Top Papers in (Parasitic) Neglected Tropical Diseases: Clinical and Epidemiology 2017-18

Joana Cortez, MD, MPH
Malaria Consortium Cambodia
ESCMID Study Group on Clinical Parasitology
Many diseases and hundreds of papers

- Buruli ulcer
- Chagas disease
- Dengue and Chikungunya
- Dracunculiasis (guinea-worm disease)
- Equinococcosis
- Foodborne trematodiases
- Human African trypanosomiasis (sleeping sickness)
- Leishmaniasis
- Leprosy
- Lymphatic filariasis
- Mycetoma, chromoblastomycosis and other deep mycosis

- Onchocerciasis (river blindness)
- Rabies
- Scabies and other ectoparasites
- Schistosomiasis
- Soil-transmitted helminthiasis
- Snakebite envenoming
- Taeniasis/Cysticercosis
- Trachoma
- Yaws (Endemic treponematoses)
Chagas disease
Chagas disease: epidemiology

- Migration
- Definition of migrants
- Screening programs
- Blood bank
- Transplant recipients and donors*
- Pregnant women

TABLE 1
Estimated prevalence of *T. cruzi*-infected people living in endemic countries and the estimated prevalence of *T. cruzi*-infected immigrants from endemic countries living in nonendemic countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Estimated prevalence (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>8.2% (1990)</td>
</tr>
<tr>
<td>Bolivia</td>
<td>15.4% (1990)</td>
</tr>
<tr>
<td>Brazil</td>
<td>1.3% (1995)</td>
</tr>
<tr>
<td>Chile</td>
<td>2.8% (1990)</td>
</tr>
<tr>
<td>Colombia</td>
<td>3.9% (1990)</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>4.3% (1990)</td>
</tr>
<tr>
<td>Ecuador</td>
<td>1.2% (1990)</td>
</tr>
<tr>
<td>El Salvador</td>
<td>6.1% (1990)</td>
</tr>
<tr>
<td>Honduras</td>
<td>5.6% (1990)</td>
</tr>
<tr>
<td>Guatemala</td>
<td>7.9% (1990)</td>
</tr>
<tr>
<td>México</td>
<td>0.7% (1990)</td>
</tr>
<tr>
<td>Nicaragua</td>
<td>1.7% (1990)</td>
</tr>
<tr>
<td>Panama</td>
<td>9.0% (1990)</td>
</tr>
<tr>
<td>Paraguay</td>
<td>9.3% (1990)</td>
</tr>
<tr>
<td>Peru</td>
<td>3.0% (1990)</td>
</tr>
<tr>
<td>Uruguay</td>
<td>1.2% (1990)</td>
</tr>
<tr>
<td>Venezuela</td>
<td>4.0% (1990)</td>
</tr>
<tr>
<td><em>T. cruzi</em>-infected immigrants from endemic countries living in nonendemic countries</td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>3.8% (2006)</td>
</tr>
<tr>
<td>Canada</td>
<td>3.5% (2006)</td>
</tr>
<tr>
<td>Europe (15 countries excluding Spain)</td>
<td>2.9% (1999-2005)</td>
</tr>
<tr>
<td>Spain</td>
<td>5.2% (2008)</td>
</tr>
<tr>
<td>USA</td>
<td>2.0% (2007)</td>
</tr>
</tbody>
</table>

Adapted from: Schmunis G.A and Yaco Z.E.®

*Lígia Pierrotti et al. Chagas Disease Recommendations for Solid-Organ Transplant Recipients and Donors. Transplantation 2018;102 (2S-2)
Opportunistic infection in HIV
Retrospective study from January 2005 to December 2014 in Buenos Aires
Vector-borne, intravenous drug use
Serological assays for T. cruzi infection may be negative in severely immunocompromised patients.
Direct parasitological techniques
HIV patients with a lower CD4 count have higher chance of reactivation

