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MALARIA: SITUAZIONE GLOBALE E STATO DELL'ARTE SUL TRATTAMENTO

Biella, 28 gennaio 2011

I. Note di storia
II. Epidemiologia
III. Roll Back Malaria
IV. Le linee-guida OMS

Giovanni Verga, Novelle Rusticane, 1883 .

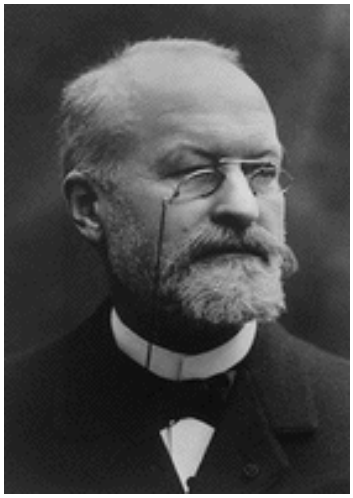
"È che la malaria v'entra nelle ossa col pane che mangiate, e se aprite bocca per parlare, mentre camminate lungo le strade soffocanti di polvere e di sole, e vi sentite mancar le ginocchia, o vi accasciate sul basto della mula che va all'ambio, colla testa bassa …"

"…. spopolate, e li inchioda dinanzi agli usci delle case scalcinate dal sole, tremanti di febbre sotto il pastrano, e con tutte le coperte del letto sulle spalle."

Carta della malaria in Italia, 1882

Carta della malaria in Italia, 1900

Charles Louis Alphonse Laveran
(1845-1922)



1907: Premio Nobel per la medicina

"a riconoscimento del suo lavoro nella scoperta del ruolo giocato dai protozoi nel causare malattie"

Camillo Golgi: 1843-1926

1906: premio Nobel per la medicina

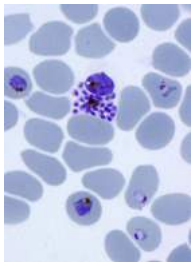
"come riconoscimento del suo lavoro sulla struttura del sistema nervoso"

www.nobelprize.org

E. Marchiafava

A. Celli

Marchiafava, Bignami, Bastianelli e Celli dimostrano che le due forme erano diverse da una terza specie conosciuta come *P. falciparum* che era la più letale.



Ronald Ross

1902: Premio Nobel per la Medicina

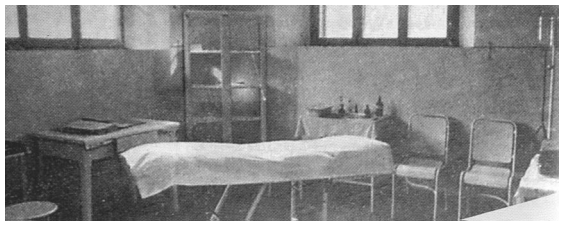
20 AGOSTO 1897: "MOSQUITO DAY"

Vide un parassita pigmentato della malaria crescere nella parete dello stomaco di una"dappled-winged" zanzara che 4 giorni prima si era nutrita del sangue di un paziente con malaria.

La “crociata” antimalarica

Enti locali
- Stazioni sanitarie rurali
- Tassa ai datori di lavoro
- Scuole contadine

Croce Rossa Italiana



La Grande Guerra

Medici e sanitari al fronte

Contadini maschi al fronte

Campi coltivati da donne e bambini non immuni

Mancata bonifica dei canali

Risorse rivolte alle attività belliche

Movimento di masse portatrici di parassiti

Trincee, scavi, crateri di bombe

LA "BONIFICA INTEGRALE"

Bonifica idraulica

Bonifica agricola

Bonifica igienica

- Profilassi con chinino
- Controllo dei vettori
- Organizzazione delle acque
- Sanificazione ambientale
- Utilizzazione di larvicidi
- Utilizzo di dispositivi di protezione

Legge 24 dicembre1928 o legge "Mussolini"

Casi di malaria da *P. falciparum* nelle truppe alleate

An. labranchiae

Malaria eradication campaign, Italy
(from A. Coluzzi historical photo-set)

17 Novembre 1970

L'Organizzazione Mondiale della Sanità dichiara l'Italia libera dalla malaria.

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MALARIA EPIDEMIOLOGY

TYPE	SPLEEN RATES	PARASITE RATES	DESCRIPTION
Hypo-endemic	Not exceeding 10% in children aged 2-9 years	Not exceeding 10% in children aged 2-9 years but may be higher for part of the year	Areas where there is little transmission and the effects, during an average year, upon the general population are unimportant
Meso-endemic	Between 11% and 50% in children aged 2-9 years	Between 11% and 50% in children aged 2-9 years	Typical found among rural communities in subtropical zones where wide geographical variations in transmission risk exist
Hyper-endemic	Constantly over 50% in children ages 2-9 years; also high in adults (over 25%)	Constantly over 50% among children ages 2-9 years	Areas where transmission is intense but seasonal and where **the immunity is insufficient in all age groups**
Holo-endemic	Constantly over 75% in children ages 2-9 years, but low in adults	Constantly over 75% among infants ages 0-11 months	Perennial, intense transmission resulting in **considerable degree of immunity** since early childhood

Snow, R.W.; Gilles, H.M. The epidemiology of malaria, "Essential Malariology", 2002

MALARIA EPIDEMIOLOGY

WHO REGION	CASES/year		DEATH/year	
	NUMBER (MILLION)	P. falciparum (%)	NUMBER (THOUSAND)	UNDER 5 (%)
AFR	208	98	621	88
AMR	1	32	1	30
EMR	9	75	32	77
EUR	0	4	0	3
SEAR	24	56	27	34
WPR	2	79	2	41
TOTAL	243	93	708	85

World Malaria Report, 2009

Human malaria parasites

Plasmodium falciparum	tertian	non relapsing	malignant
Plasmodium vivax	tertian	relapsing	benign
Plasmodium ovale	tertian	relapsing	benign
Plasmodium malariae	quartan	non relapsing	benign
Plasmodium knowlesi	daily	non relapsing	malignant (?)

