Recommandations aux voyageurs : malaria - fièvre jaune

Séminaire de Pathologie infectieuse
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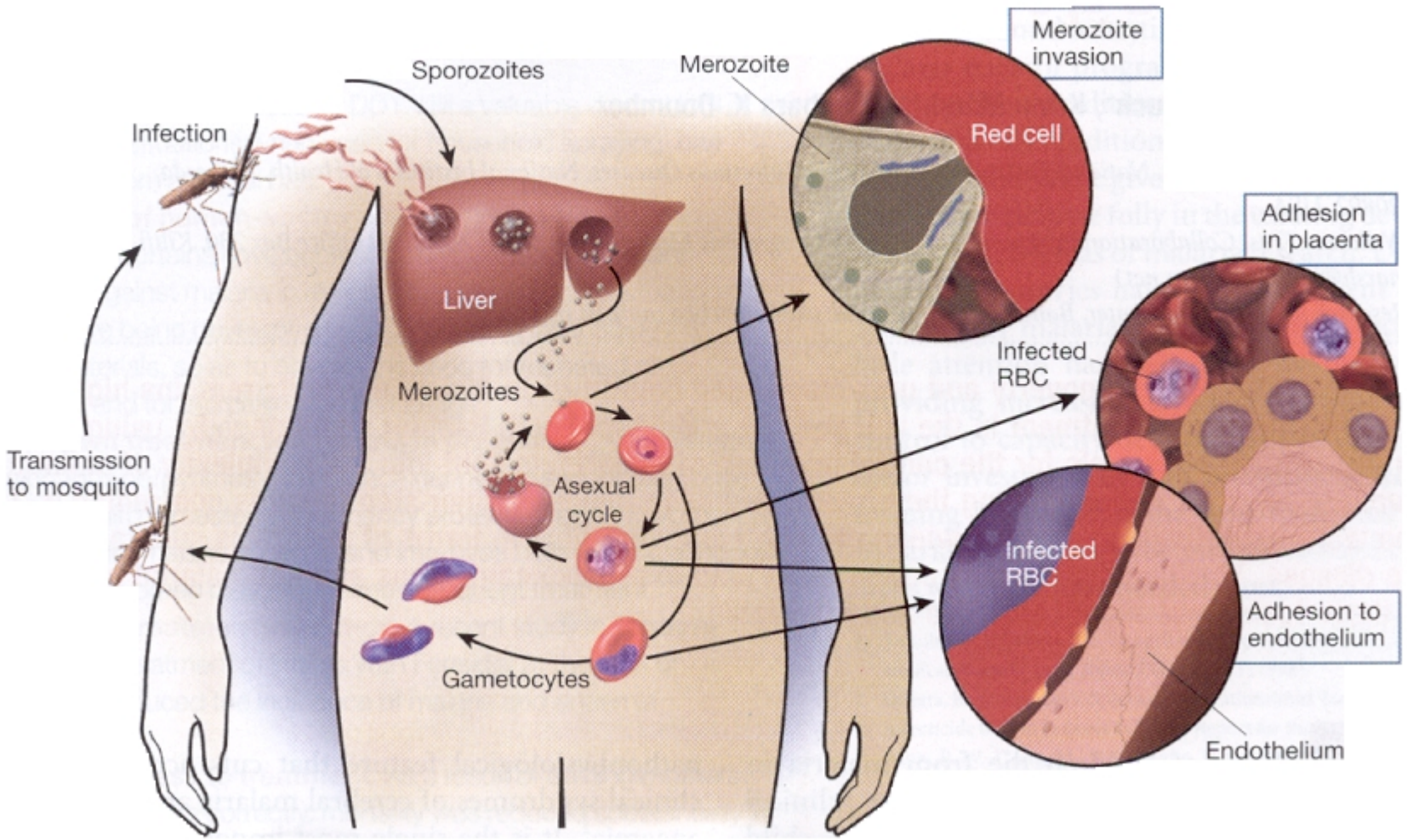

Merozoite invasion
Sporozoites
Merozoite
Infection
Red cell
Adhesion in placenta
Liver
Infected RBC
Merozoites
Transmission to mosquito
Asexual cycle
Infected RBC
Adhesion to endothelium
Gametocytes
Endothelium

