other medicines not donated through WHO.
- 4. The role of RPRGs for NTD programmes remains vital. The challenges of the expanded RPRGs are substantial, with 5 diseases, evolving guidelines, and unique country contexts. A systematic way to support the expanded RPRGs is needed to perform their functions. The WHO M&E Working Group should provide technical support to RPRGs to enhance the capacity of expanded RPRGs to review country readiness to conduct TAS and other disease-specific assessments. A first step to assist the expanded RPRG could initially be provided through an immediate, time-limited technical support provided through WHO's M&E sub-group of NTD-STAG, composed of disease-specific and TAS experts from WHO, regions, technical and implementing partners, and NTD support centres.
 - a. The expanded RPRGs should work in tandem with concurrent efforts to support M&E in high-burden countries which collectively account for nearly half of the current global coverage implementation deficit.
- 5. Improvements are needed to recognize and promote country ownership of PC data as well as the benefits of sharing data to monitor progress and inform decisions. Standard practices and processes for data sharing between all NTD stakeholders should be should

established and promoted. WHO should convene a technical meeting with representatives from national programs, drug donation programs, researchers, partners to arrive at a consensus agreement around data sharing.

- 6. Interim processes are needed to acknowledge the achievements of countries that have achieved the LF elimination goals. In the absence of definitive global guidance, RPRGs should provide this recognition to countries for their achievement of LF elimination goals. It is important to countries and donors that this achievement be recognized, even if it is not as formal as the elimination certification for polio and eradication of guinea worm.
 - a. A Common Submission Dossier Template (CSDT) format for national authorities to use in submitting the required information for processing requests for verification of elimination should be developed.
- 7. The WHO M&E Working Group should develop a systematic process to evaluate new diagnostic tools for NTDs, to review their utility for programs, and to develop recommendations for programs on their use. Evaluations should be conducted for diagnostics for which development is most advanced and could be introduced for use in national programmes in the near future. Key diagnostics for which evaluations need to be undertaken for the;
 - a. utility of the CCA assay for mapping schistosomiasis should be investigated in the program context.
 - b. comparability of the STH three multi-parasite PCR assays to Kato-Katz performance
 - c. current prototype of Ov-16 Rapid Test.
- 8. Noting the various activities that need to be implemented at regional and global levels to monitor and evaluate programme progress against the NTD roadmap goals, a strategic plan to guide the implementation and allocation of resources for M&E should be drafted. This plan should highlight the anticipated timing of key activities, provide estimates of what technical, logistical and human M&E resources are required towards the 2015 and 2020 timelines, and provide suggestions on which entities would implement the various roles. This guiding document should reflect different stages countries are in and benchmarks, and guide how national authorities, WHO and NTD partners mobilize resources for field-level activities in order to improve coordination and use of the limited resources available to monitor and evaluate progress towards control and elimination goals.
 - a. Countries should be supported to complete the development of their national multiyear M&E plans in which they should detail resources required at each phase, and particularly include a scale down plan for the diseases targeted for elimination.
- **9.** WHO should convene a technical consultation to develop a body of evidence around the global distribution of Strongyloides and its importance, and potentially develop public health recommendations that could include preventive chemotherapy of Strongyloides and to ensure that appropriate medications are made available for this purpose.

- **10.** With the substantial risk that SAEs can pose on successful program implementation, it is important to **clarify response mechanisms and strengthen capacity for SAE management**.
 - a. SAE response mechanisms should pro-actively involve national pharmacovigilance and medicines regulatory authorities
 - b. a document outlining the peculiarities of PC should be developed to collate information for the European Medicines Agency in order to develop the appropriate set of reporting requirements for PC.
 - c. the Loa loa database should be shared with appropriate stakeholders, including APOC, AFRO, and WHO HQ.
 - d. capacity building for clinical management of cases and clarifying response mechanisms during PC are needed.
- 11. Programme evaluation should be prioritized and conducted on a periodic basis in order to further improve the management and effectiveness national NTD programs. A handbook and eTool with a standardized methodology for joint evaluations (by evaluators and stakeholders) of integrated NTD control programmes needs to be developed.
 Programme evaluation needs to become an integral part of regular programme planning and implementation.
- 12. National NTD programmes and projects should be supported to harness the immense potential of mHealth technologies to collect and transmit data from the field, and even routine reporting of key indicators. A common framework to describe the constituent parts of mHealth for NTD programmes should be constructed around standard goals, placing intended users and beneficiaries in central focus against the context of several applications currently in use. WG M&E should facilitate the development of such framework of mHealth applications in which a shared language and technological approach is provided to guide the use of mHealth tools in national NTD programmes.

