Do schistosomes maximize fitness over changing environments?

Professor Joanne P. Webster

Chair in Parasitic Disease Epidemiology/Director M&E Schistosomiasis Control Initiative

Imperial College, London

Talk outline

Schistosomes and schistosomiasis.

Do schistosomes maximize fitness over changing environments?: Laboratory

Do schistosomes maximize fitness over changing environments?: Asia *('older' selective pressures*)

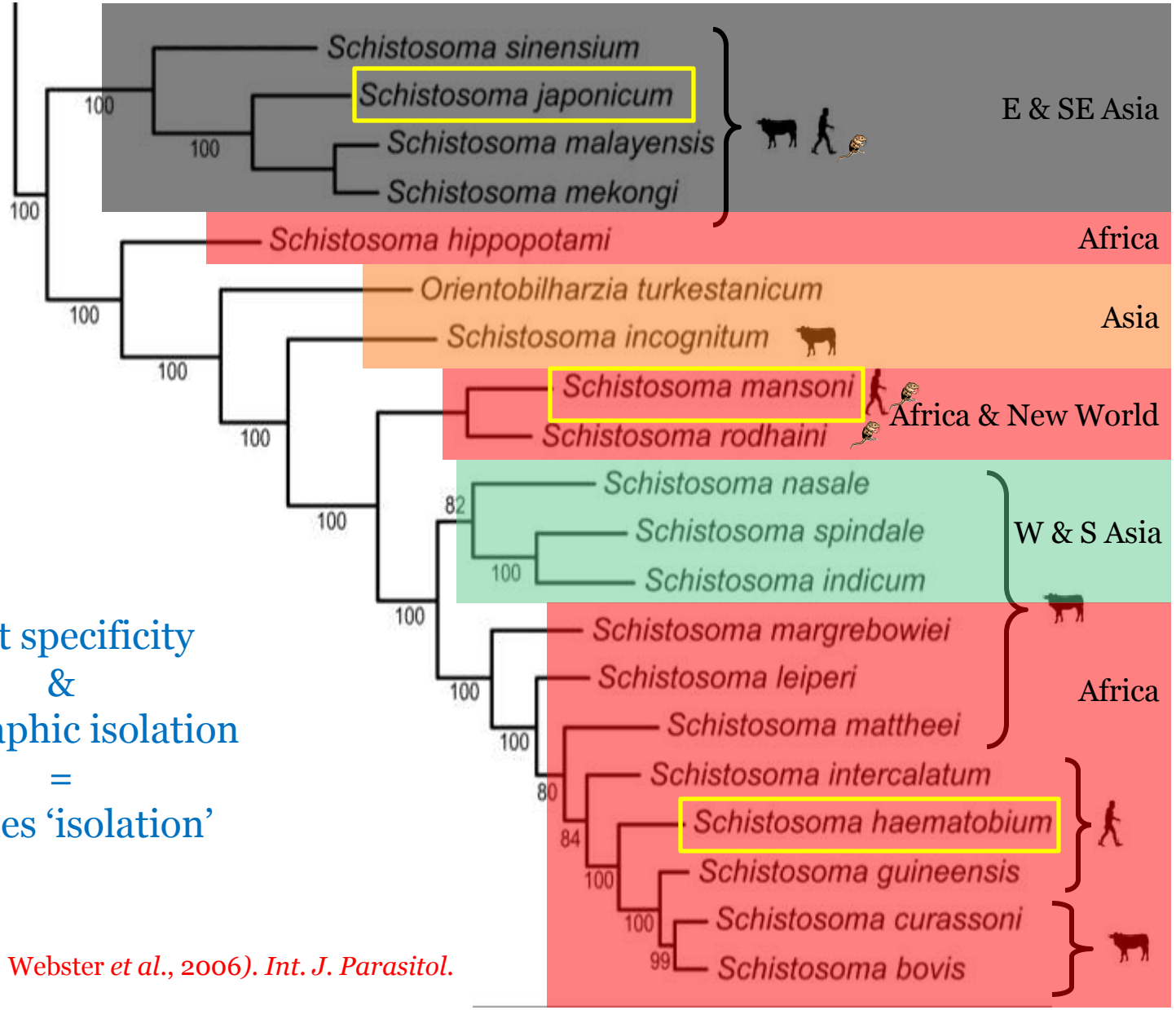
Do schistosomes maximize fitness over changing environments?: Africa *('recent' selective pressures)*

Implications and Applications

Schistosomiasis is one of the Neglected Tropical Diseases (NTDs)

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

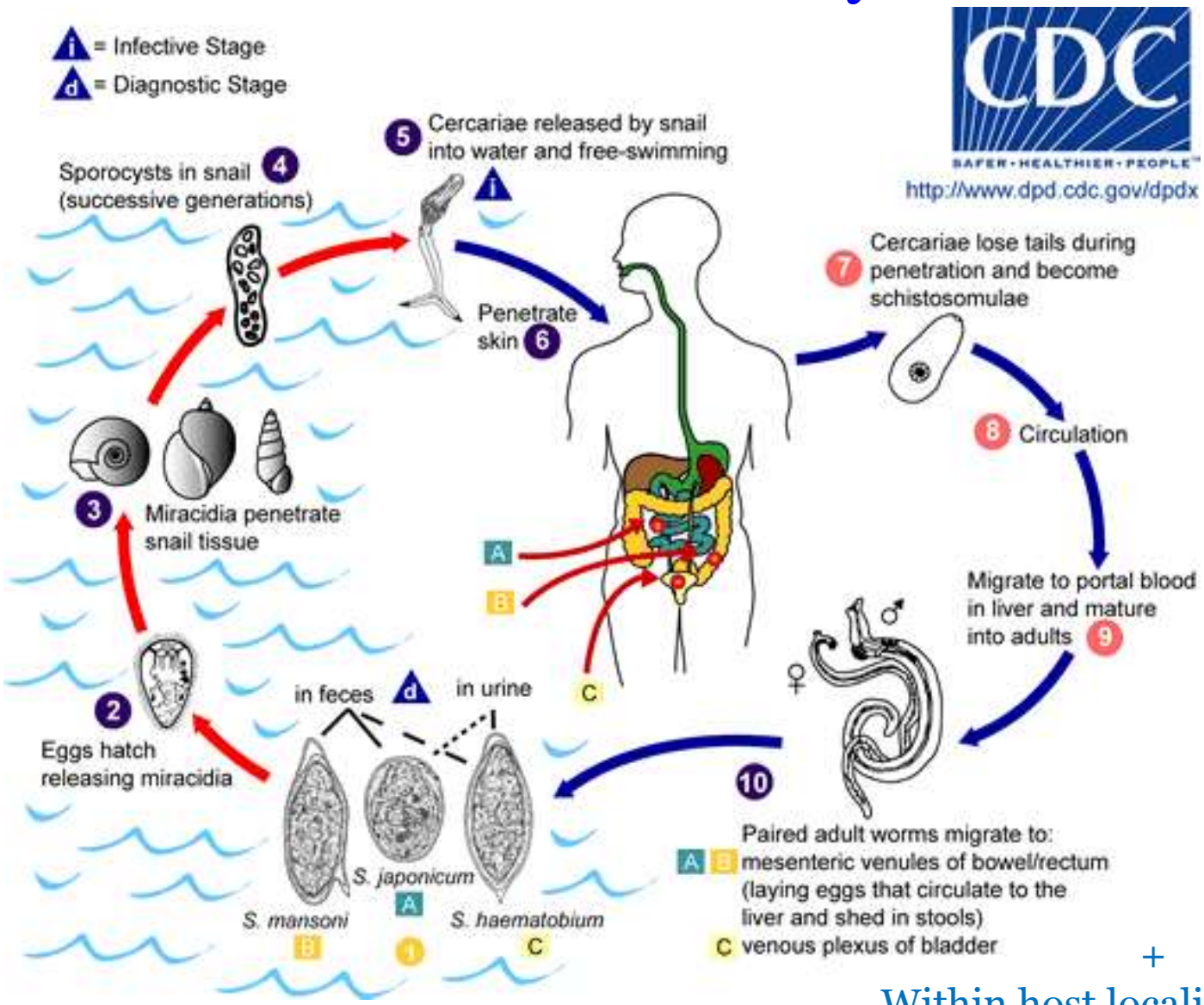
Schistosoma spp. - Phylogenetic distances



Host specificity
&
Geographic isolation
=
Species 'isolation'

(Adapted from: Webster *et al.*, 2006). *Int. J. Parasitol.*

Schistosome Life Cycle



+

Within host locality 'isolation'

=

Species 'isolation'

Schistosomiasis mortality and morbidity

Total infected
>207 million

Mortality (annually)

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

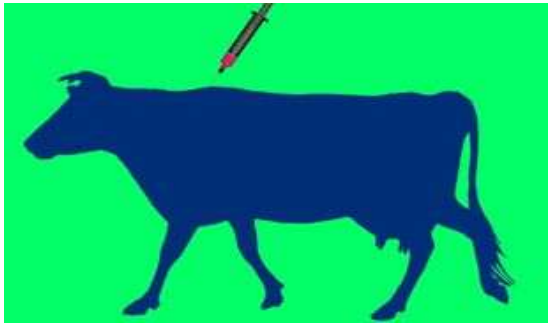
Persons with major morbidity:

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

Persons with 'subtle' morbidity:

+++++++ !

Changing environments for schistosomes



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Implications and Applications

Artificial Selection Experiments demonstrate potential for rapid change/evolution:

E.g.

snail

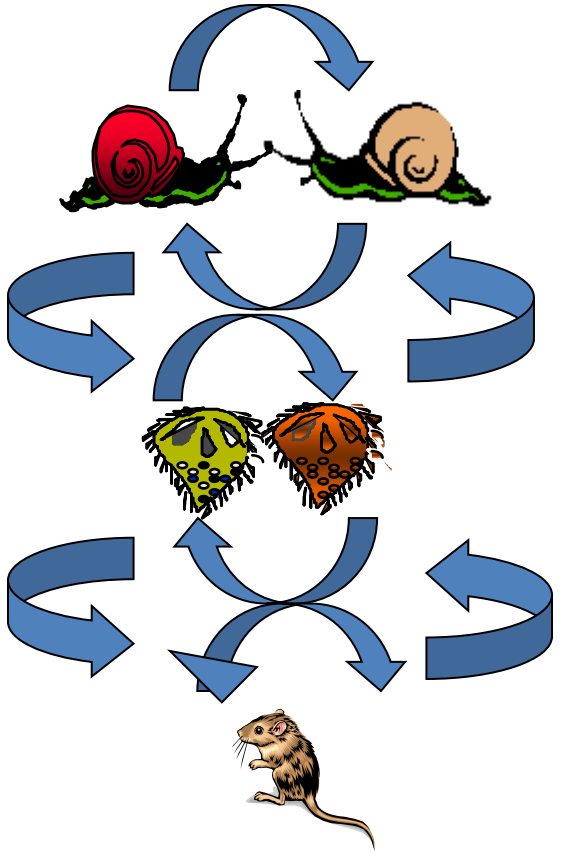
- Resistance/Susceptibility;
- Strain specificity;
- Mating potential.

& parasite

- Infectivity;
- Virulence/Avirulence;
- Reproductive rate;
- Mating potential;
- Resistance/susceptibility (drug).

