Top papers in Neglected Tropical Diseases: Epidemiology 2016-17

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> 250 PAPERS REVIEWED for 2016-17

1. Buruli ulcer
2. Chagas disease
3. Dengue and Chikungunya
4. Dracunculiasis (guinea-worm disease)
5. Echinococcosis
6. Foodborne trematodiases
7. Human African trypanosomiasis (sleeping sickness)
8. Leishmaniasis
9. Leprosy (Hansen's disease)
10. Lymphatic filariasis
11. Onchocerciasis (river blindness)
12. Rabies
13. Schistosomiasis
14. Soil-transmitted helminthiases
15. Taeniasis/Cysticercosis
16. Trachoma
17. Yaws (Endemic treponematoses)
18. Mycetoma (28 May 2016, 69th World Health Assembly)
CYSTICERCOSIS / T. SOLIUM


- **Information considered from each country**
  - Peer reviewed publications
  - Grey literature research
  - Number of pigs in the country
  - Type of pig production (commercial or “backyard”)
  - Notifications to the OIE
  - Inequality-adjusted Human Development Index (IHDI) produced by the United Nations Development Programme

- **Country categories (classification)**
  - Endemic
  - Suspected
  - Few pigs with risk factors
  - Non-endemic
  - No data / possible transmission in some communities

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CYSTICERCOSIS / T. SOLIUM: interruption of transmission is possible

- Strategies (screening + treatment of humans and pigs) to show the feasibility of interrupting the transmission of *T. solium* infection in a region of highly endemic disease in northern Peru (Tumbes province, 107 villages)

- HUMANS (81,170 people): mass treatment & health education, over 1 year, with Niclosamide po 3 doses (85% of the entire population received at least 1 dose)
- PIGS (55,638 pigs): mass treatment & vaccination, over 1 year, with Oxfendazole im every 2 months + vaccination with TSOL18

- Effect of intervention in pigs
  - Seroprevalence in pigs: from 25-50% to 29%
  - Necropsy of 342 seropositive pigs to detect live, nondegenerated cysts capable of causing new infection: from estimated 20% to 1%
  - Transmission of *T. solium* infection can be interrupted. The intervention will probably result in a decrease in the incidence of seizures and epilepsy over the next 5 to 10 years

CYSTICERCOSIS / T. SOLIUM

- endemicity update
- interruption of transmission is feasible
DENGUE / CHIKUNGUNYA / ZIKA
Before 1970, only 9 countries had dengue epidemics. Currently endemic in >100 countries.

Average number of suspected or confirmed dengue cases reported to WHO, 2010–2016

http://www.who.int/denguecontrol/epidemiology/en/
### DENGUE / CHIKUNGUNYA / ZIKA: a threat to Europe?


- August-September 2015
- 7 authochtonous cases, DENV1
- An imported case from French Polynesia as probable source
- *Ae. albopictus*

#### Dengue and other *Aedes*-borne viruses: a threat to Europe? Rezza G. *Euro Surveill.* 2016;21(21)

- *Ae. albopictus* first detected in Europe in 1979 and spread to Mediterranean countries
- *Ae. albopictus is not* an efficient vector for DENV and ZIKV, but CHIKV has adapted to it
- Autochthonous *dengue* in France (3 small outbreaks) and Croatia (17 cases)
- Autochthonous *chikungunya* in Italy in 2007 (>250 cases), from an imported case of India, and in France Montpellier in 2014 (12 cases), from an imported case of Cameroon

- To date, no autochthonous cases of *zika* in mainland Europe
- *The cool winter months will restrict transmission and prevent zika being established*
Ae. albopictus has proven to be a vector for the transmission of dengue and chikungunya viruses in Europe there is growing experimental and ecological evidence to suggest that it may also be competent for Zika virus
Analysis of the monthly flows of airline travellers arriving into European cities from Zika affected areas across the Americas, the predicted monthly estimates of the basic reproduction number of Zika virus in areas where Ae. mosquito populations reside in Europe, and human populations living within areas where mosquito-borne transmission of Zika virus may be possible.
DENGUE / CHIKUNGUNYA / ZIKA

