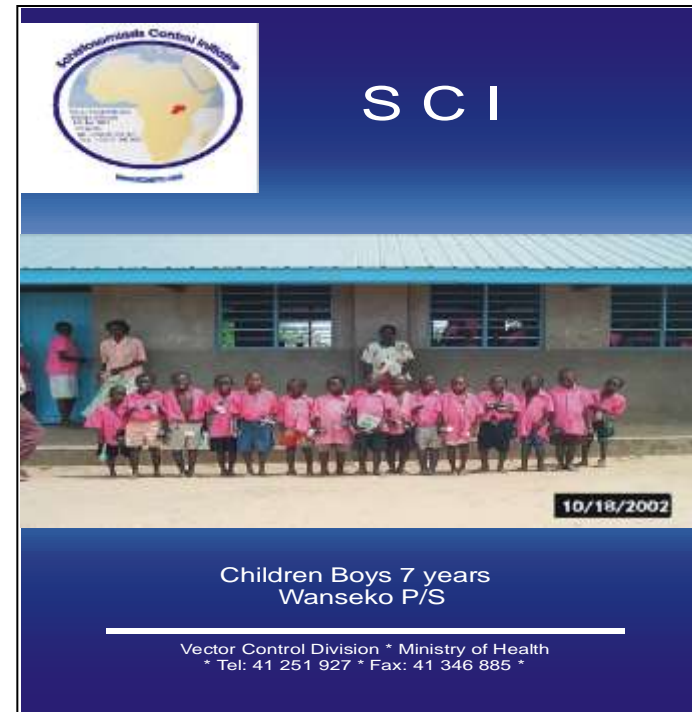


Schistosomiasis transmission and control in sub-Saharan Africa



Professor Joanne P. Webster

Talk outline

1. MDGs, NTDs and SCHISTOSOMIASIS
2. SCHISTOSOMIASIS CONTROL INITIATIVE (SCI)
2003 –TODAY
3. IMPLEMENTATION
(e.g. Coverage and numbers treated)
4. MONITORING, EVALUATION AND RESEARCH
(e.g. morbidity and parasite dynamics)
5. SUMMARY

The United Nations Millennium Development Goals (MDGs)

1. Eradicate extreme poverty and hunger.
 2. Achieve universal primary education.
 3. Promote gender equality and empower women.
 4. Reduce child mortality.
 5. Improve maternal health.
 6. **Combat HIV/AIDS, malaria and other diseases.**
 7. Ensure environmental sustainability.
 8. Develop a global partnership for development.
- NTDs are included in "other diseases"
- 

The 'Main' Neglected Tropical Diseases

Core Group of 13

Protozoan Infections

Leishmaniasis (VL + CL + MCL)
Human African Trypanosomiasis (HAT)
Chagas Disease

Helminth Infections

Ascariasis
Trichuriasis
Hookworm
Lymphatic Filariasis (Elephantiasis)
Onchocerciasis (River Blindness)
Schistosomiasis (Bilharzia)
Dracunculiasis (Guinea Worm)

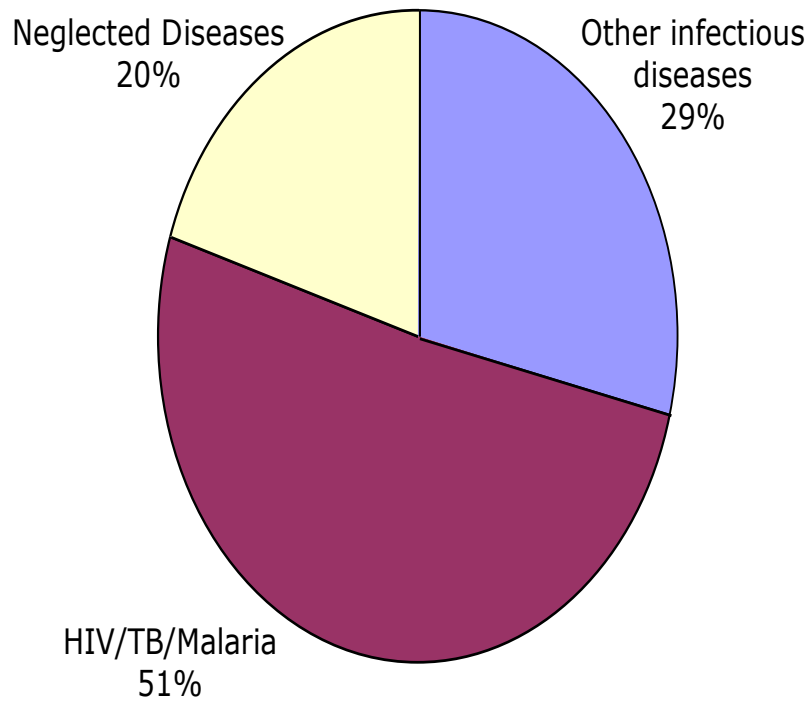
Bacterial Infections

Leprosy
Trachoma
Buruli Ulcer

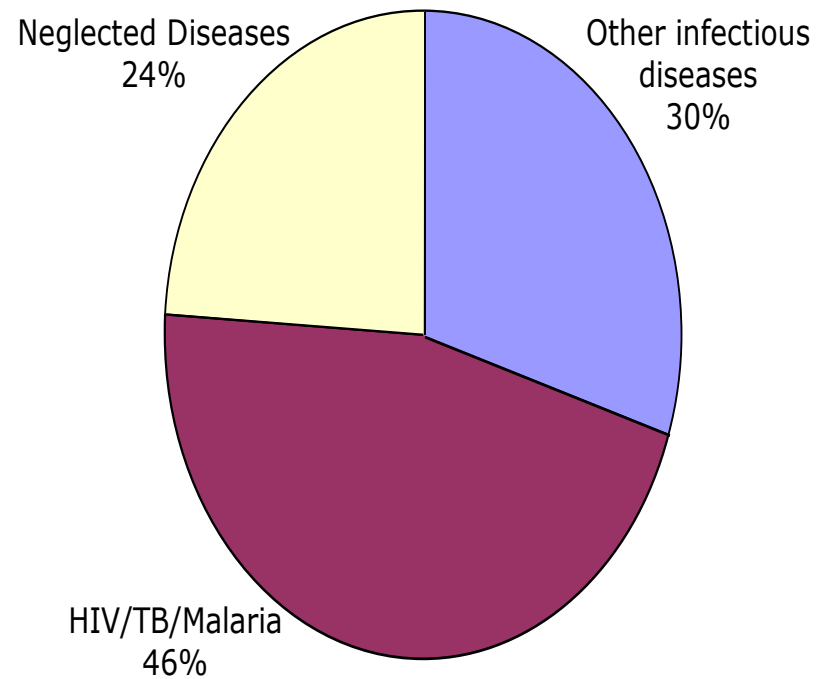
**+ 24 'Even More Neglected
Tropical Diseases'**



Deaths



DALYs



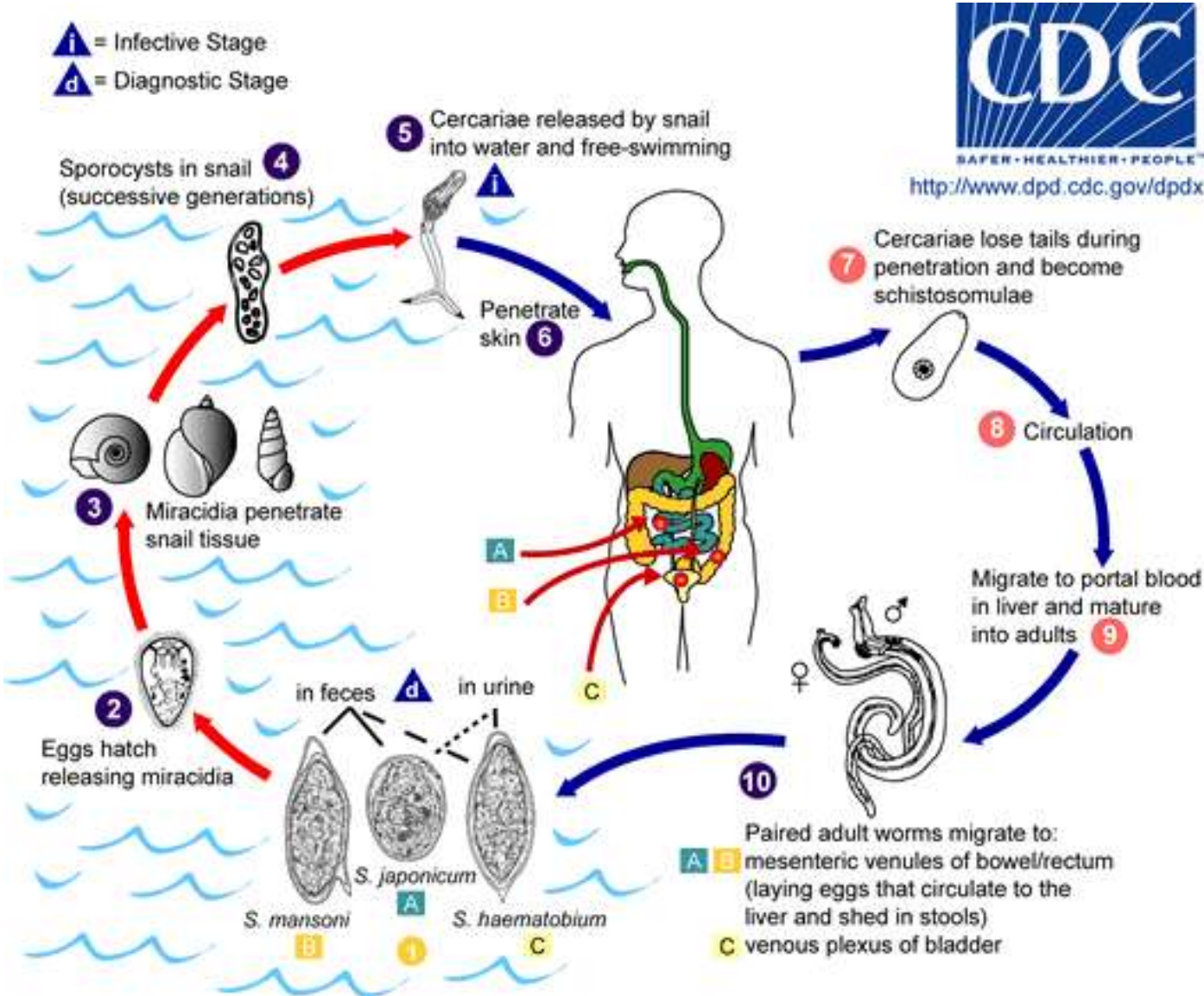
NTDs cause 20% of deaths and 24% of DALY's

Schistosomiasis is one of the Neglected Tropical Diseases (NTDs)

- Blood-born fluke
- Endemic in 70 tropical and sub-tropical countries
- 5 'human schistosome' species
 - *S. mansoni* (Africa, S. America)
 - *S. haematobium* (Africa)
 - *S. japonicum* (S-E Asia)
 - *S. mekongi* (S-E Asia)
 - *S. intercalatum* (Africa)



Schistosome Life Cycle



Schistosomiasis mortality and morbidity

Total infected
>207 million

Mortality (annually)

150,000 due to kidney failure
130,000 due to portal hypertension

Persons with major morbidity:

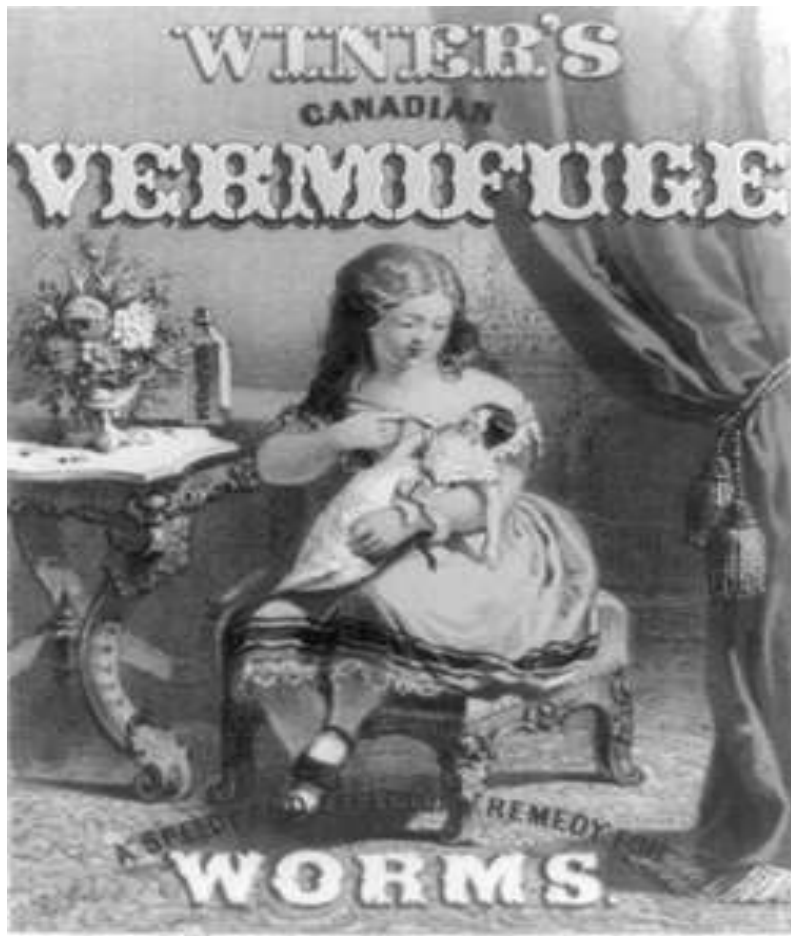
70 million with haematuria
18 million bladder wall pathology
10 million hydronephrosis

Persons with 'subtle' morbidity:

+++++++ !



