Malaria and travellers' health

Dr Behzad (Baz) Nadjm

Outline of talks

Malaria 101

Developments in treatment

Cases throughout

Ms C M

30 Yr Old

Arrived from Cameroon 2 weeks ago

Forestry research

Feeling unwell 4-5 days

Fevers, sweats, vomiting


to Europe
Tunisia
Morocco
to Middle East
Algeria
Libya
Egypt
Western Sahara
Cape Verde
Mauritania
Mali
Niger
Chad
Sudan
Eritrea
Djibouti
Senegal
Burkina Faso
Guinea
Nigeria
Cote d'Ivoire
Ethiopia
Cent Afr Rep
Ghana
Cameroon
Somalia
Togo
Uganda
Benin
Gabon
Zaire
Kenya
Rwanda
Sao Tome & Principe
Congo
Dem. Rep
Burundi
Equatorial Guinea
Congo
Tanzania
Seychelles
Liberia
Sierra Leone
Comoro Is.
Guinea-Bissau
Angola
Malawi
The Gambia
St. Helena
Zambia
Mozambique
Zimbabwe
Namibia
Madagascar
Botswana
Reunion
Swaziland
South Africa
Lesotho
Mauritius
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Ms C M

30 Yr Old

Arrived from Cameroon 2 weeks ago

Forestry research

Feeling unwell 4-5 days

Fevers, sweats, vomiting

O/E

Temp 39^{9} C

GCS 10, localising pain

Tachycardic, tachypnoeic, not shocked

No meningism, no rash, no focal CNS signs

Jaundiced

Very dark urine

Investigations

Haem

Hb 95
WCC 5.5
PLT 56
PT 1.1

Chem

Na 129
K 4.1
Ur 6.1
Cr 91

ABG

pH 7.43
pCO2 3.65
pO2 10.8
BE - 5.6

Differential Diagnosis

Malaria (falciparum)

Meningoencephalitis

Enteric fever

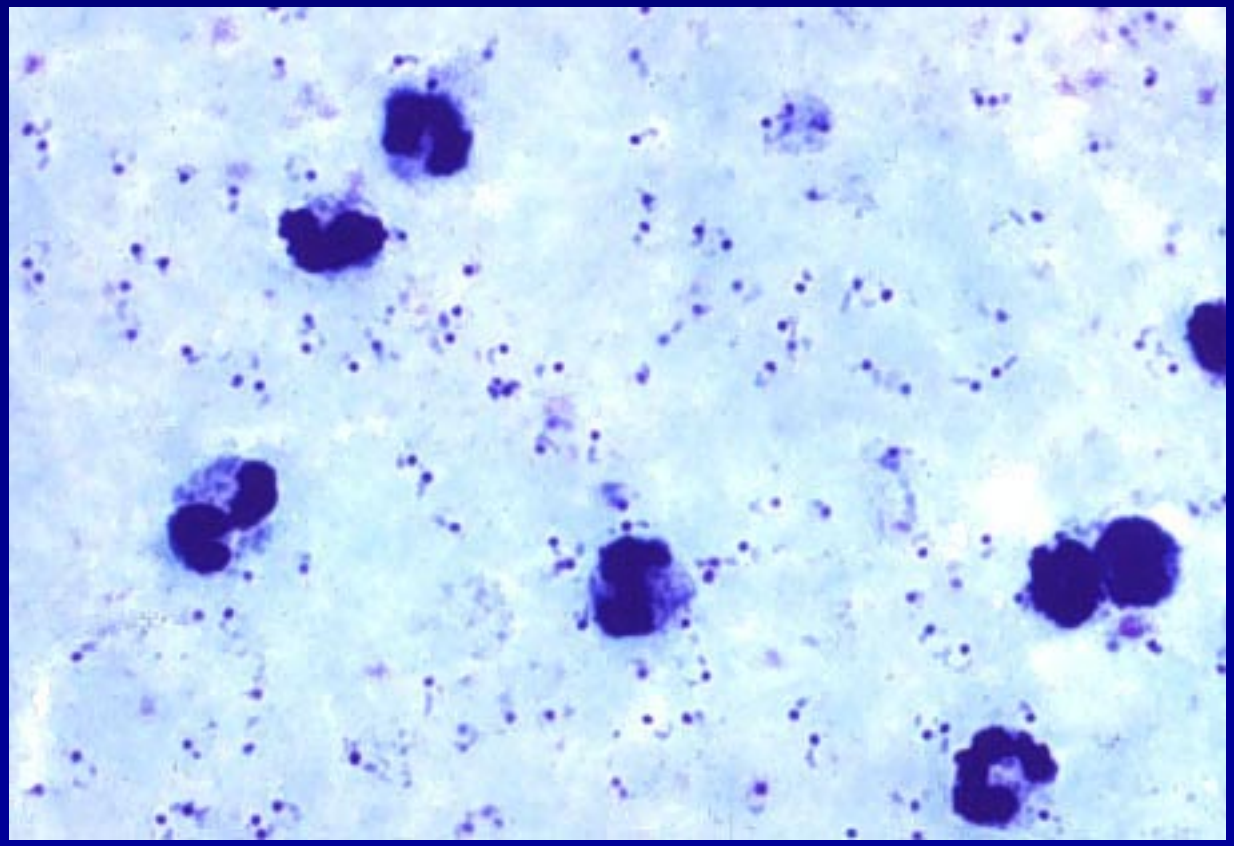
Other bacterial sepsis

+/- Cerebral venous sinus thombosis

African Trypanosomiasis

VHF

Thick Film



Parisitaemia 1% with schizonts

Initial Management

Admitted to HDU

Fluid rehydration

IV quinine, loading dose given

Clinical Course

Parasitaemia rose to 15% overnight

Remained haemodynamically stable

Urea and Creatinine rose, but good urine output maintained

Hb dropped to 7.7 - transfused

Clinical Course

By 48 hrs

- Parasitaemia down to 0.4%
- Acidosis improving
- GCS 14-15
- But QTc up to 480msec - responded to IV Mg^{2+}

