Evolution of Antimalarial Drug Resistance

Steve Meshnick, MD, PhD
Professor of Epidemiology

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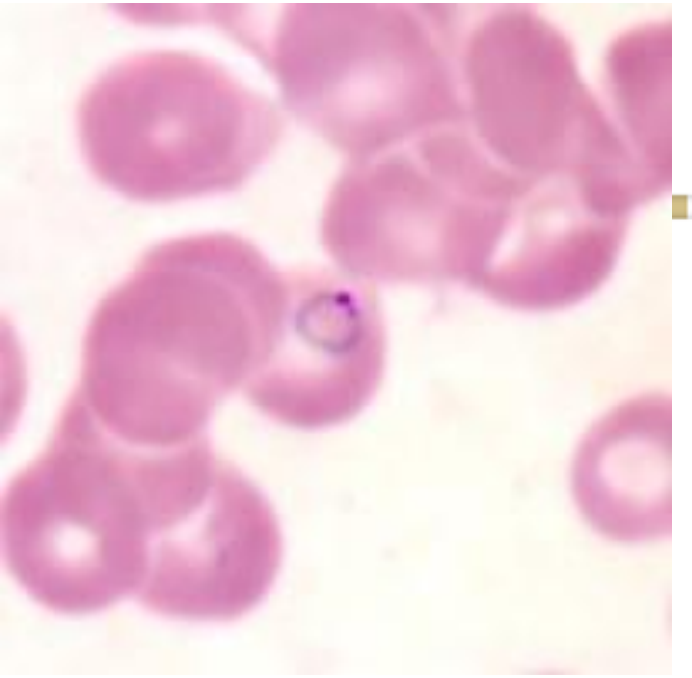
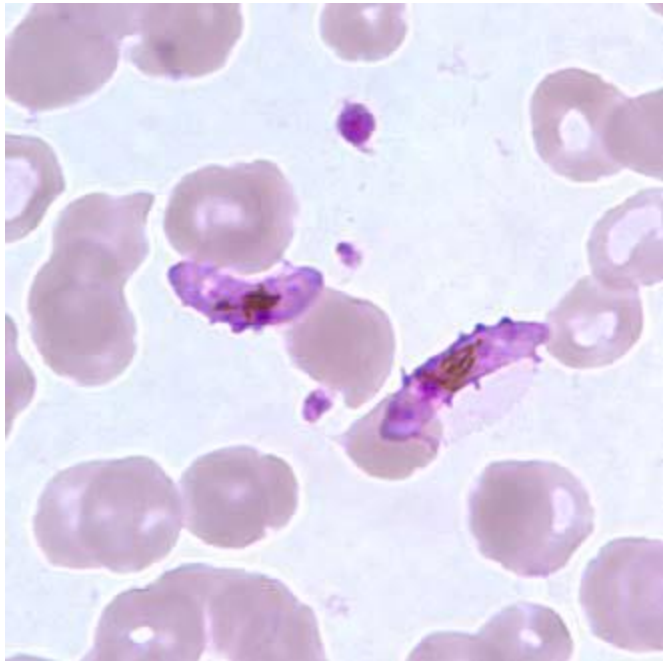
Outline

- Malaria
- Malaria as a zoonosis
- Drug-resistant malaria
- What general principals can we learn?
  - How does drug resistance evolve?
  - How can we combat it?

Malaria





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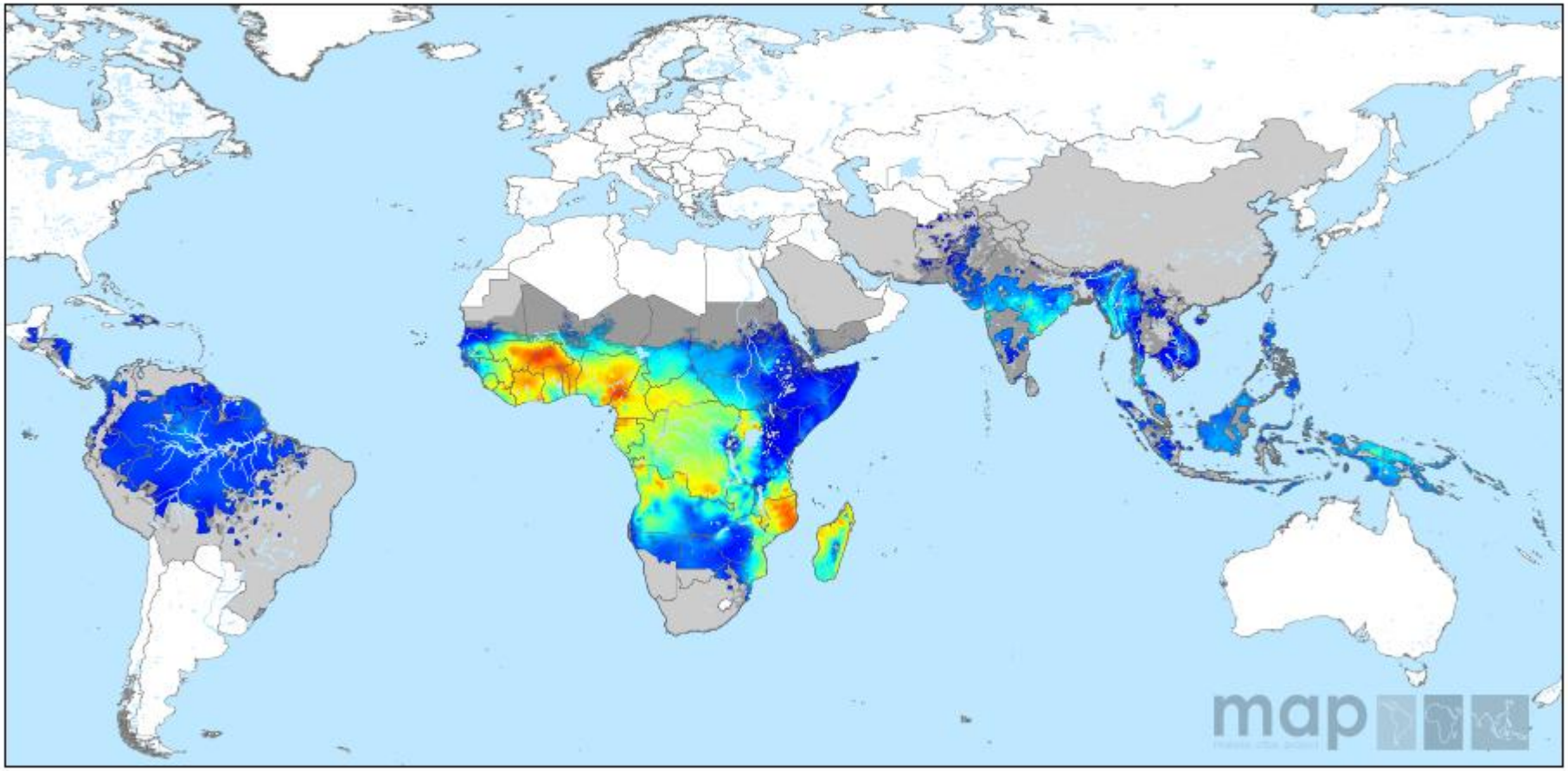
Human malarias

- ~300 million cases/year
- 1 million deaths/year, mostly children
- Infections in pregnant women
- 90% of burden in Africa

Five species

- ***Plasmodium falciparum***
  - 220 million cases
- ***Plasmodium vivax***
  - 50-100 million cases
- ***"Minor malarias"***
  - ***Plasmodium malariae***
  - ***Plasmodium ovale***
  - ***Plasmodium knowlesi***

