

# Inputs from mathematical modelling to schistosomiasis control

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## Overview

- NTD Modelling Consortium
- Modelling approach
- Current WHO strategy
- Modelling insights
  - WHO treatment guidelines for S. mansoni
  - Monitoring and evaluation programmes for S. mansoni
  - Further data needs
  - S. haematobium insights
  - Post-treatment surveillance for predicting S. mansoni elimination
- Insights from health economics
- Policy impact and future work
- Discussion



## **NTD Modelling Consortium**

- Aims to develop mathematical models of NTD transmission dynamics and the impact of control measures
  - Focus is on infections included in the London Declaration on NTDs
  - Supporting NTD community and addressing priority questions
  - Increasing engagement with WHO
  - Multiple models to increase robustness
  - Funded by the Bill and Melinda Gates Foundation
  - Includes schistosomiasis
- Schistosomiasis groups:

Oxford, ICL, LSHTM, CWRU, Surrey, Lancaster



## **NTD Modelling Consortium**

- Collections in Epidemics, CID, PLoS NTDs and Gates Open Research
- COR-NTD booklets
  - Website: https://www.ntdmodelling.org/





Reaching the 2020 Goals for Nine Neglected Tropical Diseases



PLOS COLLECTIONS

NTD Modelling Consortium: Insights on data needs

#### Gates Open Research / collections



2030 goals for neglected tropical diseases









## Modelling approach

- Static models
  - Individuals acquire infection at a rate which is not linked to the abundance of infection in the population
    - An individual's probability of being exposed to an infection is unaffected by an intervention and cannot account for the indirect benefits of interventions
- Dynamic models (used in our modelling)
  - Explicitly link the rate of infection and the abundance of infection in the population
    - Rate of infection changes over the course of an intervention. Interventions benefit the individuals treated, and reduce the risk of infection to others in the population (rate of transmission is reduced)
- Deterministic models: model output is fully determined by the parameter values and the initial conditions
- Stochastic models: include inherent randomness and chance

Turner et al. (*in prep*) Economic evaluations of human schistosomiasis interventions: a systematic review and identification of associated research needs.



- Fully age-structured deterministic and stochastic individual-based models
  - Monitor parasite transmission and control by MDA
    - Rate of infection and amount of infectious material within the environment over time
    - Age-dependent heterogeneity in risk of infection
  - MDA benefits individuals treated and reduces the risk of infection to others
- Implement treatment strategies in low to high baseline prevalence settings
  - Vary intrinsic intensity of transmission (R<sub>0</sub>) and age-specific contact rates
  - Investigate the impact of treatment strategies
- True and measured (by Kato-Katz) prevalence

## **Modelling assumptions**

- Coverage at random at each round of MDA
  - No non-adherers/non-access individuals
- No acquired immunity
  - Past infections do not impact an individual's susceptibility
- Single community with an environmental reservoir
  - No migration



- Worm aggregation parameter
  - Low prevalence settings have higher aggregation
    - Many individuals with zero/few worms and few individuals with many worms

MDA: mass drug administration

#### Truscott JE et al. (2017) A comparison of two mathematical models of the impact of mass drug administration on the transmission and control of schistosomiasis. *Epidemics.*



#### WHO treatment guidelines for S. mansoni

## **Current WHO strategy**

- Control morbidity due to schistosomiasis by 2020
  - < 5% prevalence of heavy-intensity infections in SAC</p>
- Eliminate schistosomiasis as a public-health problem by 2025
  - < 1% prevalence of heavy-intensity infections in SAC</p>
- Are current guidelines sufficient?



WHO (2011) Helminth control in school-age children: A guide for managers of control programmes.

## Low prevalence settings



- For 6 years: MDA once every 3 years
- For following 4 years: MDA once every 2 years
- Meet the WHO goal of EPHP within 6 years of treatment

EPHP: elimination as a public health problem

\*Assuming treatment coverage 75% SAC and 100% treatment adherence

Toor J et al. (2018) Are we on our way to achieving the 2020 goals for schistosomiasis morbidity control using current WHO guidelines? *CID*.

