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Can deworming at prenatal clinics prevent morbidity from infections with soil-transmitted helminths in women of reproductive age?

Carolin Vegvari on behalf of the NTD Modelling Consortium STH team

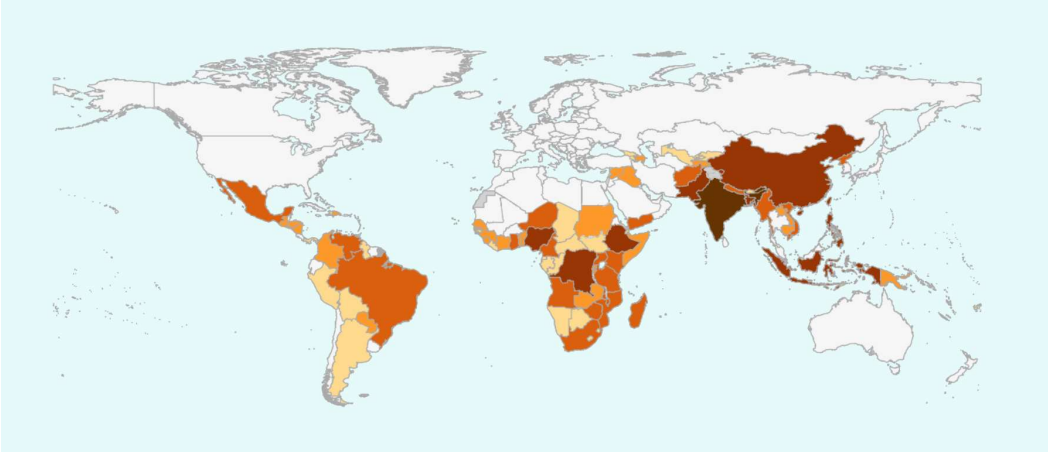
Contents

- Soil-transmitted helminths and epidemiology and morbidity
- WHO 2030 goals for soil-transmitted helminths
- Research question:
  - Can deworming during HPV vaccination and at prenatal and maternity clinics prevent morbidity from STH infections in WRA?
- Study design
- Results
- Conclusions

Morbidity from STH infections

- ~ 1.5 billion people are infected with STH worldwide
- Morbidity is associated with moderate-to-heavy intensity (MHI) infections
- Morbidity manifests as diarrhoea, abdominal pain, malnutrition, physical weakness, and impaired growth and development
- Morbidity from hookworm infections is associated with anaemia
  - Can lead to adverse pregnancy outcomes including premature births, low birth weight, and impaired lactation

How can we strengthen the connection between research and programming to beat STH?



WHO Global Health Observatory: STH prevalence 2018

WHO 2030 goals for STH and treatment strategies

Target 1: Achieve and maintain elimination of STH morbidity in pre-school and school age children

Target 2: Establish an efficient STH control programme in adolescent, pregnant and lactating women

Current treatment strategy:

School-based deworming of preSAC and SAC

Moderate prevalence Deworm 1x per year	High prevalence Deworm 2x per year

Additional treatment of WRA:

Deworming of adolescent girls at HPV vaccination

Deworming of WRA at pre-natal and maternity clinics

Research question

Can deworming during HPV vaccination and at prenatal and maternity clinics prevent morbidity from hookworm infections in WRA?

Study design

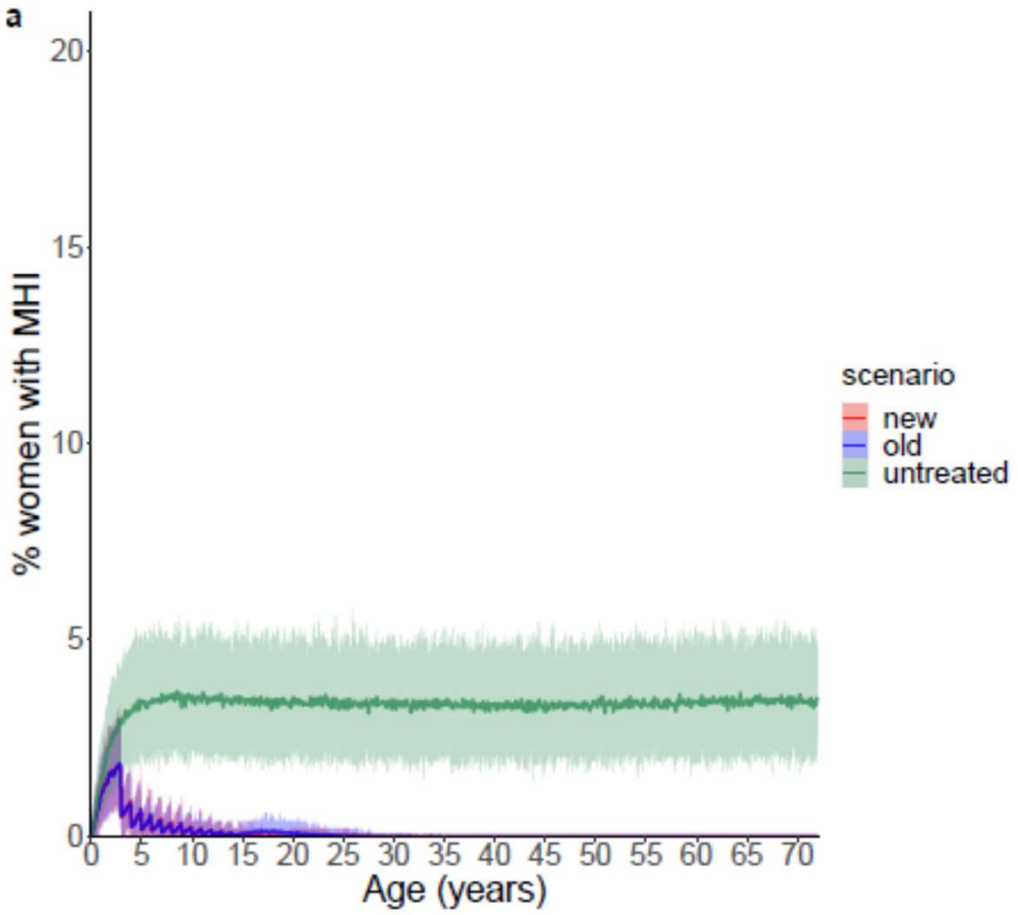
- Cohort model follows girls/women from birth to age 70
- External force of infection derived from two stochastic individual-based models of hookworm transmission and treatment
- Models differ in assumptions on age-intensity profile of infection and density-dependent fecundity of female worms
- Morbidity is measured in terms of prevalence of MHI infections

Treatment scenarios:

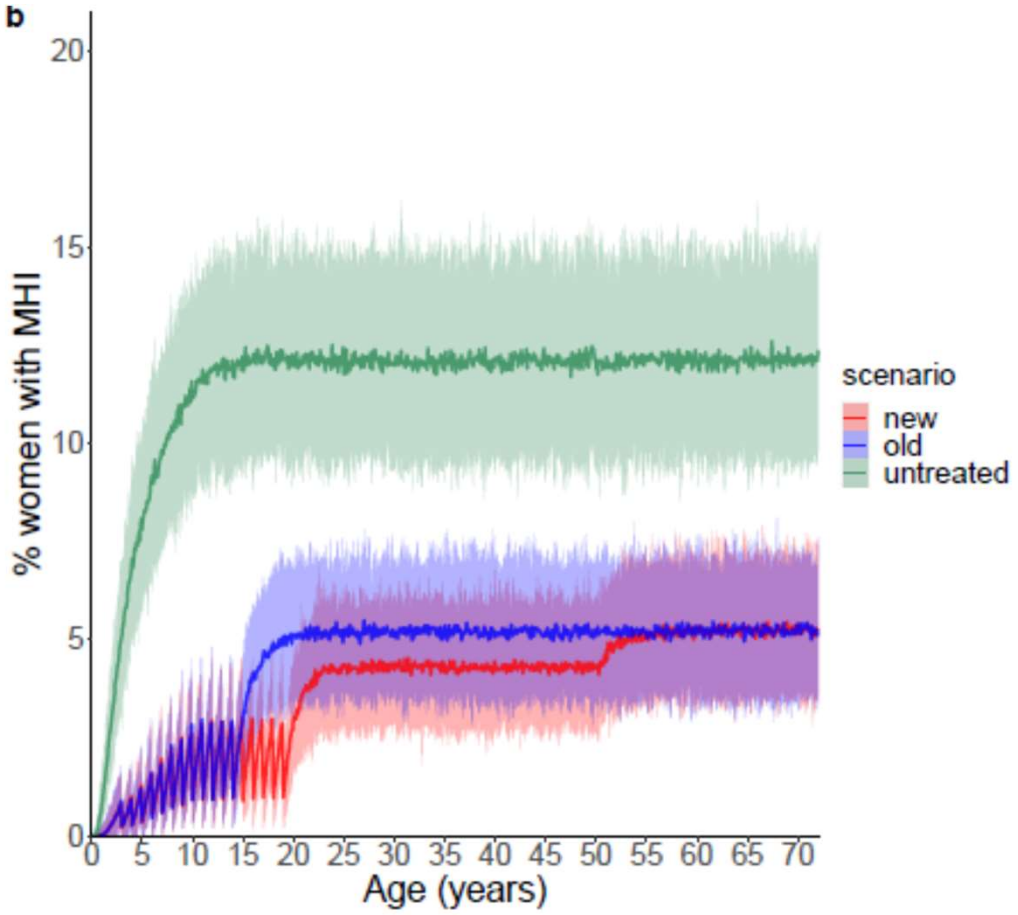
Scenario 1:	Scenario 2:	Scenario 3:
Moderate prevalence setting School-based deworming 1x per year With/without deworming of WRA according to new recommendations	Moderate prevalence setting School-based deworming 2x per year With/without deworming of WRA according to new recommendations	High prevalence setting School-based deworming 2x per year With/without deworming of WRA according to new recommendations

Results: Moderate prevalence, treat 1x per year

Force of infection from Model 1
(Imperial College London)

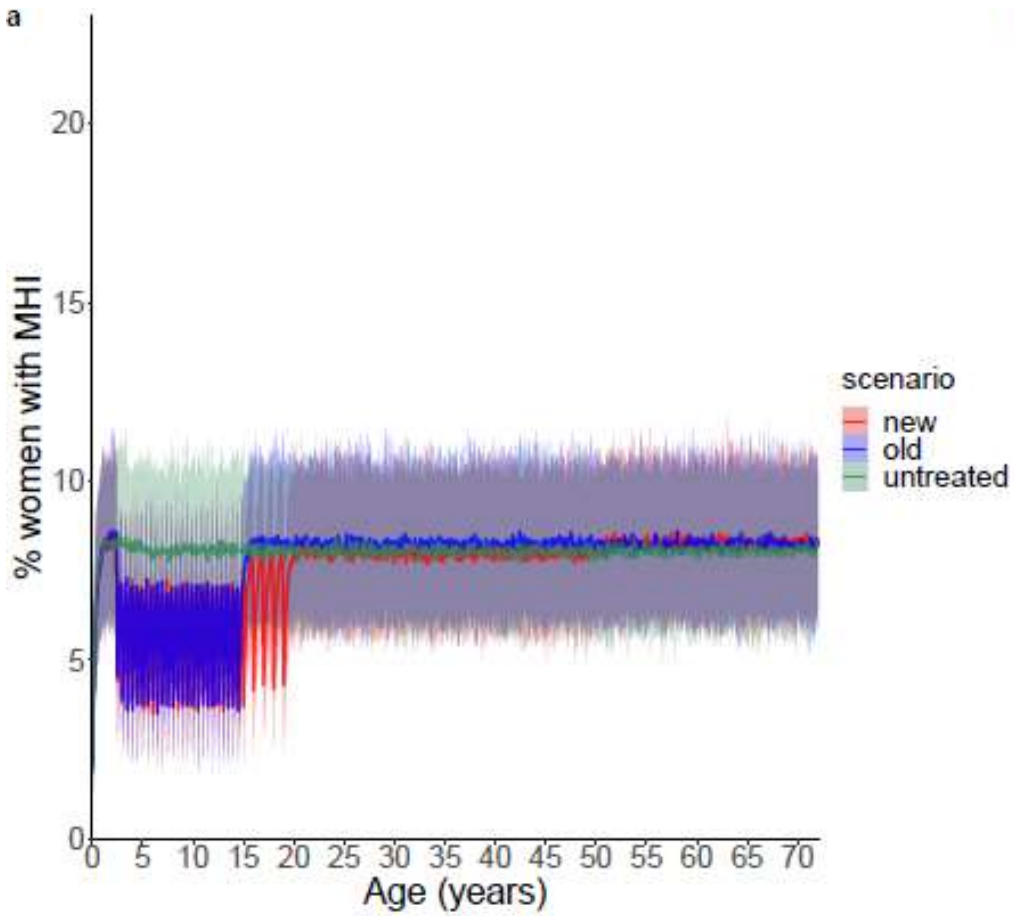


Force of infection from Model 2
(Erasmus MC)

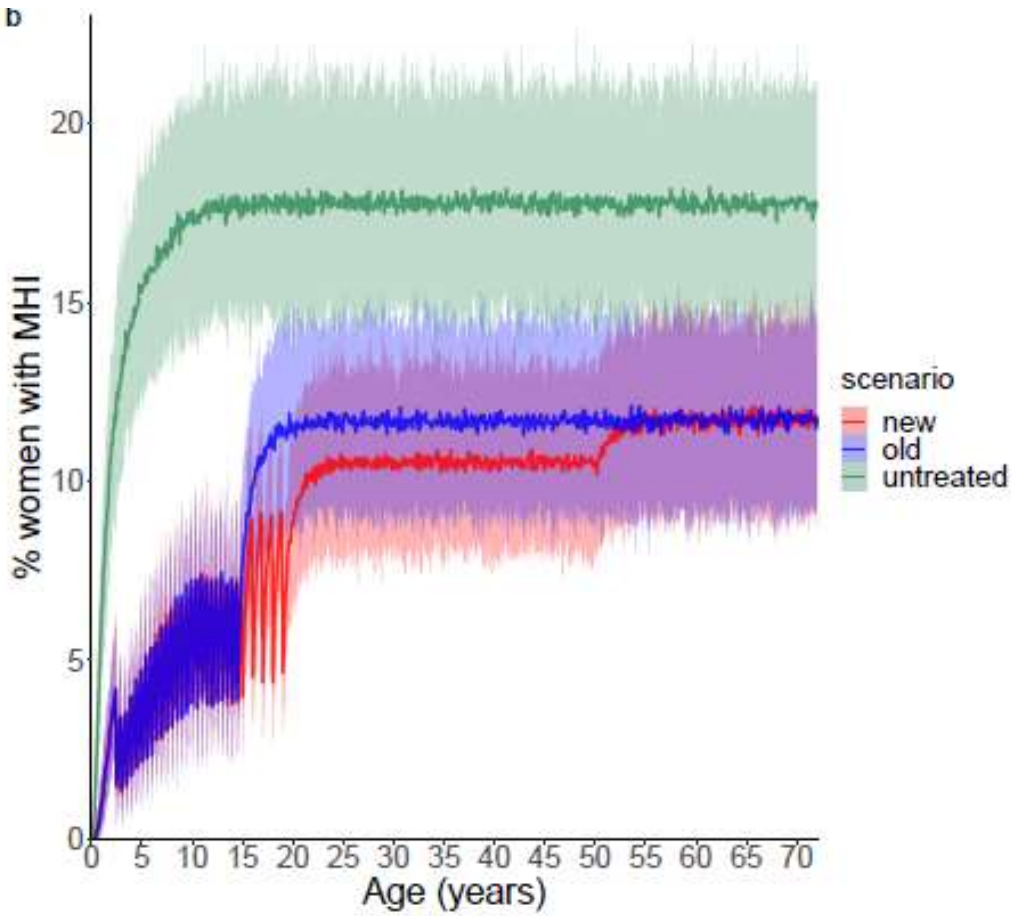


Results: High prevalence, treat 2x per year

Force of infection from Model 1
(Imperial College London)

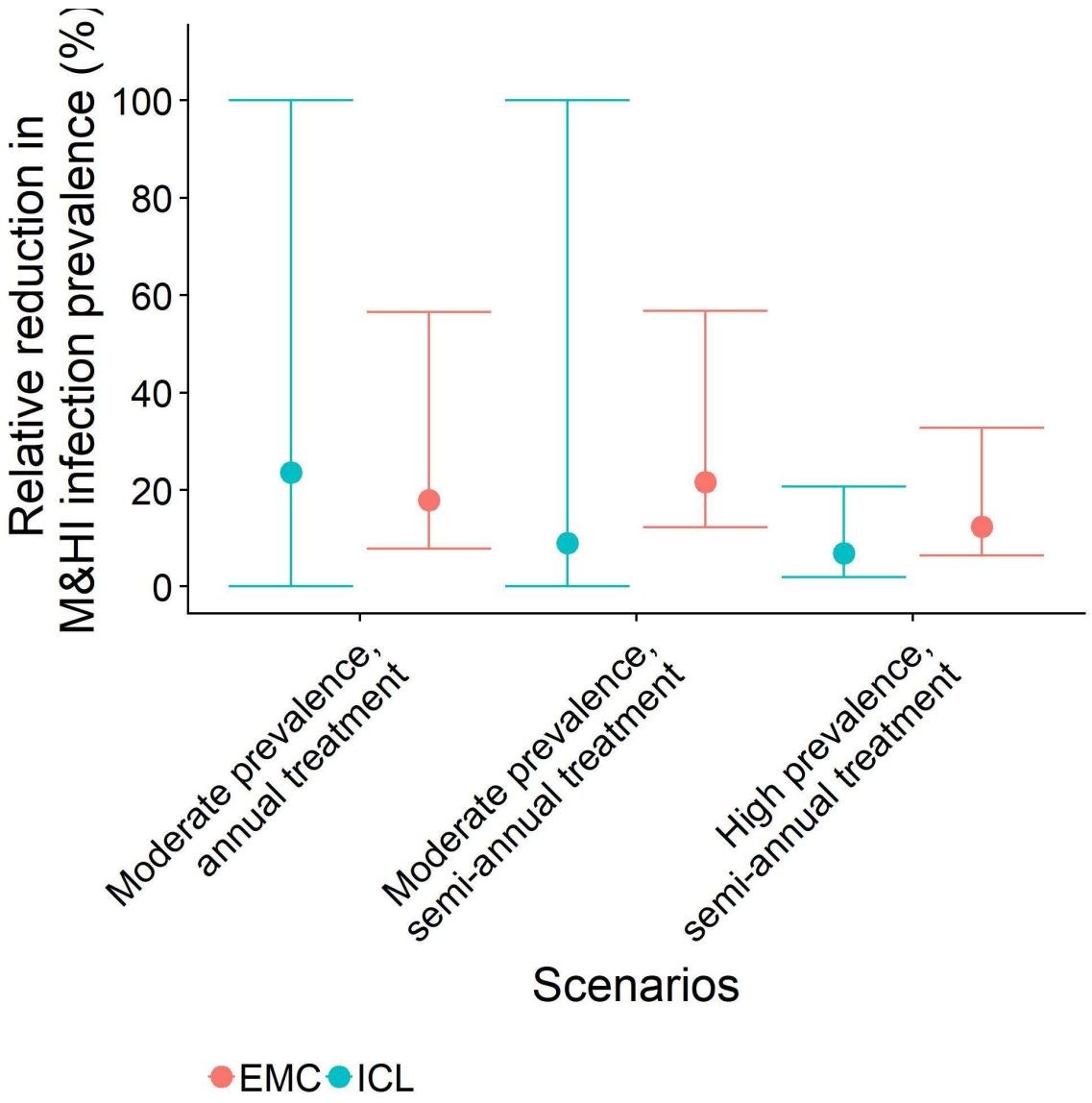


Force of infection from Model 2
(Erasmus MC)



Reasons for differences in model predictions

	Model 1 (Imperial College London)	**Model 2 (Erasmus MC)**	**Result**
Age-intensity profile	Uniform across all age classes	Higher intensity in adults than in SAC	Stronger effect of school-based treatment in Model 1
Density dependent fecundity of worms	Exponential saturation	Hyperbolic saturation	Stronger effect of treatment in high-prevalence settings in Model 2
Distribution of worm lifespan	Exponential	Weibull	Worm population is more robust to extinction by treatment in Model 2



Conclusion

Our quantitative analysis shows how research can improve programming for STH.