Distribution of falciparum malaria



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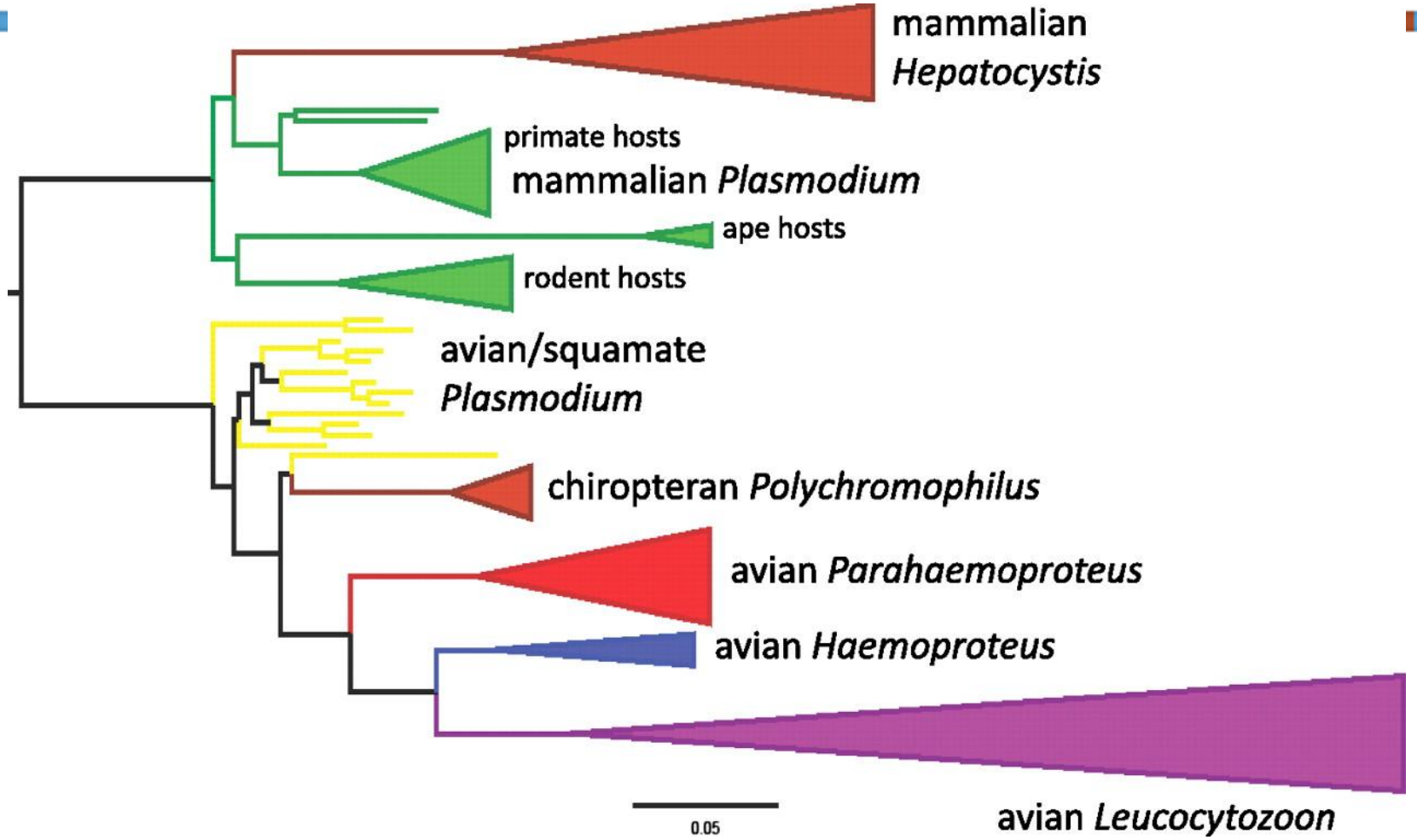
Malaria as a zoonoses

Maximum likelihood phylogram based on cytochrome b data using a GTR + gamma model of nucleotide substitution.



Outlaw D C , Ricklefs R E PNAS 2011;108:13183-13187

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Plasmodium vivax

- 100,000 – 50,000 BC
  - *P. vivax* jumps from macaques to humans
  - Becomes common in Africa
- ~60,000 BC
  - Modern humans migrate out of Africa, bring *P. vivax* to Europe and Asia

Pin.primate.wisc.edu

Plasmodium falciparum

- ~10,000 BC
  - Agriculture increases human population density
  - Mosquitoes adapt
  - Great ape malaria mutates into *P.falciparum*

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Plasmodium knowlesi

- 1931 – discovered in macaques in Malaysia
- 1965 – first human case
- 2004 – outbreak of 120 cases
- Macaques are the reservoir
- Human cases are sporadic

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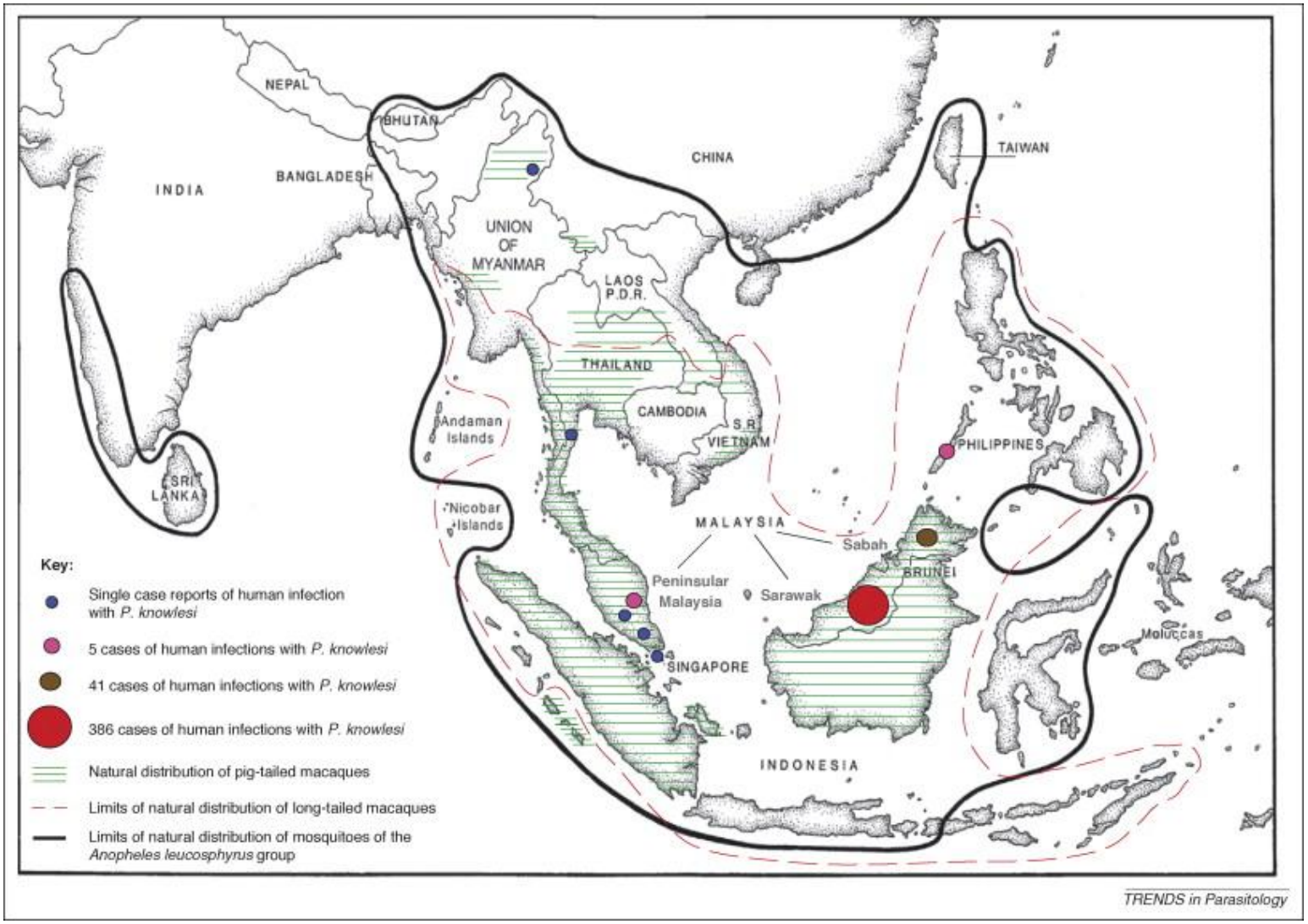
P. knowlesi distribution



Cox-Singh, Trends in Parasitol., 2008

Malaria as a zoonosis

- **Asia***:*
  - *P. knowlesi*
- **Africa:**
  - *P. falciparum, P. malariae, P. ovale and P. vivax* found in chimpanzees, bonobo, gorillas
  - Are primates a reservoir?