#### **Moderate prevalence settings**



 For 10 years: MDA once every 2 years

 Meet the WHO goal of EPHP within 10 years of treatment

\*Assuming treatment coverage 75% SAC and 100% treatment adherence

Toor J et al. (2018) Are we on our way to achieving the 2020 goals for schistosomiasis morbidity control using current WHO guidelines? *CID*.

# High prevalence settings



- For 6 years: MDA once a year
- For following 4 years: MDA once or twice a year depending on prevalence
- May or may not reach the WHO goals within 10 years of treatment depending on baseline prevalence level

\*Assuming treatment coverage 75% SAC and 100% treatment adherence

Toor J et al. (2018) Are we on our way to achieving the 2020 goals for schistosomiasis morbidity control using current WHO guidelines? *CID*.

#### **Projected outcomes of current WHO strategies**

		1 <sup>st</sup> decision (for 6 years):							
		Prevalence < 10%	10% ≤ Prevalence < 50%	Prevalence ≥ 50%					
		PCT once every 3 years	PCT once every 2 years	PCT once a year					
	Prevalence < 10% PCT once every 2 years	Prevalence: $0-9.5\% \rightarrow 0-0.3\% \rightarrow 0\%$ Heavy-intensity prevalence: $0-0.01\% \rightarrow 0\% \rightarrow 0\%$							
(for 4 years):	valence < 50% tains previous quency		Prevalence: 10.6-49.9%→0.1-27.5%→0-14.3% Heavy-intensity prevalence:	Prevalence: 50-67.8%→11.5-48.3%→3.3-40.4% Heavy-intensity prevalence: 11-32.1%→0.01-9%→0-4.7% Prevalence:					
2 <sup>nd</sup> decision	10% ≤ Prev PCT maint free		0.02-10.9%70-1.1%70-0.1%	68.1-68.4%→49.1-49.9%→41.7-42.9% Heavy-intensity prevalence: 32.5-33% → 9.6-10.2% → 5.2-5.8%					
				Prevalence: 68.6-71.3% → 50.7-58.4%→ 28.5-41%					
	e ≥ 50%		Heavy-intensity prevalence: 33.4- 37.9% → 10.8-18.5% →1.1-4.9%						
	Prevalen PCT twic			Prevalence: 71.5-75% $\rightarrow$ 58.9-67.5% $\rightarrow$ 41.8-57.9% Heavy-intensity prevalence:					
				38.2-43.9% → 19- 31.4% → 5.2- 17.9%					

 WHO goals achieved in low prevalence settings and may be achieved in higher prevalence settings depending on baseline prevalence level.



\*Assuming treatment coverage 75% SAC and 100% treatment adherence Results using age structured deterministic model (similar for mean stochastic simulations)

#### Toor J et al. (2018) *CID*.

## **Programmatic adaptations**

- Low prevalence settings: Current WHO guidelines will ensure the morbidity control and EPHP goals are met
- Higher prevalence settings: Current WHO guidelines may not achieve the goals
  - Increase coverage of SAC to 85% and include adult coverage at 40%
  - Or increase treatment frequency  $\rightarrow$  logistical challenges

#### **Recommended adaptations**





- Although WHO goals may be achieved, the overall prevalence and incidence of infection may still be high
  - Reservoirs of infection remaining in non-SAC population
  - Lower intensity infections remaining in SAC
- Settings where SAC carry the majority of infection mean that the guidelines may fail more often
  - Here more frequent or a higher coverage of treatment is needed



# Monitoring and evaluation programmes for *S. mansoni*

## M&E programmes

- M&E data typically collected from SAC as they are most likely to be infected
- Assumed 3 different burdens of infection in adults for S. mansoni
- Does the burden of infection in adults impact our recommended treatment strategies?



Toor J et al. (2018) The design of schistosomiasis monitoring and evaluation programmes: The importance of collecting adult data to inform treatment strategies for *Schistosoma mansoni*. *PLoS NTDs*.

## WHO strategy

- Followed through WHO guidelines
- Coverage levels required to achieve the WHO goals
  - Morbidity control and EPHP
  - 5, 10 and 15-year programmes



Prevalence and treatment in SAC. Treatment coverage at random. \*SAC: 5-14 years of age

WHO (2011) Helminth control in school-age children: A guide for managers of control programmes.

