Vector borne disease: global health and trends

BSc Global Health
7th November 2011

Imperial College London

Objectives

- **Describe the burden of infectious disease attributable to vector borne infection**

- **Understand the tools for malaria control**

Vector borne diseases

Viruses
- Dengue
- Chikungunya

Parasites
- Leishmaniasis
- Malaria
- Trypanosomiasis
- Filariasis

Rickettsies
- Ricketssia, Coxiella

Bacterial infection
- Yersinia, Francisella, Tularemia

Dengue Fever

2-3 billion at risk

50 million cases per year (Urban)

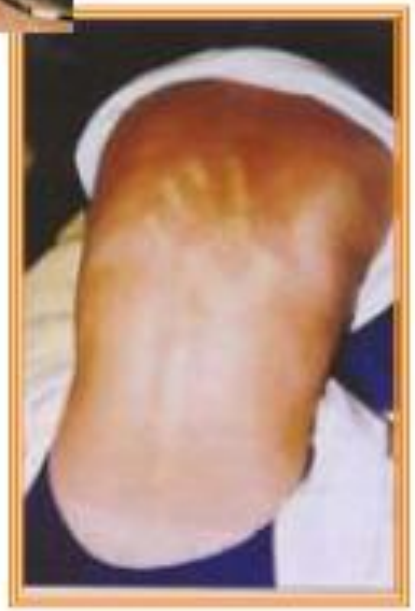
Mortality ~25, 000

4 Serotypes

Clinically

- Dengue fever
- Dengue haemorrhagic fever
- Dengue shock syndrome

A. albopictus



The rise of dengue fever

The last 50 years have seen substantial rises in cases of Dengue fever

Much of this increase is in SE Asia, driven by factors including Increased urbanisation and increased population growth/density

The disease is often asymptomatic or mild, particularly in childhood, but far more severe on reinfection

Case fatality can be as high as 10% in DHFS

The rise of dengue fever

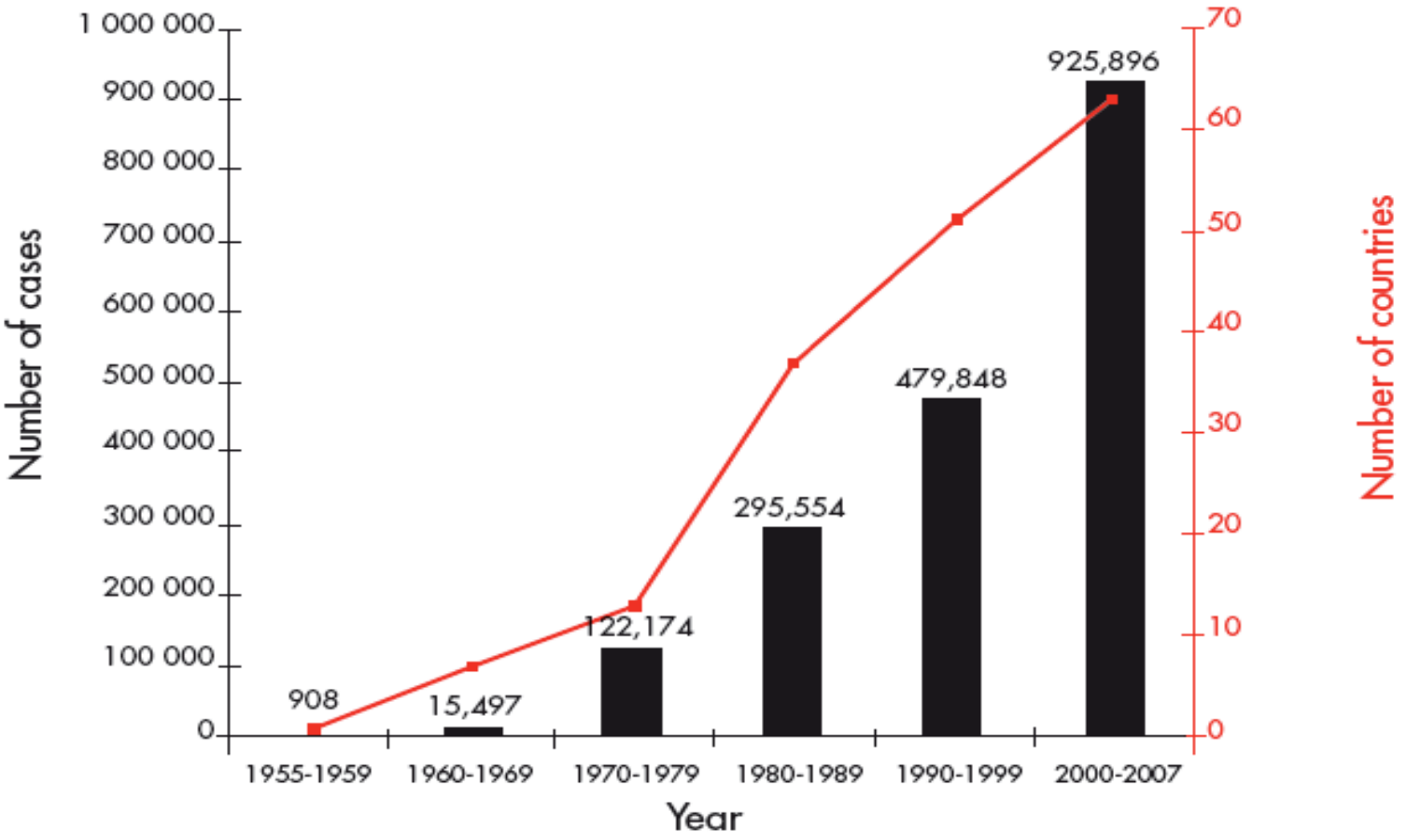
Caused by RNA flavivirus (DEN 1-4)

Vector for transmission is aedes mosquitoes (usually aegypti)

Association between rainfall, temperature and humidity and incidence of dengue fever

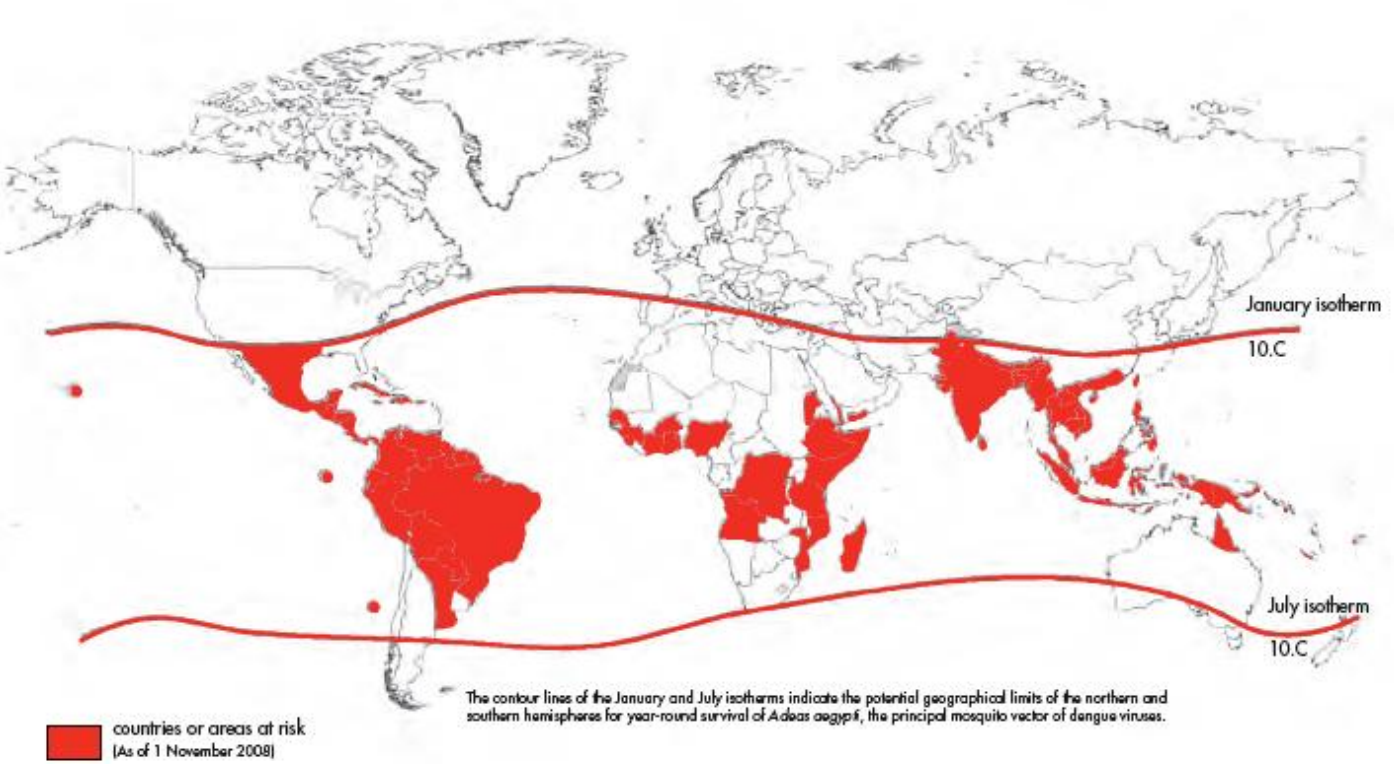
Effects primarily mediated through effect on aedes population

