TropNet

European Network for Tropical Medicine and Travel Health

15th Workshop on Imported Infectious Diseases

2014

11th – 12th April

Hamburg

TropNET Workshop – Hamburg 2014

1	Belgium	Antwerp	Jan Clerinx
2	Belgium	Antwerp	Emmanuel Bottieau
3	Netherlands	Leiden	Emile Jonker
4	Netherlands	Leiden	Meta Roestenberg
5	France	Bobigny	Olivier Bouchaud
6	France	Bordeaux	Denis Malvy
7	France	Bordeaux	Matthieu Mechain
8	Germany	Berlin	Thomas Zoller
9	Germany	Berlin	Florian Kurt
10	Germany	Berlin	Tomas Jelinek
11	Germany	Heidelberg	Thomas Junghanss
12	Germany	Heidelberg	Moritz Vogel
13	Germany	Heidelberg	Philipp Zanger
14	Germany	Tübingen	Carsten Köhler
15	Germany	München	Mirjam Schunk
16	Germany	München	Hans-Dieter Nothdurft
17	Germany	Hamburg	Jacob Cramer
18	Ireland	Dublin	Graham Fry
19	Ireland	Dublin	Andrew Lewis
20	Italy	Firenze	Marianne Strohmeyer
21	Italy	Firenze	Lorenzo Zammarchi
22	Italy	Negra (Verona)	Andrea Angheben
23	Italy	Rome	Emanuelle Nicastri
24	Italy	Torino	Guido Calleri
25	Italy	Brescia	Francesco Castelli
26	Italy	Brescia	Lina Tomasoni
27	Italy	Udine	Anna Beltrame
28	Norway	Bergen	Kristine Mørch
29	Portugal	Porto	Sandra Xará / André Silva
30	Sweden	Stockholm	Anders Björkmann
31	Sweden	Stockholm	Urban Hellgren
32	Spain	Barcelona	Joaquim Gascon
33	Spain	Barcelona	Antoni Soriano Arandes
34	Spain	Barcelona	Israel Molina
35	Spain	Madrid	Juan Cuadros Gonzáles
36	Spain	Madrid	Gerardo Rojo
37	Switzerland	Basel	Christoph Hatz
38	Switzerland	Basel	Andreas Neumayr
39	Switzerland	Basel	Esther Künzli
40	Switzerland	Bern	Olivia Veit
41	Switzerland	Geneva	Gilles Eperon
42	UK	Newcastle upon Tyre	Matthias Schmid
43	UK	London	Ron Behrens

Hamburg 2014 - 15th TropNet Workshop

Friday, 11/04/20124		
13^{00}-13^{30}	**Welcome and Introduction**	**Jakob Cramer, Hamburg** **Rolf Horstmann, Hamburg**
13^{30}-15^{00}	**Report of steering committee and coordinator** • Brief overview on TropNet membership issues • Overview on the `TropNet platforms´ with discussion and election of responsible centres/leader for individual platforms • ECTMIH 2015 – TropNET preconference travel medicine course	**Christoph Hatz, Basel &** **Andreas Neumayr, Basel**
15^{00}-15^{15}	**Break**	
15^{15}-17^{00}	**Report on ongoing TropNet studies & studies with participation of TropNet centres** • **Artesunate for severe malaria in Europe:** preliminary results • **DengueTools**: update on imported Dengue in Europe (FP7) • **Eurartesim**: update on TropNet-SigmaTau study on treatment of uncomplicated *P. vivax* malaria • **LeishMan**: update & treatment recommendations for CL & ML • **StaphTrav**: update and preliminary data analysis **Upcoming TropNet studies** • **HaemoArt**: Haemolysis after antimalarial treatment with artemisinins • **GiardiaTREAT & GiardiaREF**: studies on first- & second-line treatment of giardiasis • **Safety surveillance** of life vaccines in immunosuppressed persons **Reflection:** Institutional network collaboration for `Horizon 2020´ - strengthening capacity building	**Florian Kurth & Thomas Zoller, Berlin** **Andreas Neumayr, Basel** **Christoph Hatz, Basel** **Johannes Blum, Basel** **Philipp Zanger, Heidelberg** **Thomas Zoller, Berlin** **Andreas Neumayr, Basel** **Silja Bühler, Zurich & Christoph Hatz** **Matthieu Mechain, Bordeaux**
17^{00}-17^{15}	**Break**	
17^{15}-18^{00}	**Proposals for future TropNet studies** • Mass gatherings – WM 2014 • Imported malaria cases in Europe as sentinel surveillance of the worldwide prevalence and emergence of drug resistance • Comparison of imported *Plasmodium ovale wallikeri* and *Plasmodium ovale curtisi* • Comparison of methods used to determine the safety of N,N-diethyl-m-toluamide (DEET)	**Jakob Cramer, Hamburg** **Andreas Neumayr, Basel** **Gerardo Rojo, Madrid** **Ron Behrens, London**
18^{00}-18^{30}	Transport to University Hospital Eppendorf	**For all interested colleagues**
18^{30}-20^{00}	Visit to the centre for highly-contagious pathogens / isolation ward at the University Hospital Eppendorf	
20^{00}-20^{30}	Transport back to Bernhard Nocht Institute	
20^{30}-20^{45}	Walking tour from Bernhard Nocht Institute to dinner	**For all hungry colleagues**
20^{45}-23^{00}	**Dinner**	
Saturday, 12/04/2014		
9^{00}-9^{15}	**Introduction**	**Coordinator, SC members**
9^{15}-10^{30}	**Study proposals** • Evaluation of PCR based diagnosis of acute schistosomiasis in its prepatent and patent phase • Praziquantel pharmacokinetic • PneumoTravChild **Presentations** • A randomised blinded study of the effectiveness of topical corticosteroids and ibuprofen for the relief of Type I mosquito bite symptoms • Centre-based management of cystic echinococcosis: a model for NTD/NIDs care in Europe	**Jan Clerinx, Antwerp** **Christoph Hatz, Basel** **Antoni Soriano Arandes, Barcelona** **Ron Behrens, London** **Thomas Junghanss, Heidelberg**
10^{30}-11^{00}	**Break**	

11^{00}-12^{30}	• Internationally adopted children and screening for infectious diseases, are we doing all for final diagnosis? • Serological diagnosis of strongyloidiasis • Preliminary results: reduced-dose intradermal meningococcal vaccination using quadrivalent vaccine • Unrecognized infectious diseases in children migrating to Europe • ESBL carriage follow-up in international travellers: update and preliminary study results	**Antoni Soriano Arandes, Barcelona** **Andrea Angheben, Negrar** **Emile Jonker, Leiden** **Moritz Vogel, Heidelberg** **Esther Künzli, Basel**
12^{30}-13^{30}	**Lunch**	
13^{30}-14^{45}	• HERACLES project and the new European registry for echinococcosis • Yellow fever vaccine serology – IFA vs PRNT • Attenuated malaria parasites • The role of clinical management and infection control in reducing emerging infectious diseases threats	**Andrea Angheben, Negrar** **Emile Jonker, Leiden** **Meta Roestenberg** **Matthieu Mechain, Bordeaux**
14^{45}-16^{30}	**Clinical case presentations** • Buruli ulcer with contamination • A worm in the eye.... of the white man • A case of a traveller returning from Sri Lanka with fever, high inflammatory markers and a pustular rash • Hemoptysis & a pulmonary nodular mass lesion	 **Olivier Bouchaud, Paris** **Juan Cuadros Gonzáles, Madrid** **Andreas Müller, Würzburg** **Andreas Müller, Würzburg**
16^{30}-16^{45}	**Farewell**	**Jakob Cramer, Hamburg**

TropNet
European Network for Tropical Medicine and Travel Health

BNITM
Bernhard-Nocht-Institut für Tropenmedizin

Swiss TPH
Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse

Welcome to the 15th TropNet Workshop on Imported Infectious Diseases

11th – 12th April 2014

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Swiss TPH

Report of the steering committee & coordinator

- Membership issues
- The TropNet platforms: Where are we and how do we proceed ?
- The 2013 figures on imported diseases
- Report on ongoing TropNet studies & studies with participation of TropNet centres
- ECTMIH 2015 in Basel & a `TropNet preconference Travel Medicine Course´

Membership issues

currently **71** member sites
(no changes)

The TropNet platforms

Research

- Coordination & support for individual research groups working on communicable & non-communicable diseases:
  - Treatment of malaria
  - Dengue/Chikungunya
  - Cutaneous leishmaniasis
  - MRSA in travelers
  - Haemolyis & Artemisinines
  - Giardia treatment
  - ...

Policy development

- Harmonisation of European recommendation & guidelines to establish & provide:
  - evidence-based travel advice
  - standards in post-travel diagn. & therapeutic procedures of imported infectious diseases
- Interaction with national societies WHO, ECDC, FESTMIH, ENIVD, EuroTravNet, CDC

Teaching & Training

- Development of a curriculum / modules for a European ISTM-prep course = a TropNet Travel Medicine Course
- ECTMIH 2014 preconference Travel Medicine Course
- Setup and coordination of "hands on" training within the network

Surveillance / reporting

- Network-intern yearly report on imported diseases
- Web-based communication platform to discuss:
  - emerging diseases
  - suspicious syndromes
  - discussion & follow-up unusual events / cases

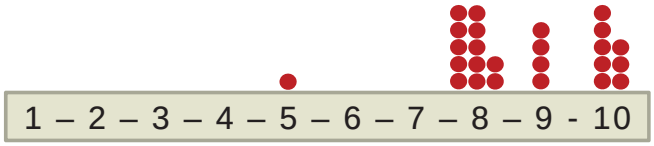
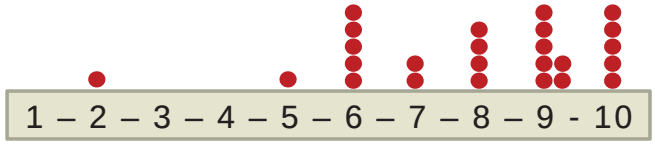
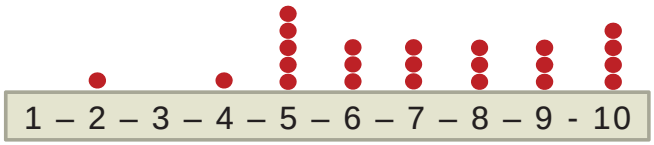
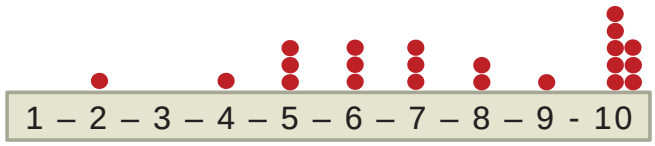
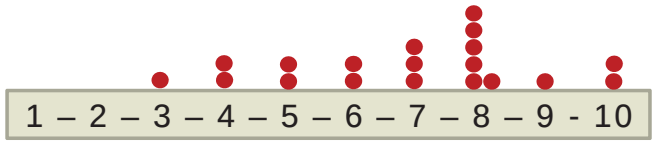
Network resources

- Database / directory:
  - Site portraits (services, resources, research)
  - Sources & network stock-list of orphan drugs
  - Web-based communication platform ("FORUM")
- Downloadable information material for councelling travelers

Public

- Website:
  - Presentation of the background, partnerships & activities of the network
  - Updated surveillance news on global outbreak situation

Survey on aims & direction of the network

n = 25	Approval	Ranking of importance
Collaborative research	100%	
Policy development	100%	
Surveillance / reporting	96%	
Network resources	96%	
Teaching & Training	90%	

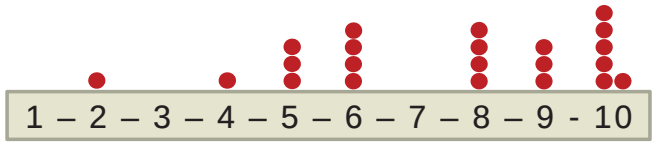
Collaborative research

Willingness to implement a own research project: 60%

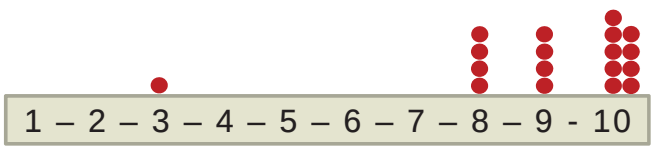
Interest in receiving support to develop own research project: 60%

Willingness to contribute to a research project: 88%

Project with need for ethical clearance



Project without need for ethical clearance



Collaborative research

Ranking of perceived obstacles:

1. Shortage of time / shortage of staff
2. Financial issues
3. Shortage of cases
4. Need for ethical board review

Willingness to lead / contribute

Research

- Leo Visser
- Thomas Zoller
- Angela Corpolongo
- Henrik Nielson
- Toni Seriano
- Israel Molina
- Graham Fry

Policy development

- Christoph Hatz
- Guido Calleri
- Andreas Neumayr

Teaching & Training

- Christoph Hatz
- Andreas Neumayr

Surveillance / reporting

Contribution to `surveillance news on global outbreak situation´:

- Joaquim Gascon
- Guido Calleri
- Andreas Neumayr
- Anna Beltrame
- Juan Cuadros
- Toni Seriano

Travel Medicine Info Material

- Jan Clerinx
- Andreas Neumayr
- Rogelio López-Vélez [Migrant health issues]
- (Graham Fry)

Website

- Thomas Zoller
- Andreas Neumayr

Possible additional strategies

Research

- FP7
- Horizon 2020
- Private Foundations at National level
- Industry

Policy development

- ECDC
- National Societies
- National Health Authorities
- WHO (collaborating centre)

Teaching & Training

- TropEd
- Rotation of hosting institutes
- Institutional modules

Surveillance / reporting

Contribution to `surveillance news on global outbreak situation´

Link with ECDC/EuroTravNet or collaboration?

Travel Medicine Info Material

- Collaboration with extra-European institutions/groups
- Financial industry support (several sponsors)

Website

The TropNet platforms

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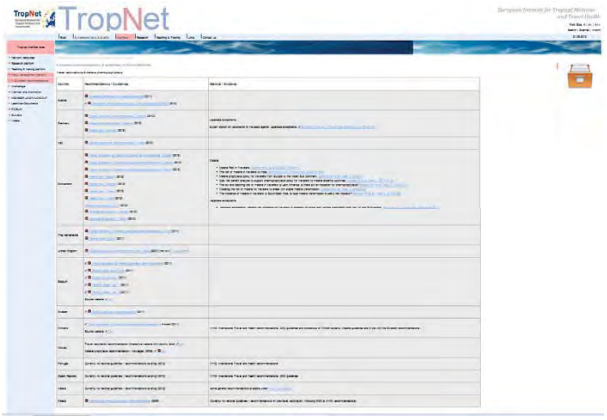
European recommendations & guidelines in Tropical & Travel Medicine

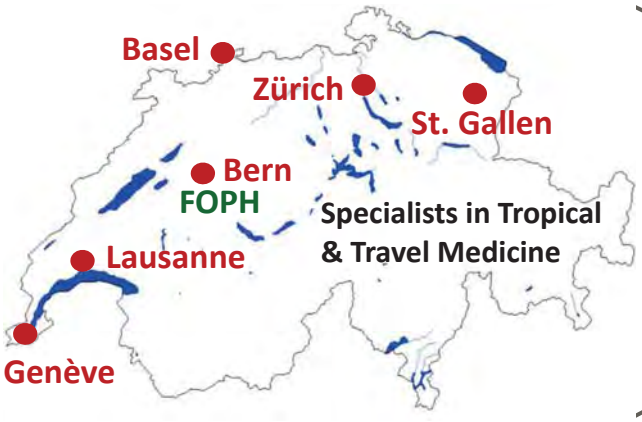


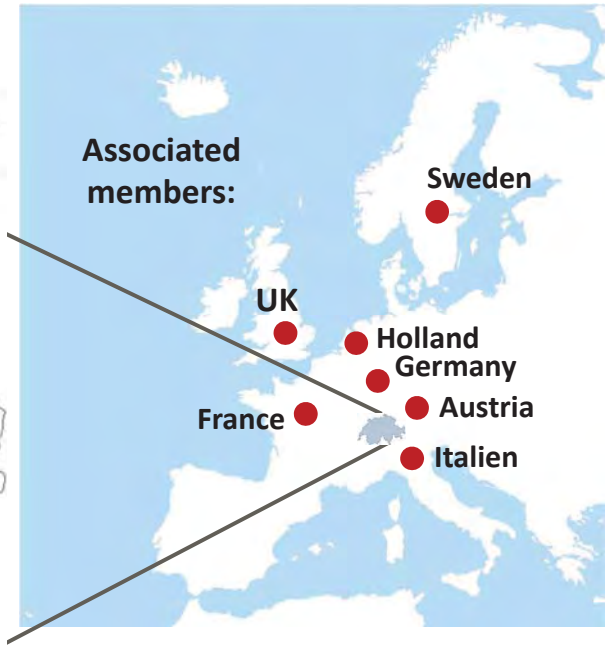
`Evidence-based European Recommendation Initiative based on Common sense´ (EERIC)

Summary analysis of current situation in the frame of a MD/MS thesis ?

Expert Committee for Travel Medicine (ECTM)

Expertenkomitee für Reisemedizin
Comité d'experts pour la médecine des voyages
Comitato di esperti per la medicina di viaggio
Expert committee for travel medicine





Aims of ECTM

- Consensus on rational recommendations for travel medicine
- Optimising pre- and post-travel health advice in European countries
- Improvement of travellers‘ compliance abroad
- Economically independent partner(s) for travel medicine issues at national and international levels

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ECTMIH 2015

The Swiss Society of Tropical Medicine and Parasitology invites you to come to Basel

Swiss TPH
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Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse

The Swiss Tropical and Public Health Institute in Basel

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Swiss TPH

TropNet preconference Travel Medicine Course

Target audience: Travel Medicine Specialists
Format: One-day pre-congress course
Saturday, September 5th 2015

- ✓ Arthropode-borne diseases & prevention
- ✓ Gastrointestinal disorders and management
- ✓ Importance of travel medicine vaccines
- ✓ High risk travel (accidents, mountains etc.)
- ✓ New approaches in travel risks and advice

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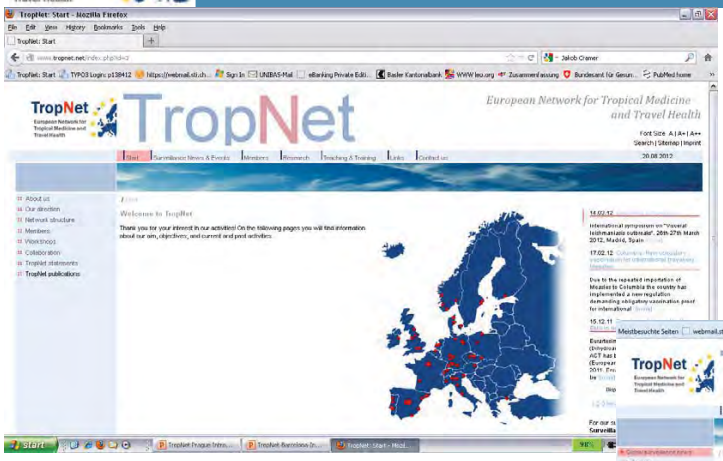
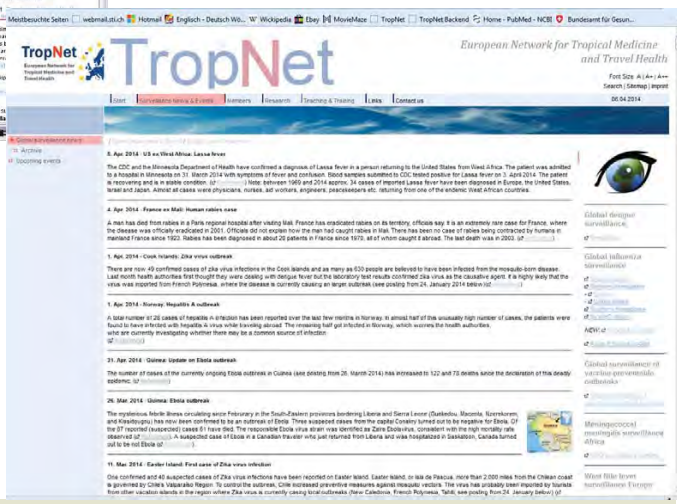


Surveillance News

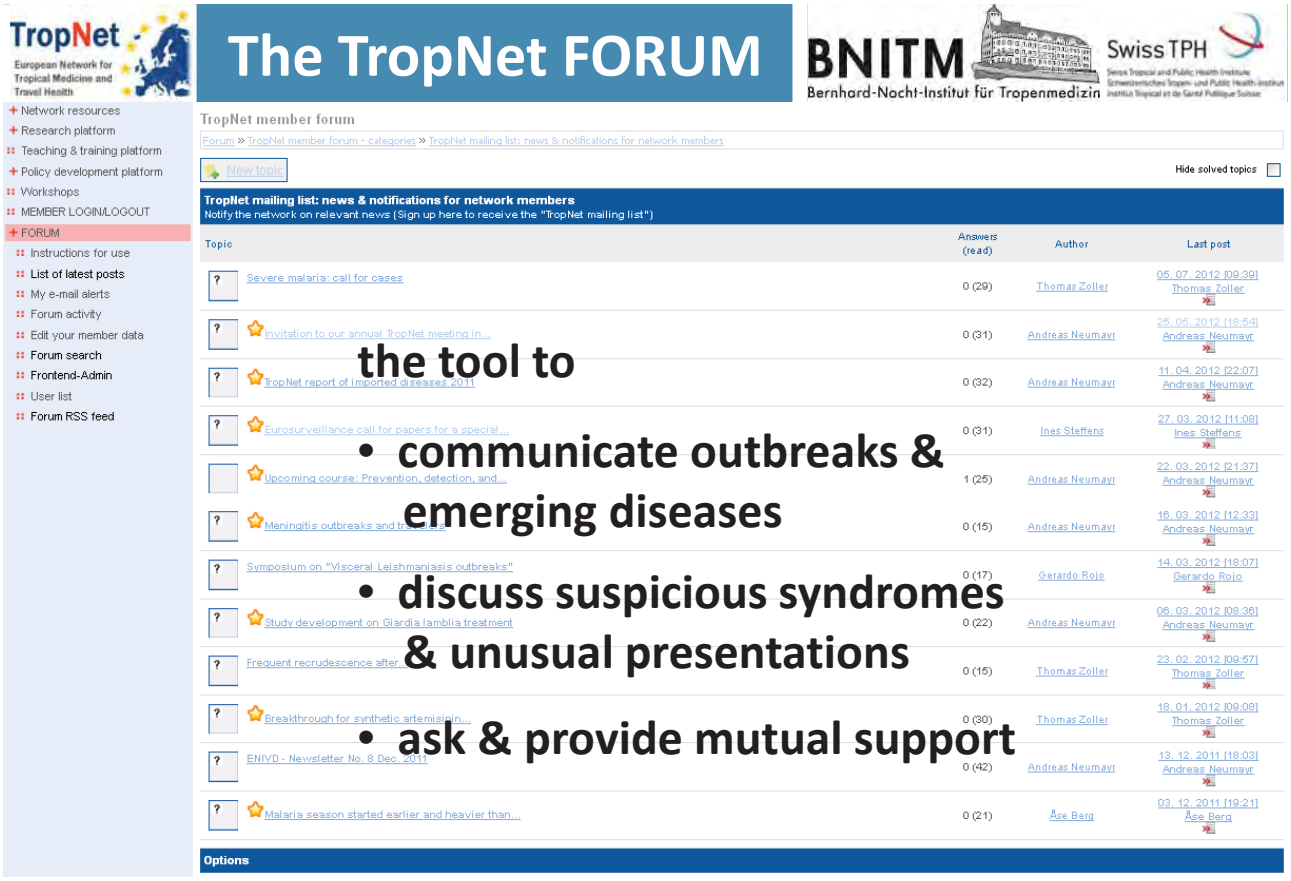


www.tropnet.net

&

www.tropnet.eu

The TropNet FORUM



the tool to

- communicate outbreaks & emerging diseases
- discuss suspicious syndromes & unusual presentations
- ask & provide mutual support

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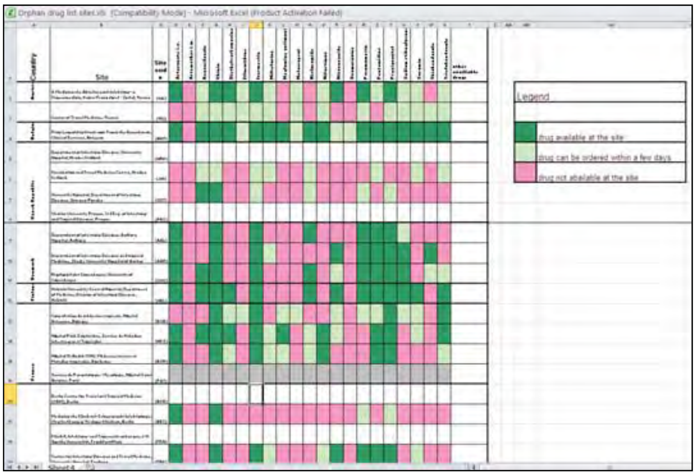
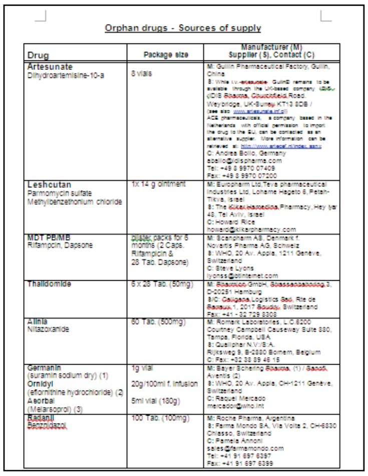
Orphan drugs: network stock-list & sources




Orphan drugs - Sources of supply

Drug	Package size	Manufacturer (M) Supplier (S), Contact (C)

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The 2011 figures on imported diseases
40 of 67 sites

Malaria	1043	(871 *falc.*; *172 non-falc.*)
Giardiasis	1089	
Schistosomiasis	672	
Amoebiasis	381	
Dengue	341	
Leishmaniasis	237	(185 CL & ML; 52 VL)
Rickettsiosis	118	
Loiasis	47	
Chikungunya	27	

The 2012 figures on imported diseases

21 of 68 sites

Malaria	552	(461 *Pf; 52 Pv; 28 Po; 12 Pm)*
Giardiasis	588	
Schistosomiasis	379	
Amoebiasis	167	
Dengue	250	
Leishmaniasis	57	(28 *CL*; 4 *ML*; 25 *VL*)
Rickettsiosis	56	
Typhoid fever	24	
Loiasis	8	
Chikungunya	4	
Sarcocystis	18	

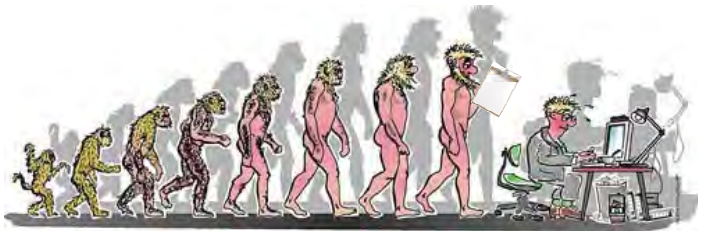
The 2013 figures on imported diseases

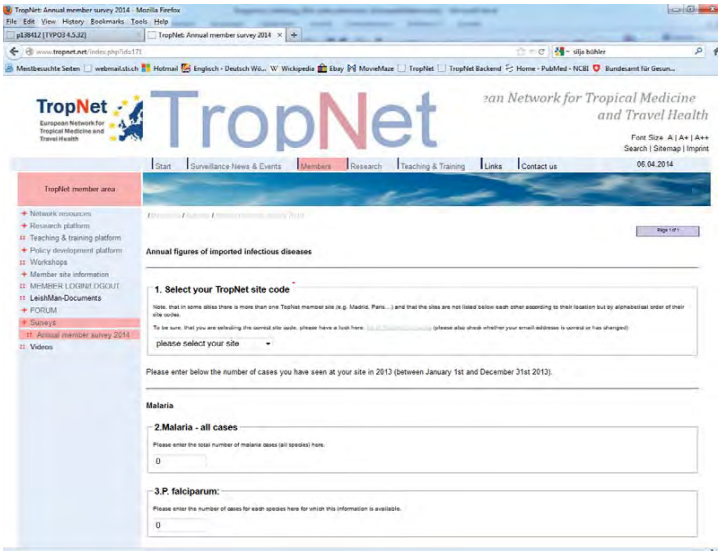
24 of 71 sites

Malaria	785	(673 *Pf; 56 Pv; 42 Po; 14 Pm)*
Giardiasis	738	
Schistosomiasis	284	
Amoebiasis	174	
Dengue	350	
Leishmaniasis	161	(133 *CL*; 2 *ML*; 26 *VL*)
Rickettsiosis	90	
Typhoid fever	42	
Loiasis	19	
Chikungunya	29	
Sarcocystis	8	

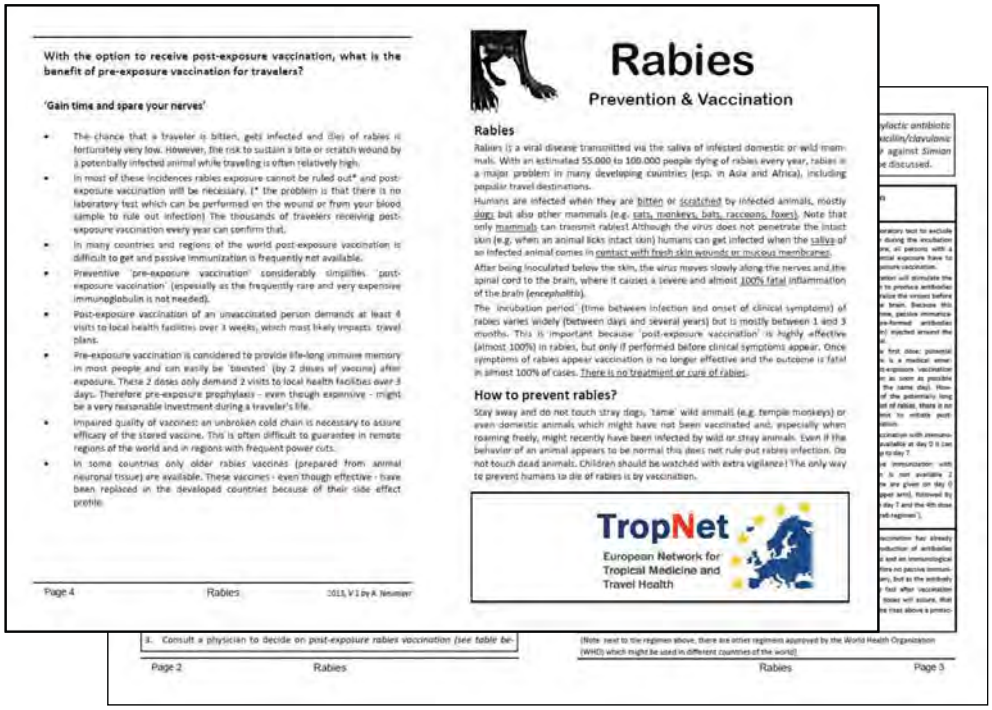
all reported by Munich

- 1 case (Antwerp, Belgium in 2013)
- 2 cases (Paul-Lechler Hospital Tübingen, Germany in Oct. 2013)
- **1 case Helsinki, Finnland 2014**





Development of TropNet travel medicine info material



With the option to receive post-exposure vaccination, what is the benefit of pre-exposure vaccination for travelers?

'Gain time and spare your nerves'

- The chance that a traveler is bitten, gets infected and dies of rabies is fortunately very low. However, the risk to sustain a bite or scratch wound by a potentially infected animal while traveling is often relatively high.
- In most of these incidences rabies exposure cannot be ruled out* and post-exposure vaccination will be necessary. (* the problem is that there is no laboratory test which can be performed on the wound or from your blood sample to rule out infection) The thousands of travelers receiving post-exposure vaccination every year can confirm that.
- In many countries and regions of the world post-exposure vaccination is difficult to get and passive immunization is frequently not available.
- Preventive 'pre-exposure vaccination' considerably simplifies 'post-exposure vaccination' (especially as the frequently rare and very expensive immunoglobulin is not needed).
- Post-exposure vaccination of an unvaccinated person demands at least 4 visits to local health facilities over 1 week, which most likely impacts travel plans.
- Pre-exposure vaccination is considered to provide life-long immune memory in most people and can easily be 'boosted' (by 2 doses of vaccine) after exposure. These 2 doses only demand 2 visits to local health facilities over 3 days. Therefore pre-exposure prophylaxis - even though expensive - might be a very reasonable investment during a traveler's life.
- Impaired quality of vaccines: an unbroken cold chain is necessary to assure efficacy of the stored vaccine. This is often difficult to guarantee in remote regions of the world and in regions with frequent power cuts.
- In some countries only older rabies vaccines (prepared from animal neuronal tissue) are available. These vaccines - even though effective - have been replaced in the developed countries because of their side effect profile.

Page 4 Rabies 2013, V 1 by A. Neumayr

Rabies

Prevention & Vaccination

Rabies

Rabies is a viral disease transmitted via the saliva of infected domestic or wild mammals. With an estimated 55.000 to 100.000 people dying of rabies every year, rabies is a major problem in many developing countries (esp. in Asia and Africa), including popular travel destinations.

Humans are infected when they are bitten or scratched by infected animals, mostly dogs; but also other mammals (e.g. cats, monkeys, bats, raccoons, foxes). Note that only mammals can transmit rabies! Although the virus does not penetrate the intact skin (e.g. when an animal licks intact skin) humans can get infected when the saliva of an infected animal comes in contact with fresh skin wounds or mucous membranes.

After being inoculated below the skin, the virus moves slowly along the nerves and the spinal cord to the brain, where it causes a severe and almost 100% fatal inflammation of the brain (*encephalitis*).

The 'incubation period' (time between infection and onset of clinical symptoms) of rabies varies widely (between days and several years) but is mostly between 1 and 3 months. This is important because 'post-exposure vaccination' is highly effective (almost 100%) in rabies, but only if performed before clinical symptoms appear. Once symptoms of rabies appear vaccination is no longer effective and the outcome is fatal in almost 100% of cases. There is no treatment or cure of rabies.

How to prevent rabies?

Stay away and do not touch stray dogs, 'tame' wild animals (e.g. temple monkeys) or even domestic animals which might have not been vaccinated and, especially when roaming freely, might recently have been infected by wild or stray animals. Even if the behavior of an animal appears to be normal this does not rule out rabies infection. Do not touch dead animals. Children should be watched with extra vigilance! The only way to prevent humans to die of rabies is by vaccination.

TropNet European Network for Tropical Medicine and Travel Health

3. Consult a physician to decide on *post-exposure rabies vaccination (see table be-*

Page 2 Rabies

(Note: next to the regimen above, there are other regimens approved by the World Health Organization (WHO) which might be used in different countries of the world)

Rabies Page 3

Focus: core information for travellers on relevant health issues

	Suggestion:
Traveler's diarrhea	_____
Protection against arthropods	_____
Malaria	_____
Dengue	_____
Chikungunya	_____
Hepatitis A	_____
Hepatitis B	_____
Influenza	_____
Japanese encephalitis	Andreas Neumayr
Tick-borne encephalitis	_____
Meningococcal meningitis	_____
Bee & wasp sting allergies	_____
Schistosomiasis	Jan Clerinx ?
Road traffic accidents	_____
Scuba diving	_____
STDs	_____
Venomous & poisonous animals	Thomas Junghanss ?
Typhoid fever	_____
Migrants / Visting friends & relatives	Rogelio López-Vélez ?

