Malaria: Treatment and Prevention: 2009

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Tropical Disease unit
Toronto General Hospital
University of Toronto

What I am going to talk about

- Malaria management approach
- Malaria management issues
- Malaria prevention

Management of Malaria

1. Is it malaria?
2. If malaria, what is the species?
3. If *P.f.*, what is the parasitemia?
4. Is the patient able to tolerate oral medication?

Management of Malaria (Cont'd)

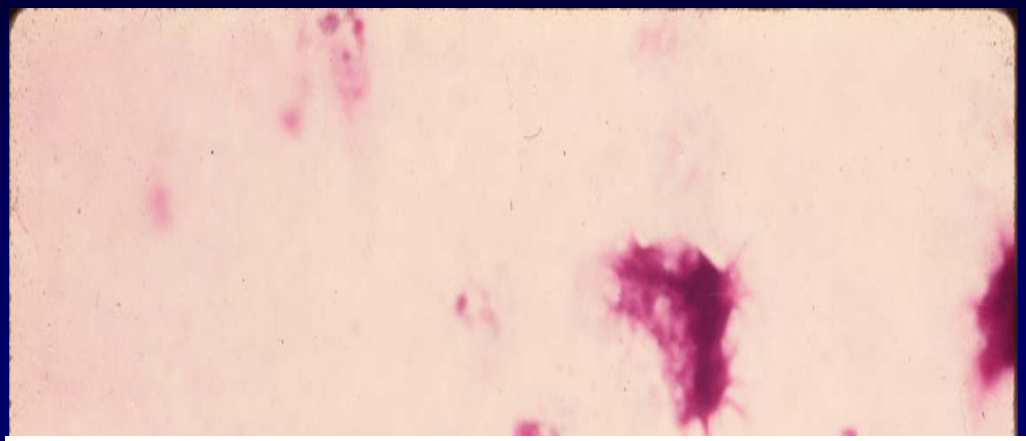
5. Is the patient from a drug resistant area?:

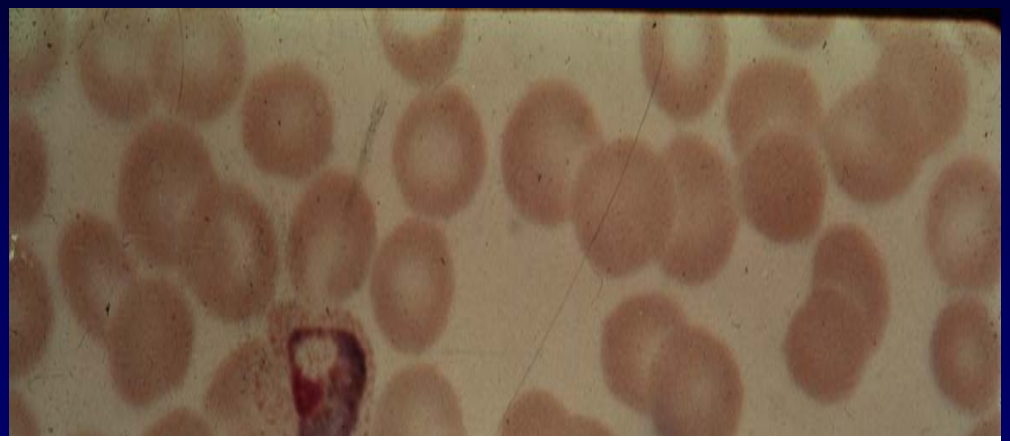
   CRPF, MRPF, CRPV, PRPV

6. Is there evidence for severe malaria?

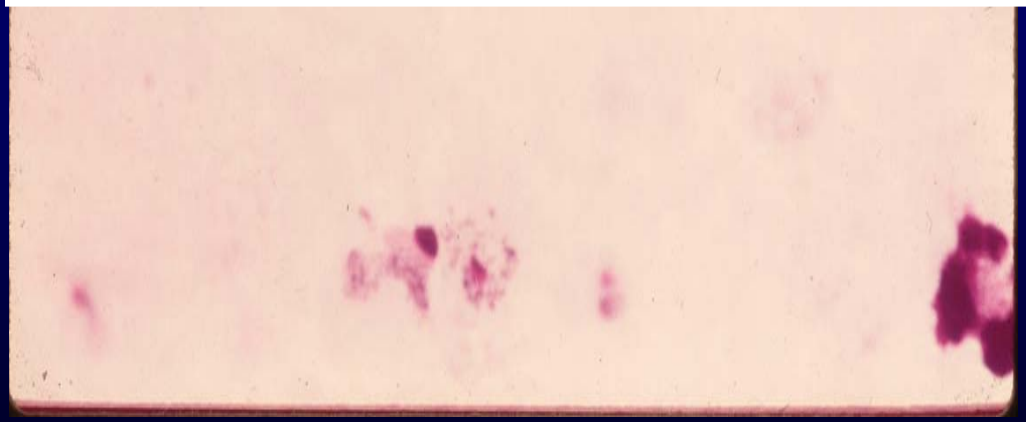
Thick film

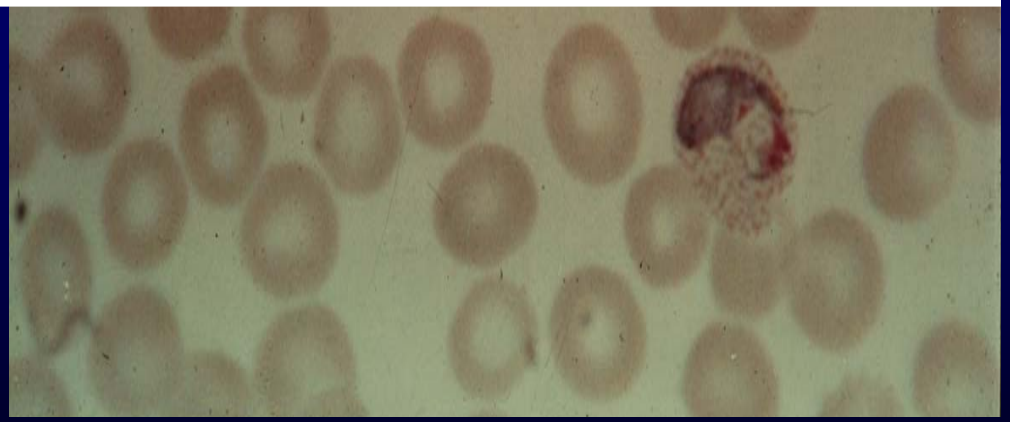
Thin film





If the first film is negative repeat it x 2 q12-24 hrs.





diagnosis

speciation

Binax ICT NOW Test *

Kain ,Am J Trop Med 60;2003:589-92

Parasitemia /µl	*P. falciparum* % Sensitivity	*P. vivax* %Sensitivity
1-100	75	50.0
101-1000	96.3	55.0
1001-10,000	97.2	94.1
> 10,000	97.1	100

