Malaria

Dr. Timothy William
Queen Elizabeth Hospital,
Kota Kinabalu, Sabah

Outline

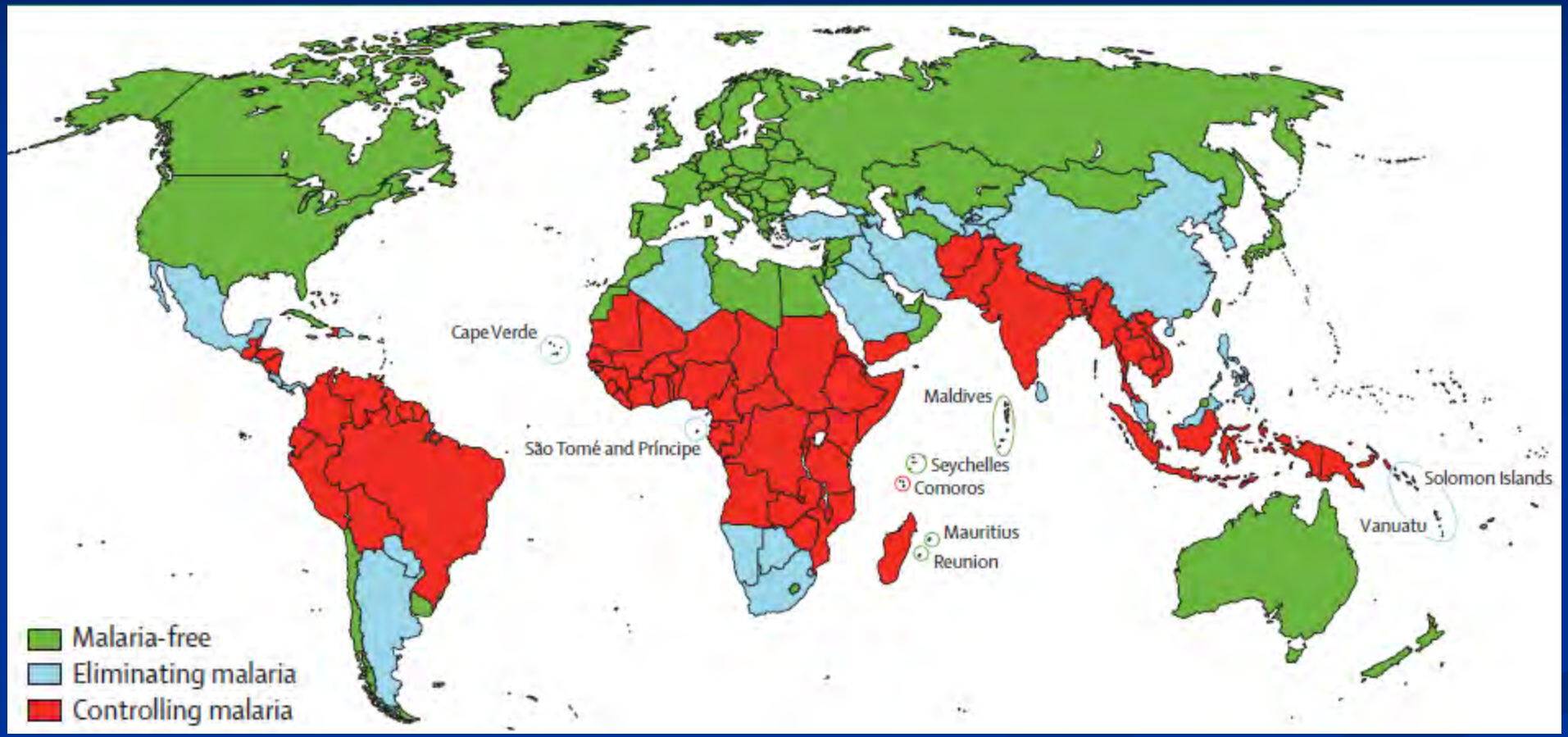
- Overview of malaria epidemiology
- Malaria pathophysiology and clinical features
- **Recognition of severe malaria**
- Management

Malaria: introduction

- 3.3 billion at risk
- Estimated 250 mill cases per year
- Nearly 1 million deaths per year
- Huge advances in malaria control over the past 5 – 10 years
- Huge increase in international funding (US$1.8 billion 2009)
- ↑ in coverage mosquito nets
- ↑ in spraying
- ↑ access to ACT
- Many countries moving towards malaria elimination