P. vivax

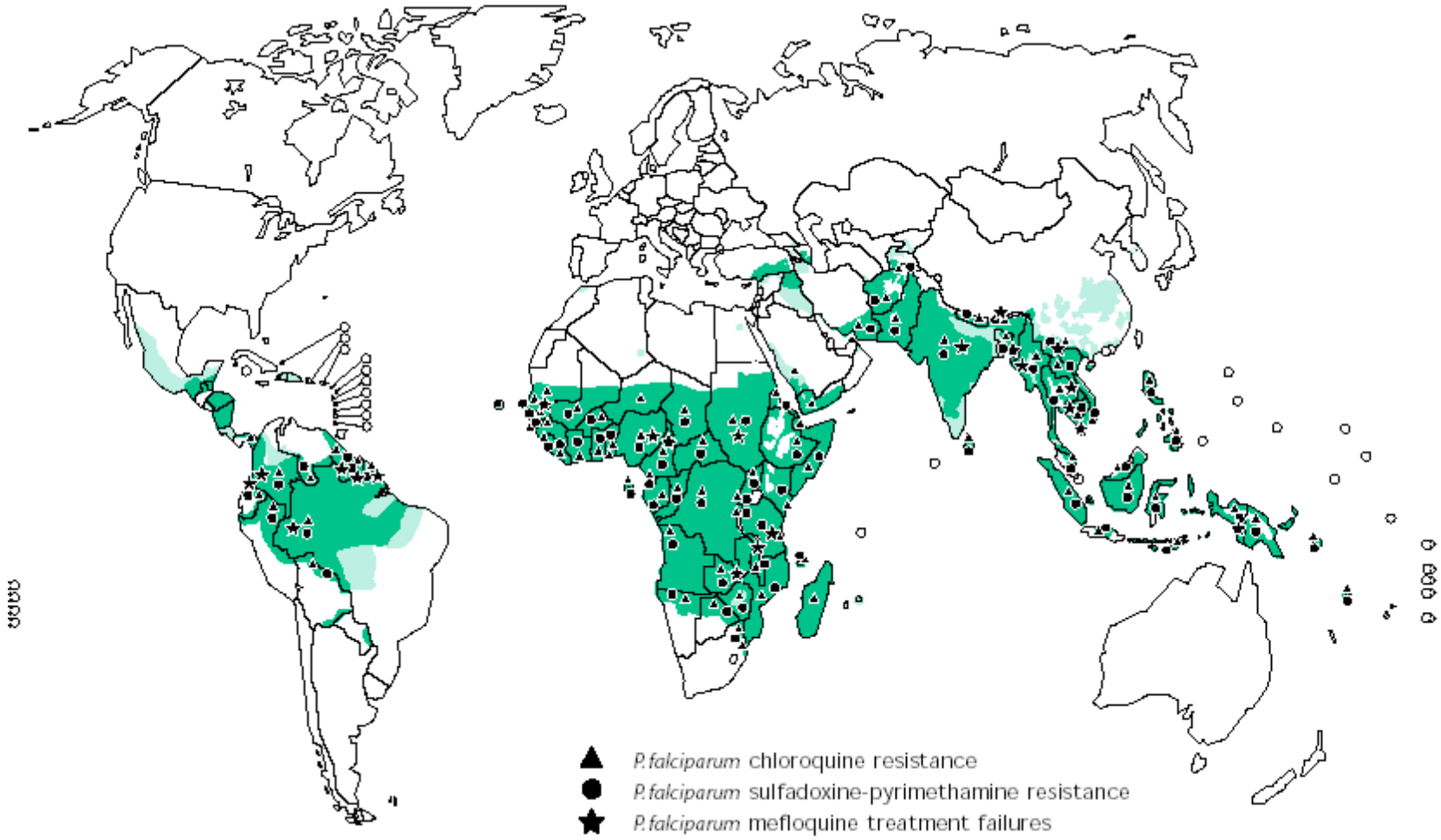
- Human populations in Africa are largely resistant to *P.vivax*, due to Duffy blood group trait
- Travelers to sub-Saharan Africa acquire infections with *P. vivax*
- Primates are a reservoir, but infections in humans relatively uncommon

P. falciparum

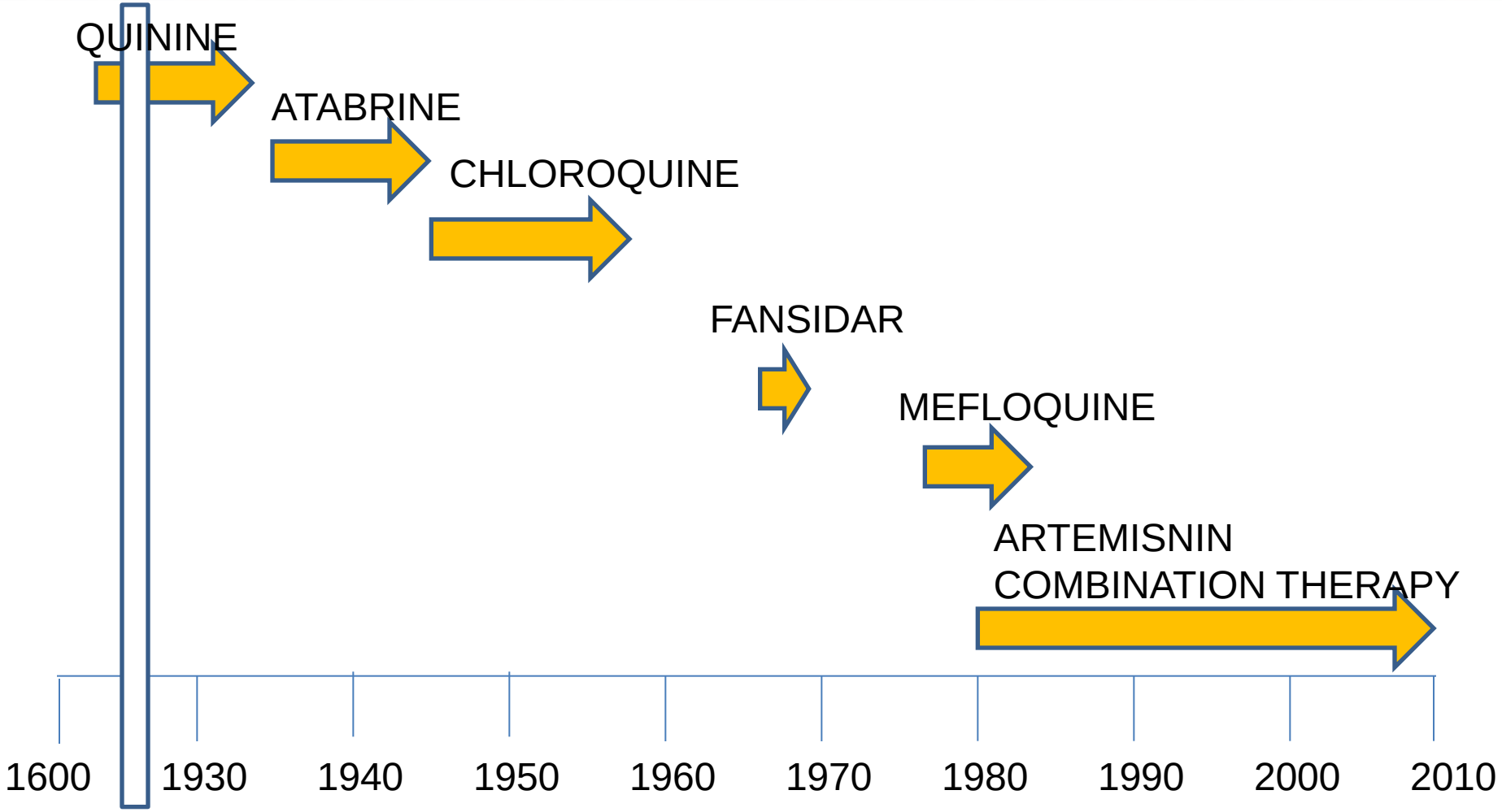
- Human population in malaria-endemic Africa >> ape population (400 million, vs 400,000)
- Contact is sporadic
- Apes are not an important reservoir currently but may play an important role when and if we are approach eradication

Drug-resistant malaria

Antimalarial Drug Resistance: 2004



Antimalarial drugs and drug resistance



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Why and when does drug resistance develop?

