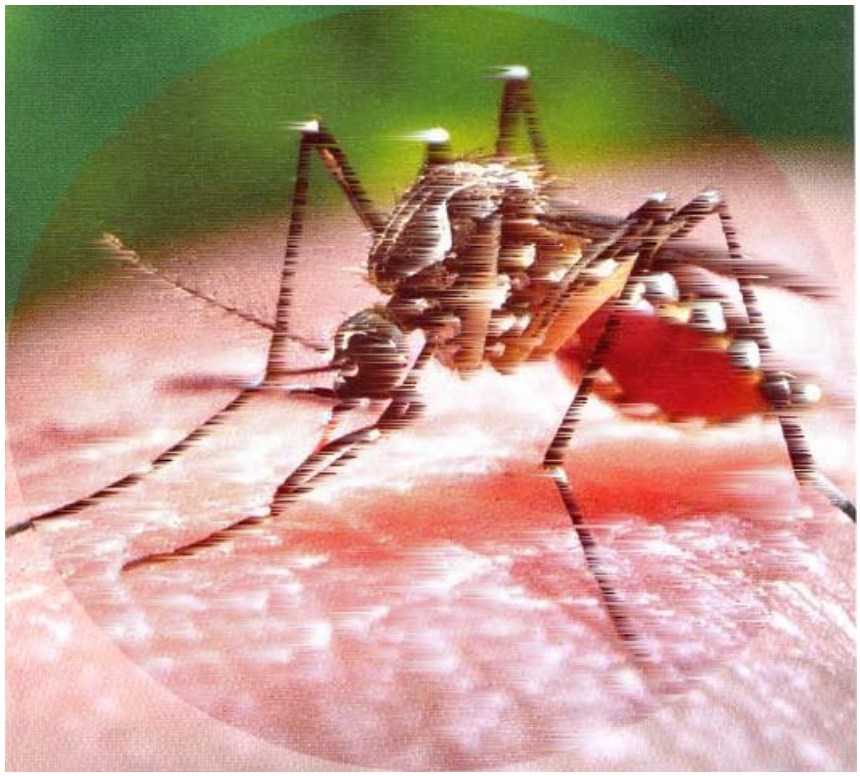
TropNetEurop

8th Workshop on

Imported Infectious Diseases

2007



September, 22th – 23th

Lisbon

European Network on Imported Infectious Disease Surveillance

www.tropnet .net

PROGRAMME

8th TropNetEurop Workshop 22-23/09/2007

Date & Time		Speakers
Saturday, 22/09/2007		
9^{00}-9^{15}	Introduction	Jorge Atouguia, Lisbon
9^{15}-10^{30}	Report of steering committee and co-ordinator • Membership issues • Reporting • Data management • ECDPC, WHO, & others	Ron Behrens, London Zeno Bisoffi, Verona Anders Björkmann, Stockholm Joaquim Gascon, Barcelona Tomas Jelinek, Berlin Nick Mühlberger, Berlin
10^{30}-11^{00}	**Break**	
11^{00}-11^{45}	Report of steering committee and co-ordinator (continued)	
11^{45}-12^{30}	The Unit Preparedness & Response, ECDC	Katrin Leitmeyer, Stockholm
12^{30}-13^{00}	The Lisbon Institute of Hygiene and Tropical Medicine and travel and tropical medicine in Portugal	Jorge Atouguia, Lisbon
13^{00}-14^{00}	**Lunch**	
	Malaria	
14^{00}-14^{30}	Multicentric study of rapid diagnosis of imported malaria with 2nd generation HPR2-f	Juan Antonio Cuadros Gonzales, Madrid
14^{30}-15^{00}	The contribution of field and laboratory studies for the understanding of putative resistance mechanisms to artemisinin derivatives in malaria parasites	Pedro Cravo, Lisbon
15^{00}-15^{30}	Should we prophylaxis against Vivax malaria ?	Ron Behrens, London
15^{30}-16^{00}	**Break**	
Malaria Chemoprophylaxis		
16^{00}-19^{30}	Consensus meeting on malaria chemoprophylaxis	
20^{30}	**Dinner**	
Sunday, 23/09/2007		
8^{25}-8^{30}	Introduction	Tomas Jelinek, Berlin
Migrants		
8^{30}-9^{00}	Epimigra: clinical and laboratorial evaluation of migrants in Lisbon	Luis Tavira, Lisbon
9^{00}-9^{30}	Chagas disease in migrants in France	Michel Develoux, Paris
9^{30}-10^{00}	Medical care for migrants in Madrid	Rogelio Lopez-Velez, Madrid
10^{00}-10^{30}	Malaria in migrants in the UK. Data from the Malaria Reference Laboratory and a plan for action	Penny Neave, London
10^{30}-11^{00}	**Break**	
Studies: TropNetEurop & Friends		
11^{00}-11^{30}	August 2007: an oubreak of Chikungunya in Northern Italy	Zeno Bisoffi, Verona - Negrar
11^{30}-12^{00}	The Exodus Software	Graham Fry, Dublin
12^{00}-12^{30}	Treatment of complicated malaria with Artesunate	Thomas Zoller, Berlin
12^{30}-13^{00}	Treatment study in uncomplicated malaria: MALTHER	Martin Grobusch, Johannesburg
13^{00}-13^{30}	JE vaccine in travellers	Ron Behrens, London & Christoph Hatz, Basel
13^{30}	**Lunch & Farewell**	

WORKSHOP ORGANIZER AND LOCAL CONTACT ADDRESS

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MEETING VENUE

The meeting will take place at the Instituto de Higiena e Medicina Tropical, Rua da Junqueira 96, 1340-008 Lisbon on Saturday 22th September and Sunday 23th September 2007.

WELCOME

Dear colleagues,

I would like to welcome you to this TropNetEurop Workshop 2007 in Lisbon.

The Instituto de Higiene e Medicina Tropical in Lisboa is 102 years old, and his history is closely related to the history of tropical medicine and infectious diseases. Portugal has always been a country connecting North and South. North, as a country of emigrants. South, as a country of colonies, and later, after their independencies, as a country with privileged relations with the new Portuguese – Speaking African Countries. This relations contribute to the recent problem of emigration that we share with other countries in the south of Europe. That is the reason why, for the first time, we include in our workshop program a discussion on migrants medicine.

The TropNetEurop Workshop 2007 includes other very important discussion topics in the malaria area, and the studies currently going on within our groups.

We are delighted to see you here in Lisbon, and hope that you enjoy the workshop.

Jorge Atouguia

Dear colleagues!

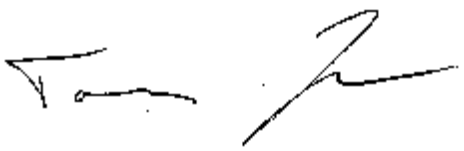
TropNetEurop has now finished its 8th successful year. Our work and the network as a provider of reliable information are experiencing increased acceptance on European and international level. Topics of the upcoming meeting reflect this, ranging from a presentation from the ECDC to discussion of a current EU proposal.

The network and its members unite 52 specialized centres all over Europe. Within the network, we see an average of 56.000 patients post travel per year. This remains by far 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 continuous success is achieved through considerable effort from all members who put in extra time and work to make the network possible. I think we can congratulate ourselves for this achievement.

I am looking forward to an exciting meeting in Lisbon.

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 Jorge Atouguia, who made the meeting possible.