* Specificity 99%

1%= 50,000/ µl

Plasmodium knowlesi: The Fifth Human Malaria Parasite

Clinical Infectious Diseases 2008; 46:172–3

N. J. White

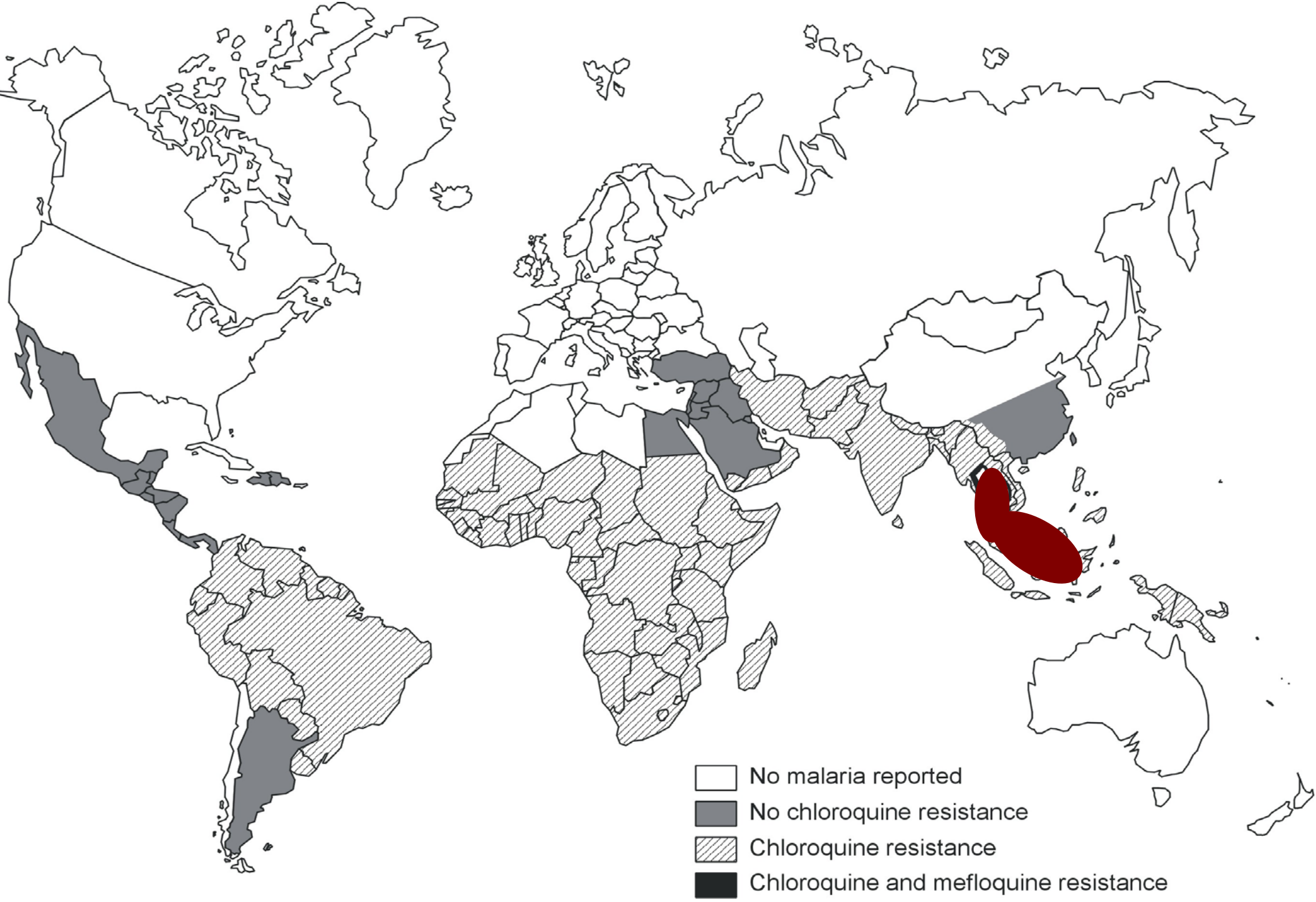
Department of Tropical Medicine, Mahidol University, Bangkok, Thailand; and Centre for Clinical Vaccinology and Tropical Medicine, Churchill Hospital, Oxford, United Kingdom

(See the article by Cox-Singh et al. on pages 165–71)

In 1932, when Knowles and Das Gupta [1] succeeded in transmitting to humans the monkey malaria they had discovered, it appeared that a new agent for malaria therapy had been discovered. Since the Nobel Prize–winning research of Julius Wagner-Jauregg, malaria therapy had become widely used for the treatment of general paralysis of the insane (neurosyphilis), one of the main reasons for admission to psychiatric institutions. But it soon became apparent that this infection simian malaria organism to humans (*Plasmodium cynomolgi*), and in 1967, Chin et al. [3] showed that *P. knowlesi* could also be transmitted from monkeys to humans. The mosquitoes used were *Anopheles balabacencis* (part of the *Anopheles leucosphyrus* group, which has undergone extensive taxonomic revision in recent years). This is an important vector of human malaria in forested areas of Southeast Asia, where the natural hosts of *P. knowlesi*—the long-tailed and pig-tailed ma-

fatal cases. There are several important practical lessons from this experience. Humans can and do acquire some monkey malarias if they share the same habitat (the reverse is also true). Molecular techniques are very useful in identifying the infection, in describing the epidemiology, and in characterizing mixed infections, which are otherwise underreported. This discovery resulted from good clinical and laboratory investigation, combined with an efficient malaria-control program. Presumably,

Macaque monkey


No malaria reported
No chloroquine resistance
Chloroquine resistance
Chloroquine and mefloquine resistance

Plasmodium knowlesi Malaria in Humans Is Widely Distributed and Potentially Life Threatening

CID 2008 46:65

Janet Cox-Singh,[1] Timothy M. E. Davis,[4] Kim-Sung Lee,[1] Sunita S. G. Shamsul,[1] Asmad Matusop,[2] Shanmuga Ratnam,[3] Hasan A. Rahman,[5] David J. Conway,[6] and Balbir Singh[1]

[1]Malaria Research Centre, Faculty of Medicine and Health Sciences, University Malaysia Sarawak, and [2]Sarawak Health Department, Kuching, and [3]Disease Control Unit, Sabah Health Department, Kota Kinabalu, Malaysian Borneo; [4]School of Medicine and Pharmacology, Fremantle Hospital, University of Western Australia, Fremantle; [5]Pahang State Health Department, Kuantan, Malaysia; and [6]London School of Hygiene

P.Knowlesi looks benign and like *P.malariae*, but kills like *P.falciparum*

(during 2003–2005), and 4 districts in Pahang, Peninsular Malaysia (during 2004–2005); and (3) 4 patients whose suspected cause of death was *P. knowlesi* malaria. For the 4 latter cases, available clinical and laboratory data were reviewed.

Results. *P. knowlesi* DNA was detected in 266 (27.7%) of 960 of the samples from Sarawak hospitals, 41 (83.7%) of 49 from Sabah, and all 5 from Pahang. Only *P. knowlesi* DNA was detected in archival blood films from the 4 patients who died. All were hyperparasitemic and developed marked hepatorenal dysfunction.

Conclusions. Human infection with *P. knowlesi*, commonly misidentified as the more benign *P. malariae*, are

Management of Malaria

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2. If malaria, what is the species?
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4. Is the patient able to tolerate oral medication?

Parasitemia (percent)

≥ 1%	usually *P.falciparum*
≥ 5%	time to get nervous
≥ 10%	time to change your underwear

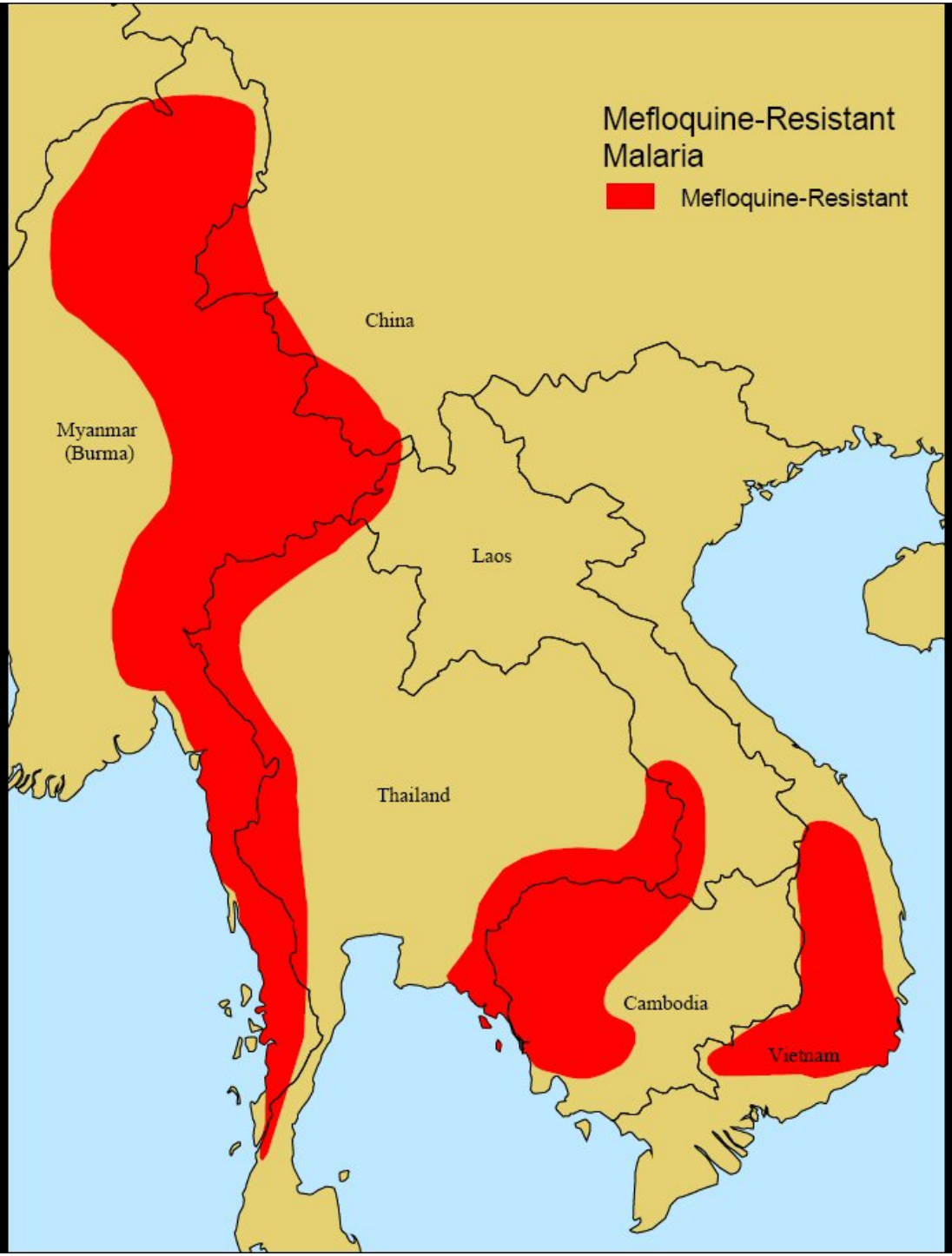
Management of Malaria (Cont'd)

