18th TropNet Workshop

(Antwerp 24th-25th March 2017)

Friday, 24th of March

1. Welcome and Introduction (Jan Clerinx & Bruno Grysels)

2. Report of steering committee and coordinator (Christoph Hatz)

Overview of the current network status

72 member sites, 1 new member site (Cambridge)

Network coordination & rotation issues of steering and research committee members

Steering Committee

Ron Behrens, Leo Visser, Thomas Zoller, Anu Kantele, Camilla Rothe, Federico Gobbi, Jill Dixon, Jose Munoz

2017 Ron Behrens will be replaced.

Suggestions as successors: Philipp Zanger, Guido Calleri, Kristine Morch, Emanuele Nicastri, Eric Caumes, Philipp Zanger, Israel Molina

- KM declines a nomination because of other commitments
- PZ declines a nominations as he feels he has not contributed enough to the network yet
- GC would prefer being part of the steering committee and instead giving up his place in the research committee
- IM suggests his place to be taken by a woman → no woman available

Votes: Guido Calleri is elected with 33 votes

Research committee

2017 Blaise Genton will be replaced.

Suggestions as successors:

- Anu Kantele, Guido Calleri or Thomas Zoller are proposed as new chair of the research committee
- Philipp Zanger, Valérie d' Acremont as successor of Blaise Genton
    - VdA declines a nomination now, as she does not have the time
    - AK declines a nomination due to other commitments (very large clinical trial in progress)

Votes for new research committee member: Philipp Zanger is elected with 28 votes

Thomas Zoller is elected with 37 votes as new chair of the research committee

Deciding on the venue for the next TropNet meeting in 2018
Suggestions were Paris, Porto and Lisbon

Decision: **Porto** was elected as next meeting venue in 2018 by a close race against Lisbon and Paris.
The dates of the next meeting are on Thursday/Friday, 17th/18th May 2018, as the majority opted for Thursday/Friday instead of Friday/Saturday.

Review of the TropNet platforms
Research:
ZikaPlan, Cutaneous leishmaniasis, MRSA in trav., Haemolysis & Artemisinins, AMR Enteropathogens, Cost, Gardia

How to overcome constraints (data base, ethical issues, "being used to collect data on a regular basis"):
Suggestions by steering committee:

- centralized open access data collection system
- sponsoring by one of the large TropNet institutions
- steering committee wants to improve network research by asking for more standardized ethical process → letter to European commission, written within the next 2-3 months
- comparing SOPs, clinical data; observational vs. interventional research crucial; standard template, allowing for "add-on" amendments rather than having separate submissions for each new project

Members of TropNet should contact members of the steering committee with their suggestions on how to improve the issue.

Policy development

- harmonization of European recommendations & guidelines
    - establish international platform to develop, implement and evaluate evidence-based and practical health recommendations for travellers
    - Andrea Angheben: how do we do this practically? On what platform? There are more topics than travel medicine (i.e. treatment of schistosomiasis etc).

Annual Figures 2016
Number of reporting centres varies each year.

- increase in Malaria → mostly P. vivax (refugees)
- increase in Chikungunya -> probably because people are testing for Zika
- Zika → high number in 2016
- Rickettsiosis is going up -> reason unclear, awareness?, more testing?

Orphan drugs: Stock list and sources haven been updated on the TropNet homepage

The Expert committee for travel medicine

CH launches the Idea to create an European expert committee for travel medicine. Basis should be the (Swiss) Expert Committee for Travel Medicine which comprises already of mmbers frm Germany, Austria, Italy, France, Spain, UK, Denmark, the Netherlands and Switzerland. Embedded in an international platform (CDC-Atlanta, CATMAT-Canada and ECDC-Stockholm attended last year's meeting (1.12.2016) in Berne, Switzerland) encourages TropNet to establish an international policy network for travel advice. The platform is generally welcomed by the members and will be further pursued.

3. Report of closed/ongoing TropNet studies & studies with TropNet participation

Eurartesim: update on TropNet-SigmaTau study on the treatment of uncomplicated *P. vivax* malaria (Andreas Neumayr)

Study closed

LeishMan: update on ongoing activities (Andreas Neumayr)

- working on cutaneous and mucosal leishmaniasis
- 8 countries, 17 groups
- genotyping leishmanial species
- visceral leishmaniasis not yet priority but the aim is to extend to it
- core publication: JTM 2014

GiardiaTREAT & GiardiaREF: update on the ongoing studies on first- & second-line treatment of giardiasis (Andreas Neumayr)

- low take up -> 3 centres contributed
- 21 cases
- 4 albendazole + choloquine → 3 fails; 17 quinacrine → 13 clinical cure, 2 improvement, 1 clinical failure; 13 parasitological cure (including the 2 with clinical improvement and the 1 with clinical failure)
- follow up on the side effects of quinacrine
- continue with the study?
    - Jose Munoz: observational study gives no additional information, clinical study to difficult
    - Kristine Morch: studies from Cuba showing that chloroquine is an option
    - Jan Clerinx: quinacrine is getting much more expensive
    - Ron Behrens: safety of the drug needs to be assessed

Update on severe malaria study & Artemisinin safety studies: HAEMO-ART & SMPS (Thomas Zoller & Florian Kurth)

- TropNet severe malaria study closed: CID 2015;61(9):1441-4

- HAEMO-ART still running
    - 88 patients

    - more sites needed

- 14 years surveillance data on Schistosomiasis: submitted to AJTMH (Lingscheid et al.)

- SMPS (severe malaria pharmacovigilance system): system for i.v. artesunate
    - standardized questionnaire
    - only 2 reporting centres

- New network study: MAL-RISK
    - Patients classified as severe with uncomplicated clinical course and vice versa
    - Retrospective analysis of severe malaria study plus literature review on scores → definition of risk factors for complications
    - development of a new score to predict complications, tested in a prospective study

<u>An update on StaphTrav – The Network for the surveillance of imported of *S. aureus* </u>(Philipp Zanger)

- ongoing surveillance
- 13 centres
- results: very different resistance pattern depending on the region the *S. aureus* comes from
- in the pipeline:
    - resistance to compounds for decolonization → paper ready for drafting
    - epidemiology of imported epidemic MRSA → poster at ECCMID 2017, paper ready for drafting
- more samples are needed

<u>Imported *P. ovale wallikeri* and *P. ovale curtisi* malaria: preliminary results </u>(Gerardo Rojo Marcos)

- 117 samples from 30 hospitals
- 61 included into subanalysis
- in *P. ovale wallikeri* more white people and more people who travel for work

<u>Malaria and diabetes mellitus: update </u>(Gerardo Rojo Marcos)

- few studies on malaria in patient with diabetes mellitus
- case-control study (1:3 ratio); cases defined as patients with diabetes mellitus suffering from *P. falciparum* malaria
- currently: 42 patients and 94 controls
- documents to enrol controls available on the TropNet homepage

<u>Loiasis: results of a comparison of different drug regimens for the treatment of loiasis – a TropNet retrospective study </u>(Federico Gobi)

- wide heterogeneity of treatments
- comparing different treatments; data from 1999-2016
- 190 patients, finally analysed: 50 patients
- IVM + ALB 81% cure, DEC + ALB 75%, DEC 57%, IVM 28%, no patient with ALB alone

- no serious side effects
- conclusion: IVM + ALB appears to be a good alternative to DEC

TropNet-ZikaPLAN WP: Zika virus infection in European travellers (Andreas Neumayr)
- 14 centres will contribute by collecting biological samples (blood, urine, +/- semen) from ZIKV infected returning travellers
- inclusion criteria: all travellers returning from ZIKV endemic regions who are diagnosed with laboratory confirmed ZIKV infection by positive PCR or positive serology results
- centres: Basel, Antwerp, Barcelona (2x), Leiden, Rotterdam, Munich, Berlin, Hamburg, Negrar, Torino, Madrid, London, Bordeaux
- linked to ZikaPLAN are 3 other studies conducted by or with participation of TropNet sites:
    - persistence & infectivity of ZIKV in semen (Ralph Huits Antwerp)
    - proof-of-concept study evaluating the feasibility of virological sentinel surveillance system using baited filter (Pie Müller, Swiss TPH)
        + smartphone App mapping travel destinations (Ulf Blanke, ETH Zurich)
    - smartphone App to collect data on arbovirus-related fever syndromes (Jose Munoz, Barcelona)

4. Upcoming and proposed TropNet studies

The ZikaPLAN research initiative (Annelies Wilder-Smith)
- funded by the EU (12.5 Mio)
- 25 partners (mostly in Europe, but also Colombia, Brazil, Carribean)
- 13 work packages
- WPs pertinent to TropNet: non-vector transmission; innovation and evaluation platform for diagnostics; burden of disease

Post-exposure screening for Zika virus antibodies in asymptomatic travelers (Ralph Huits)
- option to minimize the risk for Zika congenital syndrome
- method:
    - asymptomatic: ZIKV antibodies 20 days after exposure
    - symptomatic cases: antibody detection
- results: in asymptomatic group 1.7% confirmed ZIKV, in symptomatic group 18% confirmed ZIKV; most common symptom rash (93%), fever (59%), arthralgia (41%), myalgia (21%)

Enteropathogens causing diarrhoea in European travellers to tropical and subtropical countries – a multicenter observational cohort study on geographic distribution, symptoms and antimicrobial resistance (Esther Kuenzli)
- data on antimicrobial resistance of enteropathogens found in travllers with TD
- documents (questionnaire, protocol available on TropNet website
- David Hamer, GeoSentinel: GeoSentinel is already collecting data on ab resistance in enteropathogens; suggests to collaborate

Oral treatment of severe imported malaria (Blaise Genton)

- response to initial per os treatment (either switched to i.v. or not) for episodes of severe malaria
- multicentre observational retrospective study
- expected output: to identify a subgroup of "moderately" severe malaria which could be treated by oral treatment; results serve as a baseline for a prospective study in Africa
- investigators: Samuel Frésard, Laurence Rochat (laurence.rochat@hospvd.ch), Blaise Genton (blaise.genton@chuv.ch)

5. Presentations

Febrile rhabdomyolysis of unclear origin in refugees coming from West Africa through the Mediterranean from 2014 to 2016 (Silvia Odolini)

- 2014-2016: all cases of febrile rhabdomyolysis
- 48 cases, mainly males, all from West Africa, fever & severe muscle pain
- on average 26 days after leaving Lybia
- increased liver parameters, CPK
- serological results: CMV (10.3%), Coxsackie (18.5%), EBV (25%)
- 3 had sickle cell trait, 1 had haemophilia A
- mechanical cause? → long incubation period not consistent with this hypothesis

Saturday, 25th of March

1. Presentations

Interaction/communication with EUROSURVEILLANCE: open discussion (Ines Steffens)

- peer-reviewed, published since 2007 by ECDC, editorially independent
- impact factor 2015: 5.9
- readers and contributors: public health, microbiologists and virologists, clinicians, veterinarians, pharmacists, policy makers
- Article types
    - rapid communications: usually published within 2 weeks after submission, information could potentially lead to a prompt change in a public health situation
    - surveillance and outbreak reports
    - Euroroundups: article with an introduction, followed by the views of at least 5 European countries on a topic
- acceptance rate: 18%
- points for discussion
    - what should be communicated rapidly?
    - when are case reports interesting?
    - challenges of publishing outliers
- Andrea Angheben: there should be more publications on neglected tropical diseases

The GEOSENTINEL Network (David Hamer)

- established in 1995 by CDC and ISTM
- clinical-based global surveillance system using de-identified patient information

- 64 sites in 29 countries, 220 affiliated members
- co-funded by CDC, ISTM and PHAC (Public Health Agency Canada)
- provider-based surveillance, only basic demographics, no complete clinical record
- records with an alarming diagnosis entered into the central database triggers an immediate alarm → notification of site director, PI, CDC, Epi Team etc.
- several potential synergies with TropNet
    - AMR diarrhoeal pathogens
    - Zika
- Christoph Hatz: how do you get around the problem of ethical clearance?
    - DH: for surveillance, every institution has to go through ethics → most sites obtain a "non-research clearance" → not allowed to go back to the medical records; for research every site has to obtain ethical clearance
- Ron Behrens: non-communicable diseases/accidents/crime are not covered at all even though these kill/injure more people than infectious diseases
    - DH: as the collecting sites are tropical medicine/infectious diseases sites they do not see these type of patients; other organizations are already doing it
- Andreas Neumayr: how many sites do bio-banking?
    - DH: to date only very few sites; planned to do it prospectively

<u>Experiences with the IHR Emergency Committee: Yellow Fever</u> (Gilles Poumerol)

- purpose of international health regulation: prevent international spread of disease, avoid unnecessary interference with international traffic and trade
- measures following the 1st YF EC meeting: pre-emptive vaccination campaign for high risk population, WHO & CDC implementing an immunogenicity study, vaccination of travellers and expats
- YF fractional dose: data suggest that reduced volume dose was equivalent to a standard dose with respect to all measured immunological and virological parameters, provided a dose contained > 3000 IU
    - fractional dose only in emergency situations, not for travellers

<u>Yellow Fever vaccination in travellers: current situation and unresolved issues</u> (Olivia Veit)

- since August 2016: 4 YF cases in European tourists, between 1999 and August 2016: 4 cases in European tourists
- official recommendations:
    - WHO position: single life-time YF vaccination
        - SAGE: studies should be performed to identify specific risk groups who would benefit from a booster
    - CDC booster recommendations: pregnant women, immunosuppressed people and people in high-risk situations
- European countries: most national policies follow the single life-time policy, some give boosters for special travellers, in special risk groups and special situations
- Discussion points
    - Do we need clearer recommendations for travellers?
    - European/TropNet statement/recommendation?
- Matthias Niedrig, Berlin: problem in people vaccinated as children → European recommendations needed

- Leo Visser: protecting 80% of travellers is sufficient to prevent transmission of YF from one country to another, but what about the single traveller
    - Gilles Poumerol: SAGE did also address travellers → their recommendations are for both; it was a consensus recommendation, it is possible the decision will be changed in the future
- Olivia Veit: why, if the CDC is part of SAGE, does the CDC recommend a booster dose for high risk situations
    - Gilles Poumerol: it is confusing, but the decision was made by an expert committee
- Ron Behrens: different expert groups have interpreted the same data differently → expert consensus will always be different in different groups which is mainly due to the fact that the data is not convincing; there are two ways forward: either we accept the expert opinion of SAGE or we come to another conclusion based on the same evidence; it is important for us to come to a conclusion
- Camilla Rothe: travellers are not relevant in driving an epidemic, the problem are fake certificats etc
    - Gille Poumerol: YF vaccination should be introduced in all regions with YF in multi-vaccine programmes to prevent exportation of the disease

<u>The changing malaria risk in Southeast Asia: 2005-2008 vs. 2011-2015</u> (Ron Behrens)

- cases in travellers from the UK and USA
- denominator: WTO statistics based on arrivals to countries by nationalities
- rates for Southeast Asia declined from 2.9/100'000 to 0.9/100'0000 (USA) and from 2.4/100'000 to 0.7/100'000 (UK)
    - more than 2/3 of cases non-falciparum malaria
- rates for South America decreased 2.7/100'000 to 0.9/100'000 (USA) and 5.1/100'000 to 0.7/100'000 (UK)
- malaria chemoprophylaxis is associated with side effects in 21% → chemoprophylaxis to SE Asia and the Americas should be withheld based on current risk of *P. falciparum* malaria
- Guido Calleri: what about Myanmar?
    - RB: rates dropped dramatically (25/100'000 -> 2/100'000)
- Anu Kantele: have rates dropped because people are taking more prophylaxis in the second period?
    - RB: data and experience tell that people do not take chemoprophylaxis → effect not due to people taking prophylaxis

<u>Traveller's remote information project (the results of two pilot studies)</u> (Natalia Rodriguez)

- mobile application
    - reminding travellers to take their medication
    - questionnaires
- information downloaded real-time into a database
- used in travellers and in the Spanish Olympic team

<u>Travel medicine App</u> (Andrea Farnham)

- data collection: streaming data, daily electronic questionnaire

- good uptake by travellers
- high data output
- spatial pattern of lesser known health events
- findings support importance of research beyond infectious diseases in travel medicine

Wikitropica: a concept for knowledge management (Jan Kennis)

- originally illustrated lecture notes on tropical medicine
- when notes were online, they were used by a diversity of users
    - students
    - health-care professionals
- mobile first and offline versions are desirable
- aim: to convert the information into a collaborative project with experts providing information, freely available for health-care professionals
- Leo Visser: what is your vision on the review board
    - JK: based on expertise of the members
- Emmanuel Bottieau: also information for people working clinically under imperfect conditions?

Critical appraisal of European travel medicine websites: what's next? (Mieke Croughs)

- looked at websites mentioned on TropNet sites (language restriction: English, German, Dutch)
- in general, TropNet homepages do not provide much information on travel health information, open access, aimed at travellers, mostly no country lists
- most of them refer to national homepages
- Dutch App with travel advice available → is there a potential for a common European homepage and App?

Hydatid on the prowl (Peter Chiodini)

- 1981 to 2006 (n=53) vs. 2006 to 2016 (n=155)
- experts to not comply with existing guidelines
- what is needed: length and pattern of albendazole, role of praziquantel

S. haematobium cluster in travelers returning from South Africa: the diagnostic value of PCR (Jan Clerinx)

- Group of Flemish travelers who spent time in South Africa
- Schisto PCR positive in 24/33 (73%) during the first week of illness, a few weeks later 30/34 positive
- When to treat with what for how long?
    - Symptom relief: steroids, but no data on ideal timing, duration and dosis
        - Proposition: Methylprednisolone 0.5mg/kg/d for 3 days
        - 73% only needed one, cycle 6/21 needed 2(4) or 3(2) cycles
    - Praziquantel
        - Parasite load reduction of single dose: > 80%
        - PZQ concentration decreases if given with steroids
        - Treatment scheme: PZQ 20mg/kg at 0 and 2 hours, steroids at 4 hours

        - No symptoms: 62%, mild symptoms 26%, fever 12%, requiring steroids 9%
    - Swimmers' itch is associated with being a child
    - hypothesis: Schisto was introduced into that river by an infected person

Malaria chemoprophylaxis/standby: results and discussion of Delphi 5 survey (Guido Calleri)

- Delphi 4:
    - majority of participants changed their prescription of chemoprophylaxis significantly during the last 10 years
    - mostly due to changing epidemiology
    - mostly reduction of chemoprophylaxis
    - changes mostly in Asia, not so much in Africa
- Delphi 5:
    - 15% VFRs, one fourth of them which children
    - consent on the fact that epidemiology is changing
    - Malarone® used most often for stand-by-treatment
    - only 4/30 recommend carrying a rapid-test

Giardia lamblia infection in international travellers – a retrospective analysis (Camilla Rothe)

- Germany: 1st line treatment metronidazole 500mg for 5-7 days, most 2nd line drugs not available
- Questions:
    - Where does Giardia come from?
        - almost half from South Asia, mostly from India; followed by Africa and South America
    - What rate is failing first line treatment (defined as recurrent parasitological proof of giardia plus clinician's decision to treat again)?
        - overall, 30.2% failed; in South Asia, 46.5% failed, in Africa 15.5, South- and Central America 8.9%
    - Risk factor for failure?
        - region of travelling
    - 2nd line treatment
        - failed in 46% of cases
        - most promising: metronidazole-paramomycin or albendazole-chloroquine
    - 3rd line treatment very heterogeneous

New unexpected findings in lung nodules in African migrants with chronic schistosomiasis (Federico Gobi)

- 6 cases with lung nodules in a 18months period with schistosomiasis (7.5% of patients with schistosomiasis had lung nodules)
- lung nodules in 14 patients from sub-saharan Africa
    - tuberculosis
    - schistosomiasis
    - tuberculosis plus schistosomiasis

    - non-tuberculous mycobacterial infection
- hypothesis for lung findings: one due to eggs present in nodule, one due to eggs scattered in lung
- lung lesions can disappear without treatment

Questionnaire-based survey on clinical management of malaria in the different tropical or infectious units in Italy in 2015 (Emmanuele Nicastri)

Part 1)

- retrospective sub-analysis on severe malaria treated with combined artesunate and quinine
- 13 patients
- no benefit of this combination as compared to artesunate alone
- limitations: monocentric, retrospective

Part 2)

- 2746 cases of malaria in Italy from 2011-2014, mostly *P. falciparum*
- 322 cases of malaria
    - countries of infection: mostly West Africa, mostly in VFR
    - mostly not on prophylaxis or on incorrect prophylaxis
    - a high proportion of severe malaria was treated with oral drugs
    - only 50% of sites have access to i.v. artesunate

Antibiotics for travellers – friends and foes (Anu Kantele)

- 0.1-1% of travellers colonized after travel develop an infection
- risk factors for getting colonized: destination, suffering from TD, using antibiotics when travelling
- ESBLs found in travellers:
    - not taking ciprofloxacin while travelling: 37% co-resistance to FQ; taking ciprofloxacin while travelling: 95% co-resistance to FQ
- antibiotics and hospitalization abroad:
    - 1122 patients
    - highest risk of contracting MDR bacteria: South Asia
    - risk factor: taking antibiotics
- Benin-study
    - Etvax-vaccine against ETEC
    - study on travellers to Benin
    - 400 vaccinated, 400 receiving placebo

2. Clinical cases

A rare case of tropical fever in Norway (Kristine Morch)

Diagnosis: Rhodesiense HAT imported from Uganda, 2nd ever case in Norway

Cutaneous lesions and eosinophilia in a traveller returning from Uganda (Jara Llenas)

Diagnosis: Ectopic cutaneous Schistosomiasis

A severe case of malaria – focus on management (Angela Corpolongo): presented by E. Nicastri on Friday

Invasive strongyloidiasis in two transplant patients (Frank Olav Pettersen)
Strongyloides-positive donor

Doubt and error in focal splenic lesions (Francesca Rinaldi)
Diagnosis: Two cases of visceral leishmaniasis with focal splenic lesions