Berlin, Sept, 16th, 2007



Tomas Jelinek

ACKNOWLEDGEMENTS

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- Centro de Malária e outras Doenças Tropicais – Laboratório Associado

CONTENTS

7th TropNetEurop Workshop

Basel, September 30th-October, 1st, 2006

Workshop Minutes

Participants

No	Surname	First Name	Town	Country
1.	Atouguia	Jorge	Lisbon	Portugal
2.	Bartoloni	Alessandro	Florence	Italy
3.	Beck	Hans Peter	Basel	Switzerland
4.	Behrens	Ron	London	UK
5.	Beran	Jiri	Hradec Kralove	Czech Republic
6.	Bouchaud	Olivier	Bobigny	France
7.	Burchard	Gerd	Hamburg	Germany
8.	Calleri	Guido	Turin	Italy
9.	Clerinx	Jan	Antwerp	Belgium
10.	Domingo	Cristina	Madrid	Spain
11.	Gascon	Joaquim	Barcelona	Spain
12.	Gautret	Philippe	Marseille	France
13.	Grobusch	Martin	Johannesburg	South Africa
14.	Gundersen	Svein Gunnar	Kristiansand	Norway
15.	Hatz	Christoph	Basel	Switzerland
16.	Hellgren	Urban	Stockholm	Sweden
17.	Jelinek	Tomas	Berlin	Germany
18.	Jelinek	Claudia	Berlin	Germany
19.	Kapaun	Annette	Heidelberg	Germany
20.	Löscher	Thomas	Munich	Germany
21.	Marocco	Stefania	Verona	Italy
22.	Matteelli	Alberto	Brescia	Italy
23.	Mørch	Kristine	Bergen	Norway
24.	Mühlberger	Nick	Berlin	Germany
25.	Müller	Yolanda	Lausanne	Switzerland
26.	Muñoz	Jose	Barcelona	Spain
27.	Myrvang	Bjørn	Oslo	Norway
28.	Rossi	Isabell	Lausane	Switzerland
29.	Schmidt	Matthias	Newcastle-up-Tyne	UK
30.	Siikamäki	Heli	Helsinki	Finland
31.	Stich	August	Würzburg	Germany
32.	Treviño	Begoña	Barcelona	Spain
33.	Visser	Leo	Leiden	Netherlands
34.	Von Sonnenburg	Frank	Munich	Germany
35.	Zoller	Thomas	Berlin	Germany

Saturday

Christoph Hatz: Welcome

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

- Presentation of the network structures
- TropNetEurop mailing list:
  - Key feature of the network, average of 10 nails per month
  - 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 web site
  - Can be linked with home pagers of member institutions
- Reporting issues
  - Reported patients:9890
  - Only 54.9% of the sites are reporting electronically and only 28,9% of patients are reported that way
  - Reporting of Leishmaniasis has started, the first 55 patients have been added to the data base
  - A general decline of case reports is noticable over the past months. Several sites confirm that they see less patients than before. Reasons are discussed: is the a true decline of patients or do they present somewhere else? Ron Behrens cites data from West Africa that show a decline of malaria in urban areas. This seems to fit in with the development we see in TropNetEurop.
- Activities & changes in 2005-2006
  - TropNetEurop has moved from mere surveillance/data collection into issuing statements and recommendations. Statements were published on Artesunate use, Malaria Chemoprophylaxis in India, and on Malaria chemoprophylaxis in pregnancy. They received wide reckognition and were published in Euroseurveillance.
    Comments:
    Frand von Sonnenburg points out that issuing guidelines may be a politically risky business. Gerd Burchard and Thomas Löscher state that they were not informed about the initiative.
    During the further discussion it is agreed upon that TropNetEruop is not issuing guidelines but statements and recommendations. These are not legally binding. There were no problems in any other country regarding the statements. Urba Hellgren points out that the statement on artesunate use enabled hospitals in Sweden to acquire the drug for severely ill malaria patients which was imposible before. The coordinator comments that the statements were discussed during the last meeting and circulated afterwords by e-mail before being published.
- TropNetEurop publications:
  - 6 major papers in 2005/2006, one paper in print
  - Eurosurveillance has become interested in statements from the network
- Presentation of the map of sites, gap in the Netherlands is filled now, 51 member sites
  - Lost two sites (Leipzig, Berlin), gained 3 new sites (Leiden, Rome, Berlin)
  - Capacity of approx. 54,000 patients post travel and 190,000 visits pre travel
- Brief presentation of ongoing studies within the network
- Election of steering committee

- Candidates are Ron Behrens, Zeno Bisoffi, Anders Björkmann, and Joaquim Gascon for committee membership and Tomas Jelinek as coordinator.

Discussion:
Thomas Löscher points out that his ethical review board has a problem with reporting of data to a coordinator who is not under institutional supervision since Tomas Jelinek has changed site from the Institute of Tropical Medicine (run by the state government of Berlin) to the privately owned Berlin Center for Travel and Tropical Medicine. The point is supported by Gerd Burchard and Frank von Sonnenburg who asks for a control mechanism for the actions of the coordinator. Tomas Jelinek states that his position in regards of TropNetEurop has not changed at all and that he has only changed institutions. The steering committee is asked to discuss the issue.
Election: the candidates are confirmed in their position

Hans Peter Beck:

Molecular tools for the diagnosis of malaria

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). Commonly deployed techniques are presented and their specific application, benefit, and costs are highlighted.

Discussion

- Huge sensitivity advantage of PCR
- Cost-benefit issues of PCR for routine diagnostics

Guido Calleri: The Delphi Study revisited: VFRs

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.

Discussion:

- Disparity of recommendations by experts in the network is irritating but easily explained.
- Statements of the network seem to have impact on uniformity of results
- Further progress with the Delphi method is encouraged

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

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 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 are presented to inform the policy making process. Current national recommendations including those from CDC and WHO are distrubuted.
Data of PAHO show clear decline of malaria incidence for most countries in Latin America. Exceptions are Suriname, Guyana, and the Brasilian states of Roraima, Rondonia, and Amapa. Number of reported cases from the US, several European countries and from TropNetEurop show clear decline. Malaria incidence in travellers can be assessed by use of airport survey data., this is also declining.
Discussion:

- Impressive collection of data.
- Is the data of national notification data reliabel?
- Are the PAHO data relevant for travellers risks for malaria?
- What are the consequences for our councelling practise?

Christoph Hatz: die Schweizerische Arbeitsgruppe für Reisemedizin (SAR)

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.
Discussion (including further discussion of data presented by Ron Behrens):

- Is standby medication cost effective and ethical? Based on the data from India, about 650,000 doses of medication need to be prescribed in order to treat 5 cases of malaria.
- Can standby prophylaxis be prescribed safely?
- Round agrees that information/education is the most important prescription
- In Switzerland, Austria, and Germany, ther was no increase in malaria cases since change from prophylaxis to standby
- Several countries recommend chemoprophylaxis for low risk areas of Latin America, even though current data situation does not seem to support this
- Group recommends further data collection on Latin America, in particlar on travellers to Suriname (Leiden will provide information)
- The preparation of a statement on malaria prophylaxis in Latin America is delegated to the steering committee and Chirstoph Hatz

Sunday

Martin Grobusch: Treatment study of uncomplicated malaria: MALTHER

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.
An update on the current data is provided, and modalities for so far non-participating centers still planning to joining in into this study are discussed.
Discussion:

- To reach significant results, the study needs approx. 200 patients per study arm. This is not realistic. While the atovaquone/proguanil arm is well developed, in particular the quinine and artemether/lumefantrine arms need further inclusions.
- Retrospective inclusion of cases is discussed as possibility but viewed critically
- Martin Grobusch ask major centers whether they will be able to contribute

Joaquim Gascon: Chagas disease in non-endemic areas. The experience of Barcelona.

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.

Discussion

- Shall TropNetEurop include Chagas disease as a reporting diagnosis?
- Very few centers see any cases at all. A data collection would not add to the information on risks for travellers but rather mirror the local situation in countries of emmigration.

Stefania Marocco: Proposal of a multicentre trial on the treatment of strongyloidiasis, using serology as a tool for diagnosis and follow-up

Due to its unique autoinfective cycle, *Strongyloides stercoralis (S. stercoralis)* may persist in the host for indefinite periods. 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. 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. 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.

Discussion

- Offer of contacting Stefania and/or Zeno Bisoffi for study participation
- For many site, strongyloidiasis is not a frequent diagnosis
- How many cases are needed? Possibly outcome differences will be larger than expected?
- Should such a study be done in Africa where many cases can be expected? How to cope with re-infection? Serology cannot distinguish here.

Joaquim Gascon:

Dengue study I: surveillance of serological, clinical, and laboratory features of imported dengue

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.

