This wormy world: consequences, co-infections and the challenge of field-based study designs

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Norman Stoll, President of the American Society of Parasitologists
1947 inaugural address
“This wormy world”

Called for a world-wide effort to control worm infections
17 Neglected tropical diseases (NTDs)

NOT malaria, TB, HIV/AIDS
NOT epidemic-prone (e.g. influenza, SARS)
NOT vaccine-preventable diseases (e.g. polio, meningitis)

Over 1 billion people infected with NTDs, co-infection common, up to 99% in Sub-Saharan Africa

56.6M DALYS
534,000 deaths
Women & children particularly at risk
17 NTDs in total

Helminths (8)

- Schistosomiasis
- Lymphatic filariasis
- Onchocerciasis
- Soil-transmitted helminthiasis**

- Dracunculiasis
- Cysticercosis
- Echinococcosis
- Foodborne trematodiasis
Challenges in measuring morbidity due to helminths

- Non-specificity of clinical signs
- Ubiquity of co-infection & co-morbidity
- Difficulties in diagnosis
- Paucity of reliable and accurate epidemiological data
- Burden concentrated in countries with weak surveillance systems

Brooker, 2010
Preventive chemotherapy

- Individual level diagnosis and treatment not necessary
- Frequency based on prevalence and intensity
- Role of teachers

- Albendazole/Mebendazole: STH
- DEC or Ivermectin + ALB: LF
- Ivermectin: Oncho
- Praziquantel: Schisto
Proportion of children (1-14 years of age) in the country requiring preventive chemotherapy for soil-transmitted helminthiases, worldwide, 2010

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2011. All rights reserved

Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD)
World Health Organization
School-age children treated with preventive chemotherapy for STH worldwide

Adapted from Montresor et al., 2013
Soil-transmitted helminths* in pre-school children

- Informal consultation
  WHO 2002

- Impact of infection, approaches to control

- Implications of co-infection

*Estimated 230 million infected
Ubiquity of co-infection

Hall et al., 2008
The potential significance of Helminth-Plasmodium co-infection

- Both groups of infections are highly prevalent & co-occur
- Immune responses differ
- Large scale deworming programmes are now in place
- What is the impact of anthelmintic treatment on other infections?
The challenge of field-based study designs: a case study

Co-infection in young children: the impact of anthelmintic treatment on malaria
Objectives

To establish the prevalence of geohelminths and *Plasmodium*

To determine the effectiveness of repeated four-monthly anthelmintic treatment on *Ascaris*

To explore the impact of anthelmintic treatment on *Plasmodium* infection
Study Location

- Ile-Ife, Osun state, Nigeria

- 4 villages
  - Ipetumodu
  - Moro
  - Akinlalu
  - Edunabon
Plasmodium spp. and Ascaris in children

Prevalence of Ascaris: 0-1 yrs 2.9%, 1-2 yrs 24.7%: Kirwan et. al., 2009a
Intensity: epidemiological gold standard
**Fig. 1.1.** Frequency distribution of numbers of *Ascaris lumbricoides* per child in Ile-Ife, Nigeria (n = 808).

Holland *et. al.*, 1989
Baseline patterns of *Ascaris* infection in children aged 1–4 years (n = 1228)

<table>
<thead>
<tr>
<th>Age</th>
<th>No. Infected</th>
<th>Mean epg ± SE</th>
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<tbody>
<tr>
<td>1 (n = 422)</td>
<td>161 (38.2%)</td>
<td>504 ± 67 ± 166*</td>
</tr>
<tr>
<td>2 (n = 288)</td>
<td>157 (54.5%)</td>
<td>1386 ± 190</td>
</tr>
<tr>
<td>3 (n = 280)</td>
<td>159 (56.8%)</td>
<td>1636 ± 218</td>
</tr>
<tr>
<td>4 (n = 238)</td>
<td>108 (45.4%)*</td>
<td>1059</td>
</tr>
</tbody>
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* Significant increase with age p≤0.001, Females higher mean epg than males p≤0.011
Study Design
Double-blind, placebo-controlled randomised trial of anthelminthic treatment

Random allocation

Screen out
Severe malnutrition severe malaria

Double Blind

Treat
Placebo

Anthropometric assessments; Blood samples; Faecal samples; Questionnaire
Sample size attrition

1451 individuals assessed for eligibility

- 223 individuals excluded
  - 12 did not complete the assessments
    - 1 passed worms
    - 3 severe anaemia
    - 1 severe malaria
    - 5 died (reason unknown)
  - 201 did not submit a stool sample

1228 individuals randomised

- 625 individuals allocated to albendazole
  - 431 did not complete 14 months follow-up
  - 194 individuals for stool analysis

- 603 individuals allocated to placebo
  - 409 did not complete 14 months follow-up
  - 194 individuals for stool analysis
Mean prevalence (± C.I.) and e.p.g. (± S.E.) of *A. lumbricoides* in the treatment and placebo groups during the follow-up period (Kirwan et al., 2009b; 2010)
Studies on the interactions between helminths and malaria in humans

- 34 studies identified
- Conflicting results and difficulty in identifying clear outcomes or mechanisms
- Heterogeneity in study design precludes meta-analysis
- General lack of intervention studies (3/34)

Adapted from Nacher, 2011
Worms, wisdom, and wealth: why deworming can make economic sense

• Challenges in interpreting meta-analyses of randomized trial data for evaluation of deworming programmes
• Inclusion of the uninfected dilutes the potential impact of intervention
• Variation in study design, sample size, follow-up duration etc

Bundy et. al., 2013
Future directions and challenges

Concurrent infections and their interactions are key
Field-based studies and laboratory models in tandem
Improved surveillance of impact and consequences of large scale anthelmintic treatment

Active debate about study designs
Future directions and challenges

Exploration of the interplay between helminth infections, immune responses to their presence and that of other bystander infections and their control by chemotherapy, remains one of the most crucial challenges

Holland, 2009