Treatment of Helminth infection: Chemotherapy



J. W. WRIGHT & CO. NEW ORLEANS, LA.



Schistosomiasis treatment

Praziquantel

Safe, effective, single oral dose after food

Active against all species of human schistosome

40 mg/kg body weight - 600 mg tablets

- 10 years ago **approximately \$1 per tablet (\$4 for an adult course)**
- -= now >7 cents - **93% cheaper !**

STH

Albendazole or Mebendazole

Safe, effective, single oral dose

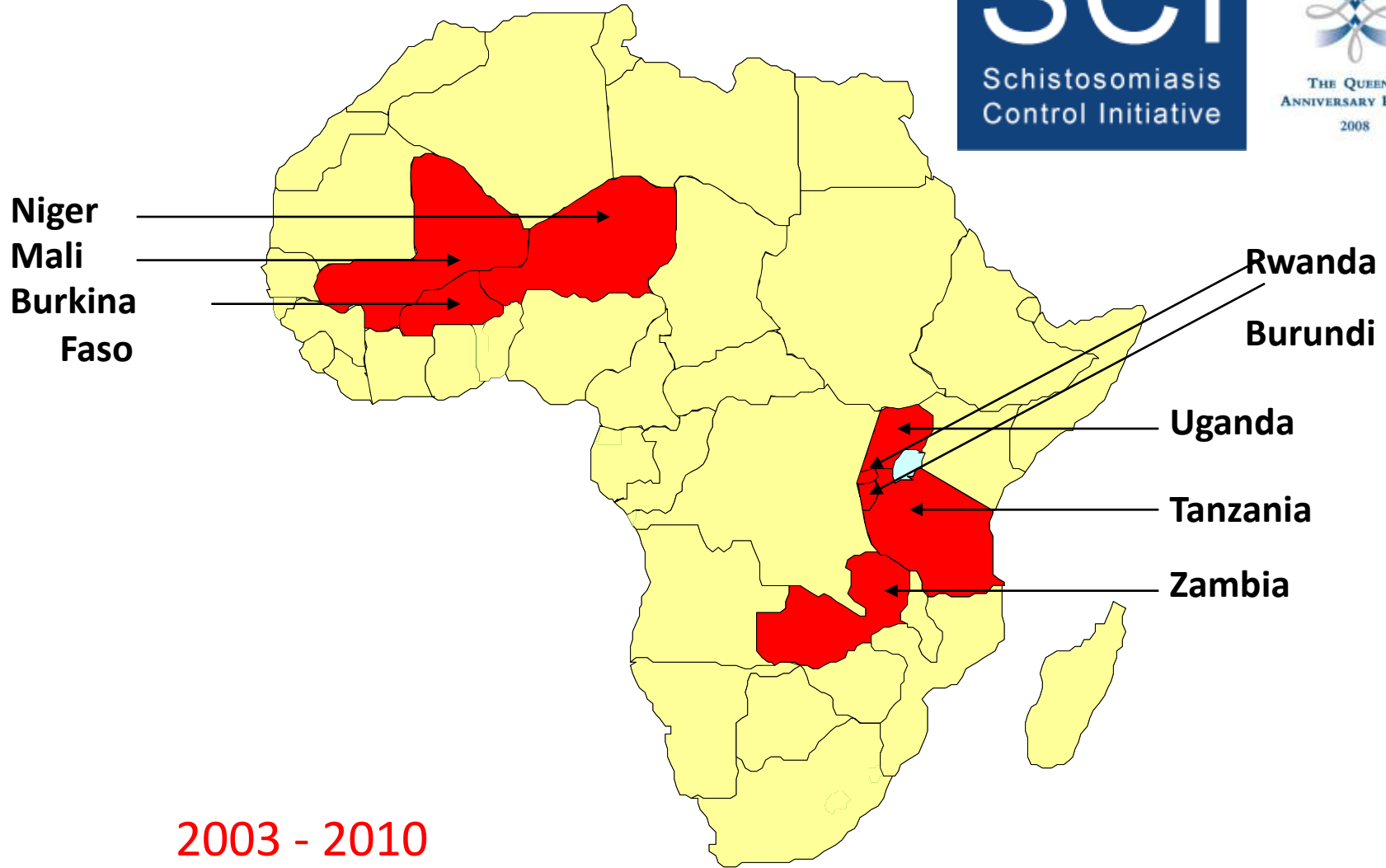
1p a treatment



The Schistosomiasis Control Initiative (SCI) Mission

- SCI, supports the WHA resolution that all member state infected regions aims “to provide regular treatment for 75% of all school-aged children for schistosomiasis and intestinal helminths”,
- To encourage treatment of schistosomiasis in sub-Saharan Africa by targeting those at high risk of developing severe morbidity, especially school-aged children, women and those in high risk occupations.
- By assisting selected countries to achieve successful **SUSTAINABLE** national control programmes, SCI expects to create a sustainable access and demand for treatment.
- To develop and implement rigorous monitoring and evaluation.
- To thereby reduce prevalence, intensity and associated morbidity of schistosomiasis and STH infections.

Sustainable schistosomiasis (*S. mansoni* and *S. haematobium*) and STH control: sub-Saharan Africa



2003 - 2010

Initially facilitated by BMGF grant

Number of persons treated (millions) in SCI-supported countries from 2003-2007.

**Cumulative Schistosomiasis Treatments delivered = 44.64 million
(& Cumulative STH Treatments delivered = > 100 million)**

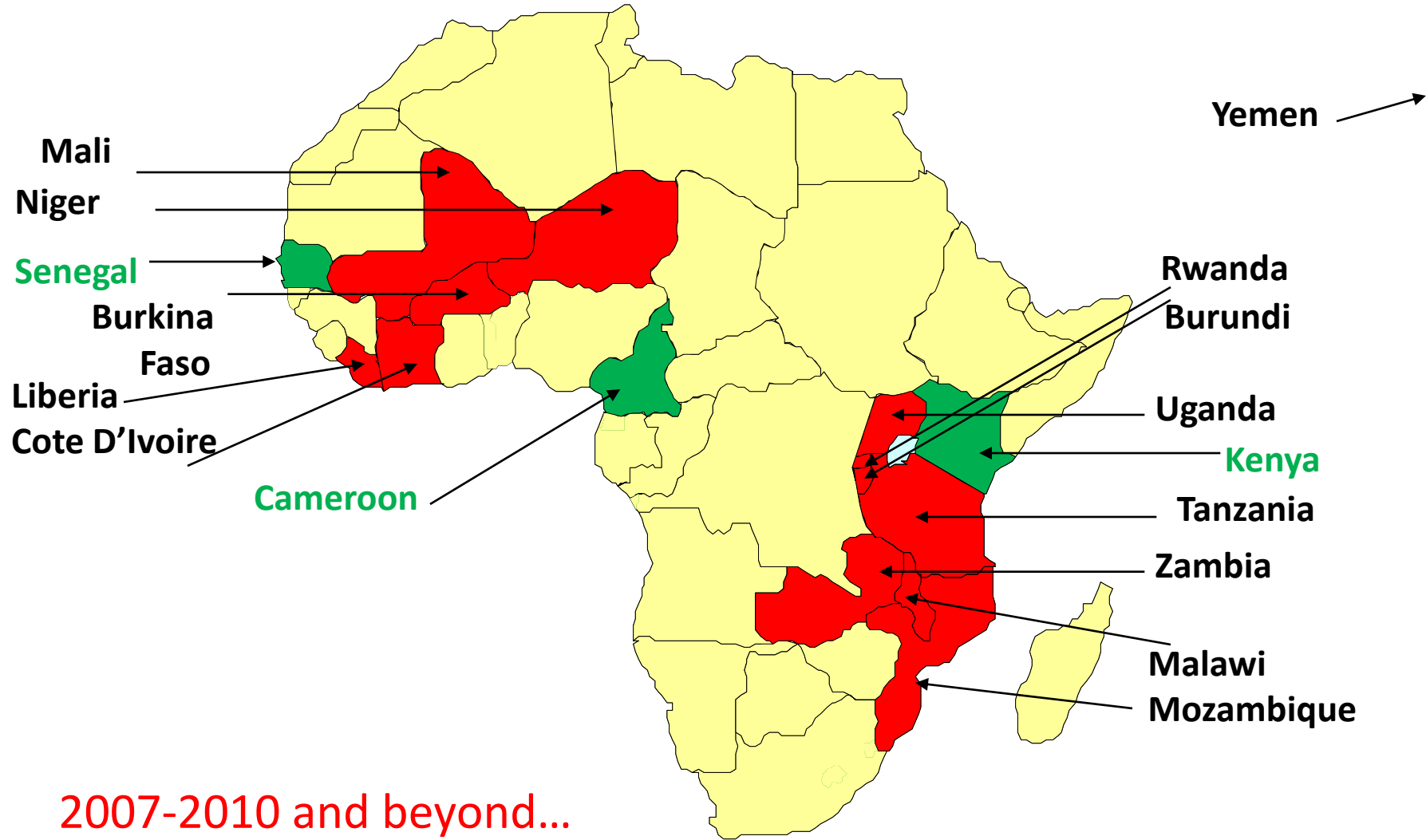
Year	Uganda	Burkina Faso **	Niger	Mali	Tanzania	Zambia	Total by year
2003	0.433	0	0	0	0.100	0	0.533
2004	1.230	1.027	0.672	0	0.442	0	3.371
2005	2.988	2.296	2.010	2.598	2.952	0	12.844
2006	1.511	2.819	1.560	2.175	0.384	0.556	9.005
2007	1.812	0.750	2.066	0.647	2.650	0.245	8.170
2008	1.497 *	2.697	5.284*	0 *	1.243	0	10.721
Total by country	9.47	9.59	11.59	5.42	7.77	0.80	44.64

* Treatment incorporated into the new integrated NTD control programme

** Burkina Faso was the first country in the WHO African Region to achieve nationwide coverage with anthelmintic drugs against three major so-called neglected tropical diseases (NTDs), namely lymphatic filariasis, schistosomiasis and STH.

90% of all treatments provided against schistosomiasis across Africa during that time

Sustainable integrated NTD Control and/or Research: sub-Saharan Africa



Plus independent research ongoing in non-SCI MDA countries

The African Neglected Tropical Diseases

- **Protozoan Infections**
 - Leishmaniasis (VL + CL + MCL)
 - African Trypanosomiasis (Sleeping Sickness)



- **Helminth Infections**
 - **Soil-transmitted Helminth infections:**
 - **Ascariasis-Trichuriasis-Hookworm**
 - **Lymphatic Filariasis (Elephantiasis)**
 - **Onchocerciasis (River Blindness)**
 - **Schistosomiasis (Bilharzia)**
 - **Dracunculiasis (Guinea Worm)**
 - **Cysticercosis**



- **Bacterial Infections**
 - Leprosy
 - **Trachoma**
 - Buruli Ulcer



Pharmaceutical companies need to recoup their investment of millions of dollars developing their drugs by selling large volumes. Sadly no-one who needs drugs against NTDs in endemic countries can afford to pay for them.

Today Pharma recognises this and so they sell their products in the West and donate the same products to those endemic countries infected with NTD's



Onchocerciasis
(Donation of Mectizan®)

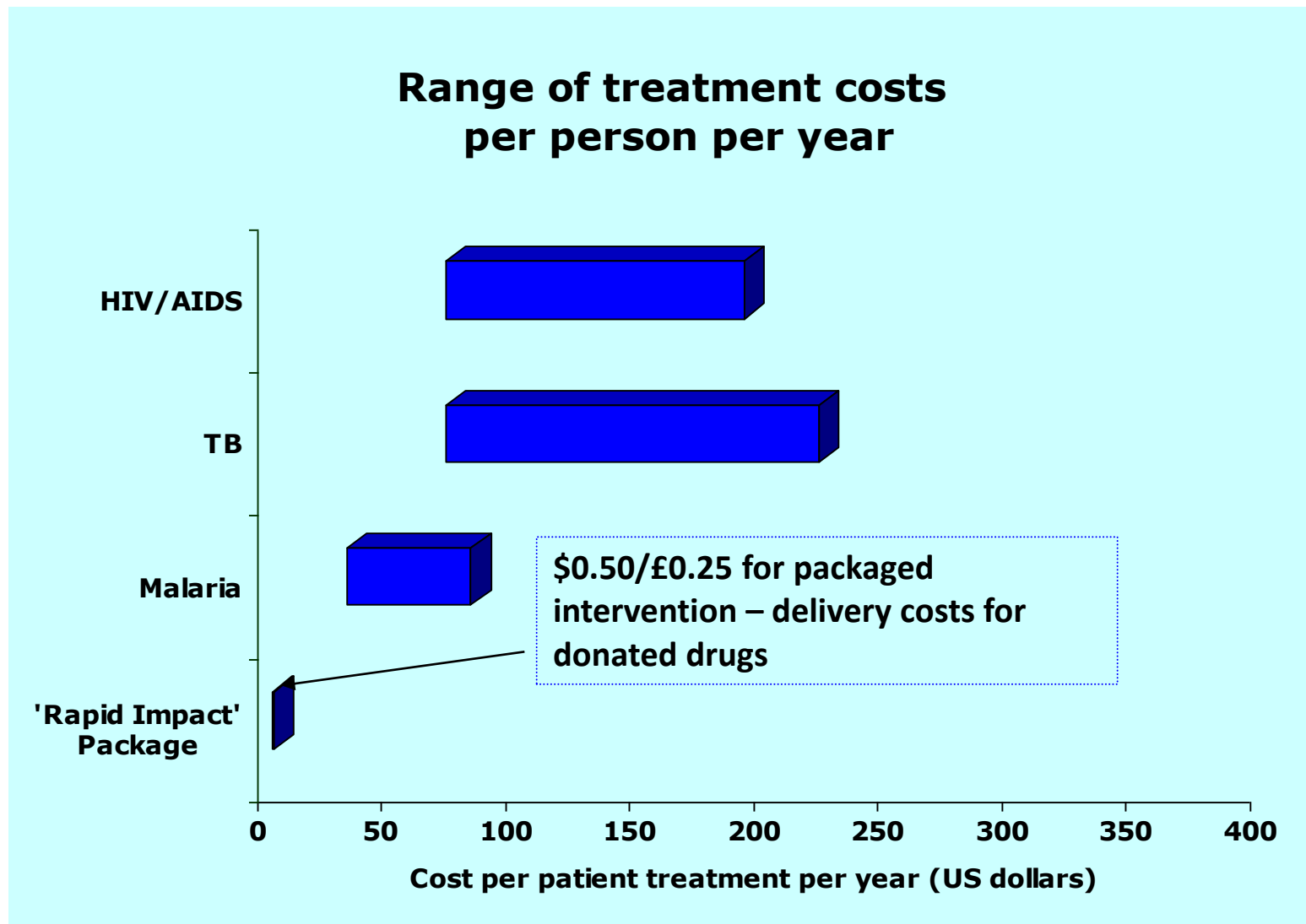
Lymphatic Filariasis
(Donation of Mectizan® and Albendazole)

Soil-transmitted Helminths
(Part donation/part purchase of Albendazole/Mebendazole)

Trachoma (Donation of Zithromax)

Schistosomiasis (& food-borne trematodes)
(Part donation/part purchase of Praziquantel)

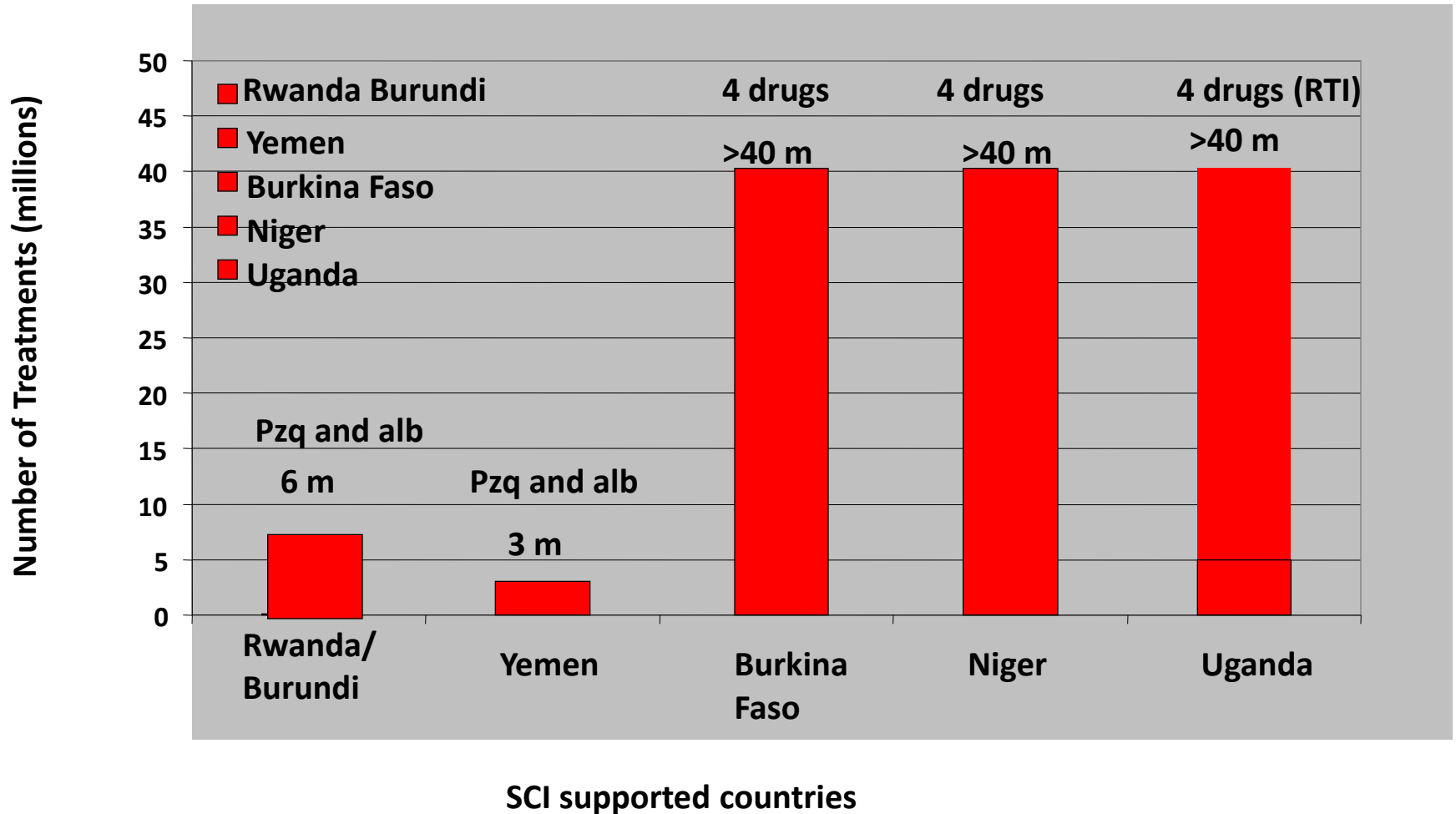
Low Cost of Interventions: mean cost of annual delivery of the chemotherapy package is just = \$0.50/25p per person



