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2° U.O. di Malattie Infettive
Azienda Ospedaliera Spedali Civili di Brescia

WHO Collaborating Center
for TB/HIV co-infection

Malaria:
nuove prospettive terapeutiche

Conflicts of interest

Related to this presentation:

✓ PI in a company-sponsored (Sigma-tau) clinical trial on DHA-PQ

✓ PI in the Sigma-tau surveillance register for DHA-PQ in pregnancy

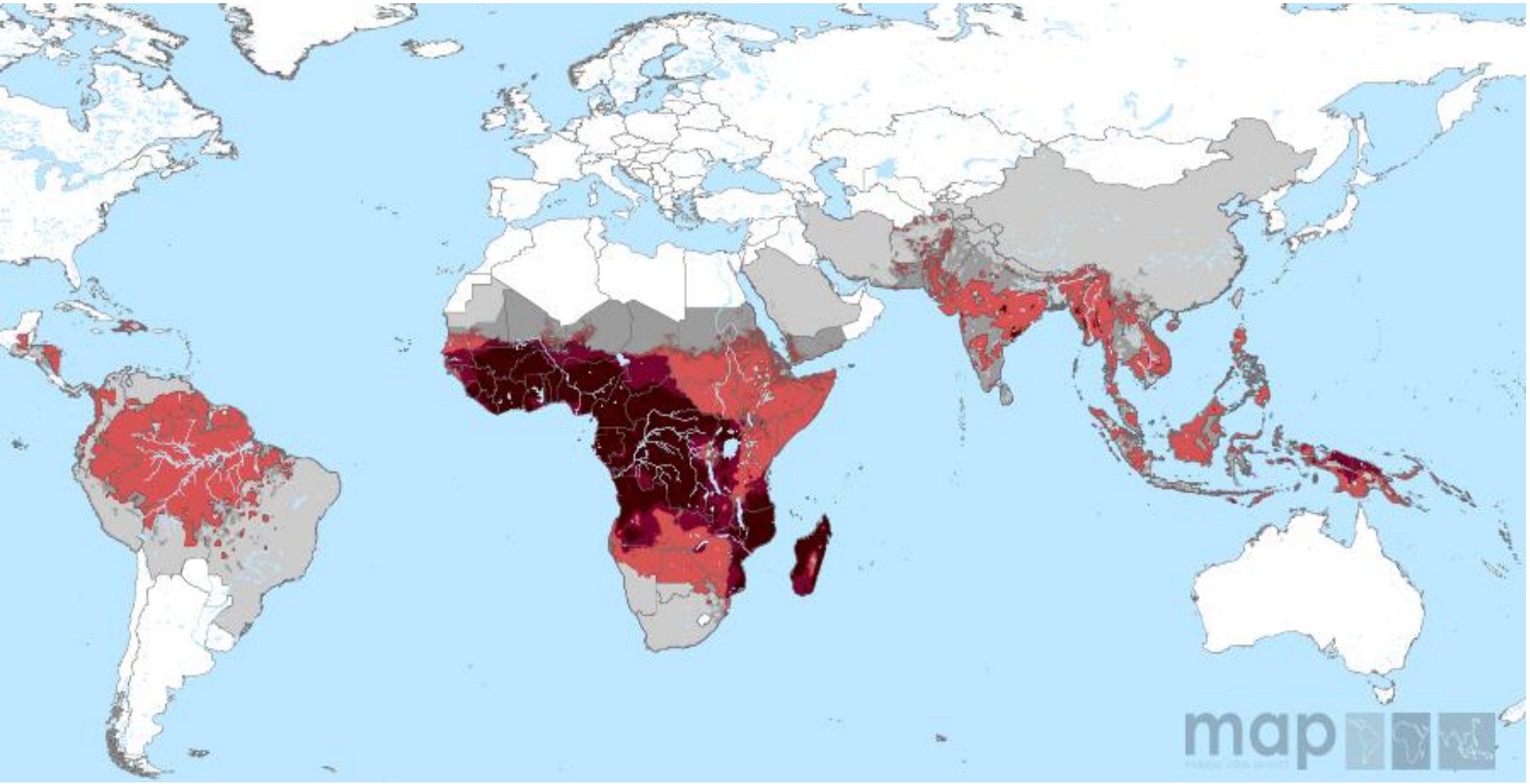
U **I suffered from malaria in february 1987 in Mali**

✓ Principal investigator of multiple company-sponsored or company-supported clinical trials on:

a) HIV infection (BMS, Medestea, VIIV, Abbott)

b) viral hepatitis (Janssen, BMS, Roche)

c) antibiotics/antifungals (Novartis)



www.map.ox.ac.uk

Roll-Back Malaria (RBM) & World Health Assembly (WHA) target

To reduce malaria cases by 75% by 2015, compared to 2000 level

Vector control:
- impregnated bednets
- indoor residual spraying
- insecticide resistance

Chemoprevention:
- intermittent preventive therapy
  a) pregnant women
  b) children
- seasonal malaria chemoprophylaxis

Diagnostic test:
- universal diagnostic testing

Treatment:
- artemisinin-based combination

Table 8.2 WHO estimates of the number of malaria cases and deaths in 2010

Region	Estimated cases ('000s)				Estimated deaths			
	Estimate	Lower	Upper	% falciparum	Estimate	Lower	Upper	% <5
African	174 000	110 000	242 000	98%	596 000	429 000	772 000	91%
Region of the Americas	1 100	900	1 300	35%	1 100	700	1 800	29%
Eastern Mediterranean	10 400	6 400	16 600	83%	15 300	7 200	23 500	70%
European	0.2	0.2	0.2	–	0	0	0	–
South-East Asia	32 000	25 900	41 900	53%	43 000	31 100	60 300	32%
Western Pacific	1 700	1 300	2 100	79%	4 000	2 400	6 100	41%
World	**219 000**	**154 000**	**289 000**	**90%**	**660 000**	**490 000**	**836 000**	**86%**

