

# Neglected Parasitic Diseases

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# The Hospital for Tropical Diseases (HTD)

- Imported parasitic and infectious diseases
- From any part of the globe
- Tourists, refugees, migrants, business people etc
- A window on the world
- Important in sentinel surveillance

# The global importance of parasites

## **MALARIA IS BY FAR THE GREATEST CHALLENGE**

### **Neglected tropical diseases (WHO)**

Apart from soil-transmitted helminthiases  
(affect >1 billion people):

- Schistosomiasis
- Lymphatic filariasis
- Blinding Trachoma (not a parasite)
- Onchocerciasis
- Chagas' disease
- Leishmaniasis

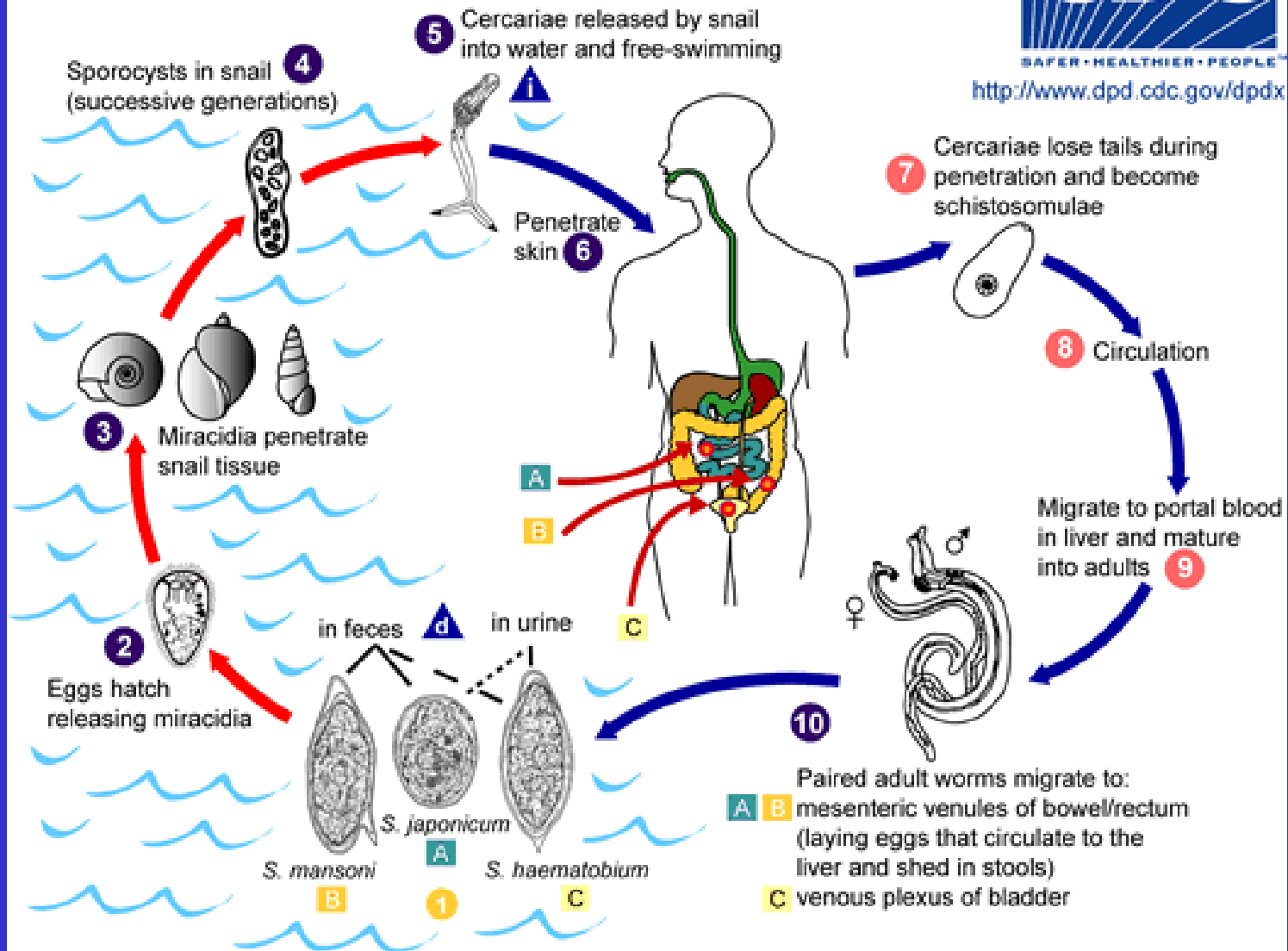
# Schistosomiasis

- **779 million people at risk**  
(Steinmann et al, 2006 Lancet Inf Dis 6: 411-25)
- **200 million people infected**
- **80% live in sub-Saharan Africa**
- **120 million symptomatic**
- **20 million with severe disease**  
(Hatz 2005 J Travel Med 12: 1-2)
- **Annual mortality 280,000**  
(Southgate et al, 2005 J Helminthol 79:181-5)

## Global distribution of schistosomiasis



**i** = Infective Stage  
**d** = Diagnostic Stage



# Pathogenesis of Schistosomiasis

Mostly due to passage of eggs and the granulomatous reaction to eggs left in tissues

