Malaria

Eskild Petersen, MD
Adjunct Professor of Tropical Medicine
Institute of Clinical Medicine
Aarhus University, Denmark
&
Senior Consultant
Department of Infectious Diseases
The Royal Hospital
Muscat
Sultanate of Oman
Human malaria

*Plasmodium falciparum*  
High mortality, drug resistance

*P. vivax*  
Persistent liverforms

*P. ovale*  
Persistent liverforms  
Classic and variant P.o

*P. malariae*  
Low pathogen, latent many years

*P. knowlesi*  
24 hours cycle, confused with  
*P. malariae* in Southeast Asia  
No known human to human transmission
Sporontocidal Drugs:
- Proguanil
- Pyrimethamine

Tissue Schizontocidal Drugs:
- Proguanil
- Pyrimethamine
- Primaquine
- Atovaquone
- Chlorproguanil

Blood Schizontocidal Drugs:
- Chloroquine
- Quinine
- Mefloquine
- Halofantrine
- Artemisinin
- Atovaquone
- Riamet
- Fansidar
- LapDap
- Amodiaquine

Gametocytocidal Drugs:
- Primaquine
- Tafenoquine

hypnozoites

P. falciparum Asexual erythrocytic stage 48 hrs

P. falciparum
Merozoite 15 mins
Liver stage 5.5 days
Sporozoite 15 - 45 mins
Gametocytes (mature) 2.5 - 22 days
Gametocytes (immature) / sequestered in deep tissues, e.g. bone marrow 10 - 12 days
Gametocytes 10 - 60 mins
Zygote
Oocyst 8 - 12 days
Ookinete
10 - 36 hrs
MOSQUITO
MAN

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ESCMID Online Lecture Library
Development in the mosquito
Exit from the liver

Release of merozoites to the bloodstream

Liver schizont
Epidemiology
Pre control
Figure 2: Global distribution of infection with *Plasmodium falciparum* malaria
Reproduced from Hay and Snow, and licensed to the Malaria Atlas Project (http://www.map.ox.ac.uk). PfAPI = *P. falciparum* annual parasite incidence per 1000 people per year. PfPR<sub>2-10</sub> = *P. falciparum* parasite rate age-standardised to 2-10 years.

ITH, WHO 2010
Malaria in the U.A.E.

Before and during the 1960s, malaria used to be a major public health problem in the United Arab Emirates (UAE), with foci on the East coast, Ras Al Khaimah, the Central Plateau and Al Ain.

Transmission was by *Anopheles stephensi* and *Anopheles culicifacies* breeding mainly in deep wells, shallow wells, basins, drums, and irrigation channels ("farms").

The prevailing parasite species were *Plasmodium vivax* and *Plasmodium falciparum*, with a sporadic occurrence of *Plasmodium malariae*.

Local malaria transmission in UAE has come to an end in 1997. From 1998 to 2004, no autochthonous cases have been reported, and UAE was certified to be a malaria free country.

Substantial importation of malaria cases from abroad, concerning both UAE nationals and especially immigrants from malarious countries with a total number of cases of 2,119 in 2007.

**Plasmodium vivax** malaria: A re-emerging threat for temperate climate zones?

Eskild Petersen a,*, Carlo Severini b, Stephane Picot c,d

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Table 1: Latest year of autochthonous malaria transmission in Europe.

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greece</td>
<td>1973</td>
</tr>
<tr>
<td>Rumania</td>
<td>1963</td>
</tr>
<tr>
<td>Hungary</td>
<td>1962</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>1961</td>
</tr>
<tr>
<td>Finland</td>
<td>1947</td>
</tr>
<tr>
<td>Former Yugoslavia</td>
<td>1964</td>
</tr>
<tr>
<td>Spain</td>
<td>1962</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>1960</td>
</tr>
<tr>
<td>Russia (from Soviet Union areas)</td>
<td>1960</td>
</tr>
<tr>
<td>Portugal</td>
<td>1958</td>
</tr>
<tr>
<td>Poland</td>
<td>1956</td>
</tr>
<tr>
<td>Italy</td>
<td>1951</td>
</tr>
<tr>
<td>France</td>
<td>1950</td>
</tr>
<tr>
<td>Germany (West)</td>
<td>1950</td>
</tr>
<tr>
<td>Austria</td>
<td>1947</td>
</tr>
<tr>
<td>Sweden</td>
<td>1939</td>
</tr>
<tr>
<td>U.K.</td>
<td>1921</td>
</tr>
<tr>
<td>Denmark</td>
<td>1900</td>
</tr>
<tr>
<td>Norway</td>
<td>1850</td>
</tr>
</tbody>
</table>

*a* Local transmission originating from a case infected abroad not included.