- What factors facilitate:
  1. Appearance of mutations?
  2. Natural selection of mutations?
  3. Geographic spread of the mutation?
- How can we impede its progress?

Step 1: appearance of mutation

Mutations

- Mutations occur at a rate of 10^{-6}/division,
- More parasites → higher likelihood of mutations
- More parasites exposed to drug→ more drug resistant mutations

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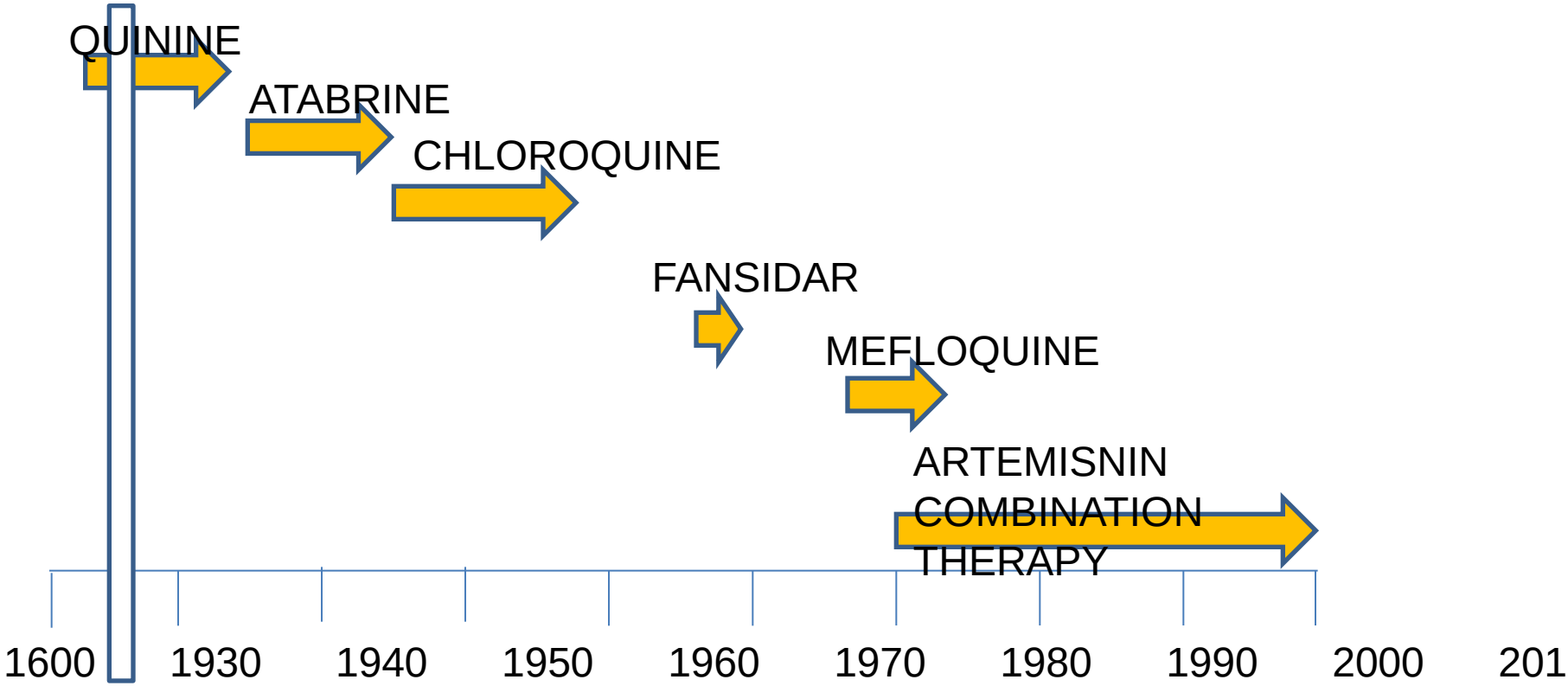
Quinine: the first antimicrobial

Bbc.co.uk
Wellcome trust library

Why was quinine effective for 300 years, when most drugs only last <10?



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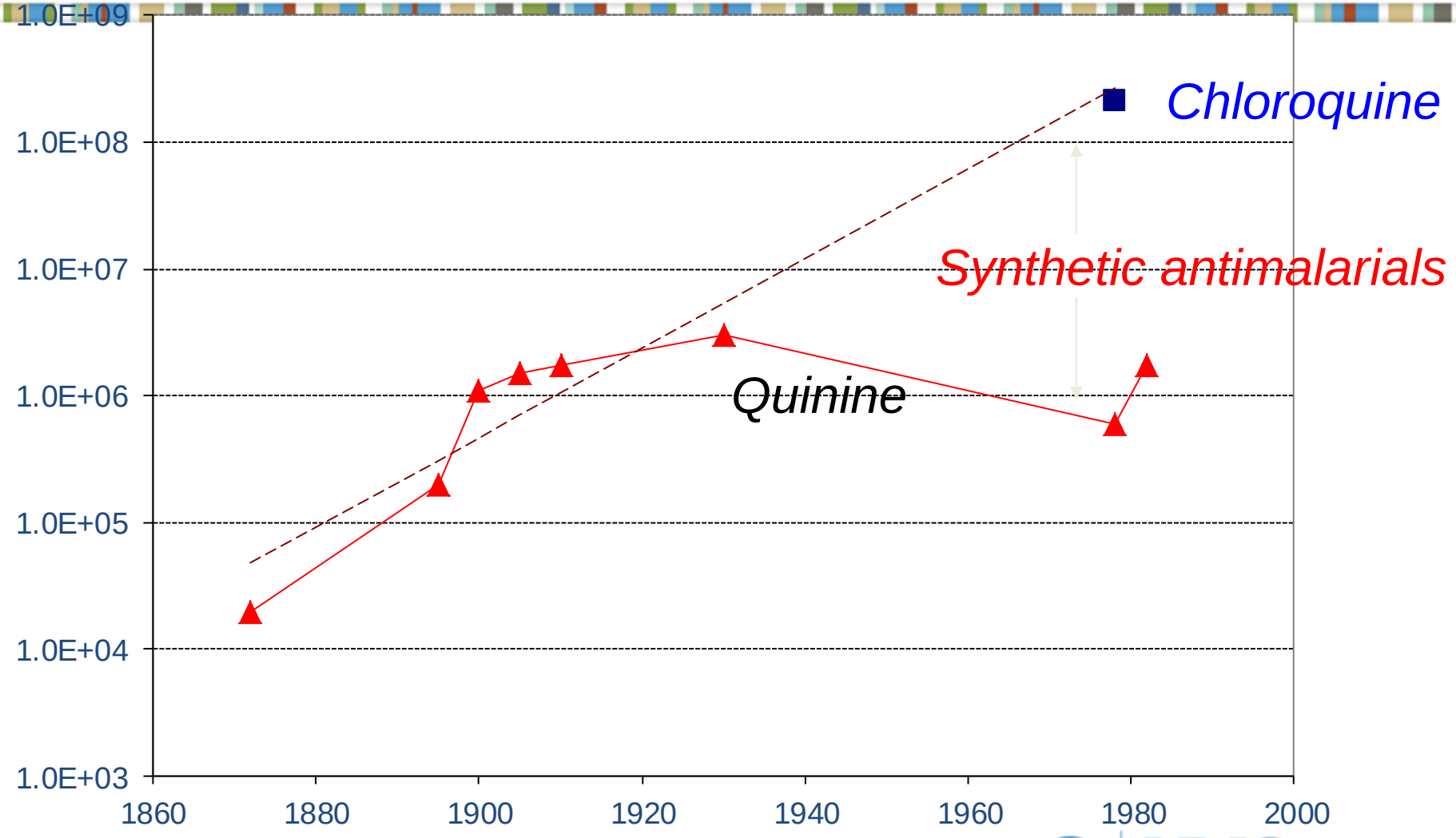
World antimalarial consumption