Format: Word document -> send to us for converting into flyer/leaflet format

Report on ongoing TropNet studies & studies with participation of TropNet centres

Currently ongoing TropNet studies

➔ Artesunate for severe malaria in Europe

➔ **EU-FP7 DengueTools & TropNet study**

Sentinel surveillance of imported dengue in returning travelers: trends and virus evolution

➔ **LeishMan working group**

Harmonization of clinical management & diagnostic methods for cutaneous & mucosal leishmaniasis in Europe

➔ **Proof of concept study of Eurartesim® in patients with imported uncomplicated *P. vivax* malaria**

Current TropNet participation

➔ **Safety registry of Eurartesim® - REGISTRAT-MAPI**

Treatment of uncomplicated malaria in returning travellers with Dihydroartemisinin/Piperaquine (France, Germany, Italy, Belgium, The Netherlands, Spain, UK)

➔ **Pregnancy registry of Eurartesim® - Sigma Tau**

European pregnancy registry

➔ **StaphTrav - European network on imported *S. aureus***

Antibiotic resistance testing and molecular typing of imported *S. aureus* in returning travelers

TropNet study: Artesunate for severe malaria in Europe

Number of recruited patients: **160**

Thomas Zoller
MD, MSc, DTM&H

EU-FP7 joint DengueTools & TropNet study:

Sentinel surveillance of imported dengue in returning travelers: trends & virus evolution

Number of recruited patients: **~ 250**
(started Sept. 2011, ending Sept. 2014
- potentially extended for 6 months)

Data analysis in the frame of a MD/MS thesis ?

LeishMan working group

Harmonization of clinical management & diagnostic methods for cutaneous & mucosal leishmaniasis in Europe

- **Improving treatment based on molecular species differentiation**
- **Harmonizing the molecular diagnostic methods** for rapid diagnosis and species determination
- **Harmonizing the therapeutic guidelines** for cutaneous and mucosal leishmaniasis in Europe

Current situation within Europe

- **Clinical management of CL & ML**
  - various treatment recommendations differentiating between Old and New World leishmania species are available
  - treatment recommendations are based on data from endemic regions
- **Species specific treatment**
  - species specific treatment recommendations are available
  - not evaluated in travelers
- **Genotyping of leishmania species**
  - done in many centers / widely available
  - no comparative evaluation / validation of the different methods

Objectives of collaborative project

- evaluation of the applied treatment protocols and outcomes with respect to the infecting parasite species
- comparison of all currently applied genotyping techniques
- obtaining genetic sequence information of all clinical isolates
- establishing a common data base of molecular and clinical data
- **long-term goal: standardization of species specific treatment protocols based on molecular species typing**

Selection of treatment regimen

- each centre is free to choose a treatment regimens based on state of the art knowledge / own experience
- species specific treatment recommendations have been compiled by the Leishman working group

Inclusion criteria

1. all patients with parasitologicaly confirmed cutaneous or mucosal leishmaniasis
2. clinical data **and** samples available
3. patient informed consent regarding the use of biopsy material and data

Exclusion criteria

- none
- pregnancy is not a criterion of exclusion, but treatment has to be adapted or postponed after delivery

The Leishman consortium

8 European countries, 17 institutions

Belgium (1 institution)

France (3 institutions)

Germany (1 institution)

Netherlands (4 institutions)

Portugal (2 institution)

Spain (2 institution)

Switzerland (1 institution)

UK (3 institutions)

Coordinators

Clinical group: Blum, Johannes

Molecular diagnostic group: Felger, Ingrid

Steering committee - members

Clinical group: Bailey, Mark
Blum, Johannes (coordinator clinical group)
Buffet, Pierre

Molecular diagnostic group: Bart, Aldert
Van der Auwera, Gert

Where we are:

- ☑ setup of database
- ☑ data collection and entering ongoing

Publications:

Clinical group:

- ☑ Local or systemic treatment for new world cutaneous leishmaniasis? re-evaluating the evidence for the risk of mucosal leishmaniasis. (International Health 2012;4:153-163)
- ☑ Clinical aspects and management of cutaneous leishmaniasis in rheumatoid patients treated with TNF-α antagonists (Travel Med Infect Dis. 2013)
- ☑ **LeishMan Recommendations for Treatment of Cutaneous and Mucosal Leishmaniasis in Travelers, 2014 (J Trav Med 2013)**

Sigma-Tau & TropNet study:

Proof of concept study of Eurartesim® in patients with imported uncomplicated *P. vivax* malaria

Study outline

Study sites: multicentre study within the TropNet network

(sites with a considerable number of *P. vivax* cases in Italy , Spain, France, Germany, Switzerland, The Netherlands, Israel)

Study subjects: 100 adult patients (18 - 65 years old), male & female, affected by uncomplicated *P. vivax* malaria. ECG day 0

Setting: patients may be followed up as in- or out-patients

Timeframe: study recruitment period: 16 months (starting Oct. 2013)

each patient will remain in the study for 42 days:

D1, D2, D3 – D7 – D21 – D42

Study objectives

Primary objective: uncorrected adequate clinical and parasitological responce (ACPR) at Day 21

Secondary objectives:

- Proportion of aparasitemic patients (at different visits)
- Proportion of afebrile patients (at different visits)
- Uncorrected adequate clinical and parasitological response at Day 42
- Proportion of patients with treatment failure

Safety & tolerability of the drug:

- Adverse events occurrence
- Change in haematology, blood chemistry and vital signs (no ECG follow-up)

Study sites & status

ITALY: study approved by coordinating EC (Brescia) & RA (AIFA)
1. BRESCIA - Clinica di Malattie Infettive e Tropicali, Spedali Civili di Brescia
2. VERONA - Centro per le Malattie Tropicali, Ospedale S. Cuore, Negrar
3. ROMA - Centro di Malattie Tropicali - INMI Spallanzani

SWITZERLAND: study approved by coordinating EC (Basel) & RA (Swissmedic)
4. BASEL (study coordinator) - Swiss Tropical and Public Health Institute
5. BERN - Bern University Hospital
6. LAUSANNE - Policlinique Médicale Universitaire

FRANCE: study approved by EC – pending approval by RA (ANSM)
7. BORDEAUX - Hôpital St André-CHU, Médecine interne et Maladies Tropicales

SPAIN: study approved by coordinating EC (Hospital Clinic Barcelona) – pending approval by RA (AEMPS)
8. BARCELONA - CRESIB-Hospital Clinic, Barcelona
9. BARCELONA 2 - Hospital Vall d'Hebron, Barcelona
10. MADRID - Tropical Medicine & Clinical Parasitology, Hospital Ramon y Cajal

THE NETHERLANDS: study approved by EC & RA (CCMO)
11. LEIDEN - Leiden University Medical Centre

GERMANY: study in the course of submission to ECs & AR (BFARM)
12. MUNICH - Dep. of Infectious Diseases & Tropical Medicine, University of Munich
13. BERLIN - Medizinische Klinik mit Schwerpunkt Infektiologie, Charite

TropNet European Network for Tropical Medicine and Travel Health | sigma-tau REGISTRAT·MAPI A Global Late Phase CRO | Swiss TPH Swiss Tropical and Public Health Institute Schweizerisches Tropen- und Public Health-Institut Institut Tropical et de Santé Publique Suisse

Safety & Pregnancy Registries of Eurartesim®

- **Safety registry** **(some TropNet Centres involved)**

  A European multi-centre study evaluating QTc prolongation with regard to co-morbidities and concomitant medications; monitoring patterns of drug utilization; treatment-assoc. adverse events

- **Pregnancy registy** **(some TropNet Centres involved)**

  A European multi-centre pregnancy registry for patients exposed to Eurartesim® for the treatment of malaria whilst pregnant

Pregnancy Registry

Study objectives:

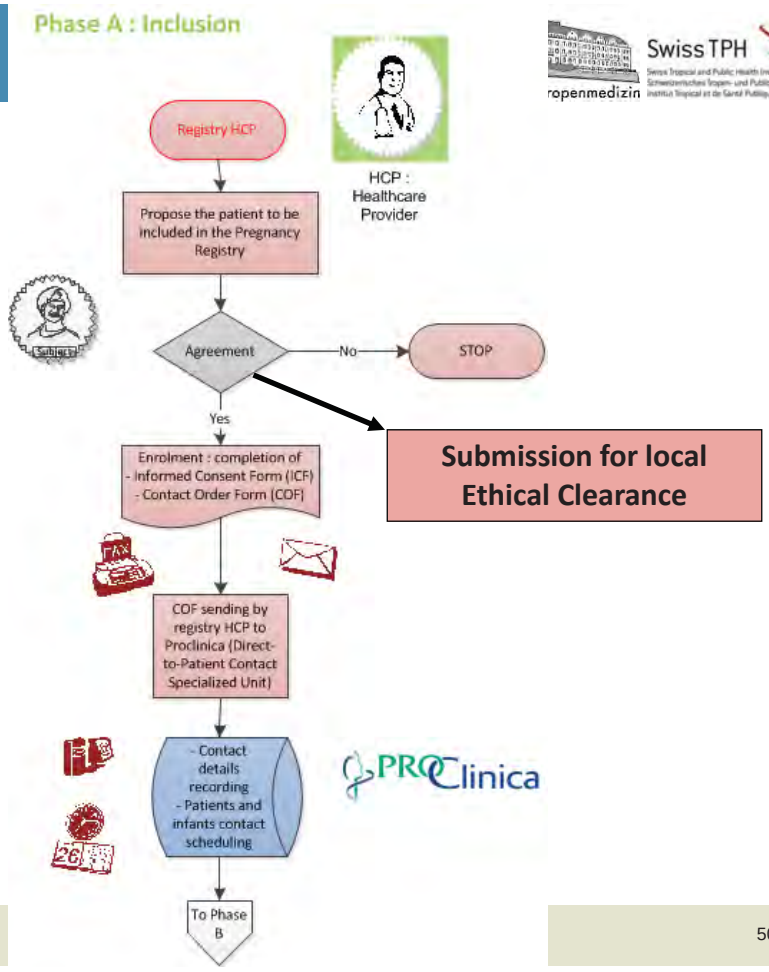
1. The primary objective is to assess the live birth incidence of minor and major congenital birth defects following exposure to Eurartesim® whilst pregnant or in the one month (30 days) prior to conception.
2. The secondary objective is to assess both maternal and fetal outcome following exposure to Eurartesim™ whilst pregnant or in the one month (30 days) prior to conception.

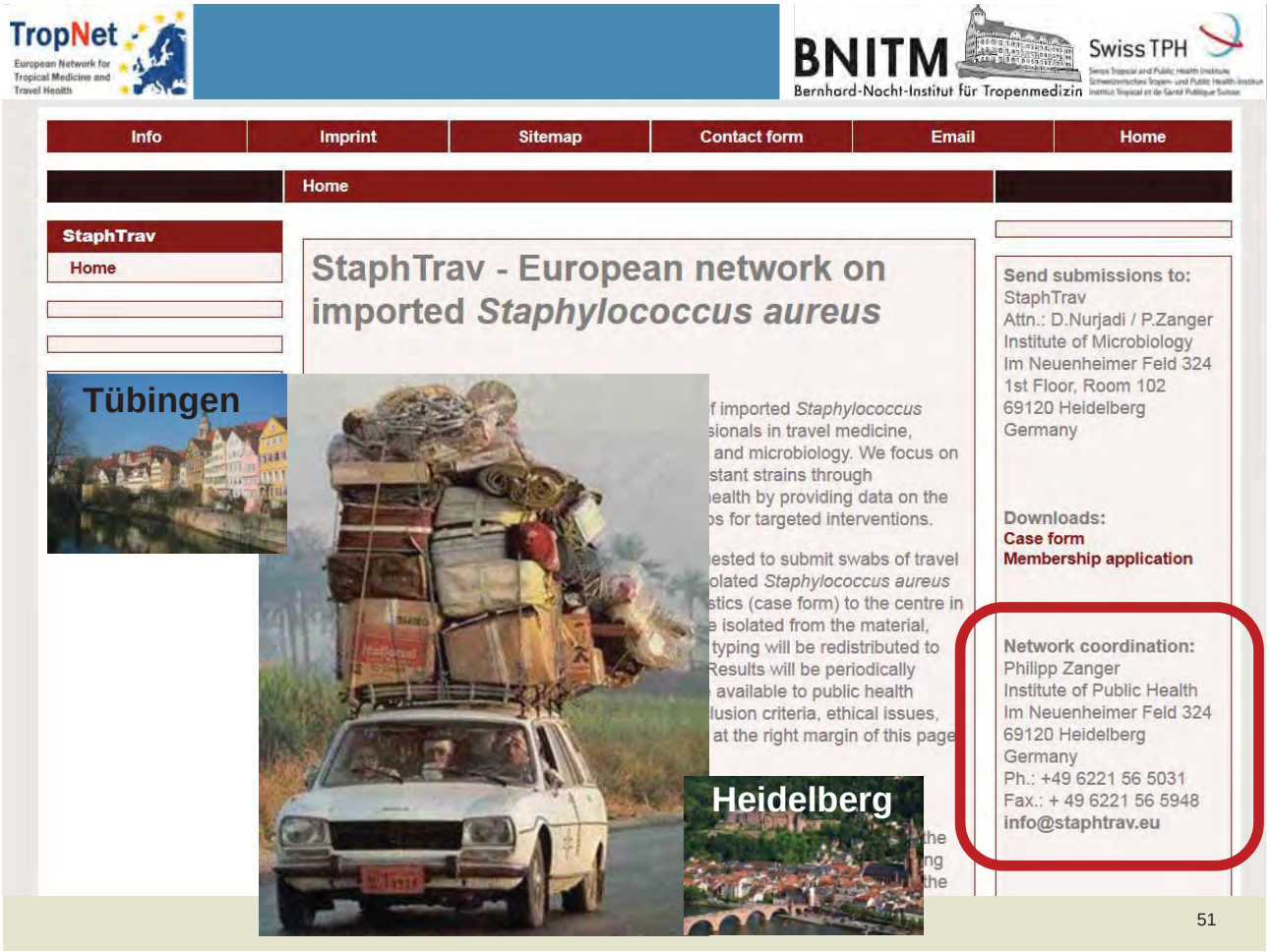
Activity	Expected Time
Set-up period	**Nov 2011 – Aug 2012**
Recruitment period	**Sept/Oct 2012 - 2017**
Follow-up period	**2018 - 2019**
Close out period	**2019**

Pregnancy registry

Patient Contact Process:

Present status: no case





StaphTrav -

a network for surveillance of imported *Staphylococcus aureus*

Philipp G. Zanger

Upcoming TropNet studies

➔ **TropNet study HaemoART**

Study on haemolysis under artemisinin therapy

➔ **TropNet studies GiardiaTreat & GiardiaREF**

Tolerability of 5-nitroimidazole 1st-line regimens &
RCT of 2nd-line regimens for refractory Giardiasis

➔ **TropNet safety surveillance of life vaccines in immunocompromised persons**

TropNet artemisinin drug safety studies

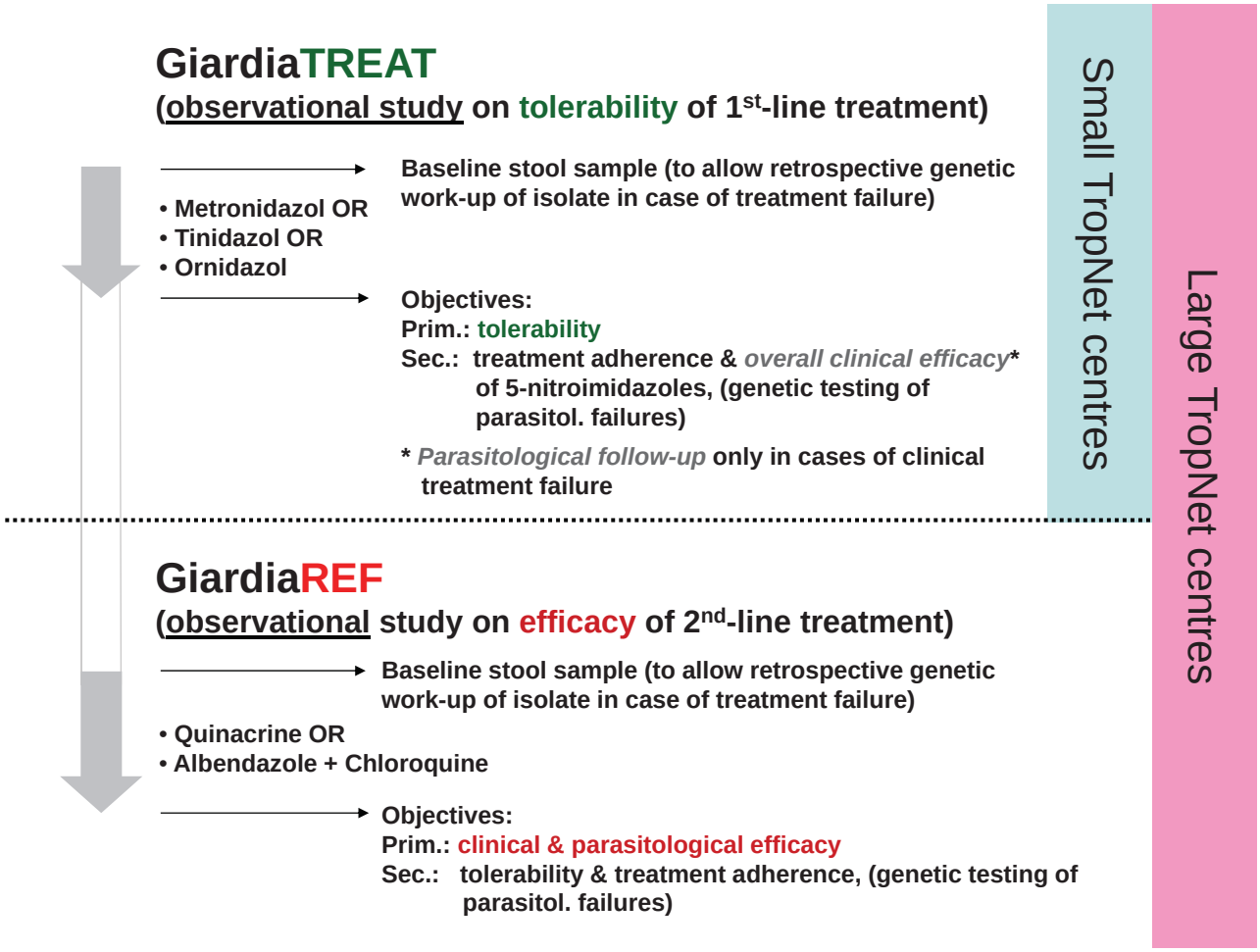
HAEMO-ART, SMPS & TOX-ART

GiardiaTREAT & GiardiaREF

1st line	regimen
Metronidazole	400 mg TID for 5 days
Metronidazole	500 mg TID for 7 days
Metronidazole	250 mg TID for 5-7 days
Metronidazole	500 mg TID, days ?
Metronidazole	750 mg - 1g for 7 days
Metronidazole	250 mg TID for 5-7
Metronidazole	500 mg BID for 5 days
Metronidazole	-
Metronidazole	250 mg TID for 5 days
Metronidazole	-
Metronidazole	500 mg TID for 7 days
Metronidazole	500 mg TID for 7 days
Metronidazole	250 mg TID for 10 days
Metronidazole	250 mg TID for 5 days
Metronidazole	250 mg TID for 7 days
Metronidazole	400 mg TID for 6 days
Metronidazole	500 mg BID for 5 days
Metronidazole	500 mg TID for 7 days
Metronidazole	250 mg TID for 10 days
Metronidazole	2 g OD for 3 days or 250 mg TID for 5 days
Metronidazole	400 mg TID for 7 days
Metronidazole	400mg TID for 6 days
Metronidazole	400 mg TID for 7 days
Metronidazole	250mg TID for 5 days
Metronidazole	500mg TID for 7 days
Metronidazole	-
Tinidazole	2 g single dose
Tinidazole	2 g single dose
Tinidazole	2 g single dose
Tinidazole	2 g single dose
Tinidazole	-
Tinidazole	2 g single dose, repeated after 5 days
Tinidazole	2 g single dose, repeated after 5 days
Tinidazole	-
Tinidazole	-
Tinidazole	-
Tinidazole	2 g single dose, repeated after 7 days
Tinidazole	2 g single dose
Tinidazole	2g single dose
Tinidazole	2 g single dose
Tinidazole	-
Tinidazole	2 g single dose
Tinidazole	-
Tinidazole	2g single dose
Tinidazole	2 g single dose, repeated after 14 days
Tinidazole	2g once daily for 2 days
Tinidazole	2 g single dose, repeated on day 10-14
Ornidazole	-
Ornidazole	500 mg BID for 5 days
Ornidazole	500 mg BID for 7 days
Albendazole	-
Nitaxozanide	500 mg BID for 3 days
Paramomycin	25-35 mg/kg/day in 3 doses for 5-10 days

2nd line	regimen
Metronidazole	600 mg TID for 7 days
Tinidazole	2 g once daily, - about duration
Tinidazole	2 g single dose
Tinidazole	-
Tinidazole	2 g single dose
Tinidazole	2 g once
Tinidazole	2 g single dose
Albendazole	-
Albendazole	400 mg TID for 5 days
Albendazole	-
Albendazole	-
Albendazole	400 mg TID for 7 days
Albendazole	400 mg QID for 5 days
Albendazole	400 mg once daily for 5 days
Albendazole or Mebendazole	-
Paromomycin	500 mg TID for 9 days
Paromomycin	500 mg TID for 7 days
Paramomycin	500 mg TID for 10 days
Nitazoxanide	Nitazoxanide 500 mg BID for 3 days
Nitazoxanide	500 mg BID for 3 days
Quinacrine	100 mg TID for 5 days
Metronidazole + Albendazole	Metronidazole: 400mg TID for 6 days + Albendazole: 400mg OD for 5-10 days
Metronidazole + Albendazole	Metronidazol 250 mg BID + Albendazole 400 mg BID for 7 days
Metronidazole + Paromomycin	Metronidazole 750mg TID for 7 days + Paromomycin 30mg/kg in 3 doses for 7 days
Metronidazole + Paromomycin	Metronidazol 2 g for 3 days followed by Paromomycin 25-35 mg/kgKG for 7-10 days
Combination therapy, no details	-
Tinidazole	2 g OD for 3 days
Tinidazole	2 g OD for 3 days
Metronidazole	250 mg TID for 5-7 days
Metronidazole	500 mg TID für 7 days
Metronidazole	-
Metronidazole	400 mg TID for 5 days (or 2g OD for 3 days)
Metronidazole	400 mg TID for 5 days
Metronidazole	-
Albendazole	-
Albendazole	-
Albendazole	400 mg TID for 7 days
Albendazole	400 mg once daily for 5 days
Quinacrine	100 mg TID for 5 days
Quinacrine	100 mg TID for 5 days
Quinacrine	500 mg TID for 5 days
Quinacrine	100 mg TID for 5 days
Nitazoxanide	-
Metronidazole + Albendazole	Metronidazole 400mg TID for 6 days + Albendazole 400mg OD for 5-10 days
Metronidazole + Paromomycin	Metronidazole 750mg TID for 7 days ± Paromomycin 30mg/kg in 3 doses for 7 days
Albendazol + Paramomycin	Albendazole 400 mg BID + Paromomycin 750 mg TID for 5 days
Albendazole + Paromomycin	400 mg TID for 7 days followed by Paromomycin 500 mg TID for 7 days
Metronidazole	-
Albendazole	400 mg BID for 3 days
Albendazole + Paromomycin	Paramomycin 500 mg TID + Albendazole 400 mg QID for 5 days
Metronidazole	-
Quinacrine	100 mg TID for 5 days
Quinacrine	100 mg TID for 5 days

TropNet survey on Giardia treatment:
53 centres, 39 different regimens, 7 drugs alone or in combination in different dosage & duration



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Swiss TPH
Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse

GiardiaTREAT

Tolerability of 1st-line *Giardia lamblia* treatment regimens

Background:

The median efficacy of 5-Nitroimidazole based 1st-line treatment regimens is similar, considered to achieve approx. 90% of clinical and parasitological cure.

Not many data exist on the tolerability of the different drug regimens, which is important to choose the regimen with the lowest rate of associated side-effects.

Study design:

Prospective, observational, open-label, multi-centre study

Optional 1st-line treatment regimens under evaluation:

1. Metronidazole 400 - 500mg* TID x 7 days
2. Tinidazole 2g OD x 1 day
3. Ornidazole 2g OD x 1 days

(*note: the dosage range of Metronidazole is based on the difference in local availability of tablets containing 400mg or 500mg respectively)

Main objective:

To evaluate the tolerability of 5-nitroimidazole based 1st-line *G. lamblia* treatment regimens

Additional objectives:

1. To assess the rate of treatment adherence and the rate of side-effect related treatment cessation of different 5-nitroimidazole based 1st-line treatment regimens
2. To assess the overall clinical efficacy of 5-nitroimidazole based 1st-line treatment regimens
3. To collect geographic data (continent/country where the infection was acquired) in order to evaluate regional differences in clinical treatment efficacy of 5-nitroimidazole based 1st-line treatment regimens
4. To obtain baseline stool samples for subsequent genetic analysis / resistance testing of *G. lamblia* isolates in cases of parasitological confirmed failure of 1st-line treatment

Inclusion criteria:

Any symptomatic person being tested positive for *G. lamblia* (by stool microscopy or stool antigen-test) with intestinal mono-infection is eligible for study inclusion.

Exclusion criteria:

- Patients who already received giardiasis-specific treatment for the current *G. lamblia* infection
- Patients with asymptomatic *G. lamblia* infection
- Patients with concomitant bacterial, helminthic or protozoal gastrointestinal infection (note: the presence of apathogenic protozoa [including *Blastocystis hominis*] is no exclusion criterion)
- Patients with contraindications (drug allergies, pregnancy, breast- feeding) for the listed drug regimens

Follow-up:

- Follow-up of the patients with assessment of tolerability and clinical efficacy of the assigned treatment regimen will be done ≥4 - ≤5 weeks after completing medical treatment by telephone, using a standardized questionnaire.
- In case the symptoms disappear after treatment, no control by stool microscopy will be performed.
- In case of persisting or relapsing symptoms, repetition of stool microscopy to test parasitological outcome will be done. Repetition of stool microscopy will be done earliest 2, latest 5 (≥2 - ≤5) weeks after completion of medical therapy.

Definition of clinical outcome:

- `Clinical cure´: absence of gastrointestinal symptoms at ≥4 - ≤5 weeks after finishing treatment.
- `Clinical improvement´: persisting gastrointestinal symptoms but improvement through medical treatment at ≥4 - ≤5 weeks after finishing treatment. To assess the subjective degree of clinical improvement, the patients will be asked to rate their persisting symptoms / max. experienced symptoms on the following, subjective scale: 10 – 20 – 30 – 40 – 50 – 60 – 70 – 80 – 90%
- `Clinical failure´: persisting gastrointestinal symptoms without improvement at ≥4 - ≤5 weeks OR relapse of the initial/similar symptoms at ≥4 - ≤5 weeks following transient resolution after finishing treatment.

Definition of parasitological outcome:

`Parasitological cure´: 3 stool samples tested negative by microscopy ≥2 - ≤5 weeks after finishing medical treatment

`Parasitological failure´: detection of *G. lamblia* by microscopy in a stool sample ≥2 - ≤5 weeks after finishing medical treatment

Storage of stool sample:

Before initiating medical treatment, a stool sample will be put aside and frozen at -80°C (alternatively -20°C) to allow later genetic analysis / resistance testing of the *Giardia lamblia* isolate in cases of `parasitological confirmed treatment failure´.

GiardiaREF

Efficacy of 2nd-line treatment

Background:

- Currently the `best´ 2nd-line treatment regimen for refractory giardiasis still needs to be defined.
- Quinacrine appears to be highly efficient and is already used by big centres, but it's availabilty is restricted.
  Therefore, a widely available and equally effective alternative treatment regimen is needed.
- As most clinicans would opt for a combination therapy and considering the wide availability of as well as existing data on Albendazole + Chloroquine this regimen may be an option.

Study design:

Prospective, observational, open-label, multi-centre study

Optional 2nd-line treatment regimens under evaluation:

1. Quinacrine 100mg TID x 5 d
2. Albendazole 400mg + Chloroquine 250mg BID x 5d

Main objective:

To assess the clinical and parasitological efficacy of quinacrine monotherapy and albendazole-chloroquine combination therapy for the treatment of refractory giardiasis after treatment with 5-nitroimidazole derivatives or other drugs.

Additional objectives:

1. To evaluate the tolerability of quinacrine monotherapy and albendazole-chloroquine combination therapy in the treatment of refractory giardiasis.
2. To assess treatment adherence and side-effect-related treatment cessation of quinacrine monotherapy and albendazole-chloroquine combination therapy in the treatment of refractory giardiasis.
3. To collect stool samples prior to 2nd-line treatment in order to allow subsequent genetic analysis / resistance testing of *G. lamblia* isolates in cases of parasitologically confirmed treatment failure of 2nd-line therapy.
4. To collect epidemiological data on the geographic background of infection.

Inclusion criteria:

Any person having clinically and parasitologically failed 1st-line *G. lamblia* treatment with a 5-nitroimidazole regimen (metronidazole, tinidazole, ornidazole, secnidazole), defined as being tested positive for *G. lamblia* by stool microscopy ≥2 weeks after completing medical treatment, is eligible for study inclusion.

To best possible exclude cases of reinfection, the upper time limit for study inclusion will be set at 3 months after completing 1st-line treatment.

Exclusion criteria:

- Patients with contraindications (drug allergies, pregnancy, breast-feeding) for the selected drug regimens.
- Female patients in child-bearing age, not able to conduct double contraception (hormonal methods [pill, coil]) combined with a mechanical method [condom, diaphragm]) during intake and over the `wash-out period´ of the selected study medication. The `wash-out´ period is anticipated to be equal to four half-lives of the used study drug

  Quinacrine: elimination $T_{1/2}$: ~14 days -> wash-out period 8 weeks;
  CQ + ABZ: CQ unproblematic; ABZ $T_{1/2}$: ~12 hours -> wash-out period 2 days
- Patients having received a non-5-nitroimidazole regimen as 1st-line *G. lamblia* treatment.
- Patients with concomitant bacterial, helminthic or protozoal gastrointestinal infection (note: the presence of apathogenic protozoa [including *Blastocystis hominis*] is no exclusion criterion)

Definition of parasitological outcome:

`Parasitological cure´: ≥2 stool samples tested negative by microscopy ≥2 - ≤5 weeks after finishing medical treatment

`Parasitological failure´: detection of *G. lamblia* by microscopy in a stool sample ≥2 - ≤5 weeks after finishing medical treatment

Storage of stool sample:

Before initiating medical treatment, a stool sample will be put aside and frozen at -80°C (alternatively -20°C) to allow later genetic analysis / resistance testing of the *Giardia lamblia* isolate in cases of `parasitological confirmed treatment failure´.

Follow-up:

- Follow-up of the patients with assessment of parasitological outcome by stool microscopy will be done ≥2 - ≤5 weeks after finishing treatment.
- Clinical efficacy and tolerability of the assigned 2nd-line treatment regimen will be assessed ≥4 - ≤5 weeks after finishing treatment by telephone using a standardized questionnaire.
- Parasitological outcome will be assessed by systematically obtaining at least two stool samples for laboratory evaluation; The logistic approach on how to collect the follow-up stool samples (e.g. re-consultation of patient at site or sending stool sample by mail) will be left to the study sites.

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Institut für Sozial- und Präventivmedizin

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Live vaccinations under immunsuppression – a retrospective and prospective data collection

Silja Bühler, Zürich
MD, MScPH, MScEpi

WHO: Individuals under any kind of immunosuppression

- Corticosteroids
- Sulfasalazine/Mesalazine
- low dose Methotrexate (<20mg/week)
- and all other medications (biologicals, ...)

WHO RECEIVE(D): a live vaccination

Yellow Fever, MMR, Varicella

FOR ANY REASON:

- inadvertently
- after careful risk/benefit assessment

Universität Zürich
Institut für Sozial- und Präventivmedizin
Swiss TPH

WHAT TO DO: USE TropNet Questionnaire

please document in detail data on:

- Demographics
- Live vaccination
- Immunosuppression
- Reason for immunosuppression (underlying disease)
- Diseases (MMR, Varicella) in the past
- Adverse reactions to vaccination
- Immunogenicity assessment (if performed)

TropNet

Live vaccinations in immunosuppressed persons

TropNet Centre Code: _____
Subject Number: ____

SECTION 1: SUBJECT VISIT

Date of visit / administration of live vaccine: __.__.____ (DD.MM.YYY) **Age in years** _____

Gender: ☐ Male ☐ Female **Weight (in kg)** _____

1. Which vaccinations were administered?

☐ MMR ☐ Yellow Fever ☐ Varicella ☐ Measles

SECTION 2: HEALTH QUESTIONS

2. What were the underlying condition(s), i.e. reason for immunosuppressive / immunomodulating treatment?

☐ Unknown ☐ Known, please specify: → Date of diagnosis or transplantation: __.__.____

→ Description: _____

3. Were there any other factors contributing to immunosuppression / -modulation?

☐ Unknown ☐ No ☐ Yes, please specify: _____

→ Further comments / information: _____

4. What was the subject's immunosuppressive/-modulating medication at the time of this vaccination?

Name / generic: *e.g. Methotrexate*			
Dosage and Interval: *e.g. 20mg/week*			
Date of last dose before vaccination:	__.__.____	__.__.____	__.__.____
Start date:	__.__.____	__.__.____	__.__.____

5. Was another immunosuppressive/ -modulating drug used in the 12 months before administration of a live vaccine?

☐ Unknown ☐ No ☐ Yes, please specify below:

Name / generic: *e.g. Methotrexate*			
Dosage and Interval: *e.g. 20mg/week*			
Date of last dose before vaccination:	__.__.____	__.__.____	__.__.____
Start date:	__.__.____	__.__.____	__.__.____

SECTION 3: PREVIOUS VACCINATIONS AND DISEASES

6. Which vaccinations were administered before this visit? If possible, check with vaccination certificates.

Type of vaccination	Number of shots	Date of last shot	Was live vaccine given before or after start of immunosuppressive/-modulatory therapy?		
Yellow Fever		__.__.____	☐ before	☐ after	☐ unknown
MMR		__.__.____	☐ before	☐ after	☐ unknown
Varicella		__.__.____	☐ before	☐ after	☐ unknown
Measles		__.__.____	☐ before	☐ after	☐ unknown

7. History of the following diseases?

	History	No history	Unclear	Serologically confirmed		
Measles	☐	☐	☐	☐ yes	☐ no	☐ unknown
Mumps	☐	☐	☐	☐ yes	☐ no	☐ unknown
Rubella	☐	☐	☐	☐ yes	☐ no	☐ unknown
Varicella	☐	☐	☐	☐ yes	☐ no	☐ unknown

SECTION 4: SAFETY ASSESSMENT

8. Were there any reactions after the administration of this live vaccine?

Definition mild: not interfering with daily activities; moderate: interfering with daily activities, but able to perform daily activities; severe: not able to perform daily activities

☐ Unknown ☐ No ☐ Yes, please specify below:

☐ Local reactions, please specify:	_____	☐ mild	☐ moderate	☐ severe
☐ Fever (>38°C)	→ If present, please specify:	☐ mild	☐ moderate	☐ severe
☐ Headache	→ If present, please specify:	☐ mild	☐ moderate	☐ severe
☐ Muscle / joint pain	→ If present, please specify:	☐ mild	☐ moderate	☐ severe
☐ Skin rash, please specify: _____	→ If present, please specify:	☐ mild	☐ moderate	☐ severe
☐ Other, please specify: _____		☐ mild	☐ moderate	☐ severe
☐ Other, please specify: _____		☐ mild	☐ moderate	☐ severe

9. Did any of the following events occur?

☐ No ☐ Yes, please specify below:

☐ Death ☐ Life-threatening event ☐ Hospitalisation or prolongation of existing inpatient hospitalisation

☐ Persistent or significant disability or incapacity ☐ Congenital anomaly or birth defect

☐ Other important medical event or reaction, please specify: _____

10. Were there any actions taken due to the above-mentioned reactions?

☐ Unknown ☐ No ☐ Yes, please specify below:

☐ Pain killer / self treatment ☐ Visit at a physician ☐ Stay at home from work / school / university or similar

☐ Other: _____

SECTION 5: IMMUNOGENICITY ASSESSMENT

11. Was an immunogenicity assessment (titer) performed?

☐ Unknown ☐ No ☐ Yes, please specify below:

	Description of test	Result	Date of test
1.			
2.			
3.			