Malaria in Greece 2012

http://www.cdc.gov/malaria/new_info/2012/malariagreece.html

COMMUNICABLE DISEASE THREATS REPORT
CDTR Week 37, 9-15 September 2012
All users
This weekly bulletin provides updates on threats monitored by ECDC.

I. Executive summary
EU Threats
Malaria - Greece - 2012
Opening date: 31 May 2012 Latest update: 7 September 2012
Since June 2012, eight autochthonous cases of malaria, caused by Plasmodium vivax infection, have been reported from Greece. Local control measures have been implemented in accordance with national guidelines.

Update of the week
No additional autochthonous cases were reported since the last update.


Indices of endemoepidemiology of Marathon District (1932 - 1939).

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of spleens examined</th>
<th>Spleen Index %</th>
<th>Parasite Index %</th>
<th>Average Spleen enlargement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1932</td>
<td>141</td>
<td>55</td>
<td>23</td>
<td>0.79</td>
</tr>
<tr>
<td>1933</td>
<td>120</td>
<td>39</td>
<td>17</td>
<td>0.64</td>
</tr>
<tr>
<td>1934</td>
<td>142</td>
<td>51</td>
<td>25</td>
<td>0.77</td>
</tr>
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<td>1935</td>
<td>129</td>
<td>31</td>
<td>10</td>
<td>0.40</td>
</tr>
<tr>
<td>1936</td>
<td>145</td>
<td>17</td>
<td>3</td>
<td>0.19</td>
</tr>
<tr>
<td>1937</td>
<td>145</td>
<td>23</td>
<td>3</td>
<td>0.33</td>
</tr>
<tr>
<td>1938</td>
<td>139</td>
<td>25</td>
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<td>0.37</td>
</tr>
<tr>
<td>1939</td>
<td>73</td>
<td>19</td>
<td>10</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Livadas GA & Sphangos JC. Malaria in Greece (1930 – 1940).
Pyrsos, Athen 1940. Vol. 2. p. 259, table CXLVI
Pathophysiology
The merozoite
Riley & Stewart Nat Med 2013;19:168-78
P. falciparum-infected RBCs bind to the postcapillary endothelial cells (sequestration) and to noninfected RBCs. Both phenomena are thought to contribute to the occlusion of blood flow and consequent severe disease.

Fig. 3. Red blood cell deformability: An unparasitized red blood cells shows considerable elongation in order to pass a rigid parasitized red blood cell adhering to the endothelium of the capillary.

Diagnostics
The malaria team, Liberia
Malaria: thick blood films

1. 
2. 
3. 
4. 

Dry the slide, and it can be send by mail.
If the thick blood film is not distributed on the slide, it will detach under transport or during staining,
Plasmodium falciparum – thin blood films

Ring forms

Ring forms

Schizont - early

Schizont - late

Schizont - burst

Schizont - burst

Gametocyte

Gametocytes
Sensitivity (parasite threshold) microscopy

COMPARISON OF TWO METHODS FOR ENUMERATING MALARIA PARASITES IN THICK BLOOD FILMS

ESKILD PETERSEN, N. T. MARBIAH, LAURA NEW AND ADAM GOTTSCHAU
Laboratory of Parasitology, and Department of Biostatistics, Statens Seruminstitut, Copenhagen, Denmark; Department of Epidemiology and Population Sciences, London School of Hygiene and Tropical Medicine, London, United Kingdom; European Community Malaria Control Project, Bo, Sierra Leone

Threshold: 2.6 parasites per microliter

(Giemsa stained thick blood films)

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Rapid diagnostic tests
Microscopy and limitations of rapid tests

Centers managing patients with malaria must be able to provide round the clock malaria microscopy of thick and thin blood films and parasite density calculations.

