Global Health aspects of

Malaria 2019

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MacLean Centre for Tropical Diseases
McGill University

DISCLOSURES

I have received in-kind research support from *BD Molecular Diagnostics and bioMerieux* for work on enteric infections in the Arctic.

Learning objectives

1. Understand the burden of malaria disease
2. Be familiar with key clinical and biological aspects of human malaria
3. **Know the main tools used for malaria control programs**
4. Know how malaria burden can be measured
5. **Understand trends in global malaria epidemiology**
6. **Understand key barriers to malaria control (and elimination)**

Outline

1. Some history and biology
2. Disease in individuals
3. Tool for malaria control
4. Where are we at in 2019?
5. Urgent threats to control (and elimination)
6. Endgame thought (?)

Outline

1. **Some history and biology**
2. Disease in individuals
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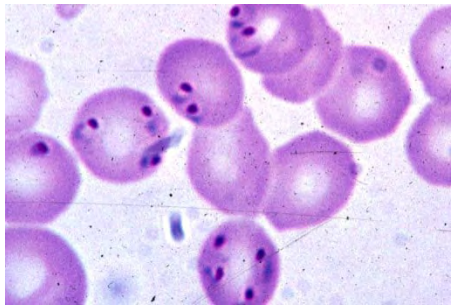
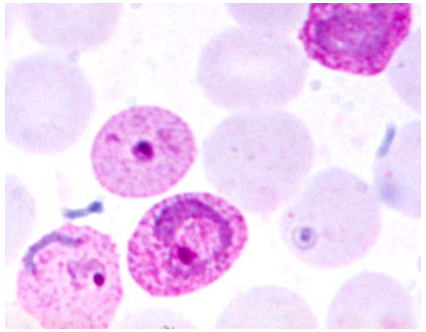
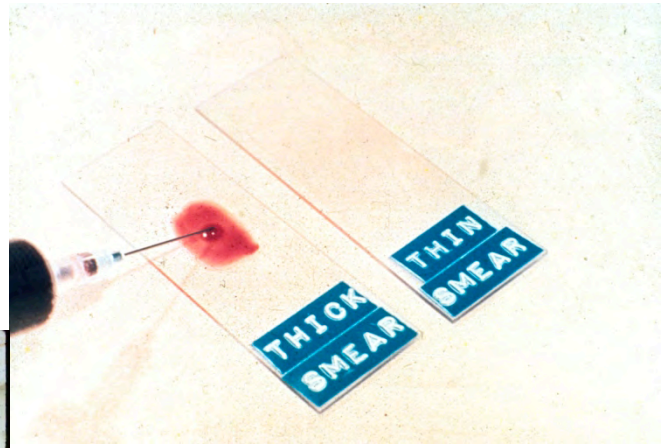
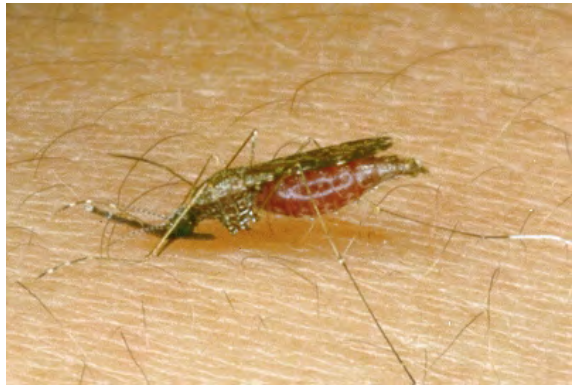
Some history and biology

malaria basics









Yangon, Myanmar; ca. 1986

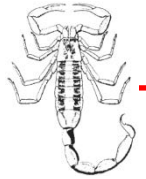
Some history and biology

malaria basics

- Parasite of human RBCs
- THE parasitic killer of human beings
  - 700,000 – 1.1 million deaths/year (>2000/day)
  - 216 million cases in 2010
- 90% of deaths in sub-Saharan Africa
- Transmitted by *Anopheles* mosquitoes

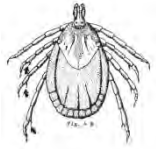
Put another way:

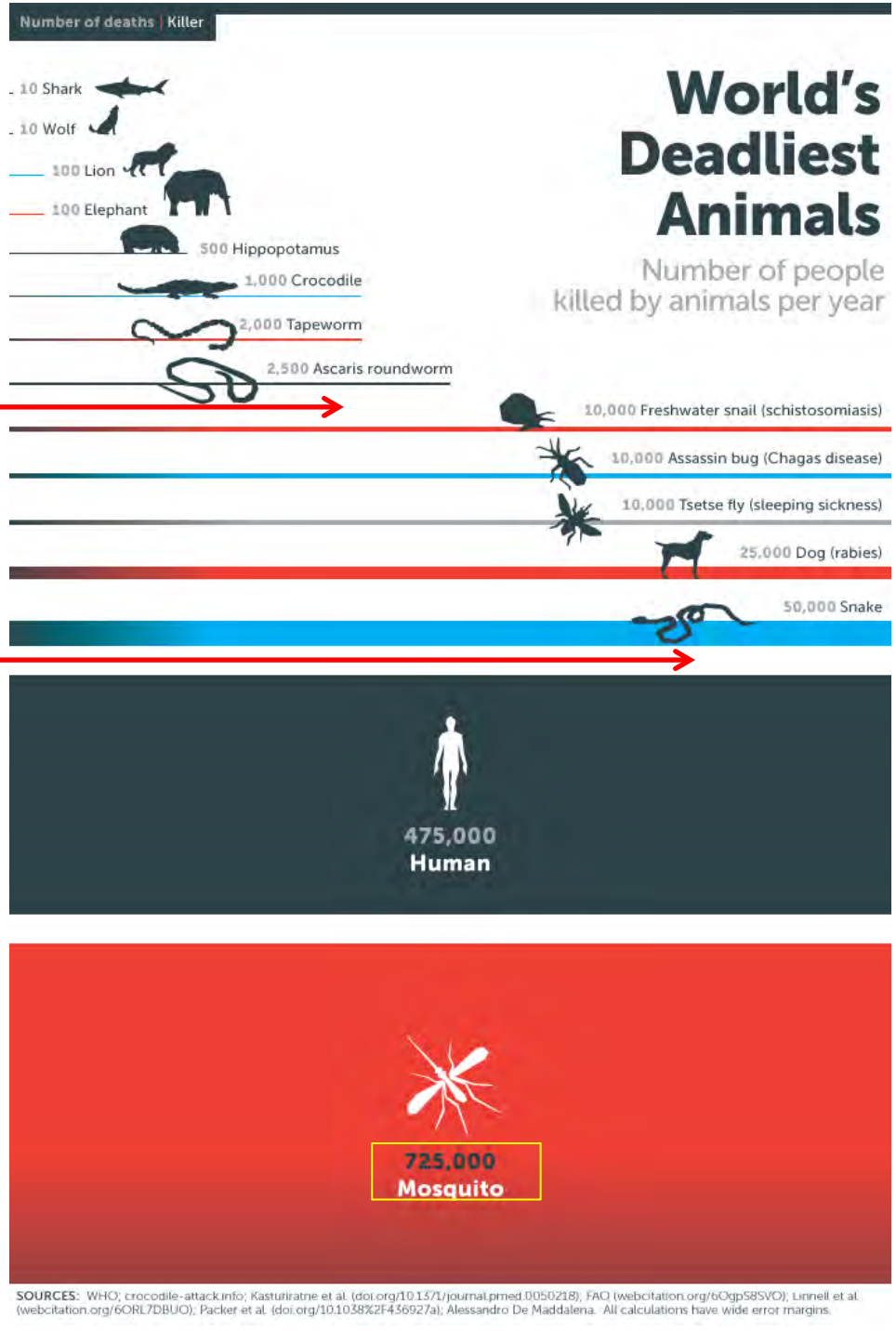
Scorpion
3,200



Sandfly
>60,000

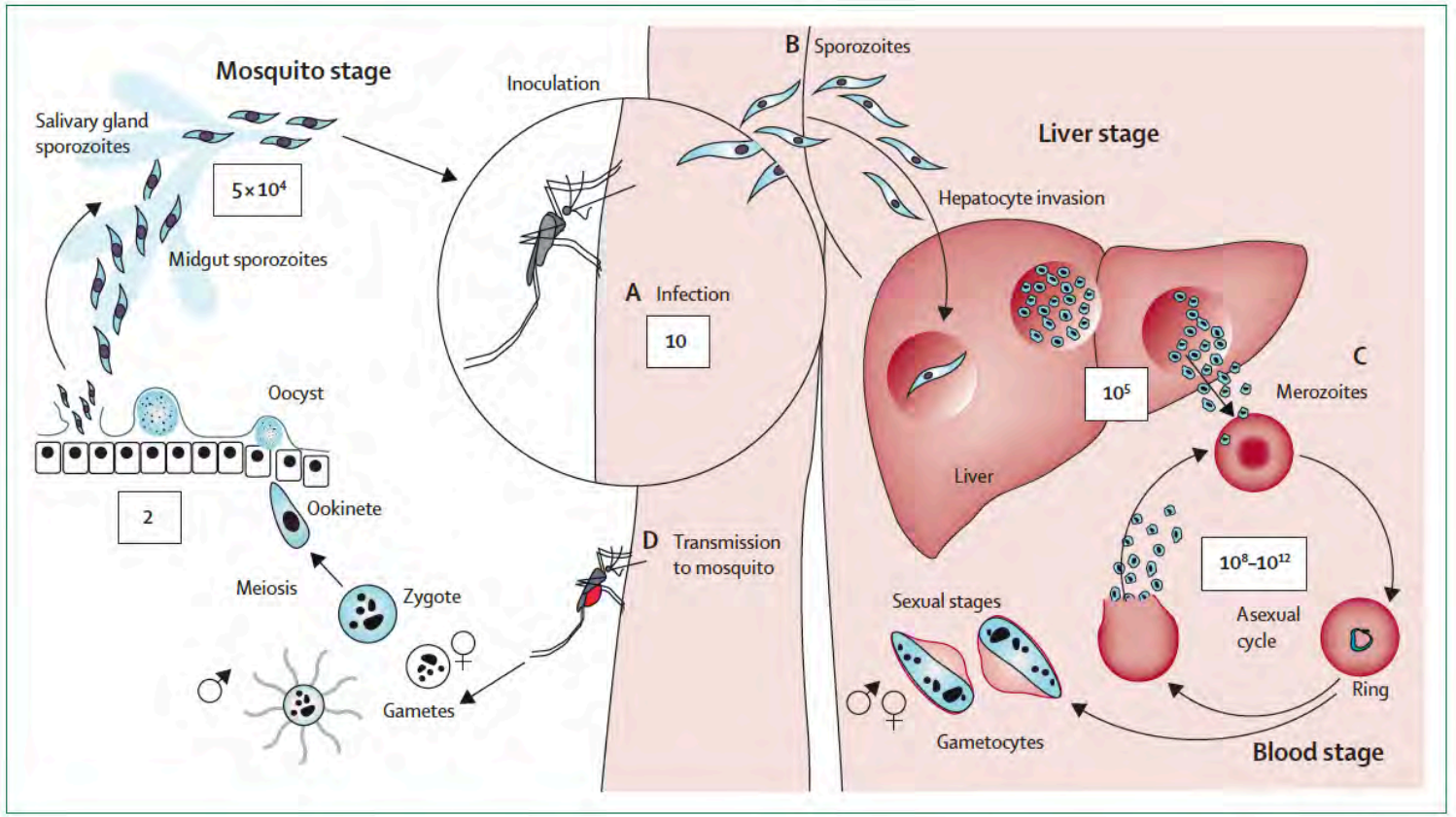
Tick
(?)





Anopheles mosquito – eg MALARIA

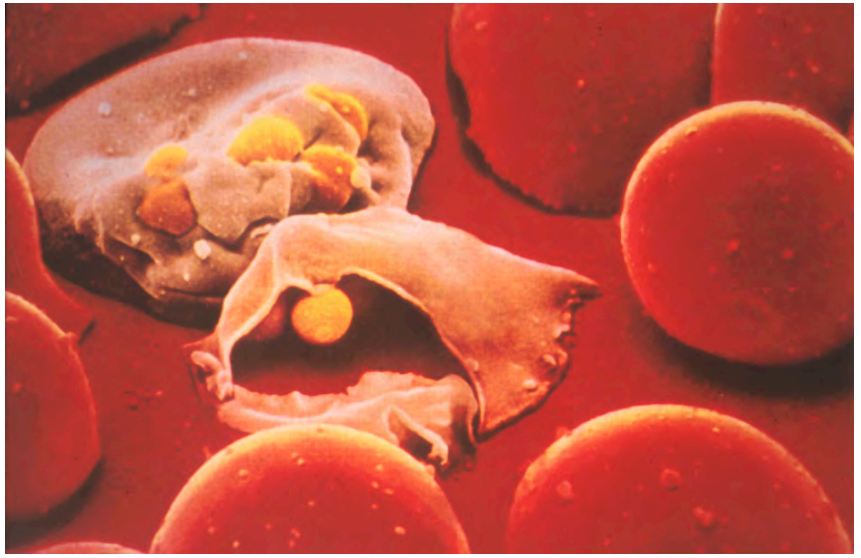
life-cycle



Lancet 2014; 383: 723–35

Some history and biology

the vector

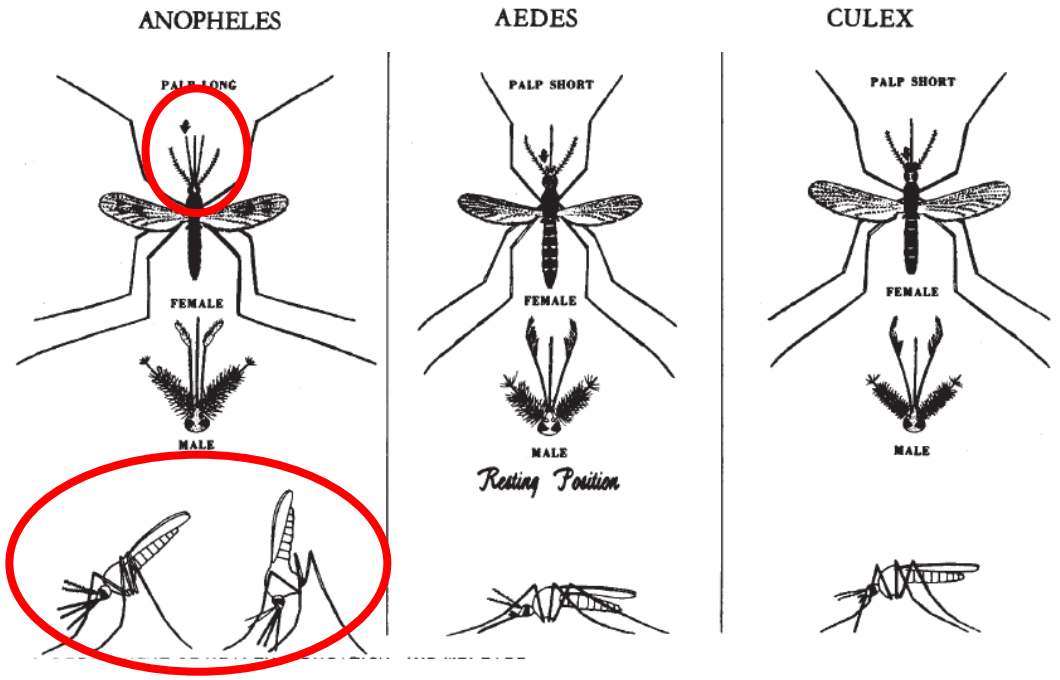


- *Plasmodium falciparum*
- *Plasmodium vivax*
- *Plasmodium ovale*
- *Plasmodium malariae*
- *Plasmodium knowlesi*

Some history and biology

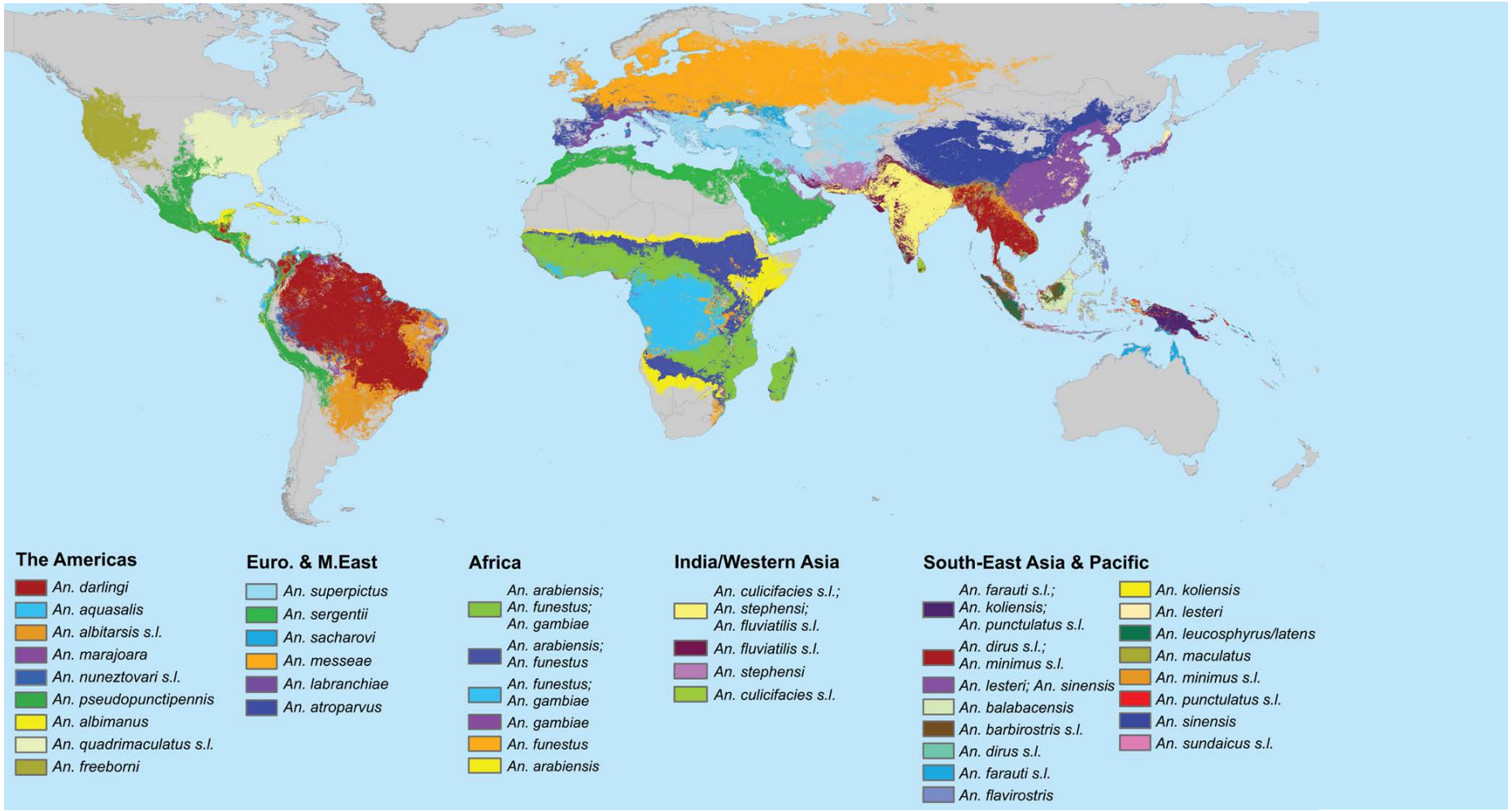
the vector

- Bite dusk to dawn
- Only females
- Inactive below 18°
- Altitude sensitive
- **DEET** and **picaridin** are the ONLY effective repellents
- Permethrin-treated clothes/nets/curtains
- Don’t like cities*