Malaria Prophylaxis: Setting the Scene

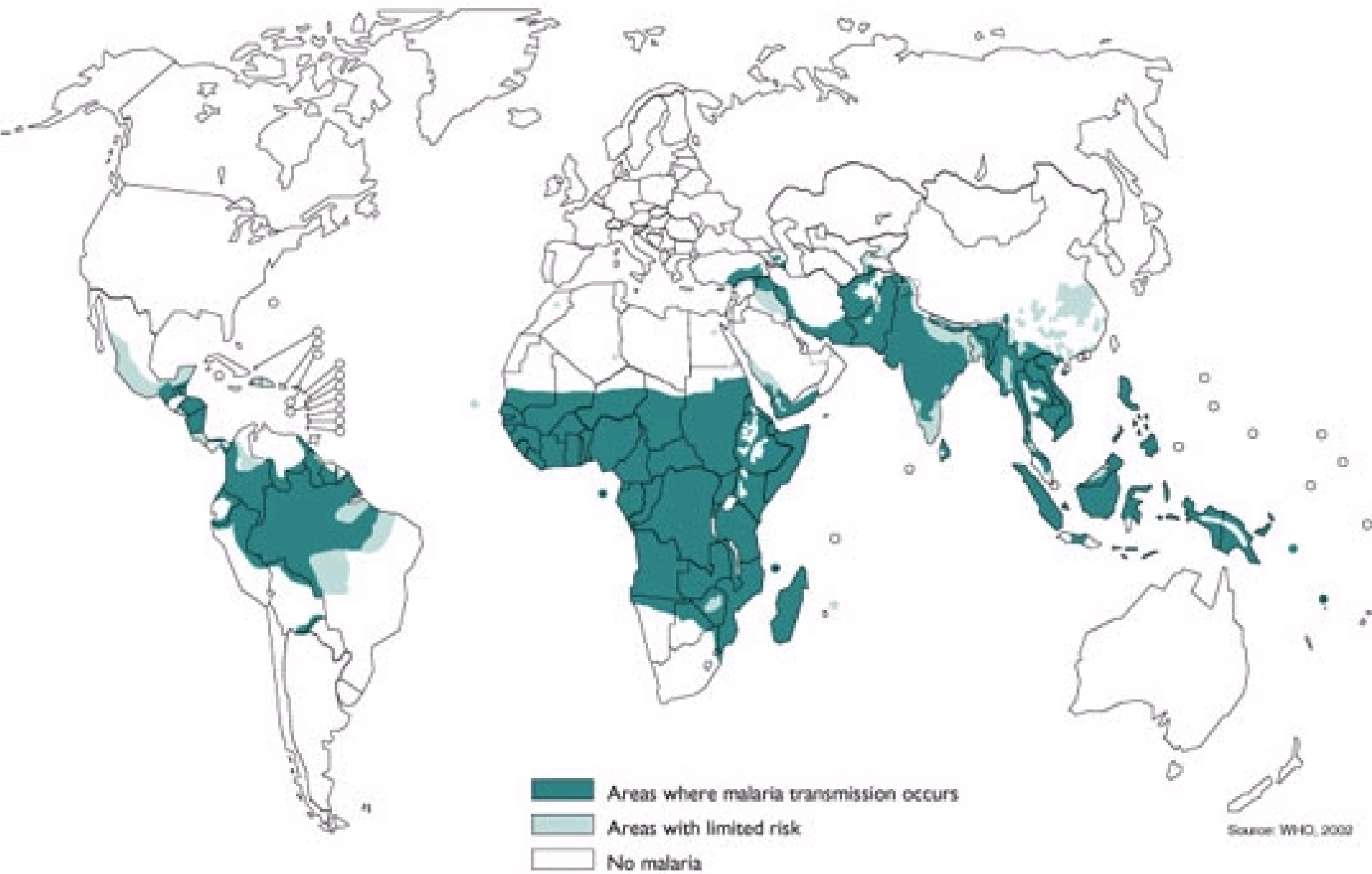
Epidemiology

- how many? — Incidence — Incidence rate
- how serious? — Case fatality rate
- where? — Towards micro-geo-epidemiology
- when? — Seasonality

Current problems

- with Travellers: — Knowledge, Attitudes and Practices
- with Medication: — Adverse reactions
- with Parasites: — Resistance