Gates Foundation – Tanzania, Burkina Faso, Niger
USAID/RTI – Uganda, Burkina Faso, Niger (Mali & Ghana)
GNNTDC – Rwanda and Burundi

Ministries of Health and Education with SCI support

Treatments delivered 2007-2010



Summary

Highly successful and expanded implementation

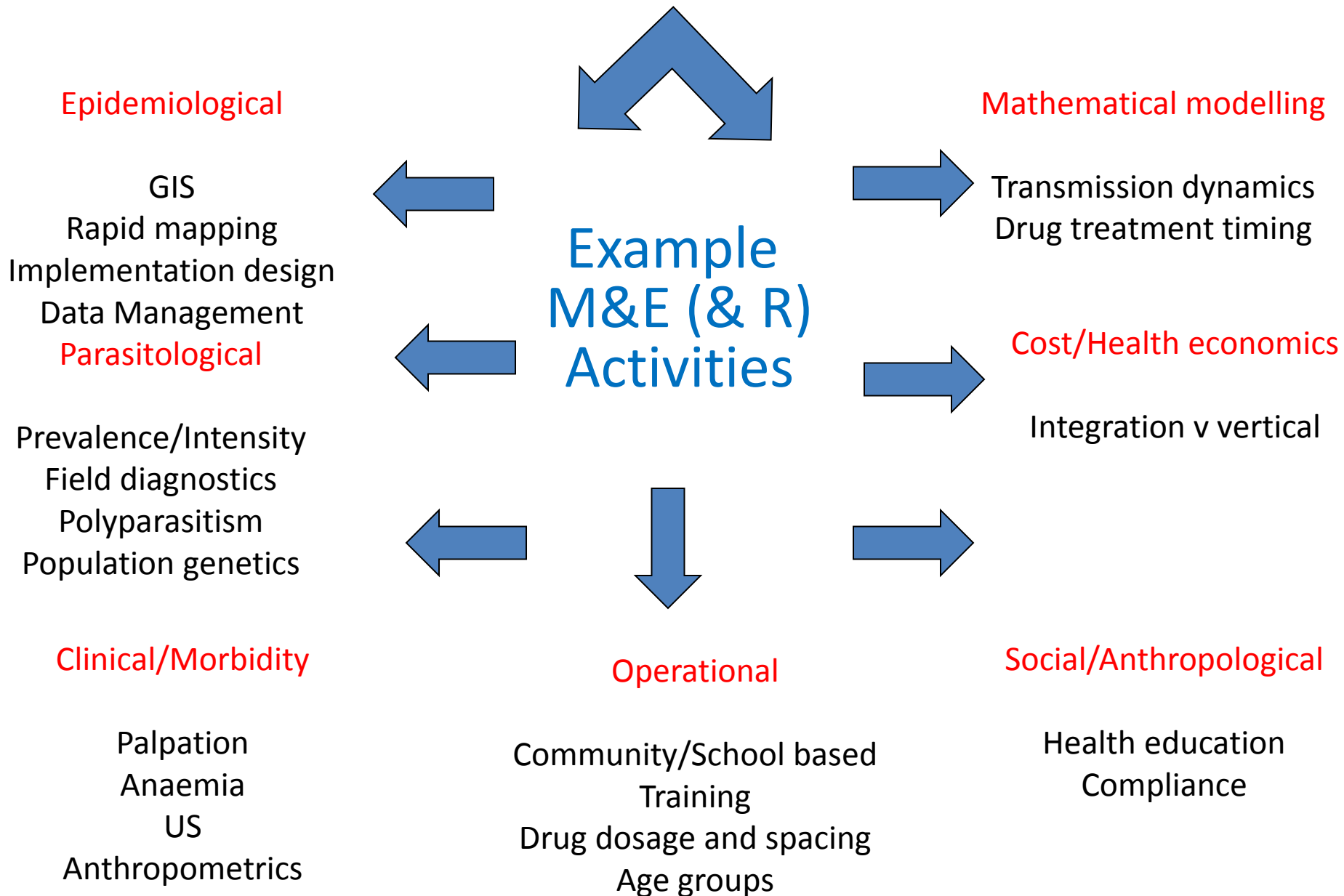
- > 273 million chemotherapeutic treatments provided for children and at-risk adults to date (2003-2010)

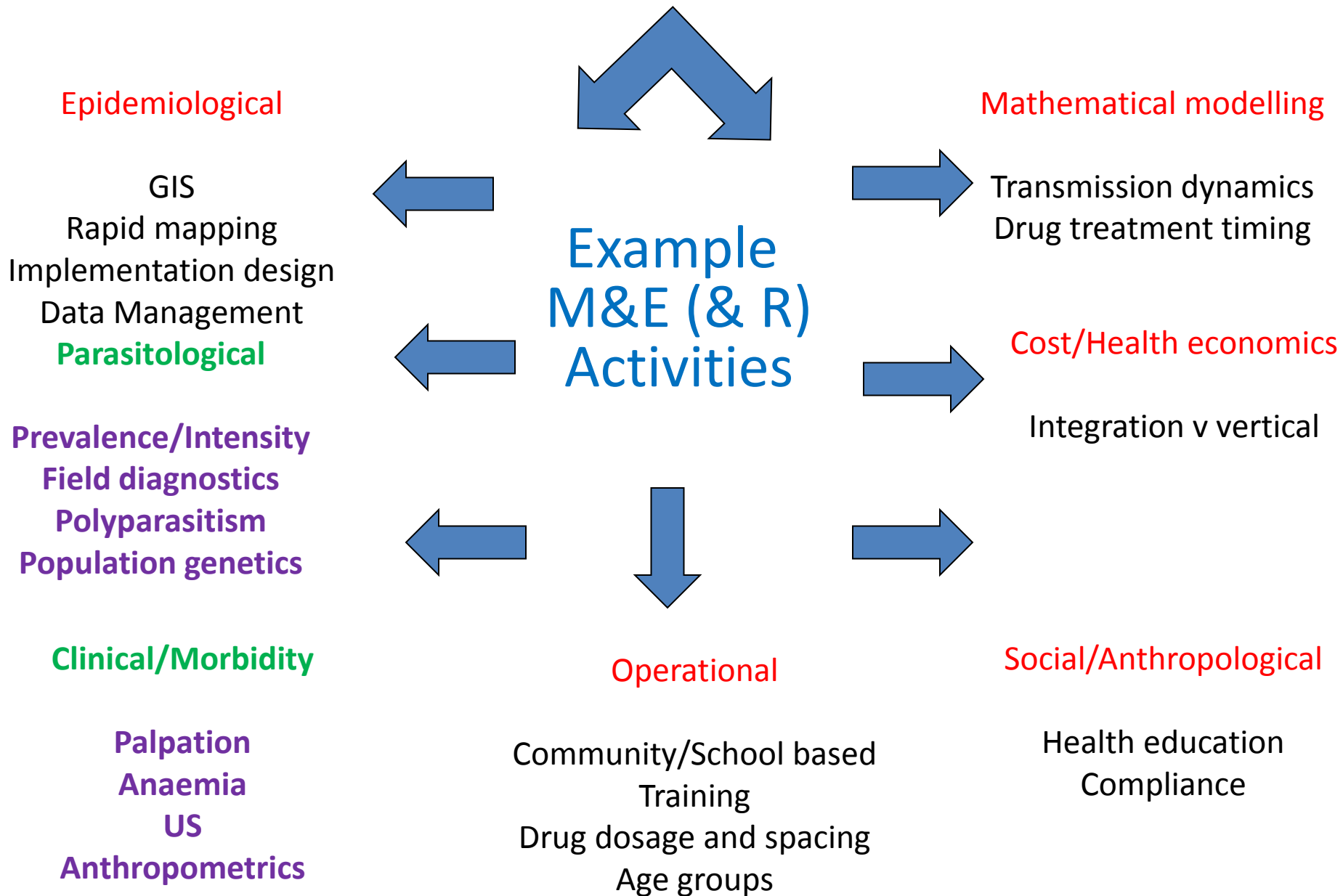
Against up to 7 major NTDs.



The Schistosomiasis Control Initiative (SCI) Mission

- SCI, supports the WHA resolution that all member state infected regions aims “to provide regular treatment for 75% of all school-aged children for schistosomiasis and intestinal helminths”, ✓
- To encourage treatment of schistosomiasis in sub-Saharan Africa by targeting those at high risk of developing severe morbidity, especially school-aged children, women and those in high risk occupations. ✓
- By assisting selected countries to achieve successful **SUSTAINABLE** national control programmes, SCI expects to create a sustainable access and demand for treatment. ✓
- To develop and implement rigorous monitoring and evaluation.
- To thereby reduce prevalence, intensity and associated morbidity of schistosomiasis and STH infections.








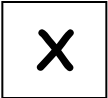
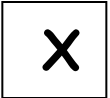































Morbidity



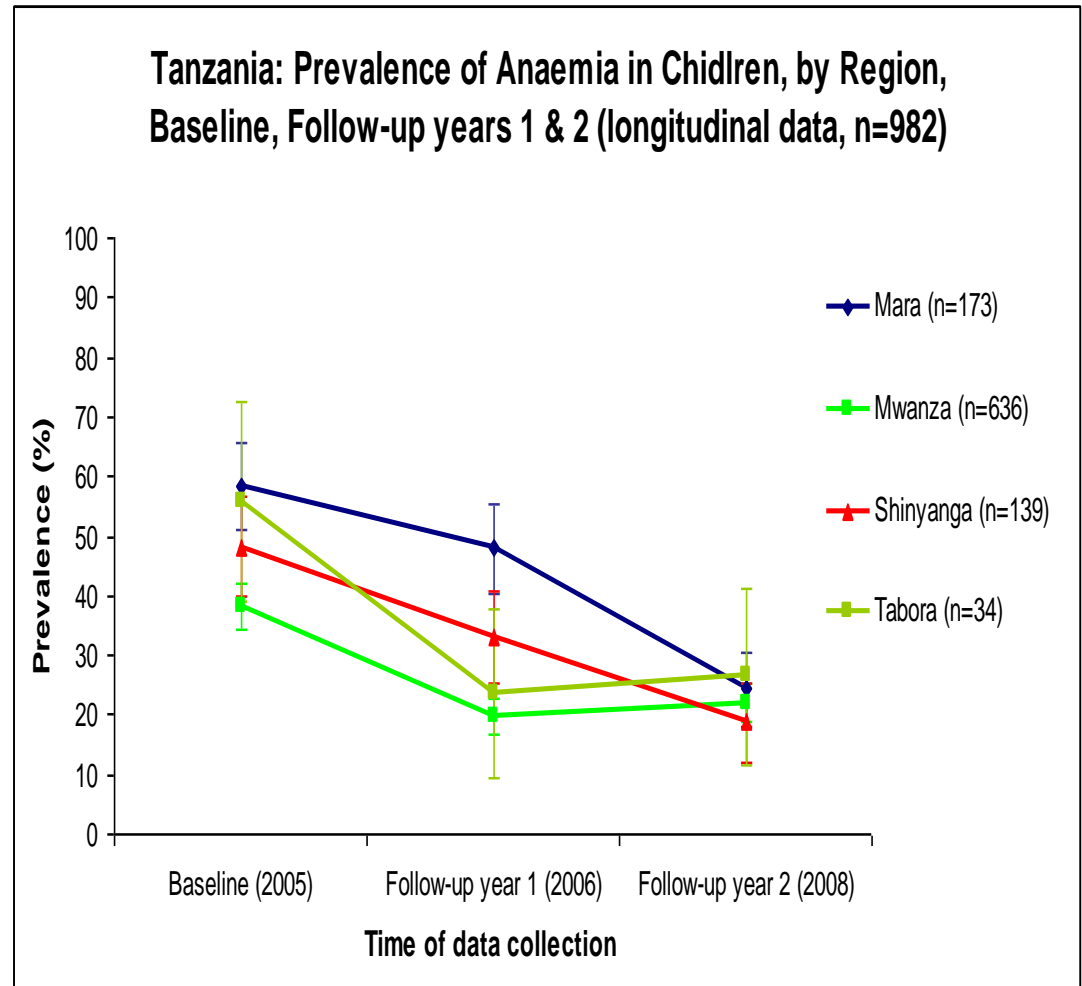
S. haematobium & *S. mansoni*

Comprehensive Monitoring and Evaluation (M&E), with associated research, incorporated into the design and implementation of all SCI mass chemotherapy right from the onset.

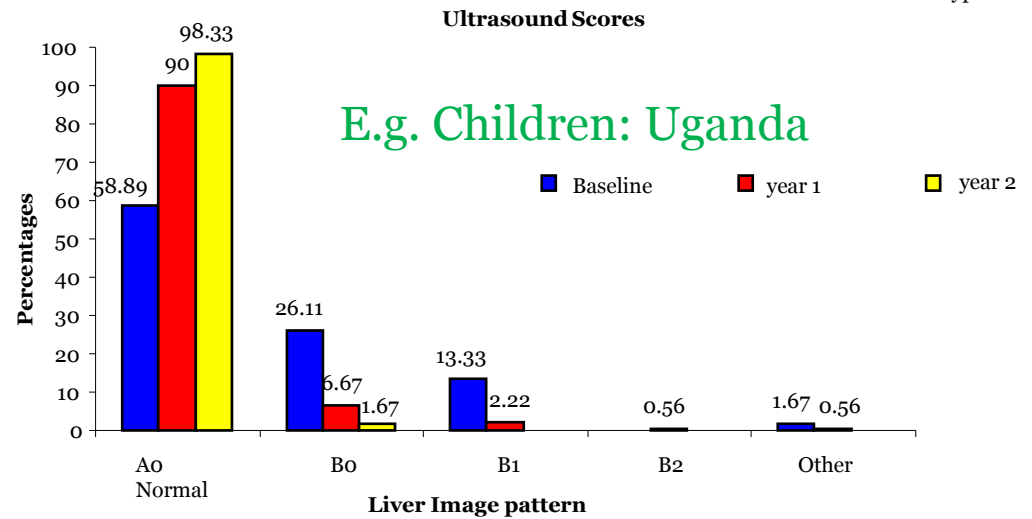
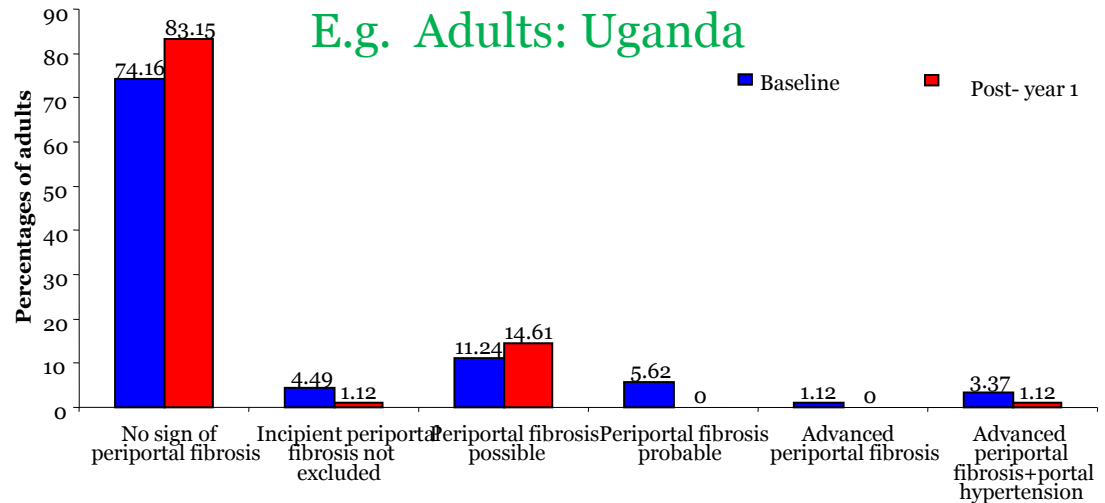
Identifiable longitudinal aged-structured cohort sampling within schools/school-aged children