SECTION 6: COMMENTS

12. If there are any important comments, please use the lines below.

_____

_____

_____

__.__.____ (DD.MM.YYYY) _____ (Signature of Investigator)

Fax Nummer : + 41 44 634 49 84 / Email: silja.buechler@ifspm.uzh.ch

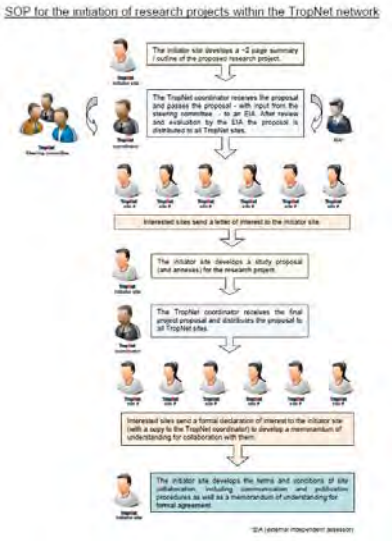
Possible TropNet projects ahead

- ➔ *TropNet study on PCR-based diagnosis of schistosomiasis in travellers*
- ➔ *TropNet study on imported multiresistant intestinal bacteria*
- ➔ *TropNet study on vaccinations in immunocompromised travelers*
- ➔ *TropNet surveillance study on worldwide distribution of polymorphisms associated with artemisinin resistance of P. falciparum malaria*
- ➔ *Pharmacokinetic study on Praziquantel in schistosomiasis*

Implementation of joint research projects within TropNet

SOP for the initiation of research projects within the network

(to be found under the member section of the TropNet website)



The infrastructure is there…
now it's about ideas, implementation & participation

Institutional network collaboration for `Horizon 2020´

Matthieu Mechain

Proposal for a joint TropNet/EuroTravNet surveillance study:

Imported malaria cases in Europe as sentinels for the worldwide distribution/emergence of polymorphisms associated with artemisinin resistance in P. falciparum malaria

International Journal for Parasitology 43 (2013) 885–889

Contents lists available at ScienceDirect

International Journal for Parasitology

journal homepage: www.elsevier.com/locate/ijpara

Succinctus

Travellers as sentinels: Assaying the worldwide distribution of polymorphisms associated with artemisinin combination therapy resistance in *Plasmodium falciparum* using malaria cases imported into Scotland

Carol W. Hunja [a,b], Holger Unger [d,f,1], Pedro E. Ferreira [e], Richard Lumsden [c], Sheila Morris [f], Rashid Aman [b], Claire Alexander [g], Toshihiro Mita [h,i,1], Richard Culleton [a,*,1]

(Nagasaki & Nairobi)

Background

- Resistance to ACTs is characterised by delayed clearance of parasites following drug treatment
- Following the first reports of parasites with delayed clearance rates in western Cambodia, it has been shown that the resistance phenotype are likely to have an underlying genetic component [1]
- This implied that genetic mutations had arisen in a subset of parasites in western Cambodia that decreased their sensitivity to ACTs and that these mutations have being selected by ACT pressure in the region
- A genomic region associated with the resistance phenotype has been described [2] followed by the identification of **4 single nucleotide polymorphisms (SNPs)** on chromosomes 10, 13 and 14, which **appear to be linked to resistance** [3]

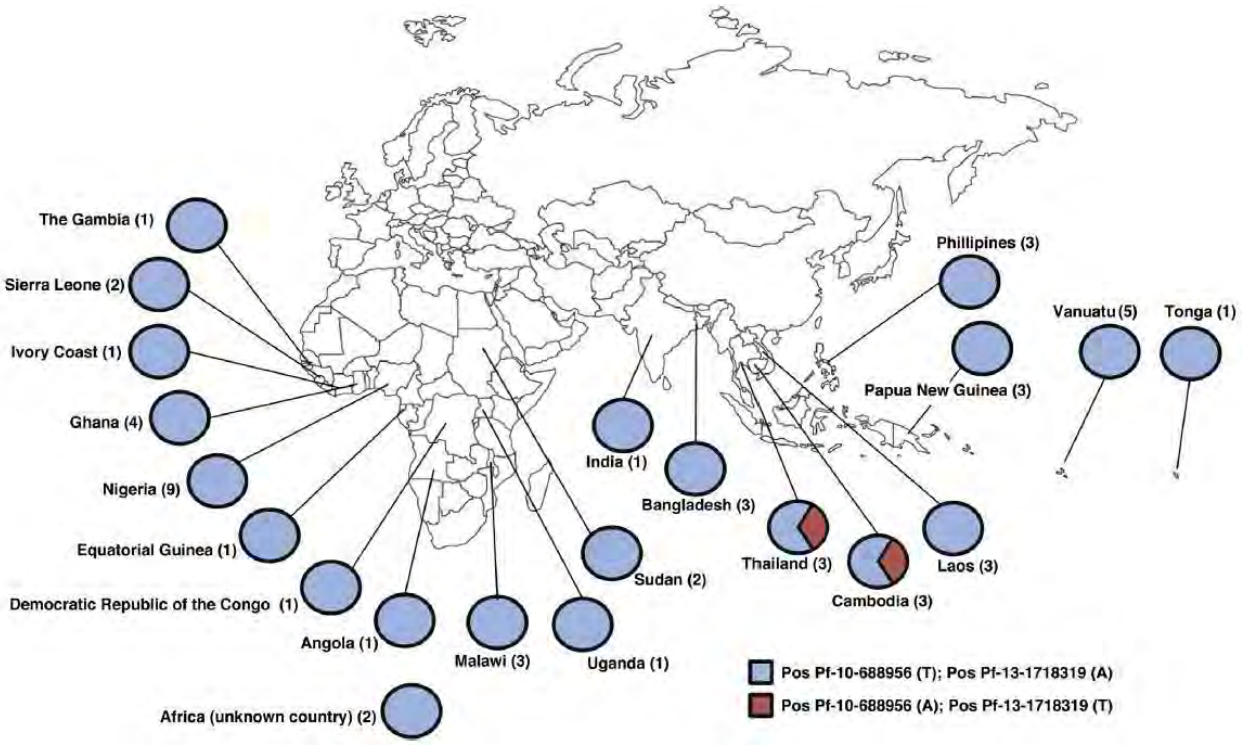
1 Anderson TJ et al. J Infect Dis. 2010;2010:1326-30
2 Cheeseman IH et al. Science. 2012;336:79-82
3 Takala-Harrison S et al. Proc. Natl. Acad. Sci. USA 2013;110:240-5

- **2 of these SNPs have been proposed to be suitable molecular markers for delayed parasite clearance**

  MAL10-688956(A) & MAL13-1718319(T)

- Although these SNPs are not thought to confer resistance themselves (and despite the fact that they have been identified in some regions before ACT resistance was reported in southeastern Asia), they could be linked to the actual genetic drivers of resistance, which could exist in parasite populations that have never been exposed to ACTs and which would be selected for when ACT pressure is applied to the population

➔ **Systematic collection and genotyping of imported *P. falciparum* malaria strains would be an ideal tool to identify geographic regions, where SNPs linked to ACT resistance are prevalent or emerging**



Hunja CW et al. Int J Parasitol. 2013;43(11):885-9

Methods:

1. Routine collection of blood samples from all malaria cases (all species?) seen at participating study sites:

   - spots of EDTA-blood on filter paper
     (air-drying & storing in sterile plastic sleeves)
   - collection of a minimal anonymized data set:
     (date, age, gender, chemoprophylaxis, countries & regions visited, result of microscopy/rapid diagnostic test)
   - establishing a sample library over the years

2. DNA-extraction ➔ PCR ➔ restriction fragment length polymorphism analysis

Case record form (Version V1.2013)

TropNet centre code: ☐☐☐ **Patient No.:** ☐☐☐ **Age:** ☐☐ years **Gender:** ☐ f / ☐ m

Date of study inclusion: ☐☐/☐☐/☐☐ (DD/MM/YY)

Malaria infection (most likely) acquired in (country): _____

☐ if not determinable: malaria endemic countries visited within the last 12 months before onset of symptoms in chronological order (1. last, 2. second last, 3. third last, etc.):

1. _____
2. _____
3. _____
4. _____
5. _____

Diagnosis established by: ☐ microscopy ☐ rapid diagnostic test

☐ mono-infection ☐ mixed-infection

☐ *P. falciparum* ☐ P. vivax ☐ P. ovale ☐ P. malariae ☐ P. knowlesi

Did the patient take malaria chemoprophylaxis:

☐ no ☐ yes, if yes: ☐ Atavaquon/Proguanil (Malarone, Malanil)
☐ Mefloquine (Lariam)
☐ Chloroquine (Resochin)
☐ Doxycycline
☐ Proguanil (Paludrine)
☐ Chloroquin/ Proguanil (Savarine)

☐ other: _____

Add-ons:

- collection of multiple blood spots would allow to re-evaluate the samples if new molecular markers are identified in the future
- & surveillance of emergence/prevalence of resistance to other chemoprophylactic drugs (malarone, mefloquin) would be possible

1. [**Molecular** epidemiological **surveillance** of markers for antimalarial drugs in Plasmodium falciparum **isolates imported** to Barcelona, Spain].
Gascón J, Mayor A, Mühlberger N, Peyerl-Hoffmann G, Oliveira I, Dobaño C, **Jelinek** T, Corachan M.
Med Clin (Barc). 2005 Sep 10;125(8):286-9. Spanish.
PMID: 16159551 [PubMed - indexed for MEDLINE]
Related citations

2. Screening for mutations related to atovaquone/proguanil **resistance** in treatment failures and other **imported isolates** of Plasmodium falciparum in Europe.
Wichmann O, Muehlberger N, **Jelinek** T, Alifrangis M, Peyerl-Hoffmann G, Muhlen M, Grobusch MP, Gascon J, Matteelli A, Laferl H, Bisoffi Z, Ehrhardt S, Cuadros J, Hatz C, Gjorup I, McWhinney P, Beran J, da Cunha S, Schulze M, Kollaritsch H, Kern P, Fry G, Richter J; European Network on **Surveillance** of **Imported** Infectious Diseases.
J Infect Dis. 2004 Nov 1;190(9):1541-6. Epub 2004 Sep 28.
PMID: 15478057 [PubMed - indexed for MEDLINE] Free Article
Related citations

3. **Molecular surveillance** of the antifolate-resistant mutation I164L in **imported** African **isolates** of Plasmodium falciparum in Europe: sentinel data from TropNetEurop.
Wichmann O, **Jelinek** T, Peyerl-Hoffmann G, Mühlberger N, Grobusch MP, Gascon J, Matteelli A, Hatz C, Laferl H, Schulze M, Burchard G, da Cunha S, Beran J, McWhinney P, Kollaritsch H, Kern P, Cuadros J, Alifrangis M, Gjørup I; European Network on **Surveillance** of **Imported** Infectious Diseases (TropNetEurop).
Malar J. 2003 Jun 25;2:17. Epub 2003 Jun 25.
PMID: 12866 [PubMed - indexed for MEDLINE] Free PMC Article
Related citations

4. **Molecular surveillance** of **drug resistance** through **imported isolates** of Plasmodium falciparum in Europe.
Jelinek T, Peyerl-Hoffmann G, Mühlberger N, Wichmann O, Wilhelm M, Schmider N, Grobusch MP, von Sonnenburg F, Gascon J, Laferl H, Hatz C, Alifrangis M, Burchard G, McWhinney P, Schulze M, Kollaritsch H, da Cunha S, Beran J, Kern P, Gjørup I, Cuadros J.
Malar J. 2002 Oct 11;1:11. Epub 2002 Oct 11.

Suggestions for partners / collaborations ?

Hospital Universitario Príncipe de Asturias
SaludMadrid
Comunidad de Madrid

Comparation of imported *Plasmodium ovale wallikeri* and *Plasmodium ovale curtisi*

Fundación de Investigación
Universidad de Alcalá
Instituto de Salud Carlos III

Background *P. ovale*

- So far considered uncommon, limited geographycally, mild and easily treated
- PCR studies:
  - Prevalence 9-15% (Nigeria, PNG, Equatorial Guinea)
  - SE Asia, Middle East, Indian subcontinent…
- Severity: ARDS, spleen rupture, anemia
- Quite ineffective prophylaxis
- Treatment failure exceptional but relapses
- Two species: *Po wallikeri, Po curtisi* . Differences?

Retrospective study

Comparison of Imported *Plasmodium ovale curtisi* and *P. ovale wallikeri* Infections among Patients in Spain, 2005–2011

Gerardo Rojo-Marcos, José Miguel Rubio-Muñoz, Germán Ramírez-Olivencia, Silvia García-Bujalance, Rosa Elcuaz-Romano, Marta Díaz-Menéndez, María Calderón, Isabel García-Bermejo, José Manuel Ruiz-Giardín, Francisco Jesús Merino-Fernández, Diego Torrús-Tendero, Alberto Delgado-Iribarren, Mónica Ribell-Bachs, Juan Arévalo-Serrano, and Juan Cuadros-González

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 20, No. 3, March 2014

12 Hospitals in Spain

Malaria Laboratory, Instituto de Salud Carlos III, Madrid

1. Príncipe de Asturias University Hospital, Alcalá de Henares, Madrid
2. Carlos III Hospital, Madrid
3. La Paz University Hospital, Madrid
4. Doctor Negrín University Hospital, Las Palmas de Gran Canaria
5. Ramón y Cajal University Hospital, Madrid
6. Gregorio Marañón University Hospital, Madrid
7. Getafe University Hospital, Madrid
8. University Hospital of Fuenlabrada, Madrid
9. Severo Ochoa University Hospital, Madrid
10. University General Hospital of Alicante, Alicante, Spain
11. University Hospital Fundación Alcorcón, Madrid
12. Hospital General de Granollers, Barcelona, Spain

Table 1. Demographic and epidemiologic characteristics of patients with imported *Plasmodium ovale curtisi* or *P. ovale wallikeri* infections, Spain, 2005–2011*

Characteristic	*P. ovale curtisi*, n = 21	*P. ovale wallikeri*, n = 14	p value
Patient sex			0.332
M	10 (47.6)	9 (64.3)	
F	11 (52.4)	5 (35.7)	
Patient age, y, median (IQR)	36.50 (23.04–52.66)	38.33 (11.79–45.27)	0.377
Age <15	3 (14.3)	4 (28.6)	0.401
Ethnicity			0.721
Black	15 (71.4)	9 (64.3)	
White	6 (28.6)	5 (35.7)	
Type of patient			0.260
Early immigrant	6 (28.6)	4 (28.6)	
Traveler	14 (66.7)	10 (71.4)	
Reason for travel			
Visiting friends and relatives	9 (42.8)	7 (50.0)	
Tourism		1 (7.1)	
Work	3 (14.3)	2 (14.3)	
Cooperation	2 (9.5)		
Unknown	1 (4.8)		
Duration of travel, d, median (IQR)	75 (23.25–91.50)	23 (15.00–81.50)	0.279
Country of infection			0.486
Equatorial Guinea	12 (57.1)	7 (50.0)	
Nigeria	2 (9.5)	3 (21.4)	
Equatorial Guinea or Cameroon	1 (4.8)	0	
Ghana	1 (4.8)	1 (7.1)	
Ethiopia	1 (4.8)	0	
Guinea-Conakry	1 (4.8)	0	
Liberia	1 (4.8)	0	
Angola	1 (4.8)	0	
Guinea-Bissau	1 (4.8)	0	
Guinea-Conakry or Senegal	0	1 (7.1)	
Côte d'Ivoire	0	1 (7.1)	
Mozambique	0	1 (7.1)	
Chemoprophylaxis			0.627
No prophylaxis	17 (81.0)	13 (92.9)	
Mefloquine, incomplete	1 (4.8)	1 (7.1)	
Mefloquine	1 (4.8)	0	
Doxycycline	1 (4.8)	0	
Atovaquone/proguanil	1 (4.8)	0	
Days from arrival to onset of symptoms, median (IQR)	94.5 (12.5–297.2)	9.5 (2.7–58.2)	0.077
Days from onset of symptoms to diagnosis, median (IQR)	8 (2.7–16.5)	3.5 (2.0–7.7)	0.206
Recent *Plasmodium* infection	3 (14.3)	3 (21.4)	>0.999
Other infections			
Hepatitis B virus			>0.999
Active	1/11 (9.1)	0/10	
Cured or vaccinated	6/11 (54.5)	5/10 (50.0)	
Negative	4/11 (36.4)	5/10 (50.0)	
Hepatitis C virus	1/7 (14.3)	0/10	0.412
HIV	1/7 (14.3)	0/10	0.412
Filariasis†	3/6 (50.0)	0/4	0.200
Intestinal parasites‡	3/6 (50.0)	1/4 (25.0)	0.571
Other underlying conditions	9 (42.8)	8 (42.8)	>0.999
Diabetes mellitus	2 (9.5)	1 (7.1)	
Drepanocytosis	2 (9.5)	0	
Hypertension	4 (19.0)	2 (14.3)	
Obesity	1 (4.8)	0	
Acute pancreatitis	0	1 (7.1)	
Policystosis and nephrectomy	0	1 (7.1)	
Oligoarthritis	0	1 (7.1)	
Glucose-6-phosphate dehydrogenase deficiency	2/14 (14.3)	0/8	0.515
Pregnancy	1 (4.8)	0	>0.999

*Values are no. (%) patients or no. positive/total no. (%) patients unless otherwise indicated. IQR, interquartile range.
†*Mansonella perstans* (n = 2), *Loa loa* (n = 1).
‡*Trichuris trichiura* (n = 3), hookworms (n = 2), *Ascaris lumbricoides* (n = 2), *Strongyloides stercoralis* (n = 1), *Entamoeba hystolitica* (n = 1).

Table 2. Microbiological characteristics of patients with imported *Plasmodium ovale curtisi* or *P. ovale wallikeri* infections, Spain, 2005–2011*

Characteristic	*P. ovale curtisi*, n = 21	*P. ovale wallikeri*, n = 14	p value
Positive thick smear, no. (%) patients	16 (76.2)	10 (71.4)	>0.999
Positive by PCR only, no. (%) patients	5 (23.8)	4 (28.6)	>0.999
Parasitemia, µL	2,800 (773.25–5,484.25)	1,243.50 (337.75–6,200.00)	0.699
Mixed infection, no. (%) patients	1† (4.8)	1† (7.1)	>0.999
Rapid diagnostic test result, no. positive/total no. patients (%)			
Common antigen positive	4/16 (25.0)	4/12 (33.3)	0.691
P. falciparum antigen positive	1/15 (6.7)	2/12 (16.6)	0.569
Leukocyte count, $\times 10^9$ cells/L	7.2 (4.9–8.7)	5.5 (4.2–8.2)	0.309
Hemoglobin, g/dL	11.6 (9.7–13.6)	10.9 (9.6–12.1)	0.364
Platelet count, $\times 10^9$ cells/L	126 (106.0–182.5)	91.5 (54.7–117.7)	**0.031**
Albumin, g/dL	3.7 (3.3–4.1)	3.4 (2.8–3.7)	0.063
Creatinine, mg/dL	0.88 (0.6–1.1)	0.97 (0.5–1.1)	0.730
Lactate dehydrogenase, IU/L	434.5 (358.7–807.7)	563 (462.5–731.7)	0.200
Aspartate aminotransferase, IU/L	24.5‡ (20.0–40.2)	31 (22–41)	0.624
Alanine aminotransferase, IU/L	25.5‡ (16.0–49.7)	23 (18.5–47.0)	0.785
Total bilirubin level, mg/dL	0.68‡ (0.6–1.2)	0.87 (0.6–1.4)	0.426

*Values are median (interquartile range) unless otherwise indicated. Boldface indicates significance.
†*P. falciparum* was second infection for both patients.
‡One patient had active hepatitis B virus infection.

Table 3. Clinical and therapeutic characteristics of patients with imported *Plasmodium ovale curtisi* or *P. ovale wallikeri* infections, Spain, 2005–2011*

Characteristic	*P. ovale curtisi*, n = 21	*P. ovale wallikeri*, n = 14	p value
Asymptomatic	3 (14.3)	0	0.259
Fever	18 (85.7)	14 (100.0)	0.259
Tertian fever	1 (4.8)	3 (21.4)	0.279
Maximum temperature, ºC, median (IQR)	38.4 (37.5–40.0)	39.7 (38.9–40.5)	0.088
Chills	3 (14.3)	3 (21.4)	0.664
Sweating	0	1 (7.1)	0.400
Headache	6 (28.6)	4 (28.6)	>0.999
Nauseas	0	3 (21.4)	0.056
Vomitus	0	3 (21.4)	0.056
Astenia	2 (9.5)	3 (21.4)	0.369
Epigastralgia	2 (9.5)	0	0.506
Arthralgia	5 (23.8)	3 (21.4)	>0.999
Myalgia	6 (28.6)	4 (28.6)	>0.999
Diarrhea	1 (4.8)	1 (7.1)	>0.999
Chest pain	1 (4.8)	1 (7.1)	>0.999
Cough	4 (19.0)	3 (21.4)	>0.999
Dyspnea	0	1 (7.1)	0.400
Dizziness	2 (9.5)	0	>0.999
Splenomegaly	5 (23.8)	3 (21.4)	>0.999
Complications or severe malaria	2 (9.5)	2 (14.3)	>0.999
Hemolytic crisis	1 (4.8)	0	
Severe anemia, hemoglobin <7 g/dL	1 (4.8)	1 (7.1)	
Acute respiratory distress syndrome	0	1 (7.1)	
Admission to hospital	13 (61.9)	13 (92.9)	0.056
Duration of hospitalization, d, median (IQR)	4 (3.0–7.5)	5 (3.5–7.5)	0.390
Treatment			0.563
Chloroquine	12 (57.1)	7 (50.0)	
Other treatment	8 (38.1)	7 (50.0)	
Quinine + doxycycline	3 (14.3)	4 (28.6)	
Atovaquone/proguanil	3 (14.3)	1 (7.1)	
Quinine + clindamycin + chloroquine/proguanil	1 (4.8)	0	
Quinine + clindamycin + chloroquine	0	1 (7.1)	
Mefloquine	0	1 (7.1)	
Atovaquone/proguanil + chloroquine	1 (4.8)	0	
No treatment	1 (4.8)	0	
Primaquine	14 (66.7)	10 (71.4)	>0.999
Compliance	19/21 (90.5)	13/13 (100.0)†	0.513

*Values are no. (%) patients or no. positive/total no. (%) patients unless otherwise indicated. IQR, interquartile range.
†One patient was lost to follow-up.

Conclusions

- **More severe thrombocytopenia** was the only significant finding among patients with *P. ovale wallikeri* infection (p = 0.031)
- Nonsignificant trends for *P. ovale wallikeri*
  - Shorter time from arrival to onset of symptoms (Nolder D 2013)
  - Lower level of albumin
  - Higher markers of hemolisis: LDH, AST, BR
  - Higher median maximum core temperature
- Is *P. ovale wallikeri* more pathogenic?
- Larger, prospective studies are needed to assess these findings

Study design

- Prospective, unrandomised, open-label, observational study

Study objectives

- Comparative study of the epidemiological, clinical, microbiological, analytical, outcome and therapeutic characteristics of both species
- Identify useful markers for differential diagnosis in the clinical practice
- Might help to complete maps of *P. ovale* circulating species in endemic countries

Number of cases available

TropNet

- 2013 (10 centres):
  - **25 *Po*** so far
- 2012 (21/68 centres)
  - 552 malaria (461 *Pf; 52 Pv;* ***28 Po****; 12 Pm)*

Spanish Malaria Lab

- 2013
  - **12 *Po***
- 2014
  - **4 *Po*** so far

Inclusion criteria

- Patients with diagnosis of imported *P. ovale* infection by thick or thin film or PCR and (All confirmed by PCR)
- No clinical restriction, from asymptomatic to severe disease

Exclusion criteria

- Lack of informed consent

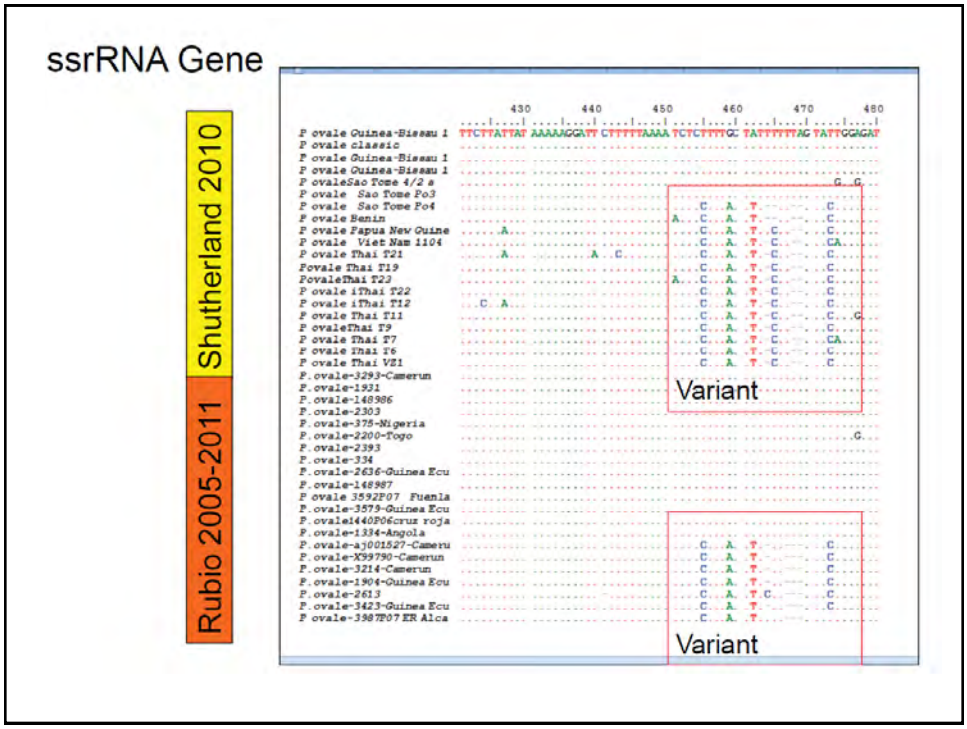
Genetic analysis

- Full blood dotted on filter paper (Whatman™) before the initiation of treatment (2-3 drops) in an individual little plastic bag

- Sent by regular mail
- Diagnosis will be confirmed by seminested multiplex PCR
- Locus amplification and sequencing of the ssrRNA gene will be carried out
- Classified as *Po wallikeri* or *Po curtisi*

Reference laboratory

- Dr. José Miguel Rubio
  Servicio de Parasitología
  Centro Nacional de Microbiología
  Instituto de Salud Carlos III
  Cra. Majadahonda Pozuelo Km. 2,5
  Majadahonda, 28220 Madrid
  España/Spain



Patient data and analysis

- Epidemiological, clinical, microbiological, analytical and therapeutic data from interview and medical reports
- Easy filling **data form** available on line (pdf)
- Statistical analysis test will be performed
- Data analysis will compare possible differences between both groups

MALARIA OVALE DATA FORM

Identification (Hospital code + number of patient. E.g. HUPA1): ____ ____

Physician name (last, first): _____ E-mail of contact: _____

Date of symptom onset of this attack (mm/dd/yyyy): ____/ ____/ ____
Asymptomatic Yes ☐ No ☐

Date of Birth: (mm/dd/yyyy) ____/ ____/ _____
Sex:
Male ☐, Female ☐ Unknown ☐

Is patient pregnant? Yes ☐ No ☐

Ethnicity: Black ☐, White ☐, Asian ☐, Other (specify) _____, Unknown ☐

Patient admitted to hospital: Yes ☐ No ☐ Unknown Date: ____/ ____/ _____
Length of stay in hospital **(days)** _____

Positive lab test result: Smear ☐, PCR ☐, RDT ☐, No test done/unknown _____

Species: Ovale ☐, Mixed ☐ (specify) _____

Parasitemia µL:_____ (%): ____

Has the patient traveled or lived outside the E.U. during the past 2 years?
Yes ☐, No ☐
If yes, specify: Country: 1. _____ 2. _____ 3. _____
Date returned/ arrived in E.U. (mm/dd/yyyy): ____/ ____/ _____
Duration of stay in country **Days:** _____
Did patient reside in E.U. prior to most recent travel? Yes☐ (specify country): _____,
No ☐ Unknown☐
Principal reason for travel from/ to E.U for most recent trip: Tourism, Military, Business, Peace Corps,

Ethical considerations

- Approval in local ethics commitees neccessary
- Patient informed consent required
- Patient **information and informed consent form** will be available in english, french, spanish and any other language under request

Contact and information

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References

- Sutherland CJ, Tanomsing N, Nolder D, Oguike M, Jennison C, Pukrittayakamee S, et al. Two non-recombining sympatric forms of the human malaria parasite *Plasmodium ovale* occur globally. J Infect Dis. 2010;201:1544-50.
- Fuehrer H-P, Habler VE, Fally MA, Harl J, Starzengruber P, Swoboda P, et al. *Plasmodium ovale* in Bangladesh: Genetic diversity and the first known evidence of the sympatric distribution of *Plasmodium ovale curtisi* and *Plasmodium ovale wallikeri* in southern Asia. Int J Parasitol. 2012;42:693–9.
- Oguike MC, Betson M, Burke M, Nolder D, Stothard JR, Kleinschmidt I, et al. P*lasmodium ovale curtisi* and *Plasmodium ovale wallikeri* circulate simultaneously in African communities. Int J Parasitol. 2011;41:677-83
- Bauffe F, Desplans J, Fraisier C, Parzy D- Real-time PCR assay for discrimination of *Plasmodium ovale curtisi* and *Plasmodium ovale wallikeri* in the Ivory Coast and in the Comoros Islands. Malar J. 2012;11:307.
- Rubio JM, Post RJ, van Leeuwen WM, Henry MC, Lindergard G, Hommel M. Alternative polymerase chain reaction method to identify *Plasmodium* species in human blood samples: the seminested multiplex malaria PCR (SnM-PCR).Trans R Soc Trop Med Hyg. 2002;96:199-204.
- Nolder D, Oguike MC, Maxwell-Scott H, Niyazi HA, Smith V, Chiodini PL, et al. An observational study of malaria in British travellers: *Plasmodium ovale wallikeri* and *Plasmodium ovale curtisi* differ significantly in the duration of latency. BMJ Open. 2013;3: e002711.
- Rojo-Marcos G, Rubio-Muñoz JM, Ramírez-Olivencia G. Comparation of imported *Plasmodium ovale curtisi* and *Plasmodium ovale wallikeri* infections among patients in Spain 2005-2011. Emerg Infect Dis 2014;20

Health care is not sold, but defended

Comparison of methods used to determine the safety of N,N-diethyl-m-toluamide (DEET). Will new EU regulations put EU travellers at risk of malaria and other vector borne diseases?

Vanessa Chen-Hussey, Ron Behrens, James G Logan

Department of Disease Control

Department of Clinical Research

malaria centre

Disease transmitted by vectors.

Vector	Diseases
Anopheles spp.	Malaria, Lymphatic filariasis
Stegomyia	Dengue, Rift Valley fever, Chikungunya, Yellow fever
Culex spp.	Japanese Enceph. Filariasis, West Nile Fever
Sandflies	Leishmaniasis
Black Flies	Onchocerciasis
Hard and Soft Ticks	TBE, Rickettsial diseases, Lyme, Borreliosis, Tick Typhus
Triatomine bugs	Chagas Disease
Tsetse fly	Trypanosomiasis

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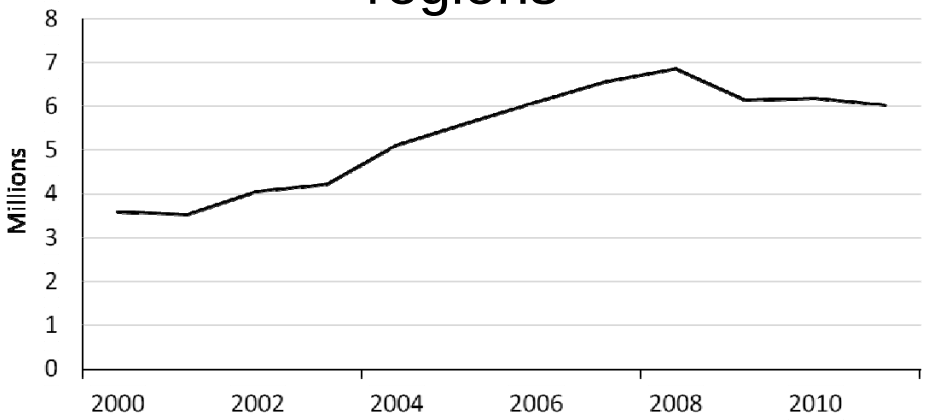
Visits by UK residents to Tropical regions$



Globally 256 Million annual arrivals in Tropical Regions of the World, 34 Million S.S. Africa*

* World Tourism Organisation report 2013 $ International Passenger Survey

Results of toxicity testing of DEET in animals reported to the USEPA

NOEL, no-observed effect-level; LEL, lowest effect-level.

Toxicologic effects and endpoints for DEET

Type of study	Endpoints (NOEL, LEL)[a]	Description of effect (nature, severity)
Acute toxicity		
Acute neurotoxicity screening study in rats (gavage)	NOEL = 200 mg/kg BW/day; LEL = 500 mg/kg BW/day	No gross or microscopic alterations were observed in the central or peripheral nervous system in comparison with controls
Subchronic toxicity		
90-day dermal toxicity study in rats	NOEL = 300 mg/kg BW/day[b]; LEL = 1000 mg/kg BW/day[b]; NOEL = 1000 mg/kg BW/day	Based on decrease in body-weight gain and increase in liver weights[b]
90-day dermal toxicity study in micropigs		Based on 13-week study in micropigs; No renal lesions in micropigs[b]
Chronic toxicity		
Combined chronic and carcinogenicity in rats (2 years)	NOEL = 100 mg/kg BW/day (females and males); LEL = 400 mg/kg BW/day	Based on decreased body weights and food consumption, and increased cholesterol levels in female and male rats[c]
Chronic toxicity study in dogs	NOEL = 100 mg/kg BW/day; LEL = 400 mg/kg BW/day	Based on decreases in food consumption and body weights, increase in the incidence of ptyalism and a decrease in cholesterol levels

[a] Endpoint abbreviations: BW, body weight; NOEL, no-observed effect-level; LEL, lowest effect-level.
[b] USEPA (1998).
[c] Schoenig et al. (1999).