ANNEX 1 - AGENDA

World Health 5th NTD-STAG Global Working Group Meeting on M&E of Preventive Chemotherapy Organization 19- 20 February 2014, Salle C, Centre de Conférence de Varembé (CCV)/Centre International de Conference de Genève (CICG), 17 rue de Varembé, Geneva

AGENDA				
Day I	Item	Name		
09:00 - 09:10	Welcoming remarks	ENGELS. D		
09:10-09:20	Introductions	ZARAMBA. S		
09:20-09:40	STAG 2013 Recommendations & Outcomes	MBABAZI. P		
	REPORT/UPDATES FOR 2011 - 2012			
09:40 - 09:50	Monitoring and Evaluation of national programmes - overview	GYAPONG. J		
09:50 - 10:05	M&E for NTDs/PCT in AFRO	AFRO		
10:05 - 10:20	M&E for NTDs/PCT in AMRO	AMRO		
10:20 - 10:30	Discussion			
10.30 - 11.00	Coffee break			
11:00 - 11:15	M&E for NTDs/PCT in EMRO	EMRO		
11:15 – 11:30	M&E for NTDs/PCT in EURO	EURO		
11:30 - 11:45	M&E for NTDs/PCT in SEARO	SEARO		
11:45 - 12:00	M&E for NTDs/PCT in WPRO	WPRO		
12:00 - 12:20	M&E for Onchocerciasis Control & Elimination activities – updates on 2012-2013 activities.	APOC		
12:20 - 12:30	WRAP-UP – Priority M&E issues for national NTD programmes	GYAPONG. J		
12:20 - 12:30	Discussion	ALL		
13:00 - 14:00	Lunch break			
14:00 - 15:30	Monitoring of disease-specific indicators 2013			
	Progress reports and updates			
14:00 - 14:20	• TAS Update: Backlog of surveys, technical questions, converting from the ICT to the LF strip test, LF strip test supply	LAMMIE. P		
14.20 - 14.40	New Tools for STH control and elimination			
14.20 - 14.40 14.40 - 15.00	 Verification issues: 	MONTRESOR. A		
11.10 15.00	 WHO Framework ; Definitions of key epidemiological terms to guide NTD programme transition 	ENGELS. D		
15:00 - 15:30	• Program Implications Discussion	LAMMIE. P		
15:30 - 16:00	Coffee break			
16:00 - 17:45	Monitoring of disease-specific indicators			
16:00 - 16:20	• Diagnostic tools: LF, Oncho antibody strip tests, Trachoma	LAMMIE. P		
16:20 - 16:40	 Update on NTD Operational Research grant: Research underway and planned 			
16:40 - 17:00	Discussion			
17:00 - 17:45	General discussion of reports of Sub-group 1 and Sub-group 2	ALL		
17:45 - 18:00	Conclusion of Day 1	ZARAMBA. S		
18:15 - 19:45	COCKTAIL – CICG			



World Health Organization **FIFTH NTD STAG WORKING GROUP MEETING ON MONITORING AND EVALUATION OF PREVENTIVE CHEMOTHERAPY.** 19 – 20 February 2014.