Discussion:

- Differences beween severe Dengue and DHF are discussed.
- Serological cross-reactions with Yellow Fever and TBE vaccination are discussed: IgG lavels may be increased in vaccinated persons with acute dengue, thus simulating secondary infection.
- At recent US conferences it was stated very clearly that DHF is seen in people living in endemic areas and in VFRs, not in travellers. The data here show that we do see DHF in European travellers, too.
- What is the consequence of these findings? Do we recommend persons who had dengue fever not to travel to endemic regions? Question remains unanswered.

Jan Clerinx: The Antwerp Fever Study

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.

Discussion:

- Differences between Katayama Syndrome and acute schistosomiasis are querried
- Significance of hyperbilirubinemia for prediction of severe malaria is diuscussed. Is this laboratory marker practical?

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

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.

Discussion:

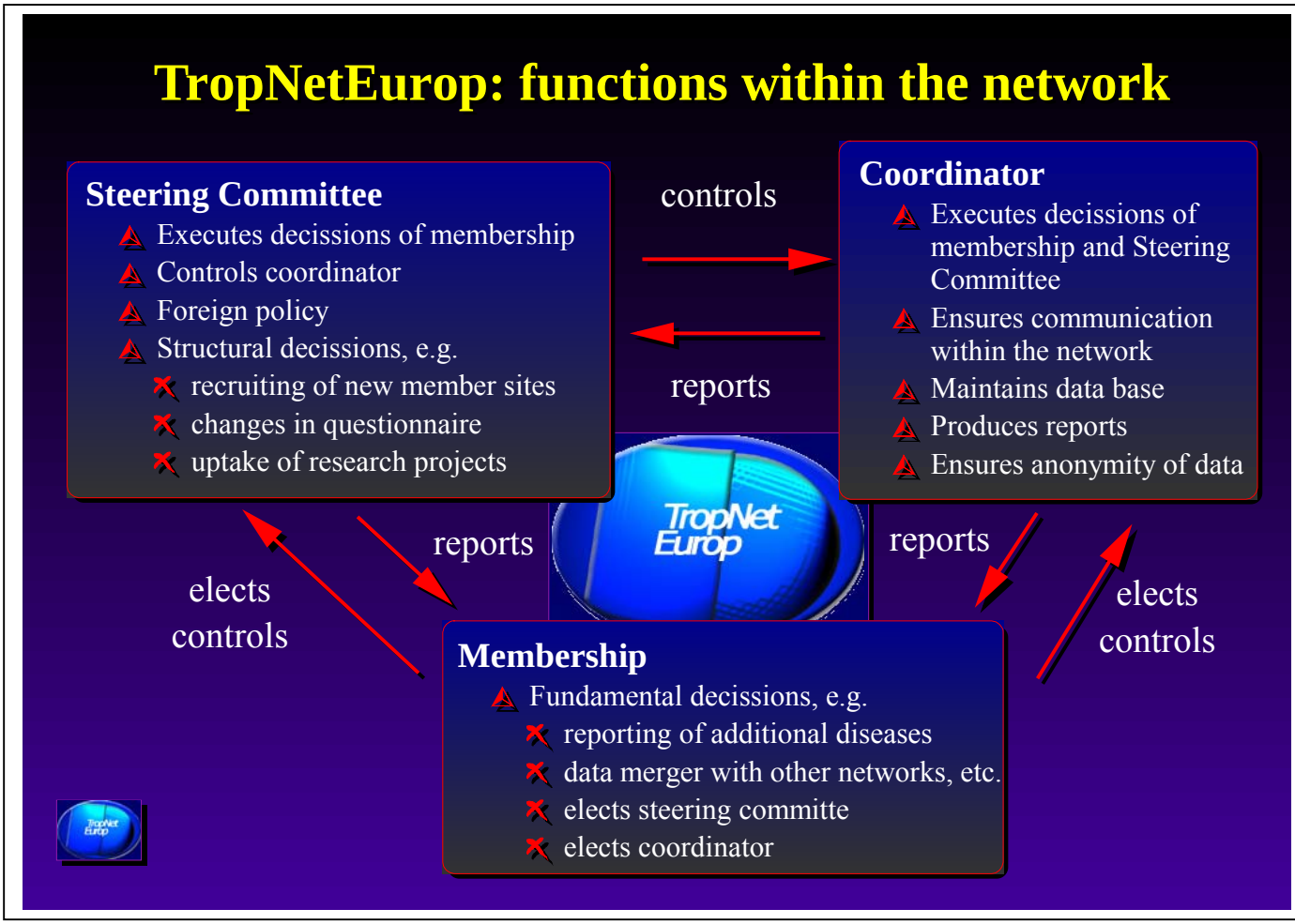
- The tool is highly recommended for educational purposes by Christoph Hatz
- Comparison of GIDEON software and fevertravel: no replacement but additional tool

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 52 members sites.

	N	%
Member Sites	52	100.0
Reported Patients	10962	100.0
Patients reported electronically	3508	32.0
Reported Diagnoses	10979	100.0
Malaria	8530	77.7
Schistosomiasis	1220	11.1
Dengue	1149	10.5
Leishmaniosis	80	0.7

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.	Division of Infectious Diseases, Department of Medicine, Center for Infectious Diseases and Travel Medicine, University Hospital, Freiburg, Germany	W. Kern
20.	Institute of Maritime and Tropical Medicine, Gdynia, Poland	Prof. A. Kotlowski
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

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.	Travel Medicine Unit, Hospital General Universitario Gregorio Marañón, Madrid, Spain	Dr. P. Martin-Rabadan
34.	Centre de Formation et de Recherche en Médecine et Santé Tropicale, Faculté de Médicine, Marseille, France	Dr. G. Soula
35.	Department of Infectious Diseases & Tropical Medicine, University of Munich, Germany	Dr. M. Schunk
36.	Centro per le Malattie Tropicali, Ospedale S. Cuore, Negrar (Verona), Italy	Dr. Z. Bisoffi
37.	Department of Infection & Tropical Medicine, Newcastle General Hospital, Newcastle-upon-Tyne, UK	Dr. M.L. Schmid
38.	Department of Infectious Diseases, Ullevaal University Hospital, Oslo, Norway	Prof. B. Myrvang
39.	Service de Parasitologie, Hôpital Tenon, Paris, France	Dr. M. Develoux
40.	Department and Clinic of Tropical and Parasitic Diseases, Karol Marcinkowski University of Medical Sciences, Poznan, Poland	Dr. M. Paul
41.	3rd Dep. of Infectious and Tropical Diseases, First Faculty of Medicine of Charles University in Prague, Czech Republic	Prof. Pavel Chalupa
42.	INMI L. Spallanzani, Rome, Italy	Dr. P. Ghirga
43.	Central Hospital of Rogaland, Stavanger, Norway	Dr. Åse Berg
44.	Karolinska Hospital, Department of Medicine, Unit of Infectious Diseases, Stockholm, Sweden	Prof. A. Björkman
45.	Karolinska Institute, Division of Infectious Diseases, Huddinge University Hospital, Stockholm, Sweden	Prof. U. Hellgren
46.	Osp. Amedeo di Savoia, Div. "A" Malattie Infettive, Torino, Italy	Dr. Guido Calleri
47.	University Hospital of Tromsø, Norway	Dr. JB Christensen
48.	Institut für Tropenmedizin, Eberhard-Karls-Universität Tübingen, Germany	Prof. J. Knobloch
49.	Clinc of Infectious Diseases, University of Udine, Italy	Dr. A. Beltrame
50.	Sektion Infektionskrankheiten, Universität Ulm, Germany	Prof. P. Kern

51.	Kaiser-Franz-Josef-Spital der Stadt Wien, 4. Medizinische Abteilung mit Infektions- und Tropenmedizin, Vienna, Austria	Dr. H. Laferl
52.	Missionsärztliche Klinik, Würzburg, Germany	Dr. G. Stich