5. Is the patient from a drug resistant area?:

   CRPF, MRPF, CRPV, PRPV

6. Is there evidence for severe malaria?

No malaria reported
No chloroquine resistance
Chloroquine resistance
Chloroquine and mefloquine resistance


Mefloquine-Resistant Malaria
Mefloquine-Resistant
China
Myanmar (Burma)
Laos
Thailand
Cambodia
Vietnam

CDC 2007

Management of Malaria (Cont'd)

5. Is the patient from a drug resistant area?:

   CRPF, MRPF, CRPV, PRPV

6. Is there evidence for severe malaria?

WHO Criteria for Severe Malaria

- >5% Parasitemia
- Altered consciousness
- Oliguria
- Jaundice
- Severe anemia
- Hypoglycemia
- Organ failure
- Seizures
- Renal failure,
- Metabolic acidosis
- ARDS
- Circulatory collapse or shock,
- Hemoglobinuria,
- Bleeding .

Five more malaria management issues

1. admit or not to admit?
2. treat or not to treat on spec?
3. oral vs. parenteral Rx?
4. which drug of choice?
5. which ancillary measures?

Interval between arrival and symptom onset USA 2003 N=1268 MMWR 2005;54:25-39

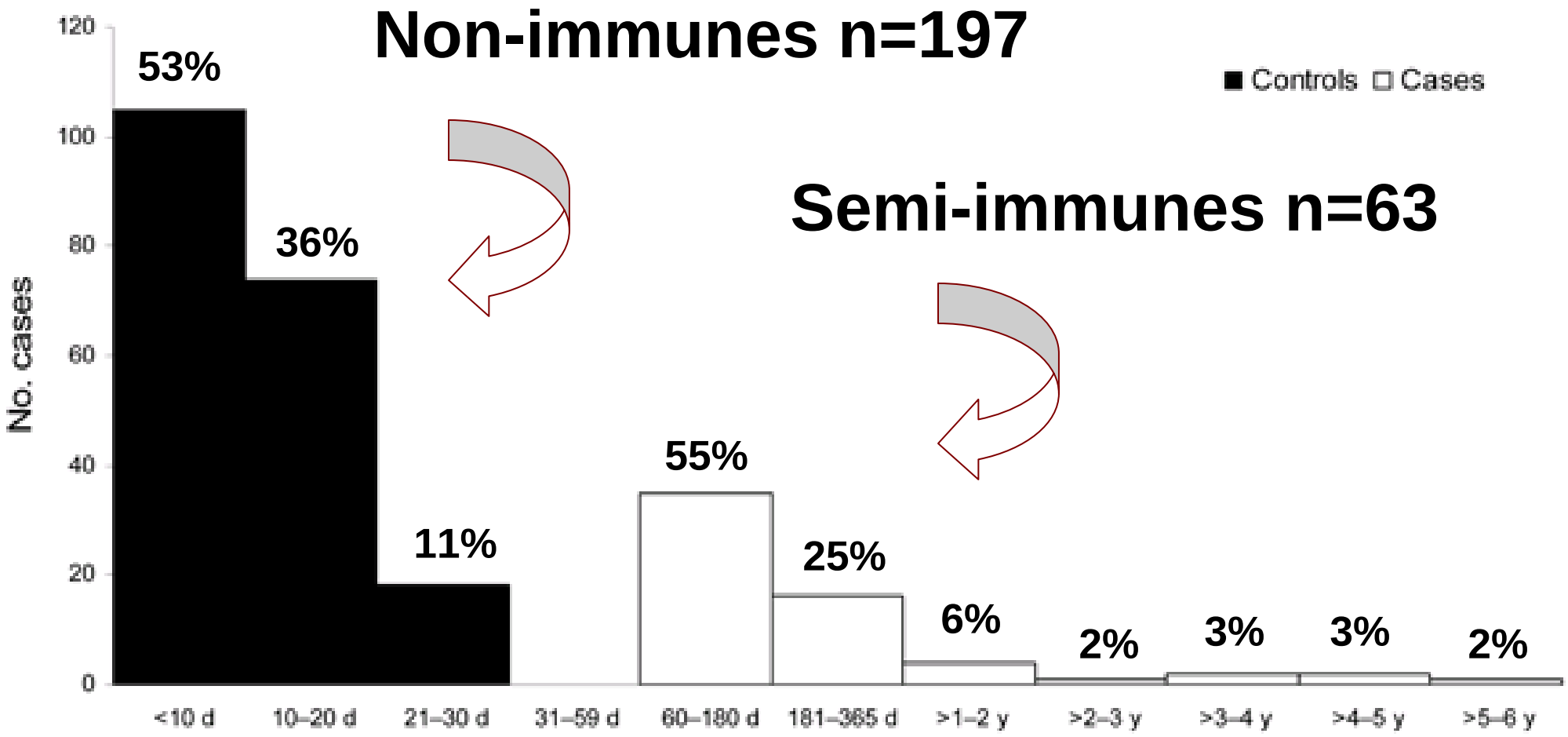
Interval mo.	% *P.falciparum* N=457	%*P.vivax* N=135
< 0	13	11
0-1	80	42
1-2	6	20
3-6	0.4	14
6-12	0.4	12
> 12	0.7	0.7

99 %

73 %

Pf Malaria onset according to pre-existing immunity

EID 2008 14 (2)–February



Source of Imported Malaria USA 2003 MMWR 2005;54:25-39 n=1268

Source	%*P.falciparum* *N=680*	% *P.vivax* *N=286*
Africa	86	17
Asia	2.7	44
C.America	4.1	16
Mexico	< 1	5
S Asia	< 1	6
Oceania	< 1	8

Kain's Rules…there are only 3, count 'em, things to remember:

1. If you have an ill patient, suspect malaria and no access to reliable dx → Rx for CRPF!!!
2. If it's *P. falciparum* → admit
3. If parasitemia ≥ 5% → give parenteral therapy and watch for complications

Why admit with low Pf parasitemia?

