MALARIA

By

Dr. Saliu Tosho ABDULSALAM

MB;BS, MPH, FMCPH,fss,mss,psc

Lecturer & Consultant Community Physician

Universityof Ilorin & UnilorinTeaching Hospital

Focus of the Lecture

- At the end of this lecture students should be able to
  - Discuss the key facts and issues in epidemiology of malaria.
  - Discuss the impacts of malaria, particularly in sub-Saharan African.
  - List and appraise existing malaria control strategies.
  - Discuss the challenges, new updates and future of research and development (R & D) in malaria.

Outline of the Presentation

Section i - Malaria Epidemiology

Section ii - Impact of Malaria

Section iii - Malaria Control Strategies

Section iv - R&D (Treatment and Vaccine)

SUMMARY

- Occurence World wide
- Organisms *Plasmodium (single celled parasite)falciparum (80%, most dangerous/devastating), P. Vivax,P malariae, P.ovale*
- Reservoir Humans
- Transmission Bite of Female Anopheles mosquioes
- Control Early diagnosis and treatment, Chemoprophylaxis, Impregnatednets and curtains, Vector control, personal protection, Environmental sanitation & ??? Vaccine protection

MALARIA

- Malaria is t he commonest cause of fever and accounts for the highest number of people visiting health facilities for treatment in Tropical Afri ca
- The disease affects those living between 60 degree N and 40 degree S but most intense in Africa

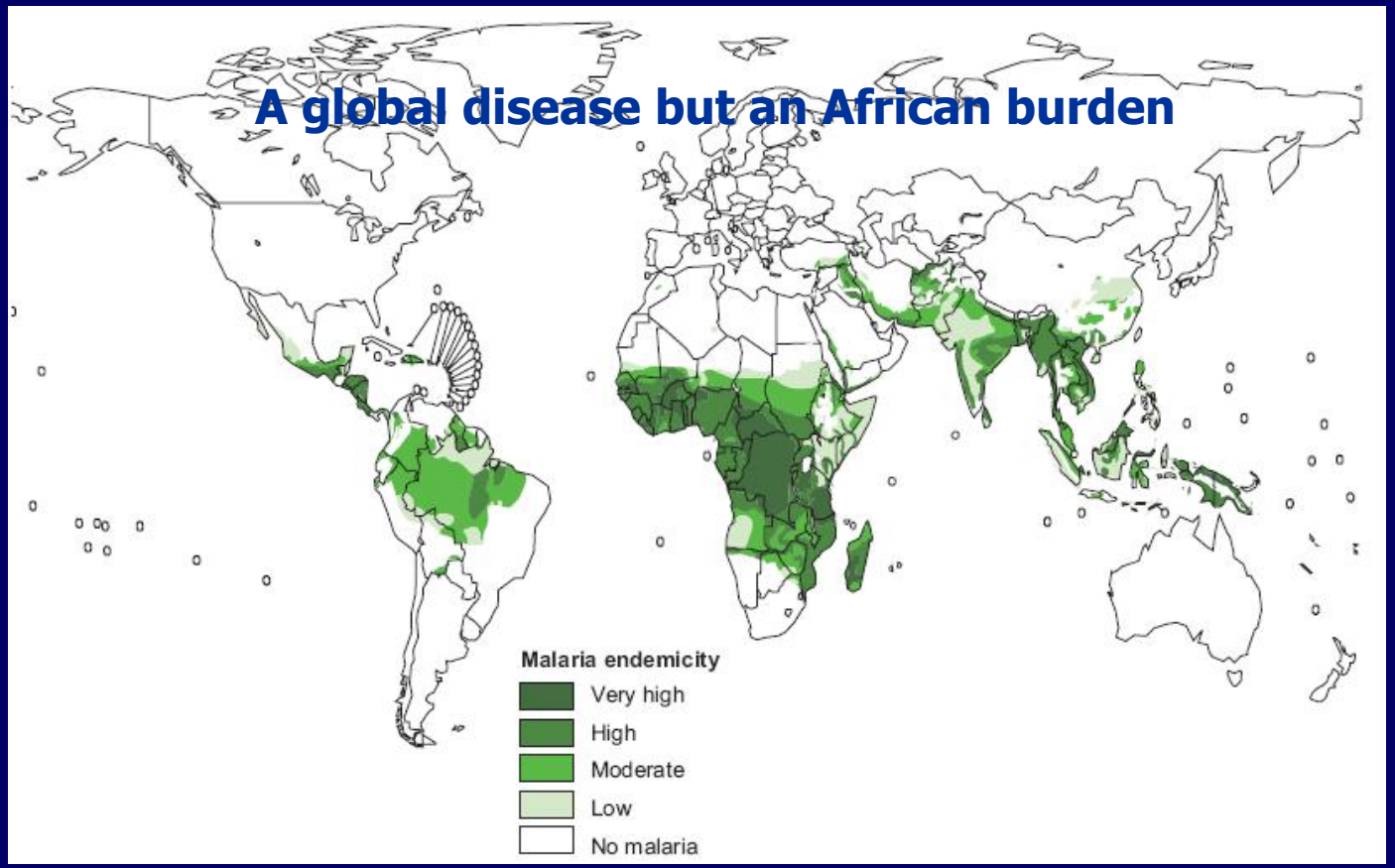
Section i

Malaria Epidemiology

Transmission intensity

- Full spectrum of malaria transmission intensity present in most countries in the sub-Saharan Africa
- Transmission intensity is partly responsible for the “quantity of disease” i.e. prevalence and incidence (→the impact of malaria transmission)
- Has no direct method of measurement; Entomological Inoculation rate (EIR) is most accurate measure but is difficult to carry out

