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

Salle C, WHO headquarters, Geneva, Switzerland
24–25 April 2012

A 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 24-25 April 2012. The list of participating members, observers and secretariat is attached as Annex 1.

**Day 1**
The Chairman, Professor David Crompton, opened the meeting by welcoming the new members of the STAG. WHO’s Assistant Director-General for HIV/AIDS, Tuberculosis, Malaria and Neglected Tropical Diseases (WHO/HTM), Dr Hiroki Nakatani, spoke on behalf of the Director-General, Dr Margaret Chan, and welcomed the participants. Dr Nakatani said that WHO was going through a comprehensive review of its priority setting, governance and administration. Member States had strongly affirmed that control of communicable diseases must stay in WHO’s list of priority areas, and that overcoming neglected tropical diseases (NTDs) remained a priority within communicable diseases. The Department of Control of Neglected Tropical Diseases (HTM/NTD) has set an example to the rest of WHO in establishing innovative, informal alliances and developing public–private partnerships to raise funds for its activities. However, he also sounded a warning that the global economic downturn has had a negative impact on the Global Fund, which could in turn reduce funding for NTDs. He stressed the importance of producing robust evidence that funding for NTDs promotes social justice.

1. **Report from the Director of WHO/HTM/NTD**

Dr Lorenzo Savioli (Director, WHO’s Department of Control of Neglected Tropical Diseases) highlighted for the period 2011–2012 the key achievements, response to recommendations made by STAG in 2011 and key issues in overcoming NTDs. These include: the update of the first WHO report on NTDs, published in 2010; the launch of the NTD roadmap for accelerating implementation of the report, in January 2012; and the London Declaration on NTDs, which affirmed commitment from many large pharmaceutical companies, including Gilead, Eisai, Johnson & Johnson, Bayer, GSK, Merck KGaA, Sanofi and Novartis. The NTD/PCT databank records indicate that more than 710 million preventive chemotherapy treatments were delivered in 2010.
Progress was made in the following areas:
- eradication of dracunculiasis;
- global coverage of preventive chemotherapy; the tools that support its roll out and scale up; and the proposed joint request, review and coordinated supply of preventive chemotherapy medicines;
- control of neglected zoonotic diseases;
- innovative and intensified disease management for human African trypanosomiasis, yaws, Buruli ulcer, Chagas disease and leishmaniasis;
- vector ecology and management;
- dengue prevention and control; and
- reporting on NTDs through the Global Health Observatory.

Upcoming events in 2012 include the 65th World Health Assembly (21–25 May) and the technical briefing on NTDs, to be hosted by Her Excellency Professor Thérèse Aya N'dri-Yoman, the Minister of Health of Côte d'Ivoire (and current President of the World Health Assembly); the second WHO report on NTDs; the Expert Committee meeting on human African trypanosomiasis; and new donations from Johnson & Johnson and Merck KGaA.

Dr Savioli reviewed the recommendations of STAG in 2011 and the department’s response to them (Annex 2), as well as the key issues currently facing the department. All 15 action points set by the STAG in 2011 have been achieved.

The Chairman and members of STAG congratulated Dr Savioli and the Department of Control of Neglected Tropical Diseases for their achievements during the past year.

2. Rolling out, scaling up and monitoring preventive chemotherapy

Dr Frank Richards from The Carter Center presented the draft of an umbrella document entitled Rolling out, scaling up and monitoring preventive chemotherapy. The NTD roadmap identifies preventive chemotherapy as one of the key strategies to accelerate work to control the global impact of NTDs. Five diseases are targeted: lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminthiasis and trachoma; 1.9 billion people in 122 countries require preventive chemotherapy for at least one disease; while 33% require the intervention for 3 or more diseases. In rolling out the integrated preventive chemotherapy package, there is a need to embed the culture of integrated and coordinated planning and management of preventive chemotherapy among disease-specific programmes and in-country partners; to facilitate national programmes to effectively integrate and scale up such programmes to full national scale; and to ensure political commitment. Preparations for scaling down after achieving the set targets must also be made well in advance.

Dr Richards presented a scorecard for monitoring progress in preventive chemotherapy, which provides a graphical representation of the progress of implementation attained each year for: the vision, as outlined in the NTD roadmap; strategy; tactical activities; and technical measures. The scorecard will have three categories of key performance indicators containing information on: programmatic indicators (national programme capacity); operational indicators (coverage); and epidemiological indicators (impact). The scorecard
was thoroughly discussed, including the placing of a scorecard to monitor progress on morbidity management.

**STAG endorsed** the further development and use of the proposed scorecard to monitor progress in preventative chemotherapy for the control and elimination of NTDs.

### 3. Practical guidelines for control, elimination and eradication of NTDs

Dr Mark Eberhard of the United States Centers for Disease Control and Prevention presented a draft document entitled *Practical guidelines for control, elimination and eradication of NTDs*. He noted that there are many concepts and definitions in this area, and stressed the need for scientific rigour in using these terms. He spoke about the principal differences between control, elimination and eradication; lessons from previous “E” programmes and the indicators of eliminability, and the use of the phrase “elimination as a public-health problem”. Precise definitions for “extinction”, “eradication”, “elimination” and “control” were presented for adoption in relation to NTDs. Dr Eberhard also spoke on the process of verification and certification of elimination and eradication, and presented suggestions for the terms that should be used in relation to each disease covered by the NTD roadmap.

**STAG endorsed** Dr Eberhard’s recommendations and recommended that the Department of Control of Neglected Tropical Diseases should hereafter use these terms as follows:

- **eradication** to mean “permanent reduction to zero of the worldwide incidence of infection caused by a specific pathogen, as a result of deliberate efforts, with no more risk of reintroduction”;
- **elimination** (interruption of transmission) to mean “reduction to zero of the incidence of infection caused by a specific pathogen in a defined geographical area, as a result of deliberate efforts; continued actions to prevent re-establishment of transmission may be required”;
- **and control** to mean “reduction of disease incidence, prevalence, morbidity, and/or mortality to a locally acceptable level as a result of deliberate efforts; continued intervention measures are required to maintain the reduction”.
- The term **“elimination as a public-health problem”** should be used only where necessary for political (rather than scientific) reasons, upon achievement of measurable targets set by Member States in relation to a specific disease.

**STAG endorsed** the Chair’s proposal that individual STAG members liaise with a member of the Secretariat to identify a single measurable indicator for each disease slated for eradication, elimination or control.

### 4. Report from the Working Group on access to quality-assured essential medicines

Professor Nilanthi de Silva, Chairman of the Working Group, presented a summary report of the activities undertaken by members and the fourth meeting held on 23 April 2012. The detailed report is attached as Annex 3.

The subgroup on access to praziquantel has estimated the projected annual need for praziquantel in 2011–2015, and the availability of donor funding and in-kind donations. As a
result of these efforts, Merck KGaA has pledged to extend its current donation of praziquantel to 250 million tablets by 2016.

The Secretariat has developed a manual for national programme managers on the prevention, detection and management of serious adverse events. The United Republic of Tanzania has already adapted this manual to suit its own needs, and the manual was successfully field tested during one of its MDA (mass drug administration) campaigns conducted in late 2011. The template is now available to all other countries that undertake preventive chemotherapy campaigns.

Based on the findings of the survey of the quality of selected medicines for NTDs (results presented to STAG in 2011), the Secretariat has also drafted a manual containing practical advice for drug regulatory authorities.

The Global NGO Deworming Inventory was carried out again for 2010, with similar results to the 2009 inventory. Once again, it was found that a significant proportion of treatments (23.3 million treatments) were not captured by WHO’s PCT Databank. Most of these “unique” treatments captured by the inventory were from small number of NGOs in a limited number of countries.

The coordination mechanism for the procurement of praziquantel now uses WHO’s Expert Review Panel in order to assure the quality of medicines procured for a number of donor organizations. The prequalification mechanism is also to be used for the procurement of finished diethylcarbamazine and mebendazole for the large donations that go through WHO.

The final report on the survey of supply chain issues (funded by the Bill & Melinda Gates Foundation), which was conducted by an independent consultant in 2011, was presented to the Working Group. The key challenges in the 10 main steps of the NTD supply chain were identified for six medicines: albendazole, azithromycin, diethylcarbamazine, ivermectin, mebendazole and praziquantel. The findings were based on the responses to a questionnaire from 75 participants in 55 countries and field visits to Niger, Nepal and the United Republic of Tanzania. Overall, efficiency was at an acceptable level, although a number of aspects for improvement were recommended.

**STAG endorsed** the recommendations made by the Working Group.

5. **Report from the Working Group on neglected zoonotic diseases**

Professor Malika Kachani, Chairman of the Working Group, presented a report on their first meeting, which took place on 23 April 2012. The detailed report is attached as Annex 4.

Professor Kachani spoke on why neglected zoonotic diseases (NZDs) are important, and why they are neglected. NZDs have dual impacts on human and livestock productivity and they perpetuate poverty. Animals are involved in transmission, so control requires concerted action between the veterinary and human health sectors, but there is a gap between veterinary, medical and other sectors.
A list of six high priority NZDs has been identified for control and elimination, based on their health and economic burdens; the availability of tools for their prevention and/or control; political commitment and funding. The priority zoonoses with a large, almost global distribution are rabies, cystic echinococcosis, cysticercosis, a group of bacterial zoonoses (e.g. brucellosis, leptospirosis), and those present only in certain regions such as human African trypanosomiasis and the trematodiases.

Surveillance of zoonoses requires capacity-building for diagnosis, which should include establishment of diagnostic laboratory networks for NZDs including regional reference centres. It is necessary to provide specific training on NZDs at regional and sub-regional levels; to share training among medical and veterinary professionals, students and technical staff; to link or share physical infrastructure and technical capacity between public and animal-health sectors; to incentivize sharing of resources and data between relevant sectors; and to establish intersectoral collaboration at policy-making and operational levels.

**STAG endorsed** the recommendations made by the Working Group.


Professor Mamoun Homeida, Chairman of the Working Group, presented the report of the third meeting of the group held on 13–14 February 2012. The detailed report is attached as Annex 5.

This working group has four subgroups working on the following:
- benzimidazoles (STH)
- ivermectin (onchocerciasis and LF)
- praziquantel (schistosomiasis)
- medicines for human African trypanosomiasis, leishmaniasis and Chagas disease

The subgroup working on STH has made progress in six aspects: the importance of anthelmintic resistance in human STH; the impact of benzimidazoles on coinfection with other pathogens; the identification of confounding factors for drug efficacy; assessment of drug efficacy; simplifying sampling procedures to monitor drug efficacy; development of a standard operating procedure (SOP) to monitor drug efficacy. This subgroup concluded that anthelmintic resistance is not a concern at present, but precautions should be taken to detect any deviation from expected drug efficacy. Progress has been made in revision of the current SOP, which will be disseminated shortly. Updated information on the efficacy of mebendazole will be available by the end of 2012, but information is lacking for other compounds such as pyrantel–oxantel. Preventive chemotherapy programmes targeting STH with benzimidazoles have a collateral impact on *Giardia* infections, and pooling samples hold promise as a cost-effective strategy to monitor drug efficacy.

The subgroup working on onchocerciasis and LF has made progress on the assessment of ivermectin efficacy in seven countries and on identification of markers for monitoring sub-optimal response to ivermectin in *Onchocerca volvulus*. The subgroup concluded that epidemiological evaluation of ivermectin treatment impact is ongoing. Simulation curves match with results and, so far, foci of lower prevalence are related to poor coverage. Development of molecular markers of response to ivermectin in *O. volvulus* is facilitated by
the availability of the *O. volvulus* genome. LF programmes monitoring ivermectin efficacy should be built up following synergies with STH and onchocerciasis monitoring.

The subgroup working on schistosomiasis has made progress in the following areas: identification of a marker for praziquantel resistance; population genetics; efficacy on *Schistosoma japonicum* and role of animal reservoir; importance of mixed *Schistosoma* infections; development of novel compounds. This subgroup concluded that several research studies are under way to monitor population genetics of schistosomes under drug pressure. Significant progress has been made towards the identification of potential markers of oxamniquine resistance, and praziquantel resistance. Funds for monitoring praziquantel resistance in preventive chemotherapy programmes are limited, but the gap needs to be identified in order to solicit more resources. SOPs exist for monitoring the efficacy of praziquantel in the field, but they need to be standardized, and one SOP should be made available via WHO.