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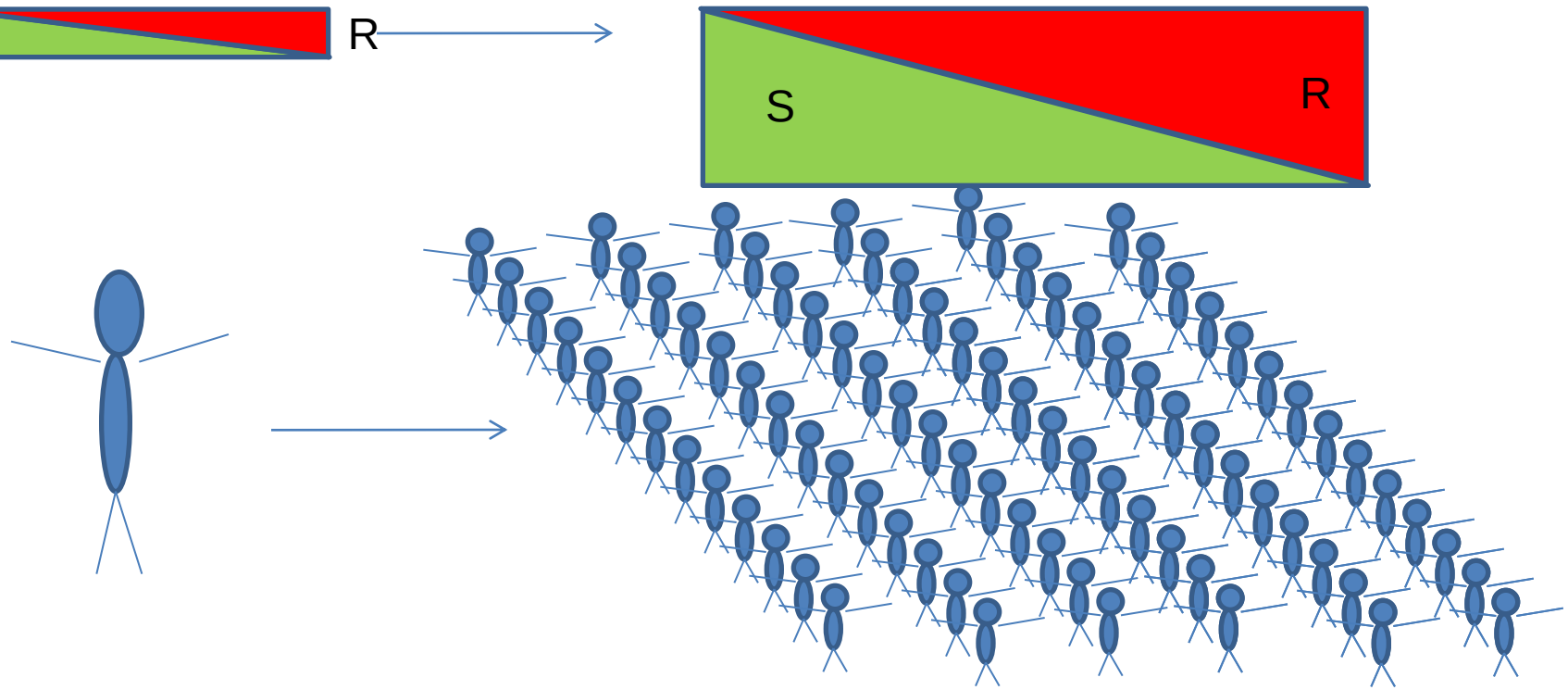
The more widely a drug is used, the more quickly resistance develops

Step 2: natural selection of mutations

How do resistant parasite populations increase?

Within-host

Within-population



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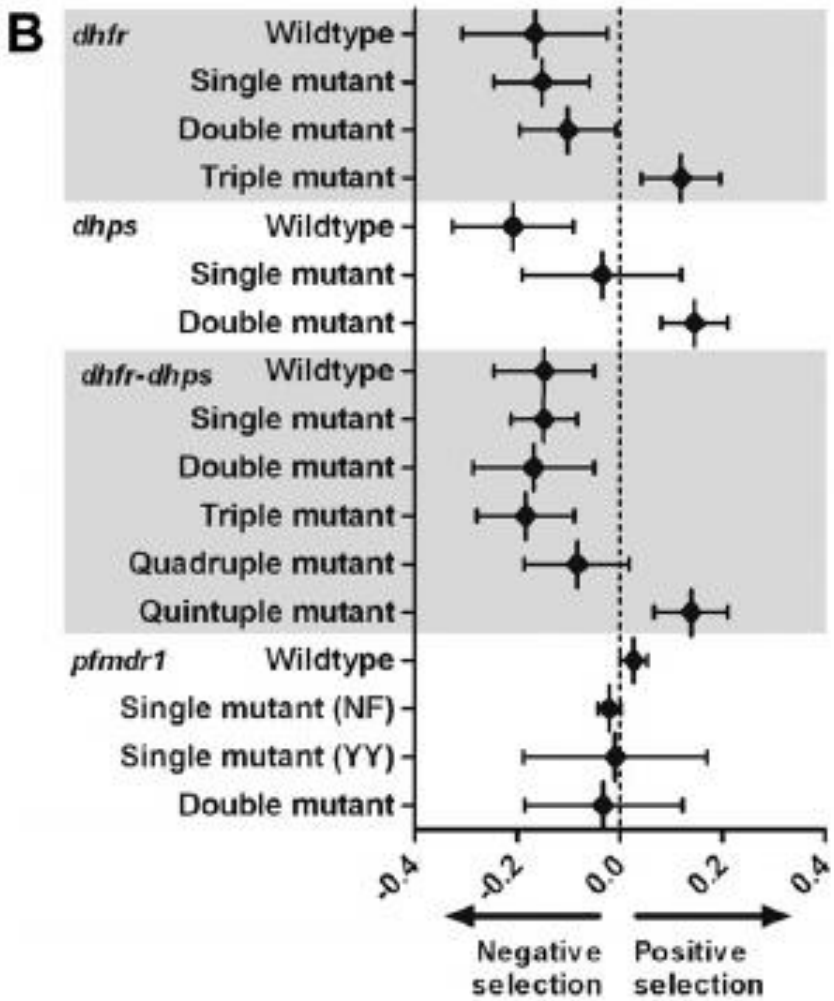
Within-host

- Resistant strain grow faster in the presence of drug
- Resistant strains also facilitate sensitive strain growth