#### **Required coverage levels**

Baseline prevalence in SAC	Morbidity control (≤5% heavy infection in SAC)	Elimination as a public health problem (≤1% heavy infection in SAC)		
Moderate (10-50%)	<u>5/10/15-year programme</u> SAC: 75%	<u>5/10/15-year programme</u> SAC: 75%		
	• Low, moderate and high burden settings: Adults: 0%	• Low, moderate and high burden settings: Adults: 0%		

## Model coverage projections

High prevalence settings (≥50% SAC baseline prevalence): annual treatment of 75% SAC and 0% adults



Toor J et al. (2018) The design of schistosomiasis monitoring and evaluation programmes: The importance of collecting adult data to inform treatment strategies for *Schistosoma mansoni*. *PLoS NTDs*.

\*SAC: 5-14 years of age

### Model coverage projections

#### Low adult burden of infection: annual treatment of 80% SAC and 16% adults

#### 100 SAC prevalence Adult prevalence SAC heavy-intensity prevalence Adult heavy-intensity prevalence 80 Prevalence (%) 60 40 20 0 5 10 n Time (years)

#### **High adult burden of infection:** annual treatment of 85% SAC and 76% adults



Toor J et al. (2018) The design of schistosomiasis monitoring and evaluation programmes: The importance of collecting adult data to inform treatment strategies for *Schistosoma mansoni*. *PLoS NTDs*.

\*SAC: 5-14 years of age

#### **Required coverage levels**

#### High prevalence settings (≥50% SAC baseline prevalence)



WHO goal of morbidity control

Toor J et al. (2018) The design of schistosomiasis monitoring and evaluation programmes: The importance of collecting adult data to inform treatment strategies for *Schistosoma mansoni*. *PLoS NTDs*.

#### **Required coverage levels**

#### High prevalence settings (≥50% SAC baseline prevalence)

WHO goal of morbidity control







5-year programme



#### Age group

Toor J et al. (2018) The design of schistosomiasis monitoring and evaluation programmes: The importance of collecting adult data to inform treatment strategies for *Schistosoma mansoni*. *PLoS NTDs*.

\*SAC: 5-14 years of age

#### **M&E data requirements**

- Moderate prevalence settings: 75% SAC-only treatment will likely reach the WHO goals within 5 years regardless of burden of infection in adults
- High prevalence settings: SAC and adult treatment is needed
  - Burden of infection in adults will impact the coverage levels required to achieve the WHO goals
- Need broader age-group data, specifically adult (as well as SAC) data at least at baseline to inform the optimal treatment strategy for a setting





#### Further data needs

#### **Data requirements**

- Parametrize models using datasets
- To improve model predictions need better quality data on:
  - Cross-sectional and longitudinal studies across all age classes
  - MDA treatment coverage
  - Adherence and access to treatment
    - Collected at multiple rounds and recorded at an individual level
  - Pre- and post-treatment age intensity of infection profiles across all age classes
  - Water, sanitation and hygiene (WASH)
  - Diagnostic techniques
  - Prevalence and intensity of infection
  - Costs

## Why do we need intensity data?

- Informs us of the morbidity
- Morbidity control and EPHP goal definitions
  - <5% and <1% prevalence of heavyintensity infections in SAC
- Cannot make assumptions about intensity based on prevalence data
  - Non-linear relationship between prevalence and intensity
  - Can have high prevalence with low or high intensity
  - Could have a small change in prevalence but large change in intensity and vice versa



Turner HC et al. (2017) Evaluating the variation in the projected benefit of community-wide mass treatment for schistosomiasis: Implications for future economic evaluations. *P* & *V*.

\*SAC: 5-14 years of age

## Why do we need intensity data?

- Prevalence and intensity data are needed to determine the optimal treatment strategy and to assess programme progress
  - Needed from SAC and adults, particularly in high prevalence settings



\*SAC: 5-14 years of age

Toor J et al. (2018) The design of schistosomiasis monitoring and evaluation programmes: The importance of collecting adult data to inform treatment strategies for *Schistosoma mansoni*. *PLoS NTDs*.