The rise of dengue fever



Source WHO 2008

The rise of dengue fever: risk of transmission



Source WHO 2008

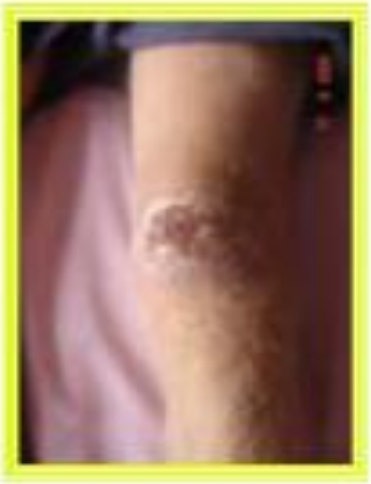
Chikungunya

- Alphavirus
- 'that which bends up' – arthritis
- *A. aegypti*
- Indian ocean – Reunion, Maldives, Sri Lanka, India
- Short incubation, fever, rash, arthritis

Aedes aegypti

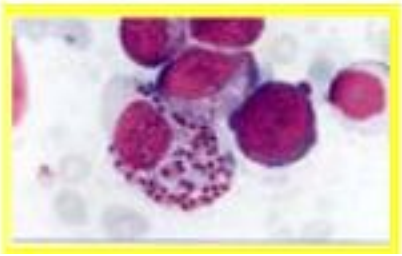
Leishmaniasis

- 350m at risk
- 1.5-2 m cases worldwide
  - » Cutaneous (1-1.5m) (eg Afghanistan, Brazil etc)
  - » Visceral (0.5m) (eg India, Sudan etc)
- 70, 000 deaths

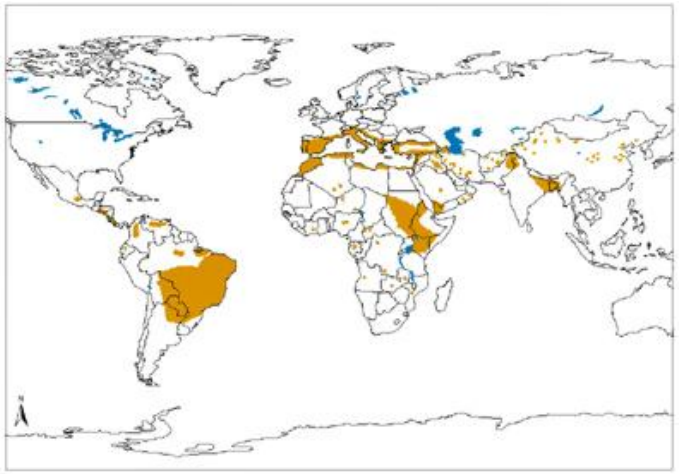


Leishmaniasis

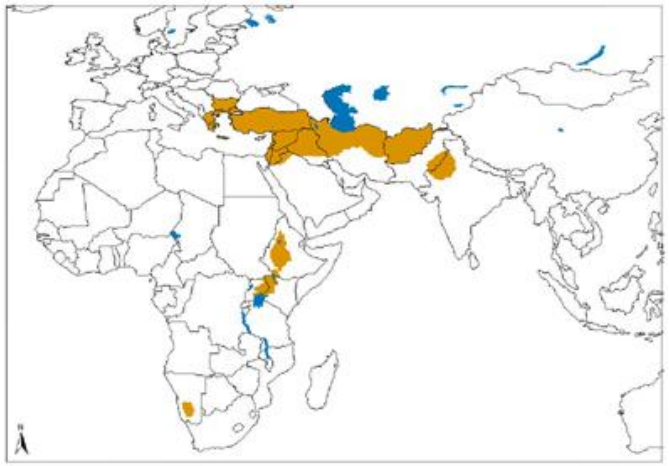
- Spread by sandflies
(*Phlebotomus.* and *Lutzomyia.*)
- Ulcer
- Sometimes indistinguishable from bacterial infection



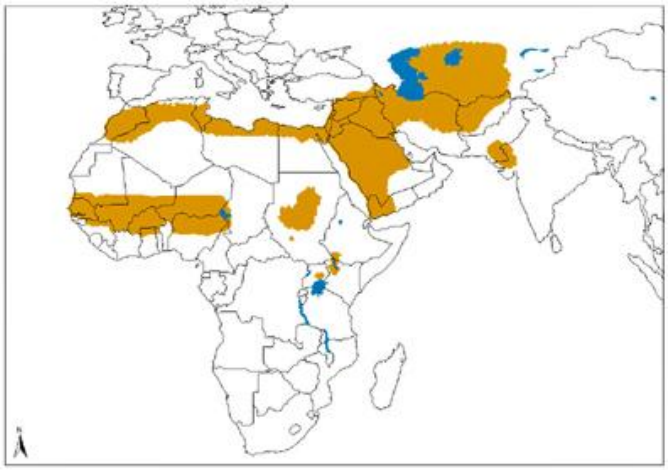
Leishmaniasis



Visceral Leish



Cut L tropica



Cut L major

Risk Factors

Migration
Urbanisation
Deforestation
Dams/water
Projects

Source WHO

Global burden of infectious disease

	Number of deaths (millions)	% of all deaths	% of all DALYs*
All infectious and parasitic diseases	**9.5**	**16.2**	**19.8**
Lower respiratory infections	4.2	7.1	6.2
Diarrhoeal diseases	2.2	3.7	4.8
HIV/AIDS	2.0	3.5	3.8
Tuberculosis	1.5	2.5	2.2
→ Malaria	0.9	1.5	2.2
Childhood infections** (inc measles)	0.9	1.4	2.0
Measles	0.4	0.7	1.0
Hepatitis B & C	0.2	0.3	0.2
Neglected tropical diseases***	0.2	0.3	1.3
STIs excluding HIV	0.1	0.2	0.7

Source: Global Burden Disease 2004 Update, 2008. www.who.int/healthinfo/global_burden_disease/

* Disability Adjusted Life Year; ** Childhood infections includes pertussis, polio, diphtheria, measles, tetanus: *** NTDs defined later

Malaria

Worldwide transmission of malaria

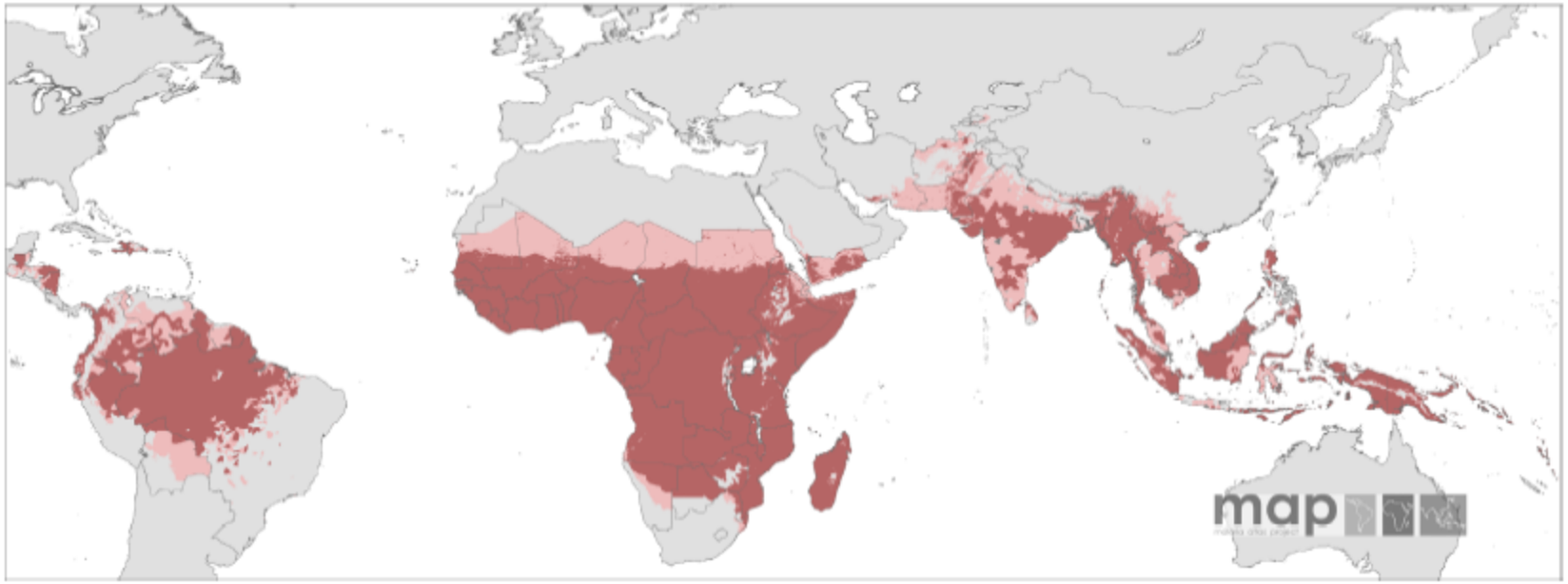


Figure 1. *P. falciparum* Malaria Risk Defined by Annual Parasite Incidence (top), Temperature, and Aridity (bottom)

Areas were defined as stable (dark-red areas, where *Pf*API $\geq$ 0.1 per thousand pa), unstable (pink areas, where *Pf*API $<$ 0.1 per thousand pa), or no risk (light grey). The few areas for which no *Pf*API data could be obtained, mainly found in India, are coloured in dark grey. The borders of the 87 countries defined as *P. falciparum* endemic are shown. Highland areas where risk was excluded due to temperature appear in light grey. The aridity mask excluded risk in a step-wise fashion, reflected mainly in the larger extents of unstable (pink) areas compared to the top panel, particularly in the Sahel and southwest Asia (southern Iran and Pakistan).

doi:10.1371/journal.pmed.0050038.g001

Source: Guerra Plos Med 08

Globally malaria is a disease that kills children

Causes maternal anaemia, LBW, prem

90% of 1 million malarial deaths/yr are African children

Non fatal consequences in endemic areas

- Prematurity - low birthweight
- Schooling missed- 11% primary, 4.3% secondary
- Cognitive development and learning (5-20% of those surviving cerebral malaria)
- Seizures

What is malaria?

