Immune Response and Vaccine Development in Schistosomiasis

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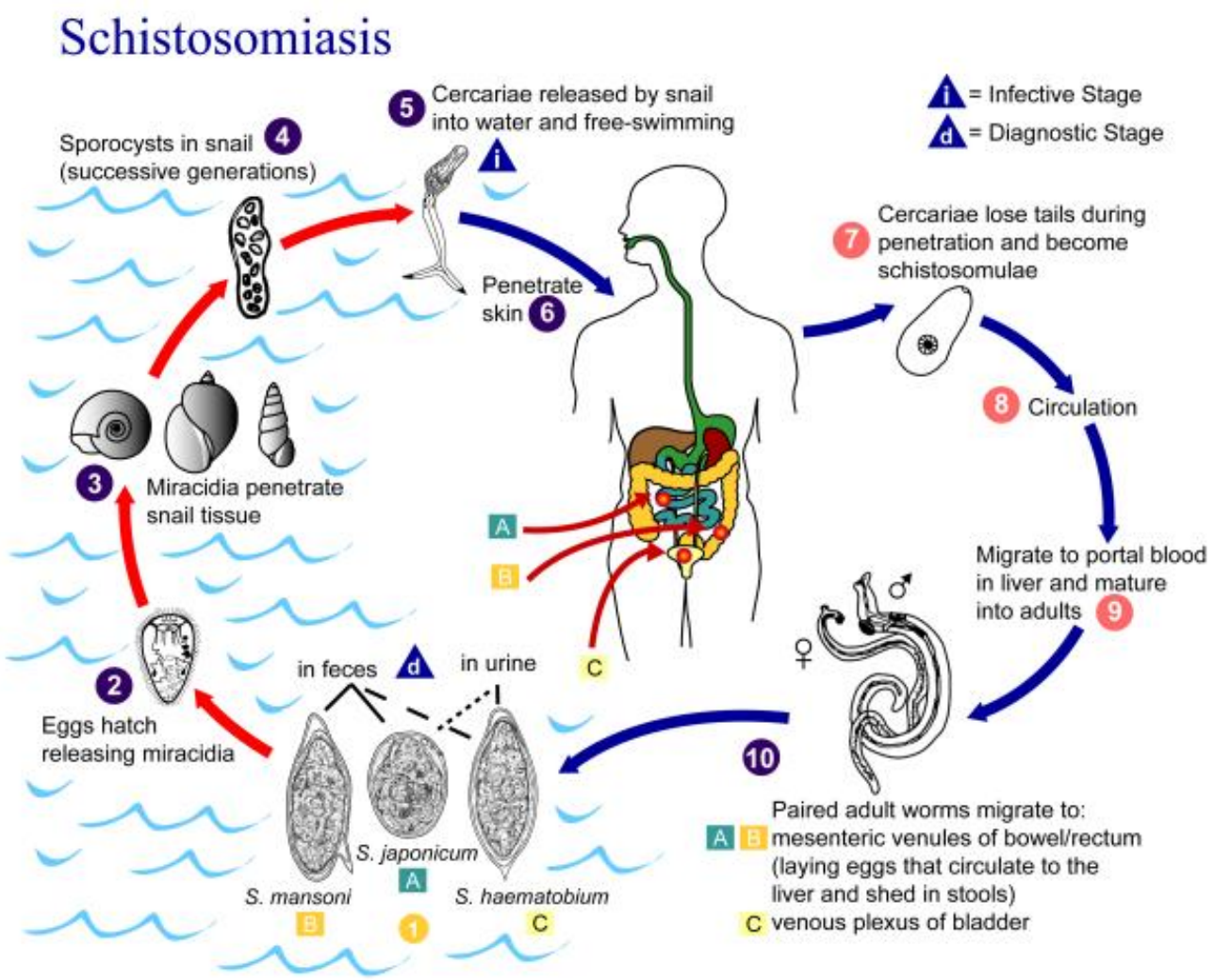
The Lifecycle