PROVISIONAL AGENDA				
Day II:	Item	Name		
09:00 - 09:10	Re-cap of Day 1	Rapporteurs		
	Updates on specific M&E issues			
09:10 - 09:30	Updates on joint mechanism for medicines request and PC data reporting	GABRIELLI. A		
09:30 - 09:50	Data Quality Assessments for NTD programmes	MBABAZI. P		
09:50 - 10:10	Prototype for national NTD databases	ZOERHOFF. K		
10:10 - 10:30	Monitoring and management of Severe Adverse Events	REGGI. V		
10.30 - 11.00	Coffee break			
	Expert Committees: Report on 2013 M&E activities & 2014 priorities			
11:00 - 11:20	- Trachoma Expert Committee	EMERSON. P		
11:20 - 11:40	- Mectizan Expert Committee/Albendazole Committee	SODAHLON.Y		
11:40 - 12:00	- Children Without Worms	ADDISS. D		
12:00 - 12:20	- Deworm the World: M&E of school-based deworming activities	ZWANE. A		
	Other M&E undates – ICOSA grant			
12:20 - 12:30	Schistosomiasis Control Initiative	FENWICK. A		
12:30 - 12:40	Centre for Neglected Tropical Diseases	REBOLLO. M		
12:40 - 13:00	Discussion			
13:00 - 14:00	Lunch break			
14:00 - 14:20	Updates: Monitoring Drug Efficacy for preventive chemotherapy (WG MDE)	MONTRESOR. A		
14:20 - 14:40	Updates: Capacity Strengthening for NTD programmes (WG CS)	RIO. F		
14:40 - 15:00	Updates: Working Group on Economics & Impact of NTD interventions	FITZPATRICK. P		
15:00 - 15:30	General discussion: linking work of WG M&E, WG MDE, WG E&I and WG CS: Identification of issues for inter-collaboration in 2014	ALL		
15:30 - 16:00	Coffee break			
16:00 - 17:00	RECOMMENDATIONS TO STAG 2014	ZARAMBA. S		
	- WG M&E work plan: 2014- 2015 and beyond			
17.00	WPAPUPAND CONCLUSION	ENCELS D		
17:00		LINGELS, D		
	Closure of Day II	1		

ANNEX 2 – LIST OF PARTICIPANTS

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Fifth Meeting of the Working Group on Monitoring of Neglected Tropical Diseases Drug Efficacy

Department of Control of Neglected Tropical Diseases Geneva, 18 February 2014

Chair: Prof Mamoun Homeida Rapporteurs: Dr Marco Albonico, Dr Bruno Levecke



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1 Background

For four consecutive years the working group (WG) on Monitoring Drug Efficacy reported independently to the STAG on its progress of ongoing work, future plans and recommendations. This WG consists of five subWG, including (i) Onchocerciasis and Lymphatic Filariasis (ivermectin), (ii) Soil-transmitted helminthiasis (benzimidazoles), (iii) Schistosomiasis (praziquantel and oxamniquine), (iv) Human African Trypanosomiasis, Leishmaniasis, Chagas disease and Yaws, and (v) DNDi and research on NTD drugs (TDR). However, at the STAG meeting in 2013 it was decided to merge the WG on Monitoring Drug Efficacy into the WG on Monitoring and Evaluation. This merge of the WGs was recommended because monitoring of drug efficacy should become part of monitoring and evaluation activities. Given the nature of the Intensified Disease Management, the subWG on Human African Trypanosomiasis, Leishmaniasis, Chagas disease and Yaws will be incorporated in the WG on Access to Essential NTD Medicines.