EPA United States Environmental Protection Agency

Human Toxicity

1. Dermal symptoms were reported in 5% of reports.
   Symptoms included irritation, redness, rash, and swelling.

2. •• Gastrointestinal symptoms following exposure to DEET by ingestion.
   Gastrointestinal symptoms included oral irritation, nausea, and vomiting.

3. •• Neurological reactions following DEET exposure are rare. The incidence of seizure following DEET ~ 1 per 100 million vc1
   Reports of neurological reactions are predominately the result of accidental or deliberate ingestion, or dermal applications not consistent with label directions. Reported neurological signs of toxicity include encephalopathy, seizure, tremor, slurred speech, coma, and death

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EPA United States Environmental Protection Agency

Based on pesticide usage information mainly for 1990, an average annual estimate of the Domestic usage of N,N-diethyl-meta-toluamide (DEET) is 4 million pounds (active ingredient). About 30% of the U.S. population uses DEET annually as an insect repellent (about 27% of adult males, 31% of adult females and 34% of children. Approximately 21% of U.S. households use DEET annually.

Agency concluded.

DEET as an insect repellent does not pose a significant health risk to the general U.S. population for the following reasons:
(1) DEET is not believed to be acutely toxic nor carcinogenic, significantly developmentally toxic nor mutagenic at the doses tested.
(2) The available data do not support a direct link between exposure to DEET and reported seizure Incidences (14 cases).

malaria centre

US EPA Special Review and Reregistration Division; *Reregistration Eligibility Decision DEET*. 1998

U.S. EPA, Toxicity and Exposure Assessment for Adults & Children

Daily exposure to DEET:

1. No-observed-adverse-effects level (NOAEL) in experimental animal studies of dermal exposure was 250-300 mg/kg/day
2. Adult males = 12 mg/kg/day
3. children <12 years = 37 mg/kg/day

"DEET insect repellents will generally not cause unreasonable risks to humans or the environment"

The AAP recommends that repellents should contain no more than 30% DEET when used on children. Insect repellents also are not recommended for children younger than 2 months

US EPA Special Review and Reregistration Division; *Reregistration Eligibility Decision DEET*. 1998

Directive 98/8/EC concerning the placing biocidal products on the market

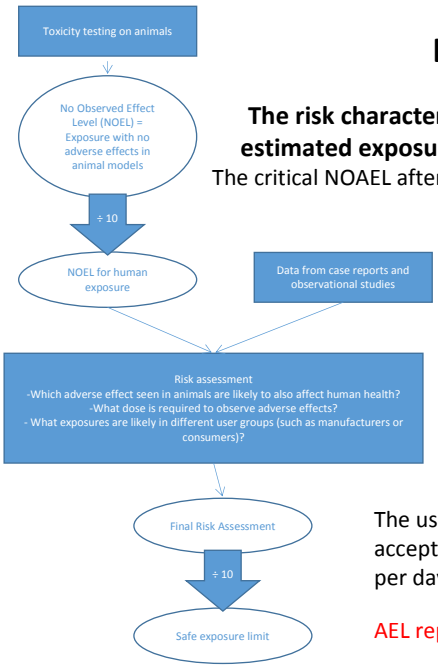
N,N- diethyl-*meta*-toluamide (DEET)

Product-type 19
(Repellents and attractants)

DEET is efficacious enough, based on the documentation received on the active substance DEET and the representative product, containing 15% DEET, for the proposed manner and areas of use of products intended as repellent without unacceptable risk neither to human health or the environment……..

Reduce the exposure in children < 12 years olds, no use in children < 2 years old. Reducing the extent of use in children < 12 years on unsuitable exposure areas i.e. hands, and around eyes and mouth, and recommendations on maximum daily number of applications.

EC: *Biocidal Products Directive (Directive 98/8/EC) Assessment Report: N,N-Diethyl*-meta-*Toluamide (DEET)*2010



EU *Human Health Risk Assessment*

The risk characterisation is based on a traditional method comparing the estimated exposure with an AEL based on the dermal 90 day study in rats.
The critical NOAEL after dermal dosing in rats is ≥1000 mg/kg bw/day

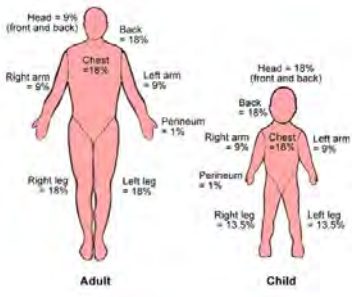
The use of the representative product (15%) 2 times per day is considered acceptable for adults and children >12 years old i.e the exposure twice per day was 47%-74% of the AEL repeated

AEL repeated is calculated as 8.2mg/kg/day

EC: *Biocidal Products Directive (Directive 98/8/EC) Assessment Report: N,N-Diethyl*-meta-*Toluamide (DEET)*2010

Daily Exposure of DEET

Adult BSA = 1.9m² = 19,000cm²



Max EU dose = 8.2 mg DEET /kg/day for 70kg = 574 mg DEET per day

Standard application rate used in laboratory testing
= 1 ml product per 600cm² (approx. 1 forearm)
= 1.7 µl/cm² or 1.7 mg/cm²

Single application:
Total product required to cover 2 whole arms(18%) OR 2lower legs = 5.7ml
An average single application used by Canadians was around 3700mg

15% DEET product contains 15g/100ml
One application of 5.7ml = 855mg DEET
One application of 3.7ml = 555mg DEET

50% DEET contains 50g/100ml
One application of 5.7ml = 2850mg DEET
One application of 3.7ml = 1850mg DEET

Why travellers might need high concentrations DEET

1. Duration of repellency
2. Compensate for under/infrequent application (safety margin in application)
3. Repellency spectrum adequate for range of vectors

Longevity of repellency of DEET

15% duration ~ 4-5hrs

Field trial DEET 20% 1.33 mg/cm2	86.9%	1h
Anopheles spp.	88.5%	2h
	87.9%	3h
	88.9%	4h
	74.5%	5h
	37.5%	6h
	72.1%	7h
Field trial DEET 20% 1.33 mg/cm2	100%	3h
Cx. annulirostris	97.4%	4h
	99.1%	5h
	99.4%	6h
	96.3%	7h
Field trial DEET 20%	100%	1h
0.76-0.84 mg/cm2	100%	2h
	97.5%	3h
Ae. albopictus	95.9%	4h
	94%	5h
	95%	6h
	100%	7h

Lupi et.al. Travel Medicine and Infectious Disease (2013) 11, 374e411

Low dosage in application of repellent by travellers

Repellency conc. Used laboratory testing ~ 1.7mg(µl)/cm²

Table 2 Mean applied dose mg/cm² (SD) of active ingredient

% Active ingredient in product	≥50%	20%–49%	<20%	Mean dose per country (mg/cm²)
Arms (mg/cm²)				
UK (*N* = 74)	0.56 (0.17)	0.23 (0.05)	—	0.41 (0.21)
India (*N* = 27)	0.57 (0.11)	0.18 (0.1)	0.13 (0.02)	0.18 (0.16)
Kenya (*N* = 23)	0.67 (0.27)	0.28 (0.94)	—	0.67 (0.29)

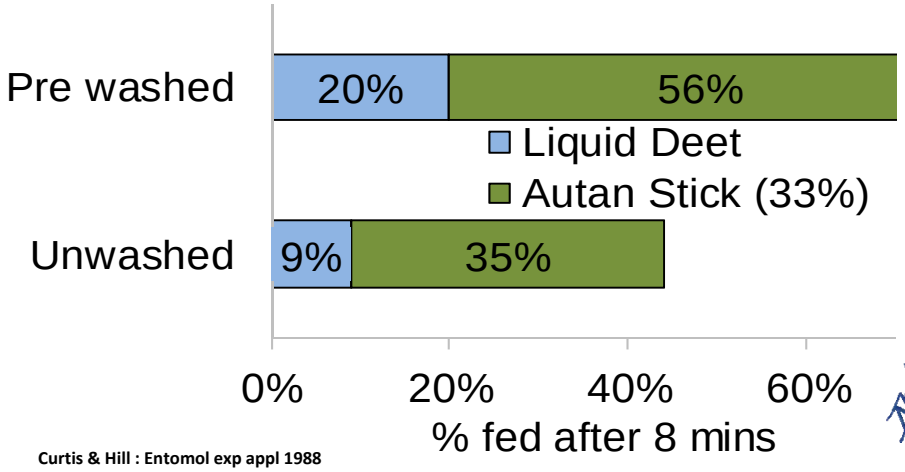
One application of 5.7ml = 2850mg DEET One application of 5.7ml = 855mg DEET

Malaria centre

Thrower & Goodyer. Application of Insect Repellents by Travelers to Malaria Endemic Areas JTM 2006

Effect of washing and formulations on the efficacy of DEET

0.4gm DEET equivalent formulation applied to lower leg with and without washing then exposed to un-fed *A. gambiae*



Malaria centre

Curtis & Hill : Entomol exp appl 1988

Summary

- The is a modelled on rat and dog toxicity studies.
- EU safety assessment will restrict DEET products to 15% to be used a maximum of twice a day.
- EU risk assessment fails to balance DEET toxicity or its historical safety record against risks of vector borne diseases.
- EPA assessment identifies not restriction on DEET in adults based on toxicity data and historical safety.
- The personal repellent protection for future EU travellers will at 15% concentration may not provide protection.

Praziquantel pharmacokinetics

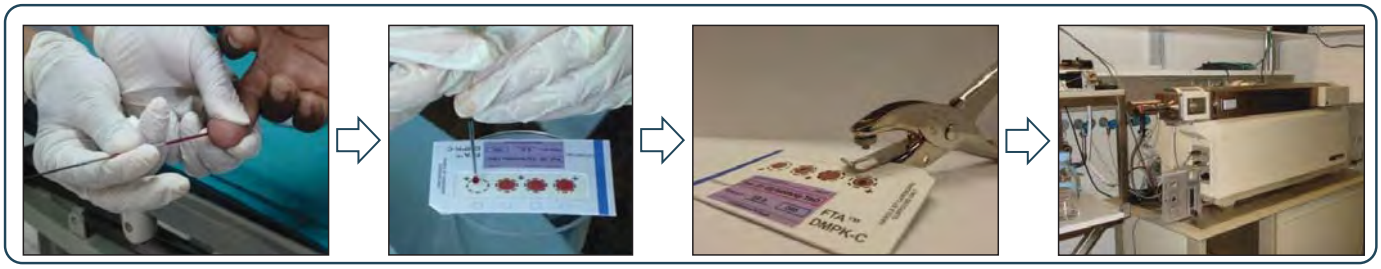
Background: perceived and true treatment failures in treated returning travellers

Approach: all schisto patients treated with praziquantel: 6 dried blood spots on filter paper samples (e.g. 1, 2, 3, 6, 8 and 24 h)

Procedure: keep patients for 3 hours to cover absorption phase and c_{max}, followed by self-pricking over 1 day (feasible?). Samples will be analysed by LC-MS at Swiss TPH

External expertise: Piero Olliaro, WHO Geneva

Outline of study design / timeframe



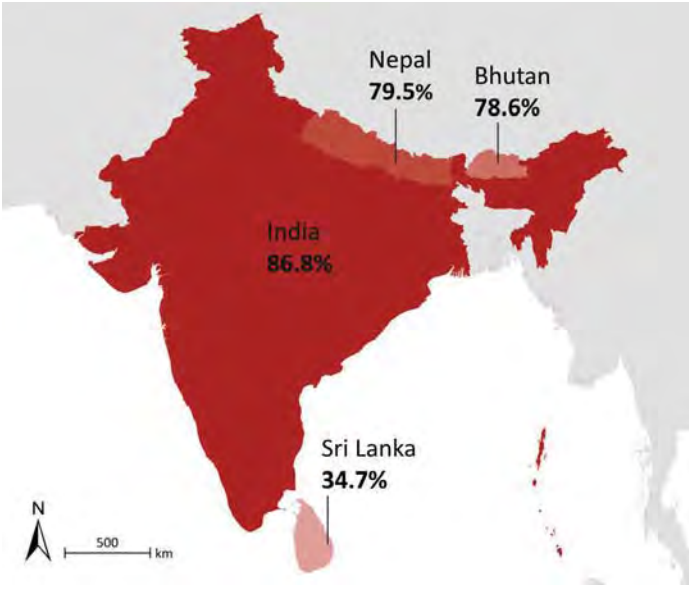
ESBL carriage follow-up in international travellers; update and preliminary study results

Esther Künzli

Study Design

- travellers to South Asia (India, Bhutan, Nepal, Sri Lanka)
- duration of stay: max. 5 weeks
- screening (rectal swab) before and after travelling as well as 3, 6 and 12 months after returning
- questionnaires to assess for travel-associated risk factors

Colonization Rates (n = 170)



3 months:
27.5% (95% CI 19.7-36.8%)

6 months:
14.1% (95% CI 7.8-24.0%)

Risk Factors

		adjusted OR	P-value
Travel Destination	India	1	
	Bhutan	0.44	0.3
	Nepal	0.46	0.2
	Sri Lanka	0.04	< 0.001
Travel Reason	Tourist	1	
	Business	1.58	0.483
	VFR	3.86	0.046
Length of Stay		1.67	0.04
Tap Water	No	1	0.03
	Yes	0.28	
Ice Cream & Pastry	No	1	0.006
	Yes	3.46	

additional factors: accommodation, eating habits, alcohol consumption, travellers diarrhoea, use of ppi

Additional Resistances

Trimethoprim-Sulfamethoxazole (*Nopil, Bactrim*)	49.0%
Ciprofloxacin (*Ciproxin*)	36.3%
Nitrofurantoin (*Furadantin, Uvamin*)	1.3%
Fosfomycin (*Monuril*)	0.7%

Clinical Relevance?

2013

OPEN ACCESS Freely available online

PLOS ONE

Risk Factors for Community-Acquired Urinary Tract Infections Caused by ESBL-Producing *Enterobacteriaceae* –A Case–Control Study in a Low Prevalence Country

Arne Søraas[1]*, Arnfinn Sundsfjord[2,3], Irene Sandven[4], Cathrine Brunborg[4], Pål A. Jenum[1]

1 Department of Medical Microbiology, Vestre Viken Hospital Trust, Bærum, Norway, 2 Department of Microbiology and Infection Control, Reference Centre for Detection of Antimicrobial Resistance, University Hospital of North Norway, Tromsø, Norway, 3 Department of Medical Biology, Research Group for Host-Microbe Interactions, Faculty of Health Sciences, University of Tromsø, Tromsø, Norway, 4 Unit of Biostatistics and Epidemiology, Oslo University Hospital, Oslo, Norway

- 100 cases and 190 controls
- Risk Factors
  - o travelling to Asia, the Middle East or Africa within the past 6 weeks (OR 21, p<0.001)
  - o travelling to Asia, the Middle East or Africa within the past 2 years (OR 2.3, p=0.017)
  - o use of quinolones (OR 16, p<0.001) and β-lactams (OR 5.0, p<0.001)
  - o diabetes mellitus (OR 3.2, p=0.051)
  - o swimming in open water (OR 2.1, p=0.040)
  - o age (OR 0.89 for each 5 years increase, p=0.014)
  - o fish consumption (OR 0.68 for each additional meal/week, OR 0.008)

Clinically relevant, but...

- What‘s the absolute risk?
- Does the absolute risk warrant a change in empirical treatment?
- When is the absolute risk highest? In the first weeks? Months? Everytime, the selection pressure is increased?

Swiss TPH
Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse
Associated Institute of the University of Basel

Universitätsspital Basel

Universität Zürich[UZH]

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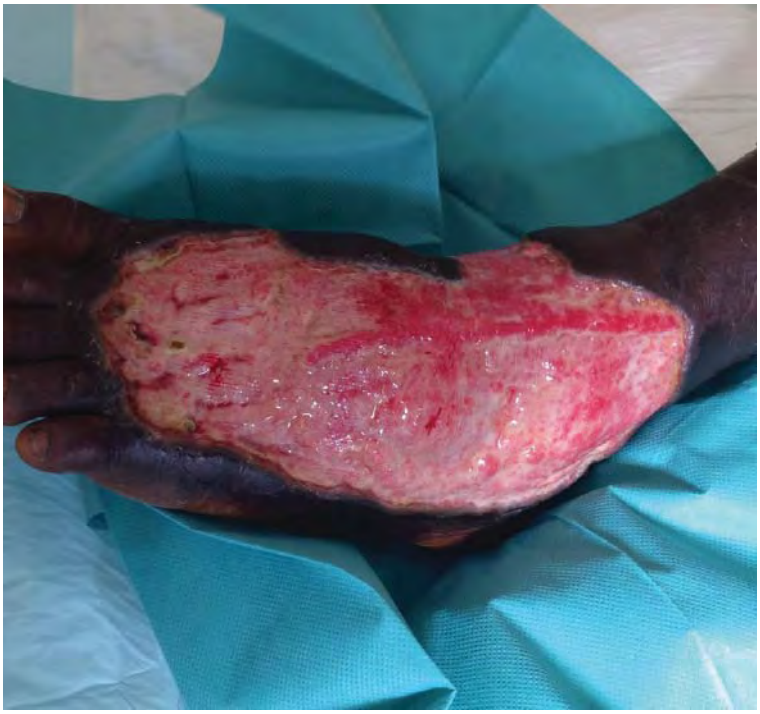
Merck Sharp & Dohme (MSD)
Freiwillige Akademische Gesellschaft Basel

- **S, 15, Mali, born and living in Bamako (no travel outside)**
- **meningitis when young with mental sequel**
- **hospitalised for left foot ulcer evolving for 6 weeks**
- **injury with tailor scissors 5 weeks ago then nodule**
- **after excision of the nodule ➔ extensive ulcer despite local care and amoxicillin**
- **because of persistance ➔ travel to France**

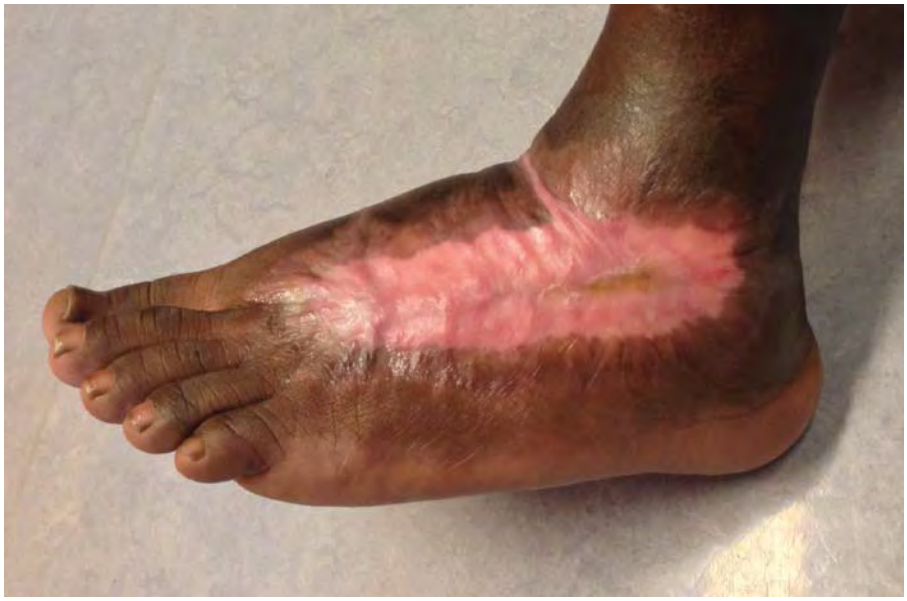
- **low painfull ulcer with no detachment of the edges**
- **oedema + local / leg heat**
- **inguinal adenopathy**
- **no fever**
- **35 kg**



examination

- **WBC : 7800 ; 5080 NPN, Hb 8,7 g/dL, platelet 388 000**
- **CRP: 30**
- **HIV negativ**
- **Biopsy of the ulcer edges :**
  - **direct exam :**
    - **bacteria / Koch bacilla / leishmania = 0**
  - **non specific inflammation**
  - ***M. ulcerans* PCR : +**

outcome under rifampicin + clarithromycine



Week 23

Buruli Ulcer

- *Mycobacterium ulcerans :* environnemental mycobacteria

- toxin (mycolacton) responsable for necrotizing lesions and large skin destruction
- transmission cycle : unclear

  – strongly linked to slow-moving or stagnant water bodies (reservoir for *M ulcerans ?)*

  – transcutaneous contamination

    – directly through local skin trauma or injuries ?

    – via water bugs bite (Africa) ?

      » experimental transmission to mice demonstrated

      » individuals highly exposed to water bug bites less infected : protective effect by frequent non infected bug bites ?

    – via mosquito bites (Australia) ?

      » evidence for prevention by mosquito nets

Jakobsen KH Int J Infect Dis 2010 ; Portaels F, PloS Neglected Tropical Disease 2008 ; Wallace JR Appl Environ Microbiol 2010 ; Marion E Plos Negl Trop Dis 2010

Buruli Ulcer

- **Clinical description :**
  - **nodule or plaque**
  - **then ulcer**

- **localisation**
  - **60% lower limb / 30% upper limb / 10% other**
  - **primary bone infection : 10 %**

- **classification according to size :**

  I: <5 cm

  II: 5-15 cm

  III: >15 cm, multiples, eye, breast , external genitalia, bone

Treatment (WHO)

- **different regimens**
  - **Rifampicin (10 mg/kg/d) + streptomycine (15 mg/kg/d IM) or amikacine**
  - **Rifampicin + clarithromycine (7,5 mg/kg/12h)**
  - **Rifampicin + moxifloxacin (400 mg/d)**

- **duration: 8 weeks**
- **alone : clas. I & II**
  - **success rate : +/- 80%**
- **clas III or failure ATB alone : ATB + surgery**

Buruli ulcer : epidemiology

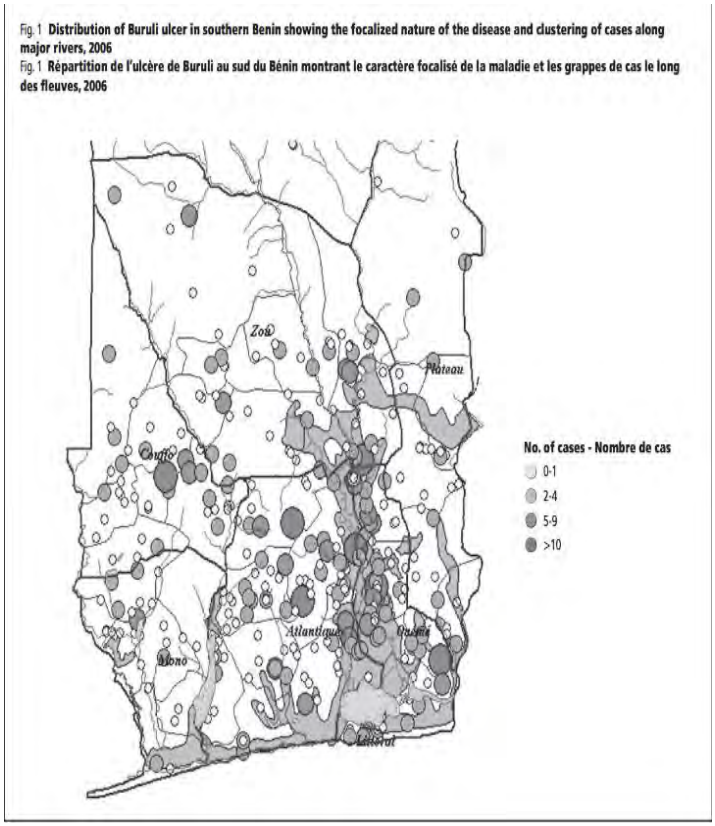
• reported in 30 « tropical » countries (Africa, America, Asia, Western pacific) + Australia, China, Japon

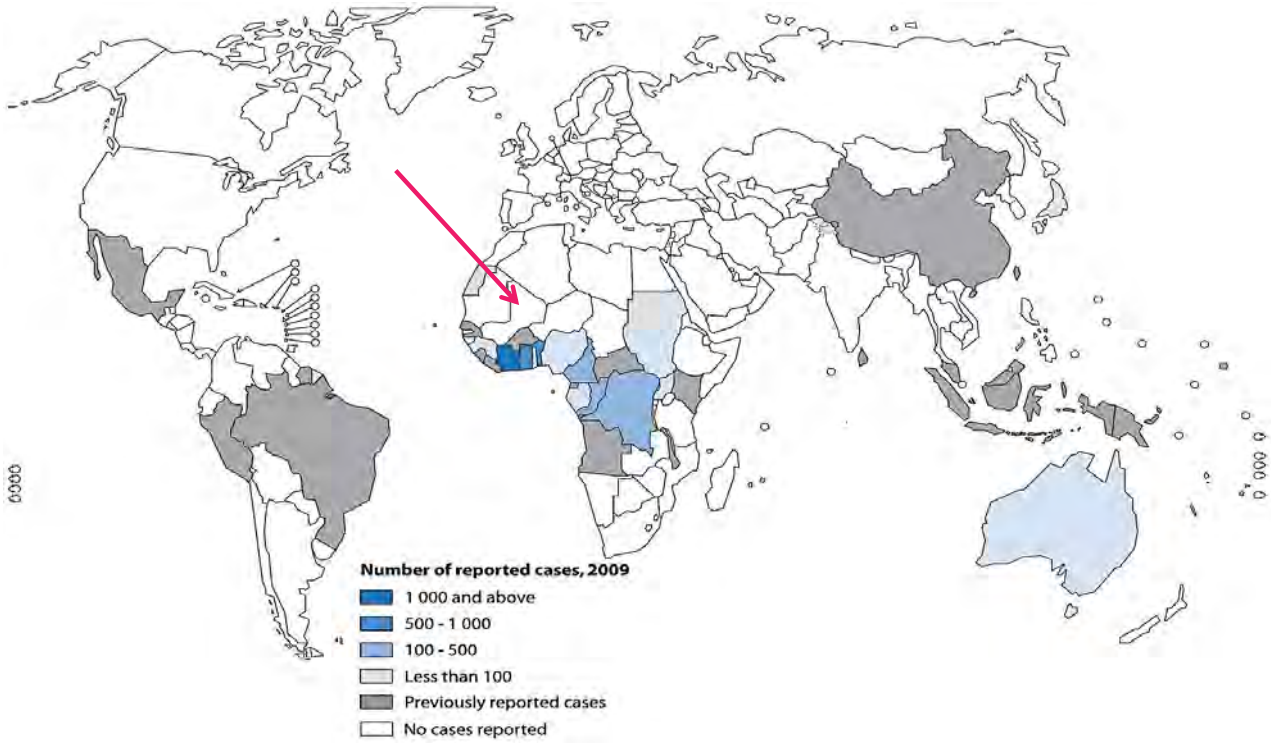
• incidence increases > 1980

• 5000-6000 cases/y by 15 among these countries
  - +++ Bénin, Côte d'ivoire, Ghana
  - Papua-New Guinea, Australia

• +++ rural area in children <15

• distribution in focus linked to river/water bodies





Merritt R. W., Walker E. D., Small P. L. C., Wallace J. R., Johnson P. D. R. et al. (2010). "Ecology and Transmission of Buruli Ulcer Disease: A Systematic Review". PLoS Neglected Tropical Diseases 4(12): e911. doi:10.1371/journal.pntd.0000911.

2 atypical aspects in our case

- **Mali : not considered as an endemic area**
  - ➔ **despite 2 previous cases**

424 *Letters to the Editor*

Painful Buruli Ulcer in a Malian Visitor to France

Acta Derm Venereol 90

Khaled Ezzedine[1], Thierry Pistone[2], Véronique Guir[3] and Denis Malvy[2]

Buruli ulcer disease

***Mycobacterium ulcerans* infection: an overview of reported cases globally**

WEEKLY EPIDEMIOLOGICAL RECORD, NO. 20, 14 MAY 2004

Deux enfants originaires de Côte d'Ivoire et un enfant originaire du Mali développent un ulcère de Buruli alors qu'ils se trouvent en France.

- **Buruli ulcer not reported in urban setting**

A worm in the eye… of the white man

Dr. Juan Cuadros, DTM&H, DTM&PH
Clinical Microbiology and Parasitology
Hospital Príncipe de Asturias
Madrid Spain

History

- A healthy 47 yo teacher
- No travel outside Europe in the last 8 years
- Living by a river with a dog and a cat
- **Rush to hospital because a mobile object in the eye**

TropNet Hamburg 2014

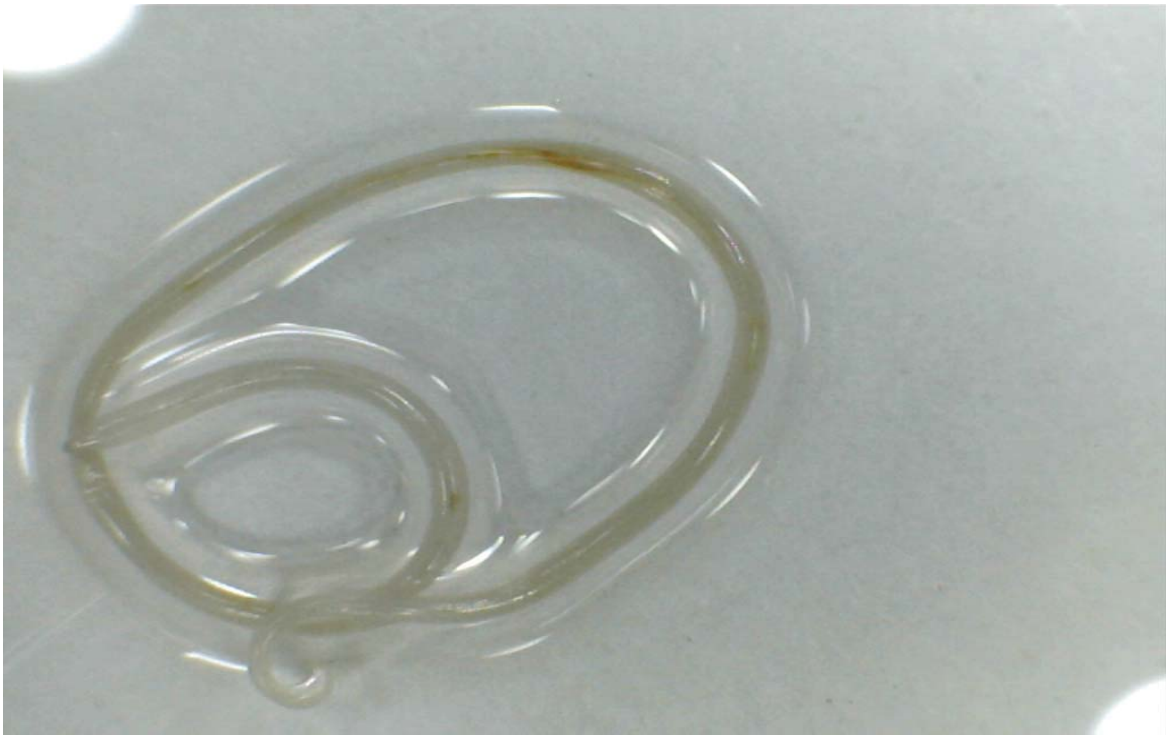
Exploration and treatment

- Slit-lamp: White helminth in superior nasal area, aprox. 4 cm
- Anesthetic eye drops → failed, the worm moved to temporal
- 1 % lidocain subconjuntival → extraction with forceps

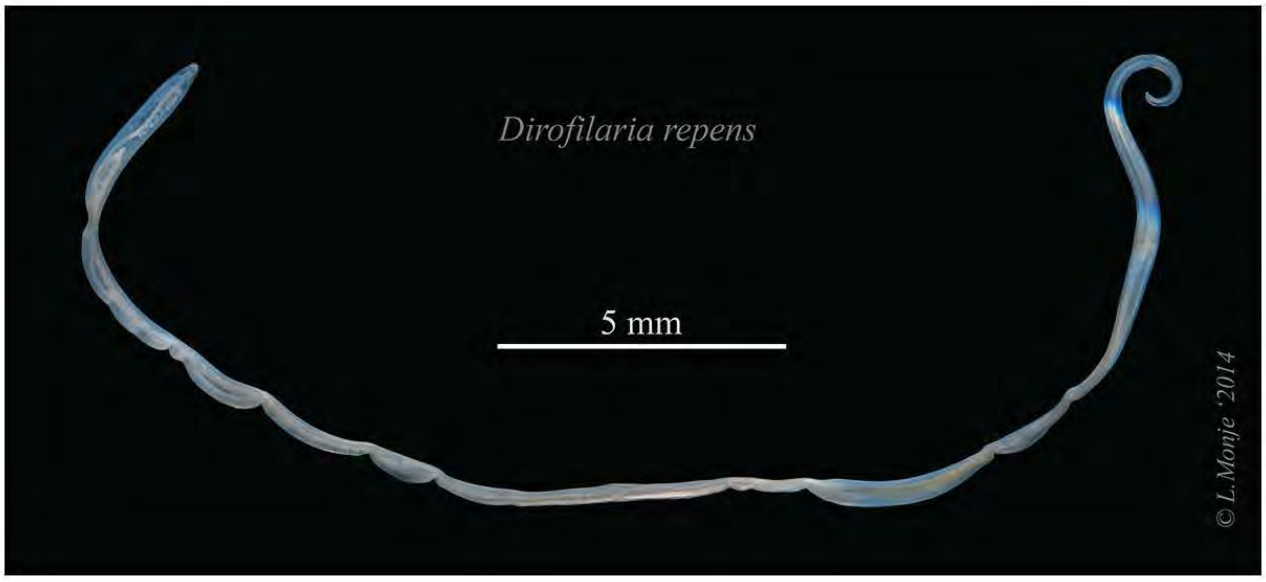
Other data

- Eosinophilia
- No microfilaria in blood
- Chest X-ray normal

The worm

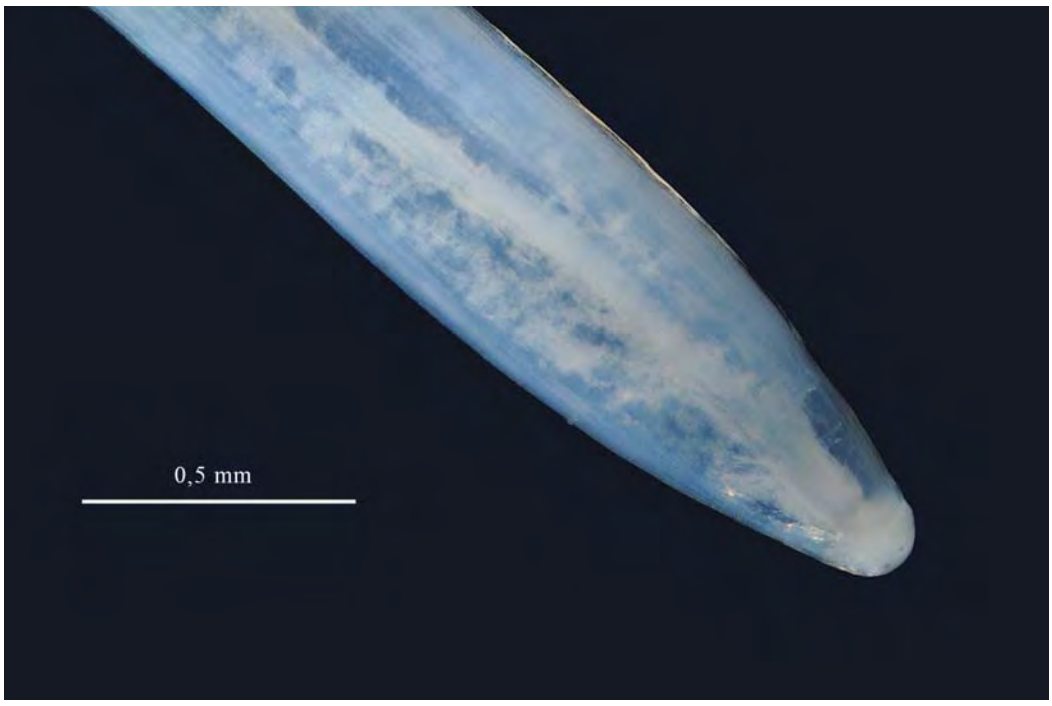


Broomed and measured



Tail

Mouth



“Ridges” in cuticula

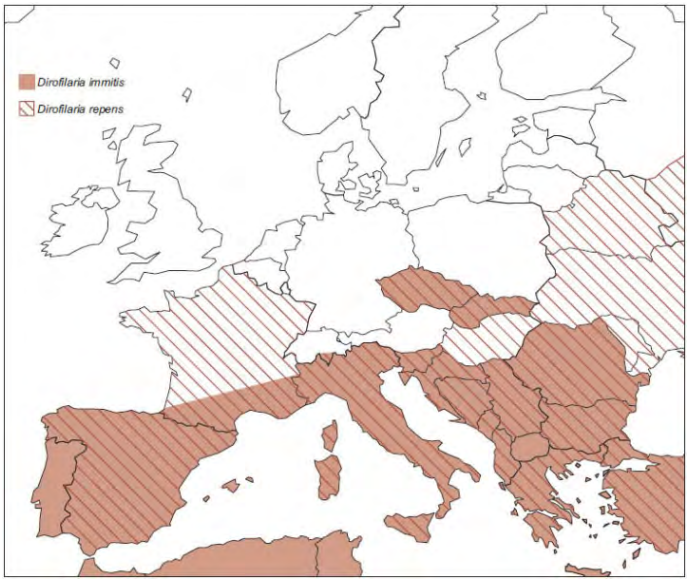
Final diagnosis

- *Dirofilaria repens*
- Something between L4 and preadult worm

Reference Labs.