The subgroup working on human African trypanosomiasis, leishmaniasis and Chagas disease have also made significant progress.

**STAG endorsed** the recommendations made by the Working Group.

7. **Report from the Working Group on monitoring and evaluation of preventive chemotherapy interventions**

Dr Sam Zaramba, Chairman of the Working Group, presented the report of the third meeting of the Group held on 15–16 February 2012. The detailed report is attached as Annex 6.

The Working Group has three subgroups: subgroup 1 (chaired by Professor John Gyapong) focuses on national programme monitoring; subgroup 2 (chaired by Dr Pat Lammie) focuses on disease-specific monitoring; and subgroup 3 (chaired by Professor Alan Fenwick) focuses on measuring enhanced outcomes and the impact of preventive chemotherapy.

Highlights from the activities of Subgroup 1 (national programme monitoring) included the development and adoption of a package of programmatic tools: (i) a Tool for Integrated Planning and Costing (TIPAC, formerly Funding Gap Analysis Tool); (ii) a joint request form for selected preventive chemotherapy medicines; and (iii) a revised joint reporting form. The advantages of the package include improved coordination between programmes; facilitation of standardized review of country information, and improved efficiency of drug requests and utilization; avoidance of double entries and minimization of errors. It would be fully automated and could be used at different administrative levels. The same subgroup noted that partners provided targeted technical and financial support to support activities at regional and country levels, while WHO maintained PCT databank and provided data updates via the *Weekly Epidemiological Record* and the Global Health Observatory.

Subgroup 2 (disease-specific monitoring) noted that there had been provision of guidance on stopping or modifying interventions in LF (Guidelines for stopping MDA: transmission assessment surveys (TAS)) and STH (Helminth control in school-age children, which includes interim guidance for adjustment of implementation strategy in ongoing programmes).
Development of a compendium of indicators for monitoring and evaluation of preventive chemotherapy is ongoing. Other activities included development of a 3-day training course for operationalizing TAS; development and testing of a protocol for xenomonitoring in settings where *Culex* spp. transmits LF, including the size of geographical area to be monitored. Work on development of an integrated platform for NTD surveillance was further advanced, including a multiplex tool for inclusion in large-scale surveys such as the Demographic Health Survey or Malaria Indicator Survey as part of a coordinated surveillance strategy. A harmonized framework for integrated monitoring of LF and onchocerciasis programmes was also developed.

Subgroup 3 (measuring enhanced outcomes and impact of preventive chemotherapy) completed an extensive literature review and identified priority activities to measure impact and document programme effectiveness and efficiency by using existing data, new data collection methods and studies of opportunity. The subgroup established a temporary Task Force on Measuring Impact of Preventive Chemotherapy, with four groups to work on health, education, socioeconomics and poverty, and water and sanitation. These groups will include broad partnerships or collaborations to complete various tasks. The Task Force will submit annual reports to STAG-NTD through the Working Group on monitoring and evaluation of preventive chemotherapy. The first report of the Task Force to the STAG will be presented in the first quarter 2013.

**STAG endorsed** the recommendations made by the Working Group.

8. **Global strategy for dengue prevention and control 2012–2020**

Since two presentations and discussions about dengue were made (Dr Raman Velayudhan, Department for Control of NTD and Dr Ronald Rosenberg, CDC) the STAG-NTD report contains a combined summary. The increasing global incidence of the disease, vector biology, pathogen characteristics (types 1, 2, 3, and 4 of a flavivirus akin to the yellow fever virus) and the pathology resulting from infection were reviewed. Progress of the development and trials for candidate vaccines was presented; the first large-scale efficacy results are expected later this year. The importance of any vaccine implementation plan to include vector control as a leveraging factor was stressed.

The recently prepared Global strategy for dengue prevention and control (2012–2020) was received and strongly endorsed by the STAG-NTD, with its main goal of reducing the burden of disease by achieving a decline in the mortality rate by at least 50% by 2020 and the morbidity rate by at least 25% by 2020.
Day 2

The first half of the second day’s session was open to partners in NTD control and other invited stakeholders.

The day began with a minute’s silence in memory of Dr Likezo Mubila, who passed away in 2011. Dr Mwele Malecela spoke a few words about Dr Mubila’s life and achievements.

9. Dengue

Presentation by Dr Ronald Rosenberg from the CDC (see section 8 above).

10. Capacity building for neglected tropical diseases

Dr Francesco Rio (WHO/HTM/NTD) explained why capacity building is a critical issue in NTDs; particularly the immediate need to build capacity for integrated preventive chemotherapy. He described the needs in capacity building: defining the needs; developing curricula; comprehensive courses for programme managers; specific modules that are tailored to different levels; and prioritized activities to guide donor support. He listed the proposed activities for 2012: an international training course for national NTD programme managers; and development of learning materials to be used in NTD control programmes.

Dr Marco Albonico (Ivo de Carneri Foundation) outlined the proposed course for NTD programme managers. The need to obtain the endorsement of all partners in NTD control for the course content was emphasized. Professor David Molyneux (Liverpool School of Tropical Medicine) spoke on the key issues in capacity building – the spectrum of needs at different levels, and the complexity of actors involved in the arena of NTD control; and the challenge in identifying priorities in allocation of resources for capacity building.

STAG endorsed the proposed outline for capacity building and recommended that WHO move forward along the presented lines.

11. Second NTD report – rolling out the roadmap

Professor David Crompton presented the purpose and the outline of the second NTD report, which follows on the London Declaration and the partners’ response to the first global report and the roadmap. He reminded the STAG and its partners of the targets set in the roadmap, and spoke on the milestones that may obstruct achievement of these milestones – conflict and population displacement; insufficient application of vector control; resistance to available medicines; expectations overtaking science; inadequate capacity for scaling up; demographic factors and urbanization; and climate change. He emphasized the need to take these factors into consideration in planning control of NTDs.
12. **Summary report of feedback of the working groups**

The chairpersons of the four working groups presented their summary reports on the work undertaken during the past year, and the recommendations that they presented for endorsement by the STAG.

13. **Summary report of STAG deliberations**

Professor David Crompton presented a summary report of the proceedings for Day 1 of the meeting. General conclusions included the following:

- Importance of veterinary public health in all countries
- Public sector matching the commitment of the private sector
- Increased political commitment to overcome NTDs
- More details and estimates of the burden (including economic) of NZDs
- All areas of NTD prevention and control in urgent need of capacity building

14. **Report and feedback of the partners’ meeting**

Julie Jacobson from the Bill & Melinda Gates Foundation presented a report on the side meetings that took place parallel to the STAG meeting. A main outcome of those meetings was to propose the establishment of the London Declaration Coordination Committee.

There is clearly an unswerving acceptance by WHO and the community of partners that the prevention, control, elimination and eradication of NTDs needs the mutual goodwill and commitment that has enabled the good progress already made to continue and be sustained. There may be a timely opportunity to build on the success of the London Declaration (30 January 2012) provided that any proposed actions do not impede or duplicate work under way to implement the NTD roadmap and reach its milestones, including the 18 targets for eradication (global) and elimination (global, regional or national) set for 11 NTDs. All present were in agreement that measures that will accelerate NTD prevention and control must have the highest priority. The members, secretariat and partners at the meeting were shown a plan of activities that would become the remit or purpose of the proposed London Declaration Coordination Committee. The STAG, while not advising rejection of the proposal, was not at this stage able to approve its establishment. More discussion would be needed with WHO and with the department to ensure that duplication of effort would not happen and that the department would not be deflected from its key task of implementing the roadmap.

15. **Points for follow-up action**

After deliberation of presentations of agenda items and discussion of reports from the working groups, STAG requested that the director and staff of the Department of Control of Neglected Tropical Diseases should work during the coming year to address the following action points:

1. Improve planning, forecasting and regularity of supplies through appropriate coordination mechanisms among donation programmes.
2. Circulate existing draft of manual for teachers involved in distribution of preventive chemotherapy medicines to a larger number of partners to seek input from a wide range of stakeholders; and take into account the need to produce local versions in national and local languages.
3. Take the lead in establishing active reporting on efficacy and safety of medicines against human African trypanosomiasis, leishmaniasis and Chagas disease.
4. Establish a global rabies control strategy in dogs and humans.
5. Map the co-endemicity of STH, schistosomiasis and neurocysticercosis, and monitor adverse and beneficial effects of preventive chemotherapy.
6. Identify the most common zoonotic causes of non-malarial febrile illness, and issue recommendations for the establishment of shared diagnostic capacities for human and animal laboratory testing.
7. Develop mathematical models (ONCHOSIM example) to predict prevalence and intensity curves during implementation of preventive chemotherapy, and finalize standard operating procedures and reference drug activities for various anthelminthics (albendazole, flubendazole, mebendazole, pyrantel−oxantel, praziquantel, etc.) to be applied in case of doubts on their efficacy.
8. Continue research to assess genetic markers of anthelmintic resistance (onchocerciasis, schistosomiasis), and new diagnostic tools (serodiagnosis) to be used towards elimination (LF, onchocerciasis and schistosomiasis).
9. Establish a Global Working Group on Capacity Building to coordinate, standardize and support the implementation of training curricula to strengthen managerial and technical capacity for NTD control. Priority activities should include:
   • identification of existing capacity building efforts;
   • recognition of gaps in capacity building efforts and prioritization of capacity building needs that must be addressed in the short and long-term;
   • coordination of partners’ efforts to harmonize and increase their contribution to fill gaps and address urgent needs that have been identified.
10. Develop tools to support implementation of technical guidance for sequential transitioning between different phases of NTD control programmes.
11. Adopt drug efficacy monitoring as an integral part of routine monitoring and evaluation of integrated NTD programmes.
12. Prepare the draft of the second WHO report on NTDs with the general objective of implementing the roadmap.
13. Advance planning for the global prevention and control of dengue including the formation of a coordination group.
14. Complete the design and development of scorecards including proposals for analysing recorded information.
15. Develop and adopt definitions of eradication, elimination and control for each NTD; identify measurable indicators for each disease slated for eradication, elimination or control.

The STAG 2012 meeting was closed by the Director of WHO/NTD, 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-MacDonald and Ms Corinne Suchet, to whom warm thanks are extended.
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1. The roadmap for implementing the first WHO report on neglected tropical diseases (NTDs) was endorsed, subject to minor editorial and textual revision, and recommended for presentation to WHO’s Director-General. Two versions should be made available: one for internal use and another for external use especially by partner organizations.

Two versions of the roadmap have been published. The summary version was announced on 26 January 2012 and presented by the Director-General of WHO at an event bringing together all NTD partners in London, UK, on 30 January 2012.

2. Countries prone to dengue epidemics should build capacity, and efforts must be coordinated at regional and global levels in order to stem the spread of possible outbreaks, through cross-border exchange of information and active surveillance of cases and vectors. The WHO Department of Control of Neglected Tropical Diseases (WHO/NTD) should coordinate prevention and control activities within WHO, and support efforts at regional and country levels.

The Director-General of WHO has requested WHO/NTD to coordinate the Organization’s response to dengue in collaboration with regional offices and all relevant departments. The department, in consultation with all interested parties, has developed a draft global strategic plan. An international consultation on prevention and control of dengue was held in Geneva, Switzerland, on 22–24 February 2012, chaired by Dr Ronald Rosenberg, United States Centers for Disease Control and Prevention.

3. WHO should continue to work with the Global Health Council to convene a second global NTD partners’ meeting in 2012.

Given the political and economical context (elections in WHO and in the USA and the global economic crisis) and the high-level awareness created by the NTD event in London, it has been agreed to postpone the second global partners’ meeting to 2013. The Global Health Council will organize an event in Washington DC, USA, in July 2012, with the participation of partners, including industry, the Bill & Melinda Gates Foundation and WHO.

4. WHO should establish a new Working Group on Integrated Control of Neglected Zoonotic Diseases in the context of veterinary public health, to assist STAG-NTD. The working group should be chaired by Professor Malika Kachani.
Membership of the working group has been defined to include eight experts. The first meeting was held on 23 April. A report will be presented to STAG by the Chair on 24 April.

5. Future work on monitoring drug efficacy and safety should focus on incorporating drug efficacy monitoring in field interventions by building expertise and creating laboratory networks.