By 72 hrs

- Bili up to 180
- Creat improving
- Remained febrile

Clinical Course

Doxycycline added on day 3,

Parasites cleared by day 4

Discharged after 6 days

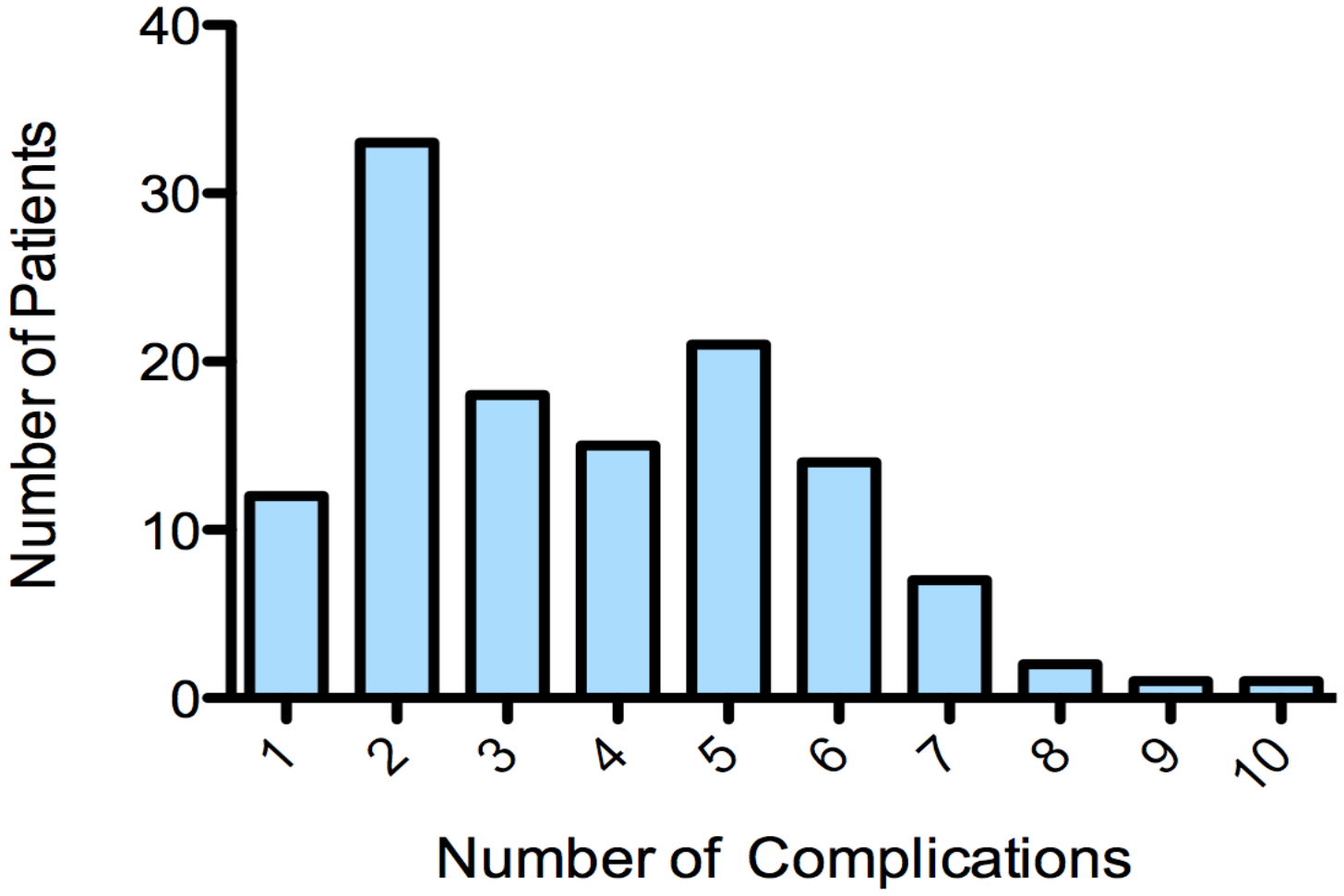
Points for Review

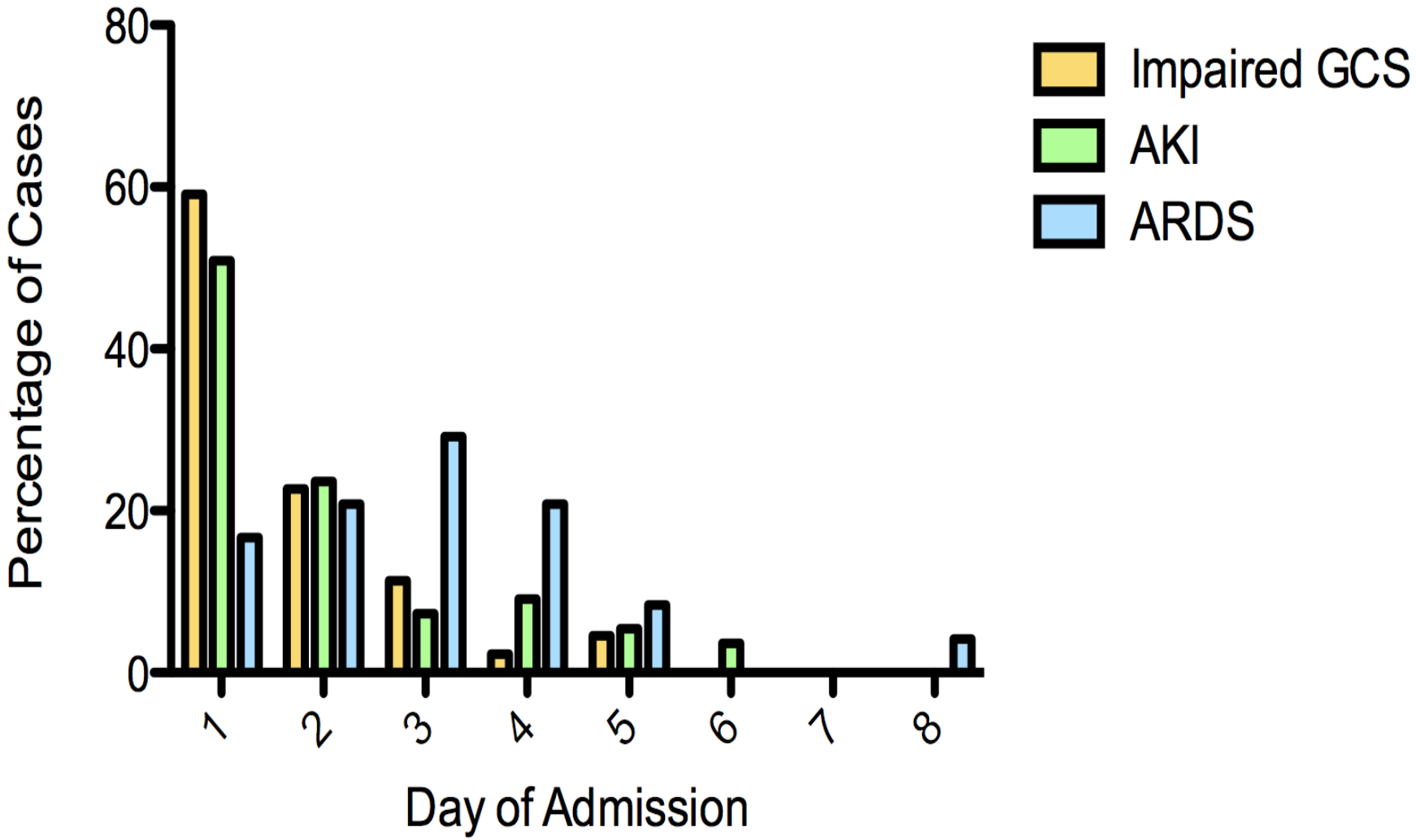
Severe disease & low parasitaemia

Parasite count rise despite adequate therapy

Reduced GCS and AKI early complications

Severe Malaria in Adults requiring ICU: Marks *et al.* BMC ID 2013





Marks *et al.* BMC ID 2013

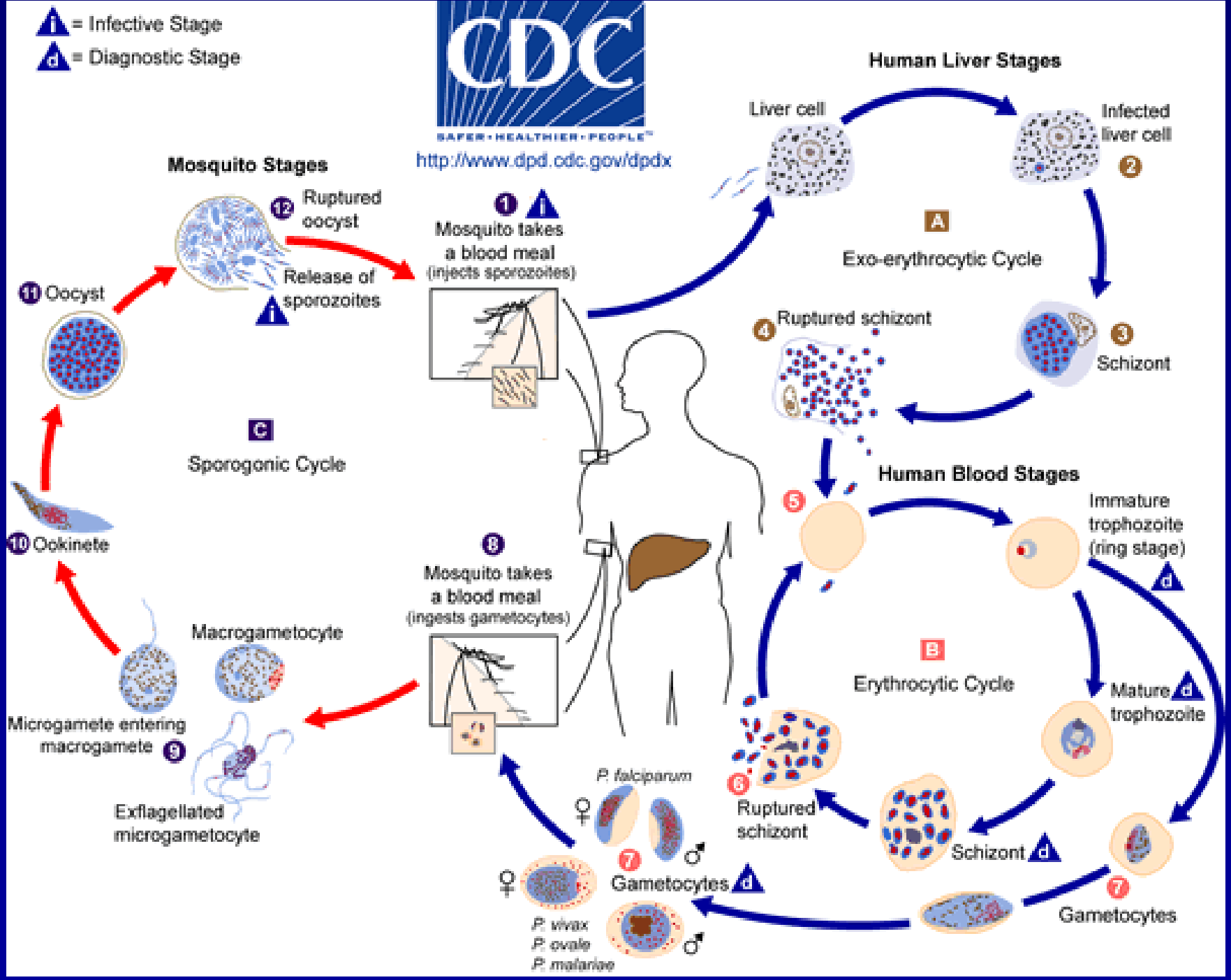
Malaria

5 species

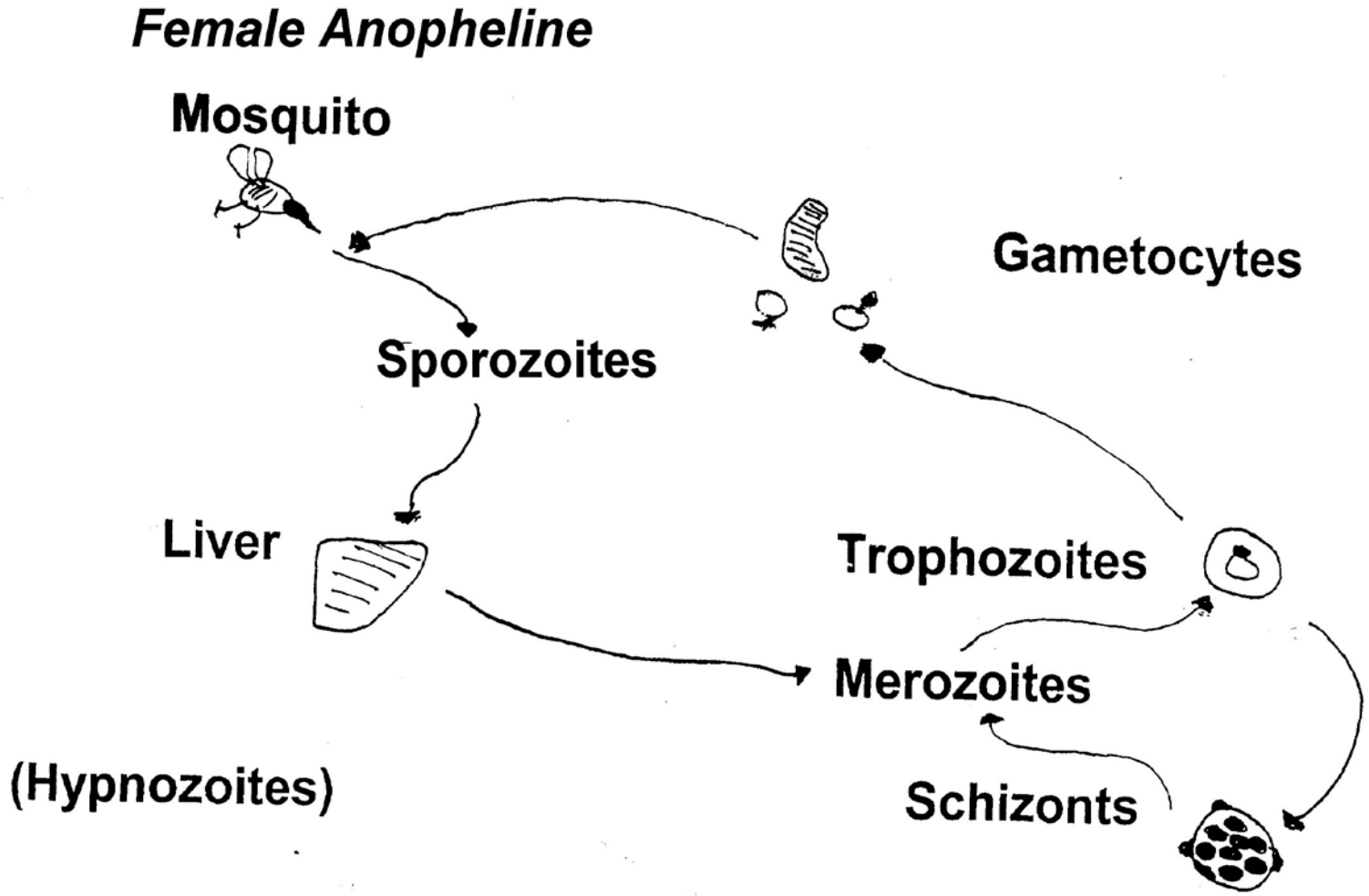
- Plasmodium falciparum