&

- Snail:Schistosome Coevolution

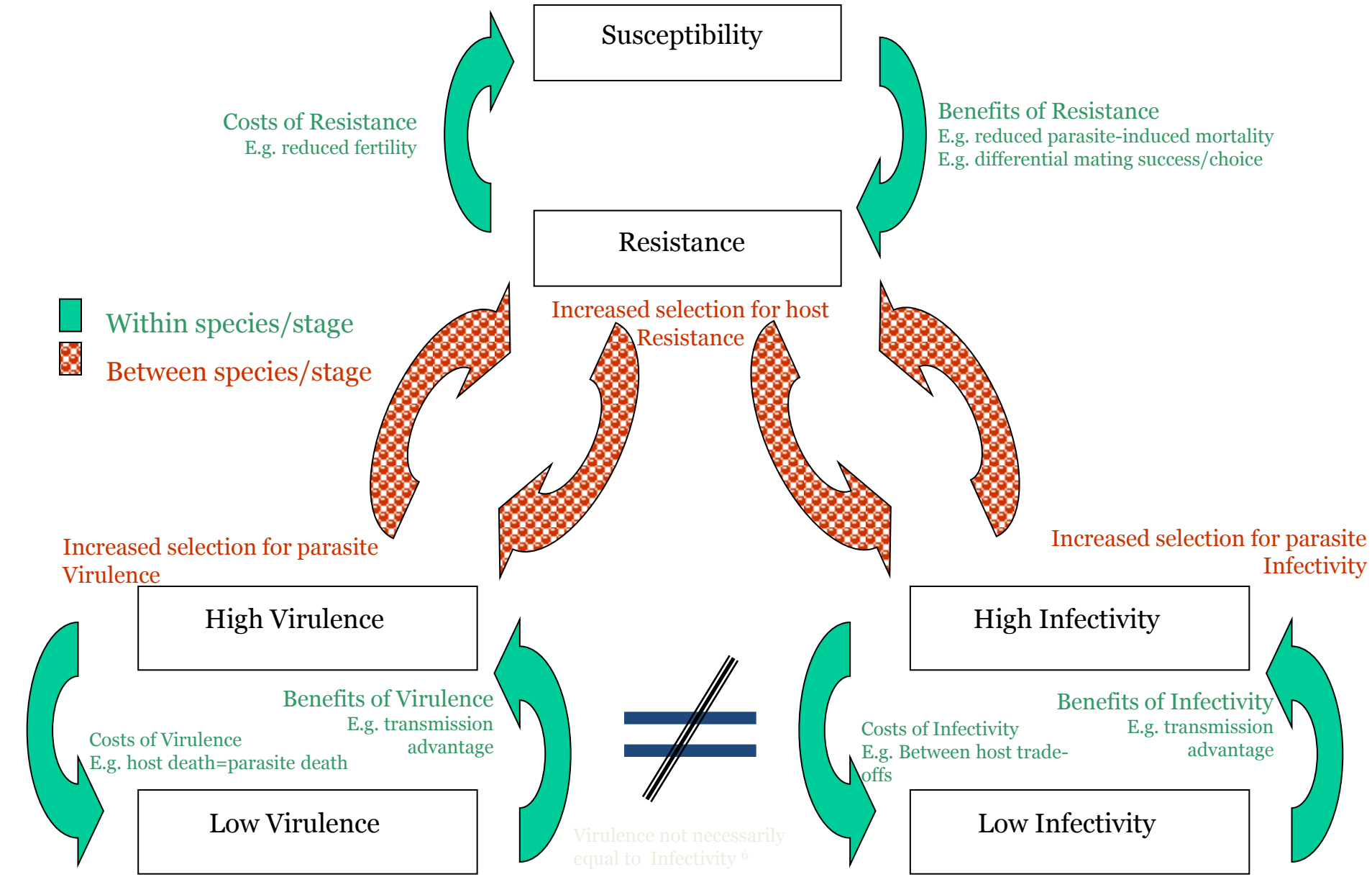


e.g. Webster, J.P., *et al.*, (2008) *Evolutionary Applications*

Webster, J.P., *et al.*, (2007) *BMC Evolutionary Biology*

Webster, J.P. *et al.*, (2004). *American Naturalist*

Woolhouse, M.E.J., Webster. J.P. *et al., (2002) Nature Genetics*



E.g. Gower, C.M. & Webster, J.P. (2004) *Evolution*
Davies, C.M. & Webster, J.P. (2001). *Proc. Roy. Soc. B. Lond*
Webster, J.P. & Woolhouse, M.E.J. (1999). *Proc. Roy. Soc. B. Lond*

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Implications and Applications

S. japoniucum - Within China, despite major control efforts over the last 50 years, (PZQ, health education, molluscididing, environmental modification etc) *Schistosoma japonicum* remains endemic in seven (out of 12) provinces and remerging in some areas.

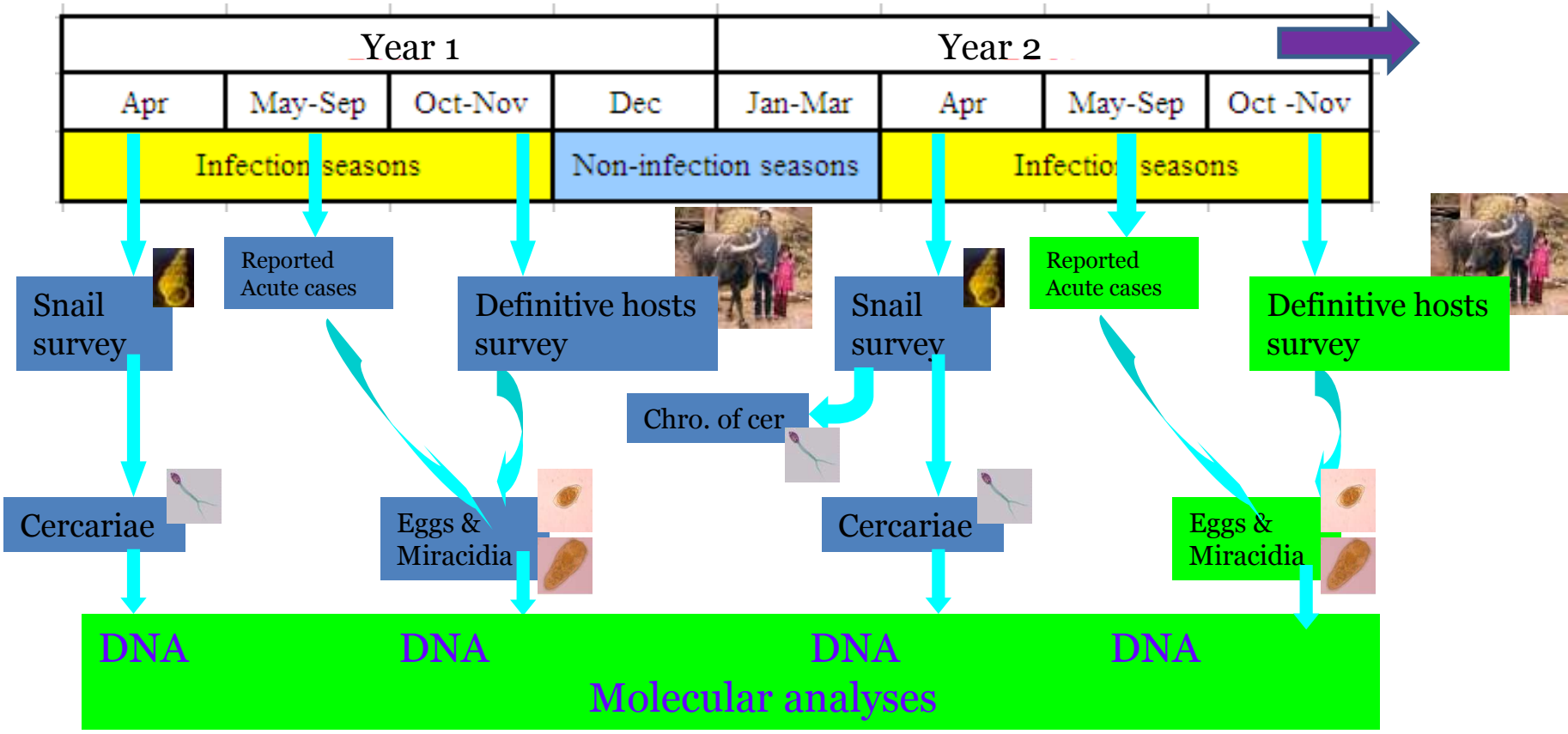
- estimated 30 million people are at risk of infection.

One of the reasons for schistosomiasis japonicum's persistance may include:

S. japonicum is unique in that it is the only schistosome for which zoonotic transmission is considered important, with over forty species of wild and domesticated animals suspected to serve as reservoir hosts for the parasite, although their relative roles remains unknown.

Field sampling scheme

Per individual Province: marshland villages VS hilly villages



e.g. Lu, D-B, Wang, T-P., Rudge, J.W., Feng, G-W, & Webster, J.P. (2010). *PLoS NTDS*
Rudge, J.W., Lu, D-B, Feng, G-W, Wang, T-P, Basáñez, M-G & Webster, J.P. (2009). *Molecular Ecology*
Wang, T-P, Shrivastava, J., Johansen, M.V., & Webster, J.P. (2006) *Int. J. Parasitol.*

Prevalence of *S. japonicum* infection by Definitive host species and habitat type
(within Province)

Mean % (range)

100
90
80
70
60
50
40
30
20
10
0

Humans 'Bovines' Dogs Cats Pigs Goats 'Rodents' Humans 'Bovines' Dogs Cats Pigs Goats 'Rodents