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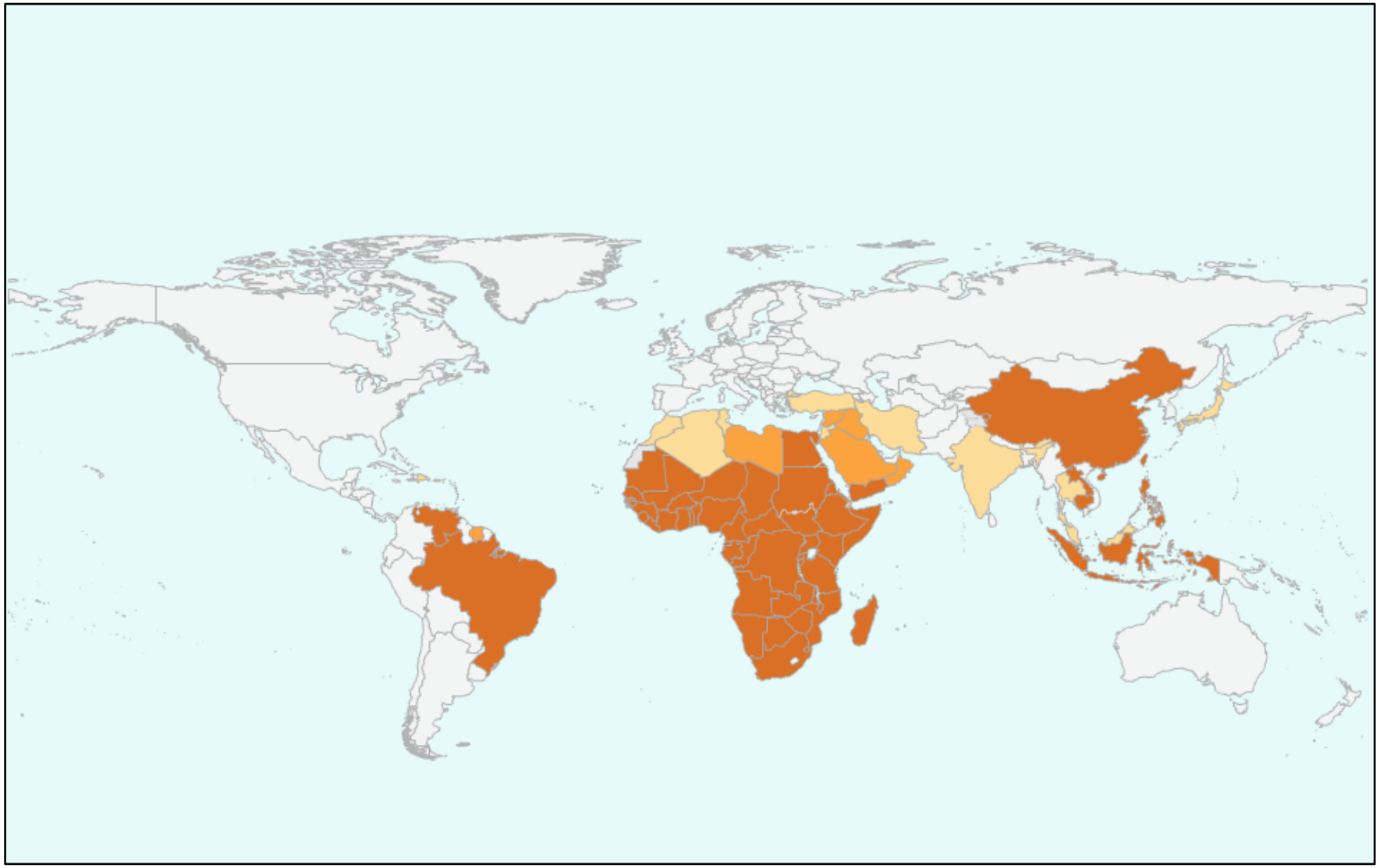


Schistosomiasis – The Numbers

750 million exposed to infection in 74 endemic countries, 200 million infected

20 million with serious morbidity, ~280,000 deaths annually

One fifth of the worlds population harbours at least one species of intestinal dwelling nematode

This equates to approximately 39 million Disability Adjusted Life Years (DALYS)

Tuberculosis gives a figure of 46 million DALYS

This is an important infection with a real cost to human productivity

Schistosomiasis – Epidemiology I

Human Pathogens

*S. mansoni (*Africa, S America)

*S. haematobium (*Africa, Near East*)*

S. japonicum *(*China, Philippines)

To understand the epidemiology of these infections, you need to recognise that the population dynamics of these parasites are fundamentally different from those of other infectious agents

They do not multiply within an individual host, and they can live in the host for up to 7 years (!)

The number of worms in a host is due to the number of infection events and is related to the degree of exposure

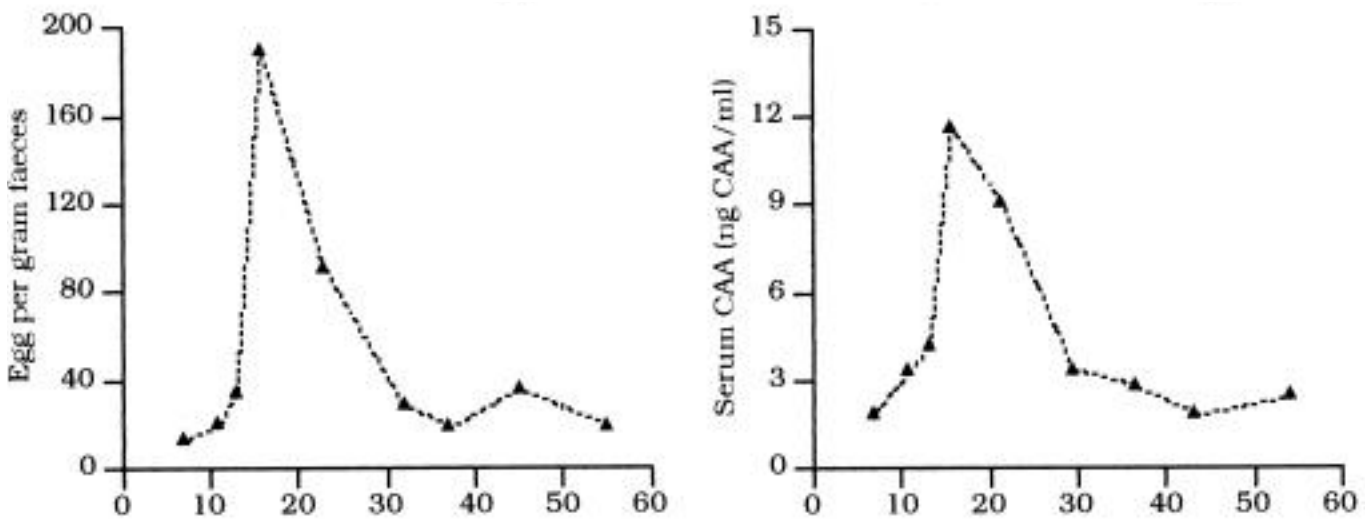
It is the number of worms in an individual that is important in the transmission of the disease

It is the **intensity** of infection that is important – not prevalence.

