Malaria Updates

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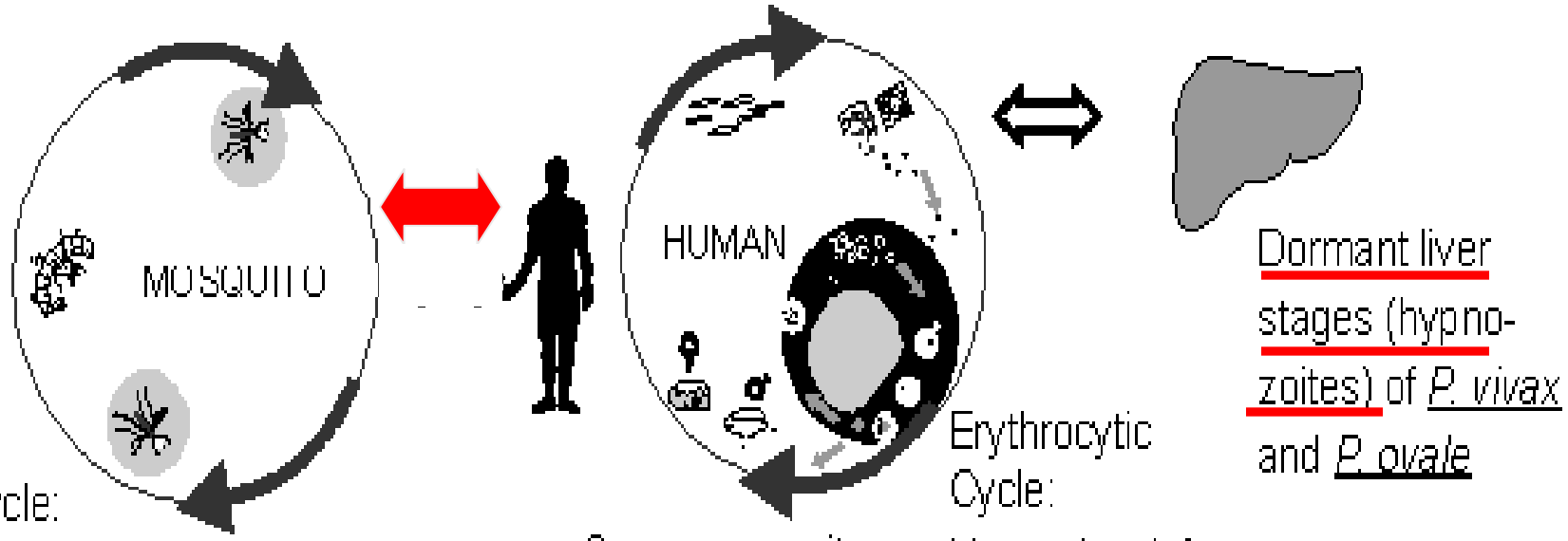
Outline

- General epidemiology of malaria in the Philippines
- *P falciparum*
  - Updates in treatment
  - Recognizing treatment failure
- *P vivax*
  - Treatment
  - Chloroquine treatment failure
  - Severe vivax malaria
- *P knowlesi*
  - Emergence
  - Diagnosis
  - Research

Sporozoites injected into bloodstream when female mosquito takes a blood meal

Exo-Erythrocytic (hepatic) Cycle: Sporozoites infect liver cells and develop into schizonts, which release merozoites into the blood



Dormant liver stages (hypnozoites) of *P. vivax* and *P. ovale*

Erythrocytic Cycle: Merozoites infect red blood cells to form schizonts

Some merozoites differentiate into male or female gametocytes

Gametocytes ingested by female *Anopheles* mosquito when taking a blood meal

Sporogonic Cycle: In the mosquito gut, gametocytes initate sexual reproduction of parasite