- Cercarial penetration
- Larval migration and maturation
- Early egg deposition
- Late egg deposition

# Clinical Features of Schistosomiasis

Common to all:

- Papular dermatitis; Swimmers' Itch
- Katayama Fever

# Katayama Fever

- Fever, myalgia, arthralgia, urticaria
- Abdominal discomfort
- Watery diarrhoea
- Hepatosplenomegaly
- Pneumonitis
- Eosinophilia

# Clinical Features of Schistosomiasis

- *S.haematobium*:

Terminal haematuria, frequency of micturition, bladder pain, pyelonephritis, hydronephrosis, pyonephrosis, haemospermia, vulval papillomata, cervical growths, bladder carcinoma

# Clinical Features of Schistosomiasis

- *S.mansoni*:

Malaise, abdominal pain, frequent stools with blood and mucus, rectal polyps, hepatomegaly (reversible at first), portal hypertension, haematemesis from bleeding oesophageal varices, ascites

# Clinical Features of Schistosomiasis

- *S.japonicum*:  
Extremely rare in travellers  
Similar to & more severe than *S.mansoni*  
Small bowel also affected  
Hepatic fibrosis with splenic enlargement  
CNS symptoms in about 5%: convulsions, hemiplegia, paraplegia, blindness

# Schistosomiasis at HTD

Whitty et al 2000 Trans R Soc Trop Med Hyg 94: 531-4

- 1107 cases over 5 years
- 28% residents of or migrants from an endemic country
- 62% travellers
- **Ova seen in only 45% of cases**

# Schistosomiasis at HTD

Whitty et al 2000 Trans R Soc Trop Med Hyg 94: 531-4

- 68% *S.haematobium*
- 29% *S.mansoni*
- 2% *S.haematobium* plus *S.mansoni*
- 1% *S.intercalatum*

# Schistosomiasis at HTD

Whitty et al 2000 Trans R Soc Trop Med Hyg 94: 531-4

- *S.mansoni* in:
  - 45% residents
  - 22% travellers
- *S.haematobium* in:
  - 94% of those exposed in Malawi
  - 60% of those exposed in West Africa

# Schistosomiasis at HTD

Whitty et al 2000 Trans R Soc Trop Med Hyg 94: 531-4

Katayama Syndrome uncommon

- *S.mansoni* 5% of cases
- *S.haematobium* 1.5% of cases

# Schistosomiasis at HTD

Whitty et al 2000 Trans R Soc Trop Med Hyg 94: 531-4

<u>Symptom</u>	<u>% cases</u>
None	50
Tiredness	25
Itch	8
Frank haematuria	19
Haematospermia	1
Semen changes	4
Bloody diarrhoea	3

# Schistosomiasis of the Nervous System

- Cerebral  
Mainly *S.japonicum*
- Slowly expanding mass lesion  
Headache, fits, speech disturbance, hemiparesis, ataxia, papilloedema
- Diagnosis by CT, MRI, serology, eggs elsewhere, biopsy

# Schistosomiasis of the Nervous System

- Spinal  
Mainly *S.mansoni* reported
- Relatively rapid onset  
Lumbar &/or lower limb pain, muscle weakness, sensory impairment, bladder dysfunction
- Diagnosis by CT, CT myelography, MRI, serology, eggs elsewhere

# Diagnosis of Schistosomiasis at HTD

- Microscopy of:  
Stool, terminal urine, [semen], rectal snips,  
[bladder biopsies]  
Only 45% of cases egg positive
- Antigen detection insufficiently sensitive
- Serology  
ELISA for IgG antibodies to *S.mansoni* soluble  
egg antigen [SEA]
- Ultrasonography for complications

# HTD SEA ELISA

- Reported sensitivity of 96% for *S.mansoni* & 92% for *S.haematobium*
- 97% specificity
- Takes approx 6 weeks to seroconvert

# HTD Treatment of Schistosomiasis

## All species:

- Praziquantel (higher dose for *S.japonicum*)
- Katayama syndrome: Steroid cover and re-treat after 6 weeks
- Neuroschistosomiasis: 3 day course under steroid cover

## Alternatives:

- Oxamniquine for *S.mansoni*
- Metrifonate for *S.haematobium*

# Problems in Practice

- Education of the traveller
- Clinical awareness in a non-endemic area
- Late referral of neuroschistosomiasis
- Misdiagnosis of genital lesions
- We lack a good test for treatment failure

