TropNet

European Network for Tropical Medicine and Travel Health

14th Workshop on Imported Infectious Diseases

2013

27th – 28th September

Bordeaux

Bordeaux 2013 - 14th TropNet Workshop

Friday, 27/09/2012		
13^{00}-13^{30}	**Welcome and Introduction**	**Philippe Vigouroux, Director General (UHC)** **Denis Malvy & Matthieu Mechain, Bordeaux**
13^{30}-15^{00}	**Report of steering committee and coordinator** • European networks in Tropical and Travel Medicine: experience of collaboration and strengthening the network • TropNet membership issues • Overview on the `TropNet platforms´ including ▪ **Research platform** - Report on ongoing TropNet studies & studies with participation of TropNet centres - Forecast on upcoming TropNet studies ▪ **TropNet figures on imported diseases in 2012** ▪ **Update on muscular sarcocystosis imported from Tioman Island 2011 & 2012**	**Christoph Hatz & Andreas Neumayr, Basel**
15^{00}-15^{30}	**Break**	
15^{30}-17^{00}	• TropNet website: using the FORUM • Network resources: sources for orphan drugs • Development of TropNet travel medicine info material • Discussion on network activities/projects: what? how? who?	**Andreas Neumayr, Basel** **Christoph Hatz, Basel**
17^{00}-17^{30}	**Break**	
17^{30}-19^{00}	**Malaria:** • PANDA and the pitting debt • HaemoArt: Haemolysis after antimalarial treatment with artemisinins • Eurartesim: Study on treatment of *P. vivax* malaria **Cutaneous leishmaniasis:** LeishMan: Surveillance of imported leishmaniasis with regard to diagnostic & therapeutic procedures **Research projects in a European context:** discussion on perspectives of efficient joint research projects	**S. Jaureguiberry, Paris** **Andreas Neumayr, Basel** **Christoph Hatz, Basel** **Andreas Neumayr, Basel** **Matthieu Mechain, Bordeaux**
19^{00}-19^{30}	Transport to City Hall	**Matthieu Mechain, Bordeaux**
19^{30}-20^{45}	City Hall with reception (cocktail pre-dinner)	**Josy Reiffers, on behalf of Alain Juppé, Mayor of Bordeaux** **Christoph Hatz, Basel**
20^{45}-21^{00}	Transport to Dinner	**Denis Malvy, Bordeaux**
21^{15}-23^{00}	**Dinner**	
Saturday, 28/09/2012		
9^{00}-9^{15}	**Introduction**	**Coordinator, SC members**
9^{15}-10^{30}	**Project proposal:** First- and second-line treatment of giardiasis **Project proposal:** Retrospective analysis of life vaccinations given to travelers with immunosuppressive therapy **Project Proposal**: Sentinel surveillance of artemisinin resistance in returning travellers with *P. falciparum* malaria	**Andreas Neumayr, Basel** **Silja Büehler, Zürich** **Andreas Neumayr, Basel**
10^{30}-11^{00}	**Break**	
11^{00}-12^{30}	**Drug resistant bacteria** • ESBL carriage in travelers: data from Basel, Switzerland • ESBL carriage in travelers: data from Leiden, the Netherlands • Colonization with resistant intestinal bacteria: a study on risk factors in Finnish travelers **New multiplex qPCR method** for assessment of intestinal pathogens in returning travelers	 **Esther Kuenzli, Basel** **Leo Visser, Leiden** **Anu Kanele, Helsinki** **Anu Kantele, Helsinki**
12^{30}-13^{30}	**Lunch**	
13^{30}-14^{45}	• The new Italian malaria prophylaxis recommendations 2013 • The new British malaria prophylaxis recommendations 2013 • Autoimmune travelers in the travel clinic: are they different? • Just published: Neurological complications of dengue	**Guido Calleri, Torino & Andrea Angheben, Negrar (Verona)** **Matthias Schmid, Newcastle upon Tyne** **Silja Büehler, Zürich** **Joaquim Gascon, Barcelona**
14^{45}-16^{30}	**Clinical case presentations** • Breast calcifications in an immigrant from Mali ? • A myxoid muscle tumor with a Russian surprise ? • Malaria ? • A family outbreak of arthritis after a beach holiday in Bali & `same same but different‘ • Migrating inflammation in travellers to Thailand • Veterinary ivermectin - a heroic remedy?	 **Michel Develoux, Paris** **Leo Visser, Leiden** **Åase Berg, Stavanger** **Leo Visser, Leiden** **Andreas Neumayr, Basel** **Anu Kantele, Helsinki** **Leo Visser, Leiden**
16^{30}-16^{45}	**Farewell**	**Denis Malvy, Bordeaux**
17^{00}-18^{45}	Eurartesim: Vivax Malaria Treatment Study - **Investigator Meeting**	**Nicola Gargano, Sigma Tau**

TropNet Workshop – Bordeaux 2013

Participants

Jan Clerinx, Antwerp, Belgium

Anu Kantele, Helsinki, Finland

Denis Malvy, Bordeaux, France

Matthieu Mechain, Bordeaux, France

Michel Develoux, Paris, France

Stéphane Jaureguiberry, Paris, France

Insa Joost, Freiburg, Germany

Jakob Cramer, Hamburg, Germany

Matthias Schmid, Newcastle upon Tyne, Great Britain

Silvia Odolini, Brescia, Italy

Andrea Angheben, Negrar, Italy

Piero Ghirga, Roma, Italy

Guido Calleri, Torino, Italy

Emile Jonker, Leiden, Netherlands

Leo Visser, Leiden, Netherlands

Kristine Mörch, Bergen, Norway

Aase Berg, Stavanger, Norway

Jorge Seixas, Lisbon, Portugal

Joaquim Gascon, Barcelona, Spain

Israel Molina, Barcelona, Spain

Toni Soriano Arandes, Barcelona, Spain

Christoph Hatz, Basel, Switzerland

Andreas Neumayr, Basel, Switzerland

Valérie D'Acremont, Lausanne, Switzerland

Silja Büehler, Zürich, Switzerland

Esther Kuenzli, Basel, Switzerland

Welcome to the 14th Workshop on Imported Infectious Diseases

27th – 28th Sept. 2013

Report of the steering committee & coordinator

- Membership issues
- The TropNet platforms: where are we?
- The 2012 figures on imported diseases
- TropNet website: update & crash course
- Implementation of joint network research projects

Membership issues

- currently 71 member sites
- 2012/2013:

  + 3 sites

University Hospital Innsbruck

Department of Internal Medicine VI
Division of Infectiology, Immunology, Tropical Medicine, Rheumatology & Pneumology

University Hospital Vienna

Department of Medicine I
Division of Infectious Diseases and Tropical Medicine

Rosa Bellmann-Weiler

Günter Weiss

Michael Ramharter

Heimo Lagler

Hôpital Tenon - Paris

Groupe Hospitalier Paris Est,
Assistance Publique Hôpitaux
de Paris

Guillaume Le Loup

Change of site coordinator

Oslo University Hospital, Ullevål Hospital
Department of Infectious Diseases, Norwegian Centre for Imported and Tropical Diseases

Bjørn Myrvang

Mogens Jensenius

The TropNet platforms

Research

- Coordination & support for individual research groups working on communicable & non-communicable diseases:
  - Treatment of severe malaria
  - Dengue/Chikungunya
  - Leishmaniasis
  - MRSA in travellers
  - 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
- 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
- Collaboration with the CDC on Sarcocystis outbreak

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

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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

➔ **Eurartesim®- Sigma Tau**

Pregnancy registry in Europe

TropNet study: Artesunate for severe malaria in Europe

Number of recruited patients: **160**

Dr. Thomas Zoller
MSc, DTM&H

EU-FP7 joint DengueTools & TropNet study:

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

Number of recruited patients: **~ 180**
(started Sept. 2011, runing over 42 months)

LeishMan working group

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

More details will be presented later

Safety & Pregnancy Registries 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

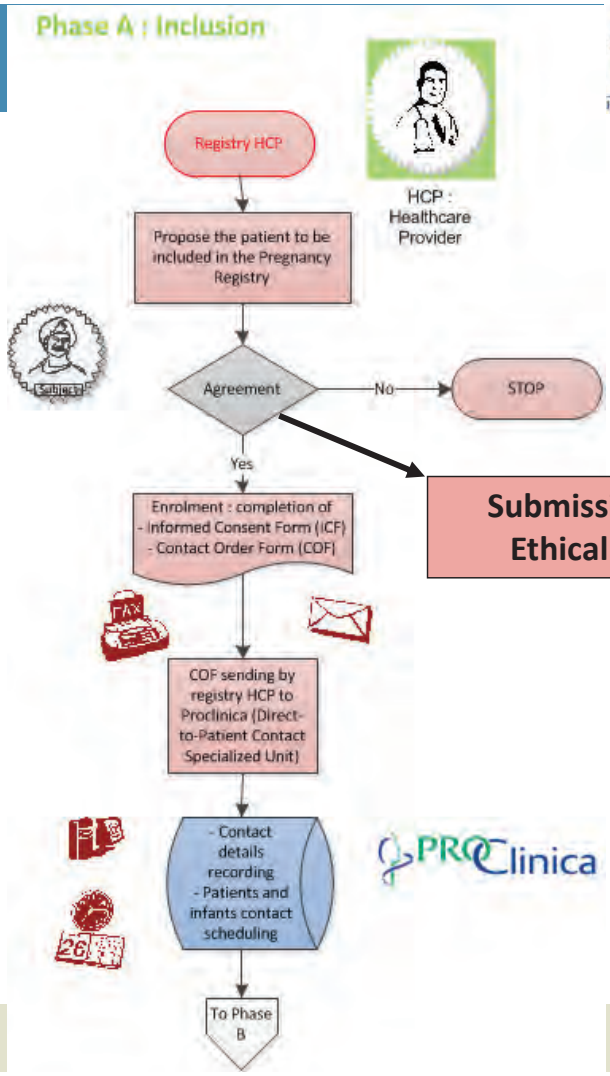
Study objectives:

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:



Current TropNet participation

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

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

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

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

New TropNet projects ahead

- **TropNet study HaemoART**

  Study on haemolysis under oral artemisinin therapy

- **TropNet/Sigma-Tau proof of concept study of Eurartesim® in patients with imported uncomplicated P. vivax malaria**

- **TropNet studies GiardiaTreat & GiardiaREF**

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

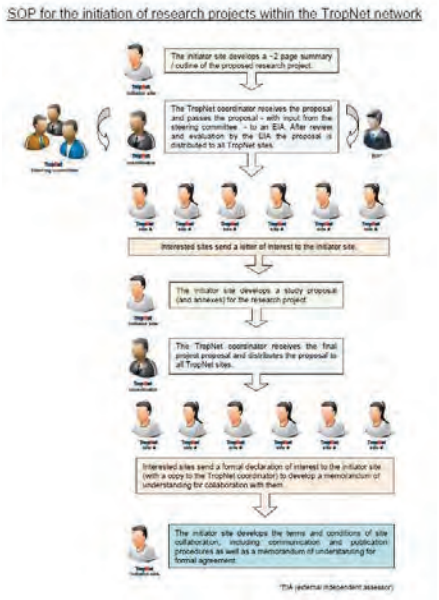
Possible TropNet projects ahead

- ***Pharmacokinetic study on Praziquantel in schistosomiasis***
- ***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***

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

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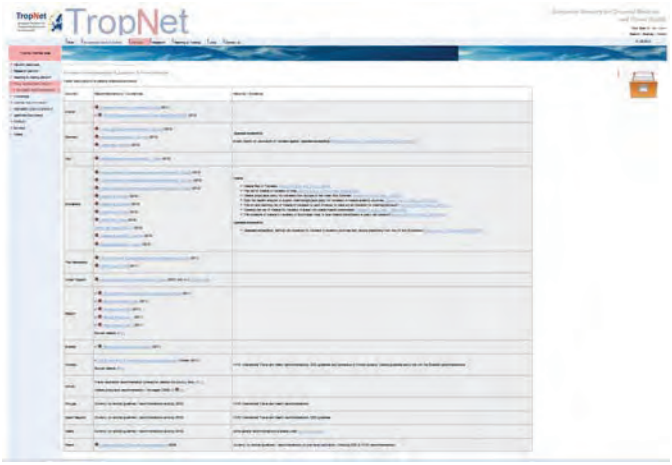
European recommendations & guidelines in Tropical & Travel Medicine



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

TropNet European Network for Tropical Medicine and Travel Health
C·H·U Hôpitaux de Bordeaux
Swiss TPH Swiss Tropical and Public Health Institute Schweizerisches Tropen- und Public Health-Institut Institut Tropical et de Santé Publique Suisse

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European Congress on Tropical Medicine and International Health (ECTMIH)
6.-10. September 2015, Basel, Switzerland

+ TropNet Travel Medicine Course ?

