Seventh meeting of the Working Group on Monitoring of Neglected Tropical Diseases Drug Efficacy

Geneva, 26–27 February 2018
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of the Working Group on Monitoring
of Neglected Tropical Diseases Drug Efficacy

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1. Introduction

Helminth control programmes based on preventive chemotherapy for the control of schistosomiasis, onchocerciasis, lymphatic filariasis and soil-transmitted helminthiasis are continuing to expand. In 2016, the global coverage of preventive chemotherapy reached 60%, with more than 1 billion individuals treated with anthelminthic medicines (albendazole, ivermectin, mebendazole and praziquantel).

The expansion of preventive chemotherapy may pose a potential risk of triggering the development of anthelminthic resistance to these essential medicines and thereby jeopardize the long-term public health benefits of the interventions. Anthelmintic resistance is not yet a public health problem in human helminthiasis, but resistance is problematic in helminths of veterinary importance.

The Working Group on Monitoring of Neglected Tropical Diseases Drug Efficacy was established by the World Health Organization (WHO) in 2011 with the purpose of promoting:

- the establishment of a standard system for monitoring drug efficacy;
- the judicious use of anthelminthic medicines in order to sustain their efficacy and delay resistance; and
- the testing of alternative medicines or combinations of medicines should resistance emerge against the anthelmintics currently used in preventive chemotherapy programmes.

At the sixth meeting of the WHO Strategic and Technical Advisory Group for Neglected Tropical Diseases (Geneva, 29–30 April 2013) it was recommended to merge the Working Group on Monitoring of Neglected Tropical Diseases Drug Efficacy with the Working Group on Monitoring & Evaluation so as to integrate monitoring of drug efficacy with overall monitoring and evaluation activities. Both working groups report to the Strategic and Technical Advisory Group on the progress of ongoing work, next steps and recommendations.

The seventh meeting of the Working Group on Monitoring of Neglected Tropical Diseases Drug Efficacy was held at WHO headquarters in Geneva, Switzerland on 26–27 February 2018. The meeting was chaired by Professor Josef Vercruysse. The rapporteurs were Dr Dora Buonfrate and Dr Antonio Montresor. The agenda is attached as Annex 1 and the list of participants as Annex 2.

2. Praziquantel

2.1 Background

In 2016, more than 80 million individuals were treated in preventive chemotherapy programmes, achieving a global coverage of the intervention in school-age children of 54%.

Praziquantel is the only medicine currently available for the treatment of schistosomiasis, yet its mode of action remains unknown. Other molecules have proven some efficacy, but they are either not available in large quantities or require further studies.

Reduced efficacy of praziquantel has not been documented in human infections, although the large number of individuals treated every year represents a concern for the future.
Morbidity in preschool children due to schistosome infection has been well documented, but preventive chemotherapy programmes targeting this age group are currently not implemented because the treatment of this group of children is expressly excluded by drug manufacturers.

2.2 Progress of ongoing work

The University of Texas Health Science Center has conducted in vitro laboratory tests to identify the genes responsible for resistance to praziquantel. A specific region in the parasite genome, which might host one or more genes responsible for reduced sensitivity to praziquantel, has been identified. The findings now need to be confirmed with further studies in the field.

Oxamniquine is a promising option for combination therapy, as it is already registered for the indication of schistosomiasis and has already been administered to millions of people, with no safety issues. However, it is effective only against *Schistosoma mansoni*.

Oxamniquine derivative molecules (e.g. CIDD 790) with efficacy also against *S. haematobium* and *S. japonicum* are under study at the University of Texas and other institutions. However, for these molecules to become available they must be registered as new compounds and a longer period of time will thus be required before they become available on the market.

In areas where schistosomiasis is endemic, animals (especially ruminants) are frequently infected by *Schistosoma* spp. In areas in which preventive chemotherapy interventions are implemented for the control of human schistosomiasis, human infection by hybrids originating from livestock is increasing (probably also as a result of a reduction of the number of human species of schistosomes).

Imperial College London has developed the first model of animal–human transmission for schistosomiasis. The model is intended to facilitate the evaluation of the role of livestock in human transmission and the impact of the possible interventions. Several aspects should be considered: (i) treating animals with praziquantel would reduce the source of the infection but would also increase the drug pressure on the parasite, reduce refugia and probably entail an increased risk of developing drug resistance; (ii) in some endemic countries, suboptimal treatment with praziquantel is given to sick animals and such misuse can promote the emergence of drug resistance; and (iii) hybrids could expand the host (snails) range and the species of animals possibly involved in transmission.

