Société belge d'infectiologie et de microbiologie clinique
Belgische vereniging voor infectiologie en klinische microbiologie

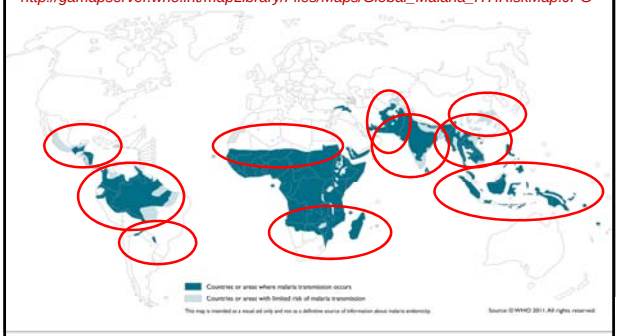
24-10-2013

Malaria chemoprophylaxis & WHO maps of the low risk areas in Asia and Latin America

Fons Van Gompel MD, DTM
Internal Medicine & Tropical Medicine
Associate Professor Tropical Medicine
Institute for Tropical Medicine Antwerp Belgium www.itg.be

Malaria, countries or areas at risk of transmission, 2010

http://gamapserver.who.int/mapLibrary/Files/Maps/Global_Malaria_ITHRiskMap.JPG



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

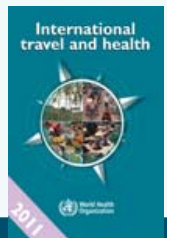
World Health Organization

Accessed 24-10-2013

- Be Aware of the risk, the incubation period, and the main symptoms.
- Avoid being Bitten by mosquitoes, especially between dusk and dawn.
- Take antimalarial drugs (Chemoprophylaxis) when appropriate, to prevent infection from developing into clinical disease.
- Immediately seek Diagnosis and treatment if a fever develops one week or more after entering an area where there is a malaria risk and up to 3 months (or, rarely, later) after departure from a risk area.

2013

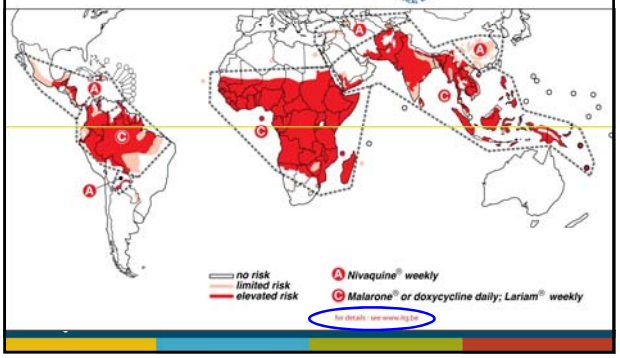
2011 = 2012 = 2013



	zone	Malaria risk	Type of prevention
Type I	A	Very limited risk of malaria transmission	Mosquito bite prevention only
Type II	A	Risk of *P. vivax* malaria only; or fully chloroquine-sensitive *P. falciparum*	Mosquito bite prevention plus chloroquine chemoprophylaxis
Type III	C	Risk of *P. vivax* and *P. falciparum* malaria transmission, combined with emerging chloroquine resistance	Mosquito bite prevention plus chloroquine + proguanil chemoprophylaxis
Type IV	C	(1) High risk of *P. falciparum* malaria, in combination with reported antimalarial drug resistance; or (2) Moderate/low risk of *P. falciparum* malaria, in combination with reported high levels of drug resistance	Mosquito bite prevention plus mefloquine, doxycycline or atovaquone-proguanil chemoprophylaxis (select according to reported resistance pattern)

2012 = 2013

Malaria 2012-2013 (source WHO 2009)



…… ALREADY NUANCED ADVICE IN BELGIUM

- Altitude
- Season
- Urban & periurban areas, popular touristic resorts *versus* rural areas, hilly forests, etc
- Travellers who spend the nights in very good conditions (luxury hotels, but also correctly applied antimosquito measures) *versus* rudimentary accomodations
- *(long term travelers and frequent travelers versus short term traveling tourists)*

5

Malaria chemoprophylaxis & WHO maps of the low risk areas in Asia and Latin America

PART I - SOME HISTORY

6

TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE (1996) 90, 680–681

The risk of malaria in travellers to Thailand

David R. Hill[1], Ronald H. Behrens[2] and David J. Bradley[3] [1]The International Traveler's Medical Service, University of Connecticut School of Medicine, Farmington, Connecticut, USA; [2]Travel Clinic, Hospital for Tropical Diseases, London, UK; [3]Department of Epidemiology and Population Sciences, London School of Hygiene and Tropical Medicine, London, UK

1996

The prophylaxis of malaria has become complex because of
- increasing drug resistance of Plasmodium falciparum and
- the availability of new antimalarial drugs such as mefloquine

In addition, **the perceived risk of malaria by both travellers and medical practitioners may differ from the actual risk and lead to inappropriate or excessive use of chemoprophylaxis**.

- These issues are particularly relevant when advising travellers to **Thailand,** one of the most popular destinations for UK travellers. In Thailand, most visited areas are **free of malaria**. However, there is **focal** transmission of **multi-drug resistant** P. falciparum.

7

TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE (1996) 90, 680–681

1996

Table. Malaria attack rates in travellers to Thailand, 1991–1993

	No. of cases	No. of travellers	Case rate
P. falciparum	7	–	1:35 012
P. vivax	13	–	1:18 853
Total	20	245 085	1:12 254[a]

[a]Overall attack rate.

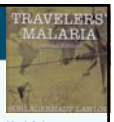
In the light of these data, which demonstrate **a very low malaria case rate**, current recommendations for malaria prophylaxis for travellers to Thailand need to be emphasized to **avoid excessive use of chemoprophylaxis**.

Following risk based recommendations would limit the use of mefloquine for Thailand and minimize risk of the rare but severe neuropsychiatric reactions to the drug which are reported in approximately one per 10000 users (STEFFEN *et al.*, 1993), a rate higher than that of the risk for falciparum malaria in Thailand.

8

Strategies of Malaria Prevention in Nonimmune Visitors to Endemic Countries

2001 & 2008



No zero-risk strategies against malaria can be offered,
- and in minimizing the risk the primary principle is, **primum non nocere** (first, do no harm)
- This dogma is valid in preventive medicine even more than in therapy; adverse events will impair previously healthy persons (who are more likely to complain), and there may be situations in treatment that force one to accept a greater risk.

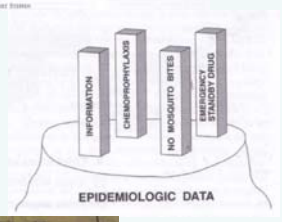
With this in mind, we must analyze the **pros and cons** of each of the **four strategic options** available for malaria prophylaxis in nonimmune visitors to endemic countries:

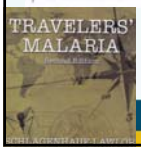
A. information,
B. personal protection measures (PPMs) against mosquito bites,
C. chemoprophylaxis (ie, chemosuppression), and
D. prompt assessment and treatment of symptoms suggestive of malaria, including emergency self-therapy (standby emergency treatment) in special circumstances.

9

2001 & 2008

STRATEGIES OF MALARIA PREVENTION IN NONIMMUNE VISITORS TO ENDEMIC COUNTRIES





Whenever possible, recommendations should be based on evidence; that is, **on recent epidemiologic** and pharmacologic **data** (Figure 1).

Unfortunately, there is clearly a **lack of reliable data relevant for travelers**.

Analyzing the available database, one becomes aware that there is great **variability in the risk of malaria transmission**, depending mainly on the duration of stay and the destination.

Whenever available, **the annual entomological inoculation rate (EIR)** may indicate the magnitude of the risk; however, the EIR rarely takes seasonality into account.

The risk for nonimmune travelers **varies enormously** between countries and even **within a country.**

10

VARIABLES USED FOR CONSTRUCTING MAPS

- **EIR**
  - = Entomological Inoculation Rate
  - = **mas**, where
    - **ma** = number of mosquito bites per night and
    - **s** = proportion of those bites positive for sporozoites
- **API**
  - = Annual Parasite Incidence
  - = annual case incidence data
  - = confirmed cases during 1 year/population under surveillance x 1000- *e,g, dark grey areas have an unstable risk of malaria transmission (i.e. annual case incidence, or API, is reported at less than 1 per 10,000).*
- **PfPR2-10**
  - = **Age-standardised *P. falciparum* Parasite Rate**
  - = the estimated proportion of 2-10 year olds in the general population that are infected with P. falciparum at any one time, averaged over 12 months