Age Intensity Curve

Egg output

Circulating antigen



Age (yrs)

Naus *et al.,* Infect Immun, 1999

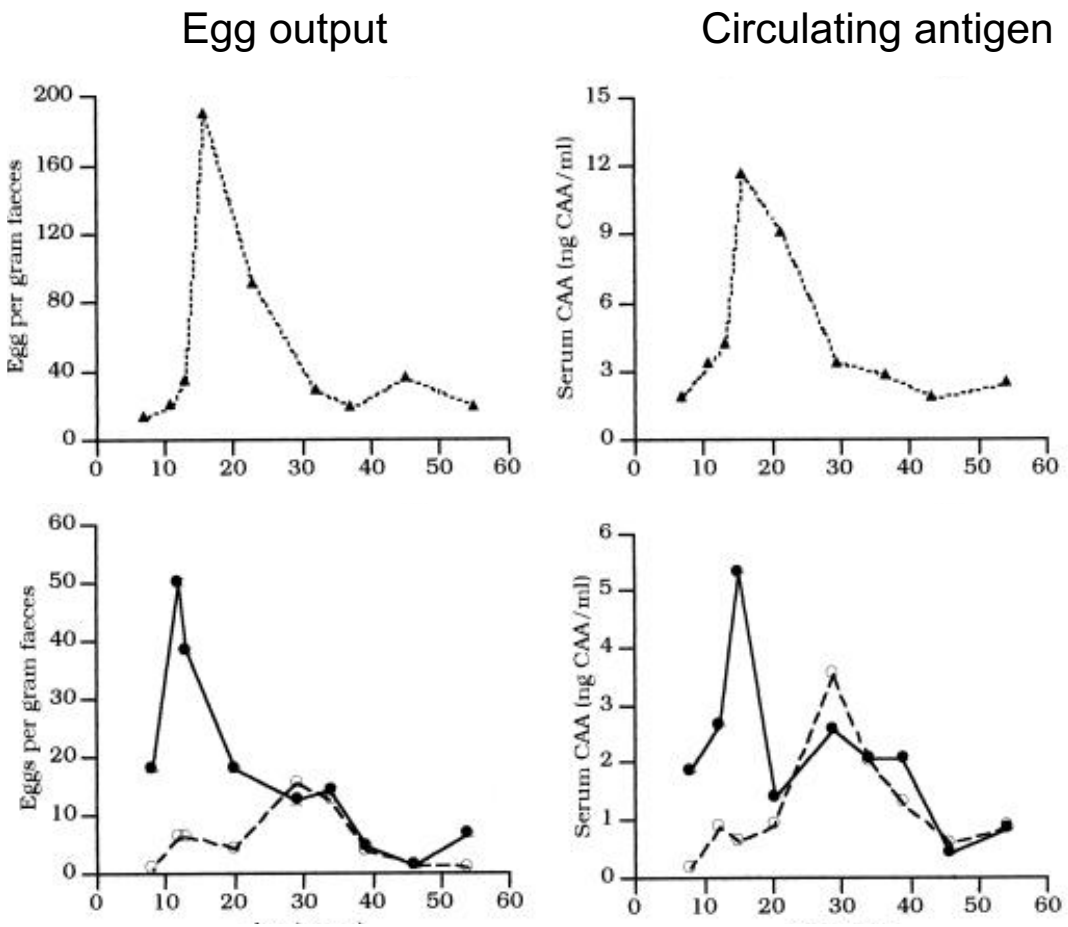
Epidemiology II

Typically, more than 70% of the worms in a population are found within less than 15% of the host individuals

The most heavily infected individuals are at greatest risk of morbidity and are also the major source of infective stages