The Working Group on Drug Efficacy is further developing standard operating procedures to monitor NTD drug efficacy. These procedures include dissemination through a network of subregional reference laboratories for which capacity will be built to act in a standardized manner following an alert of potential loss of drug efficacy from the field (see report of the third meeting in the background materials).

6. WHO should advocate for improved access to benznidazole for treatment of Chagas disease and liposomal amphotericin B for control of the leishmaniases.

WHO/NTD and GILEAD have agreed to collaborate. An agreement was signed on 8 December 2011, which provides a donation through WHO of 445 000 vials of injectable amphotericin B liposome over a five-year period, equivalent to treatment of 50 000 people with visceral leishmaniasis. A new producer of benznidazole for Chagas disease has been identified through Mundo Sano Foundation in Spain: ELEA Laboratory. The product has already been registered in Argentina.

7. WHO should be encouraged to expand its prequalification activities to essential NTD medicines.

WHO has included two essential NTD medicines in its prequalification scheme: diethylcarbamazine and mebendazole.

8. The Global NGO Deworming Inventory should be continued, and more nongovernmental organizations should be encouraged to participate and communicate their results to WHO focal points in countries and ministries of health.

The inventory, under the leadership of Children Without Worms, continues to collect information; an increasing number of nongovernmental organizations are participating (see report of the working group held on 23 April).

9. WHO should continue to coordinate the global supply of praziquantel, maintain consensus on quality standards, and engage in enhanced advocacy for Merck KGaA to increase its annual donation.

WHO continues to collect information on global forecasting and works closely with USAID/RTI, DFID/SCI and their procurement agencies to ensure access to quality-assured praziquantel. In January 2012, Merck KGaA pledged a donation of 250 million tablets, equivalent to 100 million treatments annually.
10. Sampling and testing of essential NTD medicines should be continued, and national drug regulatory authorities and nongovernmental organizations should be made aware of the need for quality assurance in procuring such medicines.

**Systematic surveys have been discontinued. WHO-qualified laboratories have agreed to test essential NTD medicines at the request of countries and/or regional offices. The WHO Western Pacific Region has used this service to test the quality of diethylcarbamazine.**

11. STAG-NTD endorses the manual on assuring the safety of preventive chemotherapy interventions for the control of NTDs and recommends final publication and strong promotion by WHO.

**The manual has been made available to WHO countries and regions.**

12. WHO should include one new member with expertise in NTDs for which no preventive chemotherapy interventions are available in the management unit of the Working Group on Access to Quality-Assured Essential Medicines.

**One member from the Netherlands has participated in the working group meeting held on 23 April.**

13. STAG-NTD recommends that WHO adopts the package of programmatic and monitoring and evaluation tools jointly developed by WHO and NTD partners for preventive chemotherapy interventions and regional distribution.

**The Funding Gap Analysis Tool, which was jointly developed by RTI, USAID and WHO, has been revised to make it more user-friendly and renamed the ‘Integrated Planning and Costing Tool’. It is currently being edited for suitability as a WHO programmatic tool. WHO has also finalized a joint drug request form for albendazole–mebendazole, praziquantel, diethylcarbamazine and ivermectin (optional); discussions are under way to include azithromycin in this form. In parallel, a joint reporting form is being developed for preventive chemotherapy to enable more accurate data management.**

14. STAG-NTD endorses current WHO guidance on stopping or modifying interventions in an evolving epidemiological situation and the proposed guidelines for stopping mass drug administration for lymphatic filariasis, including the reassessment of nine countries as not requiring the intervention. The control strategies for soil-transmitted helminthiases proposed by the Working Group on Monitoring and Evaluation should be used as interim guidelines until more evidence becomes available.
The manual for transmission assessment surveys for lymphatic filariasis has been published and a series of regional trainings are being conducted (in conjunction with Regional Programme Review Group meetings). It is expected that transmission assessment surveys will routinely be implemented from 2012 onwards. The second version of the manual Helminth control in school-age children, including interim guidelines for control strategies for soil-transmitted helminthiases in ongoing programmes, has also been published. It has been recommended that both the Working Group on Monitoring and Evaluation and the Working Group on Monitoring Drug Efficacy progress with the analysis and combination of existing monitoring data and modeling to enhance the evidence base for such strategies.

15. The Working Group on Monitoring and Evaluation should include representatives of disease-specific technical groups to enhance information exchange, consensus building and consistent information flow to national programmes.

Representatives of the Trachoma Expert Committee, the Mectizan Expert Committee/Albendazole Committee, Children Without Worms and Deworm the World have participated in the third meeting of the global Working Group on Monitoring and Evaluation of preventive chemotherapy interventions, which has led to a useful information exchange session and discussion.
Fourth Meeting of the Working Group on Access to Assured-Quality Essential Medicines for Neglected Tropical Diseases (WGA)

WHO HQ, Geneva, Switzerland – 23 April 2012

Draft Minutes

List of Participants – (see Annex 3-A)

The meeting commenced at 9.00 a.m. under the chairmanship of Professor Nilanthi de Silva. Dr Lorenzo Savioli welcomed the participants and highlighted the main issues that the WGA needs to address. Prof. Nilanthi de Silva recalled the mandate given to WGA by the STAG in 2009 and presented the objectives for this meeting.

Agenda Item 1: Global Access to quality assured praziquantel – presentation by D. Daumerie

The subgroup on access to praziquantel has estimated the projected annual need for praziquantel in 2011–2015, and the availability of donor funding and in-kind donations. The estimated need for 2012 is 428 million tablets. The current Merck KGaA donation amounts to 25 million tablets/year, while an additional 126 million tablets will be purchased by other donors (USAID, SCI, WB). The estimated need is expected to rise to 486 million tablets in 2013, and 571 million in 2014. Merck KGaA has pledged to gradually increase its current donation of praziquantel to reach 250 million tablets by 2016.

Recommendations to STAG

Continue to use WGA as facilitating platform for partners to:
- Monitor and manage response to evolving landscape of praziquantel availability
- Continue joint planning of national requirements
- Improve coordinated procurement of praziquantel
- Maintain current quality assurance policy for the procurement and provision of praziquantel tablets

Agenda item 2: Manual for teachers distributing de-worming medicines – presentation by A. Montresor

The Secretariat is developing a manual for teachers distributing deworming medicines.

Recommendations to STAG:
- Circulate existing draft of manual for school teachers on distribution of PC medicines to a larger number of partners to seek input
- Take into account need to locally produce versions in national/local languages
- Avoid details on possible adverse events and their management but rather advise to seek support, for problems teachers cannot manage, from the appropriate health system facility as instructed when preparing treatment campaign
Human African Trypanosomiasis: Sanofi has extended its donation of eflornithine, melarsoprol and pentamidine to 2016 and provision of funds for logistical support to ensure that drugs reach the point of care free of charge; also for capacity building and pharmacovigilance for health care providers. Bayer will donate suramin and nifurtimox for HAT until 2017 and 2014 respectively. The drugs are from single source suppliers but sustainability is guaranteed in binding agreements with WHO. Quarterly forecasting is done by joint WHO/donor committee. To reassure endemic countries about quality, all donated drugs for HAT are registered in Europe or USA. To ensure focused and appropriate use, HAT medicines are available only through the donation programme and are not marketed in endemic countries. The medical kit for Nifurtimox-Eflornithine Combination Therapy (NECT) includes material for four treatments, with a weight of 38 kg and costs €1152. The cost of 1 NECT treatment is therefore estimated at €288 (2010 prices) including transport to health facilities. Average cost of treatment of one patient is €336. Despite major support of Sanofi, more donors are needed to fully support scale up of screening and treatment and surveillance when incidence of disease decreases.

Leishmaniasis: the Indian subcontinent (which carries 67% of burden of visceral leishmaniasis) has set the goal to reach regional elimination by 2020 with first line treatment with AmBisome® (liposomal amphotericin B) single dose 10mg/kg infusion. In East Africa (which carries 17% of burden), compassionate treatment with AmBisome is available for selected groups of patients. WHO has signed a MoU with Gilead, on 8 December 2011 for a donation of 445,000 AmBisome® vials during the period 2012-2016. The global targets for this donation are to focus on implementation single 10 mg/kg dose regimen in Bangladesh, and alleviate the consequences of visceral leishmaniasis in East Africa (Ethiopia, South Sudan, Sudan). Miltefosine, paromomycin and antimonials are also single source drugs, with no likelihood of large scale donations. All these drugs are complex products and quality assurance is difficult. In some countries there are major issues with the quality of generic products. Ensuring regular availability of assured-quality miltefosine, paromomycin and antimonials is a major challenge.

Chagas Disease: benznidazole, which is the first line drug for this disease, was developed more than 40 years ago by Roche. Roche transferred production technology to a government manufacturer in Brazil, Laboratorio Farmaceutico do Estado de Pernambuco (LAFEPE), in July 2003. Roche stocks finished in October 2010, and LAFEPE was then the sole producer of benznidazole. However, LAFEPE did not produce any further benznidazole nor distributed any to other countries, leading to global shortage in 2011. Since then, there has been a technology transfer to Nortec Química (a private Brazilian company), which is now the sole producer of benznidazole API. After some delay, LAFEPE has restarted production with Nortec’s API. Subsequently, Laboratorio ELEA, a private pharmaceutical company based in Argentina announced production of benznidazole in February 2012. It claims that it will register and export the drug to endemic countries by May 2012. It also claims that it will synthesize the API. The product is registered in Argentina. The first batch will be donated – future price not yet calculated as will depend on the synthesis of the API. No bioequivalence studies done yet. GMP verification is needed by WHO PQ or a stringent regulatory authority.
Bayer has agreed to donate up to 1 million tablets of Nifurtimox 120 mg (Lampit® Bayer) until 2017. It has registrations in Germany and Argentina for Chagas disease. This is also a single source supplier but long term agreements for sustainability are in place.

Recommendations to STAG:

- Intensify advocacy for funding for assuring availability of quality-assured benznidazole, miltefosine, sodium stibogluconate (SSG), glucantime, paromomycin
- Advocate for donation of azithromycin for yaws and clarithromycin for buruli ulcer
- Explore feasibility of prequalification of generic versions of liposomal amphotericin B
- Approach regulatory authorities of countries that have approved generic versions of medicines for leishmaniasis to assist improving quality/efficacy

Agenda item 4: Survey on supply chain issues – presentation by G. O’Neil

As decided earlier by the WGA, a survey was carried out to better understand the NTD medicines supply chain and propose suggestions for addressing problems and hurdles to improve its effectiveness. Responses to a questionnaire were received from 75 persons from 55 countries and field visits conducted to Niger, Nepal and Tanzania. The key findings of the report are provided in annex 3-B.

Recommendations to STAG:

- Improve planning, forecasting and regularity of supplies through appropriate coordination mechanisms among donation programmes
- Simplify and streamline border control processes by systematically using WHO as consignee for all donated PC medicines
- Advocate for funding to improve in-country logistics and distribution up to the point of final use of PC medicines
- In countries where importation procedures take an unusually long time, WHO should approach national authorities to explore the possibility of obtaining a blanket import permit covering all PC medicines for a given period (e.g. one year)

Agenda item 5: Global NGO Deworming Inventory, Results 2011 – presentation by D. Addiss (via Skype)

The Global NGO Deworming Inventory was created to quantify the gap in annual reporting of treatments conducted by NGOs targeting school-age children at risk for STH. In 2010, the Inventory was carried out by Children Without Worms (CWW) to capture treatments in 2009. In 2011, CWW once again carried out the Inventory for the purpose of identifying “unique treatments” conducted by NGOs in 2010 that had not previously been reported to WHO for inclusion in the PCT databank.

NGOs reported 65.4 million STH treatments to the 2010 Inventory that were not delivered as part of the Programme to Eliminate Lymphatic Filariasis (PELF), 25% of the 260.7 million treatments in the WHO PCT databank for 2010. Of these 65.4 million treatment, the 2010 Inventory identified 23.3 million (35.6%) that had not previously been reported to WHO via Ministries of Health and were therefore considered “unique” to the Inventory. The 23.3 million unique treatments identified by the Inventory represent 8.9% of all non-PELF STH treatments in children reported to the PCT databank. Of these, 7.2 million treatments were identified in pre-school-age children (PSAC), representing 4.9% of all non-PELF STH treatments reported to the PCT databank for this age group, and 16.1
million treatments were identified in school-age children (SAC), 14.2%. Of all unique treatments identified via the Inventory, 93% of unique treatments of pre-school-age children and 97% of unique treatments of school-age children came from countries which had not submitted STH reports to WHO.