-a threat to Europe?
DRACUNCULIASIS
Update of published and unpublished surveillance data reported by ministries of health and describes progress toward dracunculiasis eradication

- From 3.5M (in 20 countries) in 1986 to 126 cases (>99% reduction), and to 22 cases in 2015 (83% reduction from 2014), in 4 countries: Chad, Mali, South Sudan, and Ethiopia

- During 2016, 25 human cases were reported in 2016

- A possible life cycle involving dogs, fish and amphibians as paratenic hosts was discovered in Chad. (~1000 dog infections recorded in Chad in 2015-6).

- The emergence of Dracunculus infections in *domestic dogs* in Chad and program disruptions caused by civil unrest and insecurity in Mali and South Sudan are now the greatest challenges to interrupting transmission.

DRACUNCULIASIS

-dogs are now identified as paratenic hosts
ECHINOCOCCOSIS
ECHINOCOCCOSIS: importance of molecular epidemiology

- Importance of molecular species identification of human CE
- Recent taxonomic revisions have suggested that *E. granulosus* s.l. consists of five species: *E. granulosus* s.s. (G1, G2 and G3), *E. equinus* (G4), *E. ortleppi* (G5), *E. canadensis* (G6, G7, G8 and G10) and *E. felidis*
- The majority of CE cases historically were attributed or presumed to be caused by *E. granulosus* s.s., mainly G1. However, recent molecular studies of CE cases have revealed that *E. canadensis* (G6/7) is not rare, but common.
ECHINOCOCCOSIS: epidemiology

- Titanic review on epidemiology of alveolar and cystic echinococcosis: 178 pages with >900 references
  - Geographical areas
  - Number of cases
  - Molecular epidemiology

Table 6 Genotypes of *Echinococcus* spp. causing cystic echinococcosis in eastern Central Europe: *Echinococcus granulosus* (G1–3), *Echinococcus equinus* (G4), *Echinococcus ortleppi* (G5), *Echinococcus intermedius* (G6/7) and *Echinococcus canadensis* (G8, G10) (no data found in the missing countries)

<table>
<thead>
<tr>
<th>Country</th>
<th>Human</th>
<th>Dog</th>
<th>Wild canids</th>
<th>Cattle</th>
<th>Pig (P), Wild boar (Wb)</th>
<th>Sheep (S), Cervids (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poland</td>
<td>G7 and G1¹</td>
<td>G1²</td>
<td>G8²</td>
<td>G10²</td>
<td>P: G7³</td>
<td>C: G8 and G10³⁴</td>
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<td>Estonia</td>
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<tr>
<td>Latvia</td>
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<tr>
<td>Lithuania</td>
<td>G7²⁵</td>
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</tr>
<tr>
<td>Ukraine</td>
<td>G1⁷</td>
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<tr>
<td>Moldova</td>
<td>G3⁷</td>
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<tr>
<td>Slovakia</td>
<td>G7⁸ and G1–3*</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

¹ (Dybiec et al., 2015); ² (Marcinków et al., 2015); ³ (Karmon et al., 2012); ⁴ (Moiks et al., 2009); ⁵ (Boukhris et al., 2009); ⁶ (Kedra et al., 2000); ⁷ (Umhang et al., 2014); ⁸ (Tarózeková et al., 2009); ⁹ Antolovi D. unpublished data.