# Prevention of Travellers' Schistosomiasis

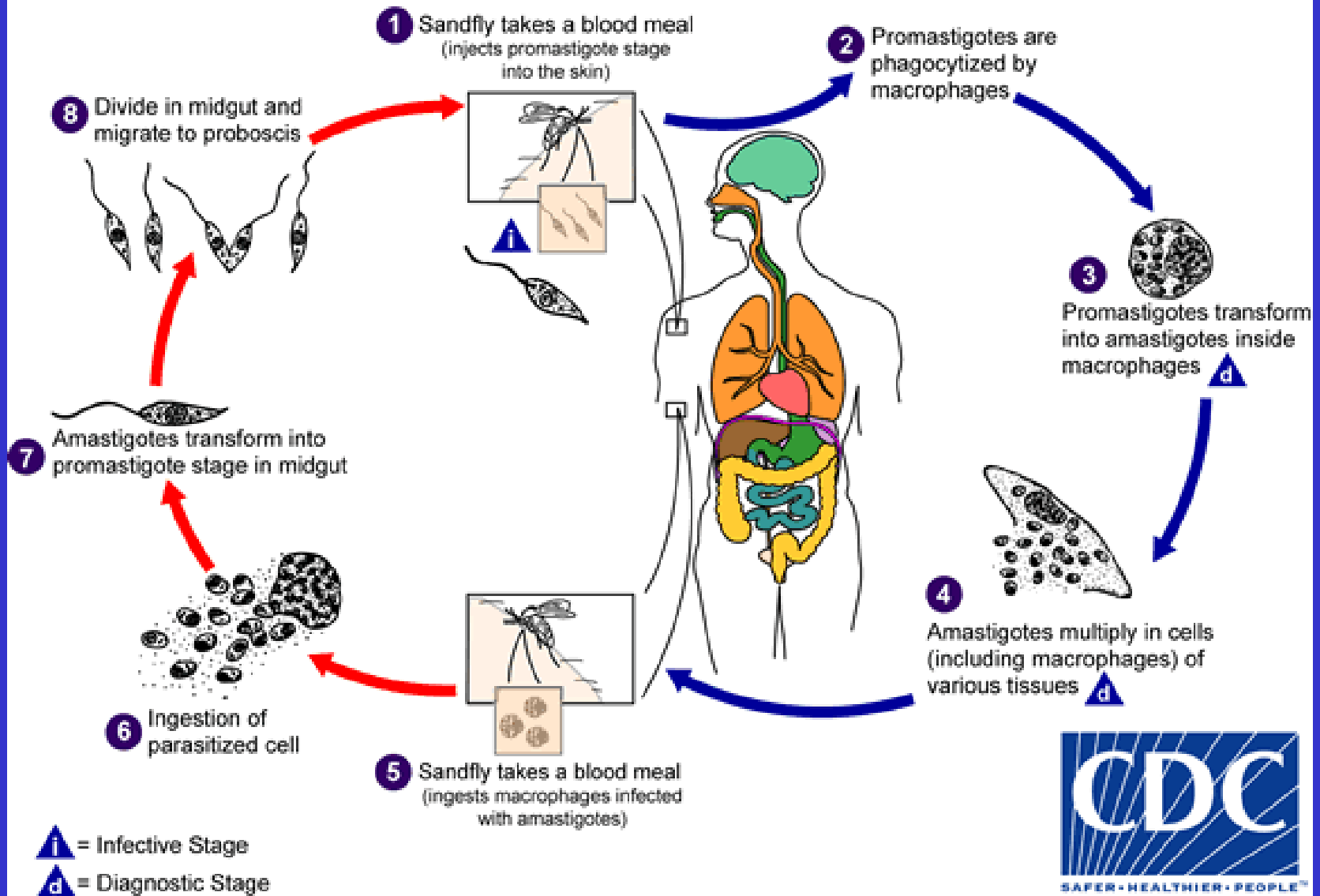
- Avoidance of freshwater exposure
  - Easier said than done
- Vigorous towelling after exposure?  
Outwater et al 2005 J Travel Med 12:265-9
- DEET or Dimeticone?  
Cooper et al 2004 J Pharm Pharmacol. 56:957-62
- Partnership with local health teams
- Control in endemic areas

# Leishmaniasis

- Infection with genus *Leishmania* - obligate intracellular parasite transmitted by the sandfly
- Identified by Leishman & Donovan in 1903
- Human infection 3 clinical syndromes
  - 1 Cutaneous Leishmaniasis
  - 2 Mucosal Leishmaniasis
  - 3 Visceral Leishmaniasis