Deworming of WRA during HPV vaccination and at prenatal and maternity clinics can **reduce morbidity over the reproductive lifespan by about 20%.**

The reduction is not massive but significant and can be achieved in current healthcare settings even in low-income countries at very **little or no additional cost**.

Acknowledgements

Imperial College London:
Sumali Bajaj, James Truscott, Robert Hardwick, Roy Anderson

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Federica Giardina, Luc Coffeng, Veronica Malizia, Sake de Vlas

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Deirdre Hollingsworth

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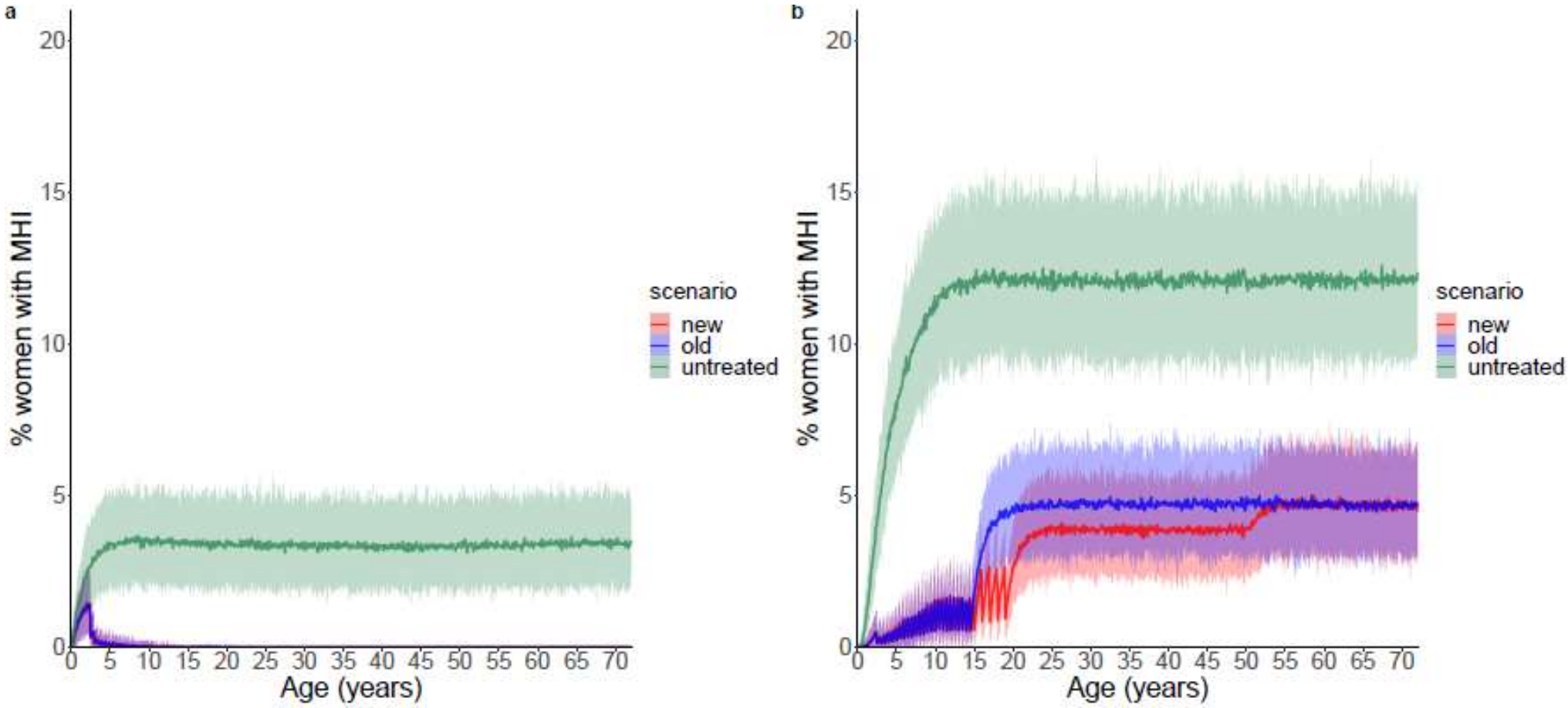
DeWorm3 Grant, Natural History Museum
UK Medical Research Council

Results: Moderate prevalence, treat 2x per year



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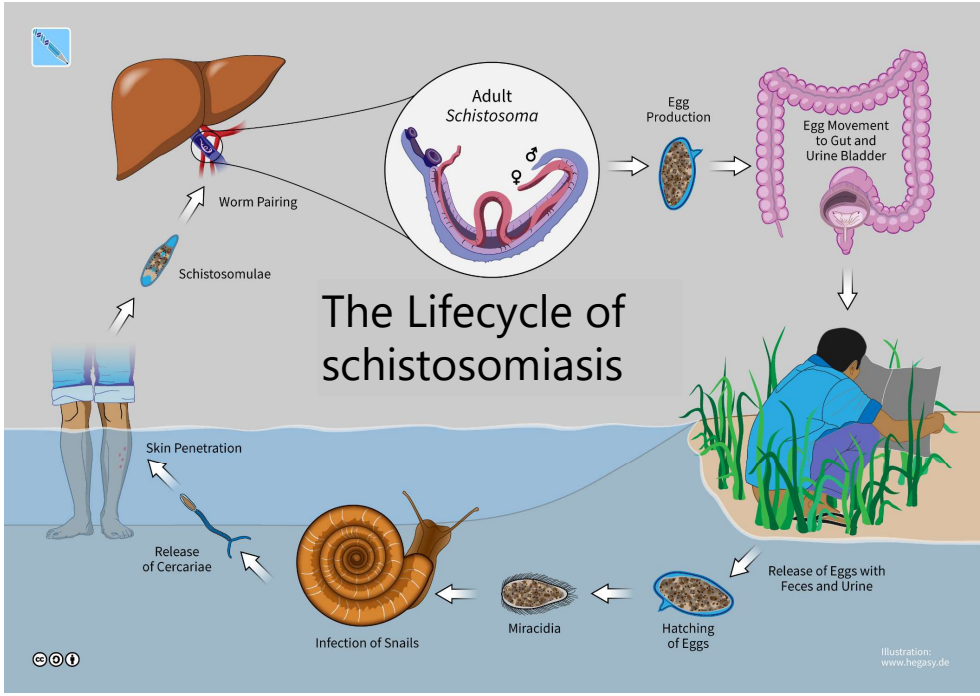
Evaluating the impact of biannual school-based and community-wide treatment on urogenital schistosomiasis in Niger

Anna Phillips, Zilahatou Tohon, Neerav Dhanani, Boubacar Sofo, Issa Gnandou, Boubacar Sidikou, Adamou Garba Noma, Bassirou Madougou, Oumarou Alto, Hannatou Sebangou, Kader Halilou, Roumanatou Andia, Amadou Garba, Alan Fenwick, Amina Hamidou

8th – 10th September 2020

Background

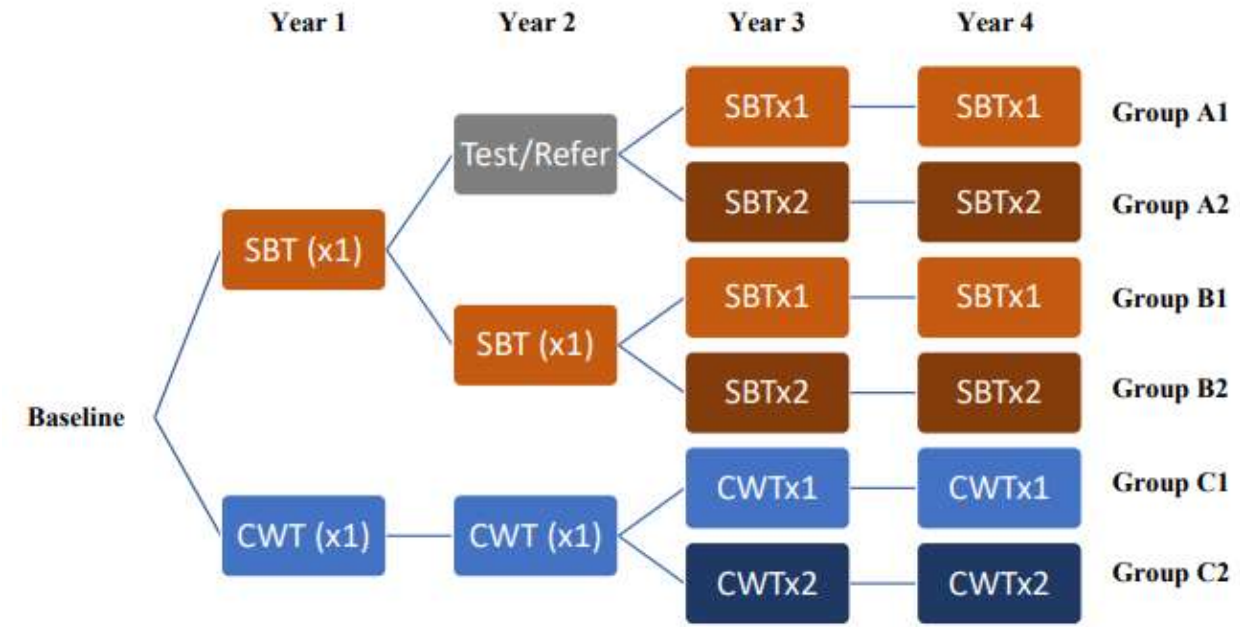
- Human schistosomiasis is a chronic, water-associated parasitic disease.
- Approx. 3.2 million people are infected with schistosomiasis in Niger alone.



- The main species is urogenital schistosomiasis (*Schistosoma haematobium*) in all regions of Niger.
- The main control strategy against schistosomiasis is school-based treatment (SBT) with praziquantel (PZQ).
- There is growing evidence of infection in pre-school-aged children (SAC) adults and their potential role in sustaining transmission.
- There is also debate around the optimal frequency of PZQ treatment.

Study design

- A cluster-randomised trial: Six possible combinations of annual and biannual community-wide treatment (CWT), SBT, and treatment holidays.
- A total of 225 communities were surveyed over five years with 100 children aged 9-12 years sampled each year.
- In addition, 100 children aged 5-to-8 years in their first year of school and 50 adults (aged 20-to-55 years) were tested in the first and final year.



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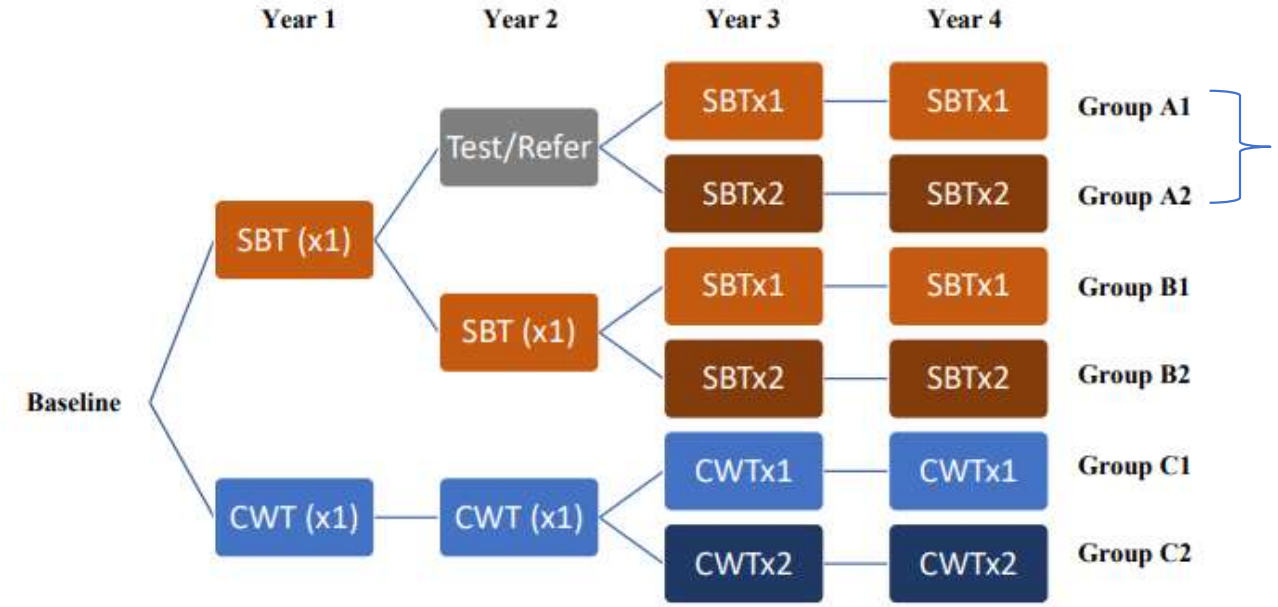

3x SBT in **MODERATE** endemic areas

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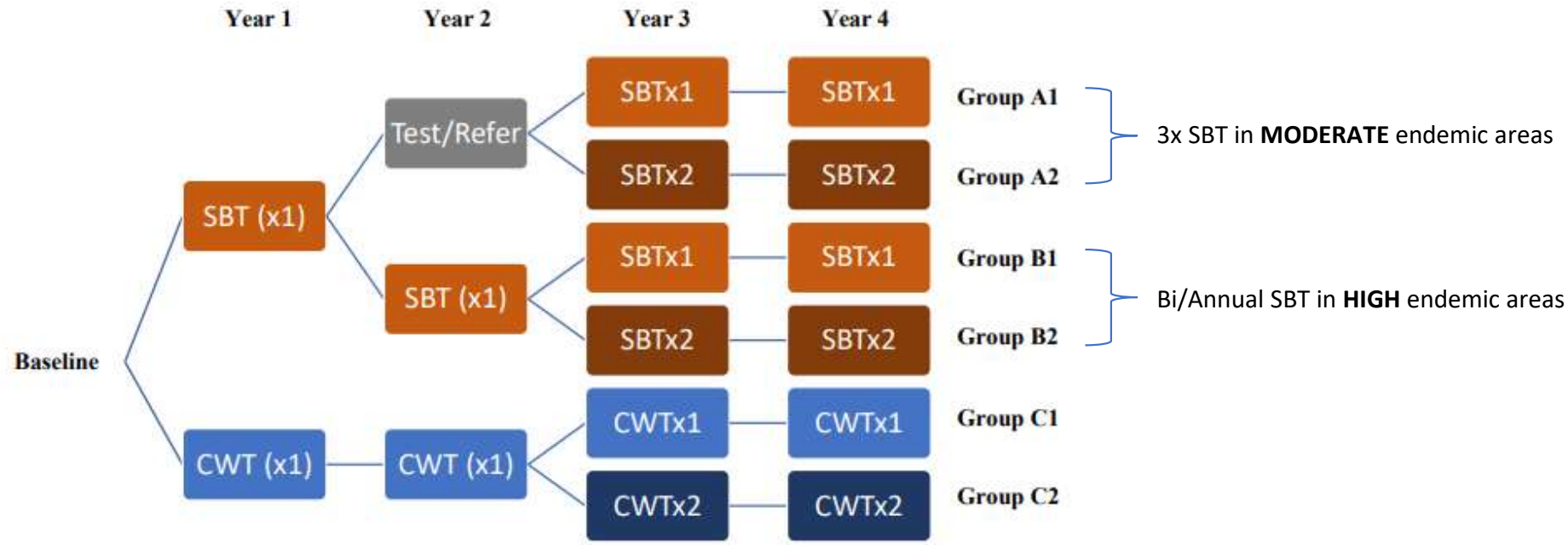