- **Definition**
- **Causative parasites**
- **Life cycle**
- **Clinical syndrome and diagnosis**

What is malaria?

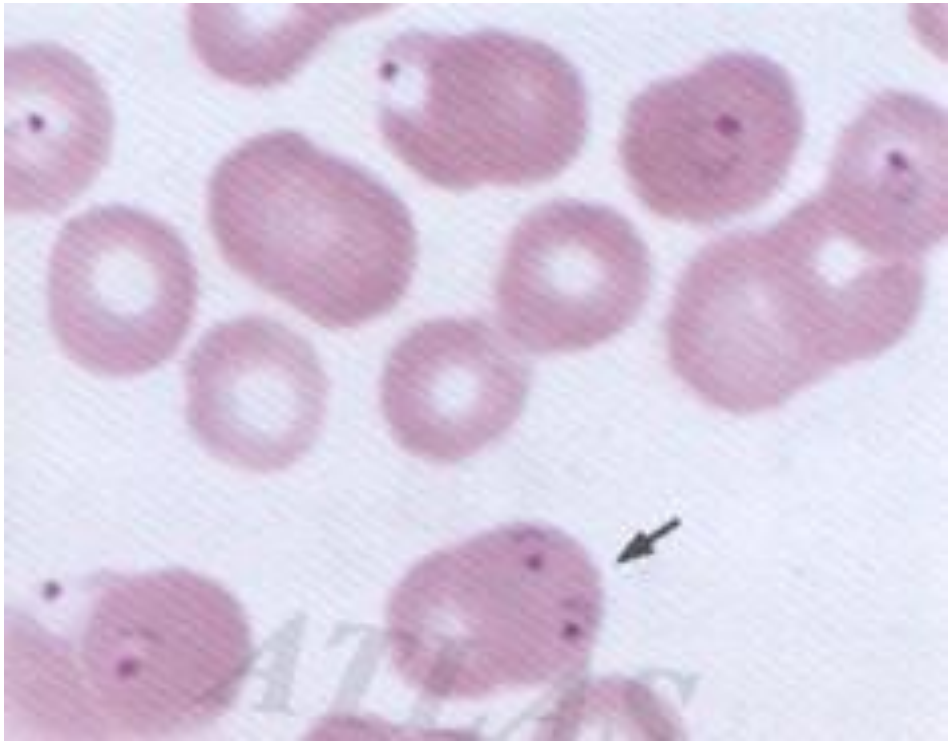
- **Mosquito transmitted disease due to infection with *Plasmodium* parasites**

- **Plasmodium species : *P. falciparum, P. vivax, P. malariae, P. ovale***

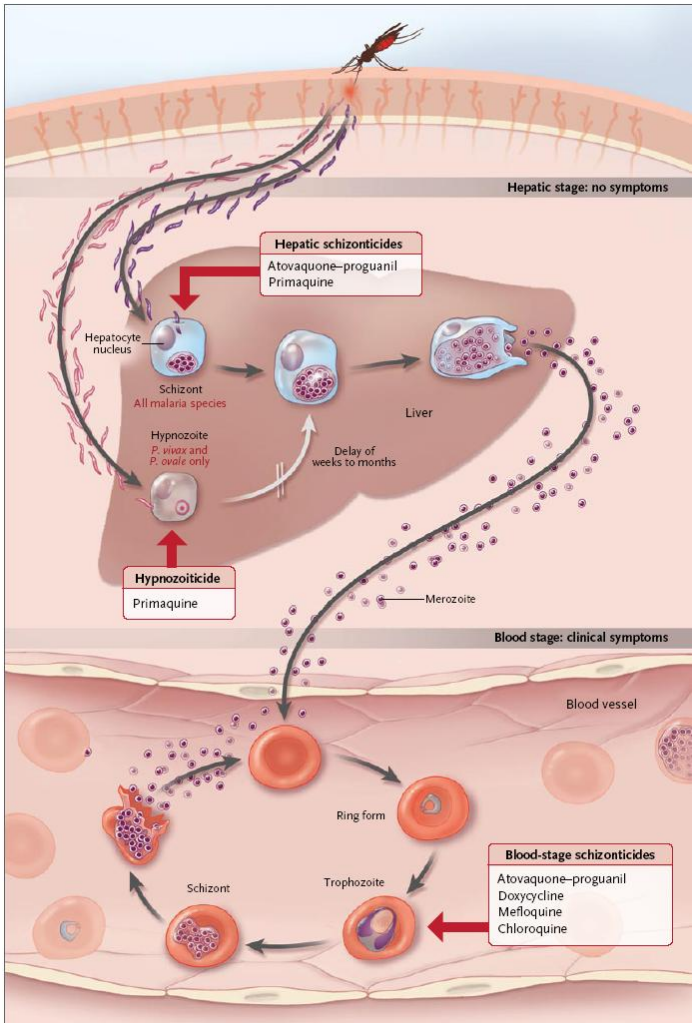
- **Fatality due to vivax, malariae, ovale very rare – hence "benign" malarias**

- **Except for a few exceptions, focus here on P falciparum**

One ring to rule them all



Life cycle



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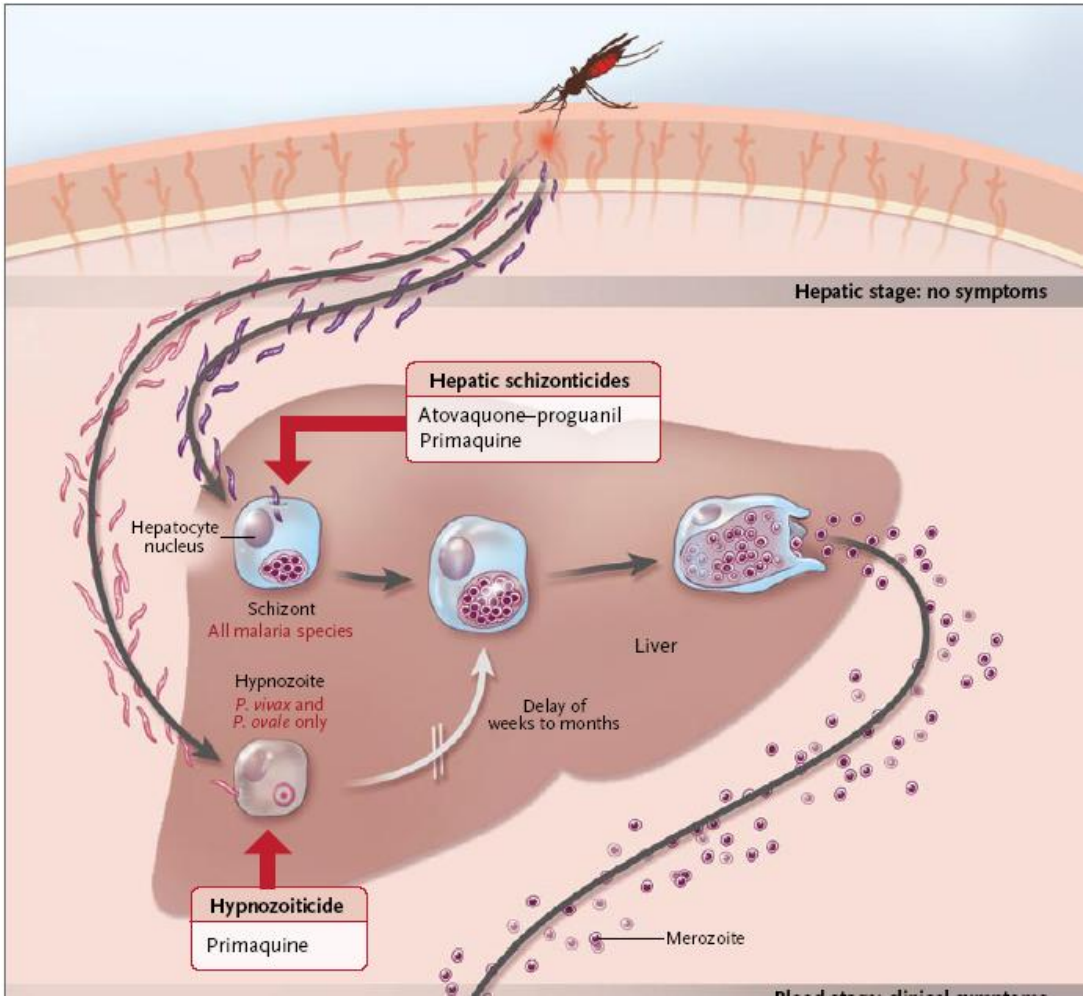
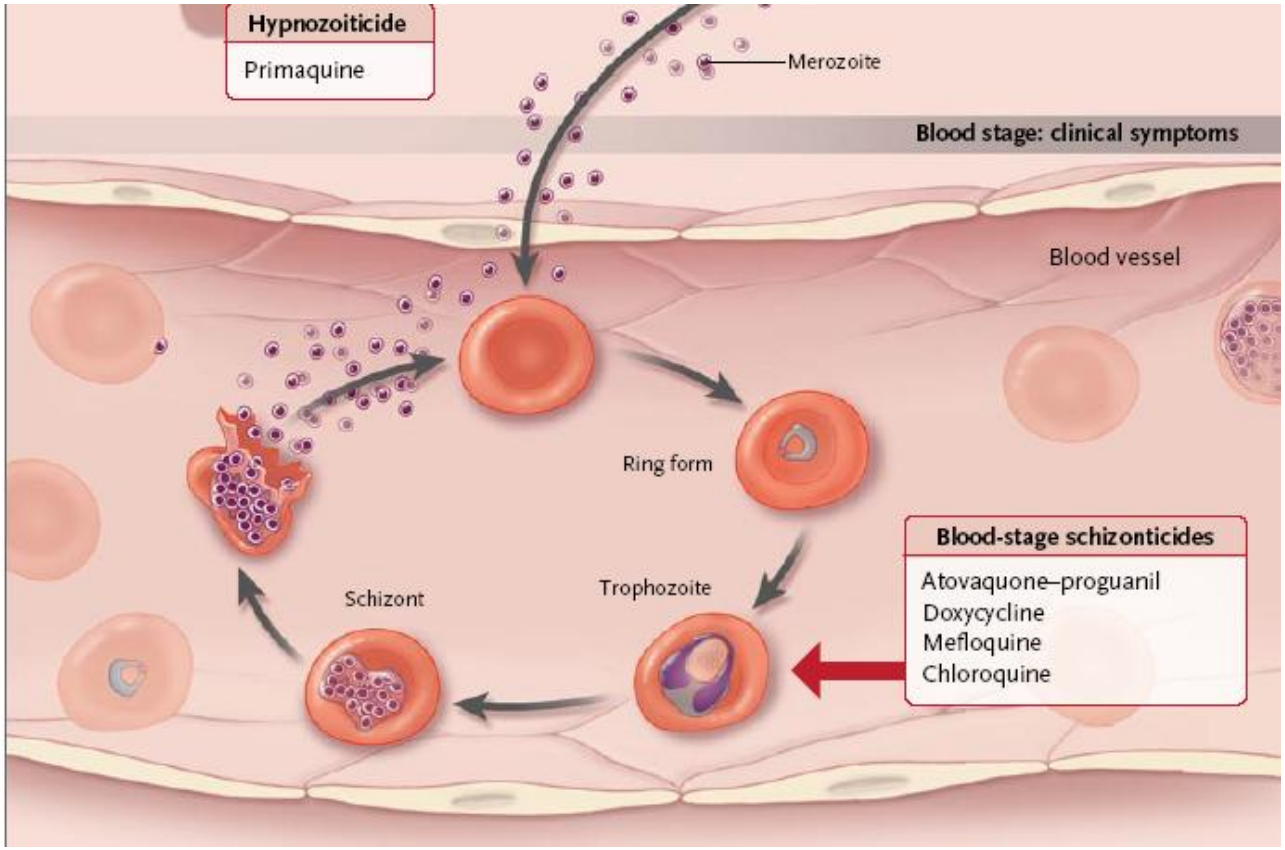
Source: Freedman NEJM 08