## Sandfly Stages

## Human Stages



<http://www.dpd.cdc.gov/dpdx>

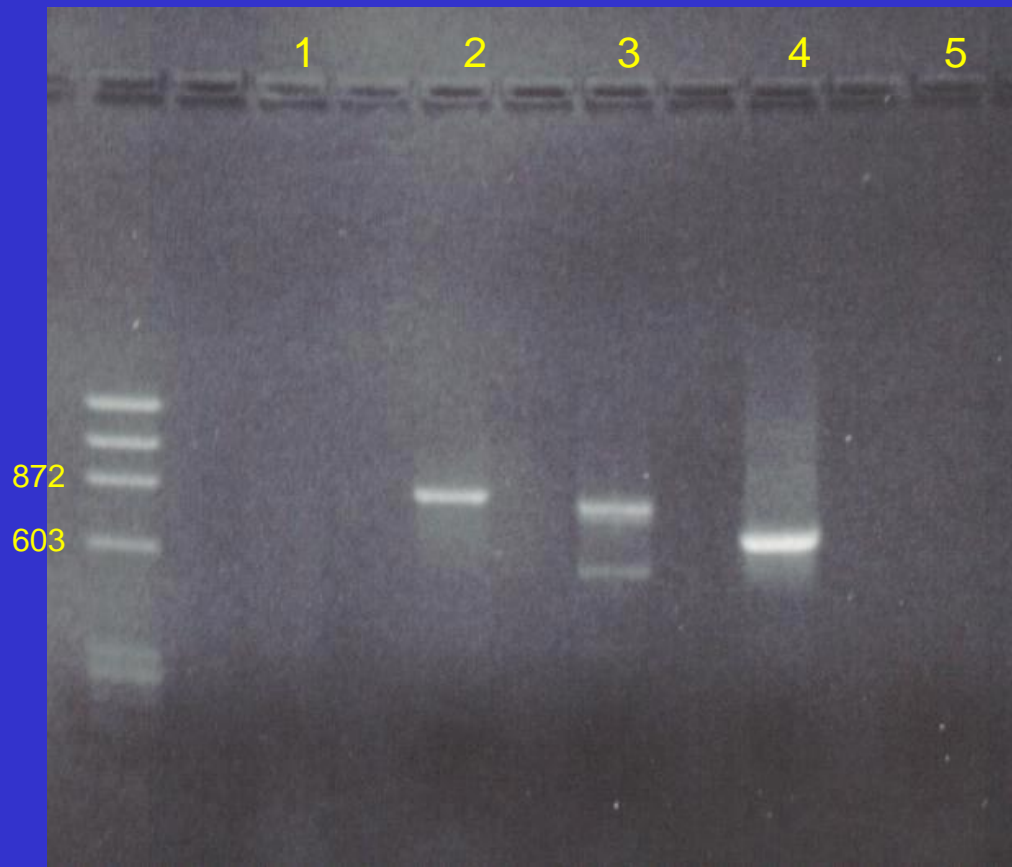
# Cutaneous Leishmaniasis

- 1.5 million cases/year globally
- Old World
  - L. tropica*, *L. major*, *L. aethiopica*
- New World
  - L. mexicana* complex, *Viannia* subgenus

# Old World Cutaneous Leishmaniasis in American troops

- Dec 2003- June 2004
- 360 suspect skin lesions in 200,000 troops returning from one year deployment in Iraq
- 237 diagnosed CL
- 181 laboratory confirmation
- PCR +ve in all 122 smear positive and 34 smear negative cases

# HTD Agarose Gel Electrophoresis - Old World Primers



- 1 - Patient: no amplification
- 2 - Patient: *L.donovani*
- 3 - *L.donovani* control
- 4 - *L.major* control
- 5 - Negative control

↑  
Marker  
(size in base pairs)

# HTD Investigations

	<b>Patients</b>	<b>+ves</b>
Skin Smear : microscopy for amastigotes	32	19 (59%)
Histology: H&E for granulomata	37	37 (100%)
H&E for amastigotes	37	25 (68%)
NNN culture	31	15 (48%)
PCR: primers for New & Old World spp.	34	32 (94%)

# Treatment of Cutaneous Leishmaniasis

Blum et al (2004)

## Indications for local Rx:

- Lack of risk of developing mucosal lesions
  - Old World cutaneous leishmaniasis
  - L.mexicana* cutaneous leishmaniasis
- Small, single lesion
- Absence of lymph node metastasis

# Treatment of Cutaneous Leishmaniasis

Blum et al (2004)

## Indications for systemic Rx:

- Presence of mucosal lesion or lymph node metastasis
- New World CL except *L.mexicana* lesions
- Lesions unresponsive to local Rx

# Treatment of Cutaneous Leishmaniasis

Bailey et al (2005)

Determine whether “simple” or “complex”

Complex:

- >2-3 in number
- >40 mm maximum diameter
- Lymphatic or lymph node involvement
- Could give cosmetic problems (eg face)
- Could give functional problems (eg hand)
- Poor response to Rx as a “simple” lesion

# Treatment of Cutaneous Leishmaniasis

Bailey et al (2005)

- ALL *L. Viannia/braziliensis*, or untyped New World lesions, whether “simple” or “complex” require Rx with intravenous sodium stibogluconate (SSG)
- Lesions due to other species:
  - “Simple”: intralesional SSG or a physical treatment
  - “Complex”: IV SSG

# Protection against leishmaniasis

- Insect repellent
- Long sleeves
- Bed nets
- Sleeping undercover
- Vector control programmes