- ***Once upon a time (2008)*** **there was 35 year old woman who returned from West Africa with 3 day history of fever.**

  -looks unwell

  -thrombocytopenia & mild anemia

  -*P.faciparum* parasitemia 1.1%

- **9 hours later : parasitemia 30%**

Treatment of uncomplicated falciparum malaria

Drug	Advantage	Disadvantage
Chloroquine	Short course,	Limited efficacy
Atovaquone/prog.	Short course	Vomiting
Mefloquine	Short course	Neuropsych.
Quinine+doxy.	Long course	Cinchonism
Quinine +clinda.	Long course	Cinch. C.difficile
Artemisinin	Short course	Availability

www.medicalletter.org

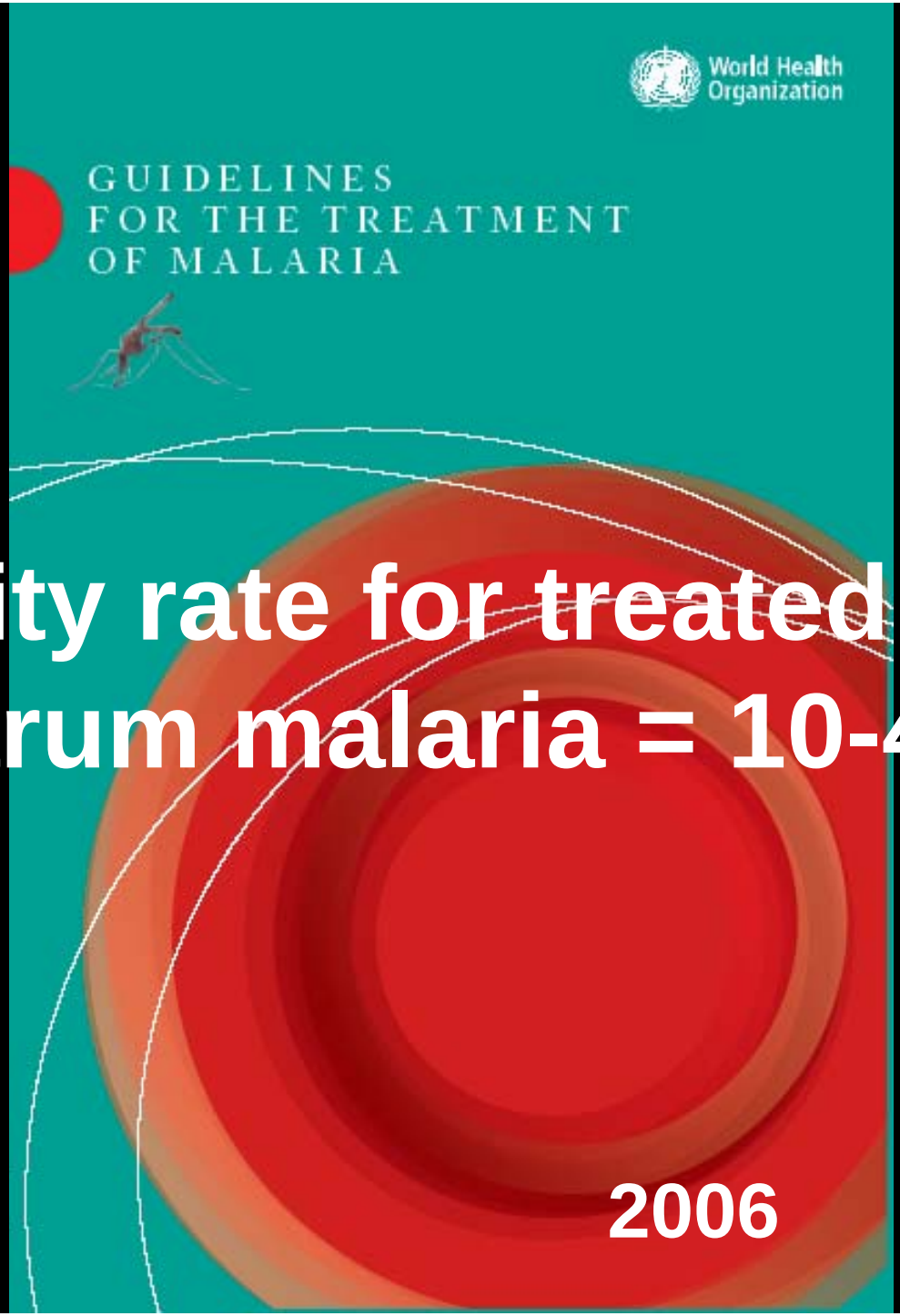
Drugs for Parasitic Infections 2007

With increasing travel, immigration, use of immunosuppressive drugs and the spread of AIDS, physicians anywhere may see infections caused by parasites. The table below lists first-choice and alternative drugs for most parasitic infections. The table on page 12 summarizes the known prenatal risks of antiparasitic drugs. The brand names and manufacturers of the drugs are listed on page 14.

Chloroquine Resistant *P.falciparum:*

1. atovaquone/proguanil
2. quinine + doxycycline or clindamycin
3. mefloquine

OR	followed by lofoquindol[c]	650 mg PO bid x 20d	30-40 mg/kg/d (max. 2g) PO in 3 doses



Mortality rate for treated severe falciparum malaria = 10-40%

2006

Department of Health and Human Services
Centers for Disease Control and Prevention

Malaria **Artemesinin Combination Therapy (ACT)**

Malaria Home >

Artesunate now available to treat severe malaria in US

Artesunate is in the class of medications known as artemesinins, which are derivatives from the "quinghaosu" or sweet wormwood plant (*Artemisia annua*).

2.4 mg/kg IV stat, 12 hr , 24hr, then daily …then doxycycline or clindamycin x 7days or Malarone x 3days

Photographer: Emmet J. Judziewicz , University of Wisconsin–Stevens Point and Madison

CDC response time to artesunate request

Time from….	Mean
Artesunate request to shipment	2.7 hours
Artesunate arrival to treatment	2.9 hours
Artesunate request to treatment	7.2 hours

Tropical Medicine and International Health doi:10.1111/j.1365-3156.2006.01690.x

VOLUME 11 NO 9 PP 1360–1366 SEPTEMBER 2006

Surveillance of the efficacy of artesunate and mefloquine combination f malaria in Car

Mey Bouth Denis[1,2], Reil Incardona[3], Pharath Lim[3]

1 National Center for Parasit
2 World Health Organization
3 Institut Pasteur du Camboc
4 World Health Organization
5 World Health Organization

Summary Artesuna line drug safety, th combinat mefloqui total dos were enr

NEJM 2008 359;24:2619

Evidence of Artemisinin-Resistant Malaria Cambodia

TO THE EDITOR: Although artem tients) or quinine (30 mg per kilogram per day) tent and rapidly acting antimala widespread use for treating patie dium *falciparum* malaria raises t emerging drug resistance.[1,2] Art therapy should not be used in a laria is endemic; it requires an e istration period and may lead to tr most frequently because of prob pliance. Recent reports of high fa ciated with artemisinin-based co apy, as well as in vitro drug-sus suggest the possibility of clinical sistance along the Thai–Cambo We studied the potential emerge nin resistance using in vivo, in v and pharmacokinetic methods signed to address the question temisinin resistance.

We randomly assigned, in a adults from Battambang Province uncomplicated *P. falciparum* malari

SYNOPSIS

Declining Artesunate-Mefloquine Efficacy against Falciparum Malaria on the Cambodia–Thailand Border

Chansuda Wongsrichanalai* and Steven R. Meshnick†

EID 2008 14;5:716

Resistance to many antimalaria drugs developed on the Cambodia–Thailand border long before developing elsewhere. Because antimalaria resistance is now a global problem, artemisinin-based combination therapies (ACTs) are the first-line therapies in most malaria-endemic countries. However, recent clinical and molecular studies suggest the emergence of ACT-resistant *Plasmodium falciparum* infections in the Cambodia–Thailand border area, where standard ACT is artesunate and mefloquine. These ACT failures might be caused by high-level mefloquine re-

in Cambodia and the provinces of Trat and Chanthaburi in Thailand, has been an epicenter of drug-resistant malaria (*3*) (Figure). Resistance to chloroquine and sulfadoxine-pyrimethamine occurred there in the late 1950s and 1960s, respectively. Mefloquine was introduced there in 1983, first on the Thai side and in the form of mefloquine in combination with sulfadoxine-pyrimethamine. Mefloquine resistance led to replacement by artesunate-mefloquine in Thailand in 1995. In Chanthaburi and Trat Provinces, con-

OPEN ACCESS Freely available online

PLoS Medicine 2008 ;5 :e128

PLoS MEDICINE

Multidrug-Resistant *Plasmodium vivax*

N=12,171 admissions:
242 (2.0%) patients died:

2.2% with Pf,
1.6% with Pv,
2.3% with mixed infections

Career Development Award affiliated to the Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme (074637).