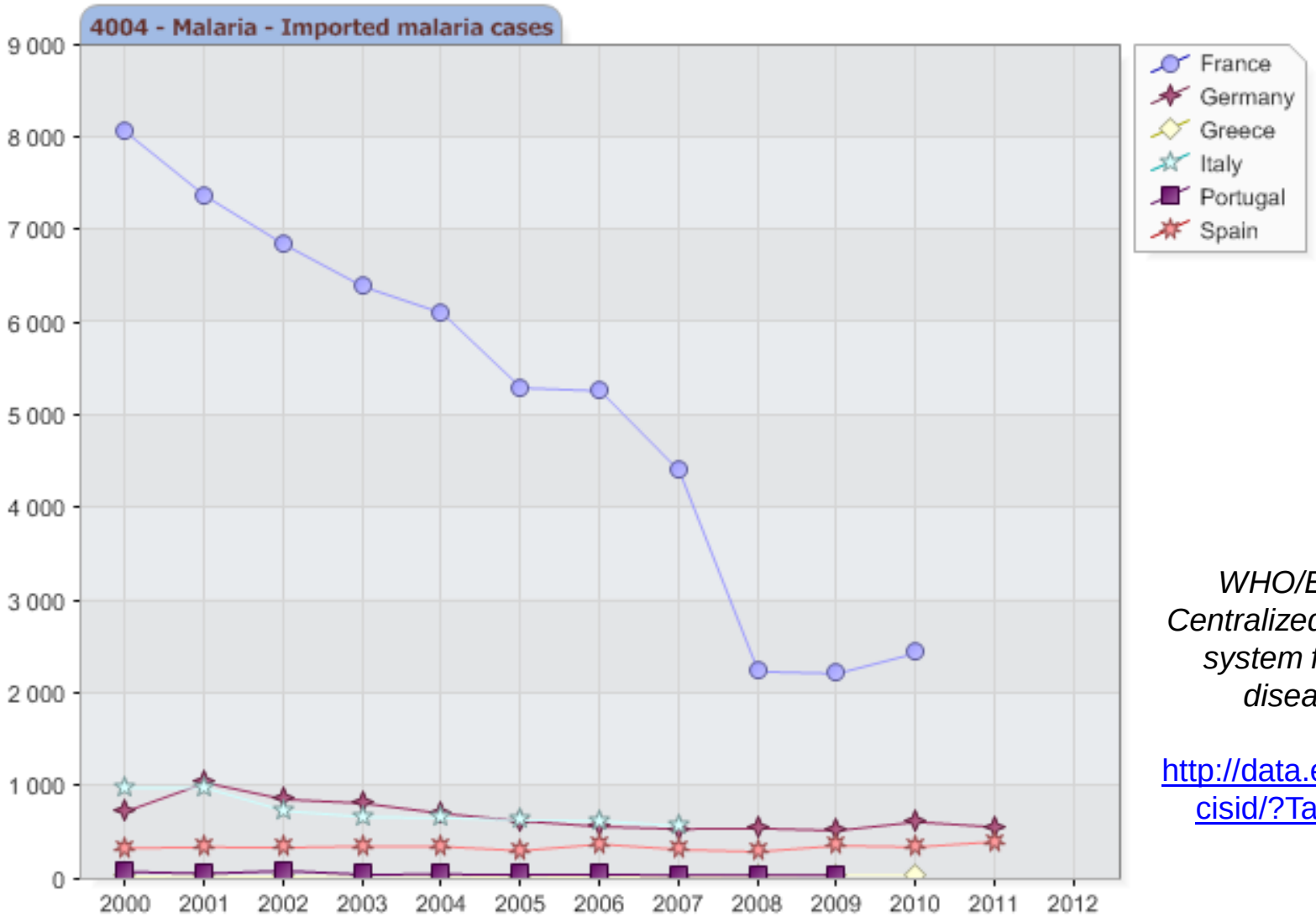
Source: WHO estimates

Cases:
80% :17 countries
40%: RDC, Nigeria, India

Deaths:
80%: 14 countries
40%: RDC, Nigeria

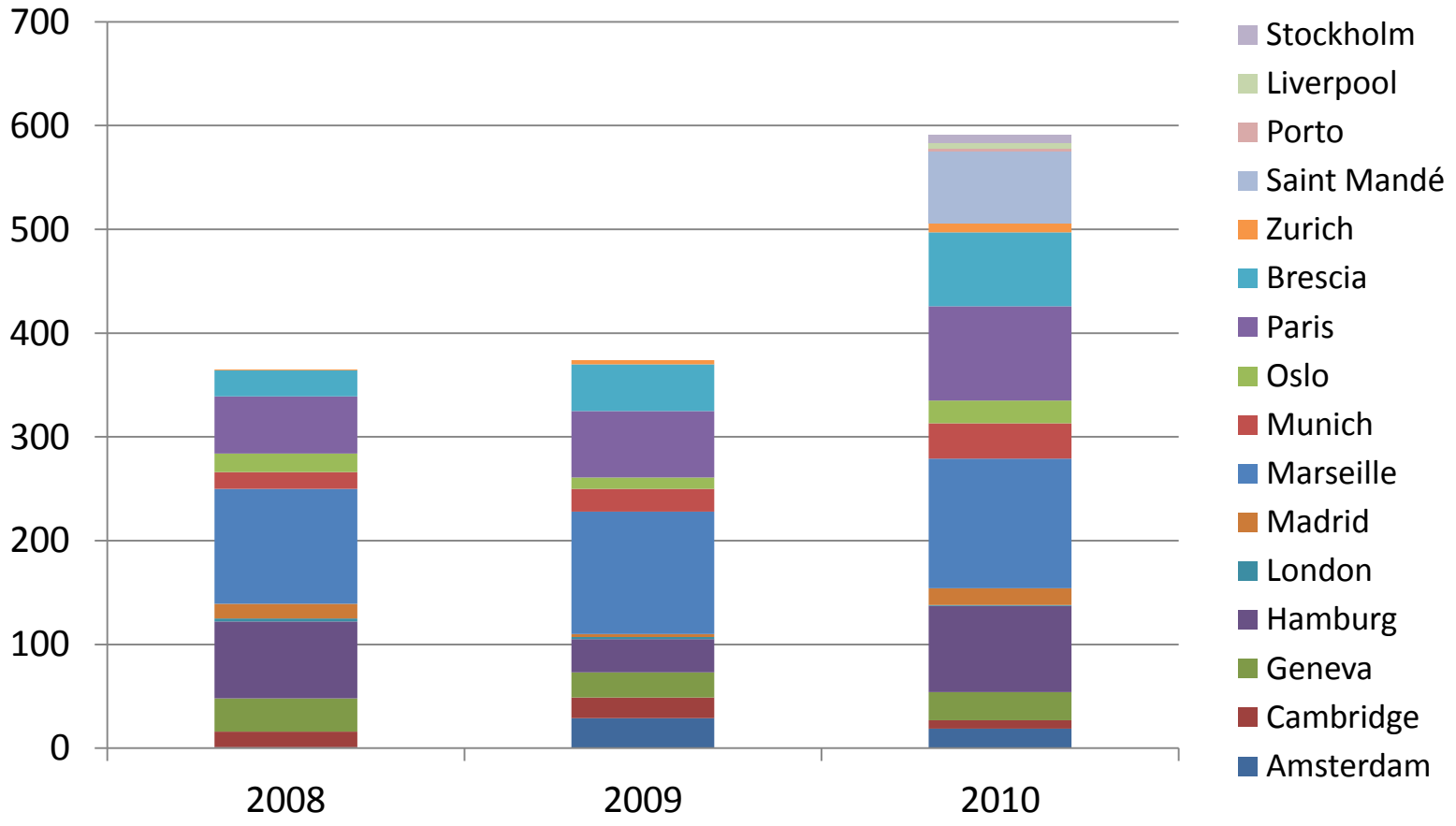
104 endemic countries:
- control phase: 79
- pre-elimination phase: 10
- elimination phase: 10
- prevention of reintroduction phase: 5

Source: WHO World Malaria Report, 2012



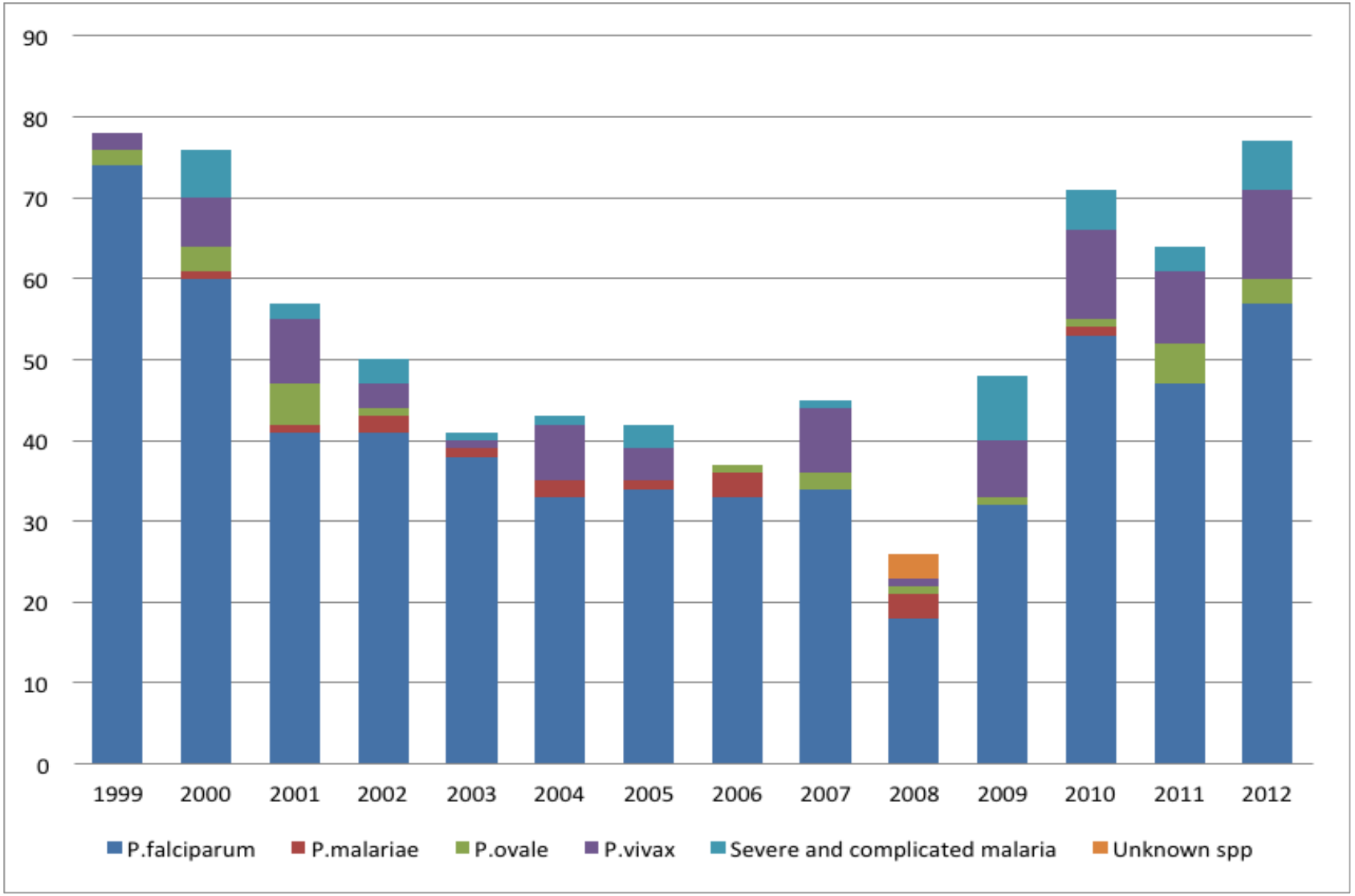
WHO/Europe 2011, Centralized information system for infectious diseases (CISID). Available at http://data.euro.who.int/cisid/?TabID=281080

- **EuroTravNet 2010**: significant increase in reported *P.falciparum* malaria observed in 2010 as compared to 2008 and 2009.