Some history and biology

global map of dominant malaria vectors



Some history and biology

where falciparum *malaria occurred in 19th C*

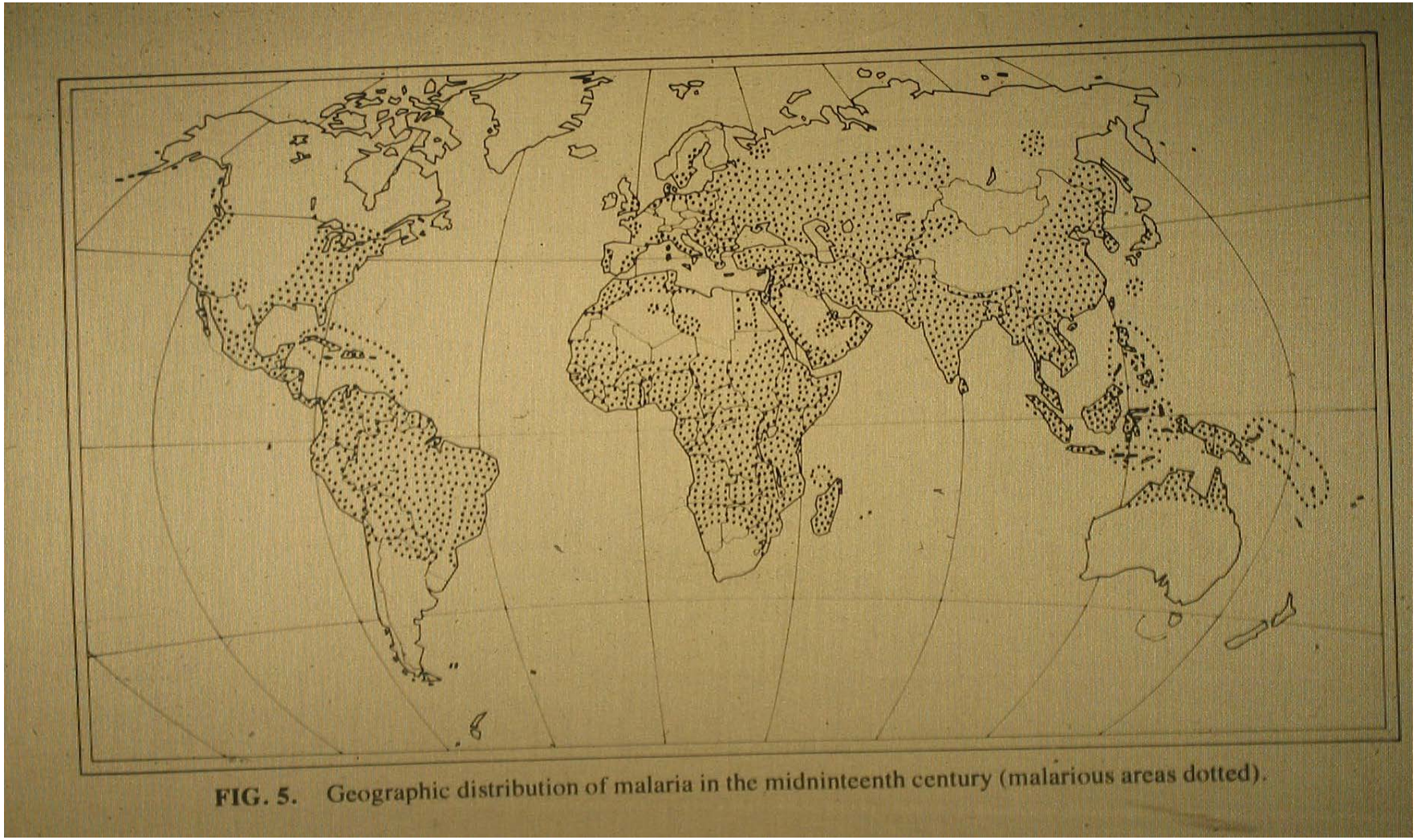
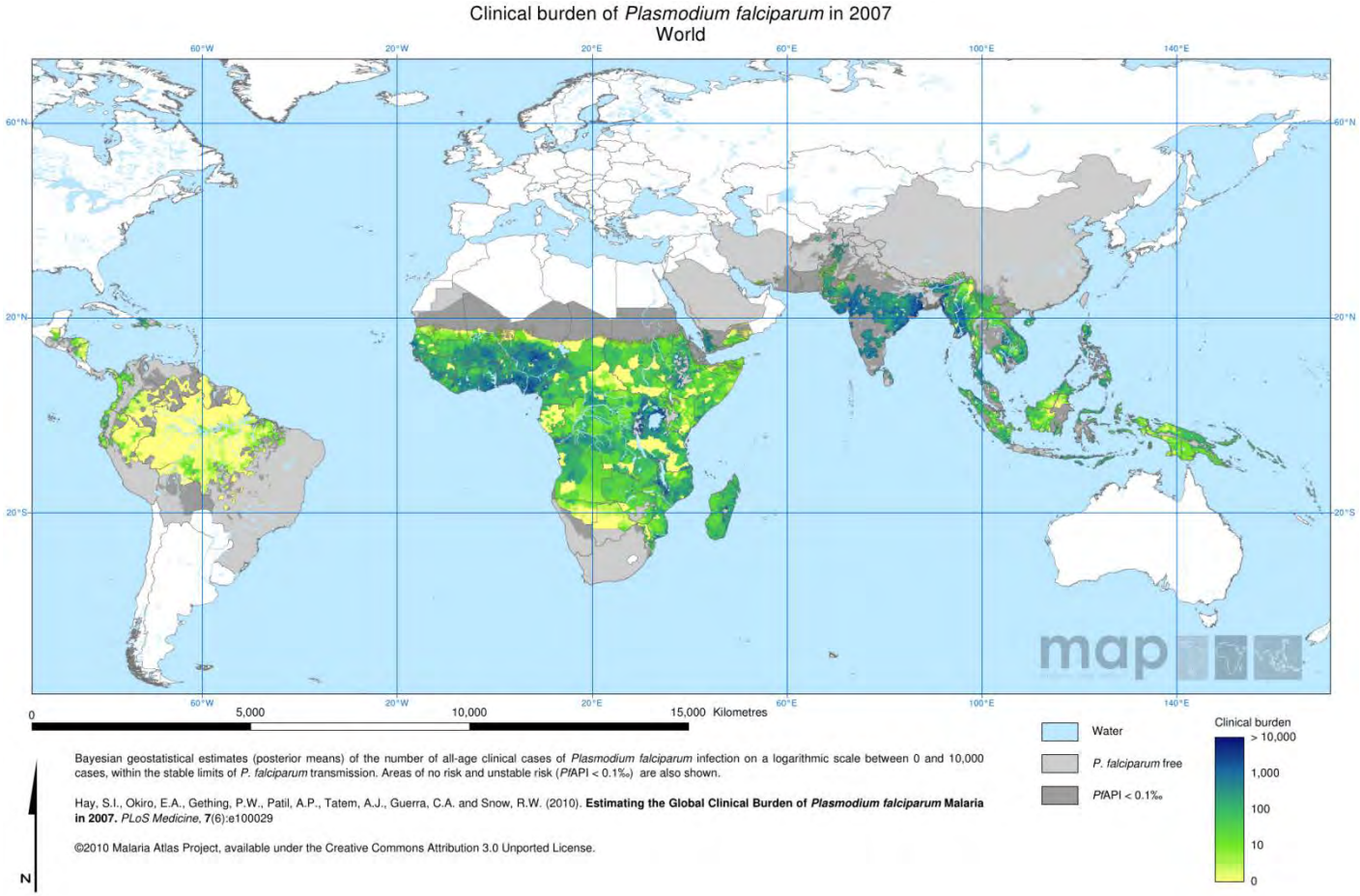


FIG. 5. Geographic distribution of malaria in the midninteenth century (malarious areas dotted).

Some history and biology

where falciparum *malaria occurs now*

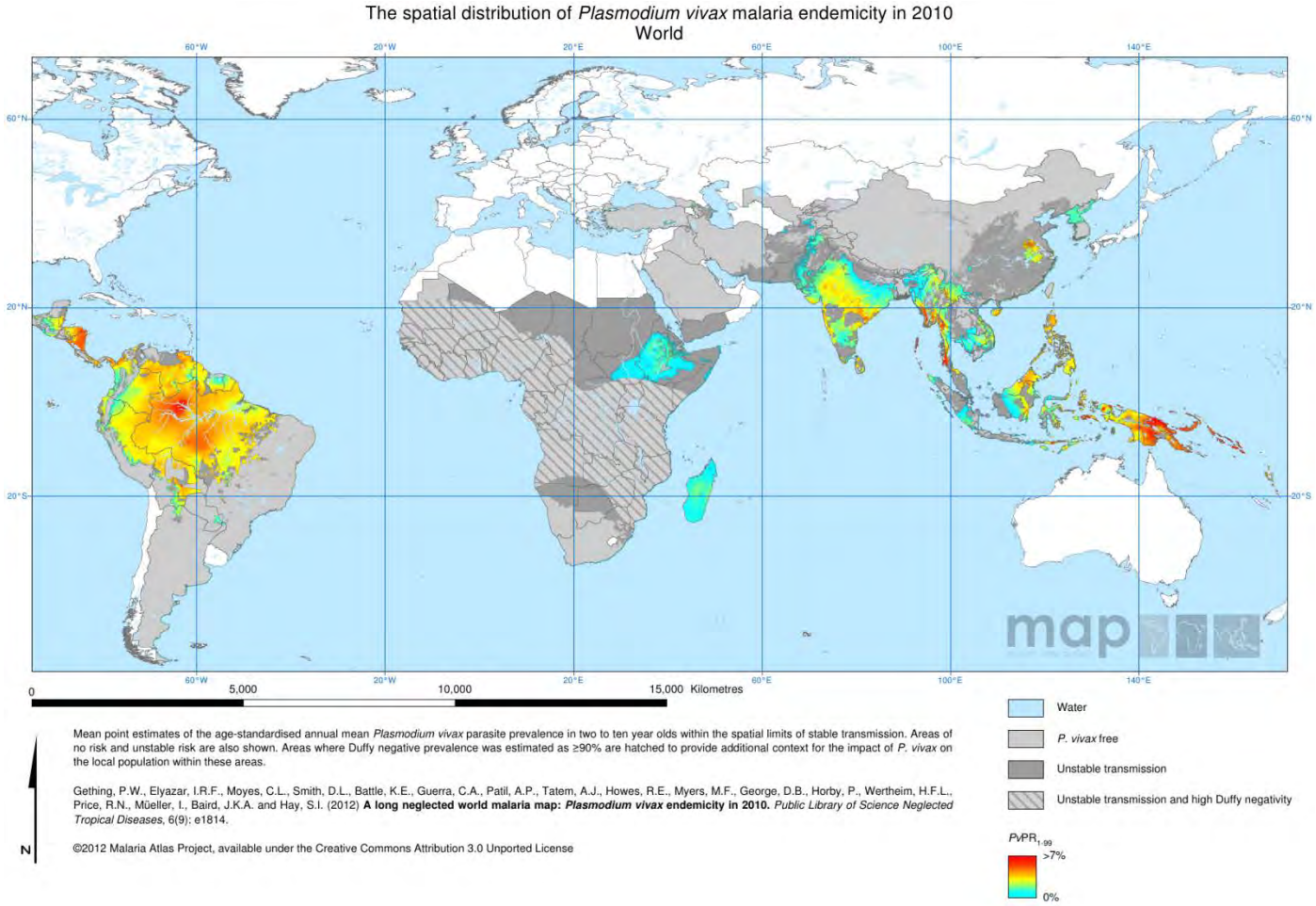


Bayesian geostatistical estimates (posterior means) of the number of all-age clinical cases of *Plasmodium falciparum* infection on a logarithmic scale between 0 and 10,000 cases, within the stable limits of *P. falciparum* transmission. Areas of no risk and unstable risk (*Pf*API < 0.1‰) are also shown.

Hay, S.I., Okiro, E.A., Gething, P.W., Patil, A.P., Tatem, A.J., Guerra, C.A. and Snow, R.W. (2010). **Estimating the Global Clinical Burden of *Plasmodium falciparum* Malaria in 2007.** *PLoS Medicine*, **7**(6):e100029

Some history and biology

where vivax *malaria occurs*



Mean point estimates of the age-standardised annual mean *Plasmodium vivax* parasite prevalence in two to ten year olds within the spatial limits of stable transmission. Areas of no risk and unstable risk are also shown. Areas where Duffy negative prevalence was estimated as ≥90% are hatched to provide additional context for the impact of *P. vivax* on the local population within these areas.

Gething, P.W., Elyazar, I.R.F., Moyes, C.L., Smith, D.L., Battle, K.E., Guerra, C.A., Patil, A.P., Tatem, A.J., Howes, R.E., Myers, M.F., George, D.B., Horby, P., Wertheim, H.F.L., Price, R.N., Müeller, I., Baird, J.K.A. and Hay, S.I. (2012) **A long neglected world malaria map: *Plasmodium vivax* endemicity in 2010.** *Public Library of Science Neglected Tropical Diseases*, 6(9): e1814.

Some history and biology

malaria is an old nemesis of humans

"Malaria is the strongest known force for evolutionary selection in the recent history of the human genome"

Am. J. Hum. Genet. 77:171–192, 2005

REVIEW ARTICLE

How Malaria Has Affected the Human Genome and What Human Genetics Can Teach Us about Malaria

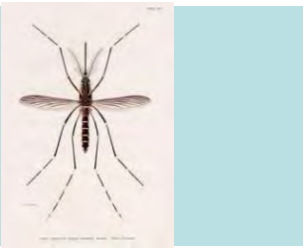
Dominic P. Kwiatkowski

Wellcome Trust Centre for Human Genetics and University Department of Paediatrics, Oxford, United Kingdom

Am. J. Hum. Genet. 77:171–192, 2005

Common Erythrocyte Variants That Affect Resistance to Malaria

Gene	Protein	Function	Reported Genetic Associations with Malaria
FY	Duffy antigen	Chemokine receptor	FY*O allele completely protects against *P. vivax* infection.
G6PD	Glucose-6-phosphatase dehydogenase	Enzyme that protects against oxidative stress	G6PD deficiency protects against severe malaria.
GYPA	Glycophorin A	Sialoglycoprotein	GYPA-deficient erythrocytes are resistant to invasion by *P. falciparum*.
GYPB	Glycophorin B	Sialoglycoprotein	GYPB-deficient erythrocytes are resistant to invasion by *P. falciparum*.
GYPC	Glycophorin C	Sialoglycoprotein	GYPC-deficient erythrocytes are resistant to invasion by *P. falciparum*.
HBA	α-Globin	Component of hemoglobin	α^+ Thalassemia protects against severe malaria but appears to enhance mild malaria episodes in some environments.
HBB	β-Globin	Component of hemoglobin	HbS and HbC alleles protect against severe malaria. HbE allele reduces parasite invasion.
HP	Haptoglobin	Hemoglobin-binding protein present in plasma (not erythrocyte)	Haptoglobin 1-1 genotype is associated with susceptibility to severe malaria in Sudan and Ghana.
SCL4A1	CD233, erythrocyte band 3 protein	Chloride/bicarbonate exchanger	Deletion causes ovalocytosis but protects against cerebral malaria.



Host Molecules That Mediate Cytoadherence by *P. falciparum*–Infected Erythrocytes and That Have Been Reported to Show Association with Resistance or Susceptibility to Malaria

Gene	Protein	Interaction with Parasitized Erythrocyte[a]	Reported Genetic Associations with Malaria
CD36	CD36 antigen, thrombospondin receptor	PE-binding receptor on endothelium and dendritic cells	*CD36* polymorphisms show variable associations with severe malaria in the Gambia, Kenya, and Thailand.
CR1	CR1, complement receptor 1	PE-binding receptor on erythrocytes	*CR1* polymorphisms show variable associations with severe malaria in the Gambia, Thailand, and Papua New Guinea.
ICAM1	CD54, intercellular adhesion molecule-1	PE-binding receptor on endothelium	*ICAM1* polymorphisms show variable associations with severe malaria in Kenya, Gabon, and the Gambia.
PECAM1	CD31, platelet-endothelial cell–adhesion molecule	PE-binding receptor on endothelium	*PECAM1* polymorphisms show variable associations with severe malaria in Thailand, Kenya, and Papua New Guinea.

[a] PE = parasitized erythrocyte.

