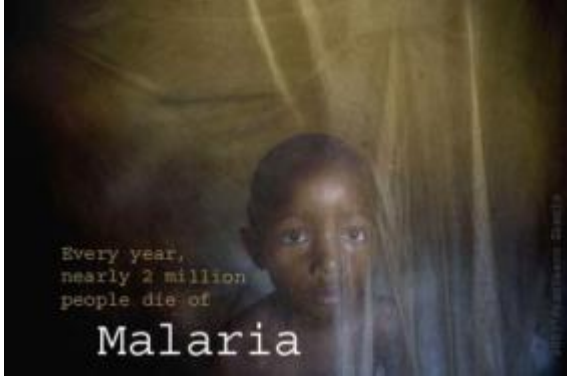

Malaria

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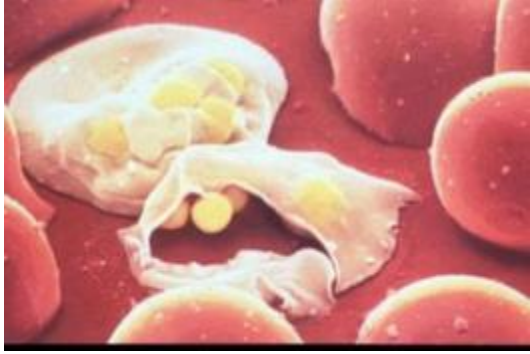
mlaurens@medicine.umaryland.edu

Malaria



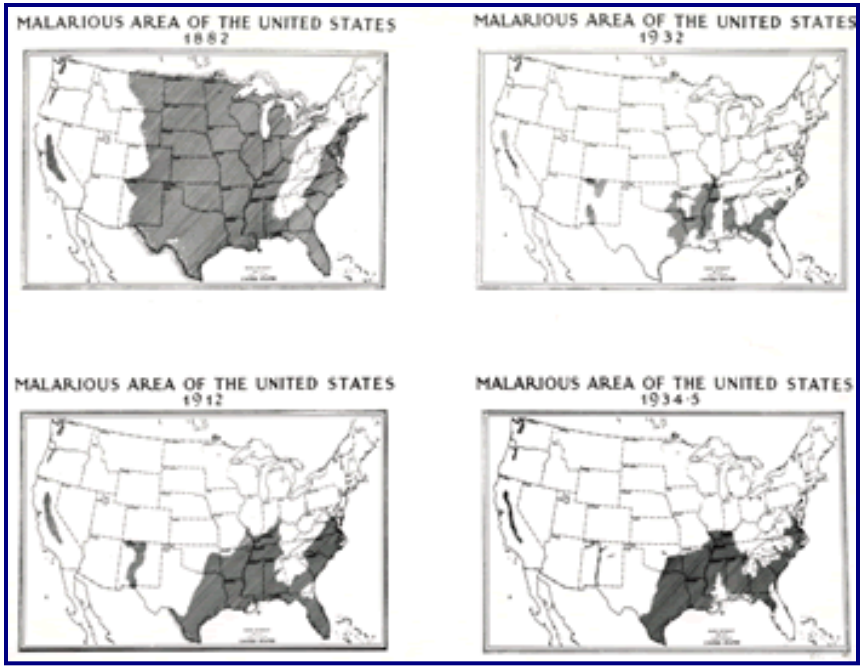
- Parasitic disease transmitted by mosquitoes
- Human-malaria interaction >100,000 years
- 198 million cases of clinical disease in 2013
- Estimated 584,000 deaths in 2013
- 80% of deaths occur in children <5 in sub-Saharan Africa
- Infants, children, pregnant women at most risk
- Worldwide decreasing incidence of disease and death since 2005
- No vaccine available

The History of Malaria

Descriptions of malaria exist from antiquity-

"Like those who shake,
Feeling the quartan fever coming on --
Their nails already blue, so that they shiver
At the mere sight of shade—such was I then ..."
Dante: Inferno Canto XVII (15)

Mummy DNA study suggests King Tut died of malaria



Malaria History:

Malaria has caused more deaths than injuries related to war.

Wars have always triggered malaria research

Quinine was first preventative treatment. British soldiers would take daily doses. The bitter medication was dosed with gin to make it more palatable. (gin and tonic)

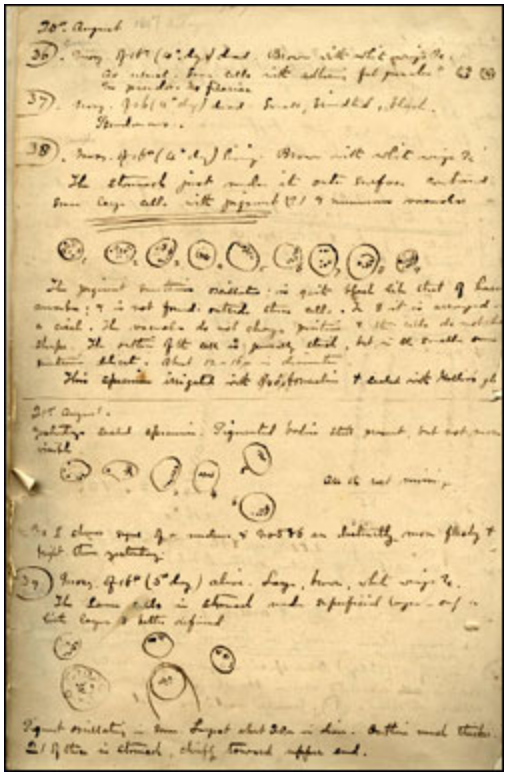
The History of Malaria, continued

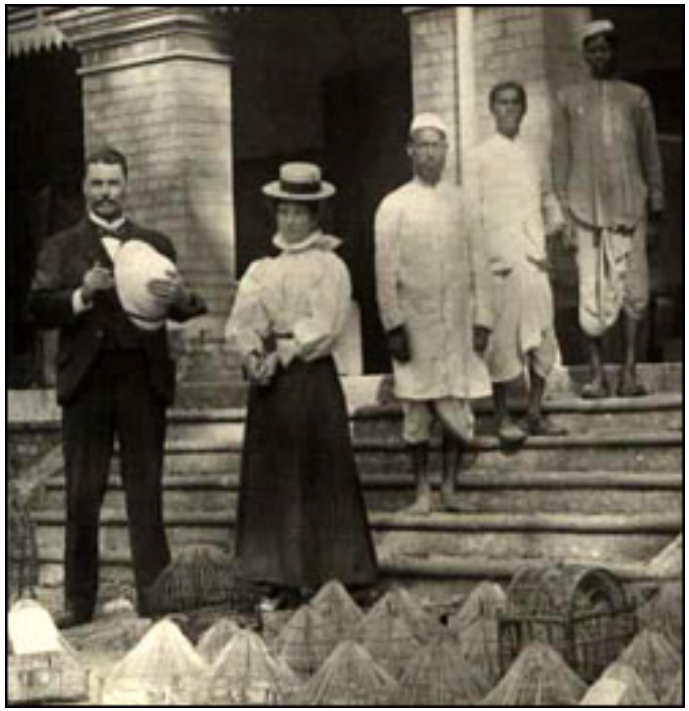
Mosquitoes transmit malaria - 1897

Sir Ronald Ross

Nobel Prize for Medicine

1902



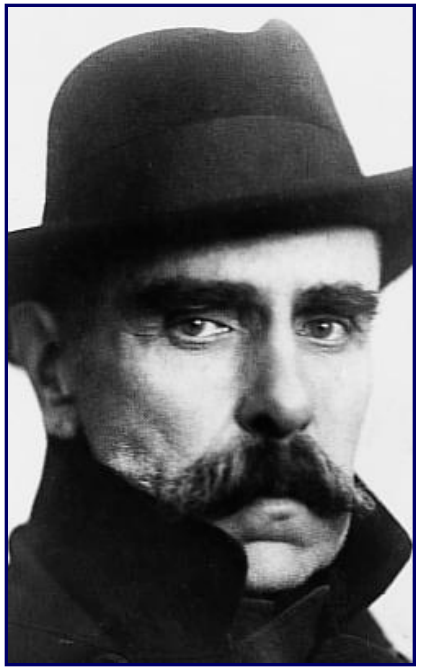


"...With tears and toiling breath,
I find thy cunning seeds,
O million-murdering Death." - Ross

The History of Malaria, continued

The Nobel Prize in Physiology or Medicine

Charles Louis Alphonse Laveran
Nobel Prize – 1907
Parasite development in erythrocytes and exflagellation of gametocytes

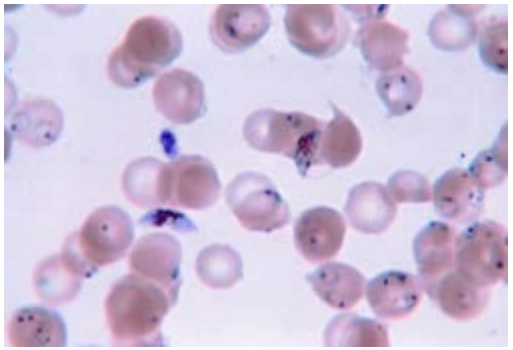


Julius Van Wagner-Juaregg
Nobel Prize – 1927
Malariatherapy to treat "general paresis of the insane" (a.k.a. late stage syphilis)

Biology and Life Cycle

Malaria is caused by *Plasmodia*: intracellular protozoa

- Four (five) human Plasmodia
  - Plasmodium falciparum
    - Most common, responsible for 90% of malaria deaths
    - Multi-drug resistance
    - Target of most vaccine efforts
  - Plasmodium vivax
  - Plasmodium ovale (2 types: classic and variant)
  - Plasmodium malariae
  - Plasmodium knowlesi
- Hundreds of animal Plasmodia



The Malaria Parasites

Phylum Apicomplexa

Class Haemosporia

Order Haemosporidia

Family Plasmodiidae

Genus *Plasmodium*

Human Malaria

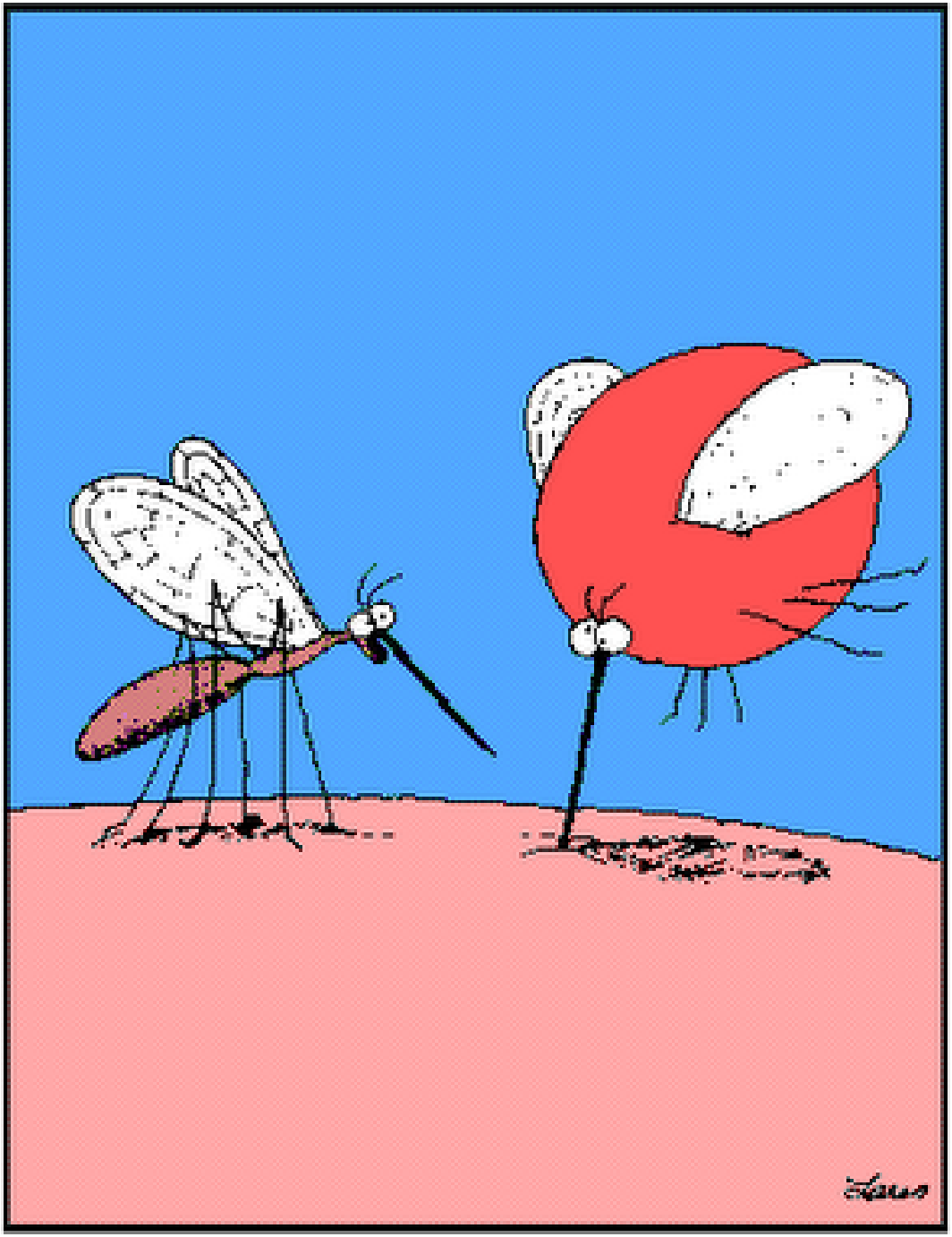
P. falciparum – malignant tertian (48 hrs) – 50%

P. vivax – benign tertian – 43%

P. ovale – mild tertian - < 1%

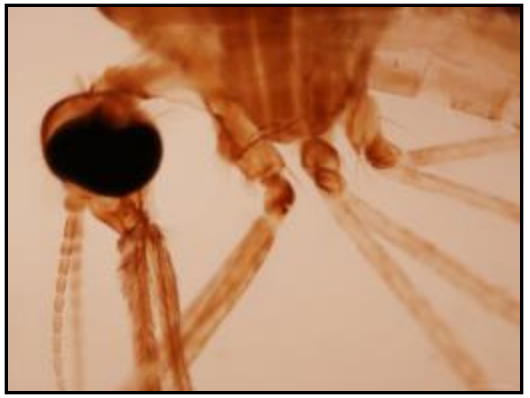
P. malariae – quartan (72 hr) – 7%

P. knowlesi – quotidian (24 hr)



"Pull out, Betty! Pull out! . . . You've hit an artery!"