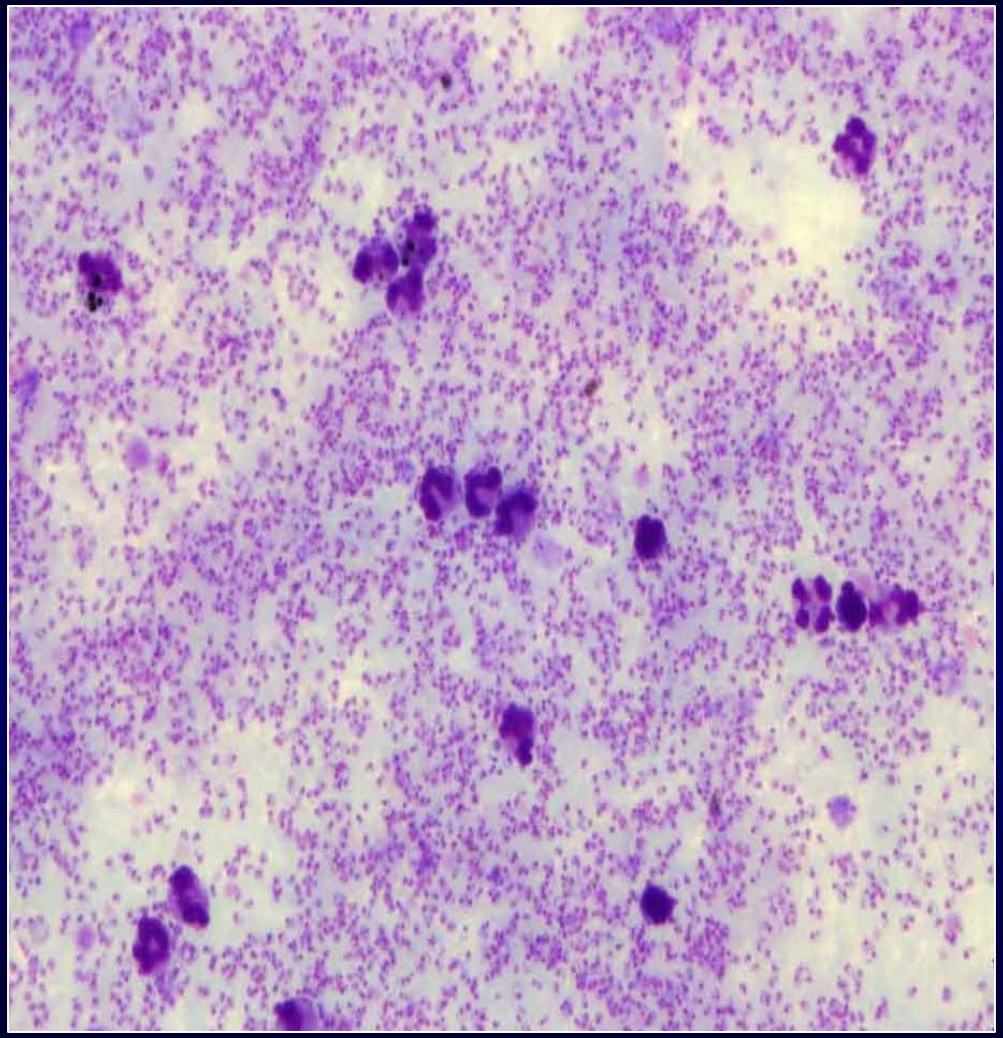
Competing Interests: The authors have declared that no competing interests exist.

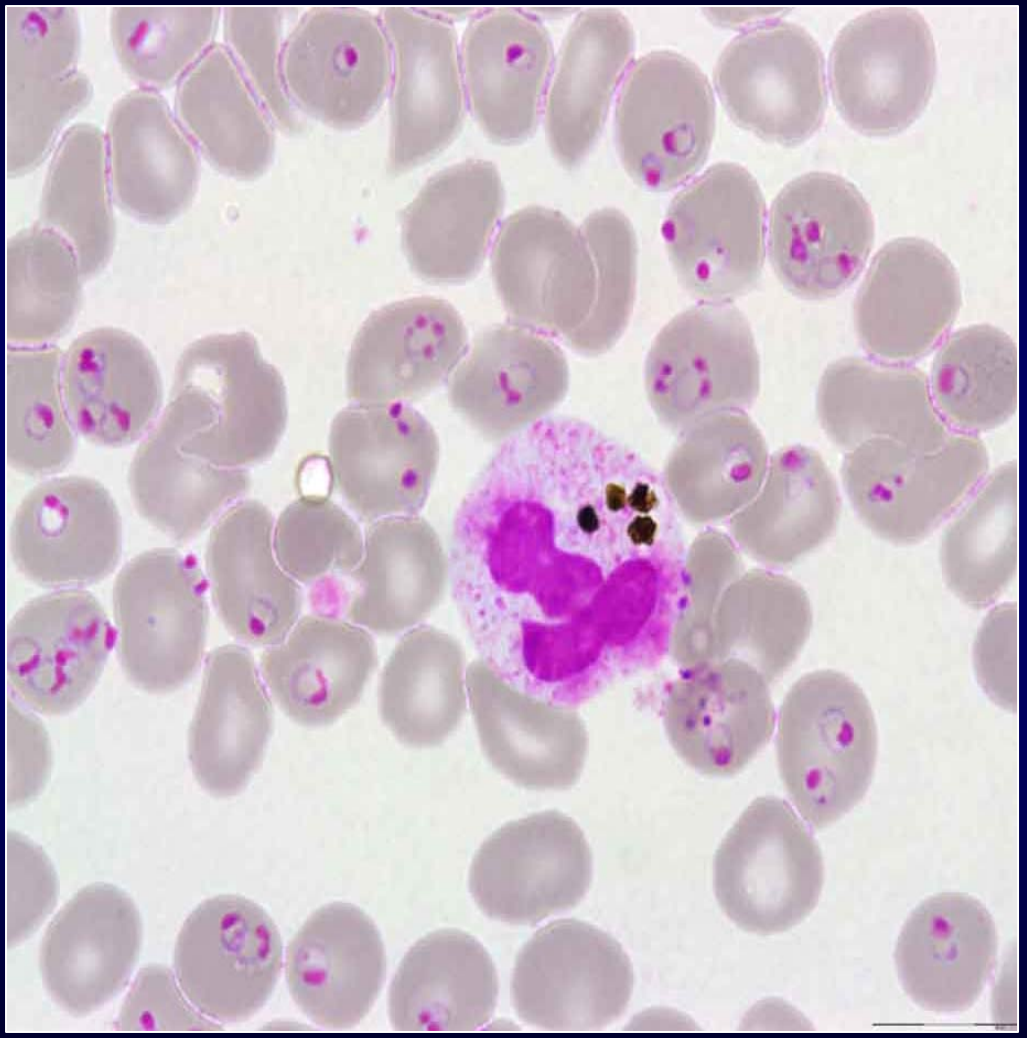
Academic Editor: Stephen Rogerson, Royal Melbourne Hospital

falciparum (*Pf*) in patients presenting to a hospital in Timika, southern Papua, Indonesia.