2 Progress of ongoing work, future plans and recommendations from the different subWGs

2.1 SubWG on ivermectin (onchocerciasis and lymphatic filariasis)

2.1.1 Progress of ongoing work

Onchocerciasis

(i) Identification of markers for monitoring for sub-optimal IVM response. Six laboratories in Australia (La Trope University), Burkina Faso (WHO/Multi-disease Surveillance Centre MDSC), Cameroon (Research Foundation in Tropical Disease and Environment), Canada (McGill University), Ghana (Noguchi Memorial Institute for Medical Research/Council for Scientific and Industrial Research) and France (Institute de Recherche pour le Dévelopment) are collaborating since 2011 with the overall objective to determine any highly significant genetic difference between sub-optimal responder and good responder worms populations in order to obtain the best unbiased marker for IVM resistance. The specific objectives are (a) identification of potential genetic markers of O. volvulus susceptible to IVM, (b) identification of potential markers of gene flow for predicting possible spread of genotypes with low susceptibility to IVM, (c) development of diagnostic tool for use by control programmes for surveillance of emerging of suboptimal responder strains and (d) capacity building in Cameroon, Ghana and WHO MDSC. To date the O. volvulus genome is available, and based on genome differences between IVM naïve subjects, 'good' and 'poor' IVM responders 800 single nucleotide polymorphisms (SNP) could be identified as potential markers. This set of SNPs has been further narrowed to 160 SNP. The research questions are (i) whether reduce efficacy in Ghana and Cameroun or in other countries is really occurring, and (ii) whether this may impair the performance of the Onchocerciasis Control Programme. Main source of funding is APOC (0.9 M US\$) and Australia (0.59 M US\$). The project is managed by TDR.

- (ii) <u>MDSC sample repository.</u> This sample repository consists of samples collected in areas differing in level of endemicity, habitat (forest vs. savannah), vectors, and history of IVM treatment (no treatment vs. >10 treatments). Currently, a total of 3,334 samples are archived at the MDSC laboratory.
- (iii) Epidemiological Evaluation Results. Epidemiological assessment has been considered as a proxy indicator of efficacy of IVM on onchocerciasis in the absence of molecular marker. Epidemiological data has been collected in 22 foci (304 villages, 76,390 persons) in 9 different countries. The epidemiological evaluation for phase 1a indicated that sites examined in Burundi, Cameroon, CAR, Congo DRC and Nigeria are progressing towards elimination. The epidemiological evaluation for phase 1b indicated that treatment can be stopped in sites examined in Ethiopia, Guinea and Tanzania, but not for Malawi (due to bordering countries where onchocerciasis is still present) and some sites in Nigeria (Cross River and Ebonyi).
- (iv) In depth situational analysis of sites with unsatisfactory results. In total five sites in DRC (Bas Congo, Uele, Ankuru), Nigeria (Kogi, Ondo-Endo) and Cameroon (Center 1 and 2) did not progress as anticipated by the ONCHOSIM model. For these sites, APOC has set up an independent group of in country experts to conduct the situational analysis. Term of References has been developed and budget has been submitted. The work will be conducted in 2014.

Lymphatic filariasis

There are two fundamental questions to be answered.

i) How to monitor drug efficacy following MDA?

Resources (grant "Filling the gap" from B&MGF, NTD modelling consortium) are now available for modelling to predict the progress after MDA, and hence allowing determining the alarm bell if progress is unsatisfactory (cfr. ONCHOSIM). WHO data from LF sentinels sites can be used to model expected declines in Mf prevalence following MDA.

ii) If reduced efficacy is expected , how do we test for it ?

WHO protocol for assessing of drug efficacy against STH can be employed in STH-TAS settings. For LF, sentinel and spot check sites may serve the same purpose.

BMGF resources are also being use to address two additional questions using modelling approaches. First, the presence of Loa loa infection has served as an important obstacle to scaling up MDA in areas where Loa overlaps with LF (or hypoendemic oncho) because of the risk of severe adverse events (SAE) following treatment with ivermectin. SAE are associated with high counts of circulating Loa MF. Models will be developed to determine if there is a community Loa loa prevalence at which LF MDA can be safely administered.

As MDA for LF is being stopped in many areas, there is a growing need to implement surveillance. Since the risk of recrudescence is related to the baseline prevalence and effectiveness of MDA, mapping approaches will be used to determine if the surveillance requirements can be stratified based on risk.

2.1.2 Challenges

Onchocerciasis

- (i) <u>Identification of markers for monitoring for sub-optimal IVM response.</u> Due to budget constrains the number of parasites to be genotyped will be reduced, and hence it is less likely to identify relevant markers.
- (ii) <u>Suboptimal response should be distinct between reduced efficacy and the tail of a normal</u> <u>response</u>. Care should be taken to deliver message to endemic countries that drug resistance is not there and IVM is still a very effective drug.
- (iii) <u>Need of having a standard protocol to assess IVM efficacy for onchocerciasis</u> and define an acceptable threshold for cure and microfilaria reduction rate.
- (iv) Eventually the model should be available also for DEC.