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The 2011 figures on imported diseases

40 of 67 sites

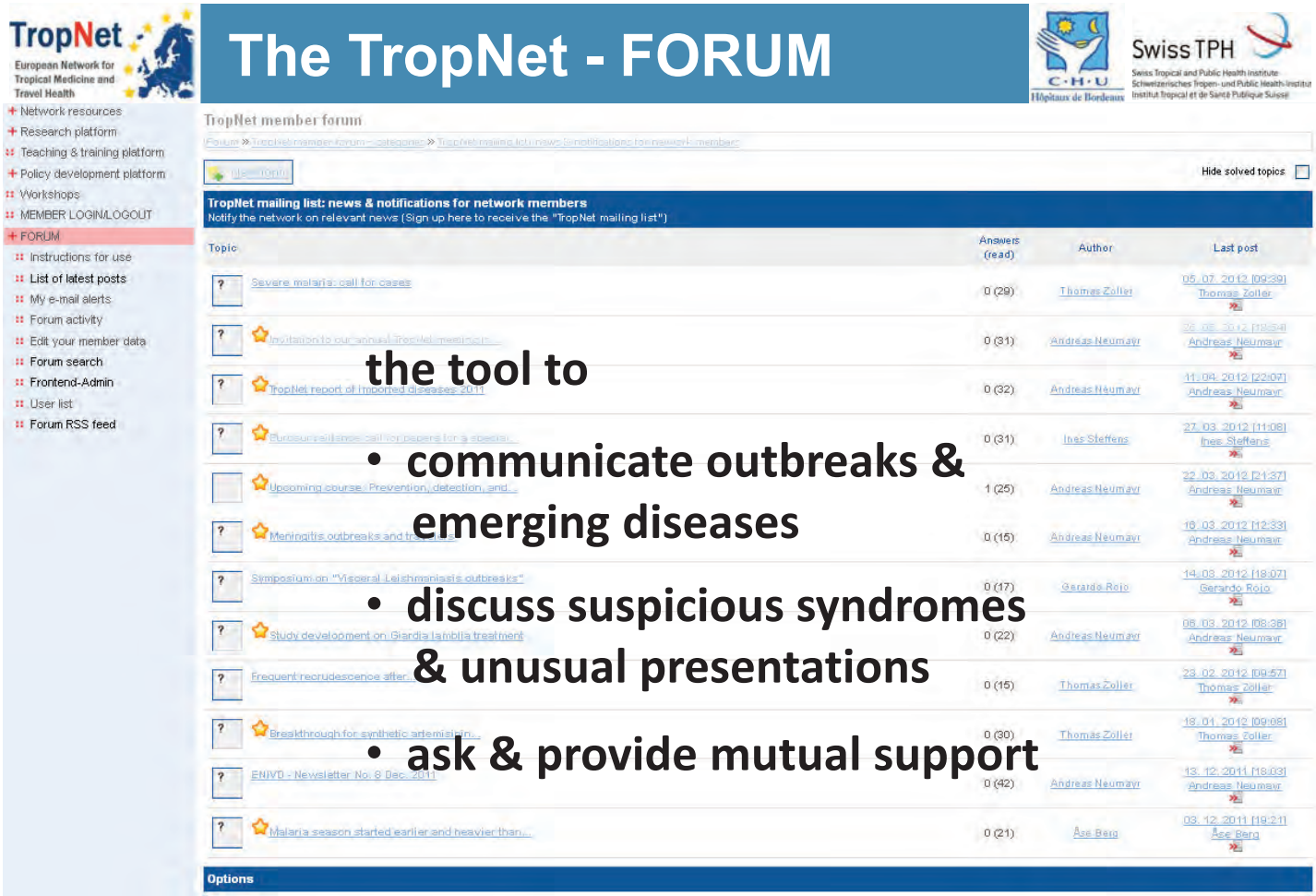
Malaria	1043	(871 *falc.; 172 non-falc.)*
Giardiasis	1089	
Schistosomiasis	672	
Amoebiasis	381	
Dengue	341	
Leishmaniasis	237	(185 CL & ML; 52 VL)
Rickettsiosis	118	
Loiasis	47	
Chikungunya	27	

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	571	(28 *CL*; 4 *ML*; 25 *VL*)
Rickettsiosis	56	
Typhoid fever	24	
Loiasis	8	
Chikungunya	4	
Sarcocystis	18	

The TropNet - FORUM



the tool to

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

Preliminary analysis & update on Sarcocystis outbreak in travellers to Tioman Island, Malaysia 2011-2012

Douglas Esposito

Division of Global Migration & Quarantine, Travelers' Health Branch
National Center for Emerging and Zoonotic Infectious Diseases, CDC

Malaysian Journal of Public Health Medicine 2012, Vol. 12(2):

ORIGINAL ARTICLE

SURVEILLANCE FOR SARCOCYSTOSIS IN TIOMAN ISLAND, MALAYSIA

Husna Maizura AM[1], Khebir V[1], Chong CK[1], Azman Shah AM[2], Azri A[3], Lokman Hakim S[4]

[1]Disease Control Division, Ministry of Health, Malaysia.
[2]Veterinary Regional Laboratory, Kuantan, Pahang.
[3]Biosecurity and SPS Management Division, Department of Veterinary Services, Malaysia.
[4]Public Health Department, Ministry of Health, Malaysia.

ABSTRACT

In October 2011, the National International Health Regulations (IHR) 2005 Focal Point for Malaysia received notification from the United States' Centers for Disease Control and Prevention (CDC) of a probable Sarcocystis outbreak amongst 23 travellers from six countries who had vacationed on Tioman Island between June and August 2011. The Ministry of Health, Malaysia (MOH) in collaboration with the Department of Veterinary Services, Malaysia (DVS) conducted a cross sectional study in November 2011 to determine the presence of Sarcocystosis among humans, animals and in the environment in Tioman Island. Epidemiological investigations conducted involved a community health survey of 44 residents in Kampung Salang, Tioman and review of outpatient attendance cards for suspected or confirmed cases of Sarcocystosis. Twenty-eight fresh stool samples were collected and sent to the National Public Health Laboratory (NPHL) for detection of Sarcocystis oocysts using fluorescence microscopy. Water samples taken from 27 water sampling points around the island were processed and analysed under the fluorescence microscope using ultraviolet (UV) light at the Institute for Medical Research (IMR) to detect the presence of Sarcocystis sporocyst. DVS collected 84 faecal samples from four types of domesticated animals and then analysed them at the Veterinary Services Centre in Tioman Island for Sarcocystis oocysts and other parasitic ova and cysts using qualitative Floatation Technique. The results showed that Sarcocystis was not present in humans, animals and in the environment in Tioman Island during the study period. Further surveillance among humans, wildlife and the environment isneeded to determine Sarcocystis endemicity in Tioman Island.

Sequencing of the DNA from the tissue of the Dutch traveler identified ***Sarcocystis nesbitti*** as the causative organism

Contents lists available at ScienceDirect

Veterinary Parasitology

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

ELSEVIER

Short communication

Phylogenetic analysis of *Sarcocystis nesbitti* (Coccidia: Sarcocystidae) suggests a snake as its probable definitive host

Ming Tian[a,b,1], Yuanxiao Chen[a,1], Lanou Wu[c,1], Benjamin M. Rosenthal[d], Xu Liu[e], Yongshu He[a], Detiger B. Dunams[d], Liwang Cui[f], Zhaoqing Yang[b,*]

[a] Cell Biology & Genetics Department, Kunming Medical University, 1168 West Chunrong Road, Kunming, Yunnan Province 650500, China
[b] Parasitology Department, Kunming Medical University, 1168 West Chunrong Road, Kunming, Yunnan Province 650500, China
[c] Pharmacology Department, Kunming Medical University, 1168 West Chunrong Road, Kunming, Yunnan Province 650500, China
[d] Animal Parasitic Disease Laboratory, Agricultural Research Service, US Department of Agriculture, BARC East Building, 1180 Beltsville, MD 20705, USA
[e] Biomedical Engineering Research Center, Kunming Medical University, 1168 West Chunrong Road, Kunming, Yunnan Province 650500, China
[f] Department of Entomology, The Pennsylvania State University, 501 ASI Bldg., University Park, PA 16802, USA

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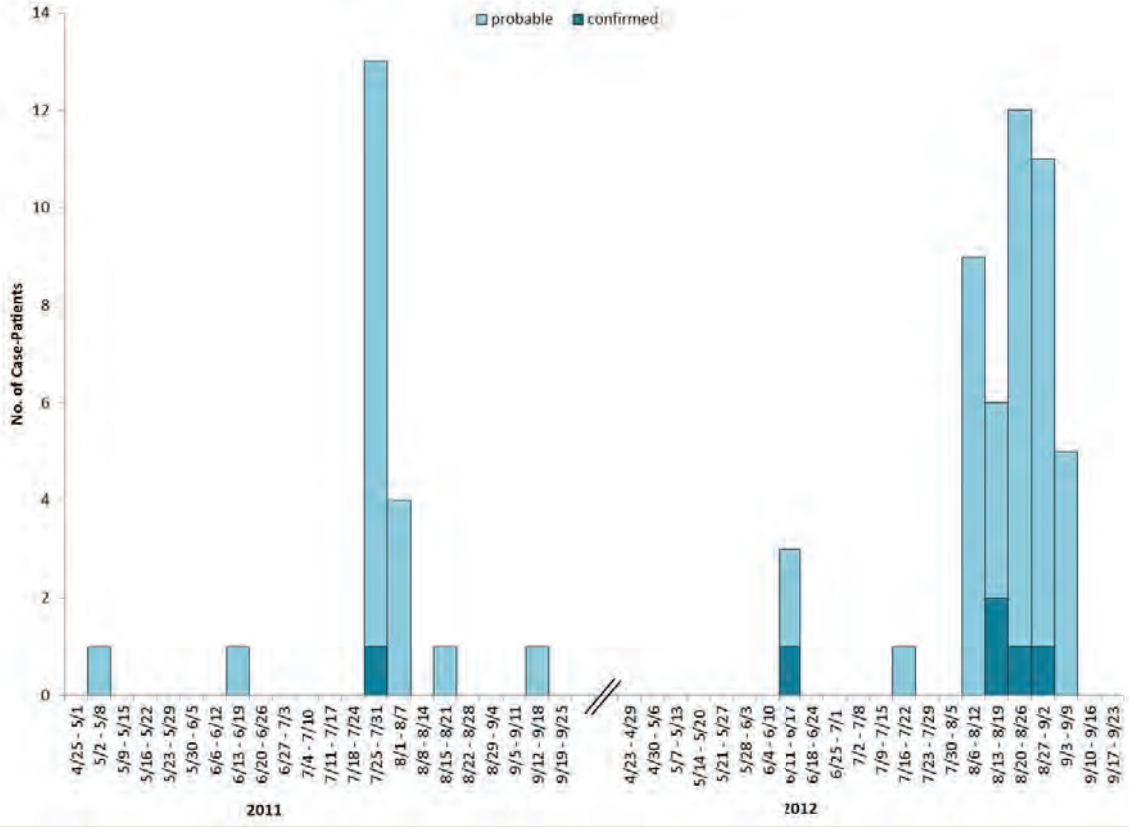
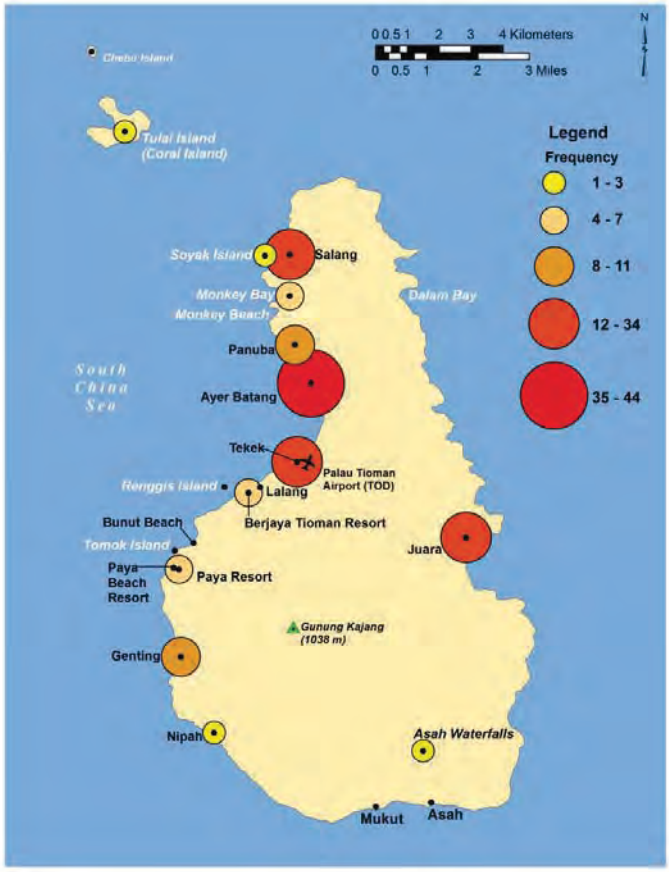
ABSTRACT

Sarcocystis nesbitti was first described by Mandour in 1969 from rhesus monkey muscle. Its definitive host remains unknown. 18S rRNA gene of *S. nesbitti* was amplified, sequenced, and subjected to phylogenetic analysis. Among those congeners available for comparison, it shares closest affinity with those species of *Sarcocystis* which use snakes as definitive hosts. We therefore hypothesize that a snake may serve as the definitive host for *S. nesbitti*.

The epidemic curve according to the week of departure from Tioman Island (n = 68 patients)



Locations visited by the patients:



TropNet
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GeoSentinel
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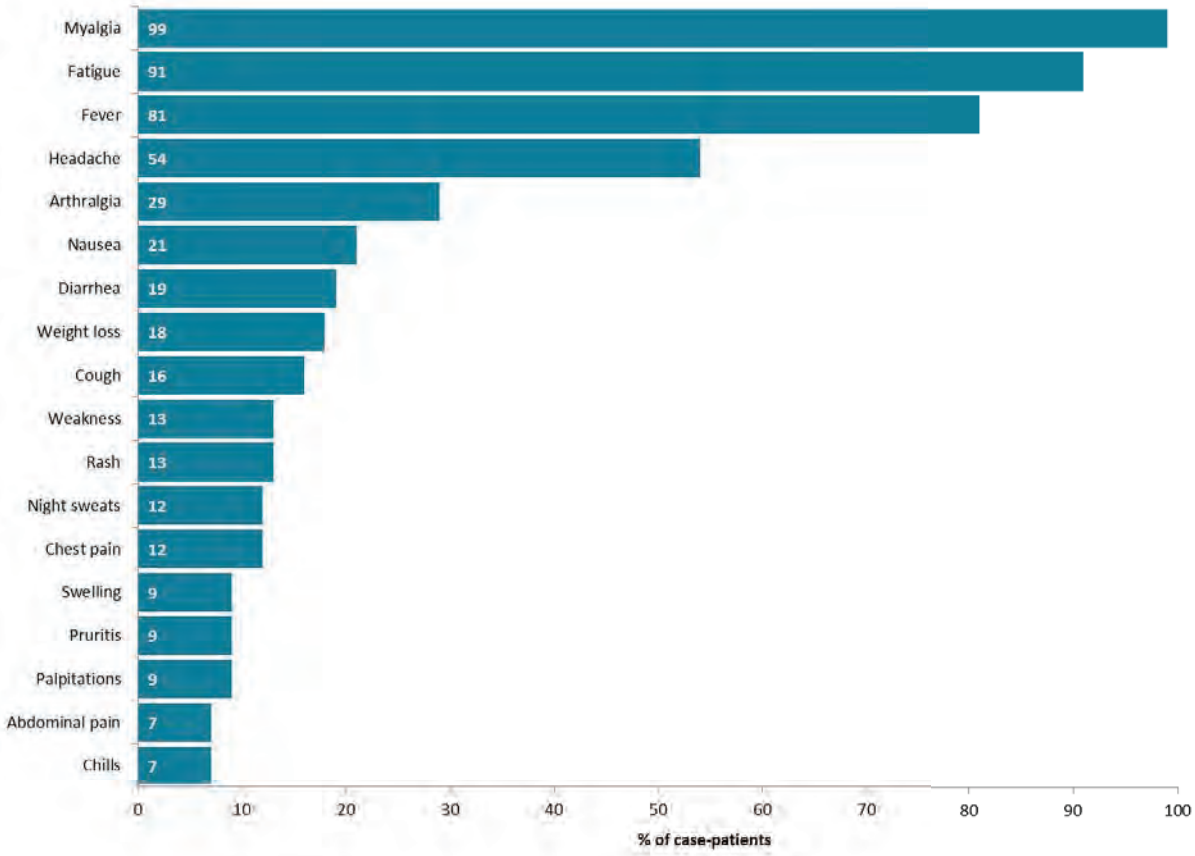
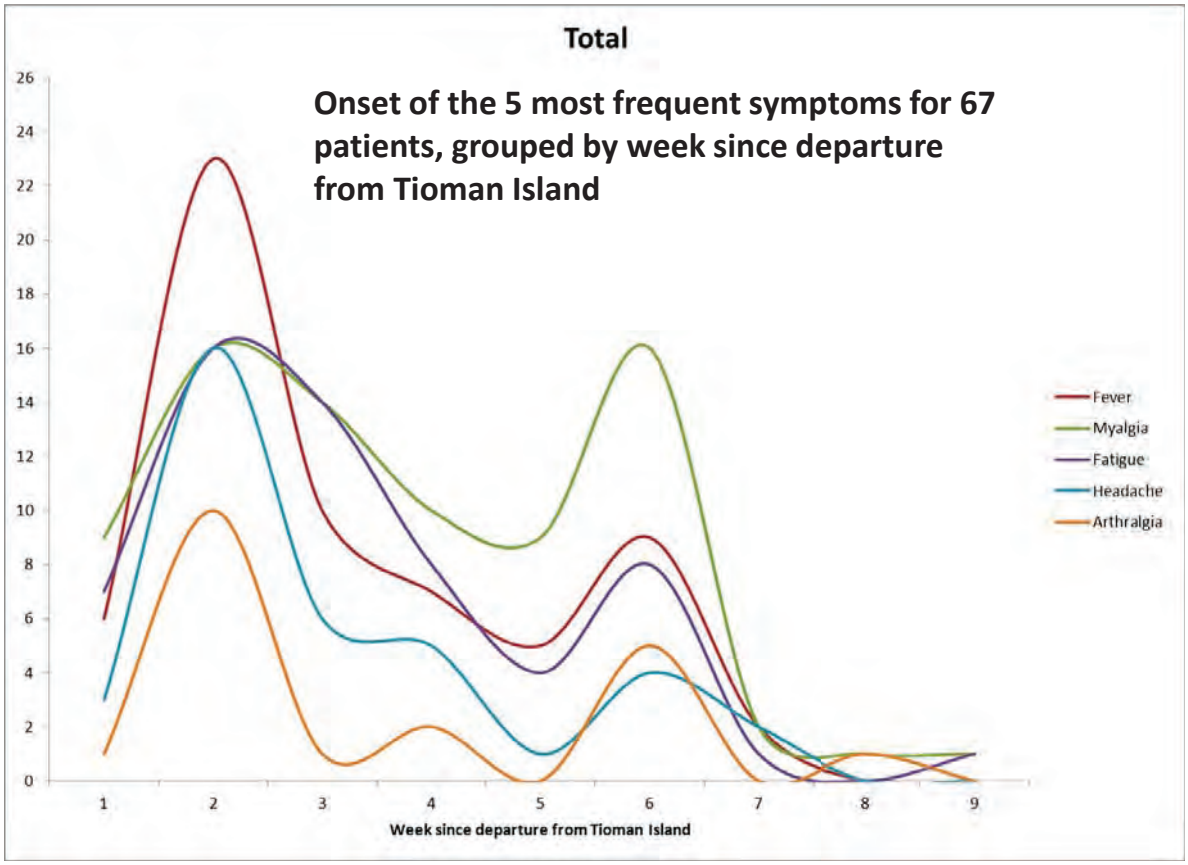
a worldwide communications & data collection network of travel/tropical medicine clinics
CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION





TropNet European Network for Tropical Medicine and Travel Health
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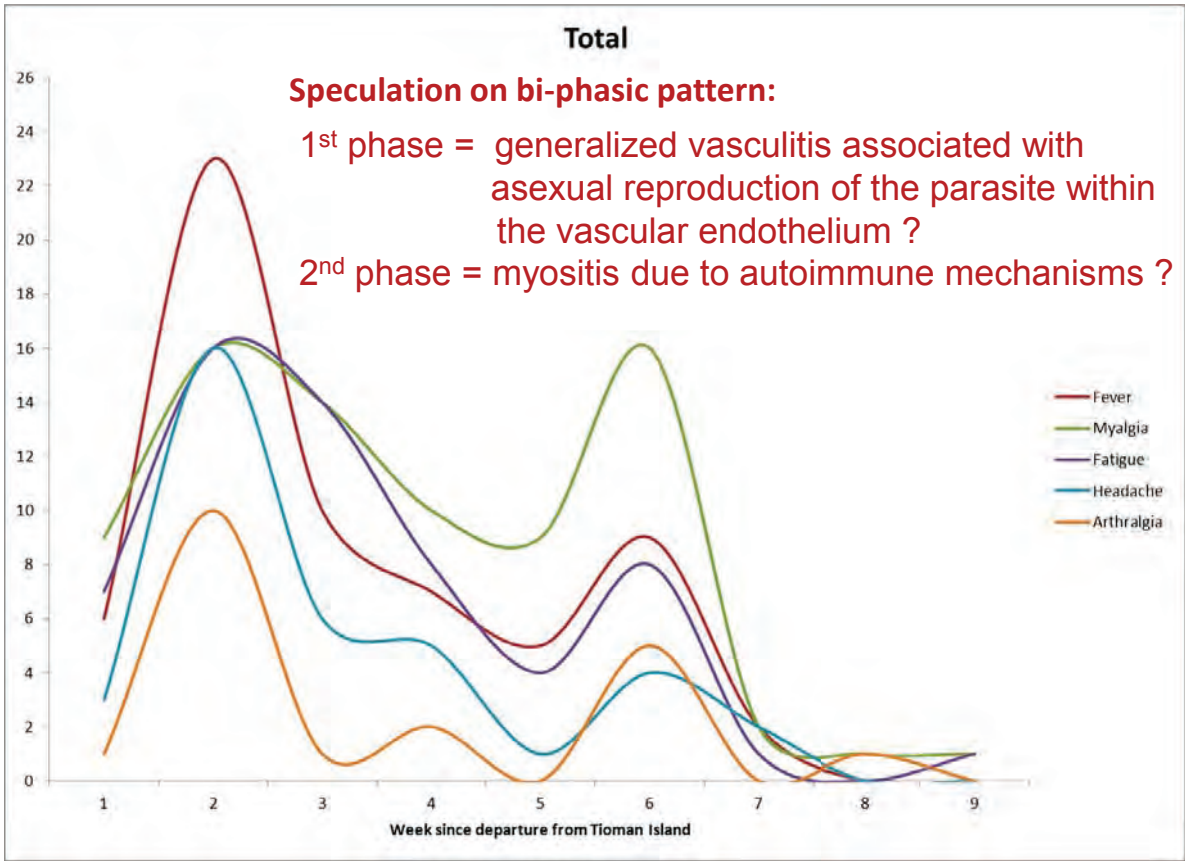
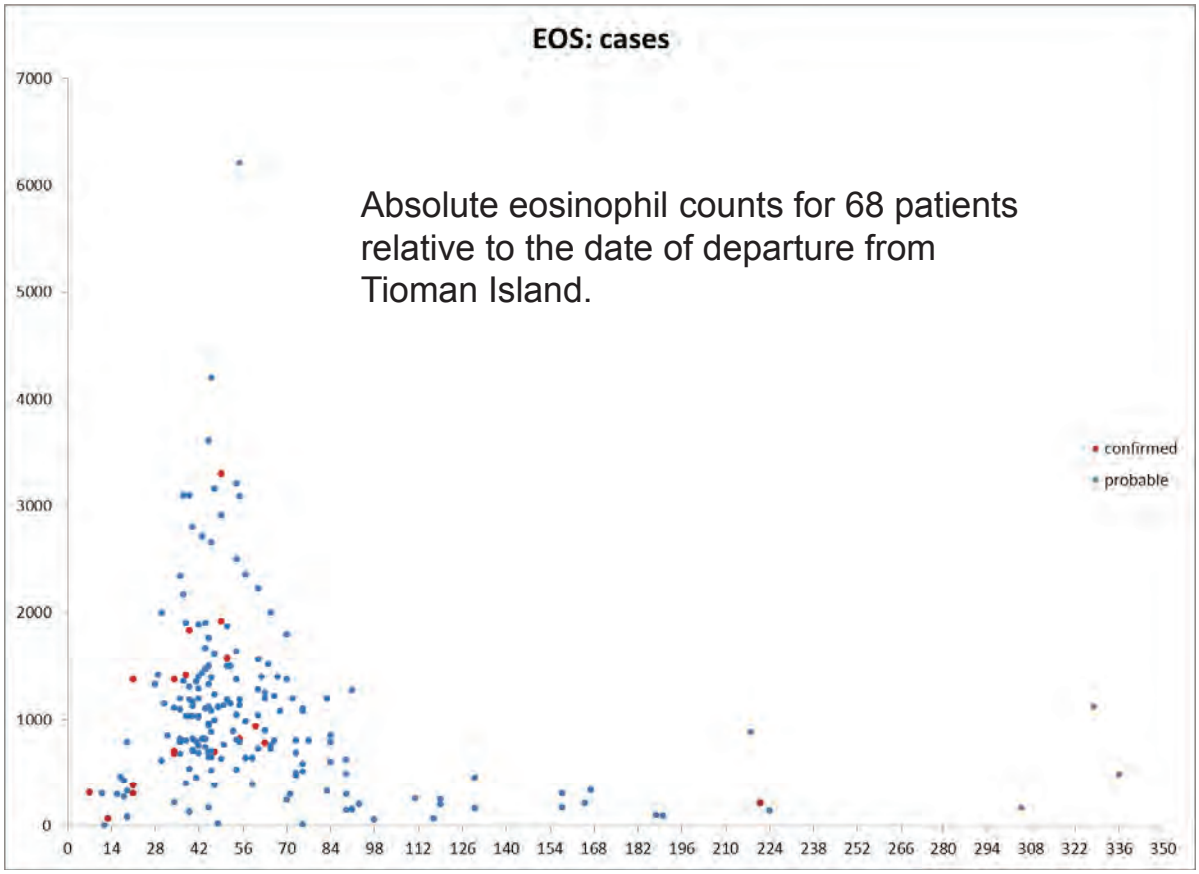
CDC Centers for Disease Control and Prevention





Absolute eosinophil counts for 68 patients relative to the date of departure from Tioman Island.

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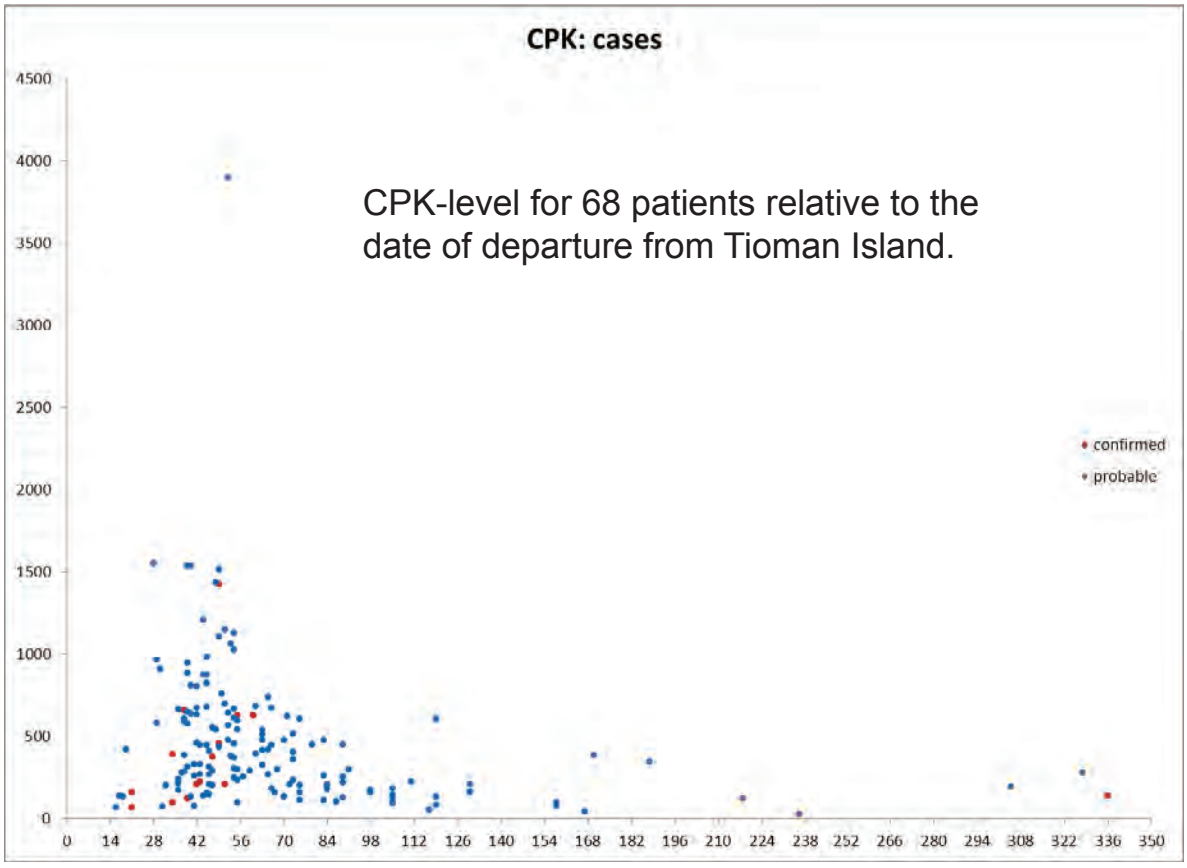
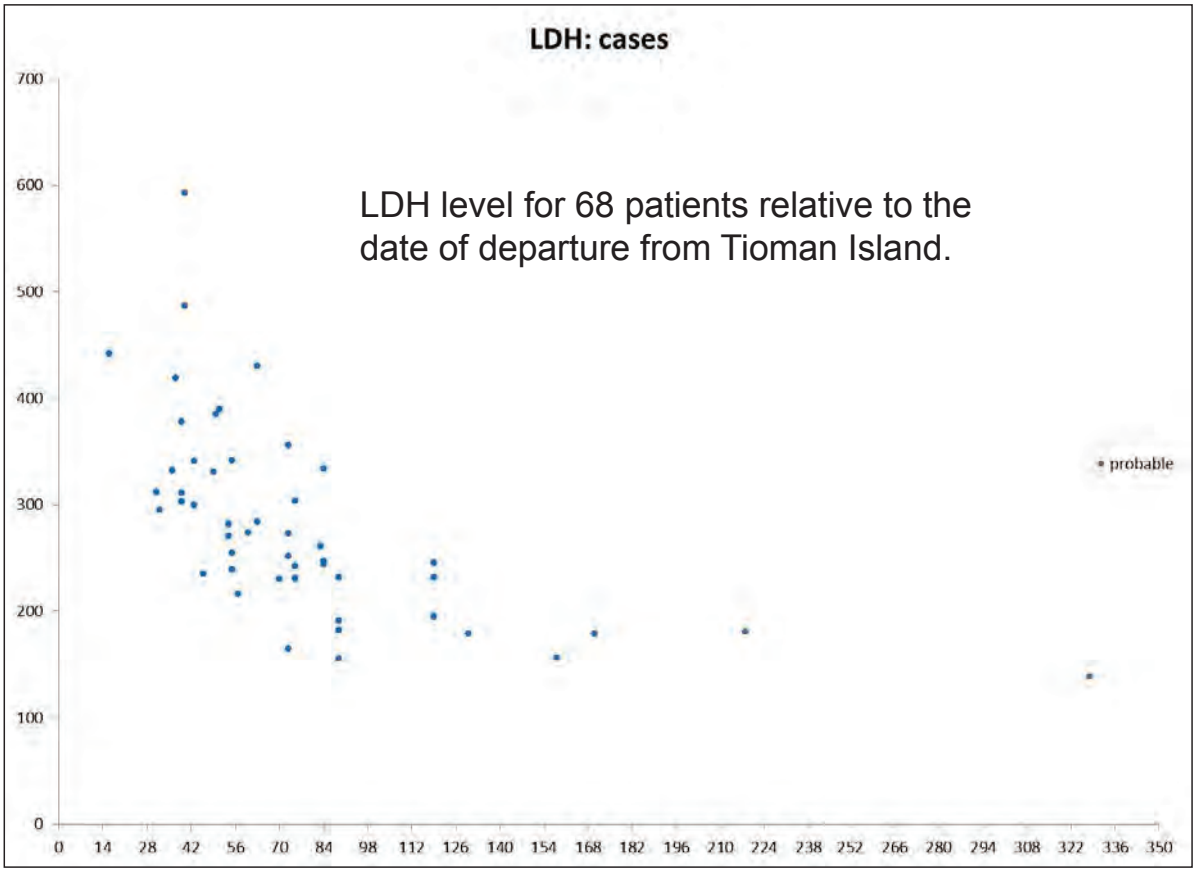


CPK-level for 68 patients relative to the date of departure from Tioman Island.