The NGO Deworming Inventory has provided a complementary approach to collecting data on STH treatments for 2009 and 2010 by estimating the treatment reporting gap for the inclusion of NGO-administered treatments for STH into the WHO’s PCT Databank. Low response rate, uncertain data quality, and imprecise case definitions limit the robustness of these findings. The Inventory results highlight the need to strengthen the reporting mechanisms for non-PELF STH treatments between Ministries of Health and the WHO, and to devise strategies to ensure that NGO-delivered treatments are integrated into Ministry of Health reports.

Recommendations to STAG:

- Strengthen reporting mechanisms for non-PELF STH treatments between Ministries of Health and WHO
- Enhance reporting by NGOs to Ministries of Health at the country level especially where unique treatments were identified by inventory work
- Reduce costs and resources for continuation of the Inventory

Agenda item 6: NTD Medicines – joint request, review and reporting – presentation by A. Mikhailov

A mechanism for a joint process of requesting, reviewing and reporting on medicines for PC is being developed by the Secretariat together with its partners in NTD control. It is proposed to set up a Joint Virtual Review Panel (JVRP), which will comprise the current chairs and members of the Regional Programme Review Groups. The JVRP will be responsible for review of applications, which will be made on the joint forms. The forms will combine both request and reporting forms into a series of linked Excel spreadsheets. These documents have already been discussed by the Working Group on Monitoring and Efficacy.

The need to engage all partners in the process of developing this process and the forms to be used, as well as the Secretariat’s urgent need to implement this protocol, was noted.

Recommendations to STAG:

- Start phased development and implementation of proposed joint review, reporting and application taking into account input from all donation programmes
Agenda item 7:  WGA – first three years and beyond – presentation by V. Reggi

WGA projects during the past 3 years were reviewed. WGA has provided a platform for discussion, coordination and information exchange. It has enhanced attention to quality of NTD medicines. Manuals on safety and quality assessment of drugs have been drawn up. A clearer understanding of supply chain issues has been achieved. The need to continue with provision of better and consistent information on formulation, quality and safety of NTD medicines was emphasized. WGA also needs to advocate for prequalification of additional products and manufacturers. It is necessary to improve pharmacovigilance, notably for implementation of preventive chemotherapy; and to assist in the development and implementation of joint requests, review and reporting for country access to donated medicines.

Other issues that could be taken up in the future were also discussed.

MDAs are a broadly accepted strategy to control certain NTDs – however, cost-effectiveness and benefit/risk ratio of MDAs have been recently challenged by recent studies conducted in Uganda. WGA could further look into this matter and identify evidence to support MDA strategy.

MDAs entail the administration of medicines to healthy persons by personnel who are not medically qualified. WGA could look into the emerging issue of informed consent and identify an appropriate approach, perhaps by emulating the immunization sector.

Sampling and testing MDA medicines has yielded worrying results concerning ALB and MEB. WGA could build on the survey done and run a new survey focusing on ALB and MEB.

Recommendation to STAG:

- Continue to provide information on formulation, quality and safety of NTD medicines
- Further promote pharmacovigilance in preventive chemotherapy through widespread adoption of the existing manual
- Revise design and implement new drug quality survey to focus on ALB and MEB
- Identify barriers hindering access to PC medicines at local level
Fourth Meeting of Working Group on Access to Assured-Quality Essential Medicines for Neglected Tropical Diseases (WGA)

Geneva, 23 April 2012
WHO, Room E. 110

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<table>
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<tr>
<th><strong>Main step of the NTD supply chain</strong></th>
<th><strong>Key challenges</strong></th>
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| **Step 1: Planning MDA**<br>
*MoH, programme managers and partners coordinate on planning MDA* | Programmes functioning separately with difficulties to ensure simultaneous/joint MDA<br>Different working methods and responsiveness of in-country partners<br>Difficulties in obtaining uniform data across programmes for planning purposes |
| **Step 2: Forecasting drug requirements**<br>
*Working groups, programme managers with support of partners forecast drug requirements for the next year(s)* | Lack of resources/experience in forecasting in MoH<br>Difficulties in collating and sending forecasts to donation programmes<br>Lack of understanding in-country of how pharmaceutical forecasting functions |
| **Step 3: Identifying resources/ sources of donations**<br>
*MoH, programme managers, partners and WHO identify potentials sources/resources* | Different standards/procedures/timing of donation programmes and donors<br>Application procedures for first-time countries<br>Challenges in commercial market to source medicines |
| **Step 4: Procuring/Ordering medicines**<br>
*MoH and programme managers with support of partners place orders with donation programmes and/or commercial companies* | Ordering medicines by individual programmes without reference to other government services<br>Incomplete or late information received from countries delaying ordering/shipping of medicines<br>Delays in ordering lead to the late shipping of medicines |
| **Step 5: Shipping of medicines**<br>
*Drugs are shipped directly from manufacturers or by shipping agents* | Challenges of shipping to landlocked countries (delays in intermediary countries) |
| **Step 6: Customs clearance**<br>
*Drugs are cleared through customs by MoH, partners, WHO or shipping agents* | Lack of coordination between MoH and other ministries on customs clearance<br>Inconsistencies in licensing requirements, exemptions and customs fees<br>Arrival in-country of drugs without all necessary clearances prepared |
| **Step 7: Transportation to central storage**<br>
*Drugs are transported to central or regional pharmacy and/or storage locations* | Availability of transport<br>Inadequate storage facilities at central and regional locations<br>Inadequate inventory management |
| **Step 8: Distribution to MDA sites**<br>
*Drugs are distributed to MDA sites for distribution* | Planning to ensure medicines arrive at the appropriate time<br>Inadequate storage facilities at MDA sites |
| **Step 9: Reception at MDA sites**<br>
*Drugs are received at the community level for distribution* | Difficulty to synchronise single treatment for multiple-drug programmes<br>Difficulty to synchronise multiple MDA across programmes |
| **Step 10: Recovering unused medicines and reporting used quantities**<br>
*Drug administering is monitored and unused drugs accounted for* | Challenges in monitoring drug use<br>Challenges in recovering or accounting for unused medicines<br>Use of out-of-date tablets |
Preliminary notes of first meeting of the Working Group on Neglected Zoonotic Diseases within the NTD Strategic and Technical Advisory Group (STAG)

WHO Headquarters, Geneva, 23 April 2012

Drs L. Savioli and F.X Meslin opened the meeting by welcoming participants and emphasizing how important the Working Group was within the STAG. Professor Malika Kachani, Chair of the working group welcomed members and thanked them for their contribution to the draft presentation which was to be discussed and finalised.

She reminded members of the objective of the meeting which was to finalize a report in form of a presentation to the STAG meeting held the following day.

An agenda for the day’s proceedings and discussions was tabled for adoption. Presentations were made by members following the agenda followed by comments and questions.

1. NZDs surveillance

1.1 Challenges and opportunities in NZDs surveillance

Professor Sarah Cleaveland introduced the first topic on NZDs surveillance and gave an overview of the challenges and opportunities in their surveillance.

She made an in-depth analysis on the following issues:

- Reversing the cycle of NZD neglect
- Purposes of collecting data for surveillance
- Challenges in responding to outbreaks of zoonotic diseases
- Early detection and early response to control; delays in reporting outbreaks especially in Africa and Asia
- Under-reporting as a challenge in surveillance of neglected zoonoses (example of human febrile illness in Tanzania) with some insights on incentives and dis-incentives to reporting for communities
- Perpetuation of inequities in geographical reporting in global surveillance of zoonoses: identifying areas where zoonoses are endemic and surveillance capacity is limited
- Building capacity in laboratory and technical competencies: case-scenario of Kenya on inclusion of zoonotic diseases demonstrating challenges in investment on diagnostic capacity and importance of integration between veterinary and medical sector
- Common elements in surveillance of emerging and endemic zoonoses.
Questions and comments

Comments were made on the feasibility of identifying sentinel areas and carrying out pilot studies on community engagement as a proof of concept. The importance of buy-in and integration with different ministries and stakeholders was also emphasized. The group should advocate use of the OIE system of surveillance and reporting and encourage a paradigm shift to all stakeholders involved. A point was raised on the huge heterogeneity of diseases and the limitations in use of animal species as indicator for zoonoses. Several points from Prof. Sarah Cleaveland’s presentation were included in Prof. Kachani’s presentation for STAG.

1.2 Surveillance of parasitic NZDs (with emphasis on echinococcosis and cysticercosis)

Prof. Phil Craig emphasized the following in his presentation:

- Focus was put on surveillance of *E. granulosus* (including Genotypic variation) and *T. solium*
- Tools for cystic echinococcosis surveillance and control in dogs, livestock and humans were highlighted.
- Tools for *T. Solium* cysticercosis/taeniasis surveillance and control in pigs and humans were highlighted.
- It was noted in the presentation that proofs of concept of combinations of control strategies for both cystic echinococcosis and *T. Solium* cysticercosis are still lacking.

Approaches to control of neglected diseases: Consideration should be taken whether human or animal is source of infection and the reservoir.

Questions and comments

Issues on genotype differences and across-host infection and in relation to vaccine efficacy was raised.
- Map the co-endemicity of the major zoonoses (including cysticercosis) with non-zoonotic NTDs (including STH and schistosomiasis).
- The use of Ag-ELISA for human cysticercosis diagnosis was added to the presentation as a useful tool.
- It was noted that guidelines for surveillance of NCC in affected communities in developing countries were missing.
2. Public health and socio-economic burdens of NZDs

2.1 Burden of Parasitic Zoonoses

Professor Paul Togerson made a presentation on the global burden of surveillance of echinococcosis and Taenia solium cysticercosis.

Burdens of NZDs and parameters considered in building a DALY score for cystic echinococcosis, alveolar echinococcosis, HAT, zoonotic leishmaniasis, etc.

Burden of epilepsy due to neurocysticercosis and burdens of zoonotic food-borne trematodes (fasciolosis, chlonorchiasis and opisthorchiasis) were highlighted.

The estimated burdens of zoonotic schistosomiasis, toxocariasis, trichinellosis, trypanosomiasis, leishmaniasis, toxoplasmosis (congenital), intestinal protozoa, brucellosis, bovine tuberculosis and anthrax were noted.

Cost-effectiveness of interventions for rabies, HAT, brucellosis and echinococcosis were shown.

Questions and comments

Questions on integrated control not being applied to NZDs was raised (at public health level, bringing diseases control managers together) and cost-effectiveness of integrated control needing to be elucidated.

2.2 Burden of Rabies

Professor Cleaveland made a presentation on global surveillance of rabies and the current challenges.

Issues related to under-reporting of the disease were raised.

Cost-effectiveness of different strategies were discussed.

The effectiveness of legislations in rabies control and prevention was also discussed.

Questions and Comments

The Group strongly agreed that rabies should be considered as public good to make prevention and control sustainable.

After the presentation on rabies the Chair proposed to amend the Agenda by omitting the presentation on “Human-animal-ecosystem interface for NZDs” in order to have more time to finalize the presentation for the STAG meeting. This was agreed by members.

Professor Samson Mukaratirwa was requested to give an overview “Review of the detailed NZDs roadmap for high-priority neglected zoonotic diseases for 2012-2020” before discussing the final presentation.
Professor Mukaratirwa referred members to the recent report on “Interagency meeting on planning the prevention and control of neglected zoonotic diseases” held in July 2011 for the detailed information regarding the road map for high-priority neglected diseases and the financial requirements needed for the control and prevention activities thereof.

Members recommended adjustments on the presentation to make it more specific on the short-term objectives.

3. Final Discussions and comments to the draft presentations

The Chair introduced the draft presentation based on contributions from members of the Working Group. It was agreed that the presentation should be shortened by removing slides on individual diseases and the option of taking one disease (rabies) as an example was agreed.

The presentation was revised and updated based on the new information from previous presentations and discussions. It was agreed that the introduction slides should emphasize the inherent characteristics of NZDs and their importance to communities. A slide giving information on the global burden of high-priority NZDs was also added.