Mosquito-borne



<u>Female</u> *Anopheles gambiae*

Prefers to bite at night

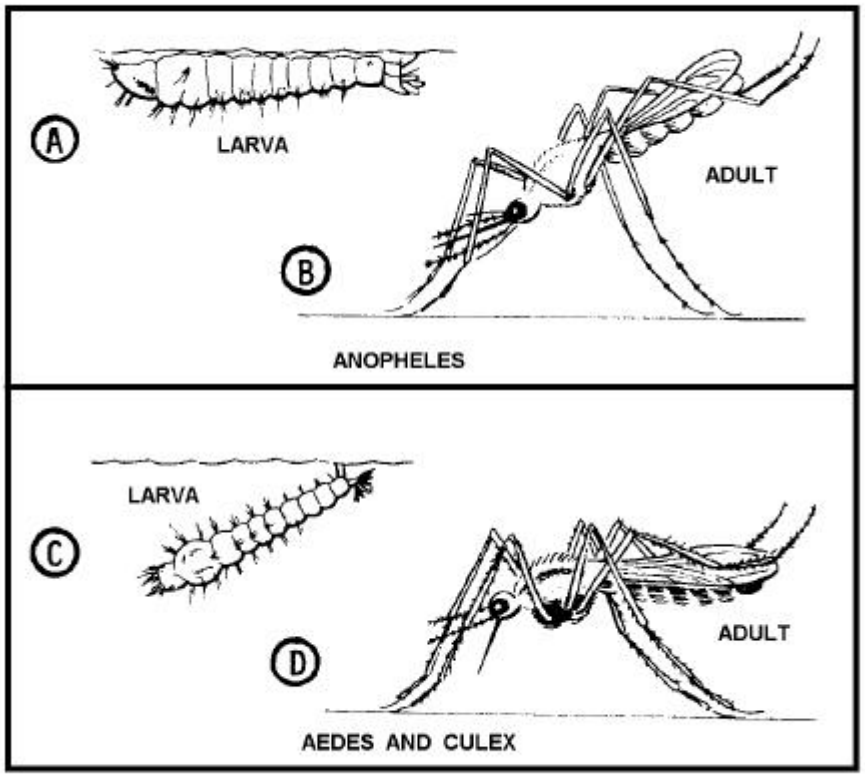
Lives for > 30 days

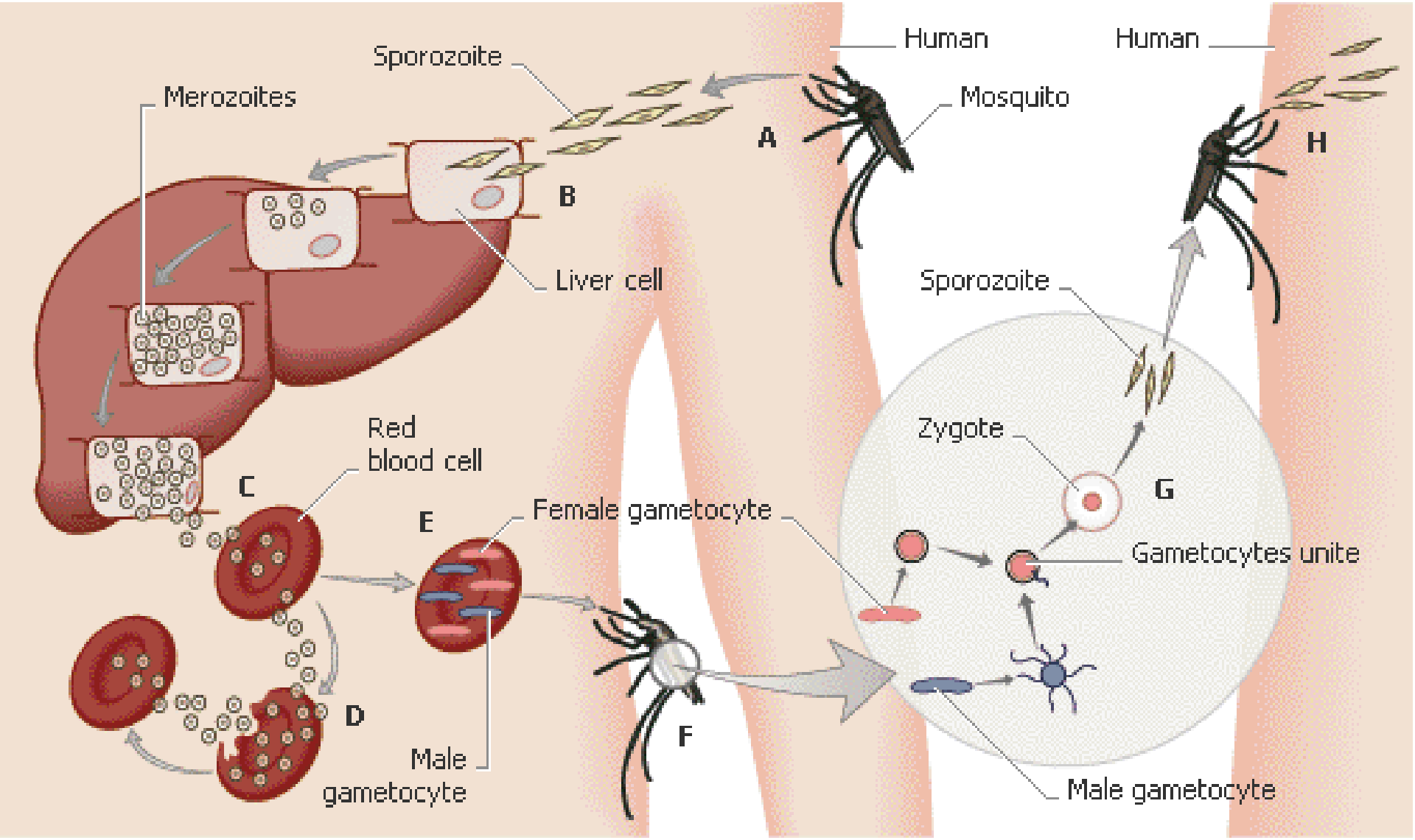
Feeds only on humans

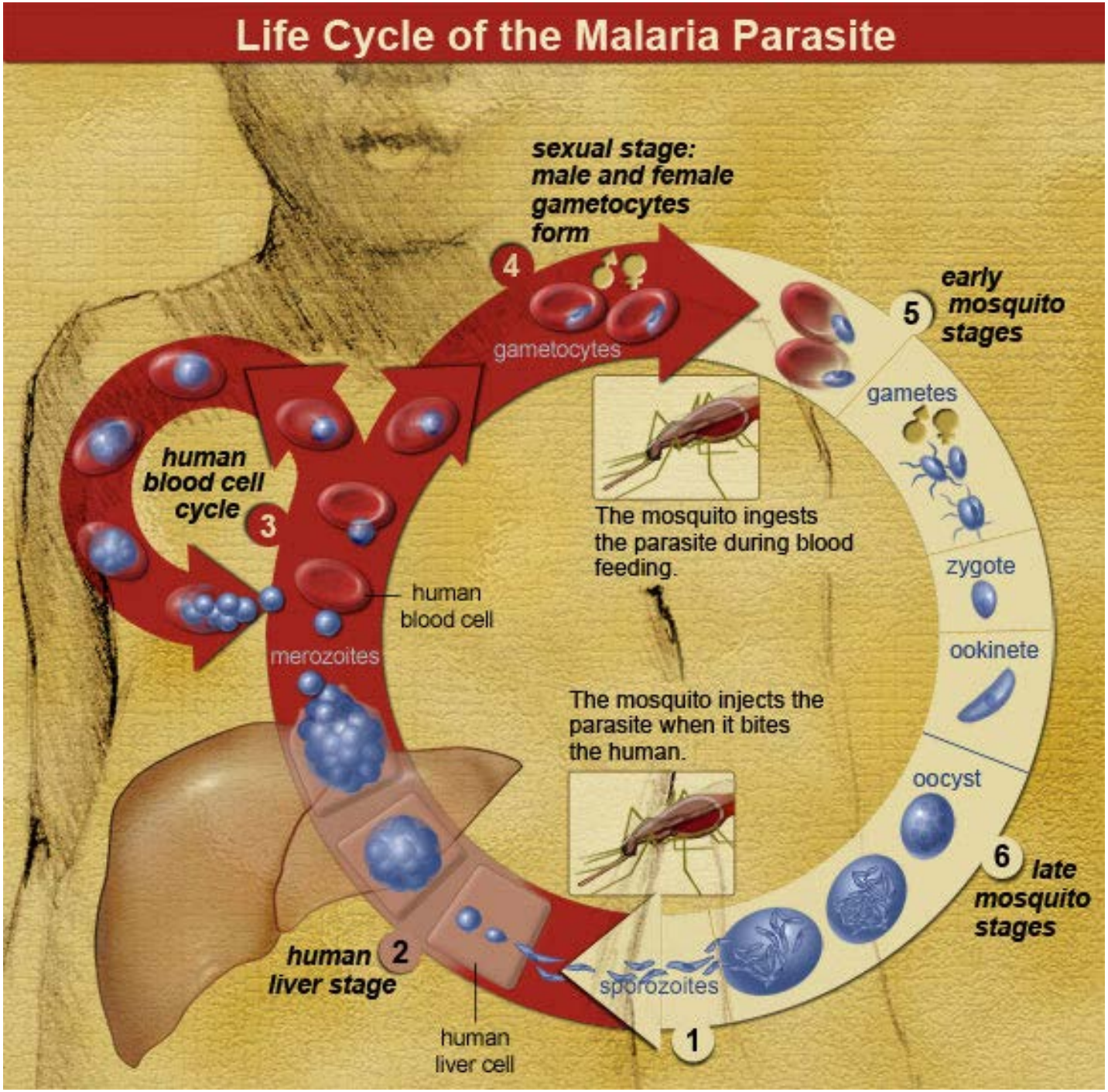
Angle of the bite

Anopheles adults usually rest and feed with the body at an angle of 45º to the surface.

The *Aedes* or *Culex* adult rests and feeds with its body parallel to the surface.



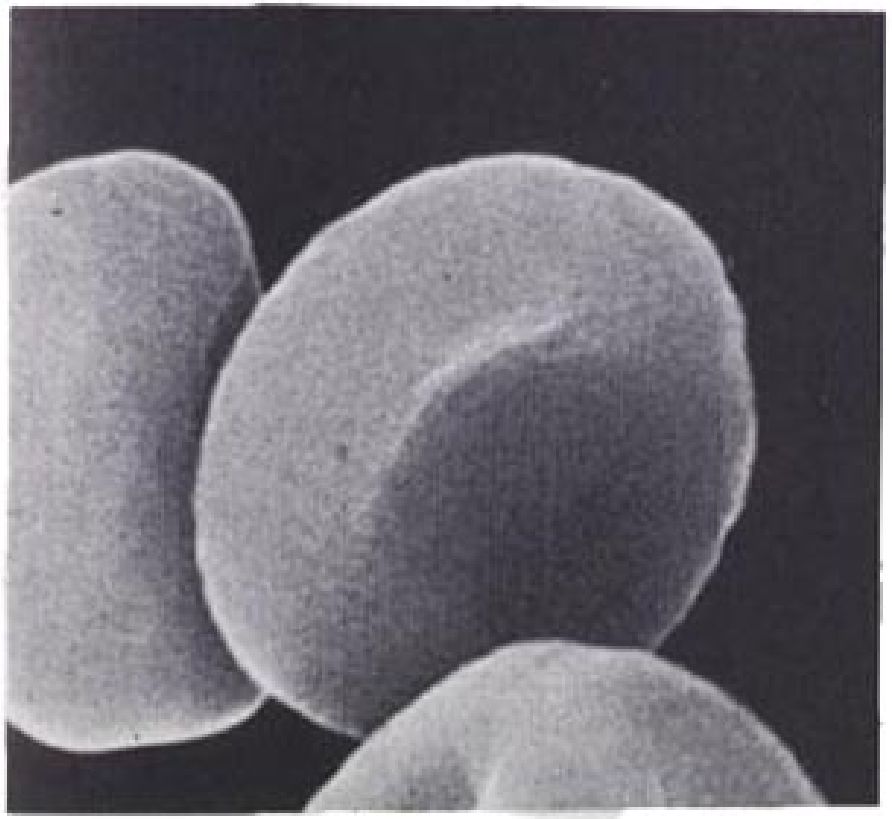

Human
Sporozoite
Merozoites
Mosquito
A
B
Liver cell
Red
blood cell
C
E
Female gametocyte
D
Male
gametocyte
F
Human
H
Sporozoite
Zygote
G
Gametocytes unite
Male gametocyte


Life Cycle of the Malaria Parasite
sexual stage: male and female gametocytes form
4
gametocytes
early mosquito stages
5
gametes
zygote
ookinete
oocyst
6
late mosquito stages
The mosquito ingests the parasite during blood feeding.
human blood cell cycle
3
human blood cell
merozoites
The mosquito injects the parasite when it bites the human.
human liver stage
2
sporozoites
human liver cell
1

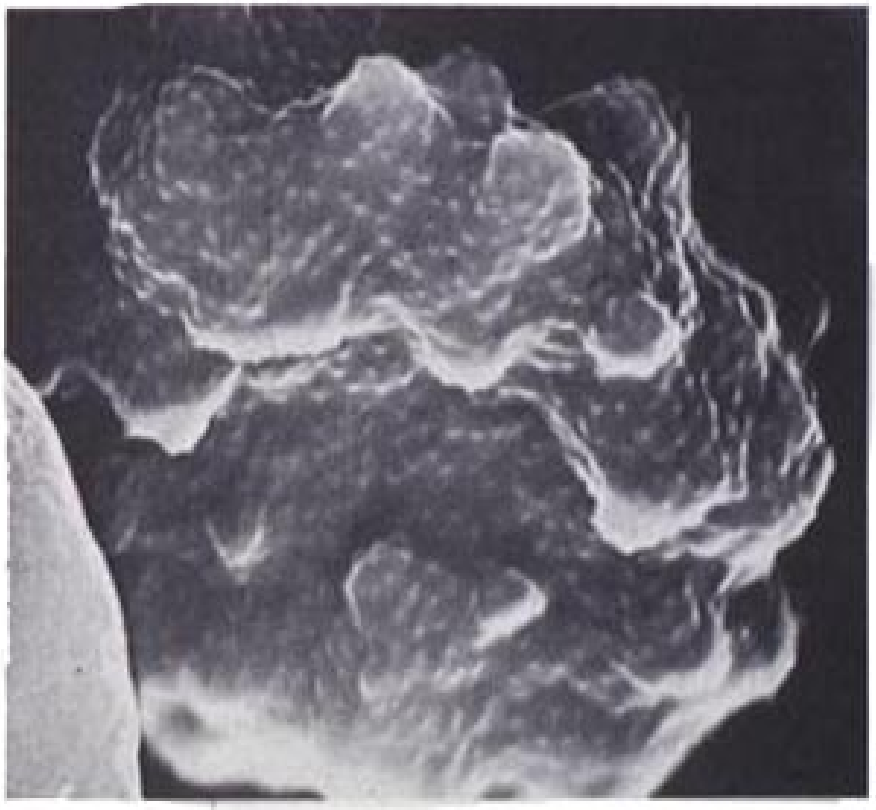
Clinical Disease and Diagnosis

How malaria causes disease

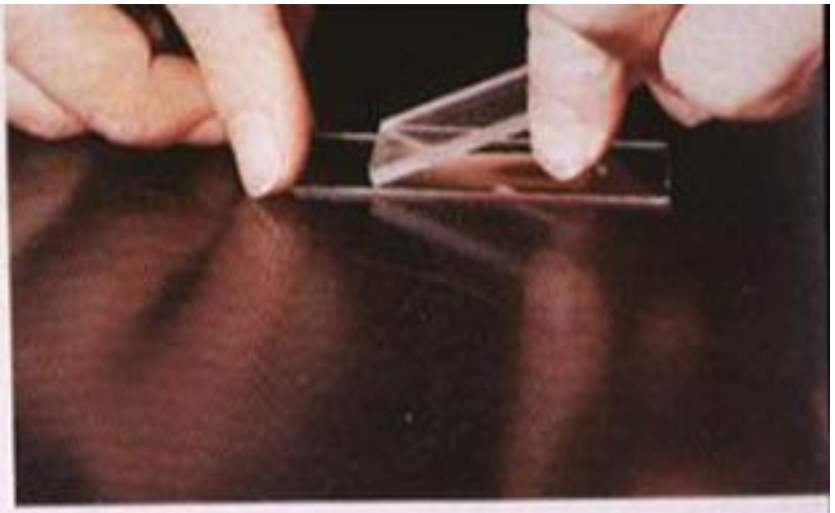
- The liver stages are asymptomatic
- Disease results from blood stages
  - Direct destruction of red blood cells
  - Adherence to vascular endothelium in organs and tissues
    - *var* genes encode parasite proteins expressed on red cell surface
    - Both infected and uninfected cells are affected
  - Stimulation of host immune response



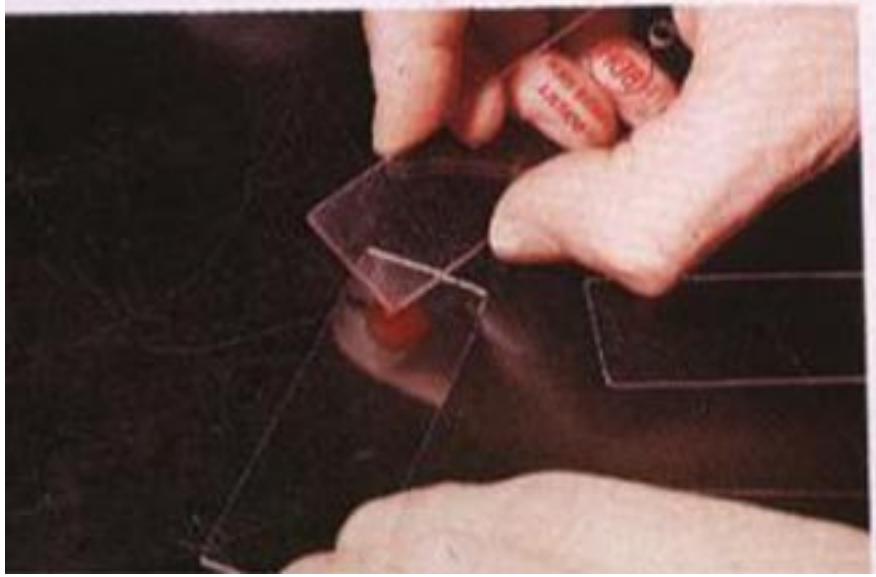
A.



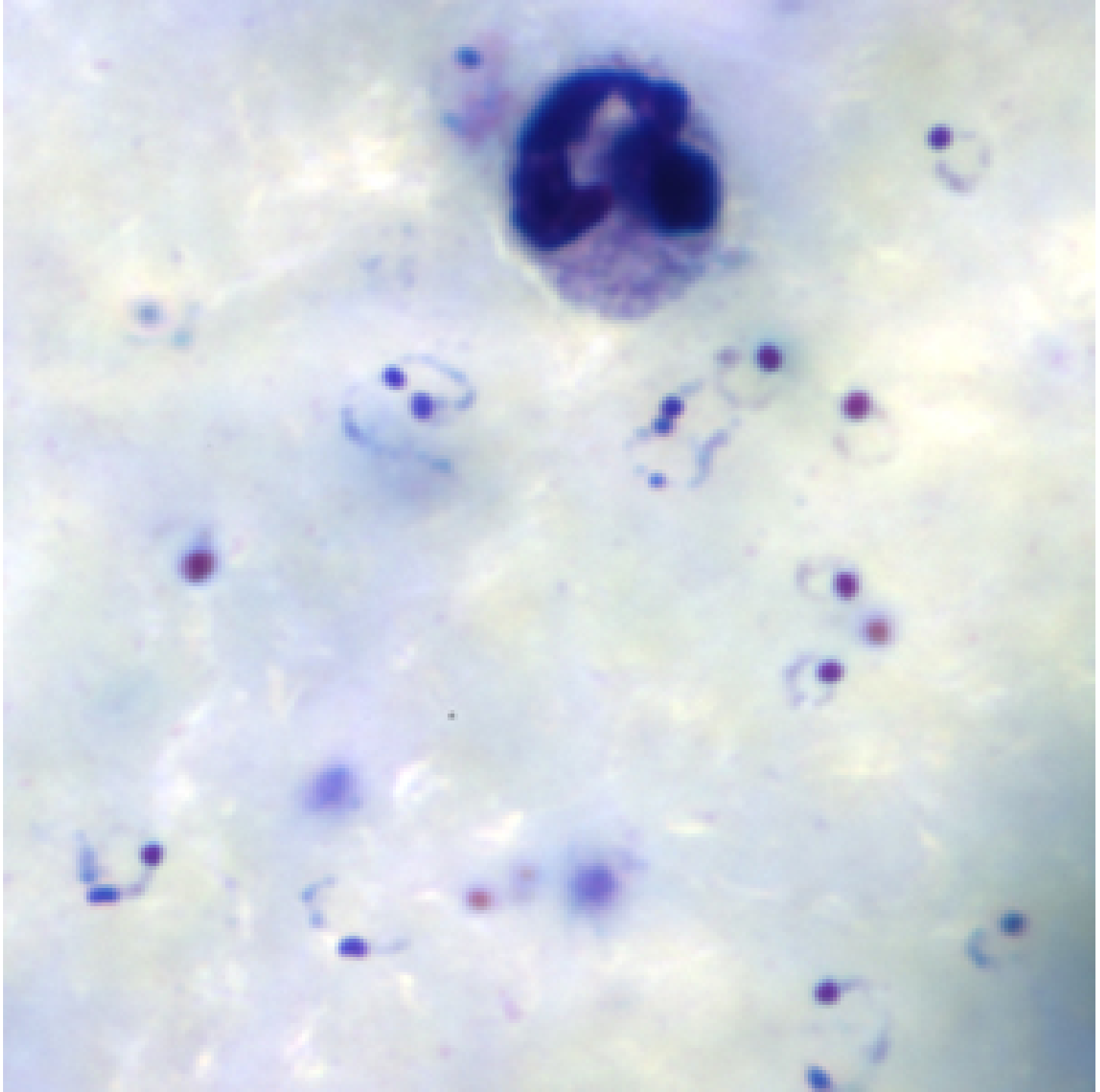
B.