	6	7	8	9	10	11
Year 0						
Year 1						
Year 2						
Year 3						
Year 4						
Year 5						

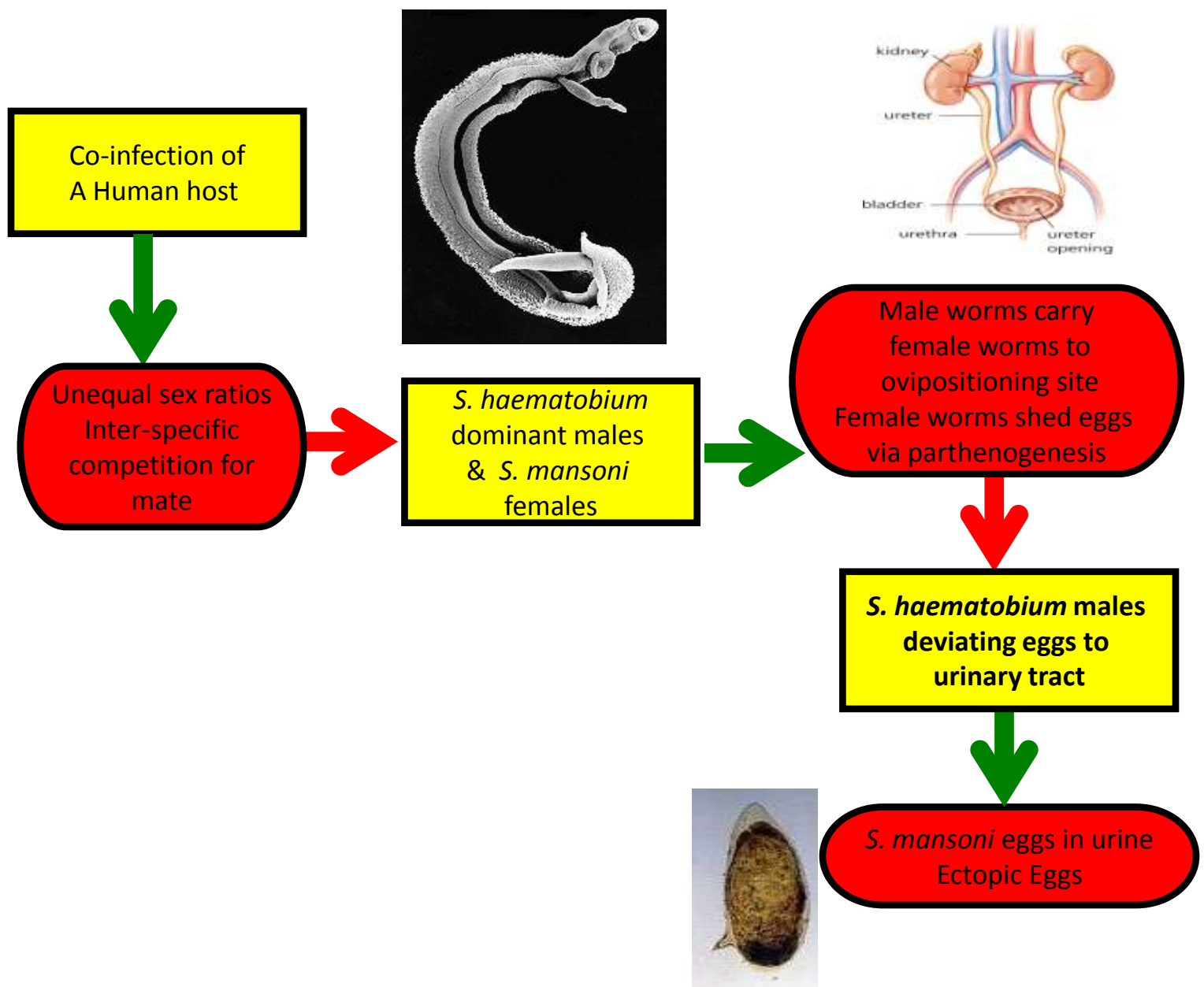
Evaluation and application of anaemia morbidity indicators for schistosomiasis in the context of MDA



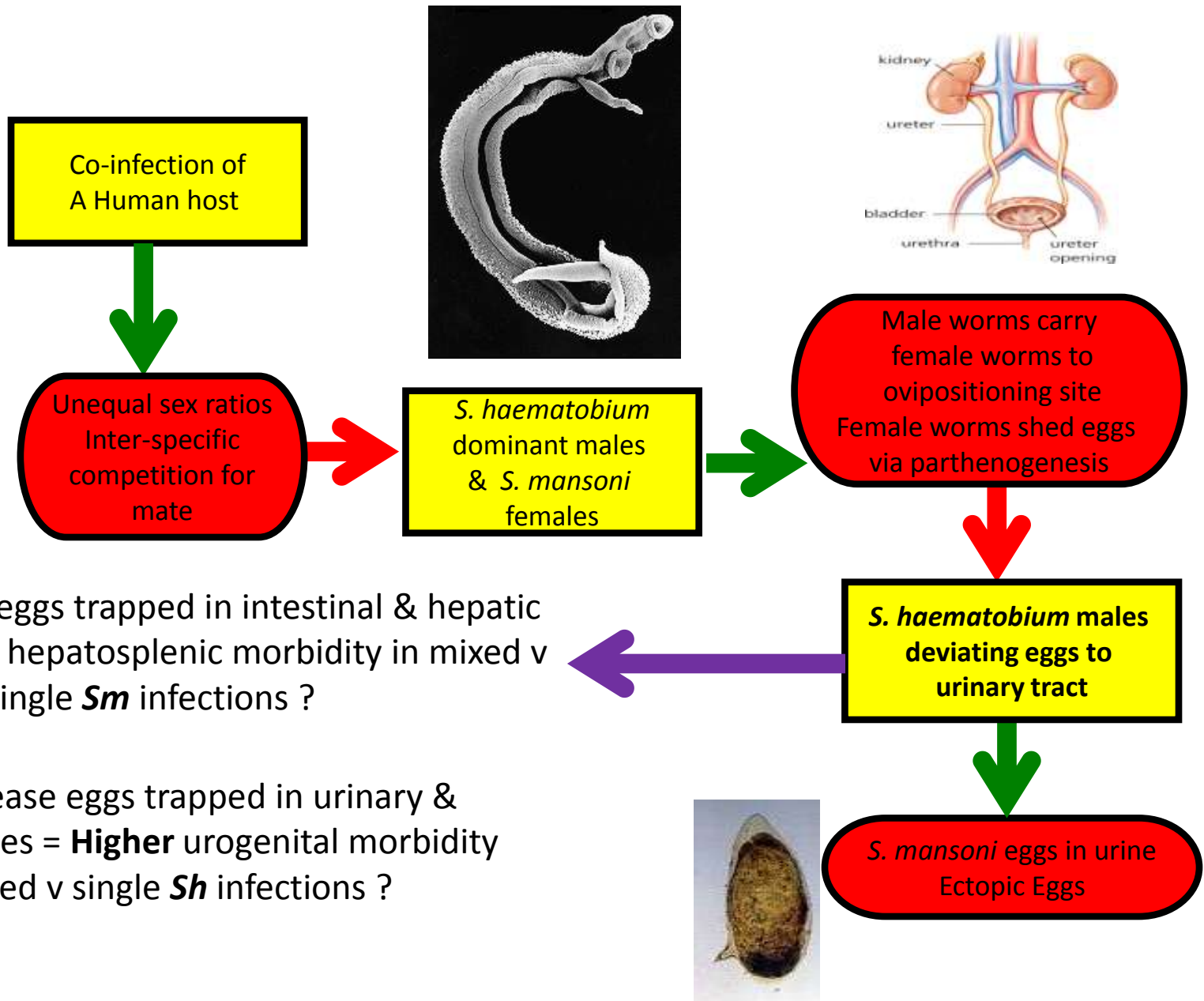
Evaluation and application of ultrasound morbidity indicators for schistosomiasis in the context of MDA



E.g. 3 Evaluation and application of mixed species morbidity indicators for schistosomiasis in the context of MDA: *S. mansoni* & *S. haematobium* coinfections



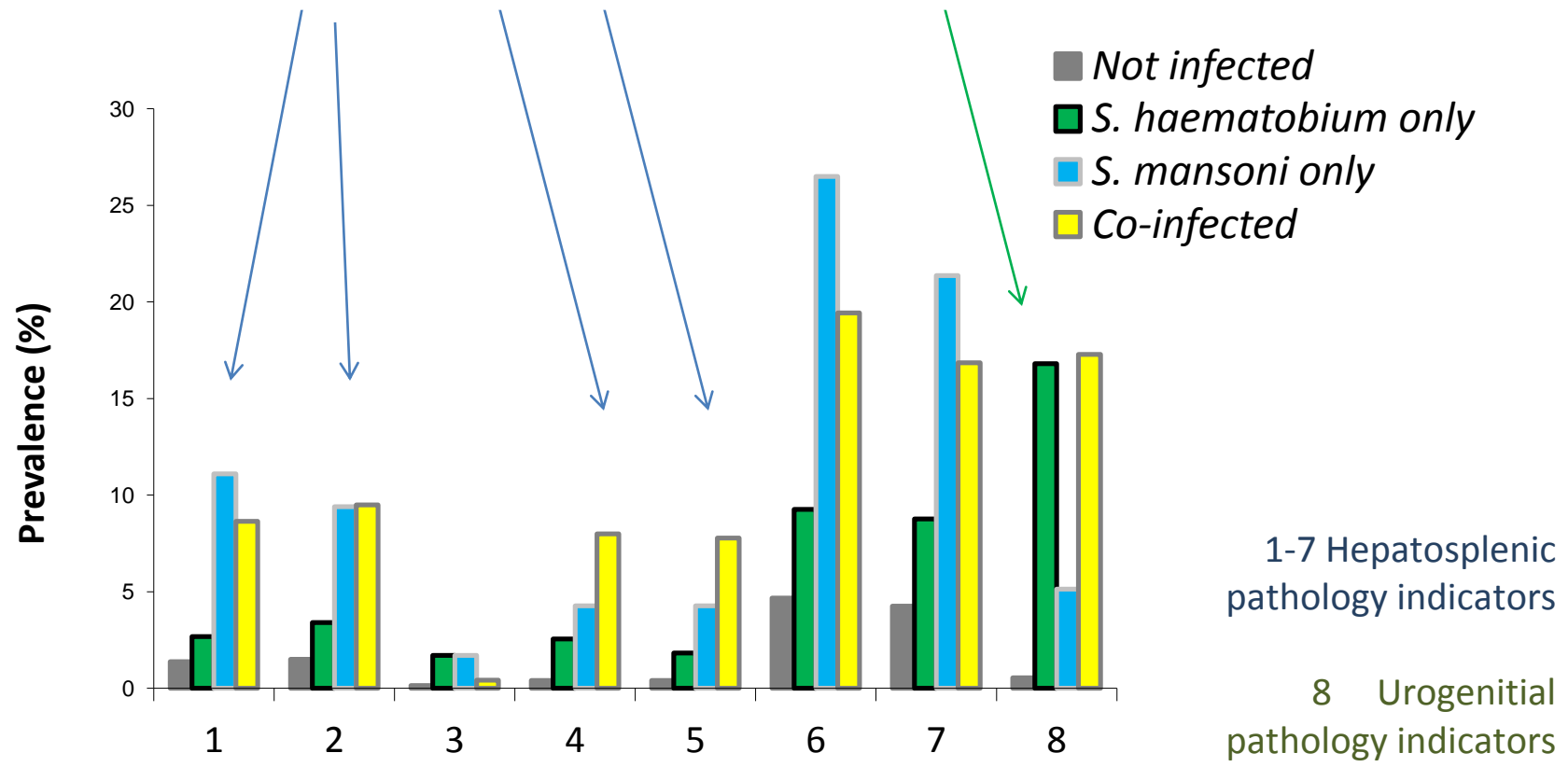
E.g. 3 Evaluation and application of mixed species morbidity indicators for schistosomiasis in the context of MDA: *S. mansoni* & *S. haematobium* coinfections



Morbidity in *S. mansoni* : *S. haematobium* infections and coinfections: e.g. Mali

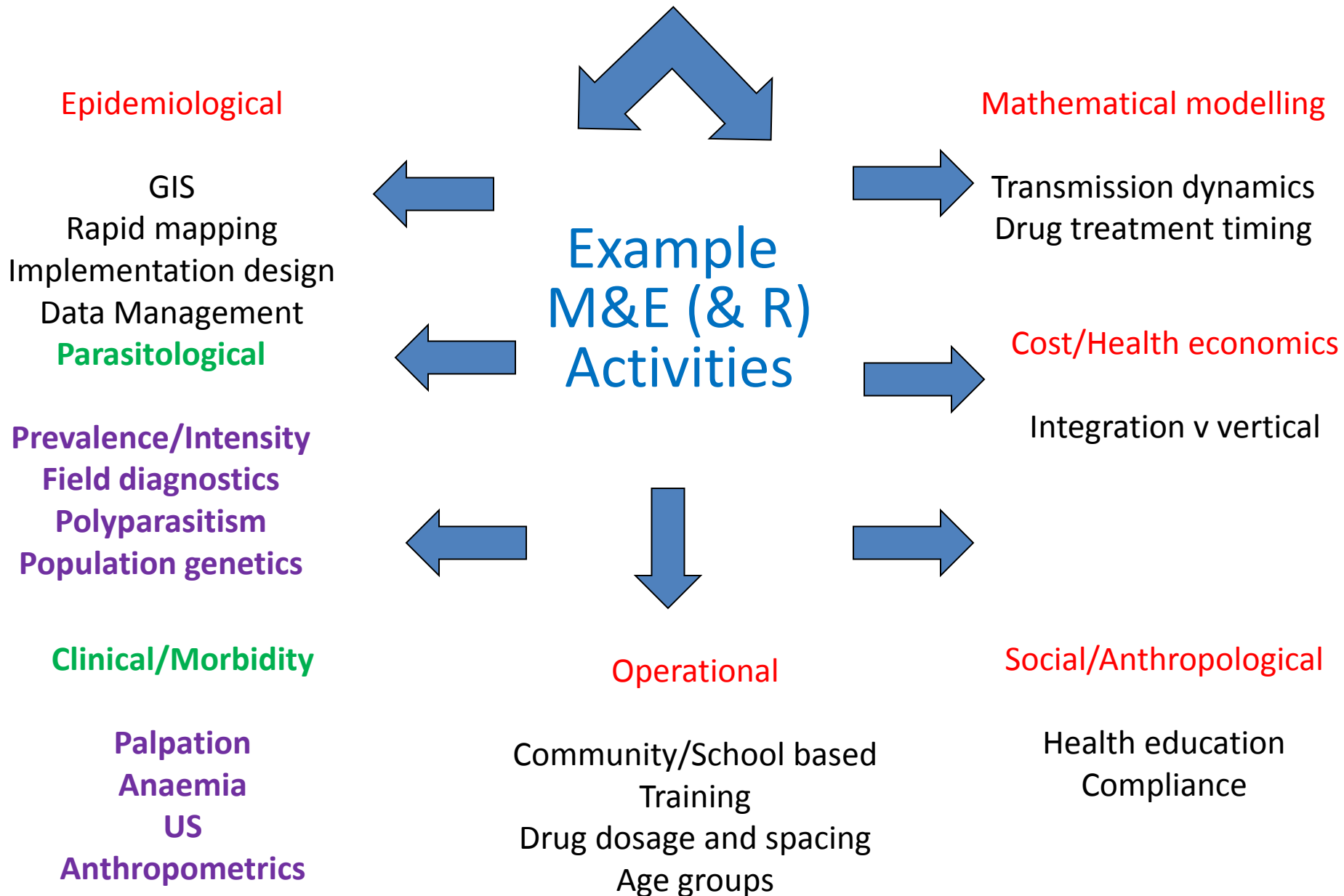
P1 := Lower hepatosplenic morbidity in mixed v single *Sm* infections ? 'Yes'