11

Risk varies enormously

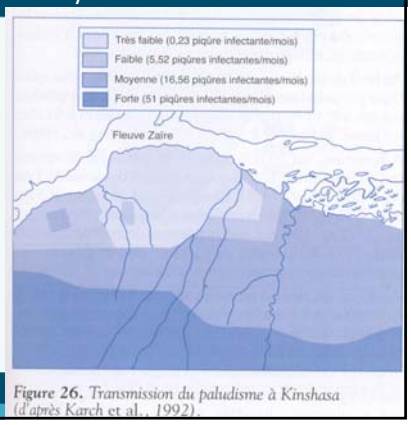


Figure 26. *Transmission du paludisme à Kinshasa (d'après Karch et al., 1992).*

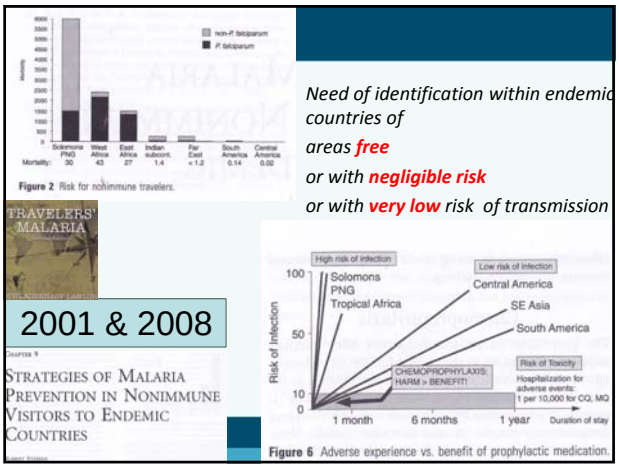
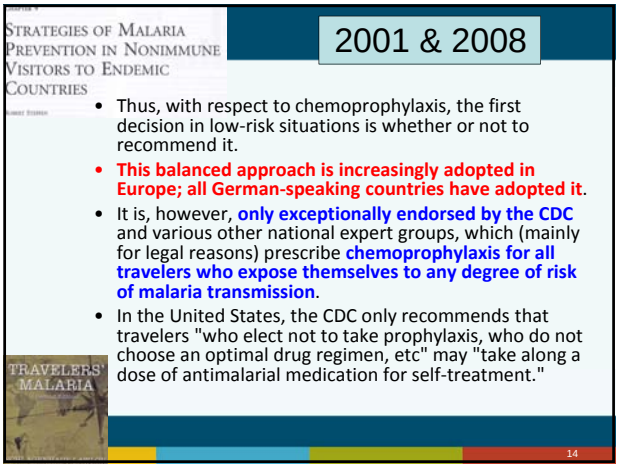
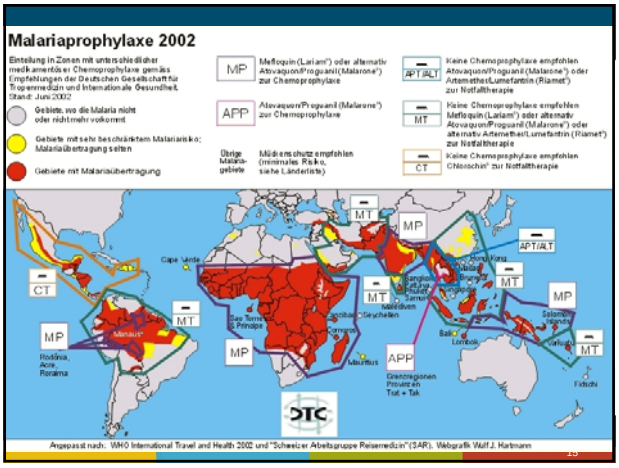
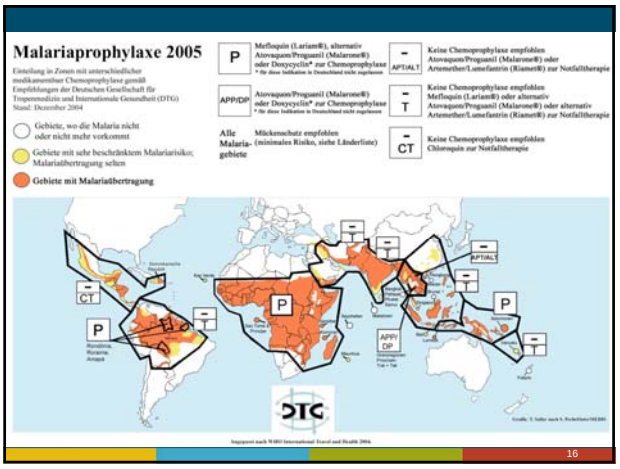
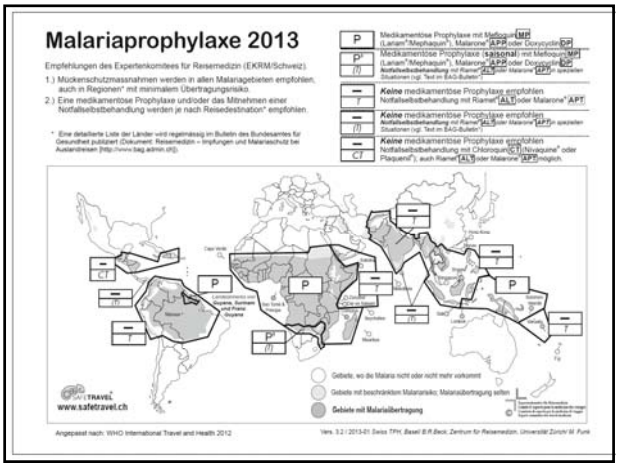


Figure 2 Risk for nonimmune travelers.
TRAVELERS' MALARIA
2001 & 2008
STRATEGIES OF MALARIA PREVENTION IN NONIMMUNE VISITORS TO ENDEMIC COUNTRIES
Need of identification within endemic countries of
areas free
or with negligible risk
or with very low risk of transmission
High risk of infection
Low risk of infection
Solomons
PNG
Tropical Africa
Central America
SE Asia
South America
Risk of Infection
CHEMOPROPHYLAXIS: HARM > BENEFIT!
Risk of Toxicity
1 month
6 months
1 year
Duration of stay
Figure 6 Adverse experience vs. benefit of prophylactic medication.


STRATEGIES OF MALARIA PREVENTION IN NONIMMUNE VISITORS TO ENDEMIC COUNTRIES
2001 & 2008
Thus, with respect to chemoprophylaxis, the first decision in low-risk situations is whether or not to recommend it.
This balanced approach is increasingly adopted in Europe; all German-speaking countries have adopted it.
It is, however, only exceptionally endorsed by the CDC and various other national expert groups, which (mainly for legal reasons) prescribe chemoprophylaxis for all travelers who expose themselves to any degree of risk of malaria transmission.
In the United States, the CDC only recommends that travelers "who elect not to take prophylaxis, who do not choose an optimal drug regimen, etc" may "take along a dose of antimalarial medication for self-treatment."
TRAVELERS' MALARIA
14


Malariaprophylaxe 2002
MP
APP
MT
CT
APT/ALT
DTG
Angepasst nach: WHO International Travel and Health 2002 und "Schweizer Arbeitsgruppe Reisemedizin" (SAR). Webgrafik Wolf J. Hartmann





In many Asian & Latin American regions
(http://www.dtg.org/21.0.html)
one can dispense with the chemoprophylaxis
(even for adventurous travellers)

- *after having an extensive talk with a **specialized doctor** who will evaluate the malaria risk depending on the type of lodgings*
- *and only when strict measures are taken against mosquito bites from dusk till dawn*
- *and malaria emergency treatment is available with complete instructions.*

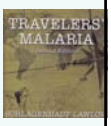
18

Comparison Europa versus US – BIG CONTRAST

CHAPTER 26

CLOSING THE CIRCLE: COMPLIANCE AND ADHERENCE

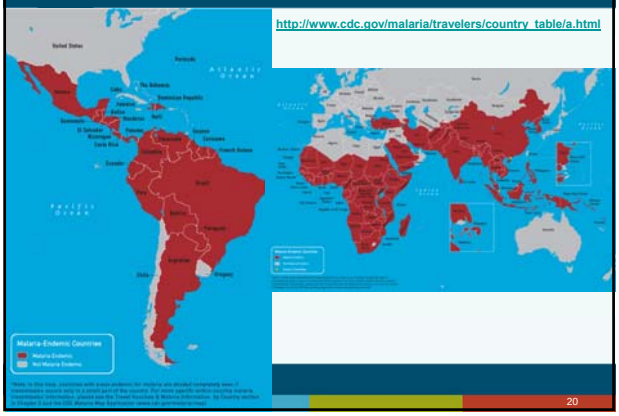
JAY KEYSTONE
PHYLLIS KOZARSKY



Every case of malaria in a traveler represents a failure: failure of public health and the travel industry to promote awareness of the risk, failure of the traveler to seek pretravel health advice, failure of the health care provider to provide appropriate advice, and most important of all, failure of the traveler to adhere to appropriate recommendations for preventing the infection. Recent data from GeoSentinel, the global surveil-

Comparison Europa versus US – BIG CONTRAST

http://www.cdc.gov/malaria/travelers/country_table/a.html

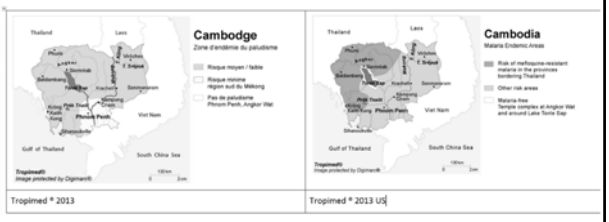


20

ZIMBABWE European advice versus US advice

21

CAMBODJA European advice versus US advice



22

Symposium 1b

ALL OR NOTHING – MALARIA PREVENTION FOR THE MINIMAL RISK TRAVELLER

Patricia Schlagenhauf Lawlor *University of Zurich Centre for Travel Medicine, Switzerland*

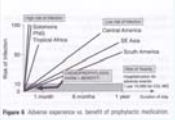
NECTM 2006

Many travellers will, however, visit countries and regions with a low risk, others will alternate between high and low risk regions and some, particularly business travellers, will have frequent albeit brief periods of exposure.

- **one size malaria recommendations are illusionary**

Advising low risk travellers is a challenge:

- What is the risk of malaria at the destination?
- Which species is pre-dominant–the life-threatening Plasmodium falciparum or the more benign Plasmodium vivax?
- What are the pitfalls of personal protective measures in areas where the perceived risk is minimal?
- **Should a chemoprophylaxis be recommended for low risk areas if the risk of drug associated adverse events outweighs the risk of acquiring malaria?**
- Can travellers be empowered to recognize and treat malaria using a standby emergency self-treatment?



The key to advising minimal risk travellers lies in

- risk-benefit analyses
- evidence based recommendations
- Individually tailored, expert advice

23

Who Needs Drug Prophylaxis against Malaria? My Personal View

2005

Lars Rombo

A long tradition of successful malaria prophylaxis with chloroquine led to a dogma that drug prophylaxis should be given regardless of risk as soon as a traveler entered endemic areas. This prevailed also when resistance to chloroquine and adverse effects of alternatives became a problem. A cost/benefit analysis of the risk for malaria versus risk for adverse effects and cost of the recommended drug is not uniformly applied and drug prophylaxis is still advocated even when the risk for severe adverse effects greatly exceeds the risk for malaria, which is unethical.

Lars Rombo, MD, PhD, DTM&H: Professor, Department of Infectious Diseases, Mälarsjukhuset Eskilstuna and Karolinska Institute, Stockholm, Sweden.

J Travel Med 2005; 12:217–221.

24

Who Needs Drug Prophylaxis against Malaria?

My Personal View

Lars Rombo

J Travel Med 2005; 12:217–221.

- The **habit of recommending prophylactic drugs** - even when the risk for malaria was only theoretical - prevailed
- The risk for malaria is often presented as **the proportion of the local population with malaria each year**,
- *for example, the **annual parasite incidence (API)**, which is how many per 1,000 in a local population have been diagnosed with malaria during a year.*
- The **API** is often given for separate districts within a country as it is most often used for national malaria programs.
  - The index cannot be used for travelers' risk assessment in countries with high endemicity as asymptomatic carriers and patients given presumptive treatment are not included.
  - The API for a district is most valid as a risk estimate for a traveler visiting relatives or friends among the local population.
- **The risk, however, is less for visitors than for the local population, for the following reasons:**

25

Who Needs Drug Prophylaxis against Malaria?

My Personal View

Lars Rombo

J Travel Med 2005; 12:217–221.

The risk is less for visitors than for the local population, for the following reasons:

1. Visitors usually spend **much less than a year** in the endemic area.
2. Visitors usually go where other people live, that is, to **urban areas**; malaria outside tropical Africa is scanty or nonexistent compared with rural areas.
3. Most tourists visit malarious areas during the **dry season** when there is generally less risk of transmission.
4. Most visitors use **some sort of protection**, whether it be repellents, protective clothing, or air-conditioned quarters.
5. The **quality of housing for visitors is generally better** than for the local population, that is, accommodations with glass windows and doors that can be sealed.