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

Shrinking the malaria map

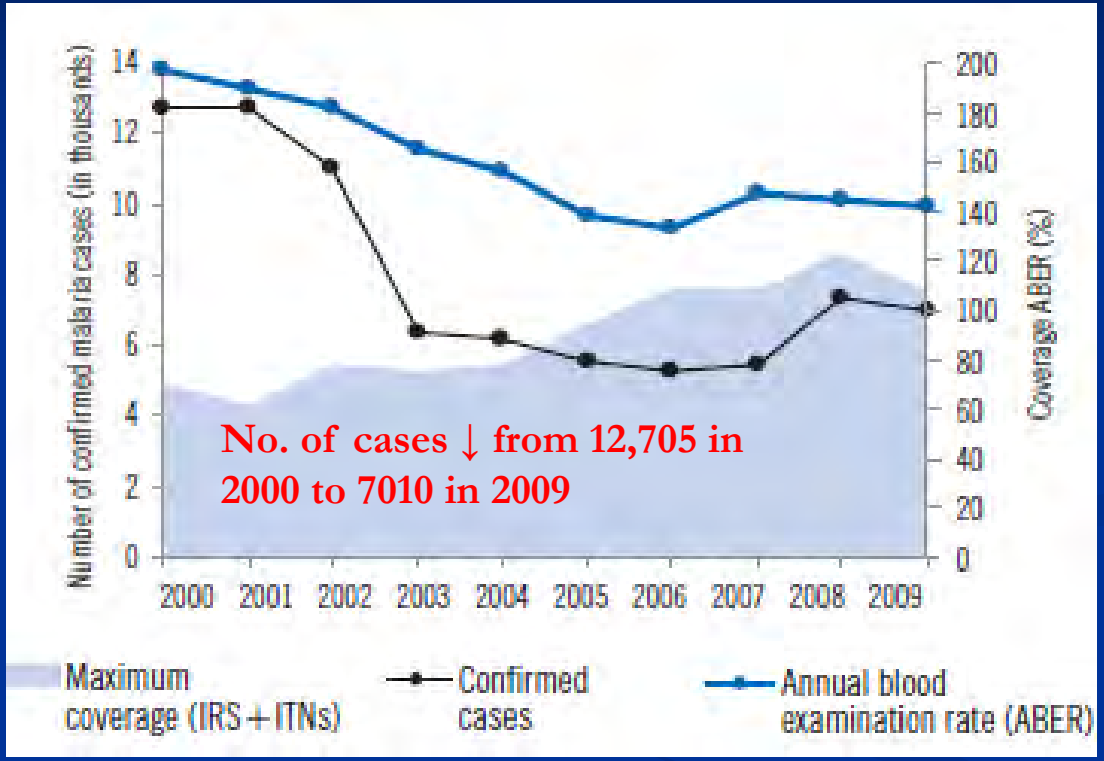


Feachem et al. Lancet 2010

PROGRESSING TO PRE-ELIMINATION OF MALARIA IN MALAYSIA

WORLD MALARIA REPORT 2010

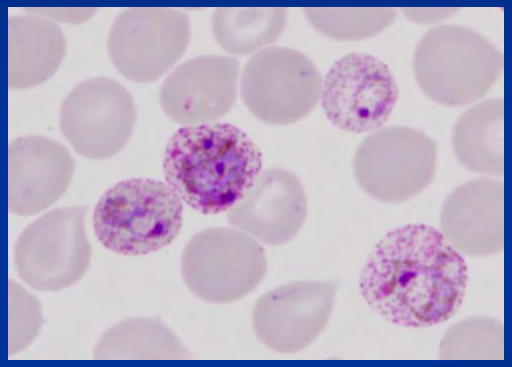
- Majority of cases occur in Sarawak and Sabah
- Incidence in West Malaysia < 0.1/1000
- Control strategies:
  - ↑ use of mosquito nets
  - ↑ spraying
  - ↑ use of ACT



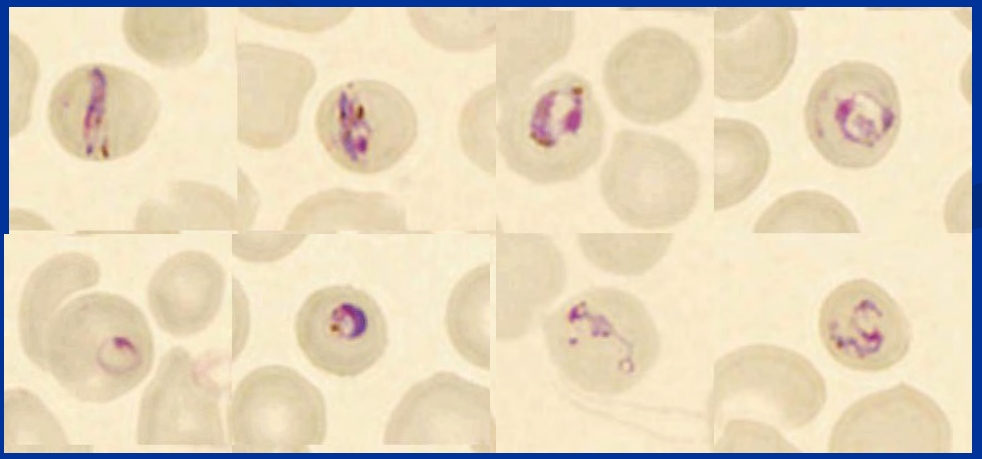
- Malaysia now in the pre-elimination phase of malaria control
- Major species: P. falciparum, P. vivax, P. knowlesi