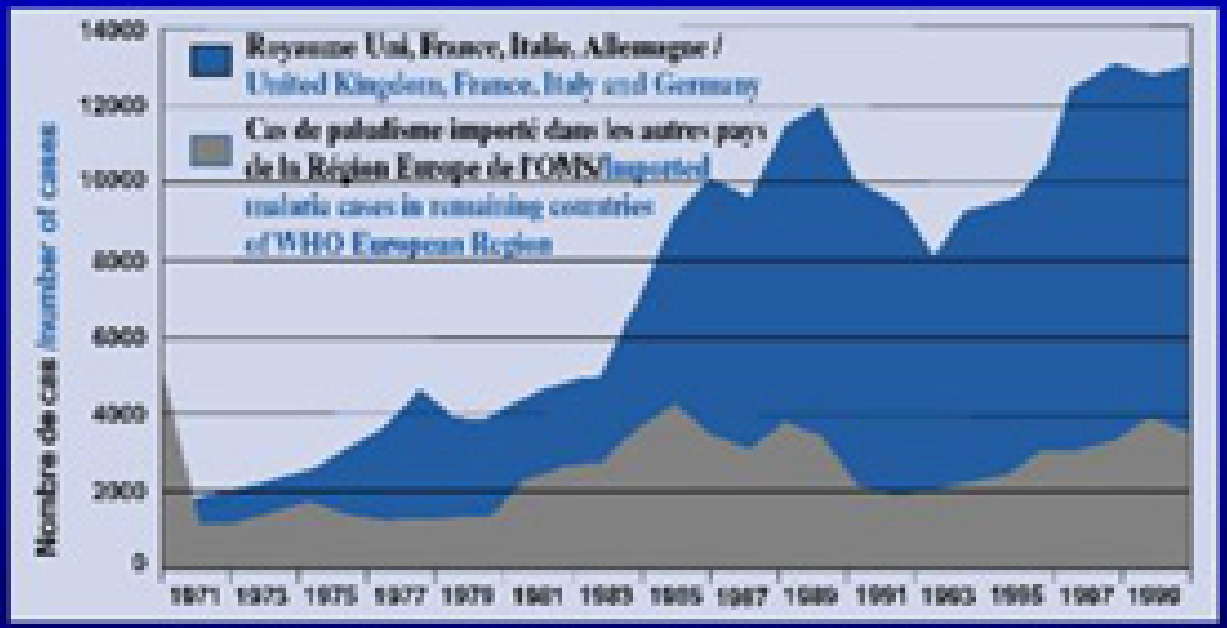
Malaria, 2002



Malaria risk pyramid for 1 month of travel without chemoprophylaxis

- Oceania 1:5
- Africa 1:50
- South Asia 1:250
- Southeast Asia 1:2500
- South America 1:5000
- Mexico and Central America 1:10 000

Malaria imported to Europe (WHO EURO), 1971-1999



- Most cases of malaria imported into WHO's European Region imported into western part of Europe, especially into European Union (EU)
- proportion of *P. falciparum* cases increased to almost 70%
- currently >80% of imported malaria acquired by Europeans* in Africa
- underreporting estimated to be 40 to 70%

Sabatinelli G et al. Eurosurveillance 2001;6:61-5
Muentener P et al. Bull World Health Organ 1999;77:560-6