Plasmodium falciparum is by far the main cause of malaria-related death

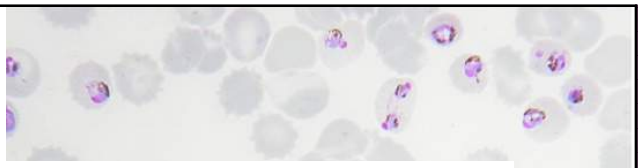


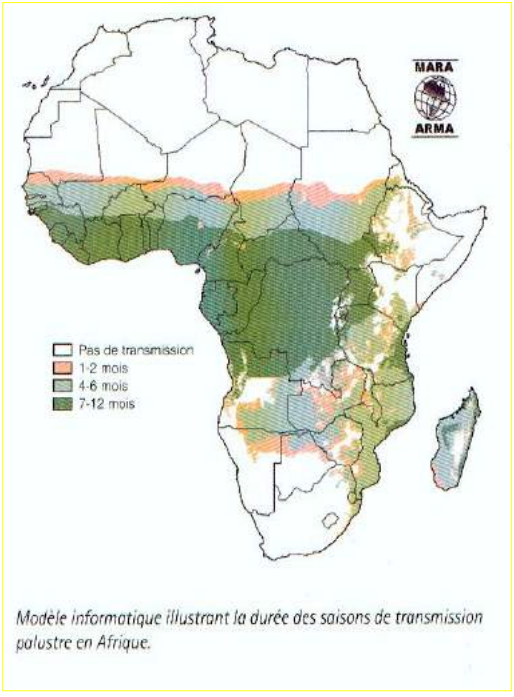
Table 1. Comparison of results for detection of *Plasmodium* species by PCR and microscopy.

PCR results	No. of cases identified by microscopy					No. of cases identified by PCR
	Plasmodium falciparum	*Plasmodium vivax*	*Plasmodium malariae*	*Plasmodium ovale*	*P. falciparum* and *P. vivax*	
P. falciparum	167	18	33	1	0	219
P. vivax	23	372	43	1	1	440
P. malariae	0	0	1	0	0	1
P. ovale	0	2	2	0	0	4
Plasmodium knowlesi	11	16	216	0	0	243
P. falciparum and *P. vivax*	11	9	4	0	1	25
P. falciparum and *P. malariae*	0	0	1	0	0	1
P. falciparum and *P. ovale*	1	0	0	0	0	1
P. falciparum and *P. knowlesi*	1	0	2	0	0	3
P. vivax and *P. knowlesi*	2	8	9	0	0	19
P. vivax and *P. malariae*	0	2	0	0	0	2
P. vivax and *P. ovale*	0	1	0	0	0	1
P. ovale and *P. knowlesi*	0	0	1	0	0	1
Total	216	428	312	2	2	960

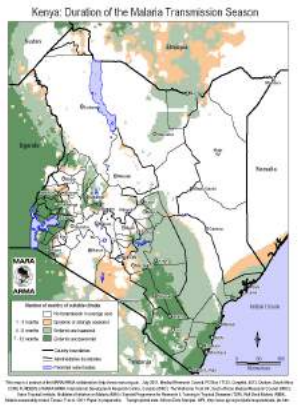
Cox-Singh j, Clin Infect Dis 2008; 46: 165

Vectors of human malaria by continent

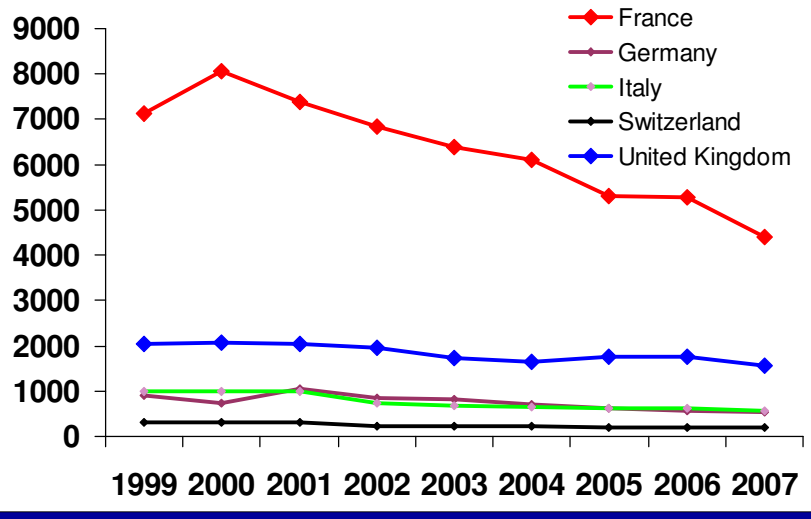
	Africa	Asia	Americas	Europe
Genus	*A. gambiae* *A. funestus* *A. nili* …	*A. minimus* *A. dirus* *A. stephensi* …	*A. albimanus* *A. darlingi* *A. acquasalis* …	*A. maculipennis* *A. atroparvus* *A. superpictus* …
Endophilia	-	-/+	-/+	++
Anthropophilia	+++	++	++	+
Larval habitat	Small vegetation-free ponds & puddles	Shallow and slow-flowing stream	Large ponds with floading vegetation	Marshes



Modèle informatique illustrant la durée des saisons de transmission palustre en Afrique.