Lymphatic filariasis

- (i) <u>Assessment of drug efficacy</u>. Protocols to assess the efficacy of STH drugs are based on the testing of 200 infected persons. Comparable approaches to examine the efficacy of LF drugs will require more infected persons than typically identified in sentinel sites; the current sample size will not be sufficient.
- (ii) <u>LF and Oncho efforts to monitor drug efficacy should be merged</u>, especially after the restructure of APOC beyond 2015.

2.1.3 Future plan of activities to fill the gaps

Onchocerciasis

- (i) <u>Identification of markers for monitoring for sub-optimal IVM response</u>: 2nd validation with 34 SNPs on male worms and microfilaria at different time points after IVM administration collected during studies in Cameroon and Ghana. A 3rd validation will be performed on field samples from other countries. Finally, these 34 SNPs will be narrowed down to 8 SNPs. These 8 SNPs will be validated as potential response markers. In addition, training, technology and capacity building will be continued. Finally, efforts will be taken to seek funding to continue the work on IVM resistance markers.
- (ii) <u>MDSC sample repository.</u> Continue archiving of parasite samples from epidemiological evaluations.
- (iii) <u>Epidemiological Evaluation Results.</u> Continue conducting epidemiological evaluation, including entomological surveys.
- (iv) <u>In depth situational analysis of sites with unsatisfactory results.</u> Conduct the in-depth situational analysis for sites where the progress based on ONCHOSIM was unsatisfactory.
- (v) <u>In 2014 a software will be available with maps and endemicity level</u> allowing countries to detect their onchocerciasis endemicity and trends towards elimination.

Lymphatic filariasis

- (i) <u>Monitoring drug efficacy</u>. A predictive model based on data from WHO should be developed. In addition, methodology on how to assess coverage will be addressed by the B&MGF grant.
- (ii) <u>Assessment of drug efficacy</u>. An appropriate protocol adequately powdered to assess drug efficacy in sentinel and spot check sites should be defined.
- (iii) <u>Merging LF and Oncho monitoring.</u> A group of experts on LF under the leadership of WHO will interact closely with APOC to explore how to best integrate LF monitoring.

2.2 SubWG on benzimidazoles (soil-transmitted helminthiasis)

2.2.1 Progress of ongoing work

- (i) <u>Assessment of drug efficacy</u>. The drug efficacy of a single dose mebendazole (MEB, 500 mg, J&J) and single dose albendazole (ALB, 400mg, GSK) against soil-transmitted helminths (STH) was evaluated in 2 multi-centric efficacy trials. The results revealed a high efficacy (measured by egg reduction rate) of both drugs against *Ascaris lumbricoides* (> 95%), a poor efficacy against *Trichiuris trichiura* (~65%). For hookworms, ALB resulted in a significant higher ERR (~96%) compared to MEB (~80%). The efficacies reported by ERR decreased as a function of increasing infection intensity for MEB (*A. lumbricoides*) and ALB (*T. trichiura*).
- (ii) Coprological techniques. To date various coprological techniques have been applied to detect and quantify STH infections, including Kato-Katz, McMaster, Mini-FLOTAC, and McMaster. In veterinary parasitology, the FECPAK^{G2} has been recently developed. The FECPAK^{G2} is a unique parasite diagnostic system that enables (i) to perform egg counts without any use of microscope, (ii) to automate FEC, and (iii) to submit results from remote locations via the Internet for analysis, interpretation, reporting and linking to expertise, and hence eliminating the need for a microscope or high skilled technicians/clinicians in the field. Although this device was initially developed for helminth infections in ruminants, preliminary studies in Ethiopia showed that its application for human STH is promising. Evaluation of coprological techniques mainly focuses on sensitivity. However, it remains unclear whether this is prerequisite. A meta-analysis was performed of six drug efficacy trials and one epidemiological survey. Prevalence and intensity of infection, CR and ERR based on collection of one or two stool samples that were processed with single or duplicate Kato-Katz thick smears were compared. It was found that the accuracy of prevalence estimate and CR was lowest with the minimal sampling effort, but that this was not the case for estimating infection intensity and ERR. Hence, a single Kato-Katz thick smear is sufficient for reporting infection intensity and ERR following drug treatment. These results are also in favour for pooling of stool samples, however this pooling strategy needs more validation.
- (iii) <u>Morbidity indicators parameters.</u> Morbidity is important to be assessed for monitoring impact. However, assessing morbidity caused by STH is difficult, as there are few morbidity indicators (growth, anaemia – hookworms) which are not specific. Faced with the same diagnostic challenges, researchers in veterinary parasitology have recently moved from stool examination towards serology-based assays to gain more insights into morbidity of helminths,