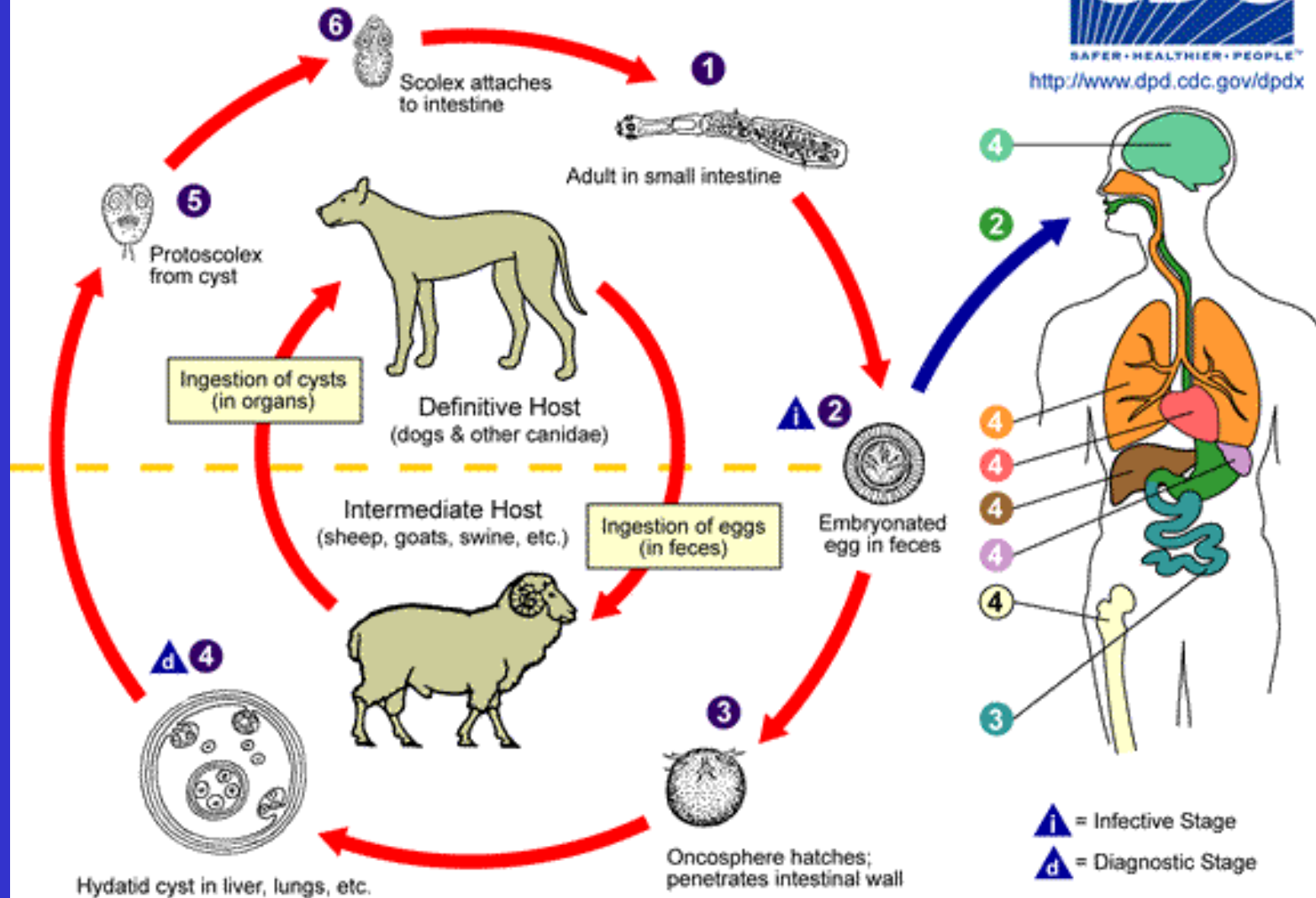
# CYSTIC HYDATID DISEASE

*Echinococcus granulosus*



SAFER • HEALTHIER • PEOPLE™

<http://www.dpd.cdc.gov/dpdx>



# Structure of hydatid cyst

Laminated membrane

Germinal membrane

Cyst fluid

## DIAGNOSIS OF HYDATID DISEASE

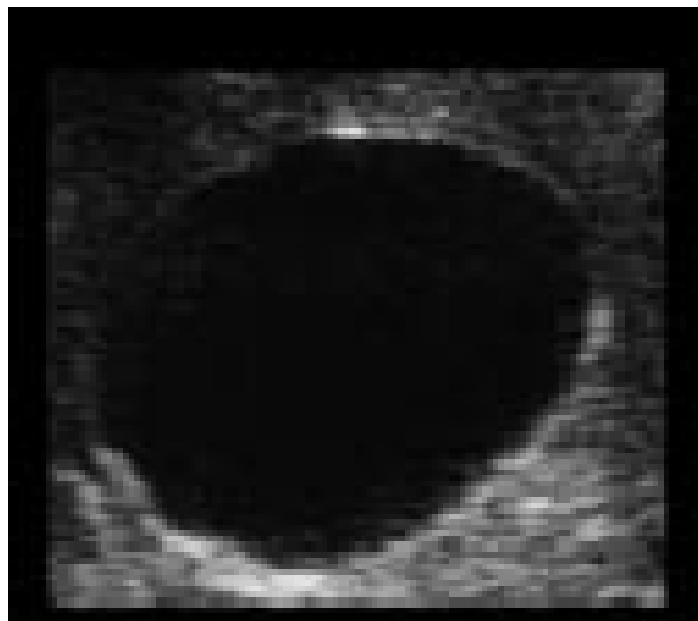
- Imaging: plain X ray  
ultrasound  
CT or MRI
- Serology
- Microscopy  
protoscoleces, hooks