Rapid tests may be false negative in cases with very high *P. falciparum* density ?? (Gillett et al. Malaria J 2009; 8:271)

(HRP2 deletion in parts of South America)

Variant *P. ovale*

(Tordrup et al. Malaria J 2011;10:15)

*P. knowlesi* HRP2 based tests will be negative sensitivity variable with other tests

Malaria Rapid Diagnostic Test Performance

Summary results of WHO product testing of malaria RDTs: rounds 1-6 (2008–2015)

http://www.who.int/malaria/publications/atoz/9789241510035/en/
Performance of Malaria Rapid Diagnostic Tests

http://www.who.int/malaria/publications/atoz/9789241510035/en/
Performance of Malaria Rapid diagnostic Tests – final assessment

Figure S3: Panel detection score of malaria combination RDTs meeting WHO procurement criteria for false-positive and invalid rates, in phase 2 of rounds 3–6 against wild-type (clinical) samples containing *P. falciparum* and *P. vivax* at low parasite density (200 parasites/μL)

- 7 NanoSign Malaria Pf/Pan Ag 3.0 RMAP10
- 8 BIONOTE MALARIA P.f. & P.v. Ag Rapid Test Kit RG19-12
- 81. Humasis Malaria P.f/P.v Antigen Test AMFV-7025

http://www.who.int/malaria/publications/atoz/9789241510035/en/
New Malaria Test, Illumigene® Malaria, Sets a New Gold Standard for Diagnosis

Meridian Bioscience collaborates with the Centers for Disease Control and Prevention and Cheikh Anta Diop University of Dakar to launch diagnostic test up to 80,000 times more sensitive than current options.

Meridian Bioscience, Inc., Cincinnati, Ohio (NASDAQ: VIVO) today announced that it has received the CE Mark for Illumigene® Malaria, a novel, highly accurate test developed by Meridian with the technical assistance of the Centers for Disease Control and Prevention (CDC) and Cheikh Anta Diop University of Dakar, Senegal. The test is up to 80,000 times more sensitive at detecting the malaria parasite than conventional tests, potentially revolutionizing malaria diagnosis and establishing a new gold standard. Using innovative molecular LAMP technology, Illumigene results are available in under one hour, and the test is easy to use as it does not rely on high level technical expertise. This is a major step forward for people with malaria as faster, more accurate diagnoses
Revolutionize your lab’s diagnostic accuracy with the molecular performance of illumigene® Malaria.

- **Sensitivity** — Analytical sensitivity up to 80,000x more than conventional methods¹,²
- **Speed** — Precise results in less than one hour
- **Simplicity** — Minimal technical expertise required
- **Affordable** — No capital investment necessary

100 parasites necessary per microliter to detect malaria by using microscopy

**ONLY 0.06-2** parasites necessary per microliter to detect malaria by using illumigene®

500-5,000 parasites necessary per microliter to detect malaria by using RT-PCR
Malaria surveillance in the Democratic Republic of the Congo: comparison of microscopy, PCR, and rapid diagnostic test

Stephanie M. Doctor a,*, Yunhao Liu a, b, Amy Whitesell a, Kyaw L. Thway a, Steve M. Taylor c, Mark Janko d, e, Michael Emch d, e, Melchior Kashamuka f, Jérémie Muwonga g, Antoinette Tshefu f, Steven R. Meshnick a

a Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC 27599, USA
b Department of Statistics and Operations Research, University of North Carolina, Chapel Hill, NC 27599, USA
c Division of Infectious Diseases and International Health, Duke University Medical Center, Durham, NC 27708, USA
d Department of Geography, University of North Carolina, Chapel Hill, NC 27599, USA
e Carolina Population Center, University of North Carolina, Chapel Hill, NC 27599, USA
f École de Santé Publique, Faculté de Médecine, Université de Kinshasa, Kinshasa, Democratic Republic of the Congo
g Programme National de Lutte contre le SIDA et les IST, Kinshasa, Democratic Republic of the Congo

Sensitivity and specificity of diagnostic methods versus PCR and LCA.

<table>
<thead>
<tr>
<th></th>
<th>Versus PCR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity (95% CI)</td>
<td>Specificity (95% CI)</td>
</tr>
<tr>
<td>PCR</td>
<td>61.6 (59.7–63.4)</td>
<td>95.1 (94.4–95.7)</td>
</tr>
<tr>
<td>Microscopy</td>
<td>71.6 (69.8–73.2)</td>
<td>86.0 (84.9–87.0)</td>
</tr>
</tbody>
</table>

CI = confidence interval.
Reduction of anti-malarial consumption after rapid diagnostic tests implementation in Dar es Salaam: a before-after and cluster randomized controlled study

Valérie D’Acremont¹²³, Judith Kahama-Maro¹²³, Ndëfiria Swai³, Deo Mtasiwa⁴, Blaise Genton¹²³ and Christian Lengeler²

![Graph showing changes in consultations, diagnosis, blood slides, RDTs, and positive tests over time.]
Limitations of RDT’s