resulting in more efficient control measures. Of these recently developed serology-based assays, the SERASCA[®] test, is probably the most promising for human application. This antibody-ELISA test allows the detection of infections of both immature and adult *Ascaris* worms in pigs. Both experimental and field studies indicated that the SERASCA[®] test is more sensitive compared to stool examination. Moreover, the output of the SERASCA[®] test correlated significantly with the daily growth of the animals, and the future for antibodies is bright. Current technology should allow to process finger-blood samples using a smartphone, (ILAb) although the development of such technology is expensive.

- (iv) <u>The subWG also developed tutorials for operational procedures for MDA programmes</u>. These tutorials have been made available on YouTube and are now also embedded in the website of the Global Atlas of Helminth infections and SCI.
- (v) Short and long term monitoring. Short term monitoring (= assessment of drug efficacy) is essential to detect any emerge of anthelminthic resistance. However, currently efficacy of drugs is poorly monitored. It is recommended that this should become an obligation for MDA programmes (every 4 years). Long term monitoring (= assessment of prevalence/infection intensity) allows evaluating and adjusting the MDA strategy. MDA programs are solely based on the frequency of drug administration. A recent study in Jimma (Ethiopia), however, indicated that there are seasonal differences in STH infections, and hence suggesting that the yearly seasonality may need also to be considered to further improve the impact of MDA.
- (vi) <u>Reporting of drug efficacy.</u> We need to strive for a reporting system similar to global atlas of helminth infections ('This Druggy World') in which the following information can be accessed (a) were are the regions at risk, (b) where are the drugs distributed, (c) where are the drugs failing, and (d) what are the potential confounding factors. The global digital revolution should play a role in this (e.g. data collection through mobiles).
- (vii) <u>Alternatives for BZ.</u> Papaya cysteine proteinases CPs) are known to have anthelmintic properties in both animals and humans. However, up-to date efficacy data are lacking. An efficacy trial assessing the efficacy of a single oral dose of ALB and CPs against two levels of *T. suis* infections in pigs, indicate a higher reduction in both egg and adult worm counts for CPs compared to ALB.
- (viii) <u>Monitoring and evaluation.</u> A Markov Chain model to ring the bell for monitoring longterm progress has been developed. This model was discussed more in detail in the meeting on mapping and modelling.

2.2.2 Challenges

- (i) Implementation of the recent guidelines on assessment of drug efficacy in the field.
- (ii) Obtaining oxantel/pyrantel to perform efficacy trials
- (iii) Development of FECPAK towards a field friendly tool

- (iv) Development of diagnostics based on mobile application
- (v) Differentiate between patent/past infections using the SERASCA test
- (vi) Use of digital platforms to capture data

2.2.3 Future plan of activities to fill the gaps

- (i) Assessment of efficacy of oxantel/pyrantel against STH
- (ii) Development of WHO tutorials for standard operational procedures on diagnostic methods, and on organization of surveys and lab work.
- (iii) Assessment of correlation between SERASCA and morbidity parameters in human population
- (iv)Monitoring effects of MDA on morbidity
- (v) Monitoring MDA programmes in relation to seasonality (dry/wet season)
- (vi) Exploring the possibility to take papaya CPs towards human application
- (vii) Testing and validation of Markov Chain model
- (viii) Further validation of pooling of samples