- Dr. Fernando Simon (Universidad de Salamanca)
- CDC. DPDx. Atlanta

Dirofilariasis in Europe



Points

- In Spain there is only a previous published case of ocular dirofilariasis
- First case outside the Mediterranean endemic area of ocular human disease for *D repens*
- Human and veterinarian cases are on the rise and spreading in Spain
- Emerging disease in Rusia and Ukranie with thousands of cases

- **Tourist in Africa Finds White Worms in Her Eyes**

  A female Russian tourist, who lived in Equatorial Guinea for six months, will have to undergo treatment for an exotic disease known as **loiasis.**

  - The woman arrived in the African country last winter. Six months later, she found a small white tumor on her shoulder.....

Special Thanks

- **Rafael Cañones**
  - Ophtalmology Service. HUPA
- **Juan Romanyk**
  - Microbiology. HUPA
- **Fernando Simón**
  - Universidad de Salamanca
- **Luis Monje**
  - Scientific Photography . Universidad de Alcalá

Membership issues

currently 71 member sites
(no changes)

Proposal:
Members*
Observers
*completed annual survey

The TropNet platforms

Research

- Coordination & support for individual research groups working on communicable & non-communicable diseases:
  - Treatment of malaria
  - Dengue/Chikungunya
  - Cutaneous leishmaniasis
  - MRSA in travelers
  - Haemolyis & Artemisinines
  - Giardia treatment
  - ...

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- Website:
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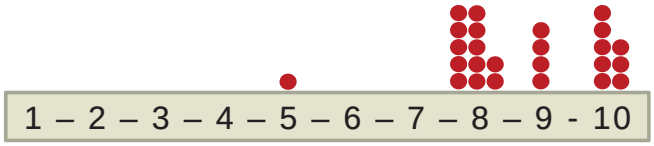
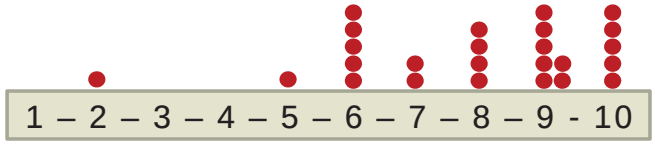
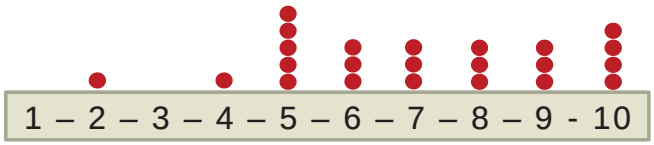
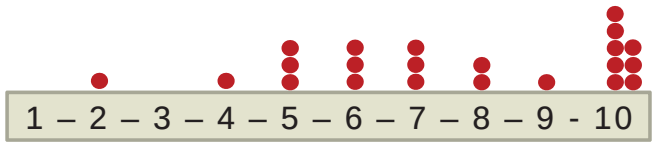
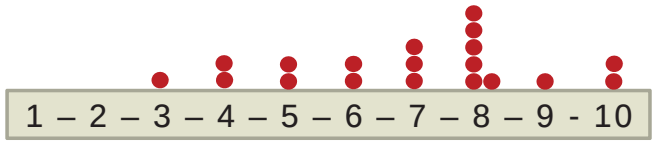
Survey on aims & direction of the network

n = 25	Approval	Ranking of importance
Collaborative research	100%	
Policy development	100%	
Surveillance / reporting	96%	
Network resources	96%	
Teaching & Training	90%	

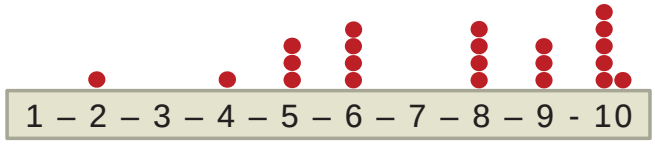
Collaborative research

Willingness to implement a own research project: 60%

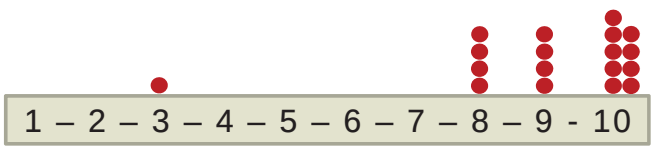
Interest in receiving support to develop own research project: 60%

Willingness to contribute to a research project: 88%

Project with need for ethical clearance



Project without need for ethical clearance



Collaborative research

Ranking of perceived obstacles:

1. Shortage of time / shortage of staff
2. Financial issues
3. Shortage of cases
4. Need for ethical board review

Willingness to lead / contribute

Research

- Leo Visser
- Thomas Zoller
- Angela Corpolongo
- Henrik Nielson
- Toni Seriano
- Israel Molina
- Graham Fry

Policy development

- Christoph Hatz
- Guido Calleri
- Andreas Neumayr
- Ron Behrens

Teaching & Training

- Christoph Hatz
- Andreas Neumayr
- Ron Behrens

Surveillance / reporting

Contribution to `surveillance news on global outbreak situation´:

- Joaquim Gascon
- Guido Calleri
- Andreas Neumayr
- Anna Beltrame
- Juan Cuadros
- Toni Seriano

Travel Medicine Info Material

- Jan Clerinx
- Andreas Neumayr
- Rogelio López-Vélez [Migrant health issues]
- (Graham Fry)

Website

- Thomas Zoller
- Andreas Neumayr

Possible additional strategies

Research

- FP7
- Horizon 2020
- Private Foundations at National level
- Industry

Policy development

- ECDC
- National Societies
- National Health Authorities
- WHO (collaborating centre)

Teaching & Training

- TropEd
- Rotation of hosting institutes
- Institutional modules

Surveillance / reporting

Contribution to `surveillance news on global outbreak situation´

Link with ECDC/EuroTravNet or collaboration?

Travel Medicine Info Material

- Collaboration with extra-European institutions/groups
- Financial industry support (several sponsors)

Website

The TropNet platforms

Research

- Coordination & support for individual research groups working on communicable & non-communicable diseases:
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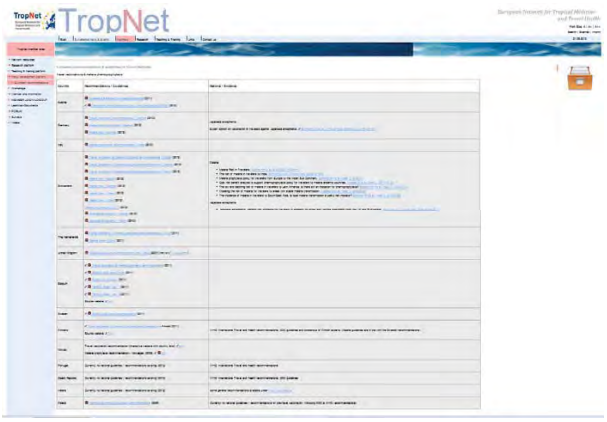
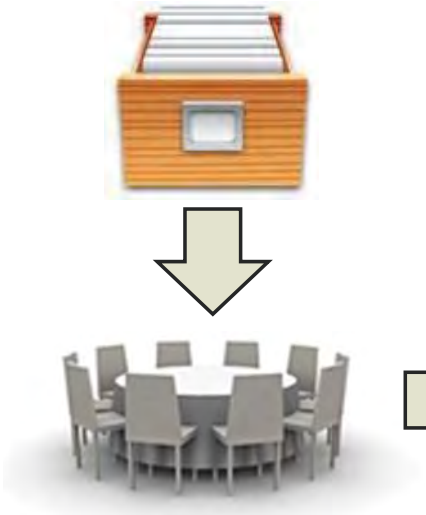
TropNet
European Network for Tropical Medicine and Travel Health

BNITM
Bernhard-Nocht-Institut für Tropenmedizin

Swiss TPH

European recommendations & guidelines in Tropical & Travel Medicine





`Evidence-based European Recommendation Initiative based on Common sense´ (EERIC)

Summary analysis of current situation in the frame of a MD/MS thesis ?

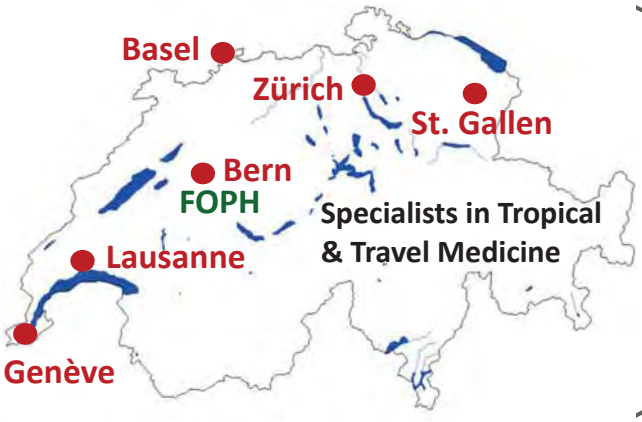
TropNet
European Network for Tropical Medicine and Travel Health

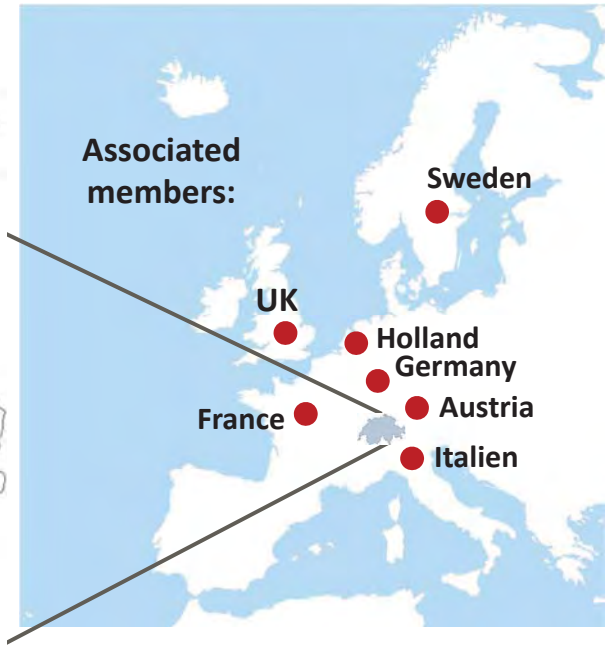
Expert Committee for Travel Medicine (ECTM)

BNITM
Bernhard-Nocht-Institut für Tropenmedizin

Swiss TPH

Expertenkomitee für Reisemedizin
Comité d'experts pour la médecine des voyages
Comitato di esperti per la medicina di viaggio
Expert committee for travel medicine





Could ECTM be the Travel and Tropical Medicine Think tank?

- AIMS of ECTM: Consensus on rational recommendations for travel medicine
- Optimising pre- and post-travel health advice in European countries
- Improvement of travellers‘ compliance abroad
- Economically independent partner(s) for travel medicine issues at national and international levels
- Expansion of membership?

The TropNet platforms

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Teaching & Training

- **Development of a curriculum / modules for a European ISTM-prep course**
- **Setup and coordination of "hands on" training within the network**
- **ECTMIH 2015 in Basel: TropNet pre-conference Travel Medicine Course**

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ECTMIH 2015

The Swiss Society of Tropical Medicine and Parasitology invites you to come to Basel

TropNet preconference Travel Medicine Course

Target audience: Travel Medicine Specialists
Format: One-day pre-congress course
Saturday, September 5th 2015

- ✓ Arthropod-borne diseases & prevention
- ✓ Gastrointestinal disorders and management
- ✓ Importance of travel medicine vaccines
- ✓ High risk travel (accidents, mountains etc.)
- ✓ New approaches in travel risks and advice

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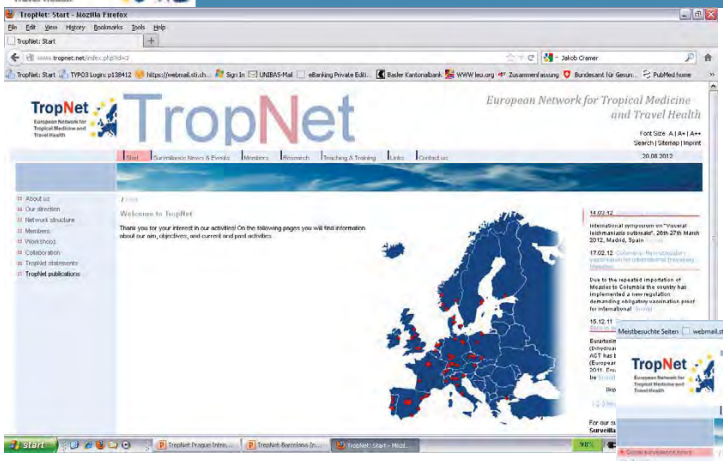
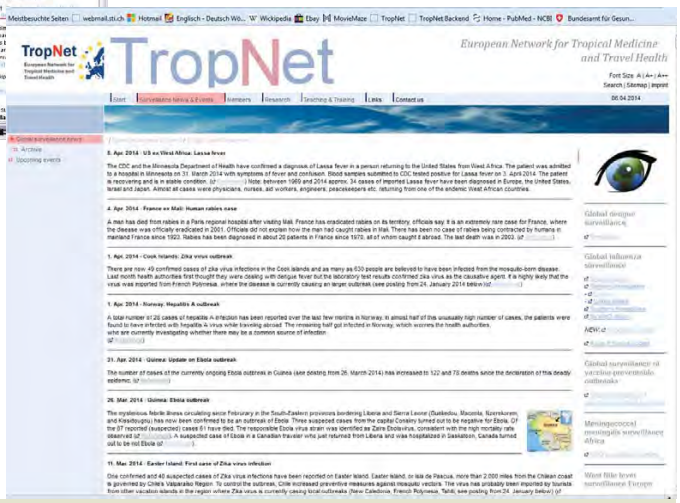


Surveillance News

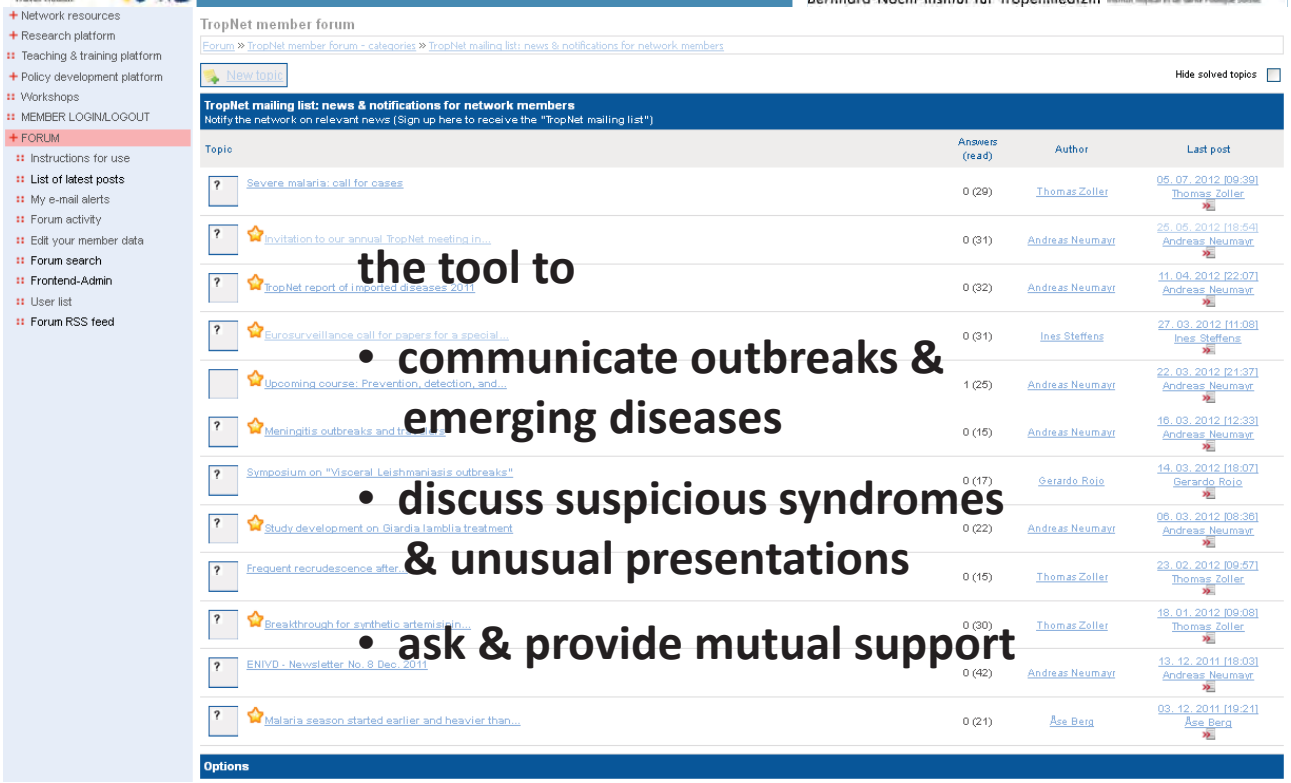


www.tropnet.net

&

www.tropnet.eu

The TropNet FORUM



the tool to

- **communicate outbreaks & emerging diseases**
- **discuss suspicious syndromes & unusual presentations**
- **ask & provide mutual support**

The TropNet platforms

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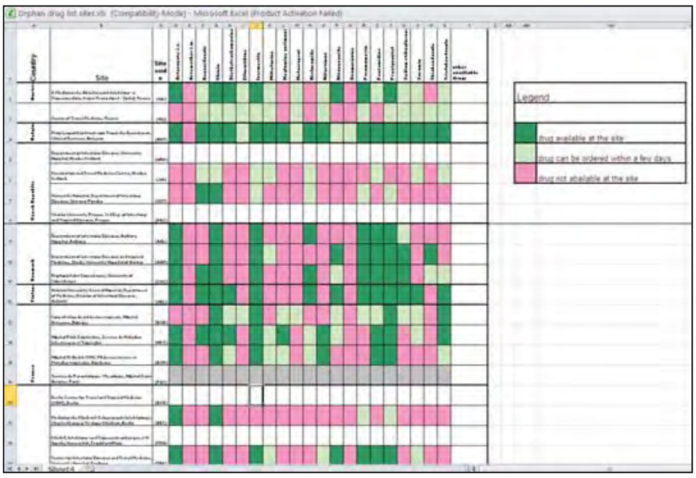
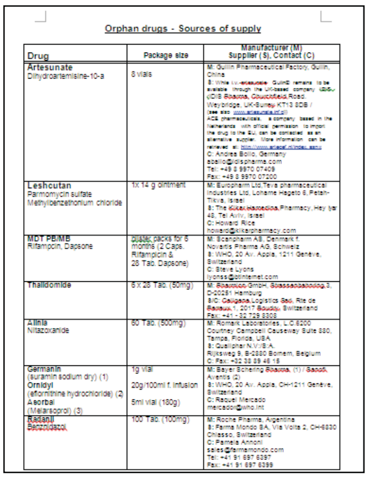
Orphan drugs: network stock-list & sources





Orphan drugs - Sources of supply

Drug	Package size	Manufacturer (M) Supplier (S), Contact (C)
Artesunate Dihydroartemisine-10-a	8 vials	M: Guilin Pharmaceutical Factory, Guilin, China S: While i.v. artesunate Guilin® remains to be available through the UK-based company IDIS, (IDIS Pharma, Churchfield Road, Weybridge, UK-Surrey KT13 8DB / (see also www.artesunate.inf.o)) ACE pharmaceuticals, a company based in the Netherlands with official permission to import the drug to the EU, can be contacted as an alternative supplier. More information can be retrieved at: http://www.artecef.nl/index.aspx C: Andrea Bolio, Germany abolio@idispharma.com Tel: +49 8 9970 07409 Fax: +49 8 9970 07200
Leshcutan Parmomycin sulfate Methylbenzethonium chloride	1x 14 g ointment	M: Europharm Ltd, Teva pharmaceutical Industries Ltd, Lohame Hageto 6, Petah-Tikva, Israel S: The Kikar Hamedina Pharmacy, Hey Iyar 48, Tel Aviv, Israel C: Howard Rice howard@kikarpharmacy.com
MDT PB/MB Rifampcin, Dapsone	blister packs for 6 months (2 Caps. Rifampicin & 28 Tab. Dapsone)	M: Scanpharm AS, Denmark f. Novartis Pharma AG, Schweiz S: WHO, 20 Av. Appia, 1211 Genève, Switzerland C: Steve Lyons lyonss@btinternet.com
Thalidomide	6 x 28 Tab. (50mg)	M: Pharmion GmbH, Strassenbahnring 3, D-20251 Hamburg S/C: Caligara Logistics Sàrl, Rte de Bassaux 1, 2017 Boudry, Switzerland Fax: +41 - 32 729 8308
Alinia Nitazoxanide	60 Tab. (500mg)	M: Romark Laboratories, L.C.6200 Courtney Campbell Causeway Suite 880, Tampa, Florida, USA S: Qualiphar N.V./S.A. Rijksweg 9, B-2880 Bornem, Belgium C: Fax: +32 38 89 46 15
Germanin (suramin sodium dry) (1) **Ornidyl** (eflornithine hydrochloride) (2) **Arsobal** (Melarsoprol) (3)	1g vial 20g/100ml f. infusion 5ml vial (180g)	M: Bayer Schering Pharma (1) / Sanofi Aventis (2) S: WHO, 20 Av. Appia, CH-1211 Genève, Switzerland C: Raquel Mercado mercador@who.int
Radanil Benznidazol	100 Tab. (100mg)	M: Roche Pharma, Argentina S: Farma Mondo SA, Via Volta 2, CH-6830 Chiasso, Switzerland C: Pamela Annoni sales@farmamondo.com Tel: +41 91 697 6397 Fax: +41 91 697 6399

The 2011 figures on imported diseases

40 of 67 sites

Malaria	1043	(871 *falc.; 172 non-falc.)*
Giardiasis	1089	
Schistosomiasis	672	
Amoebiasis	381	
Dengue	341	
Leishmaniasis	237	(185 CL & ML; 52 VL)
Rickettsiosis	118	
Loiasis	47	
Chikungunya	27	

The 2012 figures on imported diseases

21 of 68 sites

Malaria	552	(461 *Pf; 52 Pv; 28 Po; 12 Pm)*
Giardiasis	588	
Schistosomiasis	379	
Amoebiasis	167	
Dengue	250	
Leishmaniasis	57	(28 *CL*; 4 *ML*; 25 *VL*)
Rickettsiosis	56	
Typhoid fever	24	
Loiasis	8	
Chikungunya	4	
Sarcocystis	18	

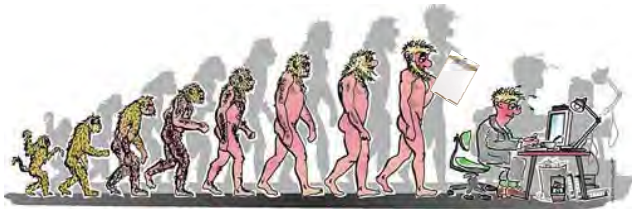
The 2013 figures on imported diseases

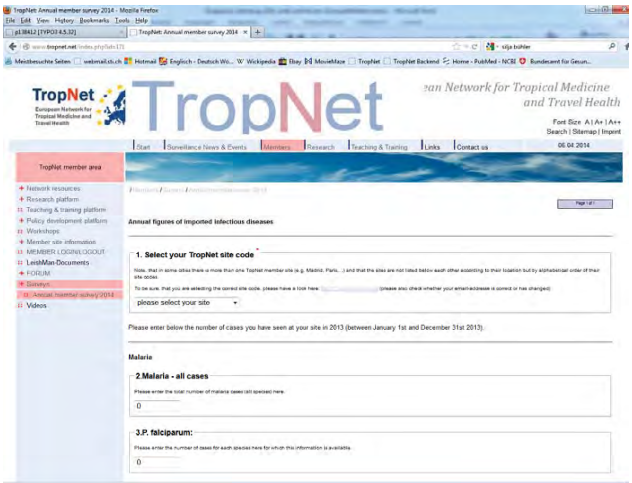
24 of 71 sites

Malaria	785	(673 *Pf; 56 Pv; 42 Po; 14 Pm)*
Giardiasis	738	
Schistosomiasis	284	
Amoebiasis	174	
Dengue	350	
Leishmaniasis	161	(133 *CL*; 2 *ML*; 26 *VL*)
Rickettsiosis	90	
Typhoid fever	42	
Loiasis	19	
Chikungunya	29	
Sarcocystis	8	

all reported by Munich

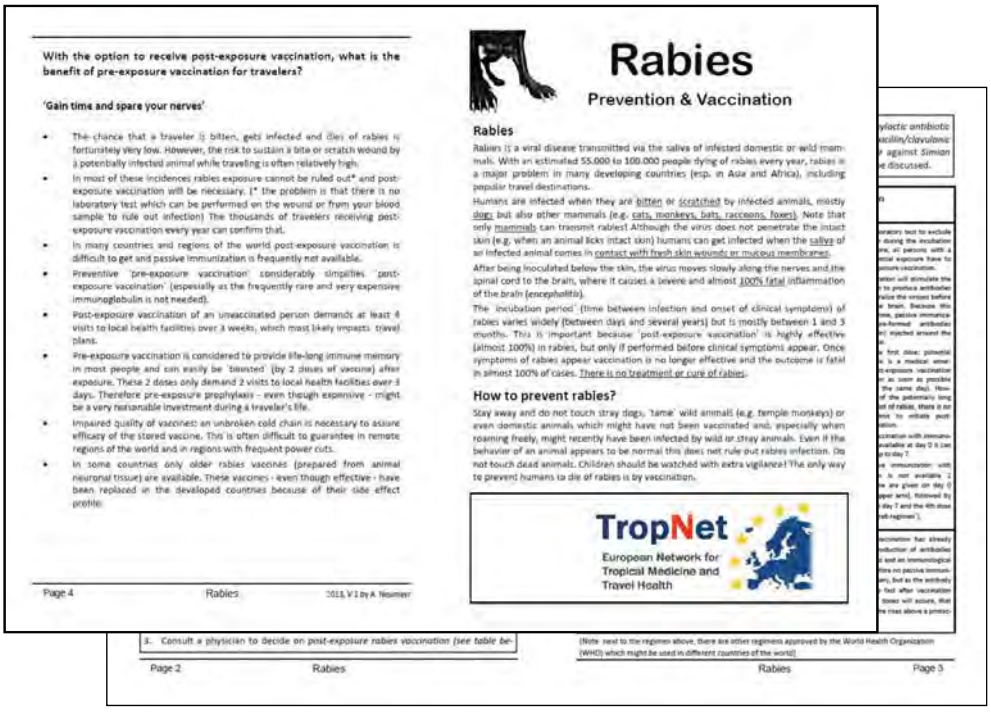
- 1 case (Antwerp, Belgium in 2013)
- 2 cases (Paul-Lechler Hospital Tübingen, Germany in Oct. 2013)
- **1 case Helsinki, Finnland 2014**





Paper-based Excelsheet → **Paperless** web-based → **Senseless ?**

Development of TropNet travel medicine info material



Focus: core information for travellers on relevant health issues

Traveler's diarrhea	Suggestion:
Protection against arthropods	_____
Malaria	_____
Dengue	_____
Chikungunya	_____
Hepatitis A	_____
Hepatitis B	_____
Influenza	_____
Japanese encephalitis	Andreas Neumayr
Tick-borne encephalitis	_____
Meningococcal meningitis	_____
Bee & wasp sting allergies	_____
Schistosomiasis	Jan Clerinx ?
Road traffic accidents	_____
Scuba diving	_____
STDs	_____
Venomous & poisonous animals	Thomas Junghanss ?
Typhoid fever	_____
Migrants / Visting friends & relatives	Rogelio López-Vélez ?

Format: Word document -> send to us for converting into flyer/leaflet format

Report on ongoing TropNet studies & studies with participation of TropNet centres

Currently ongoing TropNet studies

➔ Artesunate for severe malaria in Europe

➔ **EU-FP7 DengueTools & TropNet study**

Sentinel surveillance of imported dengue in returning travelers: trends and virus evolution

➔ **LeishMan working group**

Harmonization of clinical management & diagnostic methods for cutaneous & mucosal leishmaniasis in Europe

➔ **Proof of concept study of Eurartesim® in patients with imported uncomplicated *P. vivax* malaria**

Current TropNet participation

➔ **Safety registry of Eurartesim® - REGISTRAT-MAPI**

Treatment of uncomplicated malaria in returning travellers with Dihydroartemisinin/Piperaquine (France, Germany, Italy, Belgium, The Netherlands, Spain, UK)

➔ **Pregnancy registry of Eurartesim® - Sigma Tau**

European pregnancy registry

➔ **StaphTrav - European network on imported *S. aureus***

Antibiotic resistance testing and molecular typing of imported *S. aureus* in returning travelers

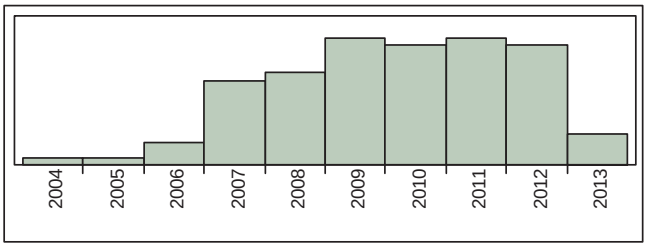
TropNet study: Artesunate for severe malaria in Europe

Number of recruited patients: **204**

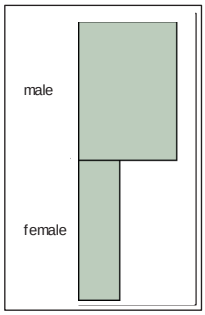
Thomas Zoller MD, MSc, DTM&H
Florian Kurth, MD, MSc

N= 204 cases

Year of Presentation



Gender Distribution



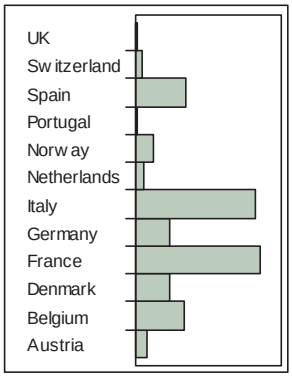
male
n=140
71%

female
n=60
29%

Most common criteria for Severe Malaria according to WHO:

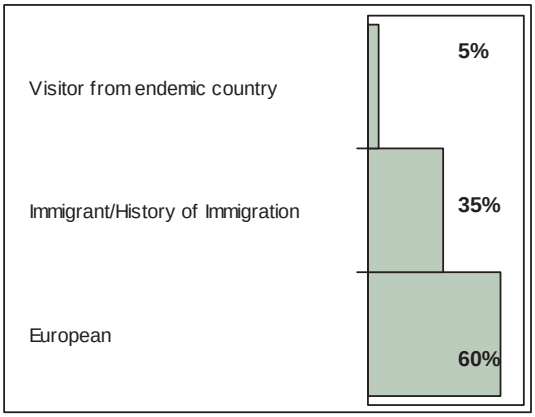
- Jaundice (91/204)
- Cerebral Malaria (46/204)
- Acute Renal Failure (43/204)

Reporting Country

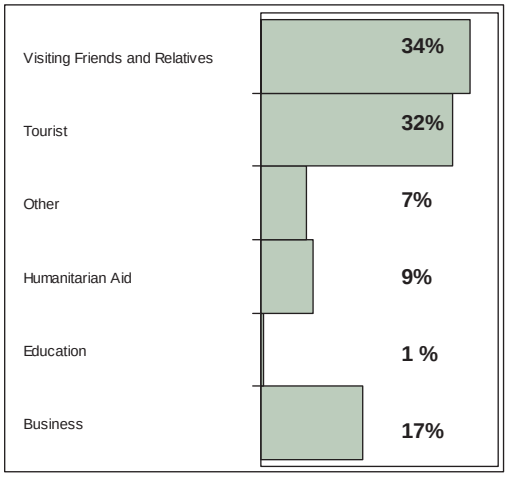


Country	Number of Cases
Austria	5
Belgium	21
Denmark	15
France	54
Germany	15
Italy	52
Netherlands	4
Norway	8
Spain	22
Switzerland	3
UK	1

Status of Patient

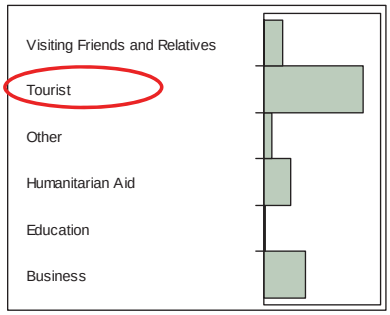


Purpose of Travel

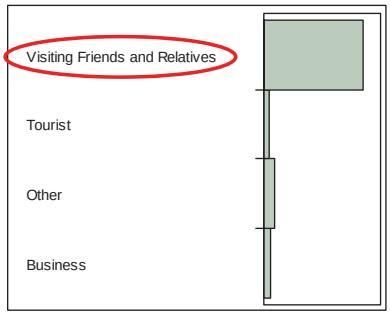


Purpose of travel for subgroups:

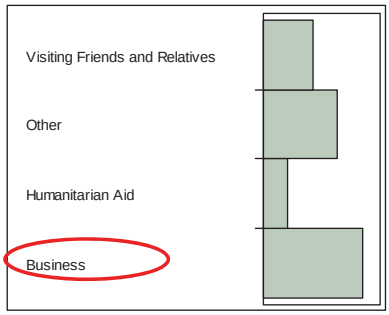
Europeans



Immigrants

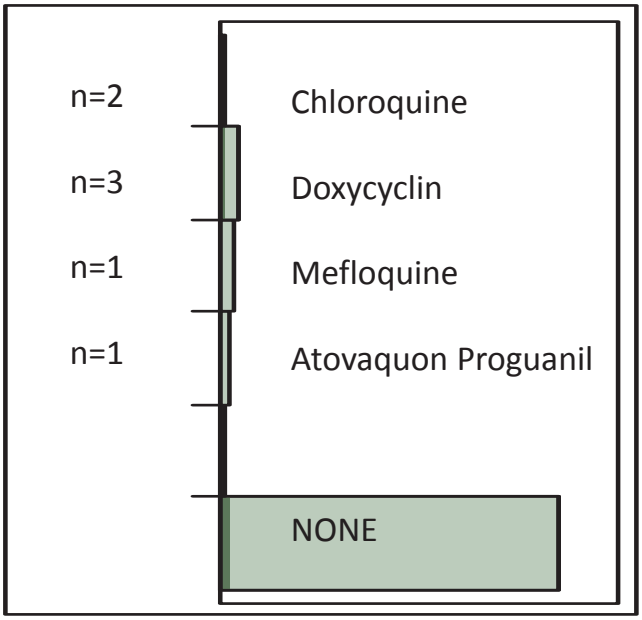


Visitors from end. countries

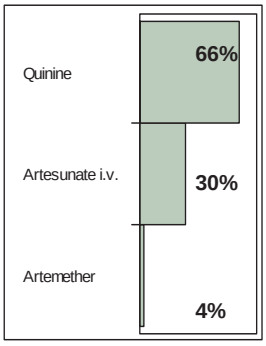


Chemoprophylaxis-

(only compliant Patients)



first line treatment:

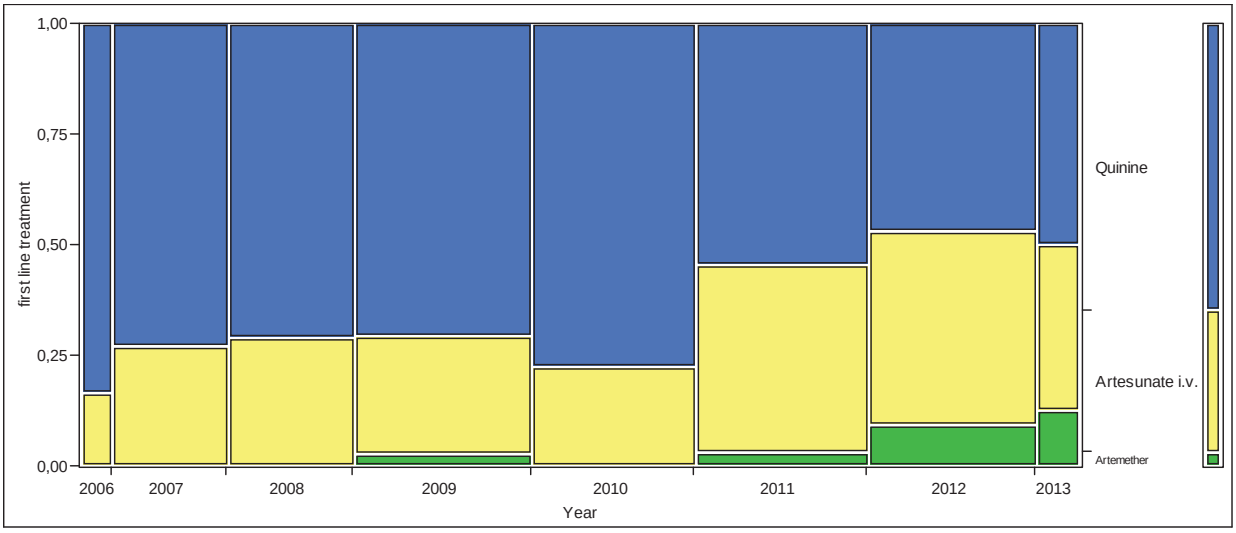


n=134

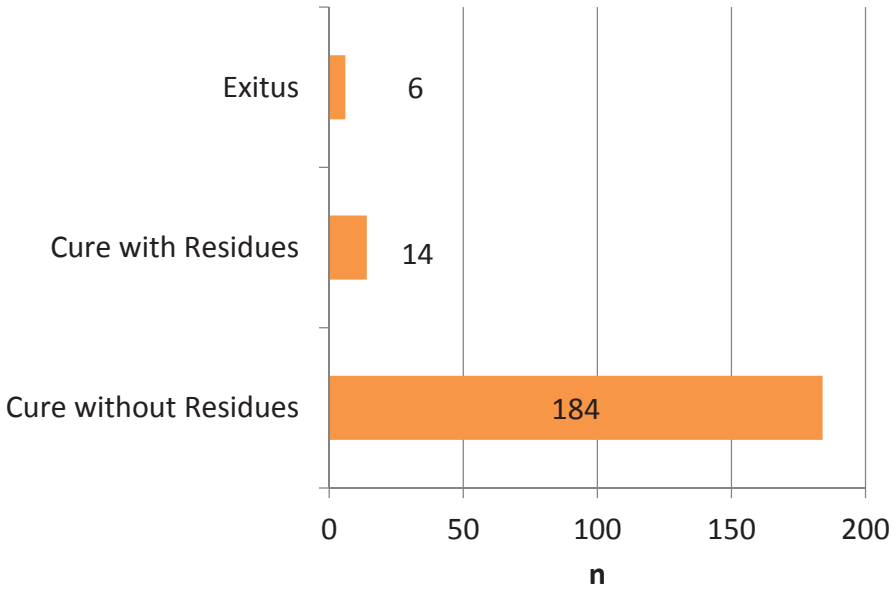
n=62

n=7

first line treatment / Year:



Outcome



TropNet
European Network for Tropical Medicine and Travel Health

Swiss TPH
Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse

EU-FP7 joint DengueTools & TropNet study:

Sentinel surveillance of imported dengue in returning travelers: trends & virus evolution

Number of recruited patients: **~ 250**
(started Sept. 2011, ending Sept. 2014
- potentially extended for 6 months)

1. **Data analysis in the frame of a MD/MS thesis ?**
2. **Related MD/MS thesis option: European Dengue**

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LeishMan working group

Harmonization of clinical management & diagnostic methods for cutaneous & mucosal leishmaniasis in Europe

- **Improving treatment based on molecular species differentiation**
- **Harmonizing the molecular diagnostic methods** for rapid diagnosis and species determination
- **Harmonizing the therapeutic guidelines** for cutaneous and mucosal leishmaniasis in Europe

Current situation within Europe

- **Clinical management of CL & ML**
  - various treatment recommendations differentiating between Old and New World leishmania species are available
  - treatment recommendations are based on data from endemic regions
- **Species specific treatment**
  - species specific treatment recommendations are available
  - not evaluated in travelers
- **Genotyping of leishmania species**
  - done in many centers / widely available
  - no comparative evaluation / validation of the different methods

Objectives of collaborative project

- evaluation of the applied treatment protocols and outcomes with respect to the infecting parasite species
- comparison of all currently applied genotyping techniques
- obtaining genetic sequence information of all clinical isolates
- establishing a common data base of molecular and clinical data
- **long-term goal: standardization of species specific treatment protocols based on molecular species typing**

Selection of treatment regimen

- each centre is free to choose a treatment regimens based on state of the art knowledge / own experience
- species specific treatment recommendations have been compiled by the Leishman working group

Inclusion criteria

1. all patients with parasitologicaly confirmed cutaneous or mucosal leishmaniasis
2. clinical data **and** samples available
3. patient informed consent regarding the use of biopsy material and data

Exclusion criteria

- none
- pregnancy is not a criterion of exclusion, but treatment has to be adapted or postponed after delivery

The Leishman consortium

8 European countries, 17 institutions

Belgium (1 institution)

France (3 institutions)

Germany (1 institution)

Netherlands (4 institutions)

Portugal (2 institution)

Spain (2 institution)

Switzerland (1 institution)

UK (3 institutions)

Coordinators

Clinical group:	Blum, Johannes
Molecular diagnostic group:	Felger, Ingrid

Steering committee - members

Clinical group:	Bailey, Mark **Blum, Johannes** (coordinator clinical group) Buffet, Pierre
Molecular diagnostic group:	Bart, Aldert Van der Auwera, Gert

Where we are:

- ☑ setup of database
- ☑ data collection and entering ongoing

Publications:

Clinical group:

- ☑ Local or systemic treatment for new world cutaneous leishmaniasis? re-evaluating the evidence for the risk of mucosal leishmaniasis. (International Health 2012;4:153-163)
- ☑ Clinical aspects and management of cutaneous leishmaniasis in rheumatoid patients treated with TNF-α antagonists (Travel Med Infect Dis. 2013)
- ☑ **LeishMan Recommendations for Treatment of Cutaneous and Mucosal Leishmaniasis in Travelers, 2014 (J Trav Med 2013)**

Sigma-Tau & TropNet study:

Proof of concept study of Eurartesim® in patients with imported uncomplicated *P. vivax* malaria

Study outline

Study sites:	multicentre study within the TropNet network (sites with a considerable number of *P. vivax* cases in Italy , Spain, France, Germany, Switzerland, The Netherlands, Israel)
Study subjects:	100 adult patients (18 - 65 years old), male & female, affected by uncomplicated *P. vivax* malaria. ECG day 0
Setting:	patients may be followed up as in- or out-patients
Timeframe:	study recruitment period: 16 months (starting Oct. 2013) each patient will remain in the study for 42 days: **D1, D2, D3 – D7 – D21 – D42**

Study objectives

Primary objective: uncorrected adequate clinical and parasitological responce (ACPR) at Day 21

Secondary objectives:

- Proportion of aparasitemic patients (at different visits)
- Proportion of afebrile patients (at different visits)
- Uncorrected adequate clinical and parasitological response at Day 42
- Proportion of patients with treatment failure

Safety & tolerability of the drug:

- Adverse events occurrence
- Change in haematology, blood chemistry and vital signs (no ECG follow-up)

Study sites & status

ITALY: study approved by coordinating EC (Brescia) & RA (AIFA)
1. BRESCIA - Clinica di Malattie Infettive e Tropicali, Spedali Civili di Brescia
2. VERONA - Centro per le Malattie Tropicali, Ospedale S. Cuore, Negrar
3. ROMA - Centro di Malattie Tropicali - INMI Spallanzani

SWITZERLAND: study approved by coordinating EC (Basel) & RA (Swissmedic)
4. BASEL (study coordinator) - Swiss Tropical and Public Health Institute
5. BERN - Bern University Hospital
6. LAUSANNE - Policlinique Médicale Universitaire

FRANCE: study approved by EC – pending approval by RA (ANSM)
7. BORDEAUX - Hôpital St André-CHU, Médecine interne et Maladies Tropicales

SPAIN: study approved by coordinating EC (Hospital Clinic Barcelona) – pending approval by RA (AEMPS)
8. BARCELONA - CRESIB-Hospital Clinic, Barcelona
9. BARCELONA 2 - Hospital Vall d'Hebron, Barcelona
10. MADRID - Tropical Medicine & Clinical Parasitology, Hospital Ramon y Cajal

THE NETHERLANDS: study approved by EC & RA (CCMO)
11. LEIDEN - Leiden University Medical Centre

GERMANY: study in the course of submission to ECs & RA (BFARM)
12. MUNICH - Dep. of Infectious Diseases & Tropical Medicine, University of Munich
13. BERLIN - Medizinische Klinik mit Schwerpunkt Infektiologie, Charite

Safety & Pregnancy Registries of Eurartesim®

- **Safety registry** **(some TropNet Centres involved)**

  A European multi-centre study evaluating QTc prolongation with regard to co-morbidities and concomitant medications; monitoring patterns of drug utilization; treatment-assoc. adverse events

- **Pregnancy registy** **(some TropNet Centres involved)**

  A European multi-centre pregnancy registry for patients exposed to Eurartesim® for the treatment of malaria whilst pregnant

Pregnancy Registry

Study objectives:

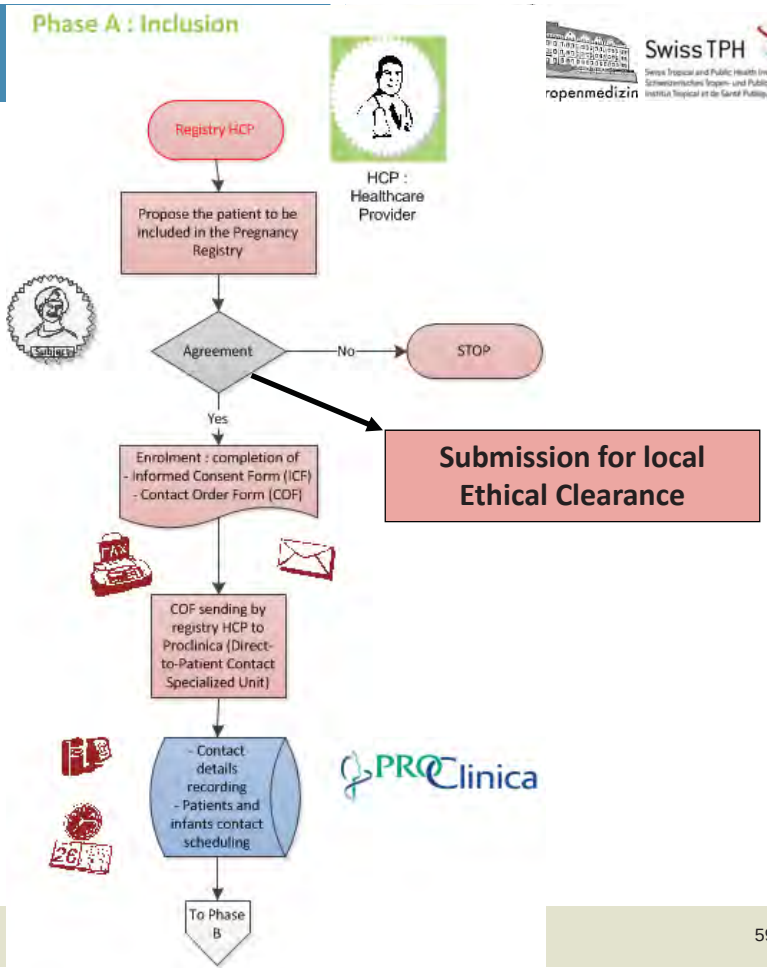
1. The primary objective is to assess the live birth incidence of minor and major congenital birth defects following exposure to Eurartesim® whilst pregnant or in the one month (30 days) prior to conception.
2. The secondary objective is to assess both maternal and fetal outcome following exposure to Eurartesim™ whilst pregnant or in the one month (30 days) prior to conception.

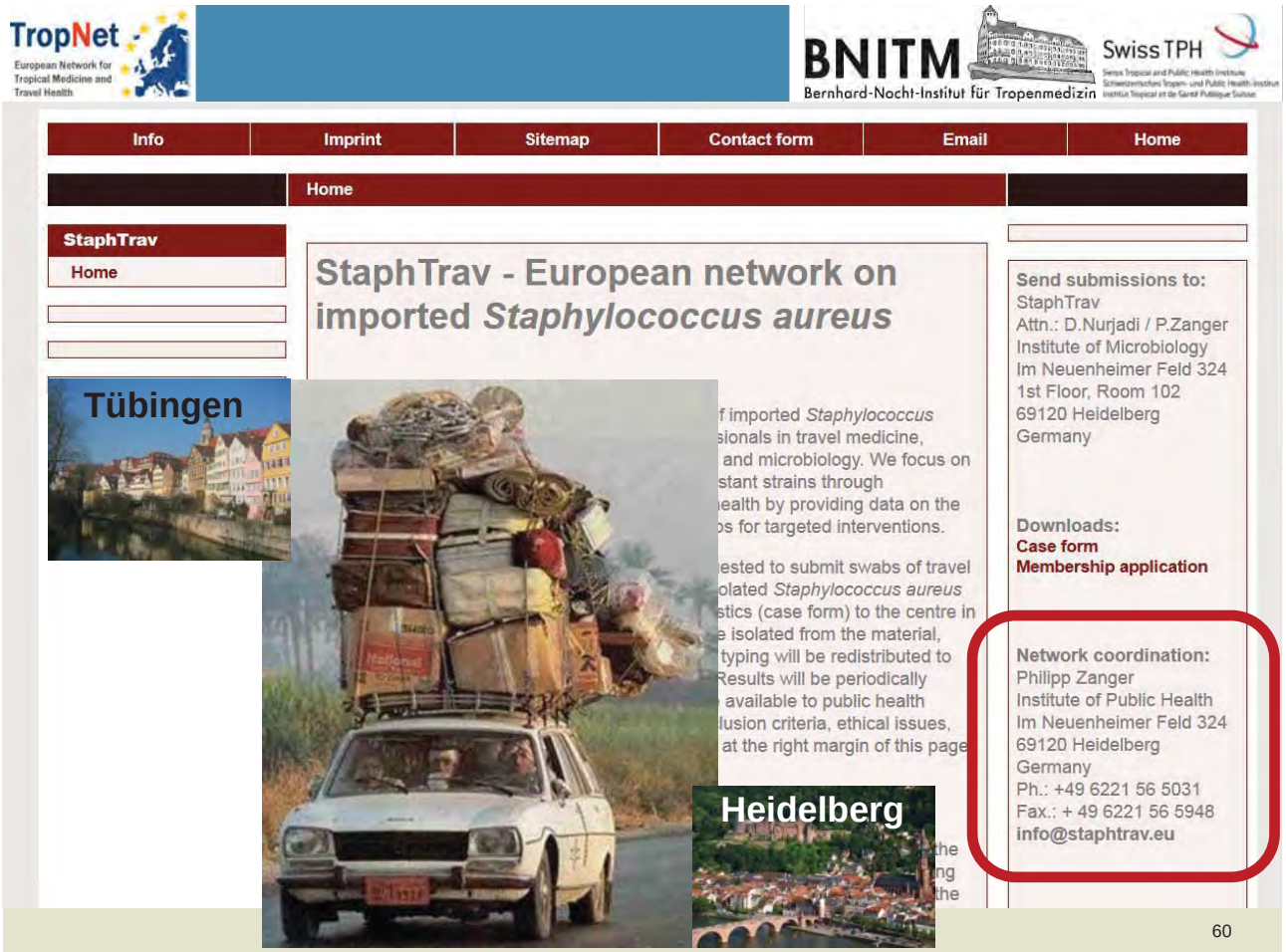
Activity	Expected Time
Set-up period	Nov 2011 – Aug 2012
Recruitment period	Sept/Oct 2012 - 2017
Follow-up period	2018 - 2019
Close out period	2019

Pregnancy registry

Patient Contact Process:

Present status: no case





Upcoming TropNet studies

➔ **TropNet study HaemoART**

Study on haemolysis under artemisinin therapy

➔ **TropNet studies GiardiaTreat & GiardiaREF**

Tolerability of 5-nitroimidazole 1st-line regimens &
RCT of 2nd-line regimens for refractory Giardiasis

➔ **TropNet safety surveillance of life vaccines in immunocompromised persons**

TropNet artemisinin drug safety studies

HAEMO-ART, SMPS & TOX-ART

Florian Kurth, Andreas Neumayr &

Thomas Zoller

Observational safety study:	Retrospective case collection / register:	Analysis of patient samples:
Haematological alterations during **any oral or intravenous** malaria treatment	Intravenous Artesunate **Pharmacovigilance** for **i.v. Artesunate**	**In vitro** study: metabolism & toxicity of artemisinins in Patient samples and *in-vitro* generated drug metabolites
HAEMO-ART	**SMPS**	**TOX-ART**
All TropNet centres	All TropNet centres	Charité + interested TropNet sites

TropNet HaemoART study:

Haemolysis and other haematological alterations after antimalarial treatment with artemisinins (and other drugs)

Background

- Intravenous artesunate causes a late haemolytic reaction in some patients
- No study has systematically investigated haematologic adverse effects of artemisinins
- Clinical observations suggest that a – mostly sub-clinical – haemolysis may occur also in patients after oral artemisinin treatment

Rationale

The proposed study analyses prospectively **haematological parameters under and after antimalarial therapy**

Study design

prospective, observational, multi-centre study

Primary endpoint

- clinical or laboratory-diagnosed haemolysis not attributable to malaria
- in a period of 6 weeks after the 1st dose of antimalarial treatment

Secondary endpoints

- occurrence of any adverse drug reactions
- degree of haemolysis in relation to risk factors
- duration of haemolysis
- clinical interventions as a consequence of haemolysis
- immunohaematologic parameters in patient samples
- Other haematologic parameters under / after treatment

Study Population:

Patients with **uncomplicated as well as severe malaria** who receive antimalarial treatment with either

- artemether-lumefantrine
- dihydroartemisinin-piperaquine
- atovaquone-proguanil
- mefloquine
- intravenous artesunate*
- intravenous quinine
- chloroquine
- chloroquine-proguanil

*** Due to legal requirements, cases will be analysed separately and retrospectively**

Inclusion criteria

- adult or paediatric patient with microscopically confirmed malaria (***any species***)
- patient or legal guardian able to provide informed consent
- patient able and willing to complete follow-up examinations at least until **Day 21**

Exclusion criteria:

- Any drug or condition inducing haemolysis (details in protocol)

Definition of post-treatment haemolysis

any

- **unexplained increase of LDH** and/or
- **elevation of LDH above normal values for ≥ 7 days after parasitological cure**

within a period of 6 weeks after the 1st dose of antiparasitic treatment

(in addition other clinical and laboratory parameters may be considered to define a case of post-treatment haemolysis)

Visit schedule

In-patient	**Visit 1**	**Day 0**	*before first dose of treatment is given:* - inclusion and exclusion criteria, informed consent - patient questionnaire - vital status, clinical examination, baseline blood sample
	Visit 2	**Day 3**	vital status, clinical examination, blood sample, urine sample
Regular Follow-up	**Visit 3**	**Day 6-10**	vital status, clinical examination, blood sample, (optional: urine sample)
Study-Follow-up	**Visit 4**	**Day 14-18**	vital status, clinical examination, blood sample, (optional: urine sample)

Note: ***- Visit 4 can take place either at the study centre or alternatively at a local GP with a reduced set of laboratory examinations:*** **RBC, WBC & LDH**
- if signs of haemolysis are detected, the patient must be referred to the study centre for Visit 5

➔ **If no signs of haemolysis, end of follow-up**

Study-Follow-up	**Visit 5**	**Day 24-28**	vital status, clinical examination, blood sample, (optional: urine sample)

Data collected

Epidemiological information

1. age
2. sex
3. ethnicity
4. parasitological diagnosis
5. non-antimalarial medication within 12 weeks prior to inclusion
6. antimalarial chemoprophylaxis taken within 12 weeks prior to inclusion
7. relevant co-morbidities
8. travel destination

Antimalarial medication

- drug
- duration
- dose

Laboratory values (all patients at each visit):

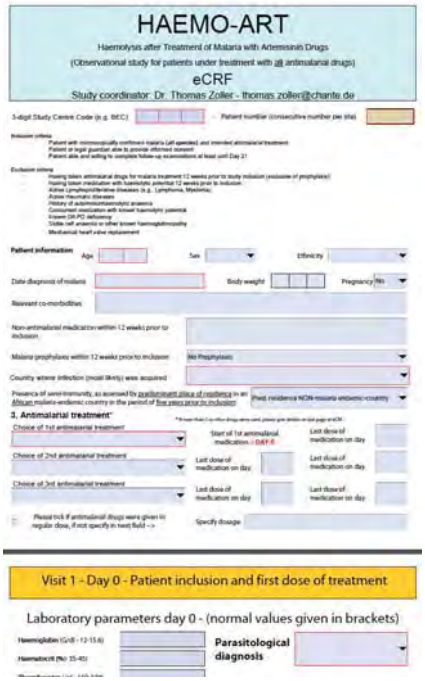
- RBC (Hb, Hct), PLT, WBC
- LDH
- AST*
- Haptoglobine*
- Reticulocytes*
- bilirubin (total, conjugated)*
- Creatinine*
- potassium*
- CRP*
- blood film*
- G6PD (only 1st blood sample)
- Coomb´s test* (6ml EDTA)
- parasitaemia*
- In selected study centres: blood sample for immunohaematol. & pharmacol. analysis (10ml serum + 6ml EDTA)

In case of haemolysis:

- haemoglobin electrophoresis
- serum & urine sample for further analysis

* these values are recommended, but **optional** when study visit takes place at local GP

Data collection


HAEMO-ART

Haemolysis after Treatment of Malaria with Artemisinin Drugs

(Observational study for patients under treatment with all antimalarial drugs)

eCRF

Study coordinator: Dr. Thomas Zoller - thomas.zoller@charite.de

Visit 1 - Day 0 - Patient inclusion and first dose of treatment

Laboratory parameters day 0 - (normal values given in brackets)

Parasitological diagnosis

- patient data will be collected using an electronic *.pdf
- ethical clearance will be obtained at the Charité University Hospital, Berlin, Germany.
- Participating study sites are responsible for ethical review according to local regulations

TropNet European Network for Tropical Medicine and Travel Health

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

Swiss TPH Swiss Tropical and Public Health Institute Schweizerisches Tropen- und Public Health-Institut Institut Tropical et de Santé Publique Suisse

SMPS

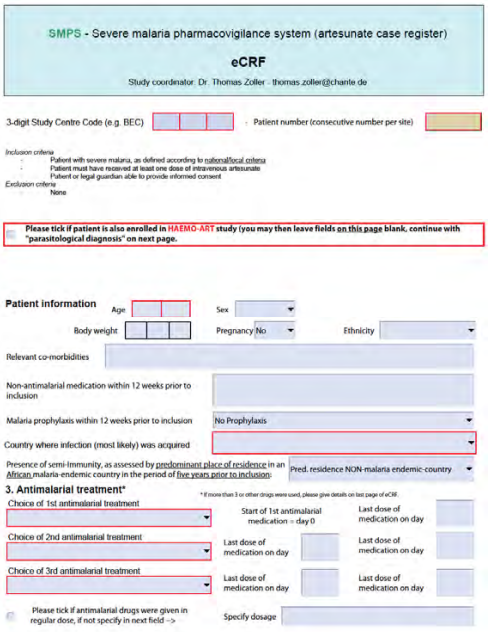
Severe malaria pharmacovigilance system

Outline

- Retrospective pharmacovigilance reporting of treatment data from patients having received at least one dose of **intravenous artesunate**
- The primary outcome is the occurrence of adverse drug reactions during or after treatment of severe malaria with **intravenous artesunate**

Design:

- No formal study (legal requirements)
- No formal registration or inclusion procedure
- Low-threshold for reporting: short eCRF, 10 minutes of work
- Reporting must be in accordance with local (ethical) rules



SMPS - Severe malaria pharmacovigilance system (artesunate case register)

eCRF

Study coordinator: Dr. Thomas Zoller · thomas.zoller@charite.de

3-digit Study Centre Code (e.g. BEC) · Patient number (consecutive number per site)

Inclusion criteria
- Patient with severe malaria, as defined according to national/local criteria
- Patient must have received at least one dose of intravenous artesunate
- Patient or legal guardian able to provide informed consent

Exclusion criteria
- None

Please tick if patient is also enrolled in HAEMO-ART study (you may then leave fields on this page blank, continue with "parasitological diagnosis" on next page.

Patient information · Age · Sex · Body weight · Pregnancy No · Ethnicity

Relevant co-morbidities

Non-antimalarial medication within 12 weeks prior to inclusion

Malaria prophylaxis within 12 weeks prior to inclusion: No Prophylaxis

Country where infection (most likely) was acquired

Presence of semi-Immunity, as assessed by predominant place of residence in an African malaria-endemic country in the period of five years prior to inclusion: Pred. residence NON-malaria endemic country

3. Antimalarial treatment*

* If more than 3 or other drugs were used, please give details on last page of eCRF.

Choice of 1st antimalarial treatment · Start of 1st antimalarial medication = day 0 · Last dose of medication on day

Choice of 2nd antimalarial treatment · Last dose of medication on day · Last dose of medication on day

Choice of 3rd antimalarial treatment · Last dose of medication on day · Last dose of medication on day

Please tick if antimalarial drugs were given in regular dose, if not specify in next field -> · Specify dosage

TOX ART

In vitro Study on the toxicity and haemolytic potential of Artemisinin metabolites

Outline

- **In-vitro artesunate metabolisation studies:** metabolism of Artemisinins on isolated hepatocytes and identification of metabolites with haemolytic potential
- **In vivo-metabolisation studies:** analysis of Artemisinin metabolites and (immuno-)haematological parameters in serum samples from selected patients from Haemo-ART or patients having received intravenous artesunate

➢ Interested TropNet centres may cooperate with providing samples of **patients with haemolysis, equipment or methodology**

Start of

HAEMO-ART → 01 May 2014

SMPS → 01 May 2014

TOX-ART (already running)

→ All documents and eCRF´s available on TropNet website

GiardiaTREAT

&

GiardiaREF

1st line	regimen	2nd line	regimen
Metronidazole	400 mg TID for 5 days	Metronidazole	600 mg TID for 7 days
Metronidazole	500 mg TID for 7 days	Tinidazole	2 g once daily, - about duration
Metronidazole	250 mg TID for 5-7 days	Tinidazole	2 g single dose
Metronidazole	500 mg TID, days ?	Tinidazole	-
Metronidazole	750 mg - 1g for 7 days	Tinidazole	2 g single dose
Metronidazole	250 mg TID for 5-7	Tinidazole	2 g once
Metronidazole	500 mg BID for 5 days	Tinidazole	2 g single dose
Metronidazole	-	Albendazole	-
Metronidazole	250 mg TID for 5 days	Albendazole	400 mg TID for 5 days
Metronidazole	-	Albendazole	-
Metronidazole	500 mg TID for 7 days	Albendazole	-
Metronidazole	500 mg TID for 7 days	Albendazole	400 mg TID for 7 days
Metronidazole	250 mg TID for 10 days	Albendazole	400 mg QID for 5 days
Metronidazole	250 mg TID for 5 days	Albendazole	400 mg once daily for 5 days
Metronidazole	250 mg TID for 7 days	Albendazole or Mebendazole	-
Metronidazole	400 mg TID for 6 days	Paromomycin	500 mg TID for 9 days
Metronidazole	500 mg BID for 5 days	Paromomycin	500 mg TID for 7 days
Metronidazole	500 mg TID for 7 days	Paramomycin	500 mg TID for 10 days
Metronidazole	250 mg TID for 10 days	Nitazoxanide	Nitazoxanide 500 mg BID for 3 days
Metronidazole	2 g OD for 3 days or 250 mg TID for 5 days	Nitazoxanide	500 mg BID for 3 days
Metronidazole	400 mg TID for 7 days	Quinacrine	100 mg TID for 5 days
Metronidazole	400mg TID for 6 days	Metronidazole + Albendazole	Metronidazole: 400mg TID for 6 days + Albendazole: 400mg OD for 5-10 days
Metronidazole	400 mg TID for 7 days	Metronidazole + Albendazole	Metronidazol 250 mg BID + Albendazole 400 mg BID for 7 days
Metronidazole	250mg TID for 5 days	Metronidazole + Paromomycin	Metronidazole 750mg TID for 7 days + Paromomycin 30mg/kg in 3 doses for 7 days
Metronidazole	500mg TID for 7 days	Metronidazole + Paromomycin	Metronidazol 2 g for 3 days followed by Paromomycin 25-35 mg/kgKG for 7-10 days
Metronidazole	-	Combination therapy, no details	-
Tinidazole	2 g single dose	Tinidazole	2 g OD for 3 days
Tinidazole	2 g single dose	Tinidazole	2 g OD for 3 days
Tinidazole	2 g single dose	Metronidazole	250 mg TID for 5-7 days
Tinidazole	2 g single dose	Metronidazole	500 mg TID für 7 days
Tinidazole	-	Metronidazole	-
Tinidazole	2 g single dose, repeated after 5 days	Metronidazole	400 mg TID for 5 days (or 2g OD for 3 days)
Tinidazole	2 g single dose, repeated after 5 days	Metronidazole	400 mg TID for 5 days
Tinidazole	-	Metronidazole	-
Tinidazole	-	Albendazole	-
Tinidazole	-	Albendazole	-
Tinidazole	2 g single dose, repeated after 7 days	Albendazole	400 mg TID for 7 days
Tinidazole	2 g single dose	Albendazole	400 mg once daily for 5 days
Tinidazole	2g single dose	Quinacrine	100 mg TID for 5 days
Tinidazole	2 g single dose	Quinacrine	100 mg TID for 5 days
Tinidazole	-	Quinacrine	500 mg TID for 5 days
Tinidazole	2 g single dose	Quinacrine	100 mg TID for 5 days
Tinidazole	-	Nitazoxanide	-
Tinidazole	2g single dose	Metronidazole + Albendazole	Metronidazole 400mg TID for 6 days + Albendazole 400mg OD for 5-10 days
Tinidazole	2 g single dose, repeated after 14 days	Metronidazole + Paromomycin	Metronidazole 750mg TID for 7 days ± Paromomycin 30mg/kg in 3 doses for 7 days
Tinidazole	2g once daily for 2 days	Albendazol + Paramomycin	Albendazole 400 mg BID + Paromomycin 750 mg TID for 5 days
Tinidazole	2 g single dose, repeated on day 10-14	Albendazole + Paromomycin	400 mg TID for 7 days followed by Paromomycin 500 mg TID for 7 days
Ornidazole	-	Metronidazole	-
Ornidazole	500 mg BID for 5 days	Albendazole	400 mg BID for 3 days
Ornidazole	500 mg BID for 7 days	Albendazole + Paromomycin	Paramomycin 500 mg TID + Albendazole 400 mg QID for 5 days
Albendazole	-	Metronidazole	-
Nitaxozanide	500 mg BID for 3 days	Quinacrine	100 mg TID for 5 days
Paramomycin	25-35 mg/kg/day in 3 doses for 5-10 days	Quinacrine	100 mg TID for 5 days

TropNet survey on Giardia treatment:
53 centres, 39 different regimens, 7 drugs alone or in combination in different dosage & duration

GiardiaTREAT

(observational study on tolerability of 1st-line treatment)

→ **Baseline stool sample (to allow retrospective genetic work-up of isolate in case of treatment failure)**

- **Metronidazol OR**
- **Tinidazol OR**
- **Ornidazol**

→ **Objectives:**
Prim.: tolerability
Sec.: treatment adherence & *overall clinical efficacy
of 5-nitroimidazoles, (genetic testing of parasitol. failures)

*** *Parasitological follow-up* only in cases of clinical treatment failure**

Small TropNet centres

GiardiaREF

(observational study on efficacy of 2nd-line treatment)

→ **Baseline stool sample (to allow retrospective genetic work-up of isolate in case of treatment failure)**

- **Quinacrine OR**
- **Albendazole + Chloroquine**

→ **Objectives:**
Prim.: clinical & parasitological efficacy
Sec.: tolerability & treatment adherence, (genetic testing of parasitol. failures)

Large TropNet centres

GiardiaTREAT

Tolerability of 1st-line *Giardia lamblia* treatment regimens

Background:

The median efficacy of 5-Nitroimidazole based 1st-line treatment regimens is similar, considered to achieve approx. 90% of clinical and parasitological cure.