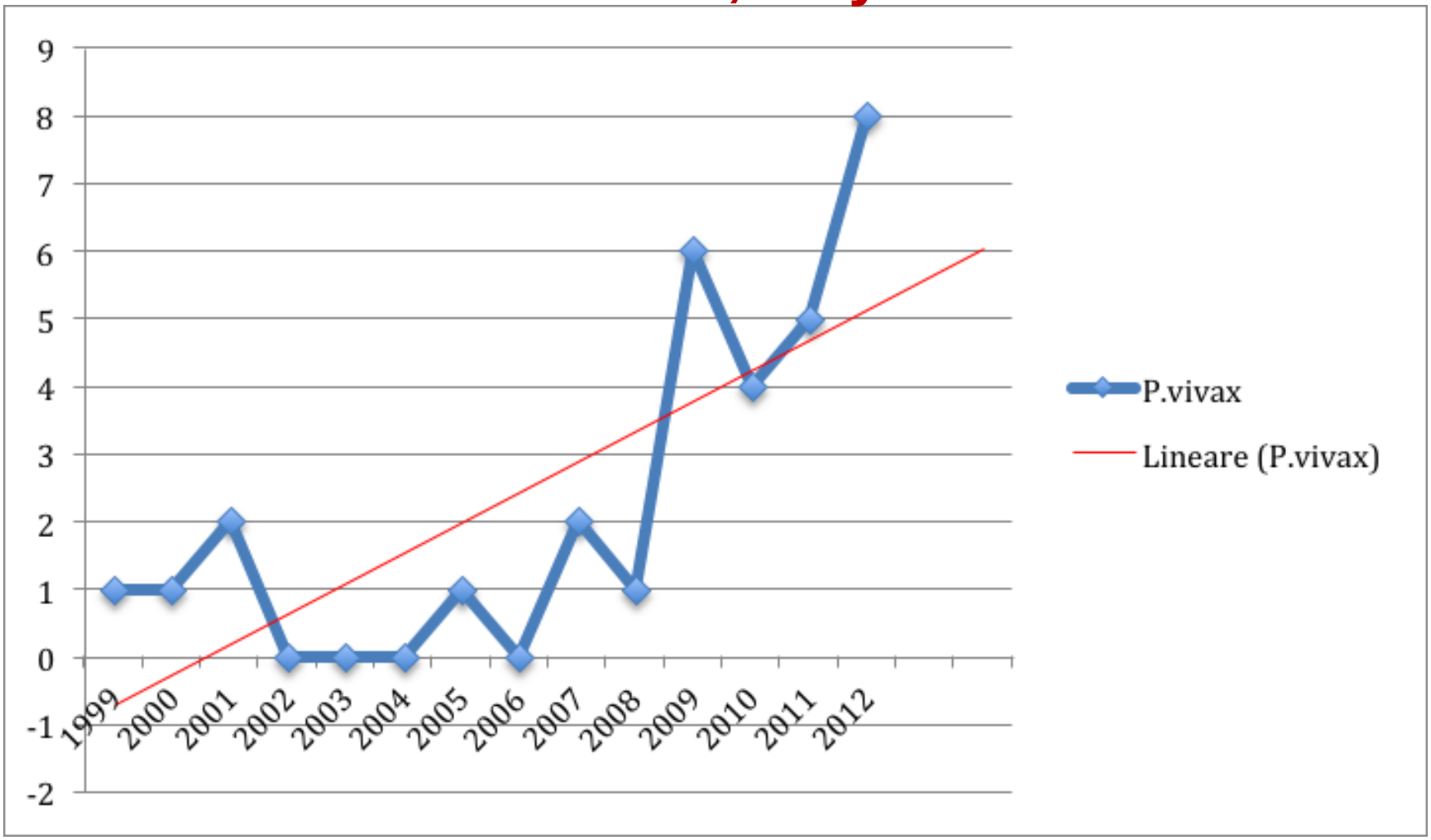
Euro Surveill. 2012;17(26):pii=20205. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20205

Imported Malaria by years in Brescia, Italy



Castelli, unpublished data

Imported *P. vivax* malaria by years in Brescia, Italy



European cluster of imported falciparum malaria from Gambia

T Jelinek (jelinek@bctropen.info)[1], C Schade Larsen[2], H Siikamäki[3], B Myrvang[4], P Chiodini[5], J Gascon[6], L Visser[7], A Kapaun[8,9], G Just-Nübling[9]

EUROSURVEILLANCE Vol. 13 · Issue 51 · 18 December 2008 · www.eurosurveillance.org

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. TropNetEurop, 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 homoeopathic 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)

Netherlands:

2 patients died = 20% (2/10)

Best practice = 0.5%

Complications in children (UK and Ireland)

In a logistic regression model,

- thrombocytopenia (OR 3.9, 95% CI 1.6 –9.2, *P* = 0.002),
- age < 5 years (OR 2.9, 95% CI 1.3– 6.8, P 0.01), and
- diagnosis outside London (OR 2.8, 95% CI 1.3– 6.1, *P* = 0.01)

remained independently associated with severe malaria.

Eleven children (6% of all cases, 7% of *P. falciparum* cases and 24% of severe *P. falciparum* malaria cases) were admitted to a pediatric intensive care unit for coma (n=5), convulsions (n=3), and 1 case each of hyper-parasitemia, circulatory shock requiring inotropic drugs and cardiac monitoring.

Ladhani et al. Pediatr Infect Dis J 2010;29:343-8

Treatment of children with malaria in the UK and Ireland

Quinine Only 45 **(30.4%)**
- Oral only 25 (16.9%)
- Intravenous only 50 (33.7%)
- Both 15 (10.1%)

Quinine with PMT-SDX 44 **(29.7%)**
- Quinine with PMT-SDX only 38 (25.7%)
- Quinine + PMT-SDX + Clindamycin 3 (2.0%)
- Quinine + PMT-SDX + ATV-PGN 2 (1.4%)
- Quinine + PMT-SDX + MFQ 1 (0.7%)

Quinine and another antimalarial 30 **(20.3%)**
- Quinine + ATV-PGN 16 (10.8%)
- Quinine + Clindamycin 11 7.4%)
- Quinine + AMT-LMF 2 (1.4%)
- Quinine + doxycycline 1 (0.7%)

Another antimalarial 29 **(19.6%)**
- ATV-PGN 25 (16.9%)
- AMT-LMF 2 (1.4%)
- Mefloquine 1 (0.7%)
- PMT-SDX 1 (0.7%)

P. vivax (n=12)
Chloroquine + primaquine 10 (83.3%)
Chloroquine + quinine 1 (8.3%)
Chloroquine only 1 (8.3%)

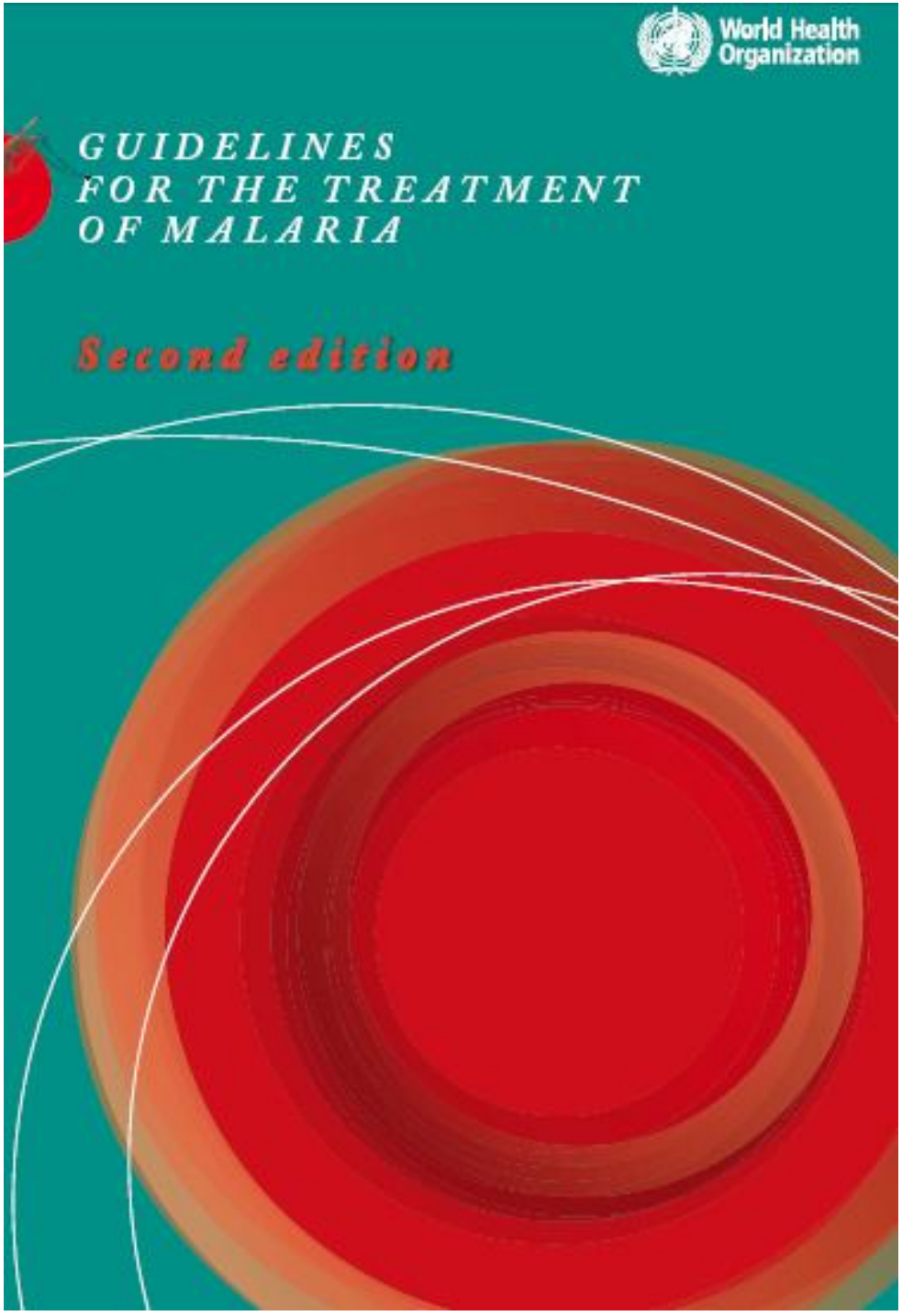
P. ovale **(n=5*)***
Quinine only 2 (40.0%)
Chloroquine + quinine 2 (40.0%)
Chloroquine + primaquine 1 (20.0%)