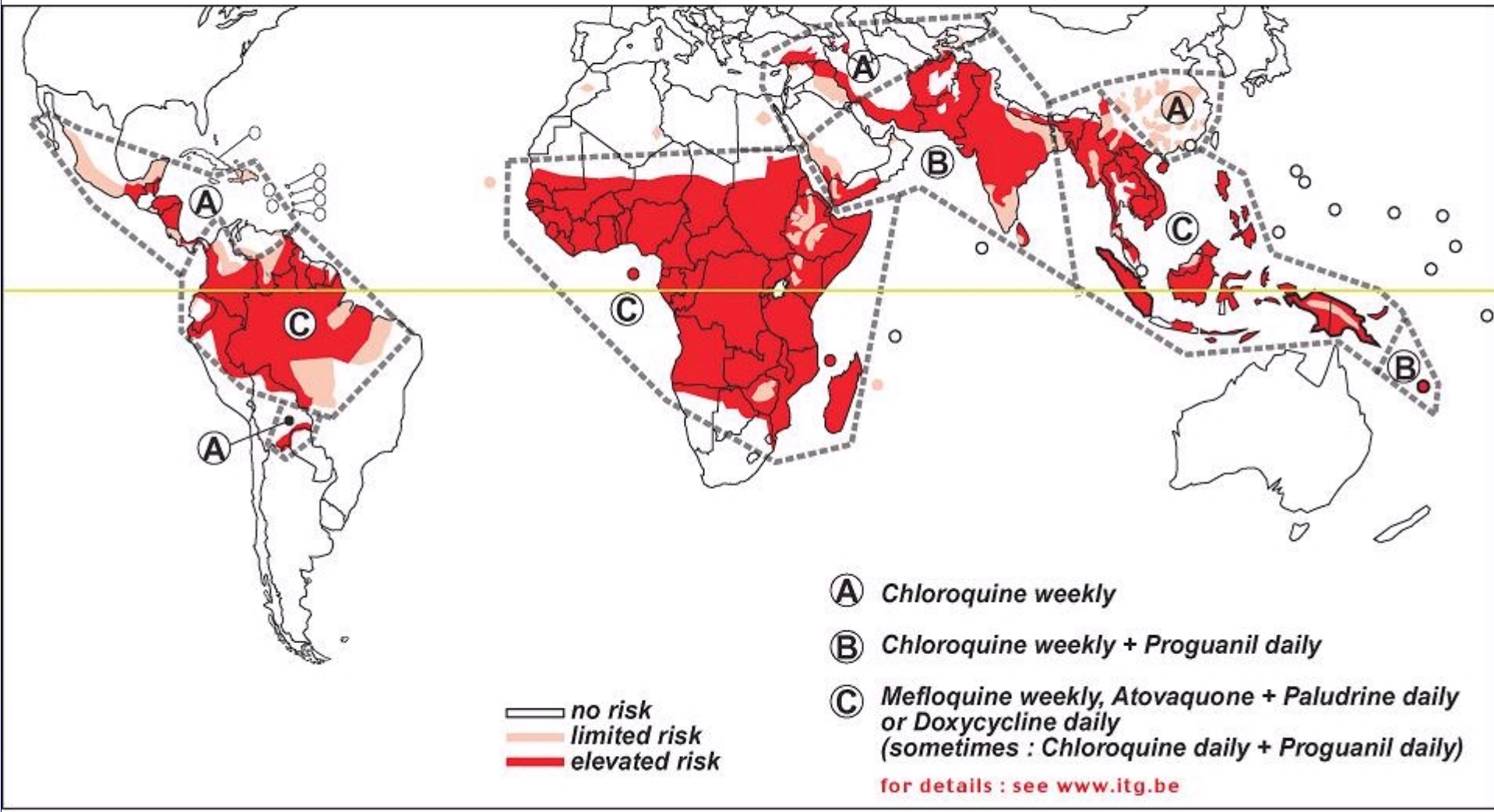
*VFR↗↗

Who dies from travelers' malaria ?

	USA & Canada (n = 21)	Total (%)
No chemo	21	100
Dealy seeking care	1	5
Missed by MD	13	62
Lab misdiagnosis	9	43
Mistreatment	11	52

MMWR July 20, 2001 & 1999; 48:SS-1
Kain K et al. CMAJ 2001, 164:654-659

Malaria 2003 (source WHO 2002-2003)



07/2003

Chemoprophylaxis palette - 2003

- Mefloquine - 250 mg weekly
- Atovaquone/proguanil - 250 mg/100 mg daily
- Doxycycline - 100 mg daily
- Chloroquine - 300 mg base daily
  (often with proguanil 200 mg daily)
- Primaquine 30 mg base daily
- ? Tafenoquine future option-dose finding 50/100/200 mg week

Medication	Use in pregnancy		Breast feeding	Commentary
Mefloquine	X	Yes (CDC, WHO)	Yes	Avoid pregnancy for 3 months post PX
Doxycycline	X	X	x	Avoid pregnancy for 1 week post PX
Chloroquine	Yes	Yes	Yes	
Proguanil	Yes	Yes	Yes	
Atovaquone/ proguanil	?	?	?	More data needed

Medication	Dose	Commentary
Mefloquine	5 mg/kg weekly	Children > 5 kg
Atovaquone/ proguanil	Paediatric tablets daily (1/4 dose)	Children > 11 kg
Doxycycline	1,5 mg/kg daily	Children > 8 years
Chloroquine	5 mg Base/kg weekly	Syrups available
Proguanil	3 mg/kg daily	Should be combined with chloroquine

AP vs CQ/Pro

Hogh et al. Lancet 2000;356:1888

- RDB, n=1083 non-Ig travellers (~65% Africa)
- Endpts: ➡ AE at D7 post travel

  2° ➡ D/C rate due to Rx

  ➡ efficacy (CS Abs) ➡ exposure

ATQ/Pro ➡ PE 100% (54-100)

CQ/Pro ➡ PE 70% (35-93%)