The Pediatric Praziquantel Consortium was founded in 2012 and has started working on paediatric formulations, namely an enantiomer L-PZQ and the racemate PZQ, both in the format of oral disintegrable tablets. The following steps have been completed: pharmacokinetics assessment, testing acceptance (taste) of the new formulations in children (both acceptable, although a bit bitter) and dose finding. A phase II study has been completed in children aged 2–6 years (part 1) and will be continued in younger ones (part 2: children aged 3 months to 2 years).

The WHO Department of Control of Neglected Tropical Diseases has supported drug efficacy tests with the standard protocol in four countries: Cameroon, Madagascar, Nigeria and the United Republic of Tanzania (Zanzibar); the results did not evidence any reduction in the efficacy of praziquantel.

2.3 Next steps

- The University of Texas will continue working on the identification of the genes responsible for drug resistance (and biomarkers of resistance) in order to develop specific tests (such as a PCR
[polymerase chain reaction] kit) to monitor the possible emergence of resistant strains of schistosomes.

- Imperial College London will collect more data on the role of animal reservoirs and will continue its modelling work to help decisions on the need for treatment of animals in areas endemic for human schistosomiasis (using the One Health approach).
- Studies on different molecules that could be used alone or in combination with praziquantel will be conducted.
- Oxamniquine could represent an ideal candidate for areas in which intestinal schistosomiasis is the main form of the disease transmitted. WHO will explore possible sources of this drug.
- The Pediatric Praziquantel Consortium will further analyse the safety of the paediatric formulations also according to different categories (stratification according to age group and by intensity of infection). The regulatory pattern should then follow according to Article 58 of the European Medicines Agency, with the aim of making the product available in 2020. Access should then be guaranteed. Merck KGaA, as the leading partner of the Consortium, does not intend to donate the paediatric formulation; hence other solutions (such as local production of generic drugs at affordable cost) could be explored.
- WHO will continue to offer technical support for the monitoring of drug efficacy in countries where preventive chemotherapy with praziquantel has been conducted for at least 4 consecutive years.
- WHO will prepare manuals for the treatment of schistosomiasis in the paediatric population.

3. **Ivermectin**

3.1 **Lymphatic filariasis**

**Background**

More than 850 million people remain at risk for lymphatic filariasis. Approximately 500 million people were treated in 2016, achieving a coverage of 58%.

Two drug combinations are currently used by the Global Programme to Eliminate Lymphatic Filariasis: ivermectin plus albendazole and diethylcarbamazine citrate (DEC) plus albendazole.

At present there are no concerns about reduced efficacy of these combinations and their administration is normally limited to 5–6 years to eliminate the parasite: long-term exposure is not a concern.

**Progress of ongoing work**

In order to accelerate elimination of lymphatic filariasis, triple drug therapy with ivermectin, DEC and albendazole will start in selected countries in 2018–2019. This combination therapy has demonstrated high efficacy against the disease in two large-scale randomized clinical trials conducted in Côte d’Ivoire and Papua New Guinea. Moreover, possible pharmacokinetic interactions between the three medicines have been excluded and no severe adverse events associated with their combined use have been observed; however, moderate and mild adverse events are probably more frequent than with the administration of two drugs. Their safety has been evaluated in a large study conducted in areas with different epidemiological situations: treatment naive (Indonesia and Papua New Guinea) and treated populations where the target thresholds of prevalence were not achieved according to the pre-transmission assessment.
surveys (Fiji, Haiti and India). No significant difference in adverse events was found between the two groups (two versus three drugs). At present, adding praziquantel to the triple drug regimen is not recommended, in order to avoid an increased rate of adverse events.

Countries where the combination therapy will be implemented can represent an ideal setting in which to test the benefits of preventive chemotherapy with ivermectin against other parasites (Strongyloides stercoralis, other soil-transmitted helminths and Sarcoptes scabiei).

Merck Sharp & Dohme AG have committed to expanding donations of ivermectin of up to 280 million tablets annually until 2025 for the Global Programme to Eliminate Lymphatic Filariasis. This amount would not be sufficient to cover all countries (especially India, in which the estimated ivermectin gap is 733 million tablets). Further contacts with Merck Sharp & Dohme AG have been pursued to evaluate the costs of additional supplies of ivermectin; however, the price so far proposed is not affordable for preventive chemotherapy programmes.