N = 148

There is a need for standardization of diagnosis and management of malaria in Europe

Ladhani et al. Pediatr Infect Dis J 2010;29:343-8

http://www.who.int/malaria/publications/atoz/9789241547925/en/index.html



Revised April 2011

Adapt to European

conditions

Askling et al. Malaria Journal 2012, 11:328
http://www.malariajournal.com/content/11/1/328

MALARIA JOURNAL

ESCMID
Study Group
on Clinical Parasitology

REVIEW Open Access

Management of imported malaria in Europe

Helena H Askling[1,2], Fabrice Bruneel[3], Gerd Burchard[4], Francesco Castelli[5], Peter L Chiodini[6], Martin P Grobusch[7], Rogelio Lopez-Vélez[8], Margaret Paul[9], Eskild Petersen[10*], Corneliu Popescu[11], Michael Ramharter[12] and Patricia Schlagenhauf[13] on behalf of the European Society for Clinical Microbiology and Infectious Diseases Study Group on Clinical Parasitology

Abstract

In this position paper, the European Society for Clinical Microbiology and Infectious Diseases, Study Group on Clinical Parasitology, summarizes main issues regarding the management of imported malaria cases. Malaria is a rare diagnosis in Europe, but it is a medical emergency. A travel history is the key to suspecting malaria and is mandatory in patients with fever. There are no specific clinical signs or symptoms of malaria although fever is seen in almost all non-immune patients. Migrants from malaria endemic areas may have few symptoms.

Malaria diagnostics should be performed immediately on suspicion of malaria and the gold- standard is microscopy of Giemsa-stained thick and thin blood films. A Rapid Diagnostic Test (RDT) may be used as an initial screening tool, but does not replace urgent microscopy which should be done in parallel. Delays in microscopy, however, should not lead to delayed initiation of appropriate treatment. Patients diagnosed with malaria should usually be hospitalized. If outpatient management is preferred, as is the practice in some European centres, patients must usually be followed closely (at least daily) until clinical and parasitological cure. Treatment of uncomplicated *Plasmodium falciparum* malaria is either with oral artemisinin combination therapy (ACT) or with the combination atovaquone/proguanil. Two forms of ACT are available in Europe: artemether/lumefantrine and dihydroartemisinin/piperaquine. ACT is also effective against *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* and *Plasmodium knowlesi*, but these species can be treated with chloroquine. Treatment of persistent liver forms in *P. vivax* and *P. ovale* with primaquine is indicated after excluding glucose 6 phosphate dehydrogenase deficiency. There are modified schedules and drug options for the treatment of malaria in special patient groups, such as children and pregnant women. The potential for drug interactions and the role of food in the absorption of anti-malarials are important considerations in the choice of treatment.

Complicated malaria is treated with intravenous artesunate resulting in a much more rapid decrease in parasite density compared to quinine. Patients treated with intravenous artesunate should be closely monitored for haemolysis for four weeks after treatment. There is a concern in some countries about the lack of artesunate produced according to Good Manufacturing Practice (GMP).

ESCMID Study Group on Clinical Parasitology

- Helena H Askling (Sweden)
- Fabrice Bruneel (France)
- Gerd Buchard (Germany)
- Francesco Castelli (Italy)
- Peter L Chiodini (United Kingdom)
- Martin P Grobusch (The Netherlands)
- Rogelio Lopez-Vélez (Spain)
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- Michael Ramharter (Austria)
- Patricia Schlagenhauf (Switzerland)

Malaria Journal 2012, ***11:328 doi:10.1186/1475-2875-11-328***

Management of Imported Malaria in Europe

Table 8 Recommendations

When should malaria be suspected?	In all ill patients with a travel history of visiting amalaria endemic area in the last year, especially inthe last 3 months.
Initial diagnosis	Microscopy of thick and thin Giemsa stained bloodfilms. Use of a rapid diagnostic test can be used ifmicroscopy is unavailable initially, but follow upby microscopy is essential.
Monitoring after diagnosis	Microscopy of thick and thin Giemsa stained bloodfilms. If this skill is not available the patient shouldbe transferred to a level where microscopy can be performed.
Treatment of uncomplicated malaria	See tables 1 and 2. Artemisinin combination therapy or atovaquone-proguanil are first linetreatment options for *P.falciparum* and can also be used for the other species. Chloroquine is the first line treatment for other malaria species.
Treatment of complicated malaria	Artesunate or quinine intravenously. If available,artesunate is preferable to quinine. These drugs must be available at the health care facility managing patients with malaria.
Treatment of non-falciparum malaria	Chloroquine is the drug of choice and ACT a pragmatic alternative. In case of chloroquine resistance an ACT is second line treatment.
	Primaquine is given after testing for G6PD at adose of 30 mg per day for patients infected in Southeast Asia; otherwise 15 mg/day.
Managing uncomplicated malaria	Patients with *P. falciparum* malaria should preferably be managed as in-patients. Under certain circumstances out-patient management may be acceptable provided there are daily assessments and daily blood films for parasitaemia until clinical and parasitological cure.
Managing complicated malaria	Patients with complicated *P. falciparum* malaria (Table4) should be managed as inpatients in anIntensive Care Unit.
	Patients receiving intravenous artesunate should be monitored twice weekly for 4 weeks following IVA for hemolysis and leucopenia.

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Who should malaria be suspected?

Diagnostic tests for malaria should be performed in

- Any ill patient who has a history of exposure, i.e. patients with a history of travel to malaria-endemic areas, whether or not they are febrile at presentation.

- Rare cases of airport malaria, transfusion malaria, sharing needles (IVDU), congenital transmission and organ transplants.

- A high proportion of migrants may be asymptomatic or present long after arrival in the host country, with periods of months up to more than 14 years recorded .

The travel history is essential and mandatory

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Microscopy and limitations of rapid tests

Centers managing patints 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 yeld false negative in cases with

1) very high *P.falciparum* density → ”pro-zone” with HRP2 (Gillet et al., 2009)

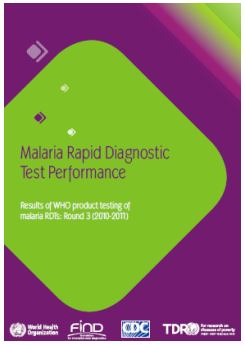
→ HRP2 deletion in South America

2) variant *P. ovale* → (Tordrup et al. Malaria J 2011;10:15)

3) P.knowlesi → HRP2 based tests will be negative

Rapid tests may yeld false positive results in cases with

1) Rheumatoid factors



http://www.who.int/tdr/publications/tdr-research-publications/rdt_round3/en/index.html