26

Who Needs Drug Prophylaxis against Malaria?

My Personal View

Lars Rombo

When Is the Risk for Malaria High Enough to Warrant the Use of Prophylactic Antimalarials?

It has recently been suggested that drug prophylaxis should only be used in areas where the risk in the local population **exceeds 10 cases of P. falciparum malaria per 1,000 inhabitants per year**, approximately 1 in 100 person-years.

Petersen E. Malaria chemoprophylaxis: when should we use it and what are the options? Expert Rev Antiinfect Ther 2004; 2:89–102.

I prefer to recommend that prophylaxis with drugs be given

if the risk for malaria despite other precautions

exceeds 1 in 10,000 travelers

J Travel Med 2005; 12:217–221.

27

Who Needs Drug Prophylaxis against Malaria?
My Personal View
Lars Rombo

J Travel Med 2005; 12:217–221.

- Antimalarial drugs are prescribed to far too many travelers.
- To prescribe a drug and feel content with the fact that you have done your part, and that it is then up to the traveler to accept the drawbacks concerning price and potential adverse effects, is not an ethical approach.

28

ONE SIZE FITS ALL DOES NOT EXIST

one size malaria recommendations are illusionary

"EENDUIDIGE RICHTLIJNEN – VOOR IEDEREEN BRUIKBAAR

EN

TOCH IN STAAT STELLEN OM ADVIES OP MAAT TE LATEN MAKEN"

29

2013

SMV

LA LETTRE
de la SOCIÉTÉ DE MÉDECINE DES VOYAGES

Lettre de liaison des centres de vaccination et d'information aux voyageurs

ÉDITORIAL

Il est temps de franchir le pas !

Oui il est temps de franchir le pas d'une réduction des indications de la chimio-prophylaxie dans les zones à faible, voire très faible risque de paludisme pour les voyages touristiques « standards ».
Ces zones correspondent essentiellement à l'Amérique tropicale et à l'Asie du Sud et du Sud-Est. La principale justification à cette évolution logique est l'application d'une règle de conduite dont la culture médicale fran-

5/10 000, a été récemment réévalué à 2/100 000 (Schmid 2009, Van Rijckevorsel 2010), celui en Amérique tropicale étant peu différent (CDC 1985, Massad 2009). De l'autre côté, le risque d'effet secondaire grave pour la méfloquine se situe entre 1/600 (Barrett 1996) et 1/20 000 (Roche 1997) et, si les données sont moins précises pour l'association atovaquone-proguanil et les cyclines, il est loin d'être nul (Jacquerioz Cochrane 2010, Boggild 2007, Banque nationale de pharmaco-vigilance France 1995-2008) et on admet que, de façon générale, il est de l'ordre de 1/100 000 pour toute

30

Il est temps de franchir le pas ! 2013

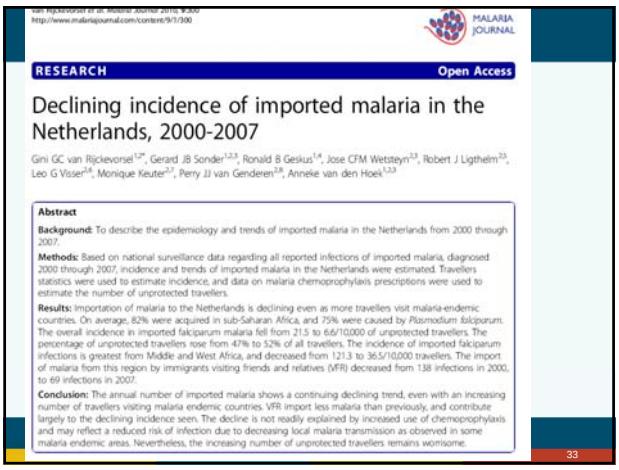
- **O**ui il est temps de franchir le pas d'une réduction des indications de la chimioprophylaxie dans les zones à faible, voire très faible risque de paludisme pour les voyages touristiques « standards ».
- Ces zones correspondent essentiellement à l'Amérique tropicale et à l'Asie du Sud et du Sud-Est.
- La principale justification à cette évolution logique est l'application d'une règle de conduite dont la culture médicale française n'est probablement pas assez imprégnée : **la balance bénéfice/risque**.

31

Il est temps de franchir le pas ! 2013

- cela fait des années que plusieurs pays d'Europe du Nord ne recommandent plus de chimioprophylaxie pour ces zones avec ces mêmes arguments, *même si un traitement de réserve est dans certains cas proposé, ce qui relève d'une certaine hypocrisie* !
- C'est le rôle d'une société savante que d'être un peu en avance sur les recommandations nationales et de contribuer à les faire évoluer,

32



MALARIA JOURNAL

RESEARCH Open Access

Declining incidence of imported malaria in the Netherlands, 2000-2007

Gini GC van Rijckevorsel[1,2*], Gerard JB Sonder[1,2,3], Ronald B Geskus[1,4], Jose CFM Wetsteyn[2,3], Robert J Ligtheim[2,5], Leo G Visser[2,6], Monique Keuter[2,7], Perry JJ van Genderen[2,8], Anneke van den Hoek[1,2,3]

Abstract

Background: To describe the epidemiology and trends of imported malaria in the Netherlands from 2000 through 2007.

Methods: Based on national surveillance data regarding all reported infections of imported malaria, diagnosed 2000 through 2007, incidence and trends of imported malaria in the Netherlands were estimated. Travellers statistics were used to estimate incidence, and data on malaria chemoprophylaxis prescriptions were used to estimate the number of unprotected travellers.

Results: Importation of malaria to the Netherlands is declining even as more travellers visit malaria-endemic countries. On average, 82% were acquired in sub-Saharan Africa, and 75% were caused by *Plasmodium falciparum*. The overall incidence in imported falciparum malaria fell from 21.5 to 6.6/10,000 of unprotected travellers. The percentage of unprotected travellers rose from 47% to 52% of all travellers. The incidence of imported falciparum infections is greatest from Middle and West Africa, and decreased from 121.3 to 36.5/10,000 travellers. The import of malaria from this region by immigrants visiting friends and relatives (VFR) decreased from 138 infections in 2000, to 69 infections in 2007.

Conclusion: The annual number of imported malaria shows a continuing declining trend, even with an increasing number of travellers visiting malaria endemic countries. VFR import less malaria than previously, and contribute largely to the declining incidence seen. The decline is not readily explained by increased use of chemoprophylaxis and may reflect a reduced risk of infection due to decreasing local malaria transmission as observed in some malaria endemic areas. Nevertheless, the increasing number of unprotected travellers remains worrisome.

33

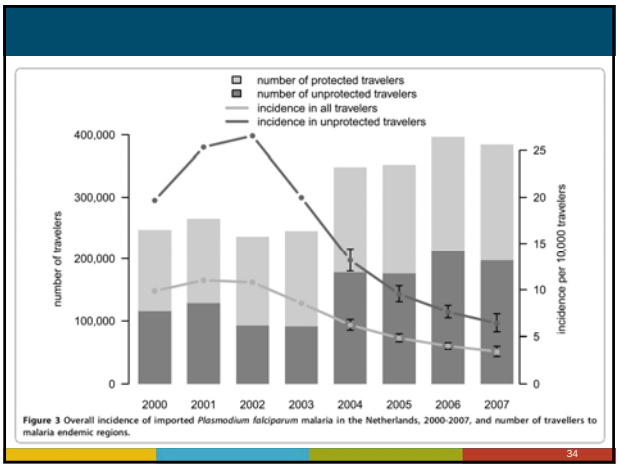


Figure 3 Overall incidence of imported *Plasmodium falciparum* malaria in the Netherlands, 2000-2007, and number of travellers to malaria endemic regions.

34

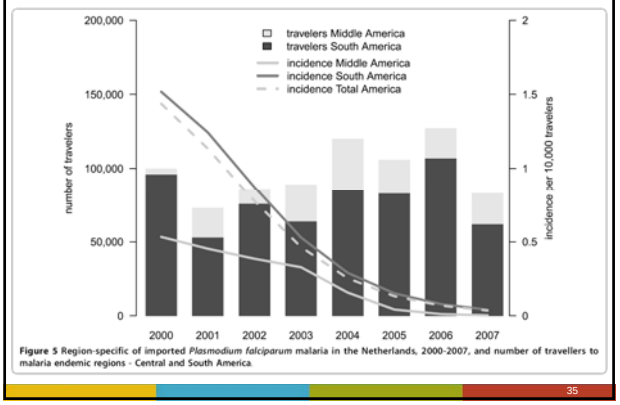


Figure 5 Region-specific of imported *Plasmodium falciparum* malaria in the Netherlands, 2000-2007, and number of travellers to malaria endemic regions - Central and South America.

35

Malaria chemoprophylaxis & WHO maps of the low risk areas in Asia and Latin America

PART II - ACTUAL MAPS

36

CISTM 13 LECTURE NOOR
www.ISTM.org
accessed at 9th October 2013

Malaria Maps: Relevance for Travel Recommendations

Dr Abdisalan M Noor (anoor@kemri-wellcome.org)
KEMRI/Wellcome Trust Research Programme,
Malaria Public Health Department

Objectives

1. Describe the process of making and updating malaria maps
2. Provide examples of malaria maps freely available on the internet
3. Discuss which kind of malaria maps and how they could be used to update travel recommendations

Mapping Malaria Transmission: The main approaches

1. Expert opinion
2. Climate suitability
3. Vector distribution & bionomics
4. Parasite rate

Mapping Malaria Risk in Africa (MARA)
http://www.mara.org.za/

Set up in 1996 with HQ in Durban, South Africa

Formally funded in 1997 by the IDRC

Focus of mapping malaria risk in Africa

Developed several malaria mapping products

MARA Malaria endemicity mapping

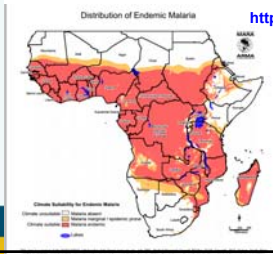
Malaria endemicity was defined as areas climatically unsuitable/suitable for malaria transmission using a Fuzzy Logic approach with temperature and rainfall as main inputs

Fuzzy Climate Suitability = $\cos^2\left(\frac{(x-U)/(S-U)*\pi}{2}\right)$

x= climate parameter
U= value when climatic conditions are unsuitable
S= value when climatic conditions are suitable