TropNetEurop: Members and Patient Encounters

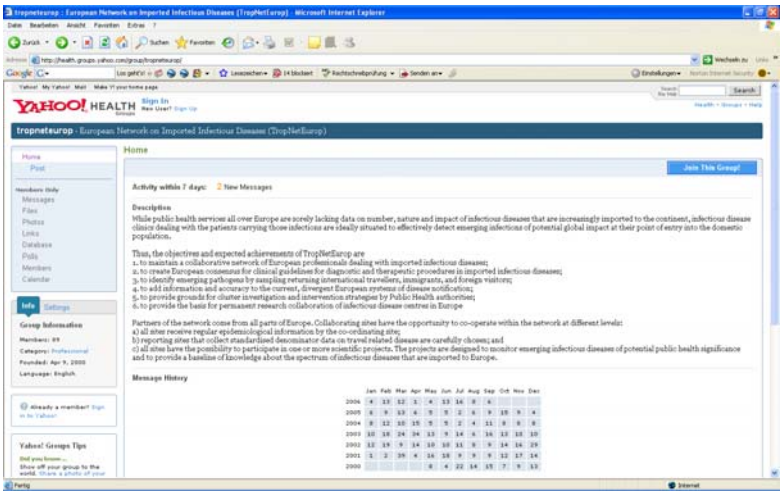
Nº	Town	Site Manager	In- and outpatients [per year]	Pre-travel advises [per year]
1.	**Aalborg**	H. Nielsen	100	200
2.	**Aarhus**	F. T. Black	350	800
3.	**Antwerp**	J. Clerinx	7700	12000
4.	**Barcelona – Hospital Clinic**	J. Gascon	1400	6000
5.	**Barcelona - Drassanes**	J. Gòmez i Prat	6000	12000
6.	**Basel**	C. Hatz	2500	10000
7.	**Bergen**	K. Mørch	50	600
8.	**Berlin - BCRT**	T. Jelinek	1000	8000
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.	**Freiburg**	W. Kern	250	350
20.	**Gdynia**	A. Kotlowski	100	200
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.	**Madrid- Gregorio Maranon**	P. Martin-Ramadan	600	150
34.	**Marseille**	J. Delmont	2500	3000
35.	**Munich**	M. Schunk	1700	13000

TropNetEurop: Members and Patient Encounters (continued)

36.	**Negrar (Verona)**	Z. Bisoffi	2000	1500
37.	**Newcastle**	M. Schmid	1500	300
38.	**Oslo**	B. Myrvang	1500	5000
39.	**Paris**	M. Deveroux	1500	6500
40.	**Poznan**	M. Paul	100	350
41.	**Prague**	P. Chalupa	600	500
42.	**Rome**	P. Ghirga	100	200
43.	**Stavanger**	A. Berg	100	0
44.	**Stockholm - Karolinska**	A. Björkman	1500	15000
45.	**Stockholm - Huddinge**	U. Hellgren	400	15000
46.	**Torino**	C. Galleri	800	2000
47.	**Tromsø**	J. B. Christensen	50	300
48.	**Tübingen**	J. Knobloch	1000	6000
49.	**Udine**	A. Beltrame	200	0
50.	**Ulm**	P. Kern	1000	2500
51.	**Vienna – KFJS**	H. Laferl	450	0
52.	**Würzburg**	G. Stich	300	450
	TOTAL		**55250**	**189905**

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:

- 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. Severe dengue infection in travelers: Risk factors and laboratory indicators. *J Infect Dis* (2007) 195; 1089-96
- Jelinek T, Behrens R, Bisoffi Z, Bjorkmann A, Gascon J, Hellgren U, Petersen E, Zoller T. Recent cases of falciparum malaria imported to Europe from Goa, India, December 2006-January 2007. *Eurosurveillance Weekly* 2007 Jan 11;12(1):E070111.1
- Behrens RH, Carroll B, Jiri Beran, Oliver Bouchaud, Urban Hellgren, Christoph Hatz, Tomas Jelinek, Fabrice Legros, Nikolai Muhlberger, Bjørn Myrvang, Heli Siikamäki, Leo Visser. The low and declining risk of malaria from Latin America: is there still an indication for chemoprophylaxis? *Malaria J* 6 (2007) 114

d) Material in preparation:

- Calleri G, Behrens R, Bisoffi Z, Björkmann A, Castelli F, Gascon J, Gobbi F, Grobusch MP, Jelinek T, Schmid M, Niero M, Caramello P. Variability in malaria prophylaxis prescribing across Europe: a Delphi method analysis. J Travel Med (submitted)
- Malaria dipstick study

Von: Malaria Journal [mailto:info@biomedcentral.com]
Gesendet: Mittwoch, 12. September 2007 14:11
An: jelinek@bctropen.de
Betreff: Malaria Journal's new Impact Factor

MALARIA JOURNAL IMPACT FACTOR 2.75

Dear Dr Jelinek,

I am contacting you, as you have previously published in *Malaria Journal*, to let you know that *Malaria Journal* has received a new Impact Factor of 2.75. The journal is now ranked first in the field of Tropical Medicine, according to the 2006 Journal Citation Report. *Malaria Journal* also ranks as the fifth most-cited journal in the general field of Parasitology for the second year in a row.

The speed with which *Malaria Journal* has established its high standing in just 5 years is in part the result of our commitment to open access. Free and unrestricted availability via the internet to all increases the visibility of research and may result in higher citations.

If you have not visited the *Malaria Journal* website recently, please do take a look at the articles published lately. *Malaria Journal* boasts a wide, international readership; last month alone, articles in the journal were accessed over 42,000 times directly from our website.

For example, this article by Ron H Behrens *et al*. has been accessed 715 times in the past 30 days:

Opinion Open Access Highly accessed
The low and declining risk of malaria in travellers to Latin America: is there still an indication for chemoprophylaxis?
Ron H Behrens, Bernadette Carroll, Jiri Beran, Oliver Bouchaud, Urban Hellgren, Christoph Hatz, Tomas Jelinek, Fabrice Legros, Nikolai Muhlberger, Bjorn Myrvang, Heli Siikamaki, Leo Visser
Malaria Journal 2007, **6**:114 (23 August 2007)
[Abstract] [Provisional PDF] [PubMed] [Related articles]

If you would like to submit your next manuscript, or sign up to receive regular article alerts, please visit the journal website.

I would like to thank you for your continuing support for *Malaria Journal*. Please do continue to read and cite articles published in the journal, submit your own research and encourage your colleagues to do the same.