Chagas disease in HIV/AIDS

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Epidemiological characteristics of Trypanosoma cruzi–HIV co-infected patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With reactivation</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>8 (88.9)</td>
</tr>
<tr>
<td>Age at Chagas disease diagnosis, years, median (IQR)</td>
<td>9 (98)</td>
</tr>
<tr>
<td>Age at HIV diagnosis, years, median (IQR)</td>
<td>7 (78)</td>
</tr>
<tr>
<td>Nationality, n (%)</td>
<td>11 (12)</td>
</tr>
<tr>
<td>Argentinian</td>
<td>7 (78)</td>
</tr>
<tr>
<td>Bolivian</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Chilean</td>
<td>0</td>
</tr>
<tr>
<td>Paraguayan</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Peruvian</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
</tr>
<tr>
<td>Risk factor for HIV, n (%)</td>
<td>0</td>
</tr>
<tr>
<td>Unprotected heterosexual contact</td>
<td>0</td>
</tr>
<tr>
<td>MSM</td>
<td>4 (445)</td>
</tr>
<tr>
<td>IDU</td>
<td>22 (22)</td>
</tr>
<tr>
<td>Vector-borne and IDU</td>
<td>0</td>
</tr>
<tr>
<td>T. cruzi infection probable acquisition route, n (%)</td>
<td>0</td>
</tr>
<tr>
<td>Vector-borne</td>
<td>5 (55.6)</td>
</tr>
<tr>
<td>IDU</td>
<td>22 (22)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
</tr>
</tbody>
</table>
| IQR, interquartile range; MSM, men who have sex with men; IDU, intravenous drug user.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Clinical characteristics of Trypanosoma cruzi–HIV co-infected patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Minimum CD4 T-cell count, cells/μL, median (IQR)</td>
<td>0</td>
</tr>
<tr>
<td>CD4 T-cell count at Chagas disease diagnosis, cells/μL, median (IQR)</td>
<td>0</td>
</tr>
<tr>
<td>Patients with opportunistic infections prior to diagnosis, n (%)</td>
<td>0</td>
</tr>
<tr>
<td>Patients on HAART at Chagas disease diagnosis, n (%)</td>
<td>0</td>
</tr>
<tr>
<td>HAART, highly active antiretroviral therapy.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Clinical and parasitological features of patients with Chagas disease reactivation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient number</td>
<td>Tissue involvement</td>
</tr>
<tr>
<td>23</td>
<td>CNS/myocardium</td>
</tr>
<tr>
<td>39</td>
<td>CNS</td>
</tr>
<tr>
<td>54</td>
<td>CNS</td>
</tr>
<tr>
<td>65</td>
<td>CNS</td>
</tr>
<tr>
<td>70</td>
<td>CNS</td>
</tr>
<tr>
<td>71</td>
<td>CNS</td>
</tr>
<tr>
<td>79</td>
<td>CNS</td>
</tr>
<tr>
<td>80</td>
<td>CNS/myocardium</td>
</tr>
</tbody>
</table>

CNS, central nervous system; Neg, negative; Pos, positive; ND, not done; RBD, benznidazole; NPT, nitrimox.
Chagas disease among Latin American immigrants in Milan

- Aim: assess the prevalence and risk factors for CD in Latin American immigrants and to evaluate the accuracy of diagnostic tests.
- Cross-sectional survey of CD among Latin Americans living in Milan (July 2013 and July 2014).
- Forty-eight (9.6%) of the 501 tested subjects were conclusively diagnosed as having CD.
- Highest prevalence: Bolivia and El Salvador.
- Older age, a Bolivian origin, being born in the department of Santa Cruz, having lived in mud houses, and having an affected relative were independently associated with CD.
- CD is highly prevalent among Bolivians and Salvadorans living in Milan.
- Regions with a large Latin American immigrant population should implement programmes of active detection and treatment.