4. Conclusion of the meeting

The Chair concluded the meeting by thanking all members of the Working Group and reiterated that their contributions to the NTD-STAG was very much appreciated. Dr Meslin made the final remarks and the meeting was closed.
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Third Meeting of the Global Working Group
on Monitoring of Neglected Tropical Diseases Drug Efficacy

Department of Control of Neglected Tropical Diseases
13-14 February 2012

Chair: Professor Mamoun Homeida

Rapporteurs: Dr Marco Albonico, Dr Bruno Levecke
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1. Background

The main goal of this Global Working Group on Monitoring of Neglected Tropical Diseases (NTD) Drug Efficacy is to come out with practical recommendation on monitoring drug efficacy that will fit into the routine monitoring and evaluation of preventive chemotherapy (PC) programme in the field. The working group is founded by the Strategic and Technical Advisory Group on NTD (STAG) in 2010 and consists of 4 subgroups (subWG) focussing on (i) soil-transmitted helminthiasis (benzimidazoles, BZ), (ii) onchocerciasis and lymphatic filariasis (ivermectin, IVM), (iii) schistosomiasis (praziquantel, PZQ), (iv) human African trypanosomiasis, leishmaniasis and Chagas disease.

Currently, we are entering a new era of combating NTD: the WHO has made a roadmap to guide implementation of the policies and strategies set out in the Global Plan to combat NTD 2008-2015; and more than 70 pharmaceutical companies, governments and global health organisations have committed to support the implementation of this roadmap in the London Declaration on NTD (January 31 2012) by sustaining or expanding existing drug donation programmes, with the support of the Bill & Melinda Gated Foundation and under the leadership and coordination of WHO. As a consequence of these increased drug donations, monitoring the efficacy of anthelminthic drugs will become even more important for the challenge of their correct use and proper monitoring, and to ensure that anthelminthic resistance is detected as it emerges in order to allow the implementation of mitigation strategies. The ultimate outcome would be to put a system in place to monitor and respond to the need of NTD control programmes and promote capacity building on monitoring PC management, with special focus on drug efficacy. This document (i) reports the progress of ongoing work, future plans and recommendations to be endorsed by the STAG in April 2012 for each of the different subWGs separately, (ii) points out the issues cutting across the SubWGs and (iii) highlights to role of WHO in the implementation of drug efficacy monitoring programmes.

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

2.1. SubWG on soil-transmitted helminthiasis (BZ)

2.1.1. Progress of on-going work

The subWG on soil-transmitted helminths (STH) has made progress on six aspects outlined below:

(i) The importance of anthelmintic resistance in human STH: A review of the occurrence of anthelmintic resistance in human STH indicated that studies reporting anthelmintic should be interpreted with care, as they have been confounded in methodological flaws. In addition, this review underscored the need for Standard Operating Procedure (SOP) to monitor drug efficacy (Vercruysse et al., 2011).

(ii) The impact of benzimidazoles on co-infections with other pathogens: The efficacy of various BZ regimens (albendazole, mebendazole, given in single dose and multiple doses) against Giardia infections was evaluated. Different regiments of BZ resulted in a significant reduction of subjects infected, but did not result in a reduction in environmental contamination.

(iii) The identification of confounding factors for drug efficacy: The level of infection intensity at baseline was identified as an important confounder of drug efficacy, especially
against *Trichuris trichiura*; a single dose albendazole being highly efficacious when the infection intensity was low, but being less efficacious when the infection intensity was high.

(iv) **Assessment of drug efficacy:** the efficacy of a single dose mebendazole is currently being evaluated in 7 countries. In addition, the occurrence of single nucleotide polymorphisms of the \( \beta \)-tubulin gene associated with anthelmintic resistance and the role of animals as reservoir for human STH are being assessed.

(v) **Simplifying sampling procedures to monitor drug efficacy:** a pilot study was performed to evaluate pooling of samples as a cost-effective strategy to monitor drug efficacy. The results indicated pooling holds promise, but further research is needed.

(vi) **The development of SOP to monitor drug efficacy:** a first explorative meeting of experts was held in WHO to develop new SOP, focussing on indicators of drug efficacy, study design, sampling strategy, diagnostic methods, statistical analysis, interpretation and dissemination.

### 2.1.2. Future plan

(i) Assessment of efficacy of pyrantel-oxantel against STH.

(ii) Establishment of reference laboratories to monitor efficacy of anthelmintics in Africa, Asia and South-America.

(iii) Coordination with the NTD London Centre working on model of predictive curves of prevalence and intensity of infections for STH to monitor PC programme impact. It is expected to have the first model ready by the end of this year.

(iv) Optimizing of PC programmes by assessing the impact of choice of drug, frequency of PC and season in which PC are implemented.

### 2.1.3. Conclusions

At present, anthelmintic resistance is not a concern, but precautions should be made to detect any deviation of the expected drug efficacy. Progress has been made to revise the current SOP, and will be shortly disseminated. Updated information on the efficacy on mebendazole will become available by the end of 2012, but this information is still lacking for other compounds such as pyrantel-oxantel. PC programmes targeting STH with BZ have a collateral impact on *Giardia* infections, and pooling samples holds promise as a cost-effective strategy to monitor drug efficacy.

### 2.1.4. Recommendations to be endorsed by the STAG in 2012

(i) Test as a priority pyrantel/oxantel in the same multinational trial as for albendazole and mebendazole.

(ii) Evaluate flubendazole in the present oral formulation against STH (see also 2.5.1 and 3).

(iii) Finalize guidelines and SOP on how to monitor drug efficacy for STH in the field (including repository of samples) - by mid 2012.
(iv) Explore the validity of pooling samples as cost-effective strategy for monitoring programme impact and drug efficacy against STH.

(v) Assess the frequency of β-tubulin SNP associated with BZ-resistance.

(vi) Contribute to the development a model of predictive curves of prevalence and intensity of infections for STH to monitor PC programme impact in coordination with the NTD London Centre – by end 2012.

2.2. SubWG on onchocerciasis and lymphatic filariasis (IVM)

2.2.1. Progress of on-going work

(i) Assessment of drug efficacy: epidemiological evaluation of onchocerciasis control based on IVM treatment has been ongoing in 7 countries (Tanzania, Nigeria, Malawi, Ethiopia, Cameroon, Central African Republic, and Democratic Republic of Congo). Results were illustrated from Tanzania, Nigeria, Malawi and Ethiopia.

Tanzania: (Tukuyu, moderate-high prevalence area; Ruvuma, high prevalence area; pre-treatment prevalence is determined by nodules). 10-12 villages were monitored for microfilaria (MF) prevalence (skin snip) and data showed that in both areas after 10 years of treatment IVM is still working very well.

Nigeria: (Enugu, high pre-treatment prevalence area), most villages were under 5% after 10 years of treatment.

Malawi: (meso-hypo endemic focus), in 20 villages selected the prevalence has been almost 0% in all villages.

Ethiopia: (Keffa, Sheka and Bench Maji, hyperendemic area; Gondar, mesoendemic area). Prevalence of MF has been less than 5% in most of the villages in hyper and almost close to 0% in mesoendemic focus.

Results of the epidemiological evaluation were matched in the ONCHOSIM predictive model by hyper, meso and hypo endemic areas and most of the data were within the expected value and some even lower.

Out of 31 sites evaluated between 2009 and 2011, 4 (1 in Democratic Republic of Congo, 2 in Cameroon and 1 in Nigeria) were outside the range, but the therapeutic coverage was checked to be low. 12 sites have achieved elimination, and the Technical Consultative Committee recommended independent treatment coverage survey for every project annually.

(ii) Identification of markers for monitoring sub-optimal ivermectin response towards O. volvulus:

The identification of markers has been ongoing with the following aims:

a. to establish whether the sub-optimal response seen in Ghana and Cameroon is due to the reduced embryostatic effect of IVM.

b. to develop diagnostic tool for use by control programmes, if putative markers are identified and validated.
c. to build capacity in West Africa (Ghana), and Central Africa (Cameroon) on multi disease surveillance in order to support use of the tool by control programmes and data analysis.

The progress made includes

a. Draft *O. volvulus* genome is now available and analysis is ongoing in populations with different response to IVM: ~800 genome sequences identified a significant difference in poor-responder groups compared with good-responder and naïve groups. Bio-informatic analysis is continuing to select most different genetic changes and DNA extractions & genome amplifications of individual samples is ongoing.

b. Multi Disease Surveillance Centre (Burkina Faso) is increasing its capacity for repositories of samples, to be used if markers are identified to assess their presence in *O. volvulus* samples from areas with different endemcity, ecology, and history of ivermectin treatment (no treatment to >10 treatments).

c. New guidelines to evaluate preventive chemotherapy programme for lymphatic filariasis have been developed. The guidelines apply on programmes that have been implemented for at least 5 years with coverage of at least 65%.

### 2.2.2. Future plan

(i) Continue conducting epidemiological evaluation (Phase 1a and 1b) in 28 APOC projects in 10 countries

(ii) Expansion of Multi Disease Surveillance Centre repository with samples from epidemiological evaluations (use for IVM response marker project, if indicated)

(iii) Implementation of research for molecular markers of response of *O. volvulus* to IVM and personnel capacity building by laboratory network

### 2.2.3. Conclusions

Epidemiological evaluation of IVM treatment impact is ongoing. Simulation curves are matched with the results and foci with lower prevalence are related so far to poor coverage. Development of molecular markers of *O. volvulus* on IVM response is under study and the recent availability of *O. volvulus* genome is facilitating this process. Lymphatic filariasis programmes monitoring on IVM efficacy should be built up following synergies with STH and onchocerciasis monitoring, and a dedicated working group should be established to develop SOP for monitoring drug efficacy of IVM against lymphatic filariasis.

### 2.2.4. Recommendations to be endorsed by the STAG in 2012

**Recommendations specific on aspects of onchocerciasis**

(i) Continue epidemiological evaluation of programme impact in APOC countries and expand repository of samples.

(ii) Validation of ONCHOSIM with new field data and model implications of the elimination effort for drug efficacy monitoring.
(iii) Continue research to assess markers of anthelmintic resistance for onchocerciasis.

Recommendations specific on aspects of both onchocerciasis and lymphatic filariasis
(i) Validate new diagnostic tools (serodiagnosis) towards elimination. Validation of OVI16 (Ag-test) is underway. Opportunities to integrate programmatic assessment of lymphatic filariasis with onchocerciasis.
(ii) Facilitate the release of DEC patch test and validate its use in the field.
(iii) Share and disseminate SOP to monitor IVM efficacy against *O. volvulus*.
(iv) Assign a working group to develop SOP for monitoring drug efficacy of IVM against lymphatic filariasis when epidemiological monitoring suggests loss of efficacy.

2.3. *SubWG on schistosomiasis (praziquantel)*

2.3.1. Progress of on-going work
(i) Identification of a marker for PZQ resistance: the genomes of *S. mansoni*, *S. japonicum* and *S. haematobium* are now available. Comparison of susceptible and resistant (to PZQ) isolates of *S. mansoni* indicated important single nucleotide polymorphisms in, for example, the β-subunit 1 and 2 of Ca$^{2+}$ channel. Markers are already developed and working for Ca$^{2+}$ channel subunit 1, under development for Ca$^{2+}$ channel subunit 2. This work will enable to design primers and sequencing in order to monitor PZQ “resistance” in the field. There is evidence that ABC transporters (p-glycoprotein) are involved in resistance to PZQ. Experiments to further identify the genes involved in oxamniquine resistance are underway, and there is potential to make oxamniquine effective against *S. haematobium* and *S. japonicum*.

(ii) Population genetics: The analysis of microsatellite loci of various isolates of *S. mansoni* and *S. haematobium* collected in more than 15 African countries suggested a large variation between and to a lesser extent within countries. Follow-up of *S. mansoni* after rounds of PZQ indicated a bottleneck in parasite diversity (i.e. reduction in alleles number). However, there was no consistent bottleneck in parasite diversity in response to PZQ treatment in villages where *S. mansoni* and *S. haematobium* were co-endemic. The development of a mathematical model to predict population genetics under PZQ treatment has been initiated.

(iii) Efficacy on *S. japonicum* and role of animal reservoir: in the near term, PZQ remains effective in treating human *S. japonicum* infection in China. Epidemiological data suggests that besides cattle, wild rodents also contribute to maintenance of *S. japonicum* transmission. In addition to this, genotypic and phenotypic differences across cercariae were observed. Differential PZQ susceptibility of schistosomes by animal definitive host is currently being assessed.