With all best wishes,

Marcel Hommel
Editor-in-Chief, *Malaria Journal*

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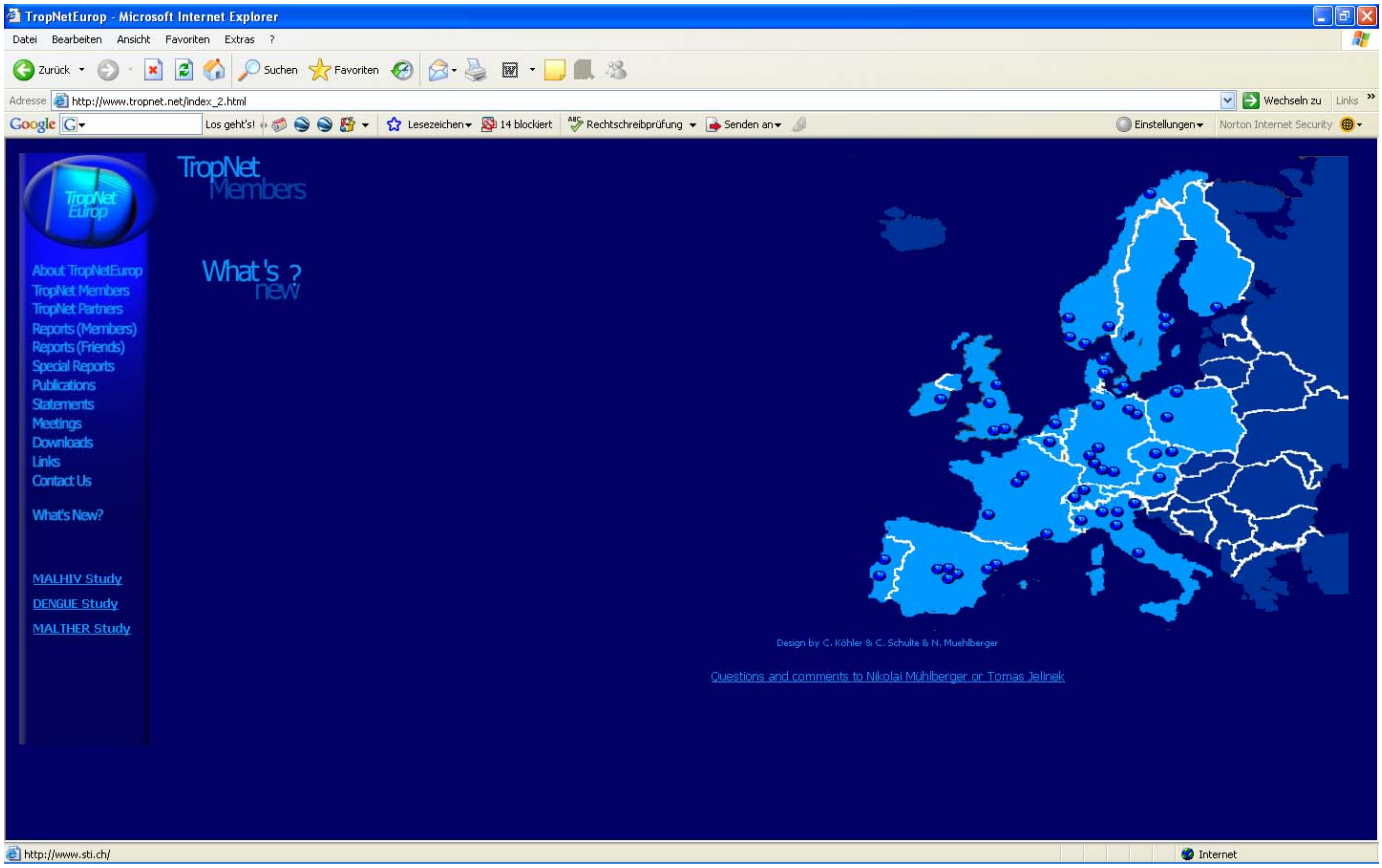
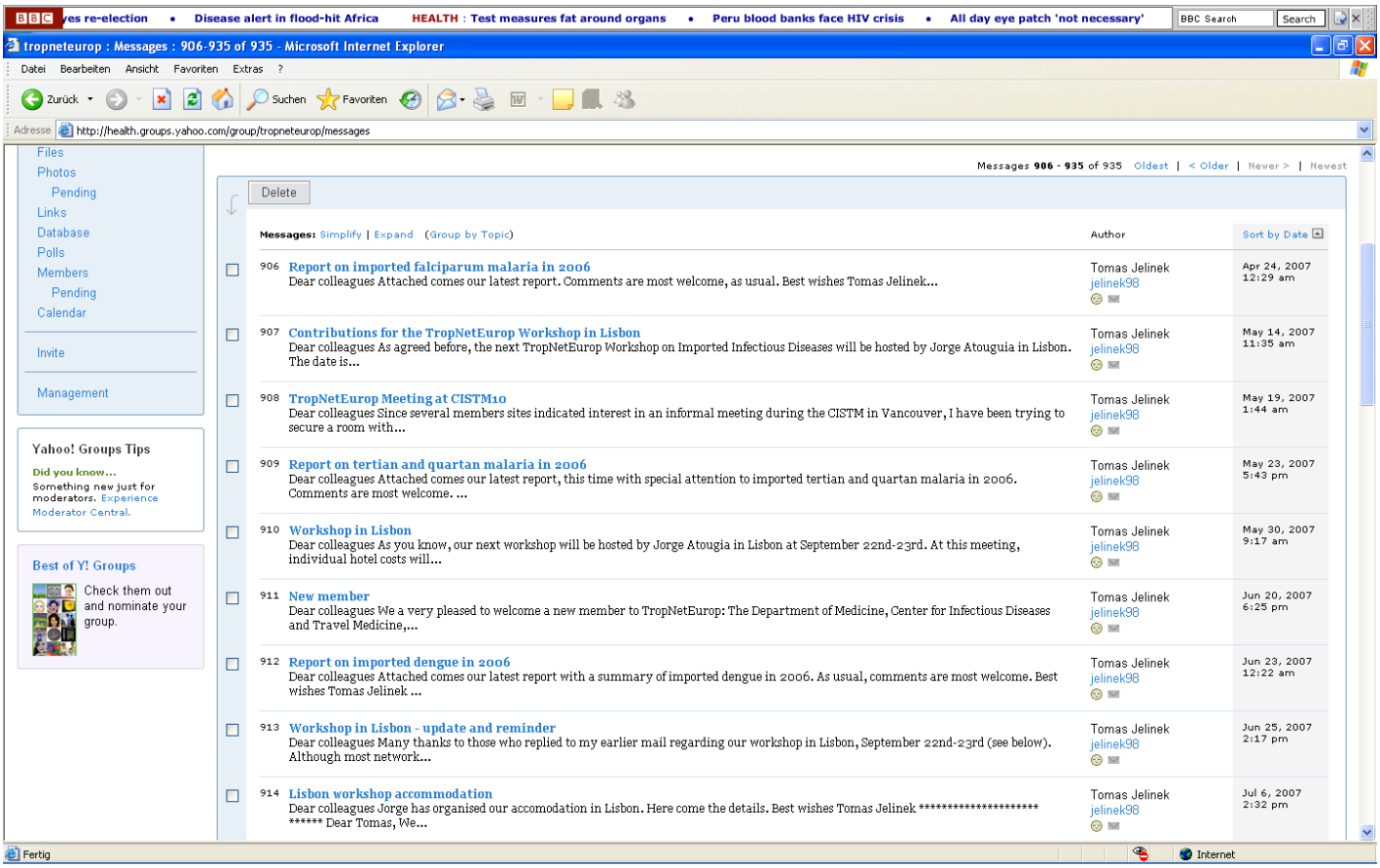
e) The Web Site

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.



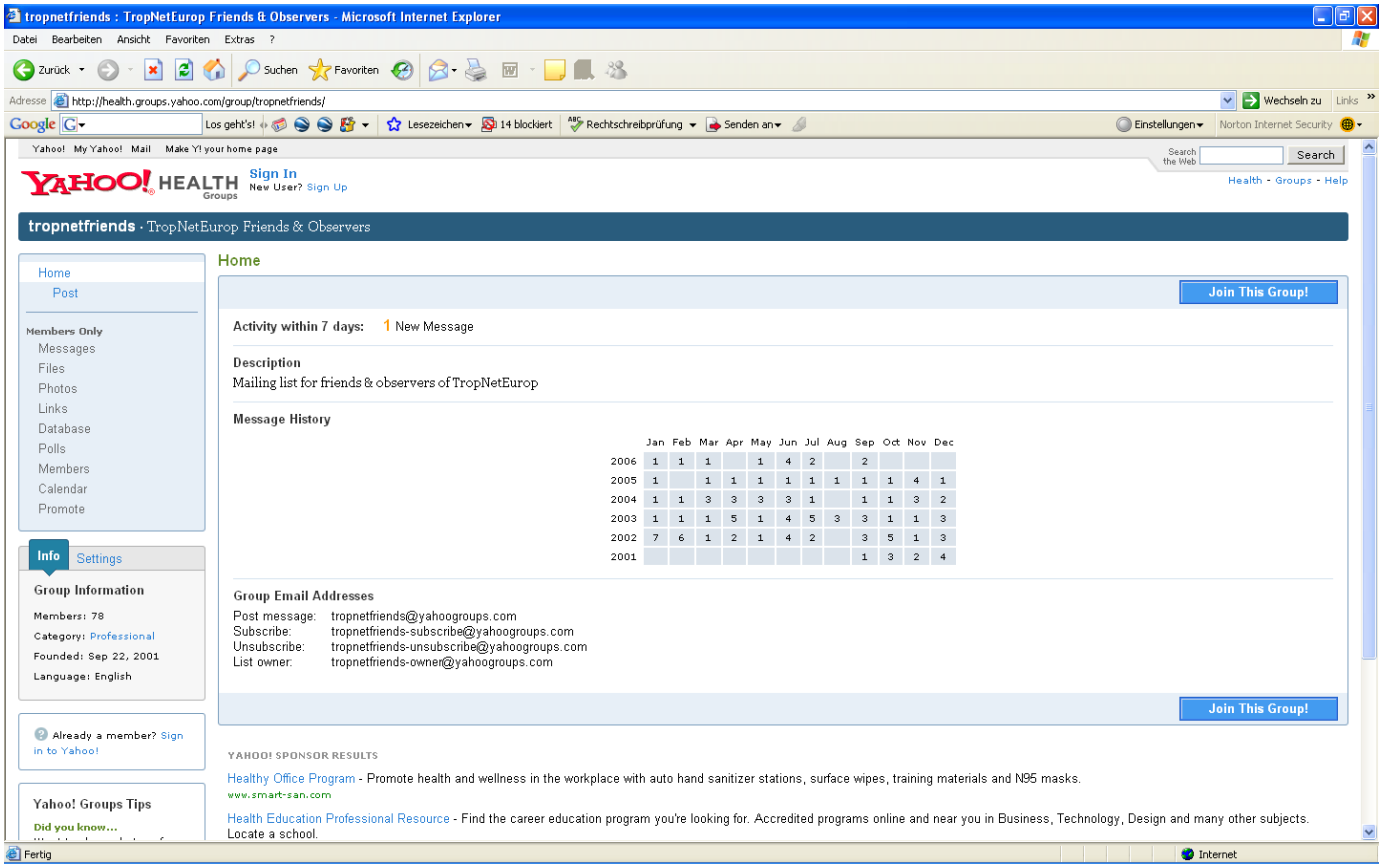
f) Special Reports and "Sentinel Events"