Chagas disease and strongyloidiasis in Latin American migrants

- Aim: evaluate association between *Trypanosoma cruzi* infection and strongyloidiasis in a cohort of Latin American migrants screened for both infections in a non-endemic setting
- 361 individuals were screened
- Factors associated with a positive *T. cruzi* serology were Bolivian origin, coming from a rural area, having lived in an adobe house and a referred contact with triatомine bugs
- More patients with a positive *S. stercoralis* serology among those who were infected with *T. cruzi*
- *T. cruzi* infection was more frequent among those with strongyloidiasis
- In multivariate analysis, *T. cruzi* infection was associated with a two-fold increase in the odds of strongyloidiasis
- *T. cruzi* infection was associated with strongyloidiasis in LA migrants attending a tropical diseases unit even after adjusting for epidemiological variables.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unadjusted OR (95% CI)</th>
<th>p value</th>
<th>Adjusted OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>0.92 (0.46–1.85)</td>
<td>0.813</td>
<td>1.02 (0.50–2.10)</td>
<td>0.952</td>
</tr>
<tr>
<td>Age ≥35 years</td>
<td>1.43 (0.72–2.84)</td>
<td>0.301</td>
<td>1.38 (0.68–2.79)</td>
<td>0.365</td>
</tr>
<tr>
<td>Bolivian origin</td>
<td>1.29 (0.47–3.55)</td>
<td>0.615</td>
<td>1.03 (0.35–3.00)</td>
<td>0.954</td>
</tr>
<tr>
<td>Rural area</td>
<td>1.13 (0.49–2.60)</td>
<td>0.778</td>
<td>0.81 (0.33–2.00)</td>
<td>0.653</td>
</tr>
<tr>
<td><em>T. cruzi</em> infection</td>
<td>2.18 (1.10–4.31)</td>
<td>0.023</td>
<td>2.23 (1.07–4.64)</td>
<td>0.030</td>
</tr>
</tbody>
</table>

Aim: investigated the safety and efficacy of three oral E1224 regimens and benznidazole versus placebo in adult chronic indeterminate Chagas disease

- Proof-of-concept, double-blind, randomised phase 2 clinical trial
- 560 adults (18–50 years), randomly assigned (1:1:1:1:1) to five oral treatment groups
- Primary efficacy endpoint was parasitological response to E1224 at the end of treatment, assessed by PCR
- E1224 displayed a transient, suppressive effect on parasite clearance, whereas benznidazole showed early and sustained efficacy until 12 months of follow-up
- Both treatments were well tolerated
Chagas disease:

- E1224 displayed a transient, suppressive effect, whereas benznidazole showed early and sustained efficacy.
- BENDITA study* is investigating the safety and efficacy of combinations of E1224 and benznidazole in shorter treatments.
- Chagas disease reactivation is an AIDS-defining illness with a high mortality rate.
- Systematic screening in non-endemic countries for Chagas and strongyloidiasis in LA individuals.

ECHINOCOCCOSIS
Echinococcus species found worldwide

Fig. 2. Map showing the 6 Echinococcus species distributed in the Northern Hemisphere, with three additional species located in Africa (E. felidis) and South America (E. vogeli and E. oligarthra). E. granulosus sensu stricto (red), E. felidis (violet), E. canadensis (orange), E. ortleppi (yellow), E. equinus (green), E. multilocularis (black) E. shiquicus (grey) E. vogeli (dark blue), E. oligarthra (light blue). E. granulosus s.s., E. felidis, E. canadensis, E. ortleppi, and E. equinus are included in E. granulosus sensu lato. E. multilocularis consists of the Asian (A), European (E), Mongolian (M), and North American (N) genotypes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
Echinococcus granulosus: relation with cancer

Echinococcosis:

• Molecular identification
• *E. granulosus* probably secretes molecules that can be developed as anticancer therapeutics in future
Human African trypanosomiasis
• In 2015, 2804 cases of HAT were reported to WHO, of which 2733 were caused by *T. brucei gambiense* (90% reduction since 1999) and 71 were caused by *T. brucei rhodesiense* (89% reduction since 1999)
• *T. brucei gambiense* – DRC, CAR and Chad
• *T. brucei rhodesiense* - Malawi and Uganda
• Drugs are available for free, low-cost RDTs and vector control tools are on the market; safe oral drugs are expected to become available soon; and, the integration of HAT diagnosis into peripheral health centres has begun.
• But History teaches a lot!
• Research priorities
Passive case detection on the transmission dynamics of gambiense HAT