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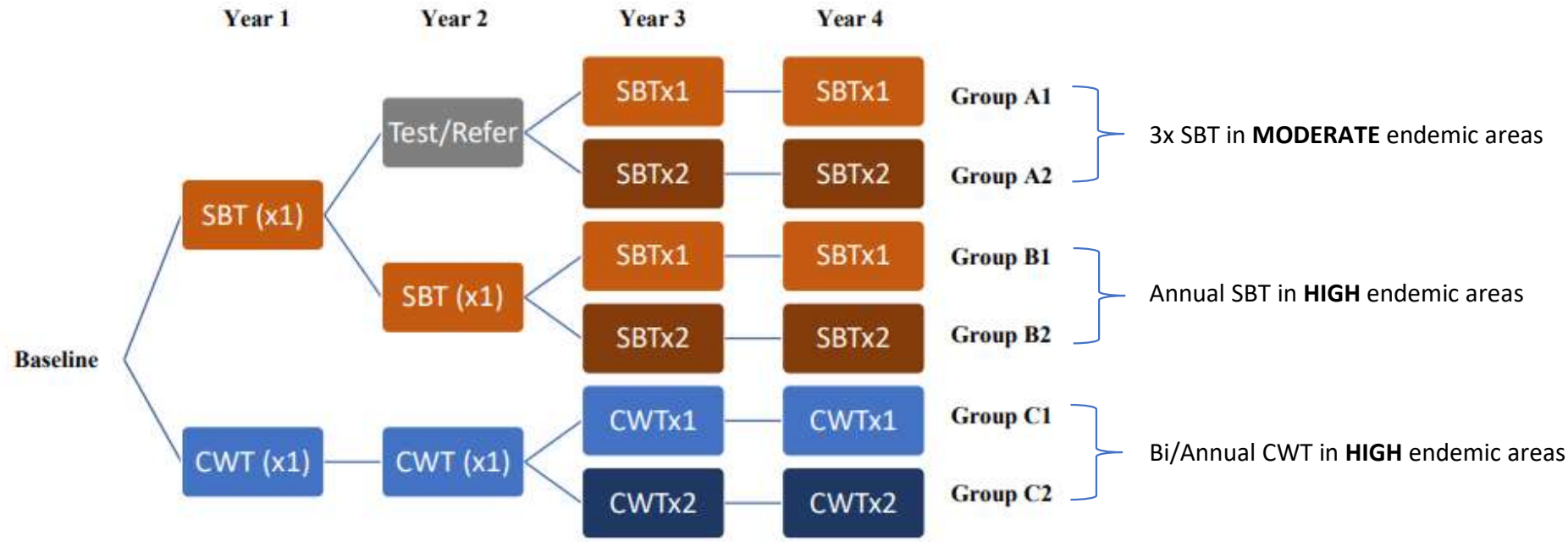
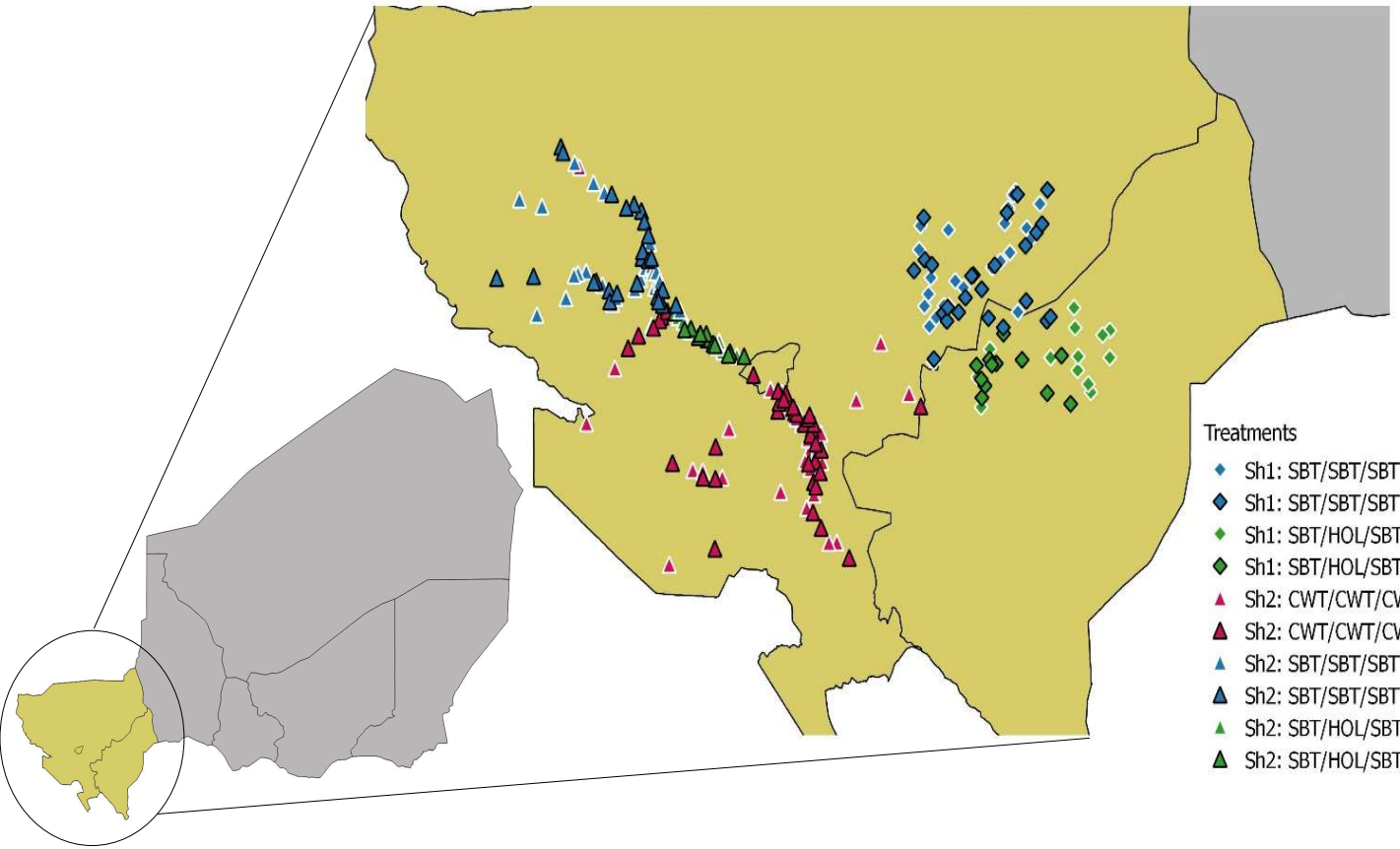


Map of the study zone



Sample characteristics by study year

	Variable	Baseline (2011)	Year 2 (2012)	Year 3 (2013)	Year 4 (2014)	Year 5 (2015)
5-8 years	No. of individuals sampled	20,220				22,364
	Proportion infected with *S.haematobium* %	17.2				9.54
	Proportion heavy intensity infection %	1.93				1.07
	Arithmetic mean*	1.08				0.62
9-12 years	No. of individuals sample	20,931	21,833	21,620	21,715	22,132
	Proportion infected with *S.haematobium* %	15.8	9.57	17.6	8.26	9.89
	Proportion heavy intensity infection %	1.32	0.45	1.35	0.67	0.66
	Arithmetic mean egg count*	3.05	1.27	3.27	1.42	1.45
Adults (20-55 years)	No. of individuals sampled	7,041				9,955
	Proportion infected with *S.haematobium* %	11.3				4.95
	Proportion heavy intensity infection %	0.50				0.28
	Arithmetic mean*	4.61				2.05

9- to- 12- year olds cross-section

Summary of infection change in 9-12 year olds

Variable	Group					
	A1	**A2**	**B1**	**B2**	**C1**	**C2**
No. of villages sampled	38	37	37	38	37	38
Prevalence at baseline (%)	3.7	4.6	24.5	22.5	14.3	23.4
Prevalence of heavy infection at baseline (%)	0.29	0.28	1.86	1.93	0.86	2.50
Prevalence at Year 5 (%)	0.6	0.2	23.2	13.4	11.5	10.5
Prevalence of heavy infection at Year 5 (%)	0.13	0.03	1.77	0.64	0.57	0.83
Absolute difference prevalence at Year 5 and baseline	-3.1	-4.4	-1.3	-9.1	-2.8	-12.9
Relative difference in prevalence at Year 5 and baseline (% change)	**-83.8**	**-95.7**	**-5.3**	**-40.4**	**-19.6**	**-55.1**
Egg reduction rate (1-Year 5 intensity/baseline)	0.82	0.9	0.12	0.73	0.23	0.59

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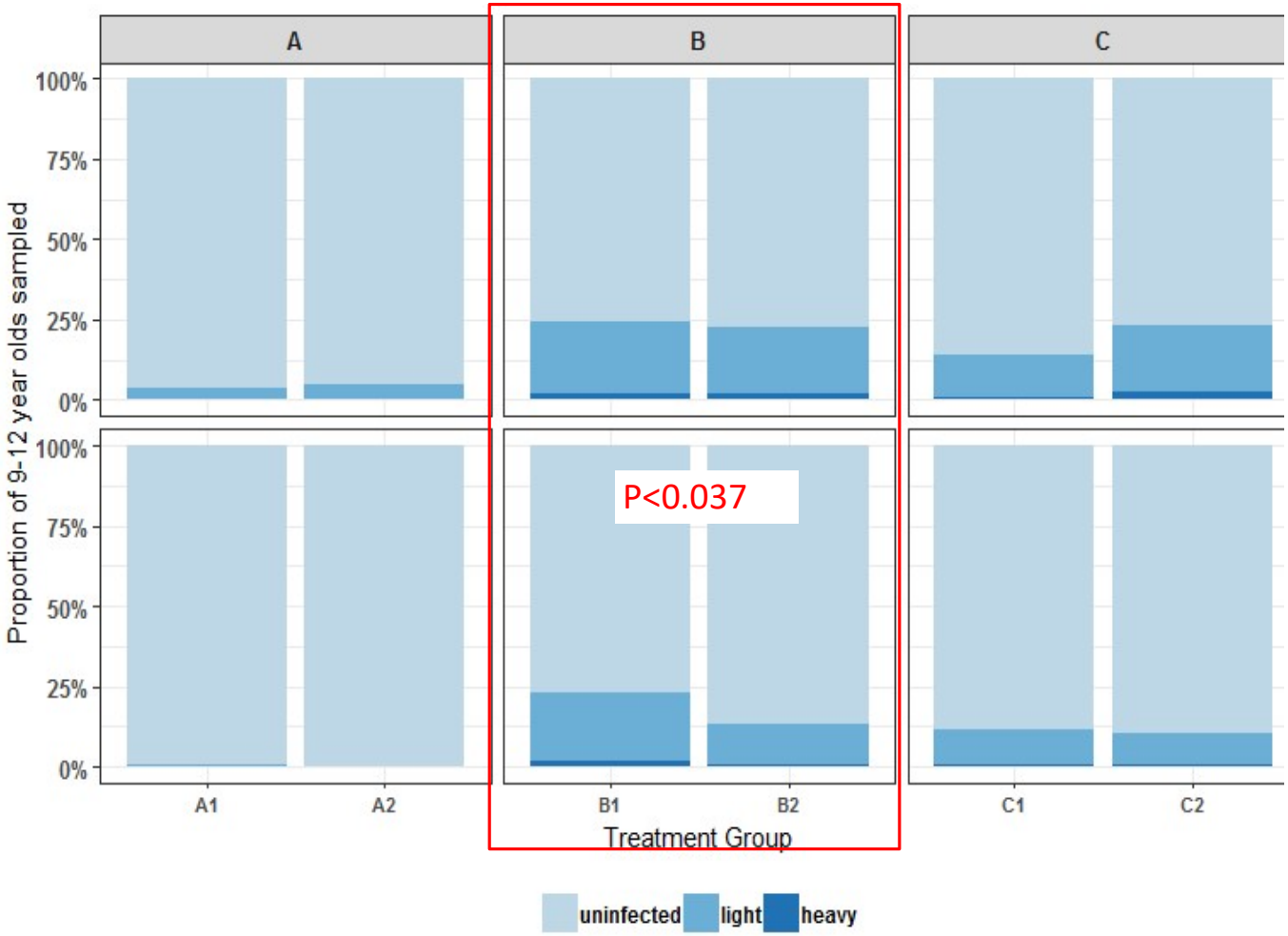
Infection status by treatment group baseline to Year 5

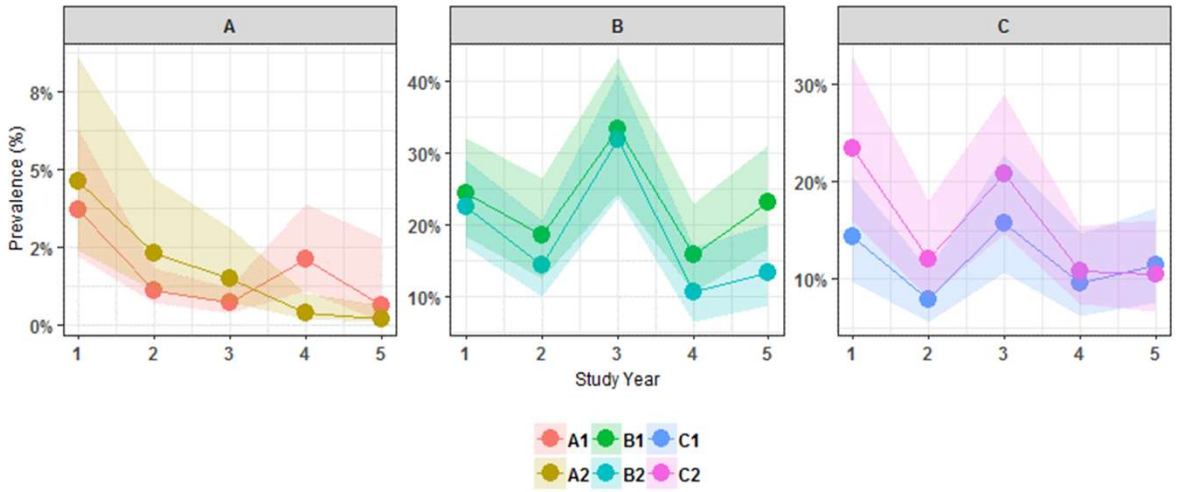


Year 1/Baseline

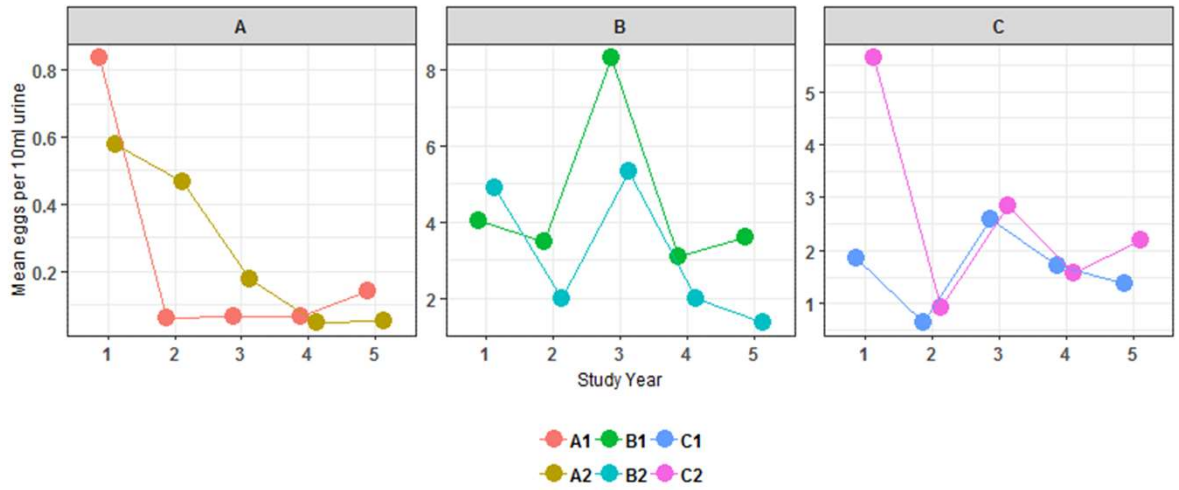
Year 5

Prevalence (a) and intensity (b) by study arm over time (9-12 year olds only)