- P. vivax & P ovale
- P malariae
- P knowlesii

Broad spread throughout tropics & sub tropics

Transmission by female anopheles mosquito


= Infective Stage
= Diagnostic Stage
CDC
SAFER • HEALTHIER • PEOPLE™
http://www.dpd.cdc.gov/dpdx
Human Liver Stages
Liver cell
Infected liver cell
2
A
Exo-erythrocytic Cycle
3
Schizont
4
Ruptured schizont
Human Blood Stages
5
Immature trophozoite (ring stage)
Mature trophozoite
B
Erythrocytic Cycle
6
Ruptured schizont
Schizont
7
Gametocytes
P. falciparum
P. vivax
P. ovale
P. malariae
8
Mosquito takes a blood meal (ingests gametocytes)
Macrogametocyte
Microgamete entering macrogamete
9
Exflagellated microgametocyte
10
Ookinete
11
Oocyst
12
Ruptured oocyst
Release of sporozoites
Mosquito Stages
1
Mosquito takes a blood meal (injects sporozoites)
C
Sporogonic Cycle

Malaria: life cycle



With thanks to Tom Doherty

Pf schizont

Falciparum malaria

0.5 – 1m deaths annually worldwide

Significant mortality in returning travellers

Prophylaxis highly effective against P falciparum

Pathogenesis multifactorial

- Infection of all ages of RBC
- Rosetting & sequestration
- Altered rheology of infected/uninfected cells
- Cytokine driven pathology