2.3 SubWG on praziquantel (schistosomiasis)

2.3.1 Progress of ongoing work

- (i) Monitoring drug efficacy.
 - a. Multi-centric drug efficacy study of PZQ against *Schistosoma* spp. is ongoing to assess the efficacy of a single oral dose of 40 mg/kg PZQ against schistosomiasis on ERR (arithmetic means) in school children. Secondary objectives are to understand the role of hybrids and animal reservoir. The study comprises 6 trials in Brazil (*S. mansoni*), Cameroon (*S. mansoni*), Ethiopia (*S. mansoni* and *S. haematobium*), Mali (*S. mansoni* and *S. haematobium*), Tanzania (*S. mansoni* and *S. haematobium*) and Philippines (*S. japonicum*).Currently, data are being collected in Ethiopia. The other sites will start soon. It is anticipated the have the final analysis by August 2014.
 - b. Generally, efficacy is measured as a population average effect, but this impedes to assess the variation among individual caused by measurable (fixed) and immeasurable factors (random factors, e.g. drug underlying resistance/tolerance of parasites). A random mixed model was developed to capture both sources of variation, allowing to identify individual sub-optimal/atypical responses by comparing against a 'reference' distribution of 'normal' responses using data from naïve populations.
 - c. Point-of-care circulating cathodic antigen test (POC-CCA) and multiple Kato-Katz were compared in *S. mansoni* drug efficacy studies following repeated PZQ. This study was conducted in three primary schools in Mayuge district (Uganda). Assessment of drug efficacy 3 weeks after PZQ revealed a reduction in prevalence and egg counts towards zero based on multiple Kato-Katz. Based on the POC-CAA the reduction of prevalence was much lower.

d. Genetic and molecular basis of drug resistance and species-specific drug action in schistosome parasites

(ii) Monitoring and evaluation.

- a. The effect of 10 years of MDA on the epidemiology and population genetics of *Schistosoma mansoni* was evaluated in Uganda. In three schools in the Mayuge district both prevalence and infection intensity remains largely unchanged. The reason for this poor progress however remains unclear. Longitudinal assessment of population genetics demonstrates in the majority of the cases re-infection. However, this analysis also indicates a bottleneck (and substructuring) in parasite diversity (reduction in number of alleles after PZQ pressure)
- b. Various models have been developed to provide insights on (*i*) the evaluation of CCA strip for pre- and post PZQ treatment, (*ii*) the dynamics of MDA selective pressure on schistosome population genetics and genomics, (*iii*) when to ring the alarm bell, (*iv*) *Schistosoma* transmission dynamics and (*v*) when to remap and to adopt alternative strategies to keep infection supressed or mover towards elimination.
- c. There is empirical evidence of hybridization between human and animal schistosomes. In 'hotspots' in Niger 87% of the children were infected with at least one of two zoonotic hybrids (*S. haematobium*: *S. bovis* and *S. haematobium*: *S. curassoni*), 52% of the children were co-infected with both hybrids and 40% of the snails were shedding *S. haematobium*: *S. bovis* hybrids. In 4 highly endemic villages, 88% of the children were infected with at least one of two zoonotic hybrids.
- d. Use of mathematical models to understand schistosomiasis transmission dynamics to improve the ability to control and eliminate infection. Available models: development of Markov model (WHO), and Transmission full age spectrum model (NTD modelling consortium).

(iii) Drug development.

- a. Oxamniquine (OXA) is currently only active against *S. mansoni*. OXA is activated in schistosomes by sulfotransferase, after which the activated OXA binds the DNA. In order to make OXA efficacious against other schistosomes, the crystal structure of enzyme-drug-cofactor complex for *S. mansoni*, *S. haematobium* and *S. japonicum* were compared. From these crystallographic analysis analogues of OXA were derived, and subsequently screened in high throughput assays for efficacy. The most efficacious compounds (analogue 74) will be screened in an *in vivo* assay of interactions between OXA and sulfotransferases.
- (iv) Drug resistance.
 - a. In Brazil 44 individual miracidia from the field were subjected to DNA sequencing. The results revealed that 14% of the miracidia were homozygous or heterozygous for OXA resistant alleles.