Selective advantage



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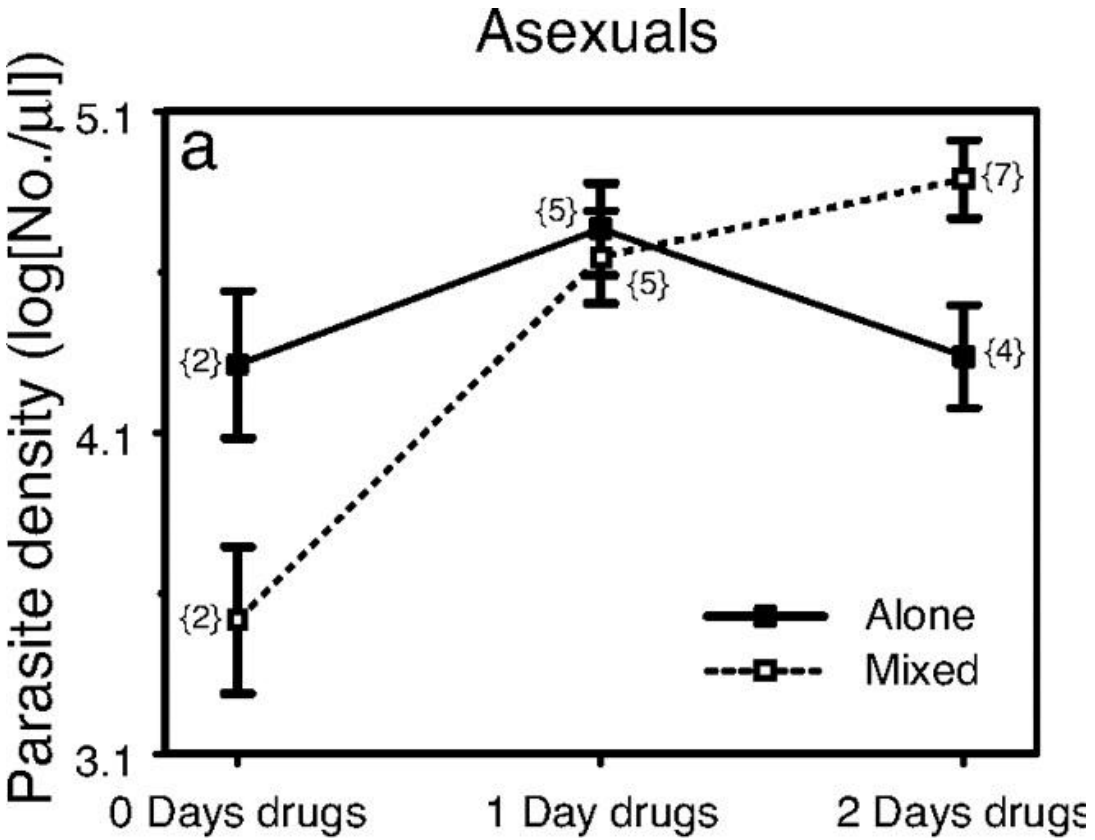
Facilitation



Mice

Wargo A R et al. PNAS 2007;104:19914-19919

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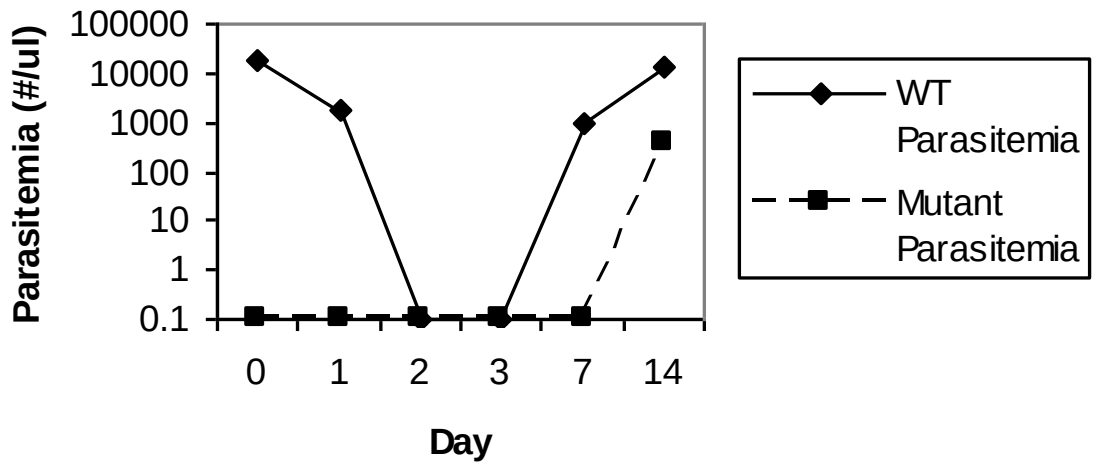
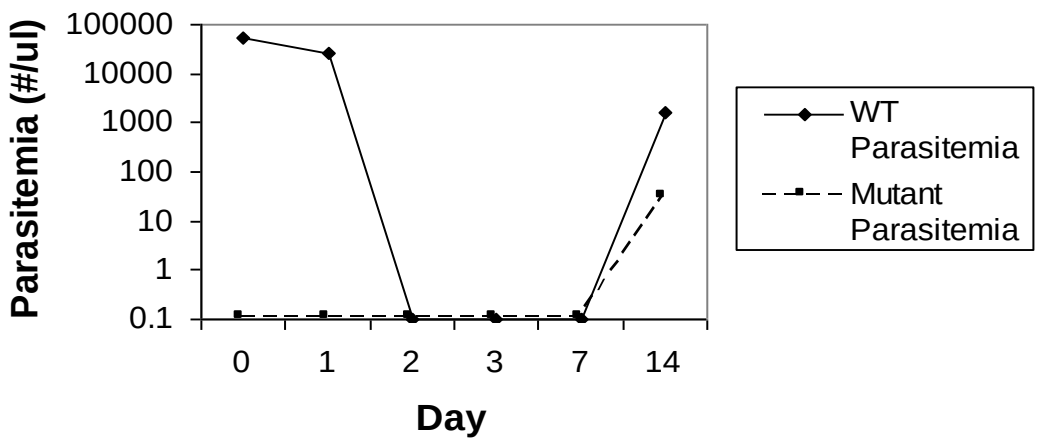
PNAS

Facilitation in humans: *pfcrt* K76T in Madagascar





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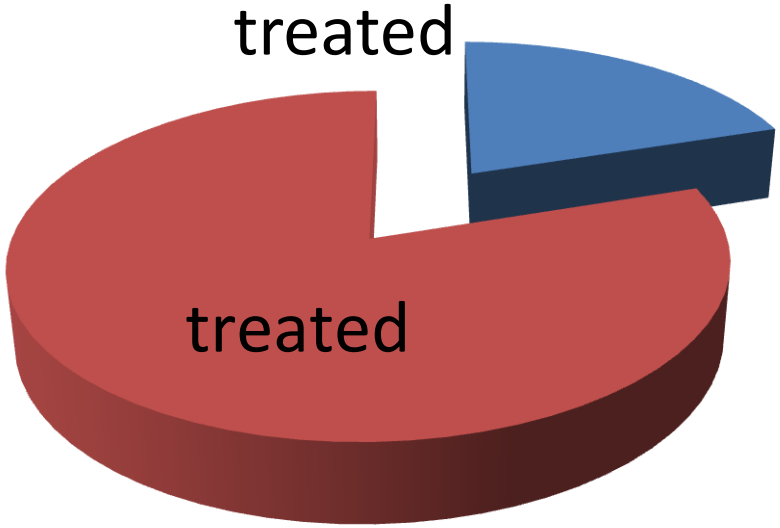
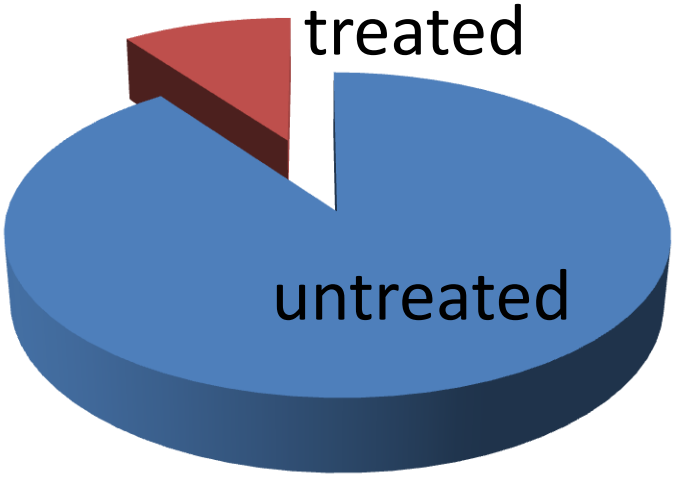
Within-host parasite responses to drugs are highly complex