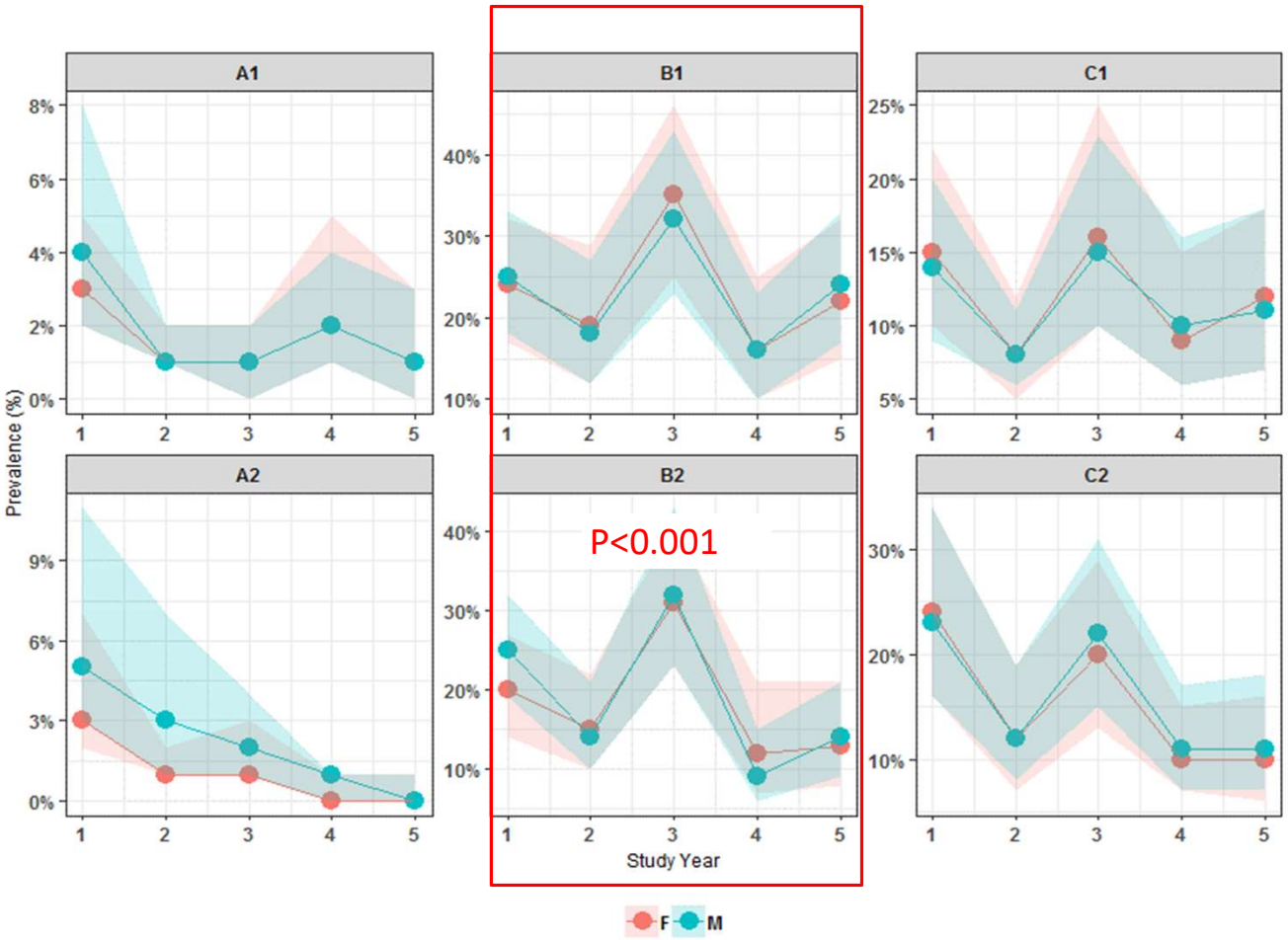
a



b

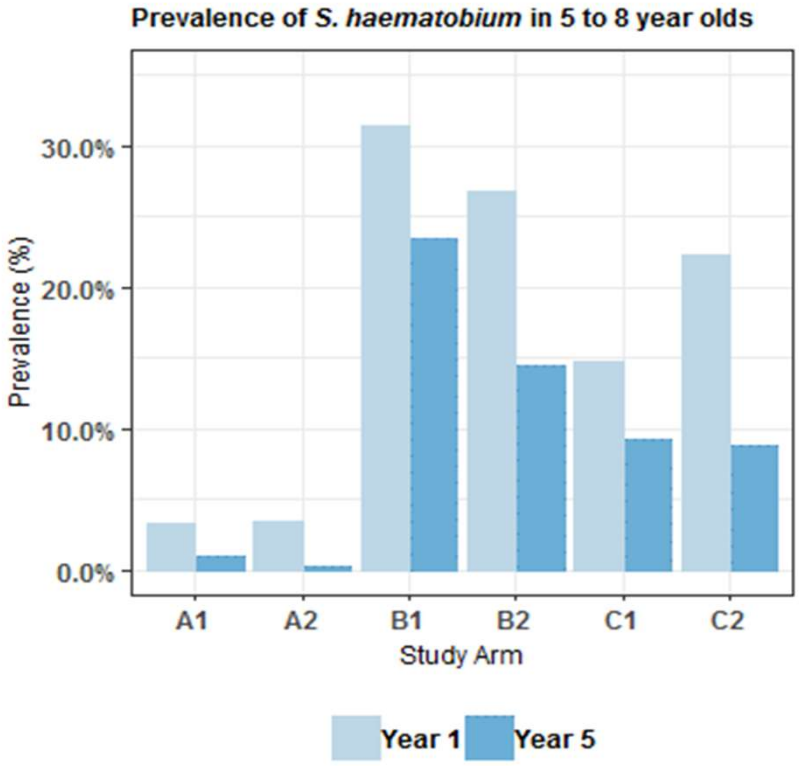


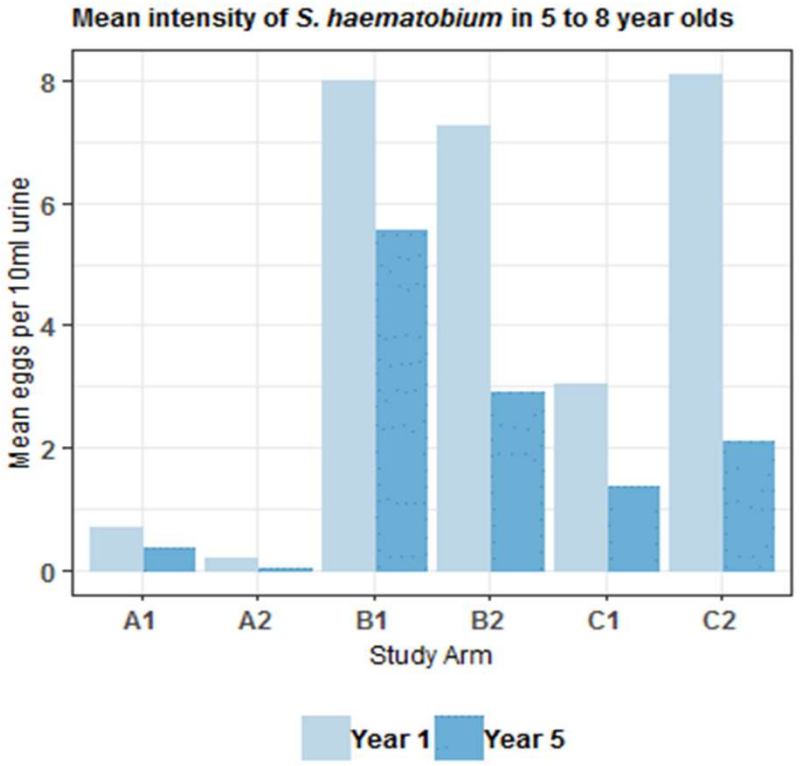
Prevalence by gender (blue=boys and red=girls) over time



First Year students (5-8 years old)

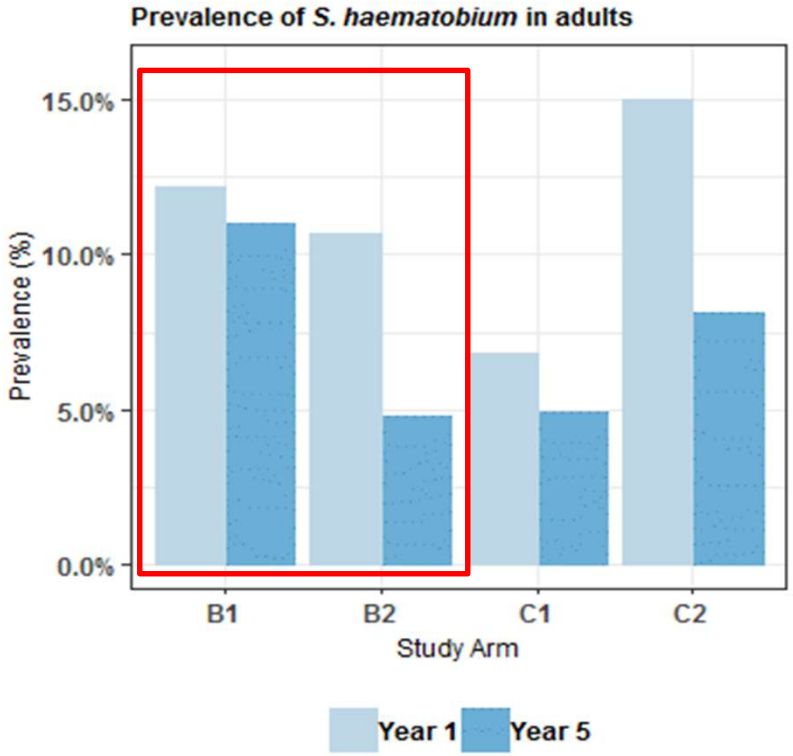
Infection in first-year students at baseline & Year 5 by study arm

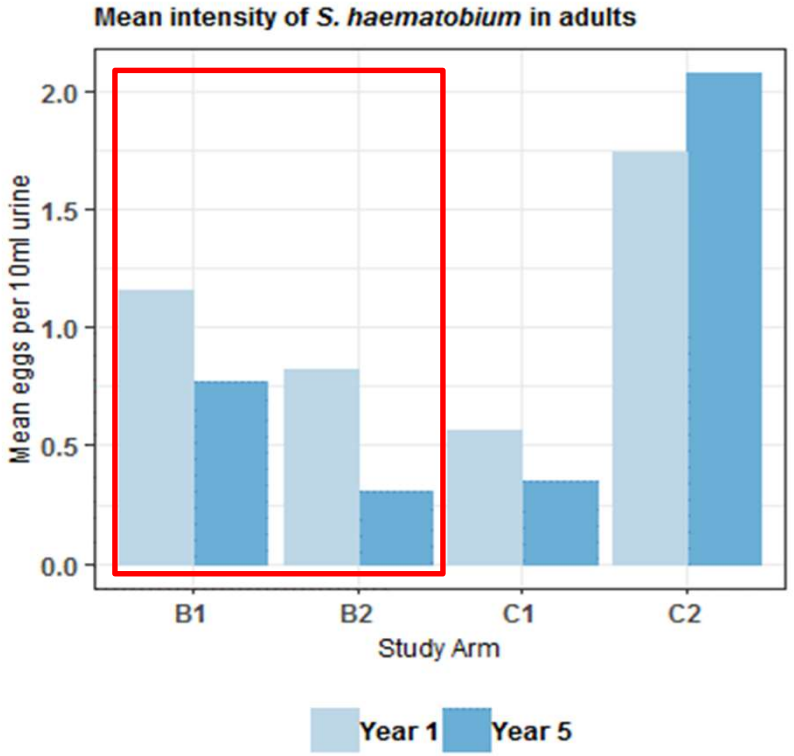




Adults (20-55 years old)

Infection in adults at baseline & Year 5 by study arm





Take home messages

- No statistically significant difference between arms with once or twice years treatment (community or school-based) in areas with **low** endemicity

- Significant impact on infection reduction from biannual vs. annual treatment in areas of **moderate to high infection**

- Prevalence decreased among adults in SBT areas, implying the rate of transmission in the whole community has been reduced.

Strengthening the connection between research and programming to beat NTDs

Current 2020 WHO Goal	Morbidity control: <5% prevalence of heavy intensity infections in SAC
Proposed 2030 WHO Goal	Elimination as a public health problem (EPHP): <1% prevalence of heavy intensity infections in SAC
How does this research move us towards the WHO road map targets?	Heavy infections were <1% in all arms at Year 5 in this study.
How can this research be used by implementors to strengthen health systems?	Prevalence and intensity of infections across all age groups (full age profile) remains poorly researched.
What further research is required to achieve shared goal?	Stopping treatment after achieving EPHP will likely lead to resurgence of infection. Elimination of transmission remains to be defined. Levels of systematic non-adherence to treatment remains unknown as well as ideal size of implementation unit.
How can research and programming better support one another?	Research Compliance: Understand and comply with WHO/ governmental regulations governing research. Data Management: Manage research data effectively and transparently throughout the research-including providing open access to research data, models, and code. Communication: Be transparent when communicating with other researchers and policy makers.

With thanks

- **Schistosomiasis Control Initiative**: Neerav Dhanani, Wendy Harrison, Alan Fenwick
- **University of Georgia/SCORE**: Dan Colley, Sue Binder, Carl Campbell, Charlie King
- The **laboratory technicians** for all their support and hard work in the field.
- The **health, education and village authorities of all communities.**
- Finally, we thank **all the children, parents, teachers and village leaders who participated in this study**.

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NATURAL HISTORY MUSEUM

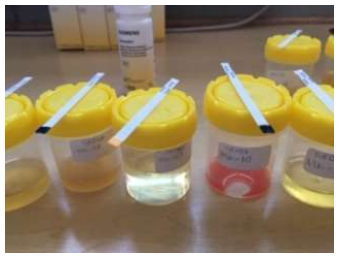
LONDON CENTRE FOR NEGLECTED TROPICAL DISEASE RESEARCH

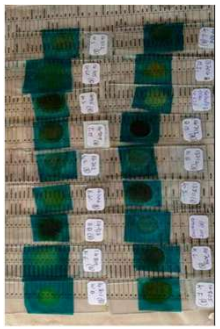
What tools are needed for schistosomiasis transmission monitoring as we move towards elimination?

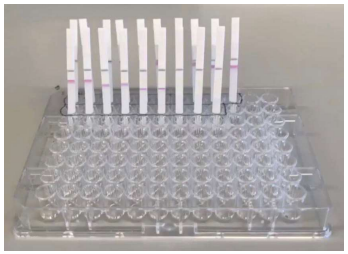
Diagnostics

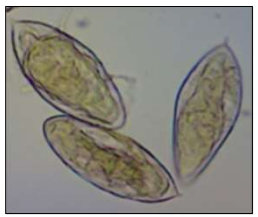
Bonnie Webster

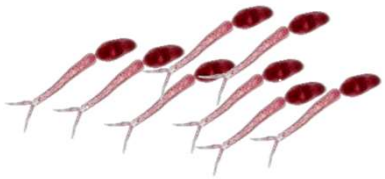
Xenomonitoring

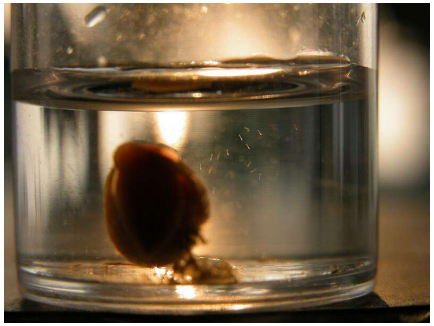












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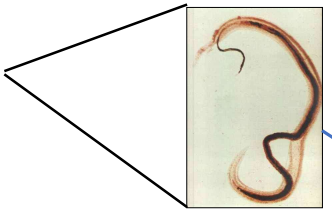
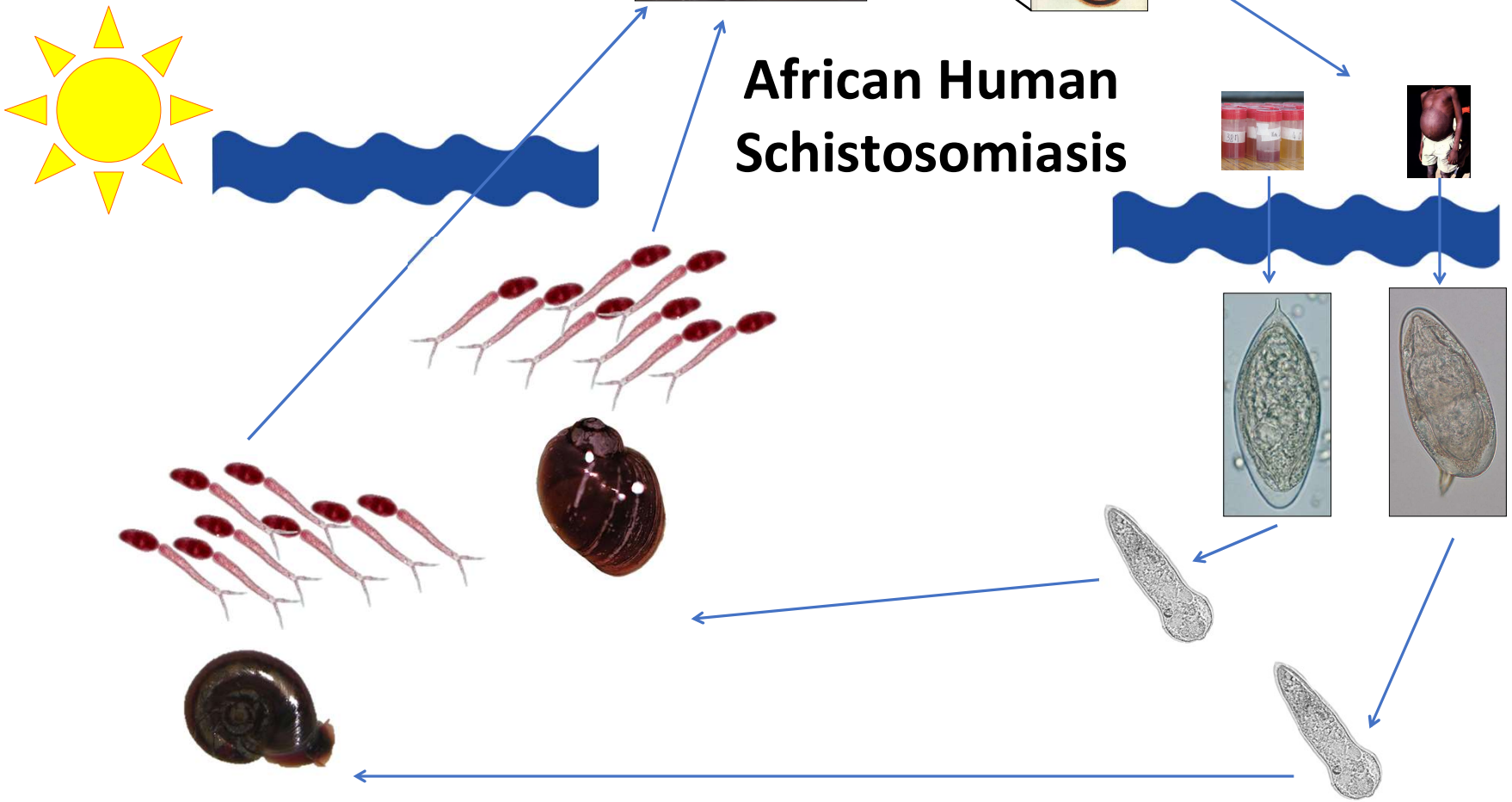
- Complexed life-cycle that makes control difficult
- Current control is via MDA but to reach and maintain elimination other interventions are vital

- >200 million infected
- Disease is chronic with morbidity associated in intensity of infection



African Human Schistosomiasis



ENDING the **NEGLECT**
to **ATTAIN** the **SUSTAINABLE**
DEVELOPMENT GOALS

A road map for
neglected tropical diseases
2021–2030

World Health Organization

We need to strengthen the connection between research and programming to support schistosomiasis elimination?