Validated only against *P. falciparum* and *P. Vivax*

Capture 2 antigens: Histidine Rich Protein 2, HRP2, and a pan malaria antigen: LDH or Aldolase

LDH and Aldolase conserved in all 5 human species

But the capture in RDT’s of the pan-malaria antigens not validated
Variant *Plasmodium ovale* isolated from a patient infected in Ghana

David Tordrup¹, Jakob Virenfeldt², Felicie F Andersen¹, Eskild Petersen²*  

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**Figure 2** Phylogenetic tree based on the concatenated sequences of *possrdna*, *poldh*, *pocysp*, *pocox1* and *pocytb*. Scale bar indicates expected number of substitutions per nucleotide site.
Droplet Microfluidics Platform for Highly Sensitive and Quantitative Detection of Malaria-Causing Plasmodium Parasites Based on Enzyme Activity Measurement

Sissel Juul,†, ‡ Christine J. F. Nielsen, †, ‡ Rodrigo Labouriau, †, ‡ Amit Roy, † Cinzia Tesauro, § Pia W. Jensen, † Charlotte Harmsen, † Emil L. Kristoffersen, †, ‡ Ya-Ling Chiu, † Rikke Frøhlich, † Paola Fiorani, † Janet Cox-Singh, † David Tordrup, † Jørn Koch, † Anne-Lise Bienvenu, ⊙ Alessandro Desideri, § Stephane Picot, ⊙ Eskild Petersen, ⊙ Kam W. Leong, † Yi-Ping Ho, ○ Magnus Stougaard, †, ○ and Birgitta R. Knudsen †, ○, *

Juul et al ASC Nano 2012
Which method should we use?

Detection levels of different diagnostic methods:

Rapid tests

200 parasites per mm$^3$

W.H.O. 2015

Microscopy

2.6 parasites per mm$^3$

(experienced microscopist)


PCR

0.2 parasites per mm$^3$

Rapid tests 20000 parasites per mm³
Microscopy 2.6 parasites per mm³
PCR 0.2 parasites per mm³

Can we use the rapid tests?

Parasites per µl
500.000 (10%)
50.000 (1:100)
5000 (1:1000)
500 (1:10.000)
50 (1: 100.000)
5 (1:1 mil.)
Comparison of sensitivity and specificity of four methods for detection of *Giardia* spp. in feces:

immunofluorescence and PCR are superior to microscopy of concentrated iodine stained samples

Running title

Compare diagnostic methods to find *Giardia duodenalis*

Helle Gottfred-Rasmussen (1), Marianne Lund (2), Heidi L. Enemark (3), Mogens Erlandsen (4), Eskild Petersen#(1)
Malaria disease

Day 0
Infective bite

Dag 5-7
The liver merozoites invade the blood

Day 10 – 14
Start of symptoms

Diagnostics difficult

Parasites per μl
- 500,000 (10%)
- 50,000 (1:100)
- 5,000 (1:1,000)
- 500 (1:10,000)
- 50 (1:100,000)
- 5 (1:1,000,000)

P. falciparum fever curve
P. vivax fever curve
P. falciparum parasitemia
Case fatality rate’s

Overall *P. falciparum* (1977-86)  
1.3

Range in Europe  
0.5 - 5.8

Switzerland 1988-2002  
2.2


A cluster of 56 patients returning from Gambia with falciparum malaria has been noted in several countries of the European Union since September this year. TropNetEuropol, the European Network on Imported Infectious Disease Surveillance, collected and reported the cases. Lack of awareness and, consequently, of prophylactic measures against malaria were apparent in the majority of patients.

The Netherlands

In the Netherlands, 10 Dutch tourists were reported with falciparum malaria after returning from Gambia between 21 September and 26 November 2008. The median age was 48 years (range 43-62), six patients were female. Three cases were related (travel companions). The median duration of stay was nine days (range 7-68). Seven travellers did not use malaria chemoprophylaxis, two used homeopathic drugs (chininum arsenicosum D8) and one tourist stopped atovaquone/proguanil prematurely. The median shortest incubation period was five days (range 0-18). The median interval between the first day of illness and the date of diagnosis was five days (range 0-17). Seven patients were admitted to hospital for treatment. Two patients, aged 45 and 49, died. Both patients had not used chemoprophylaxis. The time to diagnosis was 17 and six days, respectively [3].