The Death to Onchocerciasis and Lymphatic Filariasis dosing pole study compared the capacity of the ivermectin dosing pole to provide the appropriate dose of DEC with the currently recommended age-based dosing for DEC. The dosing pole would reduce systematic under-dosing of adults (especially males) and slightly increase the frequency of people receiving more than the recommended dosage. However, under-dosing is a greater concern because of the excellent safety profiles of DEC and ivermectin.

3.2 Strongyloidiasis

Strongyloidiasis is not included in the list of neglected tropical diseases as a separate entity. The parasite can be considered a soil-transmitted helminth as it shares the same mode of transmission as the other species in the group. However, since diagnosis and treatment differ from those for the other soil-transmitted helminths, possible interventions for strongyloidiasis would require ad hoc measures.

The burden of strongyloidiasis is probably underestimated because of poor data on its global prevalence and on the morbidity caused by infection with Strongyloides stercoralis. Although it is known that the infection can lead to death in immunosuppressed individuals, the case fatality rate is difficult to define.

Ivermectin is the drug of choice for treatment of strongyloidiasis. An interim analysis of the results of a randomized clinical trial conducted in Europe have demonstrated high cure rates with ivermectin and no statistical difference between single and multiple doses, hence supporting the use of the single dose. This indication was included in the WHO List of Essential Medicines in 2017.

A proposal was made to add ivermectin to the ongoing school-based preventive chemotherapy programmes for the control of soil-transmitted helminth infections, as this would entail lower costs compared with ad hoc programmes and would also improve the efficacy of the benzimidazoles, at least against Trichuris Trichiura infection. A tentative estimation of the need of ivermectin for possible preventive programmes aimed at the control of strongyloidiasis was done.

3.3 Scabies

Scabies was added to WHO’s list of neglected tropical diseases in 2017. The estimated global number of cases exceeds 200 million, and is likely an underestimate. The infection causes severe complications, such as secondary pyogenic infections and autoimmune sequelae including glomerulonephritis; moreover, crusted scabies is associated with higher mortality. The use of topical treatments is unpractical in endemic...
areas, while oral treatment with ivermectin would be more feasible, but this indication is presently not
included in the WHO List of Essential Medicines.

Ivermectin has no action against the eggs of the mite, so a second dose given 7–14 days after the first is
normally suggested. A recent review conducted by the WHO Regional Office for the Western Pacific
suggests that the entire region is theoretically at risk, with Pacific Island countries at especially high risk and
population prevalence documented at approximately 20% in multiple countries.

3.4 Next steps on ivermectin

• WHO and the Murdoch Children’s Research Institute (Professor A. Steer) will prepare a dossier to
include scabies among the indications of ivermectin in the WHO List of Essential Medicines.
• The WHO Collaborating Centre in Negar (Verona, Italy) and the Murdoch Children’s Research
Institute (Professor A. Steer) will refine the estimation of ivermectin for strongyloidiasis and for
scabies.
• WHO will explore the possibility of filling the ivermectin gap by identifying and supporting generic
producers (including support to prequalification).
• The Murdoch Children’s Research Institute will conduct a trial in the Solomon Islands to assess the
efficacy of single dose ivermectin on scabies (this would simplify the logistics of preventive
chemotherapy).
• WHO will establish contact with the malaria group to discuss possible sources of ivermectin.
• S. stercoralis should be more evident on the WHO web site as the fourth soil-transmitted
helminthiasis and the inclusion of ivermectin in the WHO List of Essential Medicines for this
parasite should be stressed.
• Areas where the triple drug therapy regimen will be implemented represent an ideal setting in
which to evaluate the impact of preventive chemotherapy with ivermectin also on strongyloidiasis
and scabies. Researchers are invited to collect baseline data on strongyloidiasis and scabies and to
monitor the impact of the interventions on the prevalence of these infections.

4. Triclabendazole

4.1 Background

Triclabendazole has efficacy against Fasciola hepatica, F. gigantica, Fasciolopsis buski and Paragonimus spp.
For human fascioliasis the current registered dose is 10 mg/kg as a single dose, with the option to increase
to two doses of 10 mg/kg given 12 hours apart. Professor Mas-Coma recommended that for treatment in
confirmed cases of fascioliasis the regimen should be two doses of 10 mg/kg given 12 hours apart. For mass
drug administration the regimen used is 10 mg/kg given once a year.