Challenges for Sabah…

- Vivax malaria

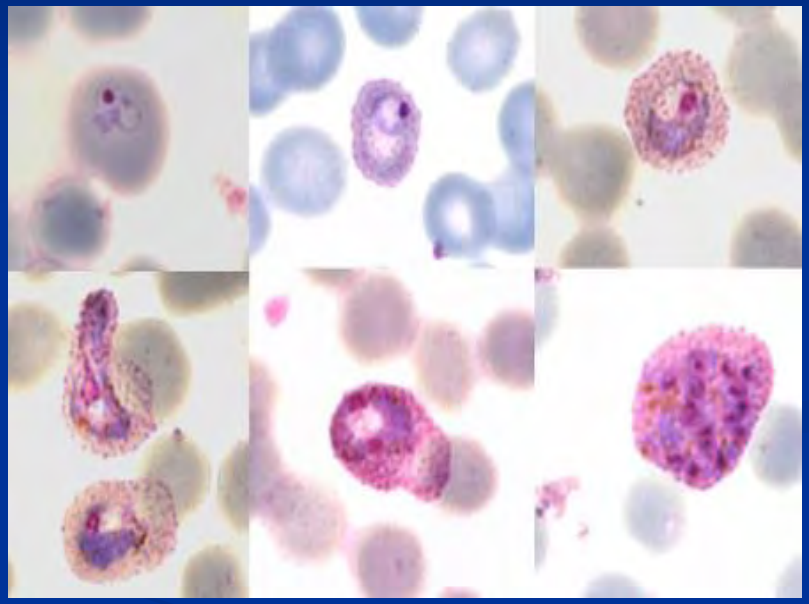


- Knowlesi malaria

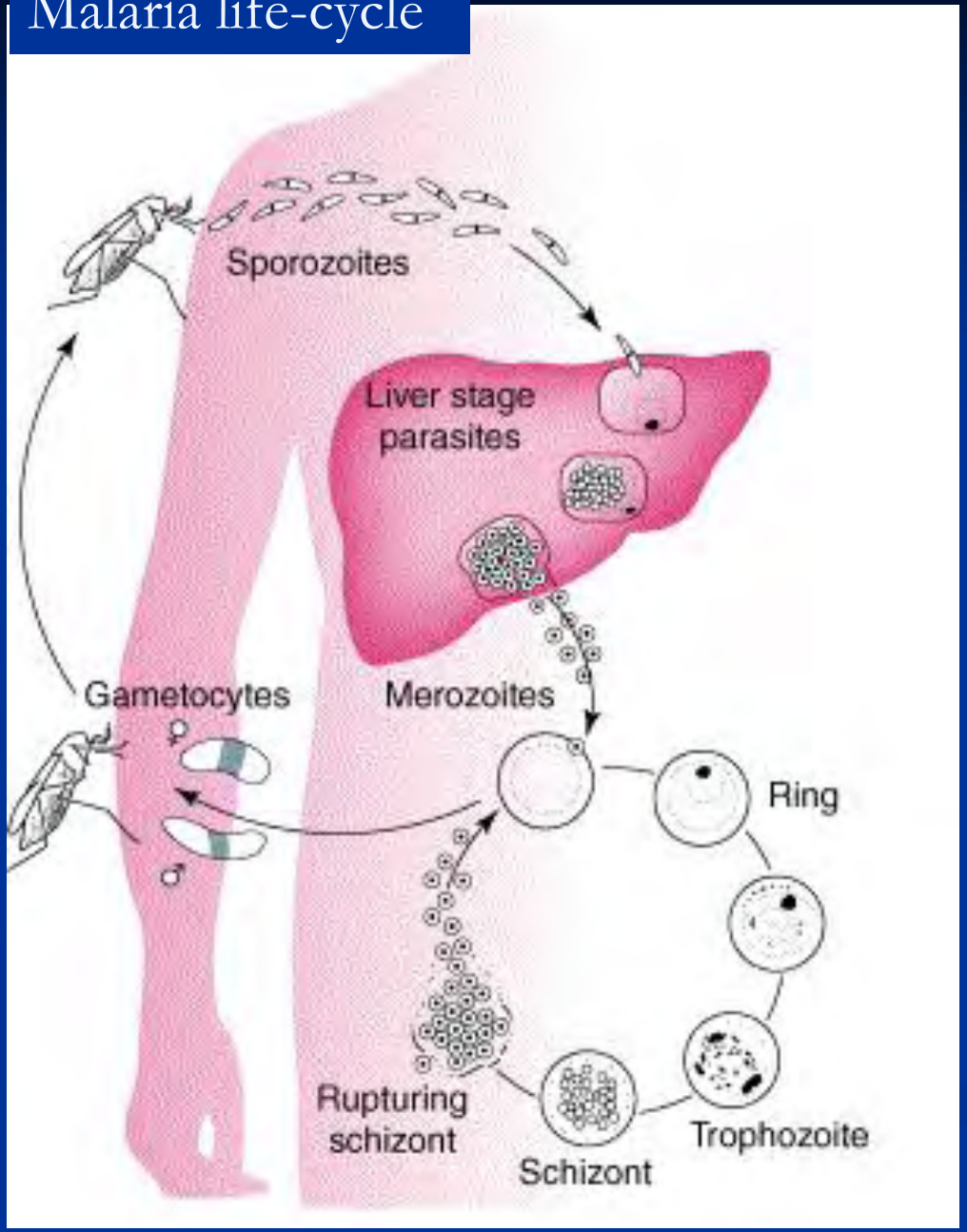


Vivax malaria

- Up to 390 million cases annually
- Accounts for at about half of malaria outside Africa
- Represents an increasing public health problem:
  - More difficult to eliminate than Pf
  - ↑ resistance to chloroquine
  - increasingly recognized as a cause of severe disease