3 failures ➡ pfcrt and DHFR mutations

AP vs CQ/Pro in children

Canus et al. ASTMH 2001;Abstr.579

- RDBPC Ped. Travellers n = 186, 3-16 yrs
- ~83% Africa
- Endpts: ➡ AE at D7 post travel
  2° ➡ D/C rate due to Rx
  ➡ efficacy (CS Abs) exposure

ATQ/Pro & CQ/Pro PE ➡ NO failures
➡ No serious AE

AP tolerability in those > 65

Beerahee et al. ASTMH 2001

- RDBPC healthy travellers > 65 yrs old
- AP vs MFQ vs CP n = 47 (~75% Africa)
- n = 47 from total n = 1998
- AP ➡ PE NO failures
- Well-tolerated
  - ➡ No serious AE
  - ➡ No treatment limting AEs

Pharmacokinetics: Special populations

- 3 studies (n = 26/study; single dosing 2 tabs)
  - ➡ elderly (>65) vs. adults (30-45)
  - ➡ renal impairment vs. normals
  - ➡ hepatic impairment vs. normals
- **Results:**
- no adjustment needed for elderly, mild to moderate renal or hepatic impairment
- ATQ/Pro C/I in ➡ severe renal impairment (CrCl <30 ml/min)

AP: What have we learned in the last few years?

- Causal active → PF non-Igs 96-100%
  → PV non-Igs 84 (45-95%)
- RCT AP better tolerated
  → MFQ, CP, Doxy
- few C/I – well tolerated: children/elderly (2-85)
- resistance → *cyto b* mutations
  → "rare"
- attractive for short-term high risk
- attractive as an agent for self treatment

PI efficacy reports

- Mefloquine (93-100 % efficacy)

  Croft 2001 systematic review of RCTs

- Doxycycline (92-100 %)

  Kain 2001 review of studies

- Atovaquone/proguanil (92-100 %)

  Efficacy in semi-immune persons in Africa and in travelers. Resistance mainly due to cytochrome b gene mutations

Färnert et al. BMJ 2003

Cost of chemoprophylaxis (swiss francs)

	Duration of travel		
Product	**3**	**14**	**28-39**
Lariam® (mefloquine)	47.10	47.10	94.20
Malarone® (atovaquone/proguanil)	63.30	126.60	253.20
Doxysol® 200 (doxycycline)	34.70	52.05	69.40
Supracyclin® 200 (doxycycline)	43.00	56.00	86.00
* monohydrate (pH7)			

Long-term travel

- MQ-unlimited (peace corps experience)
- C/C+P* - unlimited (rare retinopathy)
- At/P* - intial max 30 days, now open
- Doxy* - experience up to 3 months (wide experience with 50 mg dosage)

** Cave poor compliance with daily doses*

Allmalpro

- A randomized, double-blind four-arm chemoprophylaxis (MQ/C + P/Doxy/A+P)
- N = 680
- Tolerability study with placebo run-in phase

Schlagenhauf P et al. BMJ in press

Medication and AE profile

Medication	AE profile
Mefloquine	Neuropsychologic, headache, dizziness, seizures, sleep disturbances, depression, anxiety. Esp. WOMEN GIT events, skin events rare
Doxycycline	Photosensitivity, GIT, Candida superinfection Intracranial hypertension Cave Hyclate (pH3)
Atovaquone/proguanil	Mainly GIT Neuropsychologic rare
Chloroquine/proguanil	Neuropsychologic Skin chloroquine pruritus GIT esp. mouth ulcers

Incidence of severe* adverse events during chemoprophylaxis

Study	Population	MQ	Doxy	A + P	C + P
Phillips, 1995	Australian	11.2	6.5	-	-
Schlagenhauf 1996	Swiss	11.2	-	-	-
Barrett, 1996	UK	17	-	-	16
Steffen 1993	European	13			16
Hogh 2000**	International			0.2	2
Overbosch* 2001**	International	5		1	-
Schlagenhauf 2003	International	10.5	5.9	6.7	12.4

* Interferes with daily activity ** Stopped taking antimalarials *** Hyclate > monohydrate

Incidence of serious* adverse events during chemoprophylaxis

Study	Population	MQ	C + P	Doxy**	A + P
Mac Phearson 1992	Canadian	1/20,000		?	?
Steffen 1993	European	1/11,000	1/5,000		
Croft 1996	UK soldiers	1/6,000			
Barrett 1996	UK	1/600	1/1,200		
Roche Drug safety, 1997	Worldwide	1/20,000			