# Logistical challenges

- Data typically collected from SAC due to financial and programmatic constraints
- Difficulties in collecting adult data
  - Can require more workers, be more time-consuming and challenging to obtain followup samples
- Educating community has proven to be effective in increasing adult participance



# S. mansoni and S. haematobium treatment strategies for EPHP

## EPHP treatment strategy

- Treating annually in low to high prevalence settings
  - School-based treatment: 75% SAC-only; community-wide treatment: SAC and adults
  - Different age profiles of infection
- When is an expansion to community-wide treatment needed for achieving EPHP?



Toor J et al. (*in prep*). Achieving elimination as a public health problem for *Schistosoma mansoni* and *S. haematobium*: When is community-wide treatment required? *JID.* 

Prevalence in SAC prior to treatment	Model recommended treatment strategy for achieving EPHP for <i>S. mansoni</i> and <i>S. haematobium</i>				
Low (<10%)	S. mansoni: <b>75% SAC annual treatment for 0-1 year.</b>				
Moderate (10%–50%)	<ul> <li>S. mansoni: 75% SAC annual treatment for 1-3 years (duration increases with adult burden of infection).</li> <li>S. haematobium: 75% SAC annual treatment for 0-1 year.</li> </ul>				
	<ul> <li>S. mansoni and S. haematobium (baseline SAC prevalence is 50-51%):</li> <li>75% SAC annual treatment for up to 1 - 4 years (1 year for S. haematobium; duration increases with adult burden of infection for S. mansoni).</li> </ul>				
High (≥50%)	<ul> <li>S. mansoni (baseline SAC prevalence &lt; 73% and 59%, for low and high adult burdens of infection, respectively) and S. haematobium (baseline SAC prevalence &lt; 70%):</li> <li>75% SAC annual treatment for 7 years.</li> </ul>				
	S. mansoni and S. haematobium (baseline SAC prevalences > those above): Increase in school-based treatment coverage (i.e. over 75% SAC annual treatment for 7 years) and/or expansion to community-wide treatment. Coverage levels increase with the adult burden of infection.				

Toor J et al. (*in prep*). Achieving elimination as a public health problem for *Schistosoma mansoni* and *S. haematobium*: When is community-wide treatment required? *JID*.

## Optimal treatment strategy



Toor J et al. (*in prep*). Achieving elimination as a public health problem for *Schistosoma mansoni* and *S. haematobium*: When is community-wide treatment required? *JID*.

\*SAC: 5-14 years of age



- Low to moderate prevalence settings with good school enrolment: Community-wide treatment is not necessary to achieve EPHP
  - SAC-only annual treatment for up to 3 years is sufficient
- Certain high prevalence settings (and with low school enrolment): Community-wide treatment is required to achieve EPHP
  - Depends on the epidemiological setting: species present, prevalence prior to treatment and the age profile of infection
- In the absence of interruption of transmission, treatment would have to continue
  - Stopping treatment after achieving EPHP is likely to lead to resurgence

## Risk of resurgence

- Despite achieving EPHP, overall prevalence can still be high
  - Particularly in other age-groups and lower-intensity infections in SAC
- Stopping treatment after achieving EPHP is highly likely to lead to resurgence
  - May be feasible to maintain EPHP with less frequent treatment and WASH
  - Interruption of transmission would alleviate the need for ongoing treatment





# Post-treatment surveillance criteria for predicting *S. mansoni* elimination

# Elimination

- WHO end goal for schistosomiasis
  - Interruption/breaking of transmission
  - Achieved when the incidence of infection is reduced to zero
- Currently little guidance on what to do when stopping treatment programmes
  - Elimination vs resurgence/bounce-back
  - How can we predict whether elimination will occur?