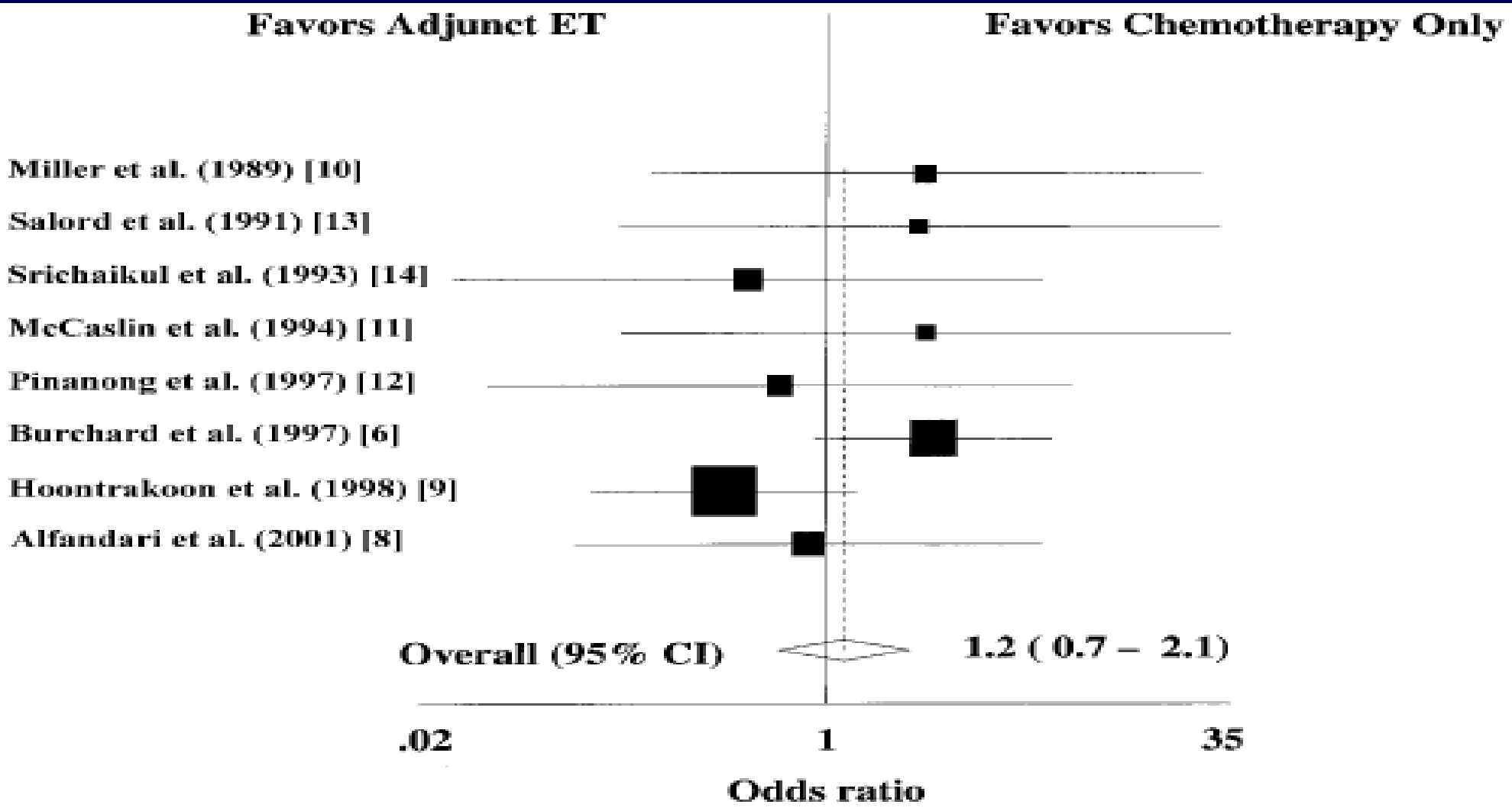
Methods and Findings

Data were prospectively collected from all patients attending the outpatient and inpatient departments of the only hospital in the region using systematic data forms and hospital computerised records. Between January 2004 and December 2007, clinical malaria was present in 16% (60,226/373,450) of hospital outpatients and 32% (12,171/37,800) of inpatients. Among



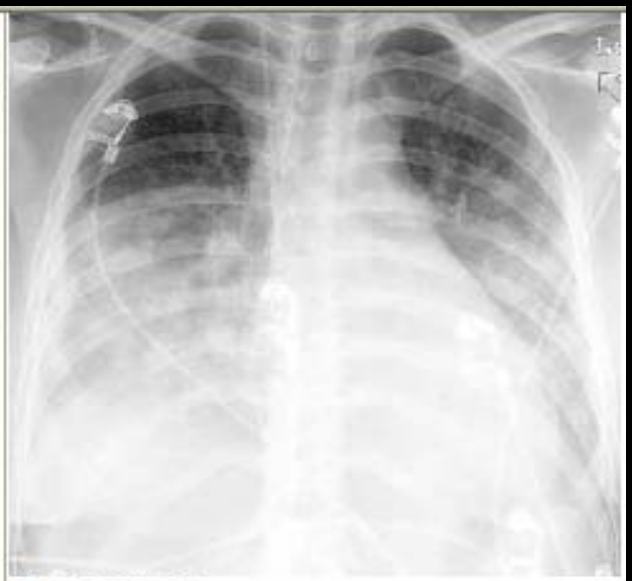


Exchange transfusion for severe *P.faciparum* malaria met-analysis CID 2002;34:1192-8

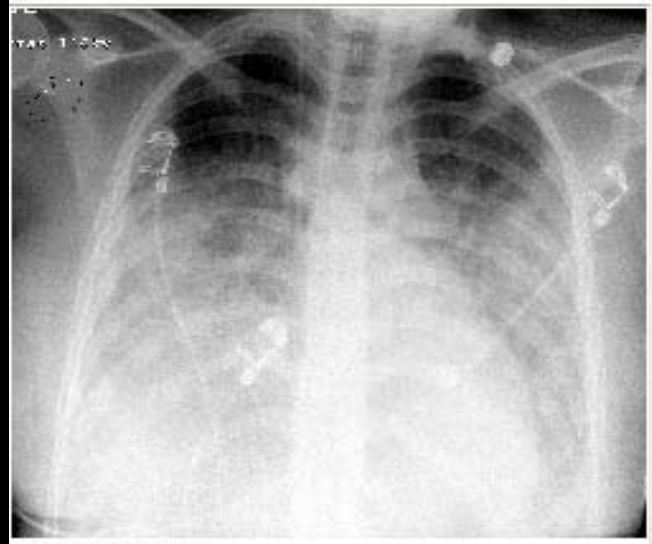


July 2

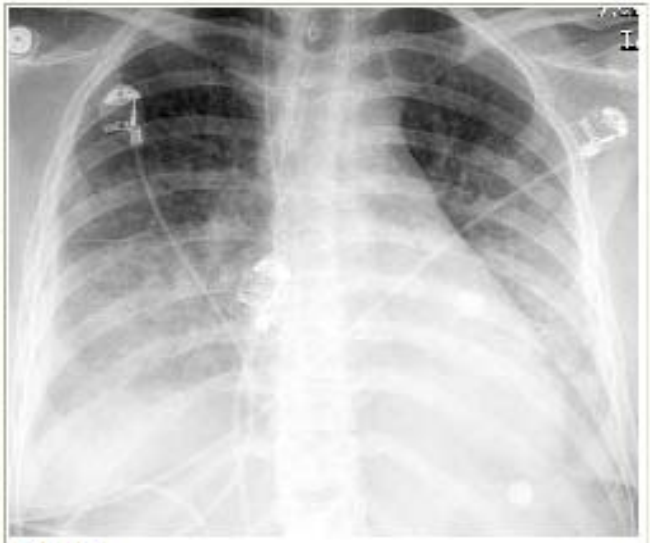
July 4 16:27



July 5 01:40



July 5 09:12



July 6

July 7

http://www.medicine.mcgill.ca/tropmed/

Treatment summary

- Fever from the tropics is malaria UPO *and* a medical emergency
- Admit *P.falciparum* to hospital
- Species and parasitemia are critical
- Rx uncomplicated unknown malaria as CRPF; Atov.Prog.= D.O.C.
- Think artesuante in severe infections

Malaria chemoprophylaxis considerations

1. Is the traveler going to a malarious area?
2. Will the traveler be *exposed* to malaria?
3. Is the area chloroquine or mefloquine resistant?
4. Are there any contraindications to antimalarial use (pregnancy, cost etc) ?
5. What is traveler's experience and preference ?

Malaria Chemoprophylaxis

Chloroquine Sensitive malaria: 😐

chloroquine

Chloroquine Resistant Malaria ☹

DOC
- mefloquine
- doxycycline
- atovaquone/proguanil

primaquine

Drugs for Chloroquine Resistant Malaria

Drug	Advantage	Disadvantage
Mefloquine *Lariam*	Weekly Moderate cost $$	Neuropsychiatric ADR 1-2 wks pre;4 wks post

Now hear this…..the M word!

If you prescribe mefloquine without discussing adverse events *and* alternative chemoprophylactic agents, you will likely meet ….