Immune Genes Reported to Be Associated with Different Malaria Phenotypes

Gene	Protein	Function	Reported Genetic Associations with Malaria
FCGR2A	CD32, low affinity receptor for Fc fragment of IgG	Clearance of antigen-antibody complexes	Association with severe malaria in the Gambia
HLA-B	HLA-B, a component of MHC class I	Antigen presentation that leads to cytotoxic T cells	HLA-B53 association with severe malaria in the Gambia
HLA-DR	HLA-DR, a component of MHC class II	Antigen presentation that leads to antibody production	HLA-DRB1 association with severe malaria in the Gambia
IFNAR1	Interferon α receptor component	Cytokine receptor	Association with severe malaria in the Gambia
IFNG	Interferon γ	Cytokine with antiparasitic and proinflammatory properties	Weak associations with severe malaria in the Gambia
IFNGR1	Interferon γ receptor component	Cytokine receptor	Association with severe malaria in Mandinka people of the Gambia
IL1A/IL1B	Interleukin-1α and -1β	Proinflammatory cytokines	Marginal associations with severe malaria in the Gambia
IL10	Interleukin-10	Anti-inflammatory cytokine	Haplotypic association with severe malaria in the Gambia
IL12B	Interleukin-12 β subunit	Promotes development of Th1 cells	Association with severe malaria in Tanzania
IL4	Interleukin-4	Promotes antibody-producing B cells	Association with antimalarial antibody levels in Fulani people of Burkina Faso
MBL2	Mannose-binding protein	Activates classic complement	Association with severe malaria in Gabon
NOS2A	Inducible NO synthase	Generates NO, a free radical	Various associations with severe malaria in Gabon, the Gambia, and Tanzania
TNF	Tumor necrosis factor	Cytokine with antiparasitic and proinflammatory properties	Various associations with severe malaria and reinfection risk in the Gambia, Kenya, Gabon, and Sri Lanka
TNFSF5	CD40 ligand	T cell–B cell interactions leading to immunoglobulin class switching	Association with severe malaria in the Gambia

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Severe malaria: new insights

P. vivax
P. malariae
P. ovale

rendent malade mais ne tuent pas

P. falciparum →

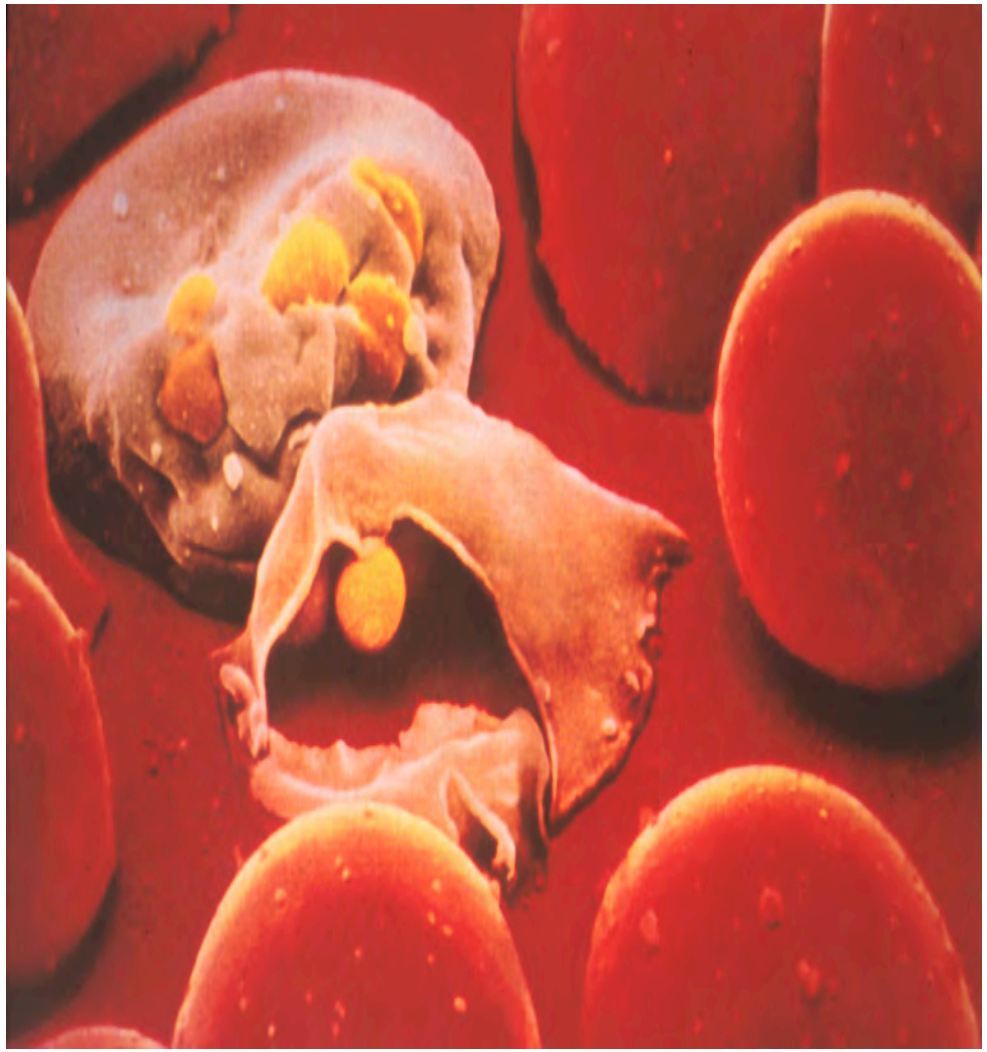
peut tuer (accès pernicieux)

(*P. vivax*)

(*P. knowlesi*)

Physiopathology severe malaria: *P. falciparum*

- Severe hemolysis



Severe malaria: hemolysis

- Anemia
- Jaundice
- Splenomegaly
- Thrombocytopenia (bleeding)
- Acute tubular necrosis

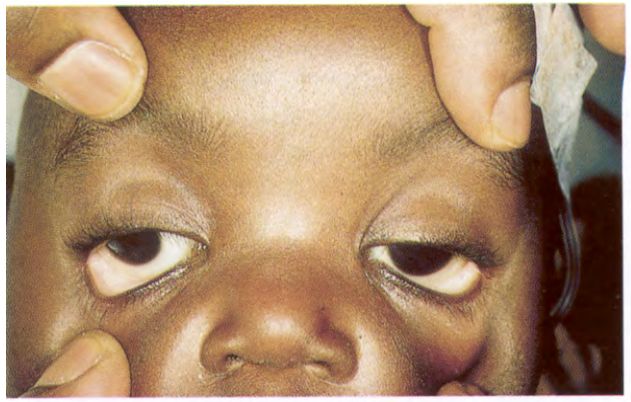


Plate 4 *Profound anaemia (haemoglobin 1.2 g/dL) in a young Kenyan boy with heavy* Plasmodium falciparum *parasitaemia. (Copyright DA Warrell.) See p*

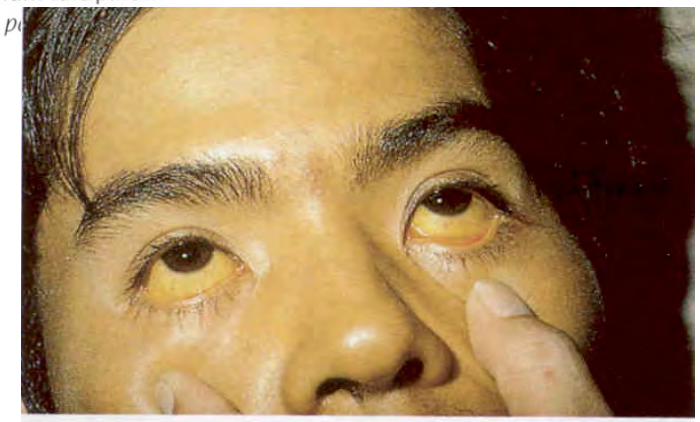


Plate 6 *Deep jaundice in a Vietnamese man with severe falciparum malaria. (Copyright DA Warrell.) See page 198.*

Physiopathology severe malaria: *P. falciparum*

- Severe hemolysis
- Sequestration

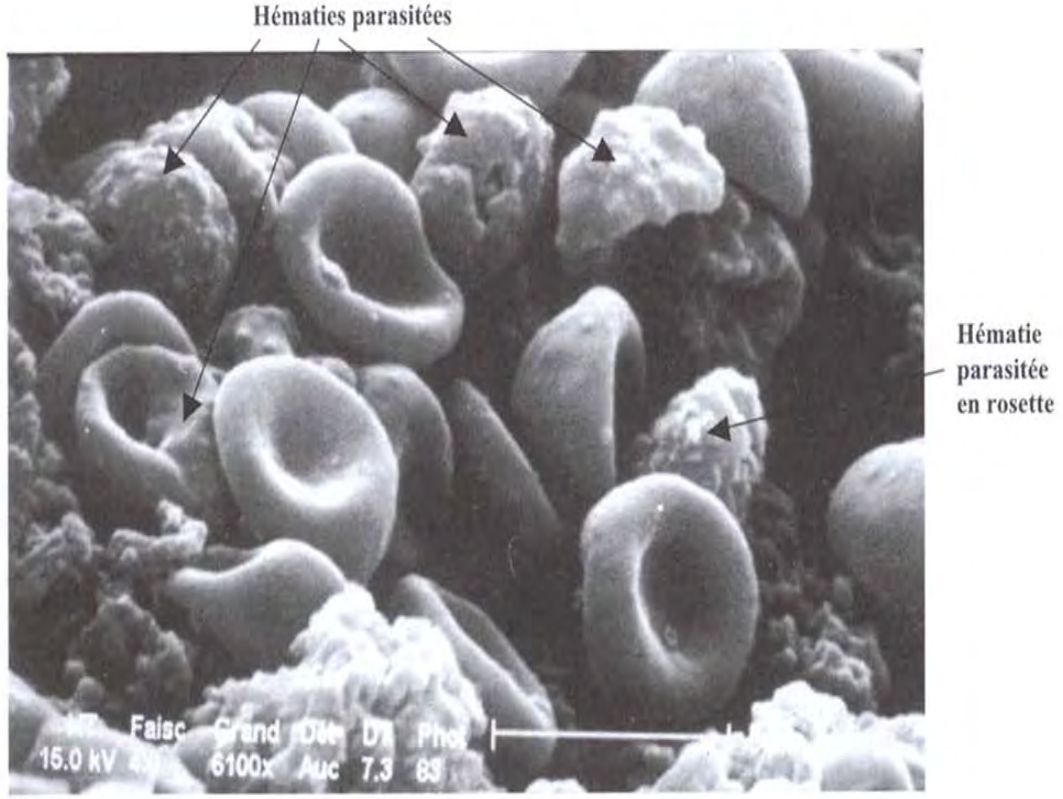
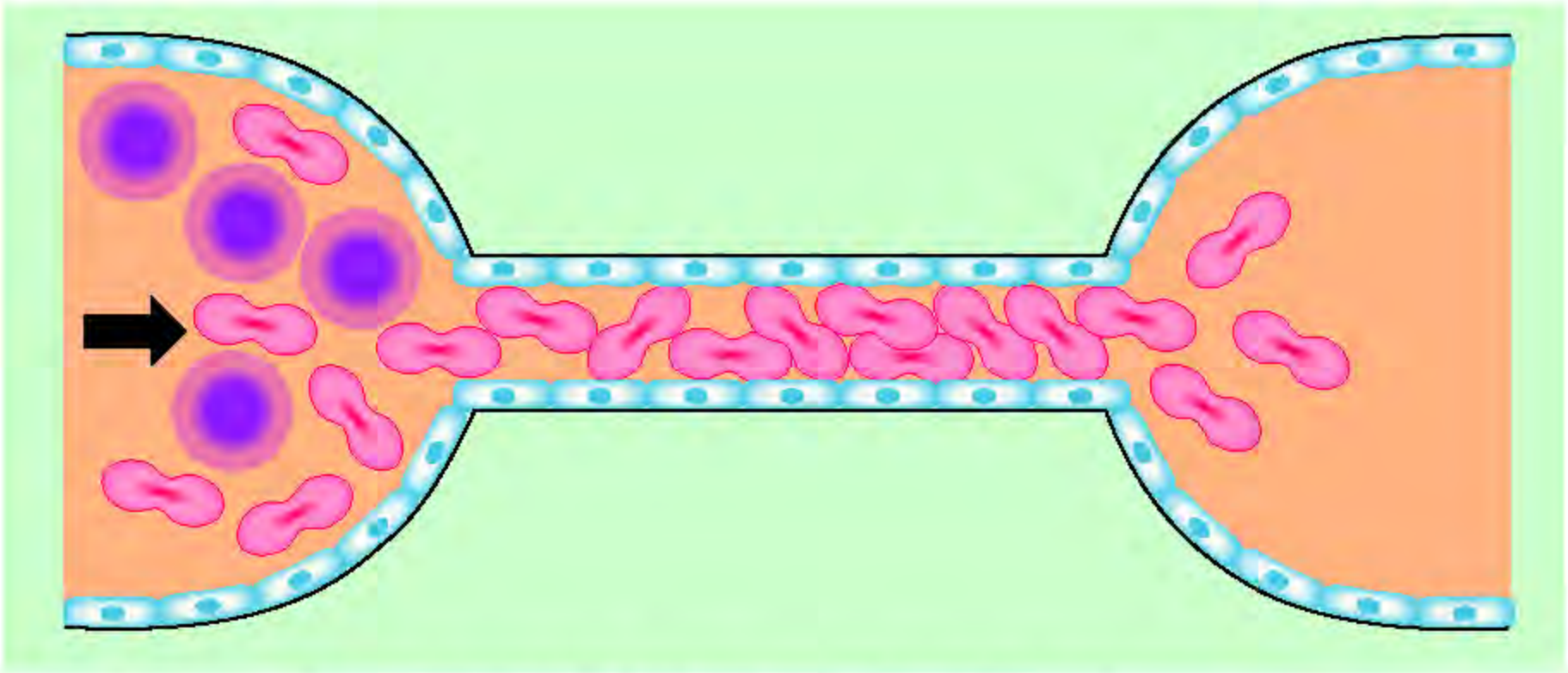


Fig. 1 – Séquestration d'hématies parasitées sur endothélium vasculaire et rosettes (Jurg Gysin, Unité de parasitologie expérimentale, URA IPP/Univ-Med/IMTSSA EA 3282, Faculté de médecine, Marseille, avec autorisation).

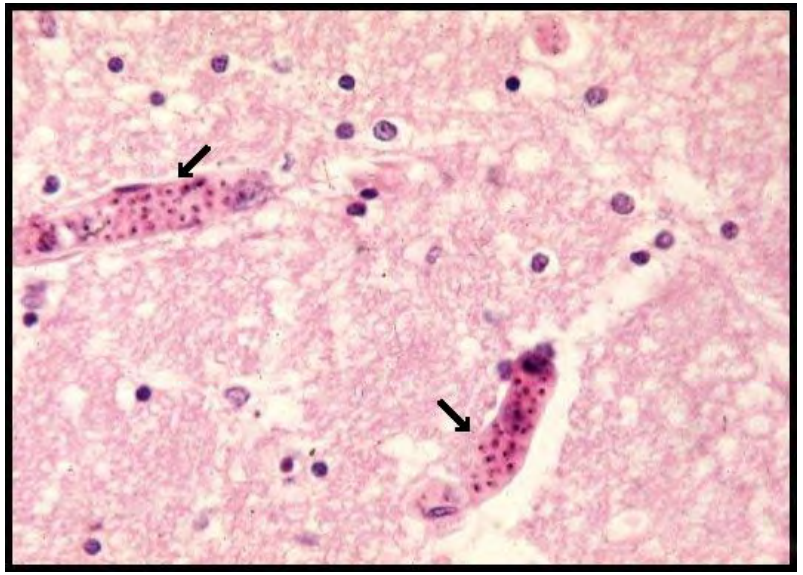


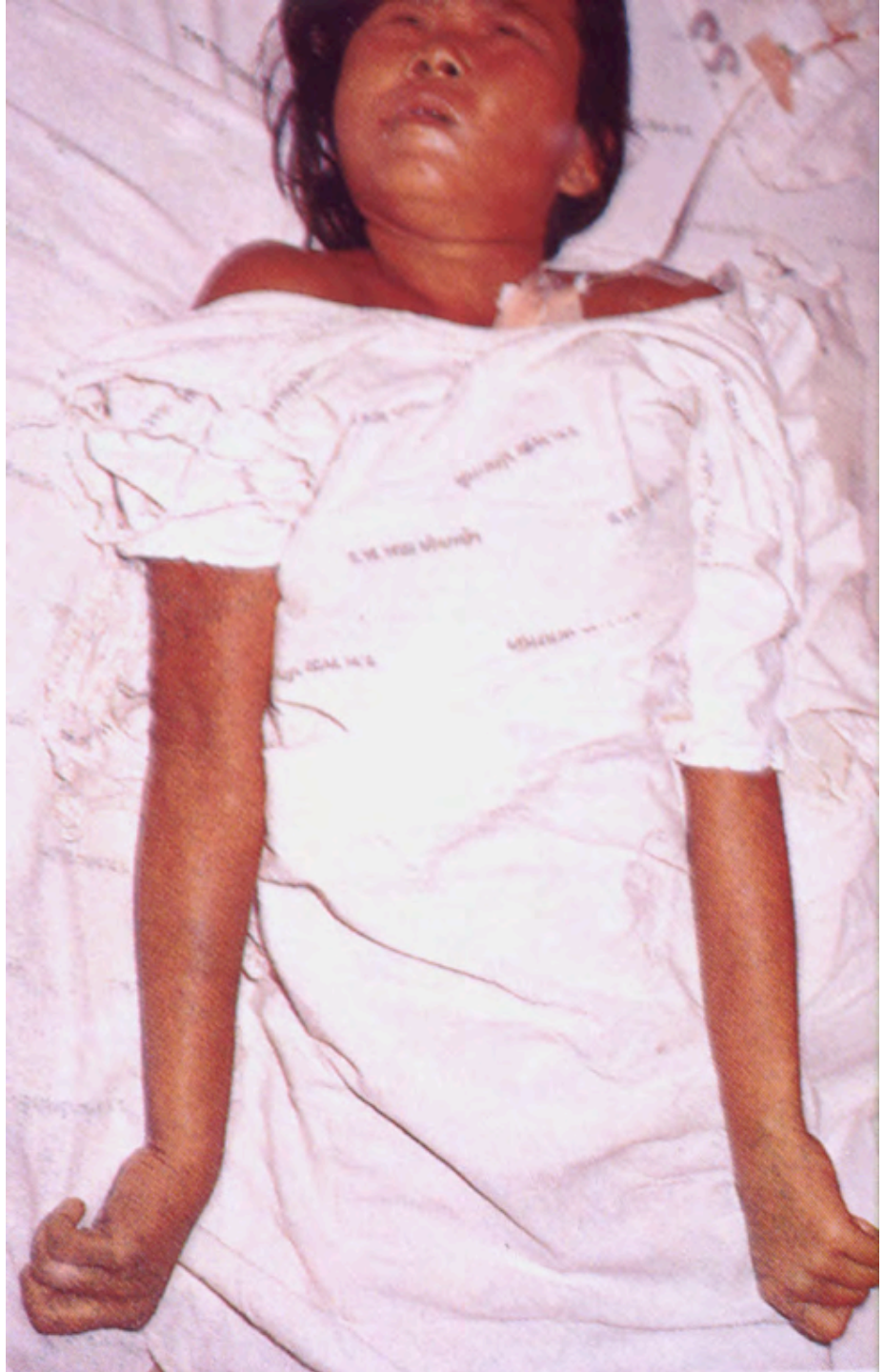
Representation of blood flow through microchannel

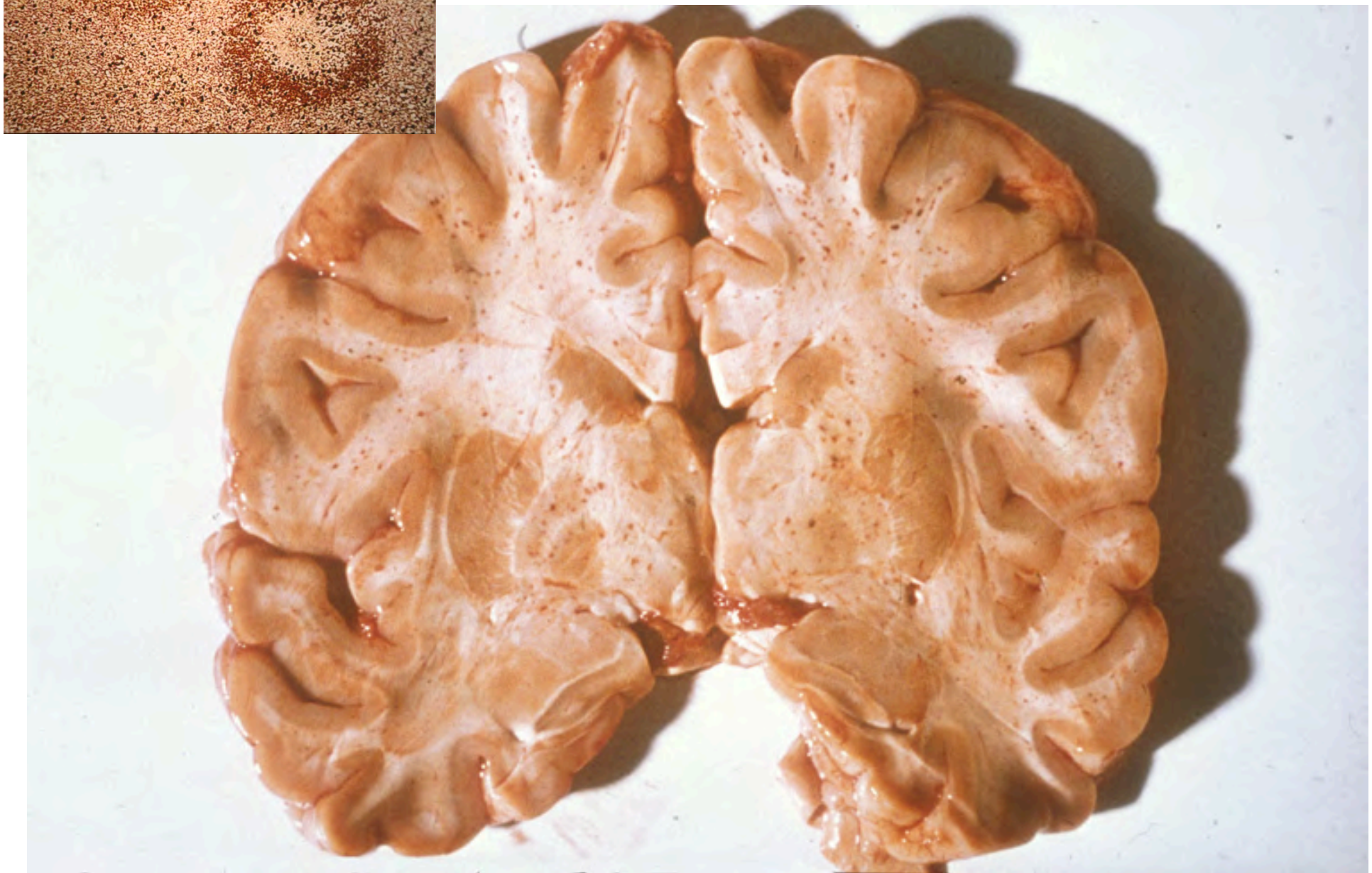
Although 8 μm in width, normal, uninfected erythrocytes are flexible enough to pass through central constriction of 2 μm diameter. By contrast, when infected with *P falciparum*, erythrocytes become spheroid and decreasingly deformable, such that, as shown, they block 6 μm constriction.