#### **Post-treatment surveillance factors**



**Post-treatment surveillance time point** 

**Community sample size** 

**Treatment programme** Likelihood of elimination

**Diagnostic** Prevalence measured by Kato-Katz

> **Species** Schistosoma mansoni





Positive/negative predictive value (PPV/NPV) proportion of eliminations/bounce-backs detected by the threshold statistic\* that result in long-term eliminations/recrudescence

\*epidemiological measure based on prevalence

#### Prevalence threshold and time point

Sample size = 200,
 population size = 500,
 1000 iterations

1% Kato-Katz prevalence after 2 years gives PPV > 0.9





- Sampling across entire community (all age groups)
  - Population size = 500, 1000 iterations, using 1% threshold 2 years after stopping MDA

Sample size ≥ 200 gives PPV > 0.9



#### Setting impact on elimination

#### Low adult burden

	Coverage of adults (%)					
	0%	20%	40%	60%	80%	95%
0%	NA	NA	NA	NA	NA	NA
20%	NA	NA	NA	NA	NA	NA
40%	NA	NA	NA	NA	NA	NA
60%	13	12	11	11	11	11
80%	11	9	9	9	9	9
95%	10	8	8	8	8	8
	0% 20% 40% 60% 80% 95%	Co 0% NA 20% NA 40% NA 60% 13 80% 11 95% 10	Covera           0%         20%           0%         NA           0%         NA           20%         NA           40%         NA           40%         NA           40%         13           60%         11           9         95%	Coverage of           0%         20%         40%           0%         NA         NA         NA           20%         NA         NA         NA           20%         NA         NA         NA           40%         NA         NA         NA           40%         NA         NA         NA           60%         13         12         11           80%         11         9         9           95%         10         8         8	Coverage of adult           0%         20%         40%         60%           0%         NA         NA         NA           0%         NA         NA         NA           20%         NA         NA         NA           40%         NA         NA         NA           40%         NA         NA         NA           60%         13         12         11           80%         11         9         9         9           95%         10         8         8         8	Coverage of adults (%)           0%         20%         40%         60%         80%           0%         NA         NA         NA         NA         NA           0%         NA         NA         NA         NA         NA           20%         NA         NA         NA         NA         NA           20%         NA         NA         NA         NA         NA           40%         NA         NA         NA         NA         NA           60%         13         12         11         11         11           80%         11         9         9         9         9           95%         10         8         8         8         8

		Coverage of adults (%)							
	()		0%	20%	40%	60%	80%	95%	_
	6	0%	NA	NA	NA	NA	NA	NA	
Low	SAC	20%	NA	NA	NA	NA	15	15	
transmission		40%	8	8	8	8	7	7	
cotting		60%	5	5	5	5	5	5	
setting		80%	4	4	3	3	3	3	
	20	95%	3	3	3	3	2	2	

#### High adult burden

#### Coverage of adults (%)

	0%	20%	40%	60%	80%	95%
0%	NA	NA	NA	NA	NA	NA
20%	NA	NA	NA	NA	NA	NA
40%	NA	NA	NA	14	13	12
60%	NA	NA	13	11	10	10
80%	NA	15	11	10	9	9
95%	NA	14	11	9	9	8

	Coverage of adults (%)										
	0%	0% 20% 40% 60% 80% 95%									
0%	NA	NA	NA	NA	NA	15					
20%	NA	15	11	9	8	7					
40%	NA	9	7	6	5	5					
60%	12	7	5	4	4	3					
80%	10	6	4	3	3	3					
95%	9	5	4	3	2	2					

- The projected number of years of annual treatment required to achieve elimination of S. mansoni.
  - Results assume 5% systematic non-compliance.
  - NA = not achievable within
     15 years of annual treatment.

Turner et al. (2017) Evaluating the variation in the projected benefit of community-wide mass treatment for schistosomiasis: Implications for future economic evaluations. *P* & *V*.



- Burden of infection in adults will impact coverage levels required to reach elimination
  - High prevalence setting: treating 85% SAC + 40% adults for 15 years annually





- Sampling across entire community for low and high adult burdens of infection
  - Population size = 500, 1000 iterations, using 1% threshold 2 years after stopping MDA

Sample size ≥ 200 gives PPV > 0.9



#### Treatment programme

Prevalence threshold changes with treatment programme

- Higher chance of elimination being achieved then higher threshold
- Lower chance of elimination being achieved then lower threshold



### **Post-MDA surveillance**



#### Post-treatment surveillance threshold and time point

1% prevalence threshold by Kato-Katz after at least 2 years

#### **Community sample size**

200 individuals across entire community (population size 500 - 1000)