3 patients died = 5.3% (3/56)
The development of immunity to malaria

Figure 1. Age-specific parasite rates and positive parasite densities for asexual parasites of *Plasmodium falciparum* and *Plasmodium malariae*. Left axis shows geometric mean positive parasite density as parasites per microliter; right axis shows parasite rate. Category axis shows age groups in days (to age 182 days) and in years. Pregnant women were excluded.
Severe and/or complicated malaria

Clinical features:
- impaired consciousness or unrousable coma
- prostration, i.e. generalized weakness so that the patient is unable walk or sit up without assistance
- failure to feed
- multiple convulsions – more than two episodes in 24 h
- deep breathing, respiratory distress (acidotic breathing)
- circulatory collapse or shock, systolic blood pressure < 70 mm Hg in adults and < 50 mm Hg in children
- clinical jaundice plus evidence of other vital organ dysfunction
- haemoglobinuria
- abnormal spontaneous bleeding
- pulmonary oedema (radiological)

Laboratory findings:
- hypoglycaemia (blood glucose < 2.2 mmol/l or < 40 mg/dl)
- metabolic acidosis (plasma bicarbonate < 15 mmol/l)
- severe normocytic anaemia (Hb < 5 g/dl, packed cell volume < 15%)
- haemoglobinuria
- hyperparasitaemia (> 2% / 100 000 /µl in low intensity transmission areas or > 5% or 250 000 /µl in areas of high stable malaria transmission intensity)
- hyperlactataemia (lactate > 5 mmol/l)
- renal impairment (serum creatinine > 265 µmol/l).

Can be both *P. falciparum* and *P. vivax*
Severe and/or complicated malaria

Can be both *P.falciparum* and *P. vivax*

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- hyperlactataemia (lactate > 5 mmol/l)
- renal impairment (serum creatinine > 265 µmol/l).
Vital signs in children with malaria during the first 24 hours

Figure 1. Vital Signs of Children during the First 24 h after Admission

Figure 1. Mortality in severe falciparum malaria. The mortality (indicated as a percentage) of the common syndromes of severe malaria are clinically defined by: (i) impaired consciousness (cerebral malaria); (ii) deep breathing (respiratory distress) and severe anaemia (haemoglobin <5 g dl\(^{-1}\)). Adapted from Ref. [13].
Management of imported malaria in Europe

Helena H Askling1,2, Fabrice Bruneel3, Gerd Burchard4, Francesco Castelli5, Peter L Chiodini6, Martin P Grobusch7, Rogelio Lopez-Vélez8, Margaret Paul9, Eskild Petersen10*, Cornelia Popescu11, Michael Ramharter12 and Patricia Schlagenhauf13 on behalf of the European Society for Clinical Microbiology and Infectious Diseases Study Group on Clinical Parasitology, ESGCP
Treatment of uncomplicated malaria

*P.falciparum*

Treatment should provide rapid clinical and parasitological cure within three days.

Oral ACTs are the standard treatment of uncomplicated malaria.

Currently, the ACTs artemether-lumefantrine, ATM/LUM, Riamet™ and dihydroartesmisinin-piperaquine, DHA/PIP, Euartesim™

Alternatives: proguanil/atovaquone, Malarone ™ or mefloquine, Lariam ™

*P. vivax, ovale, malariae, knowlesi*

Chloroquine or ACT

Primaquine for *P.vivax* and *P.ovale* hypnozoites
Policy brief on single-dose primaquine as a gametocytocide in *Plasmodium falciparum* malaria

January 2015

In low transmission areas, give a single dose of 0.25 mg/kg primaquine with ACT to patients with *P. falciparum* malaria (except pregnant women, infants aged < 6 months and breastfeeding women of infants aged < 6 months) to reduce transmission. Testing for G6PD deficiency is not required.
Treatment of severe malaria

Intravenous Artemisinin hemisuccinate, Artesunate™, IVA, is superior to intravenous quinine (IVQ) in overall survival, and IVA should be the drug of choice for treatment of severe imported malaria in Europe.

Intravenous quinine hydrochloride, IVQ, is the drug of choice if IVA is not available.

Oral follow up treatment
ACT as soon as the parasite density has decreased adequately (< 2%).

If ACT is not available:
Doxycycline (adults only) (or clindamycin during pregnancy) should be used combined with quinine.
Mefloquine should be avoided in patients with cerebral malaria even in the recovery phase.