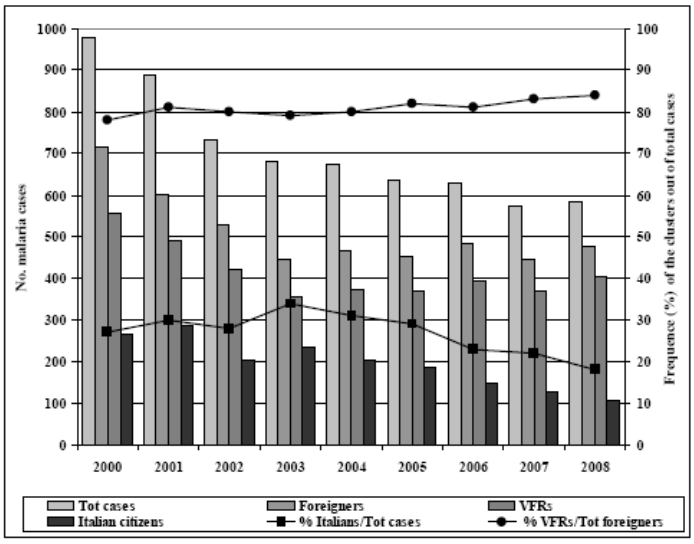


TREND OF IMPORTED MALARIA CASES IN SELECTED EUROPEAN COUNTRIES



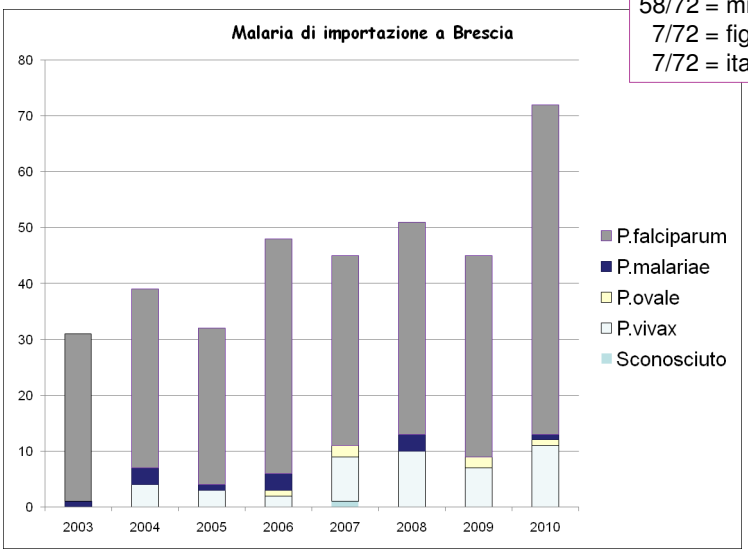
http://ecdc.europa.eu/en/Health_Topics/malaria
http://data.euro.who.int/CISID

IMPORTED MALARIA IN ITALY



Romi et al, Giorn. It. Med. Trop., 2010: 35-38

I NOSTRI DATI
2003-2010



2010:
58/72 = migranti
7/72 = figli di migranti
7/72 = italiani

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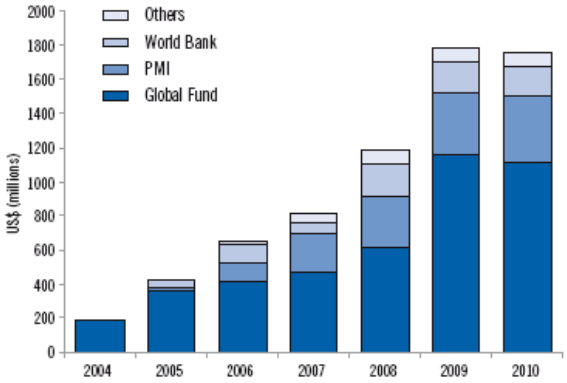


Figure 3.1 Funding commitments of the Global Fund, the US President's Malaria Initiative, World Bank, and other agencies

World Malaria Report, 2010

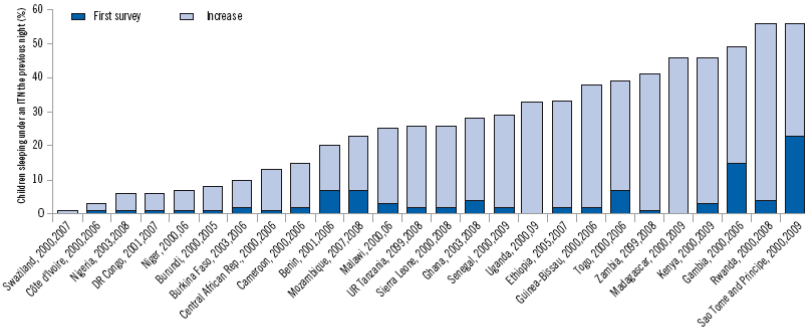


Figure 4.4 Trends in percentage of children sleeping under an ITN for countries with more than one survey, 2000–2009