The same pattern is seen regardless of environmental or cultural differences

Age Intensity Curve

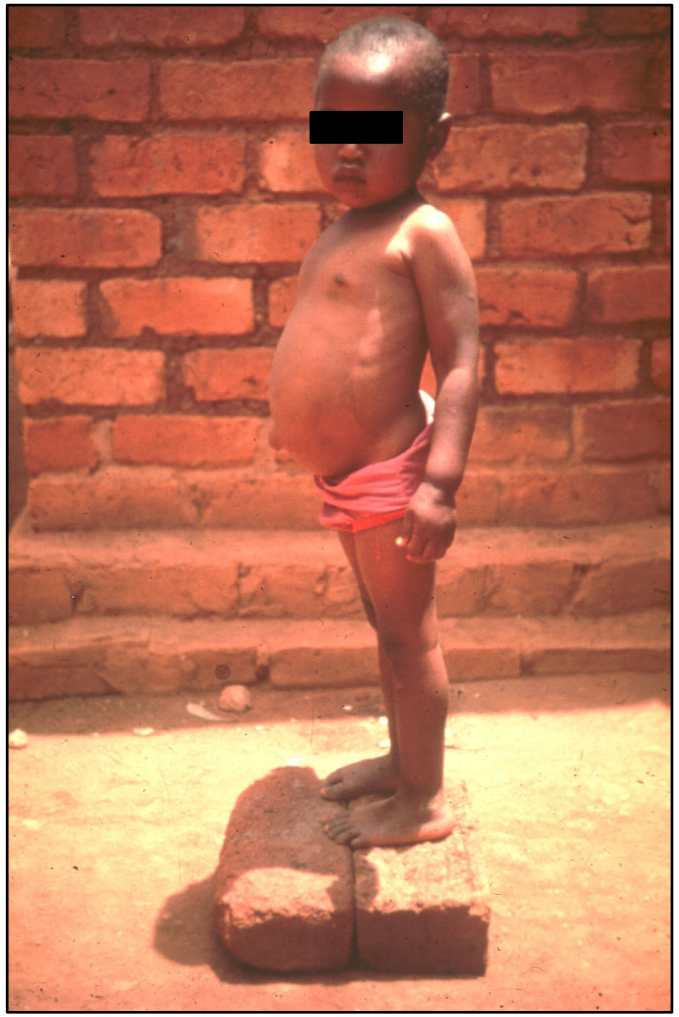


Resident Cohort

Immigrant Cohort

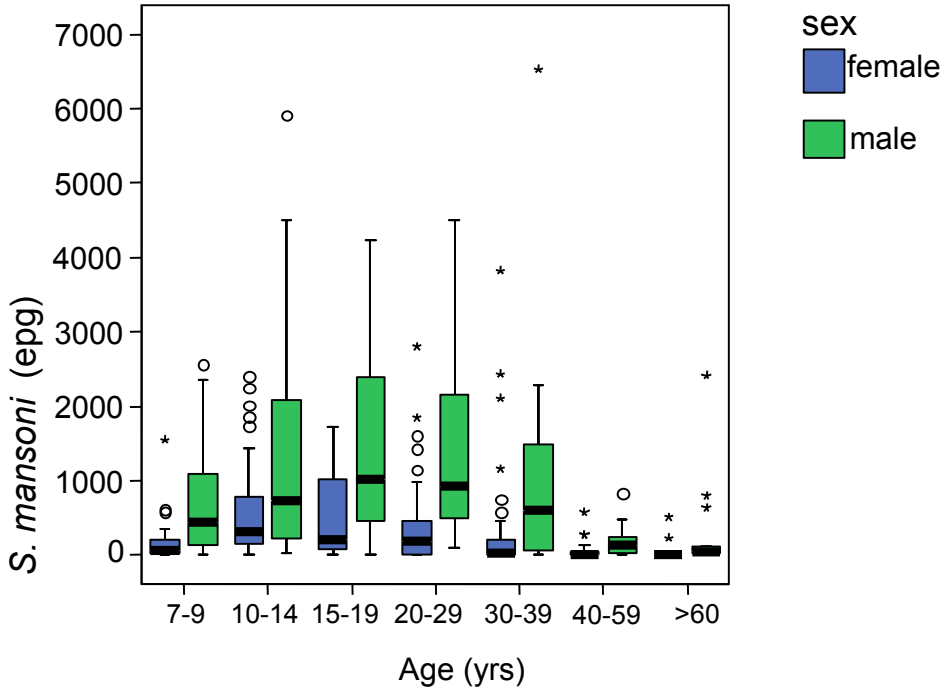
Naus *et al.,* Infect Immun, 1999

Before and after Treatment



A Word of Caution…

When conducting human studies, be careful about potential bias



Males frequently have heavier infections than females
Hormone-related differences in immune response?
Behaviour, socio-cultural differences?

Schistosomiasis – The Immunology

What are the immune correlates of protection?

Eosinophils

Antibodies (IgE/IgG4)

Cytokines (IL-4, and IL-5)

Eosinophils

Peripheral eosinophilia is a characteristic feature of helminth infections

In vitro - cytotoxic to schistosomula in the presence of parasite specific antibodies

In Kenya[1], children with eosinophil counts > 400,000/ml had significantly reduced rates of *S.mansoni* re-infection

Gambian children[2] with elevated eosinophil counts were less susceptible to *S. haematobium* re-infection

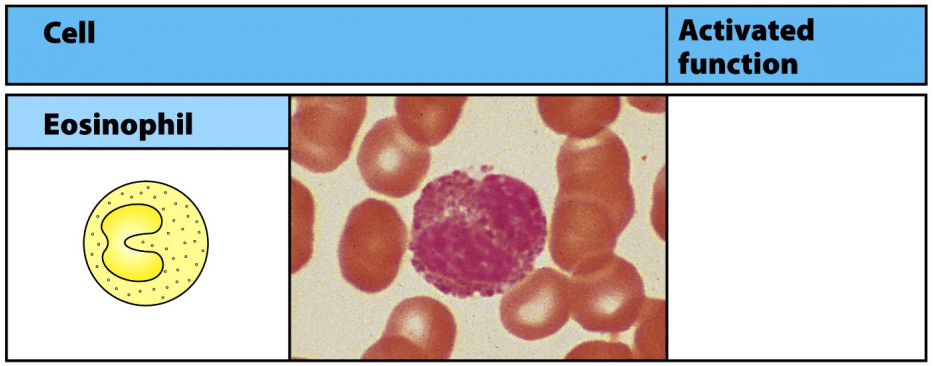
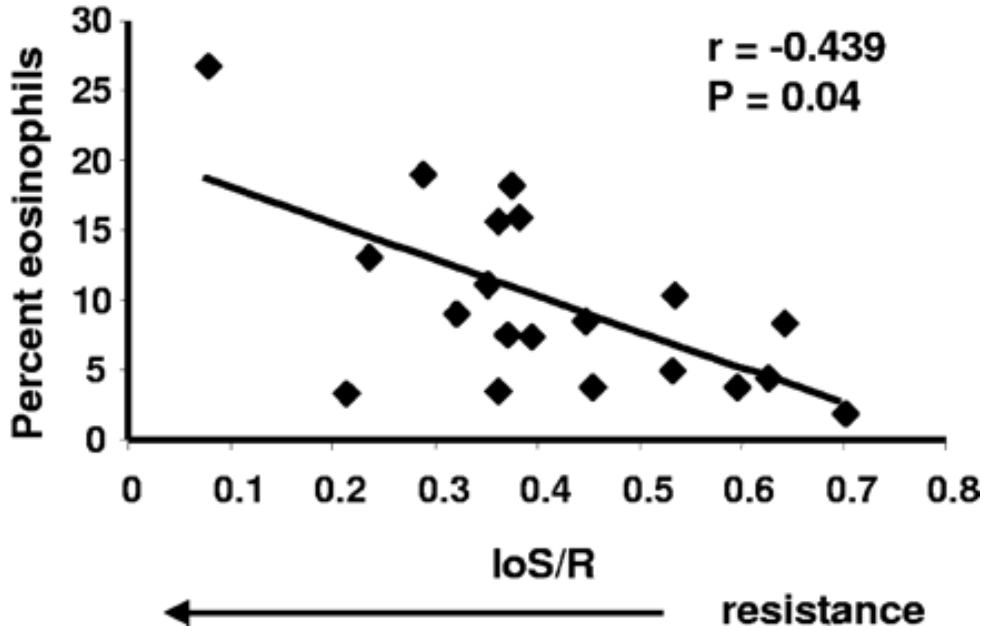