Disease-specific targets

Targets relevant to individual diseases

Disease	Indicator	2020	2023	2025	2030
TARGETED FOR ELIMINATION AS A PUBLIC HEALTH PROBLEM (public health problem)					
Schistosomiasis	Number of countries validated for elimination as a public health problem (defined as < 1% proportion of heavy intensity infections)	**26** (33%)	**49** (63%)	**69** (88%)	**78** (100%)

Assessment of diagnostic gaps and priorities

Disease	Mapping	Starting treatment	Stopping treatment	Post-treatment surveillance	Priorities
Schistosomiasis					▪ Develop or introduce standardized, sensitive point-of-care diagnostic for use in various prevalence settings and all schistosome species; use for mapping. ▪ Create a repository of sera, urine and stools for development, validation and evaluation of diagnostics. ▪ Develop test for resistance to praziquantel. ▪ Develop molecular test for xenomonitoring and surveillance. ▪ Develop point-of-care diagnostic for genital manifestations.

Adequate diagnostic exists, and no work required to reach 2030 targets

Adequate diagnostic exists, but modifications are required to reach 2030 targets

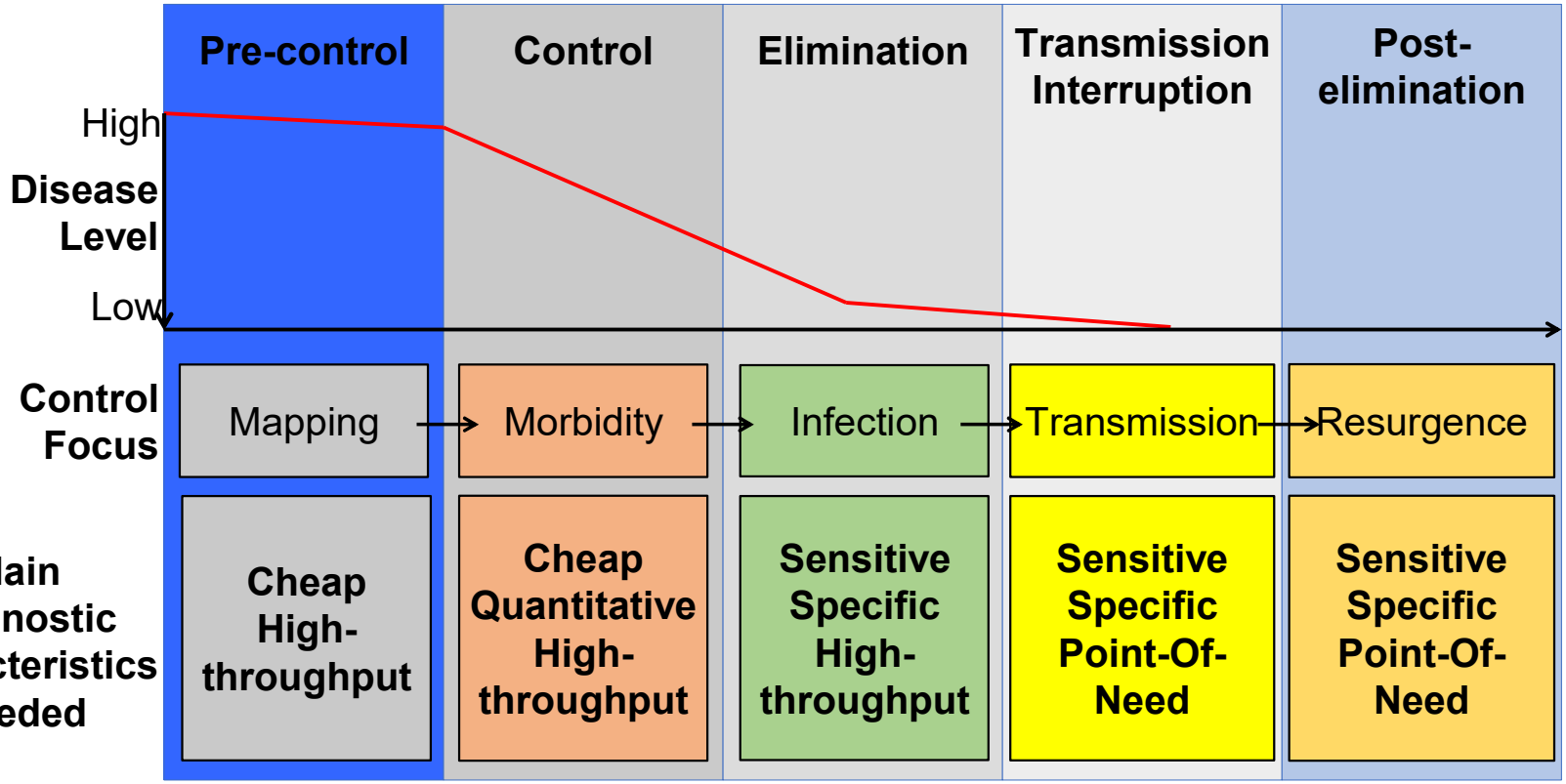
Diagnostic exists, but either requires major modifications or considered inadequate to reach 2030 targets

No diagnostic exists

Not applicable

Human Diagnostics

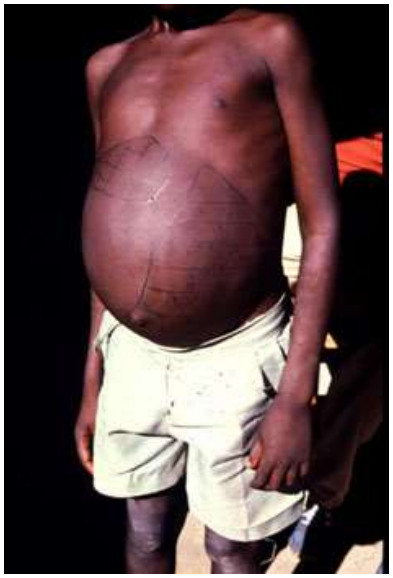
Different diagnostics are needed at different levels of NTD disease and / or phases of control



cost, infrastructure / resource needs, simplicity, reproducibility

Adapted from Utzinger *et al.*, 2015

Medical Schistosomiasis



Intestinal schistosomiasis

(mainly *S. mansoni,* *S. japonicum*

***S. intercalatum, S. guineensis,* *S. mekongi*)**

Morbidity:

- liver and intestinal fibrosis
- hepatosplenomegaly
- portal hypertension
- genital disease

Urogenital schistosomiasis

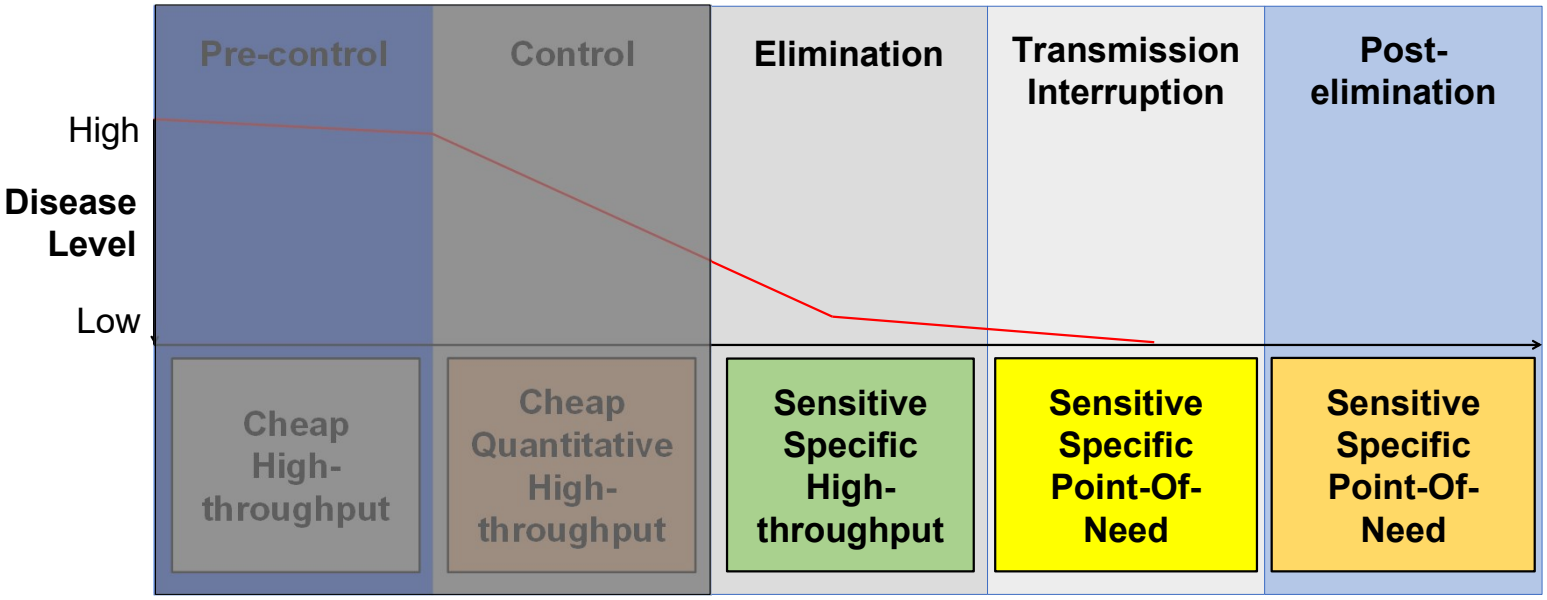
(*S. haematobium*

***S. haematobium* group hybrids)**

Morbidity:

- haematuria
- bladder wall and kidney pathology
- hydronephrosis
- genital disease (infertility, ectopic pregnancy, HIV, STI, etc.)

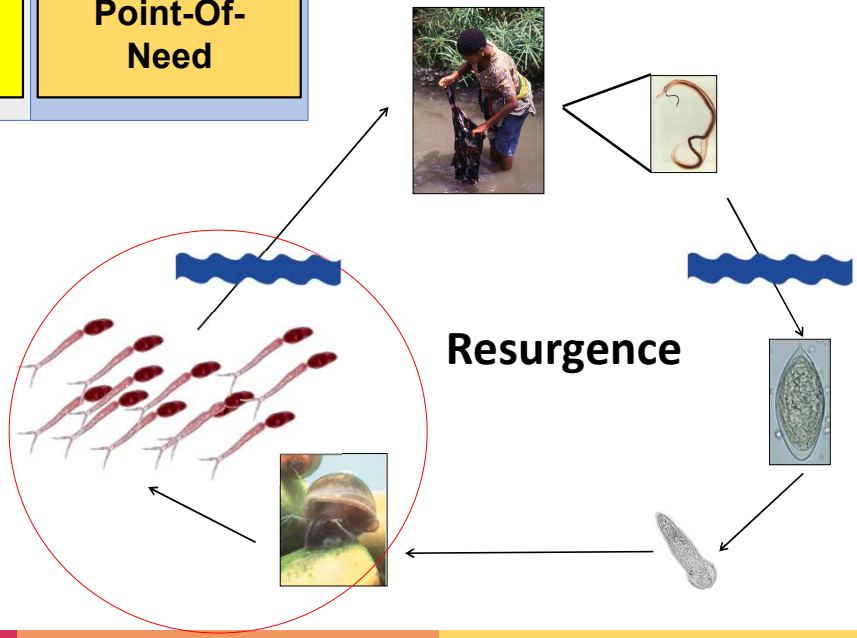
To achieve and maintain elimination advanced diagnostics are needed



Infections are hard to detect

MDA fatigue

Eggs hard to detect
(? egg negative)



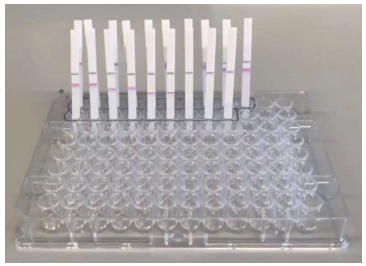
Available Diagnostics

POC-CCA

S. mansoni

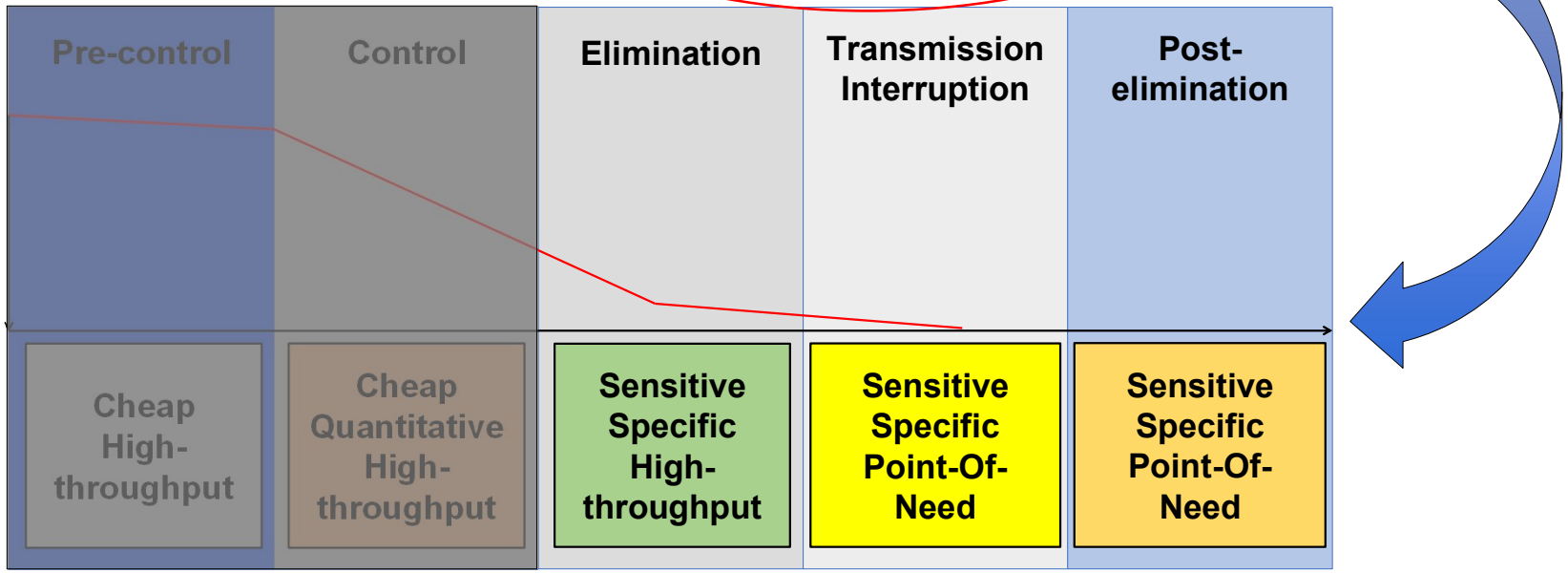
Diagnostic		Detection	SEN	SPE	PON	Cost
Microscopy		Eggs	✓	✓✓✓	✓✓	✓✓✓
Reagent strip		Blood	✓	×	✓✓✓	
Elisa		Antigen	✓✓	×	✓✓	✓✓
CCA and CAA		Antigen	✓✓✓	✓✓(✓)	✓✓(✓)	
Molecular	qPCR	DNA	✓✓✓	✓✓✓	×	?
	LAMP	DNA	✓✓✓	✓✓	✓✓	
	RPA	DNA	✓✓✓	✓✓✓	✓✓(✓)	?