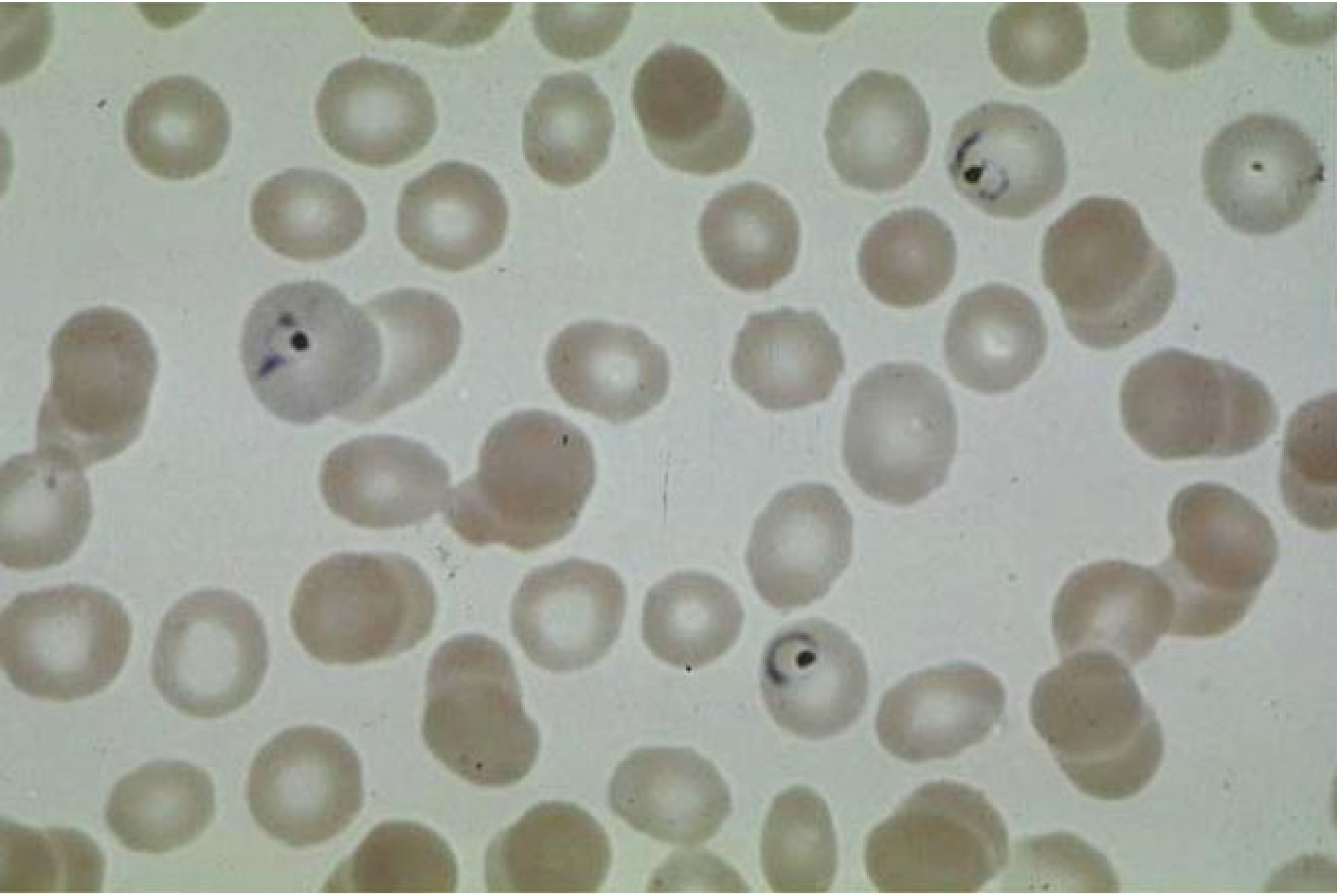


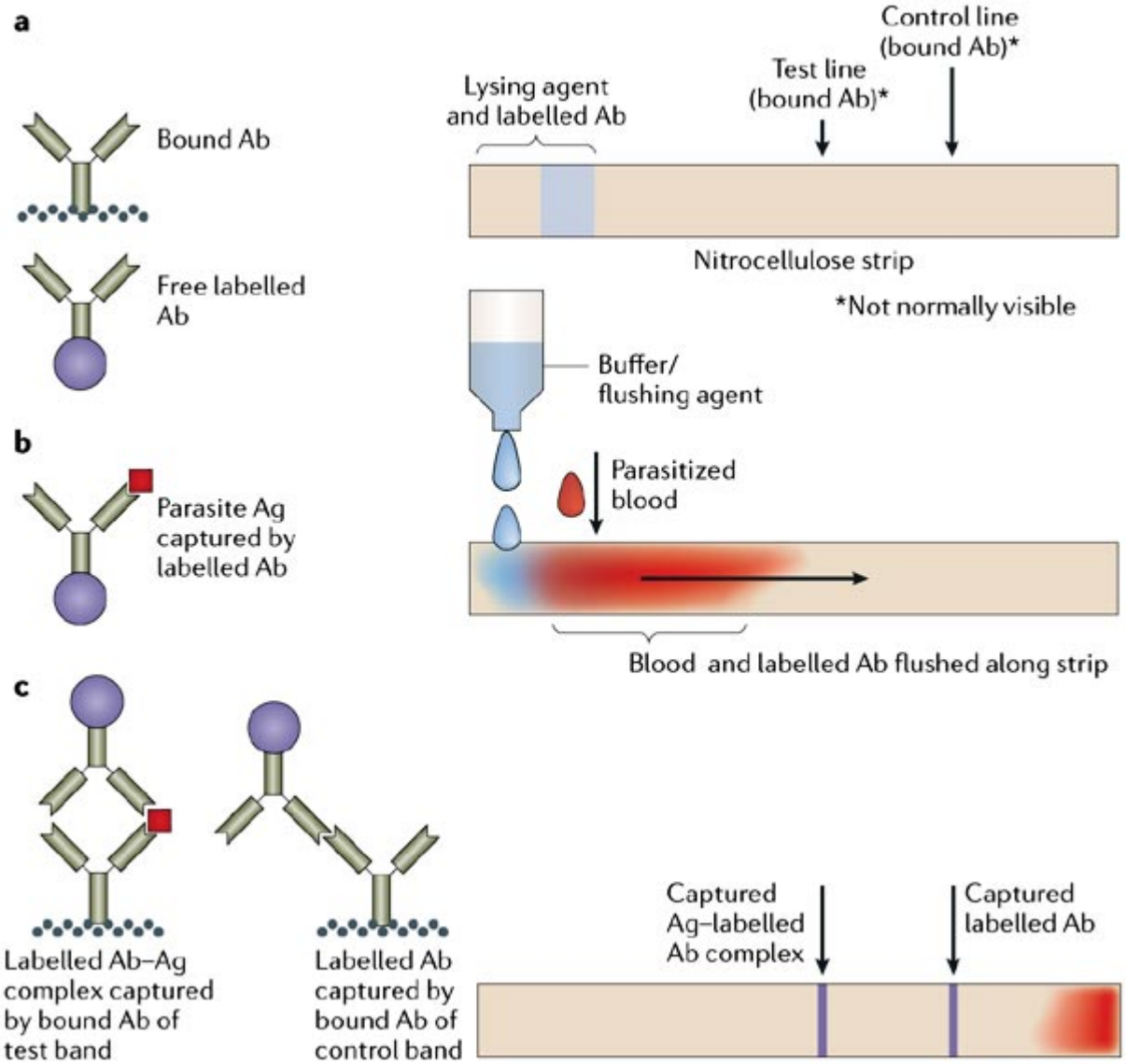
77

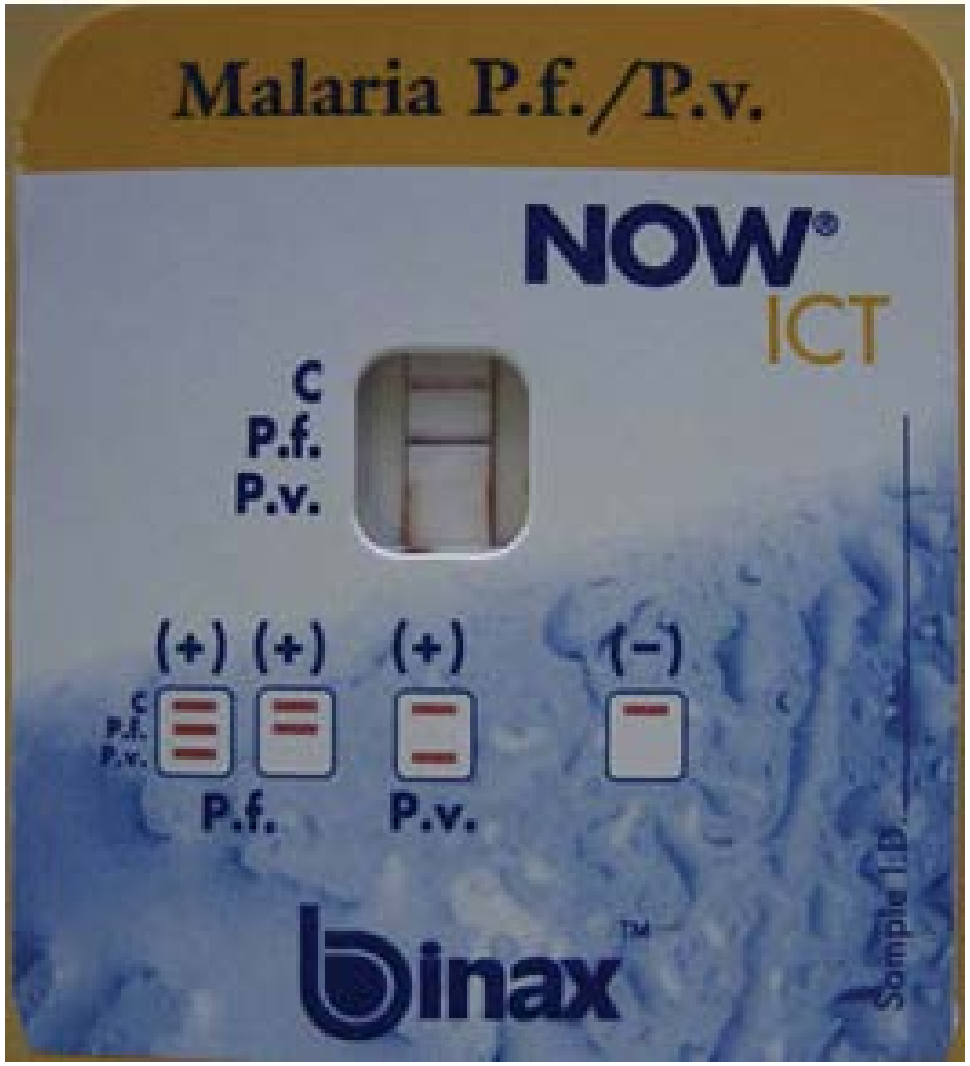



eppendorf






a
Bound Ab
Free labelled Ab
b
Parasite Ag captured by labelled Ab
c
Labelled Ab–Ag complex captured by bound Ab of test band
Labelled Ab captured by bound Ab of control band
Lysing agent and labelled Ab
Test line (bound Ab)*
Control line (bound Ab)*
Nitrocellulose strip
*Not normally visible
Buffer/ flushing agent
Parasitized blood
Blood and labelled Ab flushed along strip
Captured Ag–labelled Ab complex
Captured labelled Ab



Sensitivity: 95%
Specificity: 94%

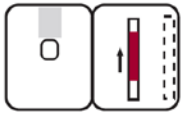
IMPORTANT: The instructions below are abbreviated and are intended for users familiar with the test procedure. Consult the Product Insert for detailed instructions and performance characteristics.

TEST PROCEDURE

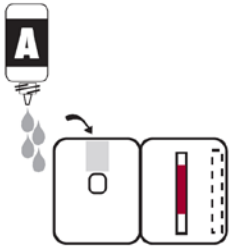
1) **SLOWLY** add 15 µl of blood from an EDTA tube (or from an EDTA capillary tube) to the **PURPLE** sample pad.
See figure 1 on test device.
IMPORTANT: Incorrect addition of sample may lead to an invalid or uninterpretable test.

2) Hold the Reagent A bottle vertically and add **two (2)** free-falling **drops** of Reagent A to the white pad immediately below the purple sample pad. Allow the first drop to absorb into the pad before adding the second drop. See figure 2 on test device.

3) Allow the blood sample to run up the full length of the test strip. See figure 3 on test device. NOTE: If blood flow up the test strip appears to stall or is less than halfway up the strip after one minute, add one additional drop of Reagent A to the white pad at the bottom of the test strip.



4) Just before the blood sample reaches the base of the white pad at the top of the test strip, **SLOWLY** add **four (4)** free-falling drops of Reagent A to the wash pad on the top left-hand side of the device.
See figure 4 on test device.



5) Remove the adhesive liner and close the device.
See figure 5 on test device.

6) Read the test result 15 minutes after closing the test device.

RESULT INTERPRETATION

TEST	RESULTS	DESCRIPTION / INTERPRETATION
T1 Positive		Positive result for *P. falciparum* (P.f.)
T2 Positive		Positive result for *P. vivax* (P.v.) or *P. malariae* (P.m.) or *P. ovale* (P.o.) In some cases the appearance of only the T2 Line may indicate a mixed infection with two or more of P.v., P.m., and P.o.
T1 + T2 Positive		Positive result for *P. falciparum* (P.f.) In some cases the appearance of both the T1 and T2 Lines may indicate a mixed infection of P.f. with another species.
No T1 or T2 Lines		Negative result (no malaria antigens were detected)

Invalid and / or Uninterpretable Test Results
The test is invalid if the Control (C) Line does not appear, whether a Test Line(s) is present or not.

The test is uninterpretable if the background color hinders reading of the test result at 15 minutes.

inverness medical

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Scarborough, Maine 04074
US: 877-441-7440
OUS: +1-321-441-7200
www.invernessmedicalpd.com

CE EC REP

EMERGO EUROPE
Molenstraat 15
2513 BH, The Hague
The Netherlands

Rev. 2 4/13/09
IN665001

Waiting 15 minutes for an RDT test result . . .

WHO recommendations for diagnosis

1. Prompt parasitological confirmation by microscopy or RDTs in all patients suspected of malaria before treatment is started; and
2. Treatment solely on the basis of clinical suspicion should only be considered when a parasitological diagnosis is not accessible.

*Major paradigm change from presumptive treatment, especially for <5 years at high risk for severe malaria

Infection ≠ Disease

- Malaria infection occurs in many individuals
  - Those with semi-immunity have no illness
    - Asymptomatic parasitemia
  - Those with less immunity may or may not develop disease

Malaria disease

- Uncomplicated malaria
  - Fever paroxysms with shaking chills
  - Other common symptoms: headache, myalgia, cough, diarrhea, abdominal pain, anorexia
  - Treat with oral antimalarial drugs
- Severe malaria
  - Most common manifestations in children in endemic areas:
    - cerebral malaria
    - severe anemia

Case Definitions

- Uncomplicated malaria: no evidence of vital organ dysfunction
- Severe malaria: malaria and “danger signs”

Severe malaria clinical features

1. Impaired consciousness or unrousable coma
2. Prostration, i.e. generalized weakness so that the patient is unable walk or sit up without assistance
3. Failure to feed
4. Multiple convulsions – more than two episodes in 24 h
5. Deep breathing, respiratory distress (acidotic breathing)
6. Circulatory collapse or shock, systolic blood pressure < 70 mm Hg in adults and < 50 mm Hg in children
7. Clinical jaundice plus evidence of other vital organ dysfunction
8. Haemoglobinuria
9. Abnormal spontaneous bleeding
10. Pulmonary oedema (radiological)

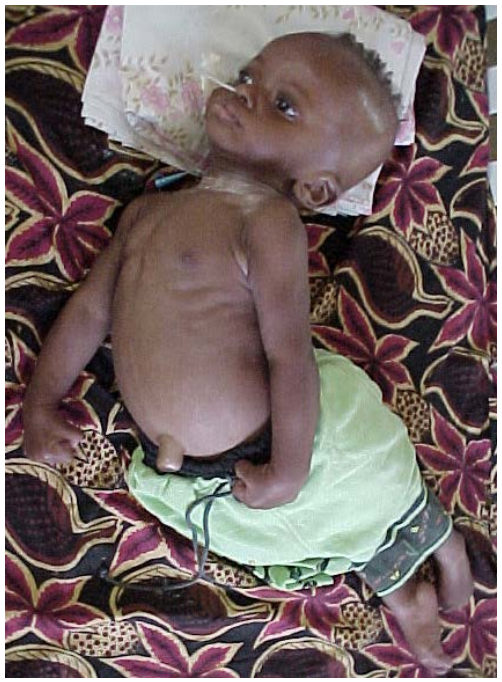
Severe malaria laboratory features

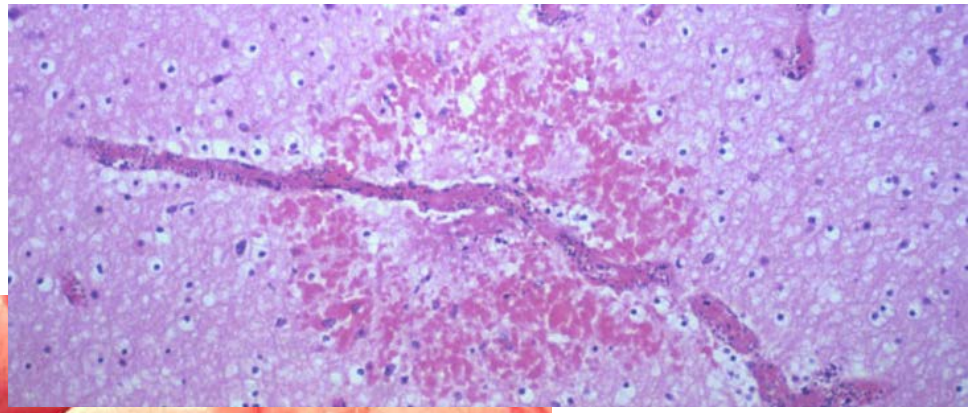
1. Hypoglycaemia (blood glucose < 2.2 mmol/l or < 40 mg/dl)
2. Metabolic acidosis (plasma bicarbonate < 15 mmol/l)
3. Severe normocytic anaemia (Hb < 5 g/dl, packed cell volume < 15%)
4. Haemoglobinuria
5. Hyperparasitaemia (> 2% or 100,000/µl in low intensity transmission areas or > 5% or 250,000/µl in areas of high stable malaria transmission intensity)
6. Hyperlactataemia (lactate > 5 mmol/l)
7. Renal impairment (serum creatinine > 265 µmol/l).