Within-population





FAST

SLOW

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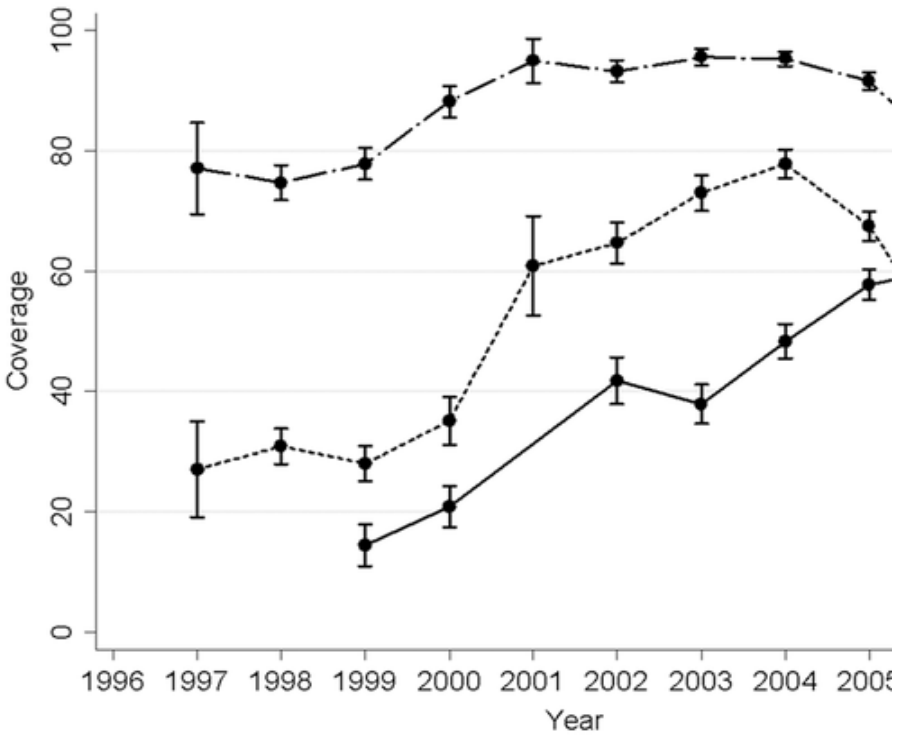
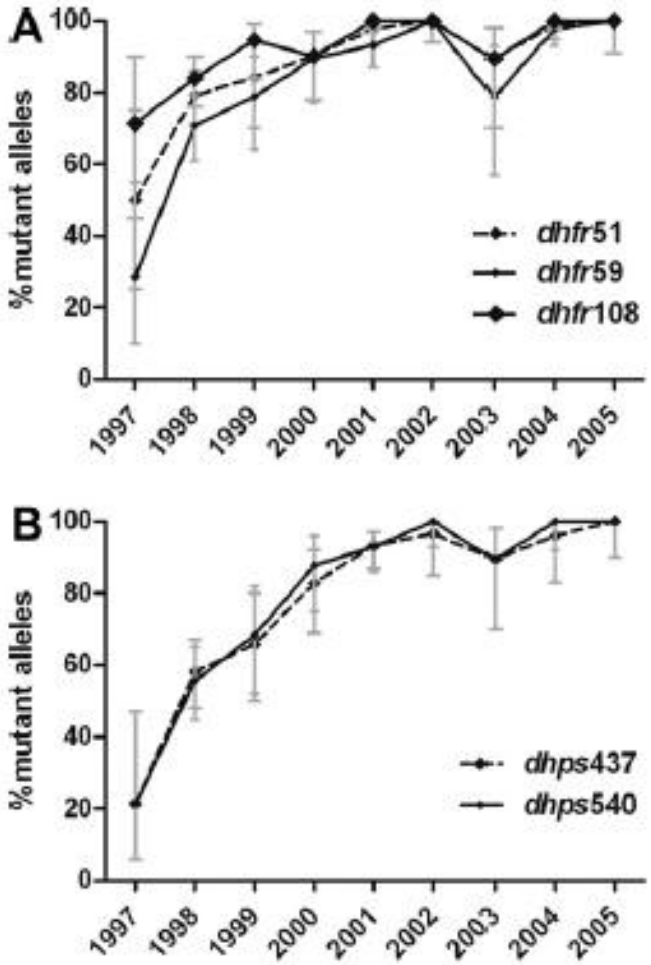
Malawi





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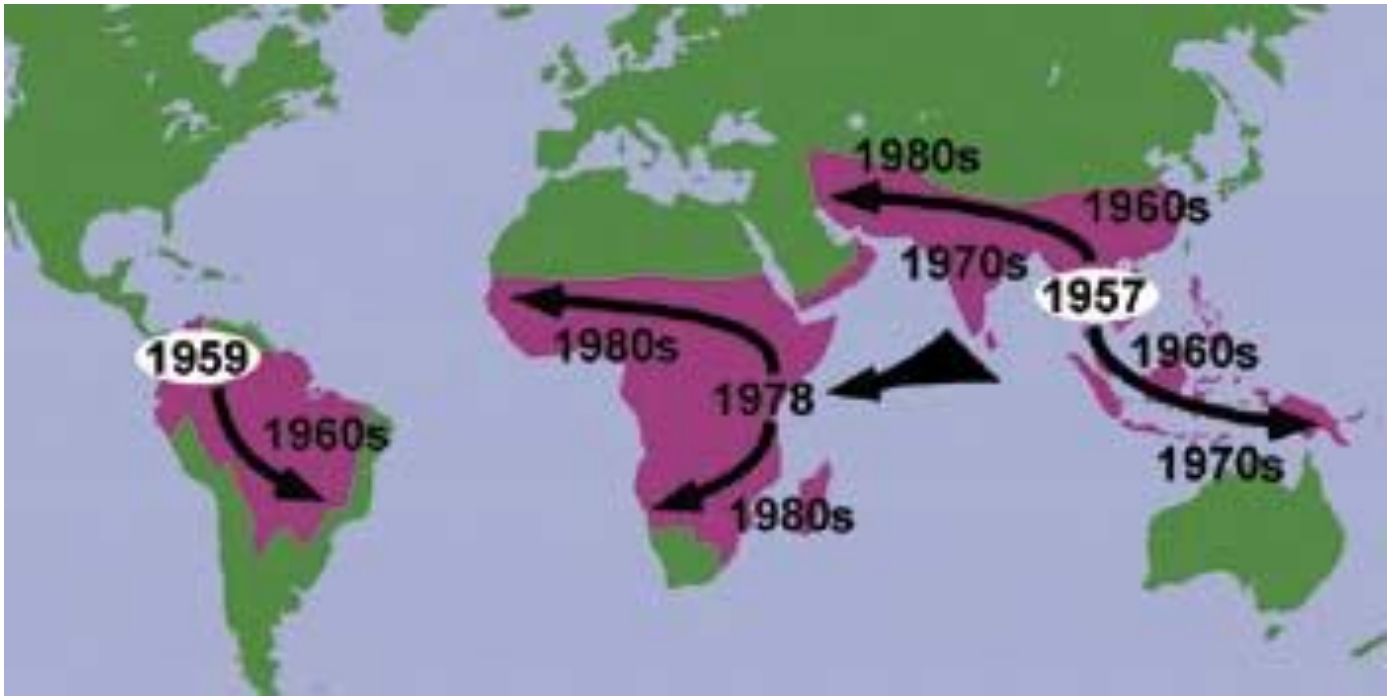
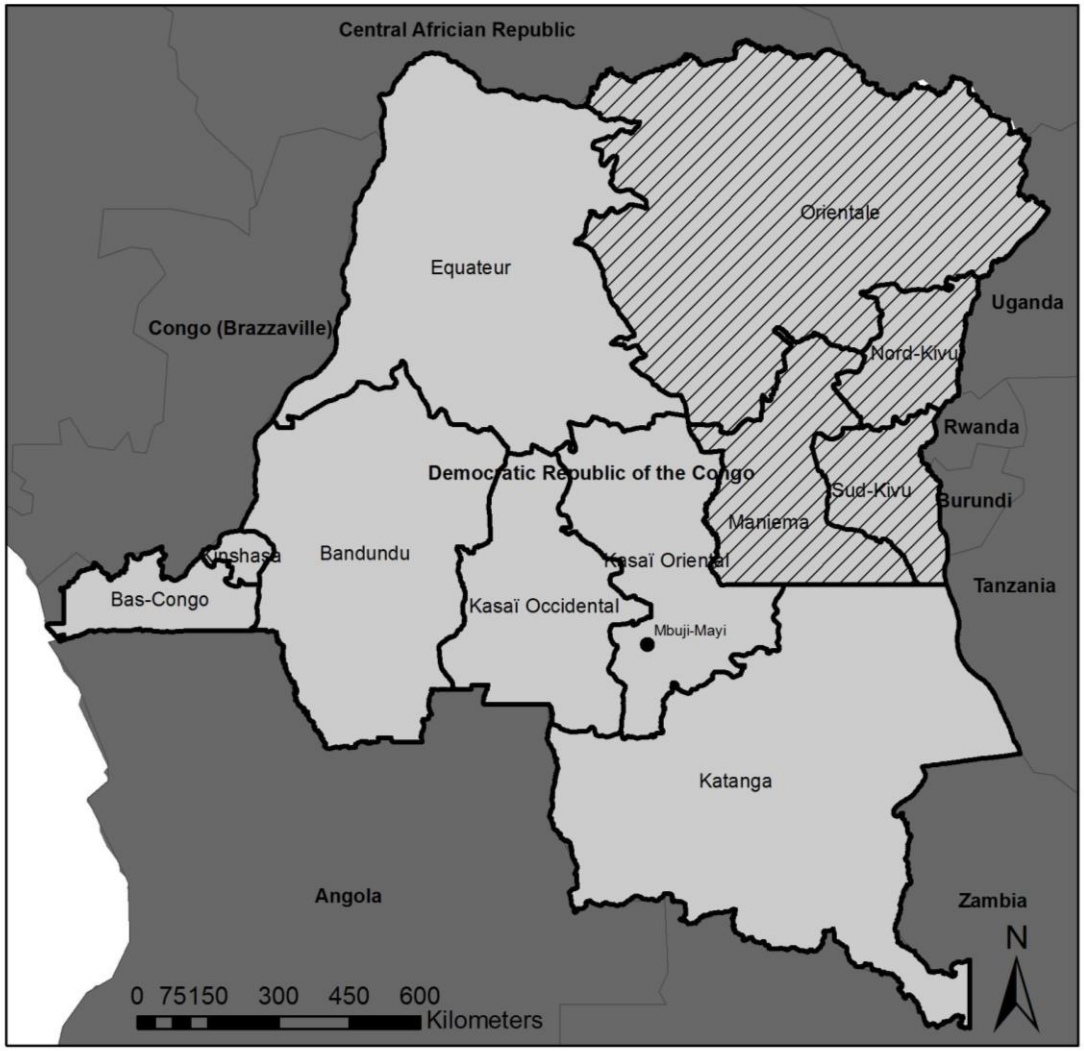
Step 3: resistance spread