ESCMID Study Group on Clinical Parasitology. Malaria J 2012;11:328
Retrospective analysis of severe malaria cases
7 centres: 4 Germany, 1 Denmark, Norway, Sweden
25 patients with severe malaria (1 child, 24 adults)
18 travellers from Europe, 7 Visiting Friends and Relatives
Clinical presentation: 80% hyperparasitaemia, 32% cerebral malaria
All treated with iv artesunate (Guilin Pharma)

Estimation of Frequency of Haemolysis

Analysis based on retrospective cohort studies (n=4) and prospective study (n=1)

Total number of patients: 192
Total number of haemolysis cases: 24 (13%; 95% CI: 9-18%)

Information about RBC transfusion (n=27)
Transfusion necessary: 23 (85%; 95% CI: 67-94%)

Estimated 11% of treated patients required RBC transfusions
Implications for Clinical Practice

1. Be aware of potential of post-treatment haemolysis!!!

2. Assure follow up for 4-6 weeks post treatment with Hb measurements two times every week
   • in returning travellers
   • in African children!!!

1. iv Artesunate remains treatment of choice for severe malaria

2. Consider more prudent use of artesunate in moderately severe malaria?

3. Further research is needed to fully understand pathophysiology of haemolysis associated with the use of artemisinin derivatives
Malaria risk from blood transfusion and organ donation

Malaria risk from blood transfusion is well known.

Patients with fever, thrombocytopenia and disseminated intravascular coagulation without an explanation should be investigated for malaria in they have received a blood transfusion within the past 3 months.

Prevention:

1. Exclude donors from risk areas
2. Screen blood with a test for malaria-specific antibodies  
   (Rapid tests, microscopy and PCR not sensitive enough)
3. Give treatment to all recipients (highly endemic tropical Africa)
Drugs
Treatment
and
Prophylaxis
<table>
<thead>
<tr>
<th>Area</th>
<th>Population</th>
<th>Malaria cases per number of noninfected travelers</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghana</td>
<td>Visiting friends and relatives</td>
<td>1 : 77</td>
<td>[14]</td>
</tr>
<tr>
<td>Nigeria</td>
<td>Visiting friends and relatives</td>
<td>1 : 106</td>
<td>[14]</td>
</tr>
<tr>
<td>Ghana - <em>P. falciparum</em></td>
<td>All travelers</td>
<td>1 : 137</td>
<td>[2]</td>
</tr>
<tr>
<td>India - <em>P. vivax</em></td>
<td>All travelers</td>
<td>1 : 286</td>
<td>[14]</td>
</tr>
<tr>
<td>Kenya</td>
<td>Business travelers</td>
<td>1 : 215</td>
<td>[14]</td>
</tr>
<tr>
<td>West Africa - <em>P. falciparum</em></td>
<td>All travelers</td>
<td>1 : 322</td>
<td>[14]</td>
</tr>
<tr>
<td>Gambia - <em>P. falciparum</em></td>
<td>All travelers</td>
<td>1 : 634</td>
<td>[2]</td>
</tr>
<tr>
<td>East Africa - <em>P. vivax</em></td>
<td>All travelers</td>
<td>1 : 1,159</td>
<td>[14]</td>
</tr>
<tr>
<td>Indonesia - all species</td>
<td>All travelers</td>
<td>1 : 1,320</td>
<td>[2]</td>
</tr>
<tr>
<td>Tanzania - <em>P. falciparum</em></td>
<td>All travelers</td>
<td>1 : 2,804</td>
<td>[2]</td>
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<tr>
<td>East Africa - <em>P. falciparum</em></td>
<td>All travelers</td>
<td>1 : 3,478</td>
<td>[14]</td>
</tr>
<tr>
<td>West Africa - not <em>P. falciparum</em></td>
<td>All travelers</td>
<td>1 : 6,441</td>
<td>[14]</td>
</tr>
<tr>
<td>Thailand - all species</td>
<td>All travelers</td>
<td>1 : 15,000</td>
<td>[12]</td>
</tr>
<tr>
<td>Latin America - <em>P. vivax</em></td>
<td>All travelers</td>
<td>1 : 16,666</td>
<td>[14]</td>
</tr>
<tr>
<td>India - <em>P. falciparum</em></td>
<td>All travelers</td>
<td>1 : 18,079</td>
<td>[14]</td>
</tr>
<tr>
<td>Thailand - <em>P. vivax</em></td>
<td>All travelers</td>
<td>1 : 19,391</td>
<td>[2]</td>
</tr>
<tr>
<td>Thailand - <em>P. falciparum</em></td>
<td>All travelers</td>
<td>1 : 35,000</td>
<td>[12]</td>
</tr>
<tr>
<td>Thailand - <em>P. falciparum</em></td>
<td>All travelers</td>
<td>1 : 58,173</td>
<td>[2]</td>
</tr>
<tr>
<td>Latin America - <em>P. falciparum</em></td>
<td>All travelers</td>
<td>1 : 100,000</td>
<td>[14]</td>
</tr>
</tbody>
</table>

Resistance

S  Susceptible, hvor parasitæmien er borte efter senst 7 dage

RI  hvor parasitæmien initialt forsvinder, men kommer igen enten indenfor 7 dage (early), eller efter 7 dage (late)

RII  hvor parasitæmien mindsker, men aldrig forsvinder

RIII  hvor behandlingen ikke påvirker parasitæmien overhovedet
Artemisinins are isolated from the leaves of the *A. annua* (wormwood).