Global distribution of malaria transmission risk



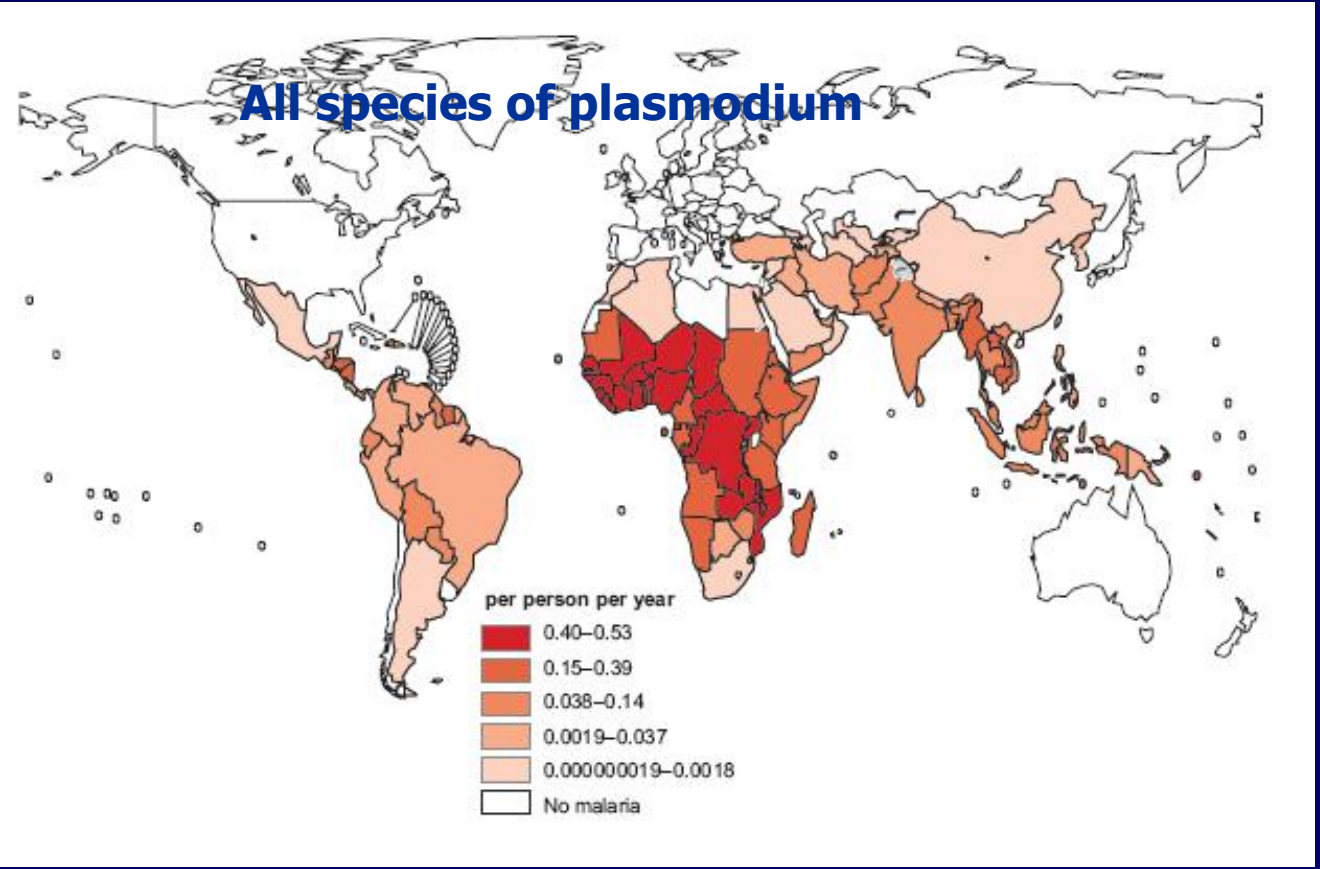
Source: World Malaria Report 2005

Transmission intensity

Transmission intensity can be estimated from any of the following proxy measures at population level:

- a) malaria disease incidence/prevalence
- b) parasite prevalence
- c) spleen rates

Estimated incidence of clinical episodes resulting from local transmission, country level averages