(iv) Importance of mixed *Schistosoma* infections: mixed *S. mansoni* and *S. haematobium* infection have a different impact on health compared to mono infections. For *S. mansoni*, mixed infections result in lower hepatosplenic morbidity compared to mono infections, whereas for *S. haematobium*, mixed infections result in higher urogenital morbidity compared to mono infections. Difference in epidemiology (higher re-infection) and control (potentially lesser susceptibility to treatment) of mixed infections were observed, but this
needs further research. *S. haematobium*-*S. bovis* hybrids are prevalent in Western Africa, but its impact on health, transmission and control is not clear.

(v) **Development of novel compounds:** further development of furoxan, an antischistosomal drug which is also effective against juvenile schistosomes, was put on hold as it was impossible to develop a pharmokinetics assay. Various analogues and hybrids of PZQ have been made, yet they did not always show a higher efficacy compared to PZQ.

2.3.2. **Future plan**

(i) Continue and expand upon modelling of *Schistosoma* transmission dynamics evaluated using empirical data. Liaise with the London Centre on NTDs to adapt the simulation model for monitoring STH control also for monitoring schistosomiasis control.

(ii) Assessment of susceptibility to PZQ of schistosomes by animal definitive host

(iii) Continue with development of markers for anthelmintic resistance (PZQ and oxamniquine) and SOP to monitor efficacy.

2.3.3. **Conclusions**

Several research studies are underway to monitor population genetics of schistosomes under drug pressure. Significant progresses have been made towards the potential identification of markers of oxamniquine resistance, for markers of PZQ resistance progress is underway. Funds are limited for monitoring PZQ efficacy in PC programmes, but gap needs to be identified in order to solicit more resources. SOP for monitoring PZQ efficacy in the field exist but they should be standardised and made centrally available via WHO.

2.3.4. **Recommendations to be endorsed by the STAG in 2012**

(i) Standardise existing SOP for monitoring PZQ efficacy (for uro-genital and intestinal schistosomiasis) in the field for WHO guidelines. Liaise with subWG on STH for similar approach.

(ii) Generalize mathematical modelling to predict prevalence and intensity curves and transmission over time after multiple rounds of PZQ taking into account baseline intensity and prevalence of infection.

(iii) Continue to carry out population genetics study to understand the impact of (a) refugia, (b) development of PZQ resistance and (c) PZQ on the parasite diversity, (d) timing and frequency of treatment

2.4. **SubWG on human African trypanosomiasis, leishmaniasis and Chagas disease**

2.4.1. **Progress of on-going work**

**Human African trypanosomiasis (HAT)**

(i) International efforts through the first decade of the 21st Century appear to have driven the decline of incidence for HAT of fewer than 10,000 cases and its elimination is envisaged by 2020. Notwithstanding, a number of issues remain with regard to HAT, relating to drug efficacy.

a. Pentamidine: few reports of resistance in the field, difficult to select in the laboratory; probably due to loss of uptake through loss of transporters.
b. Suramin: few reports of resistance in the field, but selected in the laboratory; mechanism unknown (easily selected using an RNAi approach; loss of endocytosis).

c. Melarsoprol: increasing treatment failure in the field into the mid 2000s (up to 60% in some foci in DRC); probably transporter mediated (loss of P2-TbAT1 and other transporters).

d. Eflornithine: increasing treatment failure in the field (DRC, Uganda (21% reported at the Omugo treatment centre 2004-2009), South Sudan 10% relapses), and selected in the lab; mechanism probably transporter mediated (amino acid transporter, AAT6) and due to reduced uptake.

e. Nifurtimox plus Eflornithine combination (NECT): Resistance is not known in the field but resistance to both drugs alone easily selected in the lab (loss of transporters for eflornithine, diminished nitroreductase for nifurtimox). A pharmacovigilance system for NECT is in place in 22 sites in 9 countries.

(ii) A system for monitoring efficacy of drugs was implemented in the early to mid 2000s (HAT SENTINEL) – a collaboration between WHO, Swiss Tropical Institute and CDC). A cost of $10,000 dollars/year from WHO allowed monitoring across sentinel sites in Tanzania, Uganda, Democratic Republic of Congo, Angola, Sudan (subsidised by CDC providing staff and additional feedback from STI). That system is no longer operative, although WHO does continue to collect for NECT data across Africa.

(iii) Challenges:

a. Standardised reporting system for NECT treatment failure is in place and it should be extended to other drugs.

b. Mechanisms of resistance still poorly understood and no definitive tests for resistance are available.

c. Little national or international coordination for responding to drug resistance.

d. Few drugs to replace failing compounds.

Visceral Leishmaniasis

(i) Issues relating to drug efficacy

a. Pentavalent antimonials (PA): resistance is widespread especially in India (Bihar), with regional variability.

b. Amphotericin B: resistance is not common in the field, but is easily selected in the laboratory and there are some reported field cases are sporadic (changes in sterol metabolism restricting ergosterol production appear to be the mechanism). A limited quantity (445,000 vials of the liposomal formulation AmBisome) is donated through WHO until 2017. Within the donation programme, a pharmacovigilance system with monitoring efficacy and safety will be built up. A single dose of liposomal amphotericin B proved effective in India. Roll out in the Indian subcontinent is underway. In Africa, the effective dose of L-Amb needs more research, is much higher, and shows regional variability.
c. Paromomycin: resistance is not yet known in the field, but is induced in the laboratory due to possible surface changes limiting uptake. Paromomycin is currently only used in Africa in combination with PA. As paromomycin monotherapy is not likely to be rolled out anywhere, resistance may not become an issue.

d. Miltefosine: resistance is easily selected in the laboratory through reduced transporter expression and reports of treatment failure at 25% are now known in Nepal and 7-9% relapse rates in other countries; WHO’s recommendation is to use this drug only in combination therapy. Studies involving MF in combinations are underway in Africa as well as Asia.

e. Drug combinations (e.g PA + paromomycin/amphotericin B (particularly AmBisome) with other drugs): combinations reduce length of treatment, improve efficacy, and potentially reduce the selection pressure for resistance. Moreover, choices of suboptimal doses of partner drugs will become a problem if parasites are resistant to the other partner (i.e. conditions ideal for selecting resistance to the second drug will be in place). The first examples are already starting.

f. In Europe, there is concern about the veterinary use of miltefosine and PA (in dogs). Resistant strains could easily be generated and transferred to humans.

(ii) Challenges:

a. WHO has no control of distribution of anti-leishmanial drugs as has for HAT and Chagas, that regulates price, quality, and facilitates monitoring. At the moment, GSK is planning to halt production of pentostam (but other antimony formulations remain available. WHO has continued negotiating with all anti-leishmanial drug manufacturers to continue production.

b. Improve and strengthen the monitoring of treatment response in the field.

c. Test and monitor efficacy and safety of drug combinations. In addition, the feasibility of its use at the PHC level need to be verified.

d. Few drugs are available to use in case of resistance in endemic areas.

Chagas disease

(i) Benznidazole and nifurtimox: naturally refractory strains have been reported in the field. Laboratory studies indicated lower levels of the nitroreductase enzyme(s) required to activate the drugs. A global shortage of Benznidazole has occurred due to temporary halt of production from the drug manufacturer. Nifurtimox has been used as contingency plan. Pharmacovigilance efforts have started with support from WHO.

(ii) Challenges:

a. T. cruzi has wide genetic diversity, which influences transmission, progression of disease and response to treatment.

b. Diagnosis and especially markers of cure are difficult to develop.
c. Global shortage of benznidazole.

2.4.2. Future plan

(i) As new drugs/combinations become available, WHO should take the lead in establishment of pro-active reporting on efficacy AND safety. Stakeholders should be invited to contribute to agreed procedures.

(ii) Those administering drugs need to be encouraged and supported in acquiring a culture where reporting efficacy and adverse events is essential.

(iii) An expert in assessing/reporting efficacy/safety should join the committee to advise on best practice.

(iv) Controlled distribution of donated drugs (for HAT and Chagas) has allowed tight regulation and facilitates monitoring. (Can such a system be introduced for Leishmaniasis?).

(v) Develop surrogate end-point markers for “cure”.

(vi) Establish markers/assays to distinguish “resistance” and “inefficacy”.

2.4.3. Recommendations to be endorsed by the STAG in 2012

(i) WHO should take the lead in establishment of pro-active reporting on efficacy AND safety (with focus on new drugs / drug combinations).

(ii) Reporting of drug efficacy to WHO for drugs against Leishmaniasis is recommended.

(iii) Develop/validate surrogate end-point markers for ‘cure’.

(iv) Establish markers/assays to distinguish efficacy/failures, tolerance and resistance.

2.5. DNDi and research on NTD drugs

2.5.1. Progress of on-going work

(i) DNDi is working to develop several products in preclinical, clinical and implementation phase as follows.

a. HAT:
   Preclinical phase: nitroimidazole and oxaborole back up.
   Clinical phase: fexinidazole, Oxaborole SCYX-7158.
   Implementation: nifurtimox-eflornithine co-administration (NECT).

b. Leishmaniasis:
   Preclinical phase: nitroimidazole back up (VL), VL2098 (VL), alternative formulations of Amphotericin B (VL).
   Clinical phase: new VL treatments (AmBisome and Miltefosine) in Bangladesh, Africa and Latin America.
   Implementation: SSG/PM co-administration (VL in Africa) New VL treatments in Asia (SD AmBisome, 3 drug combinations)

c. Chagas:
   Preclinical phase: fenarimol series, K777.
Clinical phase: azoles E1224 and Biomarkers.
Implementation: benznidazole paediatric dosage formulation.

(ii) DNDi with funds from Bill & Melinda Gated Foundation has made progress on formulation, pharmacokinetic, efficacy and safety of flubendazole as a macrofilaricide. An oral formulation is under development and pharmacokinetic and pharmacodynamics studies have been conducted in various animal models. The outcome of these studies indicated that pharmacokinetic patterns differ across animal species and formulations. PK studies indicate that oral bioavailability is improved with beta-cyclodextrine. Safety data shows that *in vitro* toxicity is comparable to that of albendazole.

2.5.2. Future plan (flubendazole)
Assessment of:
(i) *In vitro* toxicity (so far, = albendazole)
(ii) *In vitro* pharmacology: *Brugia malayi* vs. human cells
(iii) Efficacy testing in infected animals to choose the formulation for development
(iv) *In vivo* toxicity

2.5.3. Recommendations to be endorsed by the STAG in 2012
(i) Finalize research on flubendazole oral formulation, PK/PD, toxicity and efficacy as macrofilaricide.
(ii) Finalise research to develop new products as macrofilaricide.
(iii) Incorporate flubendazole in the subWG on STH

3. Issues cutting across the different subWGs
Across the different subWGs the following cross cutting issues were identified and discussed.

(i) Define and identify of supra-national reference laboratories in Africa, Asia, and Latin America and draft Terms of Reference. The establishment of ring testing of *in vivo* and *vitro* assays.
(ii) Speed up capacity building to monitor drug efficacy at programme and supranational laboratory level
(iii) Coordinate with Monitoring and Evaluation WG to set up a standardized framework to monitor both drug efficacy and impact of PC programmes to control NTD.
(iv) Speed up and coordinate development of a disease-specific model to predict impact of PC programmes, detect outliers, and solicit response.
(v) Assure drug quality and sensitize implementing partners on substandard drugs and best practices, through the NGDOs inventory (mailing list) that is available to the WHO.
(vi) Speed up development and coordination of SOP to monitor efficacy of all NTD drugs (by end June 2012).

(vii) Genetic polymorphism in relation with low-efficacy phenotype should be studied in order to identify markers of putative resistance against all NTD drugs and ultimately develop assays to be used.

4. The role of WHO in the implementation of drug efficacy monitoring programmes

The following suggestions for actions to be taken and to sustain the leadership role of WHO in monitoring drug efficacy in NTD control programmes have been discussed.

(i) Sensitize implementing partners on drug quality and best practices, among others through the NGDOs inventory (mailing list) that is available to the WHO;

(ii) Publish an editorial commentary (in e.g. Lancet, PloS NTD) to stress the importance of SOP, best practices to monitor drug efficacy, and to sensitize the different partners involved in NTD control programmes;

(iii) Disseminate SOP and best practices for monitoring drug efficacy to be included as integral part of programme monitoring (e.g. websites of WHO and publications);

(iv) Coordinate and connect different working groups to improve synergies (monitoring and evaluation, and drug efficacy working group);

(v) Establish a separate working group on capacity building.
Summary Points and Recommendations

Chair: Dr. Sam Zaramba

Rapporteurs: Ms. Katie Zoerhoff, Dr. Reda M.R. Ramzy

Introduction

Welcome remarks by Dr. Lorenzo Savioli, (Director, Department of Control of NTD World Health Organization, HQ):

The meeting participants were informed of a landmark meeting, convened in London (January 30th 2012), focused on a Roadmap for NTD Control and Elimination which was announced on January 26 by WHO.