Known in Chinese herbal medicine under the name Quinghao.

The antimalarial activity was rediscovered in China in 1971.

Intravenous Artesunate for severe malaria

- Comparison of iv artesunate versus i.v. quinine

- **SEAQUAMAT trial**
  - South East Asia (adults)
    - N=1461
    - ~35% reduction in mortality

- **AQUAMAT trial**
  - Africa (children)
    - N=5425
    - ~23% reduction in mortality

Riamet

- Artemether 20mg
- Lumefantrine 120mg
- Blister packages with 24 tablets

- Tbl. Riamet® contains 20 mg artemether and 120 mg lumefantrin.
- Adults and chld. > 35 kg: Tbl. Riamet 4 tabl. at hours 0, 8, 24, 36, 48 and 60
- Children 25-35 kg: Tbl. Riamet 3 tabl. at hours 0, 8, 24, 36, 48 and 60
- Children 15-25 kg: Tbl. Riamet 2 tabl. at hours 0, 8, 24, 36, 48 and 60
- Children 5-15 kg: Tbl. Riamet 1 tabl. At hours 0, 8, 24, 36, 48 and 60
Tolerability of malaria chemoprophylaxis in non-immune travellers to sub-Saharan Africa: multicentre, randomised, double blind, four arm study

Patricia Schlagenhauf, Alois Tschopp, Richard Johnson, Hans D Nothdurft, Bernhard Beck, Eli Schwartz, Markus Herold, Bjarne Krebs, Olivia Veit, Regina Allwinn and Robert Steffen

Table 1 Incidence of adverse events in antimalarial prophylaxis arms according to severity. Values are numbers (percentages, 95% confidence intervals) unless stated otherwise

<table>
<thead>
<tr>
<th>Type of adverse event</th>
<th>Melloquine group* (n=153)</th>
<th>Chloroquine and proguanil group (n=150)</th>
<th>Doxycycline group (n=153)</th>
<th>Atovaquone and proguanil (n=164)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severity of adverse event:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild†</td>
<td>135 (86, 83 to 93)</td>
<td>131 (86, 80 to 91)</td>
<td>128 (84, 78 to 90)</td>
<td>134 (82, 75 to 88)</td>
<td>0.42</td>
</tr>
<tr>
<td>Moderate‡</td>
<td>64 (42, 34 to 50)</td>
<td>69 (45, 37 to 53)</td>
<td>51 (33, 26 to 41)</td>
<td>53 (32, 25 to 40)</td>
<td>0.048</td>
</tr>
<tr>
<td>Severe§</td>
<td>16 (11, 6 to 15)</td>
<td>19 (12, 7 to 18)</td>
<td>9 (6, 2 to 10)</td>
<td>11 (7, 2 to 11)</td>
<td>0.14</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>6 (4, 1 to 8)</td>
<td>8 (5, 2 to 9)</td>
<td>5 (3, 0 to 6)</td>
<td>3 (2, 0 to 4)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

*One participant had a transient ischaemic attack outside follow up; history of two episodes was not declared (mefloquine serum concentrations were negligible).
†Trivial but some discomfort noted.
‡Interferes with daily activity.
§Medical advice required.
Current Challenges in Travelers’ Malaria
Patricia Schlagenhauf • Eskild Petersen
# Malaria Chemoprophylaxis: Strategies for Risk Groups

Patricia Schlagenhauf\textsuperscript{1} and Eskild Petersen\textsuperscript{2},

*University of Zurich Centre for Travel Medicine, WHO Collaborating Centre for Travellers’ Health, Institute for Social and Preventive Medicine, University of Zürich, Zürich, Switzerland\textsuperscript{1} and Department of Infectious Diseases, Aarhus University Hospital—Skejby, Aarhus, Denmark\textsuperscript{2}*

## TABLE 1. Risk of malaria in short-term travelers at different levels of endemicity in the indigenous population and mortality from malaria in short-term travelers