Source: World Health Report 2005

Transmission intensity

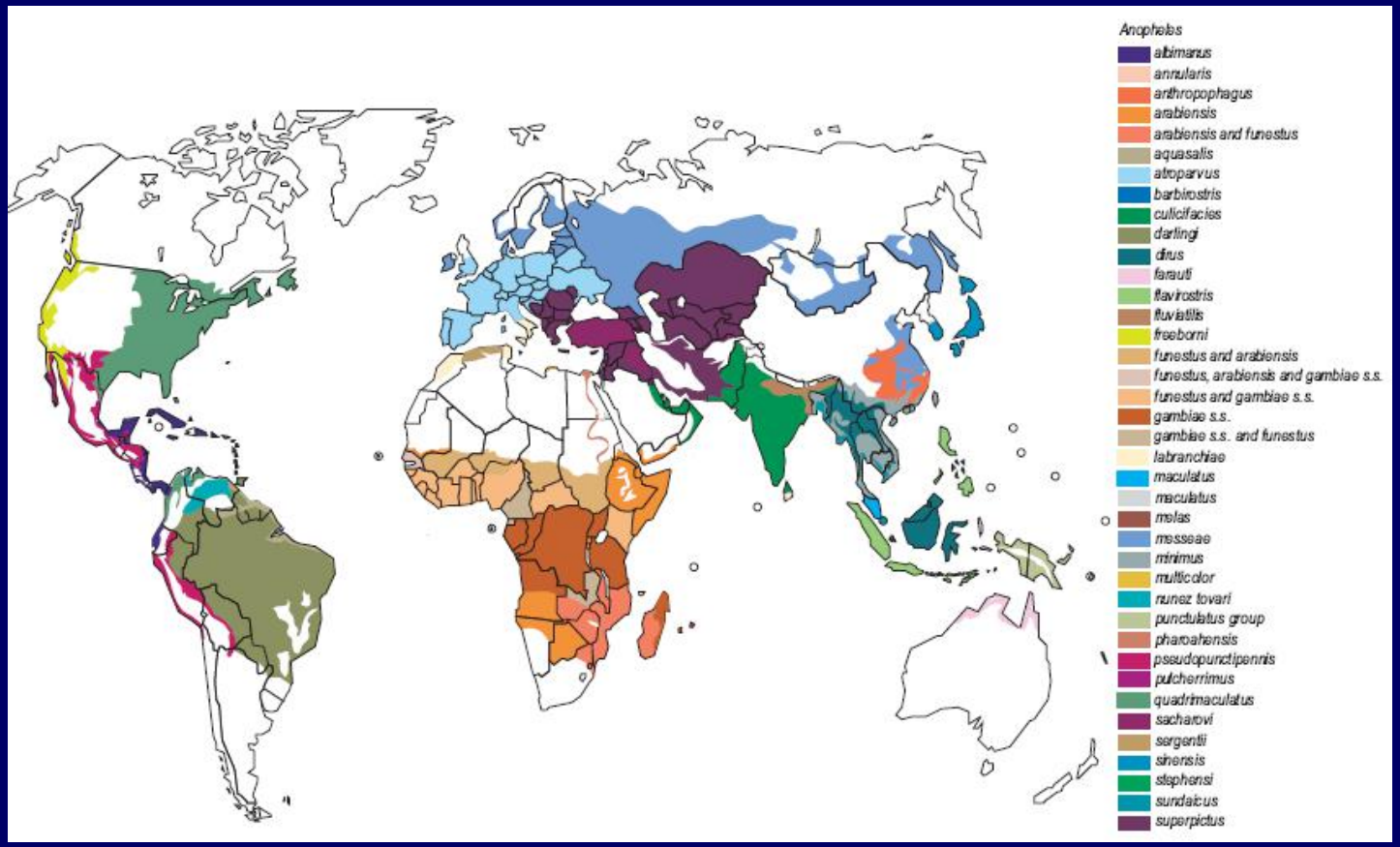
Main factors responsible for transmission intensity in an area are:

- Vectorial capacity [vector]
- Climatic conditions especially rainfall and temperature [environment]
- Presence of susceptible human hosts [host]

Transmission intensity

Vectorial capacity = The mean number of probable inoculations transmitted from one case of malaria in a unit of time

Global distribution of dominant malaria vectors



Source: World Health Report 2005

Vectors

- Female Anopheles mosquito solely responsible for transmission
- Main species found in sub-Saharan Africa include:
  - An. Gambiae → most efficient malaria vector
  - An. Funestus
  - An. Arabiensis

Transmission intensity

Climatic conditions

- Rainfall, humidity
- Temperature

Transmission intensity

Basic case reproduction rate = The number of new cases of a disease that will arise from one current case when introduced into a nonimmune host population during a single transmission cycle

Anderson and May, 1992

Malaria risk

Malaria Parasites

- Four human species of Plasmodium
  - *P. falciparum*
  - *P. vivax*
  - *P. ovale*
  - *P. malariae*
- P. falciparum is the most prevalent species in the selected countries
- P. falciparum causes severe malaria

Susceptible Human hosts

- Stable transmission areas
  - Children aged under five years
  - Pregnant women
- Unstable transmission areas
  - All age groups
- Other affected host groups
  - People living with HIV
  - Travellers from malaria-free areas to endemic areas
  - Elderly
  - Children with sickle cell disease

Section ii

Impact of malaria

The Burden of malaria

- A major public health problem worldwide.
- 107 countries are at risk of malaria
- 3.2 billion people live in malaria area
- 300 – 500 million suffer from malaria yearly
- Over 1` million people die worldwide from malaria annually

- Source – WHO, 2005

The Burden of malaria

Sub-Saharan Africa:

- 60% of case of malaria worldwide
- 75% of global P. falciparum malaria
- 80% of the deaths from malaria
- 25-35% of all outpatients
- 20-45% of hospital admissions
- 15-35% of hospital deaths

The Burden of malaria

- Malaria kills 100,000 non-immune adults annually in Asia and the Americas
- Malaria cost over US$ 2 billion to economy in Africa alone
- Major cause of poor child development: Impairment of cognitive function.

