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# Schistosomiasis and soil-transmitted helminthiases research agenda

Version 0.4 April 2020 - prepared by IDDO Secretariat and Scientific Advisory Committee, with input from expert reviewers.

For stage 3, open consultation.

The proposed schistosomiasis and soil-transmitted helminthiases (Schisto-STHs) research agenda set out below has been developed by the Schisto-STHs research theme Scientific Advisory Committee (SAC, see Appendix for current membership), and has been revised with input from expert reviewers. The purpose of this agenda is as follows:

1. The IDDO Schisto-STHs data platform is facilitating the collation, curation, standardisation, archiving and sharing of existing data on responses to the medicines used to treat schistosomiasis and soil-transmitted helminthiases. The data are managed collectively.
2. This research agenda will guide how data shared through the Schisto-STHs platform could be reused to answer outstanding research questions. It is intended to encourage collaboration and engagement with the platform.
3. This agenda reflects research areas highlighted by the community. It aims to identify research questions related to either schistosomiasis or STHs (primarily ascariasis/roundworm, trichuriasis/whipworm and hookworm) that have not, or cannot, be satisfactorily addressed in single studies or meta-analyses of aggregate data and are of urgent concern. IDDO will support individual patient data (IPD) meta-analyses of these archived data.
4. The targeted datasets primarily originate from clinical trials (see Julé et al. 20161  and Halder et al. 20172). The requested and shared datasets are IPD and include (primarily but not exclusively parasitological) measures of responses to treatment, measures of medicine safety and tolerability, and other individual-level and cohort-level (i.e. metadata) covariables.
5. This agenda is a working document. As research priorities are addressed and new prospective data collected, additional questions and capabilities for analysis will arise. The research agenda will be updated as required, with subsequent development guided by the SAC and the wider research/global health community.
6. The agenda will remain online as a ‘living document’ and will be updated as the data platform and the research needs of the disease communities evolve.
7. The development of this research agenda is following a 3-stage process:
8. first draft developed by the Schisto-STHs data platform SAC
9. version sent for comments to experts, from across the schistosomiasis and STHs communities
10. version posted on the IDDO website until 4th June 2020, with publicity and outreach activity to encourage comments from all interested parties.

The following priority research areas have been identified for which sufficient datasets are available and outcomes should be available within 2-3 years. Other questions may be identified for which at present there are insufficient data, or which are out of the current scope, but which may shape the future directions of the platform or spur new research across the disease communities. Research questions are organised thematically, with specific examples given of studies that have motivated the questions, both for schistosomiasis and STHs.

# Priority research areas

## 1. Variation in treatment responses

Responses to anthelmintics are typically reported at a group/population level in terms of an average efficacy, most frequently using traditional parasitological techniques. Because of differences in study methodologies and reporting, quantifying different sources of variation on group/population-level responses becomes difficult to impossible. Comprehensive IPD meta-analyses would permit better understanding of the geo-temporal, methodological (e.g. study design/use of diagnostics for assessing treatment response), individual participant, and treatment factors that drive variation in treatment responses.

### Geo-temporal factors

*Research questions*

* Is variation in treatment responses associated with duration and/or intensity (frequency/coverage) of mass drug administration (MDA)?
* Have treatment responses systemically changed during the past decade of MDA scale-up?
* At what geographical scale is variation detectable and when does variation become clinically and/or epidemiologically relevant?
* Is geographical variation associated with economic and/or environmental factors in studies with longer follow up times?

*Motivating examples - schistosomiasis*

* The duration of MDA has been associated with reduced efficacy of praziquantel against intestinal schistosomiasis among school children in Uganda.3
* Repeated praziquantel doses required to achieve adequate efficacy against urogenital schistosomiasis in South Africa.4
* Reduced susceptibility to praziquantel of *Schistosoma mansoni* in Kenya5
* Geographical resolution of studies identified through landscaping1 requires further analysis.

