Minutes 14th TropNet Meeting Bordeaux 2013

Meeting 27 september 2013

Welcome by Philippe Vigouroux, Director General UHC

Short introduction by Christoph Hatz, TropNet coordinator, on the history of TropNet since the Leiden Meeting when the objectives of TropNet were shifted from mainly surveillance to capacity building of a collaborative network of clinicians.

Report of the Steering Committee (Christoph Hatz)

Membership issues
71 member sites
Three new sites
- University Hospital of Innsbruck
- University Hospital Vienna
- Hopital Tenon - Paris

Change coordinator Oslo University

TropNet platform
Examples of possibilities and opportunities
- research: Leishman
- policy development: European malaria recommendations, further developed from German speaking countries' document which is regularly updated, based on new eveidence plus expert opinion of expert group for travel medicine. Open for discussion
- surveillance and reporting: importance of surveillance for unexpected cases remains, importance for visibility
- network resources - call for contributions by other centers
- public site

We need contributions from the sites, otherwise TropNet cannot function. What is the reason members cannot contribute? All members present have to fill out the survey. What are you prepared to contribute and what do you actually expect from TropNet and please specify.
Ron Behrens suggested to help setting up a study in other members centers. Invitation is still open to visit center to learn new techniques (for example how do you organize your travel clinic). Experience can be presented and published.

Fifty centers did not enter the data on number of cases. Some centers have difficulties to produce these numbers retrospectively. Suggestion for those members to score the cases prospectively so that the data can be send once a year.
Update information on available drugs at the different sites is also very important.

Andy has made a flyer on high altitude sickness in 2012 as a first example on how such common flyers could look like.
Now Andy has made a second flyer on rabies. Interested members are invited to participate in working on future flyers and to support translating of the existing flyers in their language.

Surveillance news - the web page on surveillance news is visited most. Tony Soriano Arandes helped Andy out during the summer holidays, which was much appreciated. Centers who are engaged in similar activities themselves are asked to join this group.

Research - TropNet studies

EU-FP7 dengue tools
- study period sept 2011 - feb 2015
- dengue 180 recruited patients
- 40 samples in Madrid for sequencing
- logistics will be discussed with collaborating centres: numbers of cases, numbers of entered cases, numbers of samples in store, and when to sendi samples to Madrid. Please respond

Safety registry (some centres of TropNet participate, under coordination of MAPI)

Pregnancy registry (TropNet as coordinator)
If a pregnant woman has received Eurartesim, medical follow-up is necessary. If you happen to hear of such a case. Please act and follow this up. It should be reported to TropNet and medical ethical clearance will be asked for that specific country.

Research - TropNet participation

StaphTrav – more centres are invited to participate. Contact PD Dr. Zanger in Tübingen (Philipp Zanger Philipp.Zanger@med.uni-tuebingen.de)

Registrat-Mapi: responsible for Safety registry, follow up of pregnancy registry upon alert of case (pregnant woman having taken Eurartesim® 'accidentally')

Research - TropNet projects ahead (lead, active participation, interested)
- HaemoART
- P. vivax - Eurartesim
- Giardia – (1) adverse events following different treatment schedules, (2)treatment of refractory cases

Research - Possible TropNet projects ahead
- PQ PK/PD in schistosomiasis
- TropNet Study PCR-based diagnosis schistosomiasis in travellers
- TropNet imported multiresistant intestinal bacteria
- TropNet vaccinations in immunocompromised travelers (retrospective YF)
- TropNet surveillance on artemisinine resistance
- TropNet questionnaire cost related to dengue (FP7 tools)

Discussion on ethical clearance in different European countries. Harmonization?

Evidence-based recommendation initiatives
What other subjects should be included

All available documents of all member countries are on the website
Comparison of similarities and differences on advices between countries or break-down in subjects such as malaria for further group discussion
(Could be a subject for master or bachelor paper)

Teaching and hands-on training: invitation is still open

FESTMIH 2015, 6 - 10 September Basel, Switzerland: “The best Science for Global Health Challenges”. Will be preceded by a TropNet Travel Medicine Course! Member sites that are interested can contact C. Hatz.

Presentation results Sarcocystis outbreak (Andreas Neumayr)
Sarcocystis nesbii sequences in Antwerp patient
Tioman island is famous for the monitor lizard - potential source of *S. nesbii*?

Bordeaux is currently tracking all travellers to Malaysia who had visited the pre-travel clinic for a questionnaire. Members sites that are interested can contact Bordeaux.
No new cases reported 2013

Presentation www.tropnet.net (Andy)
Surveillance data/ right column: real-time maps and special issues (for example yellow fever booklet in Nigeria)
Member page opens in the FORUM
All accounts have been set on receiving e-mails alerts. You can delete items on which you do not want to receive mails in “my e-mail alerts” in the left column
All sites are invited to enter also the file where the drugs are acquired.
All sites are invited to provide updates on national recommendation and treatment guidelines
All members are asked to enter the data on their site.
Suggestions for improvement can be sent to Thomas or Andy
Conference or courses coming up at your site? You make advertisement in upcoming events!

Development TropNet info material
Travel Medicine Network resources are available at “Library of travel clinic info material”
High altitude flyer - basic information in PP available (voor Annemieke Croughs). Dutch guidelines are lacking
Rabies flyer - translation? (Emile Jonker)
Antwerp Tropical Institute has a large library for info material (Maybe Fons van Gompel would be willing to coordinate this further?)
Usefulness - in discussing evidence into discussion on guidelines
If revision on own guidelines of member site, Library TropNet website can be used as part of the reference material. This is a win-win situation: help with revision own guideline, and add to building Library in TropNet website

As an example: in Italy representatives of all societies involved in tropical and travel medicine were invited to construct guidelines (via e-mail and limited number of meetings)

Discussion proposal Steering Committee
Meeting 2014, March - 6 months to keep the pace up and to analyse what can be achieved
- research may need shorter interval than a yearly interval
- some members prefer combination with a conference (for example NECTM Bergen)
- increasing frequency of the meeting is not feasible
- for research discussions we may need more time (add an extra day?)
- alternative suggestion combine with NECTM Bergen 2014 and other year visit a center

Vote: 18 members are in favor for separate meeting and 6 for combined meeting
- earlier meeting opens possibilities to discuss the Horizon 2020 program
- morning before start meeting opens opportunities to visit the venue
- think of rules of engagement or strategies how to proceed in the different platforms
- suggestion how to organize a consensus conference - define aims, circulate the project, requires a leader. One day reflection in a meeting that everyone (also interested non TropNet members) attends (Khaled Ezzedine, Bordeaux can share experience how this was realized in International Tropical Dermatology meeting)
  Look for evidence and to identify areas with lack of knowledge
- questions on the structure of the network
  - research committee - specific task, specific coordinator
  - number of sites - 71 centers and 25 people in the meeting - does the high number of centers have a value? what is more useful?

Presentation Post artesunate non-parasitemic deferred anemia (PANDA)
15 % of cured patients after treatment with AS have PANDA
pitting in vivo occurs in patients treated for severe malaria (RBC sparing moment in which parasite is removed without lysis). Is deferred drop in once infected RBC (OIRBC) in AS treated patient explanation for late anaemia?
Population: severe malaria, anemic, hemolysis - no transfusion
Intervention: pitting rate (FACS)
Case definition: rising after hemolysis before d8 (19); persistent (10), late (12), complex
PANDA: peak reticulocytes 3rd week, hemolysis 2 nd week
Pitting is the main factor for parasitic clearance with AS, highly variable
PANDA: high number of pitted cells in first week (more than 50%)
Pitted cells are smaller (projected surface 9% reduction in OIRBC) (17% is threshold for splenic retention)
95% PANDA have high parasitaemia; 95% have more than 0.18 Giga OIRBC/L

Discussion: observation of one LDH-peak in non-immunes and African children suggests other mechanisms such as an immunological mechanism. PANDA may be influenced by age of cells. Effect on distribution of phosphatidylserine not known.
For practice - check Hb for one month according to French guidelines. In Switzerland, the check is performed at week 2. Severe malaria most likely to develop PANDA, should be followed for one month. No experience with asplenic cells, but circulation of pitted cells is prolonged, clearance of parasitemia is delayed

Introduction of Haemo-ART/SMPS/Tox-ART studies (Andy)
1. haematological alterations any oral or IV malaria treatment
2. pharmacovigilance for iv AS
3. in vitro metabolism and toxicity of ART in patient samples and in-vitro generated drug metabolites

1. haematological alterations any oral or IV malaria treatment
   inclusion: confirmed malaria any patient, any drug, willing to complete follow-up ≥21d
   study follow-up between d17 - d21 (to document hemolysis, also possible at GP office)
   laboratory values at each visit. Encrypted transmission of electronic PDF form

discussion/questions
Study design? The current study design is a pharmacovigilance study. A case-control study would be more appropriate.
Sample size? 15% occurrence in ART would allow some calculation on numbers.
Discussion if clinical relevant hemolysis in patients having received oral ART. Clinical impressive hemoglobinuria has been observed.

Visit 4 sample is most important (many centers prefer visit 2 and 3 to be optional)

Meeting 28 september 2013

Presentation progress Leishman working group (Andy)
Open invitation of members from countries endemic for CL to join Leishman group (Piero Ghirga, Rome)
Discussion on clinical presentation and pathophysiology (role TNF control skin lesions) of CL under anti-TNF.

Proposal - TropNet Giardia studies (Andy Neumayr)
GiardiaTREAT
- efficacy 5-nitroimidazole 90% parasitologic cure
- aim: evaluate tolerability
- evaluate adherence and side-effect
  clinical efficacy and regional difference
  create biobank of stool samples
- exclusion: asymptomatic infection, previous treatment
- intervention: M 400-500 mg tid; T 1000 mg one day; O 500mg bid 5d (pediatric dose)
- follow-up after 4 - 5 w. discussion on sensitivity method of follow-up
- all centers can contribute to enter clinical cases

most centers can store stool samples for parasitologic follow-up studies (after informed consent)

GiardiaREF
Quinacrine may be a good candidate for second line treatment. However, it is not widely available. Because of sample size (100 patients per treatment arm) only 2 arms can be compared.

Tinidazole + Albendazole
Albendazole is widely available but expensive
Quinacrine is difficult to get; requires 6GPD screening
Chloroquine (20 mg/kg/d x 5 days in Cuban children) + Albendazole alternative? These two small studies in Cuba show similar efficacy as metronidazole.

16 members would be able to perform such a trial
Discussion on necessity of randomization.

Aim of randomization is to balance the numbers assigned to each arm. Assessment is not blinded. A center-based study would also be allowed provided that there is no diagnostic bias (need to store stool samples for PCR afterwards).
Discussion on the choice of drugs: quinacrine not widely available. Aim would be to find a second line treatment with 80% efficacy. Preference for the following study arms: quinacrine (5d) or chloroquine/albendazol. Time frame december 2013

Proposal - **Retrospective analysis life vaccination given to immunosuppressed travellers (Silja Buehler) for the Swiss Working Group (Zürich, Basel, Bern, Genva, Lausanne)**

Review of literature on primary vaccination and re-vaccination with life vaccines
Proposal for retrospective (and prospective) European wide survey on life vaccine given to immunosuppressed travellers.
A concept of the questionnaire for retrospective case finding is distributed for comments

Discussion
- retrospective study: the members present recall in total 8 cases to 15 cases
- need for prospective study in inadvertently administered life vaccines

Following members have expressed their interest in participation:
Leiden (Leo Visser, Emile Jonker), Bordeaux (Denis Malvy), Barcelona (Israel Molina) and Verona (Andrea Angheben)

Proposal - **Travellers as sentinels for artimisinin resistance (Andy)**
- SNIPs as indirect molecular markers for ART resistance
- Spot 250 µL on EDTA-blood on filter paper
- Minimal anonymized data set
- Establishing a sample library
- Huge collection of malaria samples

Discussion
- Interesting study proposal
- Ethical issues when analysis of host factors

Protocol will be worked out and distributed

Presentations on Drug resistant bacteria

Presentation Esther Künzli (Basel)
- Preliminary data 124 travellers to South Asia
- Epidemiology characterized by increasing prevalence of ESBL-producing Enterobacteriaceae
- Colonization rates India and Nepal 87% (3.2% before travel) suggests environmental source.

Questions: sentinel traveller to detect local resistance? Impact of colonization?

Presentation Leo Visser (Leiden)
- Large variation in ESBL - genes and strains

- Likely that colonization occurs with more than one strain

Presentation Anu Kantele (Helsinki)
- Importance of destination as risk factor
- Pre-travel 0.9% positive - Post-travel 21% positive
- Risk factors: antimicrobials, diarrhea, age
- Three year follow-up no infections with ESBL!

Discussion
- The clinical impact of colonization?
- Is it possible to document spread in the community of endemic specific genes?
- UK - many travellers from South Asia - prevalence of ESBL in patients originating from SA?
  Maybe UK MRSA screening on admission should be extended with screening for ESBL
- What should be done to reduce resistance in India?

- In Germany many patients coming from Eastern Europe are carrying many resistant strains (no numbers). Bordeaux has implemented systematic screening of patients returning from hospitals abroad (Africa, South America, Asia). Finland has done the same since 2010.
- Does spread of multi-resistant strain of UTI occur in family members?
- *C. difficile* is huge problem in UK- colonization also in travellers? In a recent symposium on causative agents of diarrhea; frequency *C. difficile* was very low. Asymptomatic infection clinically less relevant.

Presentation Anu Kantele - Traveller's diarrhea, news from diagnostics
- risk of diarrhea for a traveller from Finland 600-900-fold higher to India than to Middle European destinations
- Diarrheal E. coli - detection by qPCR-based method directly from stool (automated); detects 9 bacterial pathogens in 4 hours
- Validation studies Table 1 and Table 2
- a bacterial pathogen was identified with qPCR in 76% of cases; traditional stool culture would have identified a pathogen in 15%
- 37% 2 or more pathogens
- 47% EPEC and 46% EAEC most common

Discussion
- SENSIVITY to antimicrobials? only after culture
- analysis in asymptomatic travellers will follow
- discussion relevance for treatment. Importance of quantities?
- Israel Molina - enteropathogenic E. coli PCR is routinely performed in TD in Barcelona
- qPCR covers well the diagnostics in acute diarrhea as it is mostly of bacterial origin; in prolonged diarrhea also parasites should be studied
- Ordinary traveller do not need a stool culture or qPCR as the disease is mild (in >90% of cases) + spontaneous recovery

Presentation - New Italian malaria prophylaxis recommendations 2013 (www.simeweb.org) (Andreas Angheben)

- ABCDE approach
  Aware of risk / avoid being Bitten / take Chemoprophylaxis / immediate Diagnosis / standby Emergency treatment
- Quantitative risk estimate in travellers (if not available API)
- First choice / alternative
- Expert consultation of all societies involved in fields of tropical medicine

- Prophylaxis for areas with API ≥ 10 or more than 10 case/100.000 travellers (high risk areas). Diagnosis / E if API 1 -10/ 1-10/100.000. If less only diagnosis
- Grey situations: areas, risk factors (overweight, pregnancy), seasonality
- Short-term traveller - AP
- AP is used in Italia in pregnant women
- MQ in patients over 90 1.5 tbl and over 120 2 tbl per week
- Long-term travellers - C in first 6 months
- Standby treatment if no C and diagnosis not available within 24 hr
- No prophylaxis where P. vivax is prevalent

Simet conference Torino 28-30 nov 2013

Guideline malaria prevention in UK (www.hpa.org) (Mathias)
- Update 2007 version designed by body of expert
- Designed for GP and travel clinics
- Beer consumption increases human attractiveness to mosquitoes
- ABCD-approach
- Identification of risk factors/interactions
- Advice on malaria chemoprophylaxis, limited literature review
- AP in pregnant travellers only if no alternatives
- Country by country advice has not changed a lot since 2007. Small changes for India subcontinent
- Chemoprophylaxis on a number of popular tourist destinations.
- Standby treatment is not a replacement for chemoprophyalaxis
- Any malaria case in UK is confirmed by the reference lab
- Special conditions: smoking cessation drugs, HIV
- Special groups: long-term use,
- Frequently asked questions sheet useful
- www.nathnac.org; www.fitfortravel.nhs.uk; www.hpa.org;

discussion
- even if diagnostic facilities are available, there is a problem of fake drugs
- importance is stressed that travellers should look for medical advice
- report in France on occurrence of S. aureus infections in travellers taking doxycycline
- mew European regulations on mefloquine (ask on black water fever) (five point questionnaire and informed consent, required by EMEA?)
- RDT for long-term travellers?

Travellers with immune mediated inflammatory diseases (Silja Buehler)
- Data from health declarations filled out by travellers at Zurich travel clinic (N=412)
  anti-TNF: 25/412; MTX 29/412; AZA 18/412
  More female gender and older age (≥60)
- Pre-existing conditions: mental disorders, allergies, and epilepsy more common

- Do not present earlier at travel clinic (median 27 days versus 29 days before travel)
- Less back-packing; less long-term
- Yellow fever 51/412 - 1 adalimumab

Neurologic complications in Dengue virus infection (Joaquim)
- Increasing evidence possible neurotropism of dengue virus (Review - Lancet Neurol 2013;12:906)
- Large heterogeneity in defining neurological incidence
- Large difference in reported frequency of incidence
- Only few studies included NS1/PCR/serology in CSF
- Reports of fatal infections with positive finding in CNS
- Proposal for definition neurological feature of dengue

Discussion:
Liverpool is starting a big encephalitis study

Dynamics of pneumococcal serotype acquisition and carriage in travelling children Pneumotravchild - Antoni Soriano Arandes
- In Spain people have to pay for Prevenar
- Casual link pneumococcal carriage and invasive disease. Changing epidemiology?
- Pneumococcal carriage in travelling children compared to non travelling children less than 5 years old

Unit has 6000 children per year

Case presentations
Mastodynia in 35-yo woman from Mali. Micro-calcification in mammography.
Breast schistosomiasis (eggs with with terminal spine)
Mastodynia in 22-yo woman from Mali. Similar findings. One additional case in France. 14 cases have been published. Most presenting with breast nodule. In 15 of 17 cases microcalcifications were seen in mammography

Strongyloides should be screened for before start of immunosuppression
Eosinophilia in students from Bordeaux who did not travel had strongyloides
In Spain near Valencia and Gandia there is local strongyloides transmission
Interested members can enter sharepoint
Address for determination of ivermectine serum levels:
Anne Lespine - Ph.D.
Equipe "Membrane Transporters and Resistance"
INRA - ToxAlim UMR1331
180 chemin de Tournefeuille
31 027 Toulouse
anne.lespine@toulouse.inra.fr
Phone : [33] 561 28 53 87
Fax : [33] 561 28 51 45

HIV-positive patient with anaemia, with cola colour of serum and urine with negative blood smear. Died of intractable hemolysis. Blackwater fever, hemolytic uremic syndrome, hemophagocytosis, sickle cell anemia
Discussion on intravascular and extravascular hemolysis

Chikungunya fever

Mayaro fever enzootic spill over in tropical forests South America
Possibly seen very frequently in Spain!
Clinical picture very similar to Chikungunya
Ross river fever, enzootic spill over (Walibi reservoir) endemic in Northern Austrialia and PNG

Painful moving swelling after returning from Thailand (Anu Kantele)
Three cases of fever with moving reddish blotch without eosinophilia
Strongyloides serology positive; filaria serology positive
Lymphocytic inflitrate; gnathostoma antibody negative
Third patient returning from Thailand Gnatostoma serology +
ivermectin and albendazol/recurrence after which was treated with DEC

Proposal Matthieu Mechain
Preparing for horizon 2020 call. Proposal to formalize collaboration between institutions. It would allow to support each other to increase the change of receiving grants.
To have a network of institutions would enable to form a stronger consortium to reinforce the capacity building. Matthieu will prepare a summary of the proposal.

Closure by Christoph Hatz

Everybody has to return the questionnaire on contributions and requests for and from TropNet
All attending members will provide comments on the case record form (from Silja Bühler)
Response required from all interested member sites to continue membership
If no response no further invitation
Members from endemic countries are invited to apply for membership to the Leishman group

Final version of study Giardia study protocols for review and response

Proof of concept study of Eurartesim *P. vivax*
Call for participating centers from UK
Uncomplicated *P. vivax* in- or out-patients
Time frame: D1, D2, D3 - D21 and D42. No extra ECGs needed (this facilitates easier recruitment and follow-up!)

Next meeting 14 or 28 march 2014 in London or Hamburg
Bergen has Geosentinel meeting: we would not like to interfere