# Hydatid is not one disease

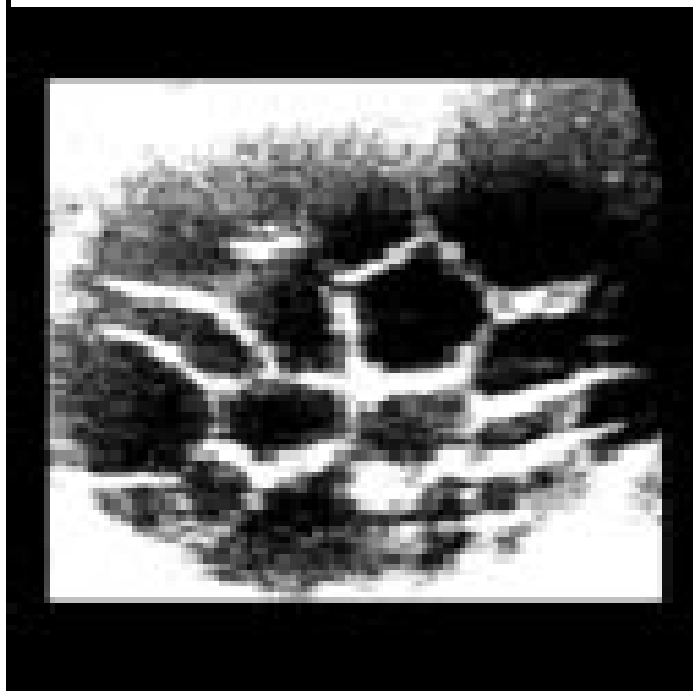
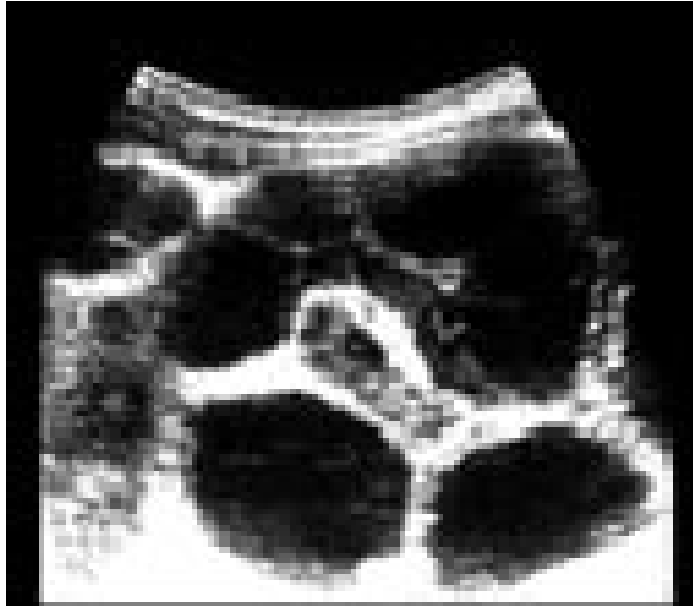
Multiple sites (any organ possible)

Different types of cyst within sites

CE 1



# CE 2



**CE3**

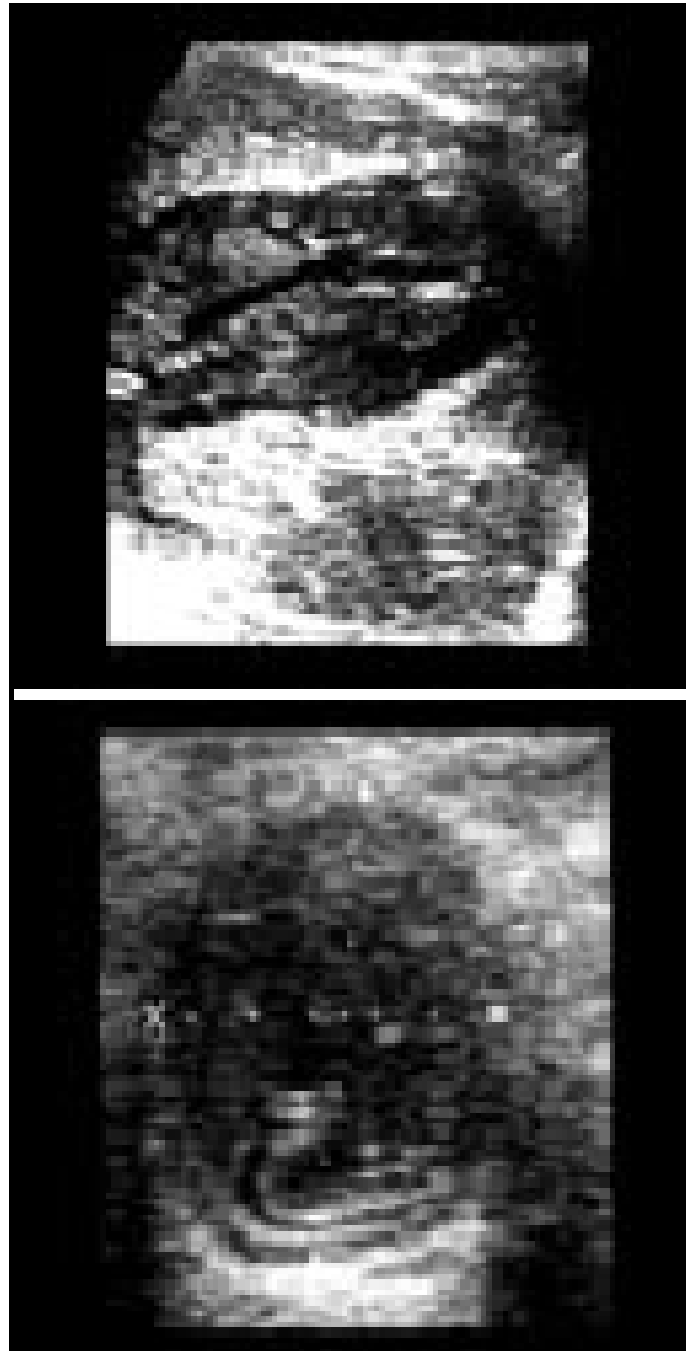
**A**



**B**



**CE 4**



**CE 5**



# HTD Hydatid Serology

- ELISA using whole cyst fluid from *Echinococcus granulosus* isolated from horses
- Optical density cut off for a positive 0.250
- Sensitivity 84-93%; Specificity 82-89%
- False positives with larval cestodes; filariases; some advanced neoplasms