Figure 1-4 part 4 of 6 Immunobiology, 7ed. (© Garland Science 2008)

[1]Sturrock *et al.*, Trans R Soc Trop Med Hyg, 1987
[2]Hagan *et al.,* Parasite Immunol, 1985

Eosinophils II

Resistance to re-infection is correlated with percentage of whole blood eosinophils



IoS/R
Index of susceptibility/resistance

number of time re-infected x 100
weeks in project x cars per week

Ganley-Leal *et al.*, Infect Immun, 2006

A Correlate of Protection: IgE

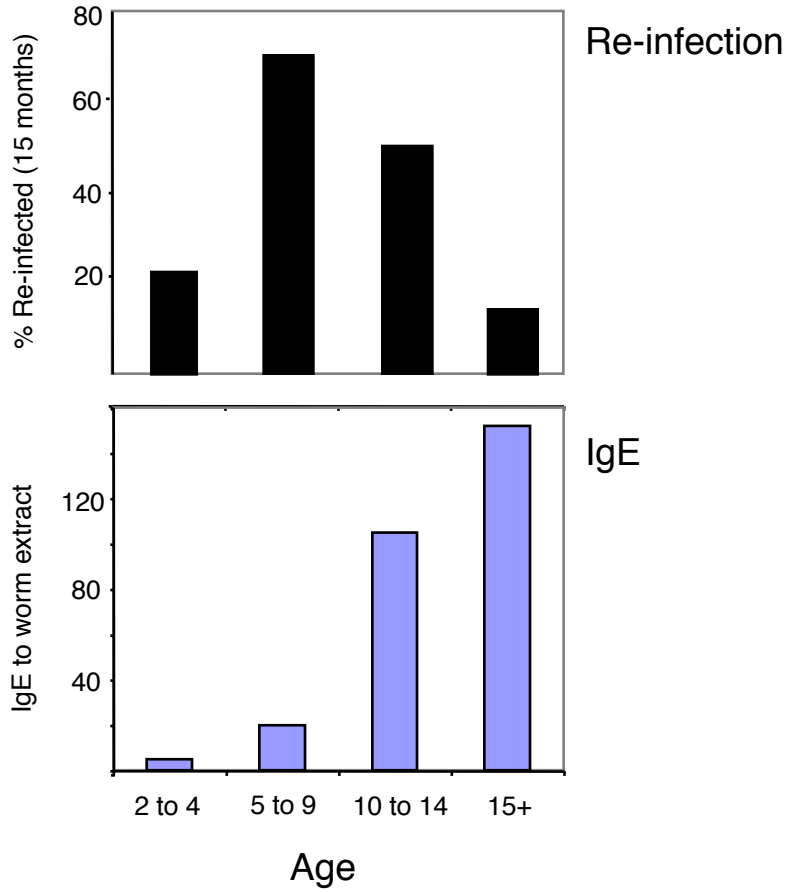
Treatment and re-infection study in The Gambia

Water contact - adults and children were as exposed to infection

Re-infection measured 15 months after treatment

Multiple linear regression used to assess the contribution of age, Ab and exposure to re-infection

Negative relationship between IgE and re-infection



Hagan *et al.*, Nature, 1991

A Correlate of Susceptibility: IgG4

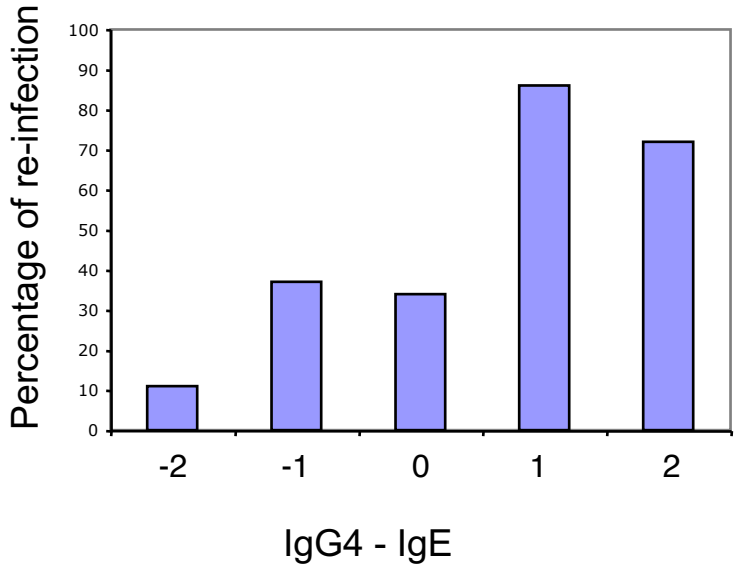
Treatment re-infection study in 118 people in Brazil

Tested relationship between re-infection and anti-schistosome larvae antibodies

Re-infection showed a negative correlation with IgE and a positive one with IgG4

High IgE:IgG4 ratio was associated with low re-infection

18 months after treatment



IgG2 Quintiles

Demeure *et al.*, J Infect Dis, 1993

The IgE/IgG4 Axis

IL-4 and IL-5 both drive IgG4 and IgE class swiching (hence their role in helminth immunity)

But IgG4 and IgE are functionally antagonistic

IgG4 competes for antigens with IgE

Thus, IgG4 blocks IgE-mediated basophil and mast cell degranulation
(also likely to block IgE-mediated eosinophil function)

A simple measure of immunity to Schistosomiasis:

IgE:IgG4

What about Regulation?

Regulation is a key element in our response to infection

Too little regulation leads to uncontrolled immune responses, pathology and organ failure

Too much regulation leads to poor immune responses and uncontrolled infection

Helminth infections are chronic infections

To survive in the host, they must regulate the immune system to stay in balance with it

Many researchers in the field are trying to understand the regulatory response, and identify the helminth proteins that generate Tregs

We may be able to use these proteins to modulate unwanted immune responses

Using Helminths to Combat Autoimmunity

Immunotherapy

Can Worms Tame the Immune System?