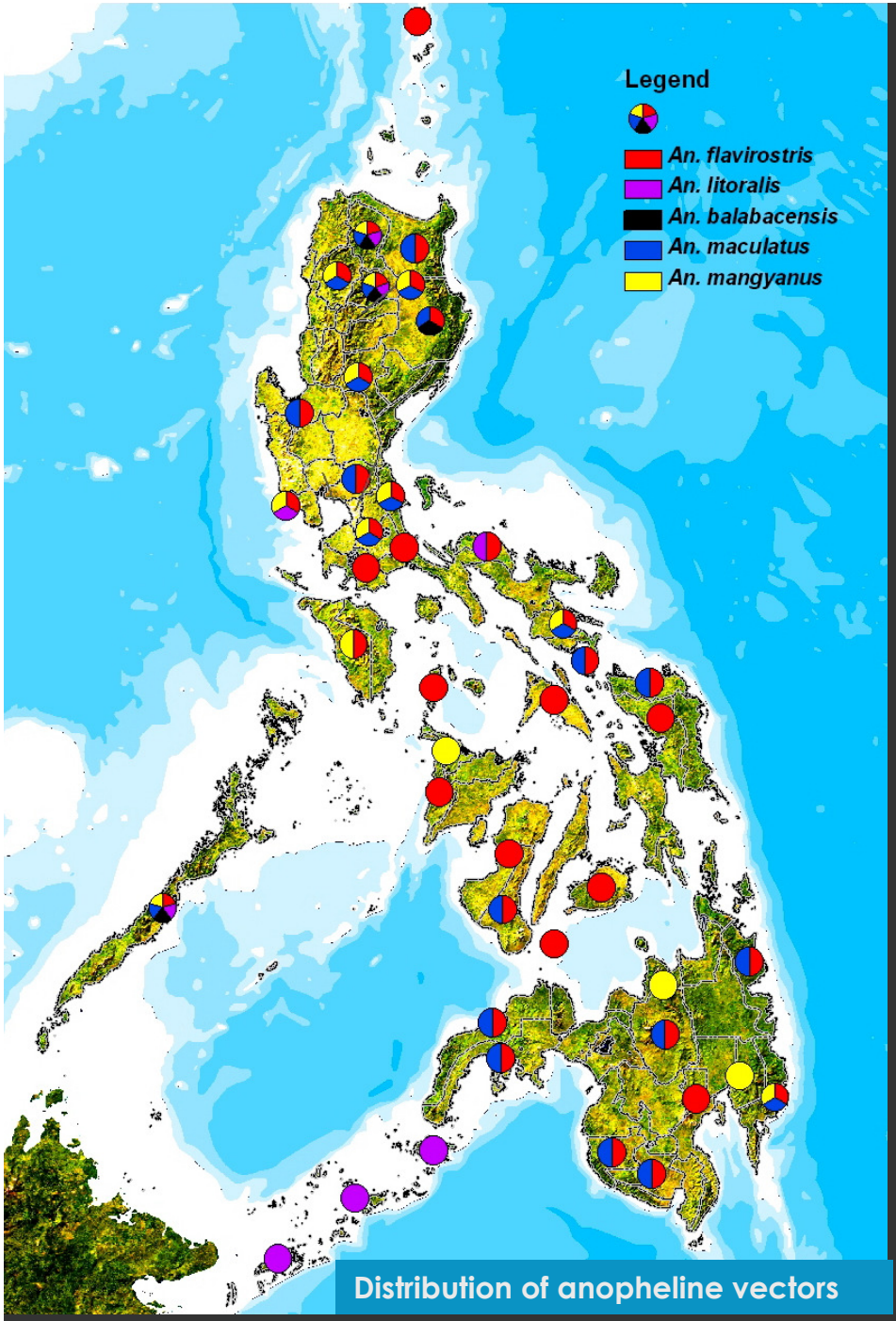
Malaria Life Cycle

Malaria Triad

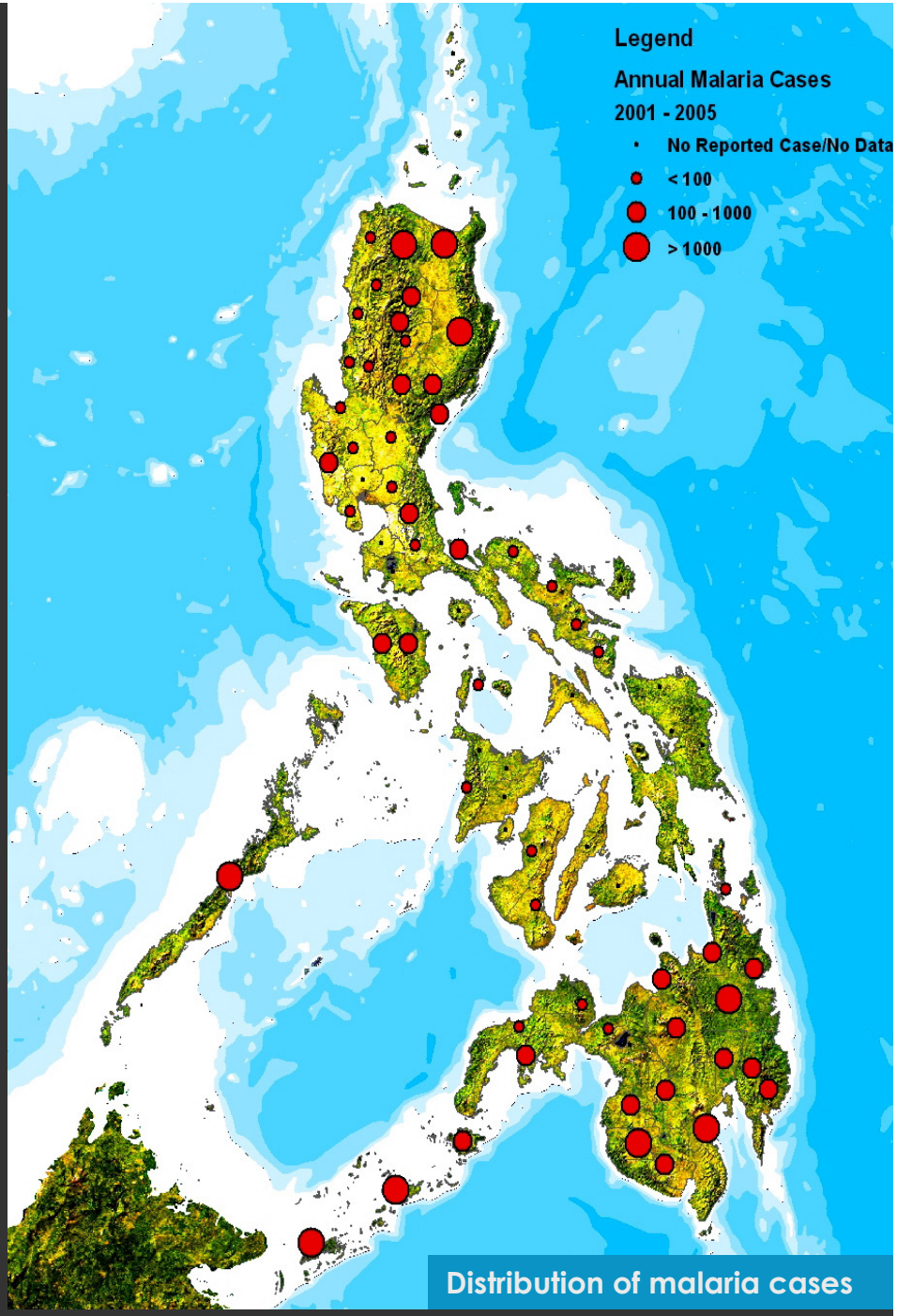
- **Human host**

- **Mosquito – *Anopheles sp.***
  - ***An. flavirostris***
  - ***An litoralis***
  - ***An. maculatus***
  - ***An. mangyanus***
  - ***An. balabacensis***

- **Parasite – *Plasmodium sp.***
  - ***P. falciparum* (60-70%)**
  - ***P. vivax* (30-40%)**
  - ***P. malariae* (?)**
  - ***P. ovale* (?)**
  - ***P. knowlesi* (?)**



Distribution of anopheline vectors



Distribution of malaria cases

Plasmodium falciparum

CQ+SP regimen for uncomplicated falciparum malaria (2002-07)

	Drug	Dose(no. of tablets)		
		Adult	Children	
Day 0	Sulfadoxine/ pyrimethamine (500mg/25mg tablet); Sulfadoxine 25 mg/kg Pyrimethamine 1.2 mk/kg	Three	0-4 mos 5-11 mos 1-6 years 7-11 years 12-15 years > 16 years	¼ ½ 1 1 ½ 2 3
