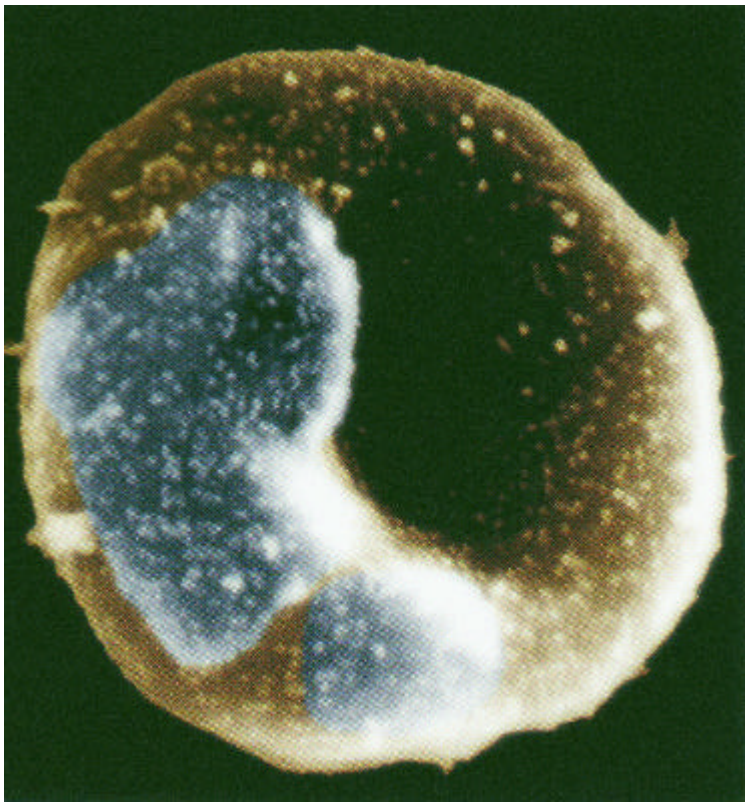
TropNetEurop

7th Workshop on

Imported Infectious Diseases

2006



September, 30th – October, 1st

Basel

European Network on Imported Infectious Disease Surveillance

www.tropnet .net

PROGRAMME

7th TropNetEurop Workshop 30/09-01/10/2006

Date & Time		Speakers
Saturday, 30/09/2006		
9^{00}-9^{15}	Introduction	Christoph Hatz, Basel
9^{15}-10^{30}	Report of steering committee and co-ordinator • Membership issues • Reporting • Data management • ECDPC, WHO, & others	Ron Behrens, London Anders Björkmann, Stockholm Joaquim Gascon, Barcelona Tomas Jelinek, Berlin Alberto Matteelli, Brescia Nick Mühlberger, Berlin
10^{30}-11^{00}	**Break**	
11^{00}-12^{15}	Report of steering committee and co-ordinator (continued) Election Steering Committee & Coordinator	
	Malaria	
12^{15}-13^{00}	The Swiss Tropical Institute & The Swiss Working Group for Travel Medicine Councelling	Christoph Hatz, Basel
13^{00}-14^{00}	**Lunch**	
14^{00}-14^{30}	Molecular tools for the diagnosis of malaria	Hans Peter Beck, Basel
14^{30}-15^{00}	The Delphi Study revisited: VFRs	Guido Calleri, Torino
15^{00}-15^{30}	Malaria prophylaxis for travel to Central and South America	Ron Behrens, London
15^{30}-16^{00}	**Break**	
	Malaria Chemoprophylaxis	
16^{00}-19^{30}	Consensus meeting on malaria chemoprophylaxis in Europe	
20^{30}	**Dinner**	
Sunday, 01/10/2006		
8^{25}-8^{30}	Introduction	Tomas Jelinek, Berlin
	Imported Infectious Diseases	
8^{30}-9^{00}	Treatment study in uncomplicated malaria: MALTHER	Martin Grobusch, Johannesburg
9^{00}-9^{30}	Chagas disease: challenges in Europe	Joaquim Gascon, Barcelona
9^{30}-10^{00}	Serology for S. stercoralis as a monitoring tool for treatment	Stefania Marocco & Marina Boscolo, Verona
10^{00}-10^{30}	Online projects in travel medicine	Richard Boyd, Dublin
10^{30}-11^{00}	**Break**	
	Studies: TropNetEurop & Friends	
11^{00}-11^{30}	Epidemiologic Surveillance on Dengue fever in Europe	Cristina Domingo, Madrid
11^{30}-12^{00}	Dengue Study	Joaquim Gascon, Barcelona
12^{00}-12^{30}	The Antwerp Fever Study and its conclusions	Jan Clerinx, Antwerp
12^{30}-13^{00}	The Feasibility and Safety Study of Practice Guidelines: current state of case inclusion	Isabelle Rossi, Lausanne
13^{00}	**Lunch & Farewell**	

WORKSHOP ORGANIZER AND LOCAL CONTACT ADDRESS

Christoph Hatz, MD, DTM&H
Professor & Head Medical Department
Swiss Tropical Institute
4002 Basel / Switzerland

Phone: +41 (0)61 2848255
Fax: +41 (0)61 2848183
Mail: Christoph.Hatz@unibas.ch

MEETING VENUE

The meeting will take place at the learning centre of the Swiss Tropical Institute at Socinstrasse 57, (www.sti.ch) on Saturday 30th September and Sunday 1st October 2006.

Accommodation is booked at the nearby Hotel Bildungszentrum-21 (www.bildungszentrum-21.ch)

WELCOME

Dear colleagues

You are warmly welcome at the Swiss Tropical Institute in the city of Basel. You will notice that Basel is a small and charming place with short distances, easy to get around, and so we are confident that nobody will get lost during the two days.

I am looking forward to a constructive and fruitful meeting of our network partners. The programme looks challenging as always and the scientific discussions ahead of us look promising for an important consensus finding on malaria protection issues.

Our team will look after you with regard to food for the body and the mind and we hope that you will also find some time to get to know the highlights of our town.

On this occasion, I would like to thank the sponsors of this meeting, namely our Institute, the Novartis Pharma Ltd, the Mepha Pharma Ltd, the GSK Ltd and the Crucell Berna Ltd for their finacial support.

On behalf of all the staff of the Swiss Tropical Institute I wish you all a pleasant stay in Basel.

Christoph Hatz

Dear colleagues!

TropNetEurop has now finished its 7th successful year. The past year showed some turbulences, but also many examples of the successful work of our network. The meeting in Basel reflects this: never before were so many delegates from members sites present.

The network and its members unite 51 specialized centres all over Europe. Within the network, we see an average of 54.000 patients post travel per year. This is the largest effort of imported infectious disease surveillance world-wide. It took only a very short time span to develop TropNetEurop to a renown reference in the field of imported infectious diseases. The large output of widely distributed material shows the value of our work. This success was achieved through considerable effort from all members who continue to put in extra time and work to make the network possible. My heartfelt thanks for all this enthusiasm!

I am looking forward to an exciting meeting in Basel.

On behalf of all members of the network, I wish to express our special thanks to the local organising team of this workshop, especially to Christoph Hatz, who made the meeting possible.

Berlin, Sept, 25th, 2006

Tomas Jelinek

ACKNOWLEDGEMENTS

Financial support for the workshop from following sources is gratefully acknowledged:

- Swiss Tropical Institute
- Novartis Pharma Ltd
- Mepha Pharma Ltd
- GSK Ltd
- Crucell Berna Ltd

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CONTENTS

PROGRAMME....2
WORKSHOP ORGANIZER AND LOCAL CONTACT ADDRESS....3
MEETING VENUE....3
WELCOME....4
ACKNOWLEDGEMENTS....5
CONTENTS....6
MINUTES OF THE 6TH TROPNETEUROP WORKSHOP....7
MISSION AND GOALS OF TROPNETEUROP....15
TROPNETEUROP: RULES & REGULATIONS....16
CURRENT SITUATION OF TROPNETEUROP....17
COMMUNICATION....23
a) The Mailing List....23
b) Monthly Reports....24
c) Recently published material:....24
d) Material submitted:....24
c) The Web Site....26
d) Special Reports and "Sentinel Events"....27
e) Friends & Observers....28
f) Publications about the Network....28
MALARIA....33
Die Schweizerische Arbeitsgruppe für Reisemedizin (SAR)....33
Molecular tools for the diagnosis of malaria....34
The Delphi Study revisited: VFRs....35
Malaria prevention policy for travellers to Central and South America. What is the evidence and what should be best practice for malaria prevention?....37
Swiss Malaria prophylaxis for Short-term Travellers....38
IMPORTED INFECTIOUS DISEASES....54
Treatment study of uncomplicated malaria: MALTHER....54
CHAGAS DISEASES IN NON-ENDEMIC AREAS. THE EXPERIENCE OF BARCELONA....55
PROPOSAL OF A MULTICENTRE TRIAL ON THE TREATMENT OF STRONGYLOIDIASIS, USING SEROLOGY AS A TOOL FOR DIAGNOSIS AND FOLLOW-UP....57
Online projects in travel medicine....59
STUDIES: TROPNETEUROP & FRIENDS....60
EPIDEMIOLOGICAL SURVEILLANCE ON DENGUE FEVER IN EUROPE....60
DENGUE STUDY I: SURVEILLANCE OF SEROLOGICAL, CLINICAL AND LABORATORY FEATURES OF IMPORTED DENGUE....61
The Antwerp Fever Study....62
www.fevertravel.ch: a website for evaluation in travel/tropical medicine and for dissemination and online feasibility study. Present status....64

6th TropNetEurop Workshop
Brescia, October, 1st-2nd, 2005

Workshop Minutes

Participants

The workshop was joined by 31 participants from 11 countries.

Bartolini Alessandro	Firenze		Jelinek Claudia	Berlin
Behrens Ron	London		Kapaun Annette	Heidelberg
Bisoffi Zeno	Verona		Manzardo Christian	Barcelona
Black Finn Trunk	Aarhus		Matteelli Alberto	Brescia
Boecken Gerd	Kronshagen		Mühlberger Nick	Berlin
Bouchaud Olivier	Bobigny		Müller Yolanda	Lausanne
Calleri Guido	Torino		Myrvang Bjørn	Oslo
Castelli Francesco	Brescia		Romi Roberto	Rome
Chiodini Peter	London		Schmid Matthias	Newcastle upon Tyne
Clerinx Jan	Antwerp		Schunk Mirjam	Munich
Ehrhardt Stephan	Hamburg		Siilkamaki Heli	Helsinki
Gascon Joaquim	Barcelona		Soula Georges	Marseille
Genton Blaise	Lausanne		Wichmann Ole	Berlin
Gobi Federico	Torino			
Grobusch Martin	Johannesburg			
Hatz Christoph	Basel			
Hellgren Urban	Stockholm			
Jelinek Tomas	Berlin			

Friday

Alberto Matteelli: Welcome

Tomas Jelinek: Presentation of the network situation (see workshop proceedings)

- Presentation of the functions within the network
- Presentation of the map of sites,still gaps in the map, still try to increase members (47 members)
- Lost two sites (Paris and Leipzig), got two new sites (Kristiansand, Firenze), currently two more interest sites (Paris,Roma)
- Reported patients:8923
- 60% of the sites are now reporting electronically
- Reporting of Leishmaniasis has been agreed upon in 2004 and will commence soon:
    - format is already installed
    - Outbreaks could be detectd (in particular in soldiers)
    - Information on the tretament outcome of miltefosine
- Proposal for a fever study / fever reporting is still pending
    - Early warning system as opportunity for TropNetEurop

- TropNetEurop mailing list:
    - The yahoo server blocks bouncing members, this can be triggered by automatic reply messages (e.g. out-of-office notices). Every member should receive at least two mails per month. If not, the mail address may be blocked – send a query to Tomas Jelinek!
    - Old mails can be accessed by members at: yahoogroups.groups.com/tropneteurop
- TropNetEurop publications:
    - 8 major papers in 2004/2005
    - Eurosurveillance has grown into an interested partner of TropNetEurop
    - Material from TropNetEurop presented at 4 big conferences in 2005
    - The website offers all information about the network
- Clinical disussions at the mailing list are recognised as helpful and interesting but follow-up on cases should be provided by those who start the discussion

Annette Kapaun:

How can we make use of the recent artesunate trial results for our patients in the EU?

- See lancet paper and hand-out
- Results :Parental artesunat will reduce case fatality rate by 1/3
- Problems:GMP standarts are not given in production, EU registration is not expected
- Guilin Pharma will become WHO supplier for Artensunate- future production by GMP?
- Fake problem in Asia - ensure use of quality product!
- Indication: Severe malaria (WHO definitions)
- Chinine is becomming unavailable in Europe- good point for Artesunate use?
- Will Artesunate use transkate in lower case fatality rate in European patients
- A list of safe suplliers should be distributed to members
- Consensus statement by TropNetEurop possible?

Sites already using i.v. Artesunate

- Hamburg
- Aarhus (imported from India)
- London

- Newcastle
- Oslo (from China)

Initial draft of TropNetEurop statement:

- Available data have to be acknowledged and connot be ignored
- TropNetEurop members would use artesunate iv if drug available
- TropNetEurop recommends use of artesuate in complicated falciparum malaria, patients treated that way should be monitored closely
- TropNetEurop recommends replacement of chinine by artesunate for i.v. use
- TropNetEurop recommends use of recongnised/effective poduct (supported by studies) as of currently by Guilin Pharma
- TropNetEurop asks for general distributions/availibility of i.v.. artesunate in Europe (if possible GMP standards)
- TropNetEurop asks national societies to join in the recommendation

Nick Mühlberger: Malaria therapy and hospital time in Europe

See also abstract in the proceedings!

The analysis included 1541 cases. Patient classification, treatment, country of treatment and codisease were found to be independent determinants of inpatient duration in multivariate analysis.

The coice of therapie varied between countries. Treatments involving quinnine were common, although they were associated with significantly longer hospital stay. With 34% longer inpatient duration the greatest difference was found comparing the quinine+sulfa-pyrimethamine combinations to artemeter-lumefantrine treatment. Atovaquone-proguanil and mefloquine treatrment did not differ significantly from artemeteher-lumifrantine.

Hospital stays of patients with uncompliceted malaria in Europe could be reduced by:

- less frequent use of quinine treatment regiments
- harmonisation of European case managment recommendations

Discussion:

- Interaction between factors may need to be re-analysed
- Results reflect rather case management, not effects of malaria therapy
- Outpatient data should be added

Matthias Schmid: UK adult malaria treatment guidelines

See also abstract and flowchart in the workshop proceedings!

The UK is developing guidelines for managment of malaria in aldults. The guidelines (see chart on page 32 in the proceedings) are being agreed between the different societies in the UK.

Discussion:

- malaria can acute without fever
- chest x-ray should not be a must
- use of dipstick tests should be included
- malaria prophylaxes has to be continiued throughout required period

- primaquine should be given as early as possible
- sent further comments to Matthias Schmid!

Roberto Rossi: EDEN Network

EDEN: Emerging Diseases European Network (2005-2009) - Eu funded
Three projects: EDEN Malaria, EDEN Nil and EDEN Leishmaniasis
Objectives:

- to define distributions of Anopheles labranchiae in Central Italy
- to evaluate the infectibiltaet of An. labranchiae

Urban Hellgren: Evidence of primaquine efficacy

See also abstract in the network proceedings!

A total of 7 relevant articels were compared. Results are: after treatment of P.vivax, recrudescence occurs within four to five weeks,while relapse occur later.There is some overlap and in epidemic countries it is not possible to differentiate between relapse, recrudescence and re-infection. The commonly used standard regimen is probably rather ineffective but the true reduction in relapse rate cannot be estimated due to follow up in areas with ongoing transmission. Short-term treatment (i.e.5 days) seems to be less evective than the 14 days standard regiment. Higher dosing might be more effective.

Discussion:

- can TropNetEurop do a randomised clinical trial?
- questionnaire study envisaged as first step

Jan Clerinx: Imported non P. falciparum malaria: a 5 year prospective study in a referral centre

- 98 patients (48 P.vivax, 34 P.ovale,16 P.malariae), confirmed with thick and thin film, antigen test as a parallel test
- observation systematically till 3 months, later patient-triggered reporting
- crude relapse rate: 31 % P. vivax (6 without primaquine), 9% P. ovale, 0% P .malariae
- relapses occured despite standard dosis of primaquine
- the standart dosis of primaquine is insufficient

Discussion:

- what about the primaquine dosis? Should it be higher?
- Study in TropNetEurop envisaged

Christoph Hatz: Experience in use of Malaria Emergency Treatment in Swiss Travellers

- Presentation of two strategies: Chemoprophylaxis and standby emergeny treatment
- Chemoprophylaxis depends on local transmission intensity and personal exposure
- Standby at low or moderate malaria risk
- In Switzerland, no increase in malaria cases since change from prophylaxis to standby
- For India, change in 2005 from prophylaxis to standby

Guido Calleri: Results from the DELPHI study

See also abstract in the workshop proceedings

Questionnairs were sent to all site managers of TropNetEurop
Round #1 distributed 47, returned 30 (64%)

- Most problematic aspects in prescribing malaria chemoprophylaxis are long term travellers and pregnancy
- Most problematic areas are Indian Subcontinent, Far East and South America
- Likely complience was of little relevance
- Efficacy is very importend, much more then costs
- Relative importance of exposure prophylaxis

2nd round: distributed 30 to those who answered 1st round, returned 22 (73%)

- Comparison of response to questionaire #1 and #2 showed a change of the median score in 8 out of 48 questions, showing general option of the group did not change between the two rounds.

Questionaire #3: started a new phase of the study (70 % returned)

- Northern Europaen countries give more prophylaxis then the South.
- Germany and the Swiss give less chemoprophylaxis than anybody else
- Experts had a split opinion on several cases of the questionnaire, no European consenus

Ron Behrens: Uk data on malaria from India

- Despite increased travel to India, incidence of malaria in European travellers has remained unchanged or has even decreased
- Type of journey and duration of stay appear not to have large influence on malaria risk

Initial draft of TropNetEurop statement on malaria chemoprophylaxis for the Indian Subcontinent

- Data on malaria in European travellers do not support the prescription of chemoprophylaxis for the Indian subcontinent.
- TropNetEurop recommends intensive advise on exposure prophylaxis. In addition, carriage of malaria emergency treatment (stand by prophylaxis) should be advised.

