NAC2013, NSTDA, Thailand Science Park
Pathumthani, April 1, 2013

World without Malaria: A Grand Challenge?

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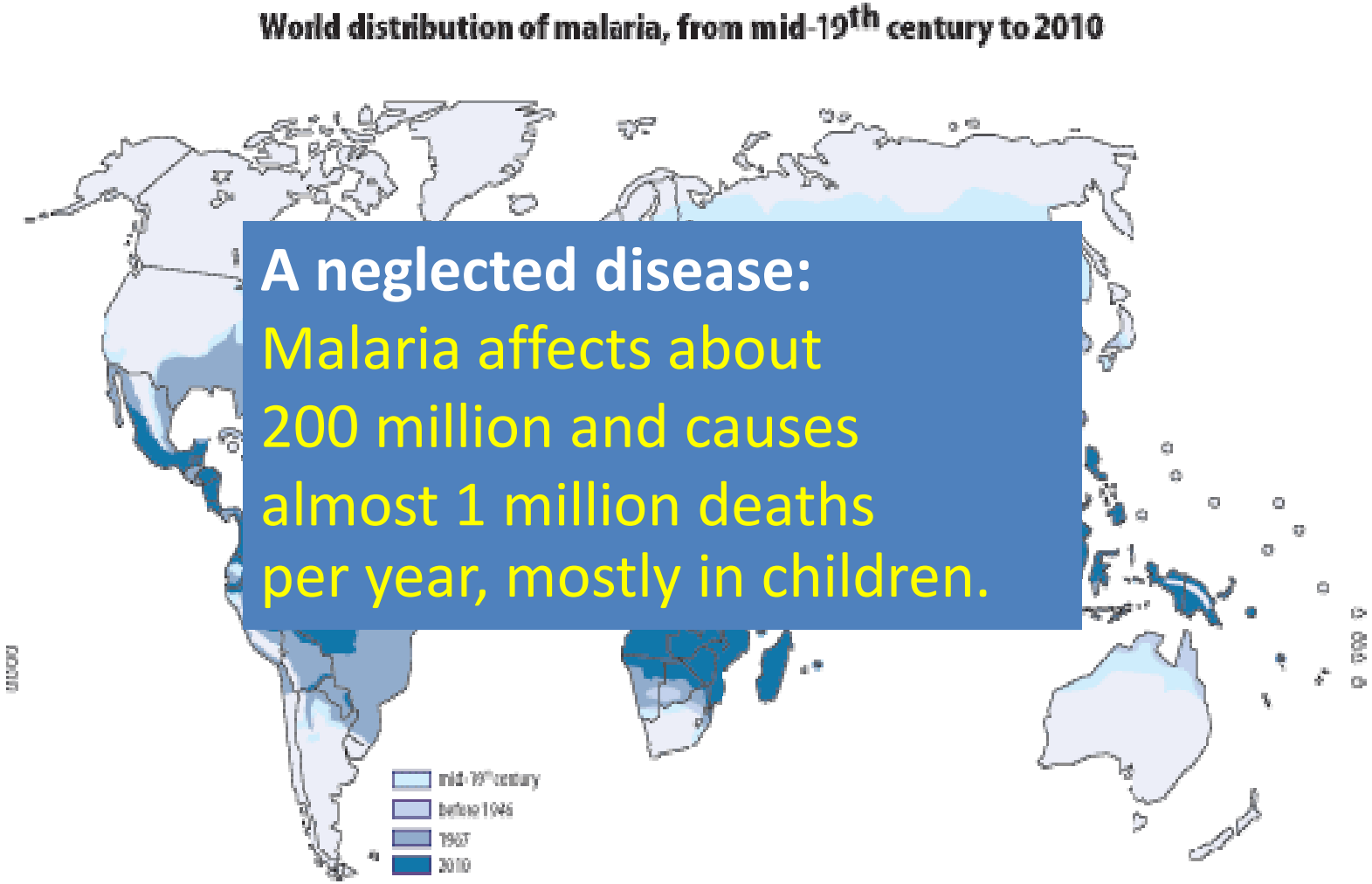
BIOTEC

National Science and Technology Development Agency

Thailand



From Roll Back Malaria (http://www.rbm.who.int/)

- Alexander the Great is believed to have died of malaria in 323 BC.
- Dante, Italian poet died of malaria 1321.
- Cause of more military casualties than bullets in every 20th century war in malarious regions.

Thai National Science Day: 18 August

Rama IV,the Father of Thai Science.

King Rama IV observed a total eclipse on 18 August 1868 at Wa Ko, Prachuab, after which he became fatally ill with malaria

Control, elimination, eradication

- Control: Reduction of incidence and burden until no longer a public health threat.
- Elimination: Interruption of transmission until disease incidence falls to zero in designated areas.
- Eradication: Interruption of transmission until disease incidence falls to zero worldwide.
- Eradication adopted as ultimate goal by Malaria Forum, 2007 (Bill and Melinda Gates Foundation) and endorsed by WHO, Roll Back Malaria and other organizations.

malERA, *PLoS Medicine*, 8(1), 2011

Disease eradication status

- Eradicated
  - Smallpox
  - Rinderpest (viral disease of measles family)
- Almost eradicated
  - Poliomyelitis
  - Dracunculiasis (guinea worm disease)
- Efforts underway
  - **Malaria**
  - Lymphatic filariasis
  - Measles
  - Rubella
  - Yaws

Possible Scenarios

- A world completely free of malaria

- Continuously shrinking pockets of malaria

- Stable, small pockets of malaria

- Still very much the same

Milestones from past efforts

- 1940s: Regional malaria elimination campaigns.
- 1955-1978: WHO Global Malaria Eradication Programme, with drugs and insecticides as main tools - malaria eliminated from Europe, North America, the Caribbean and parts of Asia and South-Central America, but parasite drug resistance and insecticide resistance appeared .
- 1975: Establishment of TDR (Special programme of WHO for tropical diseases research).
- 1998: Roll Back Malaria Programme.
- 2000s: Age of PDPs (product development programmes, PPP)

Tools for malaria intervention

- Drugs
- Vaccines
- Diagnostics
- Insecticide and other vector controls
- Bednets
- Epidemiology
- Public health and integrated approaches

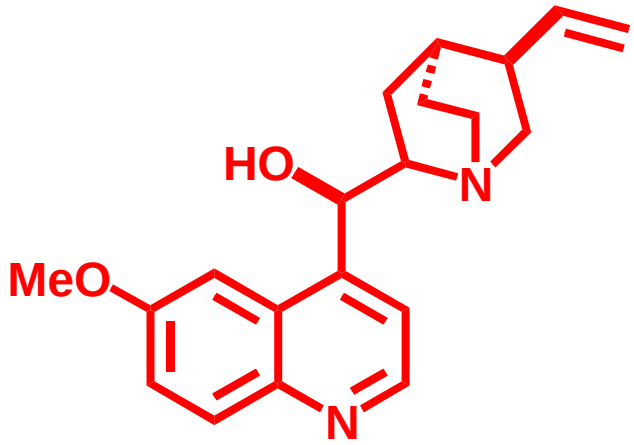
Drugs

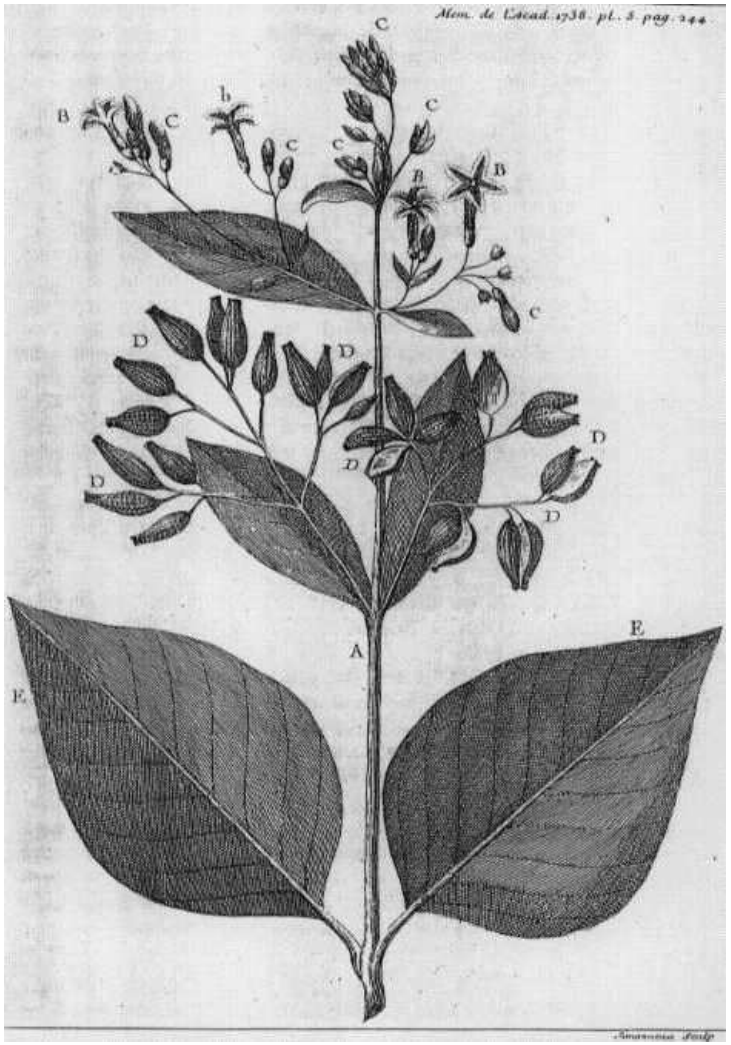
- Conventional drugs losing effectiveness.
- Many artemisinin combination therapies (ACT), eg. artesunate with mefloquine or amodiaquine, artemether with lumefantrine (Coartem ®), dihydroartemisinin with piperaquiune (Eurartesim ®) artesunate with pyronaridine (Pyramax ®)
- New drugs under development include antibiotics (azithromycin, fosmidomycin), endoperoxides, natural products, and vivax-directed (tafenoquine)