Life cycle



Source: Freedman NEJM 08

Life cycle



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Source: Freedman NEJM 08

Blood phase

- Pre-patent period –between infection and the first detection of parasites in peripheral blood

- Incubation period – between infection and first clinical symptoms

- Merozoites from liver invade peripheral (RBC) and develop causing changes in the RBC

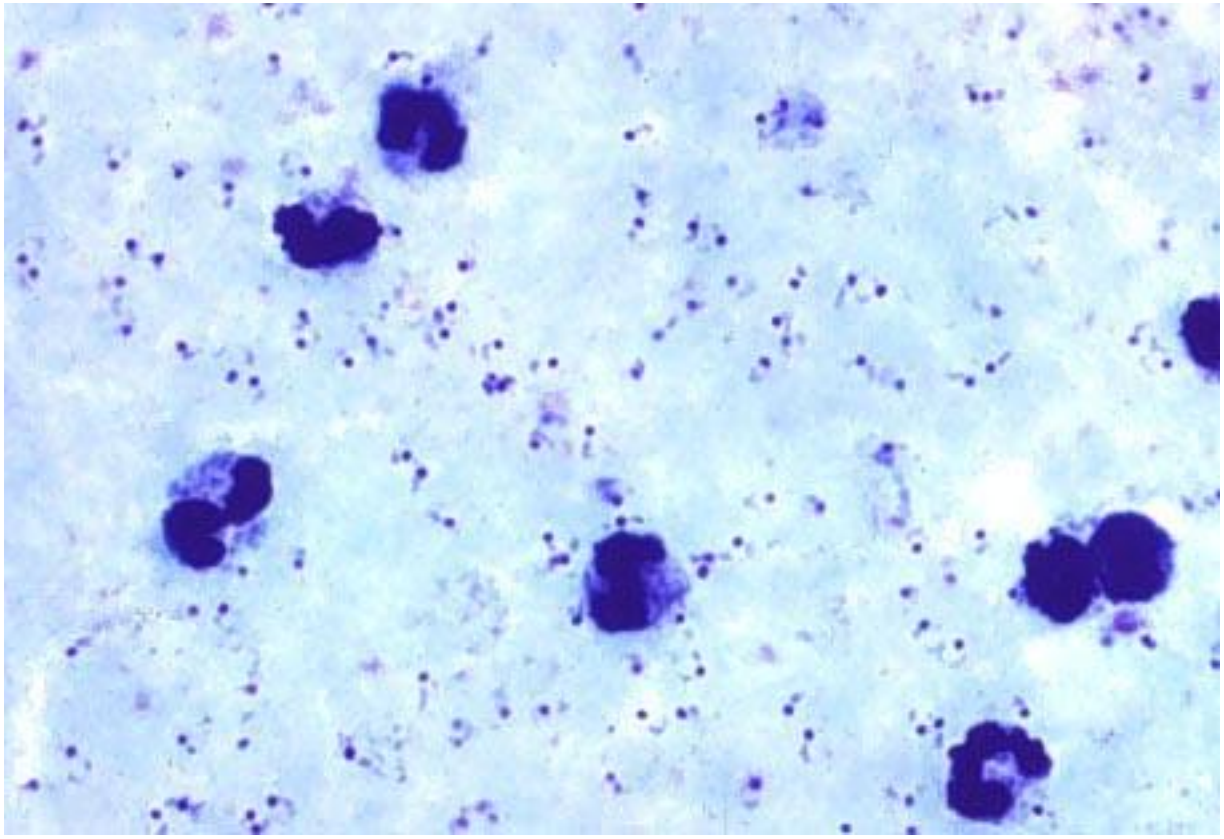
Blood phase

- Trophozoites are early stages with ring form the youngest
- Tropohozoite nucleus and cytoplasm divide forming a schizont
- Segmentation of schizont's nucleus and cytoplasm forms merozoites
- Schizogeny complete when schizont ruptures, releasing merozoites into blood stream, causing fever