Initial draft of TropNetEurop statement on malaria chemoprophylaxis in pregnancy

- Travel to high risk areas for malaria during pregnancy shopuld be discouraged.
- No effective drug is licensed for chemoprophylaxis in pregnancy.
- However, data from South East Asia show no increase of adverse events for mefloquine use in pregnancy.
- If travel is unavoidable, TropNetEurop recommends prescription of mefloquine as chemoporphylactic drug for high risk areas.

Saturday

Tomas Jelinek: Medical Care for migrants in Europe - The Berlin experience

See also abstract in the workshop proceedings on page 37!

Immigrants constitute 9 % of Germanies population and 13% of its capital Berlin.Only limited data were available regarding health status and prevalence of tropical diseases among immigrants.
The high proportion of delayed diagnosis and treatment indicates a significant lack of medical service for immigrants.The lack of an correlation between symptoms and detected infectious disease indicates the need for a standadised routine screening examination in all immigrants.

Christoph Hatz: Immigrants in Switzerland

- 40% of foreigners are living more than 10 years in the Switzerland, 20% are born there
- Nmbers of asylum seekers are decreasing
- Migrants are only checked routinely for Tbc
- Medical care for migrants tends to be more time-consuming
- Rarely written information on migrants history available
- Movement stress: patterns similar if Swiss move from one part of the country to another or if asylum seekers come into the country
- Tbc study in Geneva: Majority of irregular migrants in Geneva with TB are women from S-America and Africa

Alberto Matteellii: Immigrants in Italy

No abstract available

- Approx. 3 million foreign born persons in the county
- Large number of immigrants from Africa and SE Asia
- Pregnancy and delivery is the major reason while migrants come to hospital
- HIV in immigrants is increasing, 2/3 of newly diagnosted HIV patients are coming from foreign countries

Christian Manzardo: Medical care for immigrants in Spain

No abstract are available!

- Majority of immigrants from S-America and Africa , recently significant increase (2% in 2003, 7% in 2005)
- In some areas of Barcelona, 60 % of population are foreigners
- Immigrants can use medical services without charge
- "Community health agents" play a major role in health care delivery
- For VFR´s medcial screening is offered upon return

Ron Behrens: Trend of Importend Malaria in VFR`s to the Uk betwenn 1990 and 2004

See also abstract in the workshop proceedings on page 40!

- Travel to malaria endemic countries increased by 164 % over the last 14 years.Malaria rates among all UK residents including those visiting friends and relatives fell 64%.
- West Africa shows the largest decline. Duration of travel influences the risk per years of exposure per case. Reasons for this decrease are unclear.

Discussion:

- In the VFR group, 70% took no chemoprophylaxis
- Possibly the malaria risk in host countries has decreased?
- VFR´s are now financially much better off than 10 years ago – this may influence travel behaviour and thus malaria risk since they spend less time in rural areas
- Unrecorded self treatment when symptomatic may play a major role in decrease of notified cases
- Speed of malaria diagnosis is still of concern: 53% of the malaria cases where not diagnosed at the first GP visit (in the highest malaria risk area in UK!)
- Malaria diagnosis within the ethic communities may be missed

Dengue Studies I & II

See also abstracts in the workshop proceedings pages 41 to43!

Ole Wichmann

Dengue study within the network since August 2003, 10 member sites are participating so far. In a first analysis, a total of 97 probable and confirmed cases of acute dengue infections were reported between 8/03 and 12/04. Most infections were acquired on the Indian Subkontinent and SE Asia.

Discussion:

- Relationship betweenpositive touniquet test and rush?
- Dengue from African countries is increasing. As yet, only seen in caucasians.

Joaquim Gascon

Collaborative study between Spanish network and several TropNetEurop sites. Out of 80 patients having a suspected dengue, 71 were finally classified as a acut dengue fever. PCR results collected from travellers allow us to detect changes in serotype epidemiology. This model can serve as a sentinel system for dengue fever. A map showing the global distribution of dengue serotypes is being made (as yet, only serotype 3 in S-Amerika, serotype 1 in East Africa). Dengue from Africa was confirmed by PCR. The descripotion of new genetic lineages and their circulation and spread can contribute to the acquistion of dengue epidemiological data worldwide.

Martin Grobusch: European Observational Multicentre Study: Therapy of Uncomplicated Falciparum Malaria

See also abstract in the workshop proceedings!

2nd year of recruitment, 11 centres in 4 countries have joined, with now roughly 200 cases recorded in the database. A presentation of the accumulated data was given.

Yolanda Mueller & Blaise Genton: Web-based guidelines for the evalluation of fever in reurning travelers and migrants : promotion and appropriateness for the primary care physician (www.fevertravel.ch)

See also abstract in the workshop proceedings

Fever upon return can be caused by diseases that are rapidly fatal if left untreated.The differential diagnosis is wide. Physicians often lack the necessary knowledege to approproiately take care of such.
A website for GP´s has been created: www.fevertravel.ch .
The group is looking for more participants. European guidelines are envisaged. Travel medicine spezialist from different countries who work in collaboration with primary care or emergency physicians are welcome to act as reference centres.
Study on website use: automatic recording of the pathway the physician took, in order to find out which guidelines are often used and wich are not. Since study initiation, 161 physicians have been registered. 74 % of the physicians found the guidelines useful.

Discussion:
Website could be helpfull for GPs, but often no interest
Website is free of charge
Could this website be used for a fever study?

MISSION AND GOALS OF TROPNETEUROP

- to maintain a collaborative network of European professionals dealing with imported infectious diseases;

- to create European consensus for clinical guidelines for diagnostic and therapeutic procedures in imported infectious diseases;

- to identify emerging pathogens by sampling returning international travellers, immigrants, and foreign visitors;

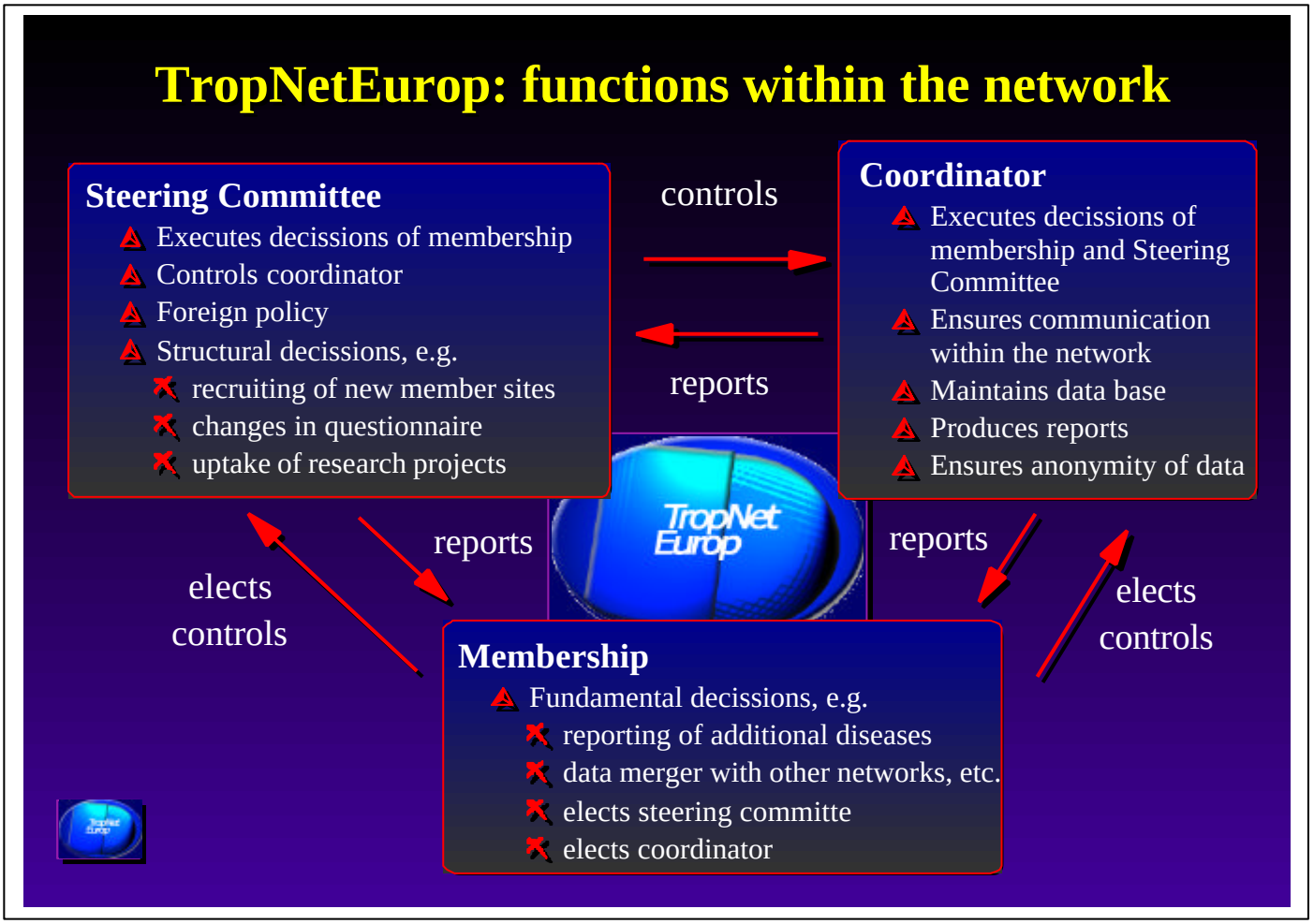
- to add information and accuracy to the current, divergent European systems of disease notification;

- to provide grounds for cluster investigation and intervention strategies by Public Health authorities;

- to provide the basis for permanent research collaboration of infectious disease centres in Europe

TROPNETEUROP: RULES & REGULATIONS

1. Membership only by clinical sites, no minimal number of patients
2. Exclusion criteria for members need to be defined, steering committee also decides on inclusion
3. Management structure: every site has one site manager and one vote (only when submitting data!)
4. Steering committee: five members including one network coordinator(elected for two years)
5. Regular meeting of membership every year necessary
6. All members decide on fundamental issues regarding the network
7. Members should decide on steering committee work at annual meetings:
   steering committee submits questions, proposals to all members, reviews research proposals
8. Network coordinator manages day-to-day work
9. Data are owned by all reporting members
10. Publication of results: all site managers of reporting sites are named as co-authors (in order of number of reported patients). TropNetEurop should always be mentioned. All publications go through review by steering committee.
11. Ownership of funds: though network infrastructure should be financed, funds will be managed by members that applied for them



CURRENT SITUATION OF TROPNETEUROP

TropNetEurop has started in April, 1999 with few selected members of TropMedEurop, the European Association for Tropical Medicine. From the beginning, support has been surprisingly strong and it has been very easy to recruit new member sites. TropNetEurop covers now 12% of all malaria patients in Europe and probably a similar percentage of patients diagnosed with dengue fever and schistosomiasis. The network has broadened its scope in membership with including sites who are not active in TropMedEurop and is now uniting many European centers of excellence in imported infectious diseases. After a major consolidation phase during the second half of 2000, when several inactive members opted to join the mailing list "friends & observers" rather then participating in the reporting system, recruitment of new member sites has continued. TropNetEurop wishes to interest all major European "centers of excellence" on Imported Infectious Diseases. Currently, the network has 51 members sites.

	N	%
Member Sites	51	100.0
Sites reporting electronically	28	54.9
Reported Patients	9890	100.0
Patients reported electronically	2857	28.9
Reported Diagnoses	9917	100.0
Malaria	7698	77.6
Schistosomiasis	1127	11.4
Dengue	1037	10.5
Leishmaniasis	55	0.6

Member sites of TropNetEurop:

No	Institution	Site Director
1.	Department of Infectious Diseases, Aalborg Hospital, Aalborg, Denmark	Dr. H. Nielsen
2.	Department of Infectious Diseasesand Tropical Medicine, University Hospital of Aarhus, Skejby Hospital, Aarhus, Denmark	Prof. F.T. Black
3.	Prins Leopold Instituut voor Tropische Geneskunde, Clinical Services, Antwerp, Belgium	Dr. J. Clerinx
4.	Sección de Medicina Tropical, Hospital Clinic, Barcelona, Spain	Dr. J. Gascon
5.	Unitat de Malalties Tropicals, Importades i Vacunacions Internationales, Institut Català de la Salut, Barcelona, Spain	Dr. J. Gómez i Prat
6.	Swiss Tropical Institute, Basel, Switzerland	Dr. C. Hatz
7.	Centre for tropical medicine and imported infectious diseases (CTID), Division of infectious diseases, Medical Dept., Haukeland University Hospital, Bergen, Norway	Dr. K. Mørch
8.	BerlinCenter for Travel & Tropical Medicine, Berlin, Germany	Dr. T. Jelinek
9.	Medizinische Klinik mit Schwerpunkt Infektiologie, Charite/Campus Virchow-Klinikum, Berlin, Germany	Dr. T. Zoller
10.	Consultation de médecine tropicale, Hôpital Avicenne, Bobigny, France	Dr. O. Bouchaud
11.	Médecine interne et Maladies tropicales, Hôpital St André-CHU, Bordeaux, France	Prof. DJM Malvy
12.	Bradford Royal Infirmary, Infection and Tropical Medicine, Bradford, UK	Dr. P. McWhinney
13.	Clinica di Malattie Infettive e Tropicali, Universitá di Brescia, Italy	Dr. A. Matteelli
14.	Surgeon General's Department, Army Medical Directorate, FASC Camberley, UK	Dr. A. Green
15.	Consulta de Medicina do Viajante, Departamento de Doenças Infecciosas, Hospital Universitário, Coimbra, Portugal	Prof. S. da Cunha
16.	Department of Infectious Diseases M 5132, University of Copenhagen, Denmark	Dr. I. Gjørup
17.	Tropical Medical Bureau, Dublin	Dr. Graham Fry
18.	SOD Malattie Infettive e Tropicali, Azienda Ospedaliero-Universitaria Careggi, Firenze, Italy.	Dr. A. Bartoloni
19.	Institute of Maritime and Tropical Medicine, Gdynia, Poland	Prof. A. Kotlowski
20.	Bernhard-Nocht-Institut für Tropenmedizin, Hamburg, Germany	Prof. G. Burchard
21.	Tropenmedizin, Abteilung Tropenhygiene und Offentliches Gesundheitswesen, Universitatsklinikum Heidelberg, Germany	Dr. A. Kapaun
22.	Helsinki University Central Hospital, Dpt. of Medicine, Div. of Infectious Diseases, Helsinki, Finland	Dr. H. Siikamaki
23.	Epidemiological Services, Military Medical Academy, Hradec Kralove, Czech Republic	Prof. J. Beran

Member sites of TropNetEurop (continued)

No	Institution	Site Director
24.	Sorlandet Hospital, Kristiansand, Norway	Prof. S.G. Gundersen
25.	Travel Clinic, Policlinique Médicale Universitaire, University of Lausanne, Lausanne, Switzerland	Dr. B. Genton
26.	Dept Infectious Diseases, Section Travel Medicine, Leiden University Medical Centre, Netherlands	Dr. L.G. Visser
27.	Universidade Nova de Lisboa, Instituto de Higiene e Medicina Tropical, Lisbon, Portugal	Dr. J. Atougia
28.	Hospital for Tropical Diseases Travel Clinic, London, UK	Dr. R. Behrens
29.	Microbiologia Clinica, Ctra. de Meco, Alcala de Henares, Madrid, Spain	Dr. J. Cuadros
30.	Tropical Medicine & Clinical Parasitology Unit, Infectious Diseases - Microbiology Department, Hospital Ramon y Cajal, Madrid, Spain	Prof. R. Lopez-Velez
31.	Hospital Carlos III, Instituto de Salud Carlos III, Madrid, Spain	Dr. S. Puente
32.	Division of Infectious Disease, Fundación Jiménez Díaz, Madrid, Spain	Dr. M. de Górgolas
33.	Centre de Formation et de Recherche en Médecine et Santé Tropicale, Faculté de Médicine, Marseille, France	Dr. G. Soula
34.	Department of Infectious Diseases & Tropical Medicine, University of Munich, Germany	Dr. M. Schunk
35.	Centro per le Malattie Tropicali, Ospedale S. Cuore, Negrar (Verona), Italy	Dr. Z. Bisoffi
36.	Department of Infection & Tropical Medicine, Newcastle General Hospital, Newcastle-upon-Tyne, UK	Dr. M.L. Schmid
37.	Department of Infectious Diseases, Ullevaal University Hospital, Oslo, Norway	Prof. B. Myrvang
38.	Service de Parasitologie, Hôpital Tenon, Paris, France	Dr. M. Develoux
39.	Department and Clinic of Tropical and Parasitic Diseases, Karol Marcinkowski University of Medical Sciences, Poznan, Poland	Dr. M. Paul
40.	3rd Dep. of Infectious and Tropical Diseases, First Faculty of Medicine of Charles University in Prague, Czech Republic	Prof. Pavel Chalupa
41.	INMI L. Spallanzani, Rome, Italy	Dr. P. Ghirga
42.	Central Hospital of Rogaland, Stavanger, Norway	Dr. Åse Berg
43.	Karolinska Hospital, Department of Medicine, Unit of Infectious Diseases, Stockholm, Sweden	Prof. A. Björkman
44.	Karolinska Institute, Division of Infectious Diseases, Huddinge University Hospital, Stockholm, Sweden	Prof. U. Hellgren
45.	Osp. Amedeo di Savoia, Div. "A" Malattie Infettive, Torino, Italy	Dr. Guido Calleri
46.	University Hospital of Tromsø, Norway	Dr. JB Christensen

Member sites of TropNetEurop (continued)