COMPLICATION OF MALARIA

- Cerebral Malaria
- Anaemia
- Pregnancy-related problems such as abortions, stillbirth, prematurity and low birthweight

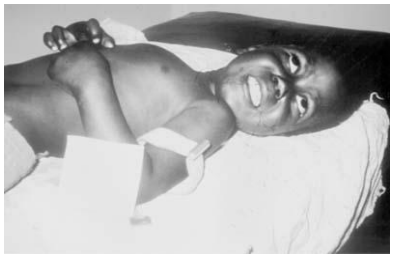
Clinical Manifestations and Consequences of malaria

Infected Mosquito

Infected Human

Acute febrile illness

Severe illness



Hypoglycemia

Anemia

Respiratory distress

Cerebral malaria

Death

Chronic effects

Anemia

Neurologic/ cognitive

Developmental

Impaired growth and development

Malnutrition

Pregnancy

Fetus

Low birth weight

Infant mortality

Maternal

Acute illness

Anemia

Impaired productivity

Distribution of malaria cases

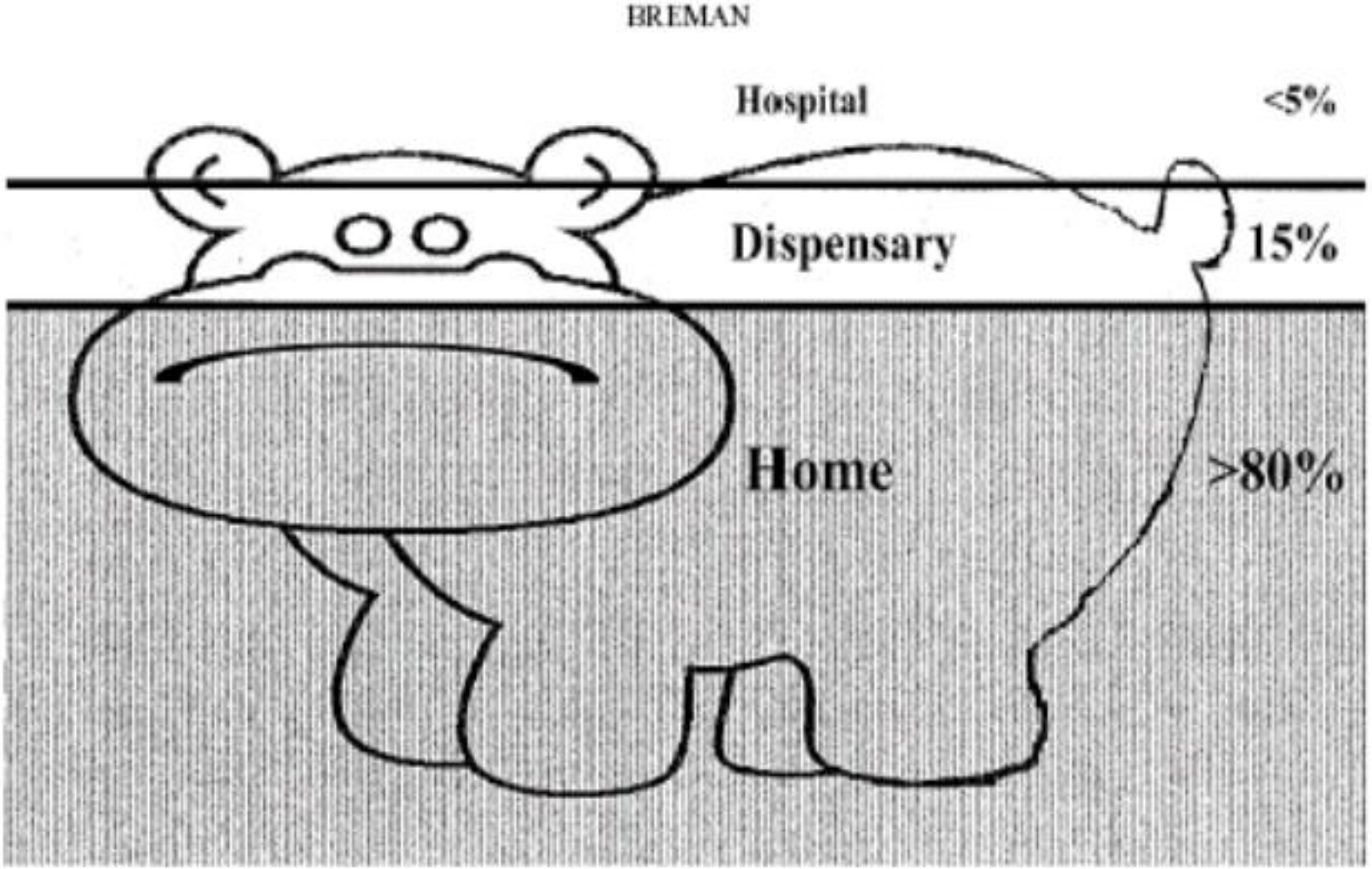


FIGURE 6. "The Ears of the Hippopotamus" where malaria patients are managed . . . and die.