Distribution of Endemic Malaria

http://www.mara.org.za/



MARA Malaria Seasonality mapping

Climate suitability index used to define spatial extent

Rainfall patterns and volume used to define seasonality

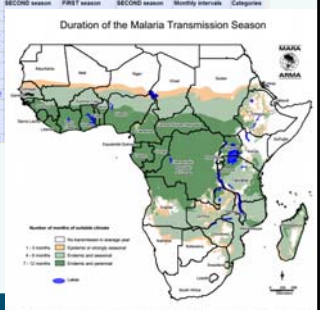
A4 maps of malaria in Adobe Acrobat (pdf) format

To view and print the maps you need Adobe Acrobat Reader software

Before using the maps, read the background information

		Distribution Model				Seasonality Model				
		Distribution of endemic malaria		First Month of the transmission season		Last Month of the transmission season		Duration of the transmission sea		
	Country Map	Gradient	Categories	FIRST season	SECOND season	FIRST season	SECOND season	Monthly intervals	Categories	
Africa		AfDistributionGrad.PDF	AfDistribution.PDF	AfFirstMonth.PDF						
West Africa										
Angola	Ang.PDF	AngDistributionGrad.PDF	AngDistribution.PDF	AngFirstMonth.PDF						
Benin	Ben.PDF	BenDistributionGrad.PDF	BenDistribution.PDF	BenFirstMonth.PDF						
Botswana	Bot.PDF	BotDistributionGrad.PDF	BotDistribution.PDF	BotFirstMonth.PDF						
Burkina Faso	Bok.PDF	BokDistributionGrad.PDF	BokDistribution.PDF	BokFirstMonth.PDF						
Burundi	Bur.PDF	BurDistributionGrad.PDF	BurDistribution.PDF	BurFirstMonth.PDF						
Cameroun	Cam.PDF	CamDistributionGrad.PDF	CamDistribution.PDF	CamFirstMonth.PDF						
Cape Verde	Ver.PDF									
Central African Republic	Car.PDF	CarDistributionGrad.PDF	CarDistribution.PDF	CarFirstMonth.PDF						
Chad	Cha.PDF	ChaDistributionGrad.PDF	ChaDistribution.PDF	ChaFirstMonth.PDF						

Duration of the Malaria Transmission Season



MAP

Malaria Atlas Project (MAP)
http://www.map.ox.ac.uk/

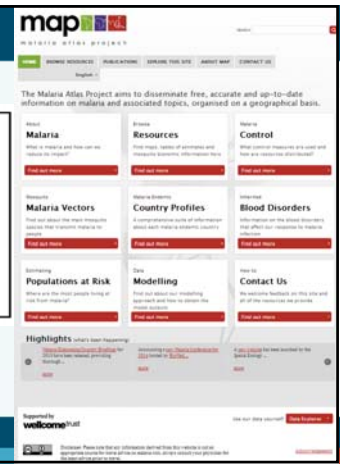
Set up in 2005 by the University of Oxford and the KEMRI/Wellcome Trust Research Programme in Nairobi

Funded by the Wellcome Trust, UK

Focus on mapping malaria globally

>20,000 geo-coded parasite survey data assembled

Developed several malaria mapping products



VARIABLES USED FOR CONSTRUCTING MAPS

- **EIR**
  = **Entomological Inoculation Rate**
  = **mas**, where
  ma = number of mosquito bites per night and
  s = proportion of those bites positive for sporozoites
- **API**
  = **Annual Parasite Incidence**
  = annual case incidence data
  = confirmed cases during 1 year/population under surveillance x 1000- *e,g, dark grey areas have an unstable risk of malaria transmission (i.e. annual case incidence, or API, is reported at less than 1 per 10,000).*
- **PfPR2-10**
  = Age-standardised *P. falciparum* Parasite Rate
  = the estimated proportion of 2-10 year olds in the general population that are infected with P. falciparum at any one time, averaged over 12 months

41

PLoS Medicine | www.plosmedicine.org 0300 February 2008 | Volume 5 | Issue 2 | e38

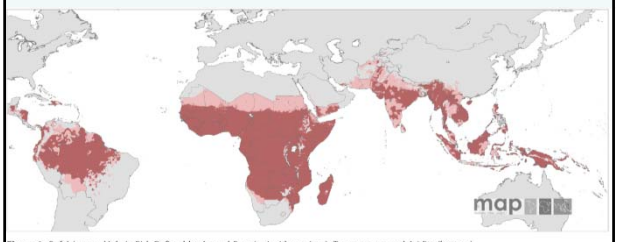
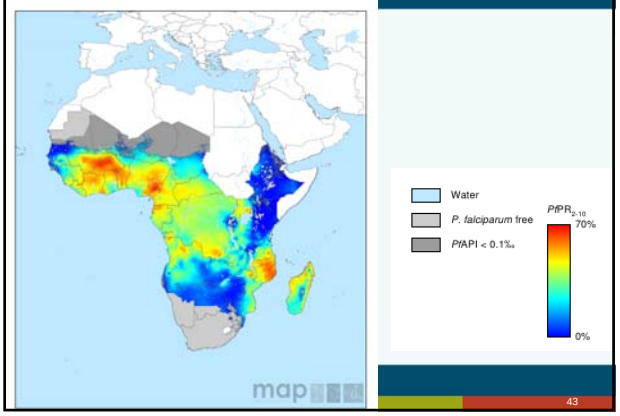


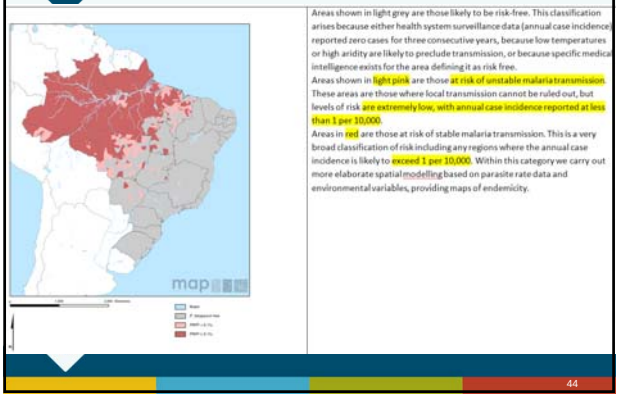
Figure 1. *P. falciparum* Malaria Risk Defined by Annual Parasite Incidence (top), Temperature, and Aridity (bottom)
Areas were defined as stable (dark-red areas, where *PfAPI* > 0.1 per thousand pa), unstable (pink areas, where *PfAPI* < 0.1 per thousand pa), or no risk (light grey). The few areas for which no *PfAPI* data could be obtained, mainly found in India, are coloured in dark grey. The borders of the 87 countries defined as *P. falciparum* endemic are shown. Highland areas where risk was excluded due to temperature appear in light grey. The aridity mask excluded risk in a step-wise fashion, reflected mainly in the larger extents of unstable (pink) areas compared to the top panel, particularly in the Sahel and southwest Asia (southern Iran and Pakistan).
doi:10.1371/journal.pmed.0050038.g001

42

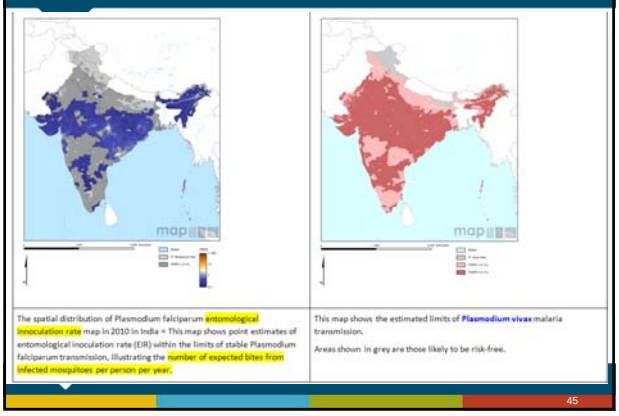
MAP http://www.map.ox.ac.uk/



MAP http://www.map.ox.ac.uk/



MAP http://www.map.ox.ac.uk/



CISTM 13 LECTURE NOOR
www.ISTM.org
accessed at 9th October 2013

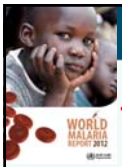
pro's and Con's

Product	Pros	Cons
Source: MARA		
Climate Suitability for transmission map	Main inputs are climatic indicators therefore easy to update dynamically	Represent a 'natural' state of risk and does not account for effect of extensive control, urbanisation etc So far developed only for Africa
Transmission Seasonality maps	Easy to update – rainfall data is main input Allows for travel advise on seasonal risk	May lead to complicated travel advice – i.e. multiple recommendations for a single year depending on season Acute and unexpected seasonal changes may lead to 'unforeseen disease risks' for travellers

Product	Pros	Cons
Source: MAP		
Parasite (*Pf* and *Pv*) rate maps	Global and empirical for both *Pf* and *Pv* – community random sample surveys used Contemporary – products available for 2010 High resolution – available at 1 × 1 km spatial resolution Robust estimates of uncertainty – Bayesian inference	Represents both 'natural' and 'controlled' states of risk depending on available data– hard to predict the magnitude of resurgence if control is interrupted Small possibility of dynamic (annual) updates – depends on infrequent and expensive community random sample surveys Large uncertainties in some countries
Entomological Inoculation Rate (EIR) map	Modeled from estimates of parasite rate hence similar strengths Number of infective bites 'easier' to translate to travel advice	Similar weaknesses to parasite rate maps, and Combines both the uncertainty in parasite rate and that of the PR to EIR model, therefore highly imprecise in some areas

46

WHO



- 1. Areas of **high** transmission, where the reported incidence of confirmed malaria due to all species was **≥1 per 1000 population per year**
- 2. Areas of **low** transmission, where the reported malaria case incidence from all species was **< 1 per 1000 population per year** but **greater than 0**.