Researchers are investigating the use of parasites as remedies for inflammatory bowel disease and other disorders of hyperimmunity

In a stunt reminiscent of the TV reality show *Fear Factor*, dozens of unpaid volunteers have recently been gulping Gatorade laced with 2500 live eggs from parasitic worms. The host, so to speak, of this experiment was gastroenterologist Joel Weinstock of the University of Iowa in Iowa City. The hoped-for reward for the participants was remission of the disruptive and painful symptoms of inflammatory bowel disease (IBD). Weinstock is among a small but growing group of researchers who believe that parasitic worms, or substances derived from them, could provide effective treatments for not only IBD but also a range of autoimmune disorders.

The idea may sound crazy, but it is buttressed by studies showing that treating mice with eggs, larvae, or extracts of helminths—parasitic worms such as flukes, flatworms, tapeworms, and pinworms—can dampen, and perhaps prevent, allergic reactions, reduce the severity of a multiple sclerosis (MS)–like disease, and block the development of type I diabetes (see sidebar). Recent data indicate that helminths may protect against disease by invigorating so-called regulatory T cells, which function as the immune system's police officers and

laboratory and clinical findings until they are reproduced, better explained, or possibly extended to other disorders. But if the data hold up, they could point the way to new medicine. The hope, says Maizels, is "to work out how helminths are doing it and reproduce that with a nonliving intervention." Adds Weinstock: "We're opening up the possibility of whole new classes of drugs."

Man and his worm. Joel Weinstock holds a dose of eggs from *Trichuris suis* (*inset*), which he is using to treat inflammatory bowel disease.

Microbe medicine

Weinstock, Maizels, and others were inspired by a decades-old theory known as the hygiene hypothesis: For millennia, the theory goes, microbes have trained the immune system—and so too much clean

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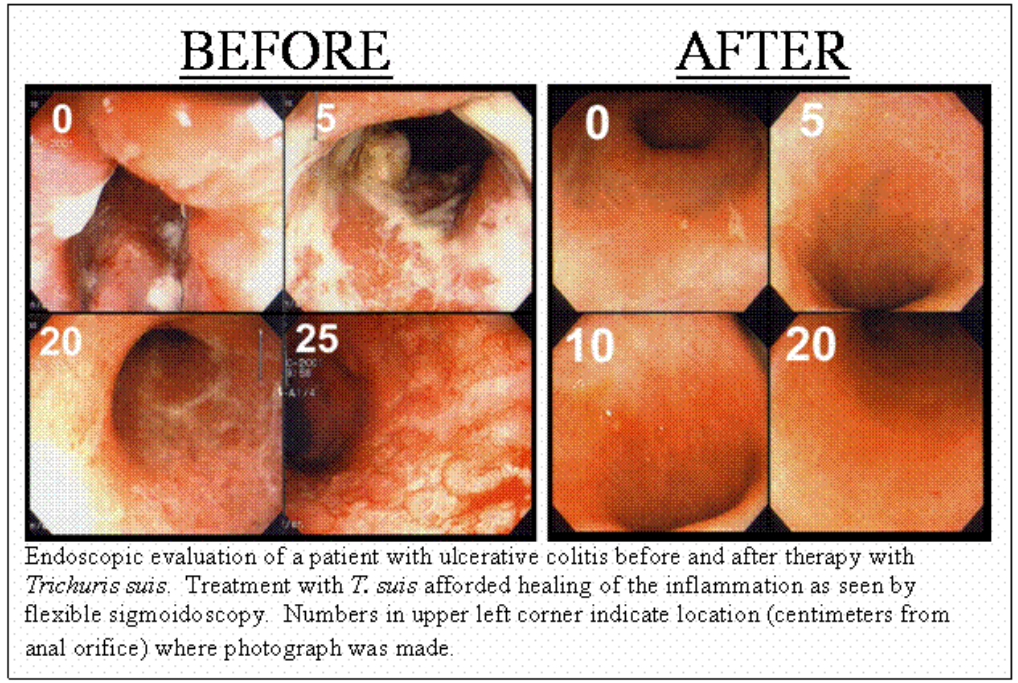