Antimalarials from nature

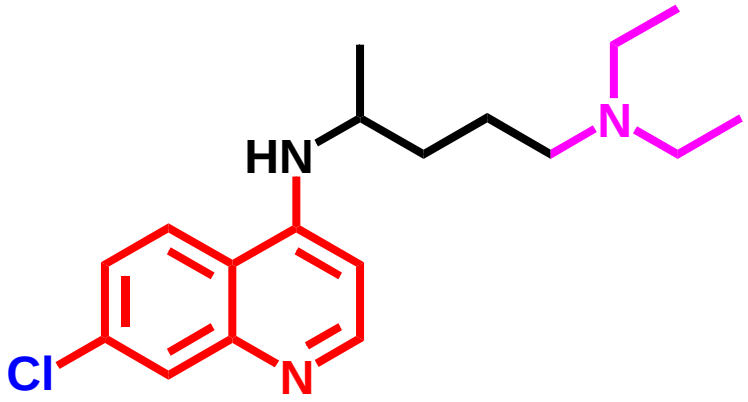
Quinine from Cinchona

(now combined with tetracycline)

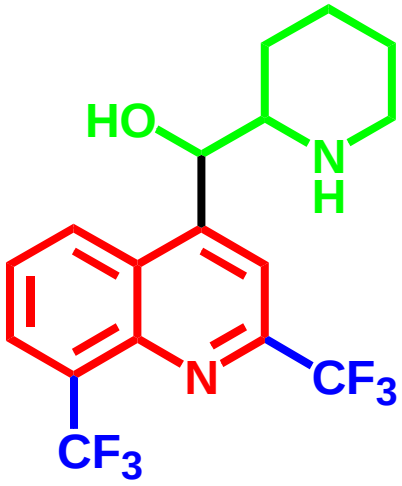




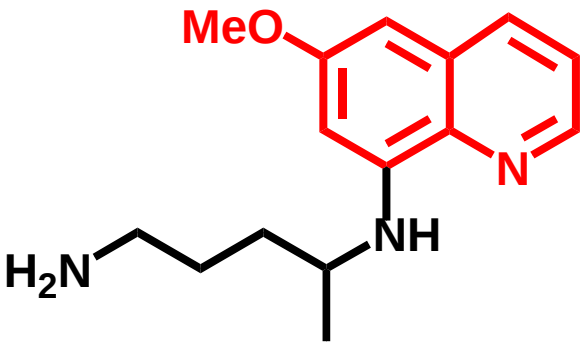
Synthetic antimalarials



CHLOROQUINE
a 4-aminoquinoline,
against blood stage



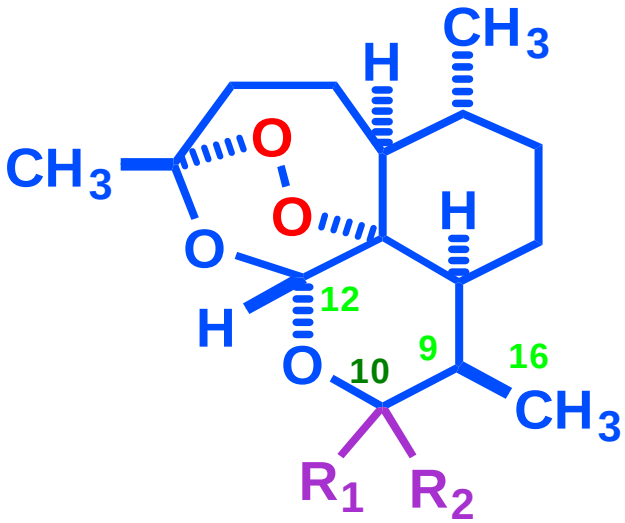
MEFLOQUINE
a quinoline-4-methanol,
against blood stage



PRIMAQUINE
an 8-aminoquinoline,
against liver stage

Antimalarials from nature

Artemisinin from *Artemisia annua* (sweet wormwood)



$R_1 = R_2 = O$ ARTEMISININ

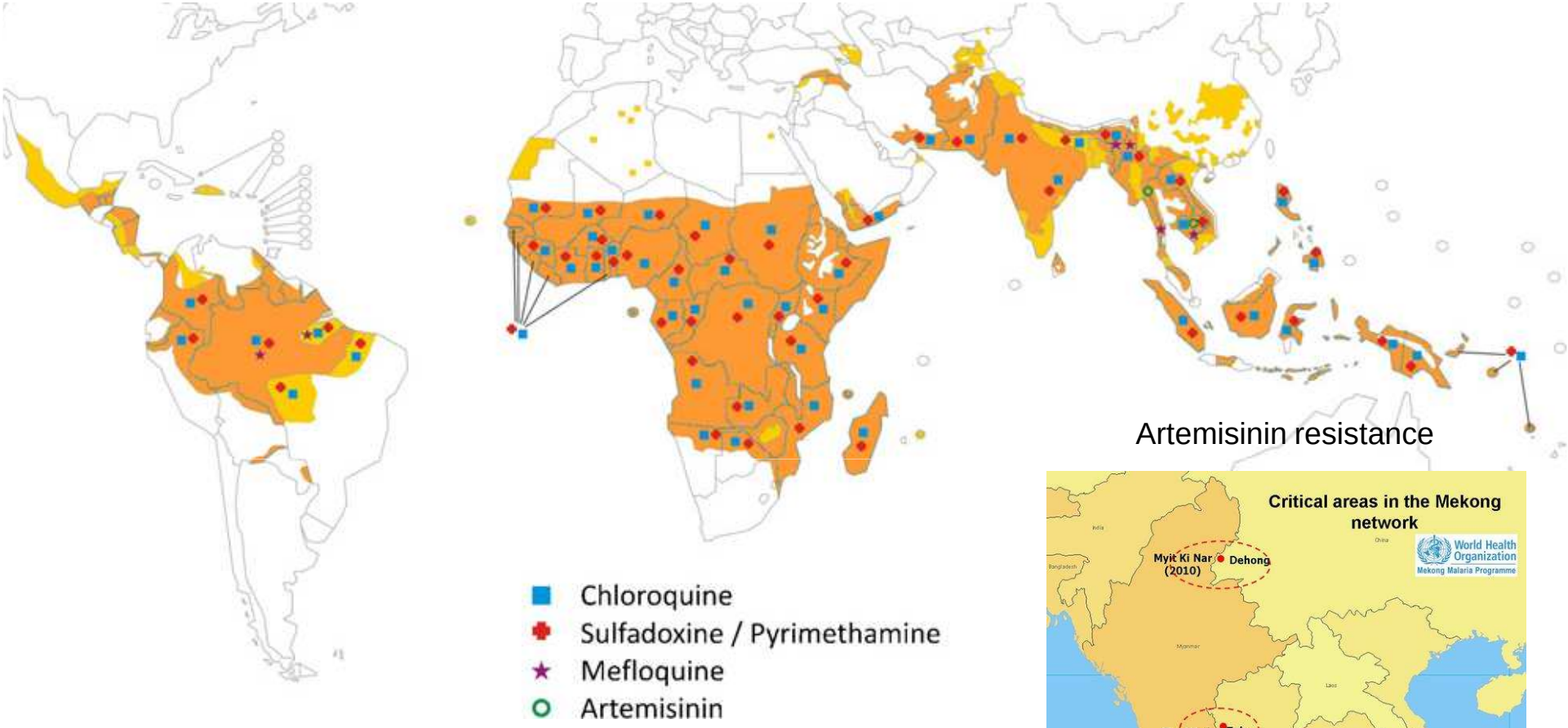
$R_1 = R_2 = OH$ DIHYDROARTEMISININ

$R_1 = H, R_2 = OMe$ ARTEMETHER

$R_1 = H, R_2 = OOCCH_2CH_2COONa$ ARTESUNATE

Used mostly in combination wirh other drugs (ACTs)