Morbidity attributable to malaria

- Fever is the most common symptom of uncomplicated malaria; not all fevers are due to malaria
- National Health Management Information Systems are routinely used to collect data on clinical episodes of malaria
- Data on malaria morbidity is limited by:
  - Lack of parasitological confirmation; misdiagnosis
  - Access to health systems and treatment seeking behaviour
  - Under-reporting
- Few Demographic Surveillance sites available
- Data is mostly prevalence; incidence data very limited

Morbidity attributable to malaria

- 11 countries (50%) with data in 2001 indicates a minimum of 12 million clinical episodes
- Snow et al. 2003, estimate that there are about 213 million episodes per year in Africa (based on 2000 data)
- Upward trend has been due mostly to increasing resistance to Chloroquine (CQ) and SP
- Introduction of Artemisinin-based combination therapy (ACT) as a more effective treatment for uncomplicated malaria; more expensive and more complex dosage than CQ or SP

Morbidity attributable to malaria

- Life threatening illness requires admission
- 25-55% of admissions are attributed to malaria
- Diagnostic criteria used to confirm severe malaria
- Quinine is the mainstay of treatment for these cases
- Timeliness of diagnosis and treatment is paramount in order to save life
- Some patients who recover have complications

Mortality attributable to malaria

- Death rate attributable to malaria is the most accurate measure but is very difficult to estimate correctly
- Under five mortality rate is not a good proxy measure because it is influenced by diarrhoeal and respiratory diseases
- Case fatality rate (CFR) drives the mortality rate
- CFR is mainly influenced by the virulence of the illness and the quality of care given

Additional effects of malaria – Macroeconomic impact

- Sachs and Malaney, 2002, estimate that the average per-capita gross domestic product of malaria-endemic countries in 1995 ($1,500) was approx. 1/5th that of malaria-free countries
- It is postulated that malaria could reduce GDP by 50% in highly endemic countries

Additional effects of malaria – Macroeconomic impact

- Malaria can hinder economic development
  - Death rate affects the demographic profile of a population
  - Leads to high fertility rates in order to compensate for those that will die
  - Sick adults are not able to work
  - Sick children miss school and need to be looked after
  - Foreigner investors may not invest in malarious areas

Additional effects of malaria – Microeconomic impact

- Household expenditure on prevention
  - $0.24 to $15 per household each month
- Household expenditure on treatment
  - $1.88 to $26 per month
- Total direct and indirect costs
  - $3.15 per person

Source: Saving Lives, Buying Time (IOM)

Section iii

Malaria Control Strategies

Current Malaria control strategies

Stable malaria transmission e.g. Benin, Chad, Côte d'Ivoire, Gabon, Gambia, Guinea, Guinea Bissau, Mali, Mozambique, Niger, Nigeria, Senegal, Sierra Leone, Togo, Uganda

- Prevention
  - Insecticide treated Nets (ITNs) for children under five, pregnant women and people living with HIV/AIDS
  - Insecticide Residual spay, where appropriate
  - Intermitent Preventive Therapy in pregnancy
  - Vector Control
- Treatment

Presumptive treatment > Diagnosis-based treatment

  - Early and effective case management (facility level)
  - Home-based management of fever (community level)

Current Malaria control strategies

Unstable malaria transmission e.g. Burkina Faso, parts of Mauritania

- Prevention
  - IRS
  - Larviciding
  - Environmental management
  - ITNs
- Treatment
  - Early and effective case management

Malaria elimination

Integrated vector management

Diagnosis-based treatment > Presumptive treatment

Current Malaria control strategies

Free of malaria e.g. Comoros

- Prevention
  - For travellers to malarious areas, chemoprophylaxis and personal protection measures
- Treatment

  Diagnosis-based treatment > Presumptive treatment
  - Early and effective treatment

Current Malaria control supporting actions at country level

- Health system strengthening
- Appropriate Information, Education and Communication
- Behaviour change communication
- Implementation planning → addressing gaps
- Operational research embedded in programme activities → Evidence-based planning and implementation
- Monitoring and Evaluation
- Programme management
- Advocacy
- Coordination and partnerships
- R & D

One size does not fit all

- Overall control strategy should take malaria epidemiology into account
- Use of cost-effective interventions either singly or in combination (evidence-based)
- Secure sufficient and sustainable financing
- “Persistent is more important than perfection”

Anti-Malaria interventions; current to future

- Prevention
  - ITN → LLIN (**Long Lasting Insecticide Treated Net**)
  - IRS (Indoor Residual Spraying) insecticides
  - Chemoprophylaxis
  - → Efficacious Vaccines
- Treatment
  - CQ/SP → ACTs
  - ACTs → New treatments
  - Ancillary treatments