The extremely high level of awareness for "sentinel events" of all network members has ensured several impressive successes of TropNetEurop. The latest example are the detection of falciparum malaria from Goa and the description of a cluster of chikungunya fever in Italy.



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 89 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.



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)	☐ Inpatient ☐ 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.	☐	**4.**	☐
2.	☐	**5.**	☐
3.	☐	**6.**	☐

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

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

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

Compliant ☐ Yes ☐….No

Patient Classification

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

Reason for most recent travel

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

Chief complaint (CHECK ALL THAT APPLY)

- ☐ Asymptomatic Screening

Or:

- ☐ Fever
- ☐ Fatigue
- ☐ Skin
- ☐ Respiratory
- ☐ Headache
- ☐ Lymphadenopathy
- ☐ Musculoskeletal
- ☐ Diarrhoea
- ☐ Vomiting
- ☐ ENT
- ☐ Genitourinary
- ☐ Neurologic
- ☐ Psychologic
- ☐ 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? ☐ Yes ☐ No If Yes, which? _____

DEATH? ☐ Yes ☐ No If Yes, why? _____

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? ☐ Yes ☐ 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? ☐ Yes ☐ 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: ☐ None	☐ Malaria-related complication	☐ Treatment failure	☐ Bacterial superinfection ☐ Other
Complications - details:			
Outcome: ☐ Cure without residues	☐ Cure with residues	☐ Exitus on day	
Outcome - details:			

Safety of i.v. Artesunate regimen:	Adverse drug reaction suspected? ☐ Yes ☐ 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**			**Relation with Artesunate**		
			mild, no specific medication needed	moderate, specific treatment needed	severe, disabling or life-threatening	No	Possible	Probable
1.			☐	☐	☐	☐	☐	☐

PRESENTATIONS

INTRODUCTION

The Unit Preparedness & Response, ECDC

Katrin Leitmeyer, Stockholm

No abstract available

The Lisbon Institute of Hygiene and Tropical Medicine and travel and tropical medicine in Portugal

Jorge Atouguia, Lisbon

As in several other Tropical Medicine Institutes all over the world, Travel Medicine started at the Lisbon Institute of Tropical Medicine and Hygiene (IHMT) back in the beginning of the 19th Century, when colons where lectured before starting a new life in Africa or some other far away country.

After the independence of the Portuguese colonies in 1975, most of the clinical activities were severely reduced. Consequently, travel advice in the Institute was limited to sporadic cases of individuals travelling to Portuguese-speaking countries for cooperation or business.

The emergence of modern patterns for international travelling forced IHMT to reorganise its clinical services. The Travel Medicine Clinic is presently able to provide up to date pre-travel information and post-travel management for international travellers, through its integration in Internet emerging diseases and Travel medicine E-mail lists. As this is an under-explored area in Portugal, much work has been done involving information and coordination activities within the framework of the Health Ministry, in collaboration with travel clinics all over the country.

Travel advice, vaccination and outpatient consultation (which also includes Tropical Paediatrics) is available 5 days a week upon personal, telephonic or E-mail contact. The annual number of travelers/patients is around 3000 and more that 1500 telephone, fax and e-mail counselling is provided to travellers, travel medicine specialists, other physicians and health workers. Since 1999 the Institute has a co-operation protocol with the Portuguese Council for Refugees (CPR), allowing refugees and asylum seekers to be directed to the IHMT for medical screening and care.

The Travel and Tropical Medicine Clinic is a WHO-approved Yellow Fever vaccination center. During 2006, 5 685 yellow fever vaccines were administered. Low consumption vaccines must be presently externally obtained. Additionally, several important anti-parasitic drugs and drug formulations can be found at the Clinic.

A Central laboratory provides valuable support, including parasitological, microbiologic, serologic tests and limited routine tests. This laboratory is a national reference in Parasitology and Mycology.

Clinical activities are integrated in IHMT's teaching and research structure in collaboration with the entomology, parasitology, microbiology, and international health divisions of the IHMT. The clinical experience of the Teaching and Research Unit of the Clinical Division is applied to the Courses the Unit offers: Travel Medicine, Tropical Medicine Clinics for Nurses and Clinics of Tropical Diseases for MDs.

Future prospects of the Travel and Tropical Medicine Clinics of the IHMT are based in the consolidation of its reference position in Portugal for Parasitic Diseases and Tropical Medicine. The strengthening of health cooperation with other travel centers in Portugal and Portuguese-speaking countries is another short-term objective of this Unit. Computerization of the reception, outpatient consultation, laboratory and vaccination activities and integration into a web-based information and clinical services supplier are also programmed, that will improve team performance and allow implementation and evaluation of collaboration/research protocols.

MALARIA

Rapid Diagnosis of Imported Malaria by a 2nd generation HRP-II based test and Expert Microscopy in Febrile Returned Travellers

J Cuadros, P Martín-Rabadán, FJ Merino, A Delgado-Irribarren, S Garcia-Bujalance, JM Rubio, Madrid-Spain

Malaria is the most potentially dangerous imported parasitic disease in Spain and other european countries and laboratories must be prepared round the clock to diagnose the disease quickly to start treatment and avoid complications. In recent years, a second generation of rapid diagnostic tests combining the detection of a soluble *Plasmodium* antigen, the histidine-rich protein II (HRP-2) and aldolase, an antigen common to all species of *Plasmodium*, has been marketed and proved to be useful. As a recent meta-analysis showed that HRP-2 based tests are superior to the lactate dehydrogenase (LDH) tests in diagnosis of malaria in non-inmune returned travellers ,we decided to perform a multicentric study to determine the performance of a HRP-2 based diagnostic kit (NOW® ICT) and expert microscopy in comparison to multiplex PCR as gold standard with a target population mainly composed by febrile semi-immune and non-immune and travellers returned from Africa.

Between 31/01/2005 and 31/08/2006, 221 patients were enrolled in the 5 centers. Sixty six (66) cases were positive by PCR (29 %; mean age, 31 years ± 16, interval, 3 months to 62 years); of those, 59, 2, 3 and 2 were identified by multiplex PCR as *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*, respectively. Absolute parasitemia was rated as negative (15, 23 %), very low (3, 5%), low (26, 39 %), moderate (8, 12 %), high (7, 11%) and undetermined (7 [11%]; in these patients parasitemia was reported only as relative proportion of parasitized red blood cells). In most cases (95 %), malaria was acquired in West Africa, mainly in Equatorial Guinea and Nigeria (83%) by recently arrived immigrants (less than 3 months, 24%) or first or second generation immigrants residing for long term in Spain and travelling back to their countries for visiting relatives and friends (65%).