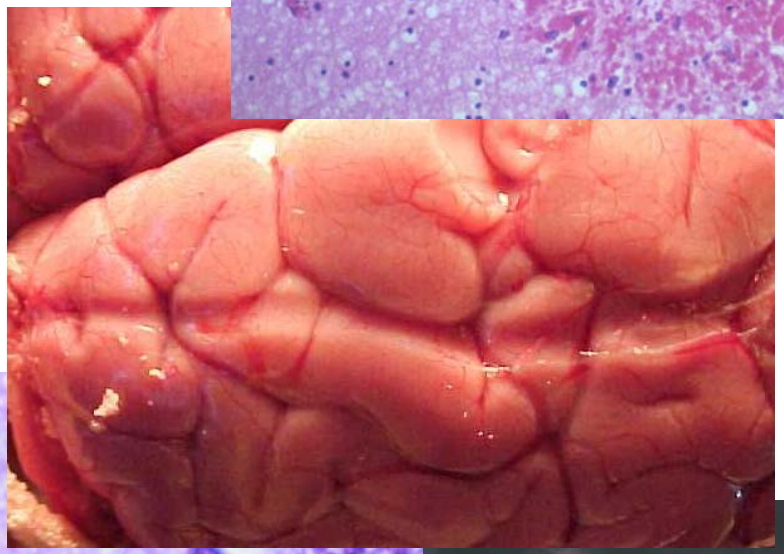
Severe malaria

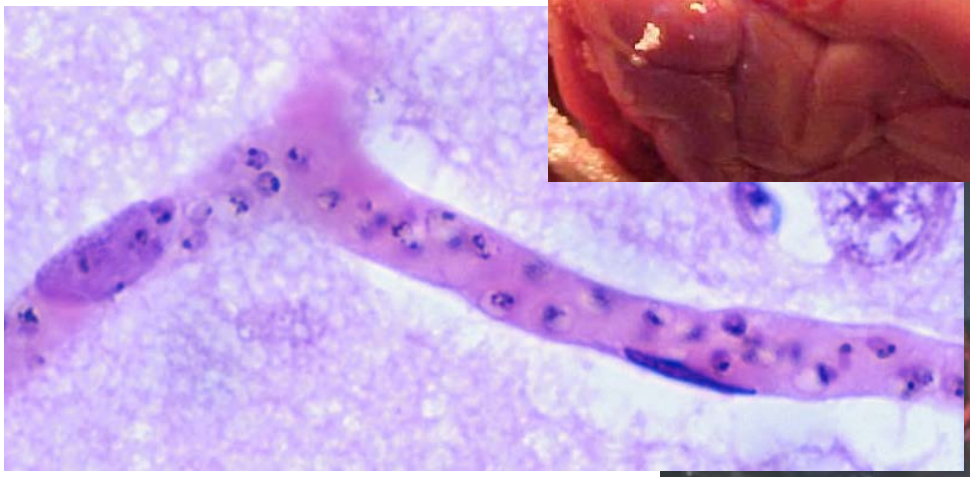
- Untreated, mortality approaches 100%
- With prompt treatment, can reduce to 15-20% mortality
- Highest mortality risk is in the first 24 hours

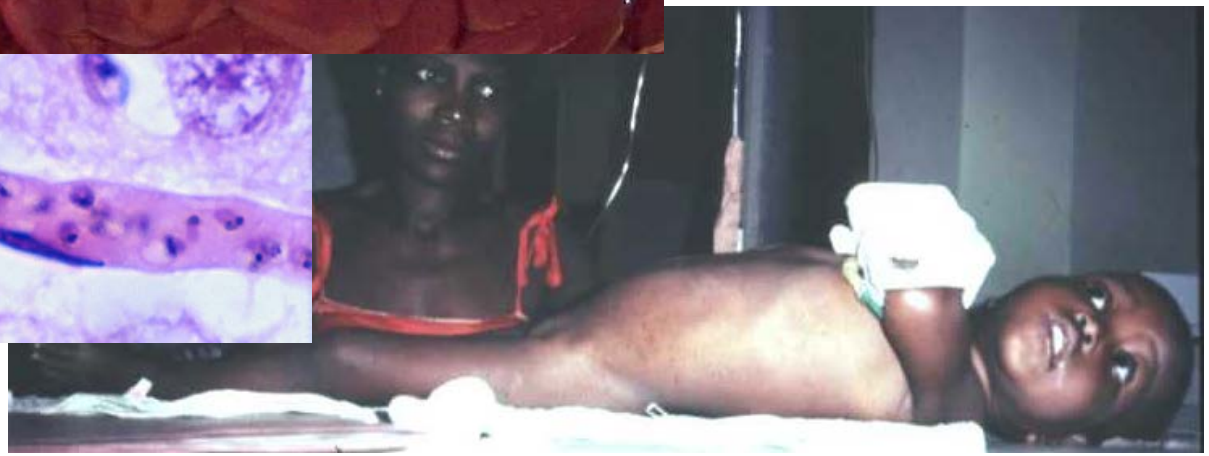
Cerebral malaria





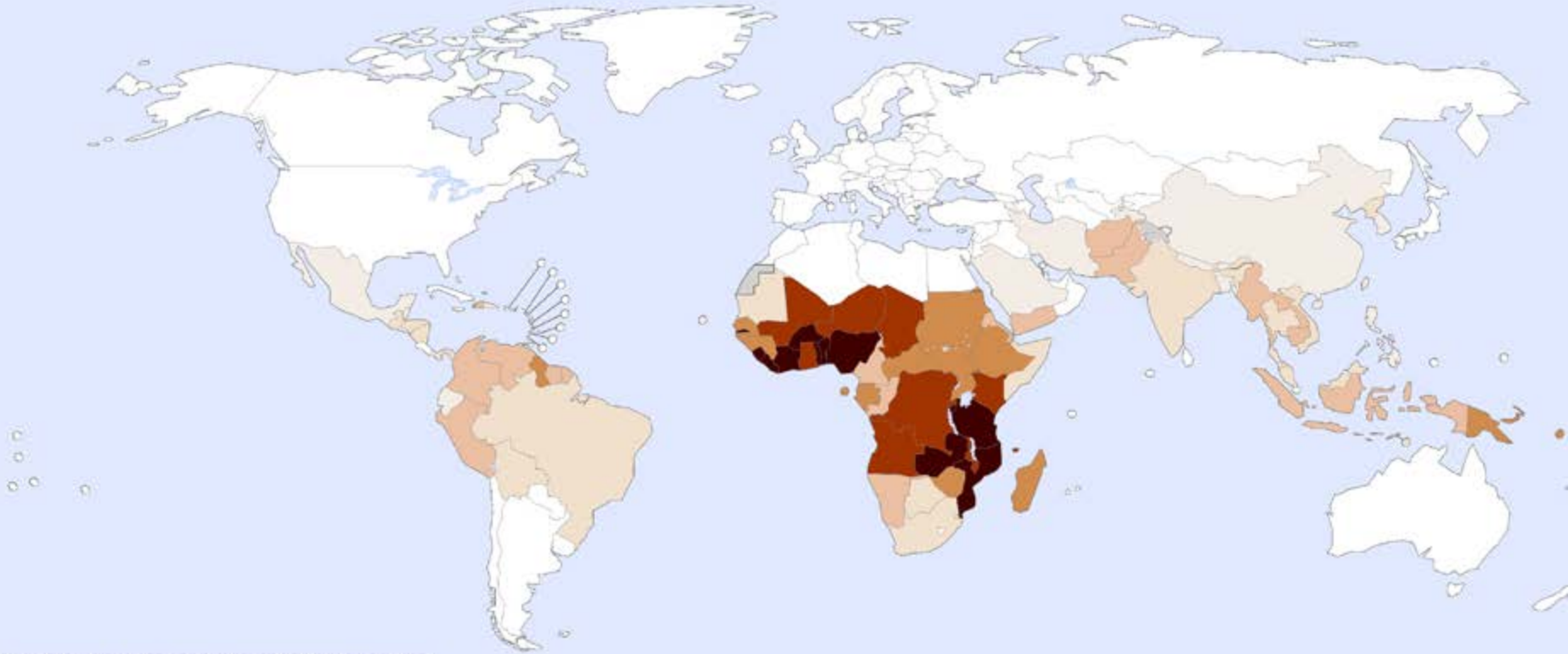






Epidemiology

Countries with ongoing transmission of malaria, 2013



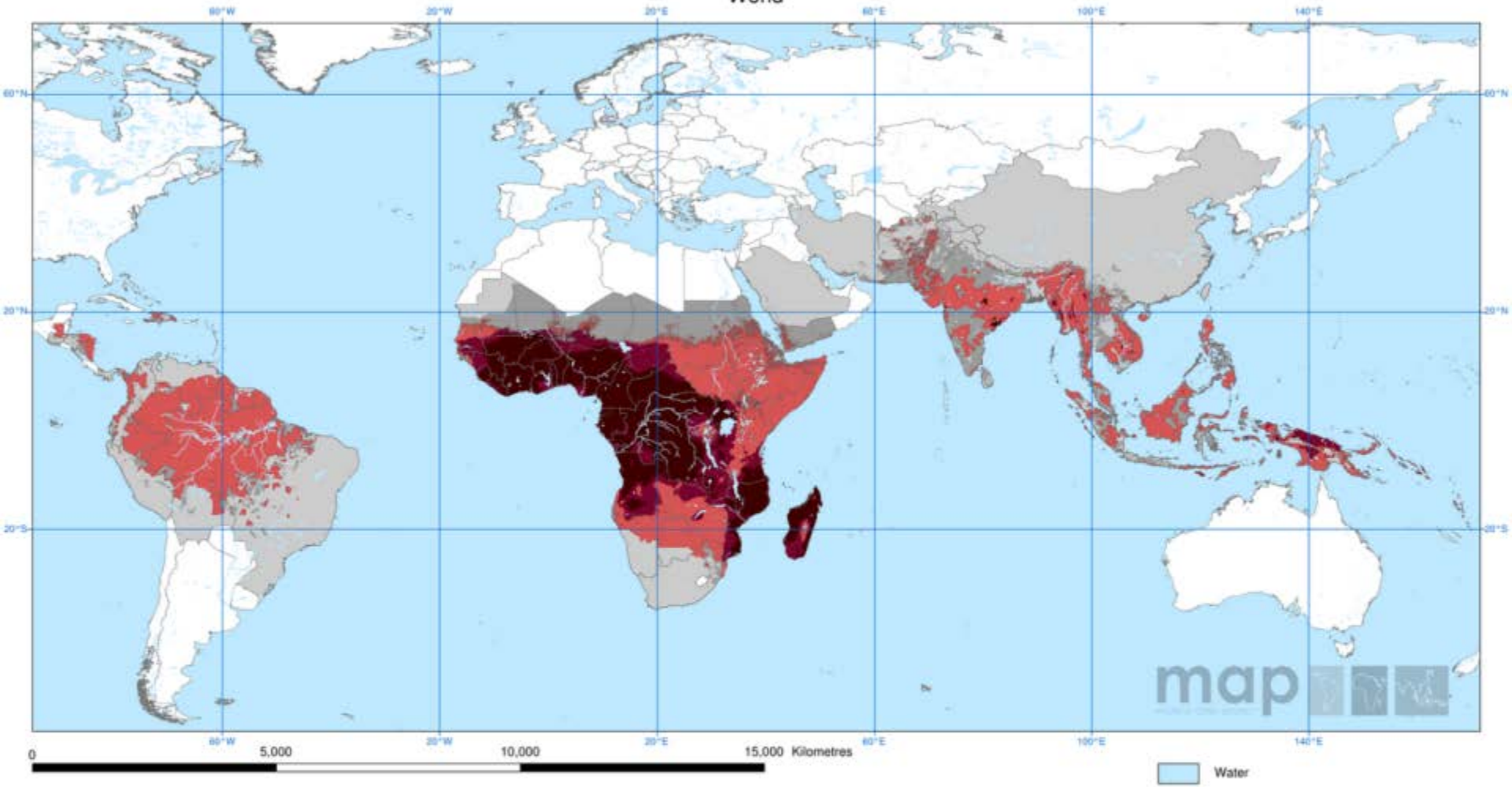
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Malaria Report 2014
Map Production: Global Malaria Programme
World Health Organization

Wor
Orga

The spatial distribution of *Plasmodium falciparum* malaria in 2010 stratified by endemicity class

World

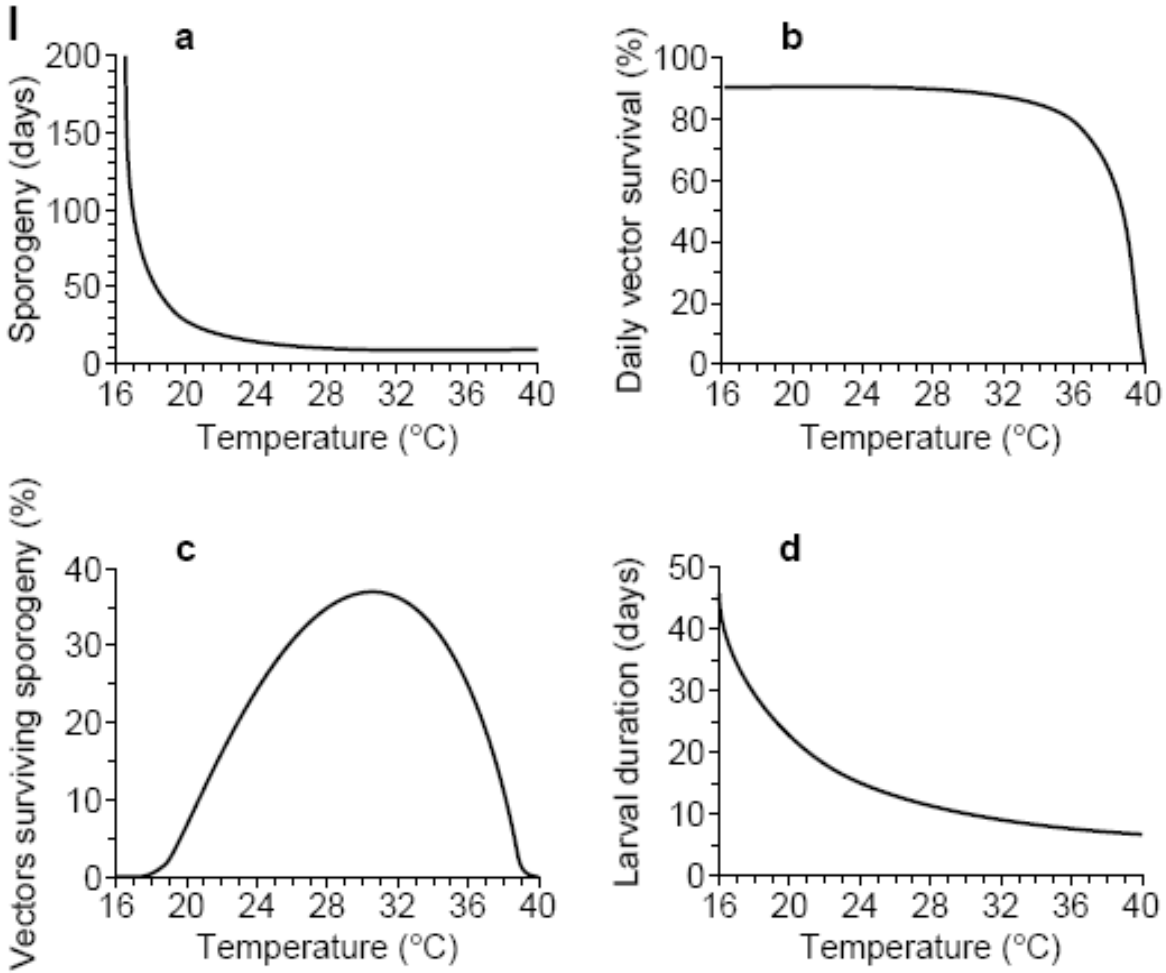


Estimates of the age-standardised annual mean *Plasmodium falciparum* parasite rate in two to ten year olds ($Pf PR_{2-10}$), within the spatial limits of stable transmission, stratified into four levels of risk. Areas of no risk and unstable risk ($Pf API < 0.1‰$) are also shown.

Gething, P.W., Patil, A.P., Smith, D.L., Guerra, C.A., Elyazar, I.R.F., Johnstone, G.L., Tatem, A.J. and Hay, S.I. (2011). **A new world malaria map: *Plasmodium falciparum* endemicity in 2010.** *Public Library of Science Medicine*, in submission.

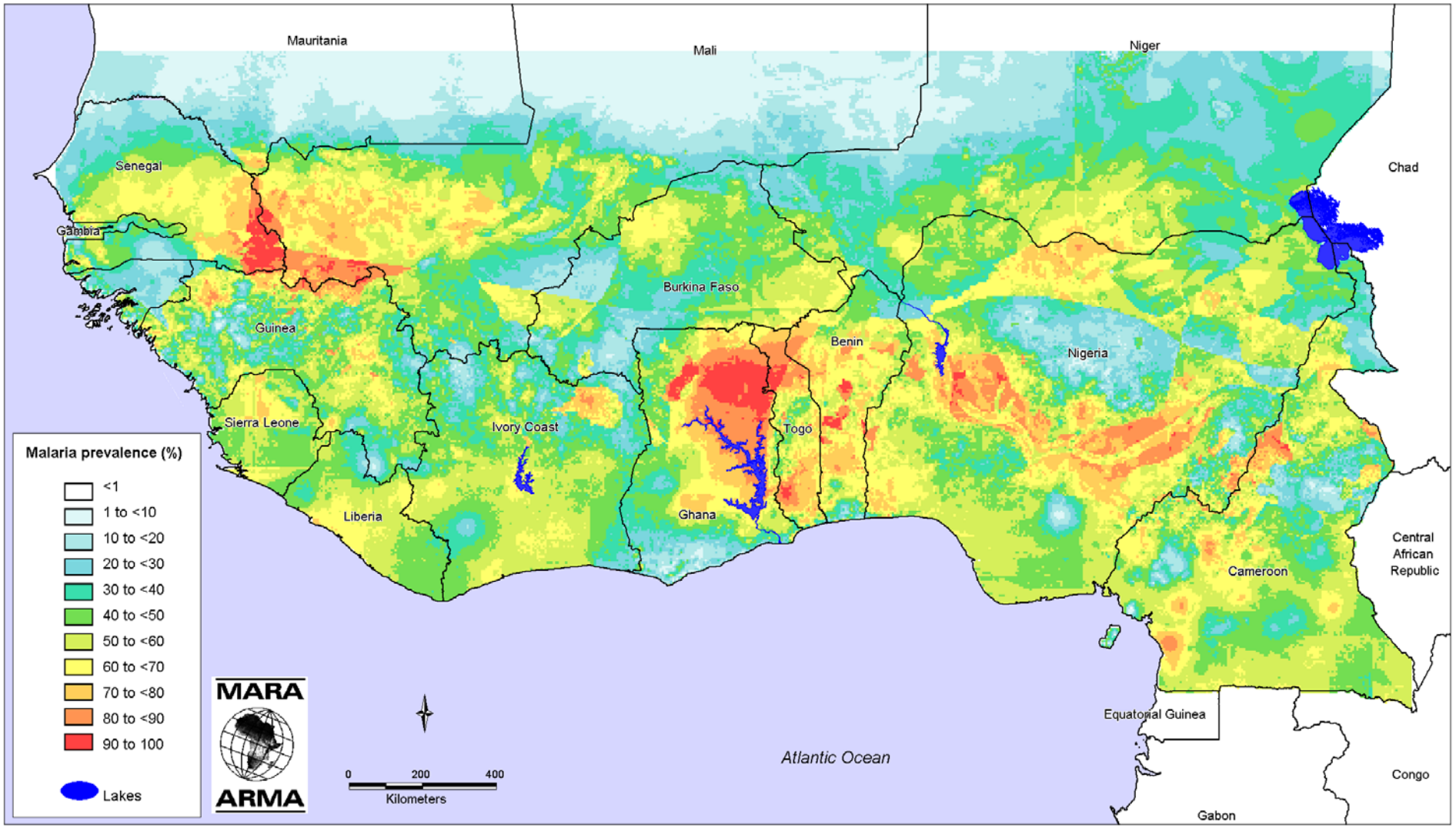
N

Box 1. Relationships between Temperature and Sporogonic Duration (n), Mosquito Survival (p) and Larval Duration



