The Global Burden of Parasitic Infections

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Impact of Malaria

• What we have been saying:
  ◦ 300-500 million infections/year
  ◦ 750,000 deaths/year - > 90% in children under age 5 in subsaharan Africa
• “New” thinking (modeling)
  ◦ 1.24 million deaths 2010 (1.14 million in Africa)
  ◦ 525,000 deaths in children < age 5
  Is this a surprise?

Impact of Malaria

What do we know about prevention efforts?
◦ Who is the target?
What do we know about malaria prevention efforts?
- What are the interventions?

Impact of Malaria

- [Image of malaria prevention efforts]
  - DDT sprayer
  - Anti-malaria netting
Impact of Malaria

What do we know about immunity to malaria?

- Only 33 individuals have been shown to have sterile immunity to P. falciparum - none of whom acquired this immunity naturally.
- Malaria naïve adults are immunologically similar to children - should we expect a different response to infection?

Entomological Inoculation Rate

\[ \text{EIR} = \frac{\text{M} \times \text{a}}{\text{S}} \]

- \( \text{M} \equiv \# \text{Anopheles/person} \)
- \( \text{a} \equiv \# \text{persons bitten by 1 Anopheles/day} \)
- \( \text{S} \equiv \# \text{Anopheles with infectious sporozoites in salivary glands} \)

Impact of Malaria

Are we going to make a sustainable difference anytime soon?

The RTS,S/AS01 vaccine

Other vaccines

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The Neglected Tropical Diseases

- Dracunculiasis
- Lymphatic filariasis
- Trachoma
- African trypanosomiasis
- Leprosy
- Soil transmitted helminths
- Schistosomiasis
- Onchocerciasis
- Chagas Disease
- Visceral Leishmaniasis

Dracunculis melinensis

No symptoms x 1 year, then:
- Slight fever
- Itchy rash
- Nausea
- Vomiting
- Diarrhea
- Dizziness
- Blister forms → burning pain → immerse foot in water to soothe → female emerges
**Dracunculiasis**

**Complications:**
- Local or systemic infection
- Tetanus
- Pain and disability

**Dracunculiasis Eradication Project**

- 1986 – 3.5 million cases in 20 countries
- 2011 – 1060 cases
  - 97% southern Sudan
  - 3% Mali, Chad, Ethiopia
- Methodology
  - Surveillance/case containment
  - Safe drinking water (filtration)
  - Vector control
  - Education

**Impact of Parasitic Diseases**

- Lymphatic filariasis
  - 110 million infected
  - 40 million disabled – the second leading cause of disability worldwide
- Onchocerciasis
  - 15-25 million infected
  - ~550,000 blind or visually impaired
Introduction Global and Public Health

Onchocerciasis – Cutaneous Manifestations

- Leopard Skin
- Chronic popular dermatitis and subcutaneous nodules

Onchocerciasis – “African River Blindness”

- "Snowflake" opacities of punctate keratitis
**Onchocerciasis**

**Diagnosis** –
- skin snips –
  - visualize microfilariae
  - PCR

**Rx:**
- Ivermectin
  - Contraindicated if concomitant loiasis (fatal encephalopathy)
- Doxycycline
- DEC contraindicated – Mazzotti reaction

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**Lymphatic Filariasis**

(Wuchereria bancrofti, Brugia malayi)

Epidemiology: tropics/sub-tropics, ~120 million
- vectors - mosquitoes, reservoirs (B. malayi)
Lymphatic Filariasis

**Diagnosis:**
- blood smear - 10 pm - 2 am
- serology (TPE) - IgG1 and IgG4
- ultrasound (visualize adults)

**Treatment:**
- DEC
- Ivermectin
- Doxycycline

**Lymphedema management:**
- Antibiotic soap
- Compression
- Surgery
- Doxycycline!

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**Impact of Parasitic Diseases**

- Intestinal helminths may occupy 2 billion GI tracts worldwide
- Consequences most notable in children - anemia, malnutrition, growth retardation, impaired cognitive development

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Parasite Public Health

- Control and eradication are a multicomponent process:
  - Sanitation/water management
  - Education
  - Vector control
  - Antimicrobials:
    - Mass administration
    - Case finding and targeted administration
  - Vaccines

All it takes is political will, manpower and lots of $.

Parasite Immunology

- In general multiple arms of the immune system are involved
  - Sterile immunity is rare
  - Premunition - persistence of viable organisms at low concentration within the host provides continued immune stimulus to control disease and prevent reinfection
A Worm's Eye View of the Immune System

- Man has co-evolved with parasites for millions of years. Observations pertinent to this relationship include:
  - Lower population risk for asthma in developing countries
  - Lower prevalence of inflammatory bowel disease in emerging nations
  - Higher prevalence of IBD in northern Europe vs. southern Europe, northern US vs. southern US
  - Rising incidence of asthma, IBD, autoimmune diseases

A Worm's Eye View of the Immune System

- Animal studies give biologic plausibility to a relationship:
  - Schistosomes or schistosomal eggs or antigens prevent type 1 diabetes, Grave’s thyroiditis, experimental allergic encephalomyelitis
  - Trichuris suis prevents Crohn’s Disease
  - Hymenolepis diminuta prevents experimental colitis
  - T. brucei prevents collagen induced arthritis

A Worm’s Eye View of the Immune System

- Human studies suggest parasite infections drive evolution of host immune responses
  - Decreased prevalence of specific interleukin and interleukin receptor genes associated with inflammatory bowel or celiac disease in populations where parasite burdens are higher

Could it be that parasite extermination leads to immune disregulation and an increase in autoimmune or allergic disease?
A Worm's Eye View of the Immune System

- ~200 million chronically infected with *Schistosoma* spp
- Complex life cycle
- Adult worms survive in the vascular space for up to 40 years
- Immune evasion -
  - Immunomodulating neuropeptides use molecular mimicry in the snail
  - Adults coat themselves with host antigens
  - Enzymatically cleave antibodies

A Worm's Eye View of the Immune System

- Immune dependence by the parasite?
  - *S. mansoni* eggs must translocate from the portal capillaries to the gut lumen
    - Process does not occur in immunosuppressed mice
    - Egg excretion is reduced in HIV infected individuals proportional to the number of circulating CD4 cells
  - Egg production in female worms appears to depend upon tissue necrosis factor (TNF)
  - Adult worms bear receptors activated by transforming growth factor β and may play a role in growth and development

Murine immune response to *schistosoma* infection:

- *S. mansoni* in the skin secrete prostaglandin D₂ which inhibits migration of Langerhan's cells to lymph nodes
- Deletion of the PGD₂ receptor results in decreased numbers of adult worms and decreased immune responses to eggs
- Eggs are potent inducers of the TH2 response by multiple mechanisms
Murine immune response to schistosoma infection:

- IL10 is generated by several sources and facilitates the development of T<sub>reg</sub>.
  - One source is schistosome-specific phosphatidylycerine which activates TLR2 at the cell surface of DCs.

- T<sub>reg</sub> further TH1 responses and polarizes the response toward TH2.
  - There is some downregulation of TH2, however, as responses to allergens such as house dust mite decrease.

How does this prevent autoimmune responses?

- Skews responses away from TH1.
- Increases T<sub>reg</sub> which can downregulate both types of autoimmune response.
- Other parasite secretory products, such as pro-opiomelanocortin-derived peptides and enkephalin, may also modulate immune response.