- Gambiense HAT - active screening and passive detection
- Drastic reduction in the global incidence of the disease over recent decades (due to active case finding and treatment)
- Coverage and transmission impact of passive case detection?
- Mathematical model
- Heterogeneity in incidence across villages
- Only a minority of prevalent cases in the haemo-lymphatic stage of the disease were detected passively (<30% in all three settings), whereas around 50% of patients in the second, meningo-encephalitic were detected
- Passive screening reduced transmission in affected areas by between 30 and 50%
- Great potential value in improving rates of passive case detection (gambiense HAT is driven towards elimination)

The incidence of gHAT in Uganda has been declining.

Early diagnosis and treatment is core.

Restricted screening and diagnosis to central health facilities (passive screening).

A novel strategy that is contributing to elimination of gHAT in Uganda through expansion of passive screening to the entire population at risk.

Full coverage of the population at risk, and is being replicated in other gHAT endemic countries. The improvement in case detection is making elimination of the disease in Uganda an imminent possibility.

Multi-centre randomised, open-label, non-inferiority trial was carried out in the gambiense-HAT endemic districts of North-Western Uganda to compare the efficacy and safety of NECT to the standard eflornithine regimen.

109 patients were enrolled.

This study shows that a 10-day course with a combination treatment of oral nifurtimox and parenteral eflornithine (NECT) is non-inferior to the standard 2-week course with parenteral eflornithine, and was well tolerated. The cure rate 18 months after starting treatment was about 91% in the NECT and 89% in the eflornithine group in all analysis sets.

These results confirm findings of earlier trials and support implementation of NECT as first-line treatment for late stage T. b. gambiense HAT.
Oral fexinidazole for HAT

- Randomised, phase 2/3, open-label, non-inferiority trial
- Success rates at 18 months were higher than expected in both treatment groups
- The primary endpoint comparing treatment efficacy of fexinidazole with nifurtimox eflornithine combination therapy was met
- No difference between groups in the proportion of treatment-emergent adverse events deemed related to treatment
- Therapeutic interest of fexinidazole in late-stage g-HAT patients, provided that safety is similar.
- Currently being tested in a phase 3b study
- Potential role to simplify the diagnostic approach
Cryptic Reservoirs and gambiense HAT

- Cryptic parasite reservoirs can be a challenge to sustained elimination of gambiense-HA
- Knowledge gaps are:
  - i) the frequency and duration of latent human infections and infections in animals
  - (ii) the infectiveness of latent human infections and animal reservoirs to tsetse flies
  - (iii) the ability of latent human infections or animal reservoirs to sustain transmission in interepidemic periods,
  - and (iv) the possible existence of an animal transmission cycle in the absence of human transmission and its ability to seed a new transmission cycle in humans.
- Prognostic and diagnostic markers
- More accurate and preferably high-throughput tests to detect and monitor *T. b. gambiense* infections in animals
- Improved mathematical models
Human African trypanosomiasis:

- NECT regimen is simpler, safer, shorter and less expensive than single-agent DFMO
- Oral fexinidazole is effective and safe for the treatment of \( T. b. gambiense \)
- Latent human infections and possible animal reservoirs may challenge the goal of gambiense-HAT elimination
Leishmaniasis in 2015

- In 2015, almost 200,000 new CL cases and 25,000 new VL cases were reported to WHO.
• TF goes far beyond DR
• WGS provides enough resolution to help clarify the molecular epidemiology of *L. donovani* in the Indian subcontinent and in the context of DR.
• The use of combination therapies is relevant for leishmaniasis control programs at the clinical level.
• AmB is currently recommended as a potential partner drug in a number of regimens, but there is a risk for resistance genes being selected during a monotherapy phase.
• Role of molecular epidemiology