Table 5 Genotypes of *Echinococcus* spp. causing cystic echinococcosis in South America: *Echinococcus granulosus* (G1–3), *Echinococcus ortleppi* (G5), *Echinococcus intermedius* (G6/7)

<table>
<thead>
<tr>
<th>Country</th>
<th>Human</th>
<th>Dog</th>
<th>Sheep</th>
<th>Cattle</th>
<th>Goat (Go)/Alpaca (A)</th>
<th>Pig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>G1²⁴⁵</td>
<td>G1²⁵</td>
<td>G1³⁴</td>
<td>G1³⁴</td>
<td>G1³⁴</td>
<td>G1³⁴</td>
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<tr>
<td>Brazil</td>
<td>G1⁶</td>
<td>G1⁸</td>
<td>G1³⁴</td>
<td>G1³⁴</td>
<td>G1³⁴</td>
<td>G1³⁴</td>
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<tr>
<td>Chile</td>
<td>G1⁹</td>
<td>G1⁹</td>
<td>G1³⁴</td>
<td>G1³⁴</td>
<td>G1³⁴</td>
<td>G1³⁴</td>
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<td>Peru</td>
<td>G1¹¹</td>
<td>G1¹¹</td>
<td>G1³⁴</td>
<td>G1³⁴</td>
<td>G1³⁴</td>
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<tr>
<td>Uruguay</td>
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<td>G1¹³</td>
<td>G1³⁴</td>
<td>G1³⁴</td>
<td>G1³⁴</td>
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<tr>
<td>Bolivia</td>
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<td>G1³</td>
<td>G1³</td>
<td>G1³</td>
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<td>G1³</td>
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</tbody>
</table>

¹ (Cocher et al., 2016); ² (Guerena et al., 2004); ³ (Kanther et al., 2002); ⁴ (Kanther et al., 1999); ⁵ (Soriano et al., 2010); (de la Rue, 2011); (Badiou et al., 2012); (de la Rue et al., 2006); (Monteiro et al., 2014); (Martin et al., 2009); (Espinosa et al., 2014); (Ito et al., 2006); (Sánchez et al., 2010); (Santamana et al., 2008); (Sánchez et al., 2012).

Table 9 Genotypes of *Echinococcus* spp. causing cystic echinococcosis in North Asia (including the European part of Russia), Central Asia and Caucasus (no data found in the missing countries): *Echinococcus granulosus* (G1–3), *Echinococcus equinus* (G4), *Echinococcus ortleppi* (G5), *Echinococcus intermedius* (G6/7) and *Echinococcus canadensis* (G8, G10)

<table>
<thead>
<tr>
<th>Country</th>
<th>Human</th>
<th>Dog (D)</th>
<th>Sheep (S)</th>
<th>Cervids</th>
<th>Pig</th>
<th>Cattle</th>
<th>Other</th>
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</thead>
<tbody>
<tr>
<td>Russian Federation</td>
<td>G1–3</td>
<td>G6⁶</td>
<td>G6/7</td>
<td>G1⁴</td>
<td>G1–3²</td>
<td>G6, G8, G10</td>
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<td>Kazakhstan</td>
<td>D: G1</td>
<td>G6/7¹⁵</td>
<td>G6/7</td>
<td>G1⁴</td>
<td>G1–3³</td>
<td>G6, G8, G10</td>
<td>Cat: G1³</td>
</tr>
<tr>
<td>Kyrgyzstan</td>
<td>D: G1, G4</td>
<td>G6/7⁷</td>
<td>G6/7</td>
<td>G1⁴</td>
<td>G1–3³</td>
<td>G6, G8, G10</td>
<td>Cat: G1³</td>
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<tr>
<td>Armenia</td>
<td>G1–3⁸</td>
<td>S: G1–3⁸</td>
<td>G7⁹ G1–3⁸</td>
<td>G1–3⁸</td>
<td>G6, G8, G10</td>
<td>Cat: G1³</td>
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</tr>
</tbody>
</table>

¹ (Konyaev et al., 2013); ² (Sharma et al., 2013); ³ (Konyaev et al., 2012); ⁴ (Sefani et al., 2004); ⁵ (Boutou et al., 2015); ⁶ (Trachsel et al., 2007); ⁷ (Zaidinov et al., 2008); ⁸ Ebi, Gevorgyan H.S., personal communication; ⁹ (Snábel et al., 2009).
ECHINOCOCCOSIS