Marshland

Hilly

Definitive Host species/Habitat Type

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Marshland

Hilly

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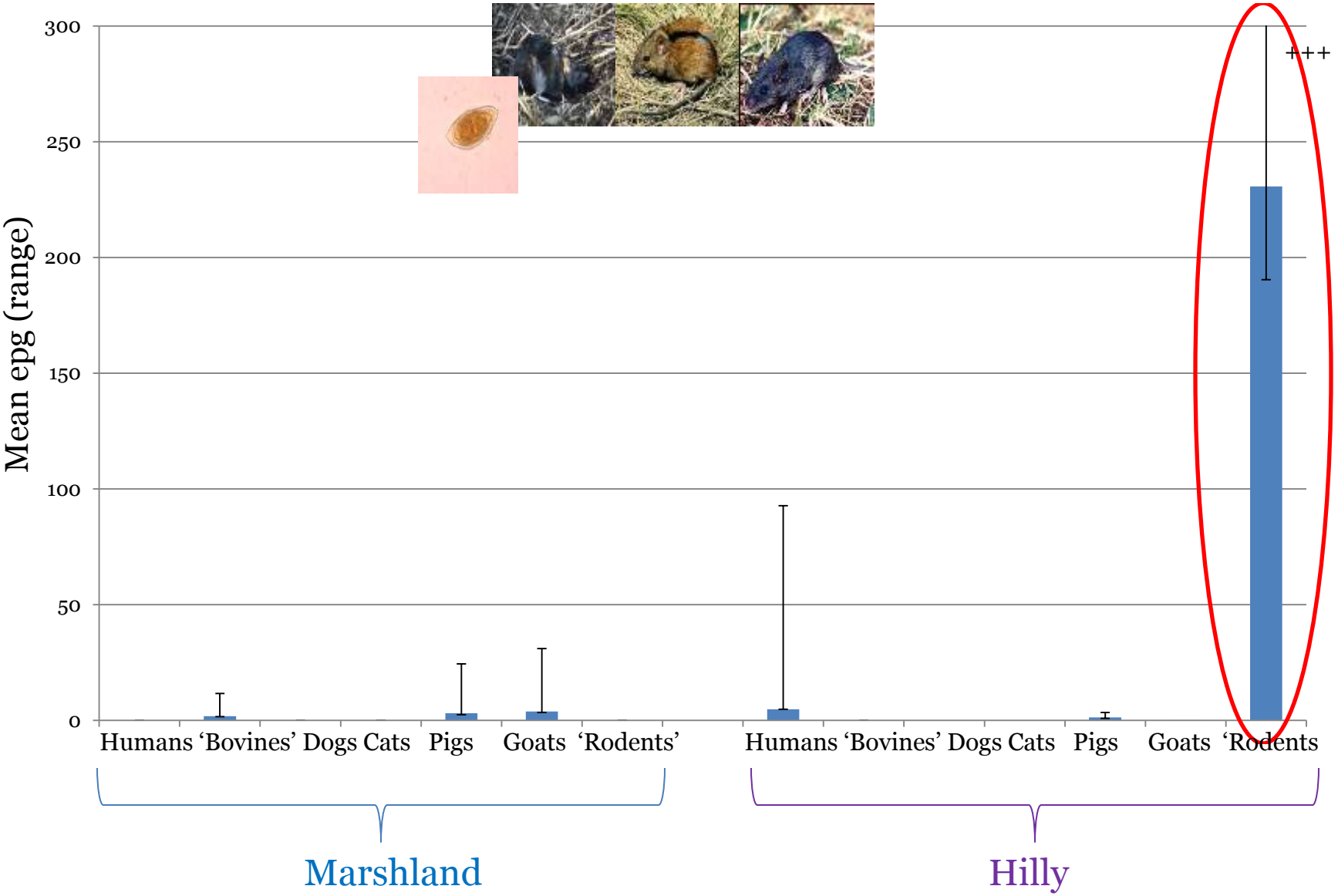
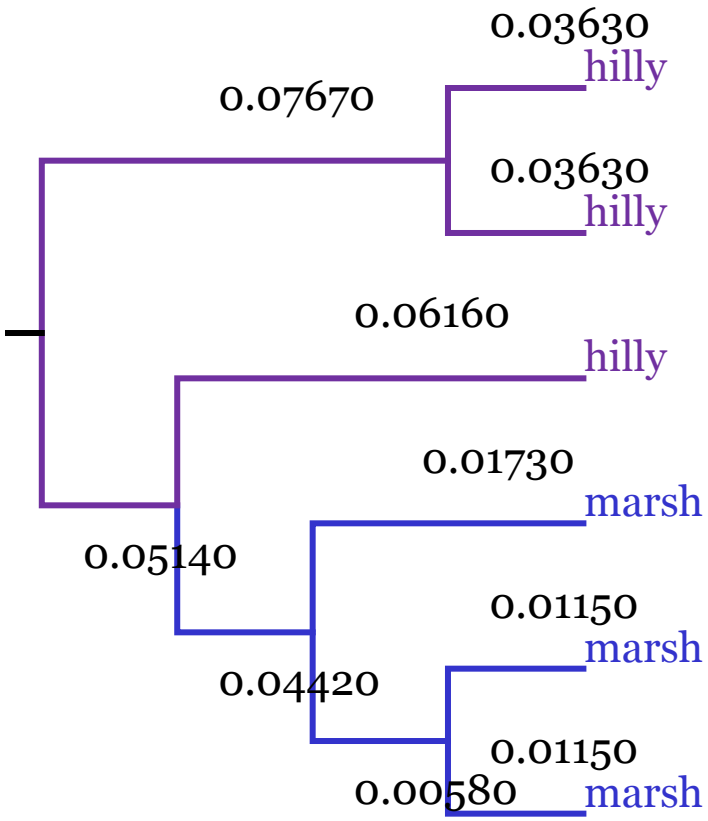
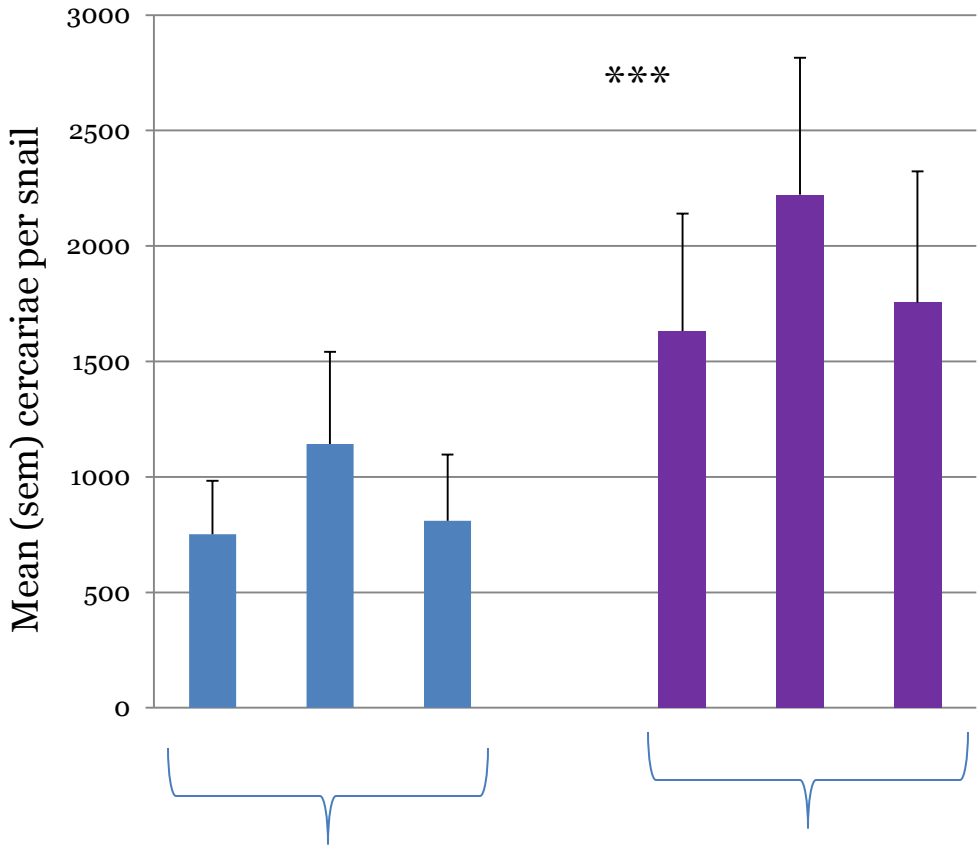


Cercarial genotypic and phenotypic differences:

Within single region of China & single snail morph





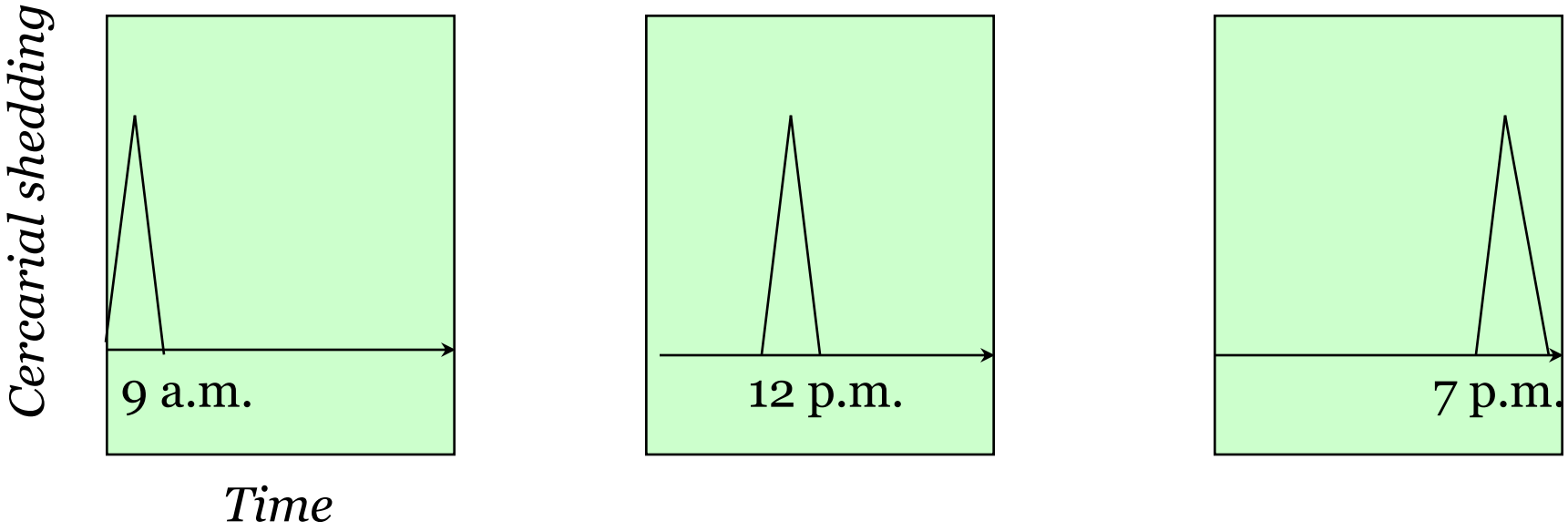
Segregation into two main clusters

Significantly higher infection intensities from Hilly >> Marshland

UPGMA phenogram depicting coancestry distance

Cercarial Behavioural data

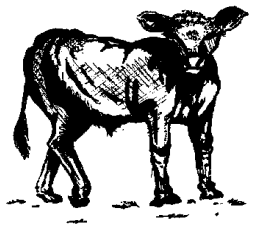
Inter-specific variation in schistosome 'shedding' in relation to host species

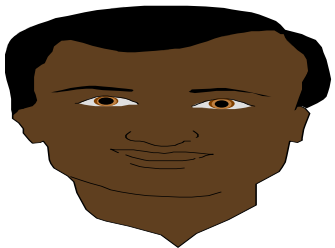


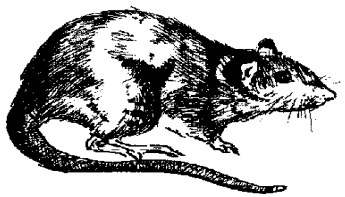
Early
Ungulates
e.g.
S. bovis, S. curassoni

Midday
Humans
e.g.
S. mansoni, S. haematobium

Night
Rodents
e.g.
S. rodhaini





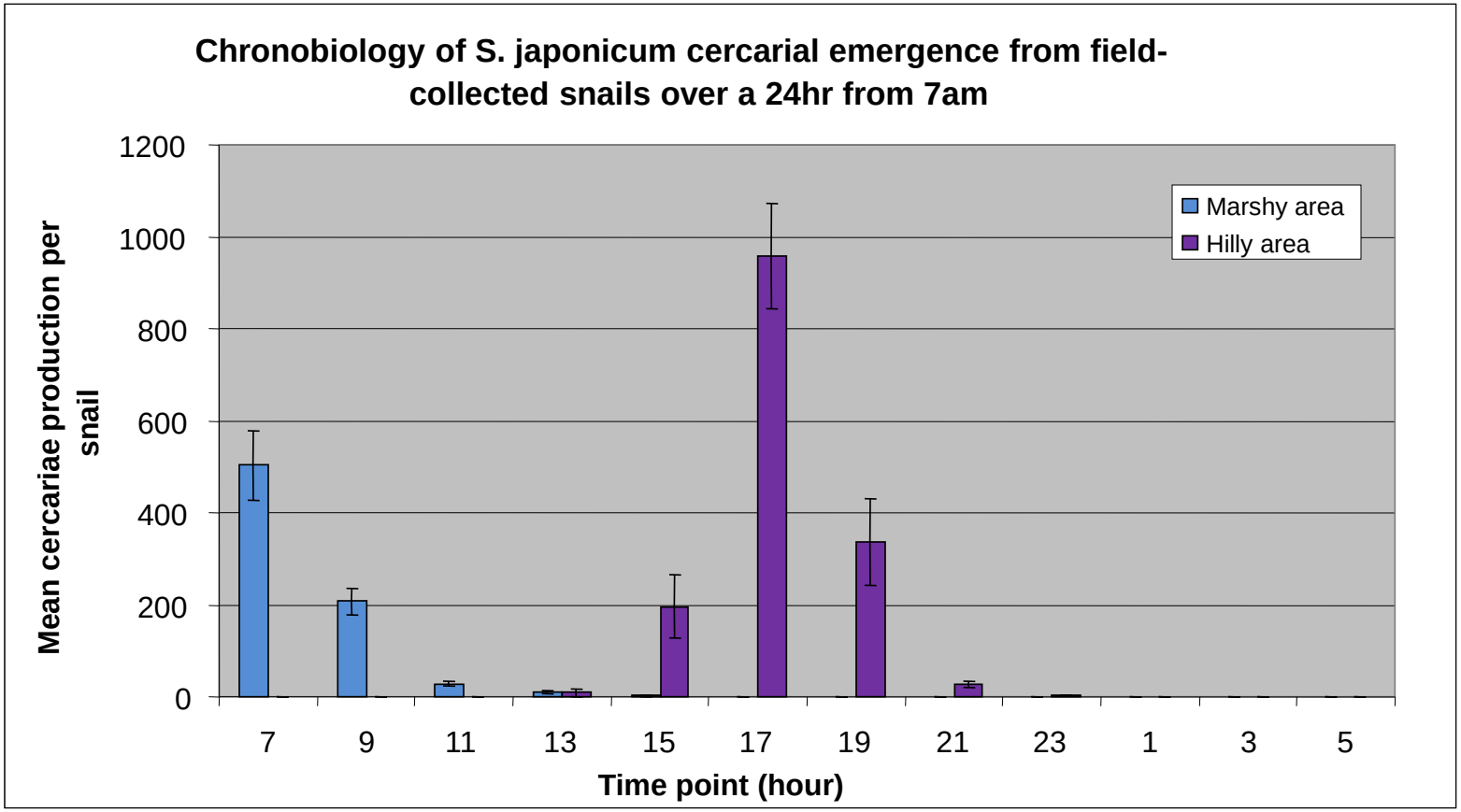


Intra-specific variation in schistosome shedding in relation to habitat and reservoir host species: ***S. japonicum***– Mainland China! ???