World Malaria Report, 2010

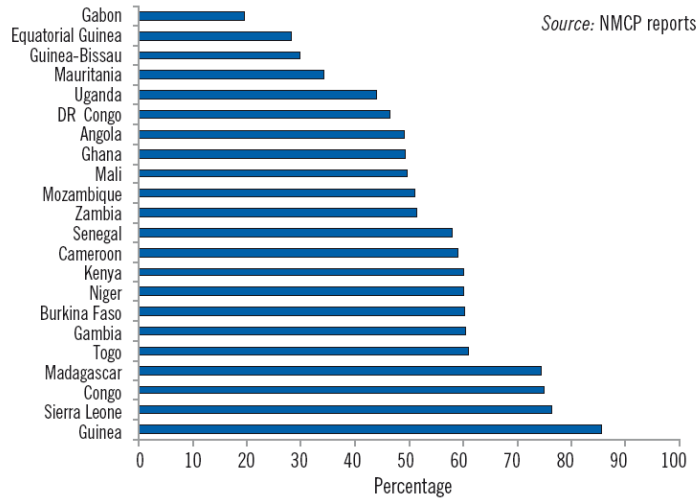
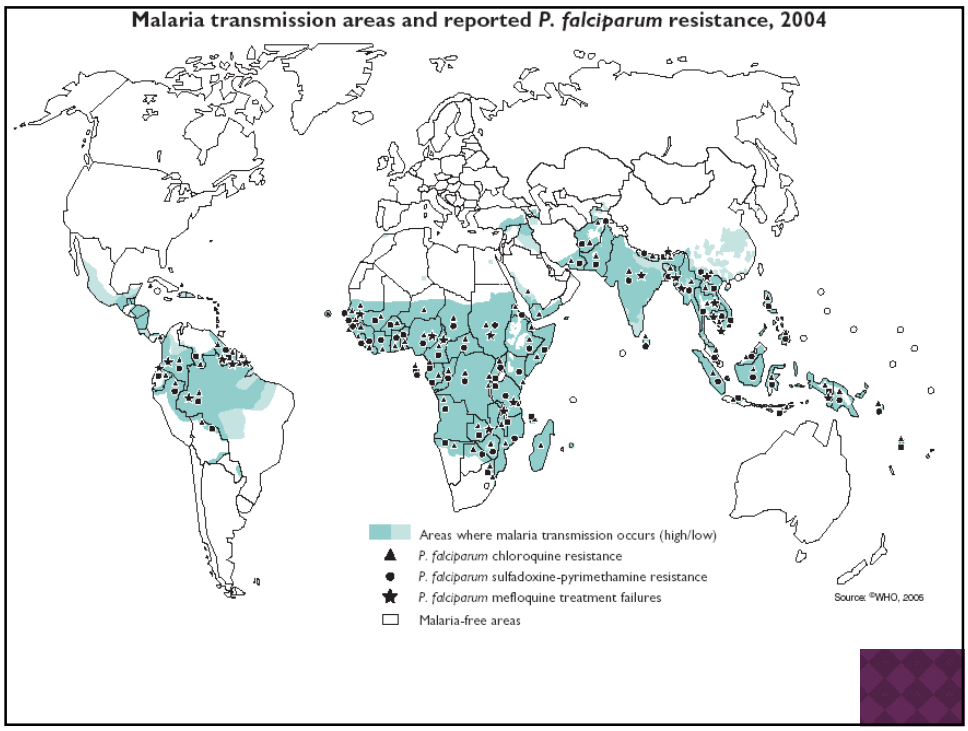
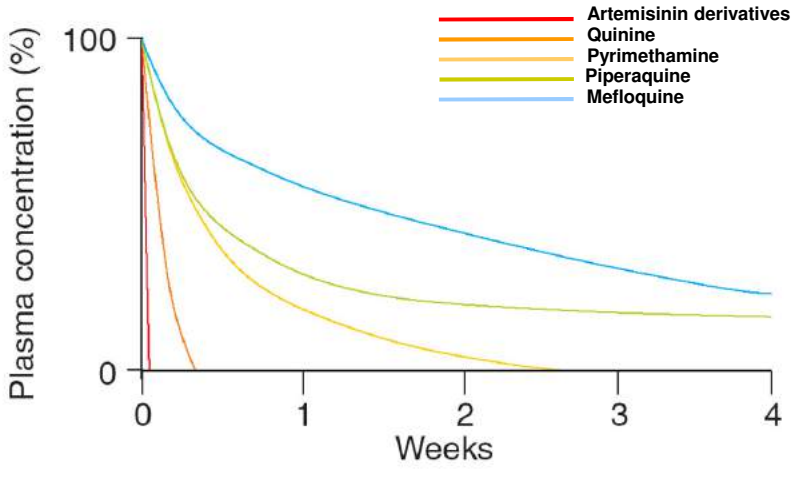


Figure 5.12 Proportion of women attending antenatal care receiving the second dose of IPT

World Malaria Report, 2010

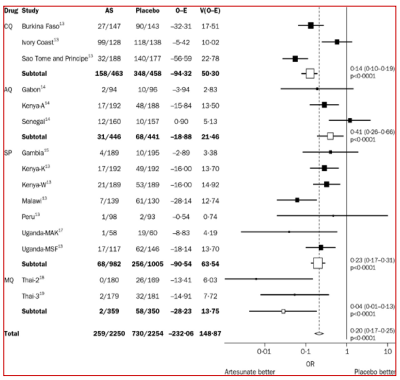


Parasite exposure to drugs in ACTs

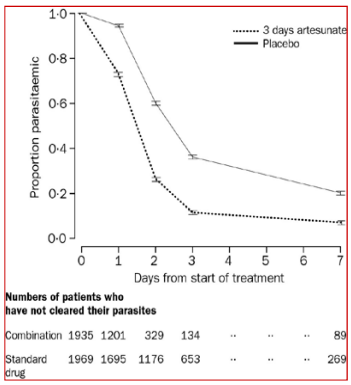


Artesunate combo for treatment of malaria: meta-analysis

Parasitological failure by day 14:
3-day artesunate vs placebo



Survival curve to time
for parasite clearance



International Artemisinin Study Group, The Lancet, 2004; 363: 9-17

ARTEMISININ–BASED COMBINATION TREATMENT (ACT)