-importance of molecular epidemiology
FILARIASIS
FILARIASIS: epidemiology and progress to eliminate lymphatic filariasis

- 946M at risk, 68M infected, 40M symptomatic
- Global Programme to Eliminate Lymphatic Filariasis launched in 2000
- Mass drug administration (MDA) is the main strategy
- 556 M received MDA for lymphatic filariasis in 2015
- During the past 13 years, ≈97 million of cases have been prevented or cured
FILARIASIS: MDA with triple-drug regimen for lymphatic filarials

• MDA: a combination of 2-drugs given once a year for at least 5-7 years (5-7 rounds) at a minimum population coverage >65-70%
  o Albendazole + Diethylcarbamazine (DEC)
  o Albendazole + Ivermectin (in areas co-endemic with onchocerciasis)

• Albendazole (400 mg) + DEC (6 mg/Kg) + Ivermectin (200 ug/Kg) is much more effective at clearing both microfilariae and adults of *W. bancrofti*


• Mathematical mode of 3-drug efficacy: acceleration progress towards elimination by 1-2 years in areas of low (5%) prevalence and by 4-5 years in areas of moderate & high (10-40%) incidence

FILARIASIS: MDA with albendazole twice a year for lymphatic filariasis in areas with loiasis (Congo, Cameroon)

- Pilot project in a village in Republic of the Congo endemic for lymphatic filariasis, loiasis and soil-transmitted helminthiasis
- Mass treatment (>2 yo) with albendazole (400 mg) every 6 months for 3 years
- Coverage was more than 80%
- *W bancrofti* antigenaemia and microfilaraemia rates in the community fell significantly, from 17.3% to 4.7% and from 5.3% to 0.3% respectively.
- Marked decrease on STH

FILARIASIS: excess mortality associated with loiasis?

- Retrospective cohort study included 3627 people from 28 villages in eastern Cameroon examined in 2001 for loiasis and followed up in 2016 for survival.

- Individuals with high numbers of *L. loa* microfilariae had increased age-adjusted and sex-adjusted risk of death

- Population-attributable fraction of mortality associated with presence of *L. loa* microfilaraemia was 14.5% (95% CI 6.5-21.8).

- Patients >25 years with >30,000 mf/mL in 2001 died significantly earlier than amicrofilaraemic patients

- Loiasis still considered a benign condition. High-grade *L. loa* microfilaraemia is associated with an increased mortality risk, suggesting that loiasis is not a benign condition and merits more attention. **Loiasis should be considered for inclusion in the WHO's list of neglected tropical diseases.**

FILARIASIS: skin snips for monitoring MDA in onchocerciasis

• Microscopic evaluation of skin biopsies is the monitoring and evaluation method currently used by onchocerciasis elimination programs in Africa.

• Repeated MDA suppresses microfilarial loads, the utility of skin snip microscopy is expected to decrease. Insufficient sensitivity of skin snip microscopy for reliable programmatic monitoring.

• At 5 years of MDA, the sensitivity improves significantly if 4 skin snips are taken.


• Pan-filarial real-time polymerase chain reaction melt curve analysis (qPCR-MCA) in skin snips can augment sensitivity and provide diagnostic confirmation.

FILARIASIS

- lymphatic filariasis: progress in elimination
- lymphatic filariasis: triple-drug regimen
- lymphatic filariasis in areas of loiasis: albendazole twice a year
- loiasis: associated with an excess of mortality?
- oncocerciasis: sensitivity of skin snips in assessing elimination
Screening of 44 ill adult Syrian refugees examined at GeoSentinel clinics worldwide, cutaneous leishmaniasis affected one in three patients.