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- Interaction with national societies WHO, ECDC, FESTMIH, ENIVD, EuroTravNet, CDC

Teaching & Training

- Development of a curriculum / modules for a European ISTM-prep 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
- Collaboration with the CDC on Sarcocystis outbreak

Network resources

- **Website member area**
  - **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

The TropNet platforms

Research

- Coordination & support for individual research groups working on communicable & non-communicable diseases:
  - Treatment of severe malaria
  - Dengue/Chikungunya
  - Leishmaniasis
  - MRSA in travellers
  - 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
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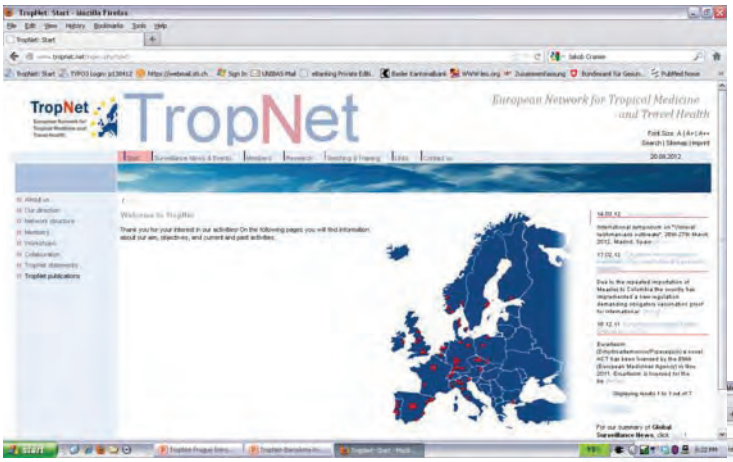
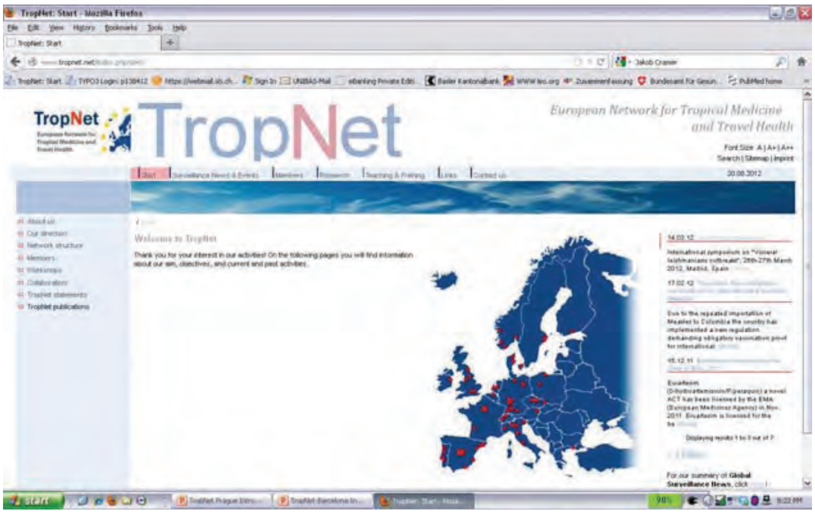


www.tropnet.net

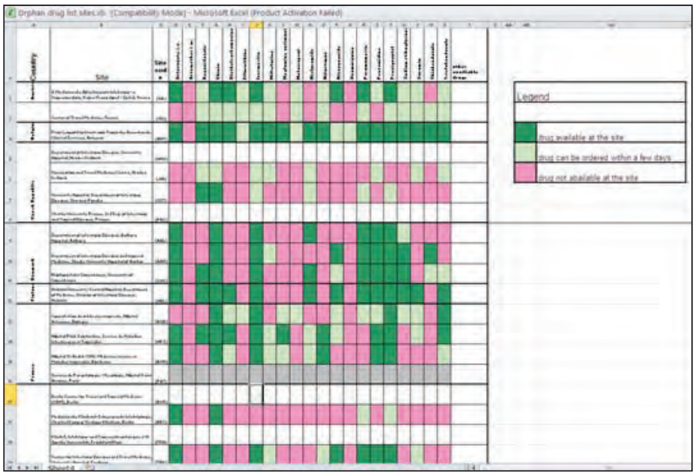
&

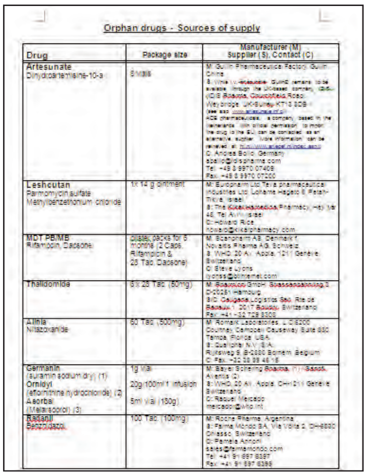
www.tropnet.eu

The TropNet website: update & crash course



Orphan drugs: network stock-list & sources





Orphan drugs - Sources of supply

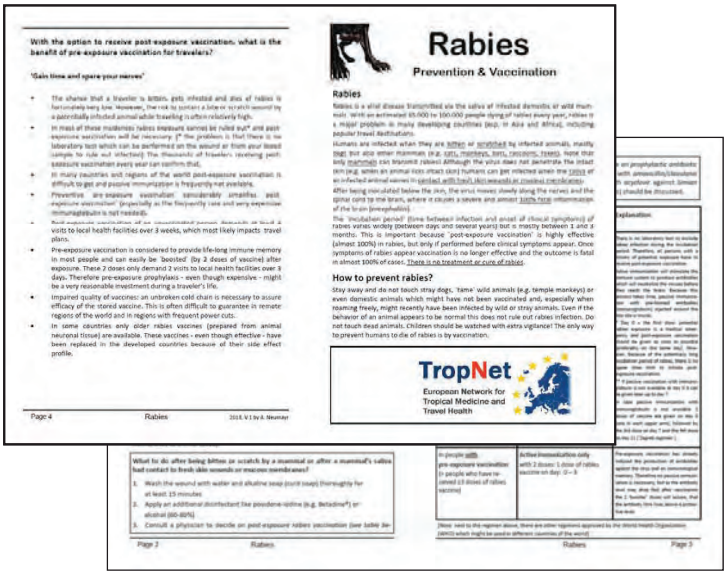
Drug	Package size	Manufacturer (M) Supplier (S), Contact (C)
Artesunate Dihydroartemisine-10-a	8 vials	M: Guilin Pharmaceutical Factory, Guilin, China S: [illegible] Weybridge, UK-Surrey KT13 8DB [illegible] C: Andrea Bollo, Germany; Tel. +49 8 9970 07409; Fax +49 8 9970 07200
Leshcutan Paromomycin sulfate Methylbenzethonium chloride	1x 14 g ointment	M: Europharm Ltd Teva pharmaceutical industries Ltd [illegible] Israel S: The [illegible] Pharmacy [illegible] Israel C: Howard Rice, howard@kikarpharmacy.com
MDT PB/MB Rifampicin, Dapsone	blister packs for 6 months (2 Caps. Rifampicin & 28 Tab. Dapsone)	M: Scanpharm AS, Denmark / Novartis Pharma AG, Schweiz S: WHO, 20 Av. Appia, 1211 Genève, Switzerland C: Steve Lyons [illegible]
Thalidomide	6 x 28 Tab. (50mg)	M: [illegible] GmbH [illegible] D-20251 Hamburg S/C: [illegible] Logistics [illegible] Switzerland Fax: +41 [illegible]
Alinia Nitazoxanide	60 Tab. (500mg)	M: Romark Laboratories, L.C. [illegible] Tampa, Florida, USA S: [illegible] Belgium C: Fax: +32 [illegible]
Germanin (suramin sodium dry) (1) **Ornidyl** (eflornithine hydrochloride) (2) **Arsobal** (Melarsoprol) (3)	1g vial 20g/100ml 1 infusion 5ml vial (180g)	M: Bayer Schering [illegible] 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, [illegible] Chiasso, Switzerland C: Pamela Annoni, sales@farmamondo.com Tel. +41 91 697 [illegible] Fax: +41 91 697 [illegible]

Where do you get your orphan drugs ?

- Send a list of your sources to complete the network's database
- We need a source for quinacrine !

Development of TropNet travel medicine info material

Current flyer



Volunteers needed: developing, translating… group-work !

Post-Artesunate Non parasitemic Deferred Anemia (PANDA) is related to pitting

Jauréguiberry S[1, 2)*], Ndour A[(2)*], Roussel C[(2)], Thellier M[(2, 3)], Ader F[(2)], Safeukui I[(4)], Nguyen M[(5)], Biligui S[(2)], Ciceron L[(2)], Mouri O[(2)], Kendjo E[(2)], Bricaire F[(1)], Vray M[(6)], Mazier D[(2, 3)], Caumes E[(1)¤], Buffet P[(2,3)¤] and the FrAWG (French Artesunate Working Group).

* & ¤: equal contributions

Affiliation

(1) AP-HP, Hôpital Pitié-Salpêtrière, Service des maladies infectieuses et médecine tropicale, Paris, F-75013, France
(2) UPMC Université Paris 06, UMR 945, Infection & Immunity, F-75005, Paris, France
(3) AP-HP, Hôpital Pitié-Salpêtrière, Service de parasitologie, Paris, F-75013, France
(4) Center for Rare and Neglected Diseases, University of Notre Dame, Notre Dame, Indiana, USA
(5) Institut Pasteur, Plate-Forme de Cytométrie, Imagopole, Paris, F-75724, France
(6) Institut Pasteur, Unité d'Epidémiologie des Maladies Emergentes, Paris, F-75724, France

ABSTRACT

Background: After being cured by artesunate, severe malaria patients sometimes experience a delayed anemic episode called Post-Artesunate Non-parasitemic Deferred Anemia (PANDA). PANDA does not jeopardize the life-saving effect of artesunate, but may impair its worldwide deployment and complicates patient management. Its mechanism is unclear. Artesunate induces pitting, a spleen-specific process whereby drug-exposed parasites are expelled from their host erythrocytes. These once-infected erythrocytes then return to the circulation.

Methods: We could follow 78 *Plasmodium falciparum*-infected travelers for more than 8 days post-treatment with intravenous artesunate for severe malaria. Sixty three of these patients did not receive transfusion, allowing a robust interpretation of hematological findings. In this group, 13 (20.6%) had PANDA, as indicated by a greater than 10% drop in hemoglobin or rise in LDH concentrations occurring after

D8. The kinetics of once-infected erythrocytes and their morphology in the peripheral blood was determined in 16 and 4 patients, respectively.

Results: In patients with PANDA, concentrations of hemoglobin and once-infected erythrocytes dropped simultaneously. Once-infected erythrocytes had an 8.9% reduction in their projected area, possibly explaining their shorter life span. Compared to patients with other patterns of post-artesunate anemia, PANDA patients were more frequently hyperparasitemic (41% v 92%, $p < 0.017$). During the first week post-treatment initiation, the concentration of once-infected erythrocytes was higher than 0.18 Giga/L in 94% (14 of 15) and 23% (3 of 13) of samples from patients with PANDA or other patterns of anemia, respectively.

Conclusion: Typical delayed episodes of post-artesunate anemia were related to the deferred loss of once-infected erythrocytes, a completely original mechanism of post-infectious anemia. The early quantification of once-infected erythrocytes may serve as a predictive marker.

PANDA and the pitting debt

Jauréguiberry S*, Ndour A*, Roussel C, Thellier M, Ader F, Safeukui I, Nguyen M, Biligui S, Ciceron L, Mouri O, Kendjo E, Bricaire F, Vray M, Mazier D, Caumes E, Buffet P and the FrAWG (French Artesunate Working Group).

AP-HP, Hôpital Pitié-Salpêtrière, Service des maladies infectieuses et médecine tropicale, Paris, F-75013, France
UPMC Université Paris 06, UMR 945, Infection & Immunity, F-75005, Paris, France
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Institut Pasteur, Unité d'Epidémiologie des Maladies Emergentes, Paris, F-75724, France
CNR du Paludisme pour la France métropolitaine

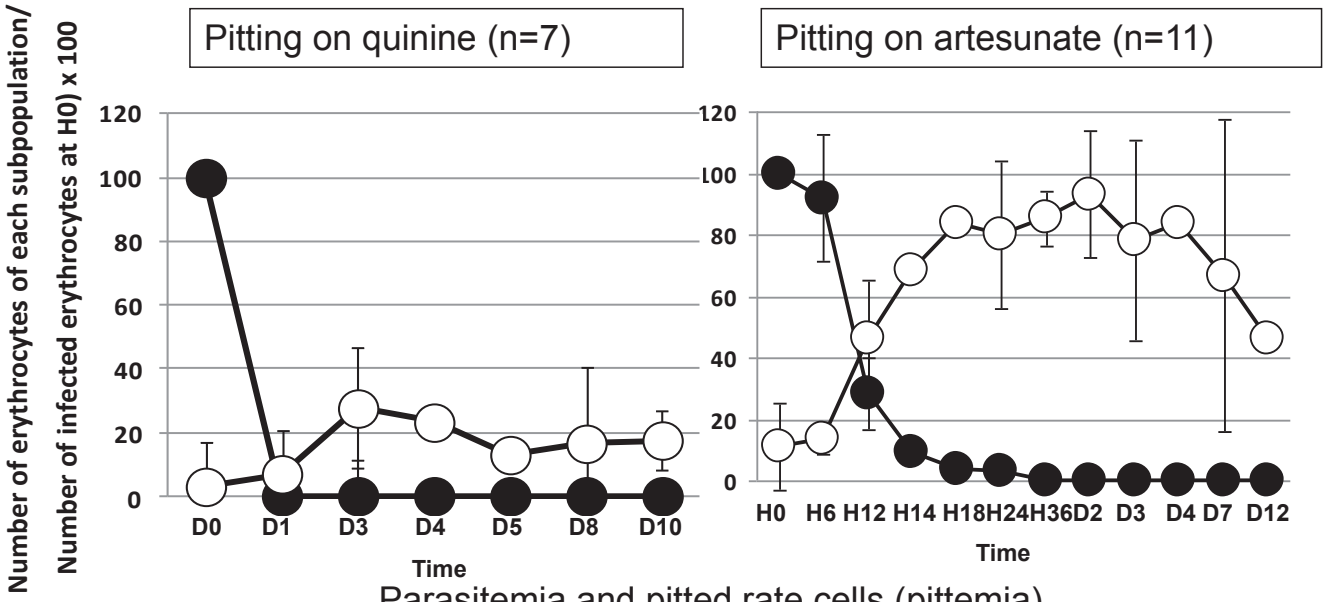
CNR Paludisme

Post Artesunate Non-parasitemic deferred Anemia (PANDA)

- No classical etiologies for late anemia
  - DAT, enzymopathy, hemoglobinopathy
- Probably other mechanism

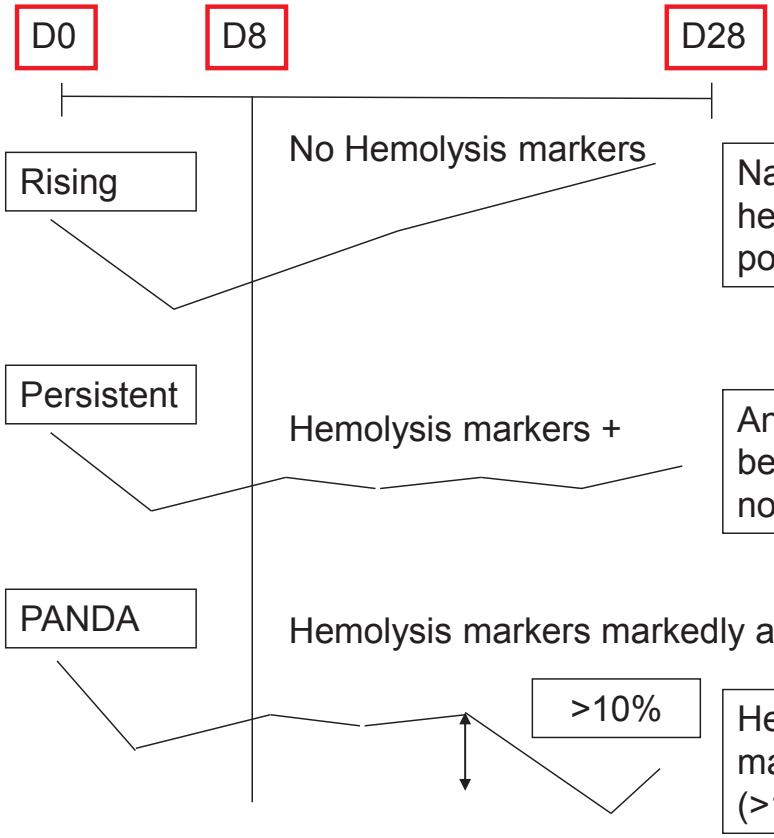
- Only patient on AS
  - But not all (15% ?)
  - Cured patient: no more parasitic infection
- ➔Post Artesunate Non-parasitemic Deferred Anemia (PANDA)

« Pitting » in vivo from patients treated for severe malaria by AS in France (unpublished data)



Parasitemia and pitted rate cells (pittemia)

Case definition



Rising

Nadir of hemoglobin and peak of hemolysis occuring before D8 without positive marker of hemolysis after D8

Persistent

Anaemia or hemolysis markers both before and after D8, and profile does not fit with Rising or PANDA definition

PANDA

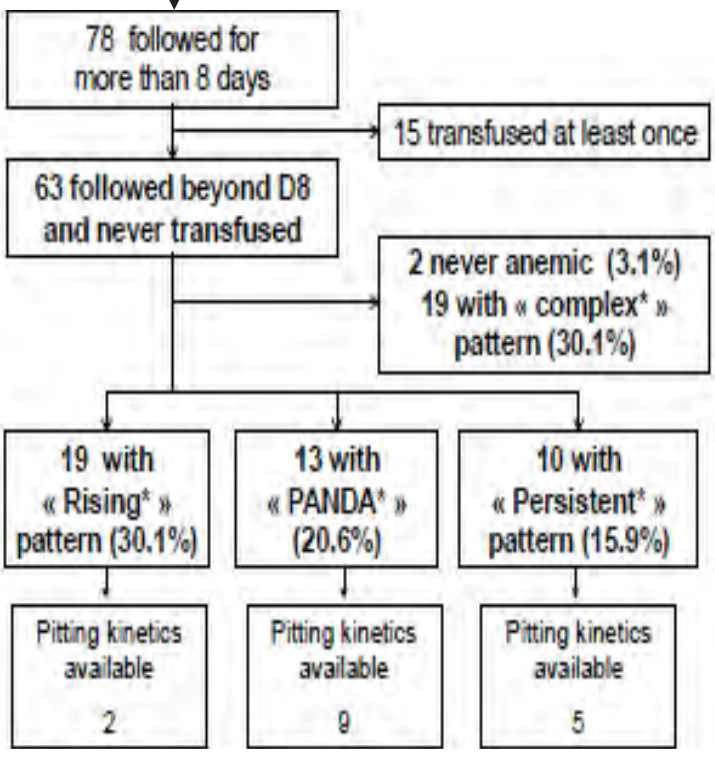
Hemoglobin level or hemolysis markers are more markedly altered (>10% variation) after D8 than before

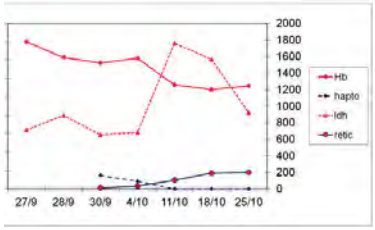
Complex

Anaemia not included in previously defined patterns

Price *et al*. JID. 2001
Zoller *et al*. EID. 2011
Buffet *et al.* MMV. 2013

French patient name program survey 2011-2013





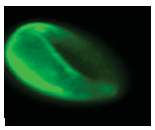
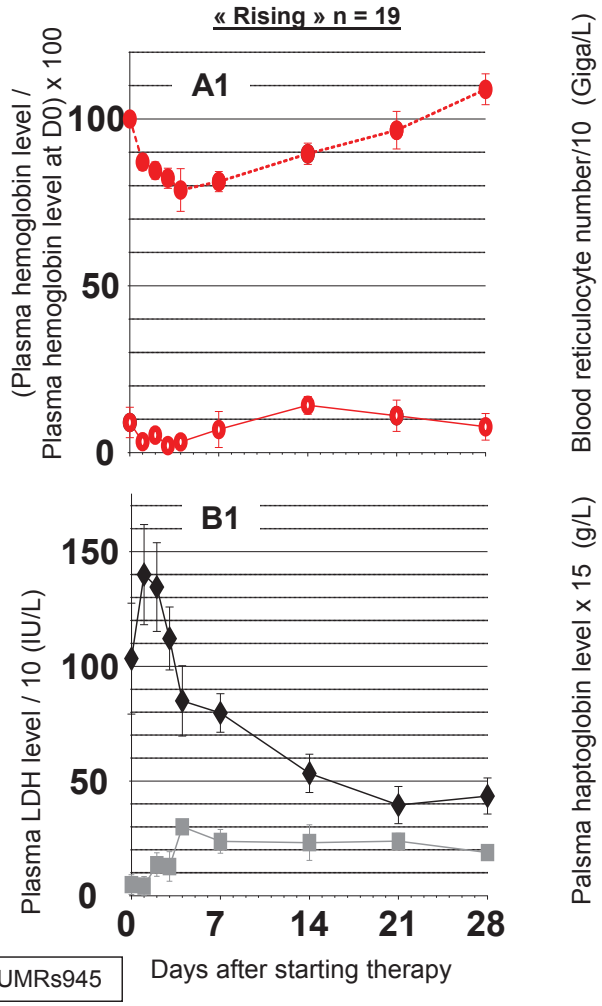


Figure 2: Anemia patterns



UMRs945

Figure 2: Anemia patterns

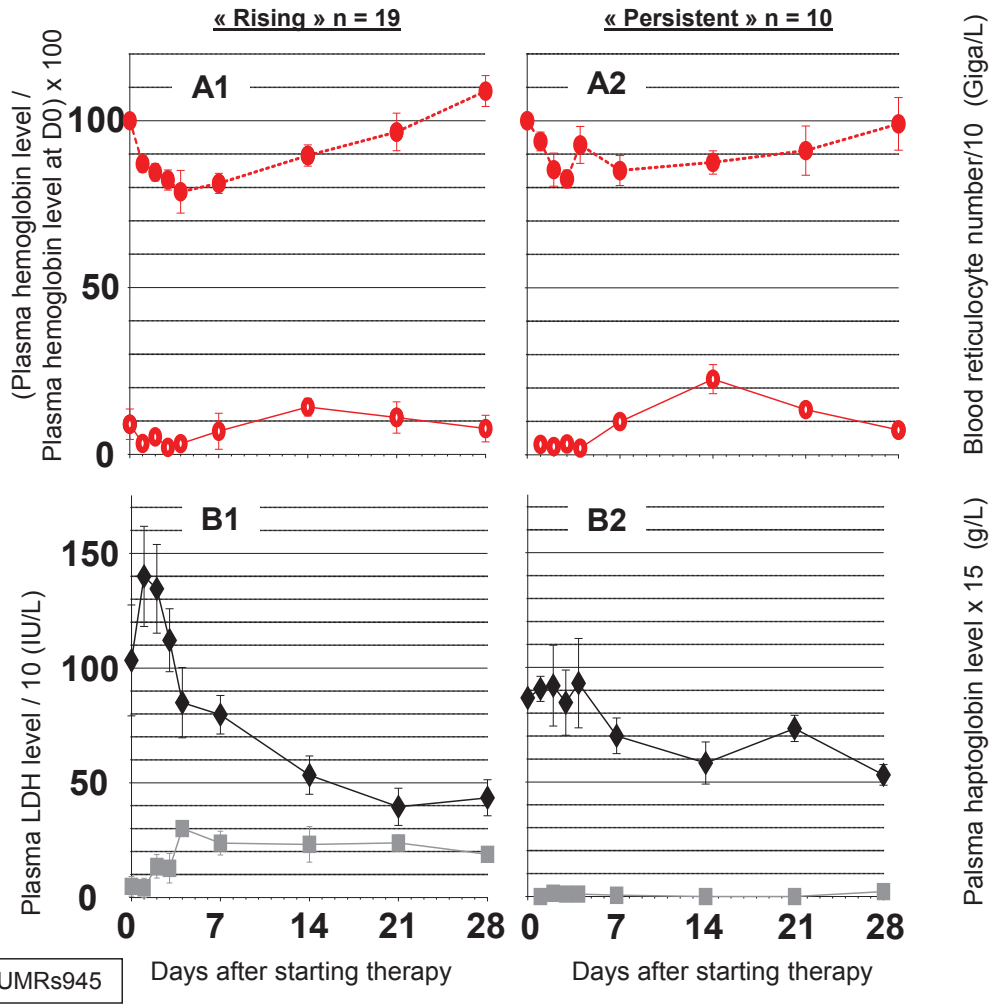


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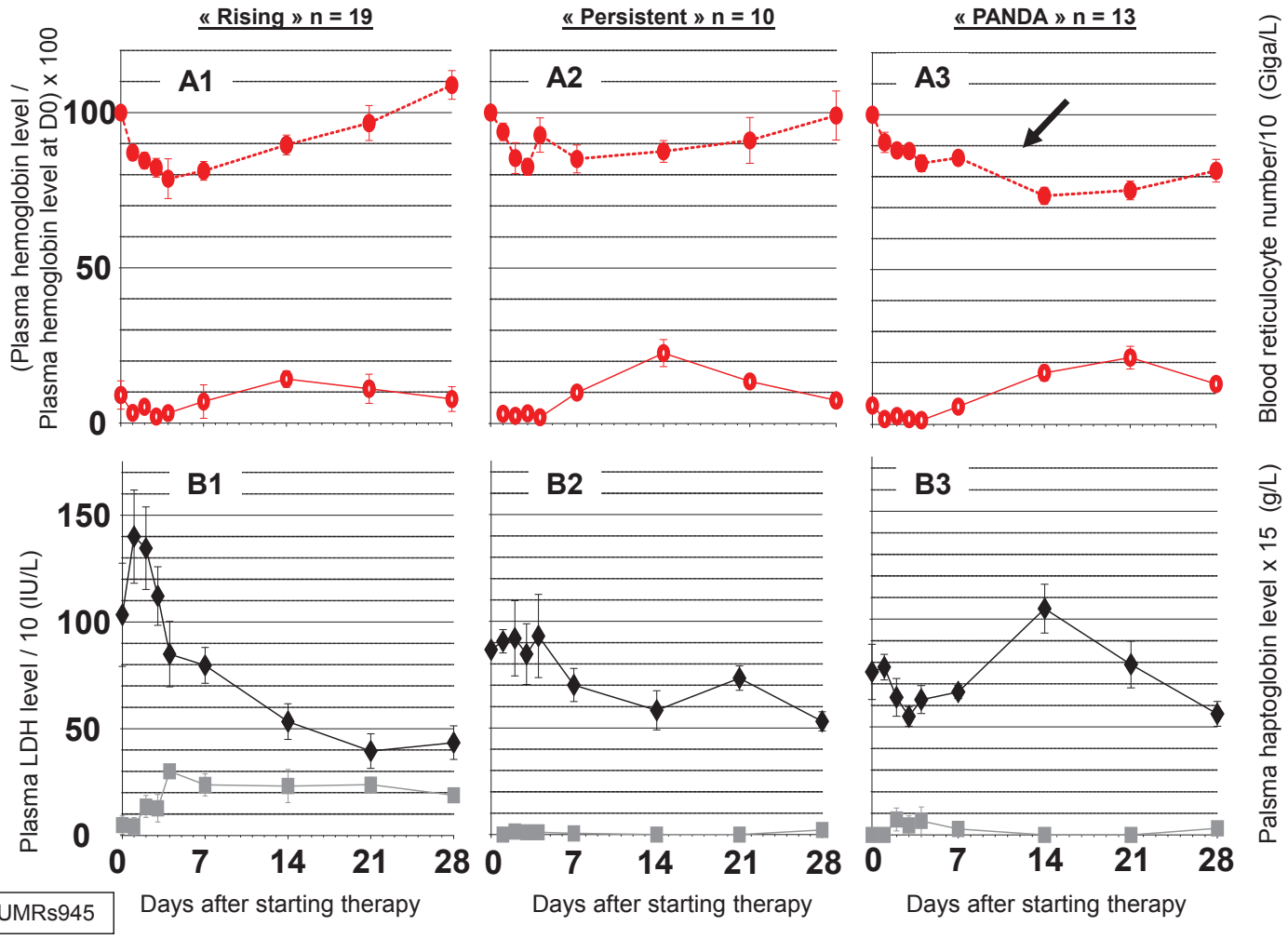
Figure 2: Anemia patterns



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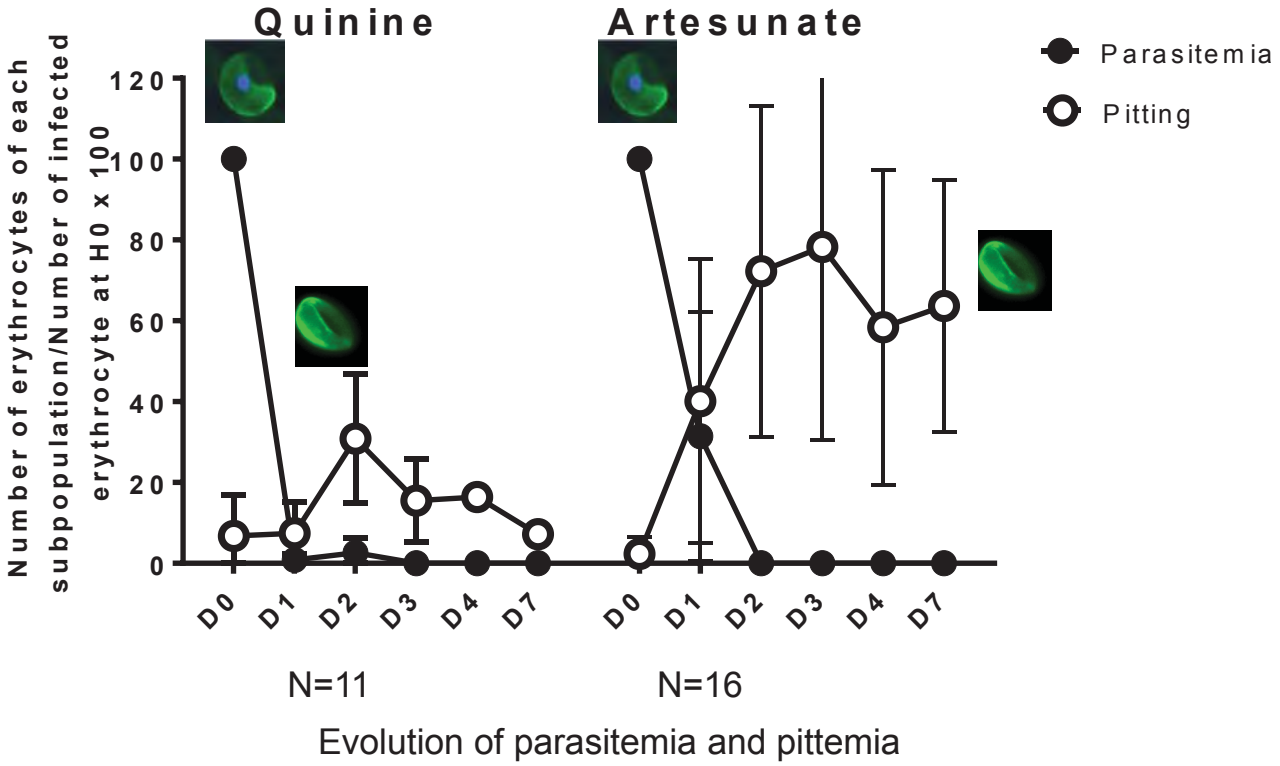
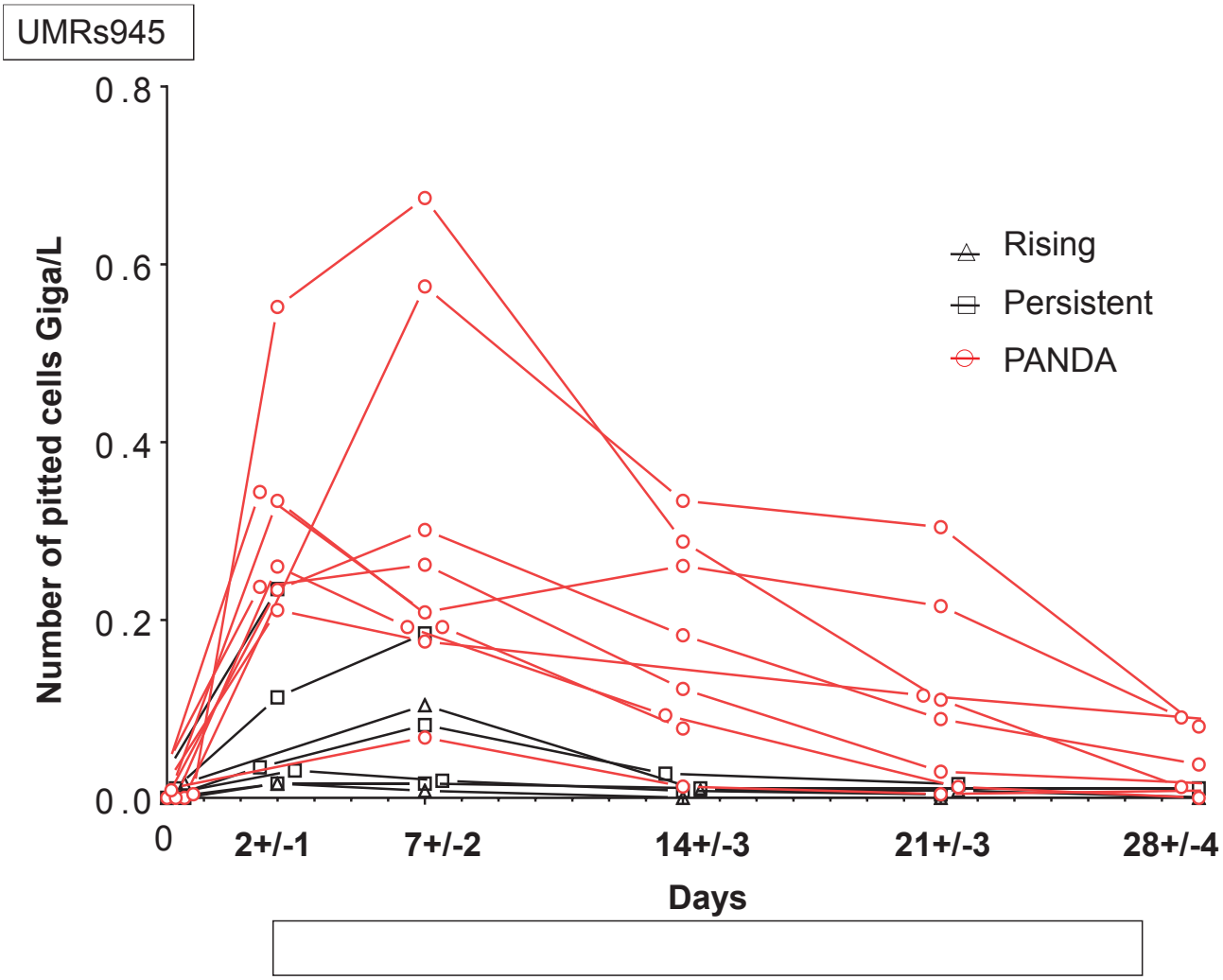
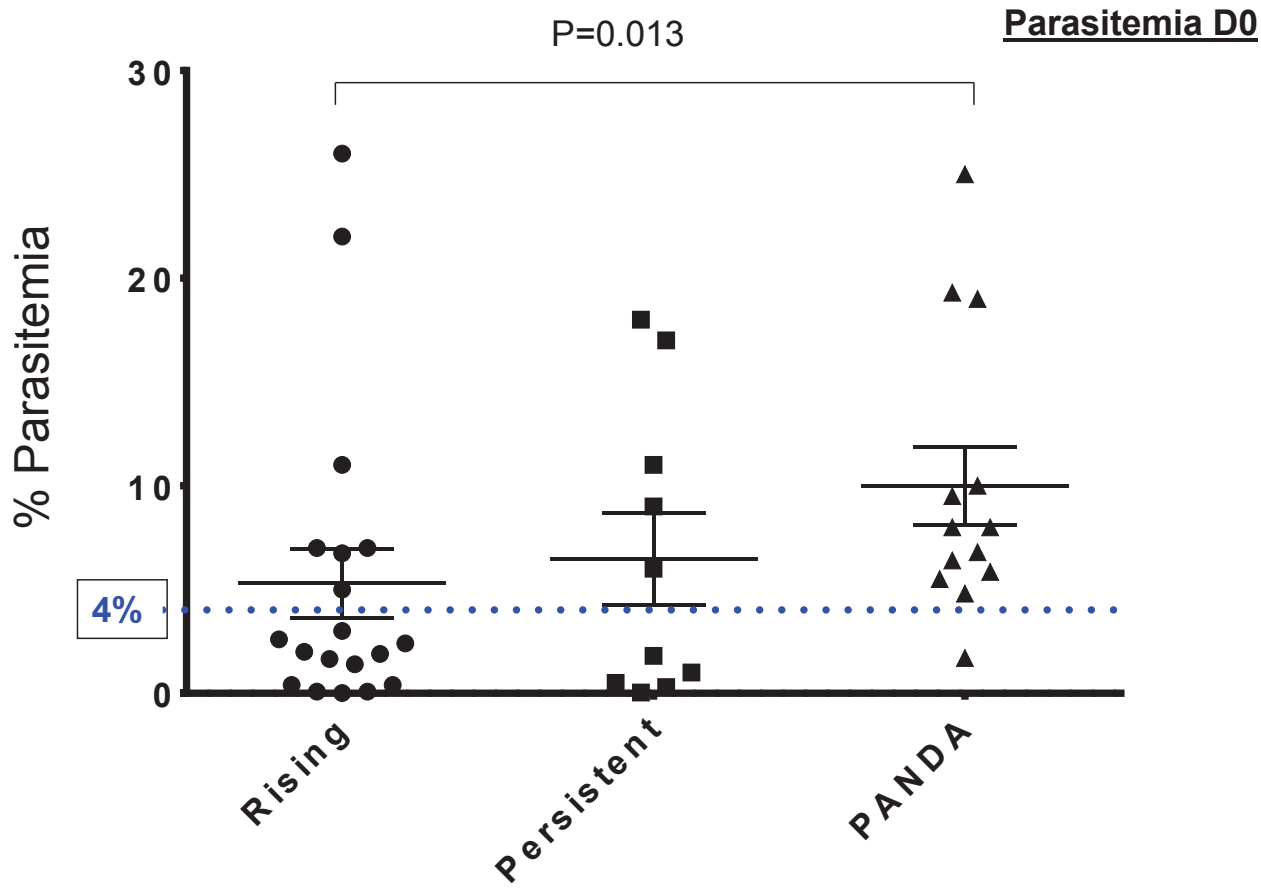


Evolution of parasitemia and pittemia

➔**Pitting is the main factor for parasitic clearance under AS**

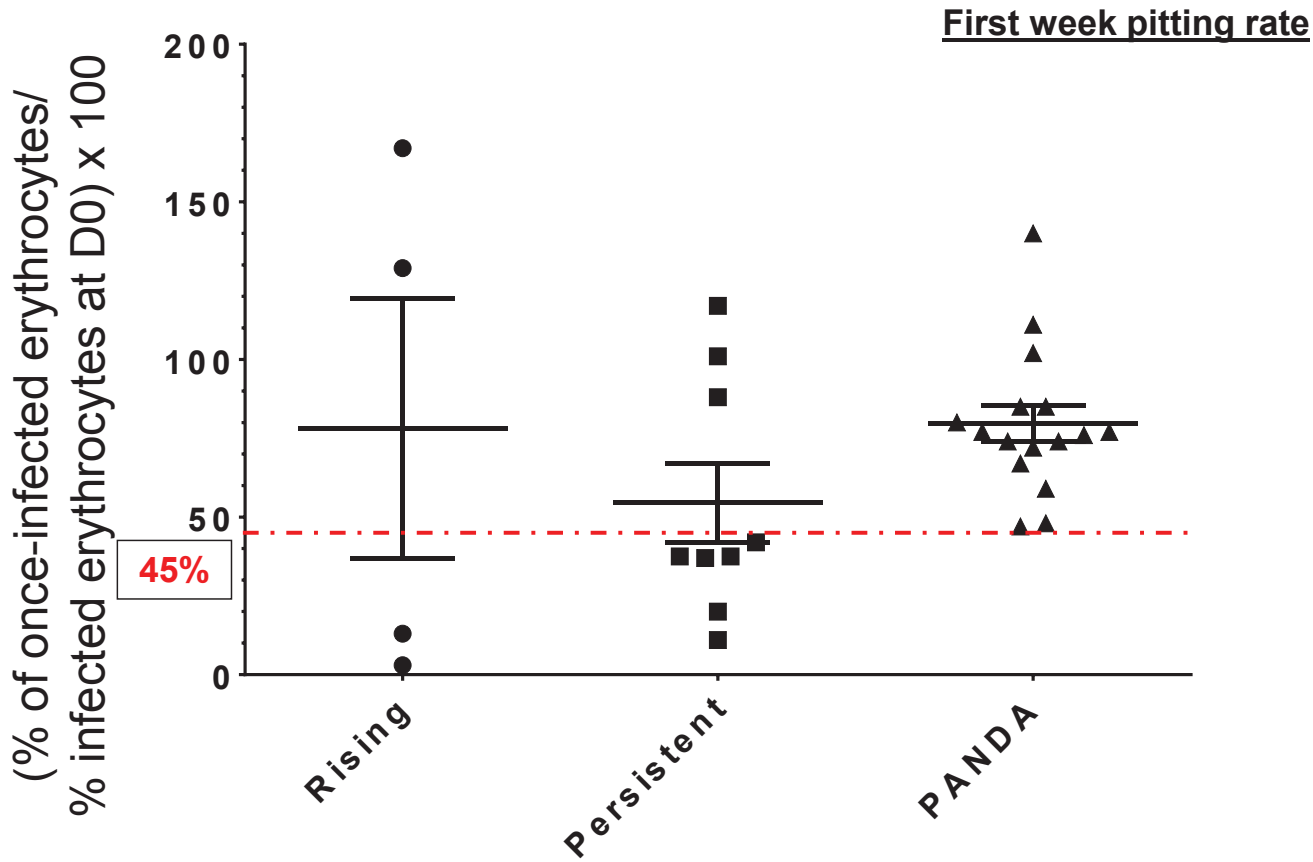
➔**Pitting rate is highly variable**


UMRs945
0.8
0.6
0.4
0.2
0.0
Number of pitted cells Giga/L
0
2+/-1
7+/-2
14+/-3
21+/-3
28+/-4
Days
Rising
Persistent
PANDA



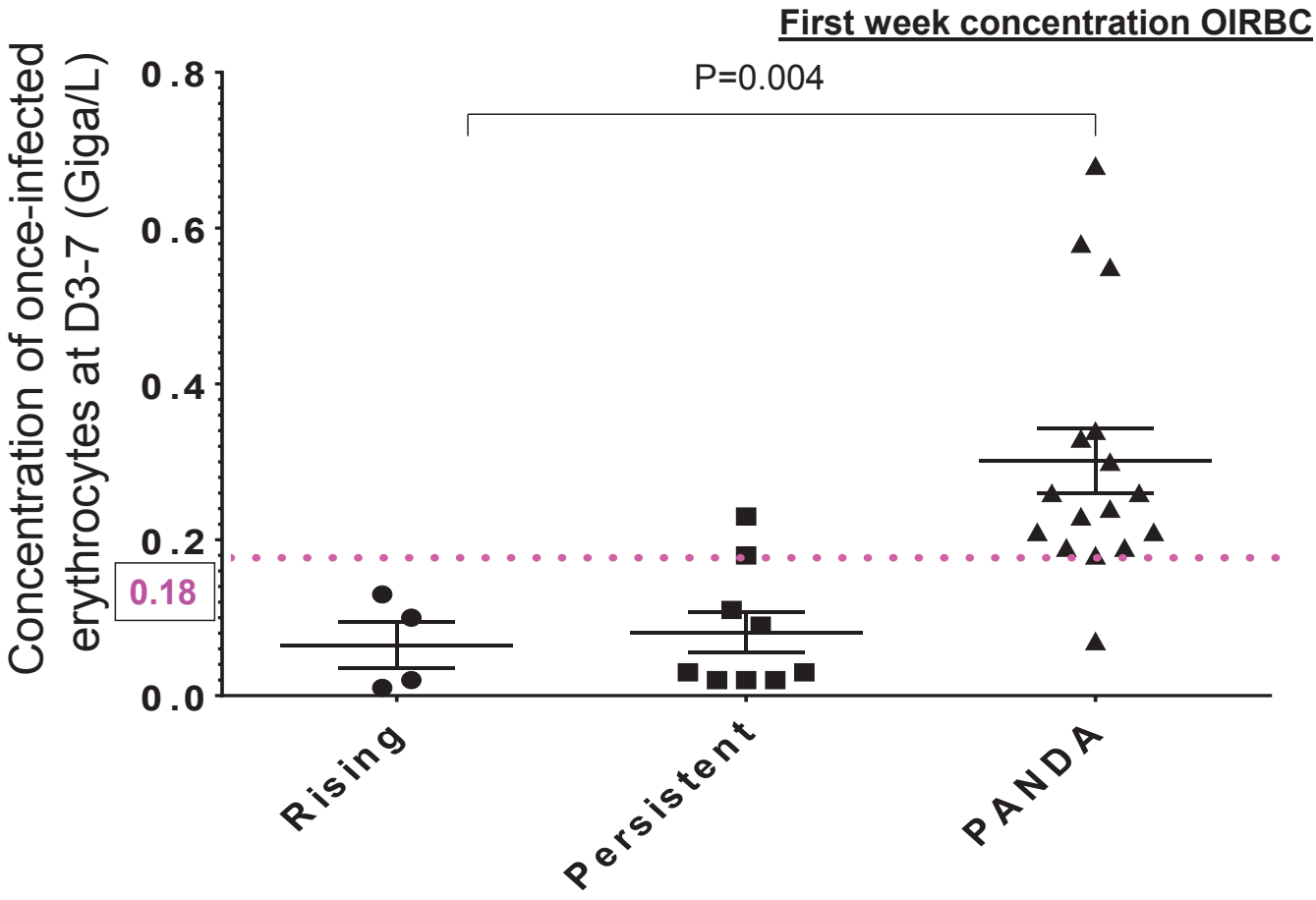
Patterns of post artesunate anemia

UMRs945



Patterns of post artesunate anemia

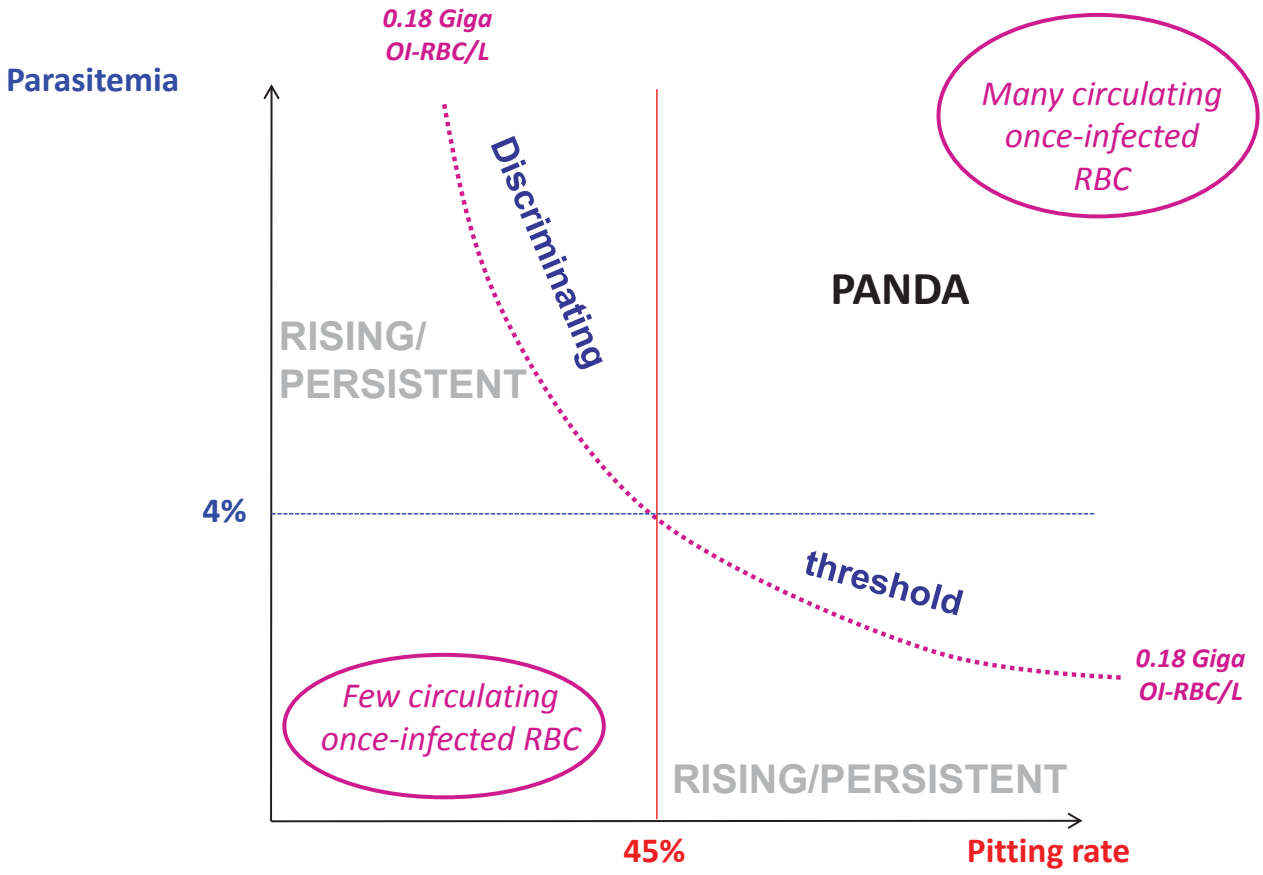
UMRs945



Patterns of post artesunate anemia

UMRs945

Frame work for risk of PANDA



Discussion

- Confirmed, inlight, classification

Zoller *et al*. EID. 2011
Kreeftmeijer *et al.* Malar J. 2012
Rolling *et al*. Malar J. 2013

- **PANDA**
  - More OIRBC during the first week:
    - Good predictive factor for the risk of hemolysis BUT maybe not the sole
  - RBC surface loss: 8.9%
    - 17% treshold for retention

Safeukui *et al.* PlosOne. 2013

  - Not in every patient because:
    - (Pi)x(PittingRate) = Nb Pc ➔ risk factor for PANDA

- Solely AS not Q

➔« Debt to pay »

  - Infected RBC initialy sparing at the beginning will be lost later
  - Cost price for survival

Questions ? Limits ?

- « Persistent pattern »
  - Overlap or transition form between Rising and PANDA pattern
  - Persisting hemolysis is already described:
    - Extra vascular hemolysis for uninfected RBC decorated by *P. falciparum* proteins
  - Not exclusive

Awah *et al.* Parasite Immunol. 2011
Woodruff *et al*. Lancet. 1979

- Size!
  - Loss is explain in part by the loss of OIRBC
  - Pi is near to the loss of hemoglobin: 10-15%
  - Findings seems to be robust but more pitting evaluation is needed

Team

Erythrocytes Parasites Physiopathology

INSERM UPMC

Alioune Ndour
Camille Roussel
Oussama Mouri
Stéphane Jauréguiberry
Sylvestre Biligui
Liliane Cicéron
Julien Duez
Seidina Diakité
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Innocent Safeukui

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Eric Caumes
François Bricaire
Stéphane Jauréguiberry

French Artesunate Working Group

Institut Pasteur

Gloria Morizot
Marie Nguyen
Muriel Vray

TropNet artemisinin drug safety studies

HAEMO-ART, SMPS & TOX-ART

Florian Kurth, Andreas Neumayr &

Thomas Zoller

Timeline of artemisinin studies

- Prague **2012**: presentation of first concept of HAEMO-ART study
- **2013**: development of *in-vitro* studies to investigate artemisinin metabolism and immunohaematologic toxicity
- **September 2013:** outline of **artemisinin drug safety project**
- **October 2013:** submission for ethical review
- **December 2013:** project start at Charité and setting up of collaborating TropNet sites

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
- Artemisinins cause other haematological abnormalities, e.g. neutropenia, reticulocytopenia…
- 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 aims to evaluate systematically and prospectively haematological parameters under and after antimalarial therapy with a focus on artemisinin treatment

Study design

prospective, observational, multi-centre, non-randomized, non-interventional, controlled safety & tolerability study

Primary endpoint

occurrence of 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 (example as in Germany)

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 7-11**	vital status, clinical examination, blood sample, (optional: urine sample)
Study-Follow-up	**Visit 4**	**Day 17-21**	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 27-31**	vital status, clinical examination, blood sample, (optional: urine sample)

Data collected

Epidemiological information
- age
- sex
- ethnicity
- parasitological diagnosis
- non-antimalarial medication within 12 weeks prior to inclusion
- antimalarial chemoprophylaxis taken within 12 weeks prior to inclusion
- relevant co-morbidities
- travel destination

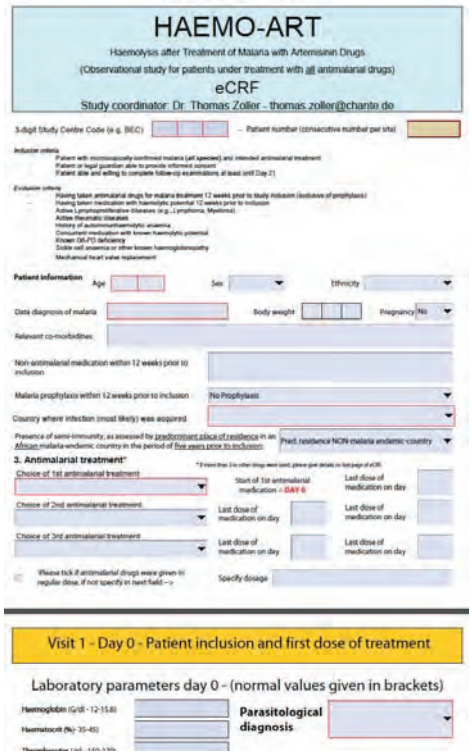
Antimalarial medication
- drug
- duration
- dose

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



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

Publication policy

- The coordinator will choose and agree with another author making essential contributions to the work on first/last authorship for each publication of study data
- Submission of at least 5 fully documented cases qualifies for co-authorship in all study publications. In publications where the number of authors is limited, co-authors will be selected according to the number of cases contributed
- Centres submitting less than 5 cases may qualify for co-authorship if they make other relevant contributions to the study, e.g. in data management or data analysis, manuscript preparation or proof-reading

SMPS

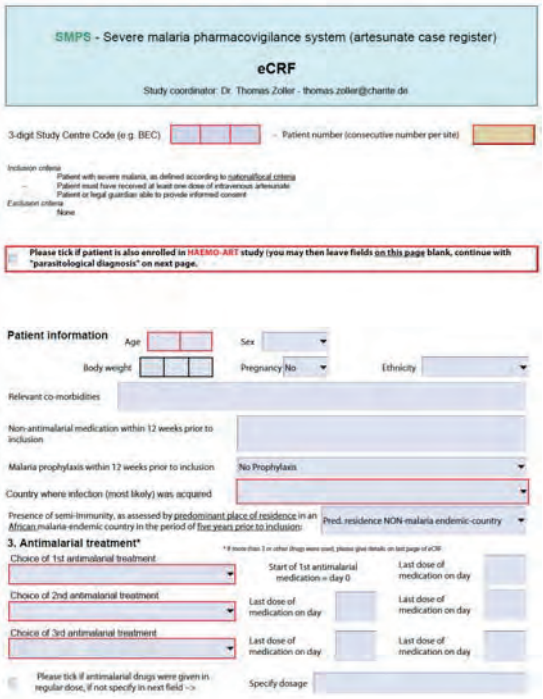
Severe malaria pharmacovigilance system

Outline

- Structured, retrospective pharmacovigilance reporting of own personal 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, less than 10 minutes work
- Data transmission must be in accordance with local (ethical) rules and requirements, reporting physician is responsible


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)

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*

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 metabolism of Artemisinins on isolated hepatocytes and indentification of metabolites with haemolytic potential
- qualitative and quantitative analysis of Artemisinin metabolites and (immuno-)haematological parameters in serum samples from selected patients from the Haemo-ART or patients having received intravenous artesunate
- Interested TropNet centres may cooperate with providing patient samples of patients with haemolysis, equipment or methodology

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
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, vital signs and ECG

Study sites

Hospital Clinic Barcelona, Spain	Jose Muñoz & Joaquim Gascon
Ramon y Cayal Hosital Madrid, Spain	Rogelio López-Vélez & Jose Antonio Perez Molina
Leiden, the Netherlands	Leo Visser
Hamburg, Germany	Jakob Cramer
Berlin, Germany	Thomas Zoller & Florian Kurth
Munich, Germany	Mirjam Schunk & Hans-Dieter Nothdurft
Verona, Italy	Andrea Angheben & Zeno Bisoffi
Tel Aviv, Israel	Eli Schwartz
Bern, Switzerland	Staehelin Cornelia & Hansjakob Furrer
Lausanne, Switzerland	Blaise Genton & Valérie D'Acremont

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: currently close to **100** cases

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): published
- ☑ Clinical aspects and management of cutaneous leishmaniasis in rheumatoid patients treated with TNF-α antagonists (Travel Med Infect Dis. 2013): published
- ☑ Species specific treatment recommendations: in press

Molecular diagnostic group:

- ☐ Comparison of different molecularbiologic methods for species determination: submitted

LeishMan project:

Travel Medicine and Infectious Disease (2013) xx, 1–9

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ELSEVIER

INVITED SUBMISSION

Clinical aspects and management of cutaneous leishmaniasis in rheumatoid patients treated with TNF-α antagonists

Andreas L.C. Neumayr [a,b,1], Gloria Morizot [c], Leo G. Visser [d,1], Diana N.J. Lockwood [e], Bernhard R. Beck [f,1], Stefan Schneider [g], Guillaume Bellaud [h], Florence Cordoliani [i], Françoise Foulet [j], Emmanuel A. Laffitte [k], Pierre Buffet [c,l], Johannes A. Blum [a,b,*,1]

47 year old man, rheumatoid arthritis

Medical history:

02/2007 - 09/2008: Prednisone 7.5 mg/d (cont.), Methotrexate 15 mg/week

06/2007 - 02/2008: Etanercept

02/2008 - 04/2009: Leflunomid 20 mg/d

02/2008 - 05/2008: Infliximab 5mg/kg/6 weeks

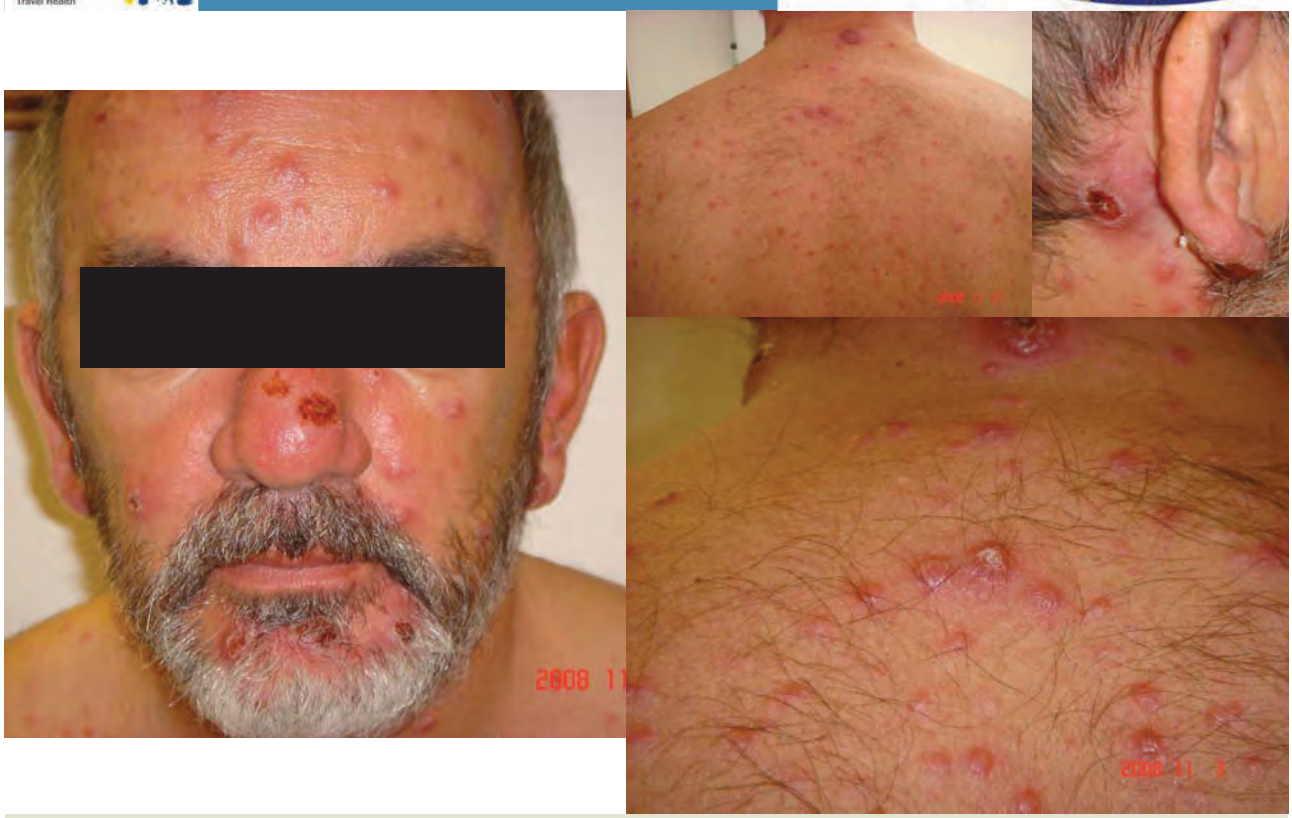
05/2008 - 10/2008: Infliximab 5mg/kg/4 weeks

Travel history:

2007: Egypt

2008: Mexico & Italy

Nov. 2008: consultation due to progressively disseminating cutaneous lesions since July

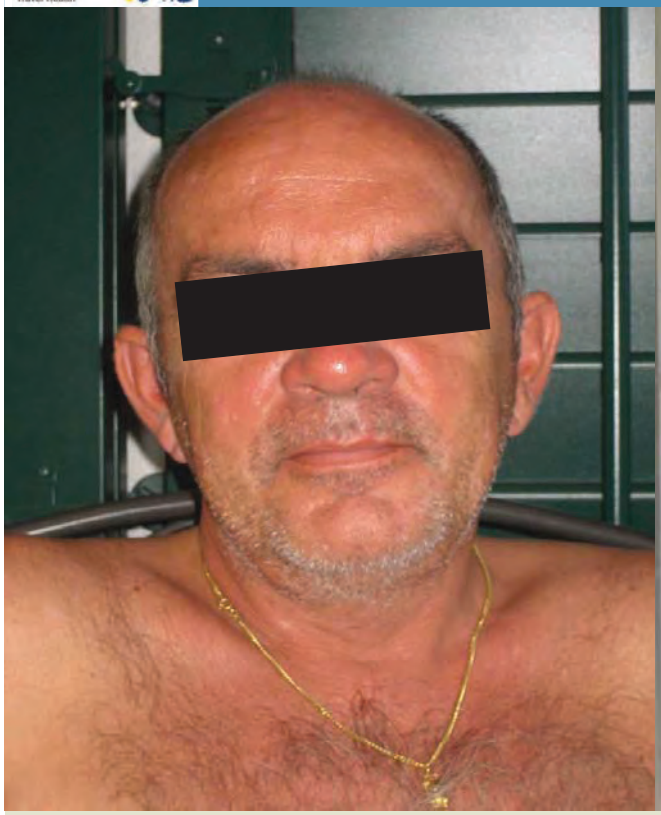


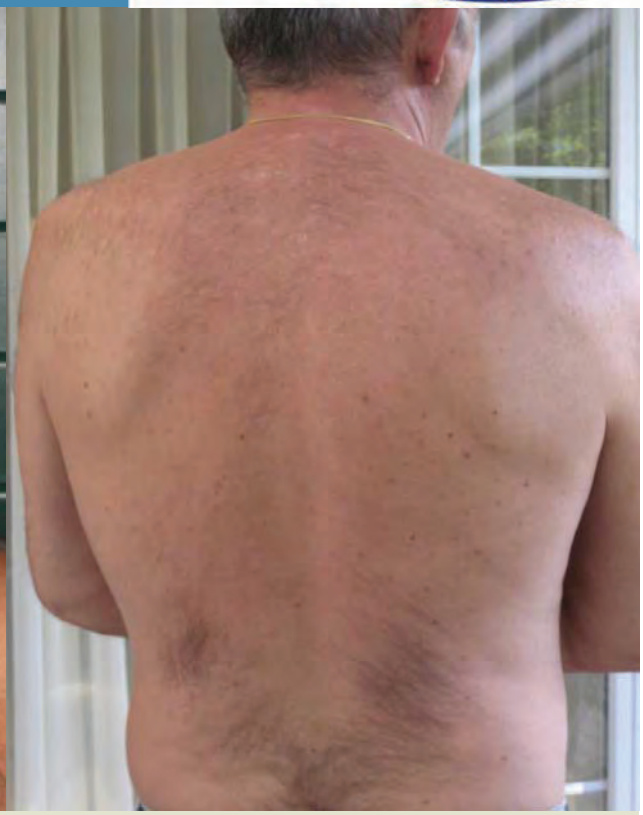
- species?
- PCR: *L. infantum*
- which investigations?
- ENT examination normal, HIV negativ, no signs of VL
- continuation of TNF-α antagonist?
- discontinuation of all immunosuppressive drugs, analgesics for rheumatoid arthritis
- which treatment?
- meglumine antimoniate 20mg/kg/day i.m. for 28 days

➔ regression of all lesions / clinical cure

➔ restart of TNF-α antagonist and MTX in lower dosage

➔ no relapse (currently under surveillance since 4 years)





Cutaneous leishmaniasis in rheumatoid patients treated with TNF-α antagonists

- an increasing problem ?!
- data currently limited to case reports

➔ we collected and summarized 16 cases: 8 cases from the LeishMan working group and 8 cases from the published literature:

- 15 CL & 1 ML
- 10x *L. infantum complex,* 2x *L. aethiopica, 4x unknown species*

TNF-α antagonist therapy after diagnosis:

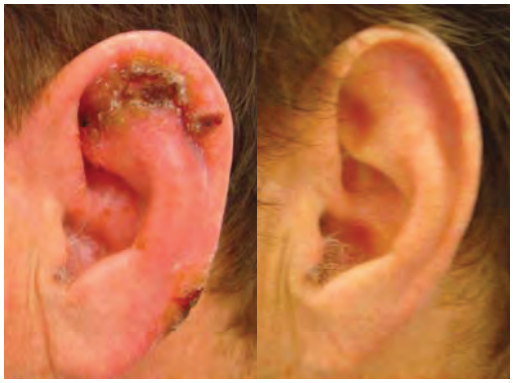
- discontinued: 7 cases
- temporarily discontinued: 3 cases
- continued: 5 cases

Outcome:

- **clinical cure achieved in all cases**
- 2 patients showed relapse after 1 and after 2 years.
- both relapses were clinically cured by retreatment without further relapses during a 1 year and a 2 years follow-up period

Antileishmanial treatment:

- 5x liposomal amphothericin B
- 4x miltefosine
- 2x systemic antimonials
- 5x local treatment with antimonials



Results

- the incubation period of CL in patients treated with TNF-α antagonists appears to be relatively long compared to non-immunosuppressed patients:

  median 7.5 months (1-15 months) vs. 28 days (5-150 days)[1]

- the median time interval between onset of CL lesions and diagnosis of CL appears to be identical to non-immuno-suppressed patients:

  4 months (1 mo.-7 y) vs. 3/4 mo. (3/19 d –5/24 mo.)[1,2]

- the number and morphology/size of CL skin lesions in patients receiving TNF-α antagonists and in non-immunosuppressed CL patients appears to be similar:

  - most patients present with 1-3 lesions [2]

  - no differences in morphology or size of lesions [2]

[1] El Hajj L. et al. Int J Dermatol 2004;43:120e5.
[2] Harms G. et al. Emerg Infect Dis 2003;9:872e5.

- all reviewed leishmaniasis patients under TNF-α antagonist therapy were treated successfully.

  we conclude that these patients can be treated by using the usual recommendations and guidelines

- should TNF-α antagonist therapy be discontinued during or after anti-leishmanial treatment ?

  currently no data from prospective studies available, but continuation appears to be possible

  ➔ suggestion:

  - discontinuation of TNF-α antagonist therapy during anti-leishmanial treatment
  - after complete resolution of the skin lesions TNF-a antagonist therapy might be restarted with the smallest needed dosage under close clinical monitoring

Research projects in a European context

Discussion on perspectives of efficient joint research projects

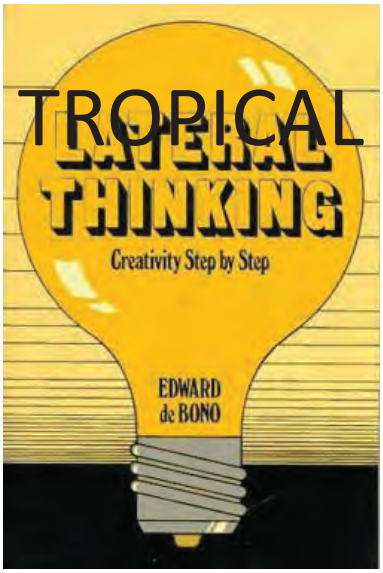
Matthieu MECHAIN
Tropical and Travel Medicine Assistant Physician
Public Health and Social Medicine Specialist
Biology, Epidemiology, Health Law Background

Lateral thinking anecdote

- It’s the story of a traveler who owes money to a money lender.
- 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.
- However, the moneylender "fixes" the outcome by putting two black stones in the bag.
- But the daughter sees this.

Ideas?

- What could be the solution for the debt being canceled?
- What would *you* recommend that the girl do?



Solution

- When she 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).

European research context

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

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 the decision makers and funders
  - Faisability for project reviewers
  - Simplicity in anticipating administrative issues and having specific guidance
  - Efficiency of joint ambitious European research projects

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

Thank you for your attention

Discussion on perspectives of efficient joint research projects

It’s up to you!

14th TropNet Workshop
On Imported Infectious Diseases
Bordeaux, 27th - 28th September 2013

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