  Transmission in these areas is generally highly seasonal, with or without epidemic peaks

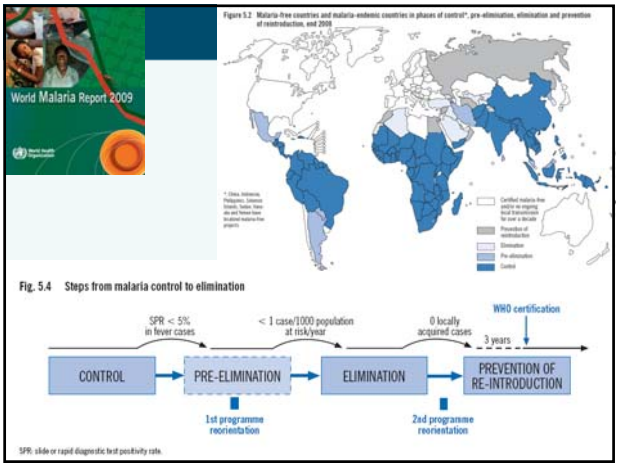
- 3. Malaria-**free** areas, where there is no continuing local mosquito-borne malaria transmission, and all reported malaria cases are imported

48

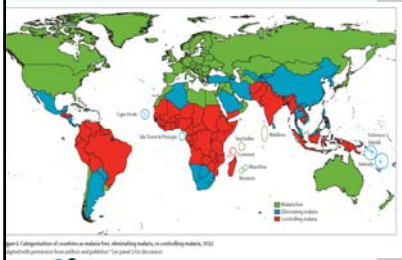
Seven levels of endemicity are shown

- >100 cases per 1000 population per year;
- > 50 cases per 1000 population per year and < 100 cases
- >10 cases per 1000 population per year but < 50 cases
- **>1 cases per 1000** population per year but < 10 cases
- > 0.1 case per 1000 population per year but < 1 cases
- **> 0 case per 1000** population per year but < 0.1 cases
- 0 recorded cases

49



Lancet 2013; 382: 900–11



2013

- **Prevention of re-introduction**

Iraq

- **Elimination**

Algeria; Azerbaijan; Georgia; Kyrgyzstan; Republic of (S) Korea; Saudi Arabia. Tajikistan; **Turkey**; Uzbekistan:

- **pre-elimination**

Argentinia; **Cape Verde**; Democratic People's Republic of (N) Korea; El Salvador; Iran; **Malaysia**, **Mexico**, **Paraguay**, **Sri Lanka**

- South Africa = C – quid subregions ?.

51

Lancet 2013; 382: 900–11

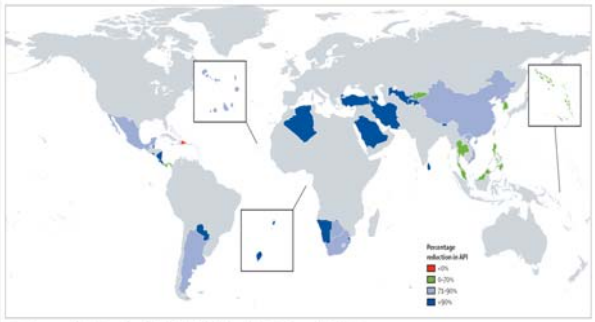
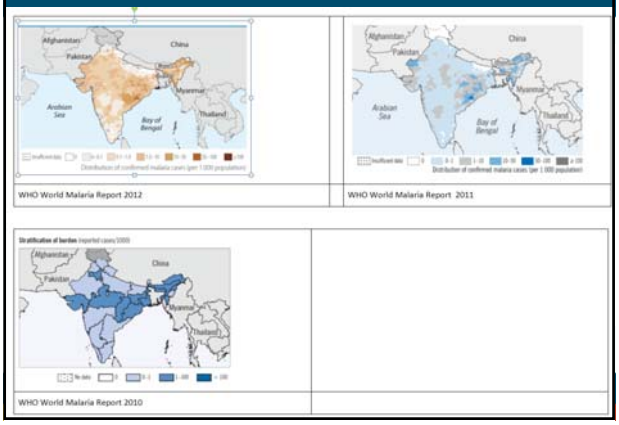


Figure 2: Percentage reduction in annual parasite incidence (API) in the 34 malaria-eliminating countries, 2000–10
The Dominican Republic is the only country with increasing malaria incidence during this time.[1]

INDIA



Possible **drawbacks** of maps

- May give a sense of (pseudo or false)-precision
- Based on incomplete or unstable / very variable data, or on rather theoretical modeling
- Maps give a snapshot of a certain moment or period, data may be outdated - malaria risk changes over time and season and most data is based on local transmission
- Different maps do not always correlate : can increase confusion …

Nevertheless = maps are very handy to give a general impression & are helpfull for the expert to form an opinion / formulate an advice

54

Possible **drawbacks** of maps : instable malaria

A malaria upsurge in the town of Maroua, in the far north [Extreme-Nord region] of Cameroon, has led to the death of hundreds of people.

- Maroua is located in the Extreme-Nord region of Cameroon, an area usually regarded as a **relatively low risk area (0.1-1.0 case per 1000 population per year)** for malaria compared with the southern part of Cameroon **(more than 1 case per 1000 population per year)** (WHO.World Malaria Report 2012
- An outbreak of this size in an otherwise endemic area is probably only possible by an increase in the transmission potential and an increase in the number of infected people. Poor compliance with insecticide treated nets is probably nothing new, and can therefore not explain the sudden increase in the number of infected people. Treatment failure could be an explanation, as most 1st line treatments are done with drugs purchased outside hospitals and clinics, and poor quality drugs used for treatment at home could be an explanation.

55

Possible drawbacks of maps : confusion

http://www.fitfortravel.scot.nhs.uk/destinations.aspx

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May not be multiplicated

Tropimed 2013

56

Possible drawbacks of maps : confusion

WHO World Malaria Report 2012

57

Malaria chemoprophylaxis & WHO maps of the low risk areas in Asia and Latin America

PART III - EXAMPLES

58

In many regions the risk for aquiring malaria for a traveler nowadays

is comparable with

"the risk for vivax-malaria in the marshes ("polders") around Antwerp 100 years ago, where my grandpa lived ..."

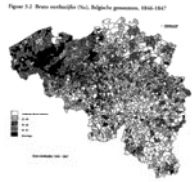
59

M Coosemans – CISTM 13 – Maastricht

Malaria in Belgium in the 19 & 20th century

'naar 't Noorden vliegen'

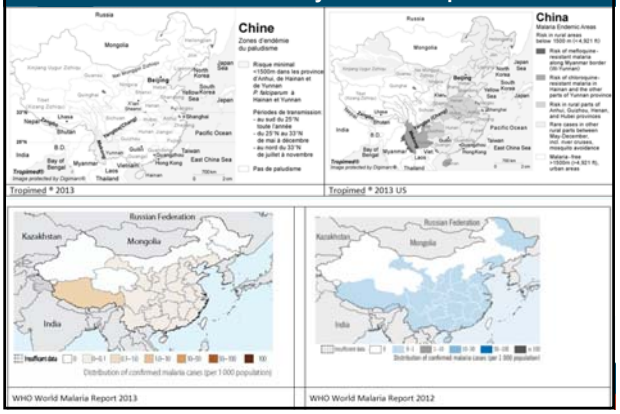
A parish priest nominated in the "Polders" was not considered as a promotion but rather a punishment



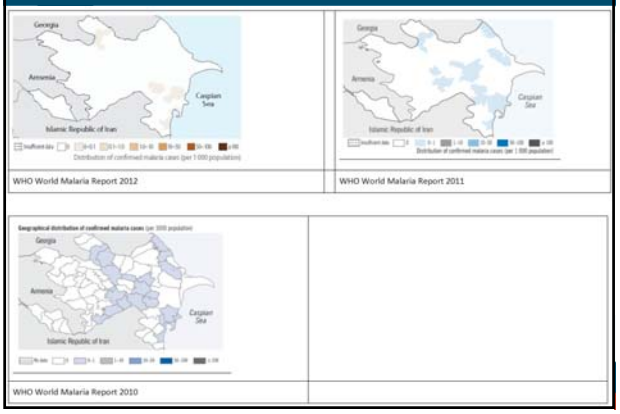
(Devos 2006)

60

China



Azerbaijan



2012

GREECE

Malaria:

- Very limited malaria risk (*P. vivax* only) may exist from May to October in villages of theEvrotas delta area in Lakonia district (an area of 20km2) in agricultural area with large migrant populations.
- There is no risk in tourist areas.
- Recommended prevention in risk area: **I**

HELLENIC CENTRE FOR DISEASE CONTROL AND PREVENTION

2012

MINISTRY OF HEALTH

EPIDEMIOLOGICAL SURVEILLANCE REPORT

MALARIA, 2012 (01/01/2012- 03/09/2012)

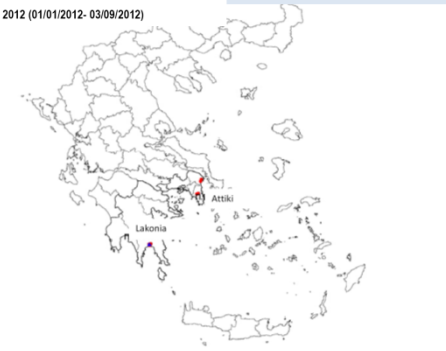


Figure 2: Distribution of locally acquired malaria cases by week of reported onset of symptoms, Greece, 01/01 until 01/09/2012 (n=8)

Malaria chemoprophylaxis & WHO maps of the low risk areas in Asia and Latin America

ASIA

65

INDIA

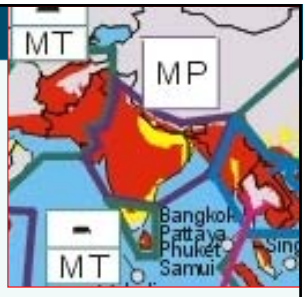
Malaria: Malaria risk exists throughout the year in the whole country at altitudes below 2000 m, with overall 40–50% of cases due to *P. falciparum* and the remainder due to *P. vivax*.
There is no transmission in parts of the states of Himachal Pradesh, Jammu and Kashmir, and Sikkim.
Risk of falciparum malaria and drug resistance are relatively higher

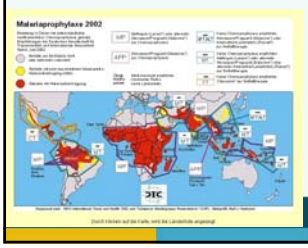
- in the north-eastern states,
- in the Andaman and Nicobar islands,
- Chhattisgarh, Jharkhand, Orissa and West Bengal (with the exception of the city of Kolkata),
- Gujarat, Madhya Pradesh,
- Maharashtra (with the exception of the cities of Mumbai, Nagpur, Nasik and Pune),
- Karnataka (with the exception of the city of Bangalore)

P. falciparum resistance to chloroquine and sulfadoxine–pyrimethamine reported.
Recommended prevention in risk areas: **III**, in the listed higher risk areas: **IV**

66

INDIA





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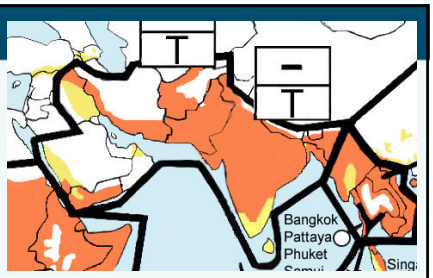
INDIA



68

Malaria Journal

BioMed Central

Commentary

Open Access

Malaria prophylaxis policy for travellers from Europe to the Indian Sub Continent

RH Behrens*[1], Z Bisoffi[2], A Björkman[3], J Gascon[4], C Hatz[5], T Jelinek[7], F Legros[6], N Mühlberger[7], TropNetEurop and P Voltersvik[8]

Malaria Journal 2006, 5:7 doi:10.1186/1475-2875-5-7

The Risk of Malaria in Travelers to India

Sabine Schmid, MD,* Peter Chiodini, MB, PhD,† Fabrice Legros, MA,‡ Stefania D'Amato, MD,§ Irene Schöneberg, PhD,¶ Conan Liu, M. App. Med. Sci.,* Ragnhild Janzon, ** and Patricia Schlagenhauf, PhD*

*Center for Travel Medicine, WHO Collaborating Center for Travelers' Health, Institute for Social and Preventive Medicine, University of Zurich, Zurich, Switzerland; †Hospital for Tropical Diseases, London, UK; ‡London School of Hygiene and Tropical Medicine, London, UK; §Centre National de Référence de l'Epidémiologie du Paludisme d'Importation et Autochtone, Paris, France; ¶Ministero della Salute, Rome, Italy; ‖Robert Koch Institut, Berlin, Germany; #Office of Health Protection, Australian Government Department of Health and Ageing, Canberra ACT, Australia; **Swedish Institute for Infectious Disease Control, Solna, Sweden

DOI: 10.1111/j.1708-8305.2009.00332.x

Journal of Travel Medicine 2009; Volume 16 (Issue 3): 194–199

69

Behrens et al. Malaria Journal 2010, 9:266
http://www.malariajournal.com/content/9/1/266

MALARIA JOURNAL

RESEARCH Open Access

The incidence of malaria in travellers to South-East Asia: is local malaria transmission a useful risk indicator?