LEISHMANIASIS: VL in high burden countries

- 30,758 total VL cases reported in 2014

In 2015 the target for elimination was achieved in 82% of sub-districts in India, 97% of sub-districts in Bangladesh, and in 100% of districts in Nepal.

1) India 9241
2) South Sudan 8015
3) Sudan 3520
4) Brazil 3453
5) Ethiopia 2821
6) Somalia 1033
7) Kenya 880
8) Bangladesh 735
9) Nepal 335
10) China 294

Leishmaniasis in high-burden countries: an epidemiological update based on data reported in 2014. WHO. Wkly Epidemiol Rec 2016;91:287-96
LEISHMANIASIS: anthroponotic / zoonotic VL

- L. donovani is responsible for anthroponotic-VL in the Indian subcontinent
- 50 stray dogs from Bangladesh screened
- 12% rK39+ in serum and 20% PCR+ in buffy-coat
- Role of domestic/stray dogs in zoonotic-VL transmission is not clear in the area


- Yemeni pediatric patients with VL. 25 isolates from Giemsa-stained bone marrow smears were successfully amplified by nested PCR and the ribosomal internal transcribed spacer-1 (ITS1) gene was sequenced.
- Phylogenetic results: L. infantum in 11 isolates and L. donovani in 14 isolates
- These data suggest the possibility of both anthroponotic and zoonotic transmission of VL in Yemen.

**LEISHMANIASIS: infection in blood donors**

- 431 healthy blood donors in Fortaleza (Northeastern Brazil). Buffy-coats tested for *Leishmania* by ELISA and PCR
  - 13.2% serology + and 4.6% PCR +
  - Overall prevalence: 17.1%


- **Review of the literature between 1948 and 2011**
  - 10 publications (14 patients): 11 newborn/children, 3 adults
  - Combination of two strategies= leukodepletion + pathogen inactivation technology (riboflavin plus UV light in plasma and PLTs, amotosalen plus UV light in PLTs, thiopyrylium in RBC), appears to provide sufficient protection against Leishmania infection by transfusion and could explain the lack of transfusion-transmitted-leishmaniasis cases in high-risk areas

LEISHMANIASIS

- CL and the Syrian conflict
- VL decrease in India & Nepal and increase in East Africa
- zoonotic VL in Indian subcontinent
- anthroponotic and zoonotic VL in Yemen
- transfusion-transmitted leishmaniasis?
SOIL TRANSMITTED HELMINTHS (STHs)
**STHs: effectiveness of mass deworming**

- Systematic review and meta-analysis: 52 studies of ≤5 years duration with >1 million children, and four long-term studies 8–10 years after mass deworming programs with more than 160,000 children.
- Mass deworming for STHs compared with controls led to little to no improvement in weight over a period of about 12 months or height, little to no difference in proportion stunted, cognition measured by short-term attention, school attendance or mortality.
- Mass deworming for schistosomiasis might slightly increase weight and has little to no effect on height and cognition.
- No indirect benefits for untreated children from being exposed to treated children in the community.
- Uncertain effect on long-term economic productivity (hours worked), cognition, literacy, and school enrolment.

- **Mass deworming for STHs +/- for schistosomiasis has little effect.**

The Cochrane Collaboration challenged the benefits of deworming for the control of STH. This finding provoked robust debate about whether RCTs are an appropriate way to measure the nutritional and educational benefits of MDA for STHs.


Most RCTs do not take into account that recovery from nutritional deficits takes much longer than 1 year. RCTs do not look to other associated morbidities such as:

- HIV: increased HIV positivity in females infected with *S. haematobium*
- Epilepsy: 30% of global epilepsy is associated with neurocysticercosis
- Cancer: bladder cancer associated with *S. haematobium* and food-borne trematode infections that cause chorioangiocarcinoma
- Malaria: hookworm exacerbate malaria pathology, particularly in pregnancy, which reduces birth weight and increases risk of neonatal and infant mortality.
- Mental health: impact of NTDs on the psycho-social status of individuals and families, particularly depressive illness and anxiety
SOIL TRANSMITTED HELMINTHS (STHs)
-the deworming debate
TRYPANOSOMIASIS: AFRICAN & AMERICAN
14-month-old boy infected with *Tr. brucei* through the transplacental route. Child referred to pediatric care unit due to psychomotor delay and axial hypotonia. Mother (from DRC) reported short visit to bush in Angola, and had arrived in France 3 years earlier.