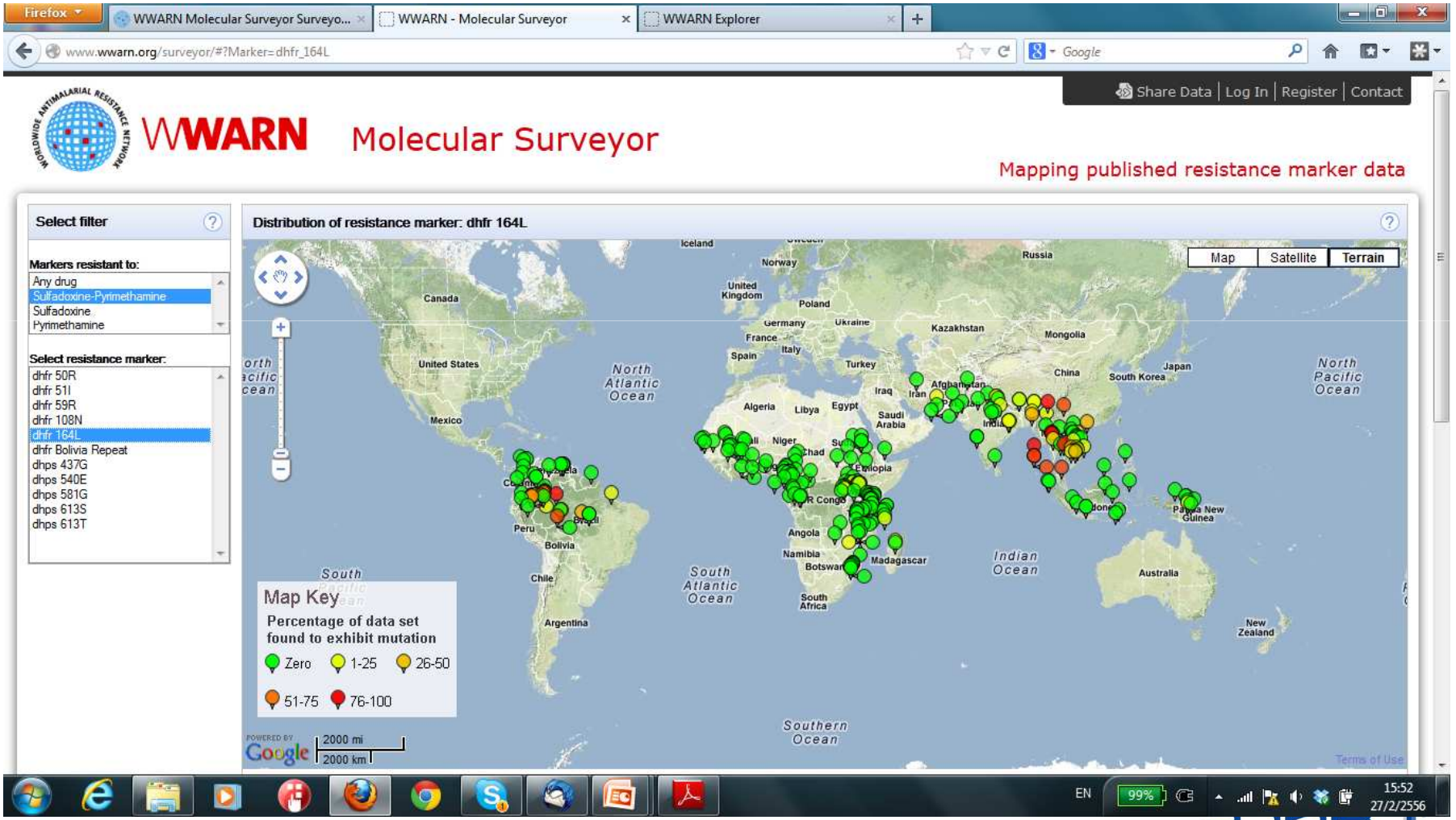
Distribution of Antimalarial Resistance



Artemisinin resistance

W. Wernsdorfer, *Acta Tropica* 121, 158-165, 2012

Worldwide Antimalarial Resistance Network



Global Antimalarial Portfolio, 4Q 2012

Research
Lead Optimisation

- Oxaboroles — Anacor
- DHODH — UTSW/UW/Monash
- Heterocycles — TCG Lifesciences
- Pyrazoles — DrexelMed/UW
- Heterocycles — Dundee
- Cell based lead — Merck Sereono /WHO/TDR
- Imidazolidinediones — WRAIR
- dUTPase inhibitors — Medivir
- 2 Projects — Novartis
- 4 Projects — GSK
- Orthologue Leads — Sanofi
- Whole cell leads — AstraZeneca
- Heterocycles — Ferrer-GSK
- 2 Projects — Liverpool STM
- Dihydro-isoquinolones — StJude/Rutgers/USF
- Aminopyridines — UCT

Translational

Preclinical

- DSM265 (UTSW/UW/Monash)
- P218 DHFR (Biotec/Monash/LSHTM)
- ELQ-300 (USF/OHSU-VAMC)
- 21A092 (DrexelMed/UW)
- MMV390048 (UCT)
- NPC-1161-B — University of Mississippi
- RKA182 — Liverpool STM
- BCX4945 — Biocryst/Albert Einstein College of Medicine
- SAR116242 — Palumed

Phase I

- GNF156 — Novartis
- Antimalarial — Actelion
- CDRI 97-78 — Ipca
- DF02 — Dilafor
- N-tert butyl isoquine — Liverpool STM/GSK
- AQ13 — Immtech

Phase IIa

- OZ439 (Monash/UNMC/STI)
- NITD609 — Novartis
- Ferroquine — Sanofi
- Fosmidomycin Piperaquine — Jomaa Pharma GmbH
- Methylene Blue AQ — Uni. Heidelberg
- SAR97276 — Sanofi
- Artemisone — UHKST

Development

Phase IIb/III

- Azithromycin chloroquine — Pfizer
- Tafenoquine — GSK
- Pyramax Paediatric — Shin Poong/University of iowa
- Eurartesim® Paediatric — Sigma-Tau
- *Nauclea pobeguinii* — DRC/Antwerp
- *Argemone mexicana* — Mali/Geneva
- Arterolane/PQP — Ranbaxy
- Co-trimoxazole Bactrim — Institut of Tropical Medicine
- ARCO — Naphthoquine/Artemisinin
- ArtiMist™ — Proto Pharma

Registration

- Mefloquine Artesunate — Farmaguinhos/DNDi
- Artesunate i.r. — WHO/TDR

Phase IV

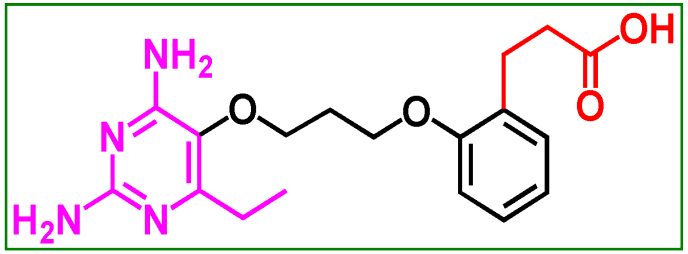
- Coartem® — Novartis (APPROVED)
- Artesunate for injection — Guilin (APPROVED)
- Eurartesim® — Sigma-Tau (APPROVED)
- Pyramax — Shin Poong/University of Iowa (APPROVED)
- ASAQ Winthrop — sanofi /DNDi (APPROVED)
- SP-AQ — Guilin (APPROVED)