P2 := Higher urogenital morbidity in mixed v single *Sh* infections ? 'Yes'

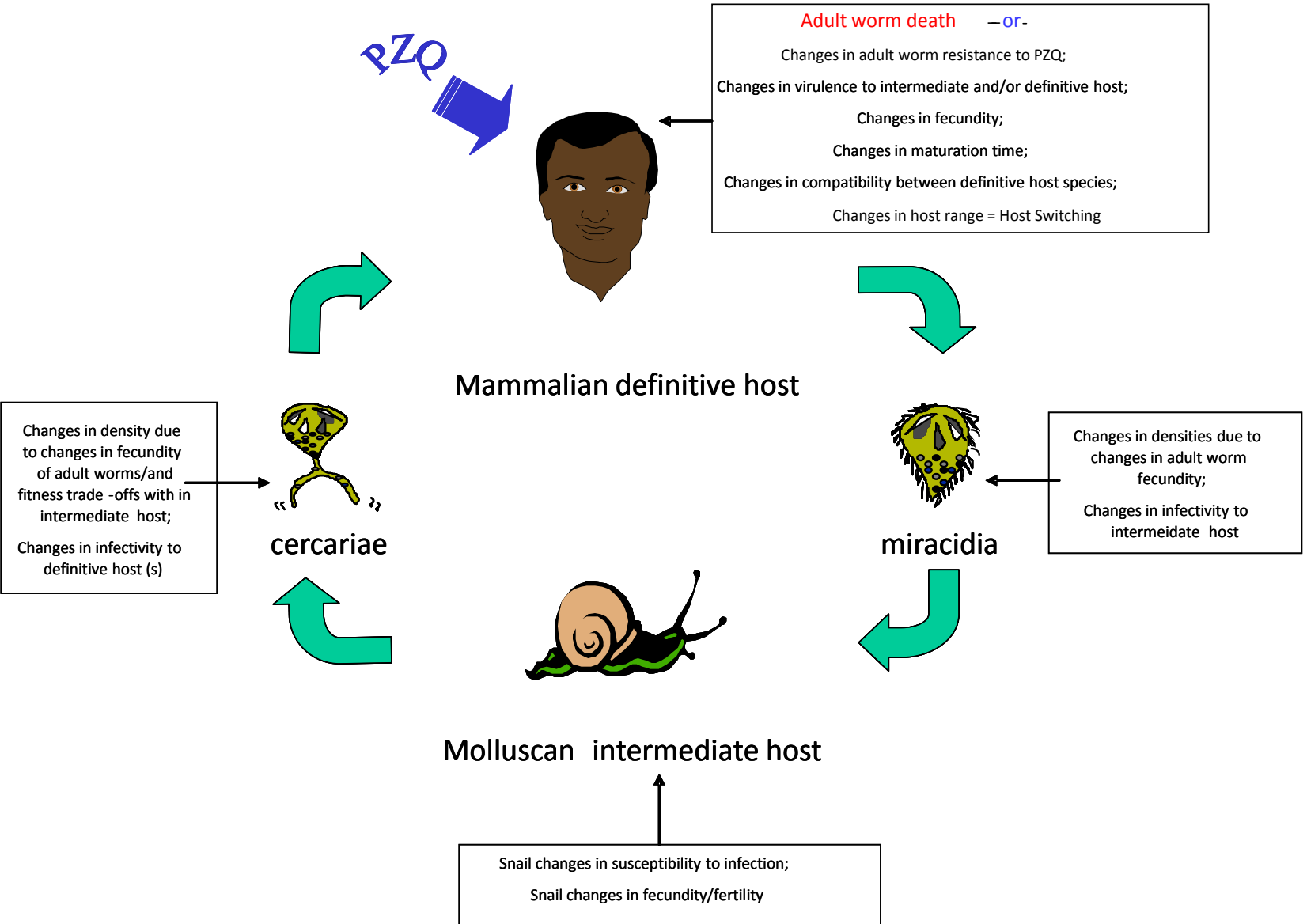


Evaluation of liver , spleen and urinary morbidity in the context of Polyparasitism and MDA

Webster, J.P., Koukounari, A., Lamberton, P.H.L., Stothard, J.R. & Fenwick, A. (2009) *Parasitology*
 Gouvas, A.N., Koukounari, A., Kariuki, C.H., Norton, A.J., Lange, C., Fenwick, A. & Webster, J.P. (2011/in press) *Acta Tropica*
 Koukounari, A., Donnelly, C. A., Sacko, M., Keita, ...Fenwick, A. & Webster, J. P. (2010). *BMC Infectious Diseases*,



Potential effects of mass chemotherapy schistosomiasis control programmes on the different parasite life stages.



Webster, J.P., Gower, C.M. & Norton, A.J. (2008) *Evolutionary Applications*
 Webster, J.P., Gower, C.M. & Blair, L. (2004) *American Naturalist*

The evolution of *Schistosoma* spp. in response to chemotherapeutic pressure.

Knowledge on how the phenotype and genotype of the parasite population changes in response to Praziquantel (PZQ) pressure is an essential component of mass chemotherapy M&E

and

could have important implications for the success of these programmes.

Schistosome PZQ R ?

AGAINST:

- No evidence from China.
- Drug resistance in Senegal? Probably not.
- No increase 10 years later in Egypt – High COSTS of RESISTANCE?
- Predicted large *refugia*
- Long generation time in human host.

FOR:

Resistance to all veterinary antihelminthics

Can select for PZQ resistance in animal models

Parasite evolution over short time periods

Non-random mating amongst schistosomes

Isolation of parasites with reduced sensitivity in Egypt

Current/Recent MDA programs are highly successful – strong selective pressures

Currently reliant on a single drug

Monitoring is difficult – no (informative or non-informative) molecular markers available; lack of mechanistic knowledge of PZQ action or R

Could rare resistance-conferring alleles be already present in untreated populations?

Development of drug resistance?

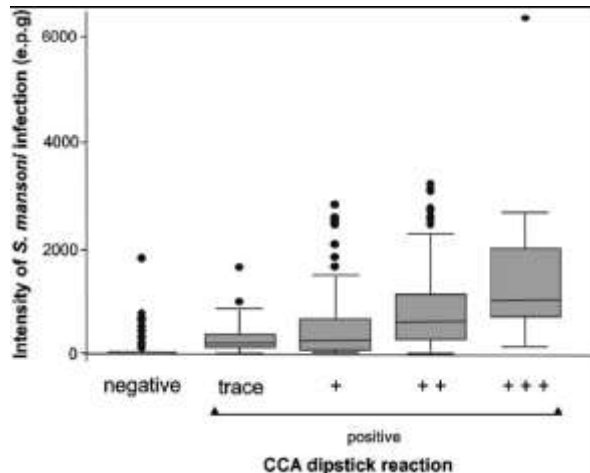
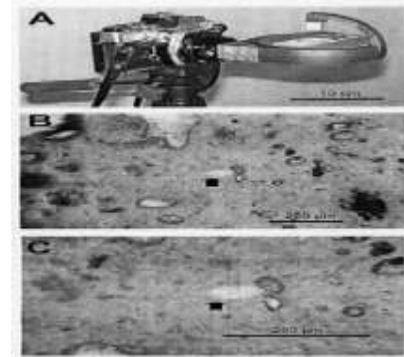
Changes in parasite population genetic structure?

Field Diagnostics Evaluation and Application

Field evaluation for rapid diagnosis of *S. mansoni*: Meade Readiview handheld microscope

e.g.

Stothard, J.R., Kabatereine, N.B., Tukahebwa, E., Kazibwe, F., Webster, J.P., & Fenwick, A. (2005). *Am J Trop Med Hyg*



Use of circulating cathodic antigen (CCA) dipsticks for detection of intestinal and urinary schistosomiasis.

Stothard, J.R., Kabatereine, N.B., Tukahebwa, E., Kazibwe, F., Rollinson, D., Mathieson, W., Webster, J.P., & Fenwick, A. (2006). *Acta Tropica*,

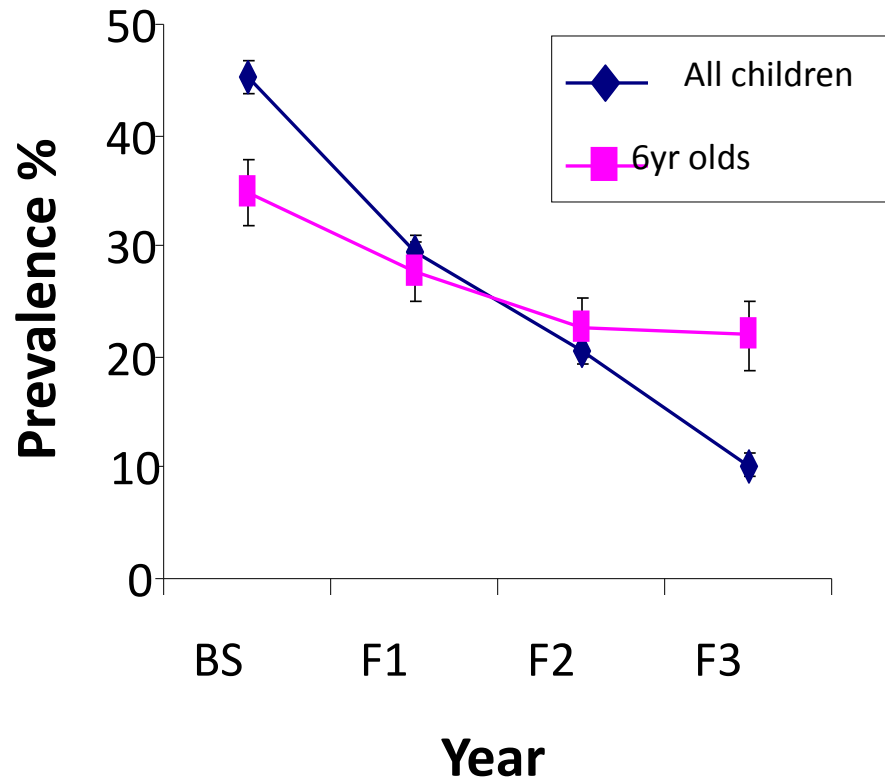
Sensitivity and Specificity of diagnostic tests

Koukounari, A., Webster, J.P., Donnelly, C.A., Bray, B.A., Naples, J., Bosompem, K. & Shiff, C. (2009). *Am. J Trop Med Hyg*