Lu, D., Wang, T-P., Rudge, J., Donnelly, C.A., Gua, C. & Webster, J.P. (2009*) Int. J. Parasitol.*

Cercarial Behavioural data:

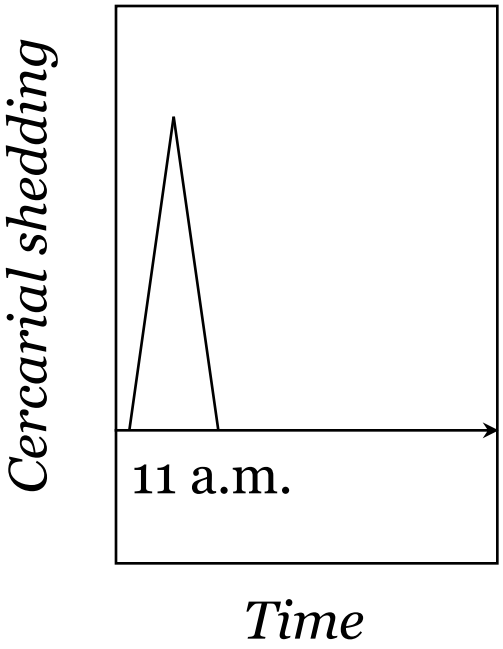
Different chronobiology of cercarial shedding emergence

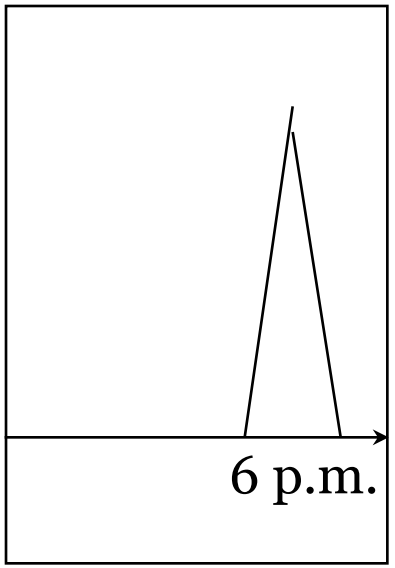


In the marshland,
7AM until 11AM

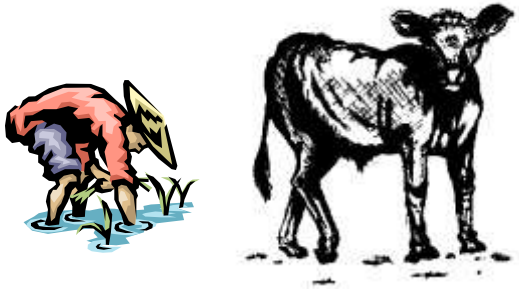
In the hilly area,
3 PM until 9 PM

Lu, D., Wang, T-P., Rudge, J., Donnelly, C.A., Gua, C. & Webster, J.P. (2009) *Int. J. Parasitol.*





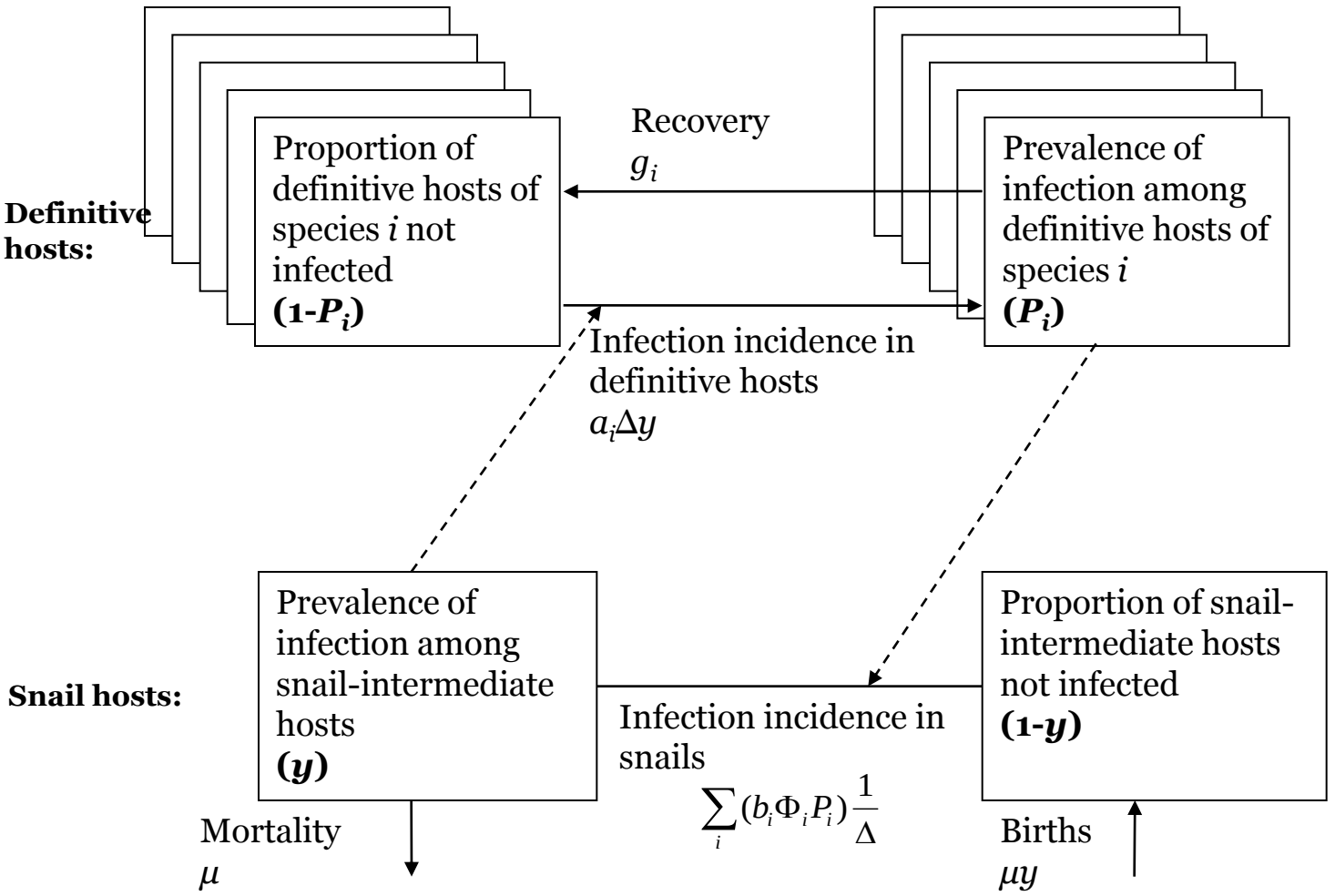
Early
Marshland foci



Late
Mountainous/hilly foci

Evolution in action? – intra-specific differentiation of *S. japonicum* chronobiology by host species and habitat type?

Mathematical modelling: Data incorporated into novel multi-host transmission models: aimed to help elucidate and predict the differential transmission and epidemiology of *S. japonicum* in relation to habitat and host.



Rudge, J.W., Webster, J.P., Lu, D-B, Feng, G-W, Wang, T-P, Basáñez, M-G (under review) *PNAS*

Basic reproduction number, R_0

R_0 estimated from local prevalence data among definitive hosts and snails & "partitioned" among the definitive host species, weighted according to their relative contribution to snail infections

	Marshland region			Hilly region		
	Guanghui	Heping	Xingzhuang	Longquan	Longshang	Yuantou
Humans	<0.01	0	<0.01	0	0.06	0.02
Buffaloes	0.11	0	0.13	0	0	0
Cattle	**1.99**	**1.41**	**11.41**	0	0	0
Goats	0	0	0.04	0	0	0
Dogs	0	0	0	0.02	0.04	0.01
Rodents	0	0	0	**1.75**	**1.31**	**1.37**
R_0 (overall)	2.11	1.41	11.59	1.76	1.41	1.40

Levels of infection among humans may be too low for transmission to be maintained in the absence of other definitive host reservoirs - "spill-over"

Rudge, J.W., Webster, J.P., Lu, D-B, Feng, G-W, Wang, T-P, Basáñez, M-G (under review) *PNAS*

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Supports the hypotheses that bovines are responsible for maintaining transmission in the marshland regions, while rodents and, to a lesser extent, dogs could be maintaining transmission in hilly regions.

Do schistosomes maximize fitness over changing environments?
– *S. japonicum* SE Asia?
Yes

Variability (without reproductive isolation) in genotype and phenotype in relation to:

- country,
- habitat type,
- Intermediate host,
- Definitive host & host availability.

Maximizing opportunities for enhanced transmission and infection persistence/parasite fitness in a changing environment.

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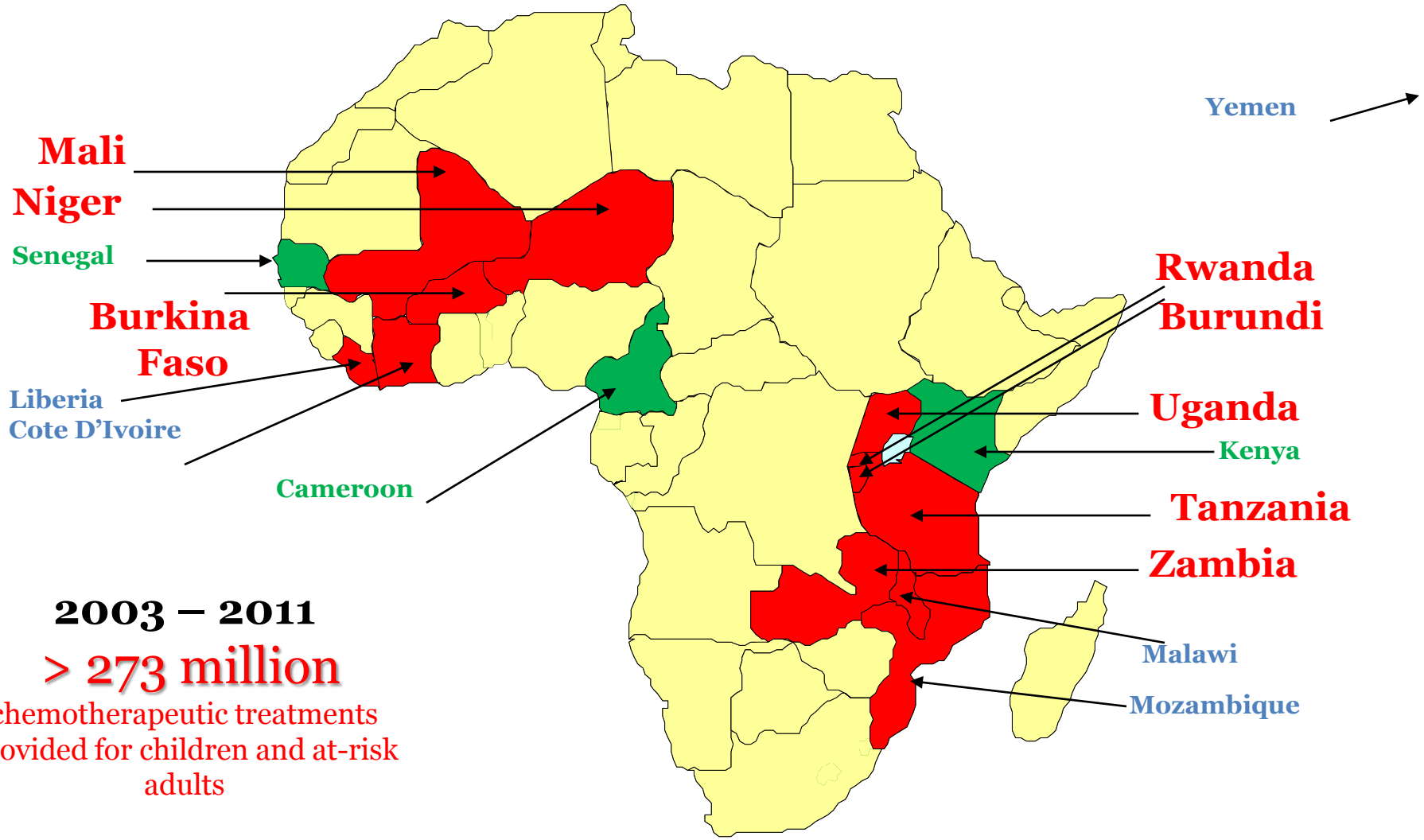
Do schistosomes maximize fitness over changing environments?: Africa *('recent' selective pressures)*

Implications and Applications

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.