# Cystic Echinococcosis

## Clinical presentation

# Clinical Presentation HTD Series

	<u>No</u>	<u>%</u>		<u>No</u>	<u>%</u>
Asymptomatic	16	28	<u>Complicated</u>	19	33
Abdominal pain	36	63	Rupture		
Abdo distension	6	10	Actual	10	17
Pruritis	3	5	Imminent	5	9
Anaphylaxis	4	7	Infected		
Fever	10	17	Primary	2	3.5
Peritonitis	1	2	Secondary	2	3.5
Jaundice	7	12			

# HTD Series

## Baseline Characteristics of the Cysts

<u>Cyst type</u>	<u>Number</u>	<u>%</u>
CE1	6	10.5
CE2	34	59.6
CE3a	1	1.8
CE3b	6	10.5
CE4	1	1.8
CE5	5	8.8
Ruptured/Post op	5	8.8

# TREATMENT OF HYDATID DISEASE

Albendazole

Praziquantel

Surgery

Aspiration: “PAIR”

Scolicide (silver nitrate, alcohol)

## RCT of Albendazole Gil-Grande et al (1993) Madrid

18 patients no drug pre-surgery

18 albendazole 10 mg/kg for 1m

19 albendazole 10 mg/kg for 3 months

US and viability studies:

50%; 72%; 94% non-viable respectively

Protoscolex ( $p=0.039$ ) and cyst viability

( $p=0.018$ ) lower in Rxd patients

## RCT of albendazole in hydatid disease Keshmiri et al (2001) Iran

Albendazole 400 mg BD for 3 6-week  
blocks vs placebo

Rx group: 134/172 cysts improved or cured

Placebo: 4/31 cysts improved or cured

$P < 0.001$

18/22 (82%) Rxd patients cured or improved  
vs 1/7 (14%) placebo improved but not  
cured

## Albendazole vs Mebendazole Franchi et al (1999) Rome

448 patients with 929 cysts

3 to 6 month mebendazole or albendazole

Follow-up 1 to 14 years

At end of Rx 74.1% degenerate cysts

(Albendazole 82.2%; mebendazole 56.1%)

25% of cysts relapsed, most often type 2  
cysts

78.5% recurred in the first 2 years

# Albendazole plus Praziquantel Mohamed et al (1998) Riyadh

## Albendazole alone

1985-90

22 patients

8 (36.4%) complete cyst disappearance (Rx in 4 was 6-24 m)

## Albendazole plus Praziquantel

1990-98

22 patients

Rx was 2-6 m

Follow-up 2m to 3y

9 (47.4%) complete cyst disappearance

5 (36.8%) >50% cyst reduction

# HTD Preoperative Praziquantel

Ayles HM et al (2002) Ann R Coll Surg Engl 84: 100-105

## Regimen

## Viabile protoscoleces

ABZ + Praziquantel

1/25

Albendazole

5/8

$p = 0.0013$

## PAIR vs Surgery; Meta-analysis Smego et al (2003)

769 patients with liver hydatid Rxd with  
PAIR plus albendazole or mebendazole  
952 era-matched historical controls Rxd with  
Surgery plus albendazole or mebendazole

## PAIR vs Surgery; Meta-analysis Smego et al (2003)

PAIR showed significantly:

- Greater clinical & parasitological cure rates
- More common fever
- More common minor allergic reactions
- Shorter mean hospital stay (2.4 days)

## PAIR vs Surgery; Meta-analysis Smego et al (2003)

Surgery showed significantly more frequent:

- Disease recurrence; major complications (anaphylaxis, biliary fistula, cyst infection, liver/abdominal abscess, sepsis); minor complications; & death
- Significantly longer mean hospital stay (15.0 days)

# Current HTD Practice (1)

## Lung cyst

- No albendazole (risk of rupture)
- Start praziquantel
- Prepare for surgery

# Current HTD Practice (2)

## Liver cyst

- Depends on WHO U/S cyst type (see below)
- Praziquantel is given for 2 weeks pre and post surgery or PAIR