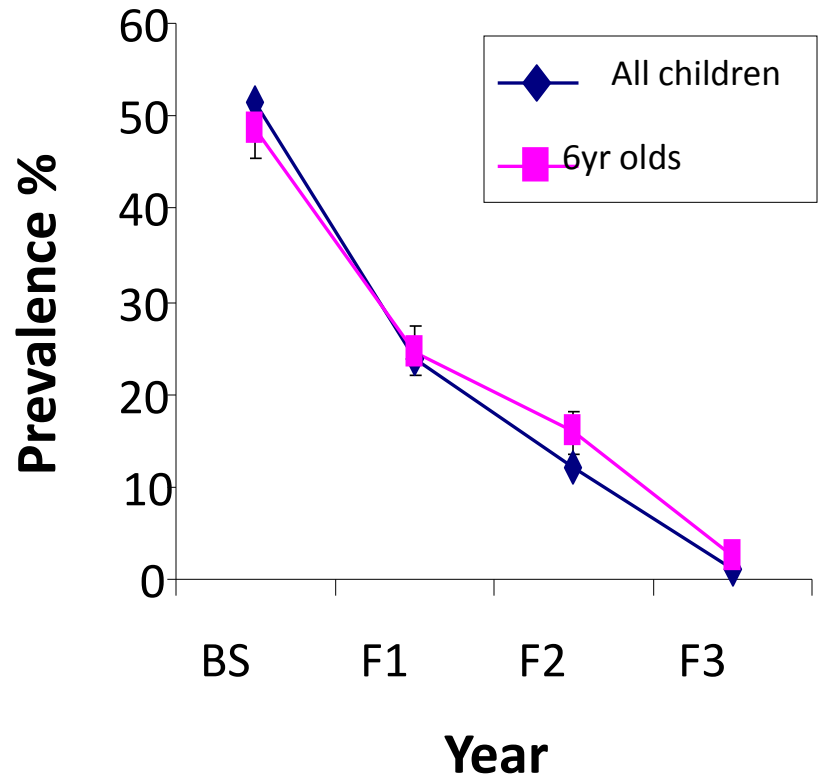


Dramatic reductions in Prevalence have been observed

S. mansoni



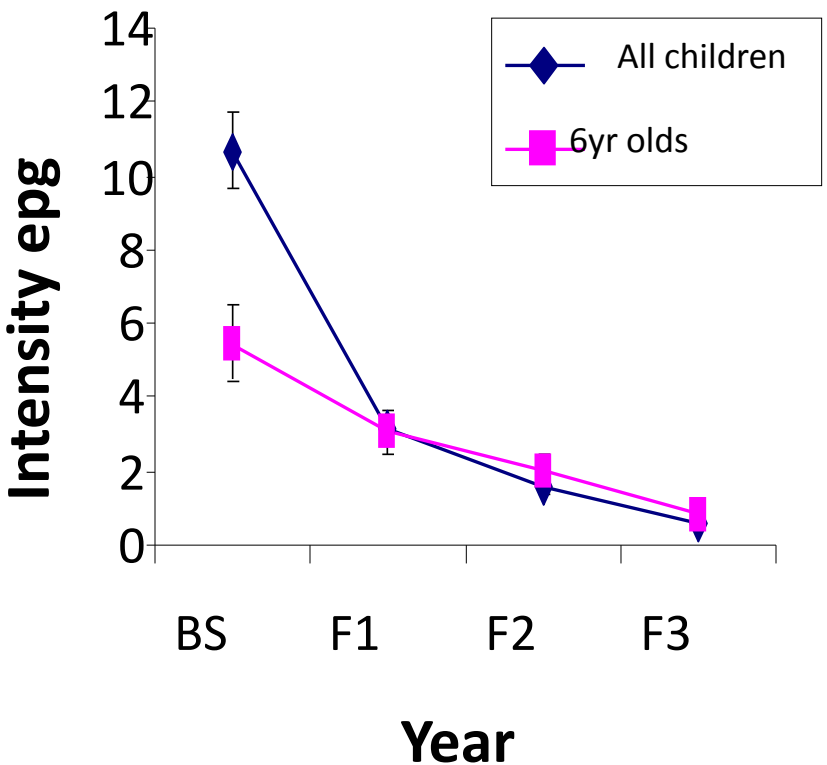
Hookworm



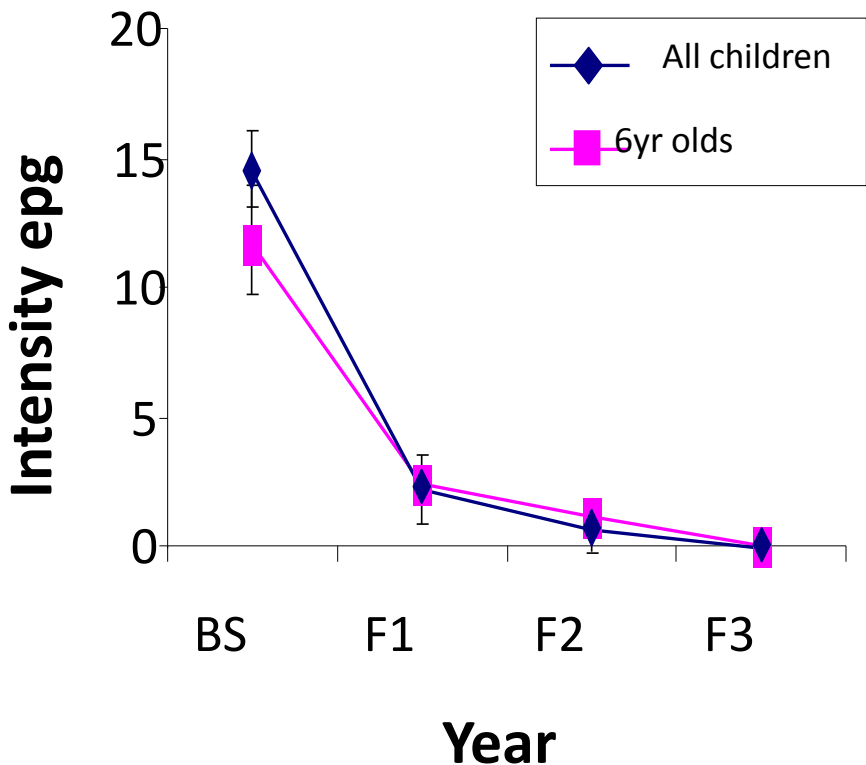
E.g. Ugandan school-aged children

Dramatic reductions in Intensity have been observed

S. mansoni



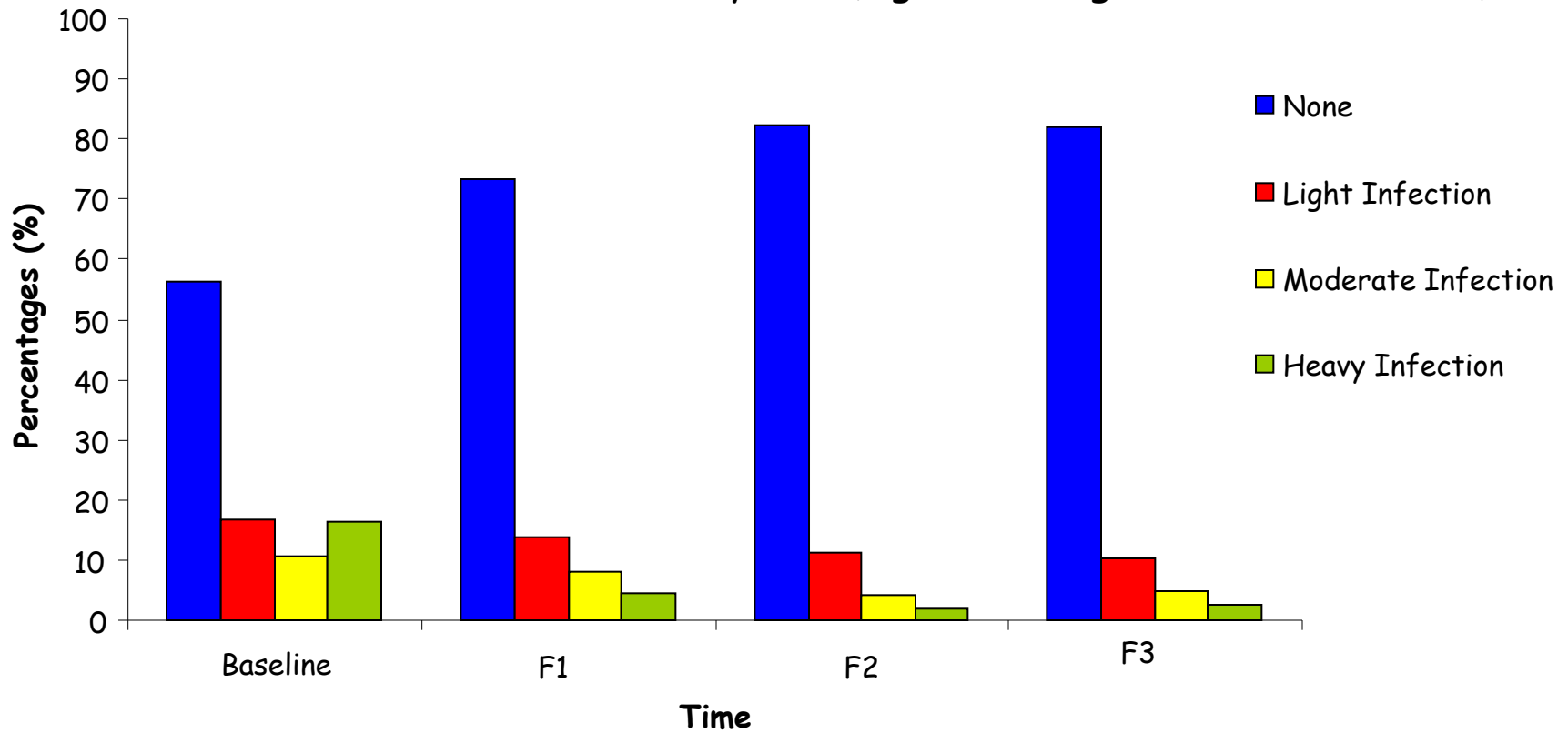
Hookworm



E.g. Ugandan school-aged children

Dramatic reductions in Highest Intensity infections

E.g. S. mansoni prevalence of light, moderate, heavy infection intensities for children over 4 years (Ugandan longitudinal data n=991)



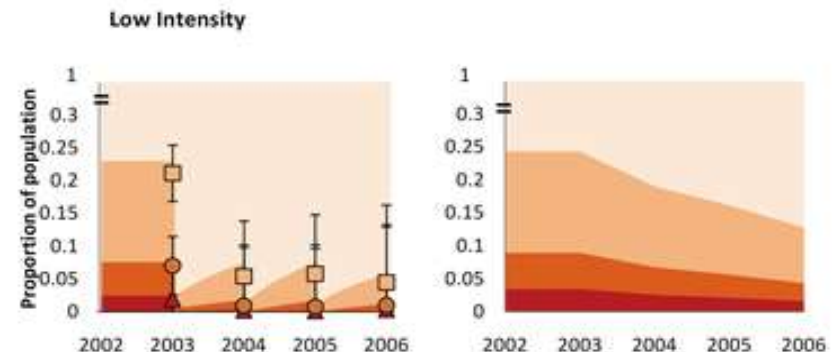
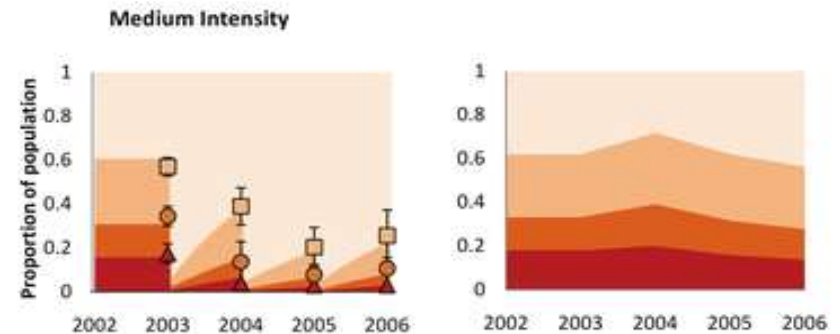
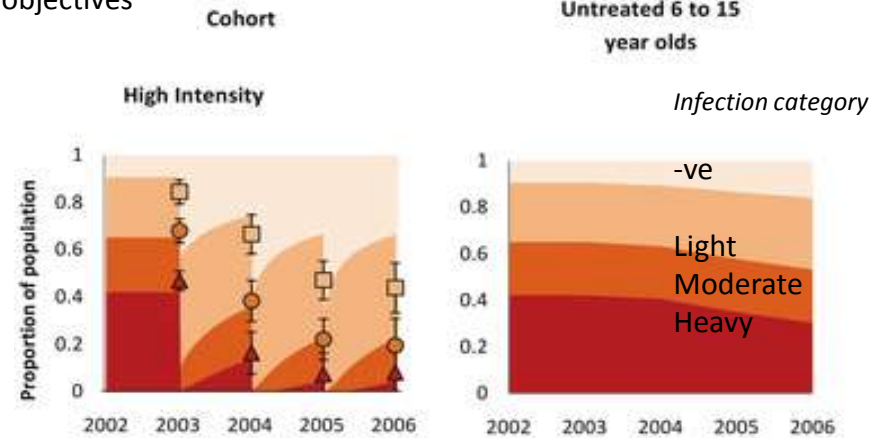
Mathematical Modelling M&E

Mathematical modelling can be used to evaluate the impact of a control programme and to investigate the optimum approaches in order to achieve target programme objectives

E.g. 1 Estimating reductions in the Force of Infection/transmission – Uganda *Sm*

- The rate at which individuals are acquiring parasites
- This will have an impact on those not receiving treatment as well as those that do. Missing this can lead to an underestimate of the impact of a control programme
- Informs policy decisions

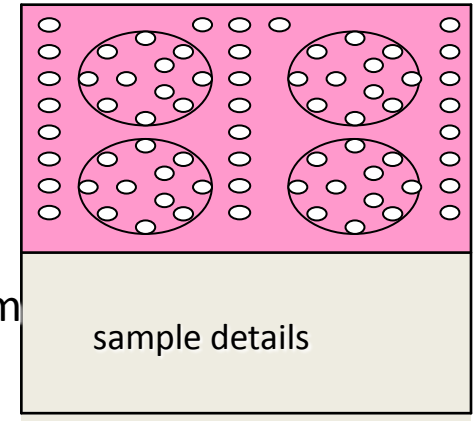
Reduction in Force of Infection	High Intensity Areas	Medium Intensity Areas	Low Intensity Areas
After 1 round of treatment	30.4% (15.6-45.3%)	6.9% (-21.2-35%)	74.7% (57.5-92.0%)
After 2 rounds of treatment	68.6% (61.4-75.7%)	62.5% (46.8-78.3%)	70.2% (58.3-82.2%)
After 3 rounds of treatment	67.9% (59.9-75.9%)	48.9% (26.5-71.3%)	79.4% (67.4-91.5%)



Significant reductions observed in high and low intensity areas following 1 round of treatment, and in medium intensity areas following two rounds. Stayed suppressed following a third round.

French, M.D., Churcher, T.S., Gambhir, M., Fenwick, A., Webster, J.P., Kabatereine, N. and Basáñez, M.-G. (2010) *PLoS NTDs*

Parasite Population genetics M&E



Miracidia are picked up from petri dish and stored on whatman cards



Faecal sample for *S. mansoni*



sieve

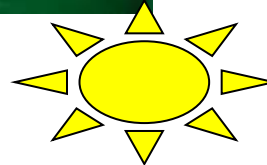


Urine sample for *S. haematobium*



Filtration through 'pitchford funnel' removes debris and washes eggs.

Miracidia hatch from eggs under the stimuli of sunlight and fresh water

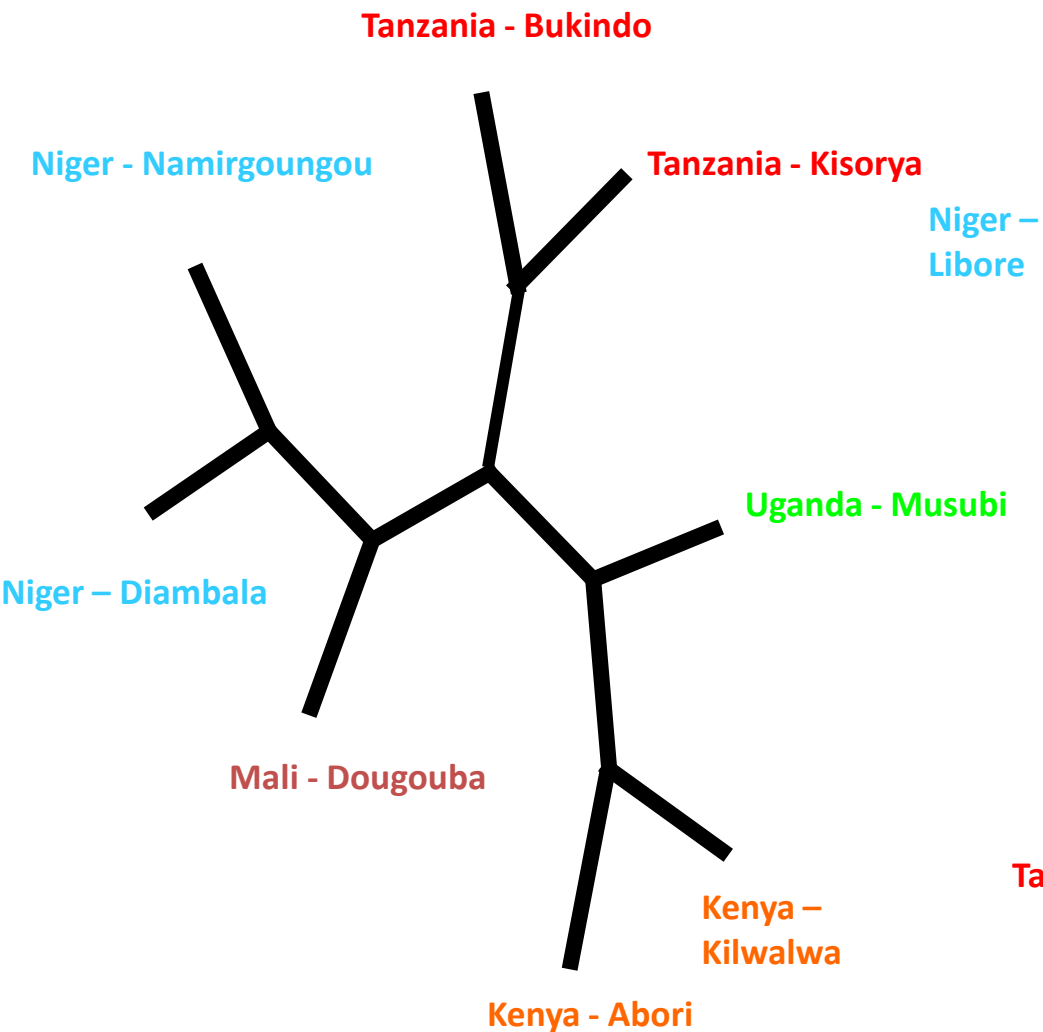


Petri dish

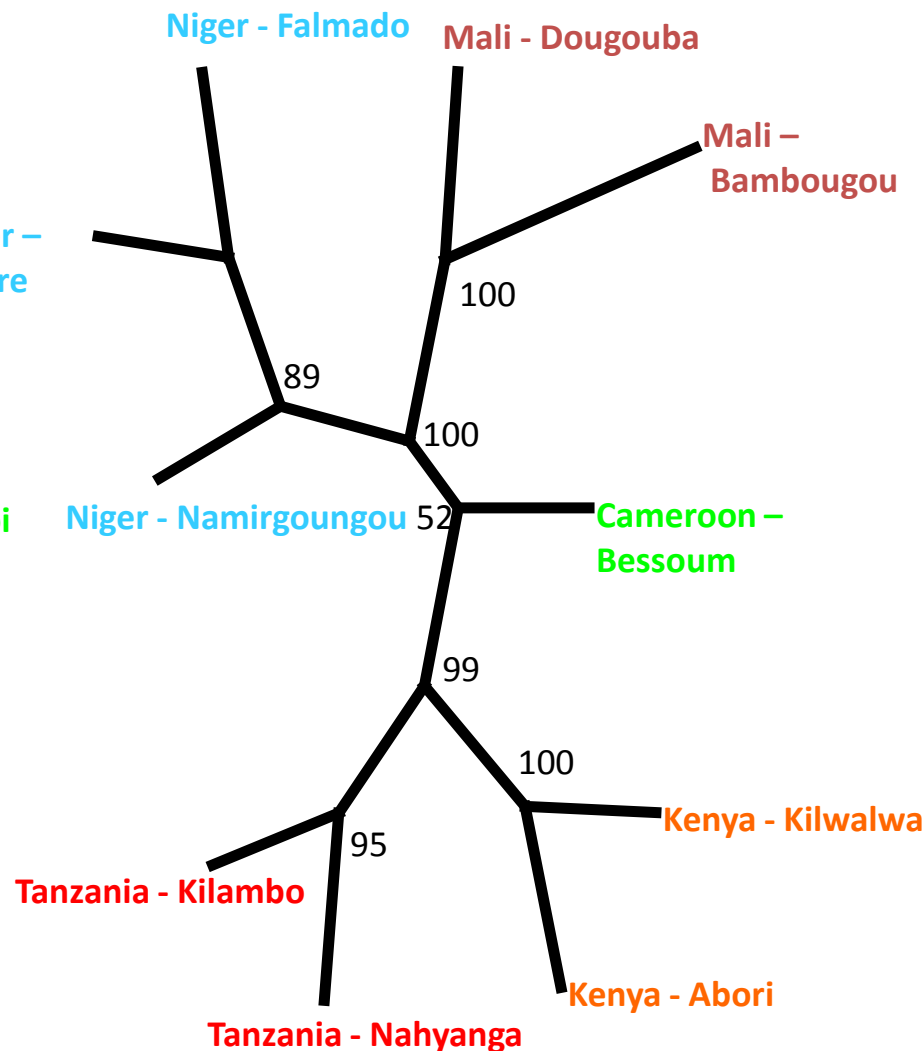


E.g. 1b: Schistosomes segregate by country.