SCI sustainable (integrated) schistosomiasis control



2003 – 2011

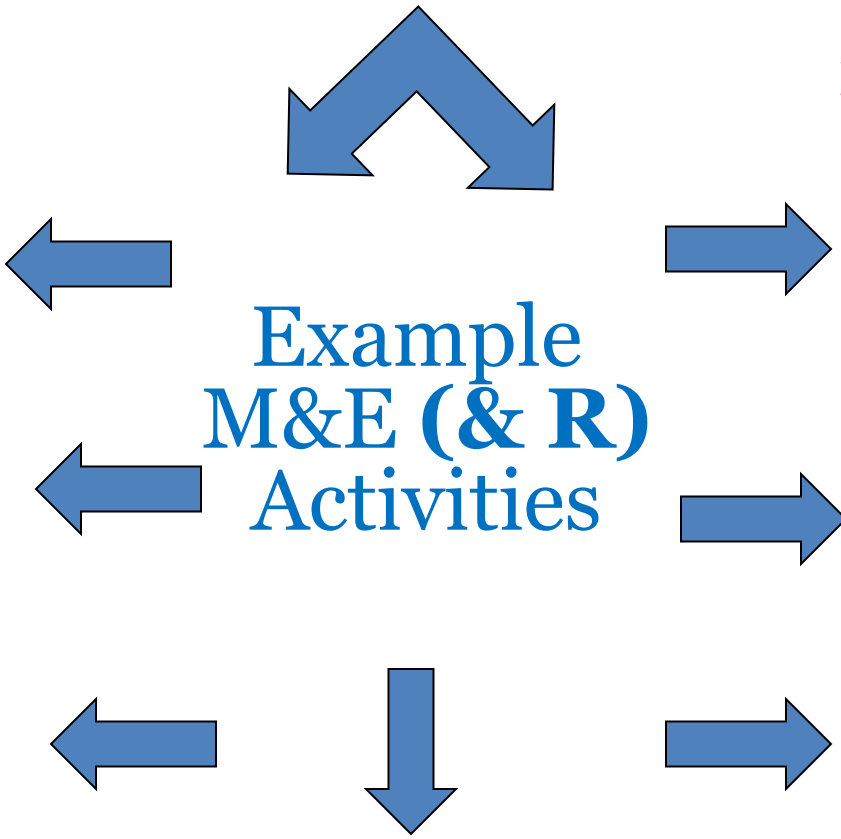
> 273 million

chemotherapeutic treatments provided for children and at-risk adults

2012 -

\+ 250 million PZQ treatments per year donation!

e.g. Koukounari, A., Webster, J.P. *et al.*, (2009). *Parasitology*
Fenwick, A. & Webster, J.P. (2006). *Current Opinion Infectious Diseases*
Koukounari, A., *et al.*, & Webster, J.P. (2007). *Journal of Infectious Diseases*



Epidemiological

GIS
Rapid mapping
Implementation design
Data Management

Parasitological

Prevalence/Intensity
Field diagnostics
Polyparasitism
Population genetics

Clinical/Morbidity

Palpation
Anaemia
US
Anthropometrics

Operational

Community/School based
Training
Drug dosage and spacing
Age groups

Social/Anthropological

Health education
Compliance

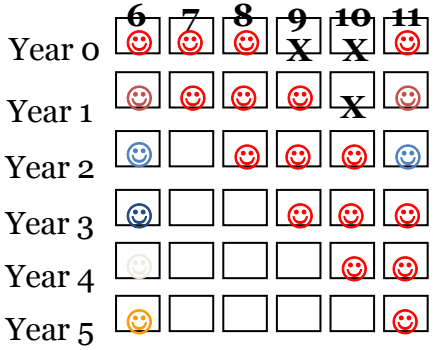
Mathematical modelling

Transmission dynamics
Drug treatment timing

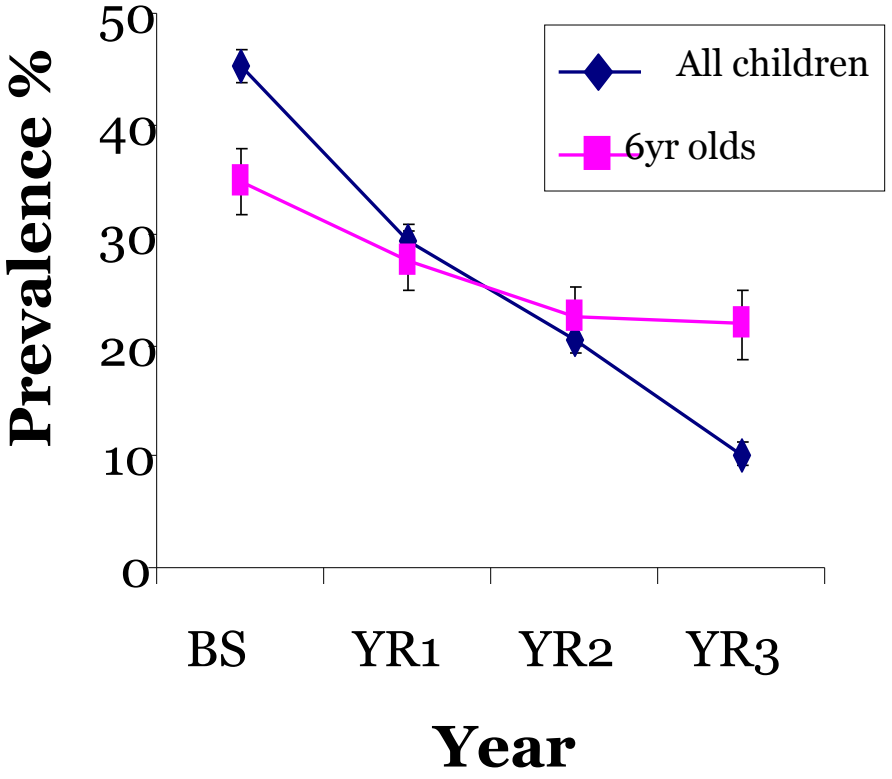
Cost/Health economics

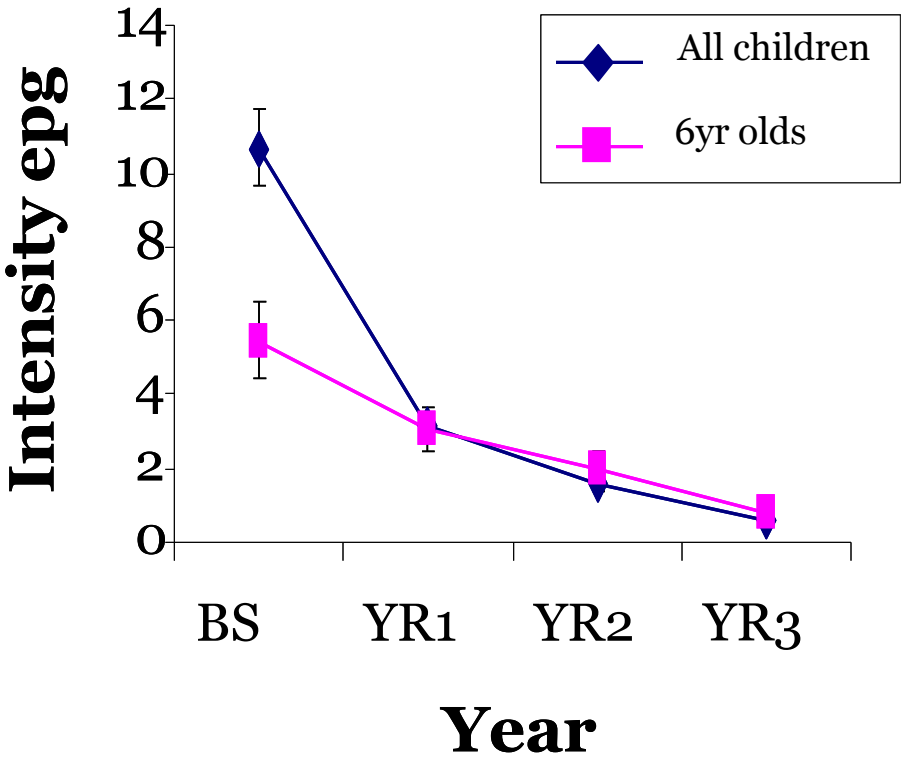
Integration v vertical

MDA =
Dramatic reductions in Prevalence and Intensity



E.g. *S. mansoni* in Ugandan school-aged children





French, M. *et al.*, Webster, J.P.. (2010) *PLoS NTDs*
Kabetereine, N., *et al.*, Webster, JP. & Fenwick. A. (2007) *Bull WHO*

Do schistosomes maximize fitness over changing environments?: Africa

('recent' selective pressures - MDA)

Evolution of Drug/PZQ Resistance?

Webster, J.P. *et al.*, (2010). *Trends in Parasitology*

Fenwick, A. & Webster, J.P. (2006). *Current Opinion Infectious Diseases*

Schistosomes 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?

Do schistosomes maximize fitness over changing environments?: Africa

('recent' selective pressures - MDA)

Evolution of Drug/PZQ Resistance?

Changes in parasite population structure?

Webster, J.P. *et al.*, (2010). *Trends in Parasitology*
Fenwick, A. & Webster, J.P. (2006). *Current Opinion Infectious Diseases*

New Biologically, Logistically and Ethically-Appropriate Tools

Parasite Population genetics

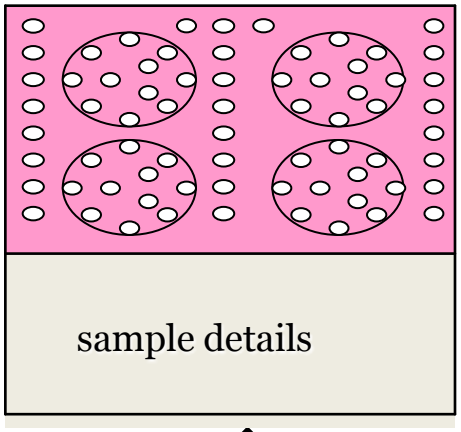
(NC3R's Prize 2007)

Faecal sample for *S. japonicum* or *S. mansoni*

Urine sample for *S. haematobium*

sieve

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



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

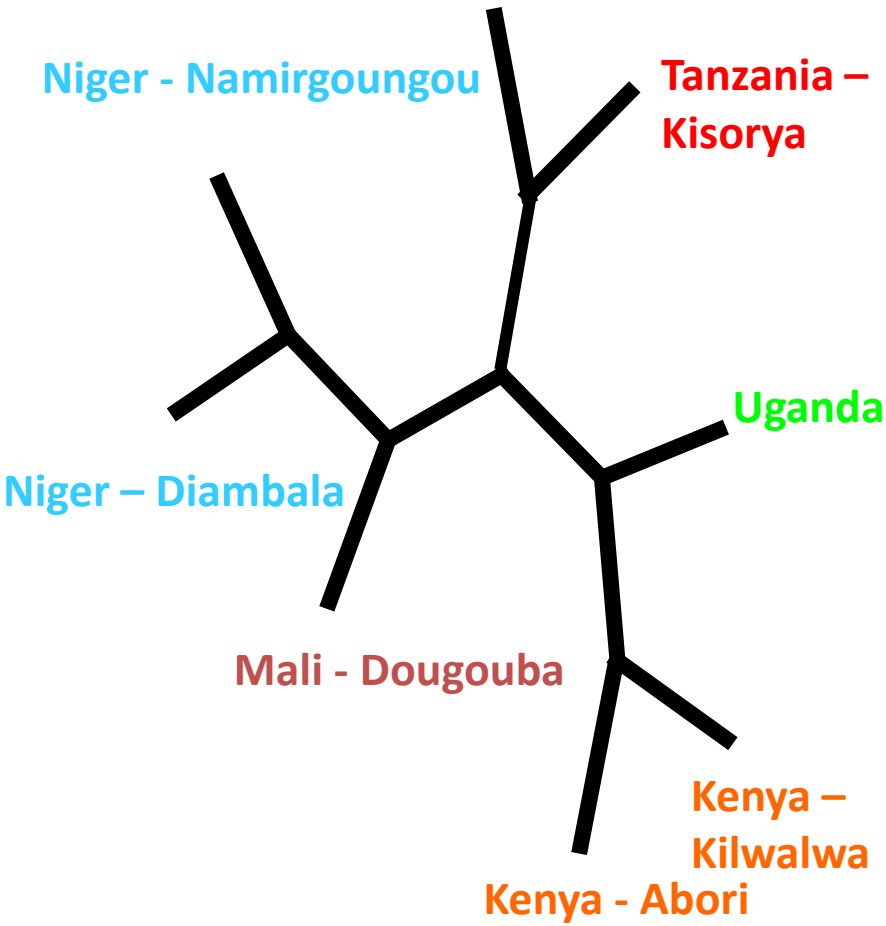
Miracidia hatch from eggs under the stimuli of sunlight and fresh water