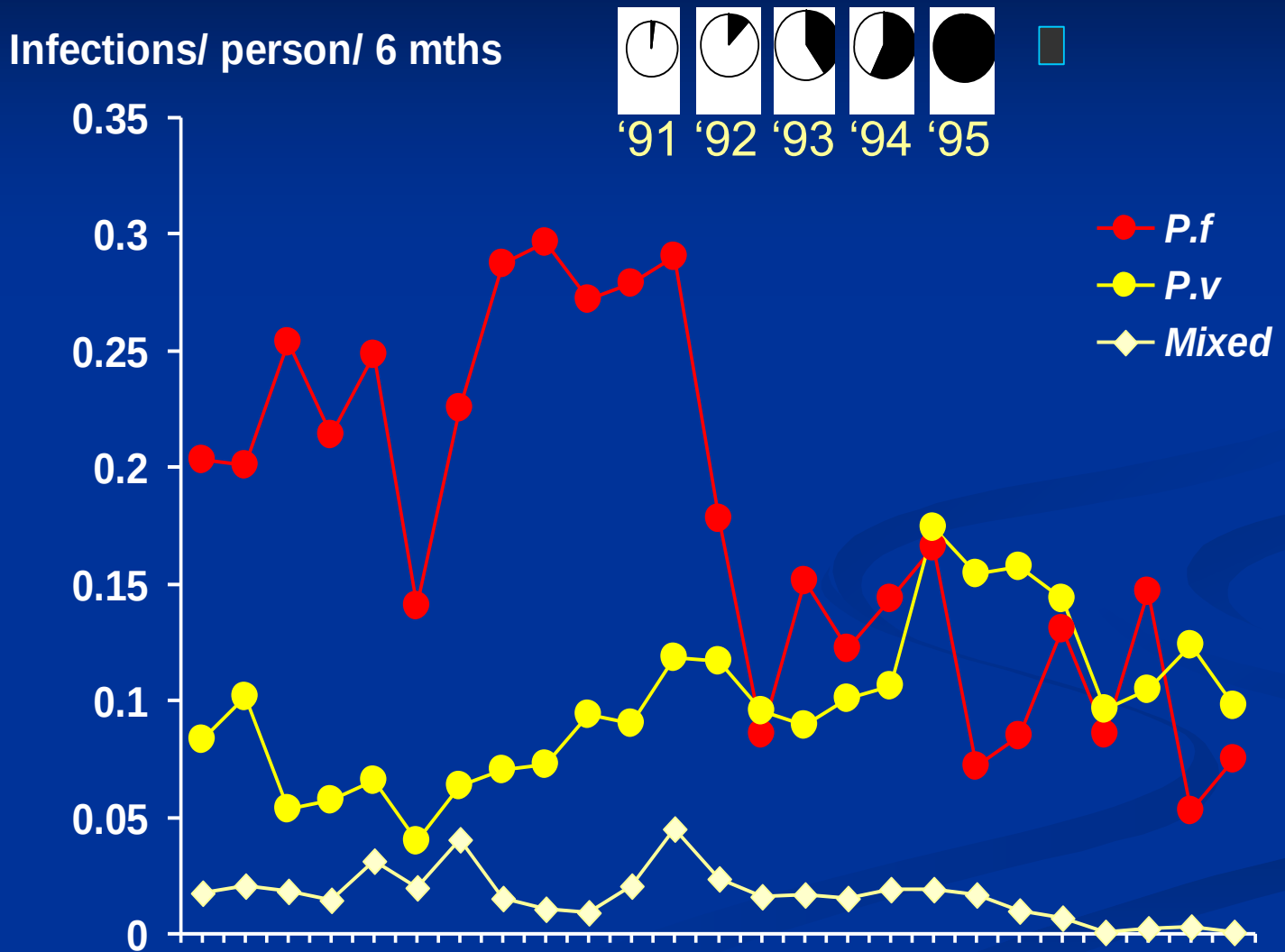
Malaria life-cycle



Vivax malaria: challenges for elimination

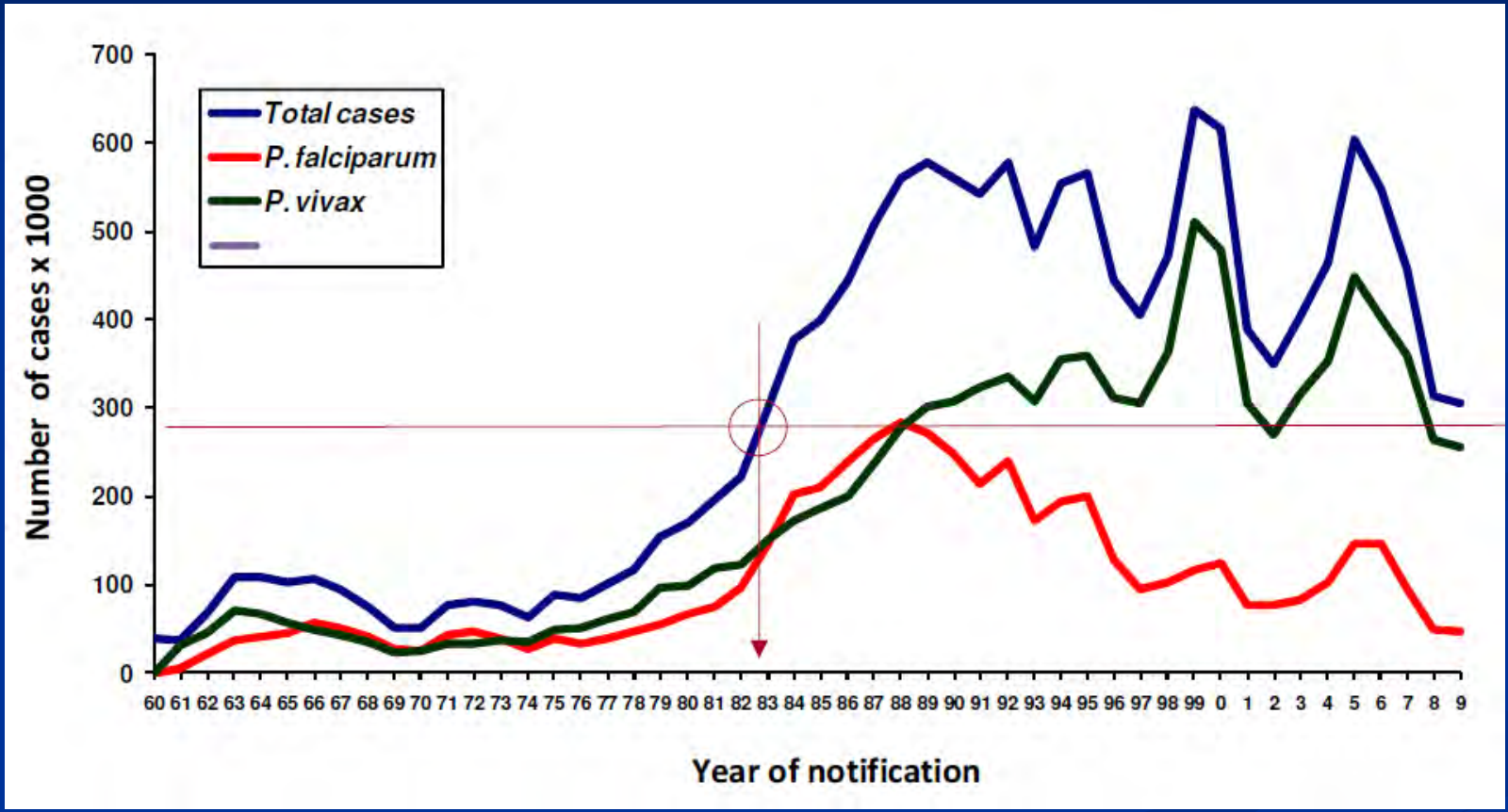
- Relapses
  - Regional variation
- Gametocytes appear earlier in infection
  - 50 – 80% of patients have gametocytes on presentation, compared to 10 – 40% with Pf
- Gametocytes more effectively transmitted to mosquitoes