*Motivating examples - STHs*

* Reduced efficacy of albendazole against whipworm & hookworm identified in Pemba Island, Tanzania which has a long history of MDA.6,7
* Efficacy of albendazole against whipworm suggested to have declined globally between 1995 and 2015.8
* Treatment known to select for *β*-tubulin mutations which may be associated with drug resistance.9,10
* Geographical resolution of studies identified through landscaping2 requires further analysis.

### Methodological factors

*Research questions*

* What is the optimal follow up time for measuring responses to treatment and does this differ between schistosomiasis and STHs and between species of infection?11,12
* Is participant dropout rate associated with study design methodology (e.g. how actively participants are followed up)?
* How do drug responses differ when measured using different diagnostics (with different performance characteristics),6 applied in different ways (e.g. repeated sampling)13 and in different transmission settings?
* How should responses measured by different diagnostics be interpreted and compared?6,14
* How do responses measured using molecular techniques compare with measures made using traditional parasitological techniques?15-17

*Motivating examples – schistosomiasis*

* Optimal timing of post-treatment follow-up may differ among schistosome species.11,18
* Levels of circulating cathodic antigen (CCA) in urine have been observed to decrease rapidly (within 24 hours) after treatment19 but may indicate lower efficacy that parasitological methods of assessment.17
* CCA and circulating anodic antigen (CAA) diagnostic tests are more sensitive that traditional parasitology,20,21 but the difference in performance will depend on the particular parasitological method (e.g. Kato-Katz, flotation methods etc.)6 and its application (e.g. repeated sampling).13,22,23

*Motivating examples - STHs*

* Quantitative PCR (qPCR) can be used to measure drug efficacy against soil-transmitted helminths15 and is more sensitive than traditional parasitology24 and can provide more precise estimates of intensity.25
* Can qPCR data (e.g. on Cq-values) be reliably compared from different laboratories?26
* How do responses measured by qPCR translate to those measured by traditional parasitology?15

### Individual participant factors

*Research questions*

* Do demographic (e.g. age, sex), socio-economic, nutritional and health indicators affect responses to treatment?
* Does the intensity of infection and of co-infections (with helminths or other pathogens) affect responses to treatment?

*Motivating examples – schistosomiasis*

* Reduced responses to praziquantel have been associated with high infection levels / transmission intensities27-29 but the association is likely different for different response measures (e.g. cure versus reduction in intensity).
* Decreased efficacy of praziquantel has been reported in older children.30

*Motivating examples – STHs*

* Responses to treatment may depend on intensity of infection31,32 (depending on the response measure; cure versus intensity reduction)33,34 which may be further confounded by the potential relaxation of density-dependent constraints on fecundity.35

### Treatment factors

*Research questions*

* What are optimal drug regimens (e.g. dose, dosing regimen, drug combinations) for the treatment of different schistosome species (and hybrids) and STHs?
* Does medicine quality (original versus generic) affect responses to treatment?
* Does co-administration of food affect response to treatment (and treatment tolerability)?

*Motivating examples – schistosomiasis*

* A 60 mg/kg dose of praziquantel has been shown in some studies (but not all36) to be more efficacious for treating schistosomiasis that the 40 mg/kg dose typically used for MDA.30,37,38
* Repeated doses of praziquantel may improve responses for treating schistosomiasis.39
* The efficacy of praziquantel somewhat variable against different schistosome species*.*40 Little is known about the efficacy of praziquantel for treating hybrid infections.41
* Evidence suggest co-administration of food increases the bioavailability of praziquantel42,43 and may therefore improve responses to treatment.

*Motivating examples – STHs*

* Benzimidazoles alone have limited efficacy against whipworm and variable efficacy against hookworm8 but combinations of existing treatments44,45 may provide an alternative.
* Mebendazole has suboptimal efficacy against hookworm in single dose.46,47
* High levels of substandard benzimidazoles have been reported in Africa48 and variation in efficacy has been associated with different brands of medicine.49

2. Responses to treatment in understudied groups

A particular strength of aggregating IPD from multiple studies is to increase the power to understand the safety and efficacy of treatment in understudied groups. Groups of interest with limited individual studies include pregnant women, preschool-aged children and individuals co-infected with HIV and other pathogens.