Petri dish

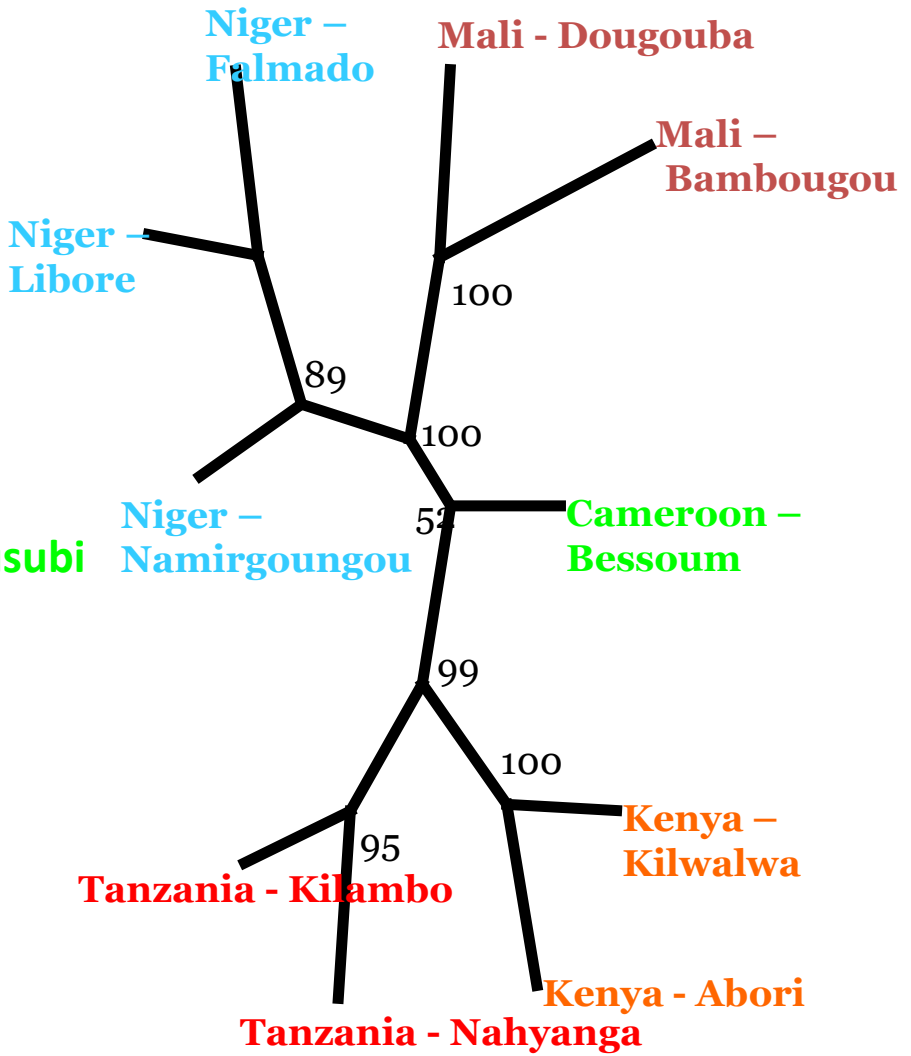
Webster, J.P., Olivera, G., Rollinson, D. & Gower, C.M. (2010). *Trends in Parasitology*

Gower, C.M., Shrivastava, J., Lamberton, P.H.L, Rollinson, D., Kabatereine, N.B. & Webster, J.P. (2007). *Parasitology*

S. mansoni by country



S. haematobium by country

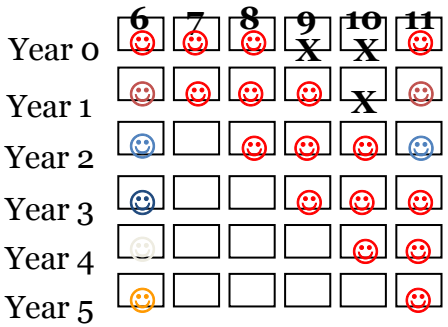


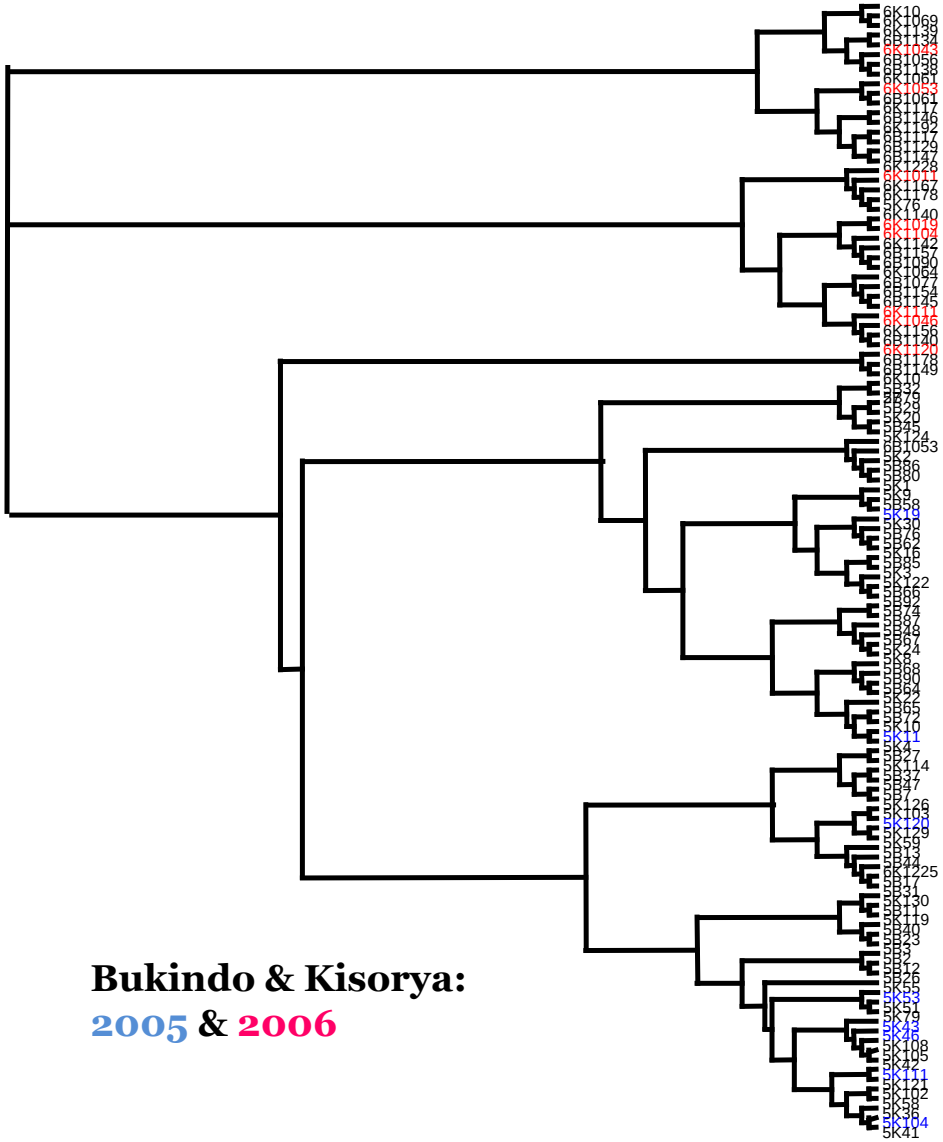
Gower, C.M., Gouvras., A., Lamberton, P.H.L., Deol, A. *et al.*, & Webster, J.P. (2012) *Acta Tropica*.

Longitudinal post-PZQ re-sampling demonstrates reinfection (and/or immature worms) NOT treatment failures in Tanzania

Multiplex microsatellite analyses

Post-PZQ re-sampling of demonstrates reinfection (and/or immature worms) NOT treatment failures – i.e. different genotypes pre and post.



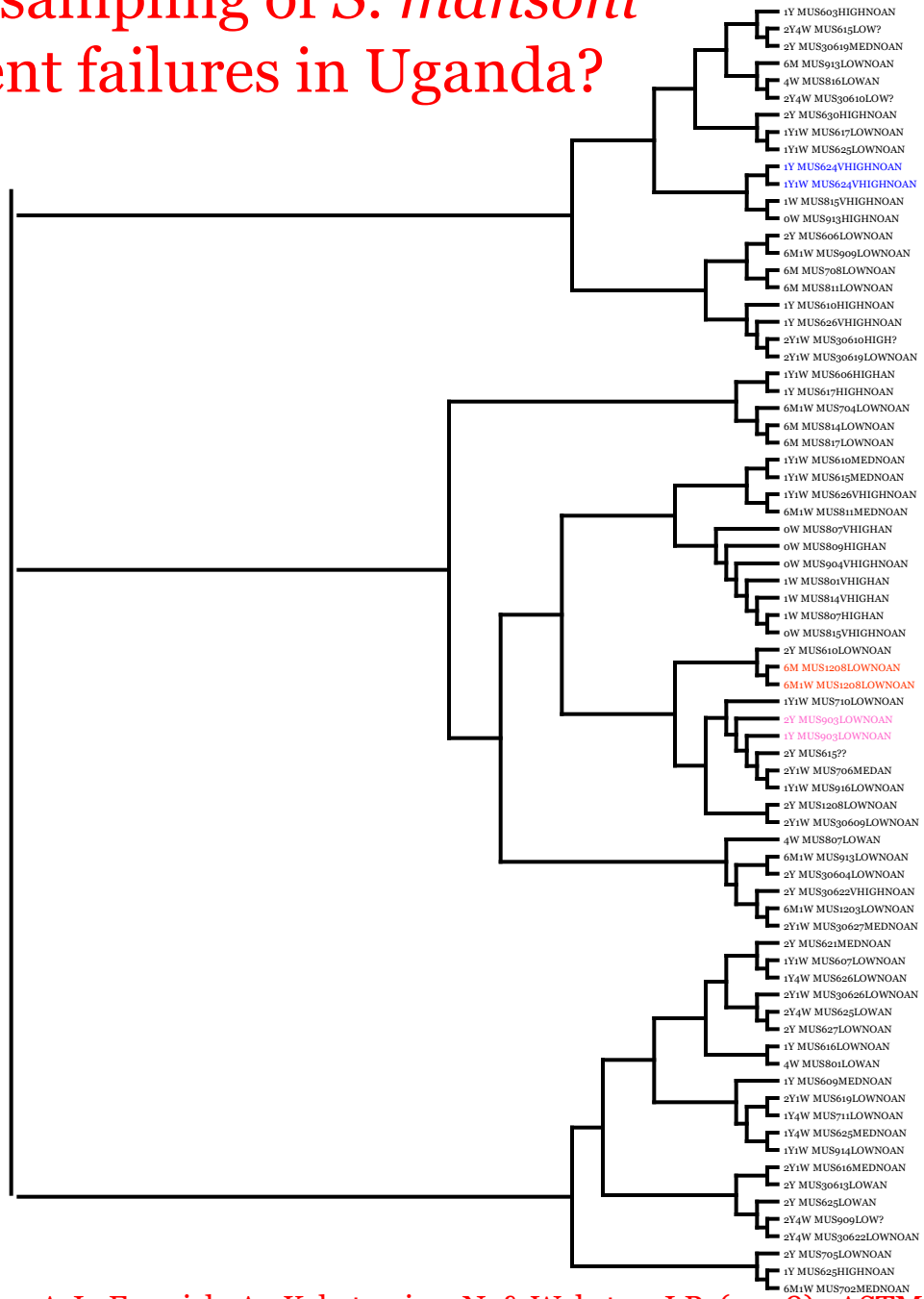


Bukindo & Kisorya:
2005 & 2006

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

Longitudinal post-PZQ re-sampling of *S. mansoni* demonstrates rare treatment failures in Uganda?