Ron H Behrens[1,2*], Bernadette Carroll[1], Urban Hellgren[3], Leo G Visser[4], Heli Silkamäki[5], Lasse S Vestergaard[6], Guido Calleri[7], Thomas Jänisch[8], Bjørn Myrvang[9], Joaquim Gascon[10], Christoph Hatz[11]

Conclusion:
The intensity of malaria transmission particularly sub-national activity did not correlate with the risk of travellers acquiring malaria in the large numbers of arriving visitors.
It is proposed to use a threshold incidence of > 1case per 100,000 visits to consider targeted malaria prophylaxis recommendations to minimize use of chemoprophylaxis for low risk exposure during visits to S-E Asia.
Policy needs to be adjusted regularly to reflect the changing risk.

70

Sri lanka

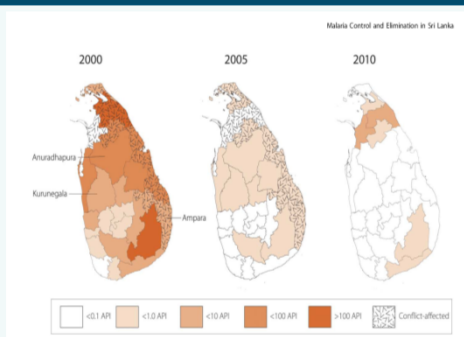
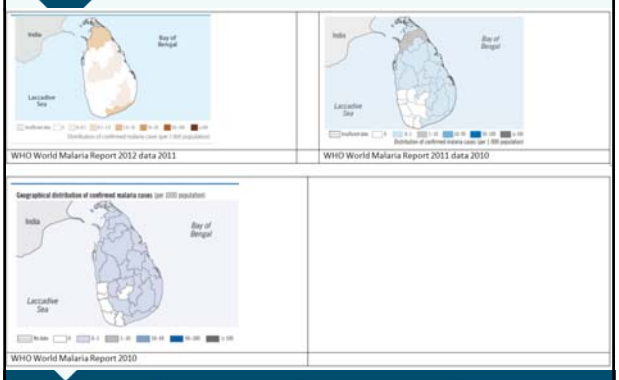
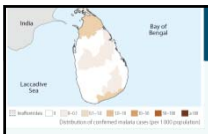


Figure 2. Map of Annual Parasite Incidence (API) (confirmed infections/1,000 population at risk) by district, 2000, 2005, and 2010. API per 1,000 population at risk. The costing analysis was conducted in Anuradhapura and Kurunegala districts. Key informant interviews were conducted with representatives from Ampara, Anuradhapura, and Kurunegala districts. The Malaria Atlas Project (MAP) and the Sri Lanka Ministry of Health provided the base district-level map of Sri Lanka. MAP is committed to disseminating information on malaria risk, in partnership with malaria endemic countries, to guide malaria control and elimination globally.
doi:10.1371/journal.pone.0043162.g002

Sri lanka



72



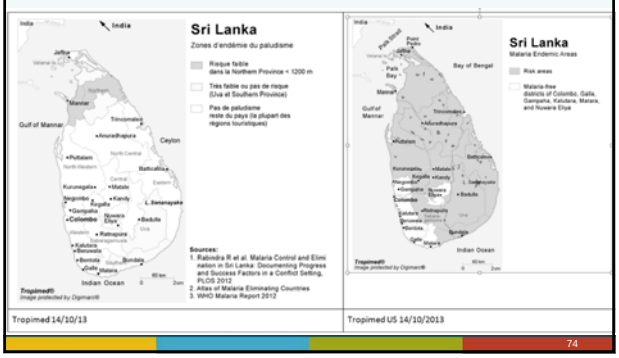
WHO 2012 Malaria:
Limited malaria risk – P. vivax (88%), P. falciparum (12%) – exists throughout the year, except in the districts of Colombo, Galle,Gampaha, Kalutara, Matara and Nuwara Eliya.
Recommended prevention in risk areas: II

Belgian Guidelines

- There is **no malaria risk** in Colombo, Galle, Gampaha (North of Colombo), the Kalutara & Matara districts (South of Colombo), nor in the central district of Nuwara Eliya.
- Measures for protection against mosquito bites in the evenings and at night are sufficient here. In case of fever, malaria should always be considered.
- However, in the rest of the country below 800 m, which is most areas, there is a **variable but limited malaria risk**, and the protective measures against mosquito bites in the evenings and at night are sufficient for travellers who spend the nights in very good conditions (exclusively luxury hotels);
- however, the recommendations for prevention of malaria discussed in **NOTE 1** apply for other travellers.
- **In case of fever, malaria should always be considered.**

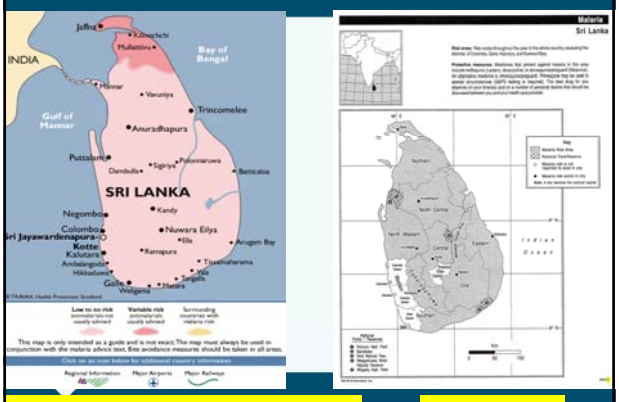
73

Sri lanka



74

Sri lanka

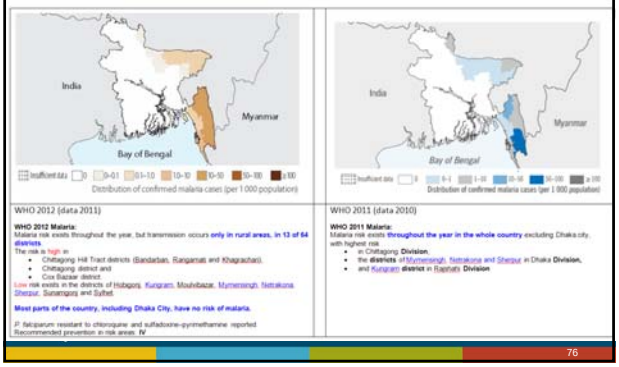


http://www.fitfortravel.scot.nhs.uk/destinations.aspx

Shoreland ® 2005

75

Bangladesh



WHO 2012 (data 2011)

WHO 2012 Malaria:
Malaria risk exists throughout the year, but transmission occurs **only in rural areas, in 13 of 64 districts**.
The risk is high in
- Chittagong Hill Tract districts (Bandarban, Rangamati and Khagrachari).
- Chittagong district and
- Cox Bazaar district.

Low risk exists in the districts of Habigonj, Kurigram, Moulvibazar, Mymensingh, Netrokona, Sherpur, Sunamgonj and Sylhet.

Most parts of the country, including Dhaka City, have no risk of malaria.

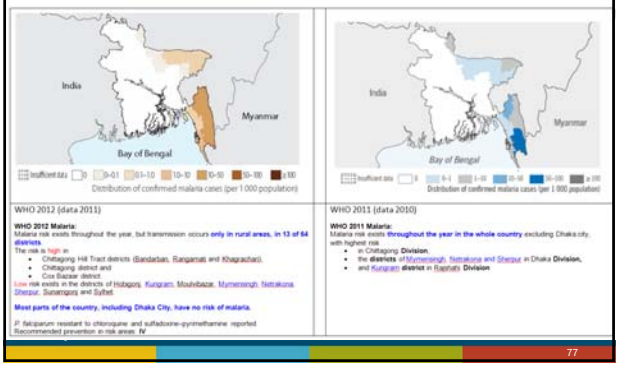
P. falciparum resistant to chloroquine and sulfadoxine-pyrimethamine reported
Recommended prevention in risk areas: IV

WHO 2011 (data 2010)

WHO 2011 Malaria:
Malaria risk exists **throughout the year in the whole country** excluding Dhaka city, with highest risk
- in Chittagong **Division**,
- the **districts** of Mymensingh, Netrokona and Sherpur in Dhaka **Division**,
- and Kurigram **district** in Rajshahi **Division**

76

Bangladesh



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77

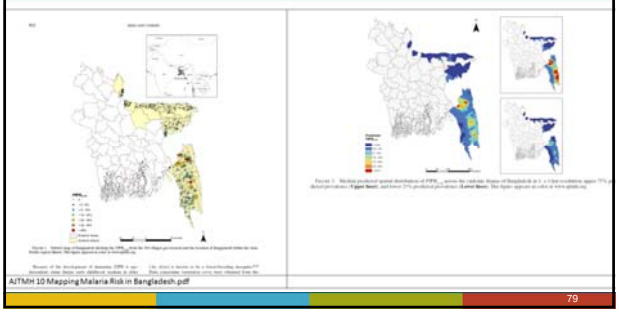
Bangladesh

Tropimed ® oktober 2013

Tropimed ® US richtlijnen oktober 2013

78

Bangladesh

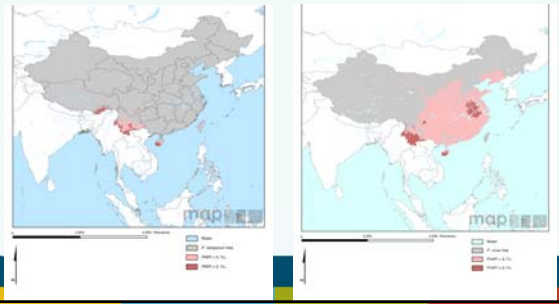


AJTMH 10 Mapping Malaria Risk in Bangladesh.pdf

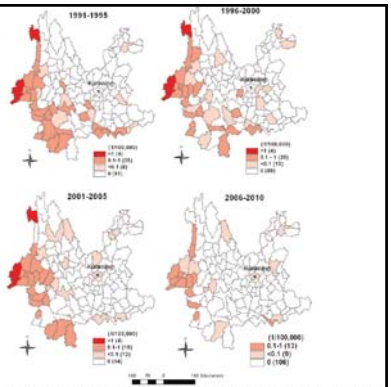
79

Southern China

WHO 2012 Malaria risk, including *P. falciparum* malaria, exists in **Yunnan** and to a lesser extent in Hainan.
Limited risk of *P. vivax* malaria exists in southern and some central provinces, including **Anhui, Ghuizhou, Henan, Hubei,Jiangsu**.
There is no malaria risk in urban areas.