- The targets contained in the roadmap are based on recommendations made by Member States in several World Health Assembly resolutions. These resolutions have been complemented by several Regional Committee resolutions and declarations. The roadmap received inputs from regional offices based on regional achievements and progress.
- The ultimate goal of the roadmap is the elimination of NTDs or reductions in their impact to levels at which they are no longer considered public-health problems.
- Progress in 2011 was highlighted thanks to pharmaceutical companies, including new donations from GSK, Johnson & Johnson, and Merck Serono.
- WHO does not have all milestones yet between 2015 and 2020; will have to do more work to further develop milestones (to be discussed at STAG meeting 2012).
- An important role of WHO is to prepare countries to receive drugs, implement preventive chemotherapy, monitor and evaluate programmes, and report progress accurately.
- The development of a Joint Request Form for Selected PC Medications has required a lot of effort. Research institutions should work in collaboration with other partners to assess impact on disease burden, morbidity, economies, etc. There should be a balance between research and implementation.

Dr. Engels reminded the participants of the seven recommendations to STAG meeting in 2011, and reported on progress made with regard to implementing the resolutions. Dr Engels concluded by pointing out to the need for determining priorities for 2012 and beyond, emphasizing the following:

- Consequent to the drug donations expansion, there is a need to enhance effort to scale-up PC interventions. This includes implementation of Strategic Plans for LF, STH and SCH and expanded "umbrella" PC interventions.
- Make drug efficacy monitoring an integral part of routine M&E of NTD programmes for PC interventions, 3-step drug efficacy monitoring:
  1. Compare routine disease monitoring data with expected values; rapidly get predicted curves for diseases and drug combinations to ring warning bell if deviated from what expected.
  2. If required, confirm with standard operating procedure (SOP).
  3. Prepare response scenario if confirmed. Some back-up scenarios are ready for some (e.g. STH), but not yet for others.
- Enhance Capacity Building to implement NTD programmes for PC interventions, focused on the following issues:

1. **National programme needs**
   - Programme management (planning, budgeting, drug forecasting & stock management, training (sub-national levels), coordination, advocacy, resource mobilization, reviews …)
   - Programme monitoring & evaluation (pharmacovigilance, coverage, disease-specific impact, drug efficacy alerts/early warning, data management – quality and quantity, …)

2. **"Supra-national" Laboratory capacity**
   - Supra national (sub-regional) reference laboratories to carry out standard operating procedures (SOPs) for drug efficacy confirmatory tests
   - Ring testing of specimens
   - Management of suspected drug resistant samples

**Report of Subgroup 1 - Monitoring and Evaluation at Regional and National Levels** (Johnny Gyapong)

The recommendations from the technical review meeting of PCT data from March, 2011 were presented, and participants were briefed on situation analyses for monitoring, evaluation, and data management practices that have recently been sent to countries.

Regional offices presented summaries of the NTD endemicity and interventions in their region, and monitoring and evaluation activities such as impact assessments and surveillance, data management practices, data quality issues, and regional and country-level M&E needs.

Several common themes included that progress was made for the control of 5 PCT/NTDs (lymphatic filariasis, onchocerciasis, schistosomiasis, soil transmitted helminthes and trachoma) in endemic countries during 2009-2010. Among the different WHO regions, various degrees of integration between disease control/elimination programmes, scaling-up mapping, MDA, and monitoring and evaluation activities were reported.

Resource constraints, inadequate capacities and delay of data flow from peripheral to central (in country) and to regional level were frequently reported. Some reported building capacities for lymphatic filariasis control, but not for other NTDs.

It is noted that international resources for NTDs are steadily increasing (drug commodities and funding), despite gloomy economic situation. However, budget gaps are still significant, as there are not enough resources to scale-up everywhere. There is a need to exploit in-country resources, such as education sector funding for deworming through school-health programs. The World Bank (WB) has initiated an International Development Assistance grant fund (up to $745 million). This fund can be used to support national NTD control programs. This requires approaching the World Bank through Ministries of Finance. To have an impact on finance officers, programmes need to rally the support and engagement of top authorities at either Ministry of Health of Ministry of Education.

Monitoring and evaluation is a key element for successful control/elimination programmes. Monitoring and evaluation activities must provide robust and credible evidence on performance and, crucially, on whether national control programmes are achieving desired outcomes. However, expenses on M&E should be limited to reasonable proportion of the overall national programme budget.
Compendium of Indicators for M&E of preventive chemotherapy

A Compendium of Core Indicators for Monitoring and Evaluation of Preventive Chemotherapy has been proposed to compile PCT NTD indicators with standardized information provided for each indicator. Similar compendiums have been developed for other health interventions. This compendium is intended to guide programme managers to select essential M&E activities in the context of multiple demands and limited funding; harmonize indicators across programs, countries, regions, partners and donors to facilitate appropriate M&E and data sharing; to facilitate integration across PCT NTDs; clearly define how to measure progress towards disease-specific control/elimination; and serve as a reference document for Health statistics.

To develop the compendium, an informal gathering of experts was held to determine criteria for "core" indicators and propose preliminary decisions about core versus specialized indicators. Various experts have been consulted to develop the information provided for each indicator. It is planned to have a pre-print draft version available in April 2012.

Training for Transmission Assessment Survey (TAS)

Many countries are now reaching a point where they have conducted five or more rounds of MDA in one or more implementation units (IUs), the potential stopping point for MDA. After much effort from many partners, a new protocol for making decisions about stopping MDA has been developed and validated. A description of this Transmission Assessment Survey (TAS) has been published as part of the new M&E guidelines for LF. Operationalizing these guidelines is a priority that is being tackled through a new training course and technical assistance to countries supported by WHO, USAID, DFID and partners. This 3-day training course has been developed to equip participants to carry out a TAS. This is one effort to address the need brought up by WHO regions for capacity building in national control programmes. There is a need to work out with regional focal points to identify optimal scheduling to roll out training in each region. In addition, countries need clearer guidance on the specific criteria that will be used to verify the elimination of LF and how to use these criteria to prepare LF elimination dossiers.

Funds from The Bill & Melinda Gate Foundation (BMGF) have been provided to a commercial firm to improve the current rapid antigen detection test (ICT). The new test prototype performed well in lab trials and will now be tested in the field. New antibody tests have also been validated; however, the utility of these antibody tools for carrying out post-MDA surveillance requires additional operational research. As with other diseases with specific elimination targets, surveillance is critical to prevent recrudescence of transmission, and additional work is needed to improve sampling methods and define cost effective surveillance strategies.

Xenomonitoring in Lymphatic Filariasis Elimination Programmes

The ability to monitor infection in vectors provides a potential measure of ongoing transmission and circumvents some of the challenges associated with monitoring infections in human populations. The onchocerciasis programs in both the Americas and Africa have pioneered the use of vector monitoring to assess transmission intensity. A protocol for xenomonitoring in settings where Culex spp. transmit LF has been developed and tested. Additional work is needed to demonstrate the practical feasibility of this approach and to determine if similar approaches can be employed where Anopheles spp. or Aedes spp. mosquitoes transmit LF infection. There is need to develop mosquito sampling strategies based on vector species and the size of geographic area to be monitored.

Xenomonitoring (XM) methods have the potential to identify low-level infection in communities and to identify recrudescence before it becomes apparent in humans. They offer cost-savings in comparison to the TAS and better acceptance by the communities concerned. Xenomonitoring can be considered as a tool for infection monitoring post-TAS (not just post-MDA). Xenomonitoring might also be a worthwhile tool for reassessment in areas initially identified as non-endemic.
With the development of new tools to monitor schistosome infections in snails, it is also important to determine how to standardize sampling techniques to permit the use of vector monitoring to support the goal of schistosomiasis elimination. Cross-discipline training for entomologists and program managers should be supported on the methodologies of xenomonitoring for lymphatic filariasis.

Second Edition of WHO Guidelines Helminth Control in School-Age Children: A second edition of WHO guidelines for Helminth Control in School-Age Children was recently released to help national programme managers plan, implement, and monitor programmes deworming school-aged children using methods based on the best current evidence and experience. It includes suggestions for the most useful indicators to monitor and evaluate the progress of the programme, including expert opinion on when to reduce the frequency of drug administration. It provides process indicators, performance indicators and impact indicators. Additional indicators for knowledge, attitudes and practices; assessment of drug efficacy; safe water and adequate sanitation, and school effects are included.

The new STH guidelines will improve program M&E and provide interim guidance for transitioning from community-based LF elimination to school-based STH programs after MDA for LF is stopped. However, these interim recommendations require validation. Evidence for the systematic deworming of women of child-bearing age has been generated in many research studies, but in the absence of drug donations to reach this population, countries still require clear recommendations on programmatic strategies.

Update on Diagnostic Tools
An update on diagnostic tools was provided for each of the PCT NTDs and an integrated platform for NTD surveillance. It was emphasized that the various stages of a control/elimination programme have different requirements in terms of tools, such as diagnostics and sampling strategies. Antigen tests are sufficient for monitoring mid-term programme achievements, but are not necessarily adequate for end-stage issues; antibody tests are the ideal marker at this end-stage. The eventual goal for an integrated platform for NTD surveillance is to develop a multiplex tool that can be included in large-scale surveys such as the Demographic Health Survey or malaria indicator survey as part of a coordinated surveillance strategy.

Onchocerciasis
With a new focus on the elimination of onchocerciasis in Africa (and Yemen), it is clear that the fates of the onchocerciasis and LF programs are intertwined; neither program can stop MDA without careful consideration of the status of the other program. This makes coordination of M&E across both diseases a priority. Initial discussions between LF and onchocerciasis programs have started and should focus on developing a harmonized framework for program evaluations. In parallel, BMGF-funded tool validation efforts will focus on: 1) validating the use of the DEC patch and Ov16 antibody test for assessing transmission; 2) developing a rapid (i.e. point-of-contact) diagnostic test based on Ov16; 3) identifying a practical survey design for human populations; 4) designing a new trap for sampling blackflies.

Schistosomiasis
The promise of expanded praziquantel donations will contribute to the evolution of the public health approach to schistosomiasis from morbidity control to transmission interruption. This will necessitate the development of clear operational guidelines to help program managers with M&E to manage these programmatic transitions from treatment of only school age children to all at risk groups. In many cases, program expansion is expected to take place in a step-wise fashion and clearer guidance is needed on how this should be accomplished. Operational research is needed to define the best programmatic approaches to lead up to the elimination of schistosomiasis.
Elimination of schistosomiasis appears to be feasible in specific epidemiologic settings, but stool-based diagnostic tests are not likely to be sensitive enough for use in this effort. The lack of diagnostic tools for monitoring very low prevalence situations, and for eventual use (with humans and snails) in determining if elimination has occurred and when monitoring can stop, is another critical barrier. Projects carried out by the BMGF-supported SCORE program are designed to validate a point-of-contact rapid antigen test for schistosomiasis. This test, though effective in some surveys, might not be sufficient for schistosomiasis elimination efforts. Efforts to develop robust antibody tests for schistosomiasis should be re-visited, particularly for those antigens with antibody responses that clear following successful treatment. As noted above, additional efforts are also needed to standardize the monitoring of snail vectors.

Trachoma
Trachoma programs are based on robust population-based prevalence estimates. Survey methodologies for trachoma are well described; however, it would be useful to explore how to harmonize these methods with those used for other NTDs. The endpoint for trachoma MDA and the strategy for post-MDA surveillance is currently based on clinical examination, and this has been problematic in some settings. New antibody tools for trachoma detection have been developed and appear promising, but their application to surveillance must be investigated.

Integrated NTD Programs
Funding for NTD programs is being provided increasingly for implementation of integrated drug delivery; greater attention to the development of harmonized M&E is necessary. Specific needs include the development of clear guidance for NTD program managers for monitoring drug efficacy and better options for monitoring program impact at intermediate stages of the program and for integrated surveillance.