Craig, et al. 1999

Malaria Prevalence Model for West Africa

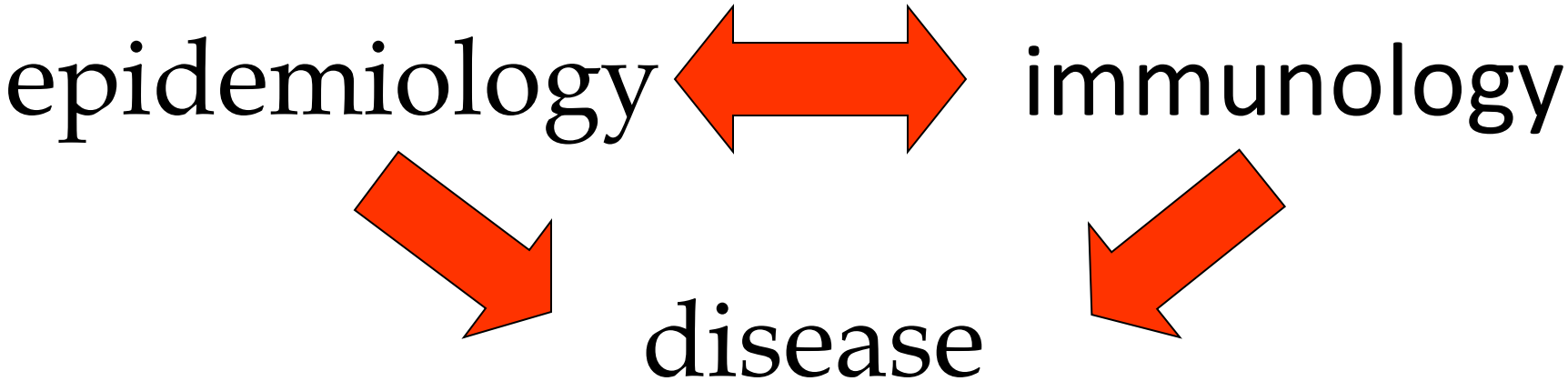


This map is a product of the MARA/ARMA collaboration (http://www.mara.org.za). March 2002, Medical Research Council, PO Box 17120, Congella, 4013, Durban, South Africa
CORE FUNDERS of MARA/ARMA: International Development Research Centre, Canada (IDRC); The Wellcome Trust UK; South African Medical Research Council (MRC); Swiss Tropical Institute, Multilateral Initiative on Malaria (MIM) / Special Programme for Research & Training in Tropical Diseases (TDR), Roll Back Malaria (RBM).
Malaria Prevalence Model: I. Kleinschmidt et al. 2001. An empirical malaria distribution map for West Africa. Tropical Medicine and International Health 6: 779-786.
Topographical data: African Data Sampler, WRI, http://www.igc.org/wri/sdis/maps/ads/ads_id

MALARIOUS AREA OF THE UNITED STATES
1882

Epidemiology of malaria

- Highly variable around the world and even within countries
- Transmission classification:
  - Perennial vs. seasonal
  - Entomological Inoculation Rate (EIR): transmission intensity
    - Can range from <1 to thousands
  - Parasite prevalence in healthy children: endemicity
    - Can get as high as 70%


epidemiology
immunology
disease

At risk groups

1. **Young children** in stable transmission areas who have not yet developed protective immunity against the most severe forms of the disease;
2. **Non-immune pregnant women** as malaria causes high rates of miscarriage and maternal death rates of 10–50%;
3. **Semi-immune pregnant women** in areas of high transmission. Malaria can result in miscarriage and low birth weight, especially during first and second pregnancies. An estimated 200 000 infants die annually as a result of malaria infection during pregnancy;
4. **Semi-immune HIV-infected pregnant women** in stable transmission areas, during all pregnancies. Women with malaria infection of the placenta also have a higher risk of passing HIV infection to their newborns;
5. **People with HIV/AIDS**;
6. **International travellers from non-endemic areas** because they lack immunity;
7. **Immigrants from endemic areas and their children** living in non-endemic areas and returning to their home countries to visit friends and relatives are similarly at risk because of waning or absent immunity.

Epidemiology of malaria

- Age-related acquired immunity
  - Related to intensity and duration of transmission
- Epidemic/unstable malaria
  - Outbreaks where transmission is low to absent
  - Population movements, environmental changes

Age-related acquired immunity protects against disease, not infection

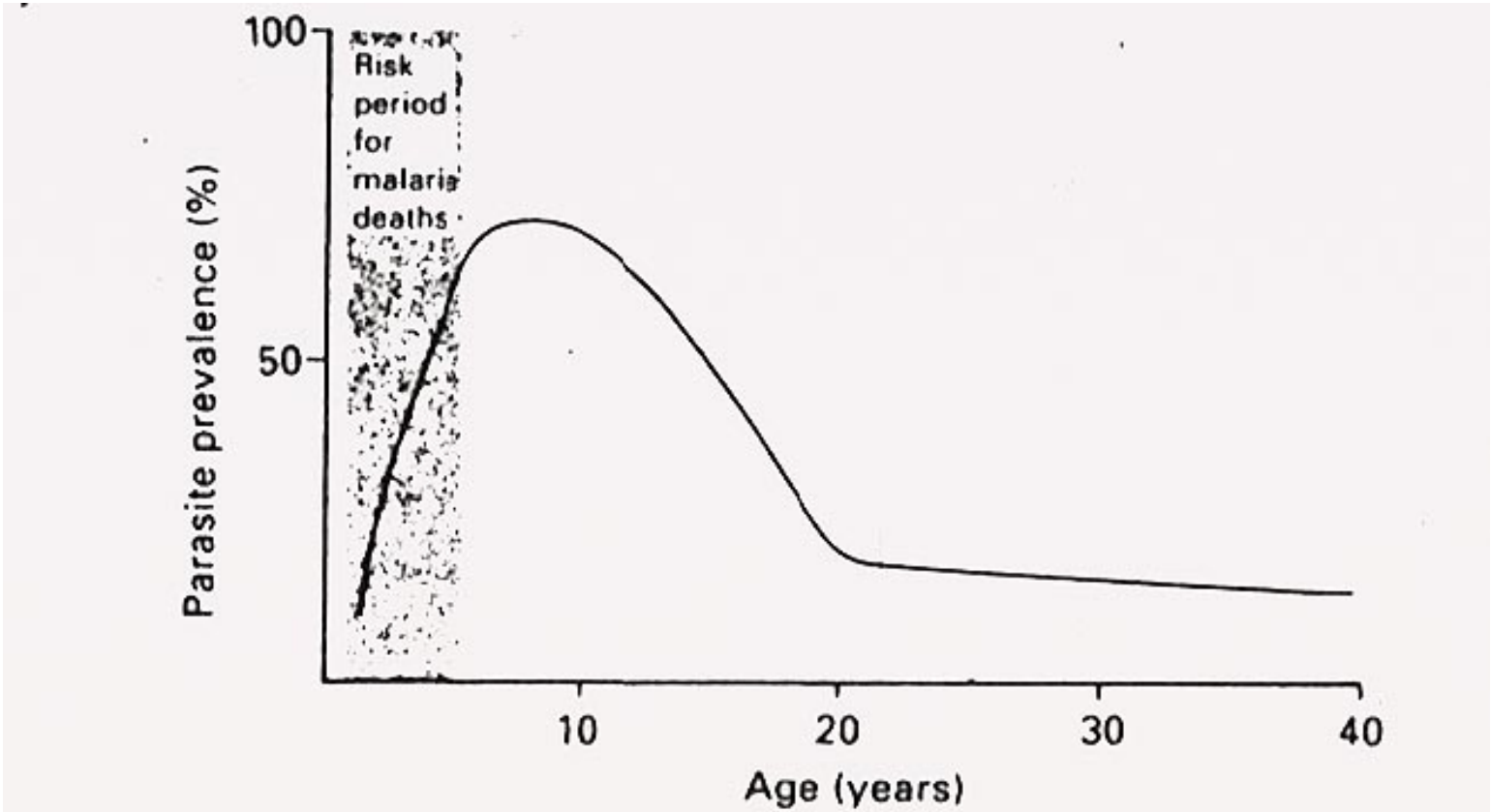
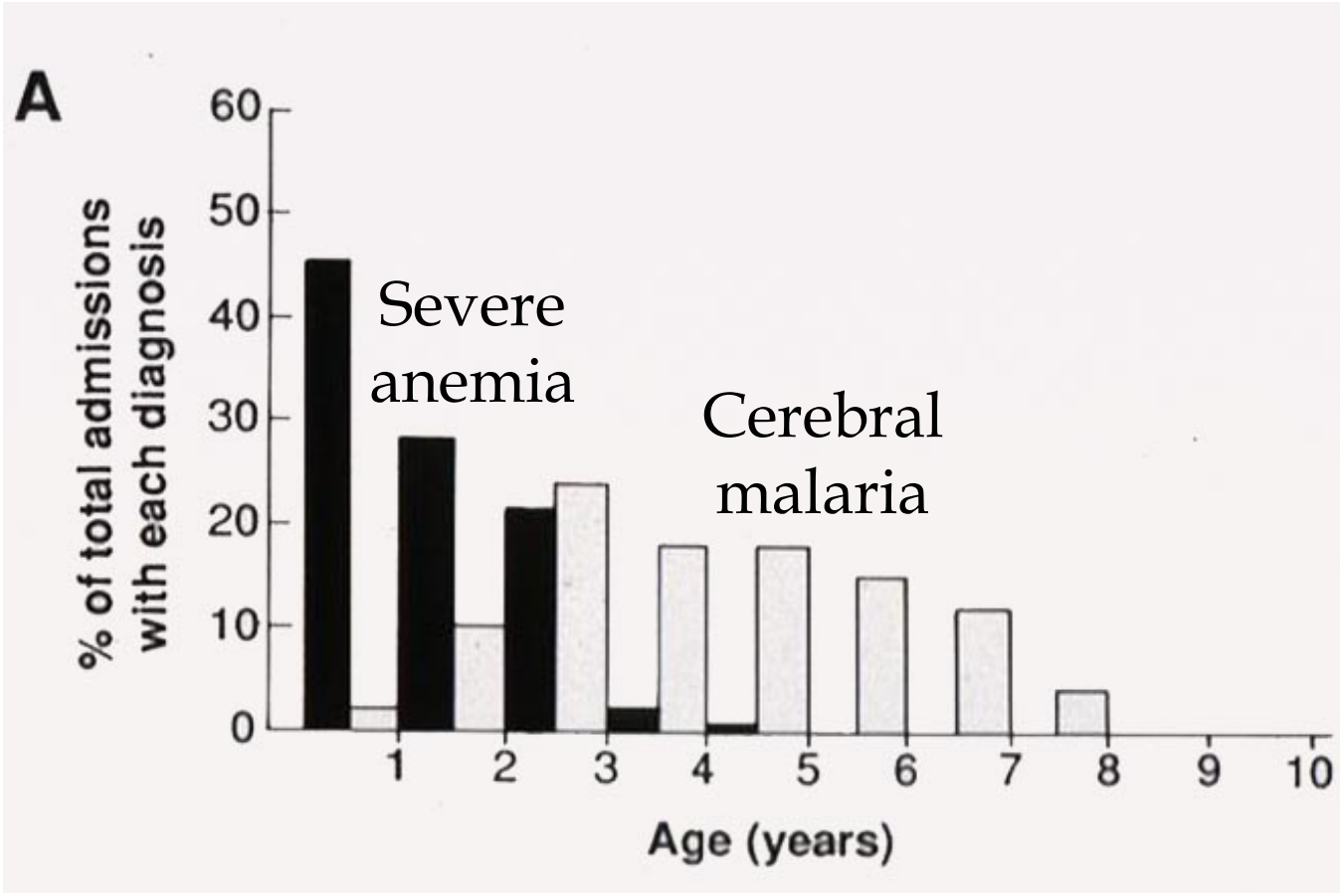


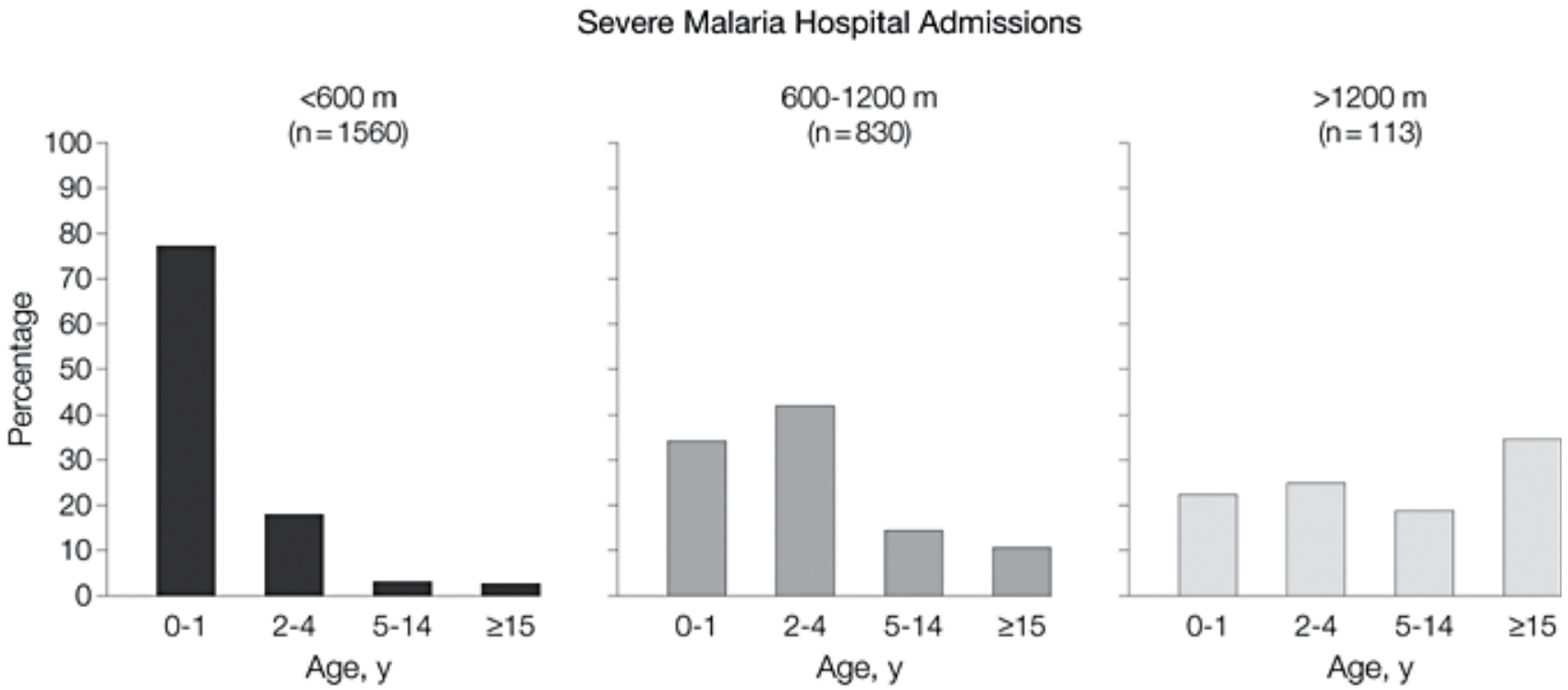
Fig. 1. Prevalence of *Plasmodium falciparum* asexual stages in a rural Gambian community. Data from Greenwood *et al.* (1987) and Marsh *et al.* (1989).

Age-related acquired immunity may also influence manifestation of disease



What are the implications for malaria vaccines and other prevention efforts?