- ✓ Combination in which one component is artemisinin and its derivatives (artesunate, artemether, dihydroartmisinin)
  - ✓ Artemeter plus lumefantrine
  - ✓ Artesunate plus amodiaquine
  - ✓ Artesunate plus mefloquine
  - ✓ Artesunate plus sulfadoxine-pyrimethamine
  - ✓ Dihydroartemisinin plus piperaquine
- ✓ The artemisinin produce rapid clearance of parasitemia and rapid resolution of the symptoms
- ✓ Rapid elimination
- ✓ Reduction of gametocyte carriage

Guidelines for the treatment of malaria, second edition, 2010

Stop malaria now!

cases

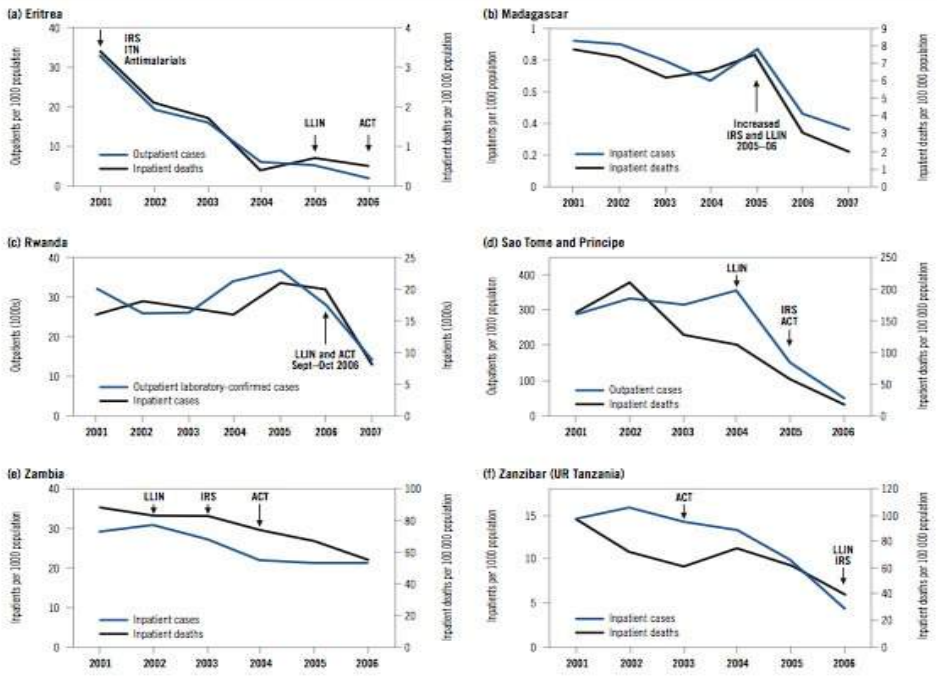
deaths

TABLE 5.2

ADOPTION OF POLICIES FOR MALARIA TREATMENT IN WHO REGIONS

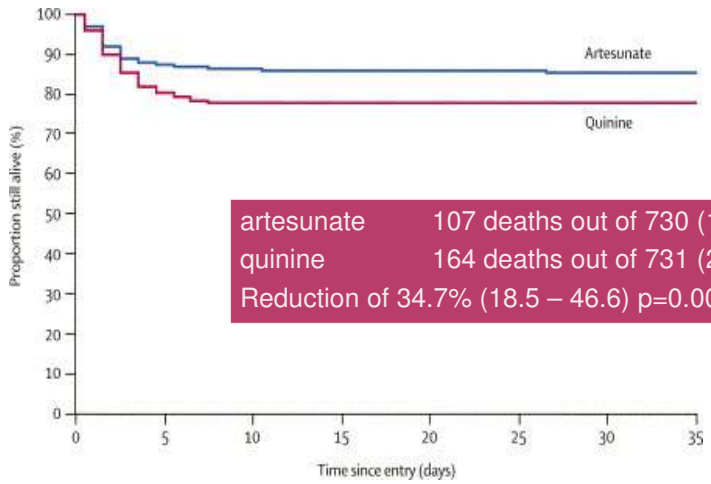
POLICY	AFRICAN	AMERICAS	EASTERN MEDITERRANEAN	EUROPEAN	SOUTH-EAST ASIA	WESTERN PACIFIC	GRAND TOTAL
Number of endemic countries and territories	43	23	12	8	10	10	106
Number of P. falciparum *endemic countries and territories*	42	18	8		9	9	86
ACT is used for treatment of *P. falciparum*	42	9	8		9	9	77
ACT is free of charge for all age groups in public sector	24	6	9		6	7	52
ACT is free of charge only for < 5 years in public sector	5				2	1	8
ACT delivered at community level	25	2	1		4	4	36
Pre-referral treatment with quinine/artemether IM/ artesunate suppositories	32	2	7		7	6	54
Therapeutic efficacy monitoring is undertaken	25	6	5		5	7	48