Malaria on the Thai-Myanmar border



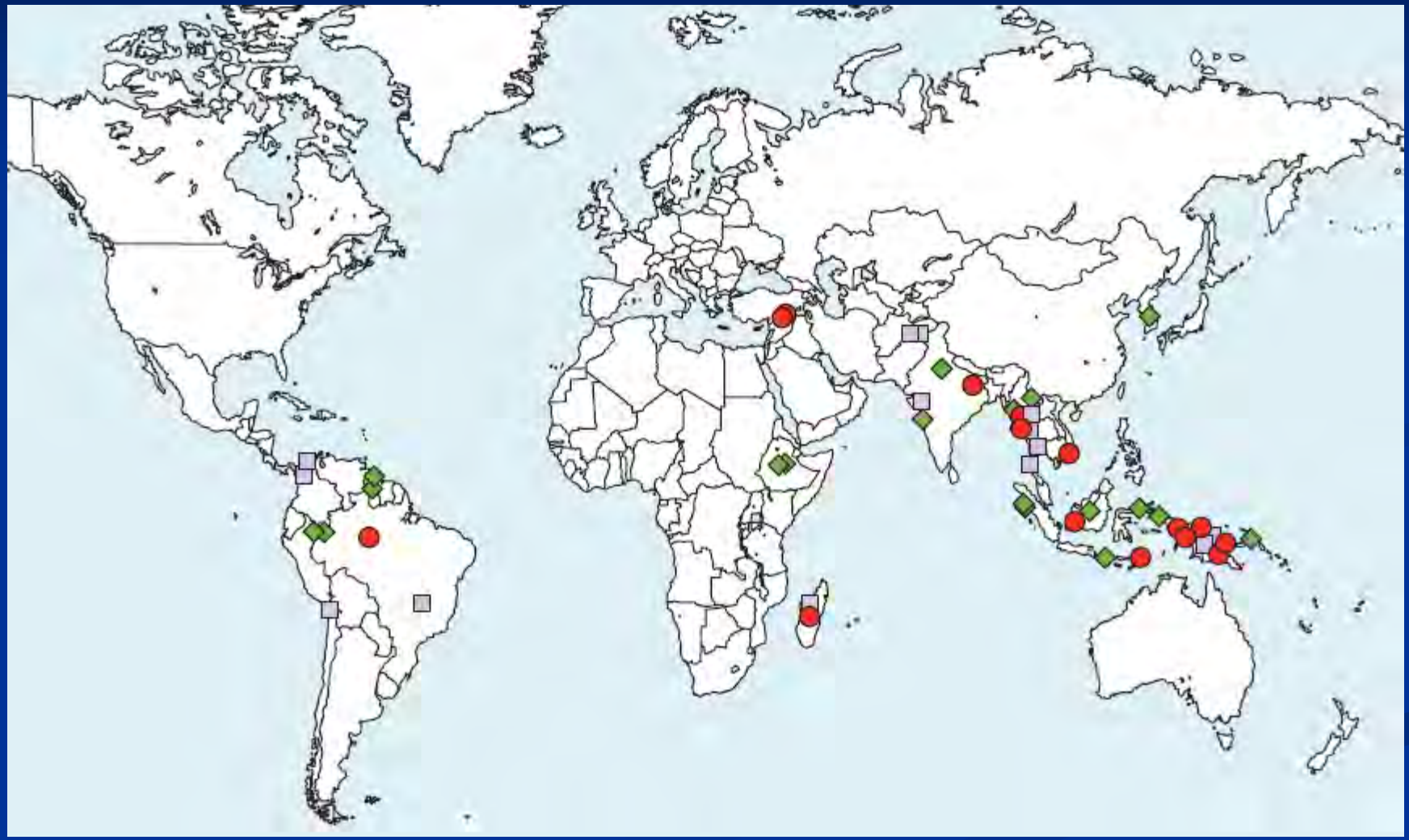
Nosten et al. Lancet 2000; 356: 297-302

Malaria in Brazil



Oliveira-Ferreira *et al. Malaria Journal* 2010, **9**:115

Chloroquine resistant P. vivax



Douglas et al. Lancet Inf Dis 2010

Am. J. Trop. Med. Hyg., 77(5), 2007, pp. 984–991

Demographic Risk Factors for Severe and Fatal Vivax and Falciparum Malaria Among Hospital Admissions in Northeastern Indonesian Papua

Mazie J. Barcus,* Hasan Basri, Helena Picarima, C. Manyakori, Sekartuti, Iqbal Elyazar, Michael J. Bangs, Jason D. Maguire, and J. Kevin Baird

OPEN ACCESS Freely available online

June 2008 | Volume 5 | Issue 6 | e127 PLOS MEDICINE

Plasmodium vivax and Mixed Infections Are Associated with Severe Malaria in Children: A Prospective Cohort Study from Papua New Guinea

Blaise Genton[1*¤], Valérie D'Acremont[1], Lawrence Rare[2], Kay Baea[2], John C. Reeder[2], Michael P. Alpers[2], Ivo Müller[2]

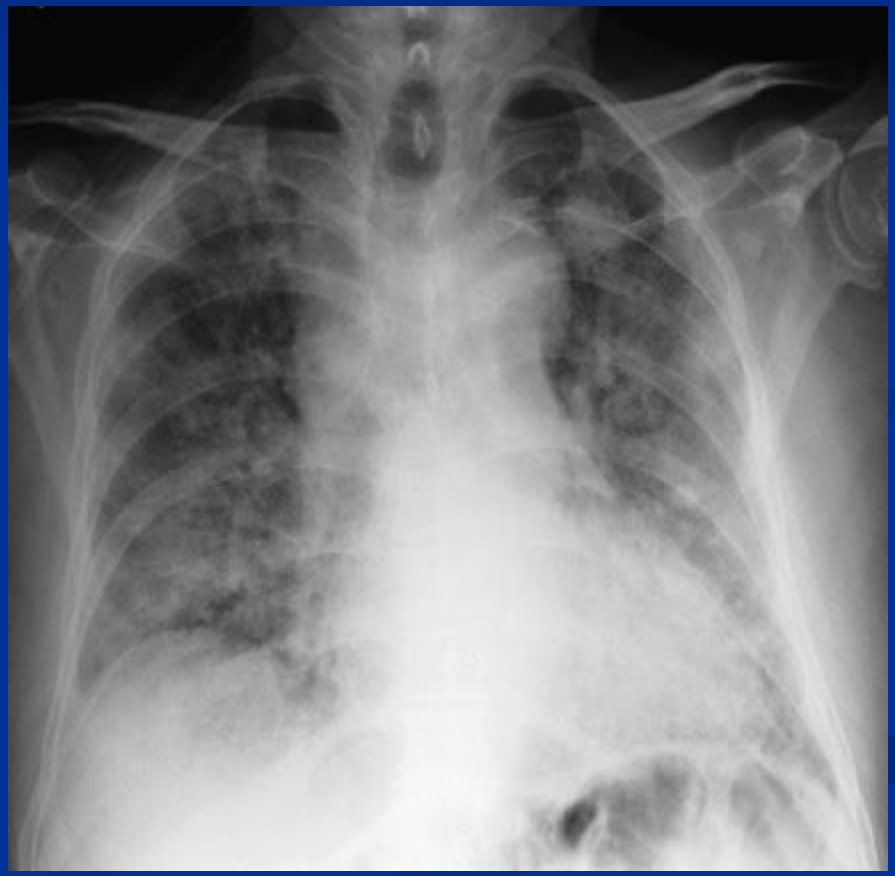
OPEN ACCESS Freely available online

June 2008 | Volume 5 | Issue 6 | e128 PLOS MEDICINE

Multidrug-Resistant *Plasmodium vivax* Associated with Severe and Fatal Malaria: A Prospective Study in Papua, Indonesia

Emiliana Tjitra[1], Nicholas M. Anstey[2], Paulus Sugiarto[3], Noah Warikar[4,5], Enny Kenangalem[4,6], Muhammad Karyana[1], Daniel A. Lampah[4,6], Ric N. Price[2,7*]

- Vivax complications
  - Severe anaemia
  - Respiratory distress
  - ARDS
  - Jaundice
  - Splenic rupture
  - Acute renal failure
  - Pancytopenia
  - Cerebral malaria



Plasmodium knowlesi: The Fifth Human Malaria Parasite

N. J. White

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

Monkey malaria in man

Balbir Singh and colleagues (Mar 27, p 1017)[1] report interesting data on the occurrence of *Plasmodium knowlesi* malaria in a human population in Malaysian Borneo.