#### **Treatment programme**

Likelihood of achieving elimination impacts threshold

#### **Species** Schistosoma mansoni



- Post-MDA surveillance criteria for S. mansoni: 1% Kato-Katz prevalence threshold after at least 2 years with a sample size of 200 individuals → 90% certainty of elimination
- Prevalence data are sufficient when checking for elimination
  - However pre-treatment, prevalence and intensity data are informative for determining the treatment strategy required
  - Intensity data also needed for tracking achievement of the EPHP goal



#### Insights from health economics

## Insights from health economics

- Economic evaluations are important in informing NTD control strategies
- Costs are not always constant and can change
- Need to think about this when considering how generalizable costs are
- Valuing the unpaid contribution of community health volunteers
- Economies of scale and scope are important when considering MDA costs
   Ignoring them can be misleading

Turner HC et al. (2018) Economic evaluations of mass drugadministration: The importance of economies of scale and scope. *CID.*Turner HC et al. (2018) Valuing the Unpaid Contribution of CommunityHealth Volunteers to Mass Drug Administration Programs. *CID.* 

#### **Economies of scale**





- Cost data across six districts over three years from Uganda for STH
  - Can be seen in other data
- Economies of scale: Cost per treatment decreases as the number of people treated increases

Turner HC et al. (2018) Economic evaluations of mass drug administration: The importance of economies of scale and scope. *CID*. Brooker S et al. (2008) Cost and cost-effectiveness of nationwide school-based helminth control in Uganda: intra-country variation and effects of scaling-up. *Health Policy Plan*.





- The lower the cost per case averted, the higher the cost-effectiveness.
- Account for economies of scale: cost-effectiveness of MDA increases as the intervention is scaled up
- Ignore economies of scale: cost-effectiveness decreases as the intervention is scaled up

# Economies of scope

- Reduction in the cost per treatment when delivering more than one intervention at once
  - Integrated control programmes for example, administering treatment for both schistosomiasis and STH within the same programme (rather than separate vertical programmes)



Turner HC et al. (2018) Economic evaluations of mass drug administration: The importance of economies of scale and scope. *CID.* Evans D et al. (2011) Cost-effectiveness of triple drug administration (TDA) with praziquantel, ivermectin and albendazole for the prevention of neglected tropical diseases in Nigeria. *Ann Trop Med Parasitol.* 



- Average cost per treatment increases as the number treated is increased
  - Opposite to economies of scale
- Programme reaches full capacity leading to resources being overstretched and inefficiencies
- Or when expanding into harder-to-reach areas (from urban to rural settings) which can be more expensive
- Important when scaling up elimination campaigns







- Although Kato-Katz is seen as the cheaper test, given the increased sensitivity of CCA, this may outweigh costs in long term
  - CCA test is faster, less labour intensive
- However, the costs vary in different settings and costs per test are not constant
- Need data relating diagnostic techniques and more accurate cost data



Turner HC et al. (2017) Economic Considerations for Moving beyond the Kato-Katz Technique for Diagnosing Intestinal Parasites As We Move Towards Elimination. *Trends Parasitol.* Turner HC et al. (2017) Evaluating the variation in the projected benefit of community-wide mass treatment for schistosomiasis: Implications for future economic evaluations. *P & V.* 



- Accurate data on which age-groups are infected are required to assess for the most cost-effective treatment strategy
- Data needs to be representative of the age-group
  - Only sampling high-risk adults → overestimate benefit of community-wide treatment



Turner HC et al. (2017) Evaluating the variation in the projected benefit of community-wide mass treatment for schistosomiasis: Implications for future economic evaluations. P & V.



#### Policy impact and future work

## Impact of modelling work

- Treatment strategies required have been shown
- Importance of adult treatment has been recognised
- Data requirements highlighted
- Modelling has informed Geshiyaro project
- NTD Modelling Consortium engagement with WHO
- WHO guidelines currently under revision
- WHO discussions
  - Mapping protocols
  - Surveillance protocols for verification of elimination



# Future work

- Sampling approaches
  - Specific age-groups or occupations
- Investigate other diagnostics
  - More sensitive diagnostics likely to have higher threshold
- Multiple communities
  - Migration, spatial heterogeneities
- Investigate acquired immunity
- Adding in zoonotic reservoirs



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