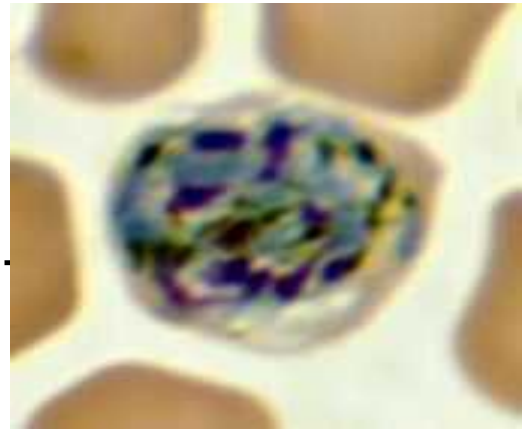
Source: Dr Philip Gothard

Diagnosis

Thick film

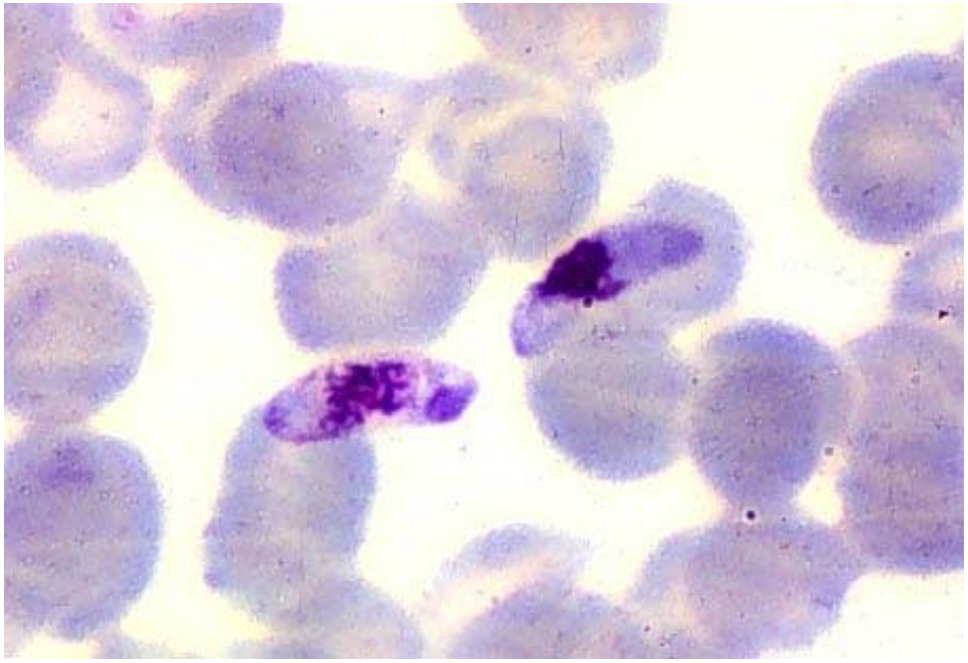


Thin film

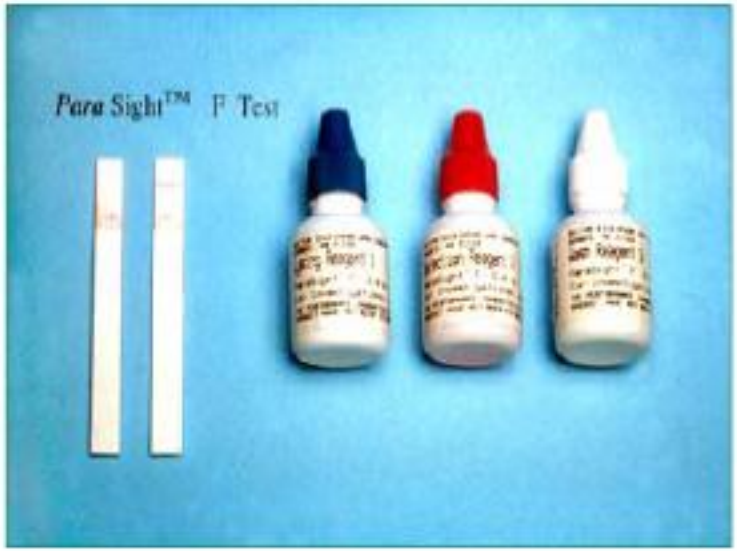


Schizonts

Gametocytes



Rapid diagnostic tests



Treatments

Mild

Quinine
Atovoquone/
Proguanil

with

Doxycycline
(Fansidar)

Severe

Quinine

Artemisinins

ACT (co-artem- artemether/lumefantrine)

Artemisinins

Artemisinins

Also known as qinghaosu (青蒿素)

Sesquiterpene lactone derived from artemisia annua

Family includes artesunate (water soluble), artemether (oil soluble) , dihydroartemesinin

Artemisisins : some theoretical advantages

Well tolerated

Little resistance

Rapid clearance of parasitaemia

Low toxicity

Good cure rates in combination therapy

Source: WHO 2006

Artemisisin : mechanism and resistance

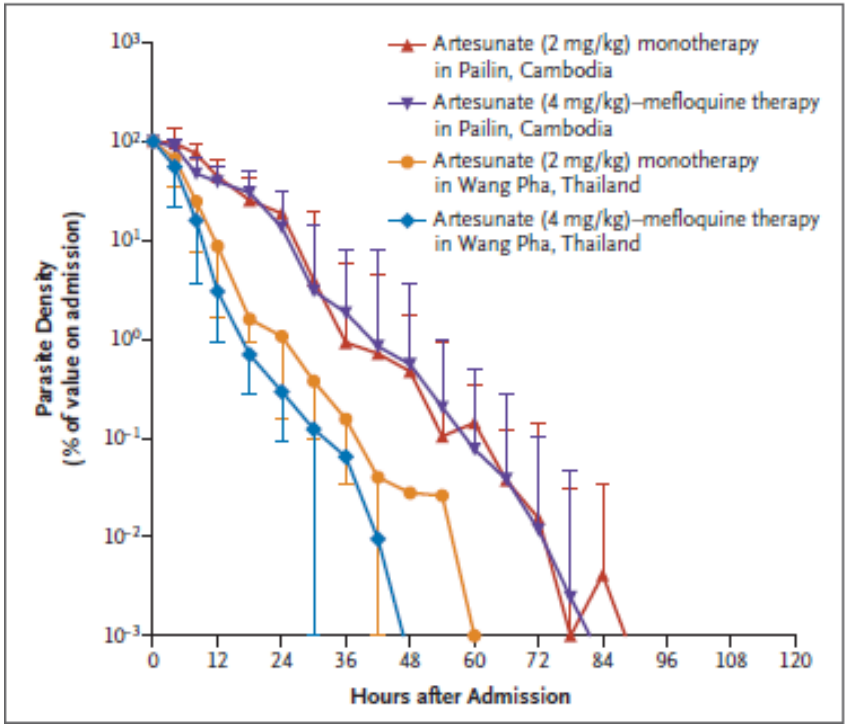
Mechanism debated

P450 metabolism (CYP2B6)

Artesunate generates RO species

Parasite target(s) not fully defined

PfATPase – PfATP6 (S769N)



Source: Dondorp-A et al NEJM 2010

Artesunate v quinine for severe falciparum malaria

- Declining efficacy of quinine in SE Asia
- Rapid parasite clearance with artesunate

- Prospective open label RCT
- 1461 adults & children (15%)
- Bangladesh (453); India (142);
- Indonesia (289); Myanmar (577)

- Severe malaria

- IV therapy plus routine care

Source: Dondorp-A et al SEAQAMAT group, *Lancet* 2005; **366**: 717-25

SEAQUAMAT

Deaths	Artesunate 15%	Quinine 22%
	107 / 730	164 / 731

Odds Ratio = 0.60

(0.45 – 0.79) p = 0.0002

RRR 35%

ARR 7%

NNT **14** (11 – 20)

Source: Dondorp-A et al SEAQAMAT group, *Lancet* 2005; **366**: 717-25

AQUAMAT

- Prospective open label RCT
- 5425 children recruited 2005-10
  11 African centres
- Median 2.9 years
- Primary outcome in-hospital mortality
- IV therapy plus routine care

Source: Dondorp-A et al AQUAMAT group, *Lancet* 2010

AQUAMAT

- Lower mortality in artesunate group

  8.5% artesunate, 10.9% quinine

  OR 0.75 95% C.I. 0.63-0.9 P=0.002

- Coma, convulsion and deterioration of coma all lower in artesunate group (followed up at 28 days)

- Significantly less hypoglycaemia

Source: Dondorp-A et al AQUAMAT group, *Lancet* 2010

Remaining Obstacles to Implementation?

- **No further RCTs forseen**
- **Questions about quality and supply of drug**
  - **Nov 2010 Guilin passed WHO pre-qualification**
  - **Capacity for 6 million pcs/year – running at 33%**
  - **Moves towards synthetic production**

Factors influencing future malaria risk

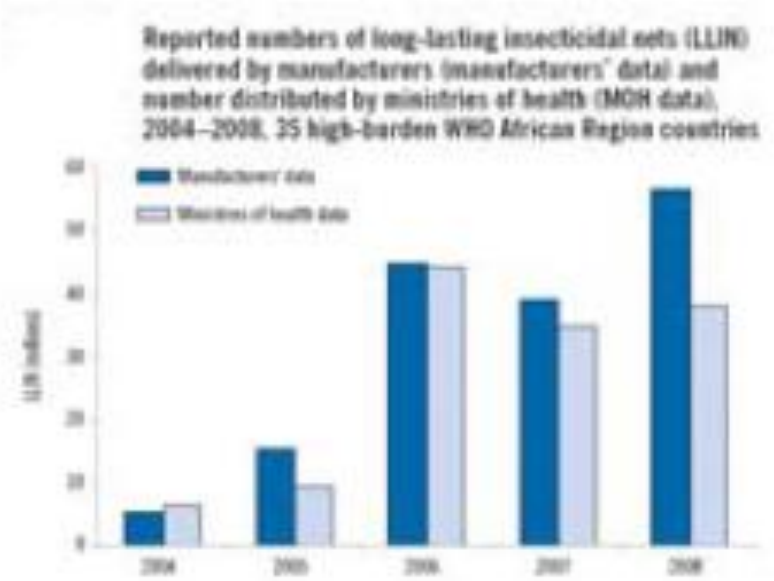
Increase

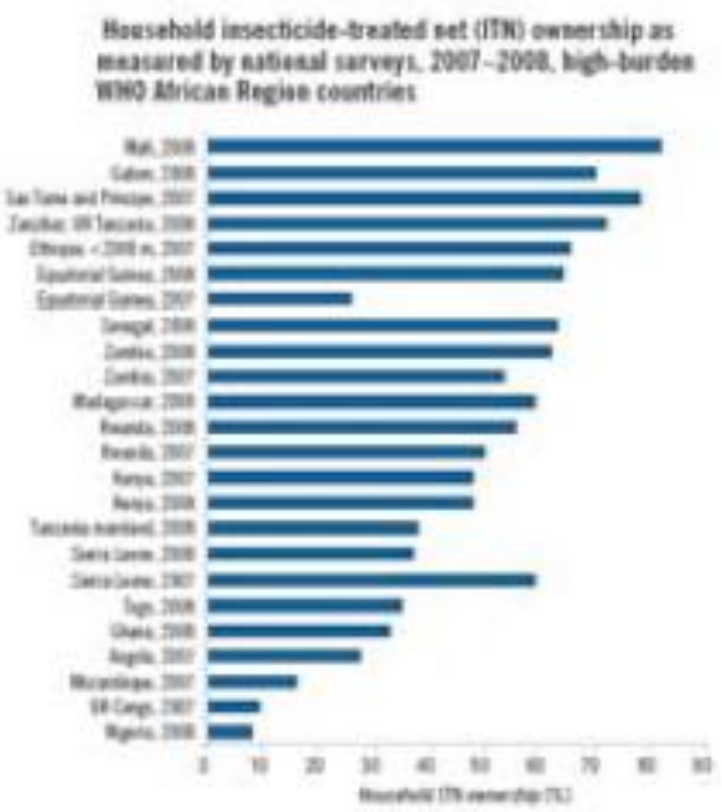
- Population movements
- Agricultural practices eg dams, deforestation
- Weakened public health systems
- Drug resistance
- More speculative- climate change

Decrease

- Long lasting insecticide treated bednets (ITN)
- Indoor residual spraying(IRS)
- Intermittent preventive treatment (IPT) for infants and pregnant women
- Rapid Diagnostic Tests (RDT)
- Artemisinin-based Combination Therapies (ACTs)
- A vaccine (eg RTS,S)

ITN ownership





Why a vaccine?