Sequestration: cerebral malaria

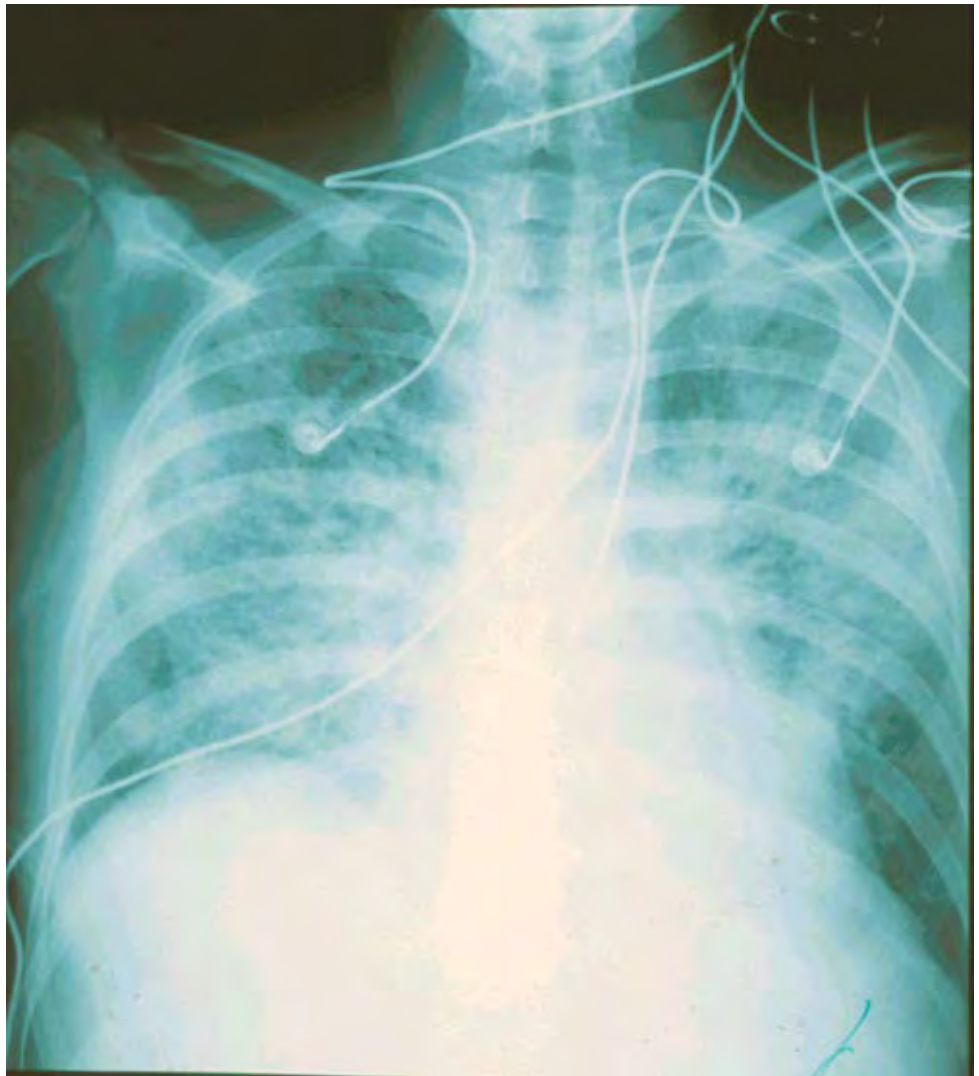
- Most important cause of death
- Obstruction microcirculation in brain
  - confusion, stupor, coma
  - convulsions
  - retina bleeding : bad prognosis
  - no neck stiffness, normal cerebrospinal fluid
  - 5-10% neurological sequellae







Sequestration: ARDS



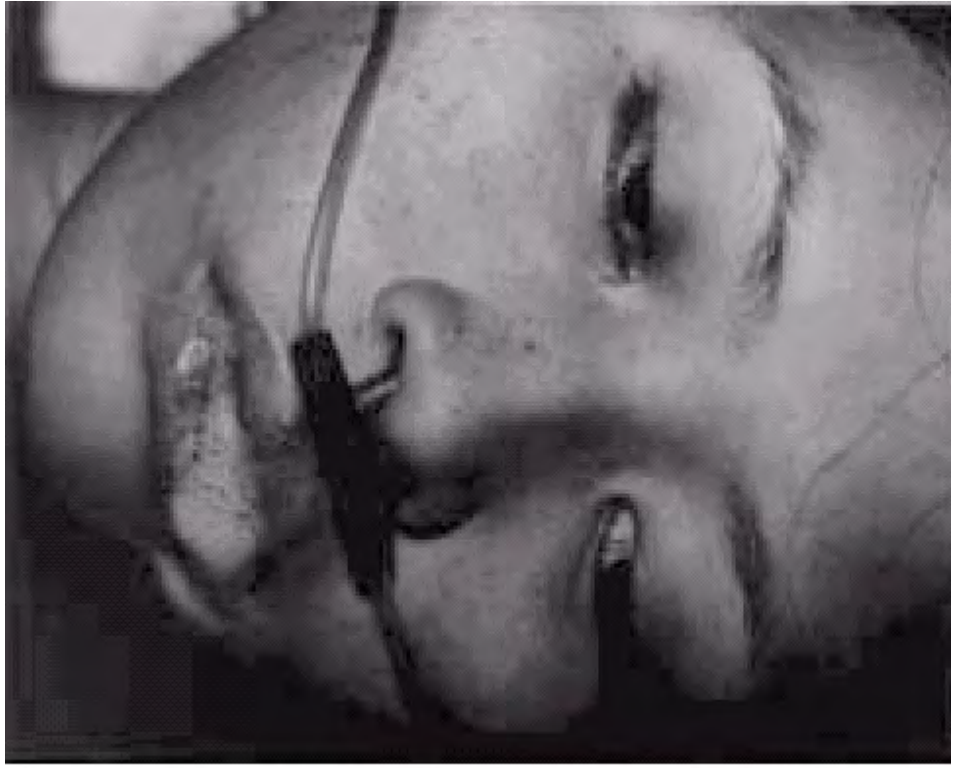


Fig. 13. **Acute pulmonary oedema developing immediately after delivery in a patient**

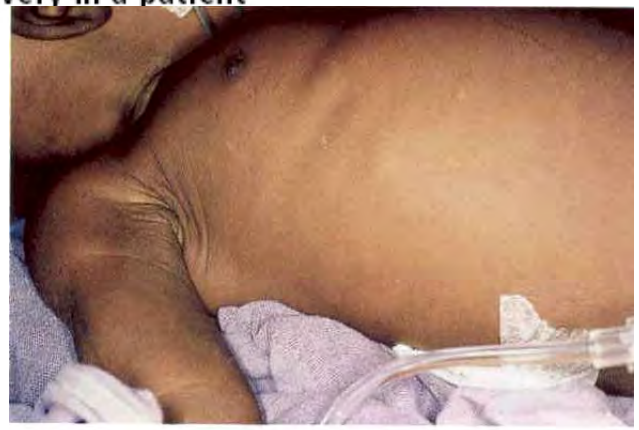
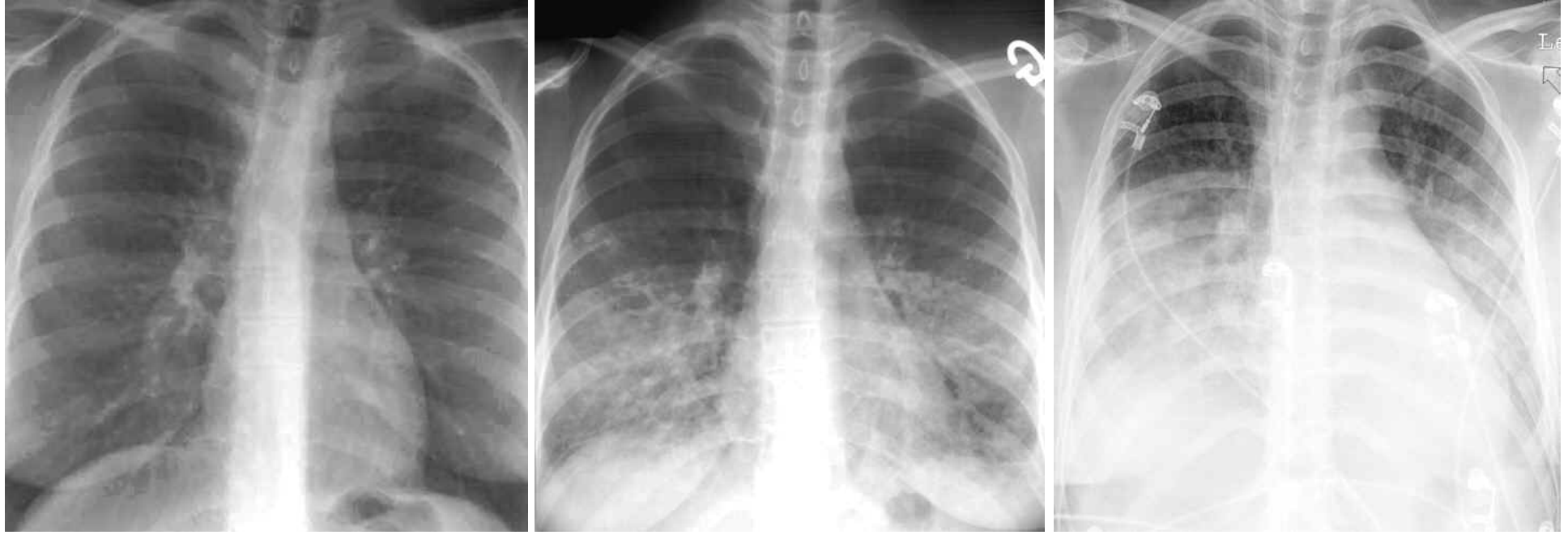
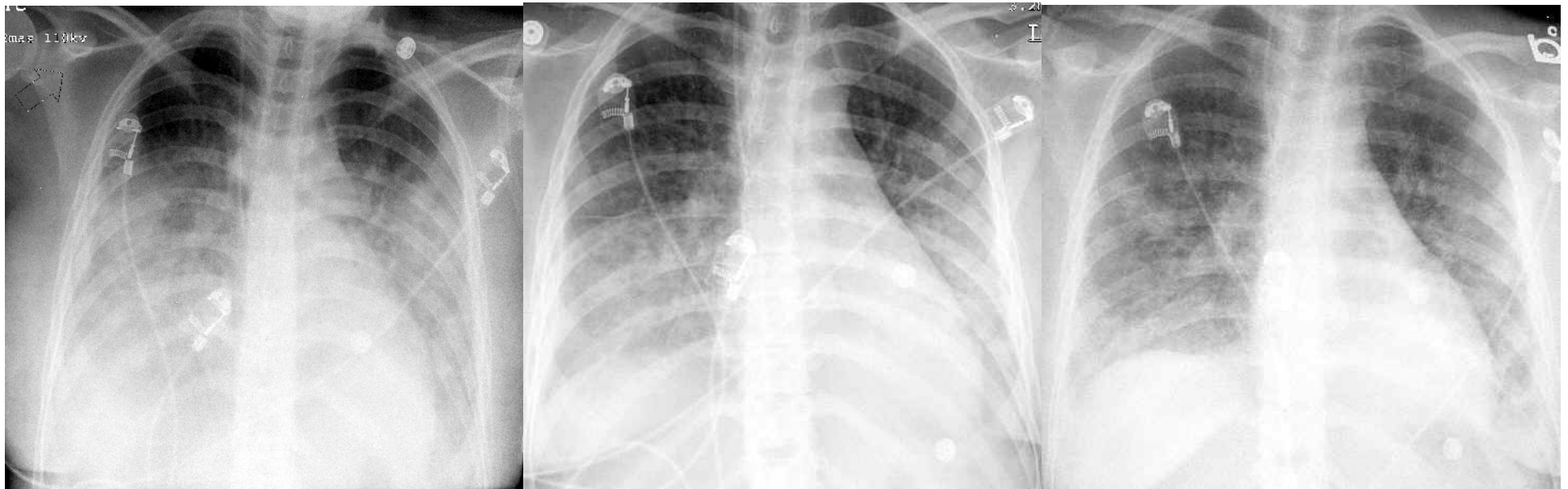


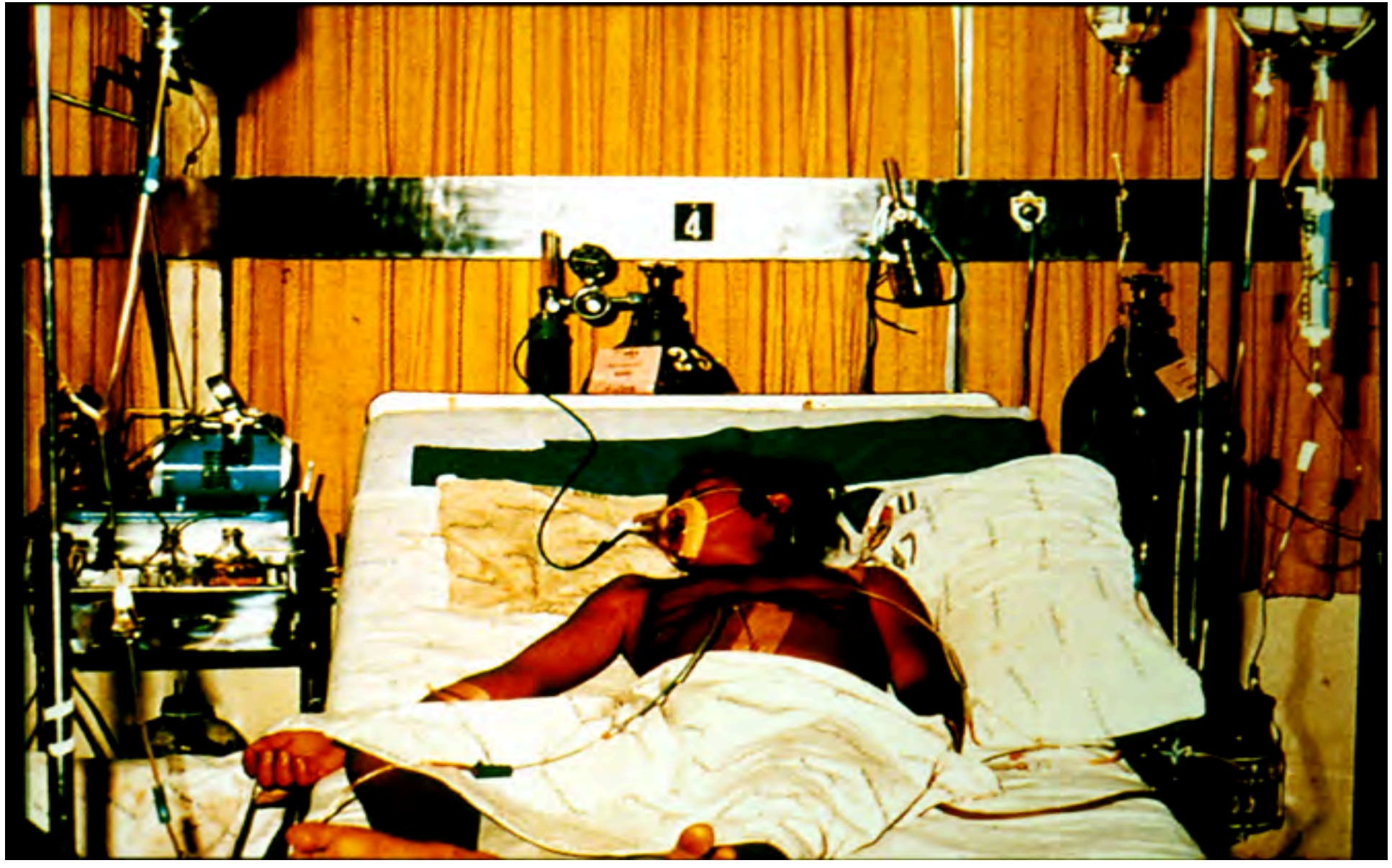
Plate 11 *Chest retraction (recession of the intercostal spaces) in a Kenyan child with respiratory distress associated with metabolic acidosis in severe malaria. (Copyright DA Warrell.) See page 212.*