S. mansoni by country

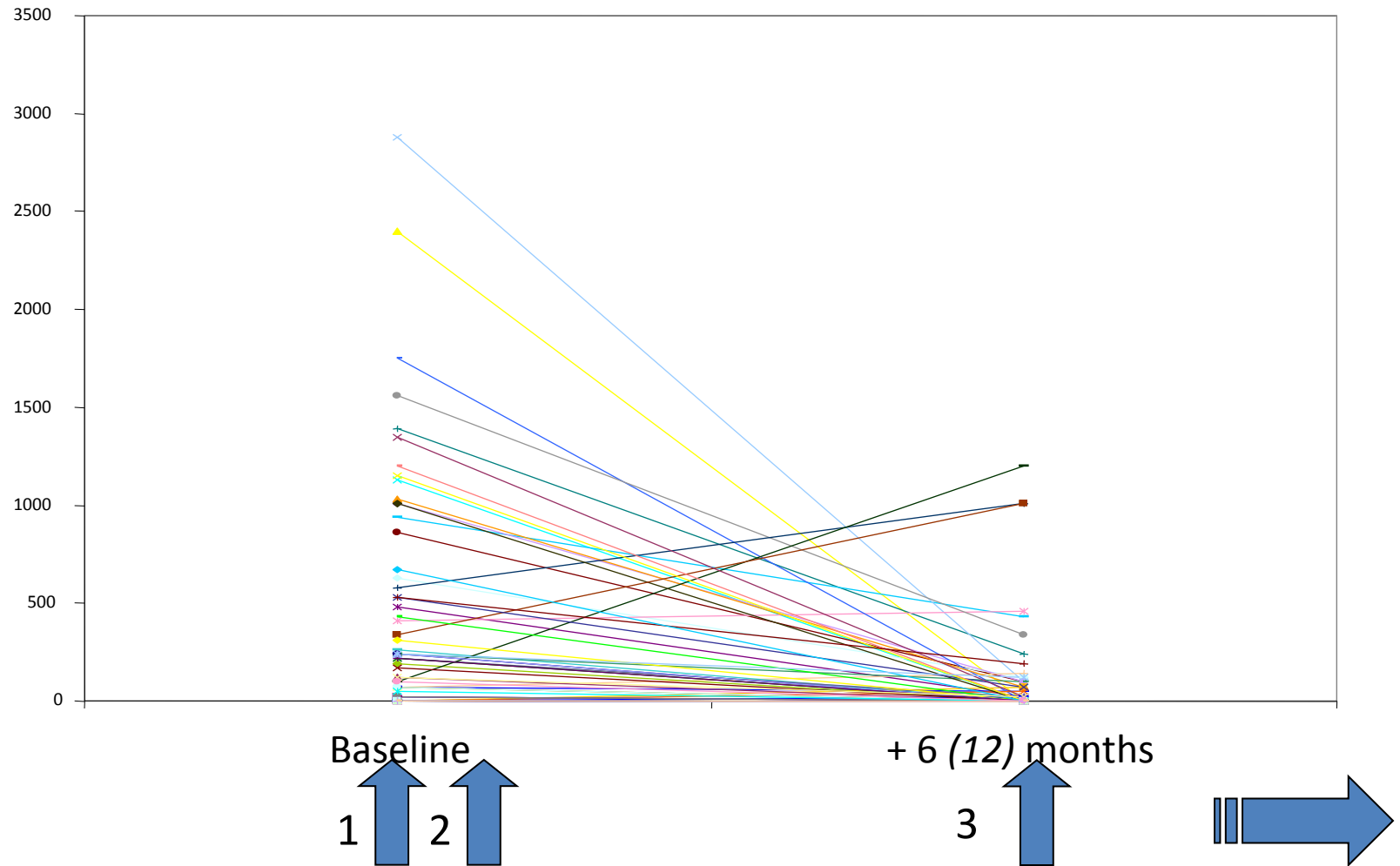


S. haematobium by country



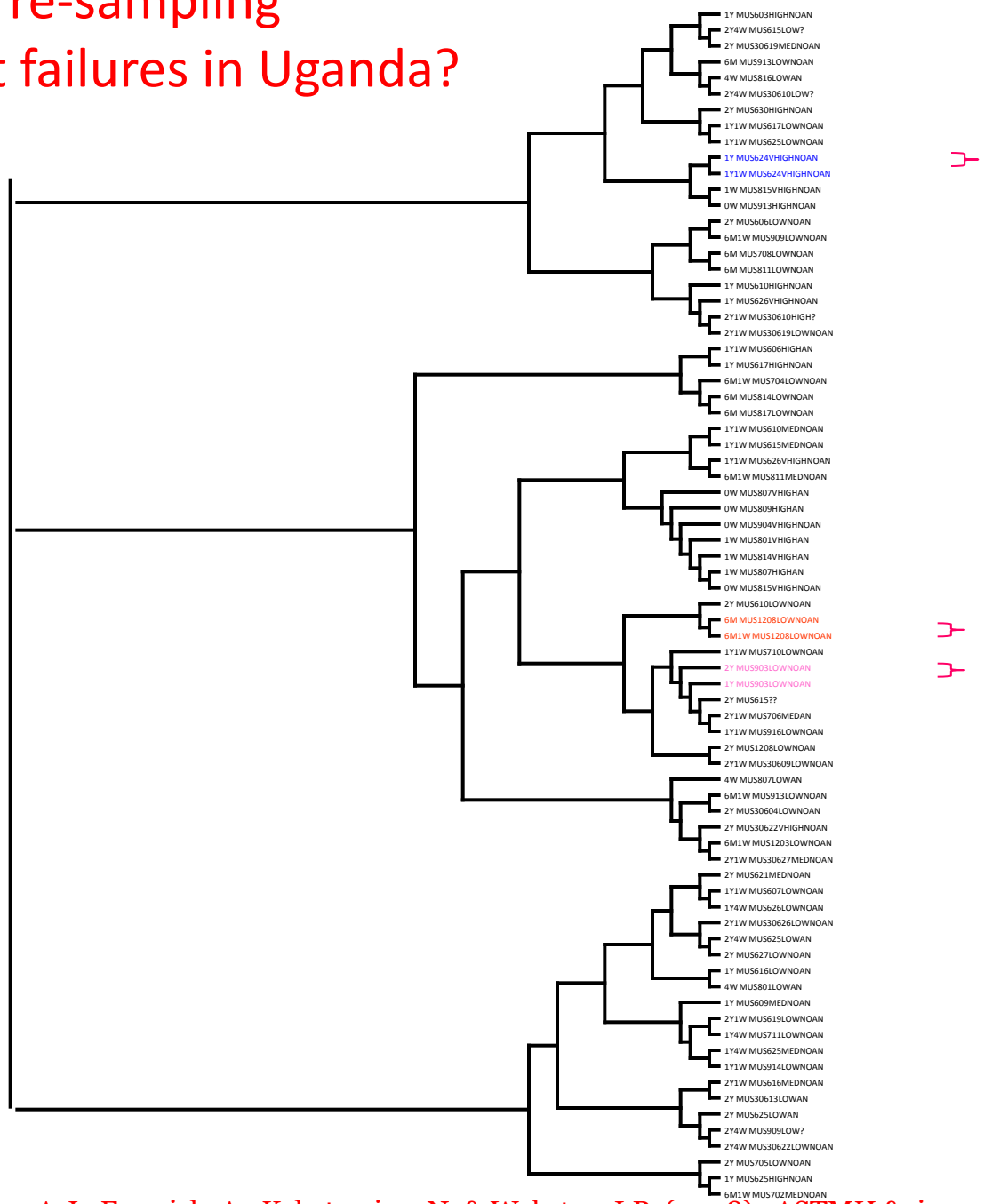
Population genetics of *S. mansoni* and *S. haematobium* linked to praziquantel drug pressure

Random and focal-sampling of *Schistosoma spp.* population genetic structure over PZQ treatment history



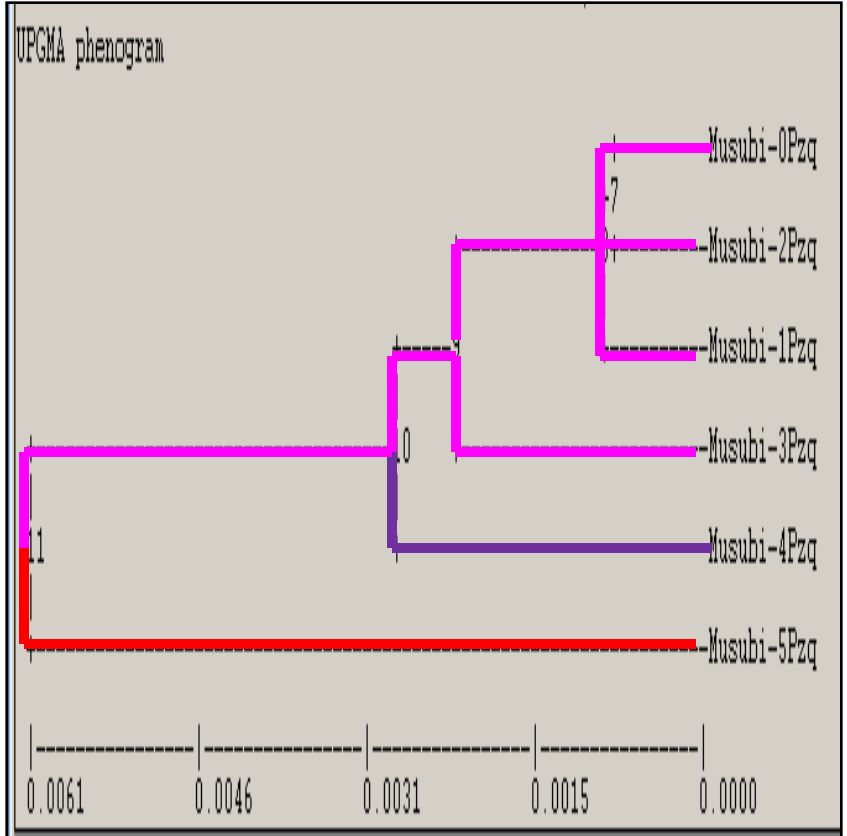
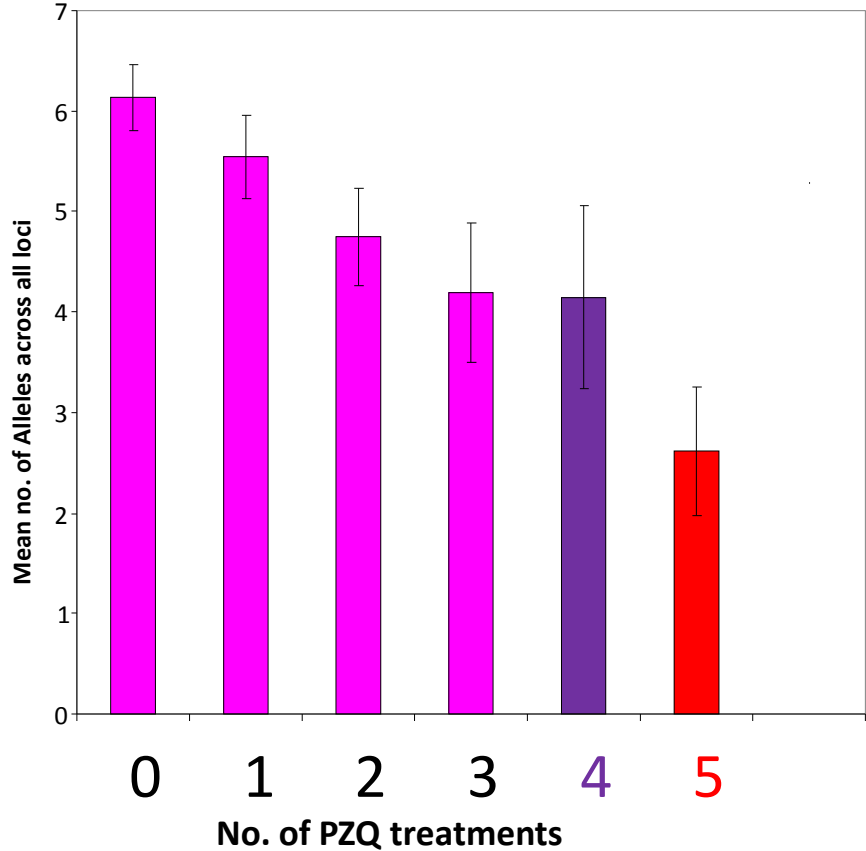
E.g. 2. Longitudinal post-PZQ re-sampling demonstrates rare treatment failures in Uganda?

- Most miracidial samples collected from the same individuals at different time points did not cluster together
- However, three children (624, 903 and 1208) did cluster between time points
- But different between children – so not one specific genotype/genotype combination associated with lack of clearance.



E.g. 3. Longitudinal post-PZQ re-sampling indicates bottleneck (and sub-structuring) in parasite diversity in response to PZQ MDA in Uganda (*and Tanzania etc*).

Fig. reduction in allele number with increasing PZQ treatments over the 3 years ($p=0.001$).



Lamberton, P.H., Norton, A.J., Fenwick, A., Kabatereine, N. & Webster, J.P. (2008). *ASTMH & in prep*
Norton, A.J., Gower, C.M., Lamberton, P.H.L., Webster, B.L., Lwambo, N.J., Fenwick, A. & Webster, J.P. (2010) *AJTMH*

Genetic consequences of Mass Human Chemotherapy selective pressures for *Schistosoma mansoni* populations

No molecular markers for PZQ Resistance available yet.

But,

Significant 'bottleneck' imposed by mass treatment on schistosome population genetics

Hence

'Effective reservoir' may be smaller than previously thought (re *refugia*)?

Continued significant reductions in diversity may reduce the schistosomes ability to adapt and survive any future novel environmental selective pressures to which they may be exposed.

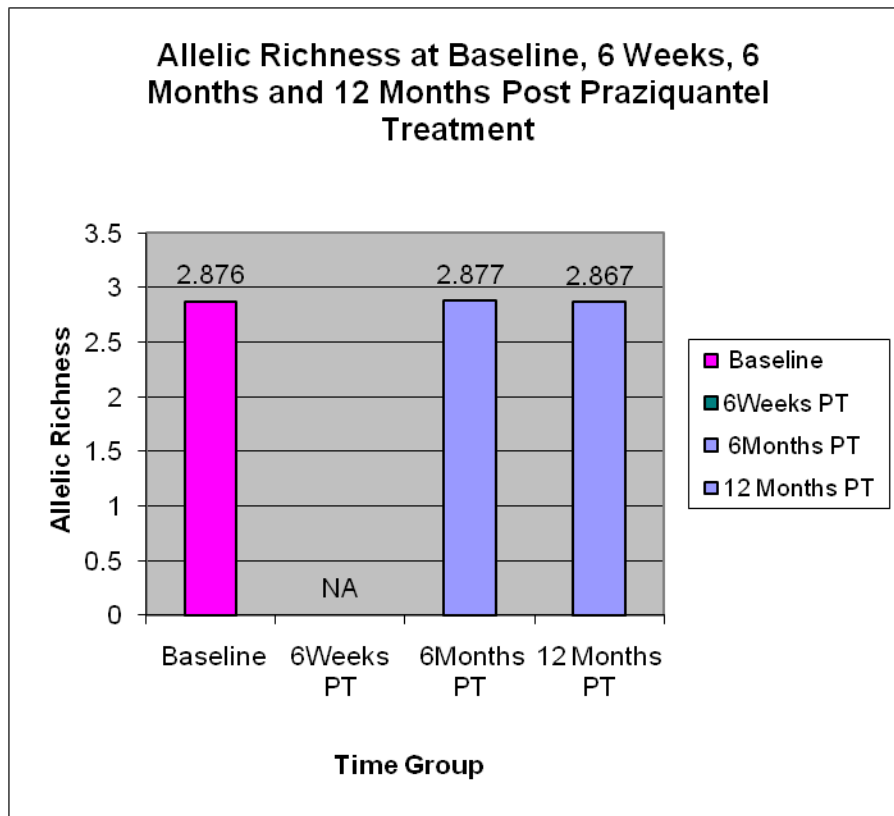
Or

Increased success of a small number of, potentially Resistant, alleles (identify selection)?