Not many data exist on the tolerability of the different drug regimens, which is important to choose the regimen with the lowest rate of associated side-effects.

Study design:

Prospective, observational, open-label, multi-centre study

Optional 1st-line treatment regimens under evaluation:

1. Metronidazole 400 - 500mg* TID x 7 days
2. Tinidazole 2g OD x 1 day
3. Ornidazole 2g OD x 1 days

(*note: the dosage range of Metronidazole is based on the difference in local availability of tablets containing 400mg or 500mg respectively)

Main objective:

To evaluate the tolerability of 5-nitroimidazole based 1st-line *G. lamblia* treatment regimens

Additional objectives:

1. To assess the rate of treatment adherence and the rate of side-effect related treatment cessation of different 5-nitroimidazole based 1st-line treatment regimens
2. To assess the overall clinical efficacy of 5-nitroimidazole based 1st-line treatment regimens
3. To collect geographic data (continent/country where the infection was acquired) in order to evaluate regional differences in clinical treatment efficacy of 5-nitroimidazole based 1st-line treatment regimens
4. To obtain baseline stool samples for subsequent genetic analysis / resistance testing of *G. lamblia* isolates in cases of parasitological confirmed failure of 1st-line treatment

Inclusion criteria:

Any symptomatic person being tested positive for *G. lamblia* (by stool microscopy or stool antigen-test) with intestinal mono-infection is eligible for study inclusion.

Exclusion criteria:

- Patients who already received giardiasis-specific treatment for the current *G. lamblia* infection
- Patients with asymptomatic *G. lamblia* infection
- Patients with concomitant bacterial, helminthic or protozoal gastrointestinal infection (note: the presence of apathogenic protozoa [including *Blastocystis hominis*] is no exclusion criterion)
- Patients with contraindications (drug allergies, pregnancy, breast- feeding) for the listed drug regimens

Follow-up:

- Follow-up of the patients with assessment of tolerability and clinical efficacy of the assigned treatment regimen will be done ≥4 - ≤5 weeks after completing medical treatment by telephone, using a standardized questionnaire.
- In case the symptoms disappear after treatment, no control by stool microscopy will be performed.
- In case of persisting or relapsing symptoms, repetition of stool microscopy to test parasitological outcome will be done. Repetition of stool microscopy will be done earliest 2, latest 5 (≥2 - ≤5) weeks after completion of medical therapy.

Definition of clinical outcome:

- `Clinical cure´: absence of gastrointestinal symptoms at ≥4 - ≤5 weeks after finishing treatment.
- `Clinical improvement´: persisting gastrointestinal symptoms but improvement through medical treatment at ≥4 - ≤5 weeks after finishing treatment. To assess the subjective degree of clinical improvement, the patients will be asked to rate their persisting symptoms / max. experienced symptoms on the following, subjective scale: 10 – 20 – 30 – 40 – 50 – 60 – 70 – 80 – 90%
- `Clinical failure´: persisting gastrointestinal symptoms without improvement at ≥4 - ≤5 weeks OR relapse of the initial/similar symptoms at ≥4 - ≤5 weeks following transient resolution after finishing treatment.

Definition of parasitological outcome:

`Parasitological cure´: 3 stool samples tested negative by microscopy ≥2 - ≤5 weeks after finishing medical treatment

`Parasitological failure´: detection of *G. lamblia* by microscopy in a stool sample ≥2 - ≤5 weeks after finishing medical treatment

Storage of stool sample:

Before initiating medical treatment, a stool sample will be put aside and frozen at -80°C (alternatively -20°C) to allow later genetic analysis / resistance testing of the *Giardia lamblia* isolate in cases of `parasitological confirmed treatment failure´.

GiardiaREF

Efficacy of 2nd-line treatment

Background:

- Currently the `best´ 2nd-line treatment regimen for refractory giardiasis still needs to be defined.
- Quinacrine appears to be highly efficient and is already used by big centres, but it's availabilty is restricted.
  Therefore, a widely available and equally effective alternative treatment regimen is needed.
- As most clinicans would opt for a combination therapy and considering the wide availability of as well as existing data on Albendazole + Chloroquine this regimen may be an option.

Study design:

Prospective, observational, open-label, multi-centre study

Optional 2nd-line treatment regimens under evaluation:

1. Quinacrine 100mg TID x 5 d
2. Albendazole 400mg + Chloroquine 250mg BID x 5d

Main objective:

To assess the clinical and parasitological efficacy of quinacrine monotherapy and albendazole-chloroquine combination therapy for the treatment of refractory giardiasis after treatment with 5-nitroimidazole derivatives or other drugs.

Additional objectives:

1. To evaluate the tolerability of quinacrine monotherapy and albendazole-chloroquine combination therapy in the treatment of refractory giardiasis.
2. To assess treatment adherence and side-effect-related treatment cessation of quinacrine monotherapy and albendazole-chloroquine combination therapy in the treatment of refractory giardiasis.
3. To collect stool samples prior to 2nd-line treatment in order to allow subsequent genetic analysis / resistance testing of *G. lamblia* isolates in cases of parasitologically confirmed treatment failure of 2nd-line therapy.
4. To collect epidemiological data on the geographic background of infection.

Inclusion criteria:

Any person having clinically and parasitologically failed 1st-line *G. lamblia* treatment with a 5-nitroimidazole regimen (metronidazole, tinidazole, ornidazole, secnidazole), defined as being tested positive for *G. lamblia* by stool microscopy ≥2 weeks after completing medical treatment, is eligible for study inclusion.

To best possible exclude cases of reinfection, the upper time limit for study inclusion will be set at 3 months after completing 1st-line treatment.

Exclusion criteria:

- Patients with contraindications (drug allergies, pregnancy, breast-feeding) for the selected drug regimens.
- Female patients in child-bearing age, not able to conduct double contraception (hormonal methods [pill, coil]) combined with a mechanical method [condom, diaphragm]) during intake and over the `wash-out period´ of the selected study medication. The `wash-out´ period is anticipated to be equal to four half-lives of the used study drug

  Quinacrine: elimination $T_{1/2}$: ~14 days -> wash-out period 8 weeks;
  CQ + ABZ: CQ unproblematic; ABZ $T_{1/2}$: ~12 hours -> wash-out period 2 days
- Patients having received a non-5-nitroimidazole regimen as 1st-line *G. lamblia* treatment.
- Patients with concomitant bacterial, helminthic or protozoal gastrointestinal infection (note: the presence of apathogenic protozoa [including *Blastocystis hominis*] is no exclusion criterion)

Definition of parasitological outcome:

`Parasitological cure´: ≥2 stool samples tested negative by microscopy ≥2 - ≤5 weeks after finishing medical treatment

`Parasitological failure´: detection of *G. lamblia* by microscopy in a stool sample ≥2 - ≤5 weeks after finishing medical treatment

Storage of stool sample:

Before initiating medical treatment, a stool sample will be put aside and frozen at -80°C (alternatively -20°C) to allow later genetic analysis / resistance testing of the *Giardia lamblia* isolate in cases of `parasitological confirmed treatment failure´.

Follow-up:

- Follow-up of the patients with assessment of parasitological outcome by stool microscopy will be done ≥2 - ≤5 weeks after finishing treatment.
- Clinical efficacy and tolerability of the assigned 2nd-line treatment regimen will be assessed ≥4 - ≤5 weeks after finishing treatment by telephone using a standardized questionnaire.
- Parasitological outcome will be assessed by systematically obtaining at least two stool samples for laboratory evaluation; The logistic approach on how to collect the follow-up stool samples (e.g. re-consultation of patient at site or sending stool sample by mail) will be left to the study sites.

Study outline	
StaphTrav - European network on imported S. aureus Study outline	Study protocol Case record form Information sheet & informed consent form (E) Information sheet & informed consent form (D) Study participation/membership form Ethical approval - Tuebingen, Germany
Eurartesim Pregnancy registry Study outline	TropNet meeting Prague 2012 - Eurartesim pregancy registry TropNet & SigmaTau - service agreement EMA - assessment report EMA - product information EMA - annex - safe and effective use
GiardiaTREAT & GiardiaREF study Study outline	GiardiaTREAT - study protocol GiardiaTREAT - patient information & informed consent form GiardiaTREAT - case report form GiardiaREF - study protocol GiardiaREF - patient information & informed consent form GiardiaREF - case report form GiardiaTREAT - study protocol GiardiaTREAT - patient information (E) GiardiaTREAT - patient information (G) GiardiaTREAT - informed consent form (E) GiardiaTREAT - informed consent form (G) GiardiaTREAT - case report form GiardiaREF - study protocol GiardiaREF - patient information (E) GiardiaREF - patient information (G) GiardiaREF - informed consent form (E) GiardiaREF - informed consent form (G) GiardiaREF - case report form
Live vaccinations in immunosuppressed persons Study outline	Live vaccinations in immunosuppressed persons - case report form

TropNet
European Network for Tropical Medicine and Travel Health

Live vaccinations under immunsuppression – a retrospective and prospective data collection

Silja Bühler, Zürich
MD, MScPH, MScEpi

WHO: Individuals under any kind of immunosuppression

- Corticosteroids
- Sulfasalazine/Mesalazine
- low dose Methotrexate (<20mg/week)
- and all other medications (biologicals, ...)

WHO RECEIVE(D): a live vaccination

Yellow Fever, MMR, Varicella

FOR ANY REASON:

- inadvertently
- after careful risk/benefit assessment

Universität Zürich
Institut für Sozial- und Präventivmedizin
Swiss TPH

WHAT TO DO: USE TropNet Questionnaire

please document in detail data on:

- Demographics
- Live vaccination
- Immunosuppression
- Reason for immunosuppression (underlying disease)
- Diseases (MMR, Varicella) in the past
- Adverse reactions to vaccination
- Immunogenicity assessment (if performed)

TropNet

Live vaccinations in immunosuppressed persons

TropNet Centre Code: _____
Subject Number: ____

SECTION 1: SUBJECT VISIT

Date of visit / administration of live vaccine: __.__.____ (DD.MM.YYY) **Age in years** _____

Gender: ☐ Male ☐ Female **Weight (in kg)** _____

1. Which vaccinations were administered?

☐ MMR ☐ Yellow Fever ☐ Varicella ☐ Measles

SECTION 2: HEALTH QUESTIONS

2. What were the underlying condition(s), i.e. reason for immunosuppressive / immunomodulating treatment?

☐ Unknown ☐ Known, please specify: → Date of diagnosis or transplantation: __.__.____

→ Description: _____

3. Were there any other factors contributing to immunosuppression / -modulation?

☐ Unknown ☐ No ☐ Yes, please specify: _____

→ Further comments / information: _____

4. What was the subject's immunosuppressive/-modulating medication at the time of this vaccination?

Name / generic: *e.g. Methotrexate*			
Dosage and Interval: *e.g. 20mg/week*			
Date of last dose before vaccination:	__.__.____	__.__.____	__.__.____
Start date:	__.__.____	__.__.____	__.__.____

5. Was another immunosuppressive/ -modulating drug used in the 12 months before administration of a live vaccine?

☐ Unknown ☐ No ☐ Yes, please specify below:

Name / generic: *e.g. Methotrexate*			
Dosage and Interval: *e.g. 20mg/week*			
Date of last dose before vaccination:	__.__.____	__.__.____	__.__.____
Start date:	__.__.____	__.__.____	__.__.____

SECTION 3: PREVIOUS VACCINATIONS AND DISEASES

6. Which vaccinations were administered before this visit? If possible, check with vaccination certificates.

Type of vaccination	Number of shots	Date of last shot	Was live vaccine given before or after start of immunosuppressive/-modulatory therapy?		
Yellow Fever		__.__.____	☐ before	☐ after	☐ unknown
MMR		__.__.____	☐ before	☐ after	☐ unknown
Varicella		__.__.____	☐ before	☐ after	☐ unknown
Measles		__.__.____	☐ before	☐ after	☐ unknown

7. History of the following diseases?

	History	No history	Unclear	Serologically confirmed		
Measles	☐	☐	☐	☐ yes	☐ no	☐ unknown
Mumps	☐	☐	☐	☐ yes	☐ no	☐ unknown
Rubella	☐	☐	☐	☐ yes	☐ no	☐ unknown
Varicella	☐	☐	☐	☐ yes	☐ no	☐ unknown

SECTION 4: SAFETY ASSESSMENT

8. Were there any reactions after the administration of this live vaccine?

Definition mild: not interfering with daily activities; moderate: interfering with daily activities, but able to perform daily activities; severe: not able to perform daily activities

☐ Unknown ☐ No ☐ Yes, please specify below:

☐ Local reactions, please specify: _____ ☐ mild ☐ moderate ☐ severe
☐ Fever (>38°C) → If present, please specify: ☐ mild ☐ moderate ☐ severe
☐ Headache → If present, please specify: ☐ mild ☐ moderate ☐ severe
☐ Muscle / joint pain → If present, please specify: ☐ mild ☐ moderate ☐ severe
☐ Skin rash, please specify: _____ → If present, please specify: ☐ mild ☐ moderate ☐ severe
☐ Other, please specify: _____ ☐ mild ☐ moderate ☐ severe
☐ Other, please specify: _____ ☐ mild ☐ moderate ☐ severe

9. Did any of the following events occur?

☐ No ☐ Yes, please specify below:

☐ Death ☐ Life-threatening event ☐ Hospitalisation or prolongation of existing inpatient hospitalisation
☐ Persistent or significant disability or incapacity ☐ Congenital anomaly or birth defect
☐ Other important medical event or reaction, please specify: _____

10. Were there any actions taken due to the above-mentioned reactions?

☐ Unknown ☐ No ☐ Yes, please specify below:

☐ Pain killer / self treatment ☐ Visit at a physician ☐ Stay at home from work / school / university or similar
☐ Other: _____

SECTION 5: IMMUNOGENICITY ASSESSMENT

11. Was an immunogenicity assessment (titer) performed?

☐ Unknown ☐ No ☐ Yes, please specify below:

	Description of test	Result	Date of test
1.			
2.			
3.			

SECTION 6: COMMENTS

12. If there are any important comments, please use the lines below.

_____
_____
_____

__.__.____ (DD.MM.YYYY) _____ (Signature of Investigator)

Fax Nummer : + 41 44 634 49 84 / Email: silja.buechler@ifspm.uzh.ch

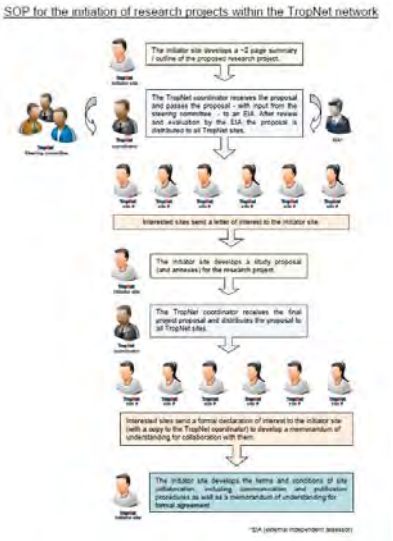
Possible TropNet projects ahead

- ➔ *TropNet study on PCR-based diagnosis of schistosomiasis in travellers*
- ➔ *TropNet study on imported multiresistant intestinal bacteria*
- ➔ *TropNet study on vaccinations in immunocompromised travelers*
- ➔ *TropNet surveillance study on worldwide distribution of polymorphisms associated with artemisinin resistance of P. falciparum malaria*
- ➔ *Pharmacokinetic study on Praziquantel in schistosomiasis*

Implementation of joint research projects within TropNet

SOP for the initiation of research projects within the network

(to be found under the member section of the TropNet website)



The infrastructure is there…
now it's about ideas, implementation & participation

Institutional network collaboration for `Horizon 2020´ - strengthening capacity building

Maladies infectieuses et tropicales
Médecine tropicale et du voyageur
CHU Bordeaux
Dr Matthieu Méchain - Pr Denis Malvy

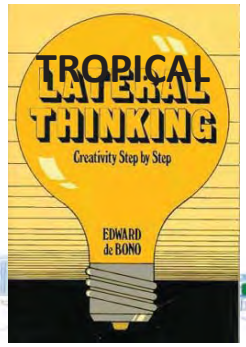
11th-12th April 2014 – Hamburg – TropNet and Horizon 2020

Lateral thinking anecdote

- It's the story of a traveler who owes money to a moneylender.
- As they were standing on a stone strewn path full of white and black stones, the traveler agrees to settle the debt based upon the choice of two stones (one black, one white) from a money bag.
- If his daughter chooses the white stone, the debt is canceled; if she picks the black stone, the moneylender gets the traveler's daughter.
- If the daughter doesn't choose a stone, her father would be thrown into jail.

Outcome fixed

- However, the moneylender "fixes" the outcome by putting two black stones in the bag.
- But the daughter sees this.
- What could be the solution for the debt being canceled? Is it possible?
- What would you recommend that the girl do?



Solution

- When the daughter picks a stone out of the bag, she immediately drops it onto the path full of other white and black stones.
- She then points out that the stone she picked must have been the opposite color of the one remaining in the bag.
- Unwilling to be unveiled as dishonest, the moneylender must agree and cancel the debt.
- The daughter has solved an intractable problem through the use of lateral thinking.

Adapted from DeBono, 1967

Creativity

- “To get a different perspective on a problem, try breaking the elements up and recombining them in a different way (perhaps randomly)”.
- Capacity to create new ways of thinking
- Powerful and useful ‘tool’, specially to face problems

European research context

- European legal context is complex
  - No unique European procedure
  - No homogenous rules - depending on the type of research project
  - Constraint of ethics and administrative burdensome (bureaucracy)
- Opportunity - Creativity
  - Facing Health (and Climate change) issues
  - Horizon 2020 proposal

Horizon 2020 topics

- WP 2015 - Health, demographic change and wellbeing
- Coordination activities
- HCO 3: Support for the European Reference Networks: Efficient network modelling and validation

From networking to institutional links

- What do you think about establishing a consortium group with institutional links based on our network?
- Why this proposal?
  - Confidence for decision makers and funders
  - Faisability for project reviewers
  - Simplicity in anticipating ethics and administrative issues and having specific guidance
  - Efficiency of joint ambitious European research projects

Similar approch:
« Research preparedness »

- “Set up a **governance:** reactivity, flexibility
- Preparation of **research tools**
- Establishment of **links** between different disciplines
- Identification of **research priorities and obstacles:** likely scenarios of emergence
- Identification of potential sources of **funding**
- Anticipation of **legal and ethical** issues”

CHU Hôpitaux de Bordeaux

How to face this challenge

- We need a small group of 2 or 3 institutions to prepare a common conventional document
- To anticipate difficulties at a European level and make a proposal to other interested institutions
- To face this challenge we need a strong adhesion to this proposal
- Vote? Questionnaire?

CHU Hôpitaux de Bordeaux

Thank you for your attention

Discussion on perspectives of
efficient joint research projects and
institutional network collaboration
It’s up to us!

CHU Hôpitaux de Bordeaux

Universität Hamburg | Universitätsklinikum Hamburg-Eppendorf

Bernhard-Nocht-Institut für Tropenmedizin

Mass Gatherings: FIFA World Cup 2014 in Brazil

TropNet, 11.04.2014

Jakob Cramer

FIFA World Cup 2014
Facts

- 20th FIFA World Cup
- June 12th – July 13th 2014
- 32 national teams
- 64 matches
- 12 stadiums (stadia)
- time delay 5 hours (Cuiabá, Manaus: 6 hours)
- temperatures in winter period (June-July)
  - 20-25°C in the North
  - 12-17°C in the South
- spectators South Africa 2010
  - 3,170,856 attended the 64 matches
  - average of 49,670 per match
- Germany 2006
  - semi-final Germany : Spain: 350,000 attended the FIFA Fan Fest in Berlin (‚public viewing')
  - estimated 715.1 million people watched the final match

Mass Gatherings: Health Risks

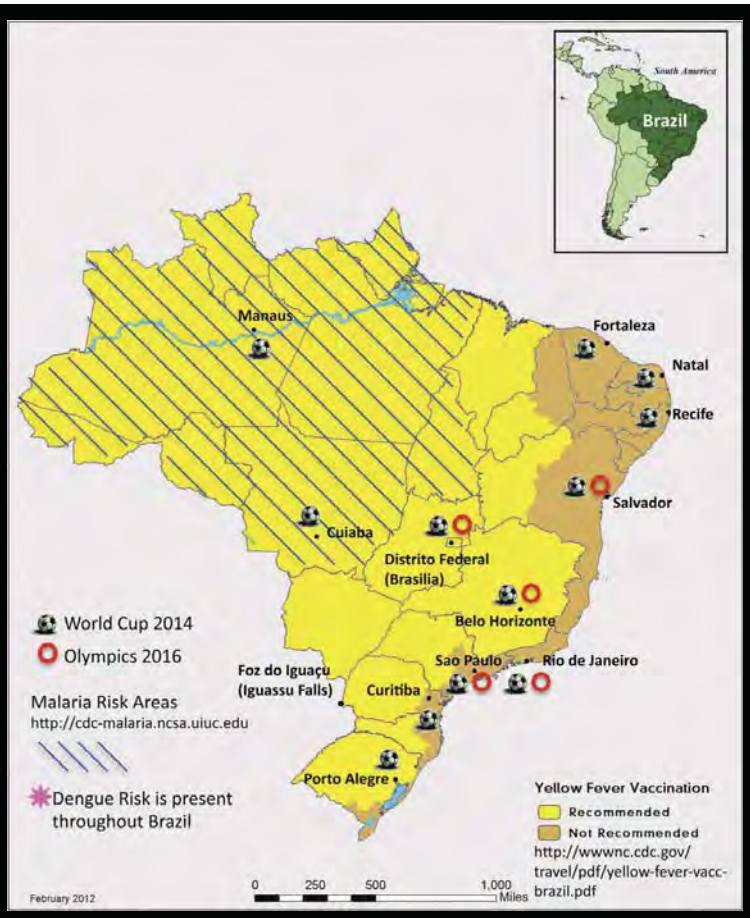
- stampede, crash injuries
- violence, crime
- terrorist attacks
- traffic accidents, trauma
- drug / alcohol intoxication
- emotional stress, aggression (in particular during sports events!)
- climate: sunburn, dehydration
- deterioration of chronic / underlying diseases (medication lost, forgotten)
- infectious diseases
  - tropical diseases
  - common diseases
  - vaccine preventable diseases
  - STDs

about 1-2% with relevant health events

[source: Süddeutsche Zeitung]

[Steffen et al. Lancet Infect Dis. 2012]

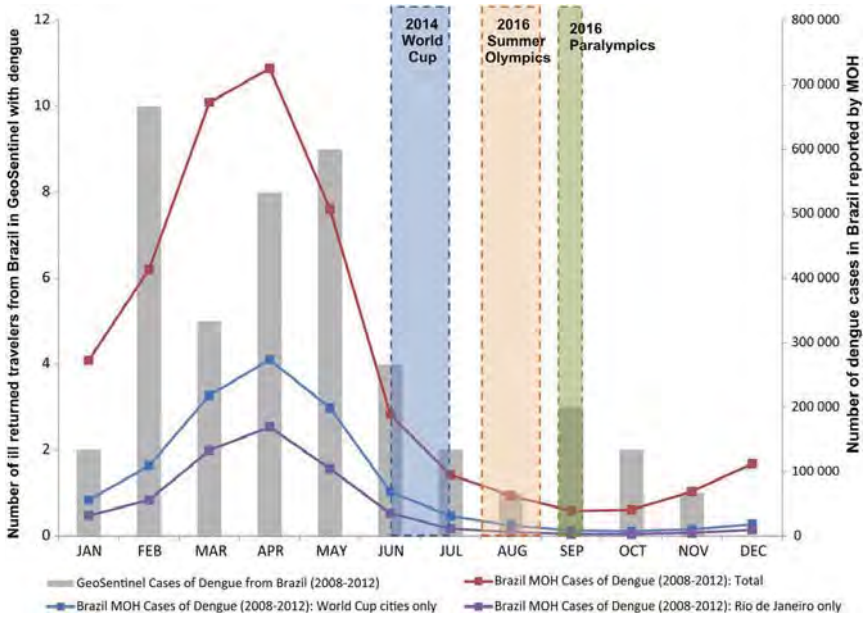
[Stadium Rio de Janeiro]



[Wilson et al. Clin Infect Dis. 2014]

Brazil: Dengue Fever

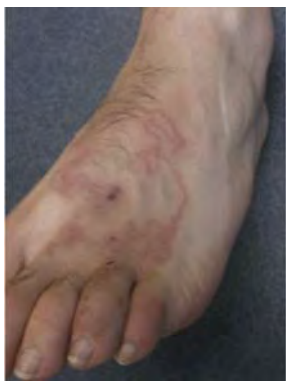
Dengue fever diagnoses of ill returned travellers exposed in Brazil seen at GeoSentinel clinics, by month, 2008–2012 (*n* = 48).



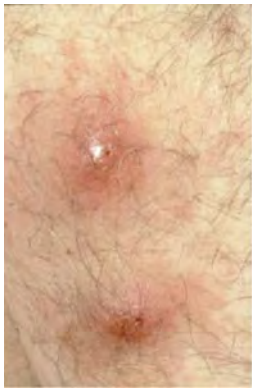
[Wilson et al. Clin Infect Dis. 2014]

Dermatologic Problems

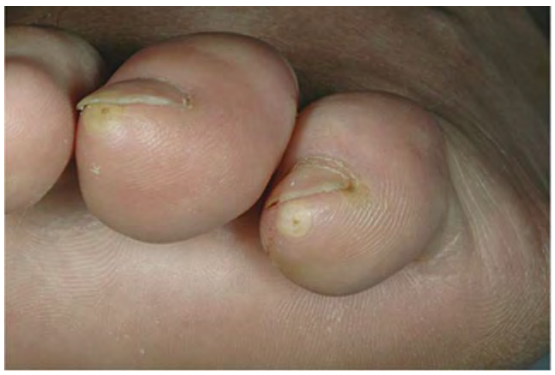
- dermatologic problems in 40%



Larva cutanea migrans (11%)



Myiasis



Tungiasis (*Tunga penetrans*)

[Wilson et al. Clin Infect Dis. 2014]

Study Design

- airport survey: Frankfurt 3 direct flights daily to Rio and Sao Paolo
- case control-approach:
  - cases = travellers to the FIFA World Cup 2014 June – July (attending a match)
  - controls = travellers after the FIFA World Cup 2014 (after July 13th)
- *n*=2.000 (minimum)
- pre-travel questionnaire
  - demographic factors
  - travel plans
  - travel preparation
- post-travel questionnaires (telephone, mail, web-based)
  - health issues
  - re-confirm some pre-travel data
- additional subjects will be recruited within our travel clinic

Inclusion Criteria

Inclusion

- ≥18 years
- travel to Brazil 1-4 weeks
- travellers: tourist, VFRs, business
- cases: plans to visit a FIFA World Cup 2014 match
- controls: travelling after FIFA World Cup 2014

Exclusion

- round trips (crossing borders for example at Iguazú permissive)
- not able / willing to provide contact details for post-travel assessment

Analysis Plan

- descriptive
  - demographics
  - travel itineraries
  - health events, categorised (climate, IDs, traffic, violence etc.)

- case control-analysis
  - # overall health events
  - # overall (para)medical consultations (hospitalisations)

- additional analyses
  - comparison of pre-travel knowledge / preparation between ‚airport-subjects' and ‚travel clinic subjects'

TropNet

- additional sites interested in participation?
  - travel clinic survey

  and / or
  - airport survey
- we could provide questionnaires (pre-/post travel), data entry, analysis
- ethical clearance not necessary – accordance with data protection regulations

Contact persons: Christof Vinnemeier, Kirsten Eberhardt, Jakob Cramer

Recommendations
for travellers to the FIFA World Cup 2014

- Yellow fever vaccination: if attending matches in
  - Belo Horizonte
  - Brasilia
  - Manaus
  - Cuiabá

  (not required for entry but some conflicting information by (regional) authorities)
- Malaria: SBET when travelling to rural areas within Amazonas basin / around Manaus and Cuiabá - risk in cities low (Atovaquone/Proguanil, Artemether/Lumefantrin)
- Dengue: Mosquito protection during daytime (entire country)
- additional vaccinations: MMR, hepatitis A, (additional risks / specific indications: influenza, typhoid fever, rabies),

- Iliaki E, Chen LH, Hamer DH, Macleod WB, Jentes ES, Barnett ED, Wilson ME; Boston Area Travel Medicine Network. Travel to Brazil: Analysis of Data From the Boston Area Travel Medicine Network (BATMN) and Relevance to Travelers Attending World Cup and Olympics. J Travel Med. 2014 Mar 28. doi: 10.1111/jtm.12117. [Epub ahead of print] PubMed PMID: 24673916.

Thank You

BERNHARD-NOCHT-INSTITUT
FÜR TROPENMEDIZIN

Universitätsklinikum
Hamburg-Eppendorf

TropNet
European Network for Tropical Medicine and Travel Health

C·H·U Hôpitaux de Bordeaux

Swiss TPH

Proposal for a joint TropNet/EuroTravNet surveillance study:

Imported malaria cases in Europe as sentinels for the worldwide distribution/emergence of polymorphisms associated with artemisinin resistance in P. falciparum malaria

International Journal for Parasitology 43 (2013) 885–889

Contents lists available at ScienceDirect

International Journal for Parasitology

journal homepage: www.elsevier.com/locate/ijpara

Succinctus

Travellers as sentinels: Assaying the worldwide distribution of polymorphisms associated with artemisinin combination therapy resistance in *Plasmodium falciparum* using malaria cases imported into Scotland

Carol W. Hunja [a,b], Holger Unger [d,f,1], Pedro E. Ferreira [e], Richard Lumsden [c], Sheila Morris [f], Rashid Aman [b], Claire Alexander [g], Toshihiro Mita [b,i,1], Richard Culleton [a,*,1]

(Nagasaki & Nairobi)

Background

- Resistance to ACTs is characterised by delayed clearance of parasites following drug treatment
- Following the first reports of parasites with delayed clearance rates in western Cambodia, it has been shown that the resistance phenotype are likely to have an underlying genetic component [1]
- This implied that genetic mutations had arisen in a subset of parasites in western Cambodia that decreased their sensitivity to ACTs and that these mutations have being selected by ACT pressure in the region
- A genomic region associated with the resistance phenotype has been described [2] followed by the identification of **4 single nucleotide polymorphisms (SNPs)** on chromosomes 10, 13 and 14, which **appear to be linked to resistance** [3]

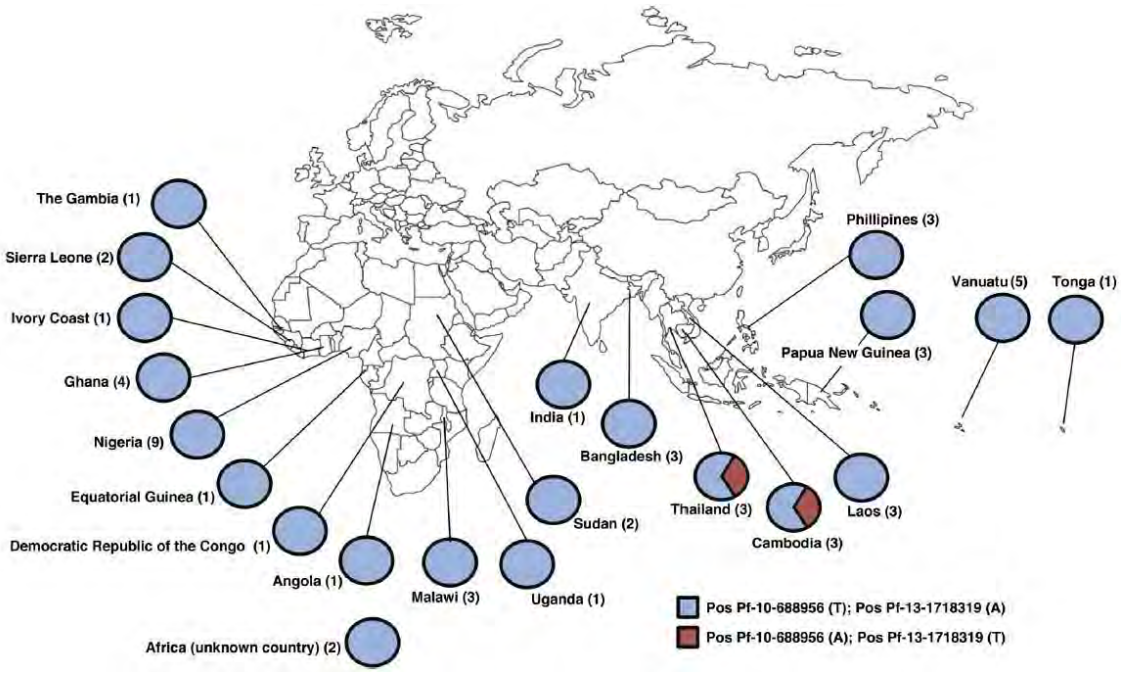
1 Anderson TJ et al. J Infect Dis. 2010;2010:1326-30
2 Cheeseman IH et al. Science. 2012;336:79-82
3 Takala-Harrison S et al. Proc. Natl. Acad. Sci. USA 2013;110:240-5

- **2 of these SNPs have been proposed to be suitable molecular markers for delayed parasite clearance**

  MAL10-688956(A) & MAL13-1718319(T)

- Although these SNPs are not thought to confer resistance themselves (and despite the fact that they have been identified in some regions before ACT resistance was reported in southeastern Asia), they could be linked to the actual genetic drivers of resistance, which could exist in parasite populations that have never been exposed to ACTs and which would be selected for when ACT pressure is applied to the population

➔ **Systematic collection and genotyping of imported *P. falciparum* malaria strains would be an ideal tool to identify geographic regions, where SNPs linked to ACT resistance are prevalent or emerging**



Methods:

1. Routine collection of blood samples from all malaria cases (all species?) seen at participating study sites:
   - spots of EDTA-blood on filter paper
     (air-drying & storing in sterile plastic sleeves)
   - collection of a minimal anonymized data set:
     (date, age, gender, chemoprophylaxis, countries & regions visited, result of microscopy/rapid diagnostic test)
   - establishing a sample library over the years

2. DNA-extraction ➔ PCR ➔ restriction fragment length polymorphism analysis

Case record form (Version V1.2013)

TropNet centre code: ☐☐☐ **Patient No.:** ☐☐☐ **Age:** ☐☐ years **Gender:** ☐ f / ☐ m

Date of study inclusion: ☐☐/☐☐/☐☐ (DD/MM/YY)

Malaria infection (most likely) acquired in (country): _____

☐ if not determinable: malaria endemic countries visited within the last 12 months before onset of symptoms in chronological order (1. last, 2. second last, 3. third last, etc.):

1. _____
2. _____
3. _____
4. _____
5. _____

Diagnosis established by: ☐ microscopy ☐ rapid diagnostic test

☐ mono-infection ☐ mixed-infection

☐ *P. falciparum* ☐ P. vivax ☐ P. ovale ☐ P. malariae ☐ P. knowlesi

Did the patient take malaria chemoprophylaxis:

☐ no ☐ yes, if yes: ☐ Atavaquon/Proguanil (Malarone, Malanil)
☐ Mefloquine (Lariam)
☐ Chloroquine (Resochin)
☐ Doxycycline
☐ Proguanil (Paludrine)
☐ Chloroquin/ Proguanil (Savarine)

☐ other: _____

Add-ons:

- collection of multiple blood spots would allow to re-evaluate the samples if new molecular markers are identified in the future
- & surveillance of emergence/prevalence of resistance to other chemoprophylactic drugs (malarone, mefloquin) would be possible

1. [**Molecular** epidemiological **surveillance** of markers for antimalarial drugs in Plasmodium falciparum **isolates imported** to Barcelona, Spain].
Gascón J, Mayor A, Mühlberger N, Peyerl-Hoffmann G, Oliveira I, Dobaño C, **Jelinek** T, Corachan M.
Med Clin (Barc). 2005 Sep 10;125(8):286-9. Spanish.
PMID: 16159551 [PubMed - indexed for MEDLINE]
Related citations

2. Screening for mutations related to atovaquone/proguanil **resistance** in treatment failures and other **imported isolates** of Plasmodium falciparum in Europe.
Wichmann O, Muehlberger N, **Jelinek** T, Alifrangis M, Peyerl-Hoffmann G, Muhlen M, Grobusch MP, Gascon J, Matteelli A, Laferl H, Bisoffi Z, Ehrhardt S, Cuadros J, Hatz C, Gjorup I, McWhinney P, Beran J, da Cunha S, Schulze M, Kollaritsch H, Kern P, Fry G, Richter J; European Network on **Surveillance** of **Imported** Infectious Diseases.
J Infect Dis. 2004 Nov 1;190(9):1541-6. Epub 2004 Sep 28.
PMID: 15478057 [PubMed - indexed for MEDLINE] Free Article
Related citations

3. **Molecular surveillance** of the antifolate-resistant mutation I164L in **imported** African **isolates** of Plasmodium falciparum in Europe: sentinel data from TropNetEurop.
Wichmann O, **Jelinek** T, Peyerl-Hoffmann G, Mühlberger N, Grobusch MP, Gascon J, Matteelli A, Hatz C, Laferl H, Schulze M, Burchard G, da Cunha S, Beran J, McWhinney P, Kollaritsch H, Kern P, Cuadros J, Alifrangis M, Gjorup I; European Network on **Surveillance** of **Imported** Infectious Diseases (TropNetEurop).
Malar J. 2003 Jun 25;2:17. Epub 2003 Jun 25.
PMID: 12866[illegible] [PubMed - indexed for MEDLINE] Free PMC Article
Related citations

4. **Molecular surveillance** of **drug resistance** through **imported isolates** of Plasmodium falciparum in Europe.
Jelinek T, Peyerl-Hoffmann G, Mühlberger N, Wichmann O, Wilhelm M, Schmider N, Grobusch MP, von Sonnenburg F, Gascon J, Laferl H, Hatz C, Alifrangis M, Burchard G, McWhinney P, Schulze M, Kollaritsch H, da Cunha S, Beran J, Kern P, Gjørup I, Cuadros J.
Malar J. 2002 Oct 11;1:11. Epub 2002 Oct 11.