ARDS in *P. falciparum* malaria Day 1 to 5

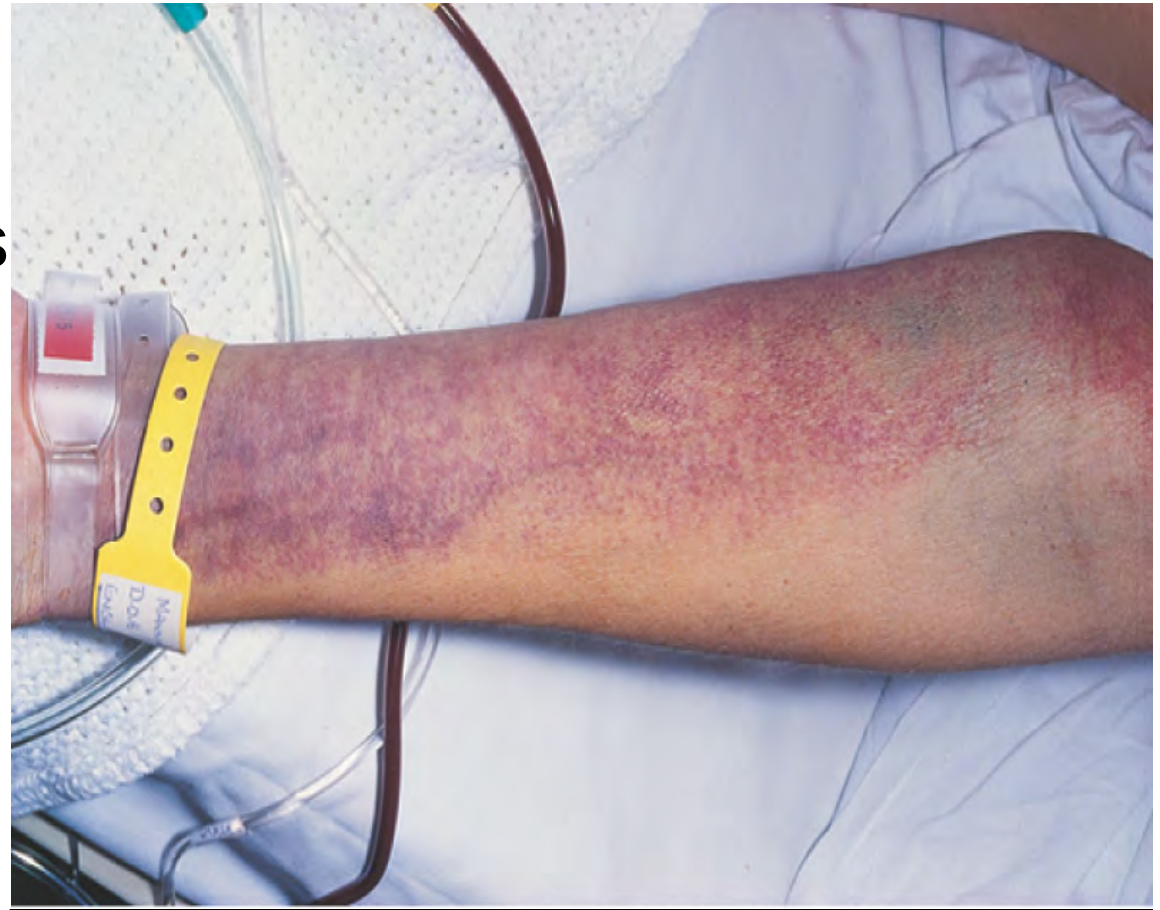


Sequestration: end-organ failure



Physiopathology severe malaria: *P. falciparum*

- Severe hemolysis
- Sequestration
- Sepsis

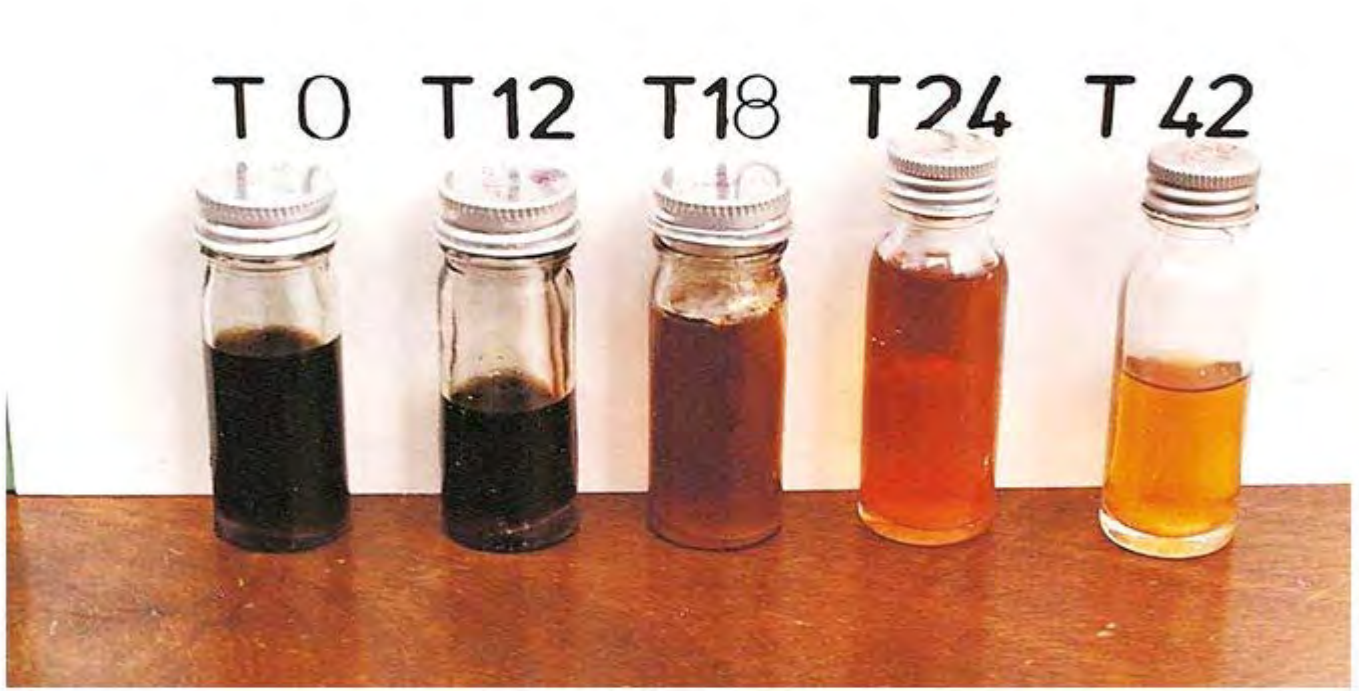


Severe malaria DIC

Severe malaria: Black water fever

5% RBC parasitized by *P. falciparum*

G6PD 28 days later was very low.



N Engl J Med 2008

Disease in individuals

complications according to age and endemicity

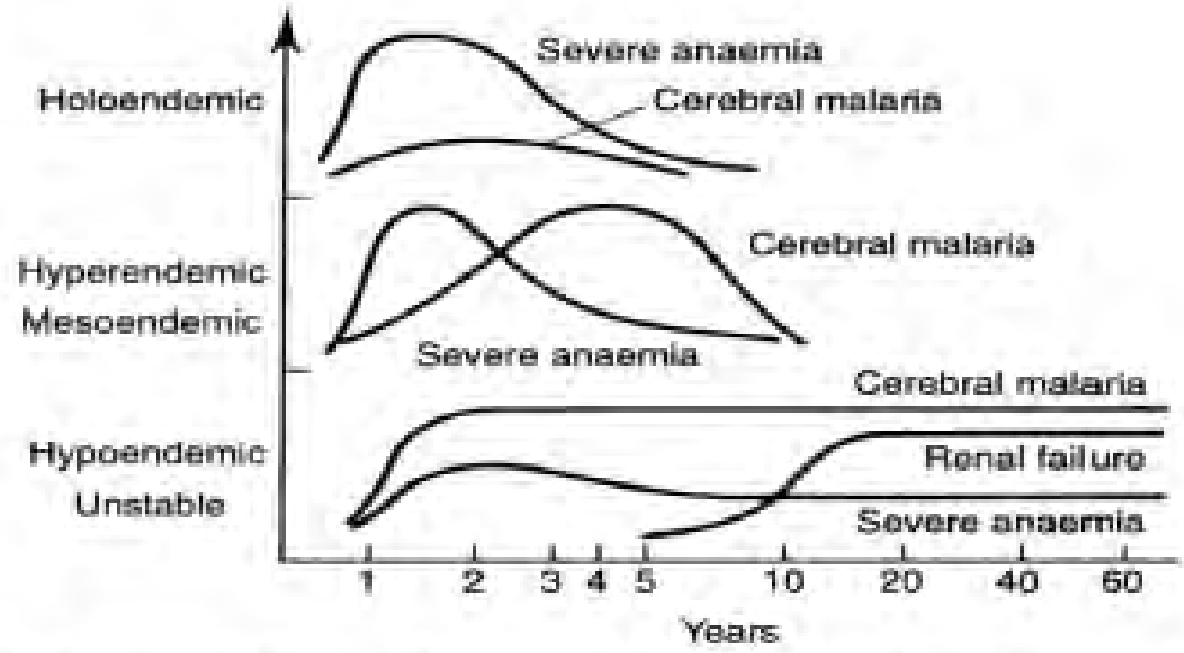


Fig. 1. The clinical presentations of severe falciparum malaria by age and transmission intensity. Nonimmune travelers are expected to behave like inhabitants of a zone of unstable transmission. (*From* White NJ. Malaria. In: Cook GC, Zumla AI, editors. Manson's tropical diseases. 22nd edition. Philadelphia: Saunders Ltd; 2009. p. 1205; with permission.)

Outline

1. Some history and biology
2. **Disease in individuals**
    - **Malaria-HIV interactions**
3. Tool for malaria control
4. Where are we at in 2019?
5. Urgent threats to control (and elimination)
6. Endgame thought (?)

Disease in individuals

malaria-HIV interactions

"Where 2 elephants meet, there grows no grass"
African proverb

Impact of HIV on malaria: summary

HIV (low CD4 count) → Malaria	
Parasitemia	↑
Clinical malaria	↑
Severe Malaria	↑
Antimalarial drug use	↑
Treatment efficacy	↓
Hemoglobin levels	↓

Impact of malaria on HIV: summary

Malaria → HIV	
Specificity HIV RDTs	↓
Transient viral load	↑
Transient CD4	↓
Progression to AIDS	?
HIV transmission	↑ (high HIV prevalence)

Outline

1. Some history and biology
2. Disease in individuals
3. **Tools for malaria control**
4. Where are we at in 2019?
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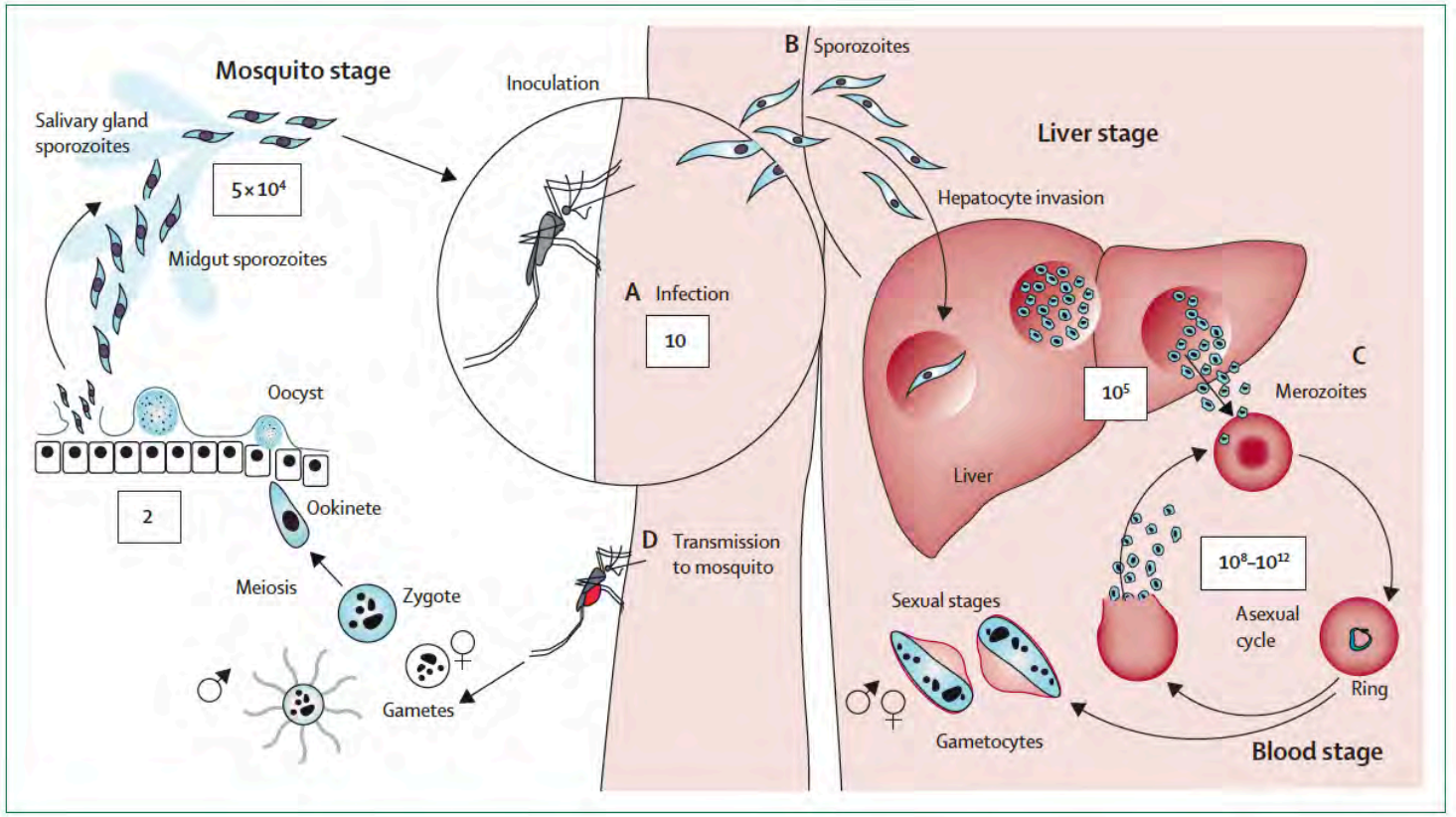
Tools for malaria community-level control



CONSULTATION MISSION
(split into groups of 4-6):

1. Determine **5 methods of malaria control** you would propose to national programmes
2. **Rank them** in order of priority
3. **What impact** do you expect?

(*10 minutes*)

MacLean Centre for Tropical Diseases McGill University

Tools for malaria community-

Malaria Journal 2008, **7**(Suppl 1):S5 doi:10.1186/1475-2875-7-S1-S5

Review **Open Access**

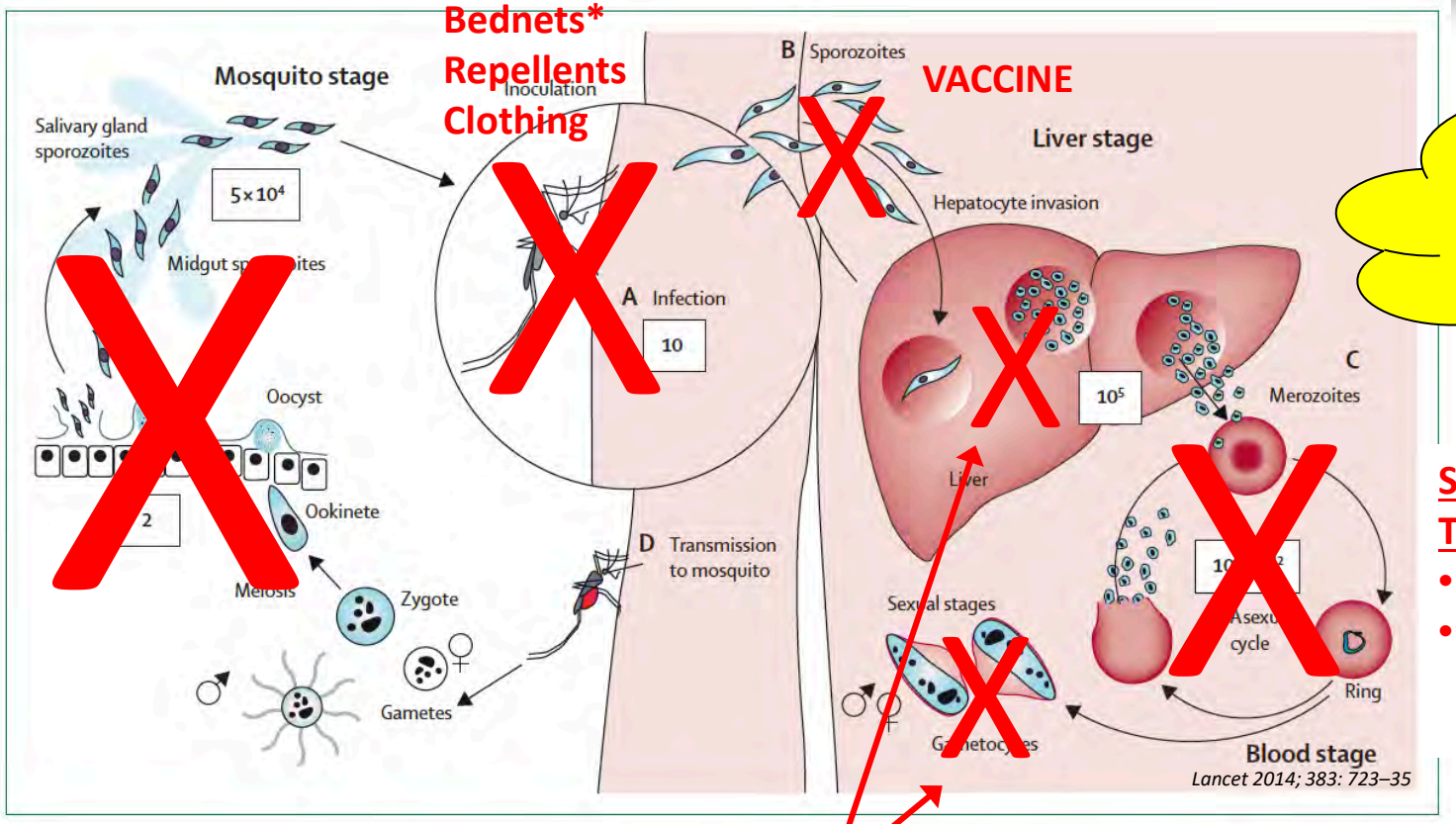
Working without a blindfold: the critical role of diagnostics in malaria control

Mark D Perkins*[1] and David R Bell[2]

BITE PREVENTION:
Bednets*
Repellents
Clothing

VACCINE

VECTOR REDUCTION:
I.R.S.
Others…

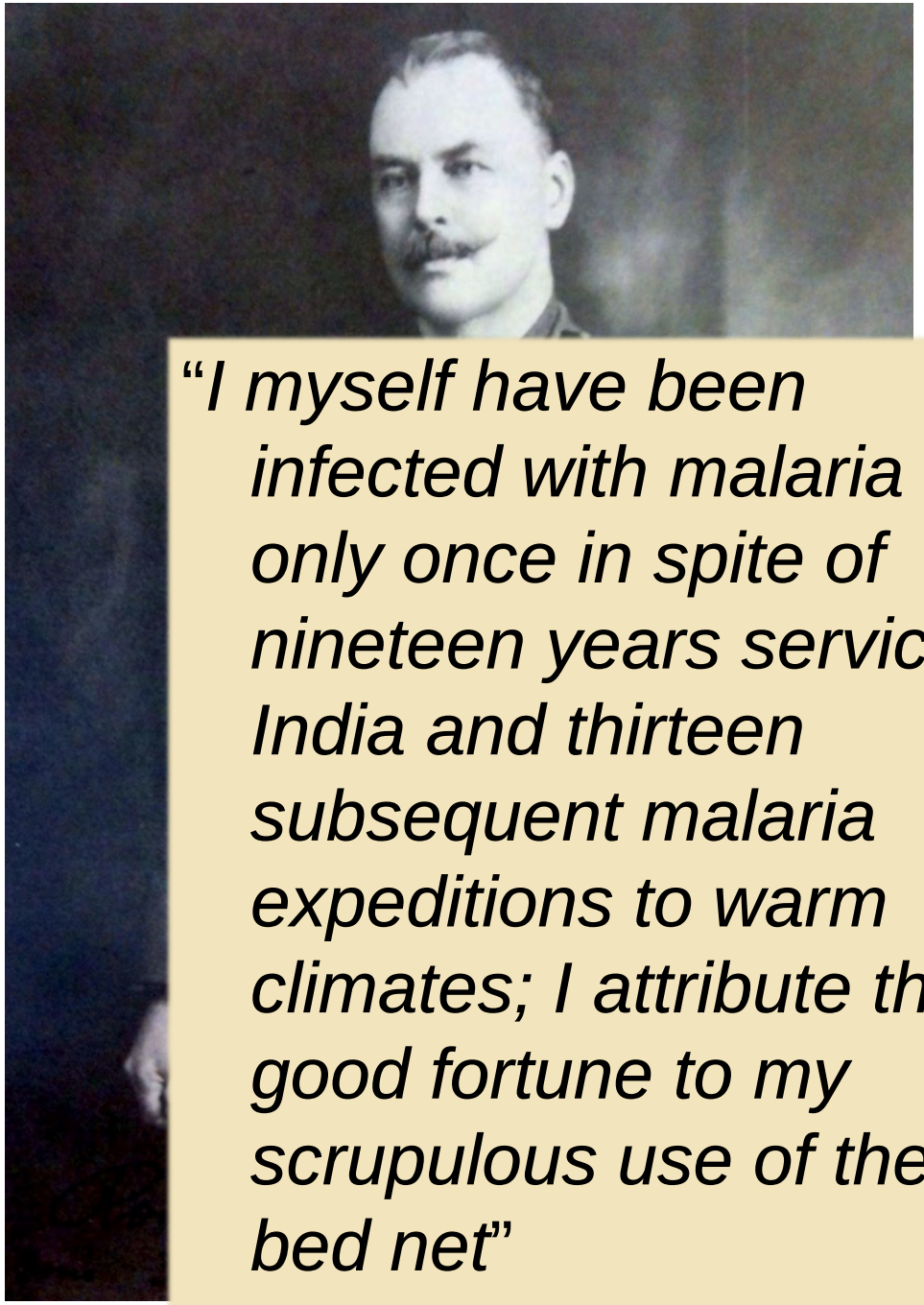


Wait a minute, WHO do we treat?
- *Passive detection?*
- *Active case-finding?*
- *Mass Rx (MDA)?*