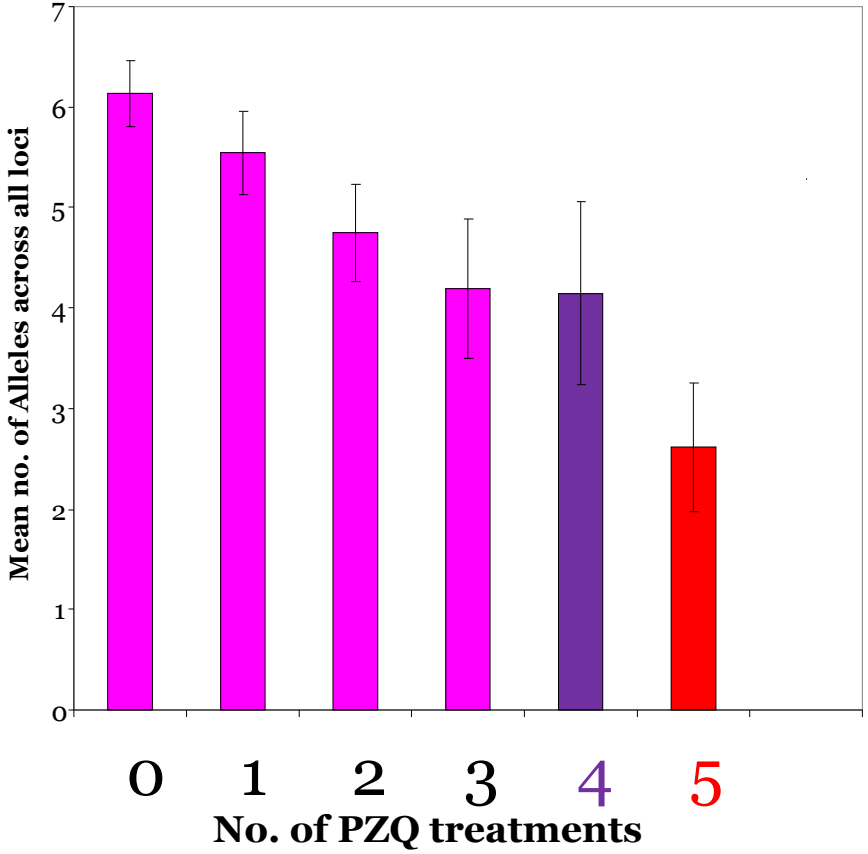
- Multiplex microsatellite analyses
- Majority post-PZQ re-sampling of demonstrates reinfection (and/or immature worms) NOT treatment failures
- But occasional clustering between time points.

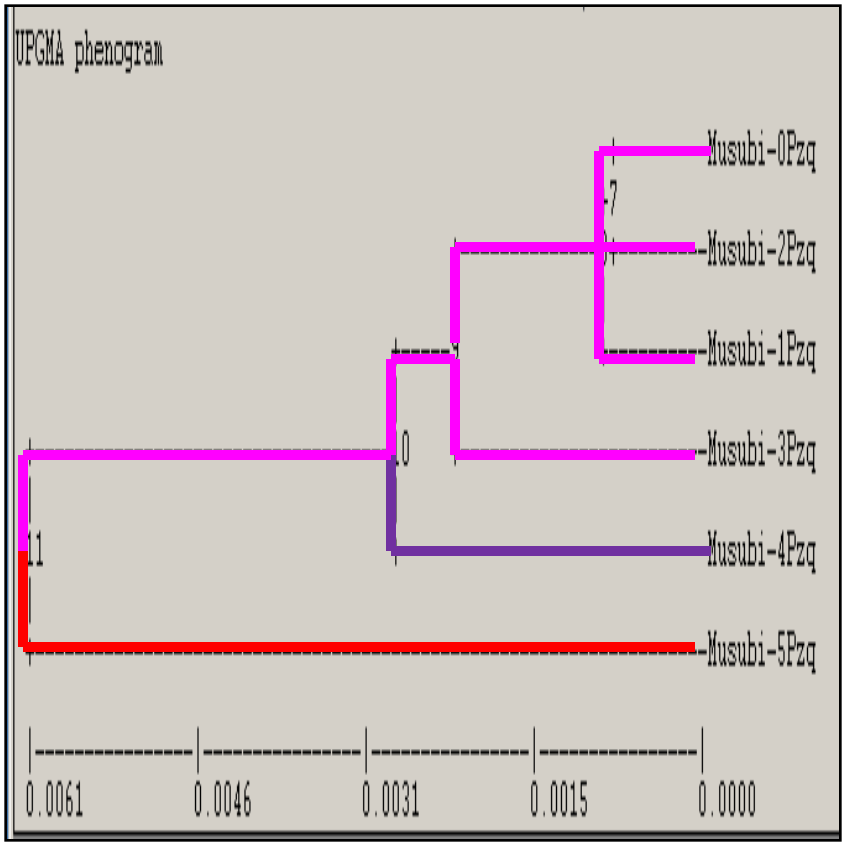


Lamberton, P.H., Norton, A.J., Fenwick, A., Kabatereine, N. & Webster, J.P. (2008). ASTMH & in prep

Longitudinal post-PZQ re-sampling of *S. mansoni* indicates bottleneck (and sub-structuring) in parasite diversity in response to PZQ MDA in Uganda and Tanzania *etc*: East Africa.

Uganda - Sig. reduction in allele number with increasing PZQ treatments over 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 MDA on schistosome population genetics

Hence

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

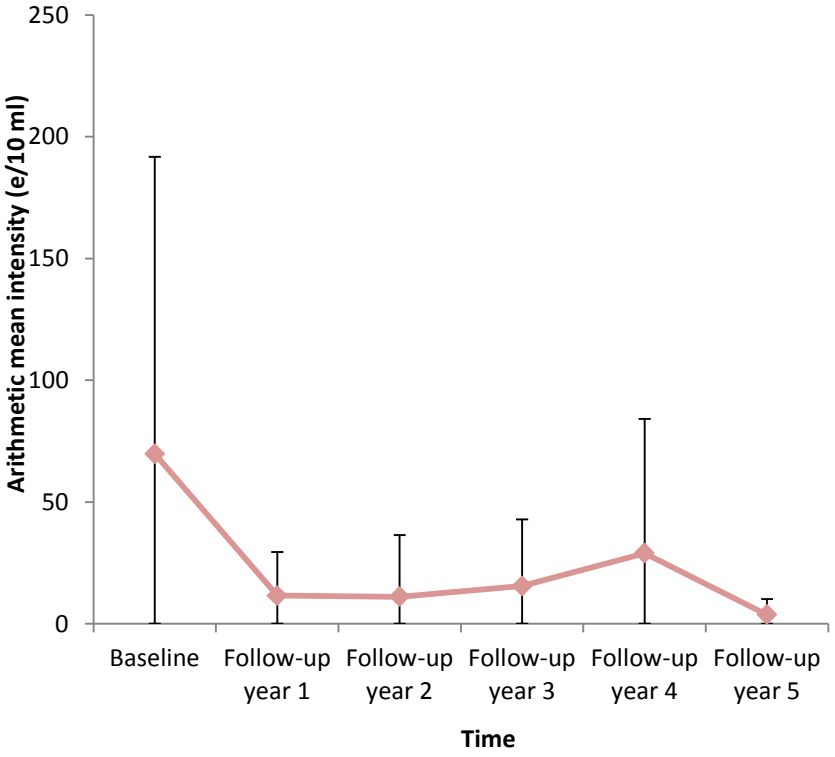
Continued significant reductions in diversity may reduce the schistsomes ability to adapt and survive any future novel environmental selective pressures to which they may be exposed?

Or

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

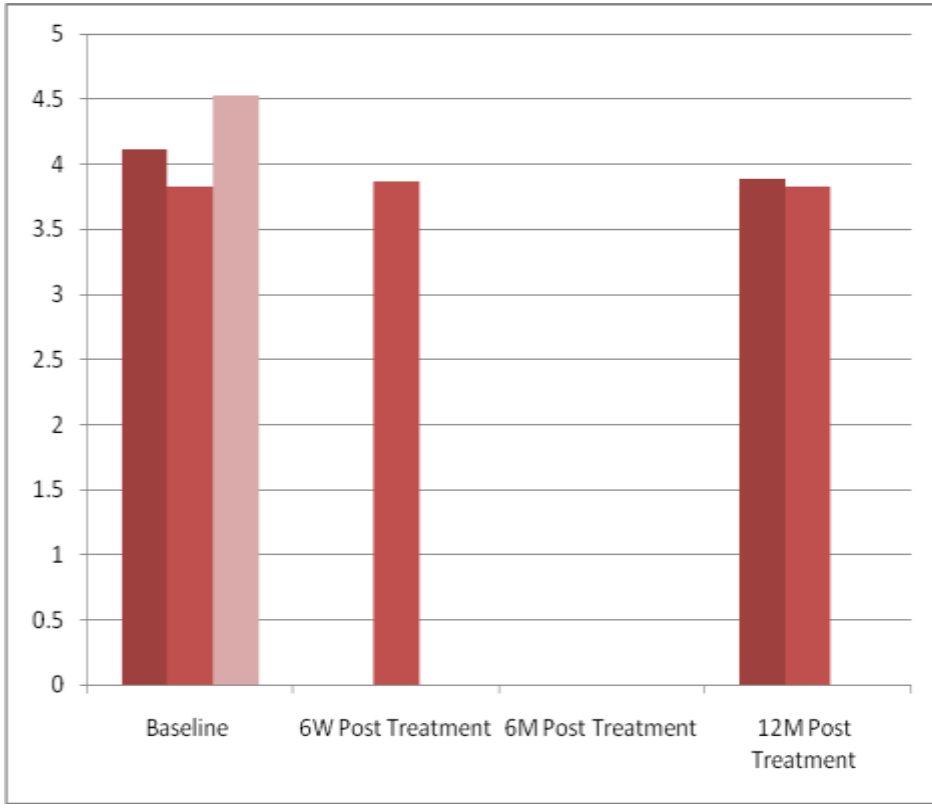
Longitudinal post-PZQ re-sampling of *S. haematobium* in Niger – West Africa (!)

Overall MDA impact on *S. haematobium* prevalence and intensity – But No genetic 'bottleneck' imposed.



Overall arithmetic mean intensity in Niger (n=433).

Error bars are 95% confidence intervals taking into account cluster sampling



Impact of treatment on Allelic Richness

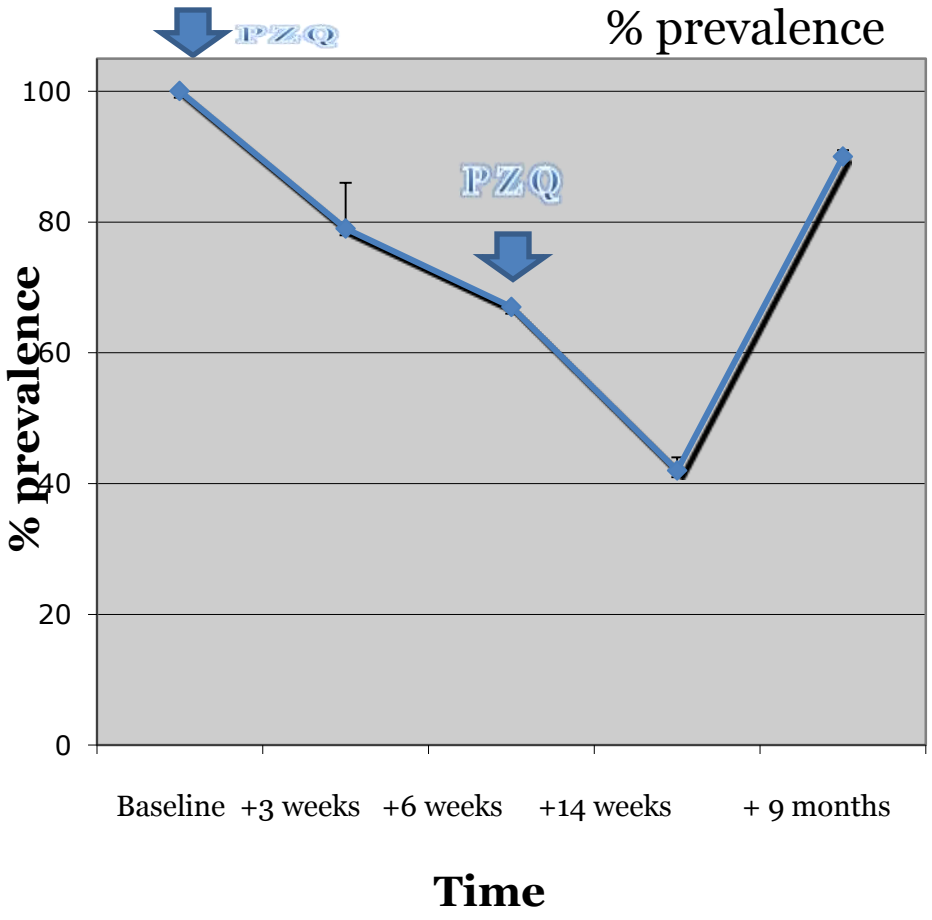
Gouvras,. A., Garba.A., Fenwick, A. et al & Webster, J.P. in prep.