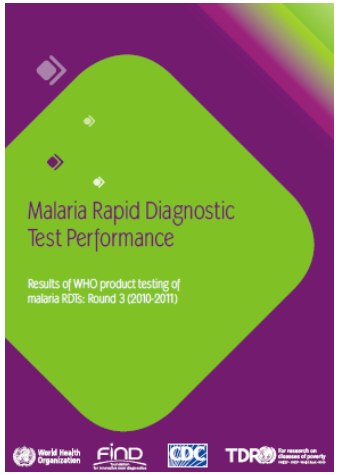
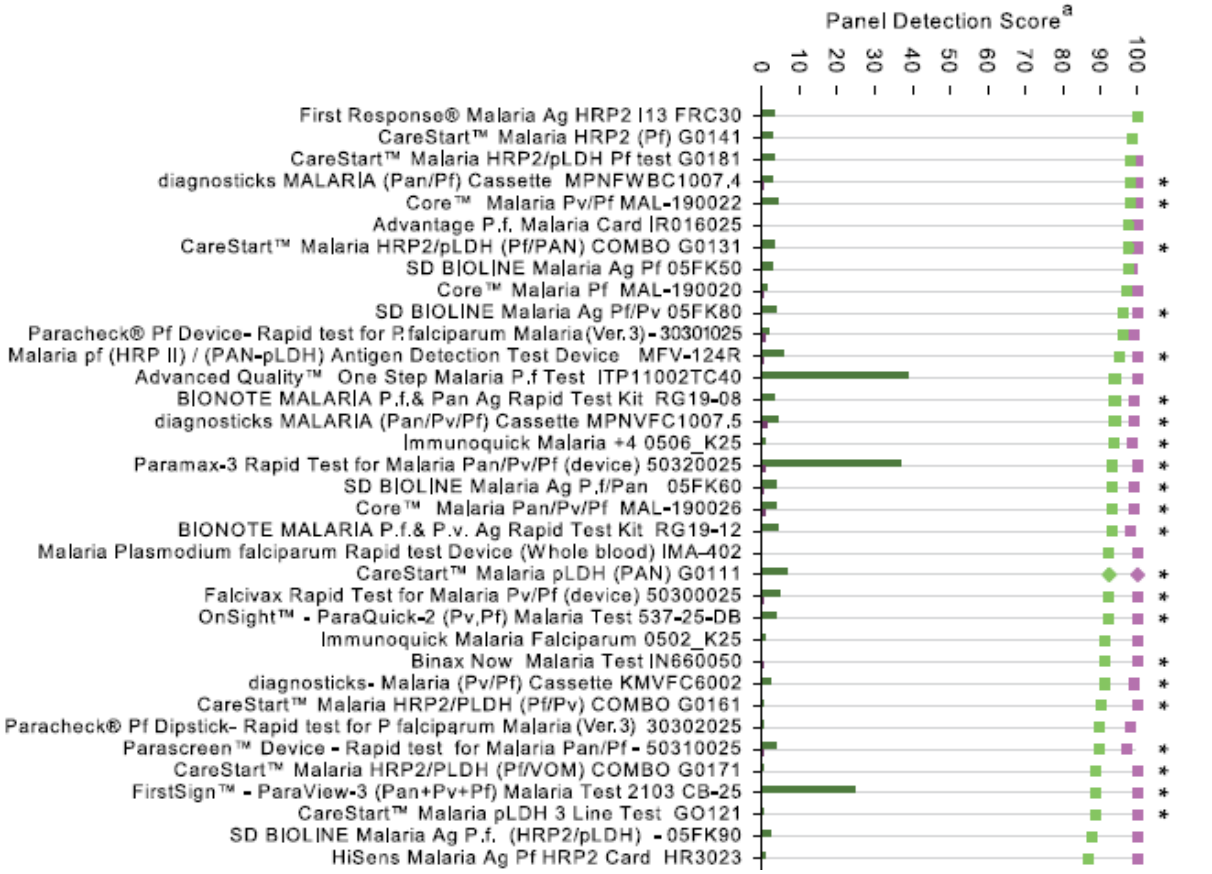


Figure S1: Malaria RDT performance in Phase 2 of Rounds 1-3 against wild-type (clinical) samples containing *P. falciparum* at low (200) and high (2000 or 5000) parasite densities (parasites/µl) and clean-negative samples



200 parasites/µl (HRP2)
200 parasites/µl (non-HRP2)
2000 parasites/µl (HRP2)
2000 parasites/µl (non-HRP2)
False-positive *Plasmodium spp.* rate (%)
Invalid rate (%)

* indicates tests that also detect other non-*P. falciparum* parasites. (see Figure S2)

[a] panel detection score - A sample is considered detected only if all RDTs from both lots read by the first technician, at minimum specified reading time, are positive.

Use a rapid test which include pan Plasmodial antigen ie. LDH or Aldolase

Take a blood sample (RDT + films) daily for three days if clinical suspicion persists

http://www.who.int/tdr/publications/tdr-research-publications/rdt_round3/en/index.html

MALARIA JOURNAL

REVIEW Open Access

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adherence and if needed, transfer to intensive care units, would normally be instantly available. Repeated monitoring of blood pressure, urinary output and oxygen saturation may be indicated. However, management as outpatients may be considered in uncomplicated cases in some health-care systems where daily follow up until clearance of parasitaemia and fever and monitoring of treatment adherence can be undertaken. Persons migrating from malaria endemic regions may fall into this category.

Management of Imported Malaria in Europe

Table 8 Recommendations

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Treatment of uncomplicated malaria in adults

1° line treatment		
Artemether/lumefantrine (20/120 mg tablets)	4 tablets BID for 3 days	Take with fatty food (reduced efficacy SEA)
Dihydroartemisinin/piperaquine (40/320 mg tbl)	3 or 4 (bw) tablets QD for 3 days	Take in fasting state
Atovaquone/proguanil (250/100 mg tablets)	4 tablets QD for 3 days	Take with fatty food

2° line treatment		
Quinine + doxycycline	10 mg/kg TID quinine + 200 mg QD doxycycline for 7 days	Off label
Quinine + clindamycin	10 mg/kg TID quinine + 10 mg/kg BID clindamycin for 7 days	Off label
Mefloquine (250 mg tablets)	3 + 2 + 1 tablet 6-8 hours apart	Take with fatty food (reduced efficay SEA)

ESCMID Study Group on Clinical Parasitology. Malaria J 2012;11:328

Paediatric doses

Table 5 Paediatric Patients

Drug	Dosage	Comment
Artemether/Lumefantrine (20/120 mg)	5–14 kg: 1 tablet per dose	Registered for treatment of patients of ≥5 kg body weight
	15–24 kg: 2 tablets per dose	Dispersible drug formulation is registered in Switzerland
	25–34 kg: 3 tablets per dose	
	> 35 kg: 4 tablets per dose	
	for 6 doses (0–8–24–36–48–60 h)[4]	
Dihydroartemisinin/Piperaquine	5 - < 7 kg: ½ tablet 160 mg/20 mg	Registered for treatment of patients of ≥5 kg body weight
	7 - < 13 kg 1 tablet 160 mg/20 mg	No paediatric drug formulation, but two strengths of tablets make use of this ACT feasible in children
	13 - < 24 kg: 1 tablet 320 mg/40 mg	
	24 - < 36 kg: 2 tablets 320 mg/20 mg	
	36 - < 75 kg: 3 tablets 320 mg/40 mg	
	75-100 kg: 4 tablets 320 mg/40 mg once daily for three days	
Atovaquone/Proguanil	5–8 kg: 2 tablets Malarone Paediatric	Registered for treatment of patients with >5 kg body weight
	9–10 kg: 3 tablets Malarone Paediatric	
	11–20 kg: 1 tablet Malarone	
	21–30 kg: 2 tablets Malarone	
	31–40 kg: 3 tablets Malarone	
	>40 kg KG: 4 tablets Malaroneonce daily for three days	
Quinine*/Doxycycline	Contraindicated in children below 8 years of age (13 years in some countries)	No drug registration
		Loose drug combination
Quinine*/Clindamycin	Thrice daily 10 mg/kg quinine plus twice daily 10 mg/kg clindamycin for 7 days	No drug registration
		Loose drug combination
Mefloquine (Lariam™)	5 - 10 kg: ½ - 1 tablet	Registered for treatment of patients of ≥5 kg body weight
	10–20 kg: 1–2 tablets	
	20–30 kg: 2–3 tablets (2 + 1)	
	30–45 kg: 3–4 tablets (2 + 2)	
	45–60 kg: 5 tablets (3 + 2)	
	> 60 kg 6 tablets (3 + 2 + 1)	
	20-25 mg/kg total dose divided in 1–3 doses 6 hours apart	

*Quinine dose provided as quinine sulphate.
°Eurartesim tablet strengths are Dihydroartemisinin/piperaquine 20 mg/160 mg (children) and Dihydroartemisinin/piperaquine 40 mg/320 mg (adults).

ESCMID Study Group on Clinical Parasitology. Malaria J 2012;11:328

Pregnancy

Table 6 Malaria treatment in pregnancy

Uncomplicated falciparum malaria		
1st trimester (1)	First line	Quinine-clindamycin quinine monotherapy
2nd and 3rd trimester	First line	artemether-lumefantrine
	Second line	quinine-clindamycin quinine monotherapy mefloquine (2)
Complicated falciparum malaria		
1st trimester	First line	i.v. quinine (+ follow on treatment)
2nd and 3rd trimester	First line	i.v. artesunate (+ follow on treatment)
	Second line	i.v. quinine (+ follow on treatment)
P. ovale*, *P. malariae* and *P. vivax (3)		
All trimesters	First line	Oral chloroquine
2nd and 3rd trimester	Second line	Oral ACT

1 Artemether/lumefantrine is not the first drug of choice due to lack of data on lumefantrine in pregnancy, but should be used if quinine is not available.
2. http://www.cdc.gov/malaria/new_info/2011/mefloquine_pregnancy.html
3. Primaquine should not be used because of the risk of foetal haemolytic anaemia

ESCMID Study Group on Clinical Parasitology. Malaria J 2012;11:328

Management of Imported Malaria in Europe

Table 8 Recommendations

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Initial diagnosis	☑	Microscopy of thick and thin Giemsa stained bloodfilms. Use of a rapid diagnostic test can be used ifmicroscopy is unavailable initially, but follow upby microscopy is essential.
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		Primaquine is given after testing for G6PD at adose of 30 mg per day for patients infected in Southeast Asia; otherwise 15 mg/day.
Managing uncomplicated malaria		Patients with *P. falciparum* malaria should preferably be managed as in-patients. Under certain circumstances out-patient management may be acceptable provided there are daily assessments and daily blood films for parasitaemia until clinical and parasitological cure.
Managing complicated malaria		Patients with complicated *P. falciparum* malaria (Table4) should be managed as inpatients in anIntensive Care Unit.
		Patients receiving intravenous artesunate should be monitored twice weekly for 4 weeks following IVA for hemolysis and leucopenia.

Malaria Journal 2012, ***11:328 doi:10.1186/1475-2875-11-328***

Severe and/or complicated malaria (*Pf, Pv, Pk*)

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)

Blood films and parasitaemia should be assessed at least daily

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).