Cross-species transmission of

Macaca fasicularis

Macaca nemistrina

Background: *Plasmodium knowlesi*

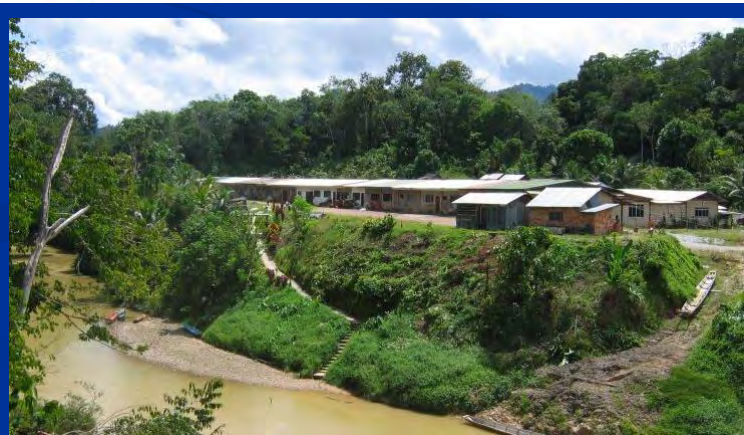
- Knowles, R. DasGupta BM. *Indian Medical Gazette* 1932
  - demonstrated infection of humans by inoculation of blood from infected monkeys
- Used as a pyretic agent for treatment of neurosyphilis - 24 hr asexual replication cycle
- Chin, W et al. *Science* 1965
  - First naturally acquired case of human knowlesi malaria

A large focus of naturally acquired *Plasmodium knowlesi* infections in human beings

Balbir Singh, Lee Kim Sung, Asmad Matusop, Anand Radhakrishnan, Sunita S G Shamsul, Janet Cox-Singh, Alan Thomas, David J Conway

Lancet 2004; **363**: 1017–24

- 1999 – 20% of malaria cases in Kapit identified as *P. malariae*
- *P. malariae* infections noted to be atypical
- PCR performed on 5 isolates – neg for *P. malariae*
- 2000 – 2002: 120 (58%) of 208 malaria cases diagnosed with *P. knowlesi* by PCR
- No cases of *P. malariae*



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

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]

Clin Infect Dis. 2008 Jan 15;46(2):165-71

- PCR performed on 960 malaria blood films from Sarawak 2001 – 2006: 28% *P. knowlesi*
- Sabah: 41/49 (84%) *P. malariae* blood films positive for *P. knowlesi*
- West Malaysia: 4/4 *P. malariae* blood films positive for *P. knowlesi*
- 4 fatal cases of knowlesi malaria
  - High parasitemia, multi-organ failure

Clinical and Laboratory Features of Human *Plasmodium knowlesi* Infection

Cyrus Daneshvar,[1] Timothy M. E. Davis,[3] Janet Cox-Singh,[1] Mohammad Zakri Rafa'ee,[2] Siti Khatijah Zakaria,[1] Paul C. S. Divis,[1] and Balbir Singh,[1]

Clinical Infectious Diseases 2009; 49:000–000

- Prospective study
- 152 adult malaria cases in Kapit, Sarawak
  - 107 (70%) *P. knowlesi*
- Most (93.5%) had uncomplicated malaria that responded well to CQ and PQ
- 8 (7.5%) had severe infection
- 2 patients died (case fatality 1.8%)

Retrospective study of clinical and laboratory features of *P. knowlesi* in children

- 24/41 (59%) of all childhood malaria
- Children with Pk older than those with Pf (mean age 8.9 vs. 5.2 years, P<0.002)
- Anaemia common
  - all had Hb<11 on admission
  - median Hb nadir 9.7
  - 1 child had Hb 6.4
- All were thrombocytopenic (mean Plt nadir 76, lowest 28)

Barber et al. Emerg Inf Dis 2011

Severe knowlesi malaria at QEH

William et al, Emerg Inf Dis 2011

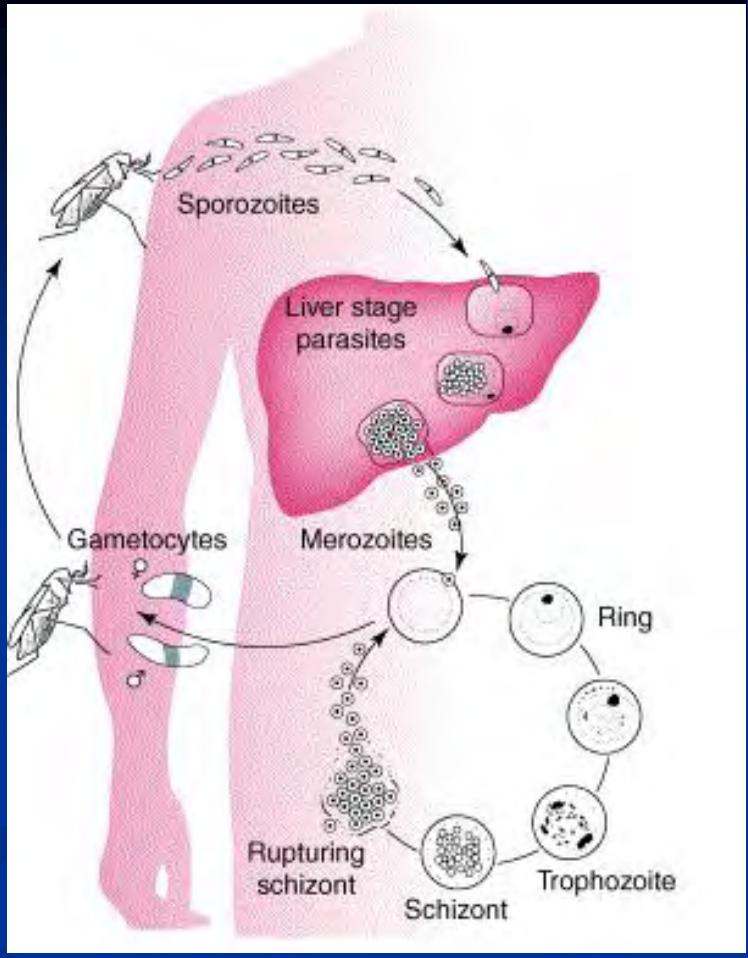
- Retrospective study from Dec '07 - Nov '09
- 56 patients with knowlesi malaria
- 22 (36%) had severe malaria, 6 (10.7%) deaths
- Complications included respiratory distress (59%), acute renal failure (55%), shock (55%)
- Risk factors for severe disease:
  - Older age