Data from mass drug administration campaigns implemented in the Northern Bolivian Altipiano have
shown cure rates of 77.8% after one treatment, reaching almost 98% after two treatments. The tolerability
of triclabendazole is excellent, and adverse events have a direct proportion with the intensity of the
infection. Hence, hospitalization is recommended to treat cases with > 400 epg (eggs per gram). At the
moment no alternative medicines are available.
Currently, only a very few reports of triclabendazole resistance have been reported in human fascioliasis, whereas the infection has been documented in animals. The mode of action of the medicine is unknown, and no markers of resistance have been identified.

Donated triclabendazole has been managed by WHO with the support of Novartis since 2006. It is used with different approaches: as preventive chemotherapy in areas of very high prevalence, with active screening in areas of moderate prevalence, and as treatment for cases reporting to health units in areas where the parasite is rarely transmitted to humans.

### 4.2 Next steps

- The Ministry of Health of Bolivia in close collaboration with the WHO Collaborating Centre on Fascioliasis and its Snail Vectors (Valencia, Spain) and the WHO Regional Office for the Americas will evaluate the impact of 10 years of preventive chemotherapy on the prevalence and intensity of human fascioliasis as well as the potential for emergence of drug resistance in the Northern Bolivian Altiplano; the results will be used to guide the next phase of control. A more robust plan is needed for elimination in high-risk areas and a One Health perspective should be considered also to mitigate the contribution of the animal reservoirs.

### 5. Benzimidazoles

#### 5.1 Background

The coverage and availability of benzimidazoles for preventive chemotherapy are increasing (global coverage of preventive chemotherapy with benzimidazoles increased from 18% in 2008 to 68% in 2016). By current projections, the 75% coverage target of 2020 for school-age children and preschool children is within reach. At present about 500 million tablets of albendazole or mebendazole are distributed annually to children in need.

The Starworms project (Stop Anthelmintic Resistant Worms) aims to strengthen monitoring and surveillance of drug efficacy and anthelminthic resistance in preventive chemotherapy programmes for soil-transmitted helminth infections.

#### 5.2 Progress of ongoing work

In the context of Starworms, a clinical efficacy trial of albendazole has been conducted in specific study sites in Brazil, Ethiopia, the Lao People’s Democratic Republic and the United Republic of Tanzania (Pemba Island). The diagnostic tests used to evaluate the efficacy of the preventive chemotherapy intervention with albendazole were single and duplicate Kato–Katz thick smear, mini-FLOTAC and FECPAK\(^2\). The FECPAK\(^2\) test consists of a device that is able to take digital images of helminth eggs that have been concentrated into one microscopic field of view. Images are stored by the associated software and can be uploaded to a remote server when an Internet connection is available. Later, a web-based laboratory technician can count the eggs visible in the images, after which the results are returned to the user by email. The FECPAK\(^2\) platform thus removes the need for skilled technicians, while the online storage of the results in the Cloud-based database allows easy access for quality control and the production of standardized analysis and reports.
For *Ascaris lumbricoides* and hookworm infections, the egg reduction rate (ERR) that resulted was basically equivalent for the different countries and techniques. These data support a good efficacy of albendazole for the two parasites (only some lower efficacy on hookworm infection was observed in the United Republic of Tanzania).

For *Trichuris trichiura* infection, the ERR result was very different among tests and countries, suggesting a doubtful efficacy of albendazole in Ethiopia and the Lao People’s Democratic Republic, and a reduced efficacy in the United Republic of Tanzania.

The sensitivity of the different tests was evaluated against a golden standard based on the combination of the results of all methods. A duplicate Kato–Katz test provided the most sensitive results across the different methods; a single Kato–Katz test proved to be the fastest to execute.

Mutations in the beta-tubulin gene (that has been linked to reduced efficacy of albendazole in animals) were found only in *T. trichiura* (this finding had already been reported in the past). The exposure to large-scale distribution history was related to the presence of mutants, which were more prevalent in the United Republic of Tanzania and less prevalent in Ethiopia and the Lao People’s Democratic Republic. However, the presence of mutations did not show a clear correlation with the individual response to the drug.