Cost will be a limiting factor

CONSTRAINTS TO MALARIA CONTROL

- Lack of Political Will
- Inappropriate use of Drugs
- Drug Resistance
- Poor Environmental Sanitation
- Vaccines
  - No vaccines
  - Efforts on for decades
  - Fighting spirit of plasmodium species
  - Undergo antigenic variation

ROLL BACK MALARIA

- Created in 1997
- Multilateral partnership
  - 4 UN Agencies (WHO, The World Bank, UNDP &UNICEF)
  - Bilateral Agencies
  - NGOs
  - National Agencies
  - The Civil Society
  - The Community

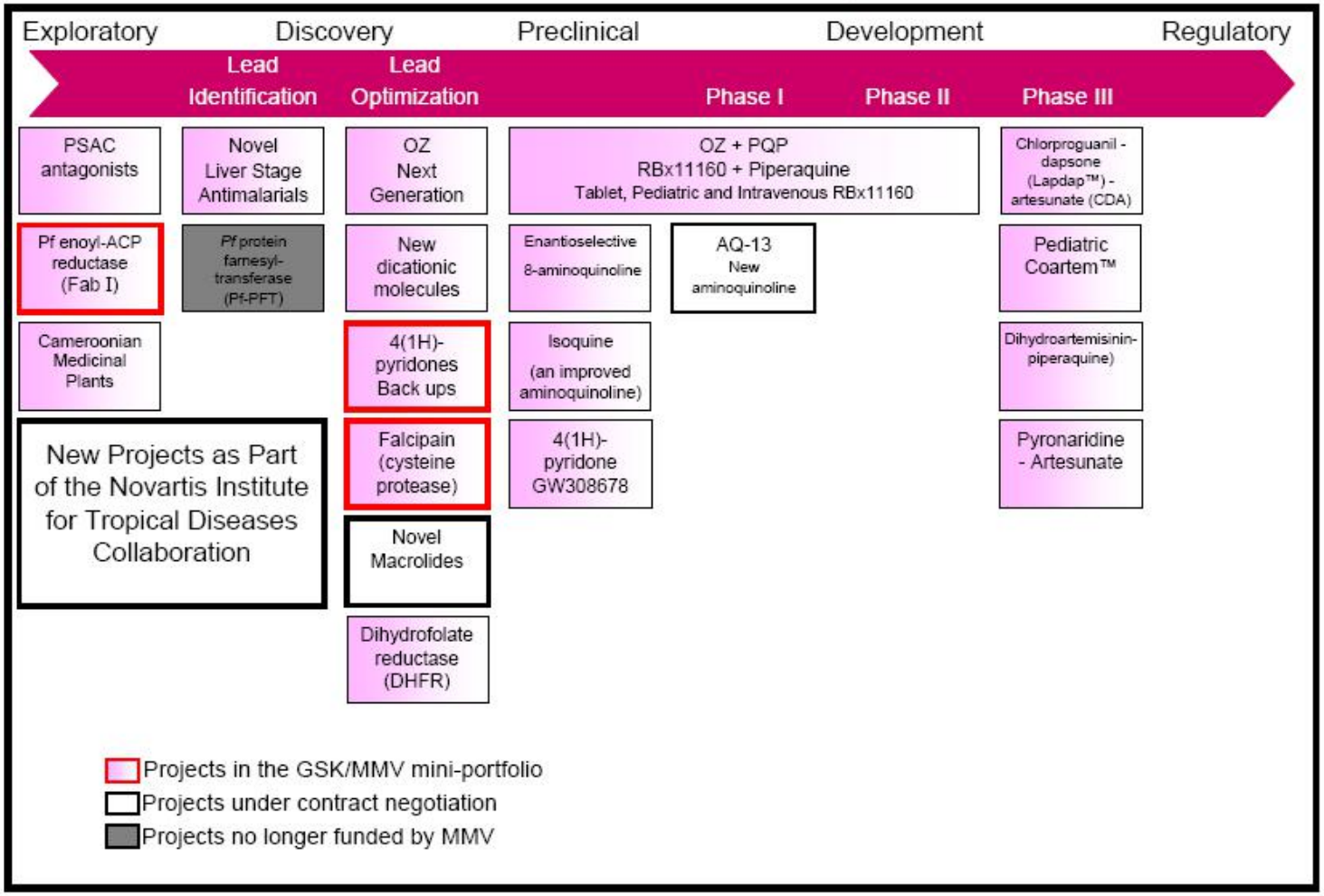
Section iv

Research and Development

Research and Development – Malaria treatment

- Between 1975 and 1999, only 4 new antimalarials out of 1,4000 new drugs
- Since 1999, improved R&D due to publicly funded initiatives
  - WHO/TDR → Medicines for Malaria Venture (MMV)
  - Public-Private Partnerships (MMV, Drugs for Neglected Diseases Initiative, DNDi)
- Walter Reed Army Institute of Research (WRAIR)