Included in MMV portfolio post registration

Non MMV – – –

Medicines for Malaria Venture

P218 as candidate



MMV/BIOTEC DHFR team

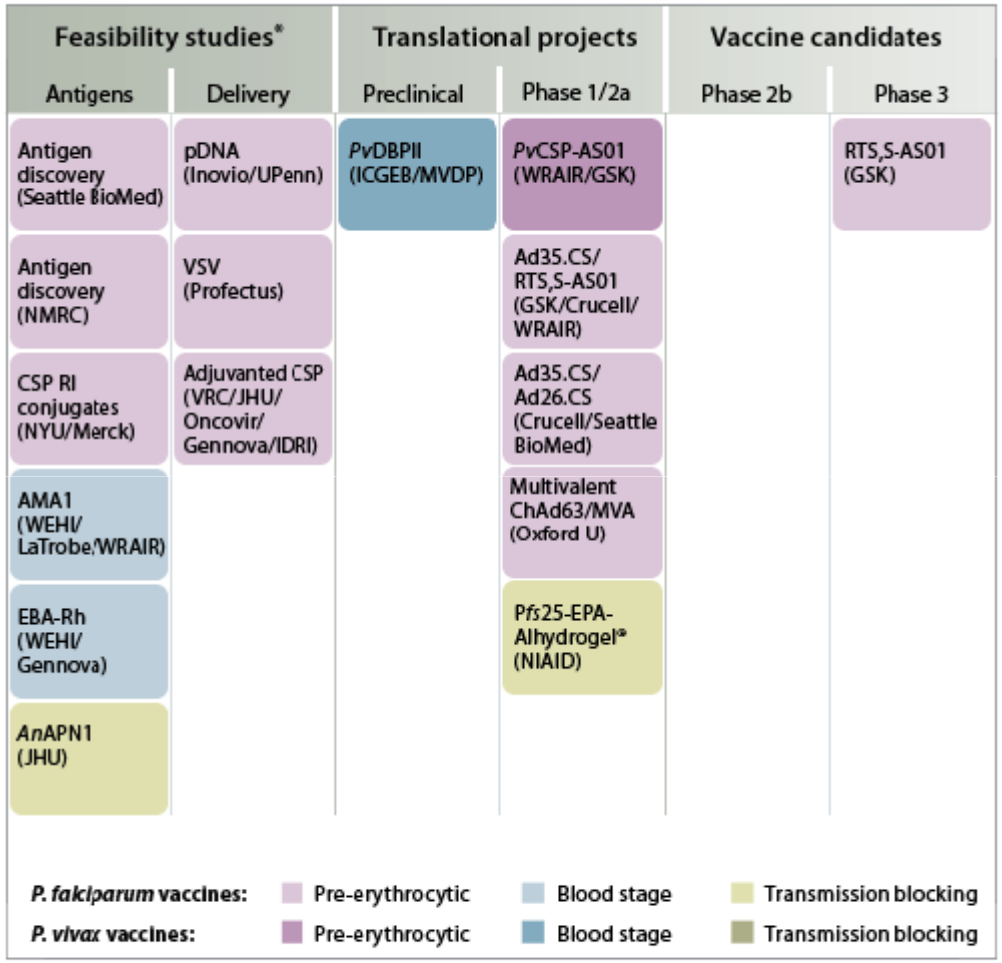
- Excellent enzyme and cell-based potency.
- Good target selectivity vs human enzyme, explained by X-ray structures.
- Good cell-based selectivity (*P. falciparum* vs human/mammalian cells).
- No cytotoxicity, mutagenicity. NOAEL (rats)≥ 100 mg/kg.
- MMV-funded project : Bangkok/Melbourne/London

Medicines for Malaria Venture

NSTDA

Vaccines

MVI portfolio



* selected projects

Aims of MVI:

By 2015—a first-generation vaccine that has 50 percent efficacy against severe disease and death, with protection lasting at least one year without the need for boosting.

By 2025—a second-generation malaria vaccine that has a protective efficacy of at least 80 percent against clinical disease and with protection lasting for many years without a booster.

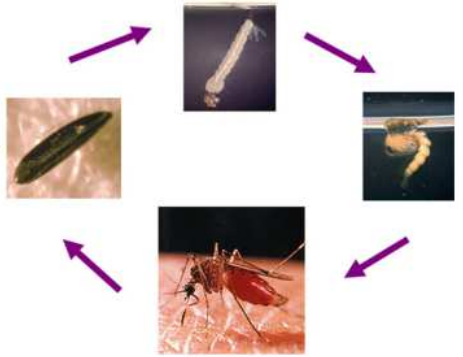
Reproduced from the Malaria Vaccine Initiative website at www.malariavaccine.org, Feb 2013

Control of vector and vector-host contact

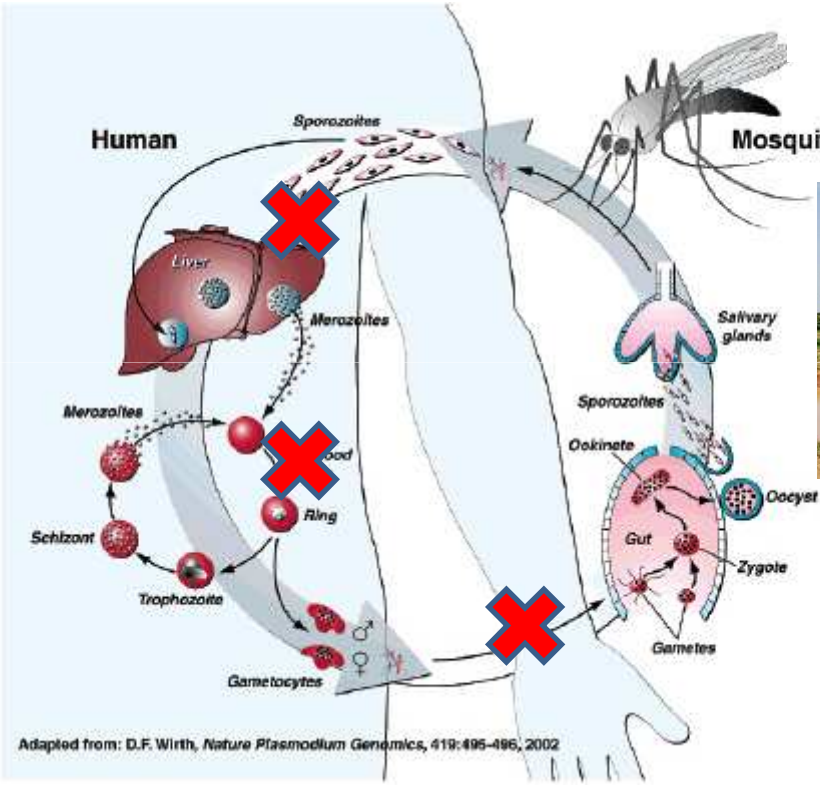
- Bednets
  - Insecticide treated, long-lasting bed nets
  - Indoor residual spraying
- New insecticides (eg selective for old mosquitoes)
- Genetically modified (GM) mosquitoes
  - Immune to malaria and spreading to offspring (homing endonuclease)
- Mosquito biocontrol and control of malaria in mosquitoes
  - Bacterial control (eg. Wolbachia)

Surveillance and rapid diagnosis

- Molecular diagnosis (Immuno-, nucleic acid-based)
- Surveillance of disease endemicity and dynamics
- Surveillance of mosquitoes (trapping-testing)
- Surveillance of habitat (remote sensing/GIS)



Amazon floating house, Peru



Western Niger

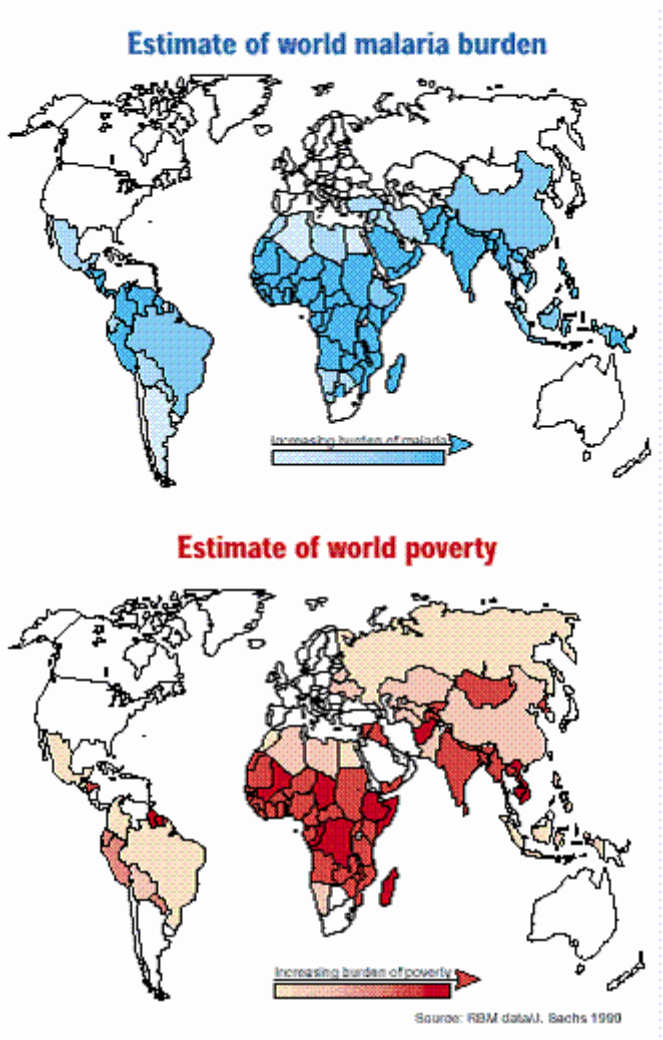
Thailand

Malaria is both medical/scientific and socioeconomic/ecological problem

- Medical/Scientific
  - Few effective drugs; widespread drug resistance
  - Few vaccines, improvements needed
  - Vector control problems (insecticide resistance, water as breeding source)
  - Host-parasite-vector interaction, complicated by immunity and drug use.
  - Epidemiology and eco-health aspects: linkage with socioeconomic/environmental aspects.