- **Malaria endemic where health care systems weak and resources poor: need cost-effective interventions**

- **Drug resistance a problem with all antimalarials**

- **Insecticide resistance a problem with vector control**

- **Recent years have seen a marked increase in available funding (particularly Gates/PATH) – more corporate approach**

It is possible to induce protective immunity

- **Radiation attenuated sporozoite challenge can protect from live malaria challenge**

Doolan JID (2002)

Nussenzweig Nature (1967)

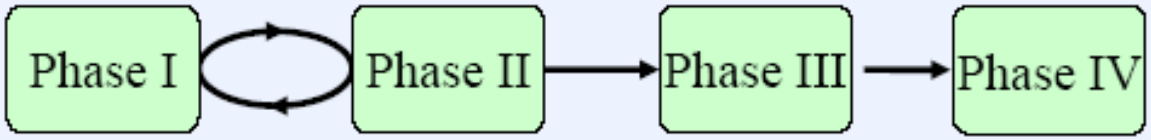
Still an area of ongoing research, e.g. manufacturing of genetically modified parasites

Protection probably largely CD8+ T cell mediated

Vaccine “pipeline”

- **Over 80 candidate vaccines in pre clinical development**
- **Pre-erythrocytic, blood stage, transmission blocking**
- **Over 20 vaccines tested in clinical testing**
- **A few have reached field trials (2b/3)**

Vaccine evaluation



Type of Trial	Proof of Principle	Dose Ranging Scheduling *Preliminary Efficacy*	Pivotal Licensure Studies	Postmarketing Studies
Endpoints	Safety Immunogenicity	Safety Immunogenicity *Efficacy in Malaria Trials*	Safety Immunogenicity Efficacy	Safety Surveillance Secondary Endpoints Effectiveness
Typical Sample Size	10s	100s	Endpoint specific (10,000-50,000)	Endpoint specific 10,000

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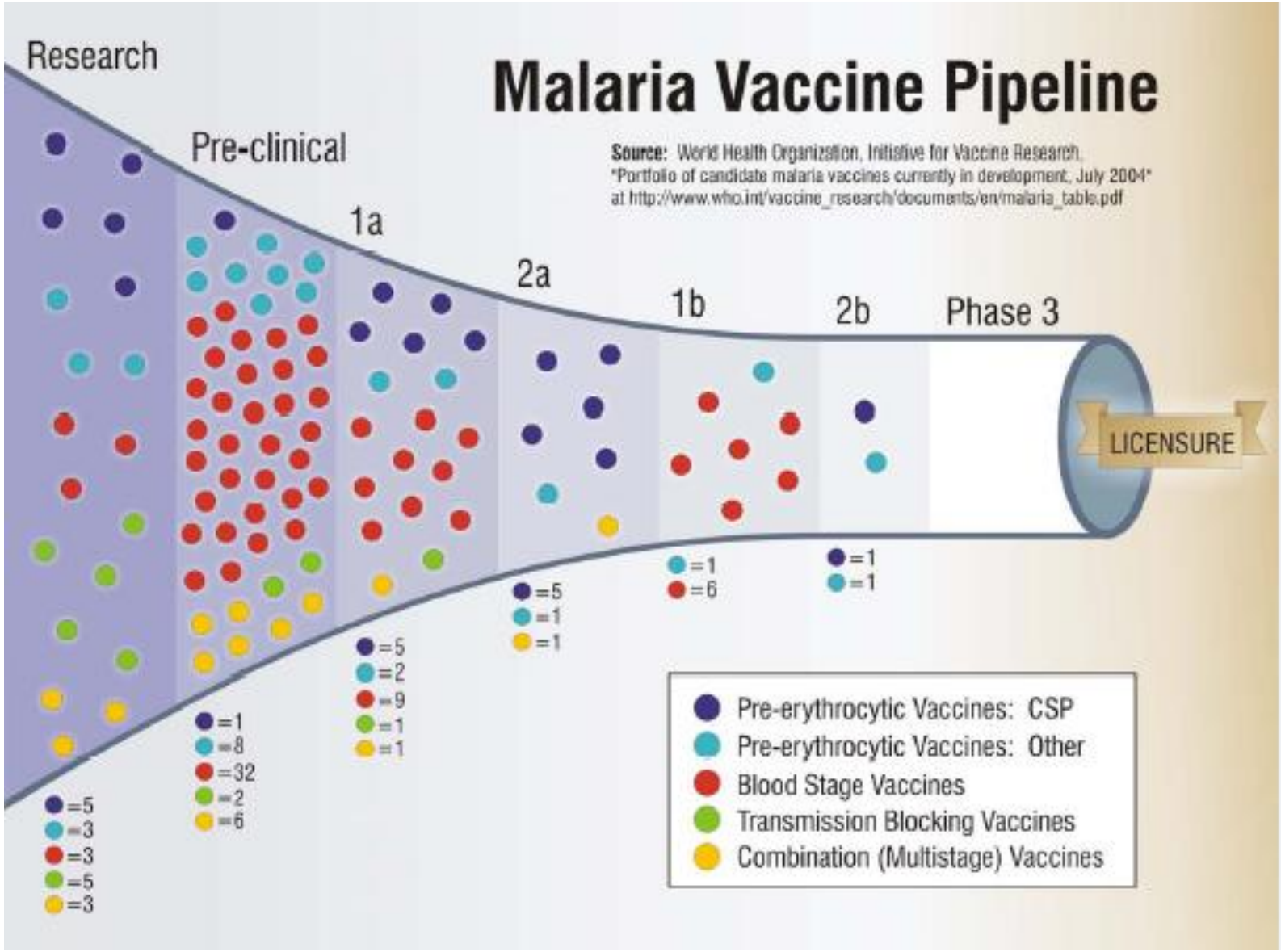
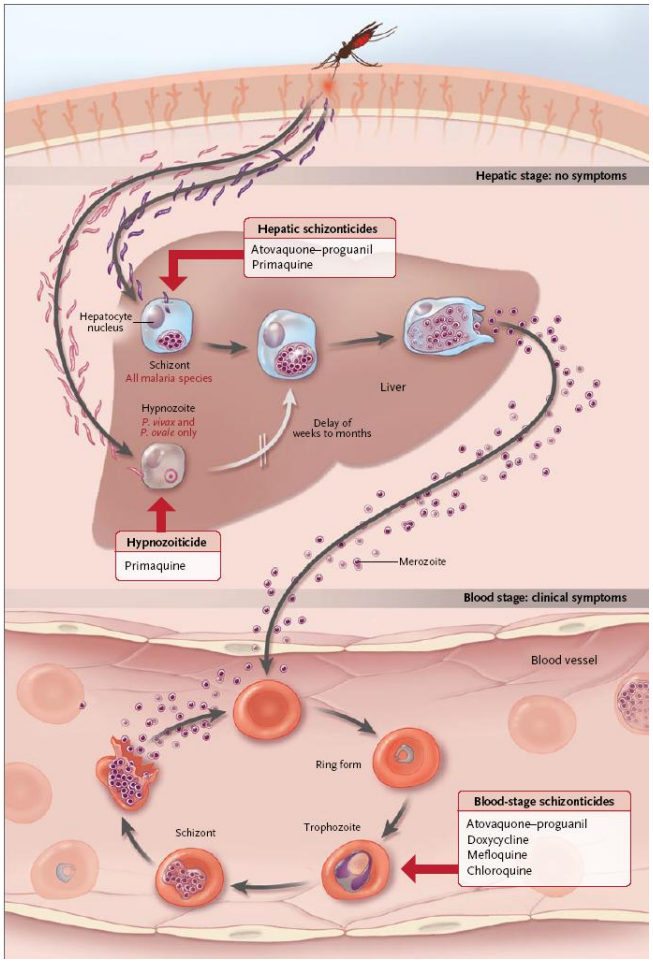
Source: Ghana MOH


Malaria Vaccine Pipeline
Source: World Health Organization, Initiative for Vaccine Research.
"Portfolio of candidate malaria vaccines currently in development, July 2004"
at http://www.who.int/vaccine_research/documents/en/malaria_table.pdf
Research
Pre-clinical
1a
2a
1b
2b
Phase 3
LICENSURE
=5
=3
=3
=5
=3
=1
=8
=32
=2
=6
=5
=2
=9
=1
=1
=5
=1
=1
=1
=6
=1
=1
Pre-erythrocytic Vaccines: CSP
Pre-erythrocytic Vaccines: Other
Blood Stage Vaccines
Transmission Blocking Vaccines
Combination (Multistage) Vaccines