The sensitivity, specificity, positive predictive value and negative predictive value of the HRP-2 based test and the thick film, respectively, in comparison with PCR for the diagnosis of malaria were: 84 % [95% CI, 76-93] *vs* 77 % [95% CI, 67-87], 98 % *vs* 98 %, 96 % *vs* 94 % and 93 % *vs* 91 %. In five patients (4 *P falciparum* and 1 *P vivax* infections; 8 % of all diagnosis) treatment was started because a positive NOW® ICT test was found, even though the thick film was negative. The PCR confirmed later the diagnosis.

In our population, mainly composed by West Africans with *P. falciparum* infection, NOW® ICT has shown to be a specific tool (98%, 95% CI, 96-100%) for diagnosis of malaria, with similar sensitivity as expert microscopy (84 % *vs* 77%) in comparison with multiplex PCR.

The contribution of field and laboratory studies for the understanding of putative resistance mechanisms to artemisinin derivatives in malaria parasites

Pedro Cravo, Axel Martinelli, Isabel Ferreira, Ana Afonso, Louise Rodrigues, Paul Hunt & Virgílio E. do Rosário

CMDT/IHMT/Biologia Molecular, Universidade Nova de Lisboa, Portugal; IIIR, University of Edinburgh, Scotland.

Artemisinin derivatives are the only compounds that still retain high efficacy against the human malaria parasite *Plasmodium falciparum*, but recent data begins to suggest that resistance may also develop against them. In an effort to identify putative modulators of artemisinin responses the artemisinin-sensitive clone *P. falciparum* Dd2 was grown *in vitro* in the presence of increasing concentrations of artemisinin. A resistant strain named *P. falciparum* Dd2-ARTmut was obtained, whose artemisinin IC50 was 100nM. Artemisinin resistance in Dd2-ARTmut proved to be unstable in the absence of drug pressure, however. Comparison of gene copy numbers between the resistant parasites and their sensitive ancestors revealed that whilst *PfATPase6* remained as a single copy in Dd2-ARTmut, the resistant parasites had gained three extra copies of the *Pfmdr1* gene during the artemisinin selection procedure. Interestingly, *pfmdr1* amplification was retained even after reversal to sensitivity, indicating that at least in our model, this genotype may be a consequence of resistance, rather than a cause.

During a large scale study in Africa (Rwanda and Sao Tome and Principe) and Brazil, samples from infected patients were collected and phenotyped for artemisinin susceptibility. The *PfATPase6* gene was sequenced in a subset of the samples for the identification of mutations potentially linked with decreased susceptibility, but no associations were detected. However, provisional analysis revealed the presence of regional genotypes. These data are providing a snapshot of the current degree of genetic variation in potential candidates for artemisinin resistance and will be of value in future drug resistance monitoring studies.

Effect of chemoprophylaxis on time to onset and diagnosis in travellers with vivax malaria

Ron Behrens Hospital for Tropical Diseases and London School of Hygiene and Tropical Medicine

Plasmodium vivax is the dominant species of malaria parasite in most areas outside of Africa. P. vivax causes considerable morbidity and infections are characterised by relapses at different intervals as a result of the activation of liver-stage hypnozoites. P. vivax strains from different geographic zones tend to display different relapse patterns. In general, strains from subtropical or tropical zones are associated with early primary infections followed by frequent relapses at short intervals, whereas strains from temperate zones are associated with primary infections that tend to be delayed, with fewer relapses. Mixed relapse patterns are observed in some areas. The determinant of P.vivax relapse patterns and other factors influencing relapses remain unclear. A number of epidemiological studies of P. vivax presentation in returned travellers highlighted that the majority of presentations occurred >2months after return and despite the use of chemoprophylaxis. These studies suggest the use of chemoprophylaxis may be a factor in this later presentation. I will review the current knowledge of the factors influencing onset and relapse of P. vivax malaria and present from two separate data sets, the association of prophylaxis use and onset of vivax malaria in returned travellers and the influence of chemoprophylaxis on the presentation of clinical disease. I will then open a discussion whether chemoprophylaxis has a role in travellers visiting areas where P. vivax predominates. I will examine the potential benefits and risks of withdrawing prophylaxis use for such travellers and alternative strategies.

Swiss Malaria prophylaxis for Short-term Travellers

January 2006
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	**11/2**	**1**	19-24	**2 1/2**	**2 1/2**	**1**
25-35	**2 x 3**	**2 x 3**	**2 x 3**					25-35	**2**	**11/2**	25-35	**3 1/2**	**3 1/2**	**2**
				31-40	**3**	**3**	**3**	36-50	**3**	**2**	36-50	**5**	**5**	**21/2**

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.

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MIGRANTS

Epimigra: clinical and laboratorial evaluation of migrants in Lisbon

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Background: For geographical and recent historic reasons, Portugal is a gateway and home for immigration from sub-Saharan countries. Misconceptions related to these populations often lead to consider them as high-frequency clusters for dissemination of infectious diseases, namely sexually transmitted infections (STI's). Epidemiological evidence-based data is needed to elucidate these issues and baseline prevalence studies are the starting point for this and thus, a project for epidemiological studies of transmittable diseases was started in 2001, denominated EopiMigra. Methodology: A prospective study was conducted in 497 migrants recently arrived in Portugal, at the time of their first consultation. Forty six percent of the individuals had clinical symptoms and in 32% was identified at least one transmittable disease, mainly intestinal parasitosis (10%) and sexually transmitted diseases (20%). In a subset of 220 African migrants (171 men and 49 women) the presence of STI´s was evaluated using a clinical syndromic approach and biological confirmation for gonorrhoea, *Chlamydia trachomatis* genital infection, syphilis, Hepatitis B and Human Immunodeficiency Virus (HIV) infection. Results: Global prevalence of the targeted infections were 1.8% for gonorrhoea, 0 % for *Chlamydia* infection, 4.1% for Syphilis, 5.9% for HBsAg presence and 7.3% for HIV infection. Globally, 16.4% of the studied persons had at least one sexually transmitted infection. Conclusions: We concluded that prevalence rates encountered in this population is similar to that of non-migrant Portuguese populations with a high risk for sexually transmitted diseases. Therefore migration from sub-Saharan Africa doesn't seem to constitute a particularly critical isolated factor for public health risk of STI´s in the community. We present and discuss the results of the identified transmittable diseases in the global migrant population studied at EpiMigra.

Chagas disease in migrants in France

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Chagas disease was an extremely rare imported infection in France. From 1980 to 2004 only two cases were published. They were two French travelers who made a short stay in South America. These two patients had an acute form of the disease. From 2004 to 2007, 13 cases were diagnosed in two teaching hospitals from Paris. All patients were Bolivian migrants recently arrived in France. Five had an indeterminate chronic form, four a chronic Chagas cardiomyopathy. Four are still under exploration, three are symptomatic. French clinicians are not familiar with the disease. In the first of our cases with cardiac involvement etiological diagnosis was missed and evocated only four months after the implantation of a pace-maker. Another problem was the lack of serological methods available in France, only immunofluorescence was used in a parasitological department of Paris. First sera had to be send for confirmation with another method to other countries (Brazil or Belgium). Now Chagas disease is a reality in France, and different methods for serologic diagnosis are used. Because of the emergence of the parasitosis in French Guiana, measures for control of transfusion risk were taken first in this department and more recently in metropolitan France.

Medical care for migrants in Madrid

Rogelio Lopez-Velez, Madrid

Malaria in migrants in the UK. Data from the Malaria Reference Laboratory and a plan for action

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There are 1500 to 2000 reports of imported malaria annually in the UK. About two thirds of all cases of falciparum malaria occur in London residents. These disproportionately affect those who go to visit friends and relatives abroad, and Nigeria and Ghana are the countries where most infections are acquired. Reports come from all areas of London, but with concentrations in particular geographical locations.