WHO 2011

Ventilator
Blood presure support
Dialysis

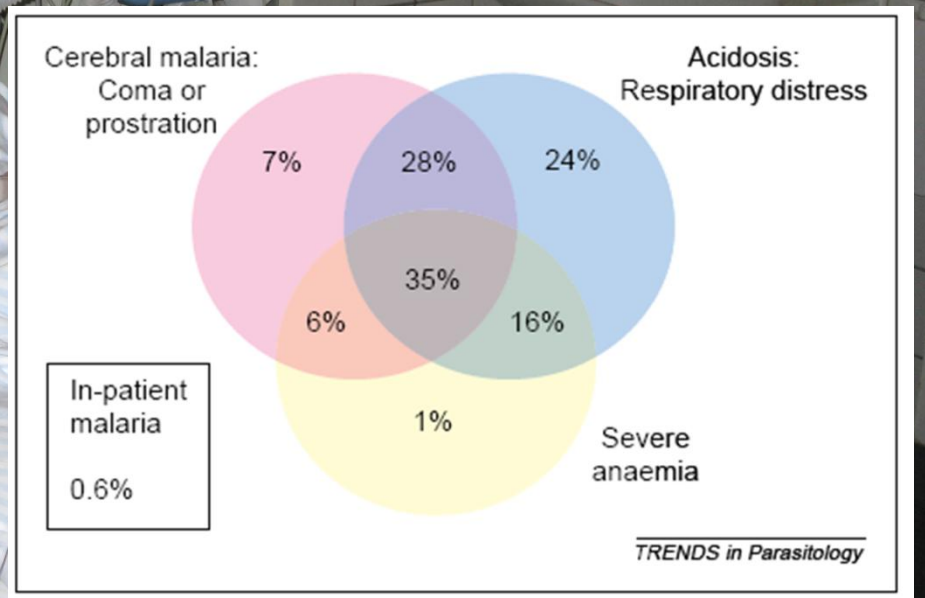
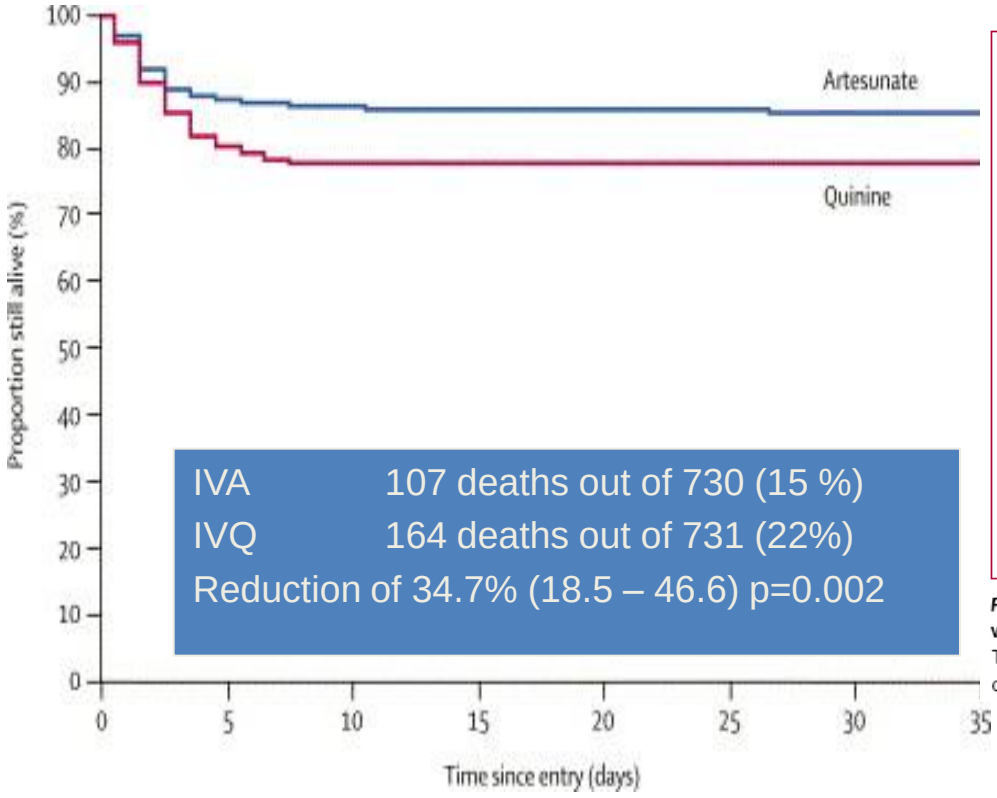


Figure 1. Mortality in severe falciparum malaria. The mortality (indicated as a percentage) of the common syndromes of severe malaria are clinically defined by: (i) impaired consciousness (cerebral malaria); (ii) deep breathing (respiratory distress) and severe anaemia (haemoglobin <5 g dl^{-1}). Adapted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

Artesunato vs chinino nel trattamento della malaria grave.

Lo studio SEAQUAMAT
In Asia
(prevalentemente adulti)



SEAQUAMAT, The Lancet, 2005; 366: 7171-25

Lo studio AQUAMAT
In Africa
(bambini)

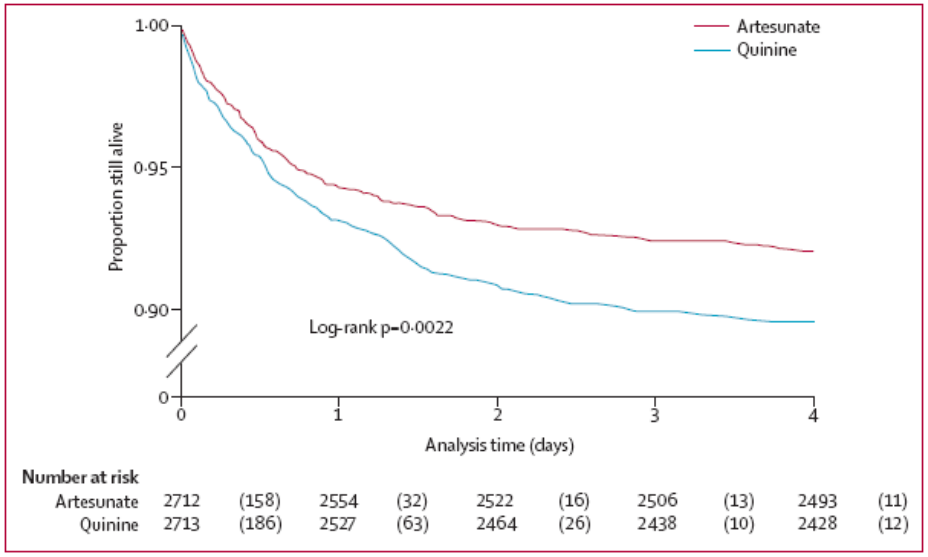


Figure 2: **Kaplan-Meier curves comparing survival in African children with severe falciparum malaria treated with either parenteral artesunate or quinine**
The numbers in parentheses are the deaths during the indicated time. In eight patients the exact time of death during the night was missing and was estimated as 2359 h.

Treatment of severe malaria

I.v. **Artemisinin hemisuccinate**, (IVA) is superior to i.v. quinine (IVQ) in overall survival, and IVA should be the drug of choice for treatment of severe imported malaria in Europe.

I.v. **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

Treatment of severe malaria

Not available in Italy

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ESCMID Study Group on Clinical Parasitology. Malaria J 2012;11:328

Am. J. Trop. Med. Hyg., 83(2), 2010, pp. 274–276
doi:10.4269/ajtmh.2010.10-0128

Case Report: Combined Intravenous Treatment with Artesunate and Quinine for Severe Malaria in Italy

Alessandro Bartoloni,* Lina Tomasoni, Filippo Bartalesi, Luisa Galli, Spartaco Sani, Sara Veloci, Lorenzo Zammarchi, Alessandro Pini, and Francesco Castelli

Clinica Malattie Infettive, Dipartimento Area Critica Medico-Chirurgica, Università degli Studi di Firenze, Firenze, Italy; SOD Malattie Infettive e Tropicali, Azienda Ospedaliero-Universitaria Careggi, Firenze, Italy; Istituto Malattie Infettive e Tropicali, Università di Brescia, Brescia, Italy; Dipartimento di Pediatria, Università di Firenze, Firenze, Italy; UO Malattie Infettive, Spedali Riuniti Livorno, Livorno, Italy

Abstract. Severe imported malaria is an important problem in European countries, where approximately 8,000 cases of *Plasmodium falciparum* malaria are reported each year. Although the World Health Organization recommends intravenous artesunate (IVA) as the treatment of choice for severe malaria in areas of low transmission, it is rarely used in Europe, because it is not yet available as a drug manufactured under Good Manufacturing Practices. We report a series of eight imported severe falciparum malaria cases treated with IVA combined with intravenous quinine (IVQ). This combined therapy was found to be efficacious, safe, and well-tolerated. The only observed death occurred in a young man who presented 10 days after the onset of symptoms. IVA plus IVQ treatment seems to be an acceptable approach, because the legal risks in using an unlicensed drug for treating a severe malaria case denies the patient the possibility of being treated with the most effective regimen.