The pregnancy, which had been initiated and monitored in France, was normal through delivery. Newborn placed with foster family as mother had vigilance disorders, aphasia, fluctuating hemiparesia and tetraparesia, convulsions associated with choreiform movements, anxiety, and severe depression. Until trypomastigotes were observed in her son’s CSF, the mother had not received a definitive diagnosis.

The foster family reported that the child did not smile and had been unable to grasp objects in the last 8 months.

HAT is a very rare imported disease: <100 cases over a 10-year period)

Congenital transmission is extremely rare: 17 probable cases reported (14 confirmed MTC transmission: 13 *Tr. b. gambiense*)
TRYPANOSOMIASIS: AFRICAN & AMERICAN

-HAT endemicity is the lowest for 75 years (from 37000 new cases in 1999 to <3,000 cases in 2015)

- *T. cruzi* and *T. brucei* in immigrants from endemic areas
NTDs GLOBAL OVERVIEW

- progress toward elimination/control
- new epidemiological tools
- excellent web sites
Key achievements include

- 1 billion people treated for at least one neglected tropical disease in 2015 alone.
- 556 million people received preventive treatment for lymphatic filariasis (elephantiasis).
- More than 114 million people received treatment for onchocerciasis (river blindness: 62% of those requiring it).
- Only 25 human cases of Guinea-worm disease were reported in 2016, putting eradication within reach.
- Cases of human African trypanosomiasis (sleeping sickness) have been reduced from 37,000 new cases in 1999 to well under 3,000 cases in 2015.
- Trachoma – the world’s leading infectious cause of blindness – has been eliminated as a public health problem in Mexico, Morocco, and Oman. More than 185,000 trachoma patients had surgery for trichiasis worldwide and more than 56 million people received antibiotics in 2015 alone.
- Visceral leishmaniasis: in 2015 the target for elimination was achieved in 82% of sub-districts in India, 97% of sub-districts in Bangladesh, and in 100% of districts in Nepal.
- Only 12 reported human deaths were attributable to rabies in the WHO Region of the Americas in 2015, bringing the region close to its target of eliminating rabies in humans by 2015.
Neglected tropical diseases (NTDs) blight the lives of a billion people worldwide and threaten the health of millions more. These ancient companions of poverty weaken impoverished populations, frustrate the achievement of health in the Millennium Development Goals and impede global public health outcomes. An appreciation of their significance to public health and economics has convinced governments, donors, the pharmaceutical industry and other agencies, including non-governmental organizations, to invest in preventing and controlling this diverse group of diseases.

- **Draconisiasis (guinea-worm disease)**
  - **99%**
  - The decrease in the number of new cases of guinea-worm disease since 1986.

- **Human African trypanosomiasis**
  - **90%**
  - The decrease in the reported number of cases of human African trypanosomiasis from 1999-2015.

- **Preventive chemotherapy**
  - **998 million**
  - People have been reached by preventive chemotherapy for at least one disease in 2016.
NTD global mapping tool: http://www.ntdmap.org/

The NTD global mapping tool provides an interactive means to assist the planning and implementation of preventive chemotherapy for NTDs, enabling visualisation of geographical distribution of diseases and the priority areas requiring mass drug administration where co-implementation should be initiated.
The Uniting to Combat NTDs initiative tracks progress on ten NTDs towards the agreed targets against a scorecard that is published annually.
Thanks very much for your attention