Mefloquine (Lariam®)

Because mefloquine is tolerated
the first time
does not mean that it will be tolerated again

Drugs for Chloroquine Resistant Malaria

Drug	Advantage	Disadvantage
Doxycycline	Lowest cost $	Daily; sun burn*; GI; vaginal yeast infection ☹ 1day pre,4 wks post (fluconazole) ☹

Sunburn: 5-15%

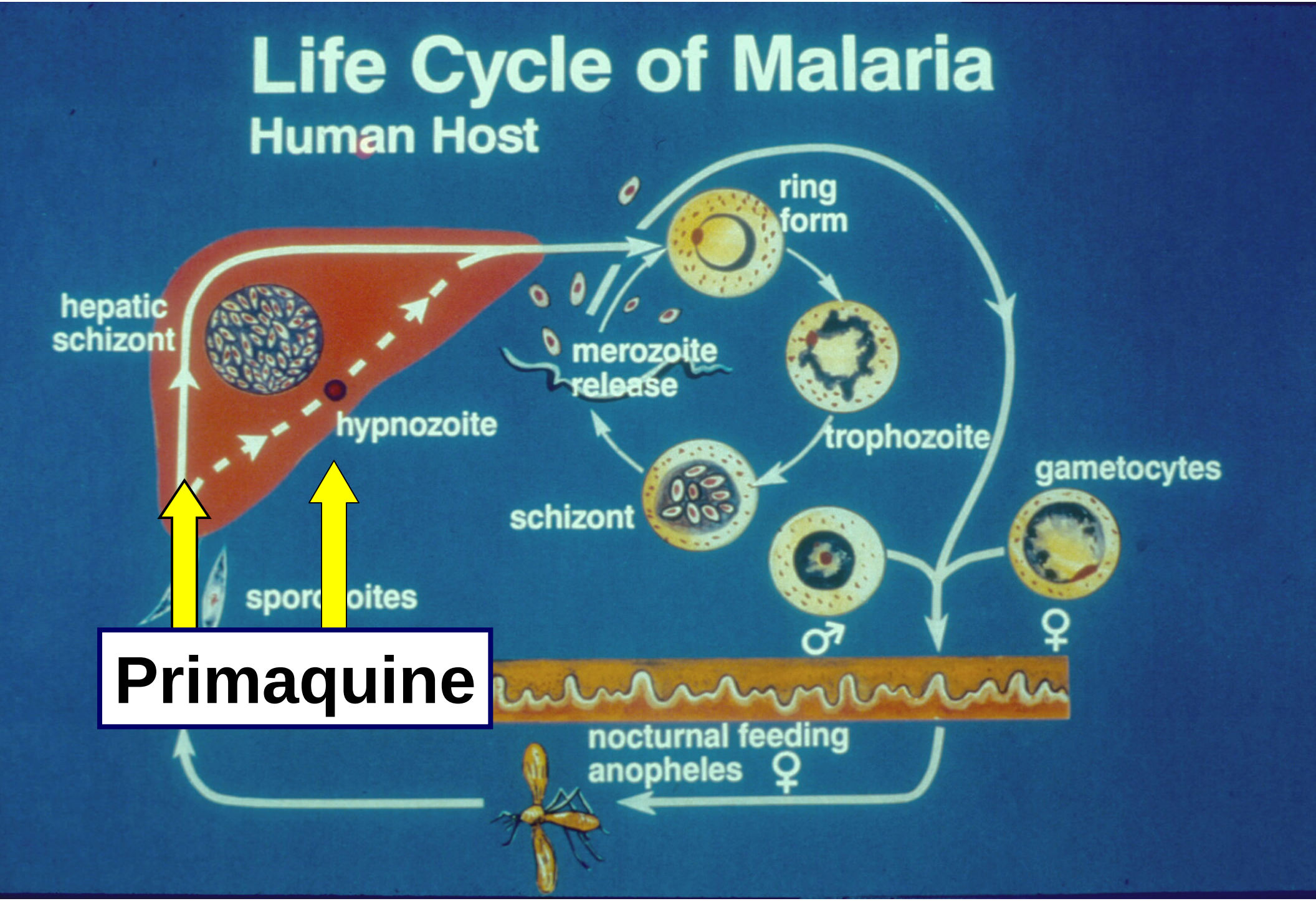
Drugs for Chloroquine Resistant Malaria

Drug	Advantage	Disadvantage
Malarone *Atovaquone /proguanil*	Safety Convenience 1 day pre;7 days post	Highest Cost $$$ headache, GI upset, insomnia; Daily?

Drugs for Chloroquine Resistant Malaria

Drug	Advantage	Disadvantage
Primaquine	Low cost $$ 1 day pre; 3 days post	*G6PD level required Daily; take with food

*Off label


Life Cycle of Malaria
Human Host
ring form
hepatic schizont
merozoite release
hypnozoite
trophozoite
gametocytes
schizont
sporozoites
♂
♀
Primaquine
nocturnal feeding anopheles ♀

Primaquine Prophylaxis

- 8-aminoquinolone
- tissue schizonticide → causal prophylaxis
- **Dose:** 30 mg (base) = 2 tabs/day, 1 day before and 3 days after exposure
- **Efficacy:** 85-95% (Pf + Pv) in 3 studies:

Irian Jaya, Kenya & Colombia

Baird K. Clinical Infectious Diseases 2003;37:1659–6

Primaquine Prophylaxis
Cont'd.

- **Adverse events:** GI upset, met Hb
- **C/I:** G6PD deficiency, pregnancy
- **Helpful hints:** take with food
  G6PD screen

Baird K. Clinical Infectious Diseases 2003; 37:1659–67

Am J Trop Med Hyg 2006:73:402

PRIMAQUINE: REPORT FROM CDC EXPERT MEETING ON MALARIA CHEMOPROPHYLAXIS I

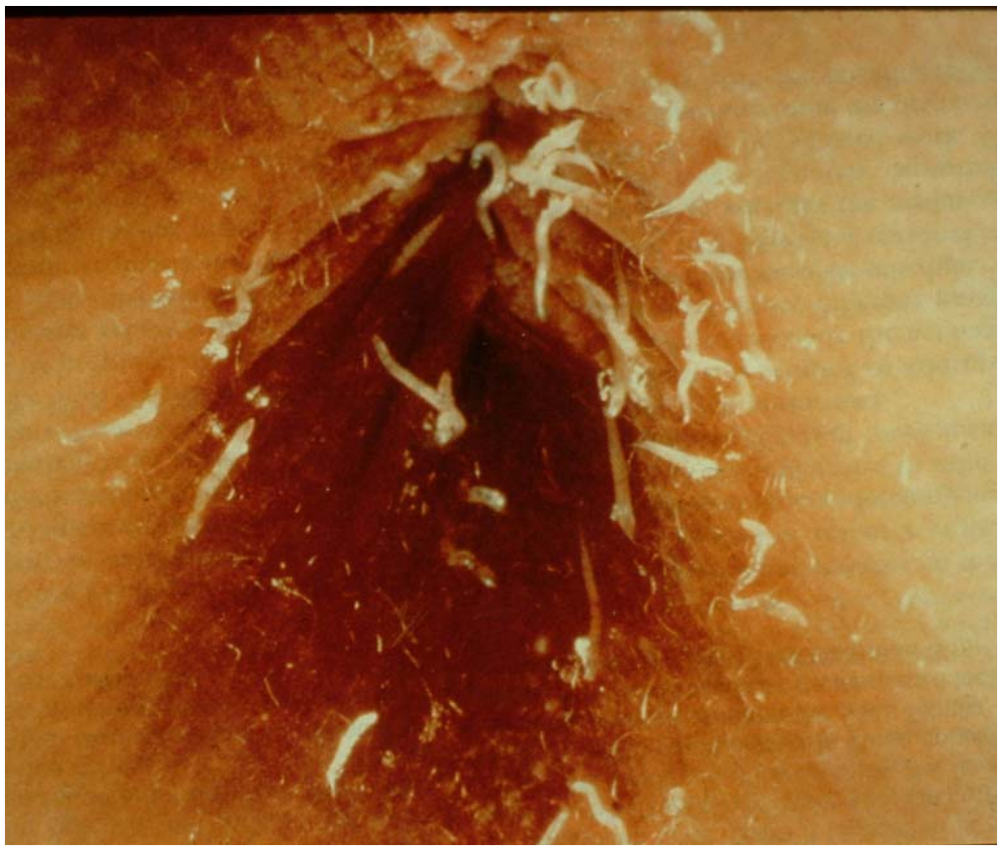
DAVID R. HILL,* J. KEVIN BAIRD, MONICA E. PARISE, LINDA S. LEWIS, EDWARD T. RYAN, AND ALAN J. MAGILL

National Travel Health Network and Centre, London, England; London School of Hygiene and Tropical Medicine, London, England; ALERTAsia Foundation, Jakarta, Indonesia; Division of Parasitic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; Butte County Department of Public Health, Oroville, CA; Division of Infectious Diseases, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; Walter Reed Army Institute of Research, Silver Springs, Maryland

Abstract. Primaquine phosphate has been used for preventing relapse of *Plasmodium vivax* and *P. ovale* malaria since the early 1950s, based on its ability to kill latent (hypnozoite) and developing liver stages of these parasites. There are three uses for primaquine in malaria: radical cure of established infection with *P. vivax* or *P. ovale* malaria; presumptive anti-relapse therapy (PART; terminal prophylaxis) in persons with extensive exposure to these parasites; and primary prophylaxis against all malaria species. All persons for whom primaquine is being considered must have a glucose-6-phosphate dehydrogenase (G6PD) enzyme level checked before use, and persons who have a deficiency of G6PD must not take primaquine for prophylaxis or PART. The recommended adult dose for PART based on clinical trials and expert opinion is 30 mg base daily for 14 days, started on return from a malarious region and overlapping with a blood schizonticide. The adult dose for primary prophylaxis is 30 mg daily begun 1 day before travel and continued for 7 days after return. This review will examine the evidence for these recommendations.