World Malaria Report, 2010



World Malaria Report, 2009

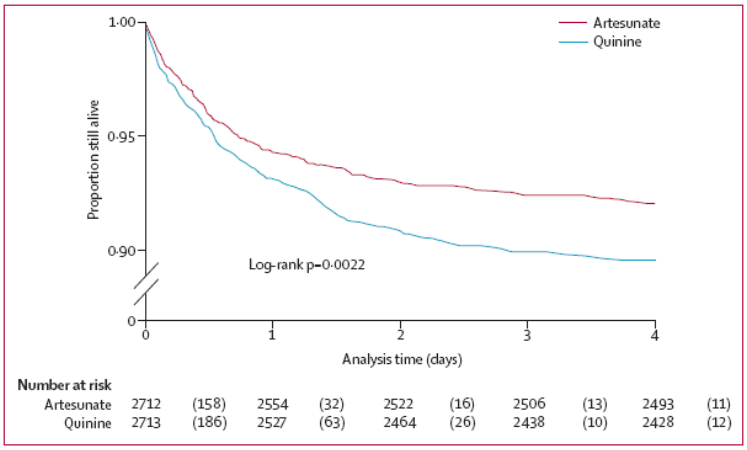
Artesunato vs chinino nel trattamento della malaria grave. Lo studio SEAQUAMAT



artesunate	107 deaths out of 730 (15 %)
quinine	164 deaths out of 731 (22%)
Reduction of 34.7% (18.5 – 46.6) p=0.002	

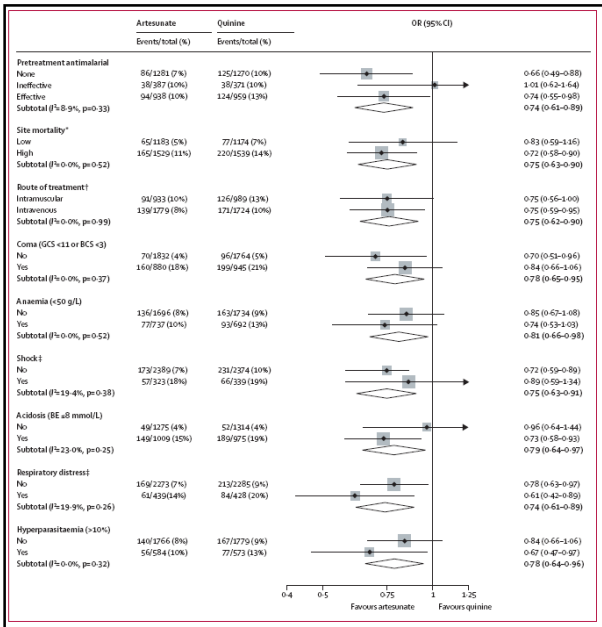
SEAQUAMAT, The Lancet, 2005; 366: 7171-25

Artesunato vs chinino nel trattamento della malaria grave nei bambini in Africa. Lo studio AQUAMAT



Number at risk										
Artesunate	2712	(158)	2554	(32)	2522	(16)	2506	(13)	2493	(11)
Quinine	2713	(186)	2527	(63)	2464	(26)	2438	(10)	2428	(12)

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.



	Artesunate	Quinine	OR (95% CI)
	Events/total (%)	Events/total (%)	
Pretreatment antimalarial			
None	86/1281 (7%)	125/1270 (10%)	0·66 (0·49–0·88)
Ineffective	38/387 (10%)	38/371 (10%)	1·01 (0·62–1·64)
Effective	94/938 (10%)	124/959 (13%)	0·74 (0·55–0·98)
Subtotal (I^2=8·9%, p=0·33)			0·74 (0·61–0·89)
Site mortality*			
Low	65/1183 (5%)	77/1174 (7%)	0·83 (0·59–1·16)
High	165/1529 (11%)	220/1539 (14%)	0·72 (0·58–0·90)
Subtotal (I^2=0·0%, p=0·52)			0·75 (0·63–0·90)
Route of treatment†			
Intramuscular	91/933 (10%)	126/989 (13%)	0·75 (0·56–1·00)
Intravenous	139/1779 (8%)	171/1724 (10%)	0·75 (0·59–0·95)
Subtotal (I^2=0·0%, p=0·99)			0·75 (0·62–0·90)
Coma (GCS <11 or BCS <3)			
No	70/1832 (4%)	96/1764 (5%)	0·70 (0·51–0·96)
Yes	160/880 (18%)	199/945 (21%)	0·84 (0·66–1·06)
Subtotal (I^2=0·0%, p=0·37)			0·78 (0·65–0·95)
Anaemia (<50 g/L)			
No	136/1696 (8%)	163/1734 (9%)	0·85 (0·67–1·08)
Yes	77/737 (10%)	93/692 (13%)	0·74 (0·53–1·03)
Subtotal (I^2=0·0%, p=0·52)			0·81 (0·66–0·98)
Shock‡			
No	173/2389 (7%)	231/2374 (10%)	0·72 (0·59–0·89)
Yes	57/323 (18%)	66/339 (19%)	0·89 (0·59–1·34)
Subtotal (I^2=19·4%, p=0·38)			0·75 (0·63–0·91)
Acidosis (BE ≤8 mmol/L)			
No	49/1275 (4%)	52/1314 (4%)	0·96 (0·64–1·44)
Yes	149/1009 (15%)	189/975 (19%)	0·73 (0·58–0·93)
Subtotal (I^2=23·0%, p=0·25)			0·79 (0·64–0·97)
Respiratory distress‡			
No	169/2273 (7%)	213/2285 (9%)	0·78 (0·63–0·97)
Yes	61/439(14%)	84/428 (20%)	0·61 (0·42–0·89)
Subtotal (I^2=19·9%, p=0·26)			0·74 (0·61–0·89)
Hyperparasitaemia (>10%)			
No	140/1766 (8%)	167/1779 (9%)	0·84 (0·66–1·06)
Yes	56/584 (10%)	77/573 (13%)	0·67 (0·47–0·97)
Subtotal (I^2=0·0%, p=0·32)			0·78 (0·64–0·96)