MALARIA JOURNAL

REVIEW Open Access

Management of imported malaria in Europe

Helena H Askling[1,2], Fabrice Brunee[3], Gerd Burchard[4], Francesco Castelli[5], Peter L Chiodini[6], Martin P Grobusch[7], Rogelio Lopez-Vélez[8], Margaret Paul[9], Eskild Petersen[10*], Corneliu Popescu[11], Michael Ramharter[12] and Patricia Schlagenhauf[13] on behalf of the European Society for Clinical Microbiology and Infectious Diseases Study Group on Clinical Parasitology

Unlicensed drugs

WHO guidelines recommend IVA in preference to quinine for the treatment of severe malaria in adults [80]. At present, no GMP (Good Manufacturing Practice) produced IVA is available in Europe. However, Guilin Pharmaceutical Factory No. 2 (Shanghai, People's Republic of China), the manufacturer of the artesunate used in major trials in Southeast Asia and Africa [87,88], may supply the drugs upon request. Artesunate manufactured by Guilin has received pre-qualification from the WHO.

Since 2011, the French National Health Agency (AFSSAPS), now named (ANSM) has temporarily authorized the import and use of IVA (Malacef®) via ACR-Pharmaceuticals, the Netherlands, granting it a temporary authorization of use [102]. However, the use of non GMP artesunate remains sensitive from a legal point of view in many European countries, and some centres

Malaria Journal 2012, 11:328 doi:10.1186/1475-2875-11-328

Haemolytic anaemia after Artesunate™

✓Haemolytic anemia have been reported in six out of 25 patients treated with IVA for severe malaria diagnosed 14–31 days after the first dose of IVA .

Zoller T et al. Emerg Infect Dis. 2011;17:771-7.

✓A study including 55 patients with severe malaria reported late onset haemolytic anaemia in six patients (9%) between 7 and 31 days after start of IVA.

Kreeftmeijer-Vegter AR et al. Mal J 2012, 11:102.

✓Three more cases have just been reported.

Rolling T et al. Malar J 2012;11:169.

Until further data are available, patients should be monitored for haemolytic anaemia and leukopenia for 4 weeks following IVA .

Management of Imported Malaria in Europe

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Treatment of complicated malaria	☑	Artesunate or quinine intravenously. If available,artesunate is preferable to quinine. These drugs must be available at the health care facility managing patients with malaria.
Treatment of non-falciparum malaria	☑	Chloroquine is the drug of choice and ACT a pragmatic alternative. In case of chloroquine resistance an ACT is second line treatment.
		Primaquine is given after testing for G6PD at adose of 30 mg per day for patients infected in Southeast Asia; otherwise 15 mg/day.
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Intensive care

✓Fluid management is very important.

✓Monitoring of plasma lactate is mandatory.

✓For children, the FEAST trial provided high quality evidence for paediatric malaria and showed that fluid bolus significantly increases mortality.

Maitland K et al. N Engl J Med 2011, 364:2483-95.

✓In the shocked and/or acidotic patient with severe malaria, bacterial co-infection should be sought by blood culture and antibiotic treatment started urgently if suspected.

Bruneel F et al. Am J Respir Crit Care Med 2003,167:684-9.

✓Cerebral malaria: corticosteroids as well as mannitol should not be given.

✓There is no consensus on the indications, benefits and dangers involved in exchange blood transfusion, so it should not be used

Guidelines for the treatment of malaria. WHO, Geneva, 2011

Recommendations I

Suspect malaria

✓Travel history

Diagnosis

✓Microscopy of thick and thin Giemsa stained blood films.

✓Use of a rapid diagnostic test does not replace the need for microscopy.

Monitoring after diagnosis

✓Microscopy of thick and thin Giemsa stained blood films to count parasites.

Managing uncomplicated malaria

✓Patients with *P. falciparum* malaria should preferably be managed as inpatients.

✓Under certain circumstances may outpatient management be acceptable provided there are daily assessments and daily blood films for parasitaemia .

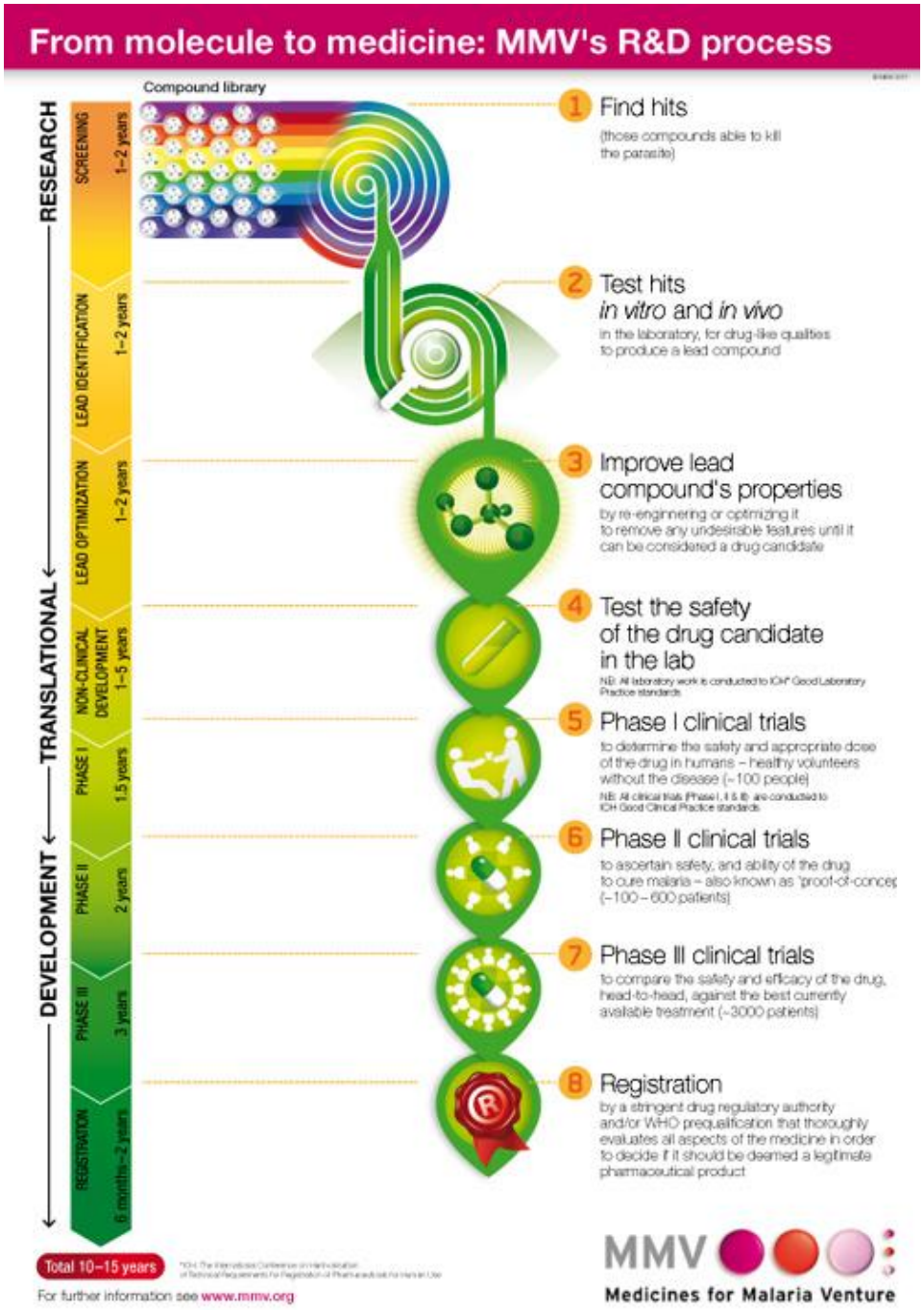
Managing complicated malaria

✓Intravenous artesunate (or i.v. Quinine) should be available

Recommendations II.

Centres managing patients with malaria should:

- Be competent in microscopy of thick and thin blood films and enumeration of malaria parasites in blood films.
- Centres with access to rapid diagnostic tests only should not manage patients with malaria.
- The Center must have access to i.v. Artesunate / Quinine and ACTs.
- The Center must have adequate intensive care facilities.



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Review

Expanding the Antimalarial Drug Arsenal—Now, But How?