Symptoms/signs

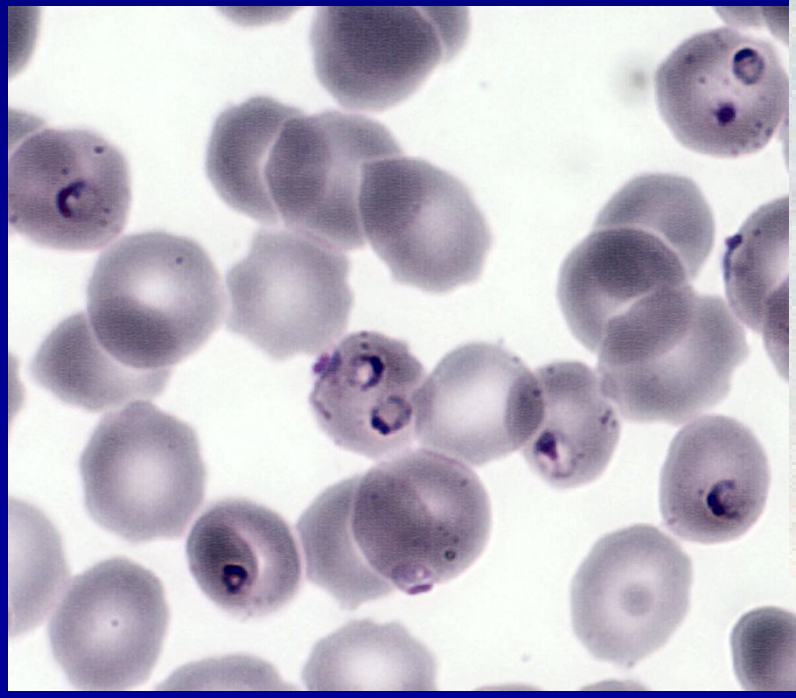
Fever

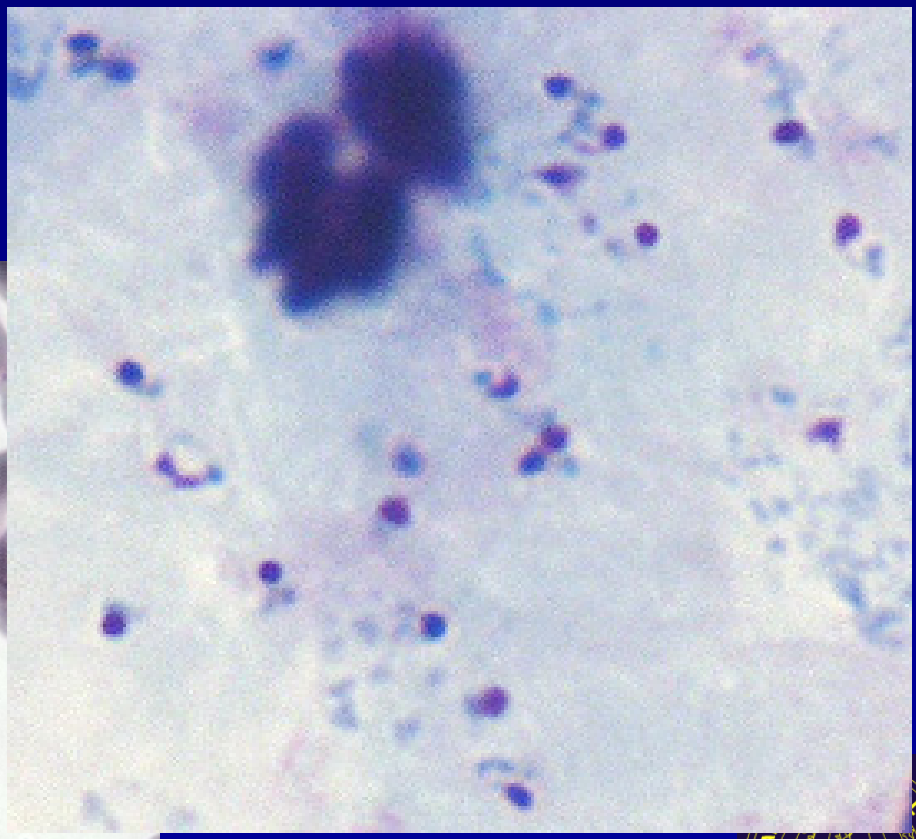
and / or

Rigors
Headache
Myalgia
N & V
Arthralgia

Dark Urine
Cough
Diarrhoea
Drowsiness
Confusion

Diagnosis – blood films





Diagnosis – Rapid Diagnostic Tests

Classification – severe disease

Any one of

- Neurological dysfunction
- Severe anaemia
- Acidosis
- Renal failure
- Hypoglycaemia
- ARDS/pulmonary oedema
- Bleeding/DIC
- ‘Blackwater fever’
- Shock
- Parasitaemia >10%
- (2% or peripheral schizonts for IV)
- (Pregnancy)
- (Elderly)

Treatment – severe disease

Artesunate

- Survival advantage over quinine

Quinine

- Remains the mainstay of treatment in Africa

Second agent in all cases (ACT, doxycycline, clindamycin)

No patient should wait untreated for artesunate

General management

Liaise with specialist centres early

Avoid over-filling

Monitor blood glucose (2hrly during infusion)

Broad spectrum antibiotics if shock/other evidence of bacterial infection

Appropriate level of care

Pitfalls

‘I lived there/had malaria before, I’m immune’

‘I thought he had flu/gastroenteritis/hepatitis/meningitis’

‘He was in for a broken leg’

‘We were waiting for quinine/artesunate/a monitored bed…’

Elderly

Non-severe Pf (UK)

Artemether-lumefantrine

DHA-piperaquine

Atovaquone-proguanill

Oral quinine sulphate for 5-7 days **plus** doxycycline or clindamycin for 7 days