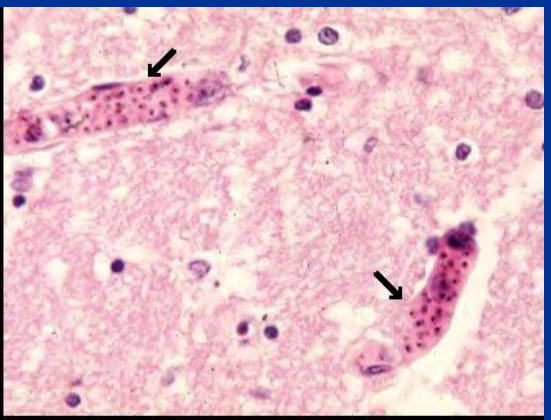
Knowlesi malaria: points to remember

- Nearly all reports of *P. malariae* are actually *P. knowlesi*
- *P. knowlesi* can be severe and potentially life-threatening
- Can present very similar to dengue
- May not appear severe on first presentation
- Older age group at ↑ risk of severe disease
- Thrombocytopenia is universal, and can be severe
- Resp complications common in severe disease
- Treatment the same as for *P. falciparum*

Pathophysiology

- Invasion of RBCs
  - → Haemolysis
  - → Release of cytokines
- Cytoadherence, rosetting, autoagglutination, reduced deformability
  - → sequestration
  - → microvascular obstruction
  - → ischaemia
  - → organ dysfunction





Clinical features

- Fever
- Headache, dizziness
- Arthralgias, myalgias, back ache
- Abdominal pain
- Nausea, vomiting
- Diarrhoea
- Cough, breathlessness
- Abnormal bleeding
- Jaundice
- Pallor
- Hepatosplenomegaly
- Petechiae, brusing
- Tachypnoea, hypoxia
- Acute abdomen

Biochemical features

- Anaemia
- Thrombocytopenia
- Hypoglycemia
- Hyperbilirubinemia
- ↑ ALT/AST (usually mild)
- Renal failure
- Metabolic acidosis

Management

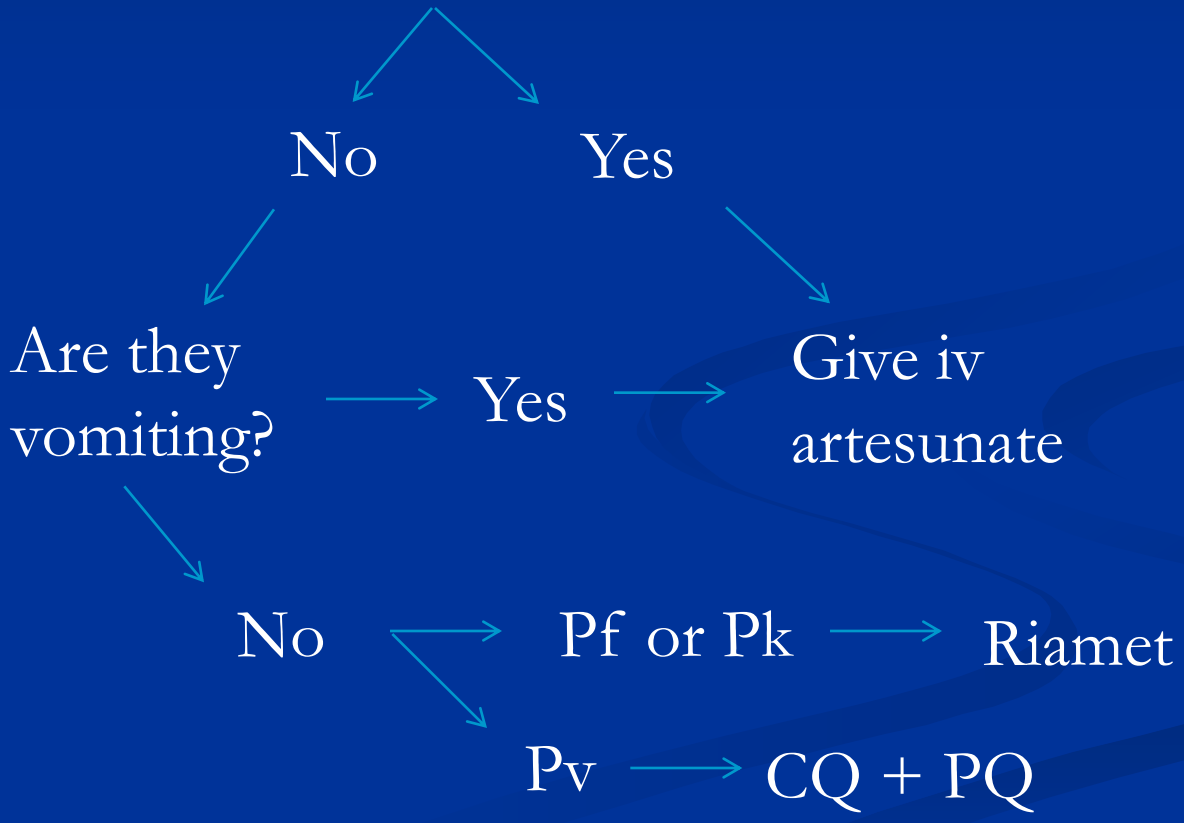
- Severe malaria
  - Malaria with any feature of severity
- Uncomplicated malaria
  - Malaria without any feature of severity