Suggestions for partners / collaborations ?

Hospital Universitario Príncipe de Asturias
SaludMadrid
Comunidad de Madrid

Comparation of imported *Plasmodium ovale wallikeri* and *Plasmodium ovale curtisi*

Fundación de Investigación
Universidad de Alcalá
Instituto de Salud Carlos III

Background *P. ovale*

- So far considered uncommon, limited geographycally, mild and easily treated
- PCR studies:
  - Prevalence 9-15% (Nigeria, PNG, Equatorial Guinea)
  - SE Asia, Middle East, Indian subcontinent…
- Severity: ARDS, spleen rupture, anemia
- Quite ineffective prophylaxis
- Treatment failure exceptional but relapses
- Two species: *Po wallikeri, Po curtisi* . Differences?

Retrospective study

Comparison of Imported *Plasmodium ovale curtisi* and *P. ovale wallikeri* Infections among Patients in Spain, 2005–2011

Gerardo Rojo-Marcos, José Miguel Rubio-Muñoz, Germán Ramírez-Olivencia, Silvia García-Bujalance, Rosa Elcuaz-Romano, Marta Díaz-Menéndez, María Calderón, Isabel García-Bermejo, José Manuel Ruiz-Giardín, Francisco Jesús Merino-Fernández, Diego Torrús-Tendero, Alberto Delgado-Iribarren, Mónica Ribell-Bachs, Juan Arévalo-Serrano, and Juan Cuadros-González

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 20, No. 3, March 2014

12 Hospitals in Spain

Malaria Laboratory, Instituto de Salud Carlos III, Madrid

1. Príncipe de Asturias University Hospital, Alcalá de Henares, Madrid
2. Carlos III Hospital, Madrid
3. La Paz University Hospital, Madrid
4. Doctor Negrín University Hospital, Las Palmas de Gran Canaria
5. Ramón y Cajal University Hospital, Madrid
6. Gregorio Marañón University Hospital, Madrid
7. Getafe University Hospital, Madrid
8. University Hospital of Fuenlabrada, Madrid
9. Severo Ochoa University Hospital, Madrid
10. University General Hospital of Alicante, Alicante, Spain
11. University Hospital Fundación Alcorcón, Madrid
12. Hospital General de Granollers, Barcelona, Spain

Table 1. Demographic and epidemiologic characteristics of patients with imported *Plasmodium ovale curtisi* or *P. ovale wallikeri* infections, Spain, 2005–2011*

Characteristic	*P. ovale curtisi*, n = 21	*P. ovale wallikeri*, n = 14	p value
Patient sex			0.332
M	10 (47.6)	9 (64.3)	
F	11 (52.4)	5 (35.7)	
Patient age, y, median (IQR)	36.50 (23.04–52.66)	38.33 (11.79–45.27)	0.377
Age <15	3 (14.3)	4 (28.6)	0.401
Ethnicity			0.721
Black	15 (71.4)	9 (64.3)	
White	6 (28.6)	5 (35.7)	
Type of patient			0.260
Early immigrant	6 (28.6)	4 (28.6)	
Traveler	14 (66.7)	10 (71.4)	
Reason for travel			
Visiting friends and relatives	9 (42.8)	7 (50.0)	
Tourism		1 (7.1)	
Work	3 (14.3)	2 (14.3)	
Cooperation	2 (9.5)		
Unknown	1 (4.8)		
Duration of travel, d, median (IQR)	75 (23.25–91.50)	23 (15.00–81.50)	0.279
Country of infection			0.486
Equatorial Guinea	12 (57.1)	7 (50.0)	
Nigeria	2 (9.5)	3 (21.4)	
Equatorial Guinea or Cameroon	1 (4.8)	0	
Ghana	1 (4.8)	1 (7.1)	
Ethiopia	1 (4.8)	0	
Guinea-Conakry	1 (4.8)	0	
Liberia	1 (4.8)	0	
Angola	1 (4.8)	0	
Guinea-Bissau	1 (4.8)	0	
Guinea-Conakry or Senegal	0	1 (7.1)	
Côte d'Ivoire	0	1 (7.1)	
Mozambique	0	1 (7.1)	
Chemoprophylaxis			0.627
No prophylaxis	17 (81.0)	13 (92.9)	
Mefloquine, incomplete	1 (4.8)	1 (7.1)	
Mefloquine	1 (4.8)	0	
Doxycycline	1 (4.8)	0	
Atovaquone/proguanil	1 (4.8)	0	
Days from arrival to onset of symptoms, median (IQR)	94.5 (12.5–297.2)	9.5 (2.7–58.2)	0.077
Days from onset of symptoms to diagnosis, median (IQR)	8 (2.7–16.5)	3.5 (2.0–7.7)	0.206
Recent *Plasmodium* infection	3 (14.3)	3 (21.4)	>0.999
Other infections			
Hepatitis B virus			>0.999
Active	1/11 (9.1)	0/10	
Cured or vaccinated	6/11 (54.5)	5/10 (50.0)	
Negative	4/11 (36.4)	5/10 (50.0)	
Hepatitis C virus	1/7 (14.3)	0/10	0.412
HIV	1/7 (14.3)	0/10	0.412
Filariasis†	3/6 (50.0)	0/4	0.200
Intestinal parasites‡	3/6 (50.0)	1/4 (25.0)	0.571
Other underlying conditions	9 (42.8)	8 (42.8)	>0.999
Diabetes mellitus	2 (9.5)	1 (7.1)	
Drepanocytosis	2 (9.5)	0	
Hypertension	4 (19.0)	2 (14.3)	
Obesity	1 (4.8)	0	
Acute pancreatitis	0	1 (7.1)	
Policystosis and nephrectomy	0	1 (7.1)	
Oligoarthritis	0	1 (7.1)	
Glucose-6-phosphate dehydrogenase deficiency	2/14 (14.3)	0/8	0.515
Pregnancy	1 (4.8)	0	>0.999

*Values are no. (%) patients or no. positive/total no. (%) patients unless otherwise indicated. IQR, interquartile range.
†*Mansonella perstans* (n = 2), *Loa loa* (n = 1).
‡*Trichuris trichiura* (n = 3), hookworms (n = 2), *Ascaris lumbricoides* (n = 2), *Strongyloides stercoralis* (n = 1), *Entamoeba hystolitica* (n = 1).

Table 2. Microbiological characteristics of patients with imported *Plasmodium ovale curtisi* or *P. ovale wallikeri* infections, Spain, 2005–2011*

Characteristic	*P. ovale curtisi*, n = 21	*P. ovale wallikeri*, n = 14	p value
Positive thick smear, no. (%) patients	16 (76.2)	10 (71.4)	>0.999
Positive by PCR only, no. (%) patients	5 (23.8)	4 (28.6)	>0.999
Parasitemia, µL	2,800 (773.25–5,484.25)	1,243.50 (337.75–6,200.00)	0.699
Mixed infection, no. (%) patients	1† (4.8)	1† (7.1)	>0.999
Rapid diagnostic test result, no. positive/total no. patients (%)			
Common antigen positive	4/16 (25.0)	4/12 (33.3)	0.691
P. falciparum antigen positive	1/15 (6.7)	2/12 (16.6)	0.569
Leukocyte count, $\times 10^9$ cells/L	7.2 (4.9–8.7)	5.5 (4.2–8.2)	0.309
Hemoglobin, g/dL	11.6 (9.7–13.6)	10.9 (9.6–12.1)	0.364
Platelet count, $\times 10^9$ cells/L	126 (106.0–182.5)	91.5 (54.7–117.7)	**0.031**
Albumin, g/dL	3.7 (3.3–4.1)	3.4 (2.8–3.7)	0.063
Creatinine, mg/dL	0.88 (0.6–1.1)	0.97 (0.5–1.1)	0.730
Lactate dehydrogenase, IU/L	434.5 (358.7–807.7)	563 (462.5–731.7)	0.200
Aspartate aminotransferase, IU/L	24.5‡ (20.0–40.2)	31 (22–41)	0.624
Alanine aminotransferase, IU/L	25.5‡ (16.0–49.7)	23 (18.5–47.0)	0.785
Total bilirubin level, mg/dL	0.68‡ (0.6–1.2)	0.87 (0.6–1.4)	0.426

*Values are median (interquartile range) unless otherwise indicated. Boldface indicates significance.
†*P. falciparum* was second infection for both patients.
‡One patient had active hepatitis B virus infection.

Table 3. Clinical and therapeutic characteristics of patients with imported *Plasmodium ovale curtisi* or *P. ovale wallikeri* infections, Spain, 2005–2011*

Characteristic	*P. ovale curtisi*, n = 21	*P. ovale wallikeri*, n = 14	p value
Asymptomatic	3 (14.3)	0	0.259
Fever	18 (85.7)	14 (100.0)	0.259
Tertian fever	1 (4.8)	3 (21.4)	0.279
Maximum temperature, ºC, median (IQR)	38.4 (37.5–40.0)	39.7 (38.9–40.5)	0.088
Chills	3 (14.3)	3 (21.4)	0.664
Sweating	0	1 (7.1)	0.400
Headache	6 (28.6)	4 (28.6)	>0.999
Nauseas	0	3 (21.4)	0.056
Vomitus	0	3 (21.4)	0.056
Astenia	2 (9.5)	3 (21.4)	0.369
Epigastralgia	2 (9.5)	0	0.506
Arthralgia	5 (23.8)	3 (21.4)	>0.999
Myalgia	6 (28.6)	4 (28.6)	>0.999
Diarrhea	1 (4.8)	1 (7.1)	>0.999
Chest pain	1 (4.8)	1 (7.1)	>0.999
Cough	4 (19.0)	3 (21.4)	>0.999
Dyspnea	0	1 (7.1)	0.400
Dizziness	2 (9.5)	0	>0.999
Splenomegaly	5 (23.8)	3 (21.4)	>0.999
Complications or severe malaria	2 (9.5)	2 (14.3)	>0.999
Hemolytic crisis	1 (4.8)	0	
Severe anemia, hemoglobin <7 g/dL	1 (4.8)	1 (7.1)	
Acute respiratory distress syndrome	0	1 (7.1)	
Admission to hospital	13 (61.9)	13 (92.9)	0.056
Duration of hospitalization, d, median (IQR)	4 (3.0–7.5)	5 (3.5–7.5)	0.390
Treatment			0.563
Chloroquine	12 (57.1)	7 (50.0)	
Other treatment	8 (38.1)	7 (50.0)	
Quinine + doxycycline	3 (14.3)	4 (28.6)	
Atovaquone/proguanil	3 (14.3)	1 (7.1)	
Quinine + clindamycin + chloroquine/proguanil	1 (4.8)	0	
Quinine + clindamycin + chloroquine	0	1 (7.1)	
Mefloquine	0	1 (7.1)	
Atovaquone/proguanil + chloroquine	1 (4.8)	0	
No treatment	1 (4.8)	0	
Primaquine	14 (66.7)	10 (71.4)	>0.999
Compliance	19/21 (90.5)	13/13 (100.0)†	0.513

*Values are no. (%) patients or no. positive/total no. (%) patients unless otherwise indicated. IQR, interquartile range.
†One patient was lost to follow-up.

Conclusions

- **More severe thrombocytopenia** was the only significant finding among patients with *P. ovale wallikeri* infection (p = 0.031)
- Nonsignificant trends for *P. ovale wallikeri*
  - Shorter time from arrival to onset of symptoms (Nolder D 2013)
  - Lower level of albumin
  - Higher markers of hemolisis: LDH, AST, BR
  - Higher median maximum core temperature
- Is *P. ovale wallikeri* more pathogenic?
- Larger, prospective studies are needed to assess these findings

Study design

- Prospective, unrandomised, open-label, observational study

Study objectives

- Comparative study of the epidemiological, clinical, microbiological, analytical, outcome and therapeutic characteristics of both species
- Identify useful markers for differential diagnosis in the clinical practice
- Might help to complete maps of *P. ovale* circulating species in endemic countries

Number of cases available

TropNet

- 2013 (10 centres):
  - **25 *Po*** so far
- 2012 (21/68 centres)
  - 552 malaria (461 *Pf; 52 Pv;* ***28 Po****; 12 Pm)*

Spanish Malaria Lab

- 2013
  - **12 *Po***
- 2014
  - **4 *Po*** so far

Inclusion criteria

- Patients with diagnosis of imported *P. ovale* infection by thick or thin film or PCR and (All confirmed by PCR)
- No clinical restriction, from asymptomatic to severe disease

Exclusion criteria

- Lack of informed consent

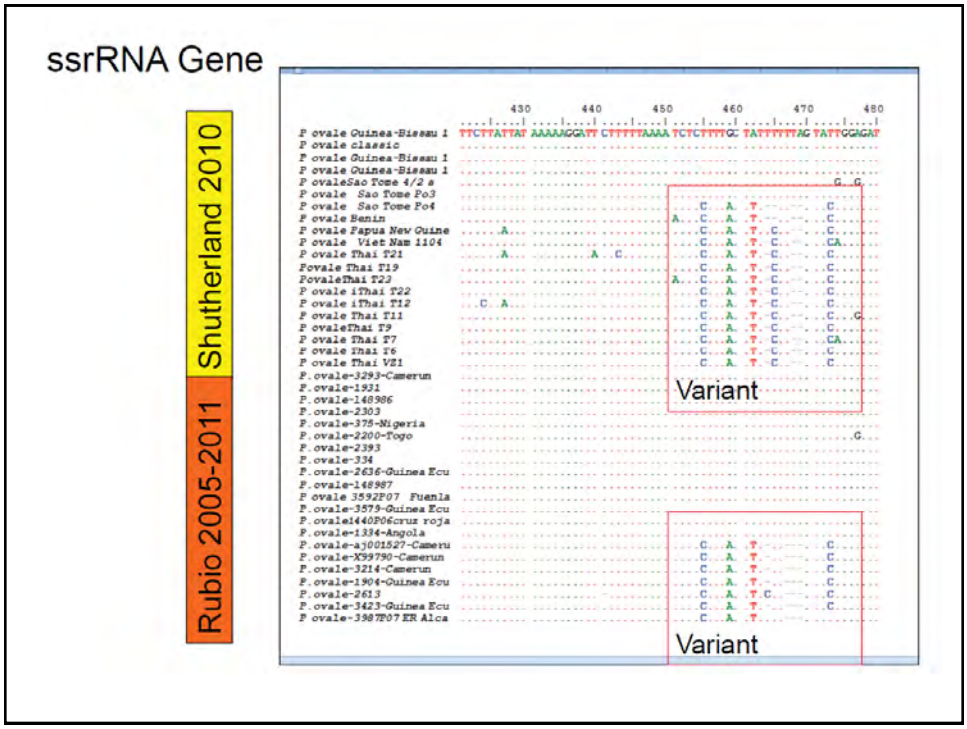
Genetic analysis

- Full blood dotted on filter paper (Whatman™) before the initiation of treatment (2-3 drops) in an individual little plastic bag

- Sent by regular mail
- Diagnosis will be confirmed by seminested multiplex PCR
- Locus amplification and sequencing of the ssrRNA gene will be carried out
- Classified as *Po wallikeri* or *Po curtisi*

Reference laboratory

- Dr. José Miguel Rubio
  Servicio de Parasitología
  Centro Nacional de Microbiología
  Instituto de Salud Carlos III
  Cra. Majadahonda Pozuelo Km. 2,5
  Majadahonda, 28220 Madrid
  España/Spain



Patient data and analysis

- Epidemiological, clinical, microbiological, analytical and therapeutic data from interview and medical reports
- Easy filling **data form** available on line (pdf)
- Statistical analysis test will be performed
- Data analysis will compare possible differences between both groups

MALARIA OVALE DATA FORM

Identification (Hospital code + number of patient. E.g. HUPA1): ____ ____

Physician name (last, first): _____ E-mail of contact: _____

Date of symptom onset of this attack (mm/dd/yyyy): ____/ ____/ ____
Asymptomatic Yes ☐ No ☐

Date of Birth: (mm/dd/yyyy) ____/ ____/ _____
Sex:
Male ☐, Female ☐ Unknown ☐

Is patient pregnant? Yes ☐ No ☐

Ethnicity: Black ☐, White ☐, Asian ☐, Other (specify) _____, Unknown ☐

Patient admitted to hospital: Yes ☐ No ☐ Unknown Date: ____/ ____/ _____
Length of stay in hospital **(days)** _____

Positive lab test result: Smear ☐, PCR ☐, RDT ☐, No test done/unknown _____

Species: Ovale ☐, Mixed ☐ (specify) _____

Parasitemia µL:_____ (%): ____

Has the patient traveled or lived outside the E.U. during the past 2 years?
Yes ☐, No ☐
If yes, specify: Country: 1. _____ 2. _____ 3. _____
Date returned/ arrived in E.U. (mm/dd/yyyy): ____/ ____/ _____
Duration of stay in country **Days:** _____
Did patient reside in E.U. prior to most recent travel? Yes☐ (specify country): _____,
No ☐ Unknown☐
Principal reason for travel from/ to E.U for most recent trip: Tourism, Military, Business, Peace Corps,

Ethical considerations

- Approval in local ethics commitees neccessary
- Patient informed consent required
- Patient **information and informed consent form** will be available in english, french, spanish and any other language under request

Contact and information

- Dr. Gerardo Rojo Marcos. Servicio de Medicina Interna. Hospital Universitario Príncipe de Asturias. Ctra. Alcalá-Meco s/n 28805 Alcalá de Henares. Madrid.

  grojo.hupa@salud.madrid.org
- Dr. Juan Cuadros González. Servicio de Microbiología y Parasitología Clínicas

  jcuadros.hupa@salud.madrid.org

References

- Sutherland CJ, Tanomsing N, Nolder D, Oguike M, Jennison C, Pukrittayakamee S, et al. Two non-recombining sympatric forms of the human malaria parasite *Plasmodium ovale* occur globally. J Infect Dis. 2010;201:1544-50.
- Fuehrer H-P, Habler VE, Fally MA, Harl J, Starzengruber P, Swoboda P, et al. *Plasmodium ovale* in Bangladesh: Genetic diversity and the first known evidence of the sympatric distribution of *Plasmodium ovale curtisi* and *Plasmodium ovale wallikeri* in southern Asia. Int J Parasitol. 2012;42:693–9.
- Oguike MC, Betson M, Burke M, Nolder D, Stothard JR, Kleinschmidt I, et al. P*lasmodium ovale curtisi* and *Plasmodium ovale wallikeri* circulate simultaneously in African communities. Int J Parasitol. 2011;41:677-83
- Bauffe F, Desplans J, Fraisier C, Parzy D- Real-time PCR assay for discrimination of *Plasmodium ovale curtisi* and *Plasmodium ovale wallikeri* in the Ivory Coast and in the Comoros Islands. Malar J. 2012;11:307.
- Rubio JM, Post RJ, van Leeuwen WM, Henry MC, Lindergard G, Hommel M. Alternative polymerase chain reaction method to identify *Plasmodium* species in human blood samples: the seminested multiplex malaria PCR (SnM-PCR).Trans R Soc Trop Med Hyg. 2002;96:199-204.
- Nolder D, Oguike MC, Maxwell-Scott H, Niyazi HA, Smith V, Chiodini PL, et al. An observational study of malaria in British travellers: *Plasmodium ovale wallikeri* and *Plasmodium ovale curtisi* differ significantly in the duration of latency. BMJ Open. 2013;3: e002711.
- Rojo-Marcos G, Rubio-Muñoz JM, Ramírez-Olivencia G. Comparation of imported *Plasmodium ovale curtisi* and *Plasmodium ovale wallikeri* infections among patients in Spain 2005-2011. Emerg Infect Dis 2014;20

Health care is not sold, but defended

Comparison of methods used to determine the safety of N,N-diethyl-m-toluamide (DEET). Will new EU regulations put EU travellers at risk of malaria and other vector borne diseases?

Vanessa Chen-Hussey, Ron Behrens, James G Logan

Department of Disease Control

Department of Clinical Research

malaria centre

Disease transmitted by vectors.

Vector	Diseases
Anopheles spp.	Malaria, Lymphatic filariasis
Stegomyia	Dengue, Rift Valley fever, Chikungunya, Yellow fever
Culex spp.	Japanese Enceph. Filariasis, West Nile Fever
Sandflies	Leishmaniasis
Black Flies	Onchocerciasis
Hard and Soft Ticks	TBE, Rickettsial diseases, Lyme, Borreliosis, Tick Typhus
Triatomine bugs	Chagas Disease
Tsetse fly	Trypanosomiasis

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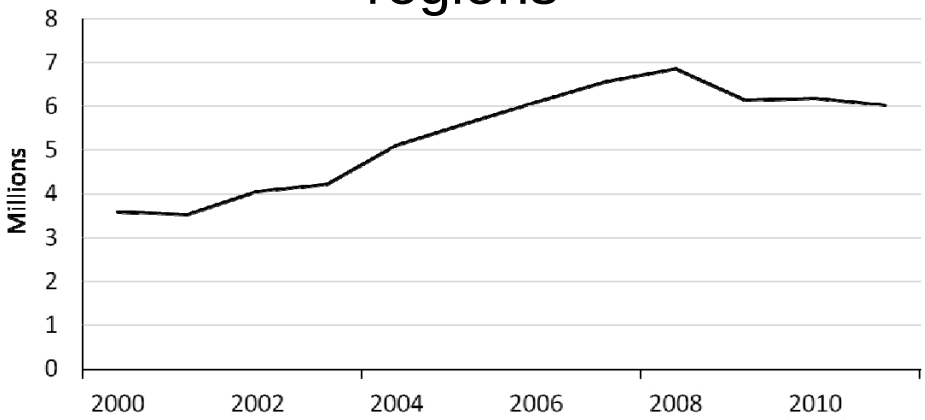
Visits by UK residents to Tropical regions$



Globally 256 Million annual arrivals in Tropical Regions of the World, 34 Million S.S. Africa*

* World Tourism Organisation report 2013 $ International Passenger Survey

Results of toxicity testing of DEET in animals reported to the USEPA

NOEL, no-observed effect-level; LEL, lowest effect-level.

Toxicologic effects and endpoints for DEET

Type of study	Endpoints (NOEL, LEL)[a]	Description of effect (nature, severity)
Acute toxicity		
Acute neurotoxicity screening study in rats (gavage)	NOEL = 200 mg/kg BW/day; LEL = 500 mg/kg BW/day	No gross or microscopic alterations were observed in the central or peripheral nervous system in comparison with controls
Subchronic toxicity		
90-day dermal toxicity study in rats	NOEL = 300 mg/kg BW/day[b]; LEL = 1000 mg/kg BW/day[b]; NOEL = 1000 mg/kg BW/day	Based on decrease in body-weight gain and increase in liver weights[b]
90-day dermal toxicity study in micropigs		Based on 13-week study in micropigs; No renal lesions in micropigs[b]
Chronic toxicity		
Combined chronic and carcinogenicity in rats (2 years)	NOEL = 100 mg/kg BW/day (females and males); LEL = 400 mg/kg BW/day	Based on decreased body weights and food consumption, and increased cholesterol levels in female and male rats[c]
Chronic toxicity study in dogs	NOEL = 100 mg/kg BW/day; LEL = 400 mg/kg BW/day	Based on decreases in food consumption and body weights, increase in the incidence of ptyalism and a decrease in cholesterol levels

[a] Endpoint abbreviations: BW, body weight; NOEL, no-observed effect-level; LEL, lowest effect-level.
[b] USEPA (1998).
[c] Schoenig et al. (1999).

EPA United States Environmental Protection Agency

Human Toxicity

1. Dermal symptoms were reported in 5% of reports.
   Symptoms included irritation, redness, rash, and swelling.

2. •• Gastrointestinal symptoms following exposure to DEET by ingestion.
   Gastrointestinal symptoms included oral irritation, nausea, and vomiting.

3. •• Neurological reactions following DEET exposure are rare. The incidence of seizure following DEET ~ 1 per 100 million vc1
   Reports of neurological reactions are predominately the result of accidental or deliberate ingestion, or dermal applications not consistent with label directions. Reported neurological signs of toxicity include encephalopathy, seizure, tremor, slurred speech, coma, and death

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EPA United States Environmental Protection Agency

Based on pesticide usage information mainly for 1990, an average annual estimate of the Domestic usage of N,N-diethyl-meta-toluamide (DEET) is 4 million pounds (active ingredient). About 30% of the U.S. population uses DEET annually as an insect repellent (about 27% of adult males, 31% of adult females and 34% of children. Approximately 21% of U.S. households use DEET annually.

Agency concluded.

DEET as an insect repellent does not pose a significant health risk to the general U.S. population for the following reasons:
(1) DEET is not believed to be acutely toxic nor carcinogenic, significantly developmentally toxic nor mutagenic at the doses tested.
(2) The available data do not support a direct link between exposure to DEET and reported seizure Incidences (14 cases).

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US EPA Special Review and Reregistration Division; *Reregistration Eligibility Decision DEET*. 1998

U.S. EPA, Toxicity and Exposure Assessment for Adults & Children

Daily exposure to DEET:

1. No-observed-adverse-effects level (NOAEL) in experimental animal studies of dermal exposure was 250-300 mg/kg/day
2. Adult males = 12 mg/kg/day
3. children <12 years = 37 mg/kg/day

"DEET insect repellents will generally not cause unreasonable risks to humans or the environment"

The AAP recommends that repellents should contain no more than 30% DEET when used on children. Insect repellents also are not recommended for children younger than 2 months

US EPA Special Review and Reregistration Division; *Reregistration Eligibility Decision DEET*. 1998

Directive 98/8/EC concerning the placing biocidal products on the market

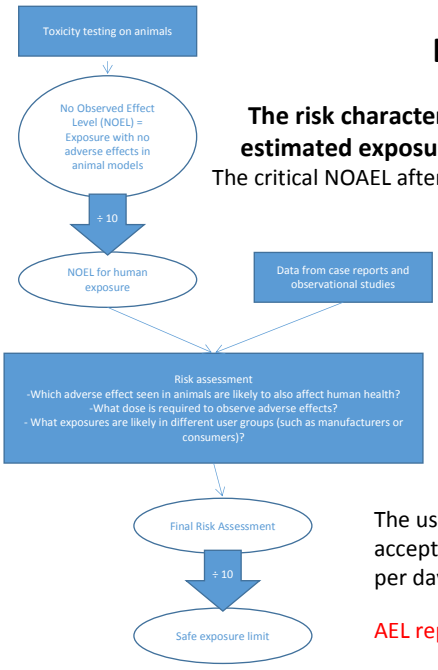
N,N- diethyl-*meta*-toluamide (DEET)

Product-type 19
(Repellents and attractants)

DEET is efficacious enough, based on the documentation received on the active substance DEET and the representative product, containing 15% DEET, for the proposed manner and areas of use of products intended as repellent without unacceptable risk neither to human health or the environment……..

Reduce the exposure in children < 12 years olds, no use in children < 2 years old. Reducing the extent of use in children < 12 years on unsuitable exposure areas i.e. hands, and around eyes and mouth, and recommendations on maximum daily number of applications.

EC: *Biocidal Products Directive (Directive 98/8/EC) Assessment Report: N,N-Diethyl*-meta-*Toluamide (DEET)*2010



EU *Human Health Risk Assessment*

The risk characterisation is based on a traditional method comparing the estimated exposure with an AEL based on the dermal 90 day study in rats.
The critical NOAEL after dermal dosing in rats is ≥1000 mg/kg bw/day

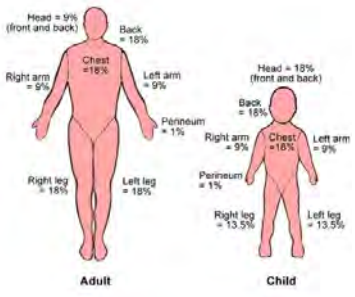
The use of the representative product (15%) 2 times per day is considered acceptable for adults and children >12 years old i.e the exposure twice per day was 47%-74% of the AEL repeated

AEL repeated is calculated as 8.2mg/kg/day

EC: *Biocidal Products Directive (Directive 98/8/EC) Assessment Report: N,N-Diethyl*-meta-*Toluamide (DEET)*2010

Daily Exposure of DEET

Adult BSA = 1.9m² = 19,000cm²



Max EU dose = 8.2 mg DEET /kg/day for 70kg = 574 mg DEET per day

Standard application rate used in laboratory testing
= 1 ml product per 600cm² (approx. 1 forearm)
= 1.7 µl/cm² or 1.7 mg/cm²

Single application:
Total product required to cover 2 whole arms(18%) OR 2lower legs = 5.7ml
An average single application used by Canadians was around 3700mg

15% DEET product contains 15g/100ml
One application of 5.7ml = 855mg DEET
One application of 3.7ml = 555mg DEET

50% DEET contains 50g/100ml
One application of 5.7ml = 2850mg DEET
One application of 3.7ml = 1850mg DEET

Why travellers might need high concentrations DEET

1. Duration of repellency
2. Compensate for under/infrequent application (safety margin in application)
3. Repellency spectrum adequate for range of vectors

Longevity of repellency of DEET

15% duration ~ 4-5hrs

Field trial DEET 20% 1.33 mg/cm2	86.9%	1h
Anopheles spp.	88.5%	2h
	87.9%	3h
	88.9%	4h
	74.5%	5h
	37.5%	6h
	72.1%	7h
Field trial DEET 20% 1.33 mg/cm2	100%	3h
Cx. annulirostris	97.4%	4h
	99.1%	5h
	99.4%	6h
	96.3%	7h
Field trial DEET 20%	100%	1h
0.76-0.84 mg/cm2	100%	2h
	97.5%	3h
Ae. albopictus	95.9%	4h
	94%	5h
	95%	6h
	100%	7h

Lupi et.al. Travel Medicine and Infectious Disease (2013) 11, 374e411

Low dosage in application of repellent by travellers

Repellency conc. Used laboratory testing ~ 1.7mg(µl)/cm²

Table 2 Mean applied dose mg/cm² (SD) of active ingredient

% Active ingredient in product	≥50%	20%–49%	<20%	Mean dose per country (mg/cm²)
Arms (mg/cm²)				
UK (*N* = 74)	0.56 (0.17)	0.23 (0.05)	—	0.41 (0.21)
India (*N* = 27)	0.57 (0.11)	0.18 (0.1)	0.13 (0.02)	0.18 (0.16)
Kenya (*N* = 23)	0.67 (0.27)	0.28 (0.94)	—	0.67 (0.29)

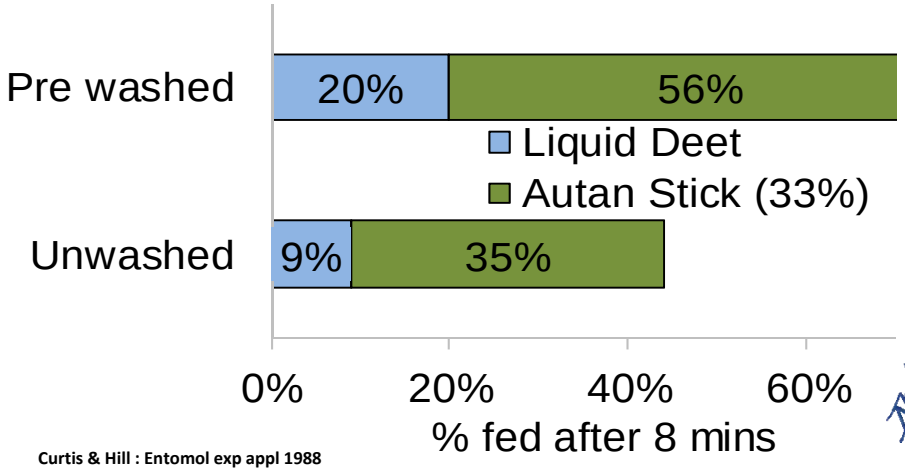
One application of 5.7ml = 2850mg DEET One application of 5.7ml = 855mg DEET

Malaria centre

Thrower & Goodyer. Application of Insect Repellents by Travelers to Malaria Endemic Areas JTM 2006

Effect of washing and formulations on the efficacy of DEET

0.4gm DEET equivalent formulation applied to lower leg with and without washing then exposed to un-fed *A. gambiae*



Malaria centre

Curtis & Hill : Entomol exp appl 1988

Summary

- The is a modelled on rat and dog toxicity studies.
- EU safety assessment will restrict DEET products to 15% to be used a maximum of twice a day.
- EU risk assessment fails to balance DEET toxicity or its historical safety record against risks of vector borne diseases.
- EPA assessment identifies not restriction on DEET in adults based on toxicity data and historical safety.
- The personal repellent protection for future EU travellers will at 15% concentration may not provide protection.