MMV Portfolio 3rd Q 2006



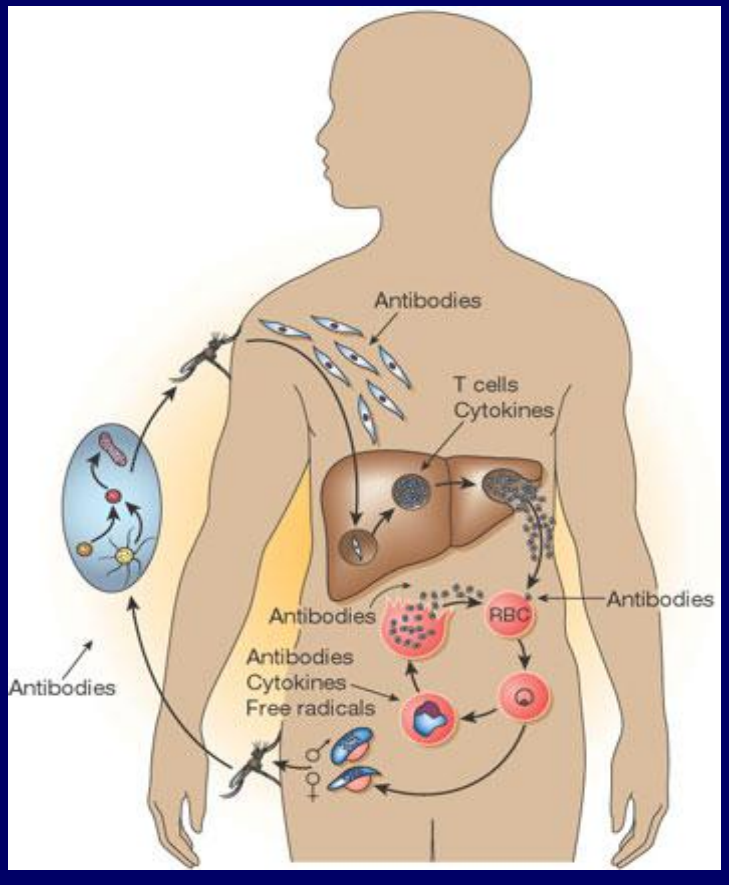
MMV portfolio

- New Combinations
  - Chlorproguanil-dapsone-artesunte (Lapdap-artesunate)
  - Pyronaridine-artesunate
  - Piperaquine-dihydroartemisinin (Artekin II)
  - Mefloquine-artesunate (→FACT)
  - Amodiaquine-artesunate (→FACT)

MMV portfolio

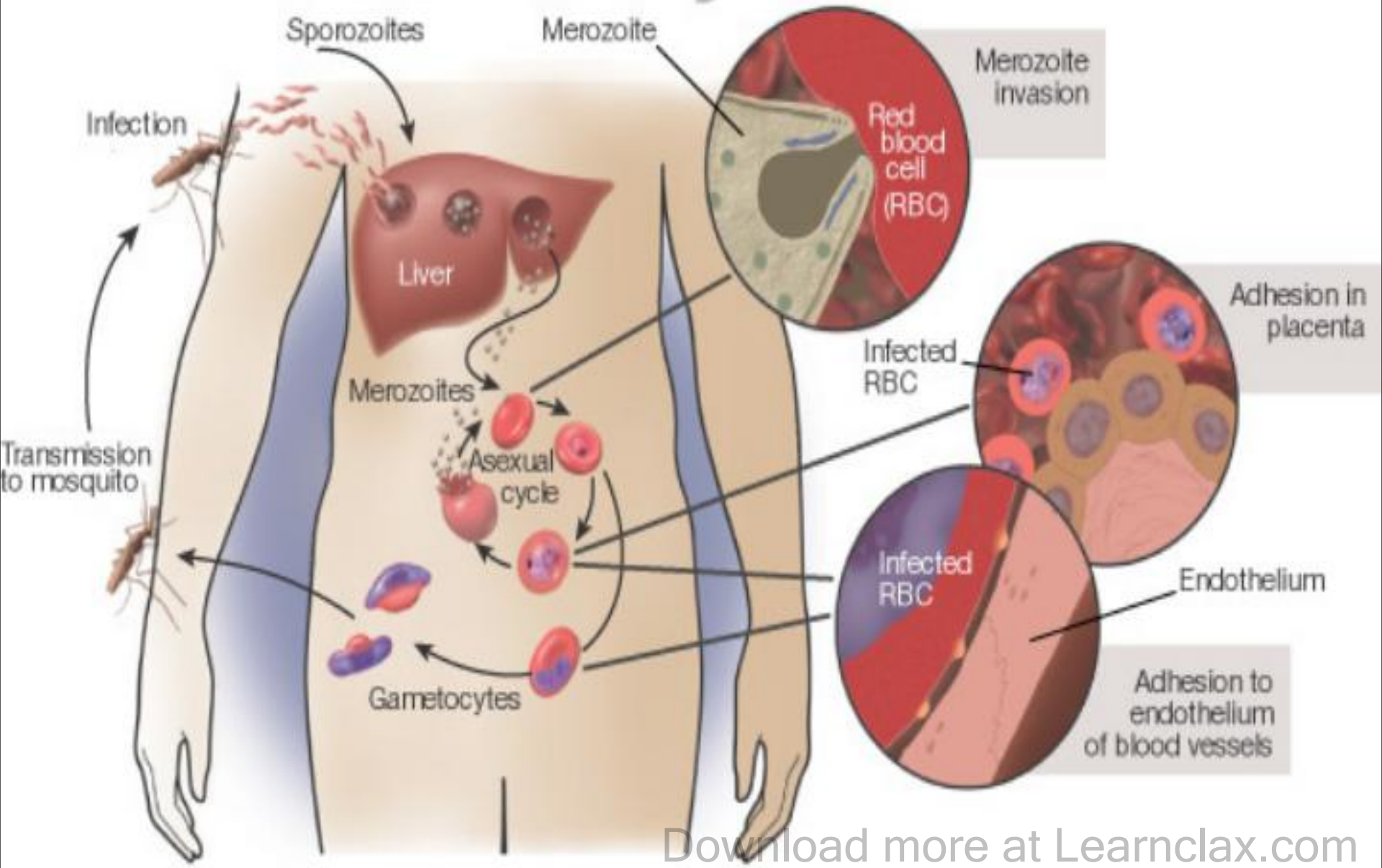
- New single agent drugs
  - Artemisone (lower neurotoxicity and ↑efficacy)
  - A new quinoline similar to amodiaquine (↑safety profile and ↑efficacy)
  - Fosmidomycin
  - A new class of synthetic endoperoxide (↑half-lives)
- Enhanced formulations
  - Paediatric Coartem
  - Rectal Artesunate
  - Intravenous Artesunate