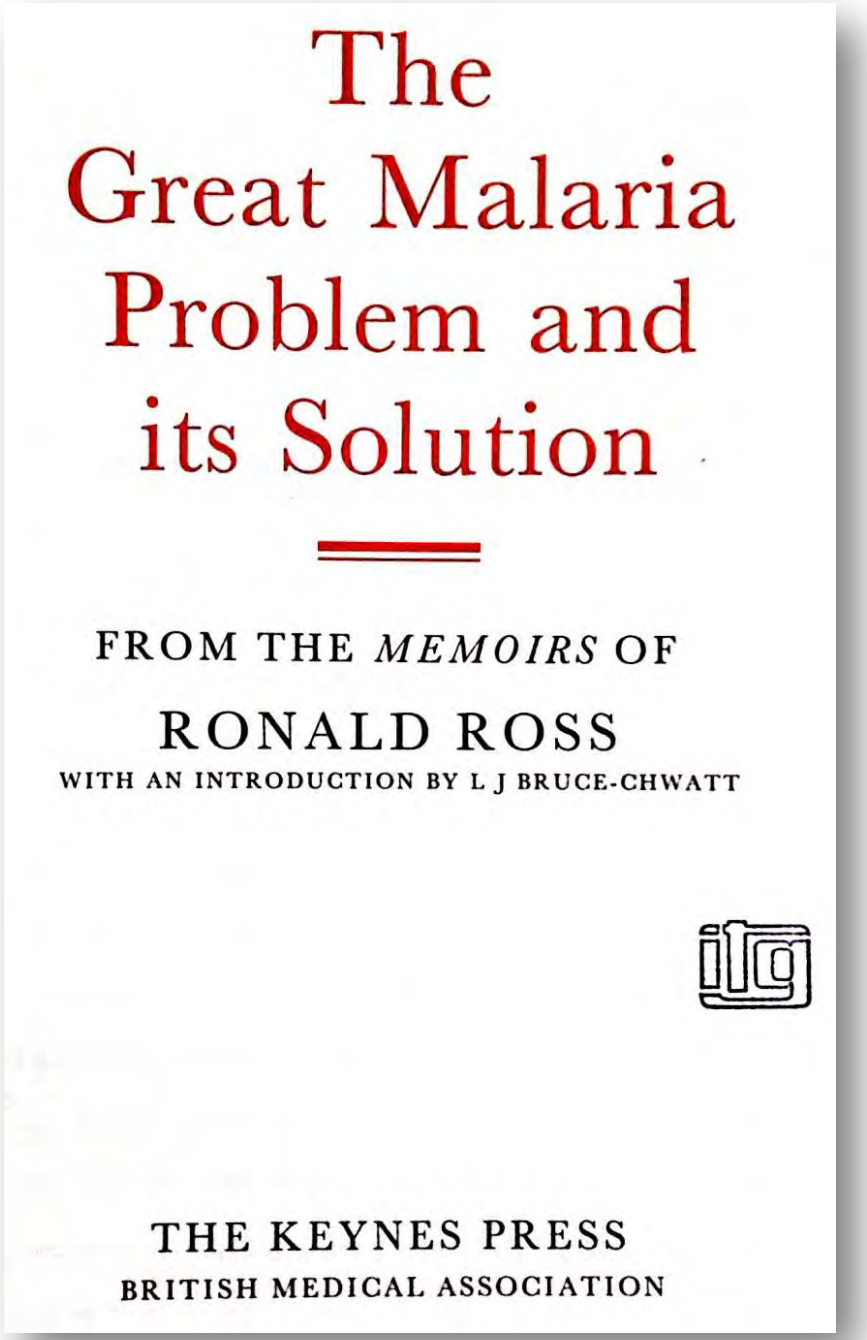
SUPPRESSIVE TREATMENT:
- **disease**
- **targetted Px**
  - **pregnancy**
  - **Infants?**

anti-hypnozoite / anti-gametocyte treatment*

MacLean Centre for Tropical Diseases McGill University



"I myself have been infected with malaria only once in spite of nineteen years service in India and thirteen subsequent malaria expeditions to warm climates; I attribute this good fortune to my scrupulous use of the bed net"



Prevention

repellent chemicals

- Important for MANY diseases and discomfort
  - Malaria, dengue, WNV, many others!
- Effective products:
  - DEET (use 35-50% solutions)
  - Picardin (use 20% solution, only 7% available is US)*
  - Permethrin on clothes and bednets
- Much less effective:
  - Eucalyptus oil, 2% soybean oil
- Not effective:
  - Citronella, ultrasonic devices, ankle/wristbands, geranium oil, baby oil

CATMAT GUIDELINES: http://www.phac-aspc.gc.ca/tmp-pmv/catmat-ccmtmv/index-eng.php

Medical Letter Vol 47 (Issue 1210) June 6, 2005 "Deet alternatives"

Prevention

wear this

7up “Uncola” ad campaign

Prevention

don’t wear this

Pictures courtesy E. Bottieau, ITM

Outline

1. Some history and biology
2. Disease in individuals
3. Tool for malaria control
4. **Where are we at in 2019?**
5. Urgent threats to control (and elimination)
6. Endgame thought (?)

Where are we at in 2019?

- Chloroquine resistance emerged in 1970s and reversed much of the gains made in Africa over the 20th Century
- Drastic increase in deaths and drug-resistant malaria 1970-2000
- MDGs and other initiatives in 2000 prompted concerted effort for control

Where are we at in 2019?

doi:10.1038/nature15535

The effect of malaria control on *Plasmodium falciparum* in Africa between 2000 and 2015

S. Bhatt[1]*, D. J. Weiss[1]*, E. Cameron[1]*, D. Bisanzio[1], B. Ma
P. A. Eckhoff[2], E. A. Wenger[2], O. Briët[3,4], M. A. Penny[3,4],
J. T. Griffin[7], C. A. Fergus[8], M. Lynch[8], F. Lindgren[9], J. M.
R. E. Cibulskis[8] & P. W. Gething[1]

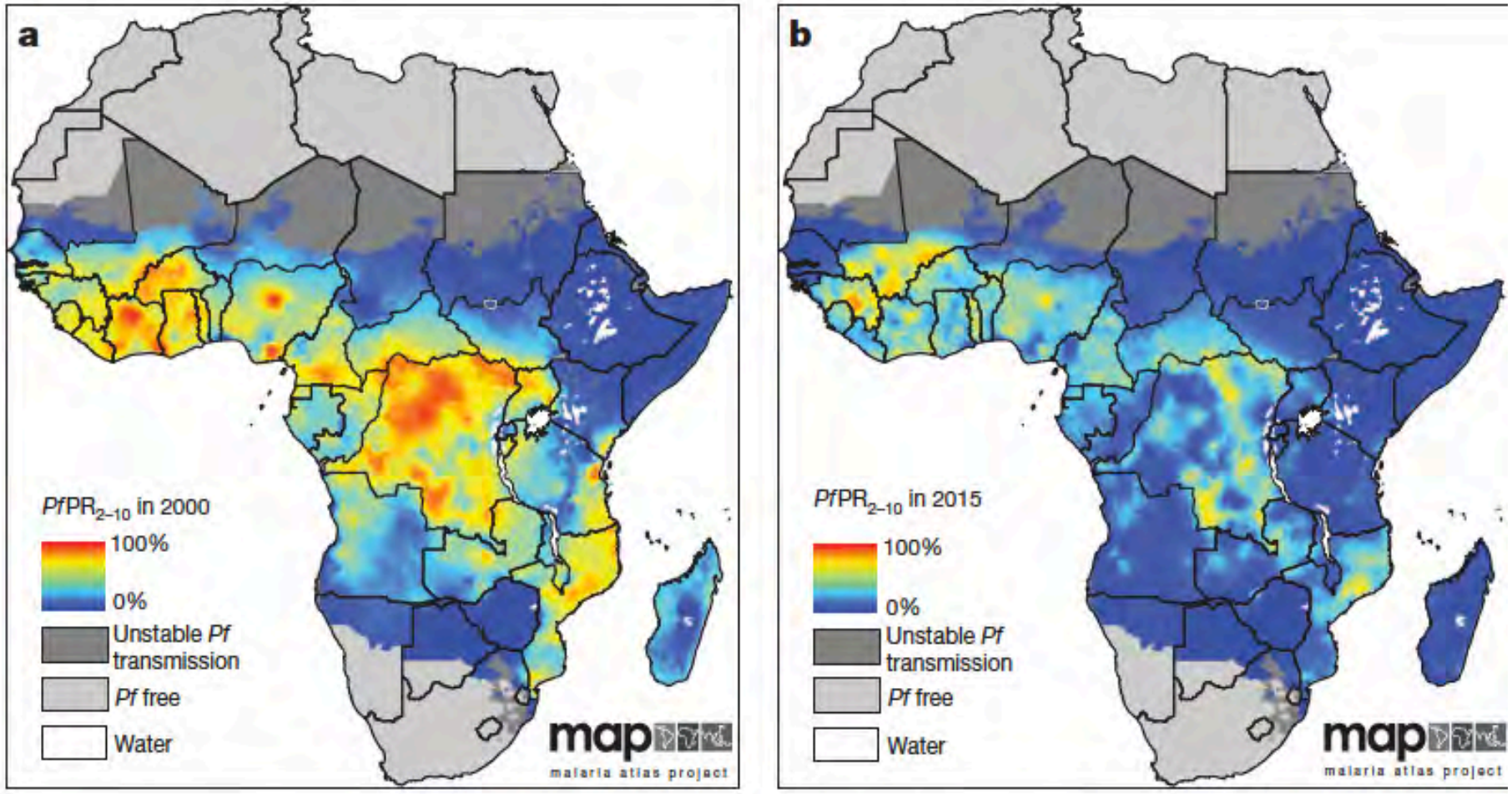
ORIGINAL ARTICLE

Mapping *Plasmodium falciparum* Mortality in Africa between 1990 and 2015

This article was published on October 10, 2016, and updated on October 20, 2016, at NEJM.org.

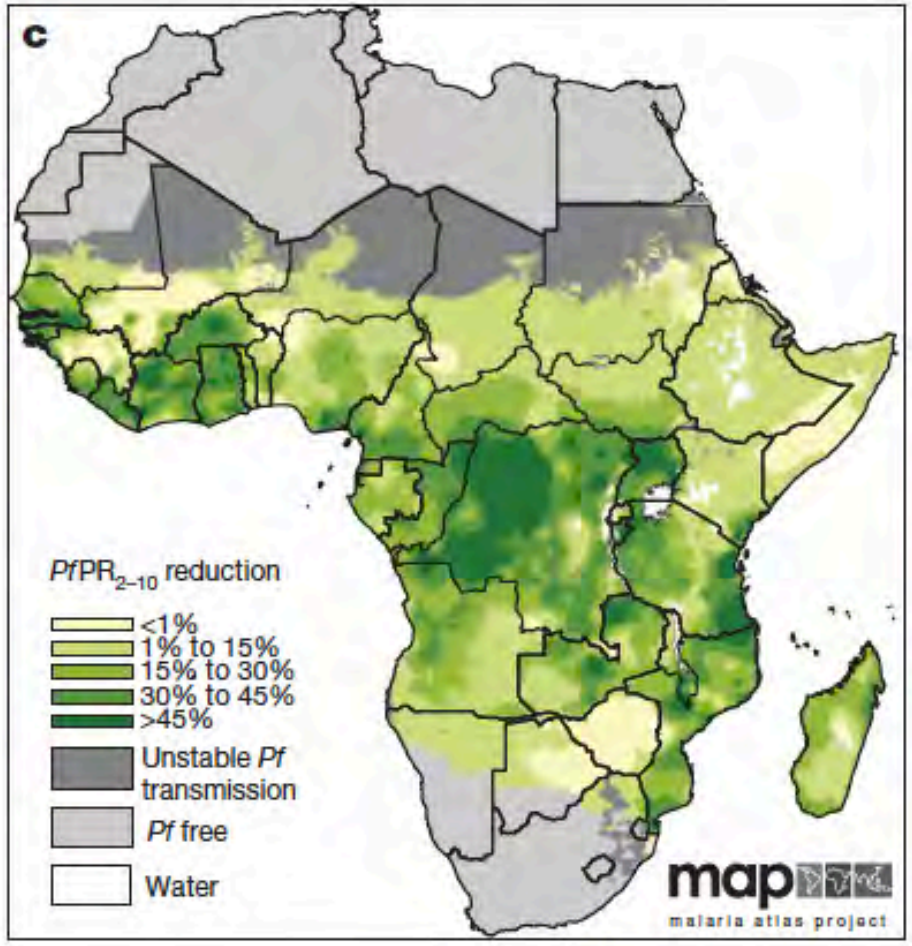
DOI: 10.1056/NEJMoa1606701

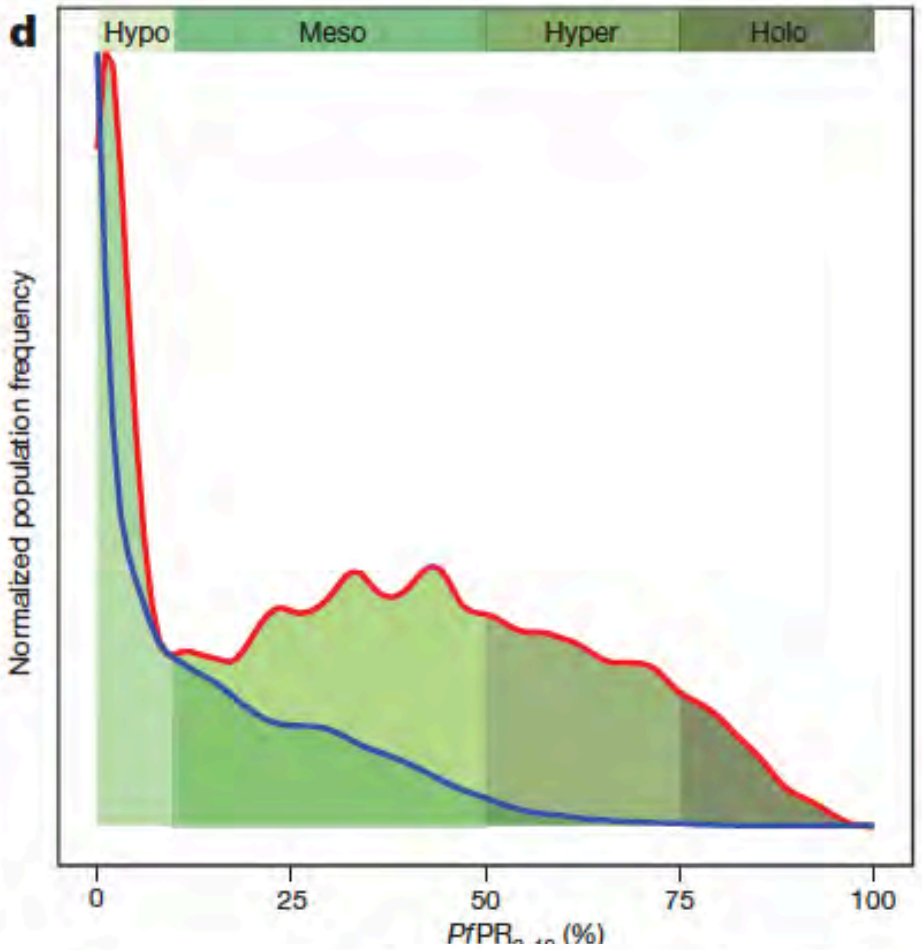
Where are we at in 2019?



doi:10.1038/nature15535

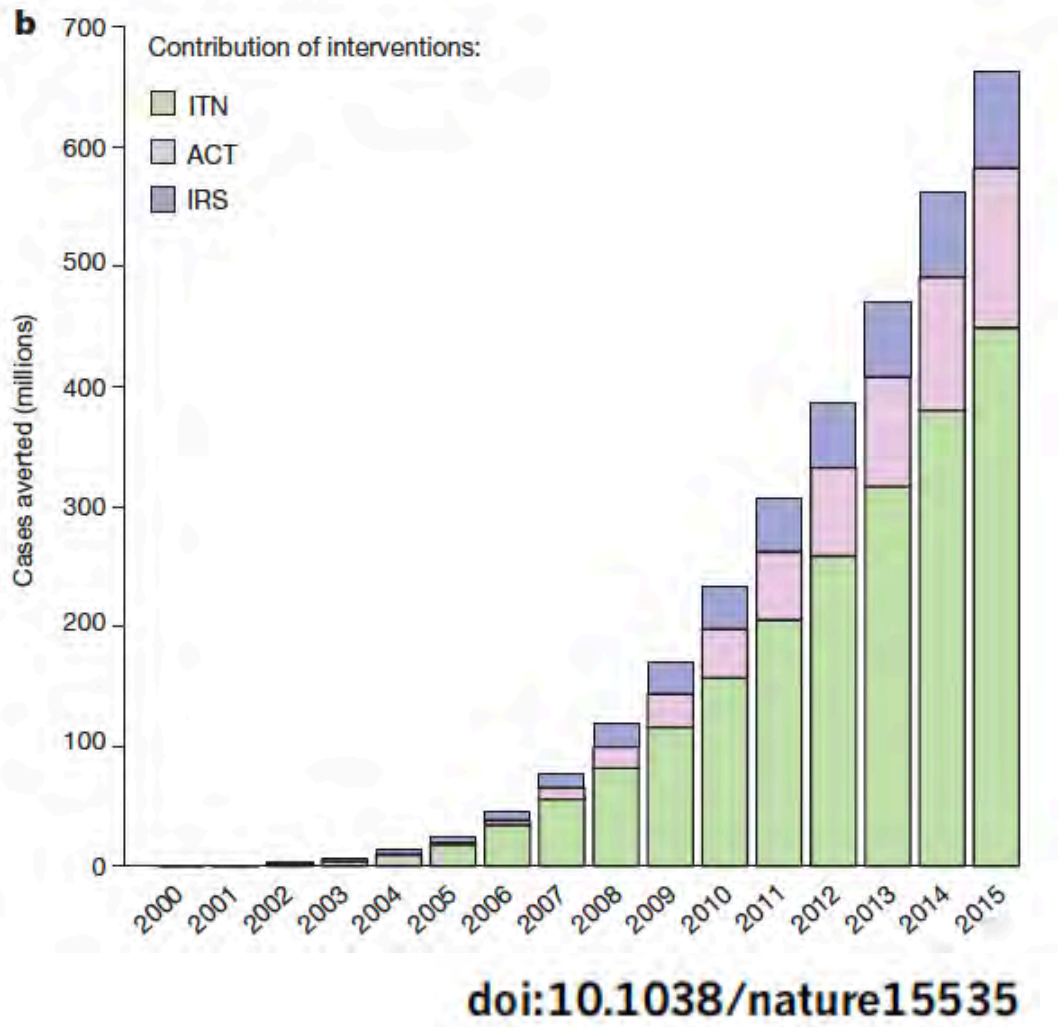
Where are we at in 2019?