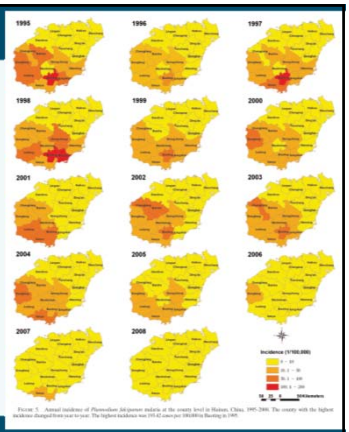
YUNNAN



Am. J. Trop. Med. Hyg., 88(3), 2013, pp. 526–535
doi:10.4269/ajtmh.2012.12-0217

81

HAINAN



Am. J. Trop. Med. Hyg., 87(4), 2012, pp. 646–654
doi:10.4269/ajtmh.2012.12-0164

82

MCQ

From: Travel Medicine Clinical Discussion List [mailto:TRAVELMED@yorku.ca] On Behalf Of ,,,

" My niece is going to work for 4-6 months in some primate research in Malaysia: Segari Melintang Forest Reserve, in the coastal region of the Perak State.

I've found some data suggesting that there is some malaria there, but no hard data for this area.

My sense is that chemoprophylaxis is probably indicated, but wanted to get any information from those who may know the area."

1. Do nothing special
2. Use only repellents If overnight stays are in a well-organized environment
3. Use only repellents & SBET (as in Switzerland)
4. Use only repellents & emergency Atov/Prog prevention
5. Take chemoprophylaxis and use repellents all the time

WHO 2012 Malaria: Malaria risk exists only in limited foci in the deep hinterland of the states of Sabah and Sarawak and the central areas of Peninsular Malaysia.
Urban, **suburban** and coastal areas are free from malaria.
P. falciparum resistant to chloroquine and sulfadoxine-pyrimethamine reported.
Human *P. knowlesi* infection reported.
P. vivax resistance to chloroquine reported.
Recommended prevention in risk areas: **IV**

Who 2011 Malaria: Malaria risk exists only in limited foci in the deep hinterland.
Urban and coastal areas are free from malaria.
P. falciparum resistant to chloroquine and sulfadoxine-pyrimethamine reported.
Human *P. knowlesi* infection reported. *P. vivax* resistance to chloroquine reported.
Recommended prevention in risk areas: **IV**

85

Malaysia

NATIONAL STRATEGIC PLANNING FOR THE ELIMINATION OF MALARIA 2011 - 2020

Target: Elimination of locally acquired malaria in Malaysia by 2020

24.5% pop. at risk

0.4% pop. at risk

19.7% pop. at risk

Sabah and Sarawak: elimination by 2020.

West Malaysia: elimination by 2015.

AREA	CRITERIA
RED	Incidence ≥ 1 / 1000 population
YELLOW	Incidence < 1 / 1000 population
GREEN	No local transmission

17

86

QUESTION 3

My niece is traveling to the Far East – 1 month in Thailand -1 month in Cambodja – 1 month in Laos – 1 month in Vietnam;

The accomodation for the nights are very varied (very primitive in a tent or with the local population to more comfortable in a motel or hostel)

After reading the information on the site of the tropical institute, ik think she needs to take Atovaq/Prog for at least 2,5 months (Laos, Cambodja, part of haïland). Is that correct ? She really does not know the exact locations she will visit

1. Do nothing special
2. Use only repellents If overnight stays are in a well-organized environment
3. Use only repellents & SBET (as in Switzerland)
4. Use only repellents & emergency Atov/Prog prevention
5. Take chemoprophylaxis and use repellents all the time

Mekong – annual parasite index

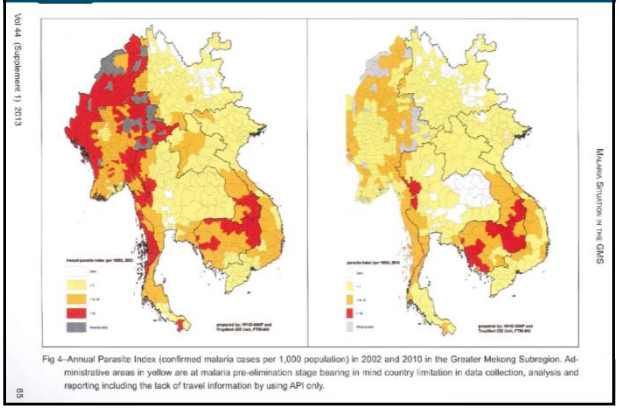


Fig 4–Annual Parasite Index (confirmed malaria cases per 1,000 population) in 2002 and 2010 in the Greater Mekong Subregion. Administrative areas in yellow are at malaria pre-elimination stage bearing in mind country limitation in data collection, analysis and reporting including the lack of travel information by using API only.

Mekong - malaria death rate

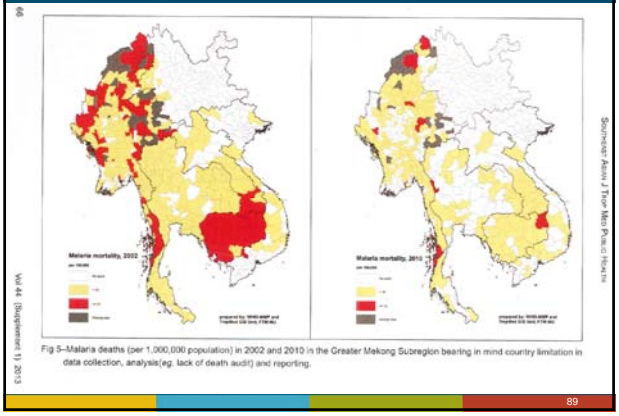
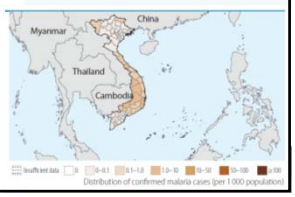


Fig 5–Malaria deaths (per 1,000,000 population) in 2002 and 2010 in the Greater Mekong Subregion bearing in mind country limitation in data collection, analysis(eg. lack of death audit) and reporting.

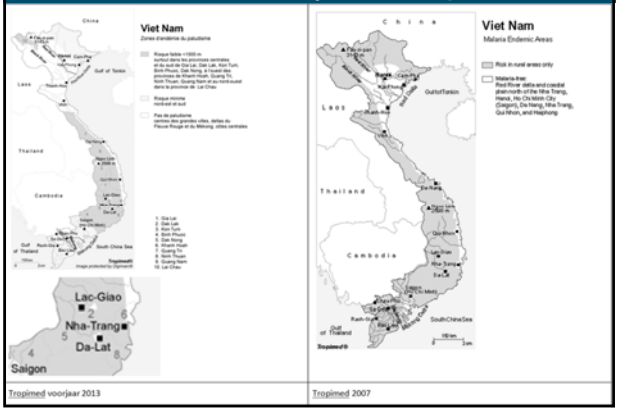
VIET NAM

WHO 2012

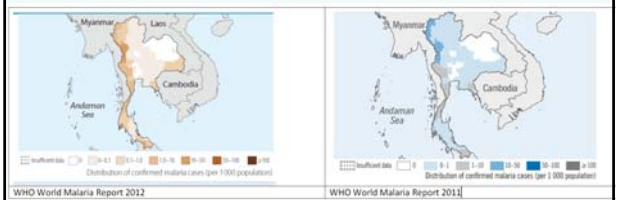
the four **central highlands provinces** Dak Lak, Dak Nong, Gia Lai and Kon Tum, Binh Phuoc province, and the **western parts of the coastal provinces** Khanh Hoa, Ninh Thuan, Quang Nam and Quang Tri.



VIET NAM

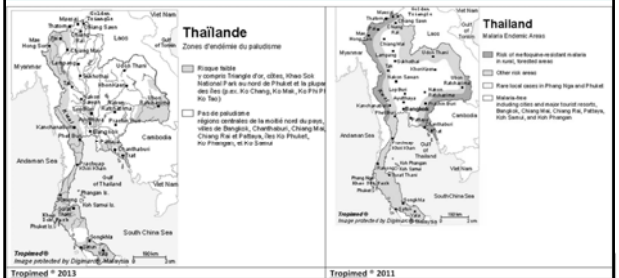


Thailand



92

Thailand



93

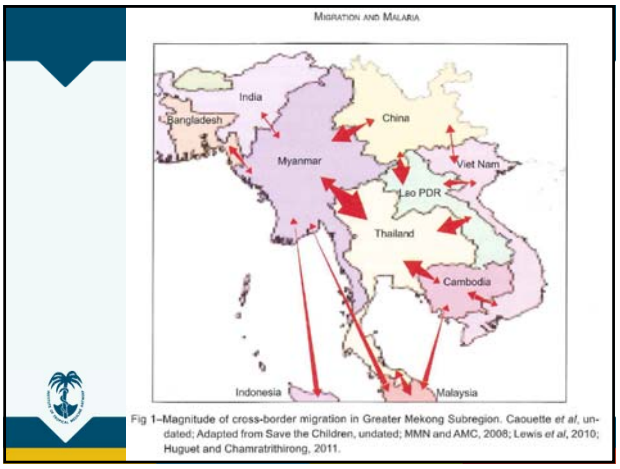
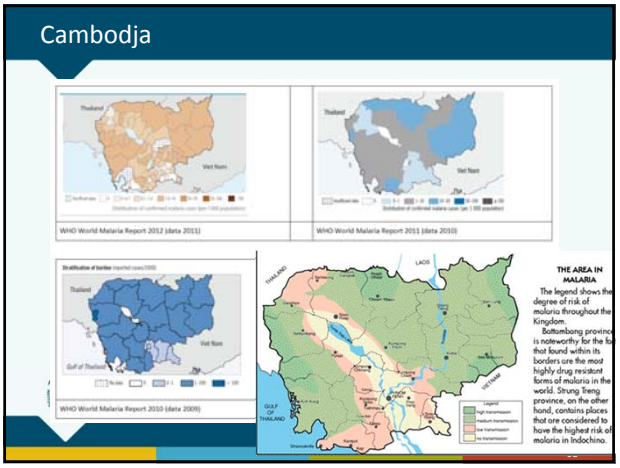
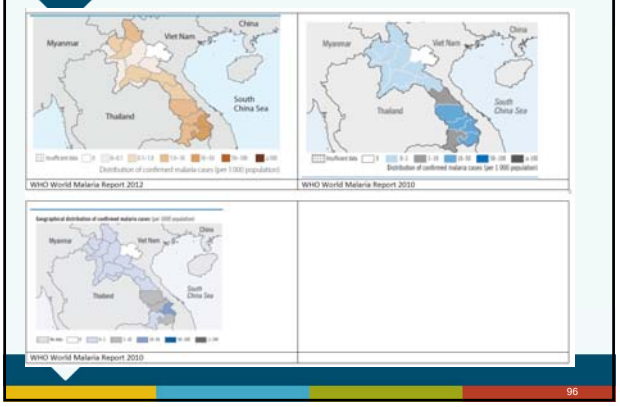