0·4 0·5 0·75 1 1·25
Favours artesunate Favours quinine

Figure 3: Treatment effect in protocol-specified subgroups
The forest plot shows odds ratios and 95% CIs. The size of the squares is proportional to the size, and therefore weight, of the subgroup. The diamonds show the combined differences. The efficacy of antimalarial pretreatment was classified before study unblinding (webappendix p 12). Hyperparasitaemia means greater than 10% of red cells parasitised. OR=odds ratio. GCS=Glasgow coma scale. BCS=Blantyre coma scale. BE=base excess. *Site mortality classified as low if the site mortality rate was lower than the overall study mortality rate, and high if the site mortality rate was higher than the overall study mortality rate. †Classified according to centre policy (ten sites); classified according to individual data (one site). ‡Decompensated or compensated shock. I^2 denotes the percentage of total variation across resulting from heterogeneity rather than chance, with the p value of significance.

www.thelancet.com Vol 376 November 13, 2010

Artesunato vs chinino nel trattamento della malaria grave nei bambini in Africa. Lo studio AQUAMAT

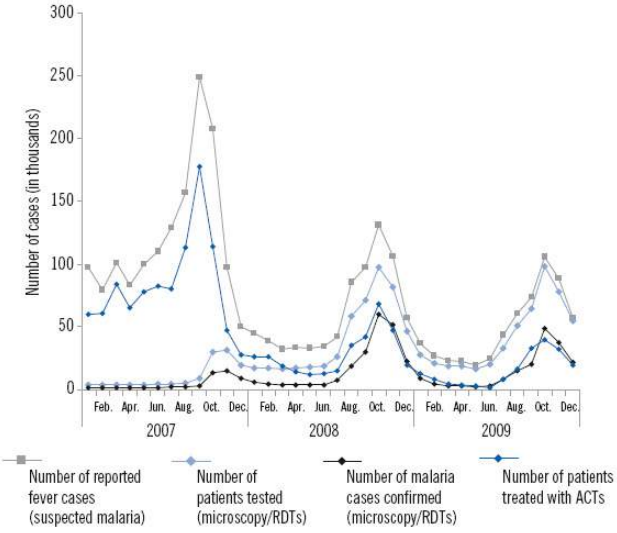


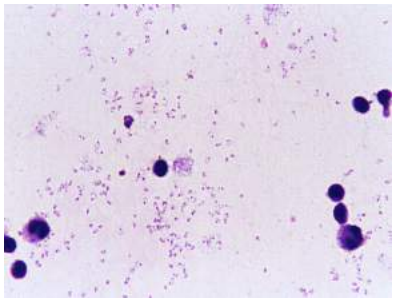
Figure Box 5.1 Trends in suspected, tested, confirmed and treated cases, Senegal 2007–2009

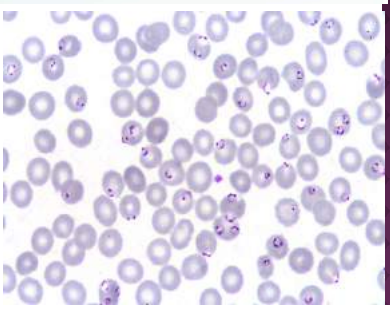
World Malaria Report, 2010

Guidelines for the treatment of malaria, 2° edition

MALARIA DIAGNOSIS

- Prompt parasitological confirmation by microscopy or alternatively by RDTs is recommended in all patients suspected of malaria before treatment is started.
- Treatment solely on the basis of clinical suspicion should only be considered when a parasitological diagnosis is not accessible.





WHO, 2010

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Guidelines for the treatment of malaria, 2° edition

TREATMENT OF UNCOMPLICATED *P. FALCIPARUM* MALARIA

- Artemisinin-based combination therapies (ACTs) are the recommended treatments for uncomplicated *P. falciparum* malaria.
- The following ACTs are recommended:
  - artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, and artesunate plus sulfadoxine-pyrimethamine.
- The choice of ACT in a country or region will be based on the level of resistance of the partner medicine in the combination.
- Artemisinin and its derivatives should not be used as monotherapy.
- Second-line antimalarial treatment:
  - alternative ACT known to be effective in the region;
  - artesunate plus tetracycline or doxycycline or clindamycin; any of these combinations to be given for 7 days;
  - quinine plus tetracycline or doxycycline or clindamycin; any of these combinations should be given for 7 days.

WHO, 2010

Guidelines for the treatment of malaria, 2° edition
(new recommandations)

TREATMENT OF UNCOMPLICATED *P. FALCIPARUM* MALARIA

- Artemisinin-based combination therapies should be used in preference to sulfadoxine-pyrimethamine (SP) plus amodiaquine (AQ) for the treatment of uncomplicated *P. falciparum* malaria.
  Strong recommendation, moderate quality evidence.
- ACTs should include at least 3 days of treatment with an artemisinin derivative.
  Strong recommendation, high quality evidence.
- Dihydroartemisinin plus piperaquine (DHA+PPQ) is an option for the first-line treatment of uncomplicated *P. falciparum* malaria worldwide.
  Strong recommendation, high quality evidence.
- Addition of a single dose primaquine (0.75 mg/kg) to ACT treatment for uncomplicated falciparum malaria as an antigametocyte medicine, particularly as a component of pre-elimination or an elimination programme.

WHO, 2010

Guidelines for the treatment of malaria, 2° edition

TREATMENT OF UNCOMPLICATED *P. FALCIPARUM* MALARIA IN SPECIAL RISK GROUPS

- Pregnancy

  First trimester:
  - quinine plus clindamycin to be given for 7 days (artesunate plus clindamycin for 7 days is indicated if this treatment fails);
  - an ACT is indicated only if this is the only treatment immediately available, or if treatment with 7-day quinine plus clindamycin fails or uncertainty of compliance with a 7-day treatment.