UCP-LF-CAA



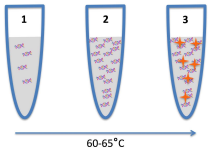
S. mansoni

S. haematobium

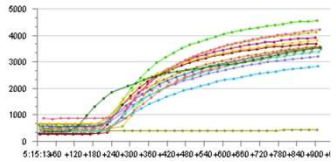


Available Diagnostics

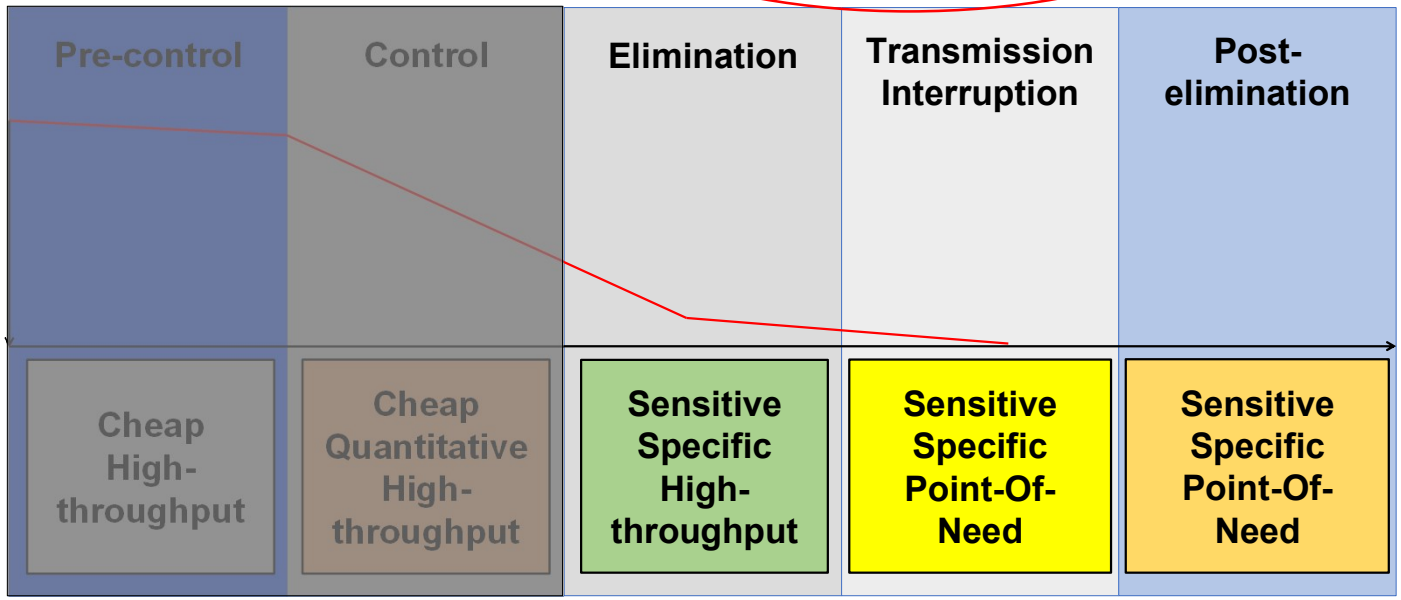
LAMP



RPA



Diagnostic		Detection	SEN	SPE	PON	Cost
Microscopy		Eggs	✓	✓✓✓	✓✓	✓✓✓
Reagent strip		Blood	✓	✗	✓✓✓	
Elisa		Antigen	✓✓	✗	✓✓	✓✓
CCA and CAA		Antigen	✓✓✓	✓✓(✓)	✓✓(✓)	
Molecular	qPCR	DNA	✓✓✓	✓✓✓	✗	?
	LAMP	DNA	✓✓✓	✓✓	✓✓	
	RPA	DNA	✓✓✓	✓✓✓	✓✓(✓)	?



Elimination of *S. haematobium* in Zanzibar (2012-2019)

Swiss TPH

Dr Steffi Knopp

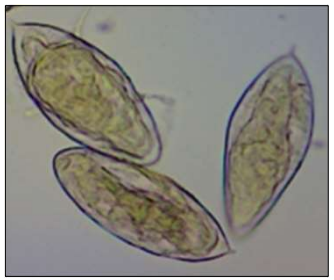
NATURAL HISTORY MUSEUM

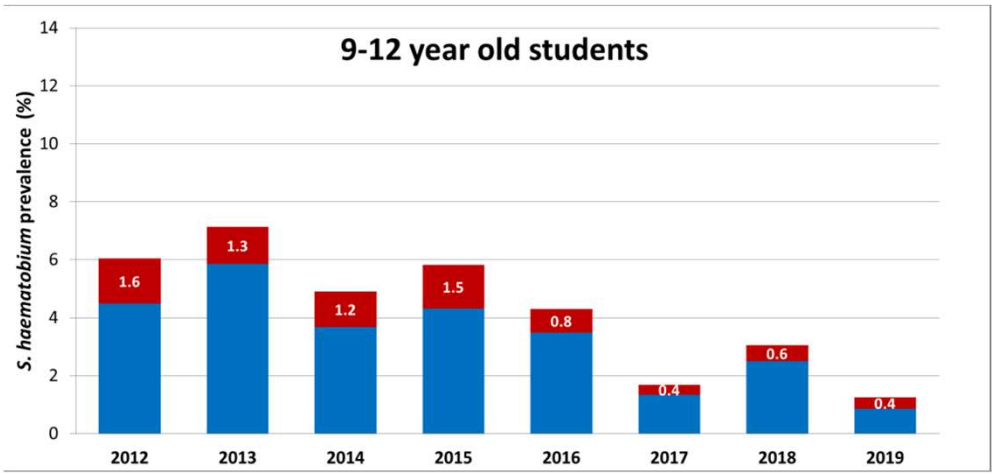
Prof David Rollinson

Interventions: biannual MDA, snail control, behaviour chang

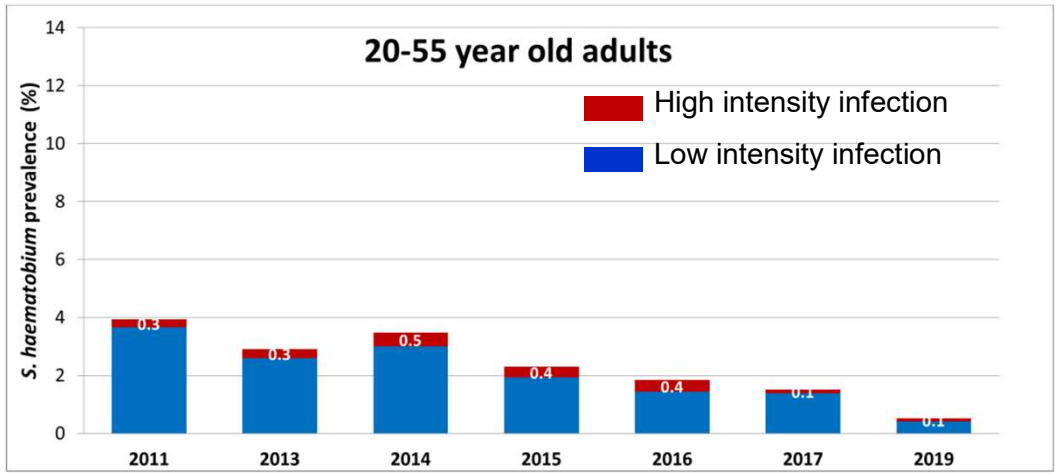
- In 2019: prevalence <2%
- In 2019: heavy intensity infections <1%

By single urine filtration microscopy…





~ 9000 samples / year

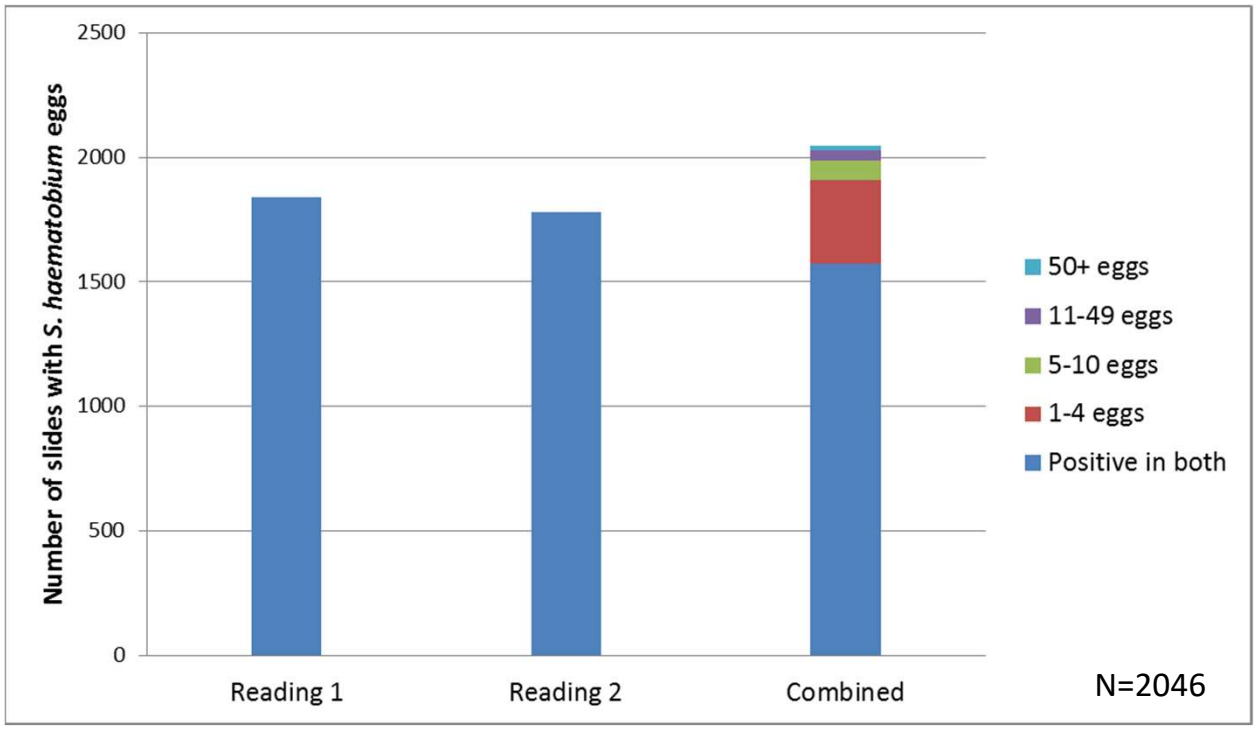


~ 4500 samples / year

SCORE RESEARCH for CONTROL and ELIMINATION

gonetwork.org

Reading the same urine filtration (UF) slides twice



Dr Steffi Knopp

Swiss TPH

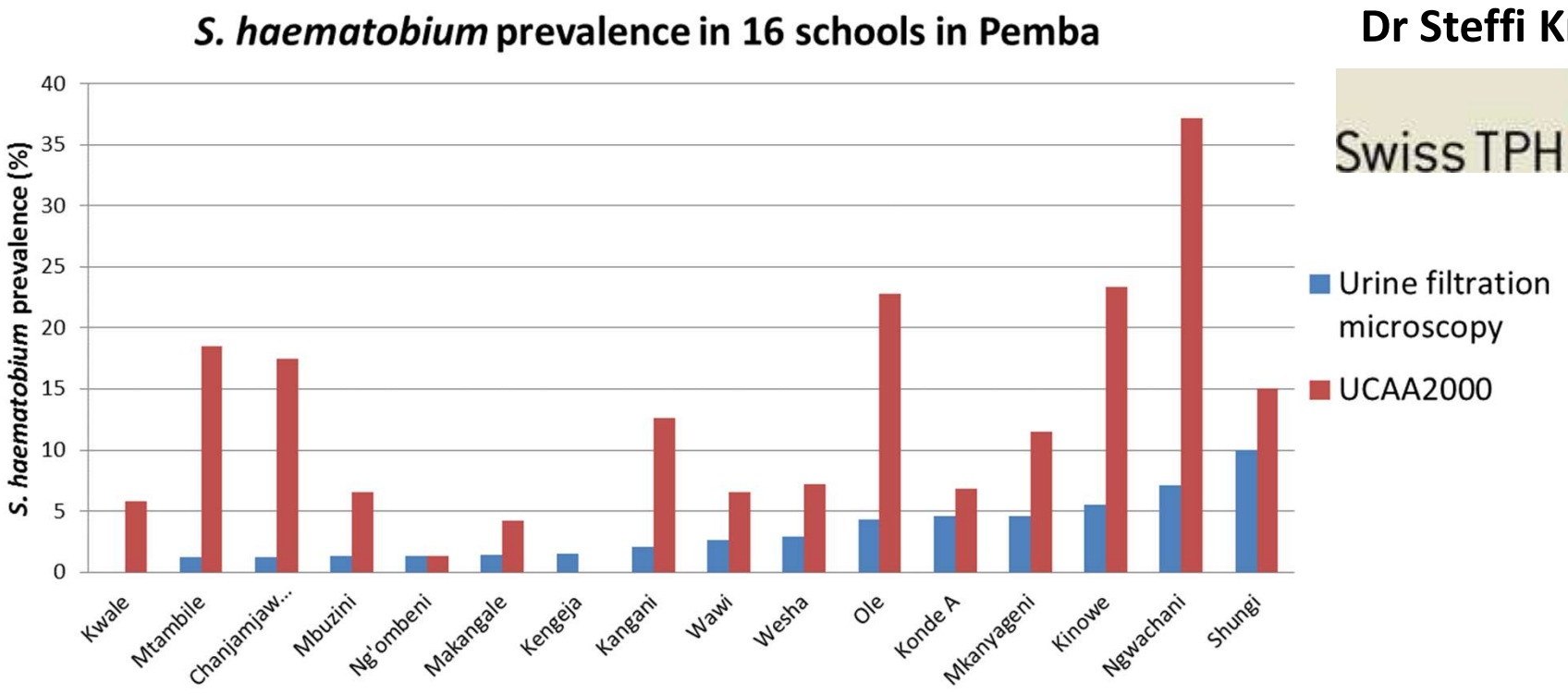
False-negative result in either of the two readings:

- 71% with eggs counts 1-4
- 17% with egg counts 5-10
- 8% with egg counts 11-49

UF microscopy becomes insensitive particularly at egg counts <5 eggs / 10mls

Knopp et al. Parasites & Vectors (2018) 11:552
https://doi.org/10.1186/s13071-018-3136-6

Urine filtration (UF) microscopy *versus* UCP-CAA2000



Dr Steffi Knopp

Swiss TPH

- UF microscopy underestimates the prevalence
- Prevalence in (elimination) settings is higher th assumed?

Knopp et al. PLoS Negl Trop Dis (2015) 9(5): e0003752. doi:10.1371/journal.pntd.0003752

Refined, improved and / or new diagnostics are needed for schistosomiasis elimination

We need to facilitate test and treat scenarios in the Zanzibar elimination setting – target hotspots and the few individuals maintaining transmission (CAA and / or PON molecular tests)

S. haematobium real time fluorescent RPA in the field

200 samples with eggs counts from 0-500 eggs /per 10ml

& / or

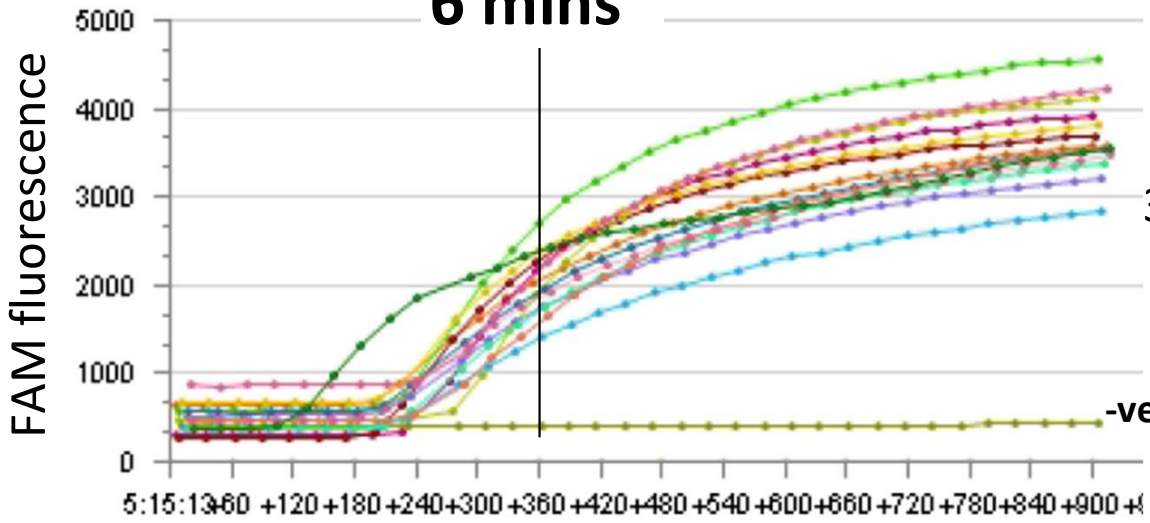
Crude DNA prep.