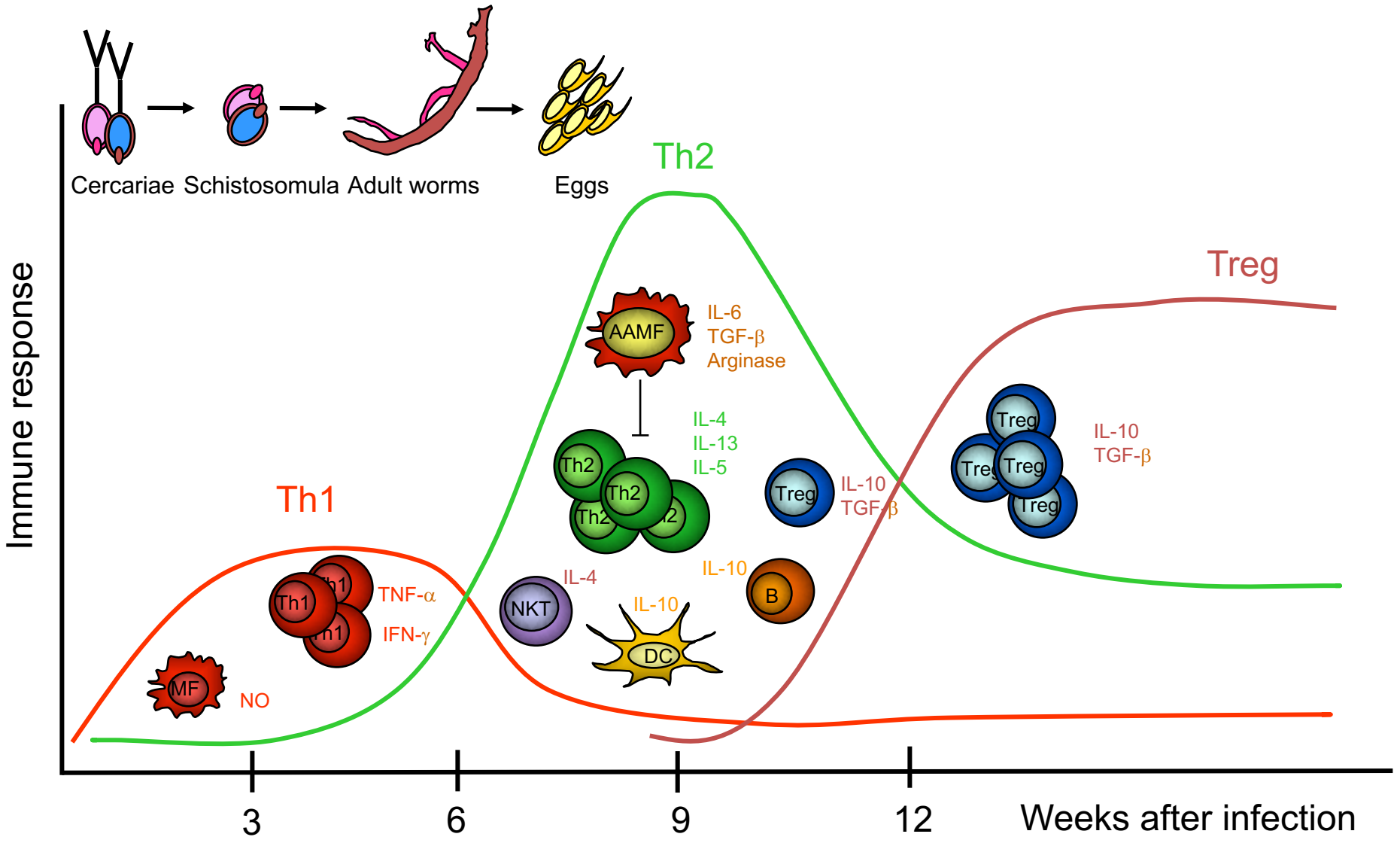
Endoscopic evaluation of a patient with ulcerative colitis before and after therapy with *Trichuris suis*. Treatment with *T. suis* afforded healing of the inflammation as seen by flexible sigmoidoscopy. Numbers in upper left corner indicate location (centimeters from anal orifice) where photograph was made.

OVAMED GmbH

Trichuris suis

A new approach to therapy for ulcerative colitis and crohn's disease?

Immunity to Schistosomiasis



Dunne & Cooke, Nat Rev Immunol, 2005

Quick Question!

Should we treat helminth infections by mass drug administration?

Another Cautionary Tale…

All the immune components associated with human immunity to schistosomiasis (and other helminths) are exactly the same as those associated with allergic disease

Eosinophils

Basophils

Mast Cells

IgE

Histamine release

Our immune system has evolved with continual helminth infection – they are not new to us

Allergies and Helminths

There is now good evidence that helminth proteins very closely resemble allergens

Example

S. Mansoni Tegument Allergen Like Proteins (SmTAL1-13)

SmTAL1 is the dominant IgE antigen in *S. mansoni*
IgE to SmTAL1 is correlated with resistance to reinfection
Increases with age

Will MDA give rise to allergic sensitivities in the absence of helminths?
What is the cost of treating allergies versus the cost treating helminths?

Should we be mass administering antihelmintics?

Fitzsimmons *et al.*, PLoS NTD, 2012
Pinot de Moira *et al.*, Infect Immun, 2013

Vaccines! And another Word of Caution…

There are quite a number of vaccines for a number of different helminth parasites

S. mansoni		
SmSynt	Schistosomula and Adult	Figueiredo, PLoS NTD 2014; 8:e3107
SmTSP-2 Sm29	Adult worms and lung-stage schistosomula	Pinheiro, Parasite Immunol 2014; 36: 303
Sm10.3	All stages	Martins, PLoS NTD, 2014; 8: e2750.
SG3PDH	Larvae	El Ridi, J Parasitol, 2013; 99: 194
Smteg	Schistosomula	Araujo, Acta tropica, 2012; 124: 140
SmStoLP	Adults and 7-day-old schistosomula	Farias, PLoS NTD, 2010; 4: e597

S. japonicum		
SjTP22.4	Adult, Schistosomulum and cercaria	Zhang, Vaccine, 2012; 30:5141
SjEsRRBL1S	Highly expressed in 14-28 day old schistosomes	Wu, Exp Parasitology. 2012; 131:383
SjMLP/Hsp70	Eggs, cercariae, schistosomula and adult	He, Parasitol Res, 2010; 107
SjPSMA5	Up-regulated in 18-day and 32-day schistosomes	Hong Y, Exp Parasitol, 2010; 126: 517

But only one Vaccine Candidate Tested in Humans to Date

Generalized urticaria induced by the *Na*-ASP-2 hookworm vaccine: Implications for the development of vaccines against helminths

David J. Diemert, MD, FRCP(C),[a,b,c] Antonio G. Pinto, MD,[c] Janaina Freire, MD,[c] Amar Jariwala, MD,[a] Helton Santiago, MD, PhD,[b,c] Robert G. Hamilton, PhD,[d] Maria Victoria Periago, PhD,[c] Alex Loukas, PhD,[e] Leon Tribolet, BSc,[e] Jason Mulvenna, PhD,[e,f] Rodrigo Correa-Oliveira, PhD,[c] Peter J. Hotez, MD, PhD,[a,g] and Jeffrey M. Bethony, PhD[b,c] *Washington, DC, Belo Horizonte, Brazil, Baltimore, Md, Cairns and Brisbane, Australia, and Houston, Tex*

This vaccine candidate was safe and immunogenic in a US trial

But it failed in Brazil

Why?