P. vivax & P. ovale:

P. vivax - Asia, South America

P. ovale - West & Central Africa

P. ovale curtisi

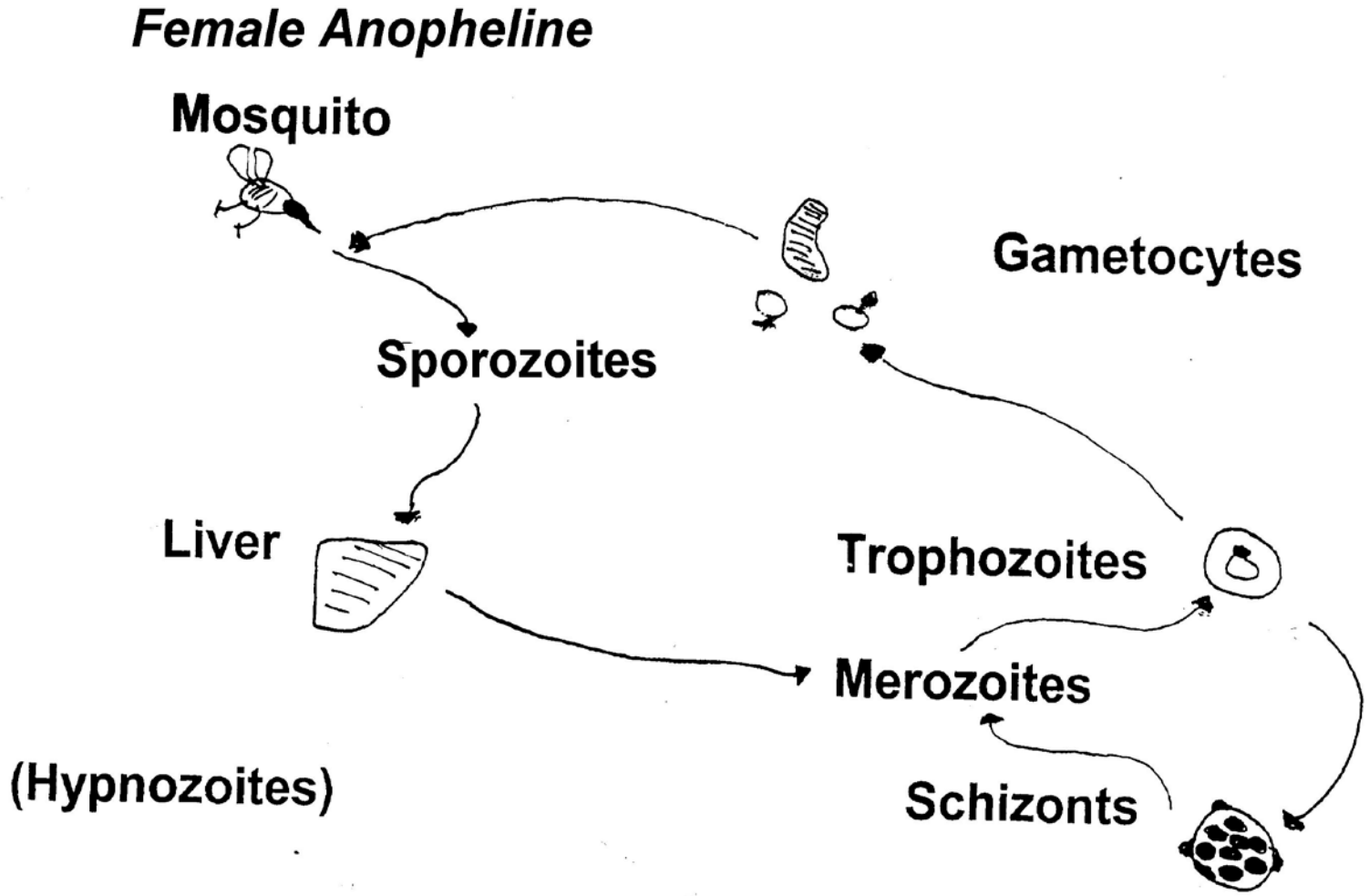
P. ovale wallikeri

Benign disease - parasitaemia never > 2%

Relapsing malaria

Hypnozoites - dormant liver stage

Malaria: life cycle



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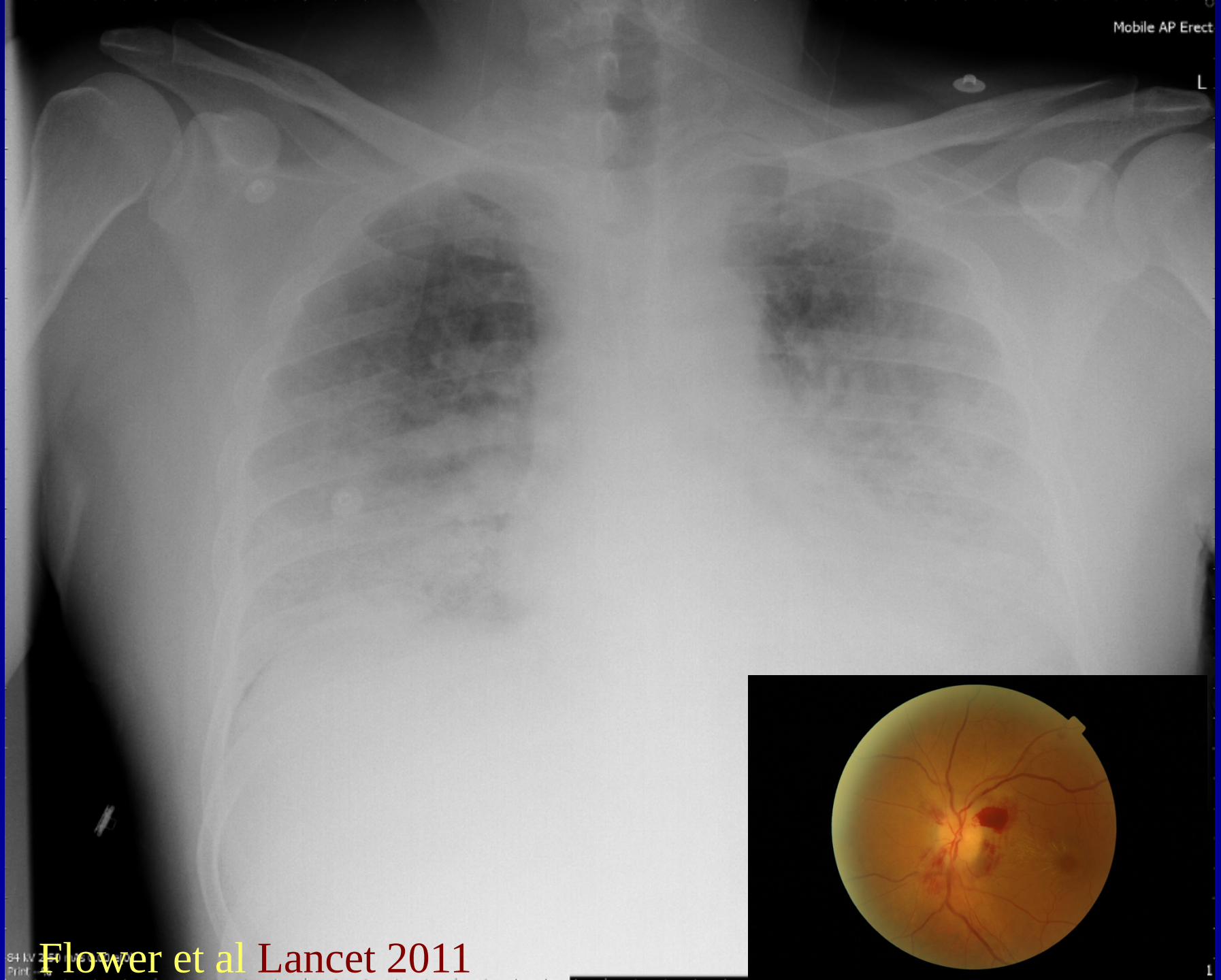
Hypnozoites – responsible for relapses