  Second and third trimesters:
  - ACTs known to be effective in the country/region or artesunate plus clindamycin to be given for 7 days, or quinine plus clindamycin to be given for 7 days.
- Lactating women:
  - lactating women should receive standard antimalarial treatment (including ACTs) except for dapsone, primaquine and tetracyclines.
- Infants and young children:
  - ACTs for first-line treatment in infants and young children with attention to accurate dosing and ensuring the administered dose is retained.
- Travellers returning to non-endemic countries:
  - atovaquone-proguanil;
  - artemether-lumefantrine;
  - quinine plus doxycycline or clindamycin.

WHO, 2010

Guidelines for the treatment of malaria, 2° edition
(new recommandations)

TREATMENT OF SEVERE *P. FALCIPARUM* MALARIA

- Intravenous (IV) artesunate should be used in preference to quinine for the treatment of severe *P. falciparum* malaria in adults.

  Strong recommendation, high quality evidence.

WHO, 2010

Guidelines for the treatment of malaria, 2° edition

TREATMENT OF UNCOMPLICATED *P. VIVAX* MALARIA

- Chloroquine combined with primaquine is the treatment of choice for chloroquine-sensitive infections.
- In mild-to-moderate G6PD deficiency, primaquine 0.75 mg base/kg body weight given once a week for 8 weeks. In severe G6PD deficiency, primaquine is contraindicated and should not be used.
- Where ACT (exception AS+SP) has been adopted as the first-line treatment for *P. falciparum* malaria, it may also be used for *P. vivax* malaria in combination with primaquine for radical cure. Artesunate plus sulfadoxine-pyrimethamine is not effective against *P. vivax* in many places.

(new recommandations)

TREATMENT OF UNCOMPLICATED *P. VIVAX* MALARIA

- In areas with chloroquine resistant *P. vivax*, artemisinin-based combination therapies (particularly those whose partner medicines have long half-lives) are recommended for the treatment of *P. vivax* malaria.

  Weak recommendation, moderate quality evidence.

- At least a 14-day course of primaquine is required for the radical treatment of *P. vivax*.

  Strong recommendation, very low quality evidence.

WHO, 2010

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

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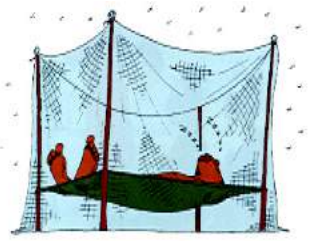
Abstract. Severe imported malaria is an important problem in European countries, where approximately 8,000 cases of *Plasmodium falciparum* malaria are reported each year. Although the World Health Organization recommends intravenous artesunate (IVA) as the treatment of choice for severe malaria in areas 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.

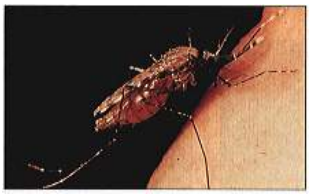
I. Note di storia
II. Epidemiologia
III. Roll Back Malaria
IV. Le linee-guida OMS
V. Surprise! Matteelli!

Protection from mosquito bites

Beneficial:
- ☒ Insecticide treated nets

Likely to be beneficial:
- ☒ Air conditioning and electric fans
- ☒ Insecticide treated clothing
- ☒ Smoke
- ☒ Protective clothing
- ☒ Topical insect repellent





Unknown effectiveness:
- ☒ Aerosol insecticides
- ☒ Insect buzzers and electrocuters

Croft, *BMJ* 2000; 321:154-60

Controversies and Misconceptions in Malaria Chemoprophylaxis for Travelers

Lin H. Chen, MD
Mary E. Wilson, MD
Patricia Schlagenhauf, PhD

CONTROVERSIES IN MALARIA

Context Controversies in malaria prevention arise from the absence of data, conflicting data between different studies, conflicting recommendations, deviation of local practice from scientific data, and varying risk thresholds. Misconceptions about the seriousness of malaria, the tolerability of chemoprophylaxis drugs, and the efficacy and safety of repellents contribute to the controversies.

Chen L. et al., JAMA, 2007; 2251-62

Variability in malaria prophylaxis prescribing across Europe: a Delphi method analysis.

Guido Calleri, Ron H Behrens, Zeno Bisoffi, Anders Bjorkman, Francesco Castelli, Joaquim Gascon, Federico Gobbi, Martin P Grobusch, Tomas Jelinek, Matthias L Schmid, Mauro Niero, Pietro Caramello, for TropNetEurop.

Calleri G. et al Journal of Travel Medicine, 2008; 15: 294-301

	Malaria risk	Type of prevention
Type I	Very limited risk of malaria transmission	Mosquito bite prevention only
Type II	Risk of *P. vivax* malaria only; or fully chloroquine-sensitive *P. falciparum*	Mosquito bite prevention plus chloroquine chemoprophylaxis
Type III[a]	Risk of *P. vivax* and *P. falciparum* malaria transmission, combined with emerging chloroquine resistance	Mosquito bite prevention plus chloroquine+proguanil chemoprophylaxis
Type IV	(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[b]	Mosquito bite prevention plus atovaquone–proguanil, doxycycline or mefloquine chemoprophylaxis (select according to reported resistance pattern)

[a] The areas where Type III prevention is still an option are limited to Nepal, Sri Lanka and Tajikistan, and parts of Colombia and India. If necessary, Type IV prevention can be used instead.

[b] Alternatively, when travelling to rural areas with multidrug-resistant malaria and only a very low risk of *P. falciparum* infection, mosquito bite prevention can be combined with stand-by emergency treatment (SBET).

ITH, 2010, WHO