Leishmaniasis and studies of vaccines for human VL

- Innovative vaccine approach for human VL
  - multi-antigen nature
  - explores the possibility of the use of Influenza virosomes as antigen-delivery vehicles
- Strong TLR-4 agonist
- No apparent adverse reactions
- Immunogenicity
- The immune responses against the VD protein were reproducibly more robust
- Priming with the VD protein alone and boosting with the complete vaccine candidate contributed towards an increase of the immune responses to the PD antigens
- Promising anti-Leishmania vaccine whose efficacy deserves to be tested in the context of the ‘natural infection’

Leishmaniasis:

- Risk of resistance with AmB
- Promising anti-\textit{Leishmania vaccine} whose efficacy deserves to be tested in the context of the ´natural infection´
FILARIASIS
Filariasis: epidemiology and global progress to eliminate LF

- Global Programme to Eliminate Lymphatic Filariasis launched in 2000
- MDA is the main strategy
- In 2016, 495.6 million persons treated in 40 reporting countries
- Program coverage ranges from 57% to 74%

Global programme to eliminate lymphatic filariasis: progress report, 2016 Weekly Epidemiological Record; 91: 594-
**Table 1. WHO recommendations on alternative MDA regimens to eliminate lymphatic filariasis**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of recommendation</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In countries using DA to eliminate lymphatic filariasis</strong> (endemic for lymphatic filariasis but without either onchocerciasis or loiasis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO recommends annual IDA rather than annual DA in the following special settings:</td>
<td>Conditional recommendation</td>
<td>Low</td>
</tr>
<tr>
<td>• for IUs that have not started or have fewer than four effective rounds of DA;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• for IUs that have not met the epidemiological thresholds in sentinel and spot-check site surveys or in transmission assessment surveys despite meeting drug coverage targets; and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• for communities where post-MDA or post-validation surveillance identified infection suggesting local transmission.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO recommends annual DA rather than biannual DA.</td>
<td>Conditional recommendation</td>
<td>Low</td>
</tr>
<tr>
<td><strong>In countries using IA to eliminate lymphatic filariasis</strong> (endemic for lymphatic filariasis and either having onchocerciasis or being co-endemic for loiasis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Onchocerciasis endemic in any part of the country)</td>
<td>Conditional recommendation</td>
<td>Low</td>
</tr>
<tr>
<td>WHO recommends annual IA rather than annual IDA.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Onchocerciasis endemic in any part of the country)</td>
<td>Conditional recommendation</td>
<td>Very low</td>
</tr>
<tr>
<td>WHO recommends annual IA rather than biannual IA, except in areas where biannual distribution of ivermectin is already being delivered for onchocerciasis.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO recommends biannual albendazole rather than annual albendazole in IUs where LF is co-endemic with loiasis and ivermectin has not already been distributed for either onchocerciasis or LF.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*DA, diethylcarbamazine + albendazole; IA, ivermectin + albendazole; IDA, ivermectin + diethylcarbamazine + albendazole; IU, implementation unit; LF, lymphatic filariasis; MDA, mass drug administration*
Although IDA is a more effective treatment strategy and a potential method for accelerating transmission elimination (this is supported by mathematical modelling studies*), this strategy is not currently applicable to most of sub-Saharan Africa (co-endemicity with loiasis and onchocerciasis).

Table 2. Recommended MDA regimen changes from existing WHO recommendations, by co-endemicity setting

<table>
<thead>
<tr>
<th>Co-endemic anywhere in the country$^a$</th>
<th>Co-endemic in the IU$^a$</th>
<th>Existing recommendations (L, 8, 24)</th>
<th>MDA regimen changes under new recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>onchocerciasis</td>
<td>onchocerciasis</td>
<td>Annual DA</td>
<td>Use annual IDA rather than DA in specified settings; use annual DA in all other settings</td>
</tr>
<tr>
<td></td>
<td>loiasis</td>
<td>Annual IA</td>
<td>No changes to the recommended use of annual IA</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>Annual IA</td>
<td>Use annual IA; biannual IA may be used as an exception when ivermectin is already being delivered biannually to eliminate onchocerciasis.</td>
</tr>
<tr>
<td></td>
<td>+ or –</td>
<td>Annual, preferably biannual albendazole$^b$ (provisional recommendation)</td>
<td>Use biannual albendazole</td>
</tr>
</tbody>
</table>