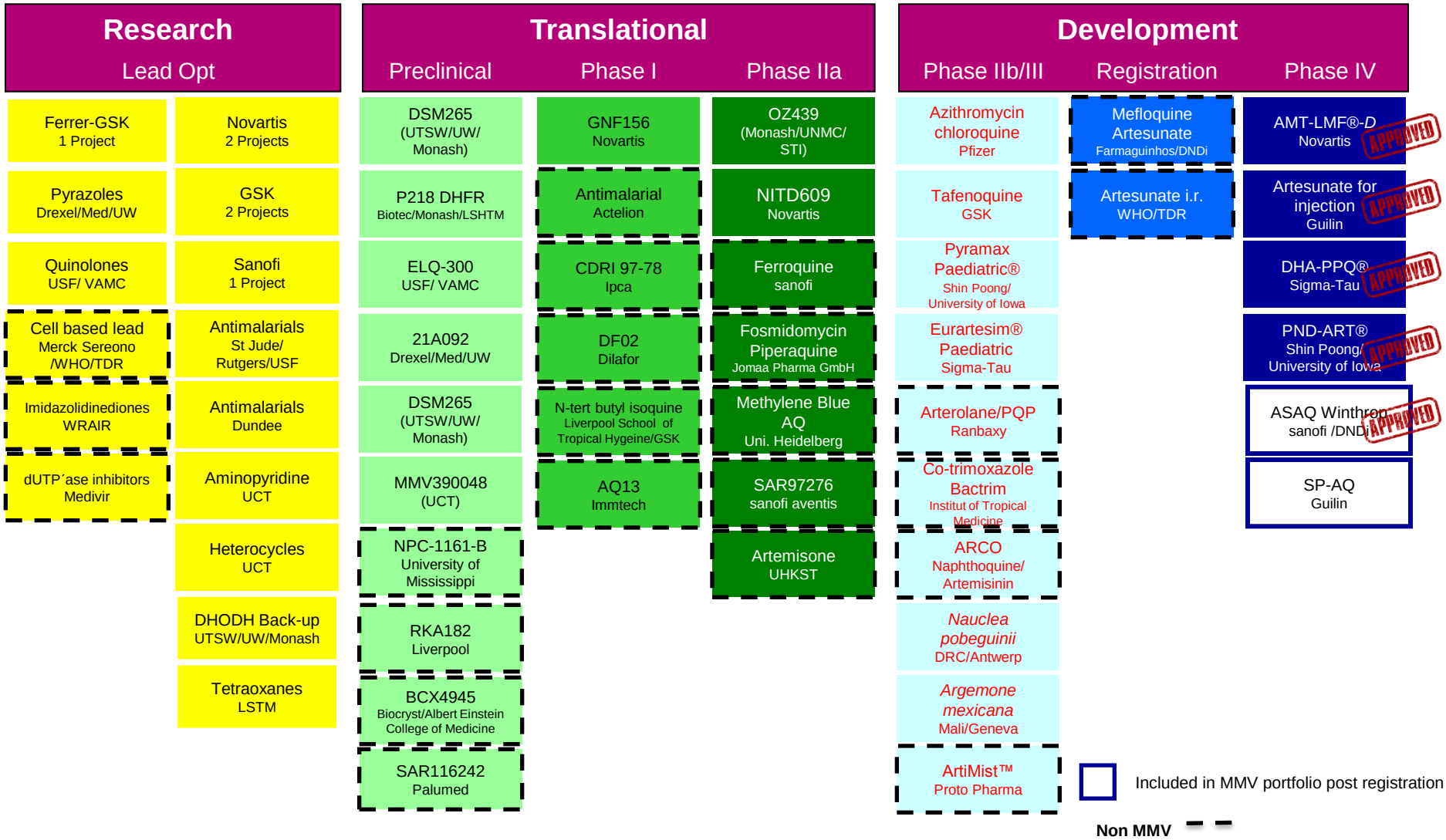
Brian T. Grimberg * and Rajeev K. Mehlotra *

Table 1. Recent antimalarial drug screening efforts.

Group	Number of compounds screened	Number of hits (effective against malaria parasites)	Number of new leads (with no reported toxicity to humans)	Pre-IND	Reference
Plouffe *et al.*	1,700,000	6,000	530	*	[141]
Gamo *et al.*	2,000,000	13,533	51	*	[142]
Guiguemde *et al.*	309,474	1,300	172	34	[143]
Rottmann *et al.*	12,000	275	17	1	[144]
Rush *et al.*	16,000	17	*	*	[145]
Grimberg *et al.*	33	28	6	3	[88]

* = Ongoing investigations, outcome pending.

Global Malaria Portfolio, 3Q 2012



Medicines for Malaria Venture http://www.mmv.org/research-development/rd-portfolio

Le nuove “indicazioni” per la profilassi antimalarica

della Società Italiana di Medicina Tropicale (SIMET) con la collaborazione di SIMIT, SIMM, SIMVIM, SoIPA

Geographical prophylaxis of malaria is based on the A-E scale

- A: Awareness
- B: Bite prevention
- C: Chemoprophylaxis
- D: Diagnosis
- E: Emergency stant-by treatment

Recommendations for antimalarial chemoprophylaxis have been based on:

1) Local incidence data
   - n. cases of yearly imported malaria / 100.000 travellers
   - API (Annual Parasite Incidence: yearly n. cases / 1.000 inhabitants
2) Presence of *P. falciparum*
   - when only *P. vivax* is present, no chemoprophylaxis is recommended;
3) Stand-by treatment is considered under specific circumstances

Le linee-guida italiane per la profilassi antimalarica

REGIONE	NOTE	AB	1°	2nd
AFRICA DEL NORD Egitto, Algeria, Capo Verde	-Riportati casi sporadici di malaria: rischio minimo	si	D	
AFRICA SUB-SAHARIANA Angola, Benin, Burkina Faso, Burundi, Camerun, Ciad, Comore, Congo, Costa d'Avorio, Eritrea, Etiopia, Gabon, Gambia, Ghana, Guinea, Guinea Bissau, Guinea Equatoriale, Kenya, Liberia, Madagascar, Malawi, Mali, Mozambico, Mauritania, Niger, Nigeria, Rep. Centroafricana, Rep. Dem. Congo, Rwanda, Sao Tomé e Principe, Senegal, Sierra Leone, Somalia, Sudan, Sud Sudan, Tanzania (eccetto Zanzibar) , Togo, Uganda, Zambia, Zimbabwe	-Eritrea (rischio nelle aree < 2000 m, ad Asmara non vi è malaria) -Etiopia (rischio nelle aree < 2000 m, ad Addis Abeba non vi è malaria) -Mauritania (rischio soltanto nella parte meridionale del Paese) -Kenya (a Nairobi il rischio è minimo, la malaria non è presente nelle aree > intorno al monte Kenya) -Senegal (rischio più basso durante la stagione secca, gennaio-maggio) -Zimbabwe (malaria presente nelle aree < , soprattutto da novembre a giugno, rischio minimo a Harare e Bulawayo)	si	C	
AFRICA SUB-SAHARIANA Zanzibar, Mafia, Gibuti	-nessun rischio nella capitale a Gibuti -rischio più elevato da ottobre a maggio nel resto di Gibuti	sì	E-D	C
AFRICA AUSTRALE Botswana (regioni settentrionali), Namibia (regioni settentrionali e lungo i fiumi Kavango e Kunene), Sud Africa (Kruger e zone limitrofe), Swaziland	-stagionalità della malaria: la chemioprofilassi è di prima scelta solo tra novembre e aprile	si	C	E-D
AFRICA AUSTRALE Botswana (escluse le regioni settentrionali), Namibia (escluse le regioni settentrionali e lungo i fiumi Kavango e Kunene), Sud Africa (escluso Kruger e zone limitrofe)		sì	D	

Le linee-guida italiane per la profilassi antimalarica

REGIONE	NOTE	AB	1st	2nd
ASIA CENTRALE E PENISOLA ARABICA Afghanistan, Arabia Saudita, Azerbaigian, Bhutan, Iran, Iraq, Kirgizistan, Yemen	- Armenia, Azerbaigian, Kazakistan, Siria, Turchia, Iran, Irak 100% *P. vivax* -Afghanistan 90% *P. vivax*	si	D	
ASIA Cina (Hainan, Yunnan, Anhui, Henan, Hubei, Ghuizhou, Jinagsu)	-nelle altre regioni della Cina la malaria non è presente	si	D	
ASIA SUBCONTINENTE INDIANO Bangladesh (regione di Chittagong), India (Assam e Orissa, in particolare nella stagione dei monsoni)		si	C	E-D
ASIA SUBCONTINENTE INDIANO Bangladesh (eccetto regione di Chittagong), India (eccetto Assam e Orissa), Nepal (Terai), Pakistan, Sri Lanka.	-India (nelle zone centrali il rischio è lievemente più alto rispetto a quelle settentrionali e meridionali) -Sri Lanka 96% *P.vivax* -Pakistan 70% *P.vivax*	si	E-D	C
ASIA SUBCONTINENTE INDIANO Nepal (Kathmandu, Pokhara)	Nessun rischio oltre i 2000 m	sì	D	
SUD-EST ASIATICO Myanmar, Cambogia (eccetto Phnom Penh, Angkor Wat e Tonle Sap), Indonesia (Lombok, Sumba, Sumbaya, Timor, Flores, Molucche, Irian Jaya), Laos (parte meridionale), Thailandia (regioni al confine con Myanmar e Cambogia),	-Segnalata la presenza di *P.vivax* resistente alla clorochina e di *P.knowlesi*	si	C	
SUD-EST ASIATICO Brunei, Cambogia (Phnom Penh, Angkor Wat e Tonle Sap), Filippine, Laos (parte settentrionale), Malesia, Vietnam, Indonesia (eccetto Lombok, Sumba, Sumbaya, Timor, Flores, Molucche, Irian Jaya)	-Segnalata la presenza di *P.vivax* resistente alla clorochina e di *P.knowlesi*	si	E-D	C
SUD-EST ASIATICO Singapore, Thailandia (escluse regioni al confine con Myanmar e Cambogia)		sì	D	

Conclusioni

1. L’infezione malarica è ancora una priorità di sanità pubblica
2. La malaria di importazione, dopo un periodo di calo, è oggi in aumento in alcune aree del Paese
3. Le combinazioni ACT rappresentano oggi lo standard of care (malaria grave e/o non complicata)
4. Necessità di uniformare le linee guida di management e profilassi malaria di importazione
   - Position paper ESCMID
   - Indicazioni SIMET/SIMIT/SIMVIM/SIMM