•Socioeconomic/Ecological Aspects of Malaria

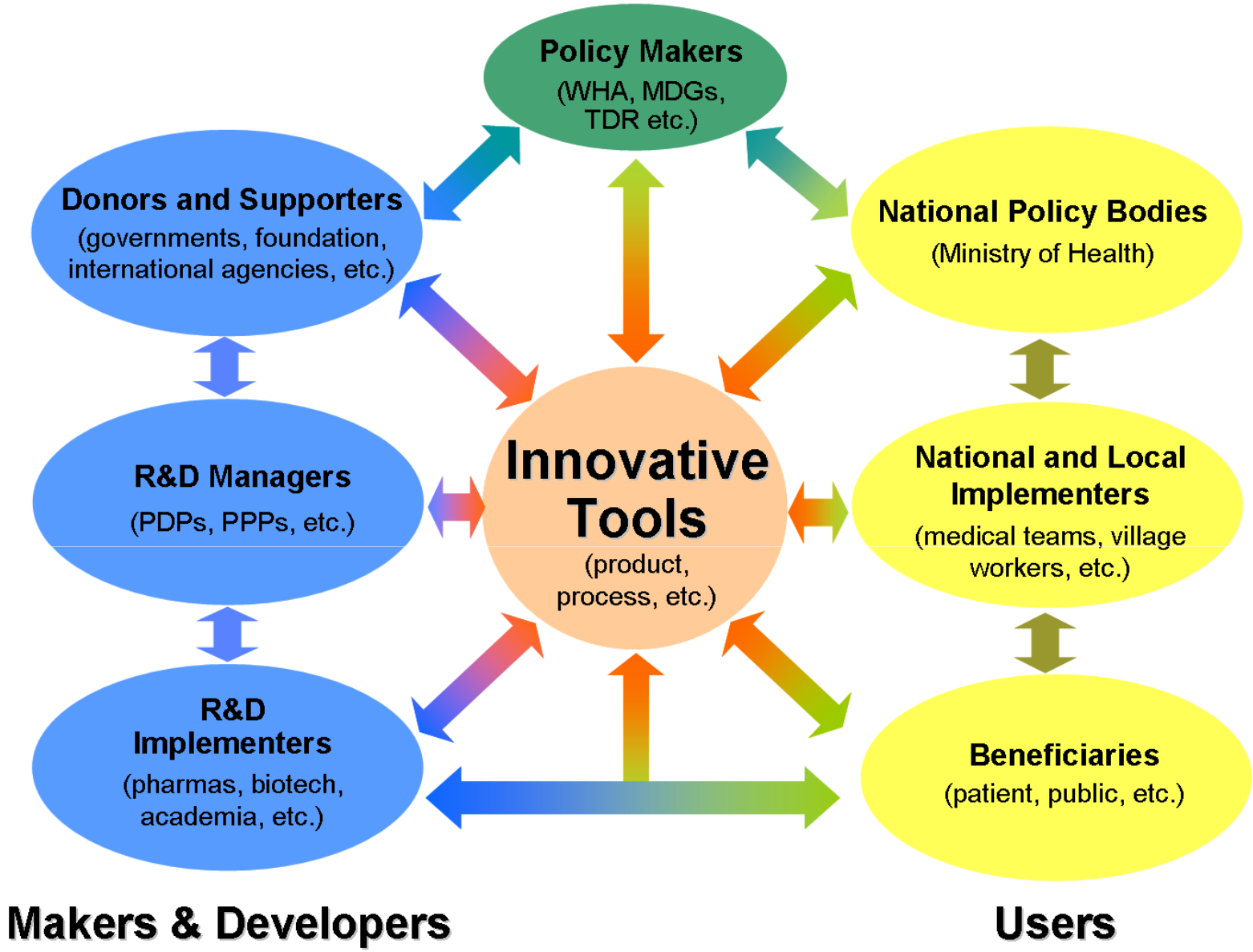
- Poverty
- Human migration
- Livelihood and behaviour
- Lack of public awareness and attention
- Poor public health infrastructure
- Deforestation
- Climate change
- Other ecological factors



WHO, 2002

Effective interventions need both technical and social approaches

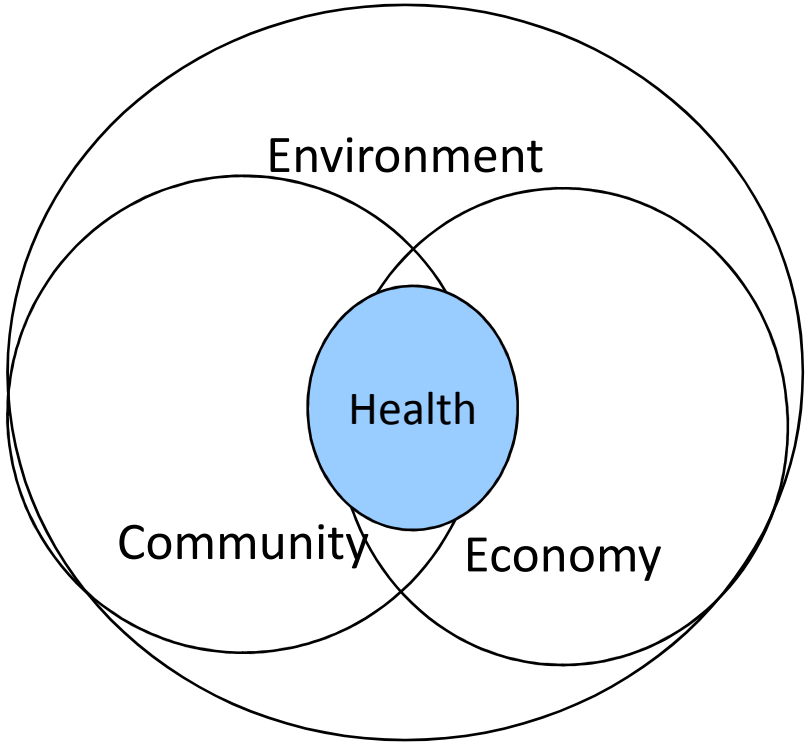
- Primary health care
  - Access to clinical care
  - Case detection
  - Access to effective drugs
  - Access to vaccines
- Vector avoidance and control:
  - Host and vector behaviour (eg. outdoor bites)
  - Insecticide-treated bednets (pyrithroids)
  - Insecticides (DDT still useful) and larvicides (eg. microbial)
  - Future: Refractory mosquitoes, sterile mosquitoes (GM, Wolbachia etc.)



Source: Y. Yuthavong *et al*., Innovation and Technology Platforms for Health Interventions in Infectious Diseases of Poverty. WHO Tech Rep Series (in press)

Ecohealth approach

An approach to addressing complex problems at the intersection of health, environment and development