Guideline: alternative mass drug administration regimens to eliminate lymphatic filariasis World Health Organization 2017

FILARIASIS

- LF and its progress to elimination
- LF and a triple-drug regimen
- LF and areas co-endemic for loaisis and onchocerciasis: research gaps
Onchocerciasis
Onchocerciasis

Distribution of onchocerciasis and status of preventive chemotherapy (PC) in endemic countries, 2016

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 2017. All rights reserved

Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD)
World Health Organization

World Health Organization
Nodding syndrome
Nakalanga syndrome
Nakalanga syndrome is observed in places where NS also occurs
Onchocerciasis associated epilepsy
High prevalence of epilepsy is currently observed in onchocerciasis-endemic regions
Two trials are ongoing to investigate whether onchocerciasis treatment is able to decrease the frequency of seizures in persons with OAE

Figure 1. The Clinical Manifestations of Onchocerciasis. An individual infected with *Onchocerca volvulus* may develop several of these complications with different degrees of severity.
Use of moxidectin in Onchocerciasis

- Annual community directed ivermectin treatment has substantially reduced prevalence
- Compared parasitological efficacy and safety of moxidectin and ivermectin
- Double-blind, parallel group, superiority trial
- Skin microfilarial loads are lower after moxidectin treatment than after ivermectin treatment
- The spread of post-treatment SmfD was greater among people treated with ivermectin compared with moxidectin
- Moxidectin was well tolerated
- Useful in areas with operational barriers to MDA and where transmission seasons are long or have two peaks
- Areas where onchocerciasis and loiasis are coendemic

The LoaScope was used to identify persons with an *L. loa* microfilarial density greater than 20,000 microfilariae per ml of blood, who were considered to be at risk for serious adverse events, and exclude them from ivermectin distribution.

- Active surveillance for post treatment adverse events.
- AE: older participants, female participants, and participants with either *L. loa* microfilaremia or anti-Ov16 IgG4 antibodies.
- High rate of participation suggests it is an acceptable strategy.
- Scalable point-of-contact tool.
Onchocerciasis:

• OAE is an additional reason for eliminating onchocerciasis
• LoaScope based test-and-not-treat approach to ivermectin treatment for lymphatic filariasis and onchocerciasis should be scaled up in other areas where *L. loa* infection is endemic
• Shorter time to onchocerciasis elimination with annual mass administration of moxidectin compared with ivermectin
Schistosomiasis
Schistosomiasis and Infertility in East Africa

- Cross-sectional multilevel semi-ecologic study
- Prevalence was extracted to georeferenced survey sample points for DHSs for Ethiopia, Kenya, Tanzania, and Uganda for 2000 and 2010
- Women living in high compared with absent S. haematobium locations had significantly higher odds of infertility
  - Women in high S. haematobium compared with high S. mansoni locations had significantly higher odds of infertility
  - Living in high compared with absent S. mansoni locations did not affect the odds of infertility
- Infertility appears to be associated spatially with S. haematobium
Meta-analysis of information from all relevant epidemiologic studies, we examined the hypothesis that *Schistosoma* infection in school-aged children (SAC) is associated with educational loss and cognitive deficits.

Thirty studies from 14 countries, including 38,992 SAC between 5-19 years old, were identified.

Compared to uninfected children and children dewormed with praziquantel, the presence of *Schistosoma* infection and/or non-dewormed status was associated with deficits in school attendance, scholastic achievement, learning and memory tests.

*Schistosoma*-infected/non-dewormed and uninfected/dewormed children were similar with respect to performance in tests of reaction time and intelligence.