	Chloroquine (150 mg base tablet); 10 mg/kg	Four	0-11 mos 1-3 years 4-6 years 7-11 years 12-15 years >16 years	½ 1 1 ½ 2 3 4
Day 1	Chloroquine (as in D0)	Four	As in Day 0	
Day 2	Chloroquine; 5 mg/kg	Two	< 3 years 4-11 years 12-15 years >16 years	½ 1 1 ½ 2
Day 3	Primaquine (15 mg base tablet)	Three	Below 1 year 1-3 years 4-6 years 7-11 years > 12 years	Contraindicated ½ 1 2 3

Coartem (artemether 20mg/ lumefantrine 120mg) regimen for uncomplicated falciparum malaria

	Adults and children 13 years and above	Children 12 years old and below		
		>8 to 12 years	> 3 to 8 years	<3 years and infants above 5 kg body weight
Day 0	4 tabs; repeat after 8 hrs	3 tabs; repeat after 8 hrs	2 tabs; repeat after 8 hrs	1 tab; repeat after 8 hrs
Day 1	4 tabs BID	3 tabs BID	2 tabs BID	1 tab BID
Day 2	4 tabs BID	3 tabs BID	2 tabs BID	1 tab BID
Day 3	Give primaquine as in uncomplicated falciparum malaria			