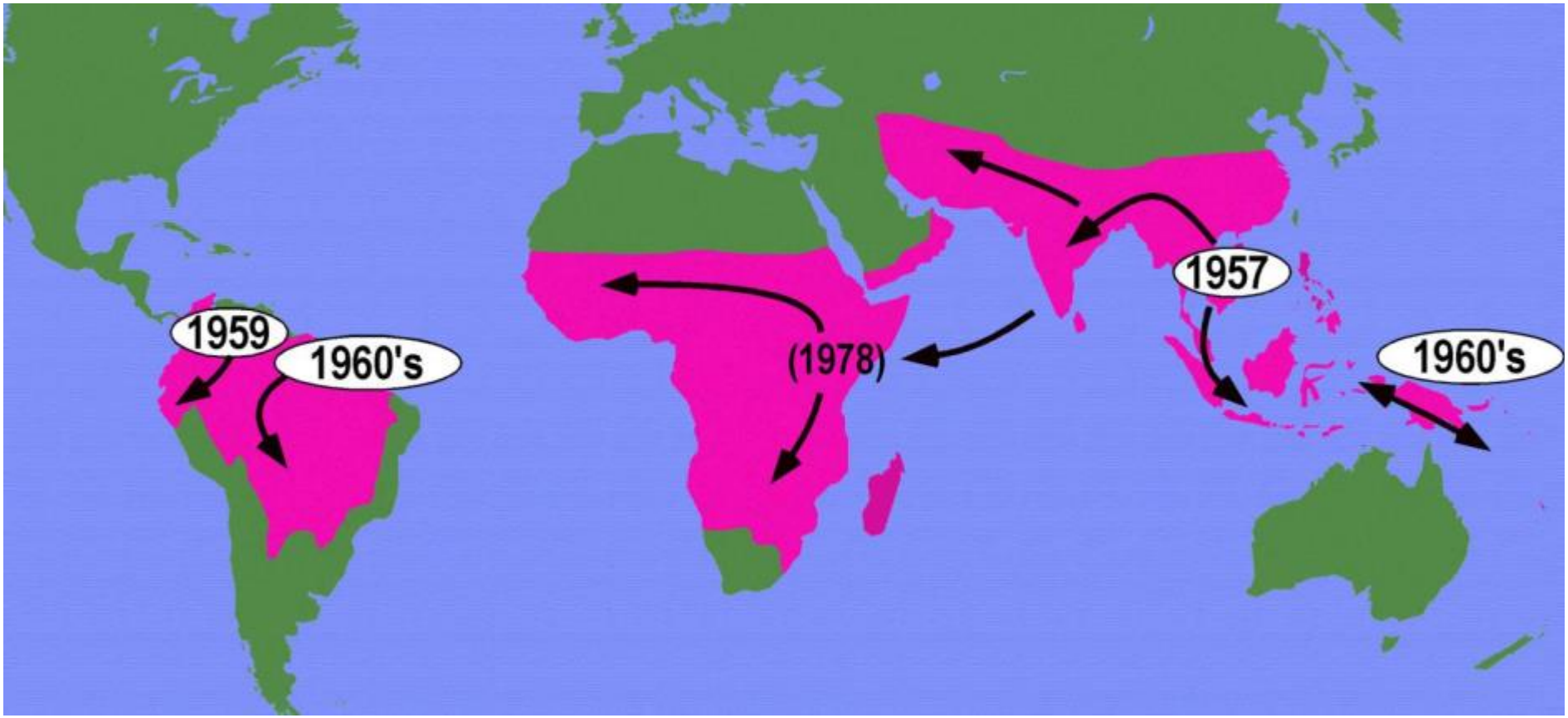
Malaria transmission intensity is related to age of risk for severe malaria



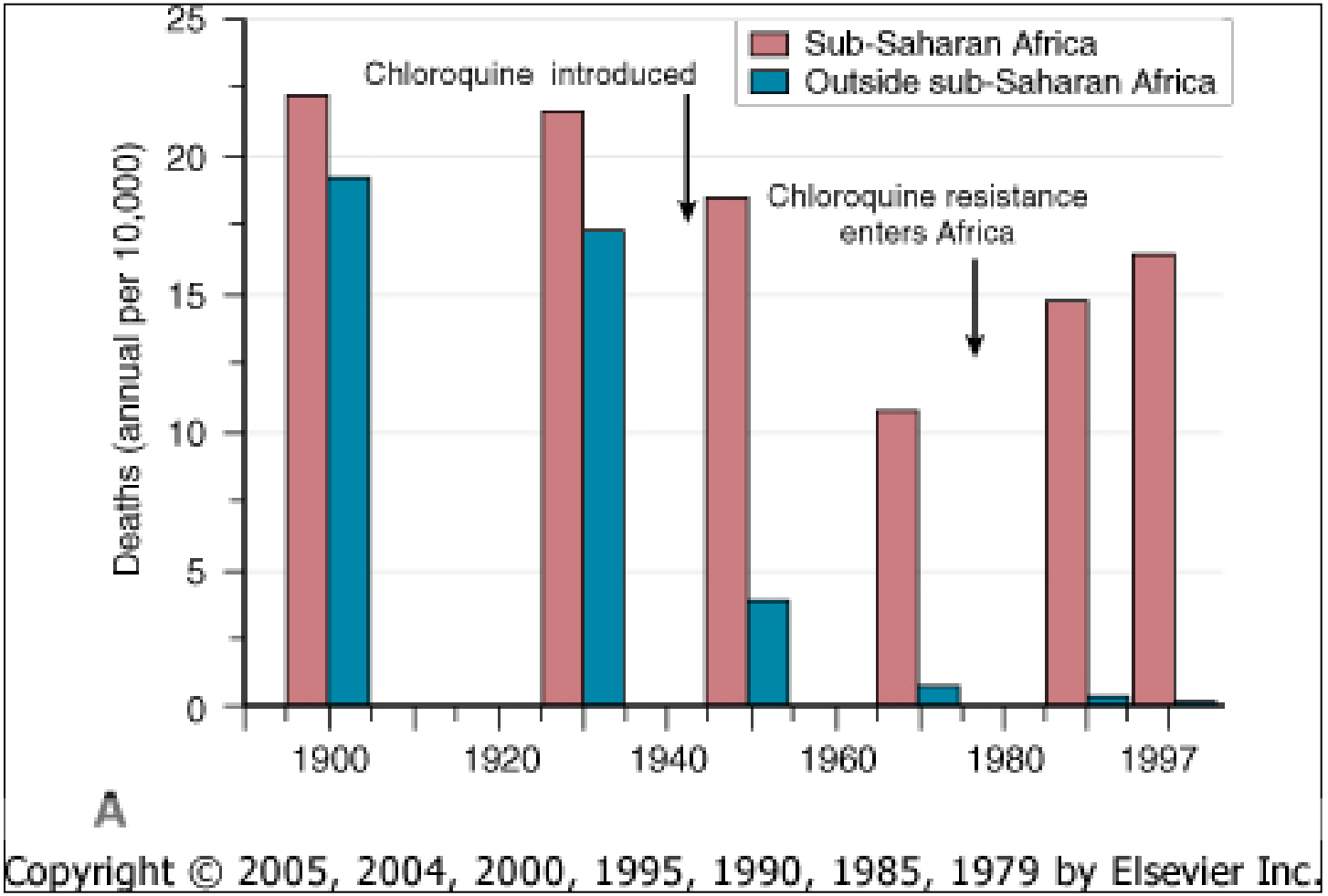
"Shifting burden of disease"?

Malaria Treatment

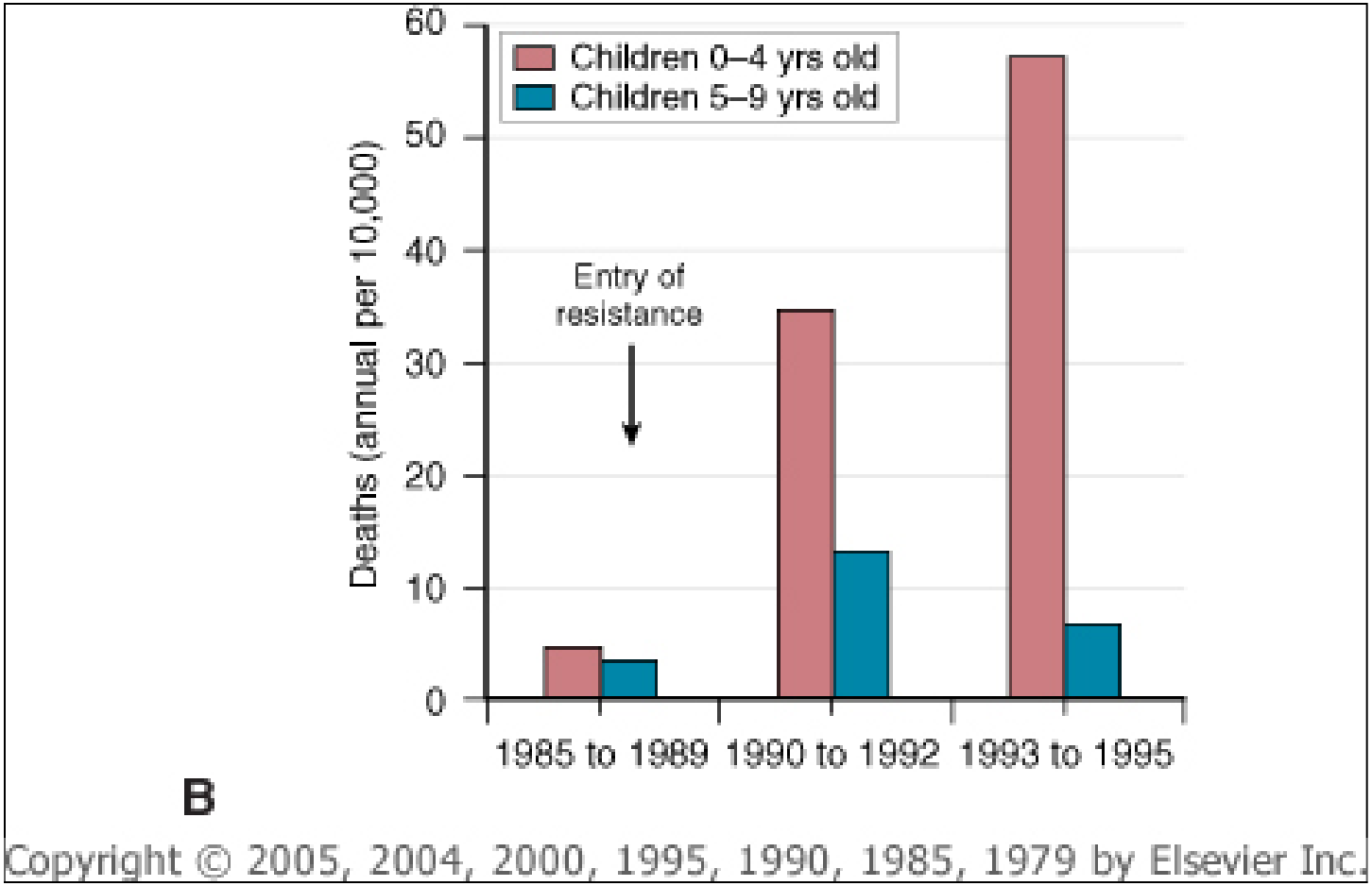
Global spread of chloroquine-resistant *P. falciparum*



Malaria deaths worldwide: Impact of chloroquine



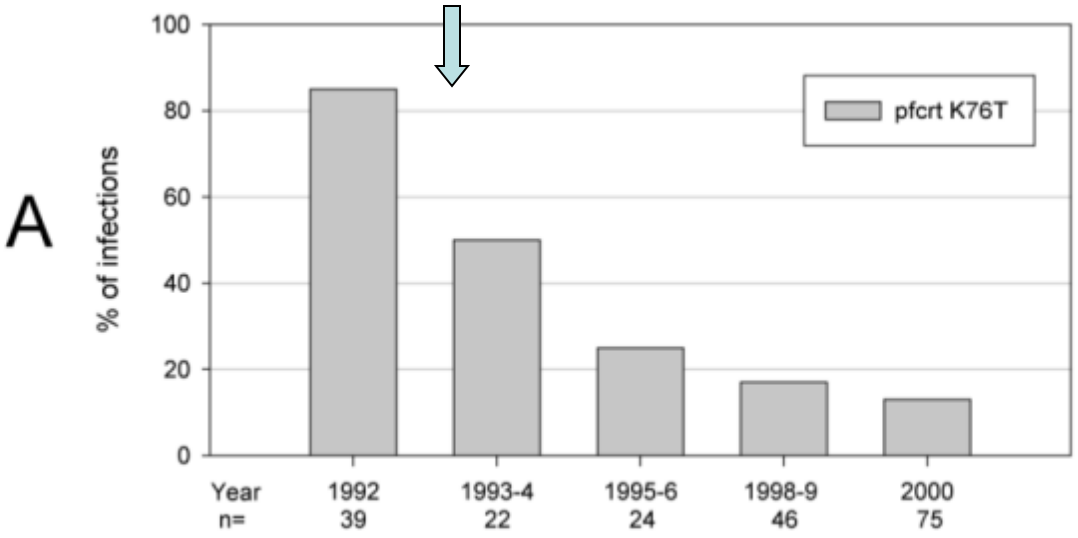
Chloroquine resistance and malaria deaths in Senegal



Chloroquine use in Malawi

- Chloroquine resistance
  - Recognized that CQ resistant malaria was on the rise in East Africa
  - In 1990, 57% of children treated with CQ failed therapy by day 28
    - At the same time, 0 failures with sulfadoxine-pyrimethamine
- Change in policy
  - In 1993, Malawi was the first country in Africa to change the first line anti-malarial therapy from CQ to sulfadoxine-pyrimethamine (SP)

Bloland et al. 1993



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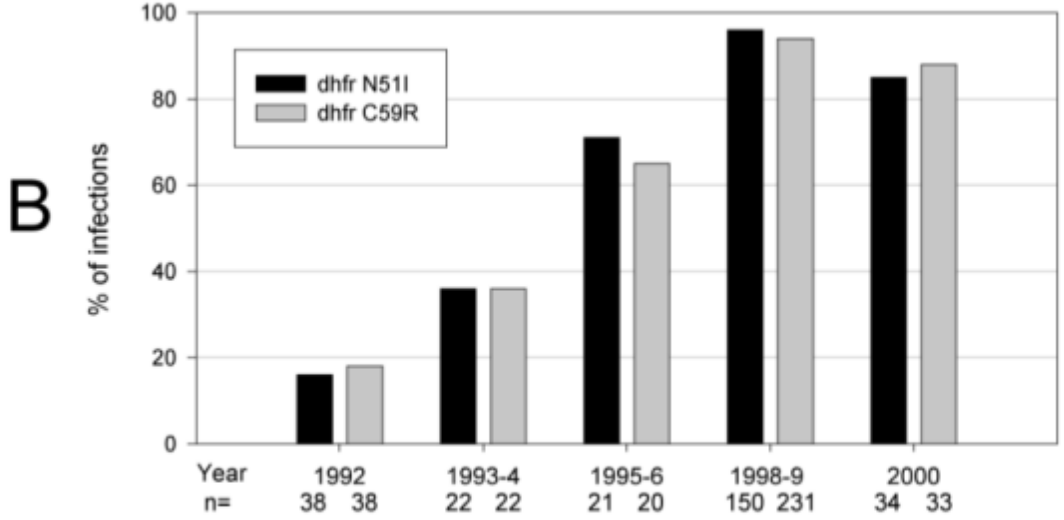


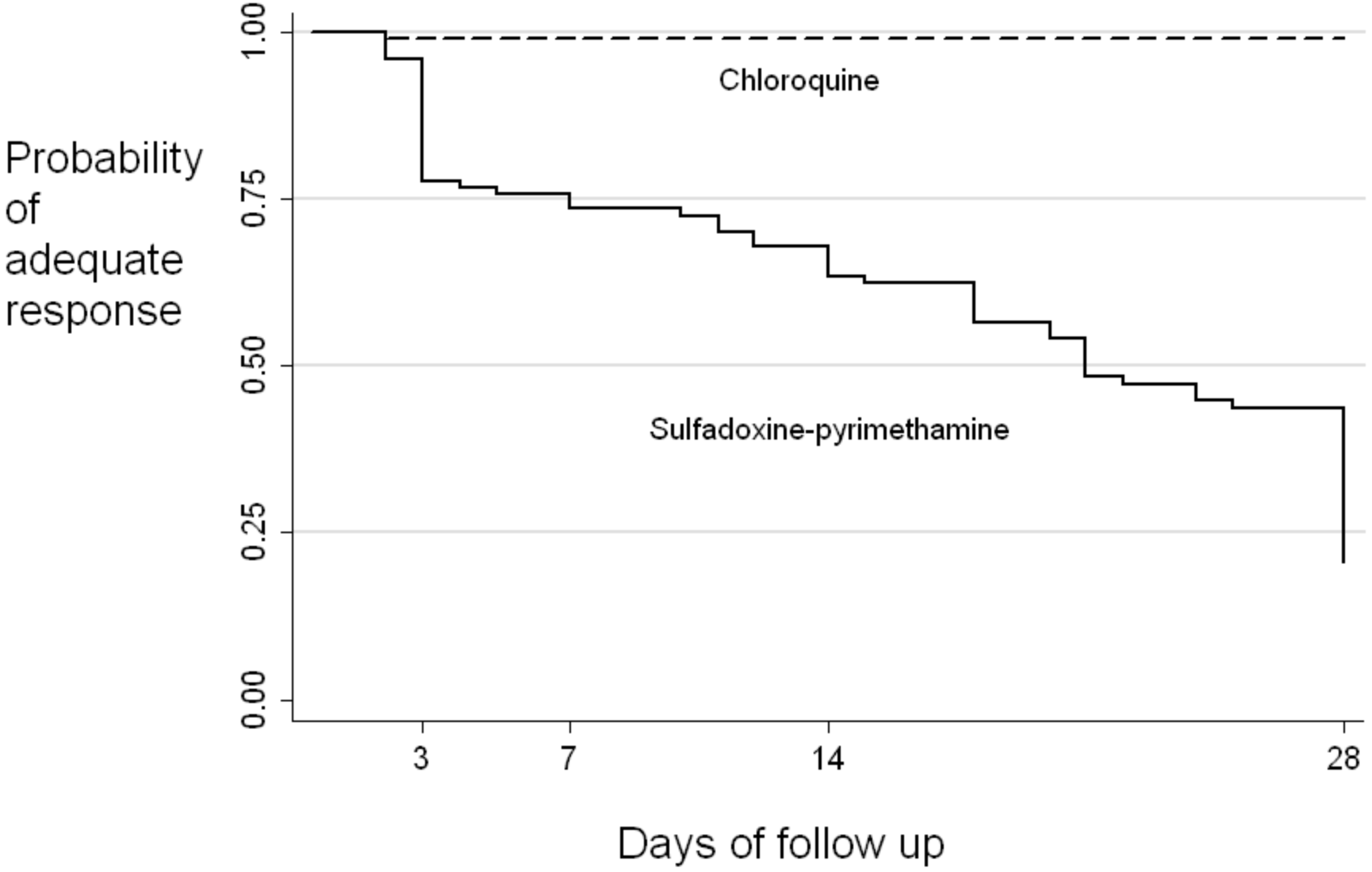
Mutations associated with SP resistance

Kublin et al. 2003

Next: clinical trial among children with symptomatic disease

- Those who would be treated for malaria in the community

Survival analysis



Laufer, et al. 2006

Sulfadoxine-pyrimethamine

- Resistance widespread in eastern Africa
- More effective in western Africa
- A lot of advantages
  - Single dose
  - Long terminal elimination
    - Gives post-treatment prophylaxis

Artemisinins

Artemesia annua

- Chinese herb used for 2000 years
- Highly efficacious but short-acting
- Active against gametocytes
  - Reduce transmission
- Combined with longer-acting drugs to deter emergence of resistance, shorten course
- Artemisinin-based combination therapy (ACT) is the first line in most of the world
  - Cost $1-5 for 3-day treatment course
  - Most common: artemether-lumefantrine (CoArtem or LA)
- Resistance in SE Asia (Thailand, Cambodia, Myanmar)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Artemisinin Resistance in *Plasmodium falciparum* Malaria

Arjen M. Dondorp, M.D., François Nosten, M.D., Poravuth Yi, M.D., Debashish Das, M.D., Aung Phae Phyo, M.D., Joel Tarning, Ph.D., Khin Maung Lwin, M.D., Frederic Ariey, M.D., Warunee Hanpithakpong, Ph.D., Sue J. Lee, Ph.D., Pascal Ringwald, M.D., Kamolrat Silamut, Ph.D., Mallika Imwong, Ph.D., Kesinee Chotivanich, Ph.D., Pharath Lim, M.D., Trent Herdman, Ph.D., Sen Sam An, Shunmay Yeung, Ph.D., Pratap Singhasivanon, M.D., Nicholas P.J. Day, D.M., Niklas Lindegardh, Ph.D., Duong Socheat, M.D., and Nicholas J. White, F.R.S.