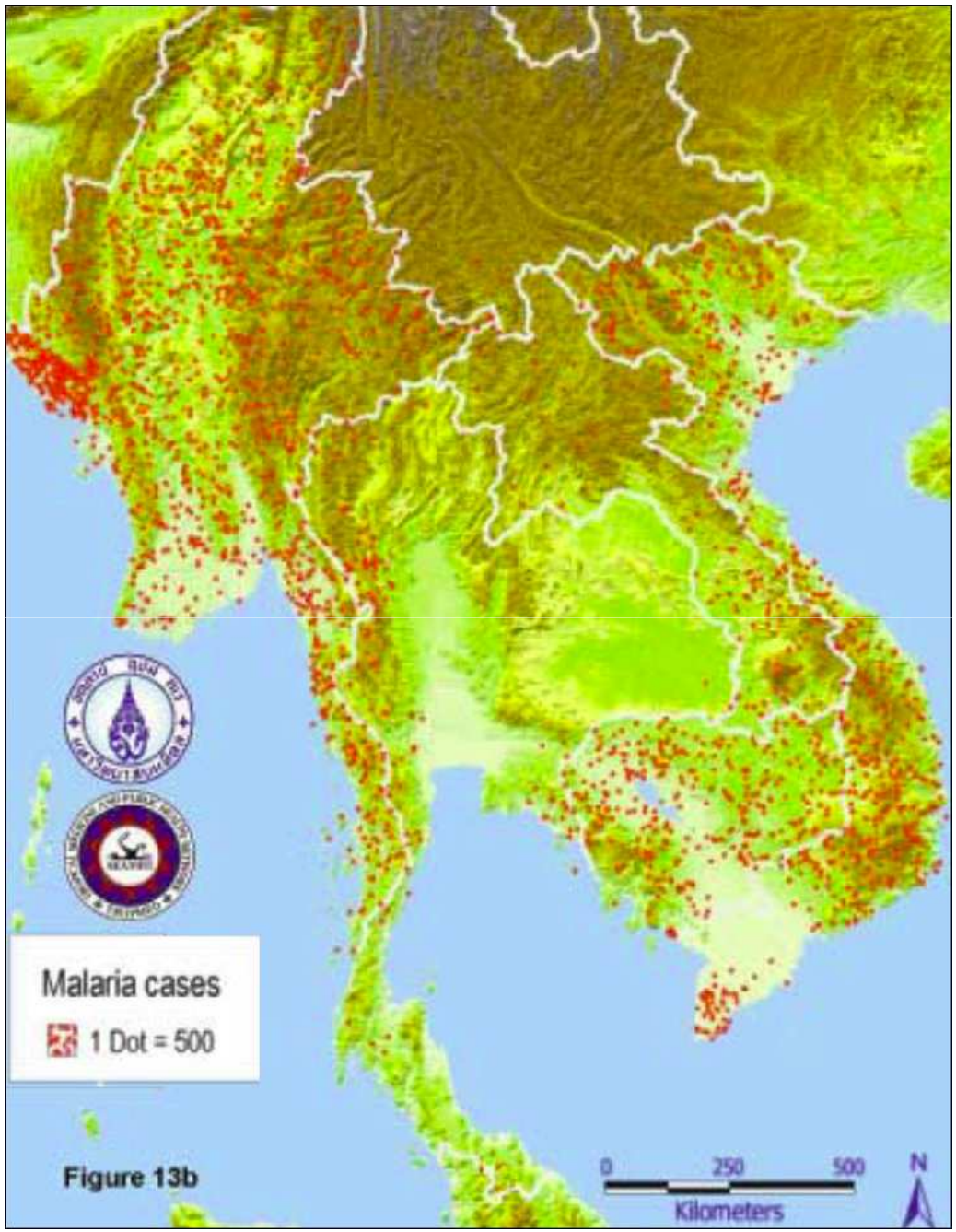


Source: Dominique Charron, IDRC

Malaria Control & Intermittent Rice Irrigation, Peru

- Collaborative research involving local agriculture association and public health officers to better understand farmers needs
- Optimum irrigation schedule: 87% reduction in mosquito larvae
- Reduction in water and pesticide use, increase in yields
- Savings of $170-240 USD per ha with new irrigation scheme

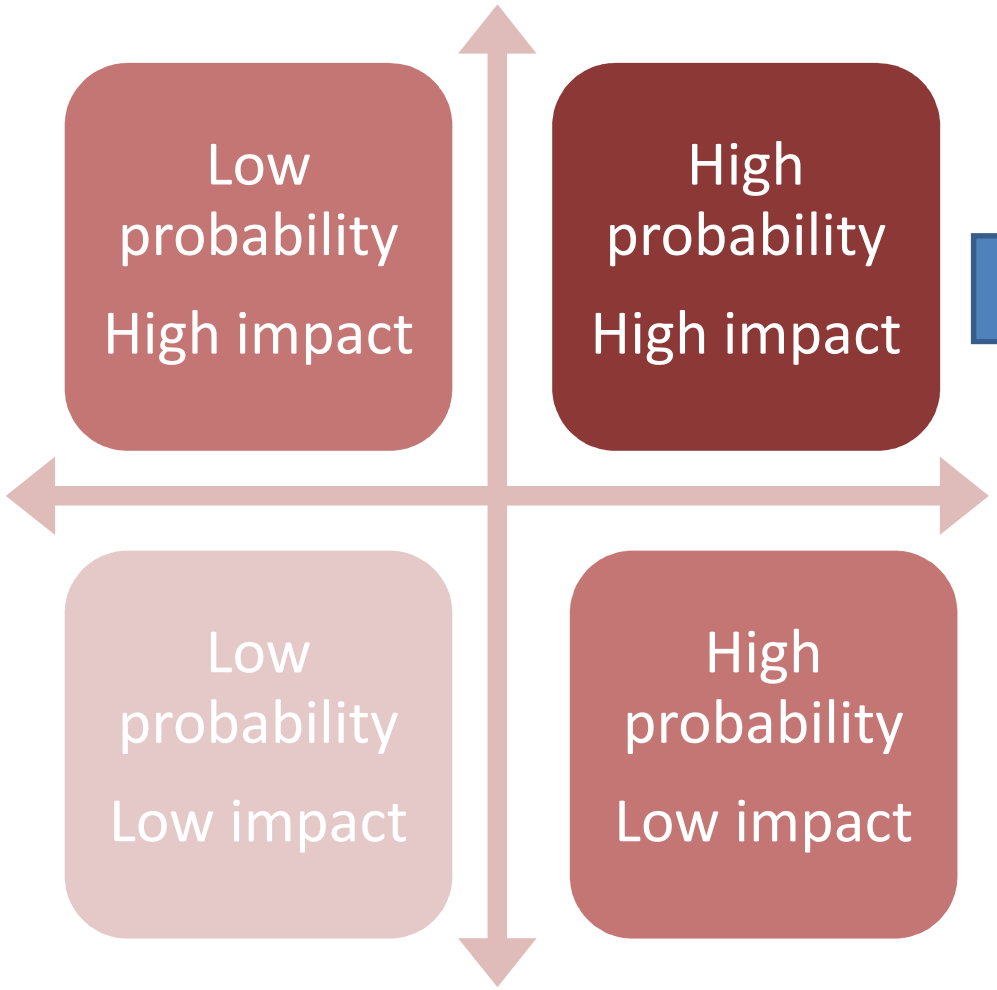
Source: Dominique Charron, IDRC



Interacting factors in malaria ecoregions

- Population
- Livelihood and poverty
- Education and awareness
- Level of natural immunity
- Migration
- Tourists and visitors
- Exposure to bites
- Mosquito habitat and ecology
- Climate and climate change
- Drugs and drug resistance
- Vaccines
- Diagnosis and surveillance
- Public health infrastructure
- Political and financial commitment
- Intervention strategies

Probability/impact diagram for control/eradication measures



- Effective tools
- Effective delivery of tools in endemic countries
- Effective surveillance of measures

Preconditions for microbial disease eradication

(Dahlem Workshop on the Eradication of Infectious Diseases, 1997)

	Malaria
• Agent can infect only human	• ☹
• No non-human reservoir	• ☹
• Infection induces life-long immunity	• ☹
• Effective tools for transmission interruption	• 😐
• Political commitment	• 😐 ☺
• Disease burden is of great public health importance with broad international impact	• ☺

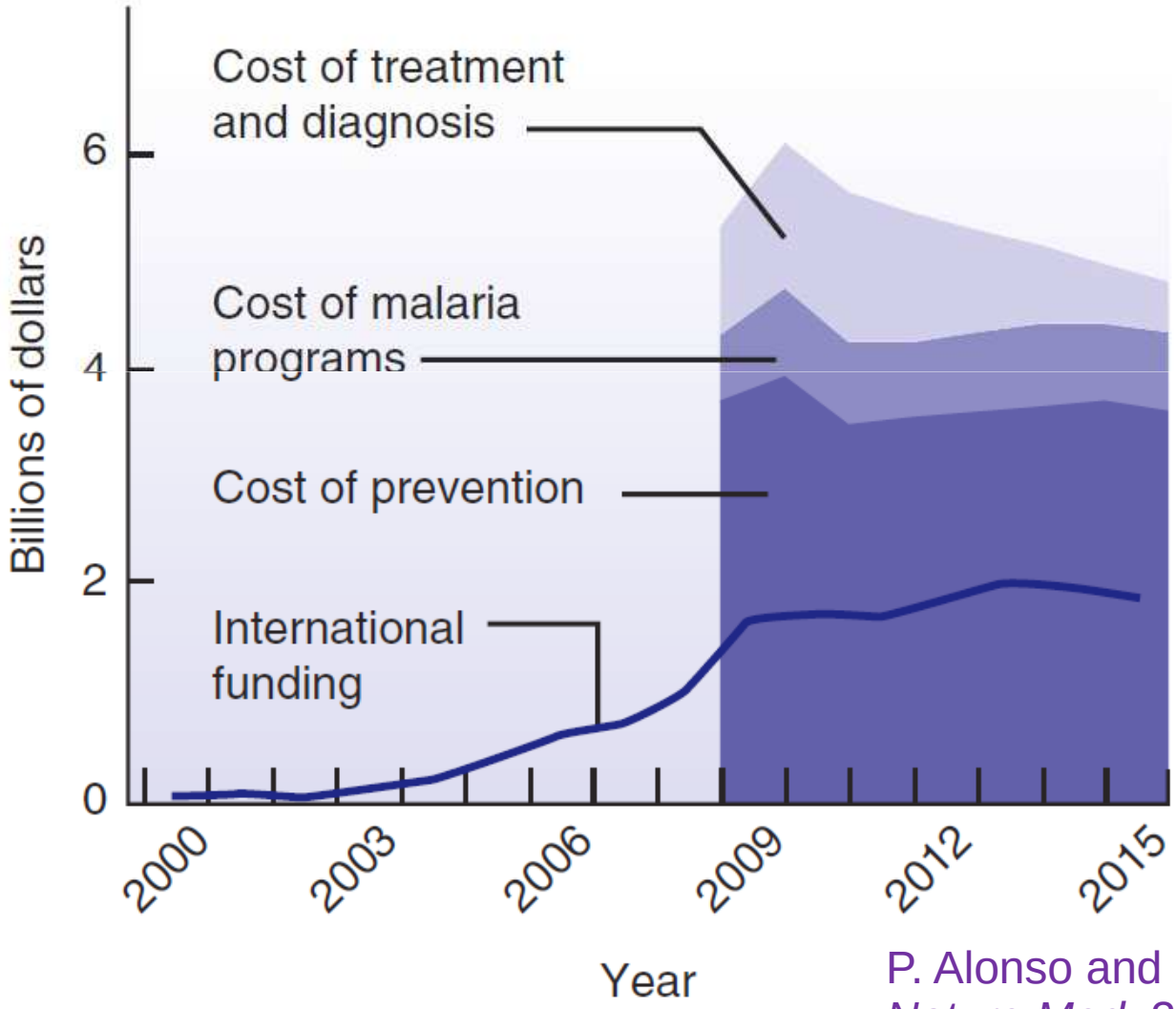
Consequences of eradication

- Positive (intended)
  - Less public health expenditure and personal medical costs.
  - Less associated costs (tourist protection,
  - Better economies from healthier populations.
- Negative (unintended)
  - Other diseases?
  - Ecological change (eg. from vector elimination)?
- Uncertain
  - Long-term human evolution