No	Institution	Site Director
47.	Institut für Tropenmedizin, Eberhard-Karls-Universität Tübingen, Germany	Prof. J. Knobloch
48.	Clinc of Infectious Diseases, University of Udine, Italy	Dr. A. Beltrame
49.	Sektion Infektionskrankheiten, Universität Ulm, Germany	Prof. P. Kern
50.	Kaiser-Franz-Josef-Spital der Stadt Wien, 4. Medizinische Abteilung mit Infektions- und Tropenmedizin, Vienna, Austria	Dr. H. Laferl
51.	Missionsärztliche Klinik, Würzburg, Germany	Dr. G. Stich

TropNetEurop: Members and Patient Encounters

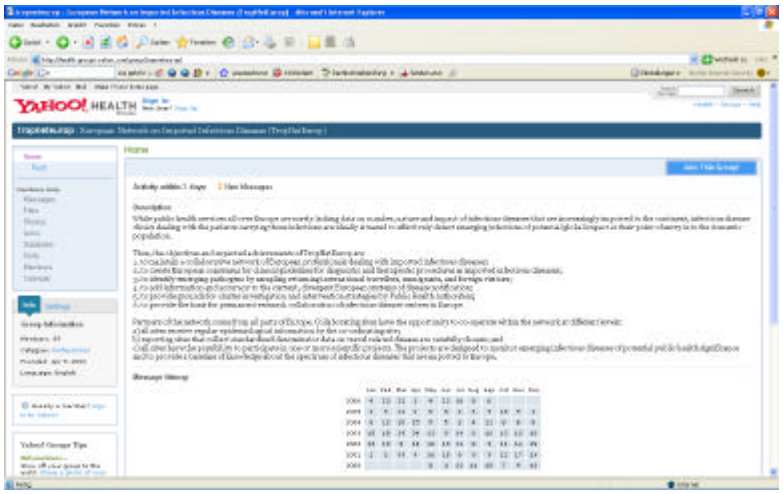
Nº	Town	Site Manager	In- and outpatients [per year]	Pre-travel advises [per year]
1.	**Aalborg**	H. Nielsen	100	200
2.	**Aarhus**	F. T. Black	350	800
3.	**Antwerp**	J. Clerinx	7700	12000
4.	**Barcelona – Hospital Clinic**	J. Gascon	1400	6000
5.	**Barcelona - Drassanes**	J. Gòmez i Prat	6000	12000
6.	**Basel**	C. Hatz	2500	10000
7.	**Bergen**	K. Mørch	50	600
8.	**Berlin - BCRT**	T. Jelinek	1000	10000
9.	**Berlin - Charite**	T. Zoller	400	0
10.	**Bobigny**	O. Bouchaud	500	0
11.	**Bordeaux**	JMD. Malvy	500	12000
12.	**Bradford**	P. McWhinney	150	0
13.	**Brescia**	A. Matteelli	400	30
14.	**Camberley (UK Armed Forces)**	A. Green	0	0
15.	**Coimbra**	S. da Cunha	50	800
16.	**Copenhagen - CMP**	I. Gjørup	300	2000
17.	**Dublin**	G. Fry	1200	12000
18.	**Firenze**	A. Bartoloni	250	0
19.	**Gdynia**	A. Kotlowski	100	200
20.	**Hamburg**	G. Burchard	5000	5000
21.	**Heidelberg**	A. Kapaun	1400	6000
22.	**Helsinki**	H. Siikamaki	300	0
23.	**Hradec Králové**	J. Beran	300	2000
24.	**Kristiansand**	S. G. Gundersen	50	0
25.	**Lausanne**	B. Genton	300	12000
26.	**Leiden**	L.G. Visser	200	2800
27.	**Lisbon**	J.V. Costa	400	3100
28.	**London**	R. Behrens	5000	8000
29.	**Madrid - Principe de Asturias**	J. Cuadros	100	75
30.	**Madrid - Ramon y Cajal**	R. Lopez-Velez	550	0
31.	**Madrid - Carlos III**	A. Benito	450	0
32.	**Madrid - Jiménez Díaz**	M. de Górgolas	100	200
33.	**Marseille**	J. Delmont	2500	3000
34.	**Munich**	M. Schunk	1700	13000
35.	**Negrar (Verona)**	Z. Bisoffi	2000	1500
36.	**Newcastle**	M. Schmid	1500	300
37.	**Oslo**	B. Myrvang	1500	5000
38.	**Paris**	M. Deveroux	1500	6500
39.	**Poznan**	M. Paul	100	350
40.	**Prague**	P. Chalupa	600	500
41.	**Rome**	P. Ghirga	100	200

TropNetEurop: Members and Patient Encounters (continued)

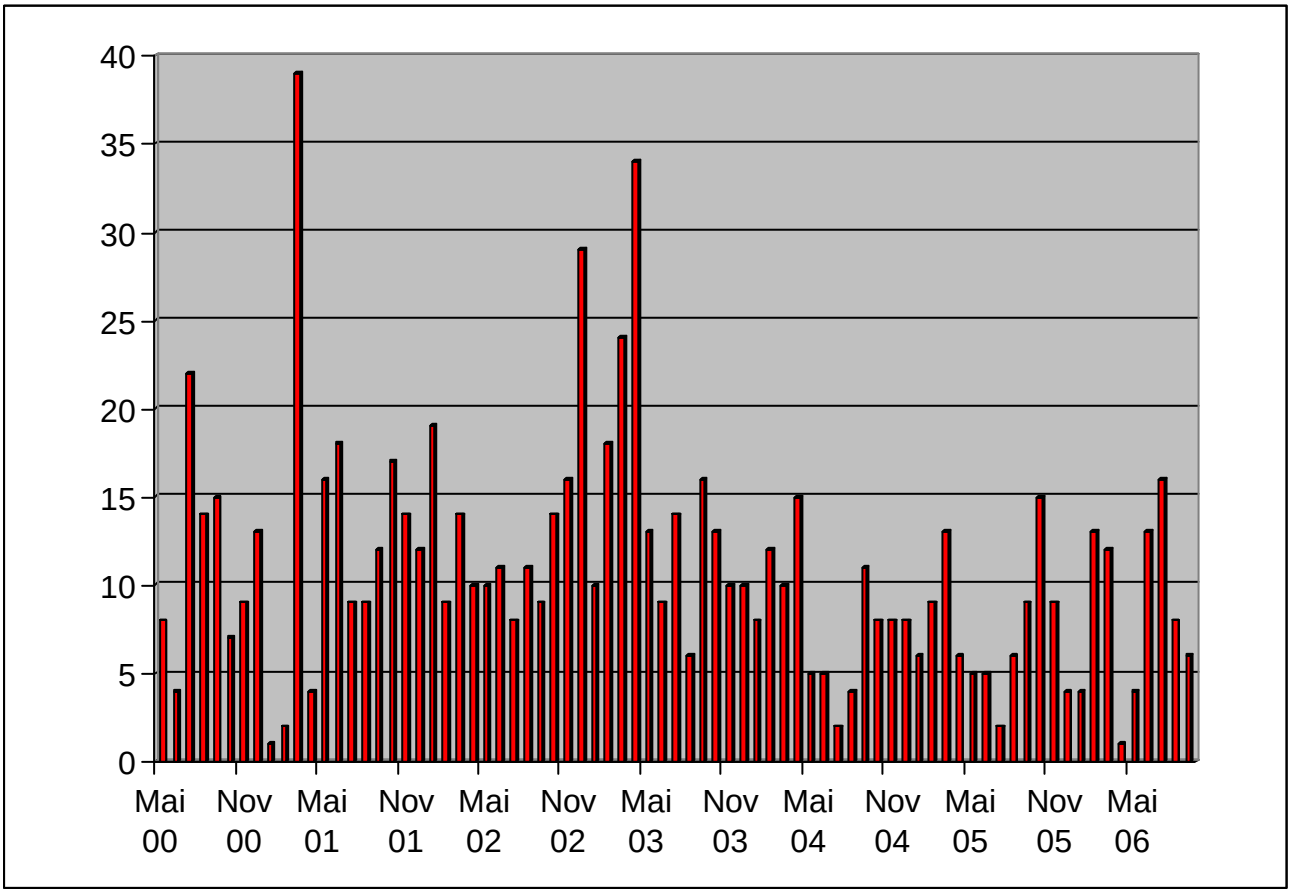
42.	**Stavanger**	A. Berg	100	0
43.	**Stockholm - Karolinska**	A. Björkman	1500	15000
44.	**Stockholm - Huddinge**	U. Hellgren	400	15000
45.	**Torino**	C. Galleri	800	2000
46.	**Tromsø**	J. B. Christensen	50	300
47.	**Tübingen**	J. Knobloch	1000	6000
48.	**Udine**	A. Beltrame	200	0
49.	**Ulm**	P. Kern	1000	2500
50.	**Vienna – KFJS**	H. Laferl	450	0
51.	**Würzburg**	G. Stich	300	450
	TOTAL		**54400**	**189405**

COMMUNICATION

a) The Mailing List



The TropNetEurop mailing list is managed by the coordinator. Primarily for reasons of convenience, a group list at Yahoo!.com has been chosen for this purpose. All mailings to TropNetEurop go through this group servers and have been approved by the coordinator. The list server cannot be accessed by non-members. Only selected messages are forwarded to the outside by the coordinator. The list is one of the most valuable features of TropNetEurop, enabling all members to communicate rapidly in an exclusive setting.



b) Monthly Reports

Monthly reports on accumulated and analysed data have been mailed on (almost) monthly basis since April, 1999. Outfit and content of the reports have changed, feedback was overwhelmingly positive. TropNetEurop members receive the reports as WinWord-files which is supposed to make use of the graphics in lectures and presentations easy. Every figure can be copied to any presentation programme (such as PowerPoint) and modified for further use. In the same way as data in the data base are owned by all TropNetEurop members, so are reports and their content. Members can use the material without further permission, yet acknowledgement of the network is encouraged.

c) Recently published material:

- Jelinek T. Intravenous artesunate recommended for patients with severe malaria: position statement from TropNetEurop. *Eurosurveillance Weekly* 2005 Nov 24;10(11)
- Weitzel T, Mühlberger N, Jelinek T, Schunk M, Ehrhardt S, Bogdan C, Arasteh K, Schneider T, Peyerl-Hoffmann G, Fätkenheuer G, Boecken G, Zoller T, Probst M, Peters M, Weinke T, Gfrörer S, Klinker H, Holthoff-Stich M-L. Imported Leishmaniasis in Germany 2001-2004. Data of the SIMPID sentinel network. *Eur J Clin Microbiol Infec Dis* (2005) 24:471-476.
- Gascon J, Mayor A, Mühlberger N, Peyerl-Hoffmann G, Oliveira, Dobano C, Jelinek T, Corachan M. Molecular epidemiological surveillance of markers for antimalarial drugs in Plasmodium falciparum isolates imported to Barcelona, Spain. *Med Clin (Barc)* (2005) 125:286-289
- Jelinek T, Mühlberger N. Surveillance of Imported Diseases as a Window to Travel Health Risks. *Infect Dis Clin North America* 19 (2005) 1-13
- Behrens RH, Bisoffi Z, Björkman A, Gascon J, Hatz C, Jelinek T, Legros F, Mühlberger M, P Voltersvik. Malaria prophylaxis policy for travellers from Europe to the Indian Sub Continent. *Malaria J* 5 (2006) 7
- Jelinek T. Importation of falciparum malaria from Thailand: should current recommendations for chemoprophylaxis be adapted? *Eurosurveillance Weekly* 11 (2006) 6

d) Material submitted:

- Wichmann O, Gascon J, Schunk M, Puente S, Siikamaki H, Gjørup I, Lopez-Velez R, Clerinx J, Peyerl-Hoffmann G, Sundøy A, Genton B, Kern P, Calleri G, de Górgolas M, Mühlberger N, Jelinek T. Clinical and laboratory spectrum of dengue infections imported to Europe. J Infect Dis (submitted)

Severe Malaria: Artesunate Use in Europe

Results of a TropNetEurop survey (date: 19/10/05)

Country	**Artesunate use**	**Dosing**	**Manufacturer**	**Procurement**
Austria	No			
France	No			
Germany	No			
Italy	No			
Spain	No			
Switzerland	No			
Sweden	No			
UK	Yes (London and Newcastle)	2.4mg/kg (Newcastle)	Guilin no. 2 Pharmaceutical Factory, Guangxi, China	London: IDIS World Medicines URL: http://www.idispharma.co.uk/ Mail: idis@idispharma.com

Oct, 31st, 2005

Intravenous artesunate for treatment of patients with severe malaria: position statement of TropNetEurop

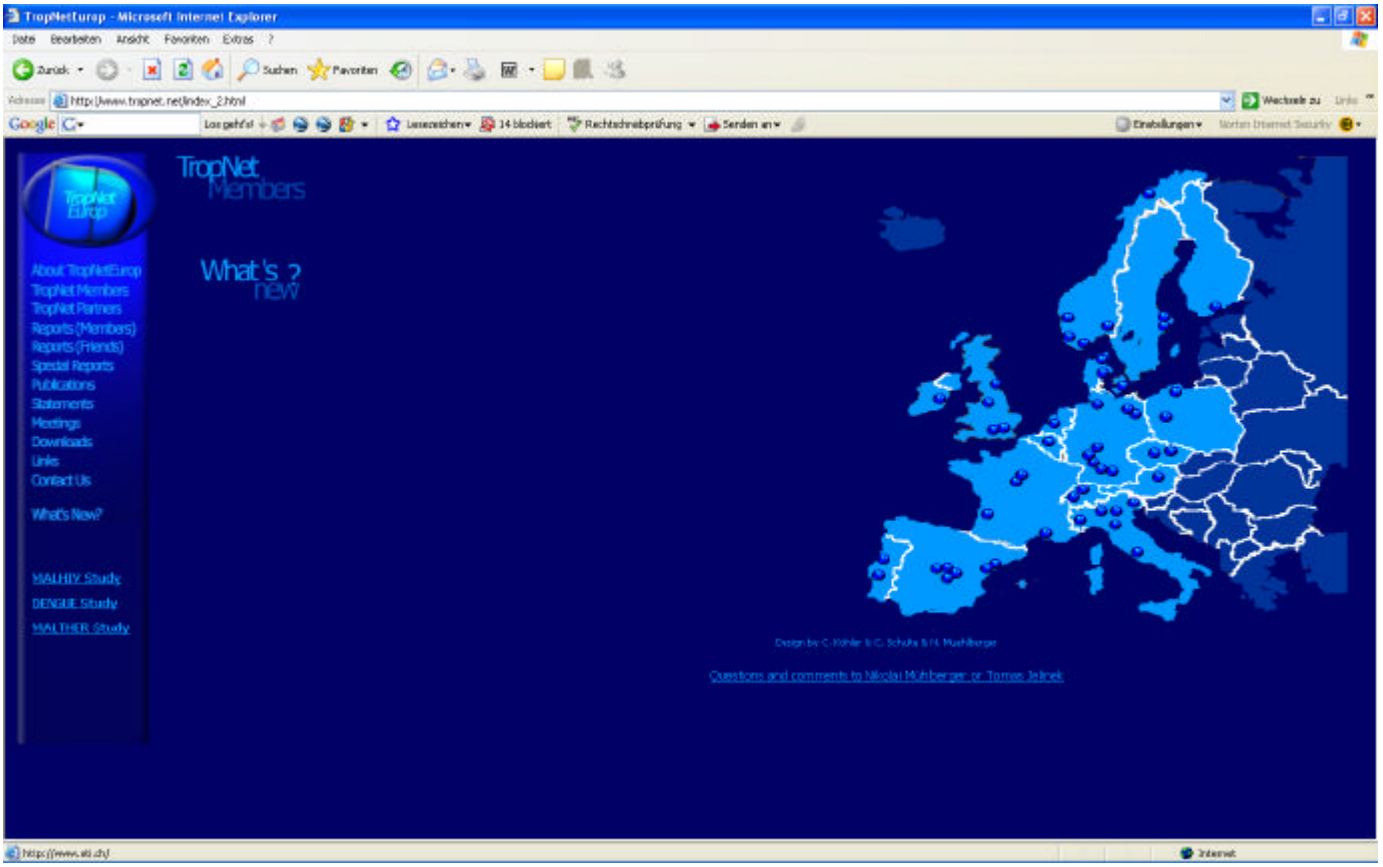
Severe falciparum malaria is an acute emergency with a very high case fatality rate, if left untreated. The condition warrants immediate onset of therapy with the most rapidly effective drug regimen possible. Quinine, the current drug of choice in Europe and the only licensed antimalarial for i.v.-use, is becoming increasingly unavailable. Thus, the survival of malaria patients is severely threatened due to supply problems.

Recent studies have shown a clinical advantage for use of i.v. artesunate versus i.v. quinine in patient survival and reduction of adverse events in severe malaria. A meta-analysis of recent work in Asia showed a highly significant mortality odds ratio of 0.57 in favour of treatment with i.v. artesunate. In the largest study of this series, mortality was reduced from 22% in patients treated with i.v. quinine to 15% in those receiving i.v. artesunate (Lancet 2005; 366:717-25). In view of optimal patient care, published data warrant the immediate use of i.v. artesunate. Unfortunately, there is currently no product available that is produced under GMP-conditions. The product that has been used in all recent studies was provided by Guilin Pharmaceutical Factory N^{o} 2, Guangxi, People´s Republic of China.

TropNetEurop recommends the application of i.v. artesunate in patients with severe malaria despite the unresolved issue of lacking GMP standards of the currently available artesunate formulation. A GMP-manufactured product of this drug should be introduced and distributed in Europe as soon as possible. The quality of the product used should be confirmed by international studies. Quality controls of single batches should be available. TropNetEurop will be monitoring patients who have received this drug.