Longitudinal post-PZQ re-sampling of *S. haematobium* in Tabalak, Niger – West Africa – 'Hot Spots' (!)

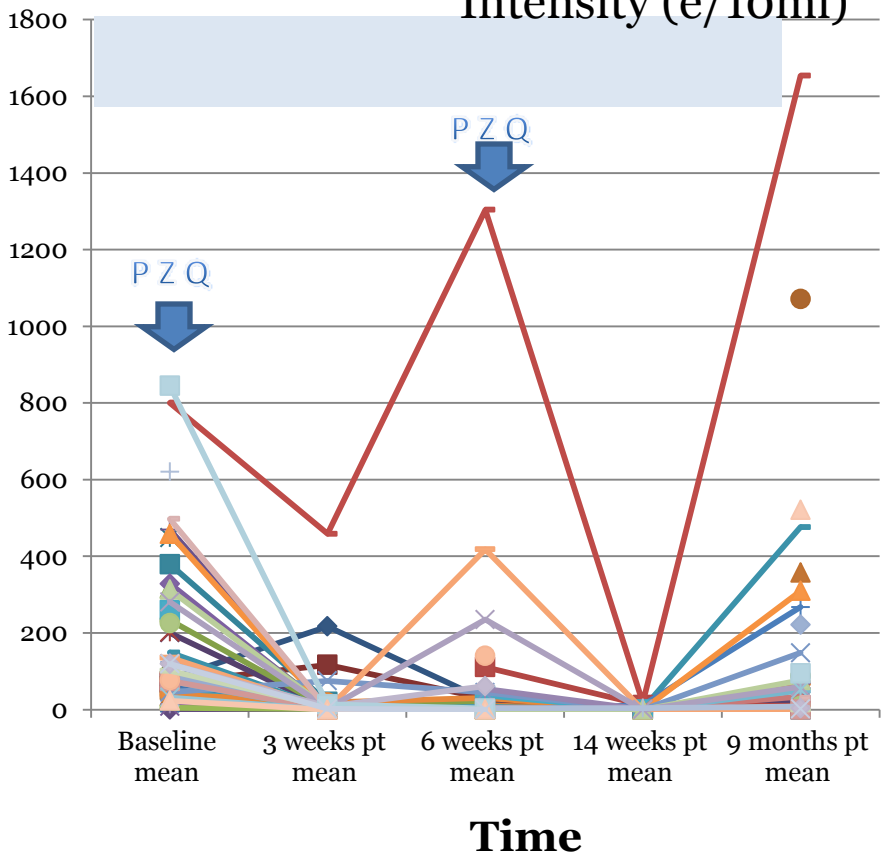
Maintained high prevalence and intensity levels of *S. haematobium* following MDA in certain region of West Africa – treatment failures and/or rapid reinfection ???

49 treated children over time

Mean (sem)
% prevalence

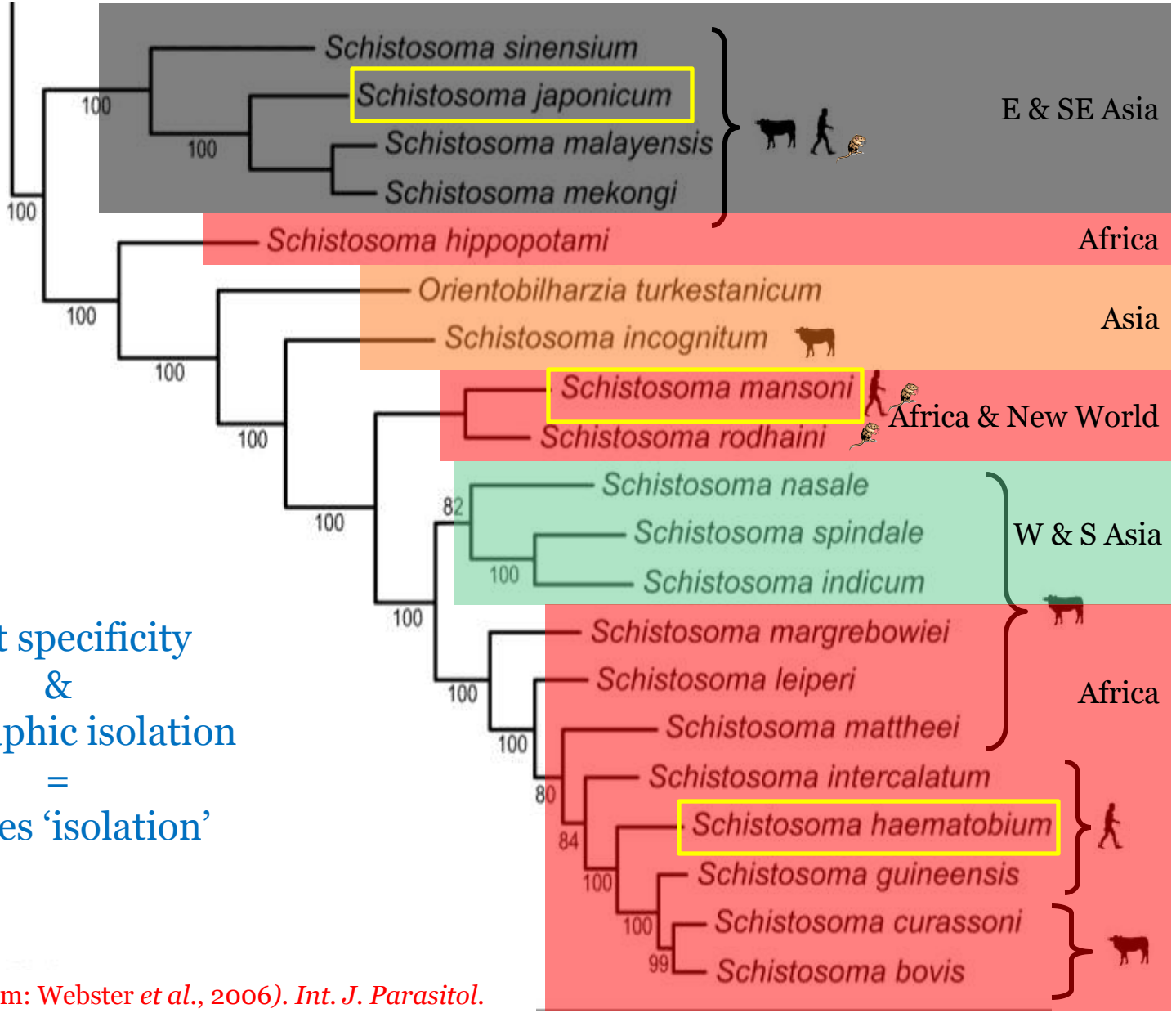


Mean (sem)
Intensity (e/10ml)



Gouvras,. A., Garba.A.,. et al & Webster, J.P. in prep.

Schistosoma spp. - Phylogenetic distances



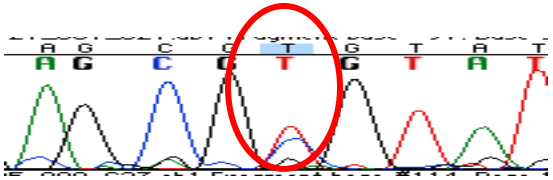
Host specificity
&
Geographic isolation
=
Species 'isolation'

(Adapted from: Webster *et al.*, 2006). *Int. J. Parasitol.*

S. haematobium Group species in West Africa

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

Hybrid detection



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)

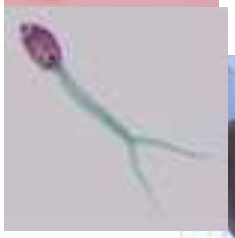
Taylor, M. (1970) *J. Helminth.*
Huyse, Webster, *et al.*, *PLoS Pathogens* (2010)

Tabalak, Niger

Preliminary results:

87 % children were infected with a hybrid species.

[52 % children with mixed both *S. haematobium* / *S. bovis* hybrids and *S. haematobium* / *S. curassoni* hybrids and pure *S. haematobium*].



40 % snails with
S. haematobium / *S. bovis* hybrid cercariae.

Webster, Webster, Rollinson, Fenwick, *et al.*, & Garba, A. in prep.

Consequences of Hybrids for MDA and morbidity control?

Why, when and what next?

Differential morbidity???

Differential PZQ efficacy???

Viable hybrids = increased transmission potential?

Do schistosomes maximize fitness over changing environments?
– *S. mansoni & S. haematobium* SSA?
Yes

Variability in genotype and phenotype in relation to:

- country,
- habitat type,
- Drug pressure
- Definitive host & host availability

Optimizing opportunities for enhanced transmission and infection persistence = parasite fitness in a changing environment.

Talk outline

Schistosomes and schistosomiasis.

Do schistosomes maximize fitness over changing environments?: Laboratory

Do schistosomes maximize fitness over changing environments?: Asia *('older' selective pressures*)

Do schistosomes maximize fitness over changing environments?: Africa *('recent' selective pressures)*

Implications and Applications

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

PZQ

Adult worm death –or-

Changes in adult worm resistance to PZQ;

Changes in virulence to intermediate and/or definitive host;

Changes in fecundity;

Changes in maturation time;

Changes in compatibility between definitive host species;

Changes in host range = Host Switching

Mammalian definitive host

Changes in density due to changes in fecundity of adult worms/and fitness trade-offs with in intermediate host;

Changes in infectivity to definitive host (s)

cercariae

miracidia

Changes in densities due to changes in adult worm fecundity;

Changes in infectivity to intermeidate host

Molluscan intermediate host

Snail changes in susceptibility to infection;

Snail changes in fecundity/fertility

Adapted from: Webster, J.P., *et al.*, . (2008) *Evolutionary Applications*

Evidence of the potential for schistosome adaptation and evolution in response to changing environments

(habitat, host, drug pressure….).

Helps understand the establishment, persistence and polymorphism of this both ‘very ancient’ and/or ‘novel’ infectious disease.

Used to develop further strategies to control schistosomiasis.

Morbidity control to ‘Elimination’?

Acknowledgements & Thank you

***Key* D.Phil/PhD students & Post docs**

& Country co-ordinators & SCI

Asia/lab.

Dr Tianping Wang,

Dr Dabing Lu,

Dr Bao-Zhen Qian,

Dr Jaya Shrivastava,

Dr James Rudge,

Africa/lab.

Dr Artemis Koukounari,

Dr Alice Norton,

Dr Poppy Lamberton,

Dr Michael French,

Dr Anouk Gouvras,

Dr Bonnie Webster,

Dr Charlotte Gower,

Miss Arminder Deol.

Africa/SCI

Prof. Alan Fenwick

Dr Amadou Garba

Dr Narcis Kabatereine

Dr Nicolas Lwambo (RIP)

CONTRAST

THE ROYAL SOCIETY

BILL & MELINDA GATES foundation

MRC Medical Research Council

NSF

SCI Schistosomiasis Control Initiative

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