* Requiring hospitalisation

** Case report

Atovaquone/proguanil 2003

PROs

- Efficacy > 95 % (Pf, Pv)
- Causal (Pf) short post-exposure
- Convenient
- Good safety profile
- Suitable for children >11kg

CONs

- Cost
- Daily intake
- Interactions
- Not for pregnancy or renal impairment
- Cytochrome b gene mutations*

Farnet et al. BMJ 2003

Mefloquine 2003

PROs

- Efficacy > 95 % (all species)
- Wide experience
- Weekly dosing
- Suitable for children, pregnant, long-term
- Reasonable price
- Rare serious events

CONs

- Negative media-neuropsychological
- Areas of Pf resistance
- Interactions
- Contraindicated in depression, epilepsy and psychoses
- Arythmia (ß$^{-}$, Ca^{++}, DIG, quinid)

Doxycycline 2003

PROs

- Effective > 95 %
- No known resistance
- Moderate price
- Monohydrate well tolerated*

CONs

- Limited applicability (not for children < 8 yrs or in pregnancy)
- Daily intake
- Interactions
- AE profile : photosensiivity, GIT, esp. with hyclate, Candida infections, intracranial hypertension**

*Pagès et al, 2002 ** Lochhead & Elston 2003

Malariaprophylaxe 2003

Einteilung in Zonen mit unterschiedlicher medikamentöser Chemoprophylaxe gemäß Empfehlungen der Deutschen Gesellschaft für Tropenmedizin und Internationale Gesundheit (DTG).
Stand: Juni 2003

Gebiete, in denen Malaria nicht oder nicht mehr vorkommt

Gebiete mit sehr beschränktem Malariarisiko; Malariaübertragung selten

Gebiete mit Malariaübertragung

P — Mefloquin (Lariam®), alternativ Atovaquon/Proguanil (Malarone®) oder Doxycyclin* zur Chemoprophylaxe
* für diese Indikation in Deutschland nicht zugelassen

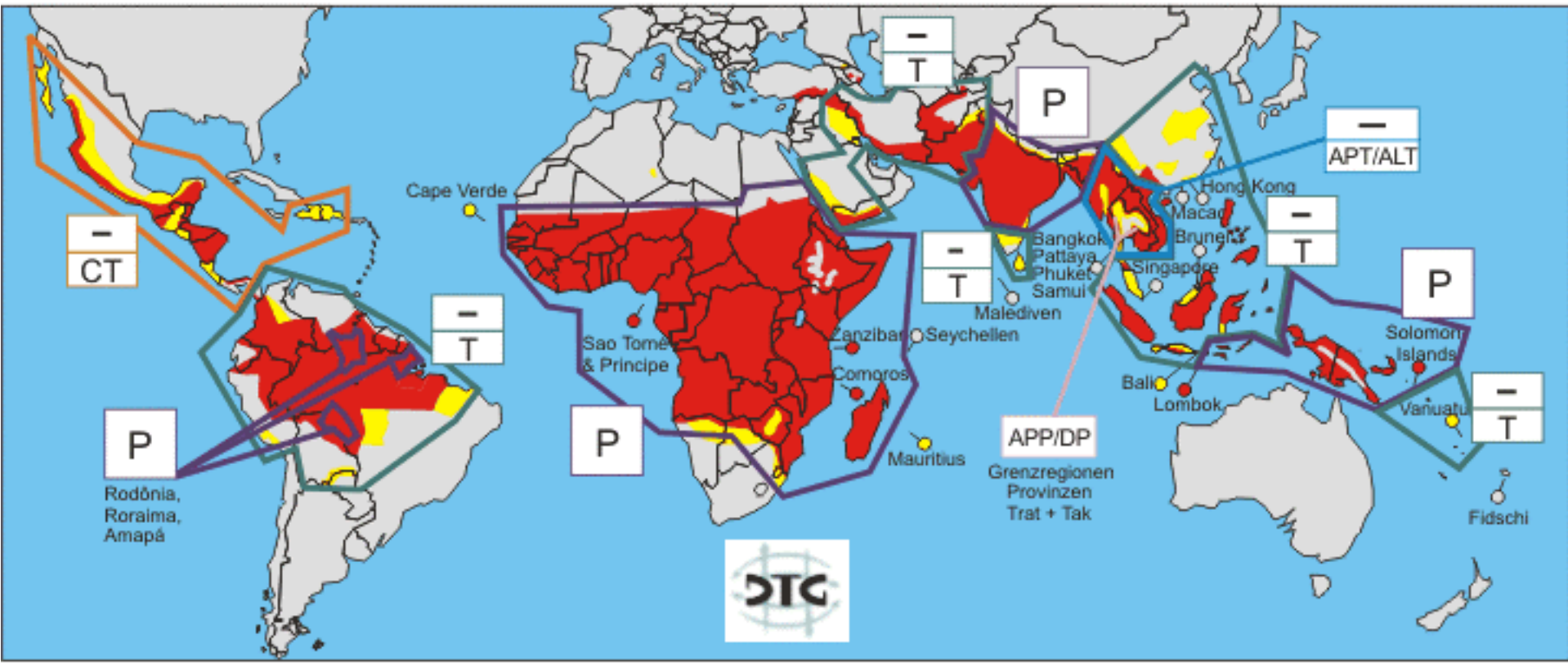
APP/DP — Atovaquon/Proguanil (Malarone®) oder Doxycyclin* zur Chemoprophylaxe
* für diese Indikation in Deutschland nicht zugelassen