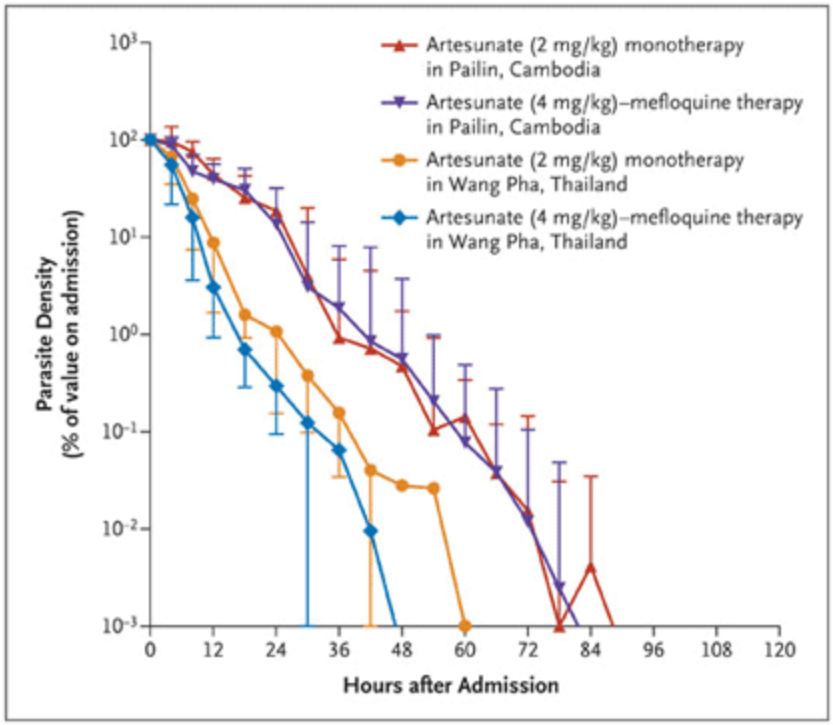
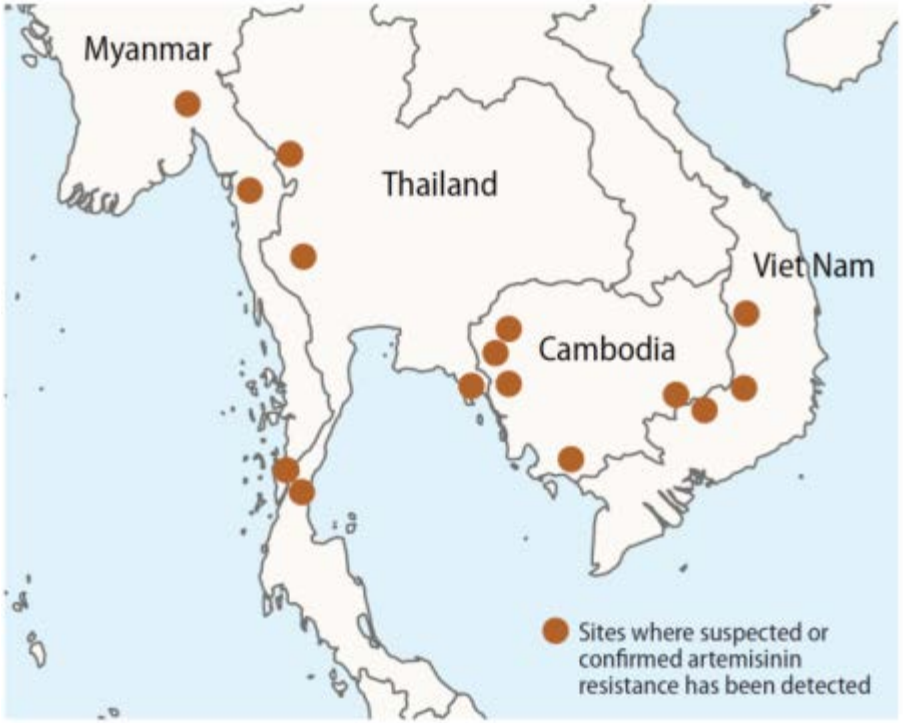


Figure 6.17 Sites where suspected or confirmed artemisinin resistance has been detected in therapeutic efficacy studies, Mekong subregion, 2007–2012



Map production: *Global Malaria Programme (GMP), World Health Organization;* ***Source of data:*** *WHO Global Database on Antimalarial Drug Efficacy, as of November, 2012*

nature 2014 Jan 2;505(7481):50-5. doi: 10.1038/nature12876. Epub 2013 Dec 18.

A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria

Frédéric Ariey[1,2]†, Benoit Witkowski[3], Chanaki Amaratunga[4], Johann Beghain[1,2]†, Anne-Claire Langlois[1,2], Nimol Khim[3], Saorin Kim[3], Valentine Duru[3], Christiane Bouchier[5], Laurence Ma[5], Pharath Lim[3,4,6], Rithea Leang[6], Socheat Duong[6], Sokunthea Sreng[6], Seila Suon[6], Char Meng Chuor[6], Denis Mey Bout[7], Sandie Ménard[8]†, William O. Rogers[9], Blaise Genton[10], Thierry Fandeur[1,3], Olivo Miotto[11,12,13], Pascal Ringwald[14], Jacques Le Bras[15], Antoine Berry[8]†, Jean-Christophe Barale[1,2]†, Rick M. Fairhurst[4]*, Françoise Benoit-Vical[16,17]*, Odile Mercereau-Puijalon[1,2]* & Didier Ménard[3]*

Plasmodium falciparum resistance to artemisinin derivatives in southeast Asia threatens malaria control and elimination activities worldwide. To monitor the spread of artemisinin resistance, a molecular marker is urgently needed. Here, using whole-genome sequencing of an artemisinin-resistant parasite line from Africa and clinical parasite isolates from Cambodia, we associate mutations in the *PF3D7_1343700* kelch propeller domain ('K13-propeller') with artemisinin resistance *in vitro* and *in vivo*. Mutant K13-propeller alleles cluster in Cambodian provinces where resistance is prevalent, and the increasing frequency of a dominant mutant K13-propeller allele correlates with the recent spread of resistance in western Cambodia. Strong correlations between the presence of a mutant allele, *in vitro* parasite survival rates and *in vivo* parasite clearance rates indicate that K13-propeller mutations are important determinants of artemisinin resistance. K13-propeller polymorphism constitutes a useful molecular marker for large-scale surveillance efforts to contain artemisinin resistance in the Greater Mekong Subregion and prevent its global spread.

WHO Treatment Recommendations

- Uncomplicated falciparum malaria: use ACTs (at least a 3-day course)
  - Artemether + lumefantrine (LA)
  - Artesunate + amodiaquine
  - Artesunate + mefloquine
  - Artesunate + sulfadoxine-pyrimethamine
  - Dihidroartemisinin + piperaquine***
  - 2nd line is another ACT
  - 1st trimester pregnancy: use quinine + clinda
  - Add a single dose of primaquine as antigametocyte for pre-elimination or elimination


ART-FANT
60ml
FOR ORAL SUSPENSION
Curative
Antimalarial
Paediatric


DUO-COTECXIN®
Dihydroartemisinin / Piperaquine phosphate
Adults
Children
over 6 years old


℞
Artemether and
Lumefantrine Tablets
Falcidoc-L
Tablets
1/D x 6 Tablets


24 g Netto
LONART
Antipaludéen
Pédiatrique
Curatif
LONART
ORAL SUSPENSION

WHO Treatment Recommendations

- Severe falciparum malaria:
  - Initial treatment with IV or IM artesunate for at least 24 hours
  - Alternatives are quinine and artemether
  - When patient can tolerate oral therapy, initiate a full oral course of treatment with ACT

WHO Treatment Recommendations

- Uncomplicated vivax malaria: chloroquine
  - In chloroquine-resistant areas, use ACT (except Artesunate + Sulfadoxine/Pyrimethamine)
  - Radical treatment with primaquine for 14 days (contraindicated in G6PD deficiency)

GLOBAL MALARIA PROGRAMME

World Health Organization

Policy brief on single-dose primaquine as a gametocytocide in *Plasmodium falciparum* malaria

January 2015

In low transmission areas, give a single dose of 0.25 mg/kg primaquine with ACT to patients with *P. falciparum* malaria (except pregnant women, infants aged < 6 months and breastfeeding women of infants aged < 6 months) to reduce transmission. Testing for G6PD deficiency is not required.

Vaccines

Malaria vaccines: Obstacles

- Natural protective immunity:
  - Partial
  - Temporary
  - Genetically restricted
- Immune response likely contributes to pathology & severe disease
- Efficiency of parasite amplification
- Complexity of parasite
- Antigenic variation
- Lack of correlates of protection and good outcome measures

Malaria vaccines: Reasons for optimism

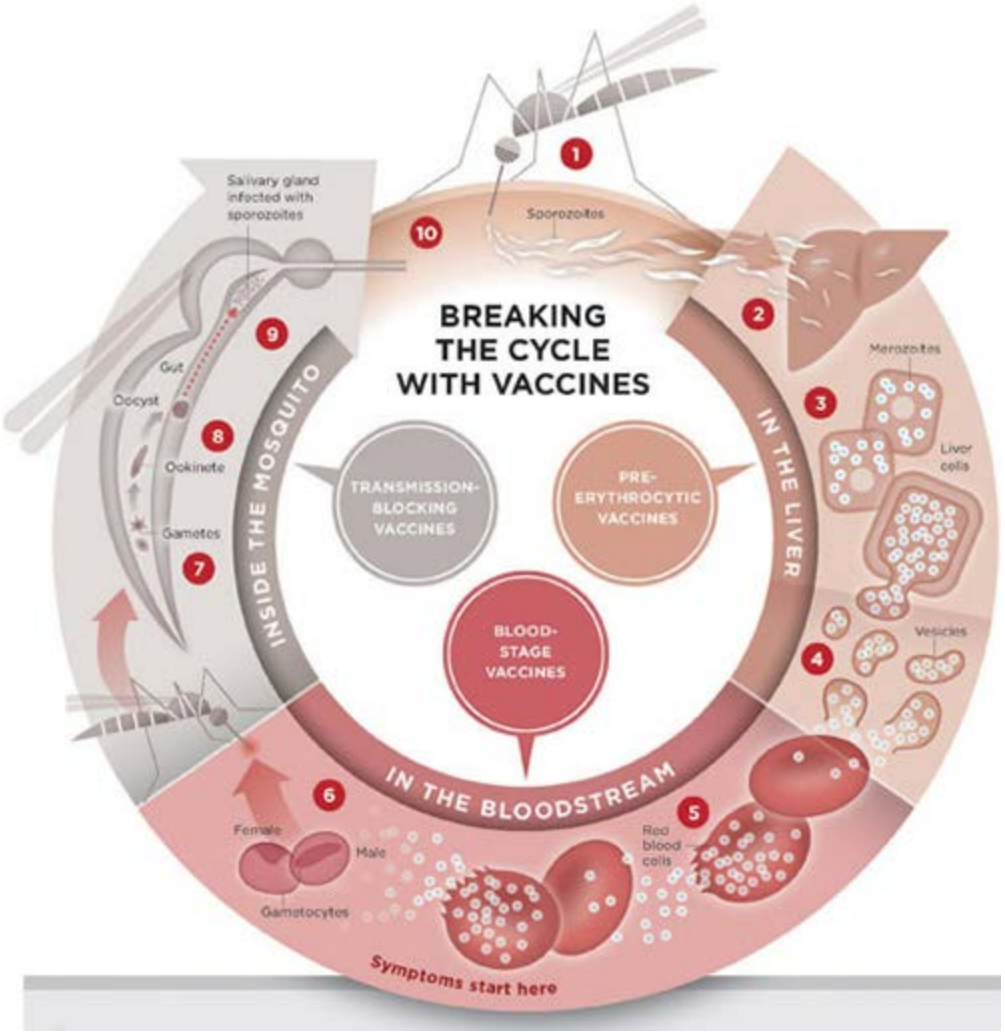
- Humans can acquire (partial) protective immunity naturally
- Irradiated sporozoites protects humans against challenge with infective sporozoites

  (Clyde et.al. 1973)

Vaccines can target different life-cycle stages

- Transmission blocking
  - Gametocyte
- Infection blocking*
  - Sporozoite/liver stage
- Disease blocking*
  - Blood stage

*In real life, may overlap



RTS,S

- Recombinant subunit vaccine based on sporozoite protein
  - Immune-boosting adjuvant AS01
  - Linked to hepatitis B surface antigen
- Moving forward toward licensure
  - Large Phase 3 trial ended in 2014
    - Administer with EPI in infants
    - 6,538 participants in 6-12 week age group
    - 8,923 participants in 5-17 month age group
  - 11 sites in 7 African countries (Gabon, Mozambique, Tanzania, Ghana, Kenya, Malawi, and Burkina Faso)
  - 50% efficacy in older age cohort in first 12 months of follow-up, then decreased
  - 25-30% efficacy in neonates, then decreased
  - European Medicines Agency approved in mid-2015
  - Awaiting WHO recommendations expected late 2015

Other promising vaccine strategies

- Whole organism approach
  - Live attenuated sporozoite
- Adenovirus-vectored candidates
- Heterologous Prime-boost strategies
- Recombinant blood-stage antigens

Sanaria's PfSPZ Vaccine

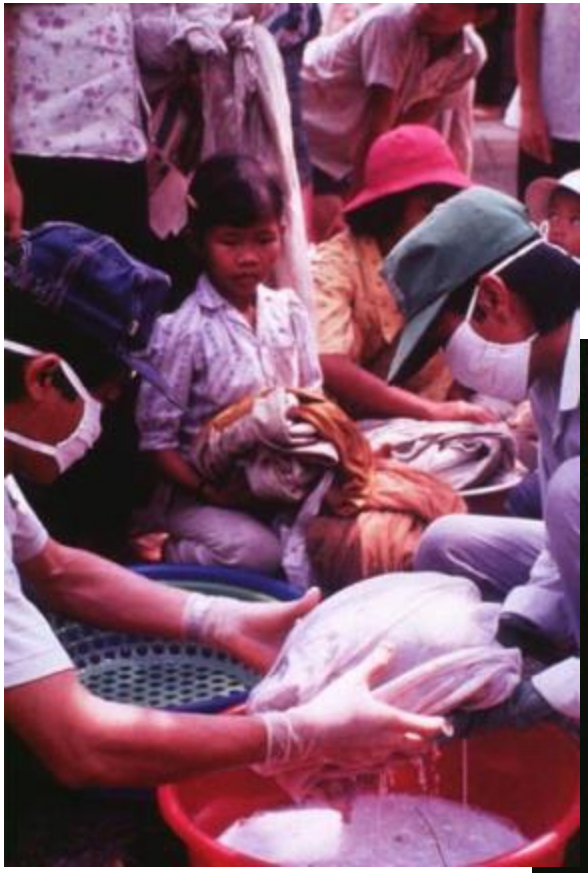
- Live, attenuated whole-organism vaccine
- 100% efficacy in 6/6 highest-dose recipients in a recent clinical trial at NIH Vaccine Research Center (*Science* 2013)
- Follow-up studies ongoing
  - NIH, University of Maryland
  - Mali
  - Tanzania
  - Gabon
  - Burkina Faso

Malaria Control

Alphabet soup of malaria control: New and old

- **ACT** = Artemisinin-based combination therapy
- **IPT** = Intermittent preventive treatment for pregnant women, infants, children
- **IRS** = Indoor residual spraying (DDT)
- **ITN** = Insecticide treated nets
- **LLTN** = Long-lasting insecticide treated nets
- **SMC** = Seasonal malaria chemoprophylaxis

ITN = Insecticide Treated Nets



Insecticide-impregnated bed nets and curtains

- Large studies have shown significant decreases in **overall** child mortality
- Most impact where transmission is high
  - Benefit less clear in low transmission areas
- "Shifting burden of disease" not seen in studies with 7+ years of follow-up
- Success now depends on effective social marketing
  - *Free vs. minimal cost*

IRS with DDT

- Short life-span of *Anopheles* means that vector control can be very beneficial
- Was the cornerstone of the first malaria eradication effort
  - Goal was to interrupt transmission for 3-5 years then conduct intensive case surveillance
  - In Africa, used in the 1940s-1960s with good results in some areas
    - Decreased vectors in all areas where implemented
    - Eliminated malaria from the border of transmission areas
  - 1962 Rachel Carson's book "Silent Spring" led to international pressure to stop using DDT
    - Banned for agricultural use

IRS with DDT

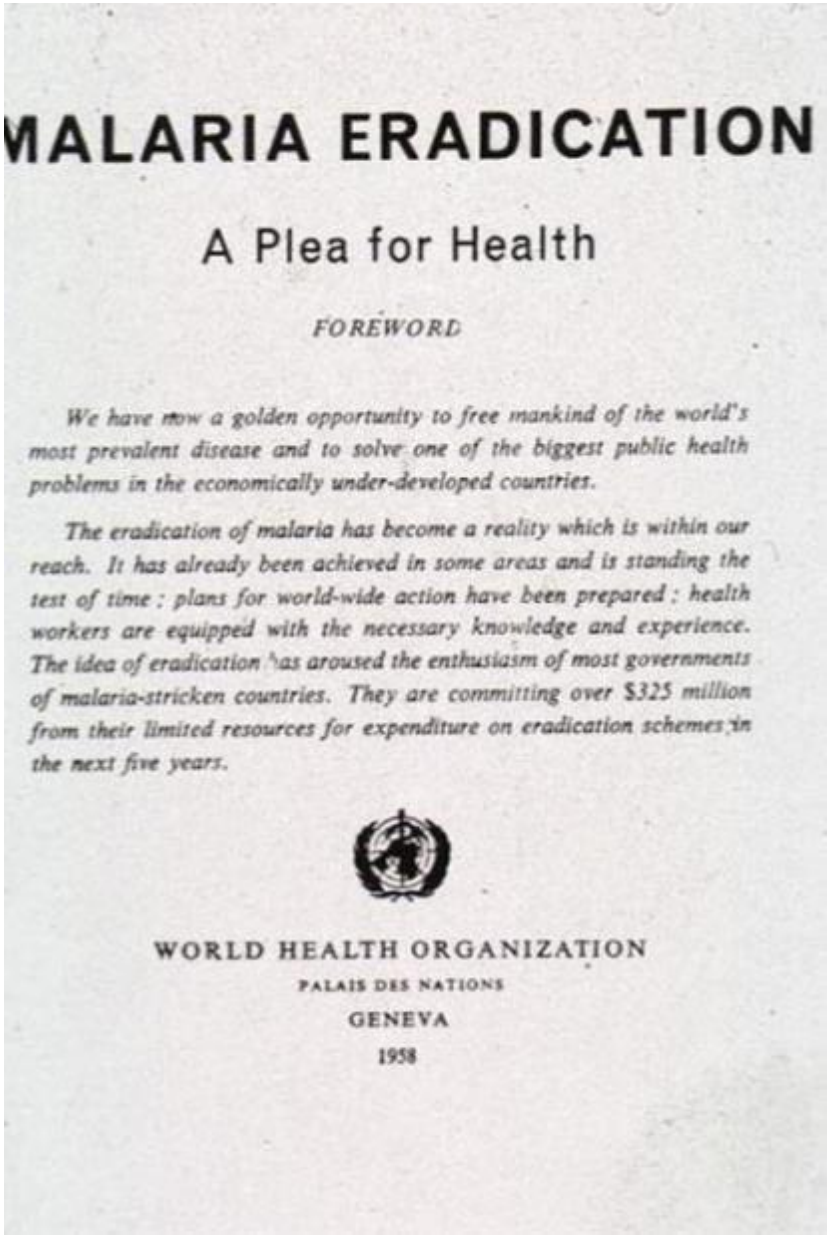
- WHO now advocates the use of DDT for indoor residual spraying
  - Spray the inside walls of houses every 6 months
- Dual activity
  - Kills vectors
  - Excitorepellent effect

IRS with DDT

- On-going concerns
  - Human toxicity
    - None have been established
    - Much less exposure than with agricultural use
  - Vector resistance
  - Effect on environment
  - Cost of second-line insecticides
  - Variability of transmission intensity

IPTi and IPTp

- Intermittent Presumptive Treatment
- IPTi recommended in moderate to high-transmission areas for infants at the time of the 2nd and 3rd DPT and MMR doses
  - Not yet adopted on country-wide level except in Burkina Faso, West Africa
- IPTp recommended at 2nd and 3rd trimesters
  - Adopted by 36 of 45 sub-Saharan African countries



MALARIA ERADICATION

A Plea for Health

FOREWORD

We have now a golden opportunity to free mankind of the world's most prevalent disease and to solve one of the biggest public health problems in the economically under-developed countries.