Dried formulation

Small Portable Detection Devices

37°C

6 mins



500 eggs / 10ml

3 eggs / 10ml

-ve control

S. haematobium real time fluorescent RPA versus microscopy (Zanzibar)

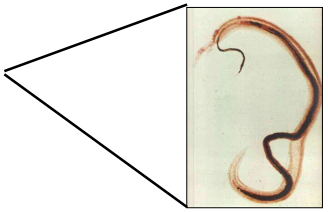
RPA versus microscopy	Ultra-high (>400 eggs/ 10 ml)	High (50-399 eggs/ 10 ml)	Low (10-49 eggs/ 10 ml)	Ultra-low (1-9 eggs/ 10 ml)	Low & Ultra-low (1-40 eggs/ 10 ml)
Total number of samples within egg-count category	9	27	52	70	122
Sensitivity % (± 95% CI)	**100 (66.4–1)**	**96.3 (81–99.9)**	**94.2 (84.1–98.8)**	**91.4 (82.2–96.8)**	**92.6 (86.5–96.6)**
Negative Predictive Value % (± 95% CI)	100 (69.2-100)	90.9 (58.7–99.8)	76.9 (64.2-95)	62.5 (35.4–84.8)	52.6 (28.9–75.6)

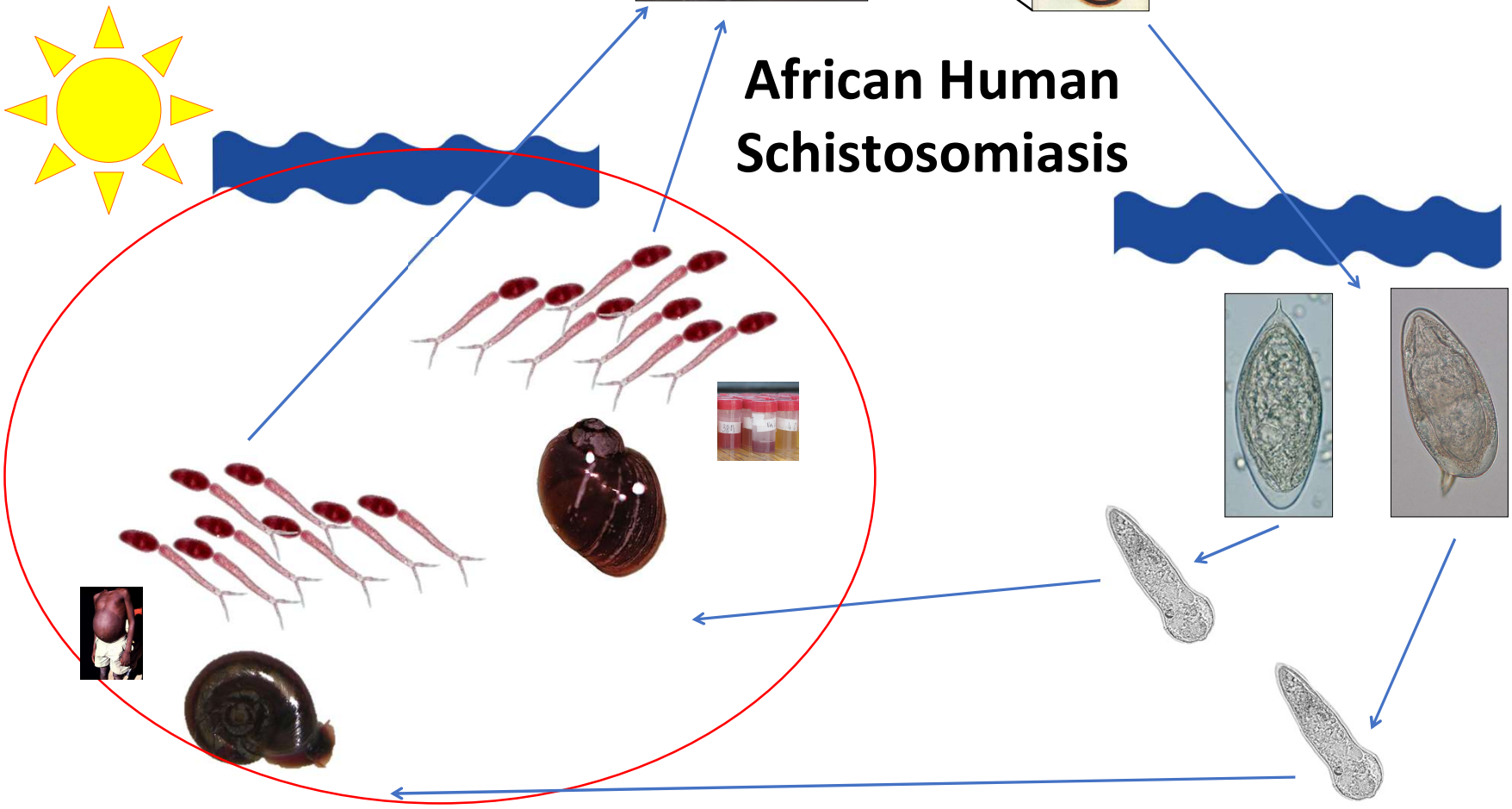
- **There are many research steps to move these types of diagnostics forward into validated tests. This takes time and funding.**
- **There is often a push for integrated diagnostics for multiple diseases and setting but sometimes this is not possible. Diagnostics may need to be targeted to specific diseases and settings.**
- **We need to strengthen the connection between research and programming**

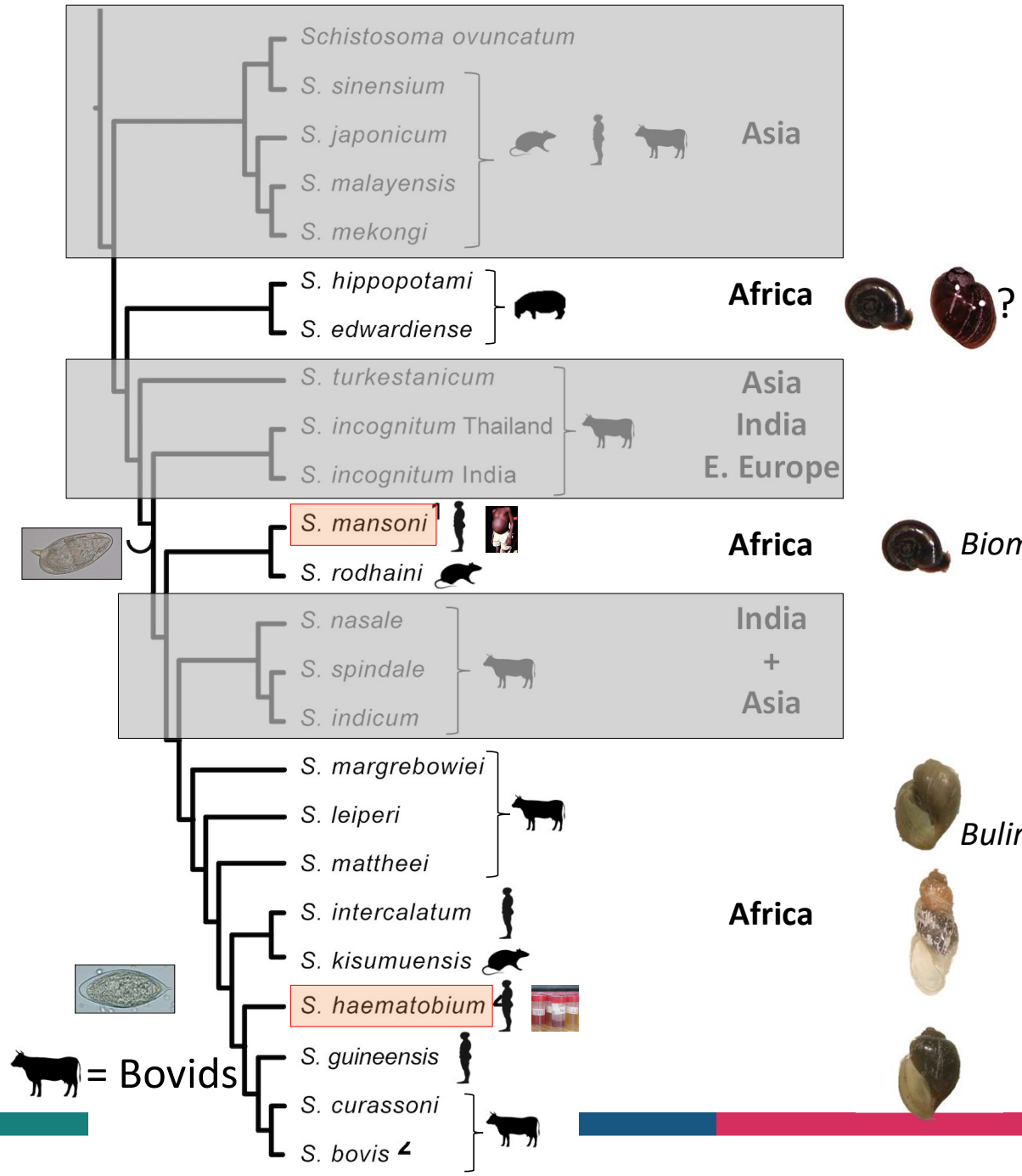
Archer et al., 2020 (under review)

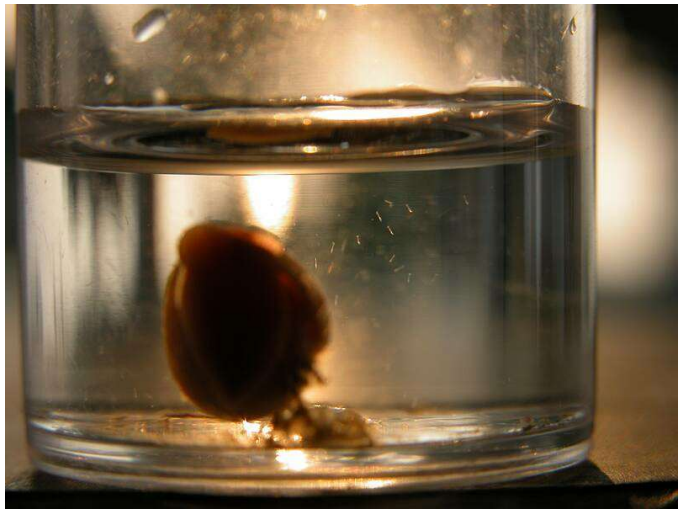
Identify transmission sites
Map snail distribution and risk of transmission
Enable targeted snail control

Snail Xenomonitoring is used to inform on transmission, to certify transmission interruption and surveillance

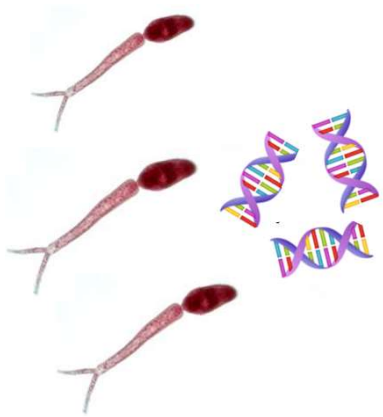








Biomphalaria spp.



Bulinus spp.

Due to the focus on human schistosomiasis snails are often assumed to be shedding human schistosomes

Snail surveys and collections

Ponds and lakes

Streams, Rivers and Paddies

Springs

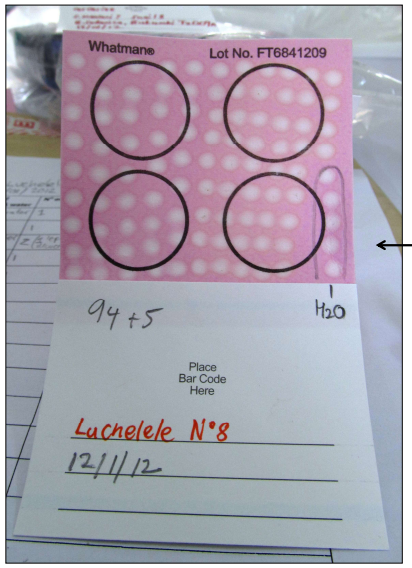
Dry sites recorded (seasonal)

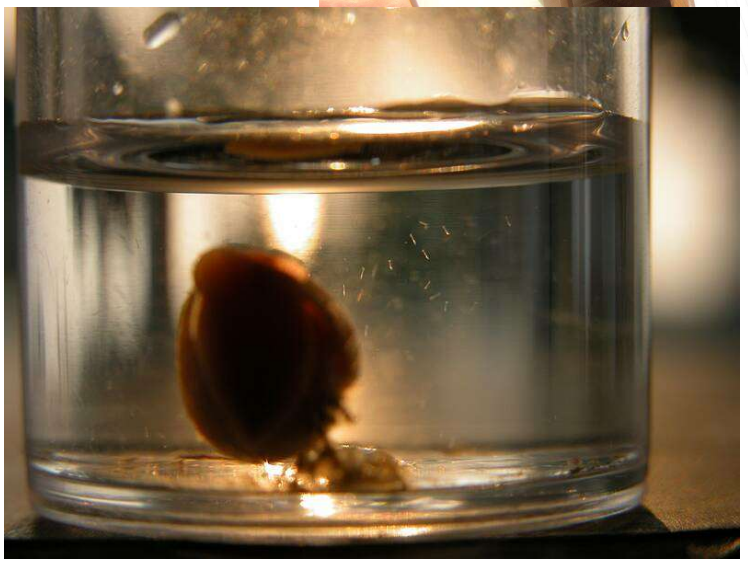
Water contact recorded

Sites mapped

Cercariae identification

All snails checked individually for shedding

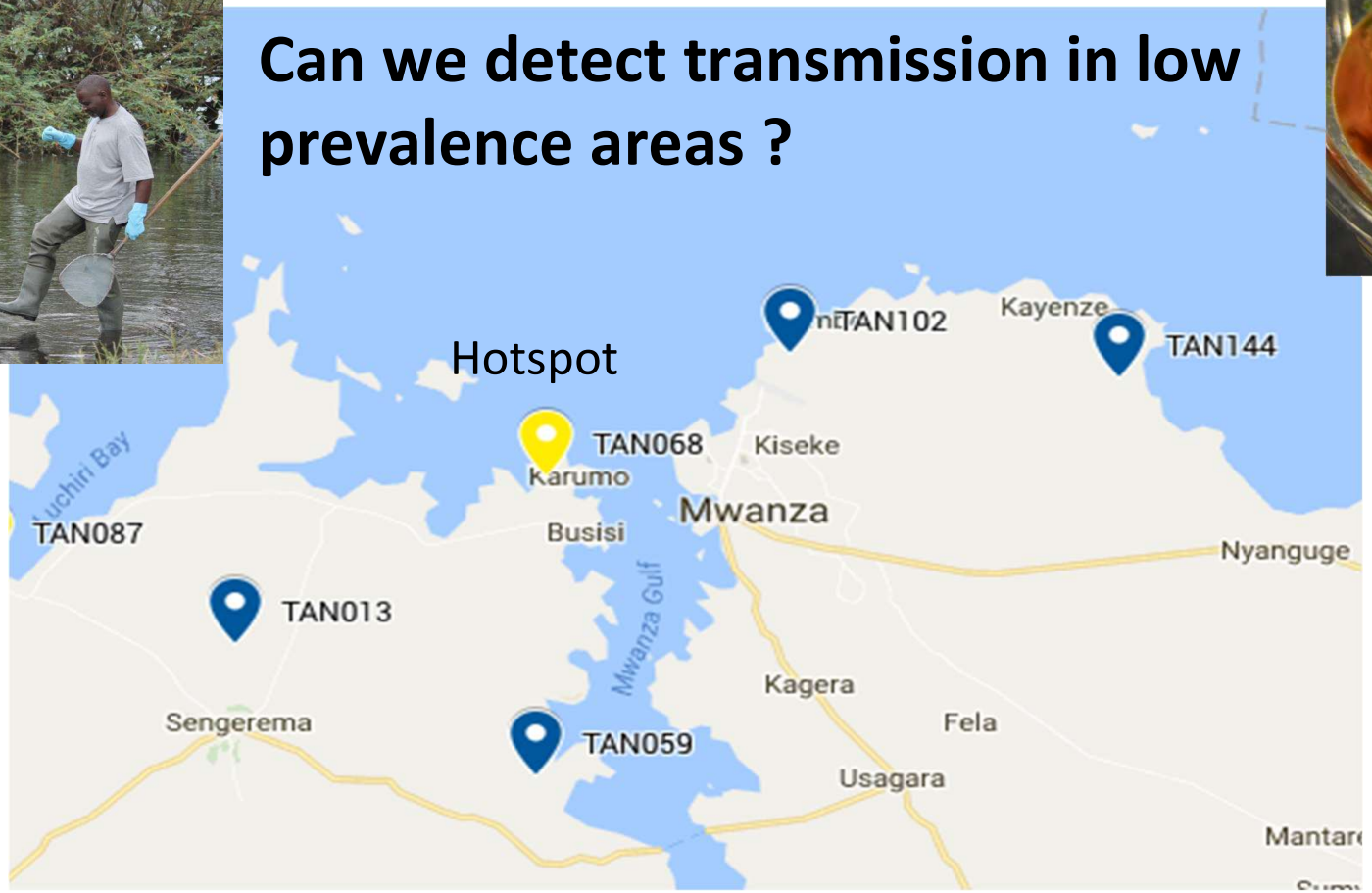


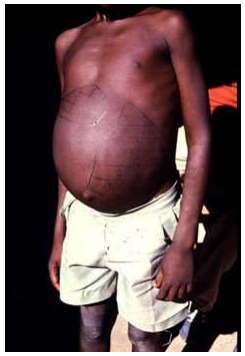


Cercariae stored for molecular identification

Tanzania, Mwanza Xenomonitoring

Can we detect transmission in low prevalence areas ?



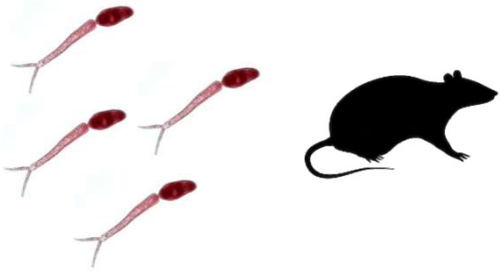


4 surveys 2016-2017; **~9000 *Biomphalaria* and ~2000 *Bulinus* were collected from 46 HWC**

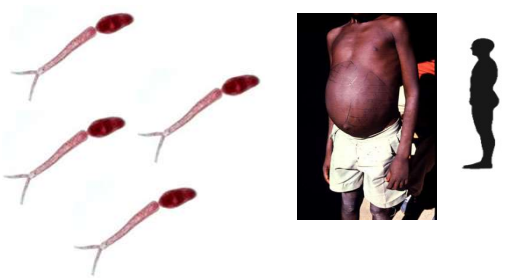
Tanzania, Mwanza Xenomonitoring

~9000 *Biomphalaria;* 11 were infected

3 shedding *S. rodhaini*



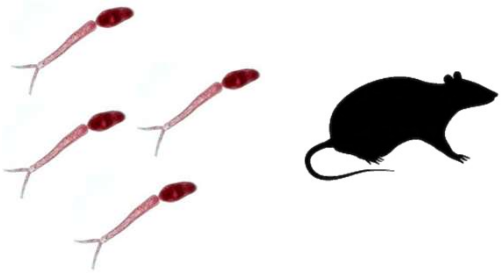
8 shedding *S. mansoni*



Biomphalaria spp.