doi:10.1038/nature15535

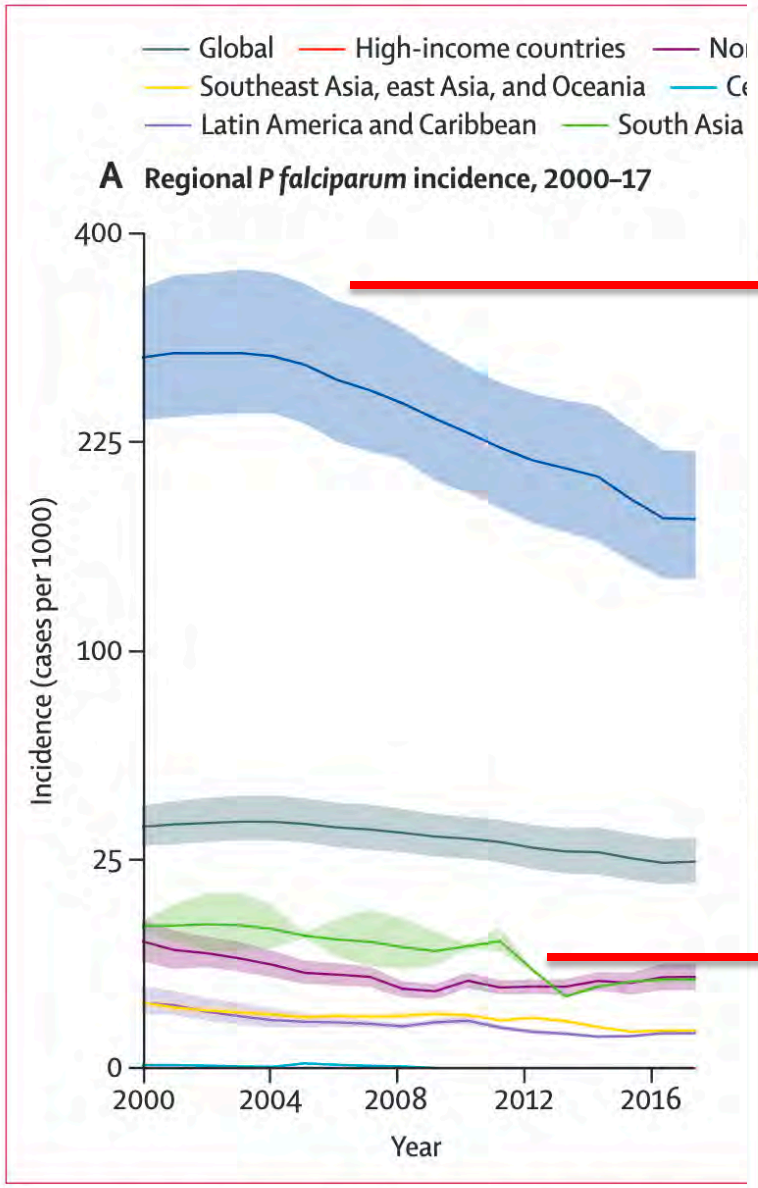
Where are we in 2019?



doi:10.1038/nature15535

- This is not the comparative efficacy of each measure!
- Reflects
  - coverage
  - time since implementation
  - Local epidemiology, age structure, and ecology

Lancet 2019; 394: 322–31



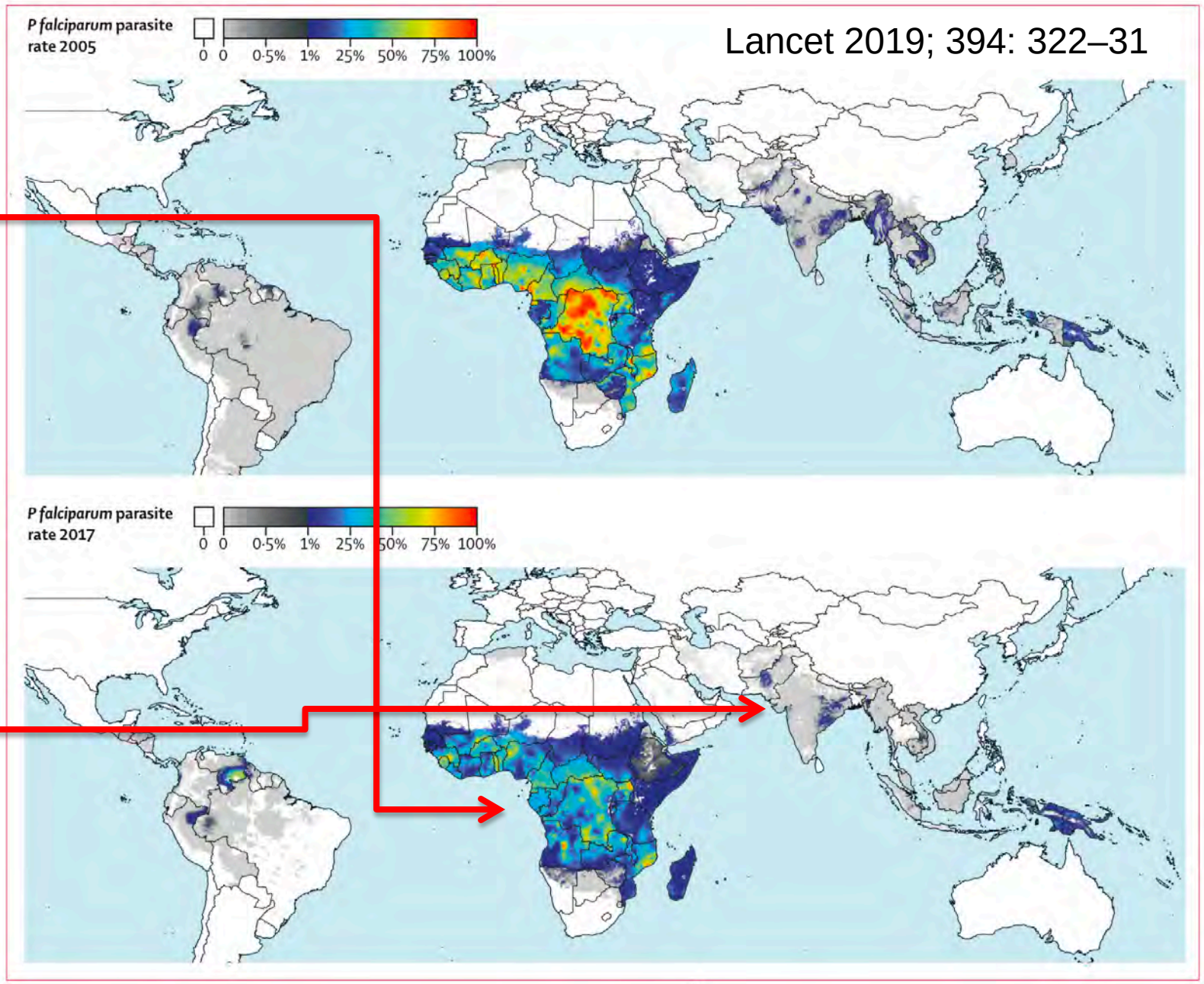
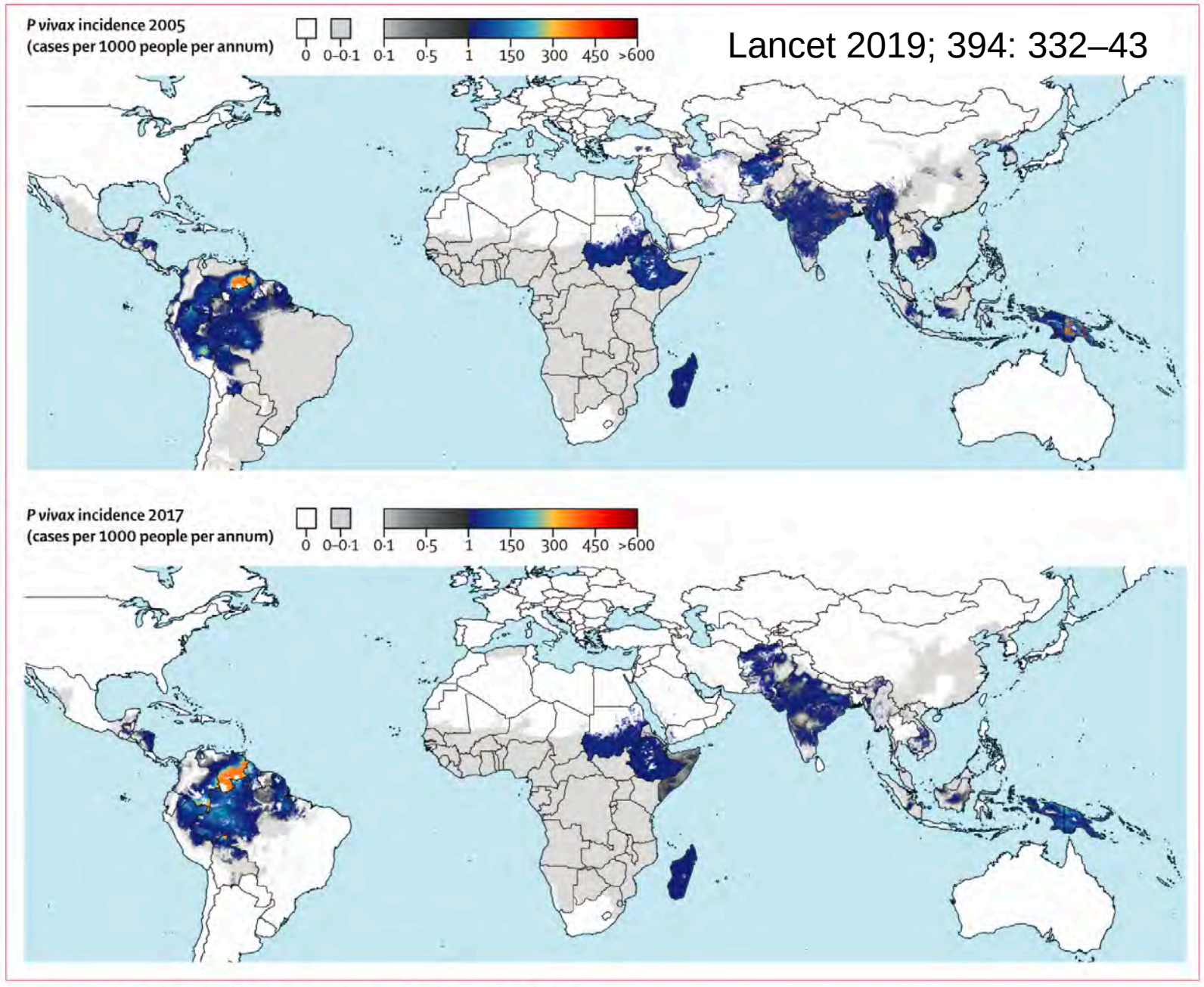


Figure 2:* Regional distribution of *Plasmodium falciparum
To show trends across regions with such different endemici
incidence (per 1000 individuals) for A and count (in million
via the corresponding coloured bands behind the mean line
endemic countries within each region.

***Figure 3:* Spatial distribution of age-standardised *P falciparum* parasite rate$_{2-10}$ in 2005 (top) and 2017 (bottom)**
Note the colour scaling is split to better differentiate within low endemic areas, with one linear scale between zero and 0·01 *P falciparum parasite rate*$_{2-10}$ (grey shades) and a second linear scale between 0·01 and 1 (colours from blue to red). Areas without endemic *P falciparum* are shown in white. *P falciparum* parasite rate$_{2-10}$=*P falciparum* parasite rate for children aged 2–10 years of age.

Where are we at in 2019?

(Vivax:)



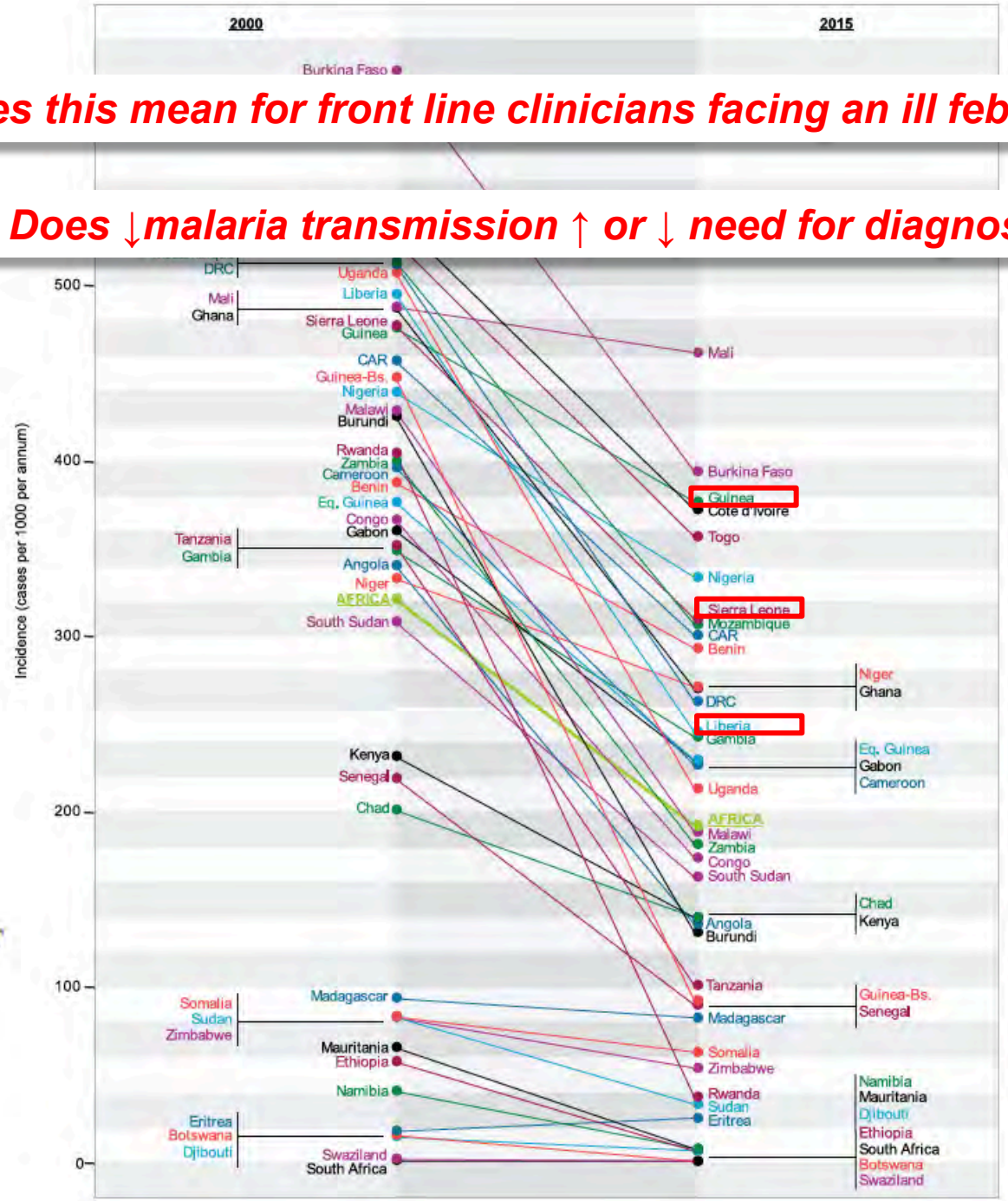
Lancet 2019; 394: 332–43

Figure 2: **Predicted incidence of *Plasmodium vivax* malaria in 2005 and 2017**
Incidence in cases per 1000 people per year are shown on a spectrum of white (zero incidence) to dark grey (1 case per 1000) and then blue to red (>1 case per 1000 to >600 cases per 1000) for the years 2005 (top panel) and 2017 (bottom).

Where are we in 2019?

Q: *what does this mean for front line clinicians facing an ill febrile child?*

Q: *Does ↓malaria transmission ↑ or ↓ need for diagnostic tools?*



Extended Data Figure 3 | Changing incidence rate by country, 2000–2015. Estimated country-level rates of all-age clinical incidence are shown for 2000 and 2015. For Sudan and South Sudan, we used the post-2011 borders throughout the time period to allow comparability. Results shown are derived from a Bayesian geostatistical model fitted to $n = 27{,}573$ *Pf*PR survey points; $n = 24{,}868$ ITN survey points; $n = 96$ national survey reports of ACT coverage; $n = 688$ country-year reports on ITN, ACT and IRS distribution by national programs; $n = 20$ environmental and socioeconomic covariate grids; and $n = 30$ active-case detection studies reporting *P. falciparum* clinical incidence.

doi:10.1038/nature15535

Where are we in 2019?

post-Ebola syndrome

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 22, No. 3, March 2016

Effects of Response to 2014–2015 Ebola Outbreak on Deaths from Malaria, HIV/AIDS, and Tuberculosis, West Africa

Alyssa S. Parpia,[1] Martial L. Ndeffo-Mbah,[1] Natasha S. Wenzel, Alison P. Galvani

Response to the 2014–2015 Ebola outbreak in West Africa overwhelmed the healthcare systems of Guinea, Liberia, and Sierra Leone, reducing access to health services for diagnosis and treatment for the major diseases that are endemic to the region: malaria, HIV/AIDS, and tuberculosis. To estimate the repercussions of the Ebola outbreak on the populations at risk for these diseases, we developed computational models for disease transmission and infection progression. We estimated that a 50% reduction in access to healthcare services during the Ebola outbreak exacerbated malaria, HIV/AIDS, and tuberculosis mortality rates by additional death counts of 6,269 (2,564–12,407) in Guinea; 1,535 (522–2,8780) in Liberia; and 2,819 (844–4,844) in Sierra Leone. The 2014–2015 Ebola outbreak was catastrophic in these countries, and its indirect impact of increasing the mortality rates of other diseases was also substantial.