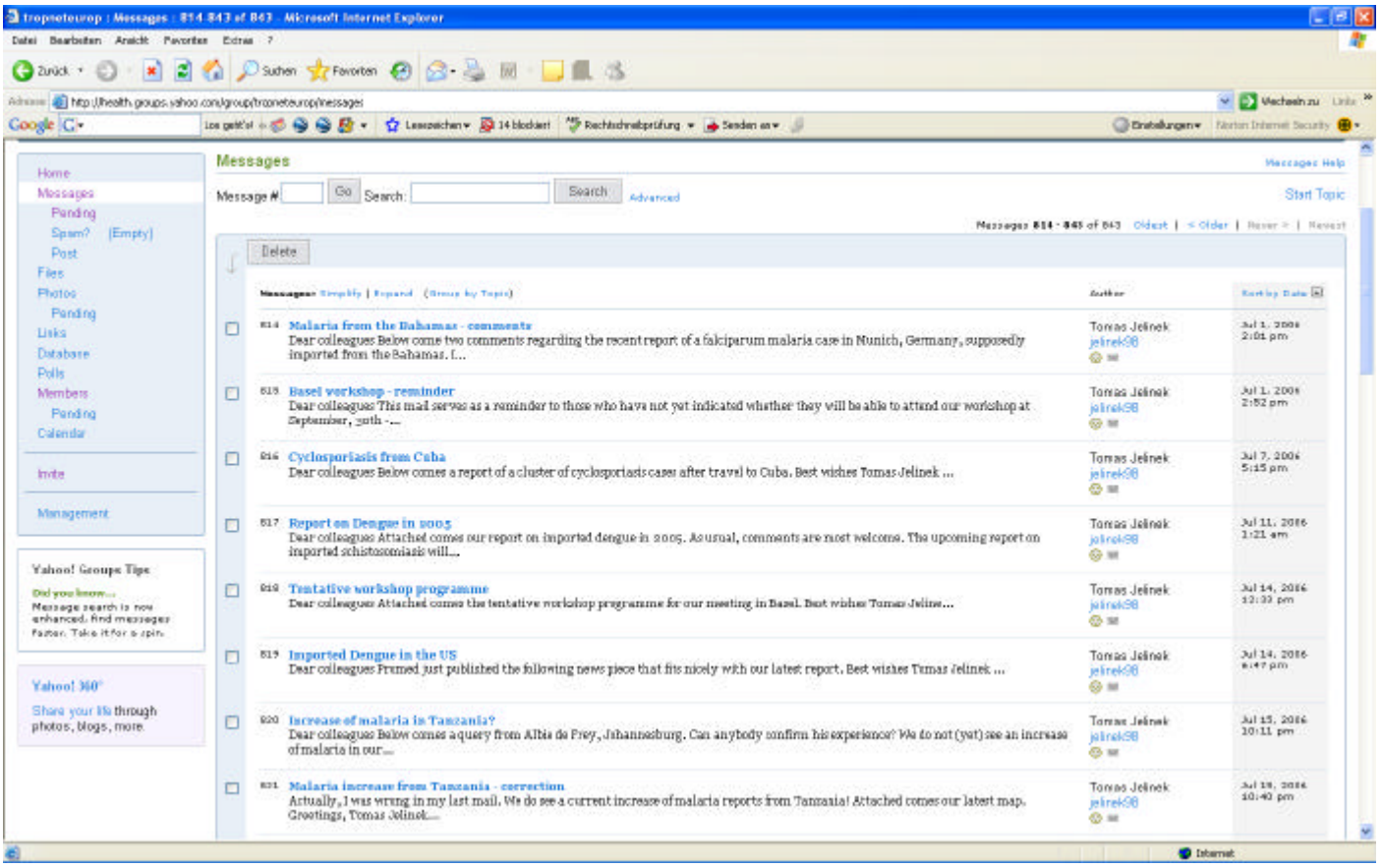
c) The Web Site

The TropNetEurop web site can be accessed by everybody at **www.tropnet.net**. The site provides basic information on the network and its members, offers contacts to the coordinator and the members and informs about recent reports and "sentinel events". A password protected area for members only gives access to all reports of TropNetEurop. We do not monitor access numbers to the web site, but feedback has been predominantly positive. The award-winning site has been created by Clemens Schulte and is now managed by Nikolai Mühlberger.



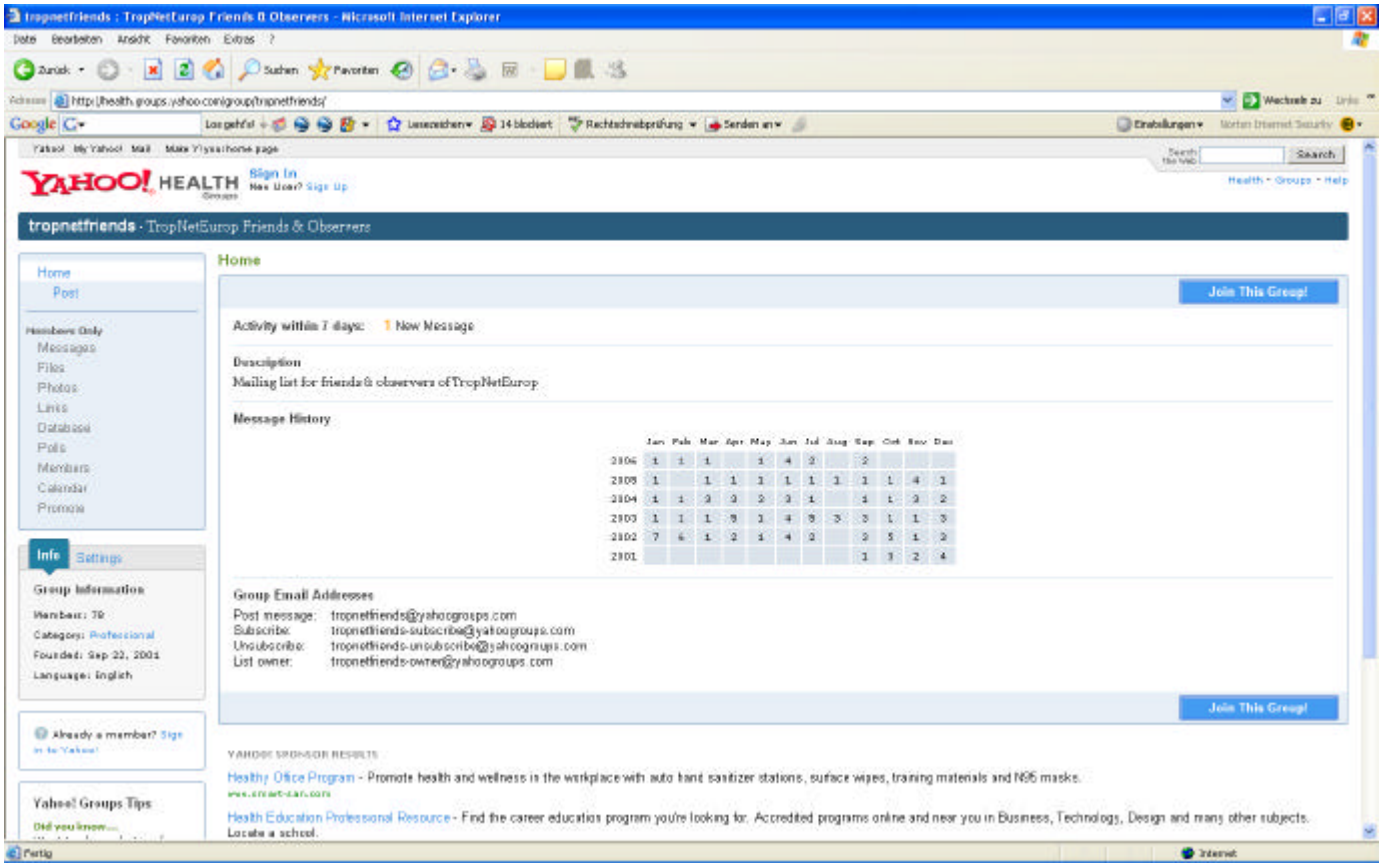
d) Special Reports and "Sentinel Events"

The extremely high level of awareness for "sentinel events" of all network members has ensured several impressive successes of TropNetEurop. The latest example is the description of a cluster of dengue fever in Thailand. TropNetEurop is contacted by several national public health agencies for information on disease activity and has formed a permanent collaboration with the German Robert Koch Institute.



e) Friends & Observers

Following increasing demand, a second TropNetEurop mailing list had to be created. This list is targeting all interested medical staff, that are not able or willing to participate actively at TropNetEurop. It also aims to include public health staff in Europe, at WHO and in countries that are visited by European travellers. This list is managed by the network coordinator and is not open for discussion. Currently it has 71 members. Feedback has been overwhelmingly positive and close contacts to several recipients have developed. This has led repeatedly to the notification of "sentinel events" through members of this mailing list to TropNetEurop.



f) Publications about the Network

- Karen Ross. Tracking the spread of infectious diseases. EMBO reports Vol 7 No 9 2006; 855-858

Surveillance Questionnaire for Imported Infectious Diseases (TropNetEurop)

(Fax to +49-30-36802844, att. Dr. T. Jelinek)

Clinic ID	Patient ID	Date Initial Visit (DD/MM/YY)	ÿ Inpatient / ÿ Outpatient	Inpatient days	Sex	Date of birth (DD/MM/YY)
		/ /			M F	/ /

Country of birth	Country of residence	Citizenship	If born outside Europe, give date of first arrival	(DD/MM/YY)
				/ /

HISTORY OF RECENT TRAVEL
List, in order, journeys to all countries relevant for this visit, and indicate most likely country of infection by checking

Trip Duration (number of days)	Trip Ended (DD/MM/YY)
	/ /

1.	ÿ	**4.**	ÿ
2.	ÿ	**5.**	ÿ
3.	ÿ	**6.**	ÿ

Detailed information on likely place of infection (town, area):

Pre-Travel counselling by health care provider? ÿ Yes ÿ No ÿ Don't know

Malaria Chemoprophylaxis: ÿ None ÿ Chloroquine ÿ Proguanil ÿ Mefloquine ÿ Doxycycline ÿ Atovaquone/Proguanil ÿ Other:

Compliant ÿ Yes ÿ….No

Patient Classification

- ÿ Immigrant / Refugee
- ÿ Foreign visitor
- ÿ European, lives/works in Europe
- ÿ European, lives/works outside Europe (urban)
- ÿ European, lives/works outside Europe (rural)

Reason for most recent travel

- ÿ Tourism
- ÿ Visiting Relatives/Friends (VRFs)
- ÿ Business
- ÿ Immigration
- ÿ Research / Education
- ÿ Missionary/Volunteer/ Humanitarian
- ÿ Military
- ÿ Other

Chief complaint (CHECK ALL THAT APPLY)

- ÿ Asymptomatic Screening

Or:

- ÿ Fever
- ÿ Fatigue
- ÿ Skin
- ÿ Respiratory
- ÿ Headache
- ÿ Lymphadenopathy
- ÿ Musculoskeletal
- ÿ Diarrhoea
- ÿ Vomiting
- ÿ ENT
- ÿ Genitourinary
- ÿ Neurologic
- ÿ Psychologic
- ÿ Other:

Date of symptoms onset: (DD/MM/YY) / /

DIAGNOSIS AND TREATMENT	1. Notification Dx	2. Notification Dx	3. Notification Dx
Working Dx			
Final Dx			
How was Dx achieved? [1]	P D A SP M G C O	P D A SP M G C O	P D A SP M G C O
Treatment (1. drug)			
Treatment (2. drug)			
Treatment (3. drug)			
Treatment (4. drug)			

[1] ***Diagnostic Procedures:*** *P=Pathogen detection D=DNA detection A=Antigen detection SP=Antibody increase in serum pair (IgM or IgG) M=IgM detection G= IgG detection C=Clinical reasoning O=Other*

Accompanying Diagnoses: **1.** _____ **2.** _____ **3.** _____

COMPLICATIONS? ÿ Yes ÿ No If Yes, which? _____

DEATH? ÿ Yes ÿ No If Yes, why? _____

TropNetEurop Questionnaire for Additonal Data on Malaria Patients with HIV (TropNet MALHIV-Study)

Fax together with surveillance report of same patient to +49-30-36802844, att. Dr. T. Jelinek. In case of electronic reporting, please fill in TropNet/SIMPID ID assigned by your Sentry Software.

CLINIC ID	TropNet/SIMPID ID: (Fill in, if malaria case has been reported electronically)	Patient ID: (Fill in, if malaria case has been reported on paper)
	/ . . / : :	

Parasitemia measured on consecutive treatment days of malaria treatment (%):					
Day 0:	Day 2:	Day 3:	Day 7:	Day 14:	Day 28:
Thrombocyte count measured on consecutive days of malaria treatment (billion/l):					
Day 0:	Day 2:	Day 3:	Day 7:	Day 14:	Day 28:
Treatment failure: ÿ Yes ÿ No					

HIV-Parameters measured before, during and after malaria episode: (please fill in measurements and dates)			
CD4 count (n/µl)		**HIV Viral load (copies/ml)**	
Last before malaria:	**DATE:** / /	**LAST BEFORE MALARIA:**	**DATE:** / /
Lowest during malaria:	**DATE:** / /	**LOWEST DURING MALARIA:**	**DATE:** / /
First after malaria:	**DATE:** / /	**FIRST AFTER MALARIA:**	**DATE:** / /
Lowest count ever:	**DATE:** / /	**HIGHEST LOAD EVER:**	**DATE:** / /

Year of initial HIV-Diagnosis:		
AIDS-defining events: ÿ Yes ÿ No	**If yes, please check applying ICD10 categories:**	
B20	Human immunodeficiency virus [HIV] disease resulting in infectious and parasitic diseases	ÿ
B21	Human immunodeficiency virus [HIV] disease resulting in malignant neoplasms	ÿ
B22; B23, B24	Human immunodeficiency virus [HIV] disease resulting in other diseases or conditions	ÿ

Current antiretroviral therapy (HAART): ÿ Yes ÿ No	If yes, please list current drugs (generic name):
1.	**2.**
3.	**4.**
5.	**6.**
Duration of current HAART (Months):	**Total duration of antiretroviral treatment (Months):**
Current prophylaxis against PCP and Toxoplasmosis (Cotrimoxazol, Sulfadiazin, Daraprim): ÿ Yes ÿ No	

TropNetEurop Questionnaire for Additonal Data on Dengue Patients (TropNet Dengue-Study)

Fax together with surveillance report of same patient to +49-30-36802844, att. Dr. T. Jelinek. In case of electronic reporting, please fill in TropNet/SIMPID ID assigned by your Sentry Software.

CLINIC ID	TropNet/SIMPID ID: (Fill in, if dengue case has been reported electronically)	Patient ID: (Fill in, if dengue case has been reported on paper)
	/ . . / : :	

ELISA
(IgM1 and IgG1 = first serum sample; IgM2 and IgG2 = convalescent sample if collected; Day#= days after onset of fever)

ÿ **PanBio-ELISA** ÿ **other:** ÿ **not performed**

IgM1: U	IgG1: U	Day#(1):	IgM2: U	IgG2: U	Day#(2):

Haemagglutination Inhibition assay (HAI) **(in paired serum samples)** ÿ **not performed**

1st :	Day#(1):	2nd :	Day#(2):	Serotype:

Laboratory measurements:

GOT/ASAT (max): U/l	**DAY#:**	**MAXIMUM HEMATOCRIT: %**	**DAY#:**
GPT/ALAT (max): U/l	**DAY#:**	**PLATELET COUNT (MIN): X10^3/µL**	**DAY#:**
Bilirubin (max): U/l	**DAY#:**	**WBC (MIN): X10^3/µL**	**DAY#:**
Duration of increased liver enzymes in days:		**PROLONGED PTT? ÿ No ÿ Yes (_____-TIMES)**	
Evidence of capillary leakage (hematocrit rises = 20% from baseline or average hematocrit for age, sex and population, or drops = 20% after sufficient fluid therapy, or hypo-albuminaemia, pleural effusion, or ascitis) ÿ No ÿ Yes, when?		**LDH: U/l Day#:**	

Relevant additional history

Duration of fever: days
History of previous dengue infection: ÿ No ÿ Yes, when?
History of previous travel to dengue endemic country? ÿ No ÿ 1-3 times ÿ > 3 times Last trip: years ago
Previous vaccination against ÿ None ÿ Yellow fever ÿ Japanese Encephalitis ÿ TBE **Time between last vaccine and febrile crisis: ÿ <2 months ÿ 2months-2 years ÿ 2-10 years ÿ >10 years**

Relevant additional clinical signs and symptoms

Bleeding disorder: ÿ No ÿ Yes: ÿ petechiae ÿ other skin bleeding ÿ positive tourniquet test
ÿ epistaxis ÿ gum bleeding ÿ GI-bleeding ÿ negative tourniquet test
ÿ others: onset of bleeding disorder:

TropNetEurop - Monitoring of Intraveneous Artesunate Treatment in Patients with severe P. falciparum Malaria

Fax together with surveillance report of same patient to +49-30-36802844, att. Dr. T. Jelinek. In case of electronic reporting, please fill in TropNet/SIMPID ID assigned by your Sentry Software.