New country specific guidance table

Country	Areas with Malaria	Drug Resistance	Malaria Species	Recommended Chemoprophylaxis
Afghanistan	April-December in all areas at altitudes <2,000 m (<6,561 ft)	Chloroquine	*P. vivax* 80%-90% *P. falciparum* 10%-20%	Atovaquone/ proguanil, doxycycline, or mefloquine
Guatemala	Rural areas only at altitudes <1,500 m (<4,921ft). None in Guatemala City, Antigua or Lake Atitlán.	None	*P. vivax* 97% *P. falciparum* 3%	Atovaquone/ proguanil, chloroquine, doxycycline, mefloquine, or primaquine



Primary care

CDC

MEXICO
Corozal
Ambergris Caye
Tikal
San Ignacio
Belize City
Flores
BELIZE
Roatan Islands
GUATEMALA
Lake Izabal
San Pedro Sula
Chichicastenango
HONDURAS
Puerto Lempira
Copan
Lake Atitlan
Guatemala City
Antigua
Tegucigalpa
San Salvador
EL SALVADOR
Lake Managua
NICARAGUA
Managua
Granada
Omelepe Island
Lake Nicaragua
PACIFIC OCEAN
CARIBBEAN SEA
COSTA RICA
Arenal Volcano
Puerto Limon
San Jose
Quepos
PANAMA CANAL
Colon
San Blas Islands
Panama City
Boquete
El Valle
Balboa
David
PANAMA
Darien Gap

P.Vivax Post-exposure Anti-Relapse Therapy (PART)

Post-exposure primaquine prophylaxis:
> 3 months stay?
30 mg /day x 14 days

map
malaria atlas project

www.map.ox.ac.uk

3 drugs of choice for CRPF

Drug	Indication
Mefloquine ***Lariam***	**Previous drug use** **Long-stay traveler** **Pregnancy, infancy**
Doxycycline	**Impecunious traveler** **Thai borders +V/N**
Atovaquone/proguanil ***Malarone***	**Short-stay traveler** **Drug plan positive** **Thai borders + V/N**

Malaria and Pregnancy & Children

Pregnancy:

- CSPF: cloroquine
- CRPF: • mefloquine safe in 2nd trimester, probably 1st

Children:

- Prophylaxis down to age zero

Tropical Medicine and International Health

VOLUME 9 NO 12 PP 1241–1246 DECEMBER 2004

Fake antimalarials in Southeast Asia are a major impediment to malaria control: multinational cross-sectional survey on the prevalence of fake antimalarials

A. M. Dondorp[1,2], P. N. Newton[2,3], M. Mayxay[3], W. Van Damme[4], F. M. Smithuis[5], S. Yeung[1,2], A. Petit[5], A. J. Lynam[6], A. Johnson[7], T. T. Hien[8], R. McGready[1,9], J. J. Farrar[2,10], S. Looareesuwan[1], N. P. J. Day[1,2], M. D. Green[11] and N. J. White[1,2]

21-92% (53%)
in 5 countries of SE Asia

If you take a proven effective antimalarial for chemoprophylaxis

… It works!!

Overdiagnosis of malaria in patients with severe febrile illness in Tanzania: a prospective study

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BMJ 2004;329:1212

Abstract

Objective To study the diagnosis and outcomes in people admitted to hospital with a diagnosis of severe malaria in areas with differing intensities of malaria transmission

N=4,450 slides in 10 hospitals

40% false positive blood films

outcome. Altitudes of residence (a proxy for transmission intensity) measured with a global positioning system.

Results Blood film microscopy showed that 2062 (46.1%) of people treated for malaria had *Plasmodium falciparum* (slide positive). The proportion of slide positive cases fell with increasing age and increasing altitude of residence. Among 1086 patients aged ≥5 years who lived above 600 metres, only 338 (31.1%) were slide positive, while in children <5 years living in areas of intense transmission (<600 metres) most (958/1392, 68.8%) were slide positive. Among 2375 people who

of district hospitals in Africa identified several problems with the organisation and planning of care.[4 5]

Given the high proportion of admissions attributed to malaria, overdiagnosis of malaria and consequent neglect of

substantially increase the costs of change.

Accuracy of hospital diagnosis of malaria is likely to depend on the epidemiological probability of the disease (defined by intensity of malaria transmission and age of patients) and is important as most of the population of sub-Saharan Africa live in areas of low or moderate malaria transmission.[7] We prospectively examined the diagnosis and outcome in all patients admitted and treated for severe or potentially complicated malaria during one year in 10 hospitals serving people for areas with

Relative Duration of Action of Insect Repellents

Ingredient	mean	range
DEET 5%	1h	0.75 2h
DEET 23%	5h	3.5 – 6h
DEET 99%	10h	8 - 12h
Citronella 10%	14 min.	7 – 60m

*Except: ultrathon & Sawyer CR DEET: 20-30%= 10-12 hr

Fradin NEJM 2002:347:13-18

“Newish” insect repellents USA

- **Picaridin** (KBR 3023,: 2-(2-hydroxyethyl)-1-piperidinecarboxylic acid 1-methylpropyl ester)
- **Oil of Lemon Eucalyptus*** or PMD (: para-Menthane-3,8-diol)the synthesized version of oil of lemon eucalyptus
- **IR3535 :** 3-[N-Butyl-N-acetyl]-aminopropionic acid, ethyl ester)

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Unforeseen misuses of bed nets in fishing villages along Lake Victoria

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Efficacy of RTS,S/AS01E Vaccine against Malaria in Children 5 to 17 Months of Age

N= 400 /group: malaria vs. rabies vaccine 3 doses 1 month apart.

Pat
Neema Mturi, M.R.C.Paed., Chris J. Drakeley, Ph.D., Barbara Savarese, R.N., Tonya Villafana, Ph.D., W. Ripley Ballou, M.D.,
Joe Cohen, Ph.D., Eleanor M. Riley, Ph.D., Martha M. Lemnge, Ph.D., Kevin Marsh, F.R.C.P., and Lorenz von Seidlein, Ph.D.

Clinical efficacy per protocol: 56% (95% CI, 31 to 72; P<0.001).

BACKGROUND
Plasmodium fa
of the malaria vaccine RTS,S (which targets the circumsporozoite protein), given
with an adjuvant system (AS02A), showed a 30% rate of protection against clinical

raphic Medi-
a Medical Re-
search Institute, Kilifi, Kenya (P.B., A.O.,
T.L., P.N., K.O.A., N.M., K.M.); the Centre

Take home points

- Fever from the tropics is a medical emergency and malaria until proven otherwise.
- There are now 5 species of malaria; vivax kills
- Speciation and especially parasitemia are critical;> 1% usually falciparum
- Rapid diagnostics are good; multiple films necessary to r/o malaria
- DOC for Tx uncomplicated Pf is atov/proguanil; artesunate for severe falciparum malaria

Take home points con't

- DOC for malaria prevention atov/proguanil, mefloquine and doxyxycline. Primaquine for vivax areas
- 20% Picaridin as good as DEET
- Globally increasing counterfeit drugs and false positive diagnosis of malaria, especially in West Africa

Additional Readings

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More additional readings

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Prevention of malaria in long-term travelers.

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Countries where *P.vivax* is >90%

- Argentina
- Azerbaijan
- Belize
- Costa Rica
- El Salvador
- Georgia
- Guatemala
- Iraq
- Koreas
- Kyrgyzstan
- Mexico
- Nicaragua
- Panama
- Paraguay
- Tajikistan