Important obstacles

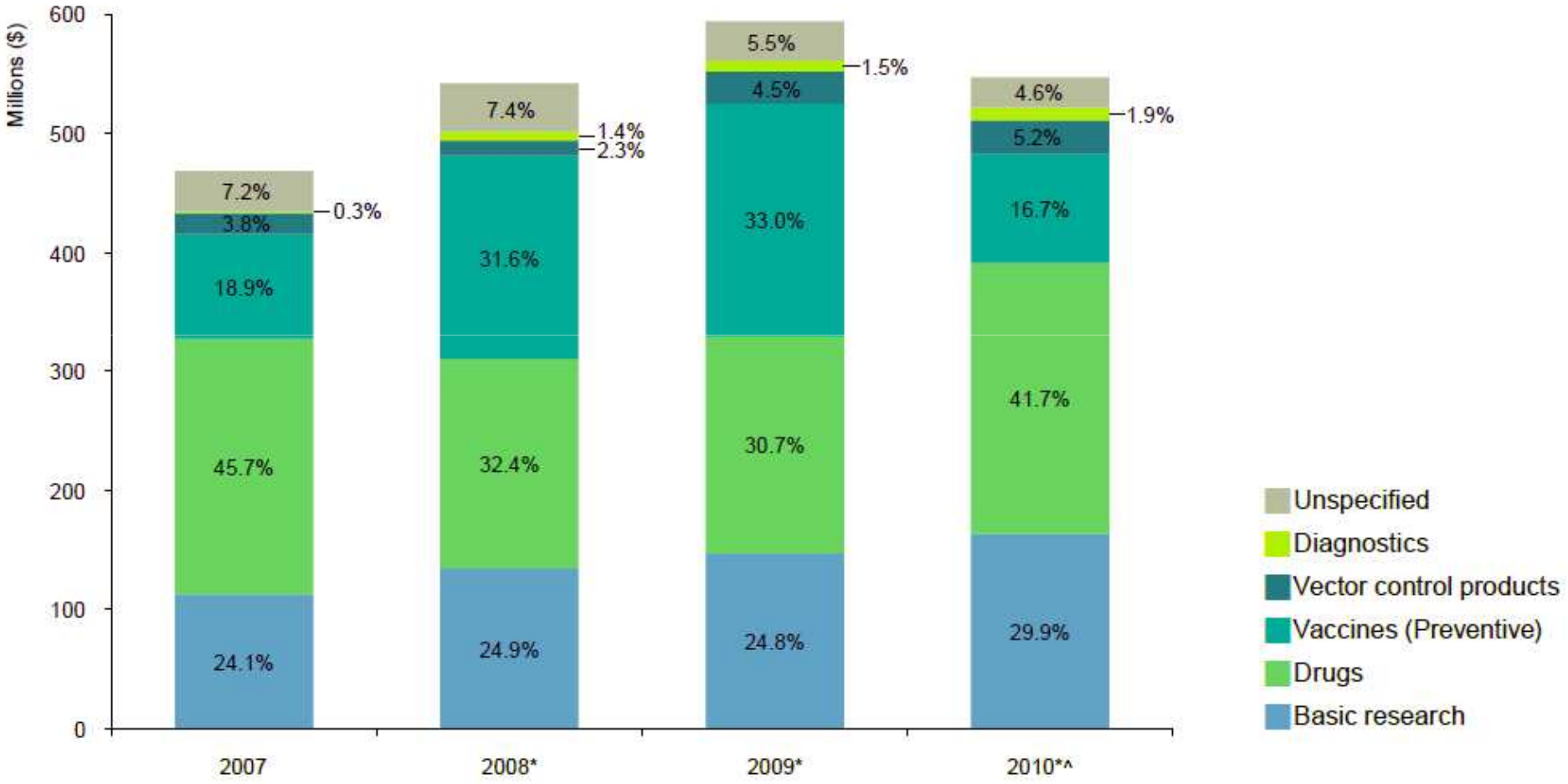
- Lack of effective vaccines
- Drug resistance
- Insecticide resistance
- Poor public health infrastructure of endemic areas
- Assessment of control programmes and tools for intervention
- FUNDING

Estimated cost and funding for malaria control



P. Alonso and M. Tanner
Nature Med, 2013, 19, 150-155

Malaria R&D funding (2007-2010)



* Figures are adjusted for inflation and reported in 2007 US dollars

^ There may be minor under-reporting as some organisations did not submit 2010 data

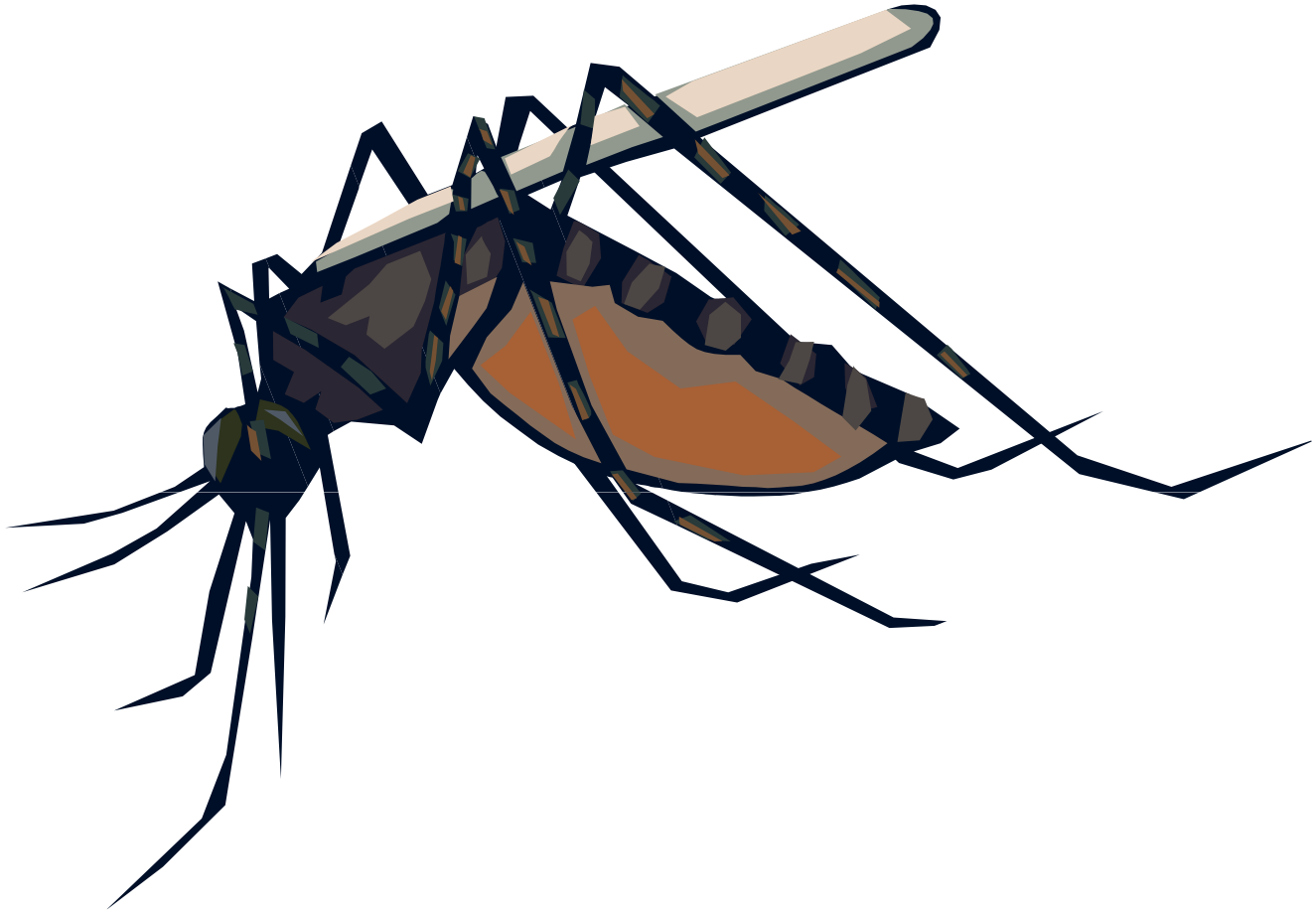
From G-Finder, Policy Cures, 2011

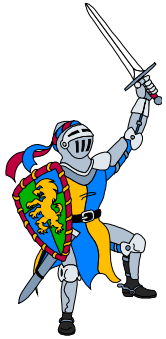
Ethical (and economic) aspects of eradication

eg. AL Caplan, The Lancet 373, 2192 (2009)