CLINIC ID	TropNet/SIMPID ID: (Fill in, if malaria case has been reported electronically)	Patient ID: (Fill in, if malaria case has been reported on paper)
	/ . . / : :	

Pre-treatment criteria of severe malaria:

Artesunate producer:	**Artesunate batch number:**

Treatment regimen including i.v. Artesunate:	First line Treatment? ÿ Yes ÿ No	
Date Day 1= Day of Dx and start of first line Tx (dd/mm/yy) / /	**Body weight**	**kg**

Administered anti-malarial substances		Start of administration	End of administration	Total dose
Drug1:	Artesunate i.v.	Day #	Day #	mg
Drug2:		Day #	Day #	mg
Drug3:		Day #	Day #	mg

Was the treatment course completed? ÿ Yes ÿ No	**if no, why**

Additional/Supportive treatment:

Efficacy of i.v. Artesunate treatment regimen:	Duration of inpatient treatment: days
Parasitemia on day 1: /µl	**Parasite clearance time** (Best estimate)**:** hours
Temperature on day 1: °C	**Fever clearance time** (Best estimate)**:** hours

Complications under treatment: ÿ None ÿ Malaria-related complication ÿ Treatment failure ÿ Bacterial superinfection ÿ Other

Complications - details:

Outcome: ÿ Cure without residues ÿ Cure with residues ÿ Exitus on day

Outcome - details:

Safety of i.v. Artesunate regimen:	Adverse drug reaction suspected? ÿ Yes ÿ No **if yes, specify below**

Adverse drug reaction (Please, fill in one line per suspected ADR)	Day of onset Day #	Day of resolut. Day #	Severity at time point of maximum intensity: mild, no specific medication needed	moderate, specific treatment needed	severe, disabling or life-threatening	Relation with Artesunate: No	Possible	Probable
1.			ÿ	ÿ	ÿ	ÿ	ÿ	ÿ

MALARIA

Die Schweizerische Arbeitsgruppe für Reisemedizin (SAR)

Christoph Hatz, Basel

The Swiss Working Group of Travel Medicine (SAR) was started in 1982 as an independent expert panel on recommendations for travel medicine issues by the two leading travel clinics in Switzerland. Within a few years, the group expanded to its present size of 12 members. Representatives of the major 5 Swiss Travel Clinics (Basel, Bern, Genève, Lausanne, Zürich), of the Federal Office of Public Health, of the Swiss International Airlines, and of the Specialist Societies for Tropical & Travel Medicine and for General Medicine FMH form the core group. In addition, one German and one Austrian member of the respective partner societies plus a member of a computer-based information company (safetravel.ch, tropimed) attend the two meetings every year in spring and autumn with the goal to reach a consensus on rational travel health recommendations and to optimize travel advice given by GPs and specialists in travel medicine. Standardized recommendations are meant to improve the compliance of travellers regarding prevention of infectious and non-infectious health problems abroad. The SAR is an independent, self-funding group providing travel medicine information at national and international level without official or legal status.

Molecular tools for the diagnosis of malaria

Hans-Peter Beck, Molecular Parasitology-Epidemiology, Medical Parasitology and Infection Biology, Swiss Tropical Institute, Socinstrasse 57, CH 4002 Basel, Basel, Switzerland

Microscopy as diagnostic tool is and will remain standard in the diagnosis of malaria. However, certain circumstance or the need for additional information sometimes requires additional techniques. For the precise determination of parasites in particular in samples with scanty or pretreated parasitemia or in mixed species infections species specific PCR are routinely deployed. Monitoring of treatment and distinction of new infections from true recrudescences in drug trials require the genetic identification of individual infections (or parasite broods). This is achieved by the analysis of highly polymorphic and discriminative molecular markers. Several applications also require the precise quantification of parasite numbers and quantitative real time PCR is the technique of choice because of its speed and accuracy.

Because drug resistance has become a major problem in malaria endemic countries the need to determine quickly the genetic profile of drug resistance a micro array based technique has been developed to rapidly analyze drug resistance associated point mutations in order to characterize the possible resistance phenotype of the infecting parasite strain(s).

In this presentation I will briefly review the commonly deployed techniques and will highlight their specific application, benefit, and costs.

The Delphi Study revisited: VFRs

Guido Calleri, Osp. Amedeo di Savoia, Div. "A" Malattie Infettive, Torino, Italy

Introduction

The access of Immigrants who return to their origin Country to visit friends and relatives (VFRs) to medical structures an finally to preventive medicine in western Countries is an important issue not only in historical immigration Countries, like U.K., France and Germany, but in almost all European Countries. The difference in health systems, in immigrant populations and in medical guidelines, as well as the result of our previous questionnaires concerning malaria prophylaxis, which showed important difference in the behaviour of experts in different Countries, induced us to investigate this topic. In VFRs, not only duration of stay, condition of stay, precise destination and season are important determinants of prophylaxis prescriptions, drug toxicity but also previous malaria history, immigration history, trust in European medicine, cost of drugs, convenience, presence of children, have to be taken into account. Thus a high degree of subjectivity is present in prescription, and a wide grey-zone is created. Trials are difficult because of the large numbers requested and the different variables involved. Consequently few data are available in literature. We tried to overcome this defect using the opinion of experts who have been working in this field for long time.

The Delphi approach is a consensus development technique, useful for situations where unanimity of opinion does not exist owing to lack of scientific evidence. Experts' views are explored to enable decisions to be made on best clinical practice. Essential requisite of the method are anonimity, iteration of questionnaires, controlled feedback, and statistical group response.

Methods.

A working group of six experts in travel medicine prepared and discussed questionnaires. These were subsequently administered to all members of Trop Net Europ.

Experts were addressed by e-mail with one questionnaire, composed of two parts. One to identify the different VFRs population observed in different travel clinics, and the most debatable areas of malaria prophylaxis in this perspective:. Experts were asked to give data about their experience (proportion of immigrants among travellers and among malaria cases, area of origin, different approach to VFRs or children) or respond to questions (about problematic situations in prescribing malaria prophylaxis, controversial areas of the world, importance of factors to be considered in prescribing prophylaxis, relevance of different drugs' characteristics and evaluation of available drugs, importance of insect bite prevention in different situations) with a score on a visual scale from 1 to 10. A second part of the questionnaire described 16 possible scenarios of malaria prophylaxis (12 adults and 4 of their accompanying children), and experts were asked about their recommendations on chemoprophylaxis.

Results were in both cases reported on a Microsoft Excel software.

Results and discussion.

Questionnaire n. 1 was sent to all managers of Trop Net Europ network centres (47 centres). 25 questionnaires were returned (53%) and were evaluable. The geographical distribution was corresponding to Trop Net Centres distribution.

Evidences from the first part are described below:

- The risk perception of malaria as well as the accessibility of travel clinics is lower but very variable in immigrants compared to other travellers, probably due to cost and cultural problems.
- 10% (median of visitors of travel clinics are VFRs (range 1-90)
- Most immigrants are from West Africa,
- Experts tend to modify their prescription when they are in front of a VFR, mostly to reduce cost.
- Experts relatively agree in taking into account area of travel, itinerary and underlying pathologies, but no consensus exist on the importance of likely compliance and cultural level of the

traveller, and partly on the duration of the travel. The relative importance of factors is similar to what seen in non-VFRs.

- The most important characteristics of drugs are efficacy and, to a lesser extent, tolerability and convenience. Cost and causal activity are relevant only for a subset of experts, but more than in non-VFRs..

The second part, including 16 practical scenarios. In 12 ceses the consensus was high. The consensus was very poor in 4 cases focusing on repeated travels, India, long stay and multiresistant area. In these case the judgement distribution was influenced by the geographic area of travel clinics.

Malaria prevention policy for travellers to Central and South America. What is the evidence and what should be best practice for malaria prevention?

Ron Behrens, Hospital for Tropical Diseases, London

Following the Delphi analysis of TropNet members by Guido Calleri, the two major areas of discrepancy amongst travel medicine experts were on advice on prophylaxis to travellers to the Indian Subconitinent and to Central and South America. Following our successful deliberation in Brescia last year we agreed a prophylaxis policy for travellers to The Indian sub-continent. A major part of of the evidence used for risk assessment for travellers was the numbers of imported cases of malaria to European countries from the areas of interest. Current malaria national guidelines from the different European countries present at the meeting contributed to the policy making process.

Data provided by National and local surveillance of imported malaria from Countries in Central and South America and data extracted from the literature will be presented to inform the policy making process. Current national recommendations including those from CDC and WHO will be available

Swiss Malaria prophylaxis for Short-term Travellers

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Schweizerische Arbeitsgruppe für Reisemedizin (SAR)*
Bundesamt für Gesundheit

* C. Hatz, Basel, B. Beck, Basel, J. Blum, Basel; *C. Bourquin, Bern, F. Brenneke, Basel, M. Funk, Zürich, *H. Furrer, Bern, *B. Genton, Lausanne, , *B. Holzer, Bern, *L. Loutan, Genève, *P.-A. Raeber, Bern, W. Rudin, Basel, P. Schlagenhauf, Zürich, *R. Steffen, Zürich, *U. Stössel, Zürich
Ausserordentliche Mitglieder der SAR: E. Jeschko, Wien, H.D. Nothdurft, München.

Important facts in brief

Every year 250-350 malaria cases and 1-3 deaths in non-immune travellers are reported in Switzerland.

Key points for malaria prevention and management:

- awareness in endemic regions and after return
- avoid mosquito bites
- compliance with chemoprophylaxis
- in case of fever: immediate diagnosis and therapy

Chemoprophylaxis: in high risk areas, with prevalence of predominant mefloquine- sensible falciparum malaria, either **mefloquine** (Lariam®), **atovaquone/proguanil** (Malarone®) or **doxycycline** (monohydrate) are recommended.

Emergency stand-by-self-treatment (further referred to a 'emergency treatment'): in areas with intermediate or low malaria risk, with prevalence of predominant mefloquine sensible falciparum malaria, **artemether/lumefantrine** (Riamet®), **atovaquone/proguanil** (Malarone®) or **mefloquine** (Lariam®) are recommended.

The importance of exposure prophylaxis should be emphasized.
It is recommended to use mosquito repellents after dusk, especially if outdoor activities are performed. Light-coloured, loose-fitting insecticide-treatedclothing with long trousers and long sleeves are suggested. Sleeping under insecticide treated bed nets or in air-conditioned rooms which are pre-treated with insecticides (knockdown spray) is recommended.

Introduction

Malaria is endemic in more than 100 countries. Every year, more than 125 million individuals travel to tropical or subtropical regions, approx. 1 million from Switzerland. In Europe 10.000 malaria cases are reported annually (1). If the estimated percentage of unreported cases in most of the countries is 40-70%, the actual number of cases is assumed to be between 20.000 and 30.000 (2).

What kind of protective measurers are available?
The complex situation of malaria transmission in various endemic areas requires differentiated recommendations for malaria prophylaxis. Malaria prophylaxis comprises of multiple components. On the one hand the malaria risk can be reduced by compliant exposure prophylaxis. On the other hand drugs for chemoprophylaxis for travels to high risk areas are available. If these substances are taken regular, protective blood concentration can be achieved which suppresses clinical disease after

infection. As a matter of course, this effect can not be guaranteed with absolute safety; therefore clinical malaria can occur in spite of appropriate chemoprophylaxis (11). With "emergency treatment" another measure for malaria prophylaxis is available. Emergency treatment is recommended in regions with intermediate or low malaria risk, if no medical doctor can be reached within 24h in case of fever.

Migrants as a risk group

As in most non-endemic countries, migrants are the biggest risk group in Switzerland (3). It is alarming that especially these people are extremely poorly informed, if they visit their friends and relatives in malaria endemic regions (4).

Delayed clinical malaria presentation

Approx. 90% of the clinical malaria cases occur after the return from endemic regions, most of them within the first two months (5). In up to one out of eight cases severe malaria is developing (6), but the overall percentage of severe cases is below 10%. In Switzerland, 1-3 patients die from malaria every year (7). They are almost exclusively non immune travellers, who get infected in Africa and who perform none or insufficient chemoprophylaxis and/or in whom the diagnosis is delayed due to variable reasons.

In the past 8 years approx. 300 malaria cases have been registered per year at the "Bundesamt für Gesundheit"(8). The actual number is estimated to be approx. 600 imported cases (9). In spite of an increasing number of tourists who travel to endemic areas, the number of malaria cases is slightly decreasing. The reason could be a lower grade of exposure. On the other hand it could be also due to insistent information from health care professionals and media to improve the individual malaria prophylaxis measures. Standardised recommendations are known to improve the travellers' compliance (10).

Epidemiology

The highest infection risk - especially for the dangerous falciparum malaria- exists in certain endemic regions (see graph) of tropical Africa (sub-Saharan Africa, Yemen), Oceania (e.g. Papua New Guinea and the Solomon Islands) and South America (Surinam, Guyana). The transmission risk is usually low at an altitude above 2000 meters (12). Most of the cities in Asia (except India) and Latin America are free of malaria. In vitro- and in vivo-resistance against almost all malaria drugs which are used for chemoprophylaxis and therapy is found in South-East-Asia. High level chloroquine resistance of P. falciparum is reported from all (except Central America) endemic areas. Increasing chloroquine resistance of P. vivax (tertian malaria) occurred in Oceania and in certain regions of Asia and South America. Rare cases of malaria, in spite of chemoprophylaxis with mefloquine, atovaquone/proguanil and doxycycline are documented.

Most of the severe and fatal cases, which have been imported to central Europe, have been acquired in Africa. Up-to-date numbers of malaria incidence are internationally scarcely available (13). On the basis of older data (1993) the infection risk for Eastern Africa is estimated 1%/month and 2-3% for Western Africa (14). Sero-epidemiological surveys (circumsporozite-antibodies) assume an even higher infection risk (15) The infection risk for most of the Asian and Latin American destinations is regarding to estimations 5-500 times smaller.

Strategy

When counselling for malaria in the travel clinic, the following four elements should be included:

1. Risk awareness that malaria infection is possible
2. Exposure prophylaxis
3. Malaria chemoprophylaxis (medication suppressing clinical symptoms)
4. Immediate diagnosis and therapy (in case of fever with suspected malaria: consultation of a medical doctor or emergency treatment, followed by a visit at a health facility for further work-up)

The following chapters describe a procedure on how short-term tourists and migrants who travel to endemic regions are counselled in Switzerland. Thereby the actual epidemiologic malaria risk and the possible possible side effects of antimalarial medication are weighed against each other. The expected compliance of the tourist is also included in the considerations. The standardized consultation of Swiss travellers, which should also include the kind and frequency of side effects helps to avoid misunderstandings and insecurity and therefore reduces poor compliance. Attention should be paid in particular to migrants ("visiting friends and relatives, VFR"). These individuals, who travel for short time to their country of origin, should get the same recommendations for malaria prophylaxis as the non-immune Swiss population (16).

In case of particular individual risk (e.g. trekking for several days in high risk rural areas) at regions, where usually emergency self-treatment is recommended, a chemoprophylaxis may be discussed and recommended in special cases.
The „Schweizerische Arbeitsgruppe für Reisemedizin (SAR) und das Bundesamt für Gesundheit (BAG)" can change the recommendations ad-hoc when special epidemiological facts require a change from emergency treatment to chemoprophylaxis or vice versa.

The following recommendations are valid for short term travellers, i.e. trips lasting up to three months. A special consultation must always be performed in long-term travellers, pregnant and lactating women, newborns, individuals with known allergies to anti- malaria drugs and immune-compromised persons.

Exposure prophylaxis

A good protection against mosquito bites with physical or chemical measures is advisable in all malaria endemic regions. The importance of malaria prophylaxis other than drug medication by means of mosquito protection should be emphasized to every traveller. The efficacy of various measures has been proven in numerous tests or studies (17).

The female anopheles mosquito, the vector of malaria feeds at dusk and at night. In high risk areas a maximum of three percent of the mosquito population is infected.
The mosquitoes can localize their victims on the basis of movement and the colour of their clothing from a distance of up to 100 meters. Light colours are less attractive for female mosquitoes than dark ones. From close-up range, besides their ability to track heat sources, their sense of smell is very effective, which helps them to detect carbon dioxide which is excreted by lungs and via the skin, and an unknown number of other substances like lactic-, hexane- and other acids which are also excreted via the skin.
The proportion of attracting and repelling scents of the transpiration will define the natural attractiveness of the individual.

How can you protect yourself?

Insecticide-trreated bed nets (ITN, e.g. with a synthetic pyrethroid) will protected the people using it and their direct surrounding very effectively for 3 or more months. ITNs are the measure of choice for newborns in perambulators, not only at home, but also outdoors. It is important to choose the appropriate mesh size (1x 1.2 mm). Air-conditioned rooms were proven to have a protective effect

one study (18). Rooms can be pre-treated by the use of insecticides (knock-down sprays) before the air conditioning is switched on. Mosquito screens at doors and windows provide additional protection, especially if pre-treated with insecticides.

Long protective clothing is recommended, but one has to pay attention that the fabric is densely woven and that the textiles are loose-fitting.
The protective effect can be increased by the application of insecticides, mostly on the basis of pyrthoids (e.g. Nobite Kleidung®, Tyra-X®, Biokill®)
Most repellents (see below) are not appropriate to apply on clothing. Their repellent effect is lower on clothing than on skin due to their mode of action.

Repellents (substances which keep away mosquitoes), are applied on exposed skin, If all exposed parts of the body are treated, they enhance the protection against mosquito bites.
Their mode of action is not fully identified. Recent studies have confirmed ongoing speculations that the repellents interfere with the mosquito's sense of orientation.
Apparently there is an interaction between the repellent and the victim's perspiration.
Furthermore, the repellent creates a "repellent cloud" in combination with the human heat radiation.

What kinds of repellents are available?

Of all the repellents, diethyl-benzamid (known as DEET, maximum concentration in Switzerland 30%), dimethylphtalate (DMP; maximum concentration 20%), ethyl-butyl-acetylamino-propionate (EBAAP IR3535), p-menthane-3.8-diol (PMD) as well as hydroxyethyl-isobutyl-piperidin (Icaridin, previously Picaridin, resp. Bayrepel) are the most effective and best documented active agents.

Repellents should be applied before performing outdoor activities. Caution with sensitive skin and infants! In general the usage is only recommended in children older than two years. In the US, DEET products with a concentration of maximum 10% are approved by the Food and Drug Administration (FDA) for children older than 6 months.
None of the thousands of products available can guarantee a protection rate of 100%.
Unpublished field studies in Tanzania have shown that the protection in a tropical-humid environment lasts -due to sweating only 2-3 hours. (C. Hatz, unpublished observations).

Light-traps and acoustic methods have no protective effect. Electrical devices are – due to unreliable power supply in tropical countries problematic.
No study could so far show a significant protecting effect of the intake of vitamins (Vit. B-complexes); this can therefore not be recommended.

Chemoprophylaxis (table 1, 2)

Definition

Chemoprophylaxis is the regular intake of a malaria drug to suppress the symptoms of the disease. The intake of the commonly used drugs starts before the departure and is continued -depending on the substance- until one to four weeks after the return from a risk area.

What is the effect of a chemoprophylaxis?