Flower et al Lancet 2011

P. malariae:

Least common

Never causes severe disease

May persist for decades

Rare cause of nephrotic syndrome

P. knowlesi

Borneo & SE Asia

Zoonosis (macaques)

24 hour erythrocytic cycle

Can cause severe disease

Treatment of benign malaria:

P. vivax & ovale:

Chloroquine + Primaquine (hypnozoites)

(Primaquine causes haemolysis with G6PD)

P. malariae & P. knowlesi

Chloroquine alone

…….but anything will do

Case

32 year old man

No previous medical history

Fever, lethargy, dyspnoea, ankle swelling

4 months backpacking in Togo, West Africa

Jarvis et al. Lancet 2013

Case

Episode of malaria diagnosed in Togo 15d ago

Hb 130g/L

Artemether IM x 3days plus 3 days DHA-PQ

Symptomatic response

Case

2 days later

Fever, dyspnoea, ankle swelling

Hb 110g/L

3 days deterioration

Hb dropped to 70g/L

IV Ofloxacin + PO Doxycycline

Evacuated to HTD

Case

On Arrival

38.5C

Tachycardic, jaundiced, pale, hepato-splenomegaly

Brown urine

Hb 41g/L WCC 4.2×10^9/L Plt 112×10^9/L

Haemoglobinuria on dip

Case

↑ reticulocytes, ↑ bilirubin, ↑LDH
↓ Haptoglobin

Malaria HRP2 test pos, malaria slides neg

No haemoglobinopathy, normal G6PD

Direct coombs test negative

Normal Iron, B12, Folate

Case

Full infection screen negative

Bone marrow – erythroid hyperplasia

No auto-antibodies/agglutinins etc

PET scan unremarkable

Case

Diagnosis –

Post artemisinin delayed haemolysis

4 blood transfusions over 6 days

Haemolysis spontaneously resolved

Jarvis et al. Lancet 2013

Post Artemisinin Delayed Haemolysis

- Now well described
- Occurs 7-14 days after parenteral artemisinin therapy
- Probably relates to pitting of erythrocytes infected with young rings stages
- However unclear why anaemia can be refractory to transfusion

http://www.mmv.org/sites/default/files/uploads/docs/events/2013/InjectableArtesunateExpertGroupMeeting.pdf

Post Artemisinin Delayed Haemolysis

Implications:

Lifesaving benefit outweighs risk

Consider check Hb 2 weeks post artesunate (UK guidance)