<table>
<thead>
<tr>
<th>Annual incidence of malaria cases in local population</th>
<th>Example of area of endemicity\textsuperscript{a}</th>
<th>Incidence per 2 wk per 100,000 travelers</th>
<th>Incidence per 2 wk per 100,000 travelers without prophylaxis</th>
<th>Incidence per 2 wk per 100,000 travelers with prophylaxis assuming 90% efficacy of prophylaxis</th>
<th>Mortality per 100,000 travelers per 2 wk without prophylaxis</th>
<th>Mortality per 100,000 travelers per 2 wk with prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 per 1,000</td>
<td>Mexico, parts of South America, Vietnam (except Binh Province)</td>
<td>1.9</td>
<td>3.8</td>
<td>0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 per 1,000</td>
<td>Parts of Vietnam (Binh Phuoc province)</td>
<td>19.2</td>
<td>38.5</td>
<td>3.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 per 1,000</td>
<td>Parts of India (Assam, Gujarat, Orissa, Rajasthan)</td>
<td>38.4</td>
<td>76.8</td>
<td>7.7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>50 per 1,000</td>
<td>Parts of South Africa</td>
<td>96.1</td>
<td>192.3</td>
<td>19.2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>100 per 1,000</td>
<td>Western Africa</td>
<td>192.3</td>
<td>384.6</td>
<td>38.5</td>
<td>8</td>
<td>0.5</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Assuming a case fatality rate of 2\%. Short-term travel is considered to be travel in a region of endemicity lasting 2 weeks or less.

\textsuperscript{b} The areas mentioned serve only as examples of areas with different levels of endemicity in the indigenous population. Risk in southeastern Asia is very unevenly distributed within each country and should be assessed at district levels based on the travelers’ planned route and using malaria maps (30).
Malaria map for travellers (adapted from WHO)

Area marked with red: chemoprophylaxis, German speaking countries
Malaria risk in Brasilien

WHO World Malaria Report 2012

Malaria risk in India

WHO World Malaria Report 2012

http://www.who.int/malaria/publications/country-profiles/
P. falciparum is increasing in India
Malaria risk in Thailand

WHO World Malaria Report 2012

http://www.who.int/malaria/publications/country-profiles/
Effect of IPTc on clinical malaria during the intervention period. AQ: amodiaquine, AS: artesunate, bi: bimonthly administration, CI: confidence interval, DHA: dihydroartemisinin, PQ: piperaquine, SP: sulphadoxine pyrimethamine.

Control
Impregnated bed nets
and
vaccines
Insecticide treated nets – ITN’s

http://www.worldmalariareport.org/map?color=41
ITN’s provide at least 50% protection

Protective efficacies on episodes of clinical malaria observed during the Weekly morbidity surveys

<table>
<thead>
<tr>
<th>Description</th>
<th>Incidence</th>
<th>Protective efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (No intervention)</td>
<td>37.7</td>
<td>0</td>
</tr>
<tr>
<td>Impregnated nets</td>
<td>19.2</td>
<td>49%</td>
</tr>
<tr>
<td>Maloprim fortnightly</td>
<td>22.2</td>
<td>42%</td>
</tr>
<tr>
<td>Nets and maloprim</td>
<td>10.7</td>
<td>72%</td>
</tr>
</tbody>
</table>

^1 Active case detection. Malaria episodes per 1000 child weeks at risk

Protection against a Malaria Challenge by Sporozoite Inoculation

Meta Roestenberg, M.D., Matthew McCall, M.D., Joost Hopman, M.D., Jorien Wiersma, Adrian J.F. Luty, Ph.D., Geert Jan van Gemert, B.Sc., Marga van de Vegte-Bolmer, B.Sc., Ben van Schaijk, M.Sc., Karina Teelen, Theo Arens, Lopke Spaarman, B.Sc., Quirijn de Mast, M.D., Wil Roefien, Ph.D., Georges Snounou, Ph.D., Laurent Réna, Ph.D., Andre van der Ven, M.D., Cornelus C. Hermsen, Ph.D., and Robert Sauerwein, M.D.

A Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in Africa
Conclusion

RTS,S/ASO2 is the only vaccine in phase III and shows only short term, limited protection (30%).

Attenuated sporozoites induce good protection

Stimulation of Cytotoxic T cells has been disappointing in humans

From discovery to phase III trials takes many years

Induction of antibodies and/or IFNγ responses are NOT equivalent to protective immunity

Impregnated bed nets provide better protection than the vaccine
Thank you