The "London Malaria Group" is a multi-disciplinary group, set up in 2003 with the aim of reducing the incidence of imported malaria in the Capital. Much of the work carried out to date has been on developing strategies for interventions to prevent and treat infections effectively. There are plans to simultaneously focus on several policy areas. These include: lobbying Governmental organisations, carrying out media campaigns and evaluating the effectiveness of prescribing anti-malarials on the National Health Service. Additionally there is a focus on ensuring local epidemiology is accurate and timely, and working with local African community groups to improve knowledge about the risk of acquiring malaria. Underlying the group's work are the Public Health principles of understanding the importance of the wider determinants of health, ensuring representation from the community most affected and using existing healthcare structures.

STUDIES: TROPNETEUROP & FRIENDS

August – September 2007: an oubreak of Chikungunya in Northern Italy

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135 cases of acute febrile illness, predominantly characterized by headache, myalgia, arthralgia and rash with dates of onset from 4 July to 28 August 2007, were observed among residents of Castiglione di Cervia and Castiglione di Ravenna, two adjacent villages in Ravenna Province, Emilia Romagna Region, divided by the River Savio. The acute phase of the illness which lasted 3-4 days was followed by prolonged severe asthenia. Eleven (11) cases required admission to hospital, including an 83-year-old man with multiple co-morbid chronic diseases who subsequently died.

The age range was 1 to 95 years, and 52% of the cases were females. The highest number of cases (11) was observed on 17 August 2007 with a marked decreasing trend in new cases noted since 21 August 2007. Preliminary epidemiological investigations conducted by local and national health authorities have identified an individual who returned from southern India at the end of June 2007 as the possible source of infection (source: W.H.O. REGIONAL Office, Europe). On 23 August 2007, local health authorities of Ravenna Province reported an outbreak of suspected arbovirus infection to the Ministry of Health, Italy. On 29 August, laboratory investigations performed on serum and blood samples obtained from potential cases at the Istituto Superiore di Sanità, Rome, confirmed chikungunya virus infection by immunoassay in 21 cases and by reverse transcription-polymerase chain reaction (RT-PCR) in six additional cases.

As of 13th September 2007, 254 cases of chikungunya (either confirmed or suspected) were notified in the Region. Chikungunya virus infection has been confirmed so far by laboratory tests in samples obtained from 78 patients (1). The majority of the cases have occurred in Castiglione di Cervia and Castiglione di Ravenna, whereas two additional clusters were detected in localities close to the towns of Cervia, Ravenna, Cesena and Forlí and Cesena Province. Additional, sporadic cases are being investigated in other localities of the following Provinces in Emilia Romagna Region: Ravenna, Forlí and Cesena, Rimini, Bologna, and Reggio Emilia (source: W.H.O. REGIONAL Office, Europe). Only a few days before the outbreak was made known, by coincidence, a description of chikungunya cases imported in Italy in 2006 was published by EID. The paper conclusion was as follows:
"The ability of A. albopictus to colonize new areas and its adaptability to the mild Italian climate allow vector populations to be active throughout the year (10). The patient is thought to be viremic for only 6–7 days (shortly before and during the febrile period) (6). We were unable to directly assess

viremia levels; however, almost half the patients were still febrile on return to Italy, which suggests a potential risk.

Although the same mosquito is a potential vector of dengue, no autochthonous case has been reported as yet, despite annual reports of many imported dengue cases in Italy. On the other hand, the clinical manifestations of both conditions are nonspecific, and a hypothetical autochthonous case would most likely go undiagnosed unless a targeted surveillance system were established. Prompt reporting of imported CHIKV infections is essential for monitoring of potential risk. The possibility of introducing CHIKV into Italy cannot be ruled out on the basis of current evidence." (2)

Although the epidemic curve is descending, it cannot be stated yet that the outbreak is over. This is the first event resulting in subsequent indigenous transmission of chikungunya in Europe, at least in recent historical times. Given the presence of the competent vector documented in at least 12 European countries (Albania, Italy, France, Belgium, Montenegro, Switzerland, Greece, Spain, Croatia, the Netherlands, Slovenia and Bosnia-Herzegovina) as well as favourable climatic conditions for the vector to persist in the coming few months in the Mediterranean basin, countries should remain vigilant for the emergence of this infectious disease (source: W.H.O. REGIONAL Office, Europe).

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The Exodus Software

Graham Fry, Dublin

No abstract available.

Treatment of complicated malaria with Artesunate

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I.v.-artesunate is a promising alternative to quinine for the treatment of patients with severe falciparum malaria. A number of recent studies in Asia have shown that treatment with i.v.-artesunate is at least equally effective to treatment with i.v.-quinine. I.v.-artesunate may offer significant advantages in treatment due to its excellent efficacy and low potential for side-effects, particularly when compared with i.v.-quinine.

Systematic data on the number of patients with severe malaria, the form and the outcome of treatment is not available since data collected on national and European level as well as data from TropNet does not allow to classify patients accurately with falciparum malaria as severe vs. non-severe. There is no published data available from patients treated under intensive-care conditions in industrialised countries.

A research initiative within TropNet with the following goals is suggested:

1. To obtain reliable data on the number, the form and efficacy of the treatment and the outcome of patients with severe malaria in Europe by adding a reporting system for cases of severe malaria to the existing TropNet reporting infrastructure
2. To systematically evaluate the efficacy, safety and tolerability of i.v.-artesunate vs. standard treatment of severe malaria in European patients
3. To provide access to i.v.-artesunate manufactured under GMP-standards for TropNet members and partners

European Observational Multicentre Study: Therapy of Uncomplicated Falciparum Malaria.

Martin Grobusch, Johannesburg

Therapy of imported uncomplicated falciparum malaria is by no means conducted uniformly throughout Europe. In fact, treatment strategies vary widely, as demonstrated by data obtained from TropNetEurop centres over the last years, and there is currently no standard therapy contributing centres would agree upon.

Centre-specific, and national, standards of care are based on data predominantly derived from therapeutic studies which have been performed in malaria-endemic areas. For epidemiological and biological reasons, these results are not always easily applicable to imported infections (large ethnically homogenous study cohorts, differences in the immune status of the hosts and vast variations of parasite strains from different geographic areas etc.).

The European multicentre MALTHER study conducted within the framework of TropNetEurop serves the purpose to observe and document current therapeutic strategies for uncomplicated falciparum malaria in order to make them comparable.

The study is now coming to a close, with recruitment ending at the end of October this year. The majority of cases (179 out of 305, or 64 %) has bene treated with atovaquoen/proguanil with approximately 15 % of all cases being treated with mefloquine and quinine and quinine combinations. This session will present a last interim analysis for efficacy of the first-line regimens, the therapeutic changes made necessary by adverse events, cure on D 28 and other key parameters prior to the final analysis to be begun towards the end of the year.

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JE vaccine in travellers

Ron Behrens, London & Christoph Hatz, Basel

The JE flavivirus causes a widespread disease in many rural parts of Asia, transmitted by Culex tritaeniorhynchus and other mosquito vectors. Children are more rarely symptomatic than older people, but the disease in endemic populations. Of those infected with the virus, around 1% develop clinical disease, one third die and one third develop permanent neurological sequelae. Fortunately, the risk of acquiring JE during travel to Asia appears to be very very low and only a handful of travel associated cases have been reported worldwide. This small risk may however be greater than contracting yellow fever. The risk has been estimated by some to be as high as, 1 in 5'000 per visit for persons staying in rural areas with paddy rice farming during the appropriate transmission seasons. Where there is a quantifiable risk, immunisation should with JE vaccine, should be recommended. The Swiss Expert Committee for Travel Medicine (ECTM) suggest that travellers spending 14 nights in endemic villages are at enough risk to require immunisation. However most travellers do not sleep close to rice paddies and this factor alone substantially reduces the risk of infection. Although the risk of severe adverse events is low in travellers and to date no fatal or anaphylactic reactions in travellers have been reported, a risk of vaccine against the benefit of avoided illness taking in to account the cost needs to be considered. We have investigated the risk of diseases, using surveillance reports of cases, serologically or clinically from the UK and Switzerland and plan to include other TropNet Europ members, along with the at risk population as the numbers of visits to endemic regions, adjusted by the numbers of travellers immunised, using doses of JE vaccine administered. This analysis will help define the risk of acquiring diseases and the likely population at risk of infection.