Diemert *et al.*, J Allergy Clin Immunol, 2012

Schistosome Vaccines – what should we do?

Generate an IgE response?

Need to avoid allergic responses

Vaccinate adults who have preexisting immunity, and probable current infection?

Lessons from the hookworm trial

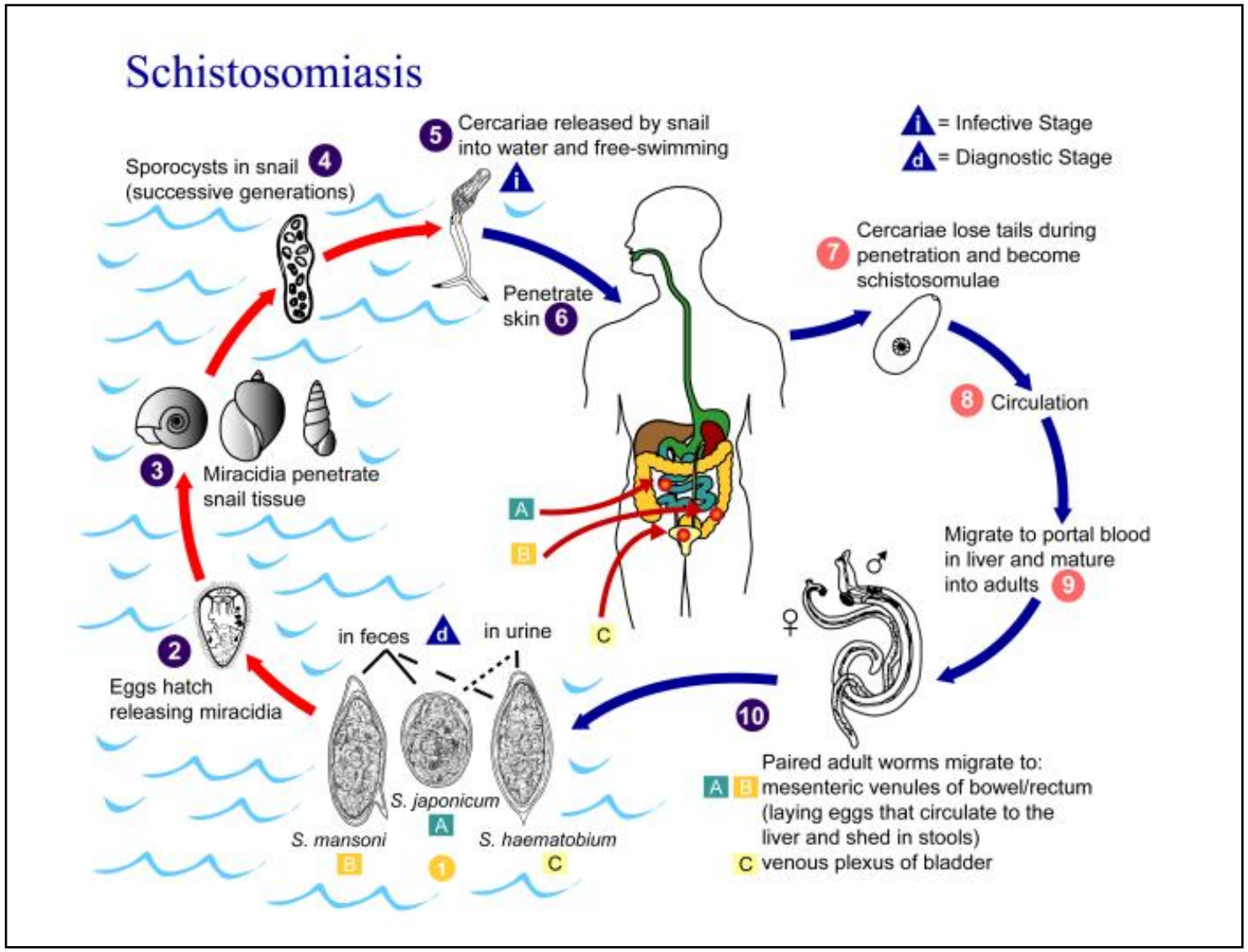
Vaccinate children without preexisting immunity?

Role of *in utero* environment

Rise in allergies in absence of schistosomiasis

Think of something else?

Targeting the Schistosomula



Can generate IgG responses to Schistosomula

Avoid allergic responses

Work at the skin stage

Prevent infection and transmission

Susceptible to innate and adaptive responses

Conclusions – more questions than answers

Protective immunity to schistosomiasis is developed over time and with continual exposure

Protective immunity correlates with

High eosinophil counts

High IgE

Th2 responses (IL-4/5)

Chronic infection means you must modulate immune system

Tregs

Can we generate a vaccine?

Allergic reactions

Effect of immunity in uninfected hosts – will it drive the emergence of allergies?

Effect of MDA?

One Last Thought

Reduced transmission of human schistosomiasis after restoration of a native river prawn that preys on the snail intermediate host

Susanne H. Sokolow[a,b,1], Elizabeth Huttinger[c], Nicolas Jouanard[c], Michael H. Hsieh[d,e,f,g], Kevin D. Lafferty[h], Armand M. Kuris[b], Gilles Riveau[i,j], Simon Senghor[j], Cheikh Thiam[c], Alassane N'Diaye[c], Djibril Sarr Faye[c], and Giulio A. De Leo[a]

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Completion of the Diama Dam in Senegal in 1986

No prawns above the dam after 1986

Schisto prevalence

1986 – 0%

1992 – 70%

1997 – 100%

Sokolow *et al.*, PNAS ,2015

Acknowledgements

I nicked a few slides from: