Minutes 13th TropNet Meeting at the Hotel ILF Prague, Budejovicka, Prague

October 5, 2012

1. Welcome by Jiri Beran of host institute
   Short introduction to the Vaccination and Travel Medicine Centre, University Hospital, Hradec Kralove, and Department for Tropical and Travel Medicine of IPME, Prague

2. Welcome by Christoph Hatz, Coordinator TropNet

3. Report of the Steering Committee and Coordinator

3.1 Meeting Eurotravnet and TropNet at FESTMIH 2011 in Barcelona sharing their views. Each organization has its own value: focus on surveillance at EuroTravnet; focus on research, evidence based recommendations and policy development, and training and teaching at TropNet

3.2 Board elections
The Steering Committee and Coordinator must stand for reelection every two years. There are no new candidates who will stand for coordinator. Christoph Hatz is reelected by unanimous vote.
Thomas Jelinek is stepping down as member of the Steering Committee. Ron Behrens, Joaquim Gascon and Leo Visser are standing for reelection. Jacob Cramer and Thomas Zoller are new candidates. After counting the votes: Ron Behrens, Joaquim Gascon, Leo Visser and Thomas Zoller were elected as members of the Steering Committee

3.3 Ongoing TropNet Studies
- EU-FP7 Dengue tools - Call to all participating centres to improve inclusion rates Portugal (Miguel Abrue) will contact Joaquim Gascon (Barcelona) to be able include their patients in the study
- Leishman working group
- StaphTrav
- Registrat-Mapi Pregnancy Registry study: TropNet has signed a study contract with Sigma-Tau for a follow-up study of pregnant women who were treated with DHA/Pip. Mother and child will be followed-up for adverse events during and after pregnancy. In case a member has a case, ethical clearance for this study will be asked for that specific centre.
  Discussion: ethical clearance is required. For practical reasons, ethical clearance will only be sought upon inclusion of a case because the input of gaining ethical clearance in all centres is technically and financially not feasible. Follow-up will be partly performed by a clinical trial bureau

3.4 Policy development
TropNet is looking for a closer interaction with international societies such as ECDC (policy making), FESTMIH (pre-meeting course)
Countrywide recommendations: call for all members to contribute to provide their national guidelines on malaria prophylaxis (and vaccination recommendations) to Andy Neumayr, <u>including if available the methodology</u> of how the recommendation were based (Ron Behrens will make short list)

3.5 Teaching and training

Two suggestions:

1) European Course in Travel Medicine according to the format of the "European Course in Tropical Epidemiology". This course will not replace current courses at several institutes at the moment, but it may in the future (role TropEd?)

2) two days pre-meeting course before the FESTMIH 2015 (Basel)

Discussion - there is a need for platform/working groups to move planned activities to a further level. We need volunteers for example to set up teaching activities

3.6 Surveillance and reporting

The yearly reporting on numbers of imported diseases (even if zero) by each centre is a basic requirement for membership to TropNet. Such information is crucial when discussing the feasibility of new initiatives and studies although in itself, it will not be used for publication as previously performed by TropNetEurope.

Centres who do not provide their data in 2013 will lose their membership.

Discussion - main reason is to get a rough estimate of how many cases are seen at the different centres to see where studies can be done. The data are not for surveillance purposes. Proposal to make a standardized form to allow members to report the data at their own pace (prospectively, regularly, retrospectively)

3.7 Orphan drugs - all members are asked to send a list of their sources of orphan drugs

3.8 Crash course on TropNet website - Neumayr and Zoller

- Request to the centres which have not yet returned their site-information questionnaire: the completed questionnaire (which was sent to all centres and is available for download in the internal section of the website) is the base to set up the member site information. Currently the questionnaires of 18 centres are pending. Please send the pending questionnaires
- Please provide source (address where the product can be ordered) of orphan drugs
- Please provide national guidelines treatment of tropical diseases (in any language) and give the methodology (evidence-based, expert opinion, consensus of national committees)
- Backbone of the TropNet website is a content management program which requires only 15 min of training for programming. Interested members can apply to learn and add text and figures.
- By using "Attach poll" to the postings in the Forum section the opinion of all members can be obtained.
- Request for volunteers to keep up the surveillance page if Andy is on holiday

3.9 Short update ongoing studies

- Severe malaria study - Thomas Zoller

  N = 103, i.v. artesunate 18

  10 centres reporting

  End of data collection 31-12-2012

  Retrospective reports can be submitted to www.artesunate.info

  Outlook: Prospective safety and tolerability with GMP-standard i.v. artesunate

  Non-comparative study (N = 150) in 11 countries requires more money

  Prospective observational study with no funding (similar to US treatment IND program)

- Short update of Leishman activities - Jan Clerinx on behalf of the Working group.
  Discussion - Patients on immunobiologicals with CL is an opportunity for funding: pharmacovigilance responsibility of companies producing monoclonal antibodies (Philipp Zanger)
  Two papers (one of Leishman) are currenty submitted to Eurosurveillance on this topic

3.10 TropNet travel medicine info material

Andy Neumayr wrote TropNet travel info on Altitude Sickness. Unsolved discussion on diamox as early treatment instead of prophylaxis.
Volunteers needed to develop info material, translating ... group-work
Discussion: original source and expiration date should be present on travel info

Proposal to form interest groups on specific topics for travel medicine info (for example rabies, JE) to discuss contents with each other. Gaps in knowledge would allow for the design of new studies.
Suggestion to use poll on Forum to find members who share the same interests and are willing to contribute

3.11 TropNet HaemoART study - Thomas Zoller

There are indication of a dose dependent late haemolytic anemia by artusunate
Aim: systematic controlled evaluation of the potential of oral artemisinin to induce hemolyse. Post treatment visit on day 18-22 is a critical visit for the study (either at local GP or study centre). Post treatment visit day 28-32 if haemolysis was detected on days 18-22

Discussion - suggestion to separate research questions, frequency of occurrence of late haemolysis from mechanism of haemolysis. It is important to explain why patients have to visit on days 8-12 and days 18-22 (to rule out haemolysis)
Proposal to keep laboratory analysis as simple as possible (days 8-12, 18-22)
If anemia is subclinical (especially in low parasitaemia), there is no need for elaborate laboratory analysis
What would be the consequence of your findings if indeed anemia is found?

3.12 Update on Eurartesim and artesunate i.v. - Andreas Diedenhofen

3.13 Pregnancy and Safety registry - Christoph Hatz

To evaluate the effect of fetal exposure to Eurartesim on frequency of congenital birth defects and outcome. Period 2012 - 2019
Patient contact process: submission for local ethical clearance once the patients have agreed to be included in the study. This will save unnecessary efforts and costs at ethical committees in centres that may not see such a case.

Discussion - numbers of pregnant travellers will be low. It is not clear what to do with the outcome. These objections have been communicated with EMEA, but they insist to perform the study

October 6, 2012

3.14 State of the art review on Giardia lamblia treatment - Andreas Mueller

3.15 Results of a recent Giardia lamblia treatment study in Barcelona - Joaquim Gascon

Results of the retrospective study:

Nitroimidazole	efficacy	78%
re-treatment	efficacy	13%
quinacrine	efficacy	100%

Guideline Barcelona:

- first line: tinidazole 2 gr single dose, control after 1 mo (2 samples)
- second line after failure: quinacrine (rule out G6PD-deficiency, ask for history psychosis)

Discussion: different availability of drugs, different experiences, and history of previous infections may explain large differences between different centres

3.16 Study proposal GiardiaTREAT - Andy Neumayr

Inclusion: any person positive for G. lamblia (GI) (travellers and autochthonous cases)
Treatment failure: GI in stool 2 samples (microscopy or antigen test) at **4 weeks** after completing full course treatment
First line: metronidazole 400 - 500 mg, 7d; tinidazole 2 g, 1 - 2 d
Second line: fixed regimen or combination or open to the expert

Discussion:

- Epidemiology: 1000 new cases will lead to 200 treatment failures per year?
- Preference for option well defined second line treatment
- In current proposal too many options for second line
- The outcome most effective first line treatment will not be met because no RCT
- Numbers too small for 3rd line and 4th line treatment
- Suggestion to exclude immunosuppressed because this patient group is different
- RCT would be the best for second line treatment of treatment failures
- Some centres have difficulties to collect 4W sample. Clinical data at 4W should be included
- Collection of data on first line treatment should have a simple design
- Clinical problem is therapy refractory giardiasis not first line treatment
- Choose for 2 treatment regimen in 2nd line
- Problem of large heterogeneity of first line, need for harmonization first line
- Observational study refractory giardiasis will not give the answer
- Clinical failures should be defined
- Information on blastocystis
- Tolerability of treatment schedule
- All fecal samples should by stored (at -20°C) for later molecular studies

Conclusion:

- Members accept study proposal `observation on tolerability and efficacy of first line therapy´ with telephone call for control of clinical symptoms and 2 additional stools (microscopy or antigen) at 4 weeks

Store an additional stool sample at -20°C for later molecular work-up - initial proposal on primary treatment and its outcome should be send for consultation on outcome measures for members

- For second line treatment of recurrences a RCT study will be designed (this had been declined the year before)

3.17 Schistosomiasis

- PCR results for serum diagnosis of early schistosomiasis (S. haematobium) (Cnops 2012 et al.) - Jan Clerinx
- Antigen detection (CCA, CAA) for parasitogical documentation of cure? - Leo Visser

Conclusion: proposal to set up a working group similar to Leishman with interested centres: Antwerp, Leiden, Hamburg, Basel, others? Combining clinicians and parasitologists. After optimalisation diagnostic possible application for other members (for example early treatment with artesunate). Crash protocol for schistosoma outbreaks among travellers

3.18 ESBL – Leo Visser

Discussion

• risk group for hospitalization: elderly, immunosuppressed
• risk group for infection: immunosuppressed
• prevalence study on occurrence of ESBL in hospitalized travellers would be interesting to members
• important public health aspect
• paper of Finland similar findings, not published
• before planning future studies we have to look at other cohorts studies going on
• possibility for funding
• is this a continuing surveillance study?

Conclusion: Initiate a working group with interested centres: Matthias Schmidt, Philippe Zanger, Leo Visser, Thomas Zoller, Esther Kuenzli, Basel, Anu Kantele, Finland

3.19 StaphTrav - Philipp Zanger

Outbreaks are often local event because *S. aureus* acquired virulence genes like mecA and PVL. Therefore, also need to look for MSSA, because they are able to acquire these virulence genes.

Results StaphTrav
N = 130 of which 73 was S. aureus (56.2%)
PVL 61%, MRSA 6.9%
Higher PVL prevalence in Sub Saharan Africa
PVL producing strains give more often recurrent infections
Ciprofloxacin resistance in South Asia; trimethoprim resistance more in South Africa
Molecular epidemiology demonstrates focal epidemiology

How can I contribute? go to www.staphtrav.eu

1. swab with transport medium (nose and pus)
2. CRF
3. TNT
4. pseudo anonymised submission

5. local ethical clearance (templates are available)
6. 15 strains is co-authorship

Discussion

- use Staphtrav setup for ESBL study?
- opens future possibilities to study for eradication treatment
- health protection agency protocol for PVL-positive MSSA

3.20 Babesiosis - Michel Develoux

Recent emergence of babesiosis in lower Hudson Valley because of enormous tick population
most trophozoites look like *P. falciparum*. Think of babesiosis if patient does not come from malaria endemic country; airport malaria. Incubation period 1- 3 W; asymptomatic infection 20% (co-infection Lyme, more frequently symptomatic)
Splenectomized travellers, need for prophylaxis?
Treatment atovaquone + azithromycine
Review NEJM 2012;366:2397

3.21 TREK study - Ron Behrens

RCT, LT enterotoxin patch over 6 hrs, repeated after 2 W
volunteers required to go on holiday
challenge design to sending to Mexico, Guatamala, India
Each site had clinical center for diagnosis
N = 723 (India) N = 2036 (L. America)
80% completion
Adverse events, 90% unpleasant local reactions an rash compared to 50% in placebo
no/minimal reduction duration
moderate to severe 3.7% vs 5.6% p = 0.06
LT ETEC alone some protection

Discussion

- 30% did not show up after screening
- mismatch between expectations and outcome
- enteric immunization more logical
- low prevalence of ETEC
- even if effective side effects prohibitive for its use

3.22 Immunocompromised traveller - Leo Visser

Inadvertent YF administration
Protocol will be written for a standardized registry for the follow-up of inadvertent YF administration in immunosuppressed travellers
Immune response to vaccination in travellers treated with monoclonal antibodies
Protocol for (hepatitis A) serology in travellers treated with monoclonal antibodies
Collect national guidelines on travel advice of immunocompromized travellers

3.23 EHEC outbreak in Germany - Jacob Cramer

mixing virulence factors EHEC and EAgEC
sprouts = stealth food (not noticed) - produced at high humidity and temperature
incubation period 3 - 11 d
time window between bloody diarrhea and HUS is 2 days 9 (Tarr et al. Lancet 2005)
132 patients with HUS 54% requiring dialysis, 42% intensive care

early drop of thrombocytes; 50% HUS also neurologic symptoms
plasmapheresis not effective
eculizumab efficacy difficult to differentiate from natural history
azithromycin (because of severity and eculizumab, reduced shedding of EHEC)
(Tarr, Nature Rev 2012; Pennington, Lancet Infect Dis 2010)

3.24 Closing - Jiri Beran
Thanks to organizers - Christoph Hatz
Overview conclusions and action points meeting - Christoph Hatz

3.25 History of malaria, from Abele Sola to Ho Chi Minh - Marco Corsi