Chemoprophylaxis doesn't provide an absolute protection from malaria. The clinical manifestation of the disease can be prevented in most cases; especially in falciparum malaria. In rare cases malaria symptoms can occur weeks to months after the discontinuation of the chemoprophylaxis. This is especially true for relapses of tertian (*P. vivax, ovale*) malaria. The drugs which are used for

chemoprophylaxis have no or only a very limited effect on the liver stages of these two parasites. Chemoprophylaxis itself has only an insufficient effect on vivax malaria (19). Though the first onset of symptoms of this infection can be prevented by regular chemoprophylaxis, relapses after weeks to months are possible due to persistent parasites within the liver cells (hypnozoites).
Chemoprophylaxis can't be continued over months after returning from endemic areas, therefore further episodes of the disease are possible. An exact diagnosis, including species identification is necessary to treat liver stages with the appropriate medication.

Drugs for Chemoprophylaxis

Chemoprophylaxis is recommended in areas with high infection risk for falciparum malaria (Africa, certain regions of Oceania und South America). Presently available drugs for chemoprophylaxis include mefloquine (Lariam®, weekly), atovaquone/ proguanil (Malarone®, daily) and doxycycline (different monohydrate products, 100mg daily).

The decision, which of the drugs for chemoprophylaxis will be recommended is made of an individual evaluation on the basis of the criteria mentioned in table 2.

Mefloquine, Atovaquone/Proguanil or Doxycycline are recommended.

Mefloquine (Lariam®)
No serious side effects were detected in a group of American Peace Corp Volunteers after an intake period of up to 3 years (23). Long-term observations have shown that a regular intake with a weekly dose of 250 mg, even for several months doesn't lead to an accumulation of the drug. A reduction of the weekly dosage is not recommended, because a protective drug level can not be guaranteed (24). Side effects are reported in 12-90% (21). The incidence of severe neuro-psychiatric side effects is up to 1/ 10.000 (25). Most of the side effects (78%) occur during the first three intakes (26). There is no negative influence on the driving ability or the diving fitness, for those individuals who tolerated mefloquine well (27).

Contraindications (epilepsy or psychiatric disorder in the medical history) must be ruled out before prescribing mefloquine. Traveller need be informed about possible side-effects and should be counselled what to do in case of their occurrence.

Some experts recommend to subdivide the weekly dosage (e.g. for females < 60 kg: 2 x ½ tablets on days 0 and 3 of the week) to enhance tolerability. However pharmaco-kinetic facts do not exist on this regimen.

Atovaquone/Proguanil (Malarone)
This combination therapy was established in recent years for the purpose of chemoprophylaxis (28). As doxycycline described below, it has significantly less side-effects than mefloquine (22). Atovaquone/proguanil works as a causal prophylaxis against P.falciparum by killing liver stages of the parasite. Therefore, it has the advantage that the duration of intake is reduced to theperiod from one day before departure until 7 days after leaving the endemic area. Side-effects are mainly gastrointestinal disturbances.
According to experts, it should only be prescribed to a maximum of 3 months (in the US unlimited). In Switzerland, the high prize of Malarone® has to be considered.

Doxycycline
The third drug registered for chemoprophylaxis is doxycycline-monohydrate (various products are available in Switzerland). It is taken on a daily basis from 1-2 days pre-travel to 4 weeks after return. The most common side-effects include phototoxic skin reactions, aphthae, gastrointestinal

disturbances and vaginal mycosis. The drug is contraindicated in children younger than 8 years and pregnant women. According to experts, it should only be prescribed for a maximum of 6 months.

Due to known resistance to mefloquine in the Thai provinces of Trat and Tak, and with special risk exposure (extreme overnight-trips outside larger settlements at the border to Myanmar, Lao and Cambodia) doxycycline or atovaquone/proguanil (Malarone®) is recommended for chemoprophylaxis.

Due to the following reasons, the combination of chloroquine/proguanil is no longer prescribed with the exception of very few special situations, as for example in the first three months of a pregnancy for women who do not tolerate mefloquine.

(1) The world-wide resistance to chloroquine/proguanil has increased dramatically. Therefore, these drugs – with the exception of Central America and Hispaniola- are insufficient.
(2) The compliance of the drug intake is unsatisfying.
(3) The range of side-effects is high when compared to the one of the other three drugs.(22)

Primaquine (30 mg/day) is also an effective drug for the chemoprophylaxis (29). It is contraindicated during pregnancy and in individuals with glucose-6-phosphate-deficiency due to the fact, that it can induce methaemoglobinuria or haemolytic anaemia. Primaquine is not registered in Switzerland.

Artemisinin derivates are not recommended for chemoprophylaxis (12). The intake of mono-substances is especially dissuaded because it can lead to resistance to artemisinins. Furthermore, the very short half-life of artemisinins is unfavourable in respect of chemoprophylaxis.

All drugs should be taken after a meal.

Possible problems of chemoprophylaxis

For multiple reasons, many travellers don't take their drugs for chemoprophylaxis correctly. The problem of non-compliance is associated with bad experience during former trips, the obliviousness of the travellers, poor pre-travel information, side-effects of the drugs – or the mere fear of side-effects (20). In some cases the reluctance not to use malaria chemoprophylaxis is deliberate.
The majority of individuals who take malaria chemoprophylaxis have no noteworthy side-effects. 25% of the travellers who take mefloquine have side-effects and 12 % are impaired in their daily activites (21). Only 1-3% have major side-effects requiring medical help. In 1/10.000 cases, severe side-effects occur and hospitalization is necessary. Usually the drugs are also well tolerated by children and the elderly. Females have a significant higher risk to experience side-effects, especially when taking mefloquine. Travellers with young infants, pregnant women and travellers with pre-existing diseases have to be counselled individually. (See section "special situations").

Why aren't there any globally binding recommendations?

The chemoprophylaxis recommendations for short-term travellers are not worldwide standardized.
That is due to the following reasons:

- Not all of the drugs are available in the different countries
- The drug- resistance of *Plasmodium falciparum* and partly also of *Plasmodium vivax* is spreading worldwide. The recommendation are not adapted equally fast in all the countries
- Due to a lack of prospective, randomized, controlled studies regarding the infection risk, most of the recommendations are not –or only insufficient evidence-based.

- Legal considerations are the reasons why in certain countries for recommending chemoprophylaxis even for trips to very-low-risk malaria areas. This is to protect the prescribing physician from compensation claims in case of clinical malaria in the traveller.

A Specialist (Tropical institutes, Travel clinics, Tropical Medicine doctors) should be consulted for travels to destinations of the beaten track (e.g. trekking at the Thai border)

Overweight

Individual dose adjustment is necessary for overweight (>90 kg) travellers (see table 1). Concerning this matter, information is scarce and no pharmaco-kinetic data are available in the literature. Experts recommend at prescribe mefloquine at 1.5 tablets/ week for bodyweight > 90 kg and 2 tablets/ week for > 120 kg (e.g. on days 1 and 3 of the week).
The manufacturers provide no recommendations for atovaquone/proguanil and doxycycline in overweight subjects. However, an increased daily dose should be considered for those drugs.

Additional emergency treatment is not usually prescribed for short-time travellers to regions where malaria chemoprophylaxis is recommended

Caveat

Strictly advise against:

- The purchase of malaria drugs in endemic regions. Counterfeits, i.e. drugs without or with only an insufficient amount of the active substance, are the role rather than the exception in many countries.

- The intake of homoeopathic substances for chemoprophylaxis or therapy. There is no evidence of the efficacy of such products against malaria. Faith in these substances can be perilous, which could be demonstrated in Switzerland several cases.

Emergency Stand-by Self-Treatment (Emergency treatment; Table 3, 4, 5)

Emergency treatment is a lifesaving action. The most important factors for surviving falciparum malaria are early diagnosis and immediate and effective therapy (30). The main purpose of an emergency treatment is to gain time before medical help can be reached, and to prevent severe or even fatal malaria.
If the parasites are sensitive to the drug, a complete elimination can be achieved during the parasites reproductive cycle. If the parasites are partly resistant, the reproduction can at least be suppressed and therefore a severe course of the infection can be prevented. A medical check for the assessment after emergency treatment is mandatory and the traveller must be duly informed about seeing a medical professional at the earliest tim possible. In Switzerland and Germany, emergency treatment is recommended for trips to regions with low or intermediate malaria risk. This strategy is recommended when the infection risk is lower than the risk of severe drug side effects.
Good information by the consulting doctor and personal responsibility of the traveller are essential for the correct handling of emergency-self-treatment.
The guidelines for the application of the emergency-self-treatment should be discussed thoroughly with the traveller, to make sure that in case of fever the correct action will be taken:

1. In case of fever (sudden onset or rapidly progressive) -body temperature in the axilla > 37.5°C (oral, tympanal or rectal >38°C) - a doctor should be seen and a malaria blood test should be performed. A working thermometer is essential in the tropics.
2. If no doctor can be seen within 24h and the traveller…
3. is in an endemic region for at least 6 days

4 the fever should be lowered
5. the malaria emergency medication should be taken with adequate amounts of fluid
6. in every case, also after the intake of the malaria drug a doctor must be consulted at the earliest possible time.

Which drugs are available for emergency treatment?

Artemether/Lumefantrine, Atovaquone/Proguanil or Mefloquine are recommended (Table 3, 4)

The high effectiveness and the well tolerability of both new malaria drugs Artemether/lumefantrine (Riamet®) and Atovaquone/Proguanil (Malarone®) have been demonstrated in various studies. However, study data regarding non-immune patients are still limited (31).

Artemether-Lumefantrine (Riamet®) (ALT) is a fixed combination of Artemether 20 mg and Lumefantrine 120mg. Artemether leads to a very fast decrease of parasite density and of fever (32). It is one of the fastest acting malaria drugs. The most common side-effects are headache, anorexia, abdominal pain, vertigo and insomnia.
A QTc prolongation in the ECG occurs in less than 10% of the patients and is not clinically significant.

Atovaquone-Proguanil (Malarone®) (APT): The treatment of adults consists of the daily intake of 4 tablets for 3 days. The common side-effects are abdominal pain, headache, vomiting, nausea, diarrhoea und cough.

The extensive experience with mefloquine, (Lariam® was licensed in 1986) has proven safe although rare neurotoxic side-effects occur. There are few data available about the tolerability of the emergency drug among non-immune persons. On the basis of available data regarding malaria therapy, it can be assumed that the incidence of neurological side effects is 60 times higher with mefloquine than with any other malaria medication (25).

The advantages and disadvantages of the three drugs for malaria emergency treatment in areas with mefloquine-sensitive falciparum malaria are listed in table 5.

Chloroquine is not sufficient for emergency treatment except for Central America (to the west of the Panama Canal) and Hispaniola.

Quinine/ doxycycline or clindamycine are no longer recommended for malaria emergency treatment due to their side effects and the complicated regimen (7 days). Halofantrine (Halfan®) is contraindicated for the emergency treatment, because of documented deaths resulting of tachyarrhythmia due to substantial QTc-prolongation.

An individual dose adjustment in case of overweight is necessary for emergency-self-treatment.

Malaria regions with a minimal risk

Neither chemoprophylaxis nor emergency treatment is necessary in various countries with a minimal infection risk. Exposure prophylaxis and laboratory diagnosis in case of fever is recommended in such areas. However, travellers to the following countries should be informed about the minimal infection risk: Mauritius, Cape Verde, Morocco, Algeria, Egypt (El Fayium), Syria, Turkey, Armenia, Georgia, Tajikistan, Kyrgyzstan, Turkmenistan, Uzbekistan and Korea. The list of these countries will be updated regularly in the Bulletin of the "Bundesamt für Gesundheit" and in 'www.safetravel.ch'.

A malaria vaccine for non-immune individuals will not be available within the next years.

Special Situations

The malaria morbidity and mortality is high during **pregnancy**. Pregnant women should be strictly discouraged from travelling to high risk areas. In many countries (e.g. USA, Canada and France), Mefloquine (or Atovaquone/Proguanil) is already recommended for chemoprophylaxis if a journey to high risk areas is inevitable during pregnancy (33). The experience with atovaquone/proguanil is however to scarce to exclude risks. Due to the experience with several hundred pregnant women, who took mefloquine for prophylaxis, it can be assumed that there is no increased risk for malformation or a foetotoxic effect. If the travel is inevitable, mefloquine is recommended during the entire duration of a pregnancy. The other malaria drugs are either contraindicated (doxycycline) or can only be recommended after a strict risk-benefit analysis. Chloroquine (risk category C) can be used, due to good long-time experience, which is however not evidence-based.

Malaria must be ruled out immediately in case of fever in pregnant women and small infants:,. If this is not possible within the recommended time frame, emergency treatment has to be initiated.

Infants:
In case of a febrile illness, a medical doctor should be seen immediately. In small infants, a malaria infection should even be considered in case of a non-febrile illness. Because of the bitter taste of malaria drugs, (table 4) it is advisable to administer the pills grinded with jam, bananas or other kinds of food. Small infants should always sleep underneath an insecticide treated bed net. A long-term and extensive exposure prophylaxis with diethylmethyl-benzamide (DEET)-containing repellents should be avoided because of the danger of a toxic encephalopathy. Repellents in general, haven't been tested in small infants.
Mefloquine can be prescribed for infants (> 5 kg). Atovaquone/Proguanil (Malarone junior) can be used in children > 11 kg body weight.
The concentration of malaria drugs, which are excreted via the mother milk, is not high enough to prevent malaria.

Immune suppressed individuals,
Especially patients after splenectomy and patients infected with HIV (34), have a higher risk to develop severe malaria. Besides chemoprophylaxis, the measures of physical and chemical mosquito protection should be conducted accurately.

Additionally, the increased risk of side-effects for travellers with organ transplants and for HIV-infected individuals has to be considered. Attention has to be paid to possible drug interactions with retroviral combination therapy (35, www.hiv-druginteractions.org). It is advisable to consult the attending infectiologist.

Interactions
Most of the malaria drugs are substrates of cytochromes, especially Cyt3A4. Numerous other drugs are metabolized with the help of cytochromes, therefore a risk for interaction exists. However, because of the short-term intake it is probably irrelevant. Almost all of the malaria drugs reduce the effectiveness of anti-epileptic drugs. Phenobarbital, phenytoin and carbamazepine reduce the bioavailability of doxycycline. Interactions with cardioactive drugs like amiodaron, diltiazem and verapamil exist, however there is no contraindication for the simultaneous intake of malaria medication. It may be advisable to start chemoprophylaxis already a few weeks prior to the trip in patients with long-term medication for chronic diseases and in anticoagulated patients, to detect interactions at an early stage before departure.

Long-term Travellers (> 3 months)

Long-term travellers usually require an exhaustive consultation with a specialist (Tropical institutes, Travel clinics, Tropical medicine doctors). Exposure prophylaxis is to be discussed in detail. The standard procedure consists of a chemoprophylaxis with mefloquine. If well tolerated, mefloquine can be taken over years. Under certain circumstances, emergency treatment can be a reasonable addition or alternative to chemoprophylaxis for long-term travellers.

Procedures in case of suspected malaria in the returning traveller

Malaria symptoms often only occur after the return from the endemic countries. Therefore, the disease has to be included as a differential diagnosis of every fever (> 37.5°C in the axilla) after the return from an endemic region (Africa, Oceania, Asia or Latin America). The first manifestation of clinical malaria can occur more than 6 months (up to 12 months) after exposure in rare cases.

Laboratory diagnosis is performed with the detection of plasmodia in the "thick film" and the species diagnostic is done with the "thin film". The rapid availability of the results is important.

- A reliable result of an experienced laboratory should be available within maximum 12 hours
- If an experienced laboratory is not immediately available, dipstick tests for rapid diagnosis and a differential blood count (exclusion of a high parasitaemia) can be performed in the clinic or in the hospital, while in the meantime 5ml of EDTA-blood is sent to a specialized laboratory.
- If laboratory diagnostics are not available and if malaria is clinically suspected, treatment should be started. As soon as the definite diagnosis from an experienced laboratory is available, therapy can be either completed or discontinued. In case of severe general conditions of the patient, a specialist should be consulted

It has to be considered, that chemoprophylaxis or simultaneous antibiotic treatment can negatively influence the detection of malaria parasites.

Serodiagnosis of malaria antibodies is irrelevant in the acute phase of the disease.

The available malaria rapid dipstick tests, which are based on the enzyme-chromatographic presentation of plasmodium-antigen or parasitic LDH, are not recommended despite high sensitivity. Multiple studies have shown that the majority of the travellers are not able to perform or to interpret the test correctly (37, 38)

Table 1: Malaria chemoprophylaxis: Dosage, indications and contraindications of different drugs (see text)

Drug	Dose	Contraindications (side-effects: SE)	Indications
Mefloquine (Lariam®) Tbl. 250 mg or 5 mg/kg/week	Start: 10 days pre-departure 1 Tbl./week Infants (>5kg): 5-19kg: 1/4 Tbl. 20-30kg: 1/2 Tbl. 31-45kg: 3/4 Tbl.	Contraindication: Epilepsy, depression and psychiatric disorder in the medical history	Sub-Saharan Africa, Papua New Guinea, Solomon Islands, Indonesia (east of Bali); Brazil: (Provinces Rondônia, Roraima, Amapá)
Atovaquone (250 mg) **plus Proguanil** (100 mg) (Malarone®) Tablets for infants: 62.5 mg Atovaquone plus 25 mg Proguanil	Start : 2 days pre-departure 1 Tbl. daily (2 days pre-departure until 7 days after return from malaria region) Infants: 11-20 kg 1 Tbl./day 21-30 kg 2 Tbl./day 31-40 kg 3 Tbl./day	Gastrointestinal disturbances, headache. Rare side- effects can't be excluded, because of insufficient experience Contraindication: Pregnancy and infants < 11 kg	The same regions like mefloquine, extreme travels to South-East Asia; last minute travellers, HIV-patients. (Cave: Interactions with certain antiretroviral substances in vitro)
Doxycycline ***(monohydrate)*** Tbl. 100 mg 1.5 mg //kg/day	Start : 2 days pre-departure 1 Tbl./day Infants > 8 years: 2 mg/kg daily	Contraindication: Infants <8 years, pregnancy	The same regions like mefloquine, extreme travels to South-East Asia
Chloroquine (Nivaquine®) Tbl. 100 mg Base (Chlorochin®) Tbl. 150 mg Base	Start : 7 days pre-departure 1 Tbl./day 1/2 Tbl./day	Contraindication: Distinct psoriasis, CQ-allergy	Trekking in Central America
Primaquine * Tbl. 15 mg Base	Start : 2 days pre-departure 30 mg daily (until 7 days after return from malaria region) Infants: 0.5 mg Base/day	Contraindication: Glucose-6-phosphate-dehydrogenase-(G-6-PD) deficiency, pregnancy	Intolerability of the above-mentioned malaria drugs, after the exclusion of G-6-PD deficiency
Chloroquine (Nivaquine®) Tbl. 100 mg Base 1,5 mg Base/kg/day **plus Proguanil*** (Paludrine®) Tbl. 100 mg** 2 mg/kg/day	Start : 7 days pre-departure 1 Tbl./day Infants 1,5 mg/kg /day plus 2x1 Tbl./day Infants: 3 mg/kg/day < 1 year: 1/4 Tbl. 1-4 years: 2x1/4 Tbl. 5-8 years: 1/2 + 1/4 T. 9-12J.: 2x1/2 Tbl.	Contraindication for chloroquine: distinct psoriasis, CQ-allergy; for proguanil: none known	Indications: Pregnancy during the first trimenon Used in rare cases, if contraindications for other malaria drugs exist.