Malaria Vaccines



- **Anti-infection vaccines**
- **Anti-disease vaccines**
- **Transmission-blocking vaccines**

Malaria life cycle



Beneficiaries of An Asexual Blood Stage Vaccine

- **Children < 5 years old**
  - **Severe anemia**
  - **Cerebral malaria**
  - **Respiratory distress**
  - **Sepsis-like syndrome**
- **Pregnant women**
  - Maternal anemia
  - Still-borns
  - Miscarriages
  - Low birth weight infants

Portfolio of candidate malaria vaccines currently in development
March 2005

Please help IVR keep this document up-to-date and send any updates/comments/changes to Zarifah Reed (reedz@who.int)

Pre-erythrocytic Vaccines							
	Research	Preclinical development	Phase 1a	Phase 2a	Phase 1b	Phase 2b	Pivotal
CSP							
RTS,S/AS02A MVI/GSK	X	X	X	X	X	X	
RTS,S/AS02D MVI/GSK	X	X	X				
RTS,S/AS01B WRAIR/GSK	X	X	X	X			
RTS,S/AS02 and Modified Vaccinia Ankara (MVA) CSP (Oxford-GSK)	X	X	X	X X			
CSP Recombinant adenovirus (NYU)	X						
CSP Recombinant adenovirus (WRAIR/Crucell Holland)	X	X					
CSP Recombinant influenza (NYU)	X						
CSP Recombinant vaccinia (NYU)	X						
CSP Recombinant Sindbis virus (NYU)	X						
CSP Recombinant Yellow Fever virus (NYU)	X						
CSP Long synthetic peptide (Biotagene/University of Lausanne)	X	X	X	X			

The Rainbow table

Activity phase / *Vaccine Type*	Development	Clinical trials	Total
Pre-Erythrocytic	13	4	27
Asexual	37	9	46
Transmission-Blocking	2	1	3
Combination	6	2	8
Total	58	16	74

Table of candidate malaria vaccines showing stage of development, collaborating institutions and sponsors; available at IVR website

http://www.who.int/vaccine_research/documents/en/malaria_table.pdf

Schedule for clinical development of SE36 vaccine

No	Phase	Place	Purpose	Target (recipient)	Test design	Usage・dose	Validity evaluation parameters	Target year
1	Phase Ia	Japan	Safety confirmation	Adult male	Single blind test with placebo	2 dose, 3 times, sc injection	Change of antibody titer (secondary evaluation)	2005
2	Phase Ib	Uganda	Safety confirmation	Adult male (SE36 antibody positive adult)	Single blind test with placebo	1 dose, 2 times, sc injection	Change of antibody titer (secondary evaluation)	2006-7
3	Phase II/III	Uganda/ Indonesia/etc	Clinical validity, Safety confirmation	6-8 years old children	dose determination test with placebo	1 dose, 2 times, sc injection	Rate of symptomatic malaria*、Rate of parasite positive, Change of Ht value, Change of antibody titer	2007-9
4	Phase III	Endemic country	Clinical validity, Safety confirmation	Children under 5 years old	To be determined	To be determined	Rate of symptomatic malaria*、Rate of parasite positive, Change of Ht value, Change of antibody titer	2009-10
5	Phase III	Japan	Validity (surrogate) Confirmation of safety	Healthy adults	To be determined	To be determined	Rate of sero-positive Change of antibody titer	2010

* Rate of symptomatic malaria: Determined according to WHO standards

** Parasitemia: number of infected erythrocyte / total number of erythrocyte

Production of malaria vaccine SE36 under GMP environments for clinical trials

In order to eliminate/eradicate malaria what we really need in addition to new interventions is

A cheap, safe and effective transmission-blocking vaccine with a long lasting effect

This and other malaria vaccine types remain elusive and is our challenge

Thank you.