ParaDrug is an available e-tool which aims to standardize the analysis and reporting of drug efficacy data (for schistosomes and soil-transmitted helminths).

5.3 Next steps

- The WHO Collaborating Centre at Ghent University in Belgium will continue the optimization of FECPAK^{62}.
- The Collaborating Centre will also offer technical support for the monitoring of drug efficacy in countries where preventive chemotherapy with praziquantel has been conducted for at least 4 consecutive years. The following priority countries were initially identified: Bangladesh, Burundi, Cambodia, Dominican Republic, Ghana, Lao People’s Democratic Republic, Myanmar, Nicaragua, Rwanda, Senegal and Viet Nam. Discussion will take place with the focal point in each Regional Office to finalize the list of countries in which to conduct the efficacy test.
- The WHO Department of Control of Neglected Tropical Diseases with the support of the WHO Regional Office for the Americas/Pan American Health Organization will translate the manual for the assessment of drug efficacy into Portuguese and Spanish.

6. Promising drugs for treatment of soil-transmitted helminth infections

6.1 Progress of ongoing work

Oxantel pamoate is well tolerated, with excellent activity against *T. trichiura* infection (better than that of ivermectin); however, it lacks activity against hookworm and *A. lumbricoides* infections. In combination with albendazole its efficacy is higher than that of the combination with either ivermectin or moxidectin. Although the drug is already registered for the treatment of soil-transmitted helminth infections, Pfizer does not seem interested in restarting its production.
Tribendimidine has been approved in China for treatment of soil-transmitted helminth infections but has poor activity against *T. trichiura* infection. A randomized clinical trial in Côte d’Ivoire and the United Republic of Tanzania comparing different regimens, including tribendimidine, for the treatment of soil-transmitted helminth infections, has demonstrated that the combination of tribendimidine and either ivermectin or oxantel pamoate was not inferior to the combination albendazole or oxantel pamoate for treatment of hookworm infection. The combinations with tribendimidine were very well tolerated.

Pyrantel pamoate has very good efficacy against *A. lumbricoides*, moderate efficacy against hookworm, and low efficacy against *T. trichiura*. A randomized clinical trial in the Lao People’s Democratic Republic has demonstrated that higher doses of pyrantel pamoate can achieve similar efficacy as albendazole on soil-transmitted helminth infections. The combination albendazole plus oxantel plus pyrantel showed higher efficacy than the coadministration of two drugs and demonstrated high efficacy also against *T. trichiura* infection.

Other drugs are in the pipeline, but the processes are still long and costs can be an issue.

### 6.2 Next steps

- Further preclinical and clinical work will be required by a Consortium of PATH, the Swiss Tropical Public Health Institute and a Chinese producer to complete the evaluation of tribendimidine for use in preventive chemotherapy programmes.
- The Consortium will work also towards the registration of tribendimidine by the United States Food and Drug Administration.
- The WHO Department of Control of Neglected Tropical Diseases will identify manufacturers that could produce a generic oxantel pamoate drug. Pfizer could be contacted with a request to support the generic producers with the transfer of technologies. Moreover Pfizer should be approached and asked to share the oxantel dossier to evaluate which studies would be required to approve the drug by a stringent regulatory authority.

### 7. Moxidectin

#### 7.1 Progress of ongoing work

Medicine Development for Global Health has conducted a large randomized clinical trial in the Democratic Republic of Congo, Ghana and Liberia to evaluate the efficacy and safety profiles of moxidectin versus ivermectin for the treatment of onchocerciasis, with positive results. The safety profile was similar and skin microfilaria loads were lower after moxidectin treatment than with ivermectin treatment, suggesting that moxidectin might reduce parasite transmission more effectively than ivermectin.

A dossier on moxidectin has been submitted by Medicine Development for Global Health to the United States Food and Drug Administration for the registration of the drug for the treatment of onchocerciasis in individuals older than 12 years.

#### 7.2 Next steps

- Studies will be conducted by Medicine Development for Global Health to identify the safe and effective dose for children aged 4–12 years.
• Medicine Development for Global Health will also submit dossiers for registration in countries endemic for African onchocerciasis using the collaborative procedure for approval by stringent regulatory authorities of medicines.