Strongyloides and Scabies
Although not a specific focus of preventive chemotherapy programs, community-based control of Strongyloides and scabies infections may be feasible using ivermectin. The widespread use of ivermectin for lymphatic filariasis and onchocerciasis is undoubtedly having an impact on these infections. Opportunities should be exploited for evaluating this impact and to refine best practices for control of these infections.

Although significant progress has been made, more work on programmatic guidelines is still needed as outlined for specific NTDs. In addition, the requirement for improved diagnostic tools has been a consistent theme for NTD programs. Overarching needs include standardized tools for assessing the impact of integrated NTD programs and better diagnostic tools for defining program endpoints and conducting post-MDA surveillance. A narrative summary of priority activities for 2012 is provided here and listed in Table 1 (Annex to this report).

Report of Subgroup 3 - Measuring Enhanced Outcomes and Impact-Overview (Alan Fenwick)

In an update from impact assessment meetings held in 2011 and literature reviews, an extensive list of potential activities were identified to measure impact and document programme effectiveness and efficiency, in order to enhance/sustain global advocacy, promote national commitment and ensure sustainability of funding and programmes. Seven priority areas for potential action were identified, and the methods proposed to address these priority areas include measuring program impact using existing data, new data collection (using existing structures), and/or studies of opportunity.

The way forward was debated, including reasons for and against the need for measuring impact. It was suggested that consultations with constituencies such as donors, pharmaceuticals, and country partners to enquire exactly what information would help them sustain or increase resources. There will be a follow-up meeting on measuring the Impact of Preventive Chemotherapy will be held in April 2012. The general objective of the meeting will be to constitute a multidisciplinary Temporary Task Force of experts to steer suggested studies that will enable the documentation of the impact of preventive chemotherapy interventions,
including the impact on education and socioeconomics/poverty in particular. Such a Task Force would then be requested to determine the most reasonable strategies to address this evidence, considering cost, level of effort, and chances of success. The Temporary Task Force will be expected to submit annual reports to the WHO Strategic and Technical Advisory Group (STAG) on Neglected Tropical Diseases (NTDs) through the Working Group on Monitoring and Evaluation of Preventive Chemotherapy Subgroup 3. The first report of Task Force to STAG will be presented in the first quarter of 2013.

**Expert Committees: Report on M&E Activities and Priorities**

Monitoring and evaluation activities and priorities were presented by the Trachoma Expert Committee (TEC), the Mectizan Expert Committee/Albendazole Committee (MEC/AC), Children Without Worms (CWW) and Deworm the World (DTW). Challenges and priorities that were highlighted include accurately assessing and validating reported coverage (numerator and denominator); determining sampling strategies for disease-specific assessments and process and performance monitoring activities; difficulties with identifying appropriate indicators; addressing the challenges co-endemic diseases particularly in the context of scaling-down of one disease while other diseases need remain to be addressed; applying and testing new guidelines; further ongoing research, including for lymphatic filariasis and onchocerciasis elimination; assessing impact and ancillary benefits of treatments; and the effects of AEs and SAEs on coverage.

**Key discussion points and Recommendations to NTD STAG 2012**

1. Capacity building is required at all levels, including for programme management, programme M&E (including data management), and laboratory capacity. It was recommended that WHO set up a Global Working Group for coordinating capacity building, in order to standardize high-quality training curricula without duplicating efforts. Some of the immediate tasks of such a working group should include:
   a. Building capacity for phased roll-out of Funding Gap Analysis Tool (FGAT), Joint Reporting Form and Joint Drug Request for selected PC Medicines
   b. Collecting all tools currently being used for data management and M&E on a (limited access) SharePoint site, agree on what should be more widely disseminated and strengthen public access to such useful information.
   c. Finalizing and disseminating the working draft of the Indicator Compendium for core indicators for preventive chemotherapy
   d. Addressing the substantial need to develop capacity for peripheral data management and develop a culture of using data in integrated national control programmes, especially at peripheral levels. This is a major priority.
   e. Database development: one single database for all targeted diseases should be developed, based on existing country data and databases. Although a lot of progress has been made with data management and reporting, there still is a need for buy-in from partners so that all routine, essential data are part of country databases. Ongoing efforts to standardize and harmonize databases across countries and partners should continue.
   f. Building capacity on prevention, management, monitoring and reporting of SAEs, (including management of rumours).
   g. Build supra-national/sub-regional laboratory capacity in support of NTD operations, such as monitoring of NTD drug efficacy. As a starting point, it was suggested to make an inventory of key regional laboratories and/or training centres, assess their status (including WHO Collaborating Centre status), select a few with the most comprehensive expertise per region, and involve them in the capacity building effort.
   h. New WHO guidelines for lymphatic filariasis ("Lymphatic Filariasis: Monitoring and Epidemiologic Assessment of Mass Drug Administration") and soil transmitted helminths ("Helminth Control in School Age Children") were published in 2011. Partners should work
together with WHO to disseminate and support the implementation of these guidelines at country level.

2. Countries require both technical and programmatic guidance; the needs vary across regions. While programmatic issues could be addressed by Regional Programme Review Groups (RPRGs) for NTD programmes, the technical experts in the various WHO Expert Advisory Panels could be used to provide additional technical guidance as required. These panels are designed to have a balanced regional representation and are regularly updated. Their more proactive involvement and use could contribute to accomplishing regional programmatic support and technical oversight in a cost-effective manner. Key issues to consider when providing this guidance is institutional memory and following WHO principles.

3. NTD drug efficacy monitoring should become an integral part of routine M&E of integrated NTD programs. Strengthening the links between the WG MDE and the WG M&E is therefore required. Further evidence is urgently needed for determining early warning signs with regard to efficacy monitoring of NTD drugs across the board (including NTDs targeted for intensified disease management). Once Standard Operating Procedures and predictive curves are ready for use, the WG MDE could be merged into the WG M&E, routine M&E aspects of drug efficacy incorporated in the work of the M&E WG, and capacity building needs related to drug efficacy monitoring in the new capacity building WG.

4. New STH guidelines can already be used to collect routine M&E data on programme impact, to be used as raw data to make decisions around drug efficacy monitoring.

5. Further evidence-base is urgently needed on determining STH and schistosomiasis treatment strategies in ongoing programmes in order to consolidate achievements or progressively move towards elimination in a cost-effective manner, as well as on constructing curves predicting the disease-specific impacts following preventive chemotherapy. WHO should engage the various NTD partners able to contribute to jointly take this area of work forward.

   a. The promise of expanded praziquantel donations will necessitate the development of clear operational guidelines to help program managers with M&E to manage programmatic transitions from treatment of only school age children to all at risk groups and eventually to a focus on interruption of transmission.

   b. Evidence for the systematic deworming of women of child-bearing age has been generated in many research studies, but in the absence of drug donations to reach this population, countries require clear recommendations on programmatic strategies.

6. With a new focus on the elimination of onchocerciasis in Africa and Yemen), it is clear that the onchocerciasis and LF programs are interdependent; neither program can stop MDA without careful consideration of the status of the other program. The LF and onchocerciasis programs should focus on developing a harmonized framework for mapping, impact evaluations and programmatic decisions.

7. WHO to develop a scorecard for M&E of the WHO Roadmap and present a draft concept for discussion to STAG in April 2012.

8. WHO to clarify concepts of “elimination” and present a concept paper for discussion to STAG in April 2012.

9. WHO to consult with NTD constituencies, stakeholders and donors to determine what information would help them sustain or increase current levels of commitment for NTD control, then request the
Temporary Task Force on Impact Assessment of Preventive Chemotherapy to steer work to acquire this information. The Task Force should report to the WG M&E through Subgroup 3 annually.

10. For NTDs with elimination targets, surveillance is critical to prevent recrudescence of transmission. Overarching M&E needs include better diagnostic tools for assessing the impact of integrated NTD programs and defining program endpoints. Additional work is needed to improve diagnostic tools, sampling methods and define cost effective surveillance strategies. New antibody tools for trachoma detection have been developed and appear promising, but their application to surveillance must be investigated. The WG calls grateful attention to the ongoing support of the Bill & Melinda Gates Foundation, USAID and other partners to develop these tools.

Additional important issues that are to be noted:

- Approval is sought for further work on xenomonitoring for vector-borne diseases to be conducted by one or more groups working under general guidance of the M&E WG of STAG.

- When scaling down treatment for one disease such as LF, it is necessary to assess needs and strategies of other diseases that use the same distribution platforms such as onchocerciasis and STH, in line with the proposal as taken forward by Subgroup 2 for integrated disease-specific monitoring.

- It is important for countries in the start-up phase to reach and maintain the required minimum coverage in the covered areas as they gradually scale up interventions. Regional programmatic review groups can review whether country programmes have adequate means (financial and technical) to achieve this. It is equally important to advocate for adequate country contributions for programme implementation.

- It is recommended that WHO take forward issue of LF elimination strategies and policies in settings where IVM + ALB cannot used, such as in Loa loa areas.
### Annex Table 1: WG M&E Subgroup 2 - Priority M&E Activities for 2012

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<tr>
<th>NTD</th>
<th>Objective</th>
<th>Activities</th>
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<tr>
<td>Lymphatic Filariasis</td>
<td>Promulgate new TAS guidelines for stopping MDA</td>
<td>- Operationalize guidelines</td>
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<td>Investigate options for conducting post-MDA surveillance</td>
<td>- Conduct TAS training and provide technical support where appropriate.</td>
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<td>Define the role for new tests for post-MDA surveillance</td>
<td>- Work with partners to explore options for collecting surveillance data.</td>
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<td>Develop clear guidance on criteria for verifying the elimination of LF</td>
<td>- Explore options for integrated post-MDA surveillance</td>
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<td>Determine best strategies for xenomonitoring</td>
<td>- Validate new ICT test format</td>
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<td>- Validate utility of new antibody assays for field use</td>
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<td>- Work with partners to test samples collected as part of TAS or other</td>
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<td>surveillance efforts for antibody</td>
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<td>- Assist countries with the preparation of dossiers documenting successful</td>
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<td>elimination</td>
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<td>- Develop and operationalize guidelines</td>
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<td>Onchocerciasis</td>
<td>Establish operational framework for coordinated M&amp;E for onchocerciasis and</td>
<td>- Consultation to develop work plan</td>
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<td>LF</td>
<td>- Develop and validate integrated monitoring approaches Prepare interim</td>
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<td>Validate tools to verify the elimination of onchocerciasis in the African</td>
<td>recommendations</td>
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<td>context</td>
<td>- DEC patch validation</td>
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<td>Establish clear sampling strategies to guide programmatic decision-</td>
<td>- Ov16 test validation</td>
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<td>making</td>
<td>- Trap testing and validation</td>
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<td>- Work with partners to evaluate sampling methods</td>
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<td>Schistosomiasis</td>
<td>Develop guidelines for programmatic transitions from treatment of</td>
<td>- WHO consultation to draft recommendations</td>
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<td>specific populations to achieve morbidity control to transmission control</td>
<td>- WHO consultation to draft recommendations</td>
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<td>Develop clear guidance for intervening in low prevalence areas</td>
<td>- Continue evaluation of CCA antigen test and</td>
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<td>Develop and validate tools to</td>
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<td>Topic</td>
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<tr>
<td>Support elimination</td>
<td>Evaluate surveillance, and document program impact without relying on fecal exams</td>
<td>Validate other tools in the field, including human antibody testing and PCR-DNA on snails.</td>
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<td>Surveillance</td>
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<td>Review data</td>
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<td>Document program impact</td>
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- Soil transmitted helminths

- Operationalize recommendations to scale down treatment frequencies or for implementing STH programs following cessation of MDA for LF
- Provide guidance on best practices for treating women of child-bearing age
- Explore options for monitoring program impact that are not dependent on Kato Katz or other stool exams.
- Validate and operationalize guidelines
- Conduct training and provide technical support where appropriate.
- WHO consultation to draft recommendations
- Develop and validate new tools.

- Trachoma

- Develop tools for outcome monitoring, to assist decision-making for stopping MDA and for post-MDA surveillance
- Continue evaluation of antigen- and antibody-detection tools and their performance in low prevalence areas
- Define options for post-MDA surveillance

- Integrated NTD programs

- Develop guidelines for monitoring drug efficacy
- Operationalize recommendations of the Drug Efficacy Working Group
- Explore alternatives for integrated sentinel sites
- Explore alternatives for integrated post-MDA surveillance