That life cycle again



That life cycle again

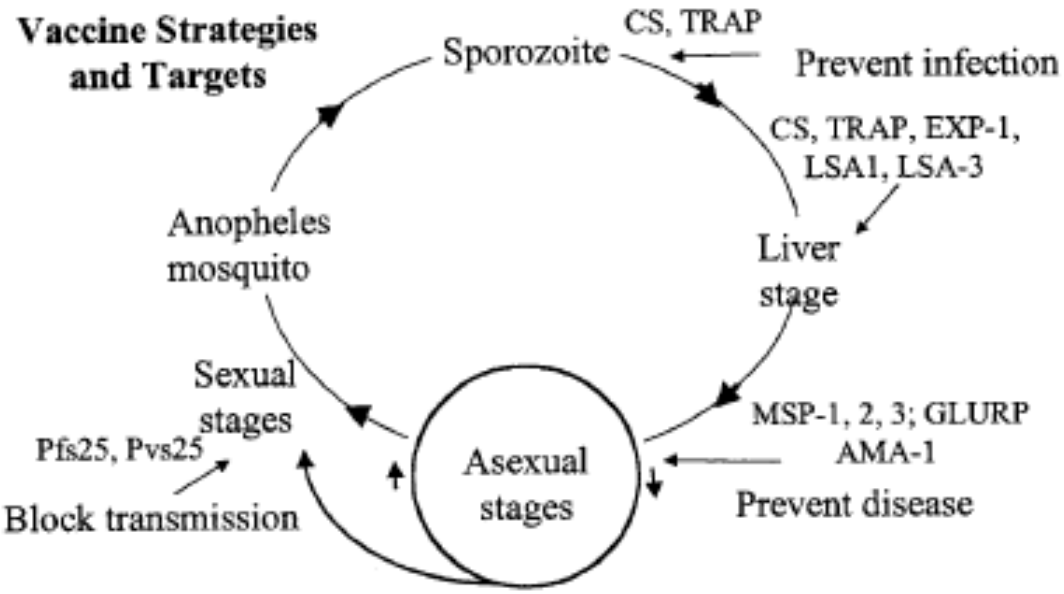


FIGURE 1. Malaria life cycle and vaccine targets. CS = circumsporozoite; TRAP = thrombospondin-related adhesive protein; EXP-1 = exported antigen 1; LSA1 = liver stage antigen 1; MSP-1 = merozoite stage protein 1; GLURP = glutamate-rich protein; AMA-1 = apical membrane antigen 1; Pf = *Plasmodium falciparum*; Pv = *P. vivax*.

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Source: Ballou AJHTM 04

Pre-erythrocytic vaccines

- **Need to be 100% effective to prevent disease**
- **Lesser reduction might be clinically relevant**
- **Circumsporozoite protein (CSP) the antigen most clearly linked to protection**
- **Induces both T cell and B cell responses**

Blood stage vaccines

- **Likely more antibody than cellular immunity, but again evidence for both**

- Materno-foetal transfer of antibody might offer window of protection to newborns
- In endemic areas, indiviudlas with repeated attacks of malaria are able to better control parasite replication
- Passive transfer of antibody can elimate P falciparum in infected humans

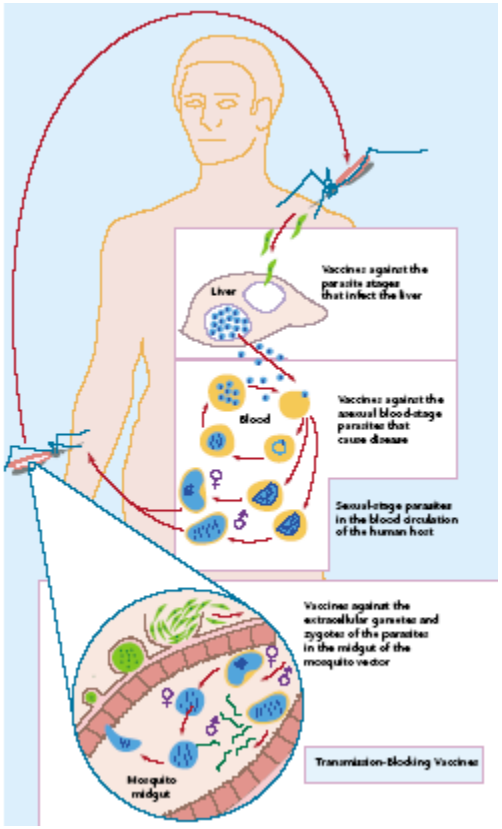
Blood stage vaccines

- **Challenges**

- Do not create sterilising immunity
- Range of target antigens (MSP-1, MSP-2, etc)
- Great antigen variability

Transmission blocking vaccines

- Poor relative of other pre-erythro/blood stage
- Rely on generating antibodies to sexual stages of parasite in mosquito midgut
- Could contribute to reducing population transmission of parasites



Source: Carter NM 2000

Selected vaccine in development 2010

Pre-erythrocytic

		Phase 1	Phase 2	Phase 3
RTS,S/AS01E	GSK			
AdCh/MVA ME-TRAP	Oxford			
Ad35 vectored CS	NIAID			
PfSPZ	Sanaria			
DNA EP1300	NIAID			

Blood stage

AdCh63/MVA MSP1	Oxford			
EBA175 RII	NIAID			
AMA1 -3D7	Us Army			
GMZ2	EVI			
MSP3	EVI			
Se36	Osaka			

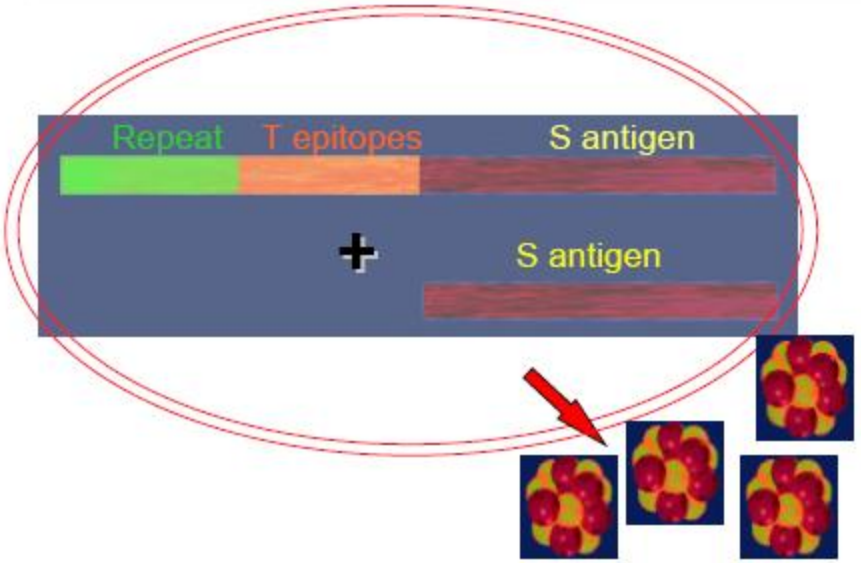
Lead vaccine product: RTS,S

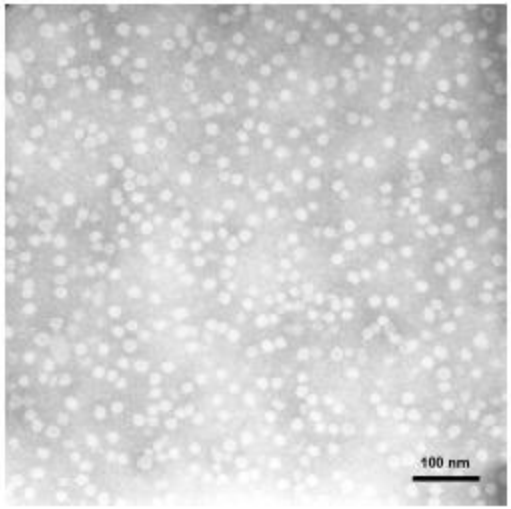
- **Product of GSK/ Walter Reid (WRAIR) collaboration began in 1987**