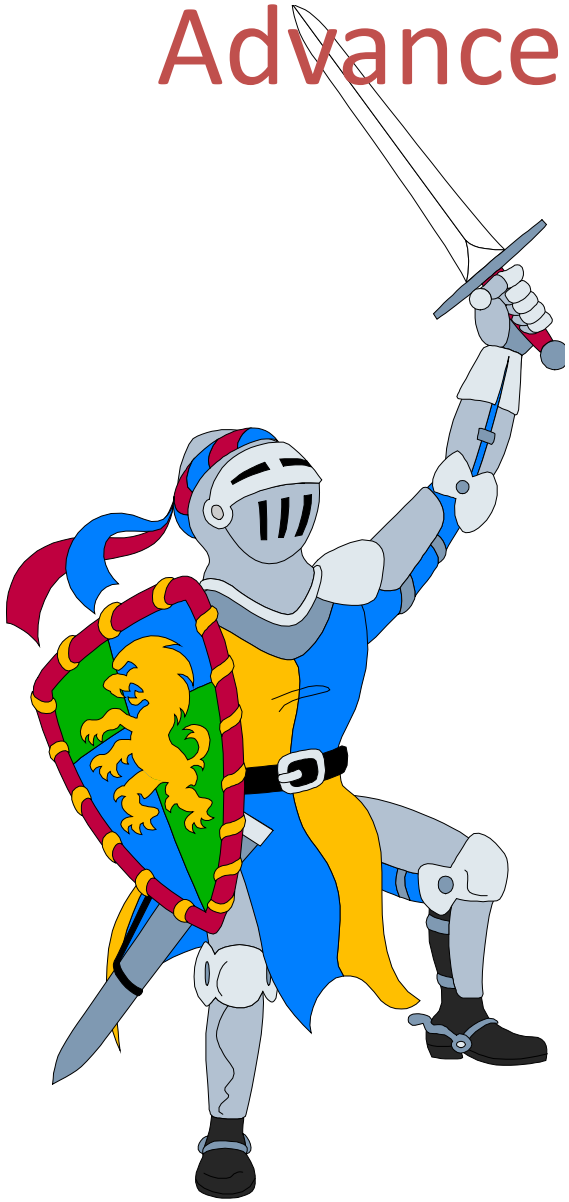
- Poor cost-benefit ratio for the “last” cases.
- Ascertaining and maintaining eradication.
- “Replacing vigilance and prophylaxis with indifference and trust”.
- Ecological risks of disease and vector elimination.

Endemic Countries



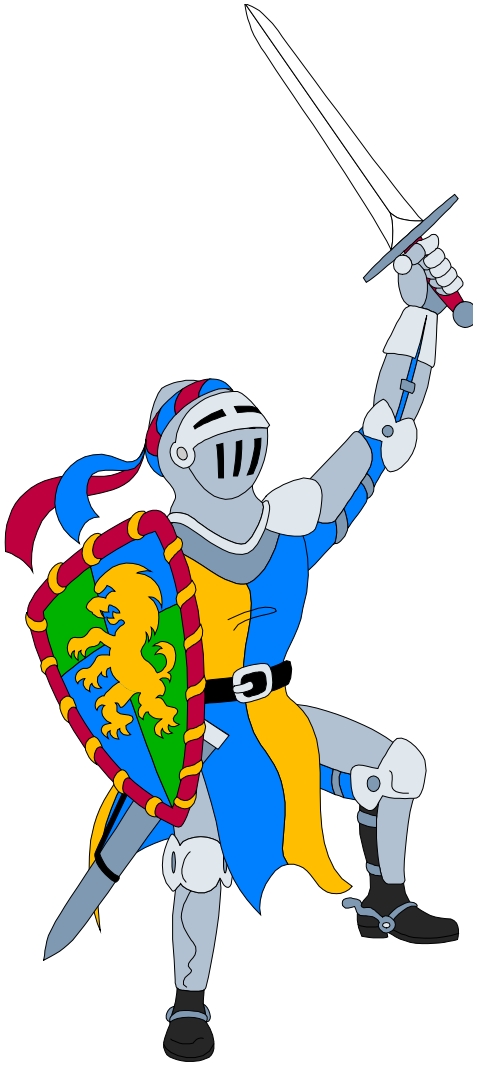


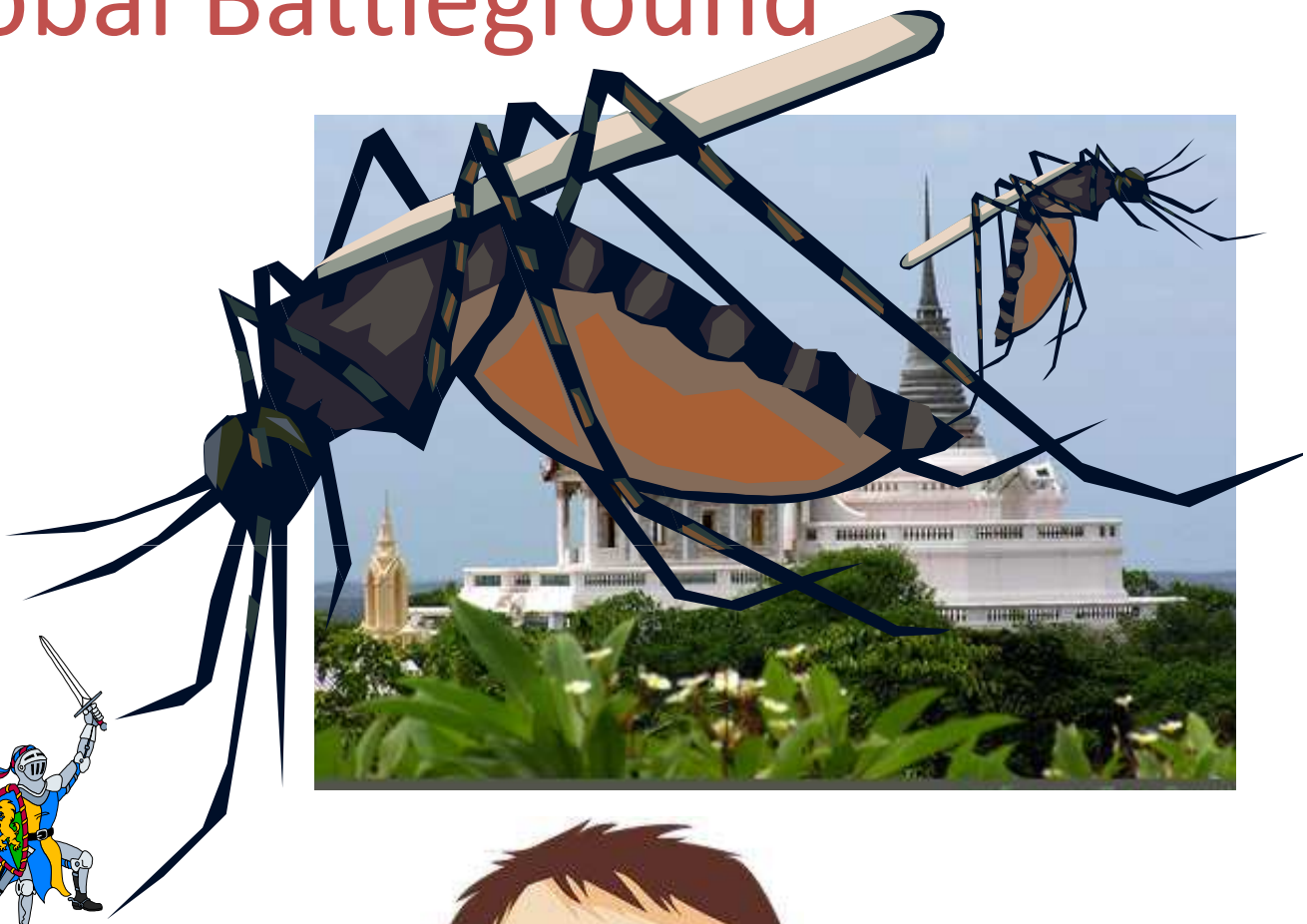
Advanced Countries



Global Battleground

Global Battleground





Conclusion

- Malaria eradication efforts have been renewed with vigour.
- Armed with new tools, the efforts are likely to be successful in some places.
- Delivery of the tools and cooperation and capability of endemic countries are keys to success.
- Best to aim for eradication where you can, but prepare for less achievement in the real world.