• The planned multi-dose study comparing the efficacy of ivermectin administered annually and biannually and of moxidectin annually and biannually for the elimination of onchocerciasis will take place in the northeastern Democratic Republic of the Congo. The trial could also represent an opportunity to collect epidemiological data on other parasitic infections such as strongyloidiasis, scabies and intestinal helminths.

8. **Recommendations**

8.1 The quantity of anthelminthic medicines presently donated will not be sufficient to cover the needs for preventive chemotherapy (that is, in groups at risk not covered by the present donations who should be included in control interventions and the expansion of triple drug combination therapy). For this reason, the generic producers of the anthelmintics currently used in preventive chemotherapy (that is, praziquantel, ivermectin, albendazole and mebendazole) should be supported in registration and prequalification.

8.2 Alternative anthelminthics are needed for use either alone or in combination with other medicines to prevent the development of anthelminthic resistance and for use as second-line drugs in case of demonstration of reduced efficacy. A number of appealing options have been identified (namely, oxamniquine, moxidectin, pyrantel, oxantel and tribendimidine); the possibility of large-scale production should be explored with generic manufacturers.

8.3 Countries in which preventive chemotherapy has been implemented for more than 4 consecutive years should be supported in evaluating the efficacy of the drug distributed with the standard protocol developed by this Working Group.

8.4 In the absence of experts on scabies in the WHO Department of Control of Neglected Tropical Diseases, it is suggested to establish an official relation (WHO Collaborating Centre) with the Murdoch Children’s Research Institute to properly follow up on the work being undertaken on this parasite.

8.5 The triple administration of ivermectin, diethylcarbamazine and albendazole that is starting in countries previously not covered by PC. Researcher are invited to collect baseline strongyloidiasis and scabies data and to monitoring the impact of the interventions on the prevalence on these infections.
### Annex 1. Agenda

#### Day 1 – 26 February 2018

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<td>10:00–10:45</td>
<td>Progress of ongoing work on praziquantel</td>
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<td>10:45–11:30</td>
<td>Progress of on-going work on praziquantel</td>
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<td>Progress on paediatric praziquantel</td>
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<td>Triple drug administration for control of lymphatic filariasis</td>
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<td>Plans to fulfil expected additional need of ivermectin</td>
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<td>Global need of ivermectin for strongyloidiasis control</td>
<td>Z. Bisoffi</td>
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<td>16:45–17:00</td>
<td>Group discussions on ivermectin, next steps</td>
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<td>08:30–08:50</td>
<td>Global need of IVR for scabies control</td>
<td>A. Steer</td>
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<td>Donation of triclabendazole</td>
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<td>09:10–09:45</td>
<td>Sub-group on benzimidazoles</td>
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<td>– STH diagnostics for the assessment of drug efficacy and emergence of</td>
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<td>– Efforts to standardize analysis and reporting of drug efficacy data</td>
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<td>– Overview of countries where monitoring of drug efficacy</td>
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<td>09:45–10:30</td>
<td>Potential alternative drug for soil-transmitted helminthiasis</td>
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<td>– tribendimidine efficacy trial</td>
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<td>– pyrantel oxantel efficacy trial</td>
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<tr>
<td>11:00–11:30</td>
<td>Group discussions on benzimidazoles and possible alternatives, next step</td>
<td>Chair</td>
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<tr>
<td>11:30–12:00</td>
<td>Preparation of draft report of the meeting</td>
<td>Rapporteur and</td>
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<td></td>
<td></td>
<td>co-rapporteur only</td>
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<tr>
<td>14:00–14:45</td>
<td>Group discussions on the report</td>
<td>Chair</td>
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<tr>
<td><strong>14:45–15:30</strong></td>
<td><strong>Closure of the meeting</strong></td>
<td>Director a.i. NTD</td>
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<tr>
<td>15:45–17:45</td>
<td>For everyone who is interested in: Starworms (Stop Anthelminthic Resistant</td>
<td>B. Levecke</td>
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<td></td>
<td>Worms), a project funded by the Bill &amp; Melinda Gates Foundation that</td>
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<td></td>
<td>unites three WHO collaborating centres</td>
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<tr>
<td></td>
<td>– Discussion on strategy work package, global patterns of drug efficacy</td>
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<td></td>
<td>and emergence of anthelminthic resistance</td>
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<tr>
<td></td>
<td>– Plans for the next year</td>
<td></td>
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</tbody>
</table>
Annex 2. List of participants

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