b. The molecular responses of *S. japonicum* to PZQ were evaluated by a transcriptional and functional approach. Numbers of differentially expressed genes between males and females after exposure to PZQ were found and more genes were changed in females schistosomes. It can be speculated that PZQ may kill mainly the males than the females. Furthermore, the analysis revealed differential gene expressions for the calcium-signalling pathway: the serine/threonine-specific protein kinase that is regulated CA2+/calmodulin complex (CaMKII) is up-regulated in response to PZQ. If CamKII transcription was reduced the IC50 dosage of PZQ increased. CamKII mitigates the effect of PZQ, probably through stabilizing Ca2+ fluxes within parasite muscles and tegument. In addition, multidrug resistance (MDR) transporters may be important for fine-tuning schistosome drug susceptibility. For example, inhibiting or knock down MDR transporters potentiate PZQ effects on motility of both juvenile and adult schistosomes.

2.3.2 Challenges

- (i) <u>Monitoring drug efficacy</u>
 - a. POC-CAA remains positive 3 weeks post treatment. The mechanism for this high infection rate needs further attention, in particular when POC-CAA is brought into assessment of drug efficacy and/or M&E
- (ii) Monitoring and evaluation
 - a. Unravel the causes and consequences of hybrids, and more important evaluate whether it is possible to control (eliminate) a zoonotic schistosome in Africa (cfr. *S. japonicum* in Asia)
 - b. Difficulty to develop a single mathematical model due to high number of variables and questions to answer.

2.3.3 Future plan of activities to fill the gaps

- (i) Completing data collection for the multi-centric PZQ study;
- (ii) Completing of mixed random model to assess drug efficacy and expand to other helminths, including schistosomes.
- (iii) Develop biomarkers to assess PZQ resistance in the field

2.4 SubWG on research on NTD drugs (flubendazole)

2.4.1 Progress of ongoing work

Flubendazole (FBZ) (i) *Preclinical phase*. Flubendazole

- a.Phase I DOLF: to develop an orally available formulation of FBZ that duplicates the efficacy of parenteral dosing as macrofilaricidal; use in *Loa loa* areas; end-stage eradication; reduce time to elimination in new sites.
- b. Phase II/Phase III (2012/2013). DND /J&J engaged resources to look at safety and to a formulation that improve compliance and systemic effect with the aim to drive FBZ into a IND filing.

c.Progress:

- Identify pharmaceutically acceptable formulations that provide bioavailability: orally available formulations (hydroxypropyl-beta-cyclodextrin, Amorphous solid dispersion (ASD), JRD formulations. The ASD formulation provides excellent bioavailability in several animal species.
- Toxicology: FBZ is as embryotoxic as albendazole and its active metabolite is even less toxic. The toxicity of FBZ on aneuplody is 10 order of magnitude less toxic than albendazole and twice less toxic than mebendazole.
- Effect of FBZ on filariae in culture on multiple animal models. Tissue damage observed on *Brugia malayi* adult females in vitro. Efficacy of ASD in 5 daily oral doses on *L. sigmoidontis* in jerds. High efficacy also of single dose (80 mg/kg). Efficacy is highly dependent on quality of formulation

2.4.2 Challenges and next steps

- 1. Attract an industrial partner to accelerate the development of FBZ oral formulation. Priority is single oral dose (not much for compliance but for safety reasons)
- 2. Final efficacy studies/formulations selection for IND filing in 2015 to enable clinical trials
- 3. Case management vs MDA (but these are not mutually exclusive).
 - i. Diagnostic needs
 - ii. Alternative route of delivery (oral FBZ needs 5/7 doses)
- 4. Susceptibility of microfilariae (*B. malayi, Loa Loa*) to concentrations attained with new oral formulations
- 5. FBZ could be used also for STH. Worth exploring the efficacy of new formulations against STH.

3 Conclusions

Important progresses and recommendations are coming out from the work of this WG. The next meeting can be planned in one year time or later, depending on the need and on the progress made. Recommendation was made to include trachoma (and azithromycin) among the diseases (drugs) of this WG in the future.