# Current HTD Practice (3)

## Liver cyst type

- CE1
- CE2
- CE3a
- CE3b
- CE4
- CE5

## Rx

Albendazole +/- PAIR

Albendazole + Surgery

Albendazole +/- PAIR

Albendazole + Surgery

Watch and wait

Watch and wait

Viability testing of operative material

Eosin exclusion test

# HYDATID DISEASE

Follow-up is long-term

# Hydatid Follow-up

- Eosinophil count sometimes helpful
- Serology
- Ultrasound or CT

# Cystic Echinococcosis

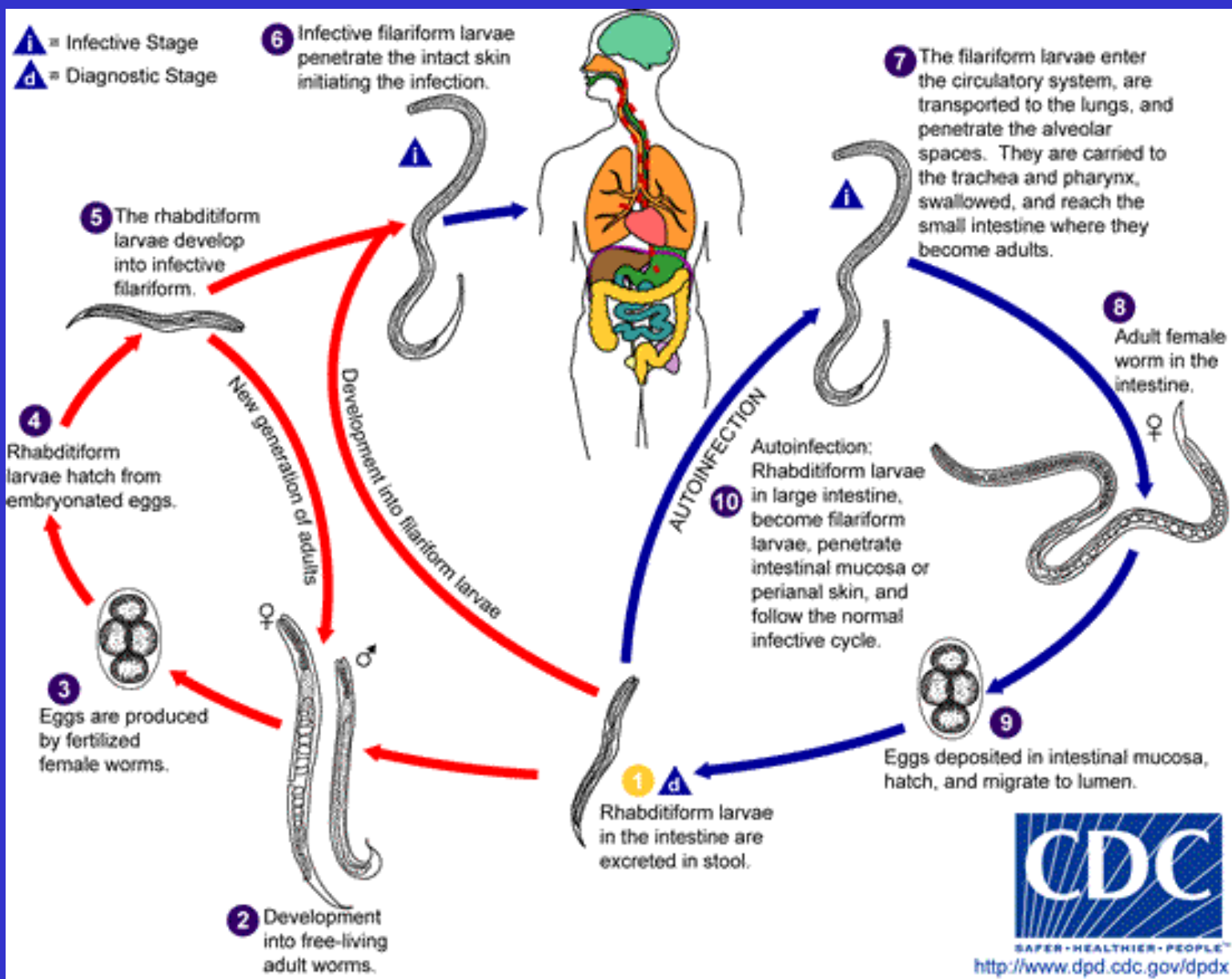
- Clinical trials on CE should assign interventions specific to the WHO CE type
- The outcome of clinical interventions should be reported for each CE type

# Hydatid Questions and Problems

- What is the optimum duration of albendazole Rx?
- What is the role of praziquantel?
- The lack of alternative drugs
- Reliably defining cure

# STRONGYLOIDES

ONCE YOU ARE INFECTED,  
*STRONGYLOIDES*  
**IS WITH YOU FOR LIFE**



# *STRONGYLOIDES*

- Asymptomatic
- Larva currens
- Diarrhoea
- Malabsorption
- Hyperinfestation

# Risk factors for hyperinfestation

- Transplant recipients
- Lymphomas
- Corticosteroid Rx
- Malnutrition
- HTLV 1 infection

# *Strongyloides* diagnosis

- Microscopy
- Culture
- String test
- Serology

98% sensitive in migrants

73% sensitive in travellers

# HTD *Strongyloides* treatment

- Oral thiabendazole      obsolete
- Oral albendazole      less effective
- Oral **ivermectin**

Hyperinfestation may require:

- Subcutaneous ivermectin

**NB unlicensed in humans**

# *STRONGYLOIDES*

- Think of the diagnosis, before it is too late
- Microscopy
- Serology
- Ivermectin
- Secondary septicaemia in hyperinfestation

<http://www.thehtd.org/>