*Research questions*

* What is the optimal dose of praziquantel for the treatment of preschool-aged children?
* Does co-infection with other pathogens affect treatment response?

*Motivating examples – schistosomiasis & STHs*

* The optimal dose and formulation of praziquantel for preschool-aged children remains to be established but is recognised as a key demographic group for the prevention of morbidity and ultimately the elimination of schistosomiasis.36,50
* Possible associations between HIV and helminth infection have received significant attention51-53 but associations between responses to anthelmintic treatment and co-infection with HIV are understudied.54

3. Methodological questions

The World Health Organization provides guidance on analysis protocols for calculating anthelmintic efficacy (as egg reduction or cure rates) on a population-level basis.55 A number of different methods have been proposed in both the human13,30,56,57 and veterinary domains58,59 for analysing individual-level data but more research is required in this area.

*Research questions*

* How do different modelling approaches for quantifying individual-level drug responses compare?
* How do the outcomes of modelling or other IPD analysis approaches relate to classical population measures of anthelmintic efficacy?
* What degree of variation among individual responses should one expect from a drug that is performing as-expected, particularly with responses measured using imperfect (and noisy) parasitological or other diagnostics?
* Can (individual) sub-optimal responses to treatment be defined?
* How should drug responses measured using molecular diagnostics be modelled or analysed?14
* How should drug responses measured using multiple (including molecular) diagnostics be modelled or analysed?
* What are the optimum sample sizes for assessing anthelmintics’ efficacy?

*Motivation examples – schistosomiasis and STHs*

* New analytical methods for conducting individual-level analyses have been outlined for both schistosomiasis13,30 and STHs56,57 but there does not yet exist consensus on the most appropriate approach.

4. Drug safety, tolerability and side effects

The drugs used to treat schistosomiasis and STHs are considered very safe and associated predominantly with only relatively mild side effects10,11 although the published research in this area is limited.

*Research questions*

* Are side effects more severe in individuals with heavy infections and/or taking concomitant medication?
* Does experiencing side effects reduce adherence with future treatments?
* What are the side effect profiles of new, repurposed or combination therapies?
* What are the side effect profiles in understudied groups?

*Motivating examples – schistosomiasis*

* Side effects of praziquantel can have a deleterious effect on adherence.60
* Studies have indicated that praziquantel is safe for pregnant women61,62 yet it is still frequently not offered during MDA to women who are pregnant or breastfeeding,63

*Motivating examples – STHs*

* Evidence on the safety of anthelmintic treatment in pregnant women is limited64 and updated analyses using pooled IPD could add significantly to the evidence base.
* Safety and tolerability of new combination treatments.65,66

5. Prospective trial design

### 5.1. Optimal trial design and case record form

The design and reporting of drug trials is highly heterogenous and has been established as a key challenge to comparing outcomes using traditional meta-analytical approaches.1,2 By collating and analysing IPD from many previous studies, guidance on optimal trial design and an associated case record form could be developed.

* Optimal follow-up time after treatment for different parasite species.
* Optimal sets of demographic and other variables to be collected that are both informative and practical to collect.
* Guidance on use of diagnostic test(s), e.g. how many repeated measures before and after treatment are sufficient to achieve a desired level of precision (i.e. sample sizes) on individual response estimates?

### 5.2 Identifying and addressing gaps

Gaps likely still exist in the clinical trials landscape where even collated IPD may be insufficient to address research questions satisfactorily. These may include:

* Geo-temporal coverage.
* Coverage of different demographic groups (e.g. gender representation and representation of at-risk occupations).67,68
* Implementation of routine monitoring and evaluation of efficacy in sentinel communities.

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