The eradication of malaria has become a reality which is within our reach. It has already been achieved in some areas and is standing the test of time; plans for world-wide action have been prepared; health workers are equipped with the necessary knowledge and experience. The idea of eradication has aroused the enthusiasm of most governments of malaria-stricken countries. They are committing over $325 million from their limited resources for expenditure on eradication schemes in the next five years.

WORLD HEALTH ORGANIZATION

PALAIS DES NATIONS

GENEVA

1958

Global malaria eradication campaign

- Optimism based on DDT & chloroquine
- Success in some areas
- Eventual failure due to:
  - Unrealistic expectations
  - Failure to integrate into existing institutions and primary health infrastructure
  - Chloroquine-resistant *P. falciparum*
  - DDT-resistant Anopheles
  - Donor fatigue

Published by AAAS

Impossible dream? At an October meeting, Bill and Melinda Gates challenged the world to eradicate malaria in their lifetimes.

MALARIA

Did They Really Say . . . Eradication?

The malaria world is all abuzz about a call by Bill and Melinda Gates to wipe the scourge from the planet. Even if it proves unfeasible, their idea could have a big impact

SEATTLE, WASHINGTON—When Bill and Melinda Gates had finished their back-to-back speeches, many researchers could barely believe what they had just heard. At a meeting hosted by their charitable foundation in their hometown, the couple had uttered the long-forgotten e-word, calling for a sweeping new plan to eradicate malaria.

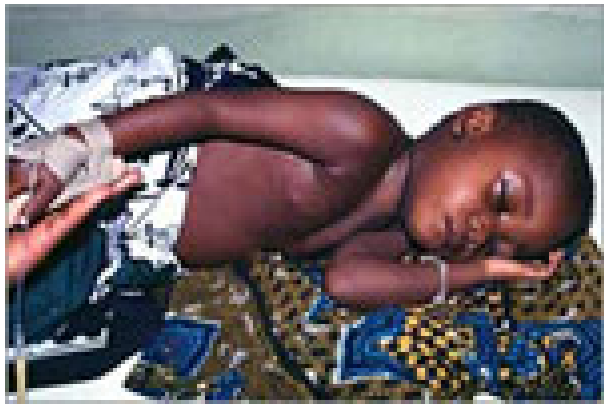
Chan and the Gateses were careful not to set a target deadline, presenting eradication as a long-term vision, not a near-term goal. "Multiple decades" is what Bill Gates told reporters afterward, noting that it is "dangerous" to offer anything more concrete. "They both hope it will happen in their lifetimes," says Regina Rabinovich, head of infectious Tuberculosis, and Malaria, who is a member of that group.

The Roll Back Malaria (RBM) Partnership, composed of all the major players in malaria, including the endemic countries, has already lent its support. Meeting in the Ethiopian capital, Addis Abeba, last week, the RBM Board agreed to set up a high-level steering committee to coordinate efforts and devise a "business plan" within 6 months. No new funding has been announced, but everyone expects the Gateses to put large sums of money where their mouths are.

Reality check

In the wake of the Seattle meeting, proponents have been trying to reassure skeptical scientists and manage expectations, in part by de-emphasizing the importance of words. Scientists use "eradication" to mean that a pathogen no longer exists anywhere on Earth—save for perhaps a few lab freezers—and control measures can stop. "Elimination" means a pathogen is no longer transmitted in a defined geographical area, although "imported" cases may still occur. By those definitions, malaria has been eliminated in Europe, measles in the Americas, and polio in most countries of the world—but smallpox remains the only disease that has been eradicated.

"I like the term 'elimination' better" than eradication, Chan told *Science* in Seat-



Diagnosing and managing malaria in endemic countries

Pre-clinical care

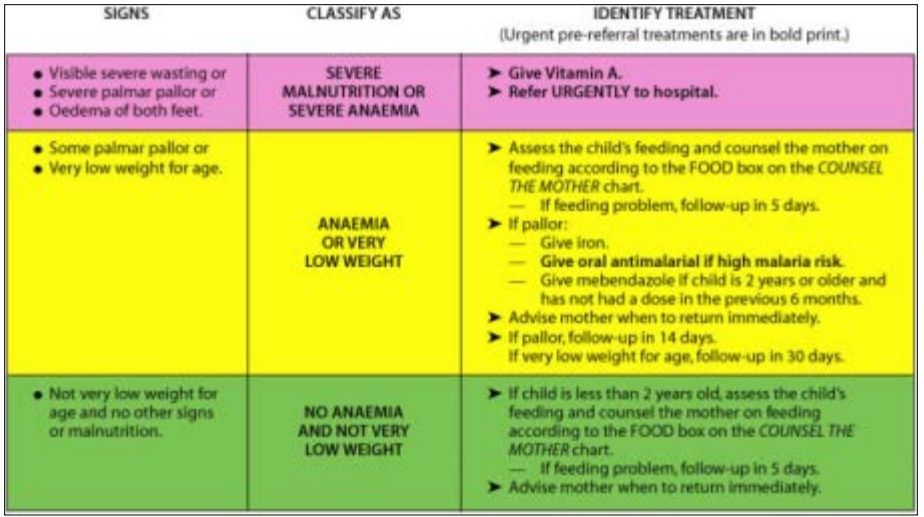
- Traditional medicine practices
- Drug seeking behavior in the informal sector
- Accessibility
  - Location
  - Cost
  - Time

Primary level of care

- Minimally trained para-professional

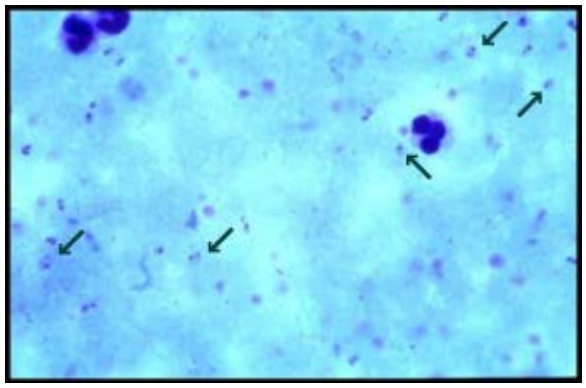
Management of febrile children by non-professionals

- Integrated Management of Childhood Illnesses (IMCI)
  - Case management based
    - Focus on pneumonia, diarrhea, malaria, measles, malnutrition
  - Ensure all providers offer basic services and refer appropriately
  - Community education

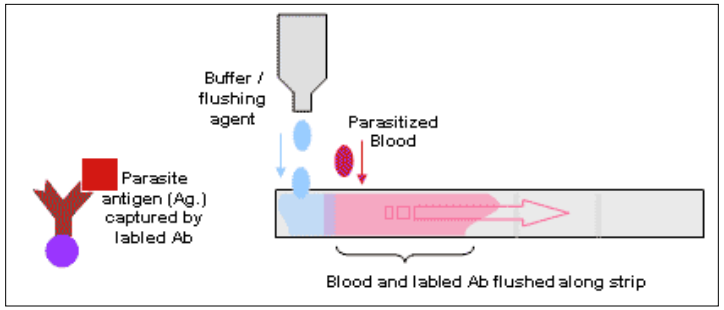


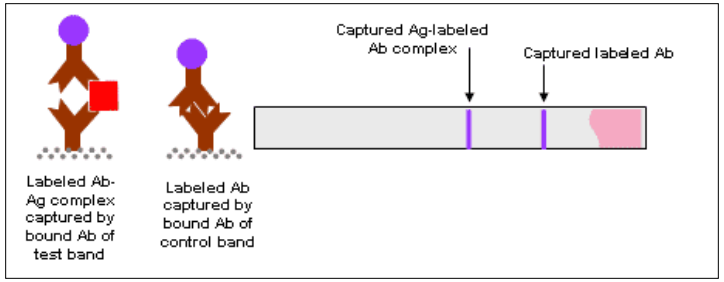
SIGNS	CLASSIFY AS	IDENTIFY TREATMENT (Urgent pre-referral treatments are in bold print.)
• Visible severe wasting or • Severe palmar pallor or • Oedema of both feet.	SEVERE MALNUTRITION OR SEVERE ANAEMIA	➤ **Give Vitamin A.** ➤ **Refer URGENTLY to hospital.**
• Some palmar pallor or • Very low weight for age.	ANAEMIA OR VERY LOW WEIGHT	➤ Assess the child's feeding and counsel the mother on feeding according to the FOOD box on the *COUNSEL THE MOTHER* chart. — If feeding problem, follow-up in 5 days. ➤ If pallor: — Give iron. — **Give oral antimalarial if high malaria risk.** — Give mebendazole if child is 2 years or older and has not had a dose in the previous 6 months. ➤ Advise mother when to return immediately. ➤ If pallor, follow-up in 14 days. If very low weight for age, follow-up in 30 days.
• Not very low weight for age and no other signs or malnutrition.	NO ANAEMIA AND NOT VERY LOW WEIGHT	➤ If child is less than 2 years old, assess the child's feeding and counsel the mother on feeding according to the FOOD box on the *COUNSEL THE MOTHER* chart. — If feeding problem, follow-up in 5 days. ➤ Advise mother when to return immediately.

Diagnostic methods



- Microscopy
  - Thick smears, usually
  - Operator dependent!
    - and operator must be there
  - For *P. falciparum*, visualize circulating ring forms
    - Other stages may be sequestered
    - Repeat smear if suspicion high
      - Especially in less immune
- Rapid tests
  - Antigen-based
  - May remain positive after therapy

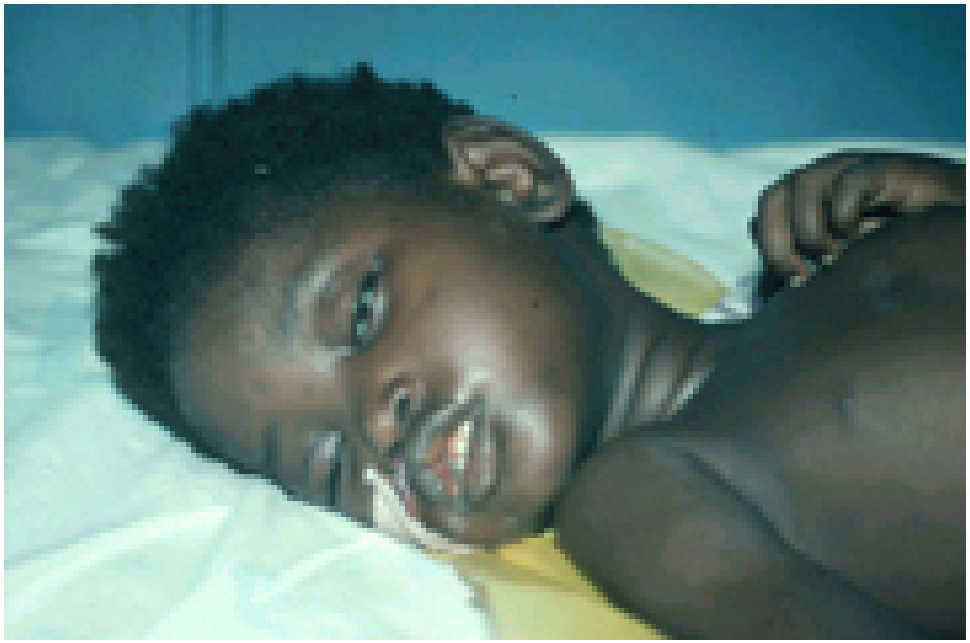




What if the test is negative?

What if the test is negative?

- Often treated for malaria anyway
- Must pursue other causes of febrile illness
- Depends on local epidemiology
  - Bacteremia
  - HIV
  - Enteric fever
  - Dengue
  - etc.



If malaria is diagnosed, must assess severity

- Danger signs
  - Altered consciousness
    - Blantyre coma score <5
  - Unable to sit or stand
  - Unable to eat or drink
  - Seizures
  - Vomiting
  - Acidotic breathing

What to look for…

- Physical examination
- Laboratory

What to look for…

- Physical examination
  - Mental status
  - Respiratory status
  - Prostration
  - Vomiting
  - Shock
- Laboratory
  - Parasite density
  - Hemoglobin
  - Glucose
  - Lactate
  - *Bilirubin*
  - *Urinalysis*
  - *Creatinine*

If malaria is diagnosed, must assess severity

- Cerebral malaria (diminished consciousness, seizures)
  - In the absence of hypoglycemia, meningitis or other cause
- Respiratory distress
- Prostration
- Hyperparasitemia (>5% or 10%)
- Severe anemia (<5 gm/dL)
- Hypoglycemia (<40 mg/dL)
- Jaundice/icterus
- Renal insufficiency
- Hemoglobinuria (“Black water fever”)
- Shock
- Cessation of eating and drinking
- Repetitive vomiting
- *Hyperpyrexia*

Blantyre Coma Scale for Young Children

Overview: The Blantyre coma scale is a modification of the Glasgow coma scale suitable to use in preverbal children. The scale uses motor and crying responses to pain and includes the ability to watch. It can be used to assess young children with cerebral malaria.

Response	Findings	Score
best motor response	localizes painful stimulus (pressure with blunt end of pencil on sternum or supraorbital ridge)	2
	withdraws limb from painful stimulus (pressure with horizontal pencil on nail bed of finger or toe)	1
	no response or inappropriate response	0
best verbal response	cries inappropriately with painful stimulus or if verbal speaks	2
	moan or abnormal cry with painful stimulus	1
	no vocal response to painful stimulus	0
eye movement	watches or follows (e.g. mother's face)	1
	fails to watch or follow	0

Blantyre coma scale = (best motor response score) + (best verbal response score) + (eye movement score)

Interpretation:

• minimum score: 0 (poor)

• maximum score: 5 (good)

• abnormal: score <= 4

General management principles

- Uncomplicated malaria
  - Outpatient therapy
    - Make sure patient can tolerate oral medication
  - Antipyretics
  - Warn about danger signs

General management principles

- Severe disease
  - Inpatient management
  - Goal: supportive management to give the antimalarials time to work

Intravenous therapy

- Artesunate
  - Can give IV, IM or rectal
    - Important in rural areas
  - More rapid acting and decreases large biomass
    - In children in Africa, improved mortality vs. quinine
- Quinine
  - Can give IM, IV or oral
  - Slow acting
  - In Africa, no resistance reported
- In both cases, must “complete” therapy with an oral medication, preferably with longer duration of action.

Supportive care

Supportive care

- Treat and prevent hypoglycemia
- Gentle fluid resuscitation
  - Increased ICP
- Monitor anemia and C-R status
  - No specific cut-off for transfusion
- Consider evaluation for bacteremia/meningitis
- Antipyretics
- Anticonvulsants as needed

The patient is anemic

- What should you do?

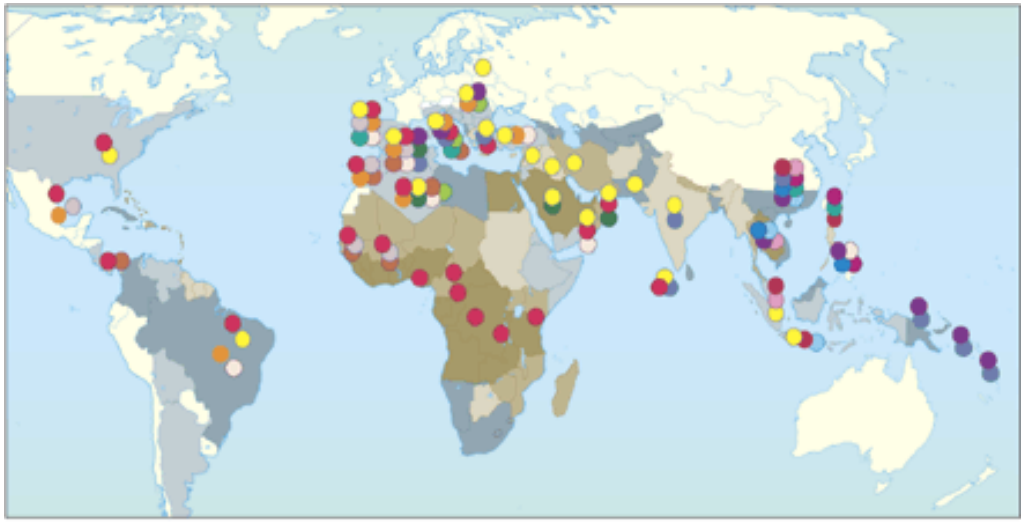
The complexity of anemia in children living in endemic countries

- Anemia is multifactorial
  - Malaria
  - Chronic inflammation
  - Hookworm and other parasitic infections
  - Nutritional deficiency
  - HIV
- Iron supplementation may lead to immune suppression and/or may exacerbate malaria infection

- You are working in the Peruvian Amazon. Your laboratory tells you that the patient has *P. vivax* infection.
- What should you do?

Non-*falciparum* malaria

- Chloroquine susceptible in most of the world
- Primaquine for terminal prophylaxis of hypnozoites of *P. vivax* and *P. ovale*
  - Often not available
  - "Should" check G6PD levels first



Malaria….
don't get it!

- Personal insecticide- Sawyers extended release
- Long sleeves and long pants
- Bed net
- Prophylaxis
- Immediate evaluation of any fever while in an endemic country or within 3-6 months after return.

A child dies every 30 seconds from malaria. It's time to Count Malaria Out.

click to join in

ROLL BACK MALARIA

world malaria day

- Visit the **World Malaria Day website** to find out more
- Add the **World Malaria Day button** to your website
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