Alle Malaria-gebiete — Mückenschutz empfohlen (minimales Risiko siehe Länderliste)

– / **APT/ALT** — Keine Chemoprophylaxe empfohlen Atovaquon/Proguanil (Malarone®) oder Artemether/Lumefantrin (Riamet®) zur Notfalltherapie

– / **T** — Keine Chemoprophylaxe empfohlen Mefloquin (Lariam®) oder alternativ Atovaquon/Proguanil (Malarone®) oder Artemether/Lumefantrin (Riamet®) zur Notfalltherapie

– / **CT** — Keine Chemoprophylaxe empfohlen Chloroquin zur Notfalltherapie



Angepasst nach: WHO International Travel and Health 2003

Grafik: Wulf J. Hartmann

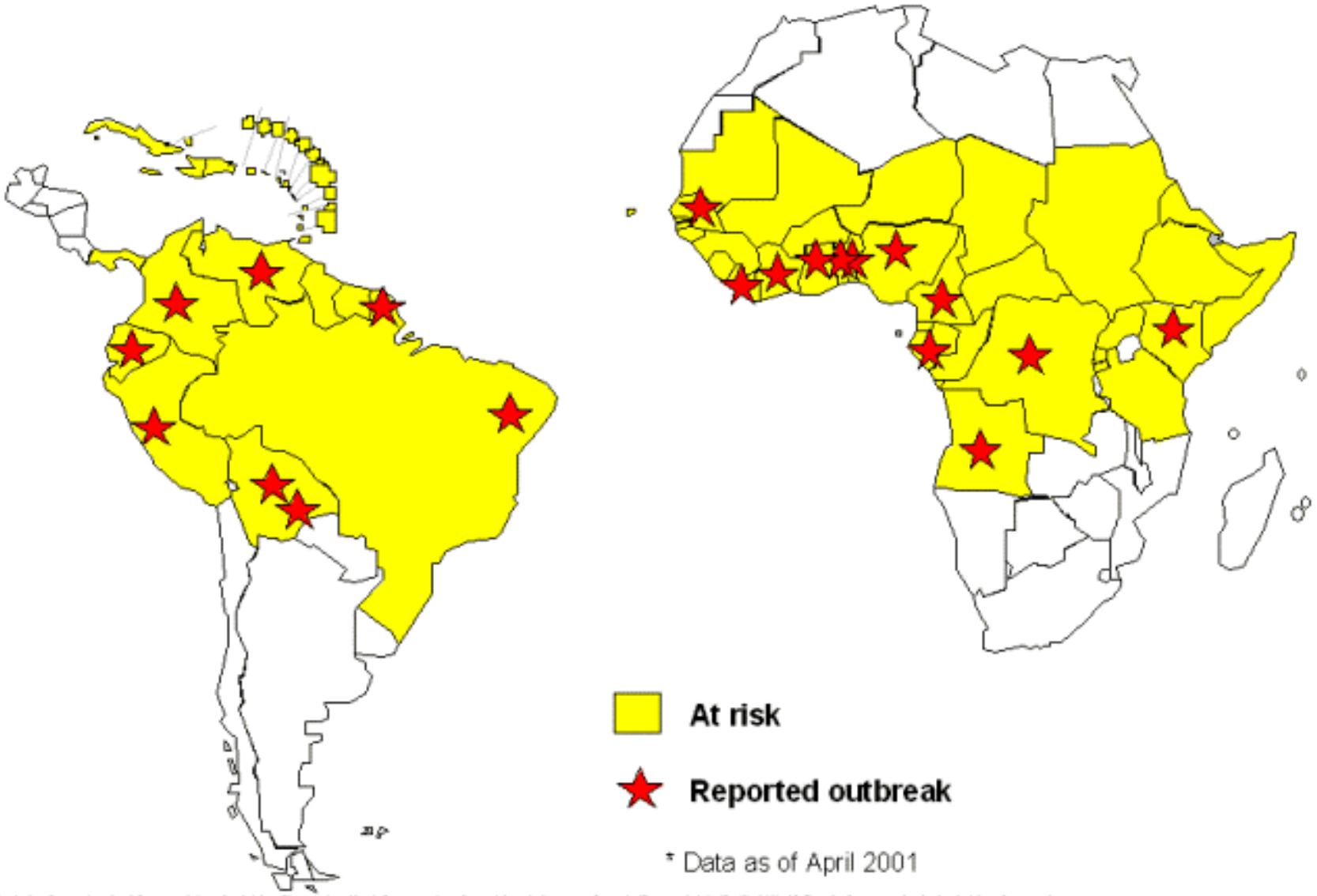
Yellow fever : global

- Flavivirus transmitted by day-biting Aedes mosquito
- Reemergence since 1980 ’s in Africa and S. America
  > 90 % cases in Africa
- ± 200 000 cases/yr (10-500 x no. reported) (30 000 deaths)
- Urban & rural in Africa ; rural & peri-urban in S. America
- Seropositivity Africa 20 - 40 %
  S.A. 1 - 3 %
  inf/illness 3,8 - 7,4 /1
- Viral hemorrhagic fever - 20% mortality

Yellow fever, 2002

* *Either yellow fever has been reported or disease in the past plus the presence of vectors and animal reservoirs create a potential risk of infection (considered to be endemic areas).*

Countries at risk for yellow fever and having reported at least one outbreak, 1985-2001*



Risk of yellow fever : Africa

Maximum risk July-Oktober

2 weeks stay	Illness	Death
Epidemics	1:250	1:1,300
Interepidemics	1:2,000	1:10,000

Montah and Cetron CID 2002, 34:1369

Risk of yellow fever : S. America

- Maximum risk : January - March (Brazil)
- Illness : 1:20,000/2 week stay