* At present (January 2006) not registered for malaria chemoprophylaxis.
** Combination (Savarine®) in France available

Table 2

Criteria for the choice of the malaria chemoprophylaxis (MP) drug in regions with predominant mefloquine-sensible falciparum-strains (adult dose)	
Pros	**Cons**
Mefloquine (Lariam®): **For MP (250 mg = 1 Tbl. weekly)**	
- Efficacy (>90%, of all Plasm.) - Safety: Experience with > 30 Mio. travellers - intake schedule (weekly) - cost - no toxic accumulation - Infants (>5kg) and adults as well as during pregnancy	- Neuropsychological side-effects - Impairing SE 11-17% (2-25%); Severe SE 1:13‘600. - Sporadic malaria breakthroughs and increasing *P.f.*-resistance - Interactions (anticoagulants, antidiabetics etc.)
Atovaquone/Proguanil (Malarone®): **For MP (250 mg/ 100 mg = 1 Tbl. daily)**	
- Efficacy> 95% (*P.f.*; *P.vivax*) - causal prophylaxis (*P.f.*): - intake schedule 1-2 days before until 7 days after travel to endemic region - favourable side-effects profile - safety: Atovaquone and Proguanil: known and tested mono-substances	- costs - Interaction with paracetamol, metoclopramide; unknown, rare SE/ interactions? - Infants with >11 kg bodyweight - gastrointestinal side-effects, headaches, aphthae - point mutation in cytochrome b gene: potentially rapid development of resistance - daily intake
Doxycycline monohydrate: **For MP (100 mg daily; Tablets with 200 mg: 1/2 Tbl)**	
- safety - Efficacy (84-98%: *P.f.*) - No known resistance - costs - active against leptospirosis, rickettsiosis - monohydrate-drugs have less GI-SE as doxycycline-hyclates	- photo-toxicity (1,4-10,5%) - vaginal mycosis - contraindicated in children < 8 years, during pregnancy and in breastfeeding mothers - gastro-intestinal SE - development of antibiotic resistance of bacteria - interactions (anticoagulants sulfonylurea, phenytoin & carbamaze-pine, antacids, bismuth, warfarin, contraceptives) - daily intake has to be continued for one month after return

Table 3

Dosage of Emergency-Self-Treatment (Adult-dose)	
Artemether 20 mg/Lumefantrine 120 mg(Riamet®):	2x4 tablets/day x 3 days: 0, 8, 24, 32, 48, 56 hours
Atovaquone 250 mg/Proguanil 100 mg(Malarone®):	4 tablets/day x 3 days: 0, 24, 48 hours
Mefloquine 250 mg (Lariam®):	3, 2, 1 (or 2, 2, 2) tablets: 0, 6, 12 hours

Table 4 – Dosage of Emergency-Self-Treatment for children (number of tablets)

Artemether+Lumefantrine[1,2], 20mg+ 120 mg				Atovaquone/Proguanil[1] 250mg+100mg				Mefloquine[3] 250mg base			Chloroquine[4] 100 mg base			
kg	**Day 1**	**Day 2**	**Day 3**	Kg	**D 1**	**D 2**	**D 3**	Kg	**Hrs. 1**	**Hrs. 6-8**	kg	**D1**	**D2**	**D3**
								5-6	**1/4**	**1/4**	5-6	**1/2**	**1/2**	½
								7-8	**1/2**	**1/4**	7-10	**1**	**1**	½
10-15	**2 x 1**	**2 x 1**	**2 x 1**	11-20	**1**	**1**	**1**	9-12	**3/4**	**1/2**	11-14	**1 1/2**	**1 1/2**	½
								13-16	**1**	**1/2**	15-18	**2**	**2**	½
15-25	**2 x 2**	**2 x 2**	**2 x 2**	21-30	**2**	**2**	**2**	17-24	**1 1/2**	**1**	19-24	**2 1/2**	**2 1/2**	**1**
25-35	**2 x 3**	**2 x 3**	**2 x 3**					25-35	**2**	**1 1/2**	25-35	**3 1/2**	**3 1/2**	**2**
				31-40	**3**	**3**	**3**	36-50	**3**	**2**	36-50	**5**	**5**	**2 1/2**

1. The available data of effectiveness and tolerability in non-immune individuals is scarce.
2. On day one: Tablets in 8 hours intervals, on day two and three in 8-12 hours intervals.
3. The total dose of 25 mg base/kg should be divided in 2-3 doses: 15 mg Base/kg on day one, after 6-24 hours a second dose of 10 mg Base/kg

The total dose consists of 25 mg base/kg divided in 3 doses (the available tablets usually contain either 100 mg or 150 mg chloroquine base)

Table 5

Criteria for the choice of the malaria emergency stand-by self-treatment (MT) drug in regions with predominant mefloquine-sensible falciparum-strains (adult dose)	
Pros	**Cons**
Mefloquine (Lariam®): **For MT (3-2-1 (oder 2-2-2) tbl à 250 mg, 6 h intervals)**	
- safety - long-term clinical experience - effective against all plasmodium species - Infants (>5kg) and adults as well as during pregnancy - short regime (18h) - low costs	- neuro- toxicity (1/216 cases) - increasing *P.f.*- Resistance (SE-Asia >50%) - interactions (e.g. anticoagulans, antidiabetics)
Atovaquone/Proguanil (Malarone®): **For MT (4 tabl/day x 3 days)**	
- Efficacy > 95% (*P.f.*; *P.vivax*) - favourable side-effects profile - safety: Atovaquone and Proguanil: known and tested mono-substances: - effective against multi-resistant falciparum-strains	- potentially rapid development of resistance - Interaction with paracetamol, metoclopramide; unknown, rare SE/ interactions? - only for patients with >10 kg bodyweight, not during pregnancy - GI-SE, headache - intake with food
Artemether/Lumefantrine (Riamet®) **For MT (2x4 tabl/day x 3 days)**	
- Safety - favourable side-effects profile - rapid effectiveness against all plasmodium species - effective against multi-resistant falciparum-strains	- short shelf-life (≤2 years) - unknown, rare SE/ interactions? - not during pregnancy - intake with food

A complete listing of side-effects is found in drug compendiums.

Literature

1. Muentener P., Schlagenhauf P., and Steffen R. Imported malaria (1985-95): trends and perspectives. Bull WHO 1999; 77: 560-566.
2. Kain K.C., and Keystone J.S. Malaria in travelers: epidemiology, disease, and prevention. Infect Dis Clin North Am 1998; 12: 267-284.
3. Angell S.Y., Behrens R.H. Risk assessment and disease prevention in travelers visiting friends and relatives.Infect Dis Clin North Am. 2005 19:49-65.
4. Dos Santos C.C., Anvar A., Keystone J.S., and Kain K.C. Survey of use of malaria prevention measures by Canadians visiting India. CMAJ 1999; 160: 195-200.
5. Leder K., Black J., O'Brien D., Greenwood C., Kain K.C., Schwartz E., Brown G., Torresi J. Malaria in travellers: a review of the GeoSentinel surveillance network. Clin Infect Dis 2004: 39; 1104-1112..
6. Miller S.A., Bergmann B.P., and Croft A.M. Epidemiology of malaria in the British Army from 1982-1986. J R Army Med Corps 1999; 145: 20-22.
7. BAG. Malaria in der Schweiz: In den Jahren 2001 und 2002 erfasste Fälle. BAG Bull 2004; 4: 44-49.
8. BAG. Meldungen Infektionskrankheiten. BAG Bull 1998-2005.
9. BAG. Die Rolle des Meldesystems für die Malaria-Prävention in der Schweiz. BAG Bull 1992; 20: 330-334.
10. Hatz C., Krause E., Grundmann H.J. Travel advice - a study among Swiss and German general practitioners. Trop Med Int Hlth 1997, 2: 6-12.
11. Wichmann O., Betschart B., Löscher T., Nothdurft H.D., von Sonnenburg F.V., Jelinek T. Prophylaxis failure due to probable mefloquine resistant P. falciparum from Tanzania. Acta Trop 2003; 86:63-65.
12. Ryan E.T., and Kain K.C. Health advice and immunizations for travellers. NEJM 2000; 342: 1716-1725.
13. Askling H.H., Nilsson J., Tegnell A., Janzon R., Ekdahl K. Malaria risk in travellers. Emerg Inf Dis 2005; 11:436-441.
14. Steffen R., et al. Mefloquine compared with other malaria chemoprophylactic regimens in tourists visiting East Africa. Lancet 1993; 341: 1299-1303.
15. Nothdurft H.D., Jelinek T., Bluml A., von Sonnenburg F, and Löscher T. Seroconversion to circumsporoite antigen of Plasmodium falciparum demonstrates a high risk of malaria transmission in travelers to East Africa. Clin Infect Dis 1999; 28: 641-641.
16. Bacaner N., Stauffer B., Boulware D.R., Walker P.F., Keystone J.S. Travel medicine considerations for North American immigrants visiting friends and relatives. JAMA 2005; 291: 2856-2864.
17. Croft A. Malaria: prevention in travellers. BMJ 2000; 321: 154-160.
18. Schoepke A., Steffen R and Gratz N. Effectiveness of personal protection measures against mosquito bites for malaria prophylaxis in travelers. J Trav Med 1998; 5: 188-192.
19. Lehky Hagen M., Haley T.J.L., Hatz C. Factors influencing the pattern of imported malaria. J Travel Med 12: 72-79 (2005)
20. Etter H. et al. Malariastudie. Schweiz. Rundschau Med. (PRAXIS) 1991; 80: 72-74.
21. Schlagenhauf P. Mefloquine for malaria chemoprophylaxis 1992-1998: a review. J Travel Med 1999; 6: 122-133.
22. Schlagenhauf P., Tschopp A., Johnson R., Nothdurft H.-D., Beck B., Schwartz E., Herold M., Krebs B, Veit O., Allwinn R. Steffen R. Tolerability of malaria chemoprophylaxis in non-immune travelers to Sub-saharan Africa: a randomised, double-blind, four-arm study. BMJ 2003; 327: 1078-.
23. Lobel H.O. et al. Long-term malaria prophylaxis with weekly mefloquine. Lancet 1993; 341: 848-851.
24. Lobel H.O. et al. Effectiveness and tolerance of long-term malaria prophylaxis with mefloquine - need for a better dosing regimen. JAMA 1991; 265: 361-364.
25. Weinke T., Trautmann M., Held T. Neuropsychiatric side effects after the use of mefloquine. Am J Trop Med Hyg 1991; 45: 86-91.
26. Winstanley P. and Behrens R..H. Malaria prophylaxis with mefloquine: neurological and psychiatric adverse drug reactions. Prescriber's J 1999; 39: 161-165.
27. Vuurman E.F., Muntjewerff N.D., Uiterwijk M.M., van Veggel L.M., Crevoisier C., Haglund L., Kinzig M and O'Hanlon J.F. Effects of mefloquine alone and with alcohol on psychomotor driving performance. Eur J Clin Pharmacol 1996; 50: 475-482.
28. Van der Berg J.D., Duvenage C.S., Roskell N.S., and Scott T.R. Safety and efficacy of atovaquone and proguanil hydrochloride for the prophylaxis of Plasmodium falciparum malaria in South Africa. Clin Ther 1999; 21: 741-749.
29. Schwartz E., and Yochay G.-R. Primaquine as Prophylaxis for malaria for nonimmune travellers: a comparison with mefloquine and doxycycline. Clin Infect Dis 1999; 29: 1502-1506.
30. World Health Organisation. Malaria (chapter 7) In. International travel and health 2005. Geneva: WHO, 2005: 137-139.
31. Hatz C., Nothdurft H.D., Gay F., Gemperli B., Andriano A., Soto J., Genton B. Open-label, uncontrolled multi-center study of the efficacy and safety of Coartem® /Riamet® in the treatment of acute, uncomplicated P. falciparum malaria in non-immune travelers: preliminary results. Proceedings of the XVIth International Congress for Tropical Medicine and Malaria, Marseille 2005; O-144: 65.

32. Hatz C., Abdulla S., Mull R. Schellenberg D., Gathmann I., Kibatala P., Beck H.P., Tanner M., and Royce C.. Efficacy and safety of CGP 56697 (artemether and benflumetol) compared with chloroquine to treat falciparum malaria in Tanzanian children aged 1-5 years. Trop Med Int Health. 1998; 3: 498-504.
33 Anonymous. Santé des voyageurs et recommandations sanitaires 2005. Bulletin Epidémiologique Hebdomadaire (Français), No. 24-25, 2005 (14.6.2005), pp 117-129.
34. Cohen C., Karstaedt A., Frean J., Thomas J., Govender N., Prentice E., Dini L., Galpin J., Crewe-Brown H. Increased prevalence of severe malaria in HIV-infected adults in South Africa. Clin Infect Dis 2005; 41: 1631-1637.
35. Oehler T., Büchel B., Hatz C., and Furrer H.J. Beratung HIV-Infizierter vor Reisen in tropische und subtropische Gebiete. Schweiz Med Wochenschr 2000; 130: 1041-1050.
36. Marx A., Pewsner D., Egger M., Nüesch R., Bucher H.C., Genton B., Hatz C., Jüni P. Accuracy of rapid tests for malaria in travellers returning from endemic areas. Ann Intern Med 142; 836-846 (2005).
37. Funk M., Schlagenhauf P., Tschopp A. and Steffen R. ParaSight F versus Malaquick (ICT) for self-diagnosis of travellers‘ malaria. Trans R Soc Trop Med Hyg 1999; 93:268-272.
38. Jelinek T, Amsler L, Grobusch M., Nothdurft H. Self-use of rapid tests for malaria diagnosis by tourists. Letter Lancet 1999; 354: 1609.

IMPORTED INFECTIOUS DISEASES

Treatment study of uncomplicated malaria: MALTHER

Martin Grobusch[1] and Nick Muehlberger[2]
[1]Infectious Diseases Unit, University of the Witwatersrand, Johannesburg, South Africa
[2]Berlin Center for Travel & Tropical Diseases, Germany

Therapy of uncomplicated falciparum malaria imported into Europe is by no means conducted uniformly. This ongoing prospective, unrandomized, open-label observational study enfolding within TropNetEurop aims to summarize data on the various treatment regimens in Europe in order to make them comparable, to harmonise treatment modalities for uncomplicated falciparum malaria, and to optimise drug treatment strategies amongst participating centres.

Primary endpoints are the rate and severity of adverse events; secondary endpoints are clinical and parasitological cure rates on days 7 and 28; and duration of hospitalisation.

During the meeting, an update on the current data is provided, and modalities for so far non-participating centers still planning to joining in into this study will be discussed.

CHAGAS DISEASES IN NON-ENDEMIC AREAS. THE EXPERIENCE OF BARCELONA

Joaquim Gascon, Hospital Clinic, Barcelona, Spain

Chagas disease is caused by the protozoan *Trypanosoma cruzi* and is an endemic zoonosis in the American continent. Transmission in endemic areas occurs through a triatomid vector that releases excreta infected with the parasite into lacerated skin or mucosa. Other routes are blood transfusion and congenital transmission through infected mothers. Oral transmission has also been described, as well as accidental transmission through contaminated medical material, and organ transplant. Chagas disease, traditionally considered to affect poor people in rural communities, is now progressively invading urban environments. Comprehensive control measures did not start in Latin America until 1980. At that time, 16-18 million people were infected by *T. cruzi* on this continent.
The seroprevalence of *T. cruzi* infection in pregnant women in Latin America varies depending on studies, and ranges from 2% to 51%, with higher rates (80%) in rural areas of Bolivia. At present, it is estimated that approximately 11 million people are infected. Fatal cases are estimated at 25,000–50,000 per year. These vectorial control measures have resulted in a relative increase in vertical transmission of Chagas disease, which may be related to the disease becoming increasingly urban and thus more frequently diagnosed. In Argentina, it is estimated that congenital cases are at least 10 times more frequent than acute cases by vectorial transmission. From de clinical point of wiew, some patients (15-30% of infected people) will develop symptomatic chronic Chagas disease, which frequently leads to cardiac disorders. Excitability and conductivity disorders, leading to cardiac arrhythmias and sudden death, and heart failure are the most threatening complications of this infection. Less frequently, Chagas disease involves the digestive tract. Chagas disease has become an imported disease in Spain, mainly due to the recent economic migration from several countries of Latinamerica to Europe, with Spain being one of the most important receptor country. In Spain, from a total population of 2 million immigrants, 32% are Latin-Americans. Thus with over 600.000 Latin-American people living and working in Spain, the potential for diagnosing *T. cruzi* infections in this country is increasing. Moreover, health care providers in non-endemic areas, like Europe, have little experience in diagnosing and managing *T. cruzi* infection. Few studies of Chagas disease have been carried out in non-endemic countries.
Through the RIVEMTI (Catalan Network on Imported Diseases) we are conducting several studies in Barcelona in order to know: de prevalence of infection in potential blood donors and pregnant women coming from Latinamerica, and consequently, the potential risk for vertical and horizontal transmission in our area; and the prevalence in the migrants from Latinamerica attended in a two specialized clinic unit. Clinical characterization, treatment and follow-up of patients with cardiac complications are other objectives of the study.
Preliminary results show that 0.65% of the latinamerican blood donors are infected by T.cruzi; 2.7% of pregnant women are also infected. We have detected 3 infected newborns. In the two specialized clinical units, 35% (150 patients) of latinamerican patients were positive for T.cruzi infection. Fifteen patients have a chronic chagasic cardiopathy.