*Schistosoma* infection/non-treatment was significantly associated with educational, learning, and memory deficits in SAC.
Schistosomiasis:

- Female genital schistosomiasis is one of the most common gynaecologic conditions of women who live in poverty in Africa.
- Early treatment of children in *Schistosoma*-endemic regions could potentially mitigate deficits in cognitive function.
SOIL-TRANSMITTED HELMINTHS (STHs)
STHs are still a problem

Figure 1: Prevalence by global regions of (A) *Ascaris lumbricoides* (for 2010), (B) *Trichuris trichiura* (for 2010), (C) hookworm (*Necator americanus* and *Ancylostoma duodenale*; for 2010), and (D) *Strongyloides stercoralis* (for 2011)

Data for (A), (B), and (C) from Pullan and colleagues. Data for *S. stercoralis* are especially scarce and may be associated with strong publication bias; estimates from data by Schär and colleagues. Data from single community-based studies suggest that *S. stercoralis* might be present also in Australia, Israel, and Japan (which is marked as non-endemic on the map).
In 2015, a Cochrane review of randomised clinical trials concluded that there was no population-level effect of deworming on a range of child health outcomes, including growth and haemoglobin levels, supported by others.

But critics of the Cochrane and Campbell reviews argue that no long-term trials have been done to determine the effect of periodic deworming, and that failure to detect diluted, population-level health benefits is an issue of measurement or statistical power.

World Bank and Harvard University health economists reported significant weight gain in dewormed children.

As such, population-level deworming in STH-endemic areas is warranted, as the health benefits of treating STH infections are well established, and MDA of anthelmintics is safe and the most cost-effective way to reach infected individuals.

No doubt that treatment reduces the severe consequences of soil-transmitted helminthiasis*


Exploratory, randomized, single-blind trial to evaluate the efficacy and safety of moxidectin (8 mg) versus ivermectin (200 μg/kg) against *S. stercoralis* infections.

127 participants were enrolled and randomly assigned to one of the two treatments.

CR of 93.7% (59/63) for moxidectin compared to 95.2% (59/62) for ivermectin. No side effects were observed.

Moxidectin might be a safe and efficacious alternative to ivermectin for the treatment of *S. stercoralis* infection.

Larger clinical trials should be conducted once the drug is marketed.

Feasibility of interrupting STH transmission using biannual MDA targeting all age groups.

Population 80,000 have been identified in Benin, Malawi and India.

Three years of twice-annual community wide MDA or standard-of-care MDA, typically annual school-based deworming.

STHs:

- Deworming debate
- Use of moxidectin in *Strongyloides stercoralis*
- De-Worm 3 project
TAENIASIS/CYSTICERCOSIS
Effectiveness of drug-free interventions in controlling human cysticercosis is not well known

Estimate the effectiveness of a community-based educational intervention in reducing the frequency of human cysticercosis in Burkina Faso

RCT between 2011 and 2014

Overall, the intervention tended towards a decrease in the cumulative incidence of active cysticercosis from baseline to after randomisation and a decrease in active cysticercosis prevalence from baseline to after randomisation.

Increase in the proportion of households with recently built latrines.

NCC and epilepsy

• Higher prevalence of epilepsy (eg: Latin-America) could be explained by parasitic infections, particularly NCC
• Important proportion of seizure cases are associated with NCC demonstrated by serology and CT scan in rural Peru
• Studies only using CT scan to determine etiology have a significant limitation - dual pathology or maybe other lesions
• Controversial to attribute that patients with positive serology for cysticercosis can make a case for NCC
• Use of MRI with proper protocols in all cases and a more comprehensive diagnostic approach can identify other etiologies lowering the rates of NCC associated with epilepsy,
• NCC associated with epilepsy has a low rate of intractability
• An individual infected with NCC has almost a three times higher risk of developing epilepsy than an uninfected individual.
• General lack of consistency in diagnostics, and lack of accurate epidemiological data

Source:
Jose F. Tellez-Zenteno et al. Epidemiology of neurocysticercosis and epilepsy, is everything described? Epilepsy & Behavior 76 (2017) 146–150
Extraparenchymal neurocysticercosis (ExPNCC), an infection caused by *Taenia solium* cysticerci that mainly occurs in the ventricular compartment (Ve) or the basal subarachnoid space (SAb), is more severe but less frequent and much less studied than parenchymal neurocysticercosis (ParNCC).