- Death : 1:100,000/2 week stay

Yellow fever immunization

- Annually ≈ 3/9 million U.S. travelers to YF areas
- 1970-2000 : 8 cases of YF in travelers
- Only 10-30 % travelers to YF endemic areas are vaccinated

Yellow fever vaccine

- Live attenuated 17D strain (204,DD)
- Protective efficacy : 90 % in 10 days; 99 % in 30 days
- Duration of immunity : probably lifetime*
  (30 - 35 years ?) : no failures in those not re-immunized
- JE immunization --> no cross protection to YF
- Dengue infection --> decreased response to YF

* Poland, TSRSTM 1981, 59:895

MMWR, 2002; 51:RR-17

Yellow fever vaccine SAE ’s

1. Hypersensitivity reaction :

   – Rash, urticaria, asthma
   – Egg allergy (chick embryo culture)
   – ? Porcine gelatin (stable)

Risk : 1:30,000 - 250,000

MMWR 2002, 51:RR-17

Yellow fever vaccine SAE ’s

2. Neutropic disease (VAND)
   - Post vaccinial encephalitis -26 cases (1945 - 2002)
   - 4-23 days post vaccination
   - 16/26 cases in children < 7 mo. of age

     Range : up to 71 years
   - 24 no sequelae; 2 deaths (HIV, child 3 years)

Risk : < 1:8,000,000

Yellow fever vaccine SAE ’s

3. Viscerotropic disease (VAVD)
   - 18 cases (19962002) : 50 % mortality
   - onset 3-5 days
   - « yellow fever » : fever, jaundice, renal failure, ARDS (multi-organ failure)

Risk (Primovax only)

- **Brazil : 1/10 000 000 doses**
- **USA : 1/200-300 000 doses**

> 60 yrs 1/40-50 000 doses

CDC, MMWR 2001, 50: 643

Yellow fever immunization is contraindicated

- Child < 6 months
  6 - 9 months : epidemics
- Pregnancy epidemics
- Allergy egg, gelatin
- Immune depression, HIV T4 < 200