~2000 *Bulinus;* 4 were infected

1 shedding *S. kisumuensis*
(Only been found in Kenya before)



3 shedding *S. haematobium*

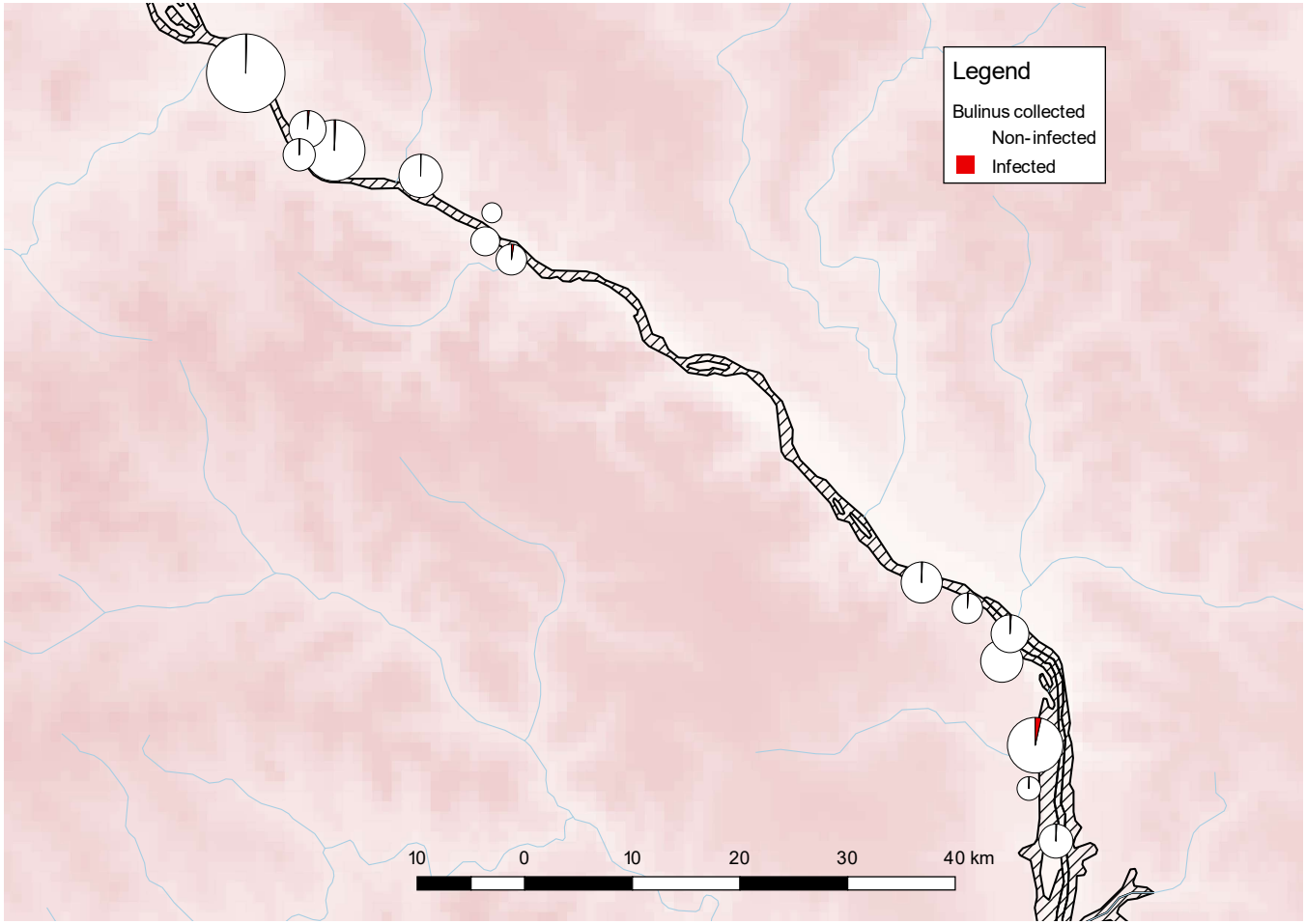
Bulinus spp.

Niger Xenomonitoring

B. truncatus

B. forskalii

B. globosus



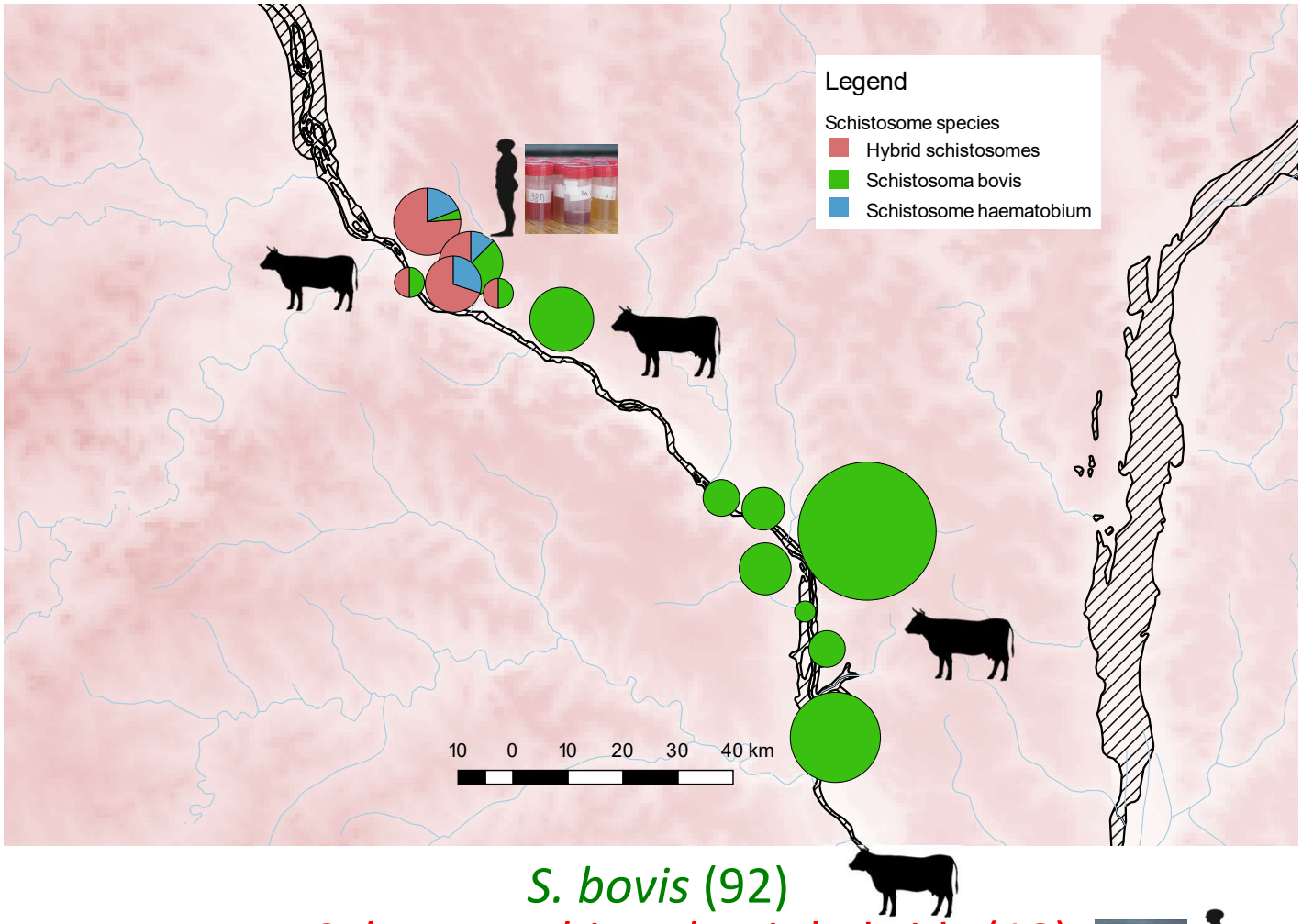
>10,000 snails collected **116 were infected**

Niger Xenomonitoring

B. truncatus

B. forskalii

B. globosus

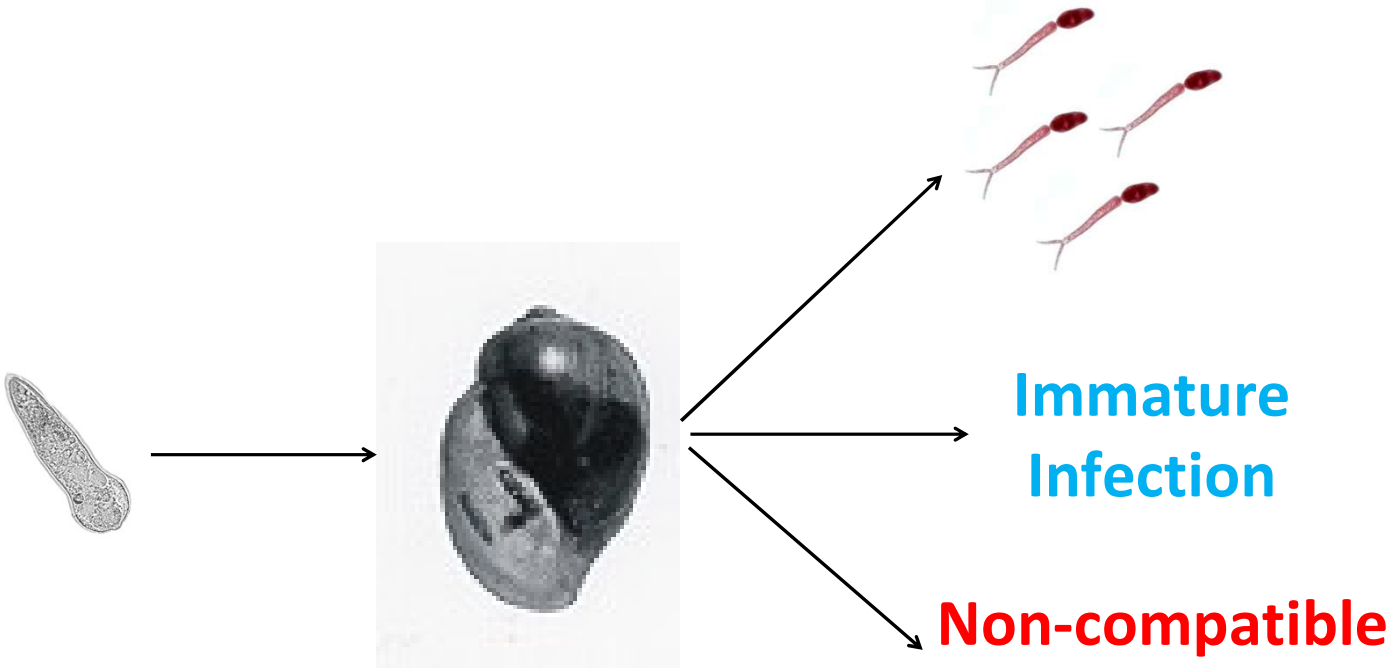


S. bovis (92)

S. haematobium-bovis hybrids (18)

S. haematobium (6)

Development of a molecular toolkit for the detection of pre-patent snail infections – **increases sensitivity for transmission monitoring**



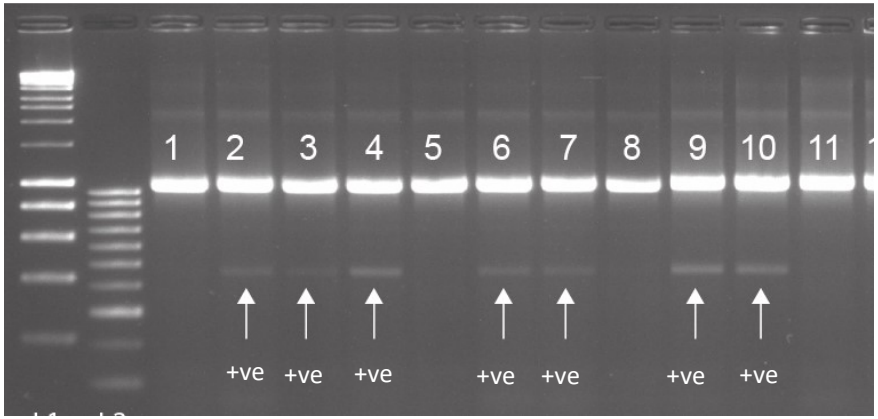
Molecular analysis of the snail tissue can identify infections within hours of miracidial penetration

Development of a molecular toolkit for the detection of pre-patent snail infections – **increases sensitivity for transmission monitoring**

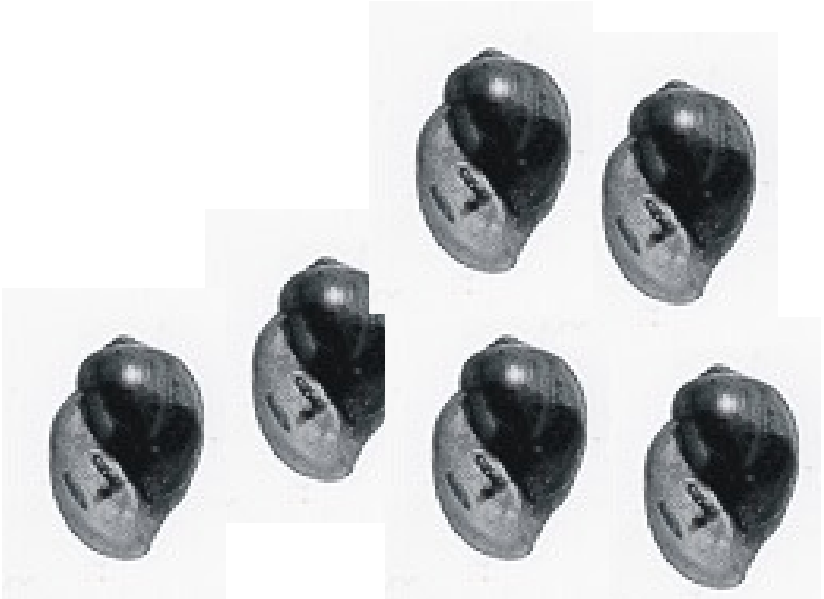
Individual

DNA

Multiplex PCR



or



Pooling (X10) snails makes this cheaper and faster

The molecular tools need to be species specific

Pennance *et al.*, 2020

Strengthening the connection between research and programming to beat NTDs (schistosomiasis elimination)

- **Advanced diagnostics that are;**
  - Highly sensitive
  - Tailored to specific setting / foci
  - Can support test and treat and enable more targeted treatment strategies
- **Snail Xenomonitoring methodologies that are;**
  - Highly sensitive and specific
  - Tailored to specific settings / foci
  - Can determine ongoing transmission or transmission interruption
  - Can support snail control strategies and risk mapping of transmission sites
- **Monitoring of infections in zoonotic reservoirs in Africa e.g. rodents and non-human primates for *S. mansoni***

- **However, significant research is needed to advance these tools so that they are feasible and can be implemented in the endemic setting.**

Thanks

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Safari Kinunghi (NIMR)

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Zanzibar Elimination of Schistosomiasis Transmission (ZEST)

All the in-country teams

NEGLECTED TROPICAL DISEASE NGO NETWORK

A global forum for nongovernmental organizations working together on NTDs

Welcome to the NNN Conference 2020

Accelerating to 2030: Building Resilient NTD Programmes in a Changing World

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Patient Pathways and Barriers to Treatment for Visceral Leishmaniasis in Bangladesh, India, Ethiopia and Sudan

Lucy Paintain, Lydia Boudarène, Jayne Webster (LSHTM)
on behalf of the KalaCORE M&E Task Team & partners

Background

- Visceral leishmaniasis (VL) is characterised by prolonged fever, substantial weight loss & anaemia, disabling patients from usual activities and requiring substantial caring support; 100% fatal within 2 years without treatment.
- Estimated 50,000 to 90,000 new cases of VL occur worldwide each year (latest WHO estimates).
- Effective case management is a cornerstone of VL control & elimination efforts.
- Earlier detection and treatment means that cases can be treated before the disease becomes severe, and the economic impact on families and on productive time is reduced

Study design & setting

- 7 cross-sectional surveys with 1,686 VL patients in Bangladesh, India, Ethiopia & Sudan (2016, 2018)
  - Patients recruited from public treatment facilities
  - Data collected on the treatment pathway and reported financial & economic cost to the household of the recent VL illness episode.
- In-depth interviews (IDIs) with recent VL patients in India and Bangladesh
  - Bangladesh: all new VL patients (15) treated in SKKRC in the previous 3 months
  - India: 25 respondents from endline survey purposively selected to get a range of experiences from VL patients
- Interventions were conducted in each country between surveys, supported by the DFID-funded KalaCORE Programme (www.kalacore.org)

- First-line treatment is one-day AmBisome (Bangladesh, India) versus 17-day SSG/PM (Ethiopia, Sudan)
- Target of elimination as a public health problem (Bangladesh, India) versus control (Ethiopia, Sudan)

Survey and in-depth interview findings

- Variable epidemiology by country e.g. age, gender of patients
- Variable treatment seeking practices e.g. number of providers, use of private sector
- Variable length of treatment pathway and time taken for each stage (symptoms to any care seeking; care seeking to first VL diagnosis; first diagnosis to start of treatment)
- Beyond the numbers… IDIs in India & Bangladesh brought out the increasing desperation of trying to get a diagnosis, and the economic impact of the illness on the household.
- Manuscripts with detailed quantitative & qualitative results are in process and will be published soon

Strengthening the connection between research and programming to beat NTDs

- To achieve effective case management of VL and reduce the economic burden, consider patient pathways to treatment.
  - Where are the biggest delays/barriers?
  - Breaking down the treatment pathway into stages can help translate research findings into interventions with the potential to achieve the greatest impact:
    - Symptoms to care seeking: patient behaviour change
    - Care seeking to first diagnosis: training of health staff and capacity of health system
    - Diagnosis to treatment: capacity of health system to respond
- Clear differences in treatment pathways in each country
  - Importance of context in understanding the data and tailoring interventions (epidemiology; treatment policy; health system)
- Are there similar patterns with other NTDs that could facilitate integration?
- Qualitative data adds depth & detail, telling the human side of the story which can be masked by numbers & percentages – powerful for advocacy

Acknowledgements

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