Categories of response to treatment of *P. falciparum*

Therapeutic response	Criteria
Early treatment failure (or ETF; days 1 - 3)	• Severe malaria and parasitemia • Day 2 – Parasitemia higher than Day 0 • Day 3 – Parasitemia and fever or parasitemia ≥ 25% of Day 0
Late clinical and parasitological failure (or LCPF; days 4 - 28)	Parasitemia and symptoms (severe malaria or fever)
Late parasitological failure (or LPF; days 4 - 28)	Parasitemia but no symptoms
Adequate clinico-parasitological response	No parasitemia and fever until Day 28

Modified from WHO, 2003

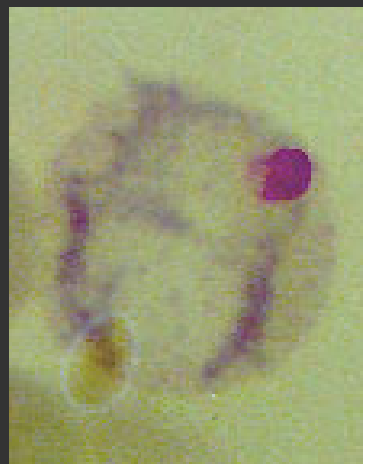
Quinine-plus regimen for falciparum malaria treatment failure

Age group/ condition	Quinine sulfate (300 or 600 mg/tablet	Plus either		Primaquine
		Doxycycline	Tetracycline	
Adults	10 mg/kg/ dose every eight hours for seven days	100 mg BID for seven days	250 mg QID for seven days	As in uncomplicated falciparum malaria
Pregnant women	As above	Contraindicated	Contraindicated	At termination of pregnancy
Children > 8 years old	As above	2 mg/kg/day for seven days	4 mg/kg QID for seven days	As in uncomplicated falciparum malaria
Children 8 < old and below	As above	Contraindicated	Contraindicated	

Regimen for severe malaria

Age group	Quinine dihydrochloride dose		Tetracycline	Clindamycin
	Loading	Maintenance		
Adult	20 mg salt/kg in D_5W x 4 hours IV drip; do not exceed 1,800 mg; do not exceed 5 mg salt/kg/hr	10 mg salt/kg in D_5W IV drip x 4 hours every 8 hours; do not exceed 5 mg salt/kg/hr	500 mg QID for seven days	10 mg/kg BID for three days
> 8 years to 16 years	15 mg salt/kg IV drip x 4 hours	10 mg salt/kg IV drip x 4 hours every 8 hours	4 mg/kg QID; not to exceed 250 mg/dose	As above
8 years and below	10 mg salt/kg in IV drip x 4 hours	10 mg salt/kg IV drip every 12 hours	Contraindicated	As above

Plasmodium vivax



CQ and primaquine (PQ) regimen for vivax malaria

	Drug	Dose (no. of tablets)		
		Adult	Children	
Days 0 to 2	Chloroquine as in *P. falciparum*			
Days 0 to 13	Primaquine (15 mg base tablet); 0.5 mg/kg	One	Below 1 year 1-3 years 4-6 years 7-11 years > 12 years	Contraindicated 1/3 ½ ¾ 1

Recognizing *P vivax* chloroquine treatment failure

- Parasitemia and clinical deterioration
- Parasitemia and recurrence or persistence of fever (>37.5C) from Day 3 to Day 28 after start of treatment
- Parasitaemia from Day 7 to 28 after start of treatment regardless of clinical condition

Surveys for chloroquine-resistant P vivax since 2000

COUNTRY	YEAR	STUDY POP'N SIZE	% RESISTANT
India	2004	287	0
	2004 (CQ+PQ)	102	0
	2001	480	0
Indonesia	2004	40	65
	2000 (CQ+PQ)	60	18
Turkey	2004	91	22
	2001	112	15
Thailand	2004 (CQ+PQ)	31	0
	2003	161	0
Vietnam	2001	113	16
Colombia	2004	210	0
Peru	2001	177	2

Modified from Baird K., 2007, TRENDS in Parasitology, Vol. 23 No. 11

Philippines	2005	37	0

Espino et al, 2006

Plasmodium vivax relapses

- Are important sources of reinfection and transmission
- Risk of relapse of tropical strains is higher than temperate strains
- Relapses can occur weeks to years after the initial infection
- Prevention targets the hypnozoites
- Primaquine is the only commercially available anti-relapse drug