Malaria morbidity and mortality in Ebola-affected countries caused by decreased health-care capacity, and the potential effect of mitigation strategies: a modelling analysis

Patrick G T Walker, Michael T White, Jamie T Griffin, Alison Reynolds, Neil M Ferguson, Azra C Ghani

Summary

Background The ongoing Ebola epidemic in parts of west Africa largely overwhelmed health-care systems in 2014, making adequate care for malaria impossible and threatening the gains in malaria control achieved over the past

Lancet Infect Dis 2015; 15: 825–32

Where are we at in 2019?

post-Ebola syndrome *(Compare these numbers to total Ebola deaths)*

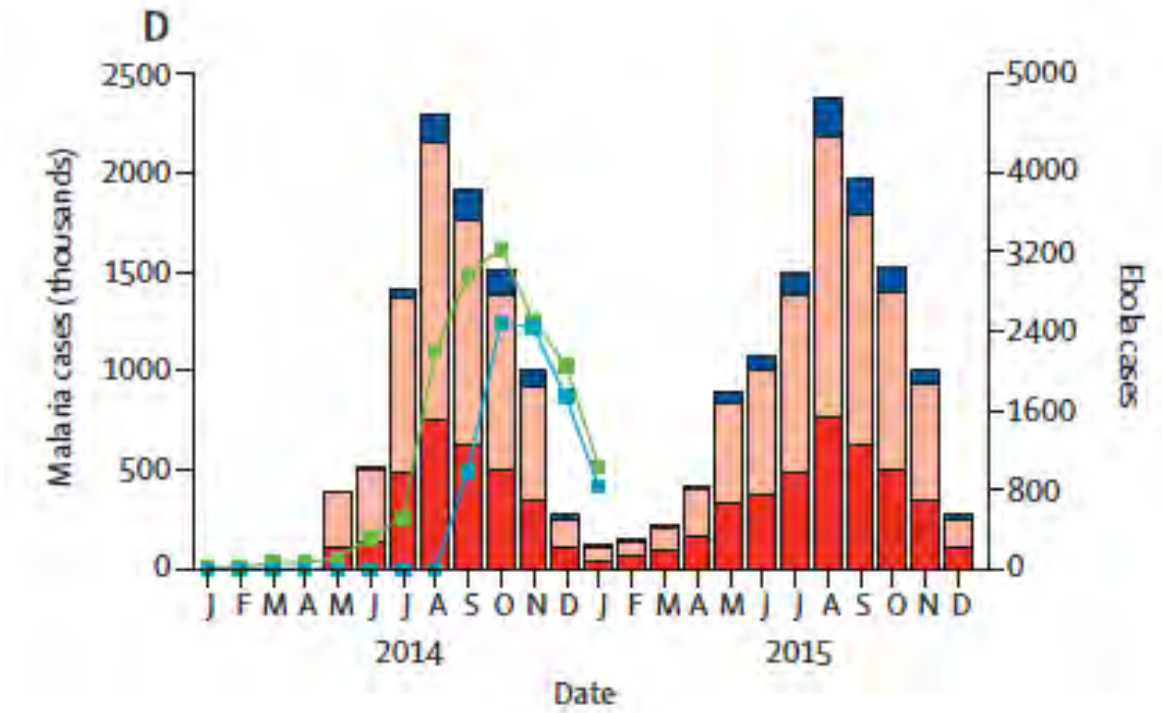


Figure 2: **Effect of health-systems failure on incidence of untreated malaria**
For Guinea (A), Liberia (B), Sierra Leone (C), and the combined total (D). Pink bars show the number of cases untreated and red bars show the number of cases treated when the system is functioning normally, blue bars show additional cases caused by increases in transmission from the additional untreated cases. The green lines show the present status of the Ebola epidemic (probable and confirmed cases from patient databases), the blue lines show Ebola cases from WHO situation reports.

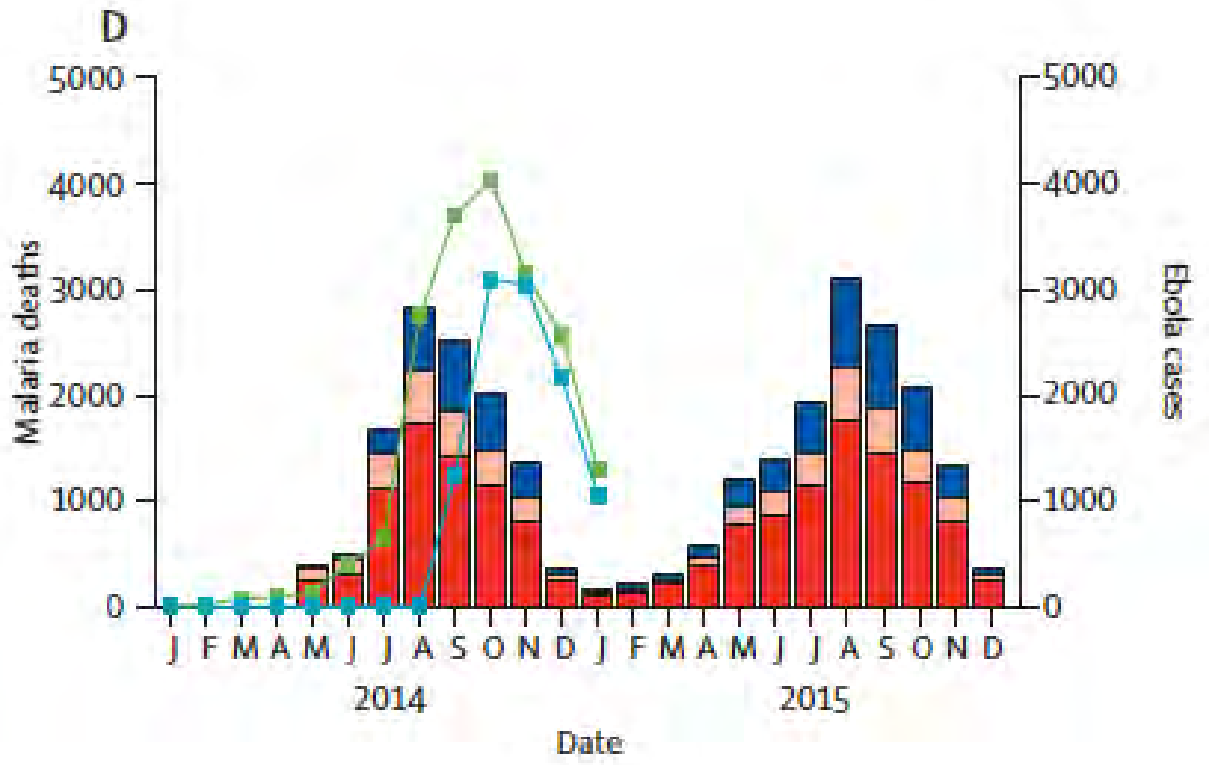


Figure 3: **Effect of health-systems failure on malaria deaths**
For Guinea (A), Liberia (B), Sierra Leone (C), and the combined total (D). Red bars show additional deaths in individuals who would otherwise have been treated with an artemisinin-based combination therapy (ACT) and recovered, pink bars show additional deaths in individuals who would not have received ACT or failed to respond to ACT but would have otherwise recovered after hospital care, and blue bars show additional deaths caused by the additional malaria cases attributable to increased malaria transmission. Green lines show probable and confirmed Ebola cases from patient databases, blue lines show Ebola cases from WHO situation reports.

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6. Endgame thought (?)

Urgent threats to control (and elimination)

- **Resistance in mosquitoes**
  - Pyrethroid resistance now widespread in some areas
  - DDT resistance
- **Resistance in *Plasmodium***
  - *ARTESUNATE RESITANCE*
- **Complacency in the face of recent gains**
  - Failing to “seal the deal” in the face of decreased prevalence
    - **Diagnostics for submicroscopic disease**
    - Establishing clinical impact of “subclinical” diasease

OPEN ACCESS Freely available online

PLOS | MEDICINE

Policy Forum

Targeting Asymptomatic Malaria Infections: Active Surveillance in Control and Elimination

Hugh J. W. Sturrock[1]*, Michelle S. Hsiang[1,2], Justin M. Cohen[3], David L. Smith[4], Bryan Greenhouse[5], Teun Bousema[6,7], Roly D. Gosling[1]

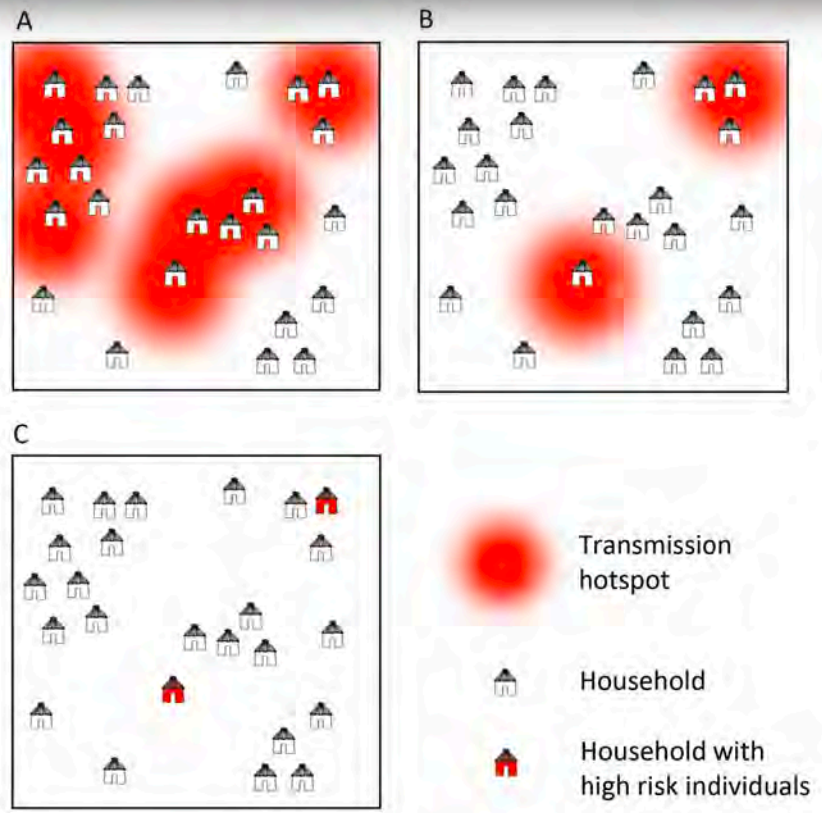


Figure 1. Microepidemiology of malaria in villages of varying transmission setting. In moderate/high transmission settings (A), hotspots coalesce to form a more homogeneous pattern. In lower transmission settings (B), risk becomes increasingly spatially discrete, with single households or small groups of households experiencing higher exposure. In very low transmission settings (C), risk shifts to individual households or, where transmission is occurring outside the house/village, to individuals.
doi:10.1371/journal.pmed.1001467.g001

Setting		Active surveillance		Presumptive treatment	
		PACD	RACD	MDA	tMDA
Transmission setting	Moderate	■		■	
	Low	▒	■	▒	■
	Elimination	▒	■	▒	■
Spatial/demographic risk	Defined	■	▒	■	▒
	Undefined		■		■
Proportion infections asymptomatic	High	■	■	■	■
	Low		▒		▒
Proportion infections subpatent	High			■	■
	Low	■	■		

■ Very suitable ▒ Could be considered □ Less suitable

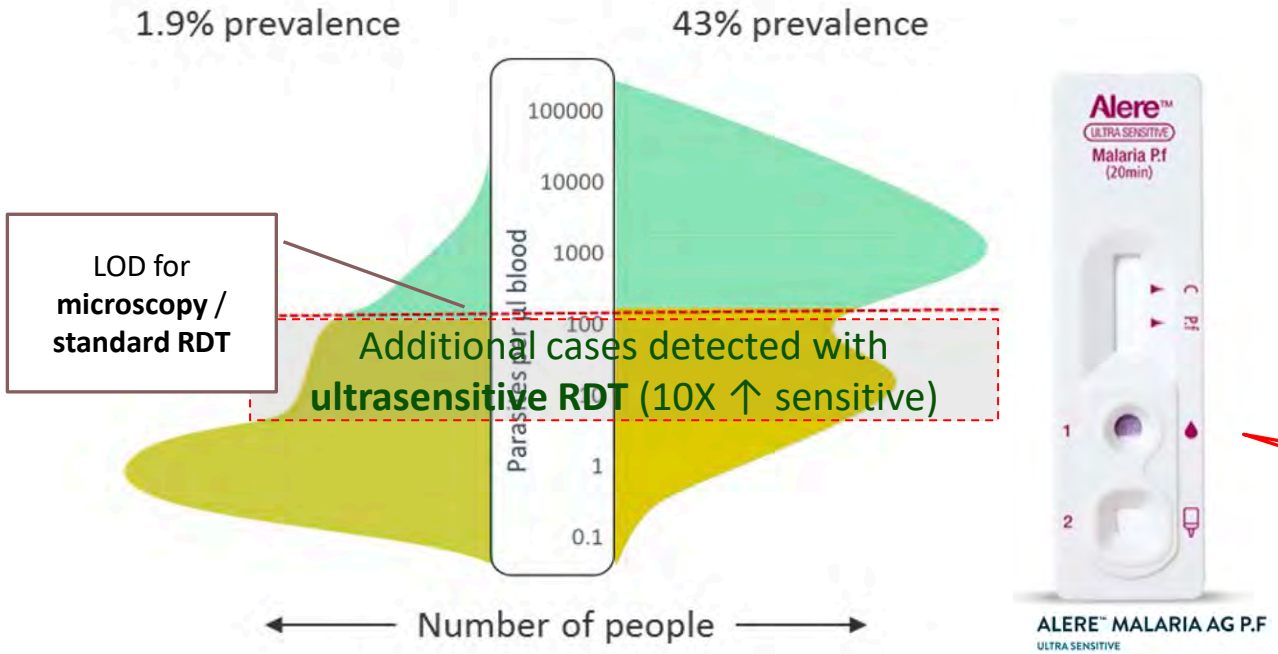
PACD – Proactive case detection, RACD – reactive case detection, MDA – mass drug administration, tMDA – targeted mass drug administration. MDA refers to presumptive treatment of pre-defined populations, whereas tMDA involves presumptively treating individuals living in close proximity, or with shared risk factors, to passively or actively detected cases.

Summary Points

- Active case detection (ACD) is a recommended intervention in low malaria transmission settings, yet evidence for its effectiveness is sparse.
- The potential of ACD to impact transmission is hampered by the ability of current field diagnostics to detect very low density infections and continued importation of parasites, as well as the operational challenges of achieving high coverage.
- The type of ACD employed should be guided by transmission setting and an understanding of risk factors.
- Standardized monitoring and evaluation of ACD strategies should be an integral component of ACD campaigns.
- In light of the current sensitivity of field diagnostic tests, targeted mass drug administration should be evaluated as an alternative or addition to ACD in low transmission settings.

PLoS Med 10(6): e1001467. https://doi.org/10.1371/journal.pmed.1001467

Parasite density distribution in malaria-infected but asymptomatic populations



PATH/Gonzalo Domingo

Setting		Active surveillance		Presumptive treatment	
		PACD	RACD	MDA	tMDA
Transmission setting	Moderate	■		■	
	Low	▒	■	▒	■
	Elimination	▒	■	▒	■
Spatial/demographic risk	Defined	■	▒	■	▒
	Undefined		■		■
Proportion infections asymptomatic	High	■	■	■	■
	Low		▒		▒
Proportion infections subpatent	High			■	■
	Low	■	■		

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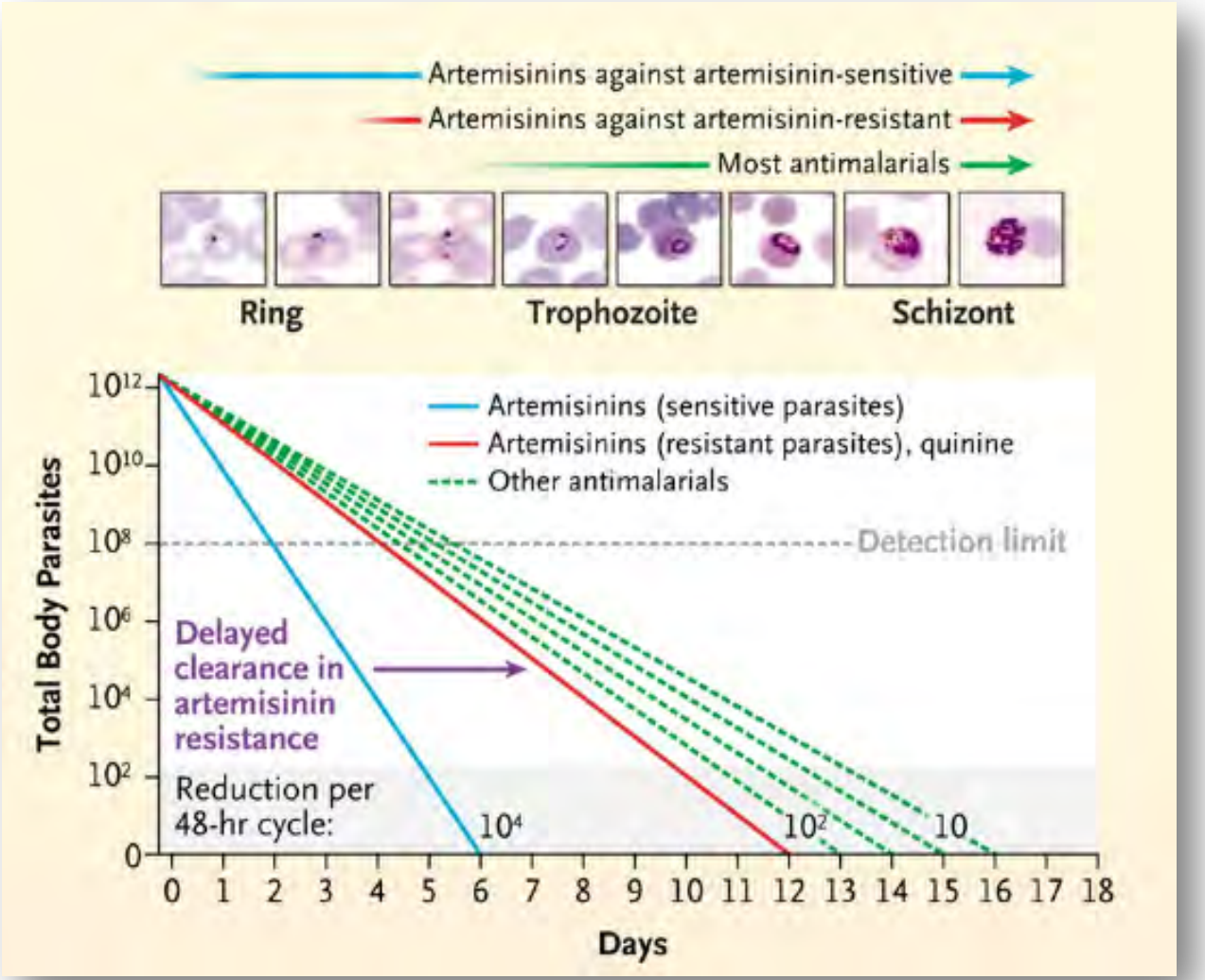
PLoS Med 10(6): e1001467. https://doi.org/10.1371/journal.pmed.1001467

The threat of artemisinin-resistant malaria

Figure 3 | **The study site in Pailin, western Cambodia.** Decreased artemisinin sensitivity was first detected in Pailin, western Cambodia, near the border with Thailand.

Dondorp AM et al. N Engl J Med 2009



Dondorp AM et al. N Engl J Med 2011

Urgent threats to control (and elimination)

artesunate resistance

- Initially thought to be contained to small pockets SE Asia
- Now documented to be widespread in SE Asia
- New foci found in Guyana
- Looming threat in Africa

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Endgame thoughts

- Malaria is one of oldest foes
- Great advances made in last 15 years
- Can be eliminated in theory
- Major threats are present, however.
- ***Endgame will require specific intensified concerted action despite decreasing cases***
  - *Much more $$ per case averted*
  - *Politically difficult to maintain*
  - *Morbidity of other species, submicroscopic disease*

Thank you