- **RTS, S is a pre-erythrocytic vaccine**

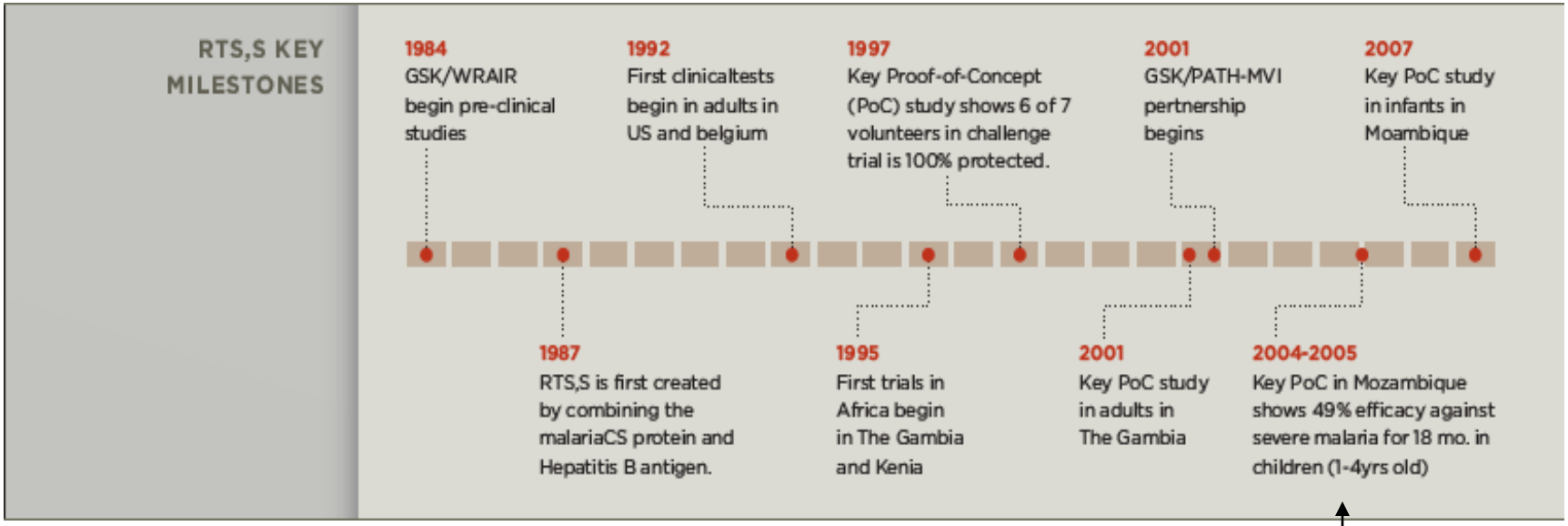
- **Comprises:** **Sequences of CSP fused to HBsAg**
  Unfused HBsAg
  Adjuvant (AS02) – QS21, 3D-MPL

The RTS,S antigen





Source: Cohen GSK 2004



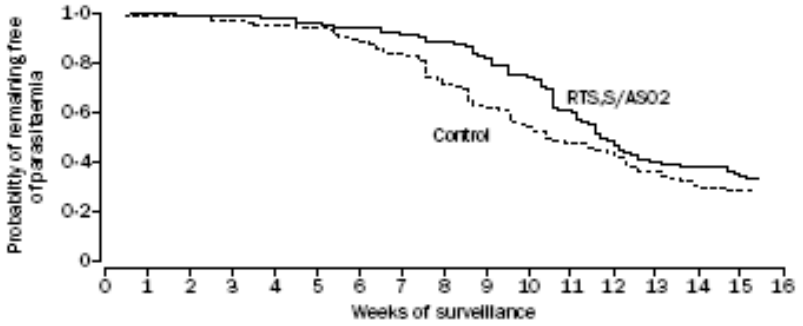
UK Gov commits to buy vaccine

Source: MVI PATH fact sheet

Lead vaccine product: RTS,S

- **Human Phase IIa studies 30-86% protection**

- **2b field studies in semi-immune adult men in The Gambia (Bojang Lancet 01)**
  - **Infections earlier in control group**
  - **Vaccine efficacy 34%**
  - **Protection waned with time**



Number at risk								
RTS,S/AS02	131	129	125	118	110	90	58	45
Control	119	118	110	101	82	60	47	33

Figure 3: Kaplan-Meier survival curves showing probability of remaining free of *P falciparum* infection during 15 weeks of surveillance in 1998
Week 0 of surveillance began in September, 1998, 14 days after dose 3 of vaccine was administered.

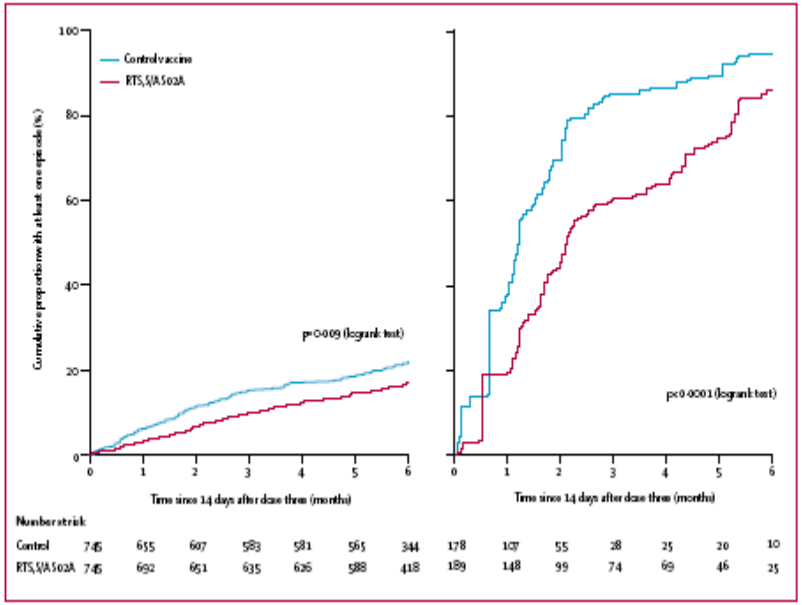
Lead vaccine product: RTS,S

- **Phase 2b in children**

- **Study in Mozambique (Alonso Lancet 04)**
  - **Two groups**
  - **Cohort 1 – time to first malarial episode (29.9% effective)**
  - **Cohort 2 – prevention of new infections (37% effective)**

Prop >1 malarial episode

Prop with malarial infection



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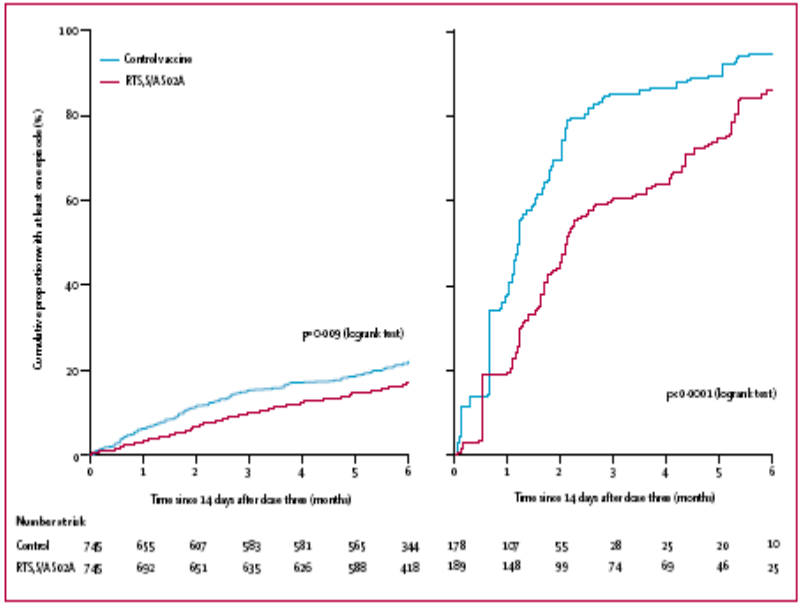
Prop >1 malarial episode

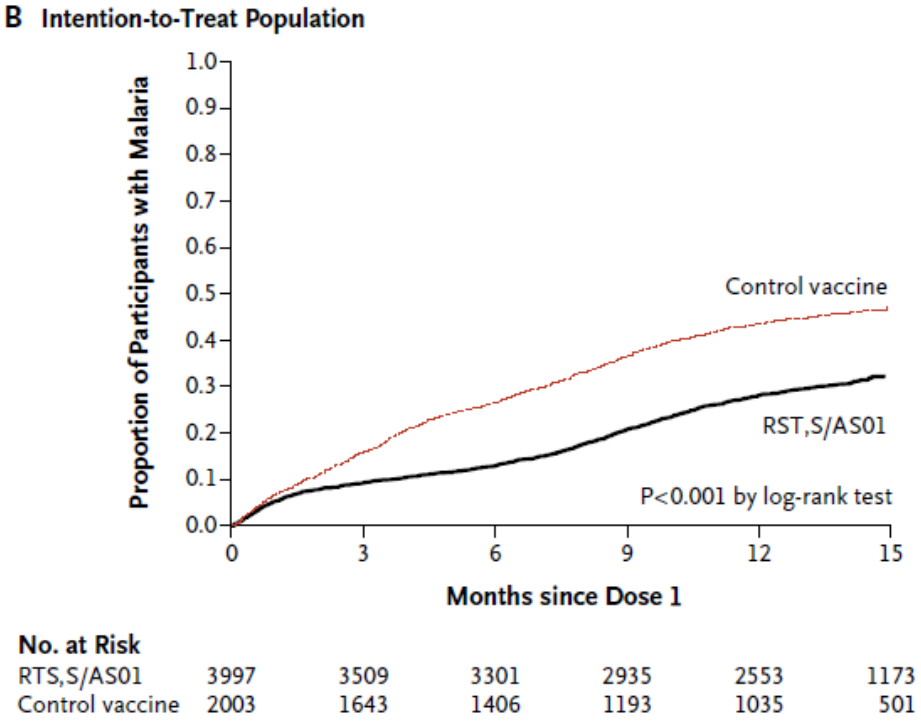
Prop with malarial infection



Phase III

- **Phase 3 in children**

- **Study in SSA (NEJM 11)**
  - **15,460 children**
  - **6-12/52 or 5-17/12**
  - **Primary endpoint malaria by 12 months**
  - **Efficacy against severe malaria 45.1%**



NEJM 2011

Need a break?

Thank You