Risk of P vivax relpase according to primaquine dose (India, Thailand and Brazil)

Primaquine dose	Odds ratio (adjusted)	95% CI
0	1.0	
75	0.42	0.34-0.52
210	**0.22**	**0.16-0.30**
315	0.01	0.00-0.08
420	0.05	0.01-0.20

(modified from Goller et al., 2007, Amer Jour Trop Med Hyg, Vol 76 No. 2)

Reports of severe and complicated *P. vivax* malaria since 1998

COUNTRY	YEAR	NO. OF CASES	PRESENTATION	FATAL CASES
Afghanistan	2004	1 adult	ARDS	0
Brazil	2000	1 adult	Thrombocytopenia	0
Columbia	1998	1 adult	ARDS	0
India	1998, 1999, 2000, 2002, 2003, 2006	56 adults; 1 child	ARDS (5) Cerebral (4) Renal failure (22 adults; 1 child) Liver dysfunction (8) Jaundice (4) Thrombocytopenia (5) Pancytopenia (1)	1 1 5
Indonesia	2000	21 children; 17 adults	ARDS (2) Cerebral (5) Renal failure (4) Liver dysfunction (10) Anemia (24) Hyperparasitemia (1) Acidosis (3)	1 3 3 1
Kenya	2004	1 adult	Splenic rupture	0
Malaysia	2003	2 adults	ARDS (1) DIC/ renal failure (1)	 1
New Guinea	2000	1 adult	ARDS	0
Pakistan	2000	1 adult	Cerebral	0
Singapore	2003	1 adult	ARDS	1
Turkey	2005	2 adults; 1 child	Cerebral (child) Splenic rupture (2 adults)	0
Venezuela	2005	1 adult	ARDS	0

Modified from Baird K., 2007, TRENDS in Parasitology, Vol. 23 No. 11

Plasmodium knowlesi

P. knowlesi – a new, emerging human parasite

- Malaria parasite of old world monkeys; isolated from Philippine macaques (*Macaca fascicularis*) in 1961
- Incriminated vector is *An balabacensis*
- First naturally acquired human infections was reported in 1965 in Malaysia
- Foci of cases reported
  - Sarawak, Malaysia – 2004, 2008
  - China - 2006
  - Thailand – 2004
  - Philippines – 2008 (in press)

P. knowlesi (cont.)

- Morphologically similar to *P malariae*; may be mistaken to be *P falciparum* because of abundant ring stages
- Rhesus monkey studies
  - High parasite densities is possible
  - No significant sequestration in microcirculation
- Reported in relatively older adults
  - May present as a mild from of malaria easily responding to chloroquine
  - Fever, headaches, intermittent chills, abdominal pain, sweating and malaise
  - May also be severe and fatal

Comparison of results for detection of Plasmodium species by PCR and microscopy

PCR \ Microscopy	Pf	Pv	Pm	Po	Mixed	# PCR identified
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
P knowlesi	11	16	216	0	0	243
Mixed infections	15	20	17	0	1	53
TOTAL	216	428	312	2	2	960

Modified from Cox-Singh et al., 2008, Clinical Infectious Diseases, 46, 165-71

Details at hospital admission of 4 fatal cases of P knowlesi

	Case 1 (66/f)	Case 2 (69/m)	Case 3 (39/m)	Case 4 (40/m)
Parasites	764,720	75,000	112,000	++++
BP	120/90	124/66	81/51	132/57
T (axilla)	36.8	38	37	36
Hb	10.6	15.2	15.4	11.9
WBC	16,700	6,600	13,400	11,400
APC	22,000	25,000	24,000	24,000
Creatinine (umol/L)	500	NA	NA	557
TB (umol/L)	79	300	NA	490
Conj. bilirubin	59	187	NA	350
AST (U/L)	122	163	NA	87
ALT (U/L)	104	77	NA	82
AlkPO4ase (U/L)	160	77	NA	151

Modified from Cox-Singh et al., 2008, Clinical Infectious Diseases, 46, 165-71

P. knowlesi – research questions

- For how long has this parasite been infecting humans in the Philippines?
- How is the parasite transmitted –
  - Primate to human?
  - Human to human?
- Clinical characteristics of knowlesi malaria
- What is the phylogenetic origin of the parasite? Molecular epidemiology?
- How are Philippine strains related to those in other countries that report this infection in humans?

Summary/ conclusion

- Epidemiology of malaria in the Philippines is changing
  - Response to treatment
  - Control of relapse
  - New species in humans
- Responsibilities
  - Suspected malaria cases must be confirmed (especially species)
  - Malaria cases treatment must be monitored during and after treatment