Conclusions:
Although triatomids and wild mammals infected with *T. cruzi* are not present in areas outside Latin America, Chagas disease is found in non-endemic countries. Transmission in non-endemic countries can occur through blood transfusions and transplacental and perinatal infections, usually with an asymptomatic course of the disease.
There is no absolute consensus concerning criteria for screening *T. cruzi* in non-endemic countries. In our setting, we consider that screening must include all pregnant women from endemic countries, the potential blood or organ donors from Latin American countries, and any of these citizens that present clinical signs compatible with Chagas´disease or evidence of immunosuppression, such as HIV infection.

The risk of infection for travellers is low, but screening is recommended for those who have lived in rural areas and in poor housing conditions for long periods of time in endemic areas. Early diagnosis and treatment will determine successful outcome in cases of vertical transmission of *T. cruzi* infection. The increase of the Latin-American immigrants in non-endemic countries requires greater epidemiological surveillance, appropriate diagnostic techniques and tools for managing the infection.

PROPOSAL OF A MULTICENTRE TRIAL ON THE TREATMENT OF STRONGYLOIDIASIS, USING SEROLOGY AS A TOOL FOR DIAGNOSIS AND FOLLOW-UP

MARINA BOSCOLO[1], MARIA GOBBO[2], STEFANIA MAROCCO[1], AND ZENO BISOFFI[1]
CENTRE FOR TROPICAL DISEASES[1], AND LABORATORY OF PARASITOLOGY[2], SACRO CUORE HOSPITAL, NEGRAR, VERONA, ITALY

Abstract
Due to its unique autoinfective cycle, *Strongyloides stercoralis (S. stercoralis)* may persist in the host for indefinite periods (1). Most infected individuals are asymptomatic or may present aspecific and intermittent clinical symptoms, and unexplained eosinophilia. However, in cases of immunosuppression, strongyloidiasis may become a disseminated, life-threatening disease (2, 3). Unfortunately, its diagnosis remains a challenge. Given the irregular and often low larval output in uncomplicated infections, the sensitivity of direct stool examination is very poor (4, 5, 6). Furthermore, currently available antiparasitic drugs do not always eradicate the infection. No conclusive trial has as yet established which treatment should be considered as first choice. Ivermectin and thiabendazole are considered of equivalent efficacy, but the former is much better tolerated and should probably be taken as the first line treatment. A randomized trial is being concluded at our Centre, comparing thiabendazole and ivermectin on about 200 patients (unpublished), and failing to find a significant difference of efficacy, while confirming the better tolerability of the latter. Nevertheless, an optimal dosage is still to be determined, and the efficacy of ivermectin at standard dosage (200µg/kg) is sub-optimal. Cases of fatal, disseminated strongyloidiasis in patients previously treated with this regimen have been reported. Empirically, higher dosages have been used/suggested, but with no conclusive evidence. A trial is needed to determine the optimal treatment schedule of this parasite, that is a widespread albeit neglected problem not only in travel medicine (some European countries, including Spain and Italy, are still endemic). A major problem with trials is, precisely, the low diagnostic sensitivity of direct diagnostic methods. A negative test after treatment, even on repeated samples and/or with stool culture, could be a true negative or a false positive, therefore the interpretation would be doubtful. We evaluated the diagnostic accuracy of an Indirect Immunofluorescence Antibody Test (IFAT) for *Strongyloides stercoralis* at different serum titres (submitted). To assess diagnostic sensitivity, sera from 156 patients with known strongyloidiasis were collected. Negative control sera were obtained from a composite group of 427 subjects (blood donors and hospitalized patients). With an area under the Receiver-Operating Characteristic (ROC) plot of 0.98, IFAT showed a high diagnostic accuracy for strongyloidiasis. An antibody titer of = 1:20, with 97% sensitivity and 98% specificity, was identified as the diagnostic threshold with the best overall performance. Cross-reactions were evaluated in 41 additional samples from patients with other known helminth infections, detecting a low-titer IFAT positivity in only one subject with filariasis. A positive IFAT at a dilution of = 1:80, was virtually 100% specific, with 71% sensitivity. To test the usefulness of IFAT as a monitoring tool, the changes in specific-antibody titers after treatment in a group of 155 patients were evaluated. A seroreversion or a decrease by two or more titers were observed in 60% of the patients. Response to treatment was directly correlated to the initial antibody titer and a baseline titer of = 1:80 was identified as the best predictor of response. In conclusion, a positive IFAT at a dilution of = 1:20 is the optimal cutoff for screening. A titer of = 1:80, with virtually no false-positive result, is a reliable cutoff for a serological assessment of treatment efficacy and for inclusion in clinical trials. Based on our findings, we propose a randomized, double blind, multicentre trial with ivermectine at two different treatment schedules for uncomplicated strongyloidiasis: a) 200µg/kg once; b) 200µg/kg for 2 consecutive days, repeated after one week. The case definition for inclusion in the trial will include IFAT serology as well as direct microscopy and stool culture in agar, and a patient will be considered cured if IFAT titre will be diminished by at list two dilutions at 6-month and 12-month follow-up.

REFERENCES

1. Grove, D. I. 1996. Human strongyloidiasis. Adv. Parasitol. 38:251-309

2. Concha, R., W. Jr. Harrington, and A. I. Rogers. 2005. Intestinal strongyloidiasis: recognition, management, and determinants of outcome. J. Clin. Gastroenterol. 39:203-211.

3. Keiser, P. B., and T. B. Nutman. 2004. Strongyloides stercoralis in the Immunocompromised Population. Clin. Microbiol. Rev. 17:208-217.

4. Dreyer, G., E. Fernandes-Silva, S. Alves, A. Rocha, R. Albuquerque, and D. Addiss. 1996. Patterns of detection of Strongyloides stercoralis in stool specimens: implications for diagnosis and clinical trials. J. Clin. Microbiol. 34:2569-2571.

5. Jongwutiwes, S., M. Charoenkorn, P. Sitthichareonchai, P. Akaraborvorn, and C. Putaporntip. 1999. Increased sensitivity of routine laboratory detection of Strongyloides stercoralis and hookworm by agar-plate culture. Trans. R. Soc. Trop. Med. Hyg. 93:398-400.

6. Sudarshi, S., R. Stumpfle, M. Armstrong, T. Ellman, S. Parton, P. Krishnan, P. L. Chiodini, and C. J. M. Whitty. 2003. Clinical presentation and diagnostic sensitivity of laboratory tests for Strongyloides stercoralis in travellers compared with immigrants in a non-endemic country. Trop. Med. Int. Health. 8:728-732.

Online projects in travel medicine

Richard Boyd, Tropical Medical Bureau, Dublin

STUDIES: TROPNETEUROP & FRIENDS

EPIDEMIOLOGICAL SURVEILLANCE ON DENGUE FEVER IN EUROPE

Cristina Domingo, Madrid, Spain

Dengue is a frequent imported disease among travellers returning from the tropics in Europe. The advances in air transport make easier that, in very few hours, an infected patient could return during the acute phase of the disease. This situation makes more feasible to perform a molecular diagnosis of the disease during the short viremia period. Viral genome detection can be useful, not only to achieve a confirmed diagnosis of dengue infection, but to obtain additional viral nucleotide sequence information which could serve to characterize the serotype and the genotype of the virus involved in the infection.

Since 2004, a collaborative research project joined by both clinical and virology groups from TropNet (European Network of Tropical Medicine) and ENIVD (European Network for Imported Viral Diseases) networks respectively, has been carried out for the study of imported dengue in Europe. In this work, acute phase samples of patients with a suspected dengue infection have been analyzed and characterized by molecular methods, and viral nucleotide sequence data and phylogenetic methods have been used to understand genetic relationships between dengue viruses as well as their epidemiology. This study could be of interest for the global epidemiological surveillance of dengue viruses in endemic areas, by monitoring the emergence of new genotypes, the co-circulation of different serotypes, and the identification of genotypes associated with a more virulent biotype.

In the 2004-2006 project, a total of 128 dengue virus strains, from a wide range of geographic areas, have been detected and characterized. The approach has demonstrated utility in plotting the distribution and circulation of different genotypes, and an up-to-date map of circulating dengue serotypes and genotypes in endemic areas has been outlined. Thus, it has been demonstrated that non endemic areas, as Europe, could act as “sentinels” of global dengue serotype and genotype circulation, since air travellers can quickly move viruses from an endemic area to a receptive area.

DENGUE STUDY I: SURVEILLANCE OF SEROLOGICAL, CLINICAL AND LABORATORY FEATURES OF IMPORTED DENGUE

Ole Wichmann, RKI, Berlin, Germany & Joaquim Gascon, Hospital Clinic, Barcelona, Spain

Dengue is the most common arboviral disease in travelers. TropNetEurop collect the data on imported dengue from the beginning of the network. Since May 2003 until December 2005, we are doing a more detailed study on imported Dengue. A total of 14 member sites have participated in the study by reporting data with an additional questionnaire sheet.

A total of 219 dengue infections imported from various endemic regions were reported during the study period. Infections were acquired in Southeast Asia (77), Indian Subcontinent (63), Rest of Asia (1) Central America (39), South America (16), Caribeean (7), East Africa (10), Rest of Africa (6).

Of the 219 reported cases, 133 had a confirmed and 86 a probable dengue infection. Confirmation was achieved in 2 cases by PCR only, in 115 cases by increasing dengue-antibody titers in paired serum samples, and in 16 cases by combining both methods. For the probable diagnosis only positive IgM-antibody titers were available from a single serum sample (in 86 cases in combination with an IgG-assay).

For 175 patients both quantitative IgM- and IgG-antibody titers were available and indicated a primary infection in 134 (77%) and a secondary (sequential) dengue infection in 40 (23%) cases. Among the 40 patients with secondary immune response 5 had a positive history of previous dengue infection. Among the 163 patients; 27 (17%) with both available quantitative IgM- and IgG-antibody titers were defined as probably having acquired a secondary dengue infection.

Blood examination during the acute phase revealed leukopenia in 76.7% (124 of 172); thrombocytopenia in 70.7% (123 of 174). Levels of LDH, and ALAT were increased in 67% (70 of 104), and 55.68% (98 of 149) respectively.

Fever (92.7%), Headache (69.4%), Fatigue (124 (56.6%), Rash (53%), Muscle pain (49.8%), Retro-orbital pain (43.8%) and Bleeding disorder (26%) were the most frequent clinical features. In 84 patients a tourniquet test was performed with results being positive in 36 (44%).

Among all patients, 2 (0.9%) fulfilled the WHO clinical case definition for dengue hemorrhagic fever as both demonstrated evidence of hemoconcentration = 20%. Serological analysis in one revealed a secondary and in the other patient a primary immune response. A total of 23 (10%) of patients demonstrated severe clinical manifestations (internal hemorrhage, n=4; plasma leakage, n=2; shock, n=1; platelet count = 50/nL, n=18).

Conclusions: In travelers, severe dengue infections are not uncommon but may be missed if the WHO classification is strictly applied. Serum alanine and aspartate aminotransferase levels could serve as indicators for disease severity.

The Antwerp Fever Study

E.Bottieau, J.Clerinx, dept.of Clinical Sciences, ITMA

From 2000 till 2005, the department of Clinical Sciences of the Institute of Tropical Medicine, Antwerp (ITMA) initiated a project research with the following 3 main objectives: (1) to investigate the etiology and outcome of imported fever (2) to improve the medical decision making for its diagnosis and treatment and (3) to describe more extensively the leading imported febrile diseases. All patients presenting with fever within one year after a stay in the (sub)-tropics at the ITMA or at the University Hospital, Antwerp were enrolled. Clinical data were recorded during consultation, first-line investigations were standardized, and diagnosis, treatment, evolution and outcome were prospectively assessed. In total, 1842 febrile episodes were investigated. Tropical (39%) and cosmopolitan (34%) infections were most common, but diagnosis remained unspecified in 24%. The spectrum and the probability of disease was largely determined by the continent visited but also by the incubation period, the traveler profile and the hospitalization status. In contrast, the referral pattern had no sizeable impact. To steer diagnosis and to initiate safe patient management, first-line laboratory tests could be restricted to a thick film, a total blood count, and kidney and liver function tests. Many diseases however, had to be diagnosed by (paired) serology leading to diagnostic delay and probable underestimation of true prevalence. Morbidity of most tropical diseases was extensive in terms of hospitalization rate, but mortality was essentially limited to *Plasmodium falciparum* malaria, which was the only tropical cause of death in the study population (5 of 9 fatalities). In contrast, fever of unknown cause had invariably a favorable outcome.

The diagnostic predictors of the most frequent tropical conditions were mainly investigated in early-onset fever (within one month of return), as almost all tropical infections other than malaria develop during this period. The classic predictors of malaria were confirmed (enlarged spleen, fever without localizing symptom, platelet count < 150,000/µL and total bilirubinemia = 1.3 mg/dL), and their respective power of confirmation was calculated. For the other tropical diseases (after excluding malaria) the diagnostic predictors were rather similar to those observed in endemic studies, but their adjusted positive and negative likelihood ratios have been specifically calculated for travelers. Combining the confirming power of common (clinical & paraclinical) features with the destination-specific pre-test probability of a given diagnosis can provide a comprehensive predictive assessment.

When several diagnoses are competing, computer-based expert systems may appear helpful as a decision-support tool. Only one such system is available for imported fever: the Global Infectious Disease and Epidemiology Network (GIDEON). We evaluated its diagnostic accuracy by entering collected data of 161 fever episodes (chosen at random) according to the developer's recommendations. Accuracy was found satisfactory (meaning correct diagnosis in the top 5 ranking, with a probability = 1%) in 63% of the cases, and the results were reproducible. However, several limitations were identified: endless lists of hypotheses with very low probability, excessive excluding power of non-related features and insufficient impact of absent clinical arguments. These conceptual weaknesses may explain the suboptimal performance of GIDEON. In particular, the finding that in about 10% a diagnosis of a severe condition was missed, makes its use hazardous for less experienced physicians.

P. falciparum malaria is by far the most frequent and severe imported disease, but its optimal management remains controversial. We demonstrated that ambulatory treatment of P.falciparum is safe when certain conditions are met. Based on these data, a new definition of uncomplicated malaria has been drawn up. Though benign, non-falciparum malaria is challenging in diagnosis and treatment. Episodes frequently occurred 3 months after exposure, in particular when chemoprophylaxis was taken. Exact diagnosis is hampered by very low parasitemia, which limits also the performance of current rapid diagnostic tests. Relapses of *P. vivax* or *P. ovale* are frequent when "recommended" dosages of primaquine have been used.

Acute schistosomiasis (or Katayama syndrome) has been confirmed in 23 patients. Diagnosis was more than often presumptive at presentation, and exacerbation of symptoms was frequent if steroids were not administered concomitantly with praziquantel. Clinical recurrence was not uncommon, and there is so far no clearcut therapeutic strategy to prevent this.

Of the cosmopolitic infections, the mononucleosis-like syndrome formed a sizeable part. Its disease spectrum was different from that observed in non-imported series, with a higher proportion of primary cytomegalovirus, *Toxoplasma gondii* and HIV infections. Diagnosis was often established lately, leading to unnecessary hospitalizations, investigations and presumptive treatments. Associated morbidity was substantial. As no single feature was found with a strong confirming power, adjusted weights of each combination of predictors were assessed in this study.

With the accumulated evidence, we are currently exploring the feasibility of developing an expert system for imported fever destined to non-referral travel clinics and hospitals.

www.fevertravel.ch: a website for evaluation in travel/tropical medicine and for dissemination and online feasibility study. Present status.

Isabelle Rossi & Blaise Genton, Lausanne, Switzerland

We have developed practice guidelines for the management of fever in travellers or migrants, based on a an evidence-based approach (AGREE methodology) and complemented by an explicit international expert opinion panel. The website www.fevertravel.ch was constructed and launched at the 8th Conference of the International Society of Travel Medicine in 2003. In order to evaluate feasibility and safety of the web-based guidelines, we integrated a research component into the website. Since October 2004, direct online recruitment began as a testing phase in our medical outpatient clinic, and then a multi-centre, international study was launched.

From its launch in May 2003 up to August 2006, 20'054 visits have been made to the website, mainly from Europe, with a 100% increase each year.
Since global study initiation 365 physician/patient pair have been recruited in several countries. 272 (74.5%) have been included in our outpatient clinic, 79 (21.6%) from reference centres, 14 (3.8%) from general practitioners or specialists in infectious disease, in internal medicine or tropical medicine.
Interim analysis shows that 53% of the physicians are fully adherent to the guidelines. The most frequent deviations are no repetition of malaria tests (27%), no chest X-ray in case of fever + cough (24%) and no presumptive treatment for fever + diarrhoea (38%), all in the absence of alternative documented diagnosis.

At the present time, we face a major difficulty in recruiting physicians outside few known European centres and would need more collaborations from primary health care facilities or emergency wards in the US, Canada, Australia and Japan, in order to assess the usefulness and appropriateness of these web-based guidelines by the target audience.

TropNetEurop could be a useful platform, although restricted to one continent, to widen the scope of assessment. If centres are including enough patients, we would be keen to involve them in the overall evaluation and in the writing of the next version of the guidelines, which are scheduled to be published and then fully computerized in 2008.