With respect to parenchymal cysts, extraparenchymal parasites were diagnosed at an older age, chiefly caused intracranial hypertension, were more frequently multiple and vesicular, and CSF from these patients showed higher protein concentration and cell count.

SAb patients were diagnosed at an older age than Ve patients, and showed more frequently seizures, vesicular cysticerci, and higher CSF cellularity.

Clear clinical, radiological, and inflammatory differences between ExPNCC and ParNCC, and between SAb and Ve patients, and demonstrated that parasite location determines different pathological entities.

Parasite location is one of the most important features of the disease.

Clinical Cysticercosis in Spain

- Retrospective descriptive study using the Spanish hospital discharge database 1997 to 2014
- Total of 1,912 hospital discharges with CC
- From 1998 to 2008, an increasing trend in the number of CC hospitalizations was observed, decreasing afterwards, in parallel with a decrease in the external migration rate.
- Differences between regions in Spain
  - 16-44 age group most represented
  - Epilepsy and convulsions, hydrocephalus and encephalitis/myelitis/meningitis
  - Few intestinal taeniases compared with clinical cysticercosis
  - Immigration from endemic areas may also play a role in the appearance of autochthonous CC by human to human transmission
  - Improving the human and animal CC surveillance

TAENIASIS/CYSTICERCOSIS:

• Low-cost, culturally appropriate intervention can be successful in controlling human cysticercosis
• Increased migration and travels from endemic regions, CC is becoming a constantly growing public health problem also in high-income countries
• NCC does increase the risk of developing epilepsy,
• Differences in parasite location actually determines distinct diseases, with wide variations in severity
Chagas

Leishmaniasis:

Lymphatic filariasis
- Benjamin G Koudou et al. Elimination of lymphatic filariasis in west African urban areas: is implementation of mass drug administration necessary? Lancet Infect Dis 2018

Onchocerciasis
- Walker et al. Macrofilaricidal Efficacy of Repeated Doses of Ivermectin for the Treatment of River Blindness. CID 2017:65

Scabies:
- Olivier Chosidow et al. Scratching the itch: is scabies a truly neglected disease? Lancet. 2017;17

Schistosomiasis
NTDs:
- Challenges for sustaining progress towards control and elimination
- Community engagement
- Integration in primary health care
- Robust, resilient and responsive health systems
- Vector control, preventive chemotherapy, new drugs and diagnostics and tools for M&E
- Discrepancy in GDB data – long-term manifestations of NTDs
- Mental health
- Partnerships

The Changing Global Landscape of NTDs

Communities

Health System

- Leadership & Governance: Health Care financing; Health Workforce; Medical Products & Technologies; Information & Research; Service Delivery; Drug Supply Chain; Strengthened Hospital Capacity; Universal Health Coverage

- + Improved community pharmacy, vigilance, solutions to drug delivery - loss of vector control capacity

- + Improved community pharmacy, vigilance, solutions to drug delivery - loss of vector control capacity

- + Committed Health Workforce dedicated to workforce change

- + Remuneration/recognition for workforce

- Lack of appropriate remuneration/recognition for workforce

- + Wide reach MDA

- Lack of patent voice; dimension of health equity; mental health exposure

- + Violence & disease

- Lack of patient voice; dimension of health equity; mental health exposure

Multi-Directional Capacity Strengthening

- + Creation of new drugs and diagnostics

- Need for vector control

- Emergence of resistance

- Complex drug resistance

- + Global stocks, conflict & distribution

- + Intersectoral collaboration

- + Sustained donor

- + Change disease

- - Emergent infections: Ebola, Zika

- - Emergent infections: Ebola, Zika

- - Global stocks, conflict & distribution

- - Intersectoral collaboration

- - Sustained donor
NTDs: Global Health Observatory
http://www.who.int/neglected_diseases/en/
Acknowledgements

• ESCMID Study Group for Clinical Parasitology

• Malaria Consortium Cambodia