WHO Criteria for severe malaria

- Clinical features:
  - Impaired consciousness
  - Prostration (severe weakness)
  - Failure to feed
  - Multiple convulsions
  - Respiratory distress
  - Shock
  - Jaundice + other organ failure
  - Abnormal spontaneous bleeding
  - Pulmonary oedema
- Biochemical features:
  - Hypoglycemia (BSL<2.2)
  - Severe anaemia (<7g/dL)
  - Lactate >5
  - Renal impairment (Cr>265)
  - Metabolic acidosis (HCO3<15)
  - Haemoglobinuria
  - Hyperparasitemia (>100,000/μL)

Reference: 2010 WHO Guidelines for the treatment of severe malaria

Approach to treatment of malaria



Severe malaria: drug treatment

- iv artesunate 2.4mg/kg stat, 12 hrs, 24 hours, then daily
- Change to Riamet when able to tolerate oral meds (usually after 3 doses of artesunate)
- consider empirical antibiotics (eg. Ceftriaxone)
  - Always take blood cultures first
  - Cease Abs if blood cultures negative

Severe malaria: supportive management

- Consider HDU/ICU referral
- iv fluids
- O2
- Blood transfusion
- Dialysis
- Monitoring –
  - BP, 02Sats, RR
  - Daily BSMP, daily FBC (platelets usually recover quickly, but Hb usually falls)

Treatment of uncomplicated Pf / Pk

- All patients should be given combination therapy
  - More effective
  - Prevents development of resistance

- Recommended treatment for uncomplicated Pf
  - Artemisinin Combination Therapy
    - Riamet (artemether/lumefantrine)
    - Artequine (artesunate/mefloquine)

Artemisinin derivatives

- Rapid clearance of parasites
  - reduce parasite density by a factor of 10,000 in each 48 hr asexual cycle
- Rapidly eliminated, so need to be combined with longer acting partner drug
  - 3 day course of artemisinin derivative will clear ≥90% of parasites
  - Remaining 10% of parasites will be cleared by partner drug
- Reduce gametocyte carriage

Practice points: Riamet

- Riamet: 20mg artemether + 120mg lumefantrine
- Dosage: 4 tabs stat, followed by 4 tabs 8 hrs later, then 4 tabs bd 2/7 (total of 6 doses)

- For children
  - 25 – 34kg: 3 tabs, 15 – 24kg: 2 tabs, 5 – 14kg: 1 tab

- Must be given with ≥ 1.2g fat to increase absorption

Riamet alternatives

- Alternatives:
  - An alternative ACT (eg. artesunate/mefloquine)
  - Artesunate + doxycycline for 7 days
  - Quinine + doxycycline for 7 days

Treatment of uncomplicated Pv

- Chloroquine still 1st line treatment for P. vivax in Malaysia
- Dose: 25mg **base**/kg over 3 days
  - 10mg/kg stat, 5mg/kg 6hrs, 5mg/kg day 1 and 2
  - 10mg/kg stat, 10mg/kg 6 hrs, 5mg/kg day 1
- Dosage refers to CQ base, not CQ Phosphate
- Commence PQ as soon as possible, if G6PD normal

Primaquine for preventing relapses

- Only drug available
- 15mg daily for 14 days initially adopted as standard regimen, but treatment failures common
- Recommended dose in Sth East Asia
  - 40 – 70kg: 30mg daily 14/7
  - Otherwise, 0.5mg/kg/day (total 6mg/kg)
  - If >90kg, 0.5mg/kg/day until total dose reached

Toxicity of Primaquine

- Abdominal discomfort, nausea, vomiting
  - Usually resolved if primaquine taken with food
  - Can given in divided doses
- Haemolytic Anaemia
  - Occurs in people with G6PD deficiency
  - Begins 24 – 72 hours after commencing primaquine
  - Severity depends on degree of enzyme deficiency
  - Haemolysis less severe or absent using primaquine 45mg or 60mg weekly for 8 weeks

Preventing relapses in pregnant women and patients with G6PD deficiency

- Moderate G6PD deficiency:
  - 45mg weekly for 8 weeks
- Severe G6PD deficiency:
  - Chloroquine prophylaxis for 6 – 8 weeks
- Pregnancy
  - Chloroquine prophylaxis until delivery
  - Primaquine post-delivery

Malaria in pregnancy

- Associated with low birth weight, increased risk of anaemia, increased risk of severe malaria and death
- 1st trimester:
  - Current data indicates no adverse effects of ACT, but more data required
  - Pf – quinine + clindamycin 7/7
- 2nd trimester
  - ACT

Case study: Mr KK

- 55 year old man, previously well
- Presented with 3/7 fever, headache, myalgias
- No vomiting, no abdo pain, no diarrhoea
- No resp symptoms, no bleeding tendencies
- BSMP at Tamparuli: Pv 3+, platelets 35

- Seen in ED - vital signs stable, hepatomegaly and jaundice noted – referred to medical MO
- Seen by MO – "uncomplicated Pv" – plan: chloroquine

Progress

- Admitted to MMW
- Repeat BSMP at QEH: Pm/Pk 4+
- BP overnight – 70/50, minimal improvement with fluid resuscitation
- Transferred to ICU later the following day

- Additional blood results on admission:
  - Platelets 20
  - Bilirubin 189
  - Na 127
  - Cr 120
  - Parasite count: 1.8 million
- Subsequent blood results day 1 - 3:
  - Bilirubin peaked at 290
  - LDH ~2000
  - Hb dropped to 7.3, transfused 2 units

Lessons…

- Microscopy reports can be wrong –
  - Assessing the patient is more important than looking at the BSMP report
- Carefully assess for *any* feature of severity (eg. Jaundice)
- Remember older patients are more at risk of severe disease
- Treat all **severe** malaria with iv artesunate – regardless of species
- Think about early ICU referral

Summary: things to remember

- P. knowlesi
  - in Sabah, "P. malariae" is nearly always P. knowlesi
  - can be severe and potentially life-threatening
  - Older age group at increased risk of severe disease
- Severe malaria
  - Know the features and complications of severe malaria
  - iv artesunate as soon as possible
  - Close monitoring for complications
- Uncomplicated malaria
  - Riamet for Pf and Pk
  - CQ + PQ for Pv