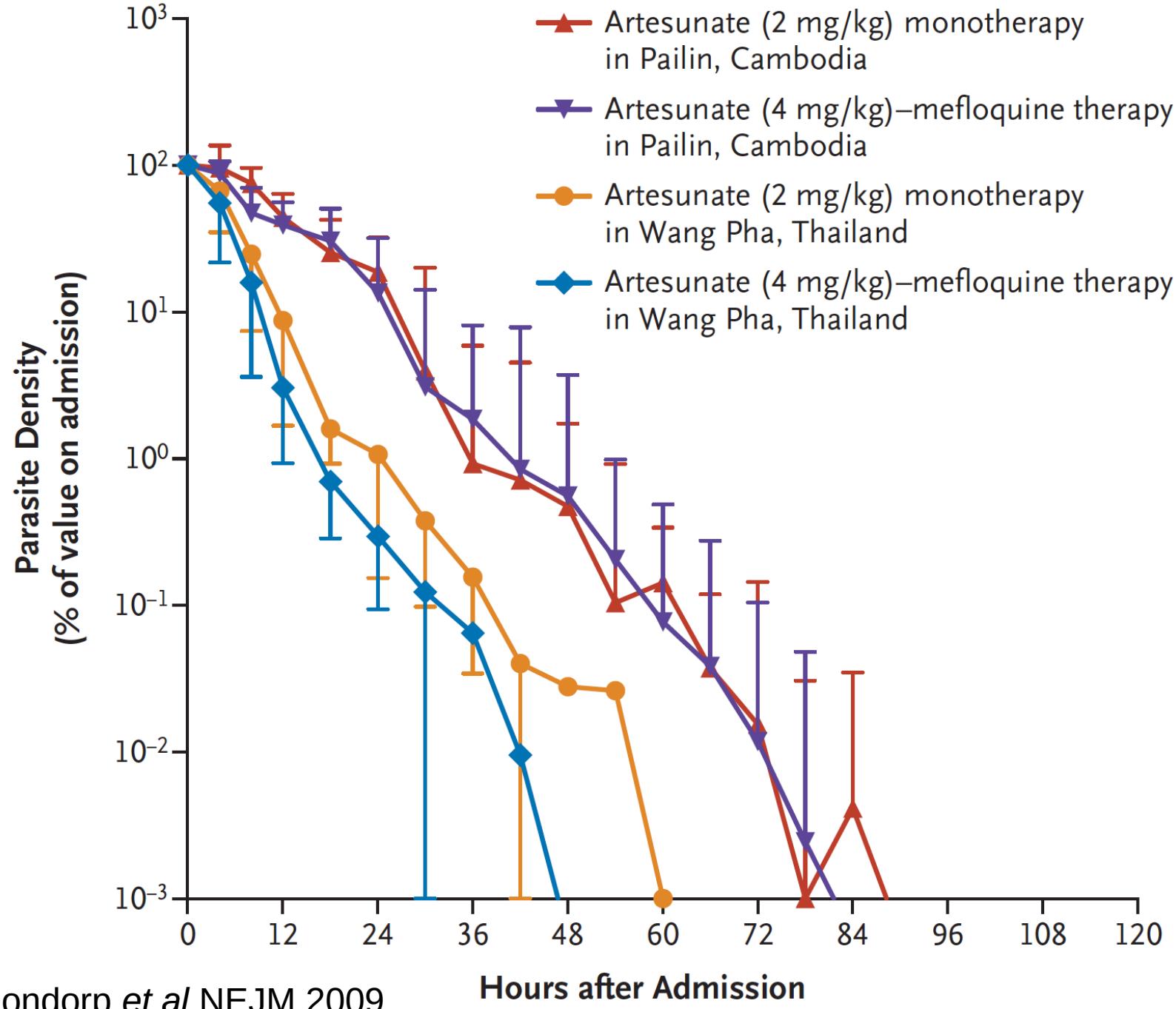
Artemisinin Resistance

Early Signs

28 day treatment success 79% in Eastern Thailand (2003)

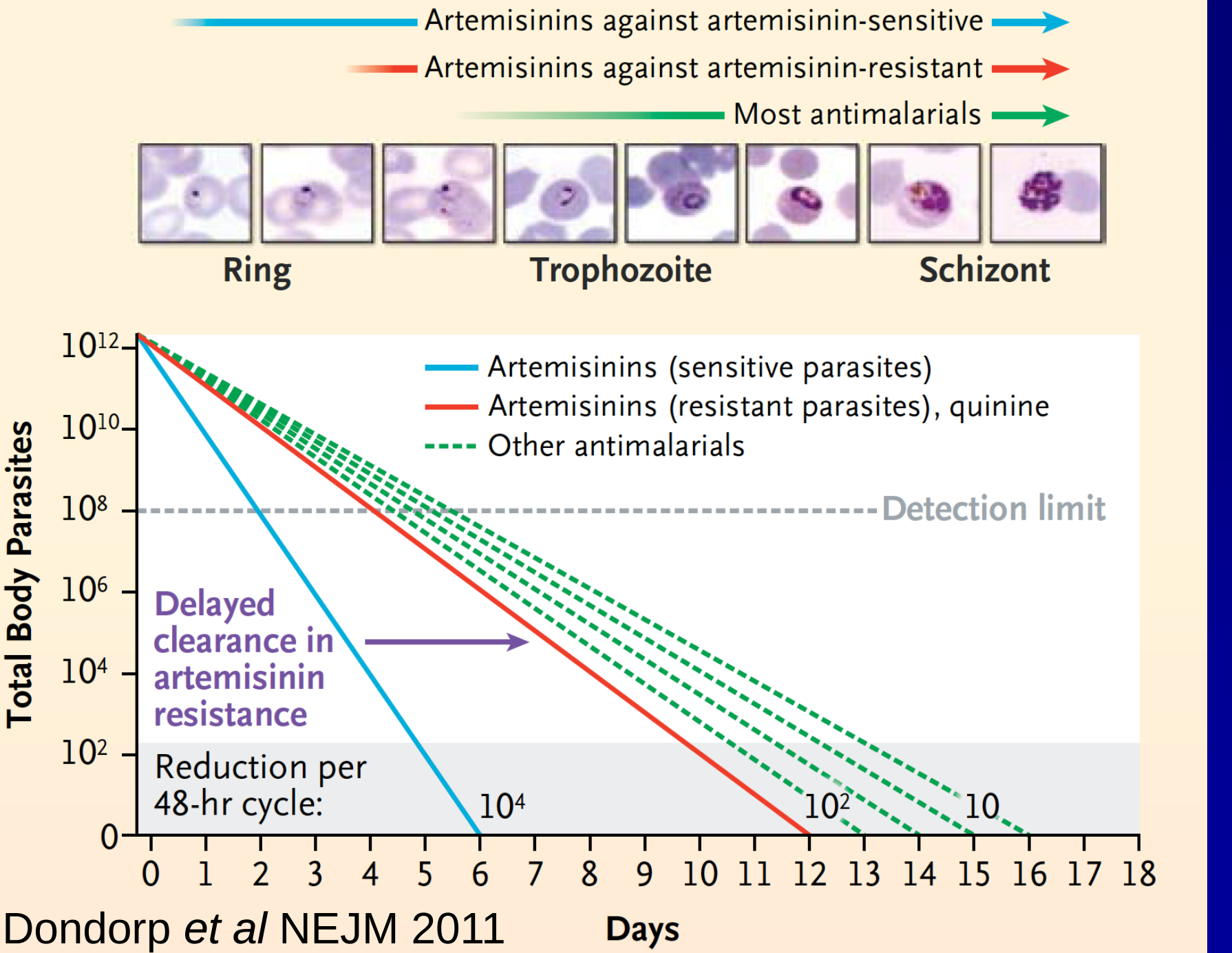
Similar reports from Western Cambodia

Vijaykadga et al Trop Med Int Health 2006
Denis et al Trop Med Int Health 2006



Dondorp *et al* NEJM 2009

Image Credit: BBC News



Dondorp *et al* NEJM 2011

Artemisinin Resistance

Difficult to track

- Required clinical studies
- Refined by quantitative PCR
- Possibility of genetic markers
- *Kelch* protein on Chromosome 13
  - K13-propellor mutations
- Currently confined to SEA

Artemisinin Resistance

Implications

- Severe malaria
  - Few
- Non-severe malaria
  - Longer course of ACT?
  - TACT (Triple ACT – DHAP-MQ)?
  - New drugs…

New Drugs

Cipargamin (KAE 609)

Tafenoquine

Cipargamin

Under development by Novartis

Completed Phase 2 studies in Thailand

Very rapid clearance of Pf & Pv infections

No safety issues as yet

White et al NEJM 2014:371 (5)

Tafenoquine

Under development by GSK

Single dose treatment of hypnozoites

Similar problems as primaquine

Undergoing phase 3 trials

Any Questions?