Fig 1–Magnitude of cross-border migration in Greater Mekong Subregion. Caouette *et al*, undated; Adapted from Save the Children, undated; MMN and AMC, 2008; Lewis *et al*, 2010; Huguet and Chamratrithirong, 2011.

Cambodja



Laos



Laos

LAOS IMT 2013:
There is no malaria risk in the capital Vientiane and a low risk in the city of Luang Prabang.
For most organized tours with overnight stay in luxury hotels, no intake of malaria tablets is necessary and precautions against mosquito bites are sufficient.
In case of fever, malaria should always be considered.
However, there is a malaria risk throughout the rest of the country.
The recommendations discussed in NOTE 2 apply

97

Malaria chemoprophylaxis & WHO maps of the low risk areas in Asia and Latin America

LATIN AMERICA

98

MCQ

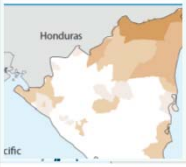
QUESTION 2

" My daughter is going to do a trip with the "Damiaanactie - Action Damien" for 4 weeks in Nicaragua – with a stay of 3 weeks in one place and a trip of 1 week in the south-western region,

Some members of the group are prescribed chloroquine"

What do you advice

1. Do nothing special
2. Use only repellents If overnight stays are in a well-organized environment
3. Use only repellents & SBET (as in Switserland)
4. Use only repellents & emergency chloroquine prevention
5. Take chemoprophylaxis and use repellents all the time

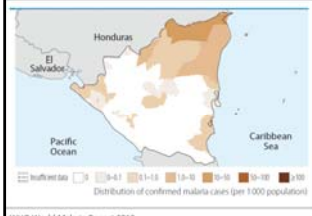


Nicaragua

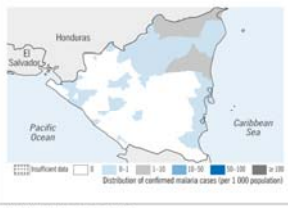
WHO 2012 Malaria:
low malaria risk due predominantly to *P. vivax* (82%) exists throughout the year in a number of municipalities, mainly in Región Autónoma del Atlántico Norte, with sporadic transmission also reported in Boaco, Chinandega, Jinotega, León and Matagalpa.
cases are reported from other municipalities in the central and western departments but the risk in these areas is considered to be very low or negligible.
to chloroquine-resistant *P. falciparum* reported.
recommended prevention in risk areas: 8

WHO 2011 Malaria:
low malaria risk due predominantly to *P. vivax* (85%) exists throughout the year in a number of municipalities in Chinandega, León, Managua, Matagalpa, Región Autónoma del Atlántico Norte and Región Autónoma del Atlántico Sur.
cases are reported from other municipalities in the central and western departments but the risk in these areas is considered to be very low or negligible.
to chloroquine-resistant *P. falciparum* reported.
recommended prevention in risk areas: 8

Nicaragua



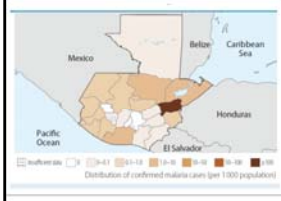
WHO World Malaria Report 2013



WHO World Malaria Report 2012

102

Guatemala



WHO World Malaria Report 2012

WHO World Malaria Report 2011

103

Guatemala

Malaria

Er is geen malariarisico in de hoofdstad, noch in de gebieden gelegen boven de 1500 m.

- Er is enkel malariarisico (hoofdzakelijk door P. vivax, de goedaardige vorm van malaria) in de landelijke laaglandgebieden (beneden 1500 m):
  Matig risico in de departementen Escuintla en Izabal
  Laag risico in de departementen Alta Verapaz, Baja Verapaz, Chiquimula, Petén, Suchitepéquez en Zacapa.
  Enkel bij een avontuurlijk verblijf op het platteland in het noordelijke grensgebied met Mexico en Belize (Petén) gelden de volgende aanbevelingen voor de preventie van malaria:

WHO 2012 Malaria:
Malaria risk due predominantly to P. vivax exists throughout the year below 1500 m.
There is moderate risk in the departments of Escuintla and Izabal, and
low risk in Alta Verapaz, Baja Verapaz, Chiquimula, Petén, Suchitepéquez and Zacapa.
Recommended prevention in risk areas: II

WHO 2011 Malaria:
Malaria risk due predominantly to P. vivax exists throughout the year below 1500 m.
There is moderate risk in the departments of Escuintla and Izabal, and
low risk in Alta Verapaz, Baja Verapaz, Chiquimula, Petén, Suchitepéquez and Zacapa.
Recommended prevention in risk areas: II

104

Guatemala

Tropimed * 2013

Tropimed * 2013 US

105

Guatemala

Castellanos et al. Malaria Journal 2012, 11:411
http://www.malariajournal.com/content/11/1/411

MALARIA JOURNAL

CASE REPORT Open Access

Plasmodium vivax congenital malaria in an area of very low endemicity in Guatemala: implications for clinical and epidemiological surveillance in a malaria elimination context

María Eugenia Castellanos[1*], Azucena Bardají[2*†], Michela Menegon[3], Alfredo Mayor[2], Meghna Desai[4], Carlo Severini[3], Clara Menéndez[2] and Norma Padilla[1]

Abstract

This is a report of the first *Plasmodium vivax* congenital malaria case in Guatemala and the first case in Latin America with genotypical, histological and clinical characterization. The findings show that maternal *P. vivax* infection still occurs in areas that are in the pathway towards malaria elimination, and can be associated with detrimental health effects for the neonate. It also highlights the need in very low transmission areas of not only maintaining, but increasing awareness of the problem and developing surveillance strategies, based on population risk, to detect the infection especially in this vulnerable group of the population.

Keywords: *Plasmodium vivax*, Congenital, Malaria, Guatemala

106

Malaria in Highlands of Ecuador since 1900

Figure 6. Number of hospital admissions for malaria in each province of Ecuador in peak malaria years of A) 1969, B) 1990, and C) 2000. Data were obtained from the Instituto de Nacional Estatísticas y Censos (38).

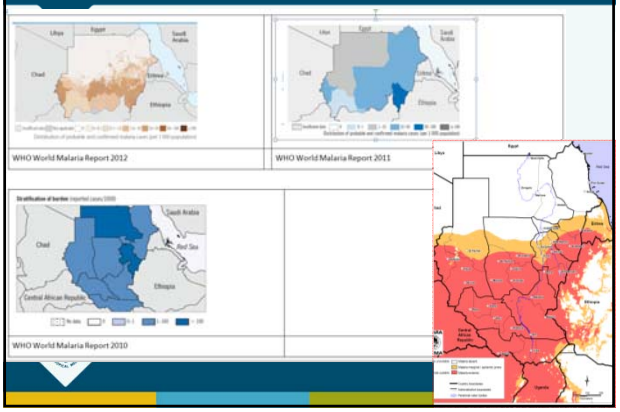
107

Malaria chemoprophylaxis & WHO maps of the low risk areas in Asia and Latin America

AFRICA

108

SUDAN



Pond *Malaria Journal* 2013, **12**:313
http://www.malariajournal.com/content/12/1/313

MALARIA JOURNAL

RESEARCH Open Access

Malaria indicator surveys demonstrate a markedly lower prevalence of malaria in large cities of sub-Saharan Africa

Bob S Pond

110

Increase of malariarisk

- Haïti !!!
- Nairobi ? ….

111

Possible drawbacks of maps

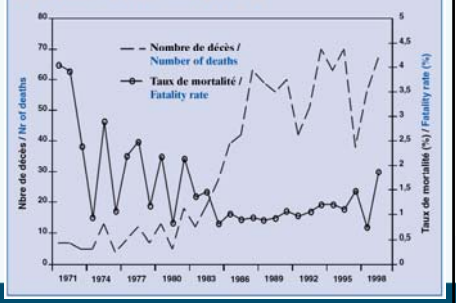
- May give a sense of (pseudo or false)-precision
- Based on incomplete or unstable / very variable data, or on rather theoretical modeling
- Maps give a snapshot of a certain moment or period, data may be outdated - malaria risk changes over time and season and most data is based on local transmission
- Different maps do not always correlate : can increase confusion …

Nevertheless = maps are very handy to give a general impression & are helpfull for the expert to form an opinion / formulate an advice

112

EUROSURVEILLANCE VOL. 6 - N° 4 AVRIL / APRIL 2001

Figure 2
Nombre de décès dus au paludisme et taux de mortalité dans la région Europe de l'OMS, 1971-1999/Number of deaths for malaria and fatality rates in WHO European Region, 1971-1999



113

ABCD – WHO

7.2 Precautions

Travellers and their advisers should note the four principles – the ABCD – of malaria protection:

- Be **A**ware of the risk, the incubation period, the possibility of delayed onset, and the main symptoms.
- Avoid being **B**itten by mosquitoes, especially between dusk and dawn.
- Take antimalarial drugs (**C**hemoprophylaxis) when appropriate, to prevent infection from developing into clinical disease.
- Immediately seek **D**iagnosis and treatment if a fever develops 1 week or more after entering an area where there is a malaria risk and up to 3 months (or, rarely, later) after departure from a risk area.

D = In case of fever, malaria should always be considered (too).

Cave !!! : **Patient's delay & Doctor's delay**

114