Genetic consequences of Mass Human Chemotherapy selective pressures for *Schistosoma haematobium* populations (!)

No (consistent) 'bottleneck' imposed by MDA on *S. haematobium* population structure.
Certain sites with very high reinfection/lowered clearance despite MDA

E.g. West Africa (*Niger*)



School v Community **X**

Established v Recent selective pressures – **X**

East v West Africa **X/?**

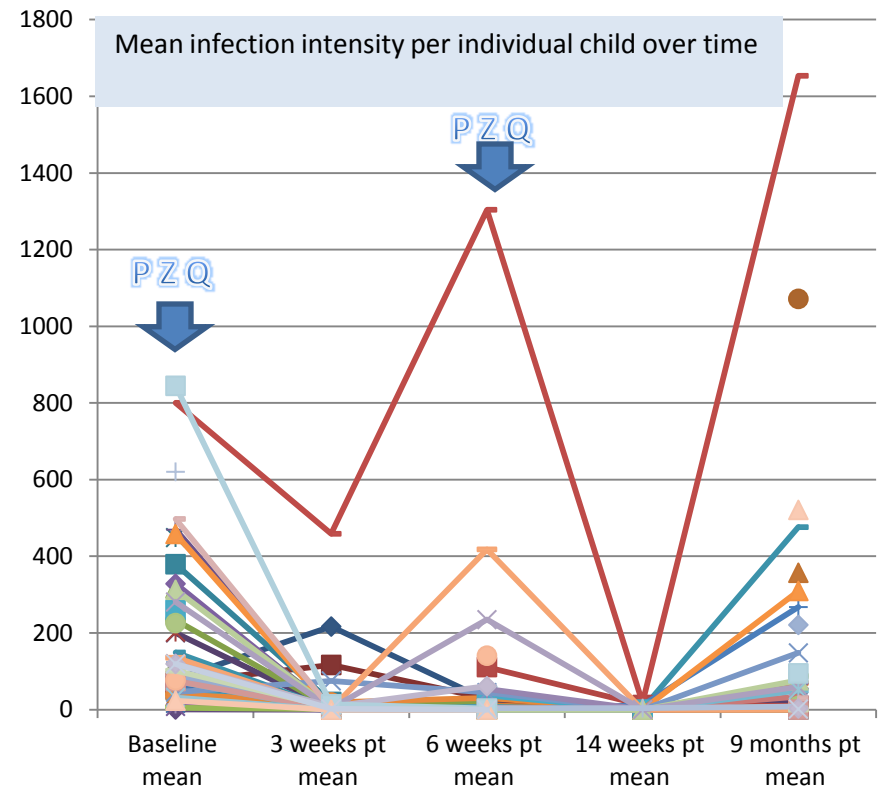
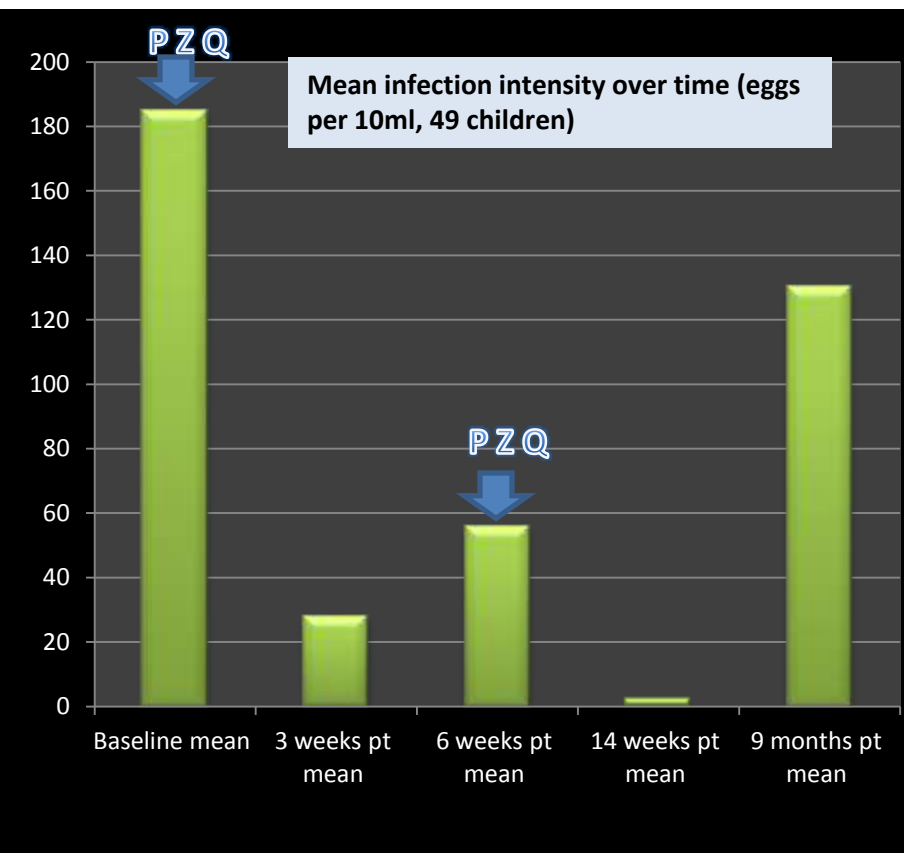
S. haematobium v *S. mansoni* ?

S. haematobium Group hybridisation ?




Consequences of Mass Human Chemotherapy selective pressures for *Schistosoma haematobium* populations (!)

Maintained high prevalence and intensity levels of *S. haematobium* following MDA in certain region of West Africa – rapid reinfection and/or treatment failures ???

E.g. Tabalak - West Africa (Niger) 49 children over time



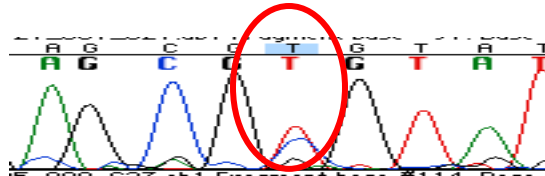
S. haematobium Clade species in West Africa

Species	Infection	Preferred Hosts	Egg
<i>S. haematobium</i>	Urinary	Humans <i>B. globosus</i>	
<i>S. bovis</i>	Intestinal	Cows <i>B. truncatus</i>	
<i>S. curassoni</i>	Intestinal	Sheep + Goats <i>B. umbilicatus</i>	

Hybrid detection

S. h ♂ X *S. b* ♀

S. b ♂ X *S. h* ♀



4 polymorphic bp in ITS1 between *S. h* and *S. b*

Dominance of *S. h* peaks

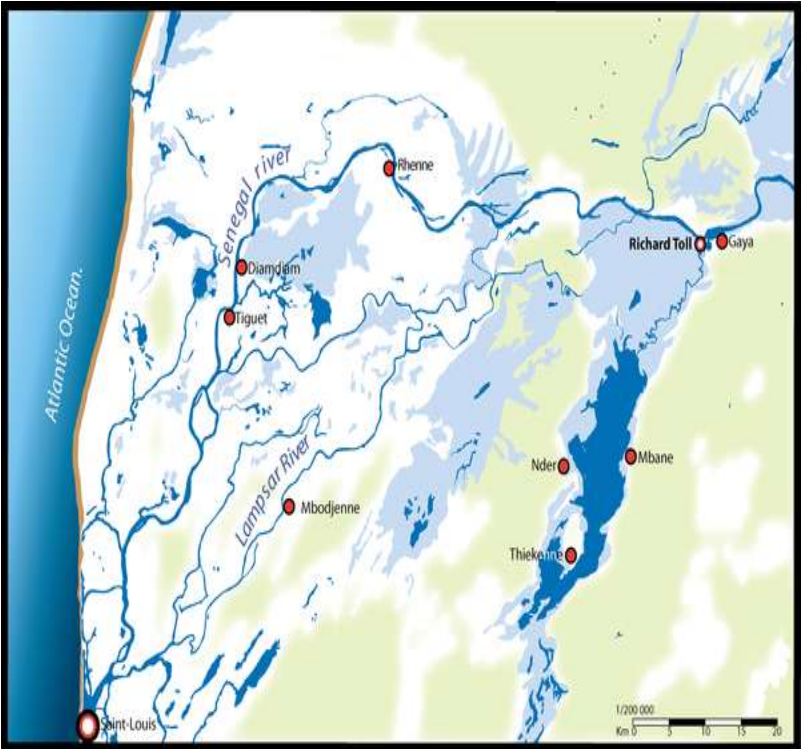
Molecular analysis of nuclear and maternally inherited mitochondrial genes that enable species identification (e.g ITS and COX1)

Senegal River Basin (SRB) ecosystem and schistosomiasis dynamics changed dramatically over the last 30 years due to the construction of the **Diama Dam**

(1)-15% of the sequenced eggs/miracidia = *S. haematobium*: *S. bovis* hybrids

(14/15 patients that were infected with hybrids were also co-infected with *S. mansoni* and *S. haematobium* – multiple polyparasitism).

Huysse, Webster, Stothard, Geldof, Stothard, Diaw, Polman & Rollinson. *PLoS Pathogens* (2010)



Northern Senegal indicating the villages where *Sh:Sb* hybrids have been observed

Tabalak, Niger

Maintained prevalence, intensity, diversity -

Preliminary data:

50% children infected with *S. haematobium*: *S. bovis* hybrids



Niger river, Niger

Consequences of *S. heamatobium*: *S. bovis* hybrids for MDA and morbidity control?

Why, when and what next? (e.g. ecological barriers between species lost due to both natural and anthropogenic recent changes – e.g. dam construction resulting in increase water contact by humans, their livestock and their shared parasites).

Viable hybrids = increased transmission potential? (e.g. Hybrid vigour: Human & bovine definitive host species; *Bulinus truncatus* & *B. globosus* intermediate host species = increased host range/zoonotic reservoir 'spill-over' hosts to maintain human infection as in *S. japonicum* across SE Asia?).

Differential PZQ efficacy?? (e.g. Sh>Sb?; Sh>Sh:Sb?)



Differential morbidity???

(e.g. more pathogenic?; mixed urogenital/intestinal symptomology?)

current ongoing research.

SUMMARY

- *So, in 50 minutes or so I have hopefully shown you that:*

SCI, initially facilitated by BMFG, has been extremely successful in implementing MDA across SSA and thereby reducing infection prevalence, intensity and the burden of disease/morbidity (= the MDGs).

Unique incorporation of detailed multi-dimensional, both 'classical' and novel, M&E&R from the outset.



The Schistosomiasis Control Initiative (SCI) Mission

- SCI, supports the WHA resolution that all member state infected regions aims “to provide regular treatment for 75% of all school-aged children for schistosomiasis and intestinal helminths”, ✓
- To encourage treatment of schistosomiasis in sub-Saharan Africa by targeting those at high risk of developing severe morbidity, especially school-aged children, women and those in high risk occupations. ✓
- By assisting selected countries to achieve successful **SUSTAINABLE** national control programmes, SCI expects to create a sustainable access and demand for treatment. ✓
- To develop and implement rigorous monitoring and evaluation. ✓
- To thereby reduce prevalence, intensity and associated morbidity of schistosomiasis and STH infections. ✓

SUMMARY

‘Caveats/causes for concern’ ?? – e.g. PZQ efficacy and the role of hybrids - NOT to detract from the impact of SCI work, but highlight, through our unique inherent M&E&R we can identify and thereby respond appropriately and swiftly to any foreseen and/or unforeseen consequences of/challenges to our MDA programmes.

Thereby helping ensure the long term success of these and future NTD programmes.

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Key personnel in highlighted summary examples here:

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BILL & MELINDA
GATES *foundation*

And



The Wellcome Trust

The MRC

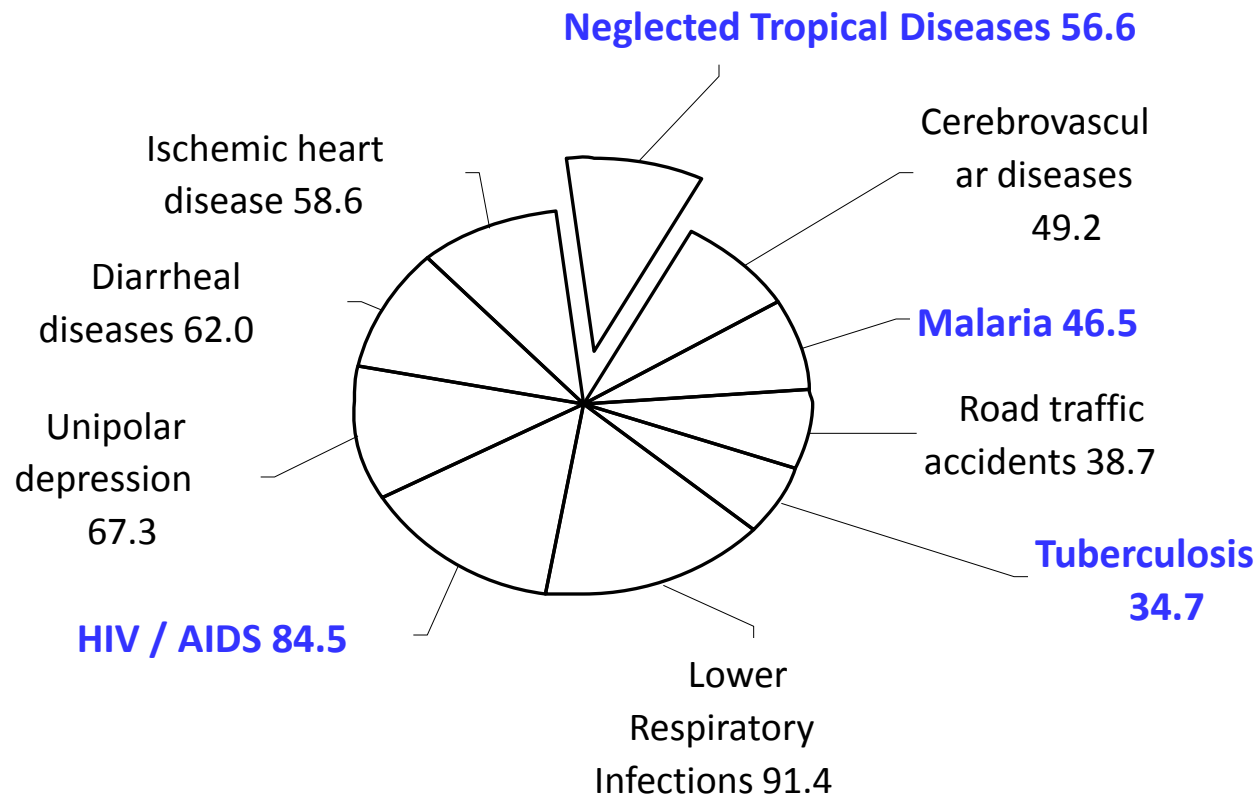


Thank you



Estimated DALYs lost from NTDs compared to other conditions

DALYs (in millions)



PZQ R phenotype

'Resistant/tolerant' miracidia 2010: Tanzania

- No clustering was observed using the neutral markers used in this study, suggesting that these parasites were not closely genetically related.
- Argues against any selective sweep of a small number of "resistant" strains in this population, but rather supports the existence of a significant minority of the population with an existing low susceptibility to praziquantel.