Spread of Chloroquine Resistance



http://www.sciencenews.org/pages/sn_arc97/11_29_97/map.jpg

SP resistance in the Congo



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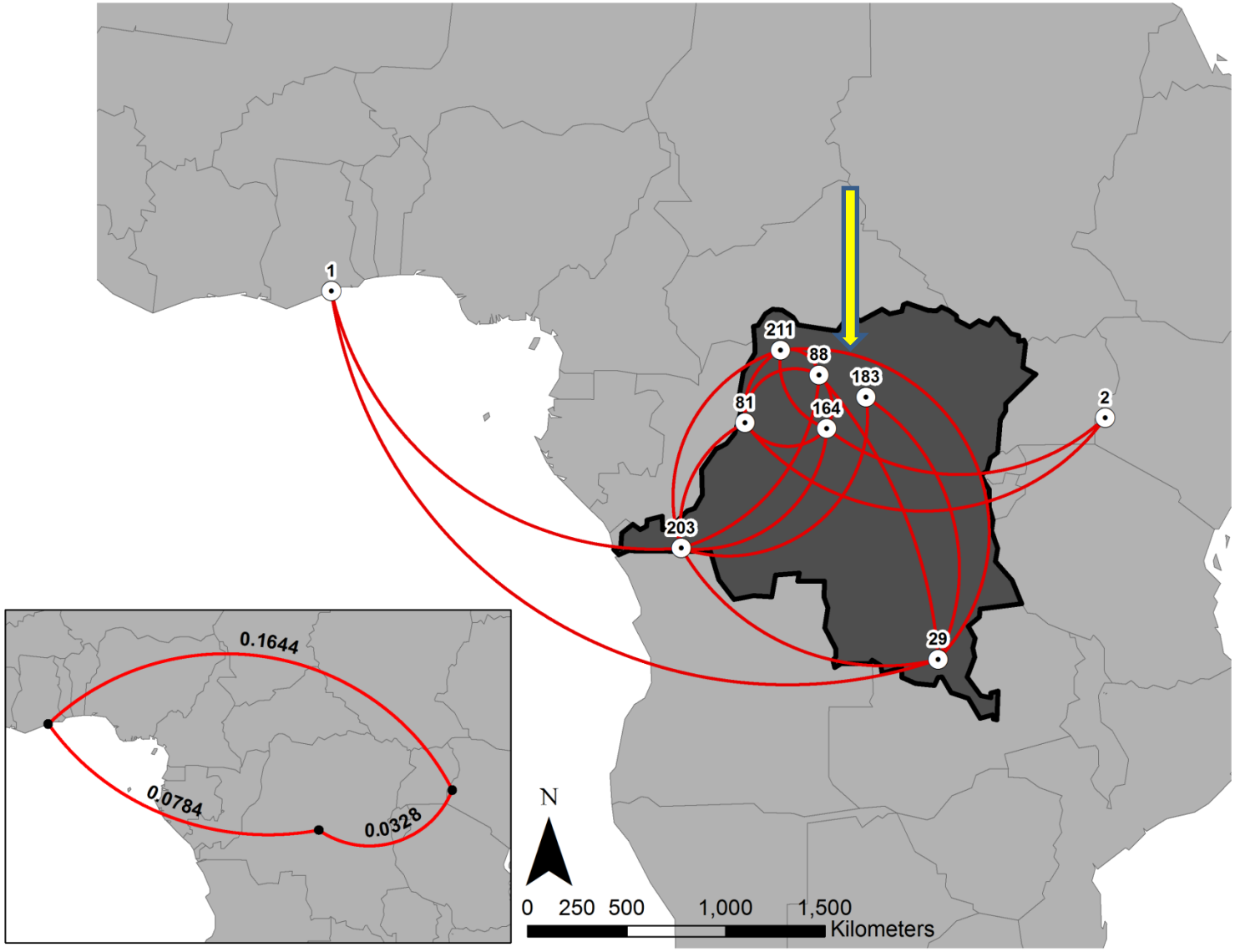
Gene flow measures migration



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How can we combat drug resistance?

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1-Plan ahead

Translational			Development	
Preclinical	Phase I	Phase II	Phase III	Approved[1]
MK 4815	OZ 439 Monash/UNMC/STI	Arterolane/ piperaquine Ranbaxy	Eurartesim Sigma-Tau/MMV	Coartem-D Novartis/MMV
GSK pyridones 2 compounds	Isoquine GSK/MMV	Artemifone UHKST/MMV	Pyramax Shin Poong/University of Iowa/MMV	Coarsucam sanofi-aventis/DNDi
(+) Mefloquine Treague	Tafenoquine Liverpool University	Fosmidomycin/ clindamycin Jomaa	ASMQ Far-Manguinhos/ DNDi	
Novartis 2 compounds	4-Pyridone GSK/MMV	Ferroquine/ artesunate sanofi-aventis	Azithromycin/ chloraquine Pfizer	
Trioxaquine Palumed/ sanofi-aventis	AQ-13 Immtech/Tulane	SAR 97276 CNRS/sanofi-aventis		
	CDRI 97/78 Ipca Laboratories & CDRI	Methylene blue/ amodiaquine Heidelberg/DSM		
		Tinidazole WRAIR		

[1]with stringent international regulatory authority or prequalified.

Olliaro & Wells, 2009

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2- Combination Chemotherapy

- Combination therapy
- Risk of 1 mutation = 10^{-6}
- Risk of 2 mutations = $10^{-6} * 10^{-6} = 10^{-12}$
- Resistance is much less likely to arise

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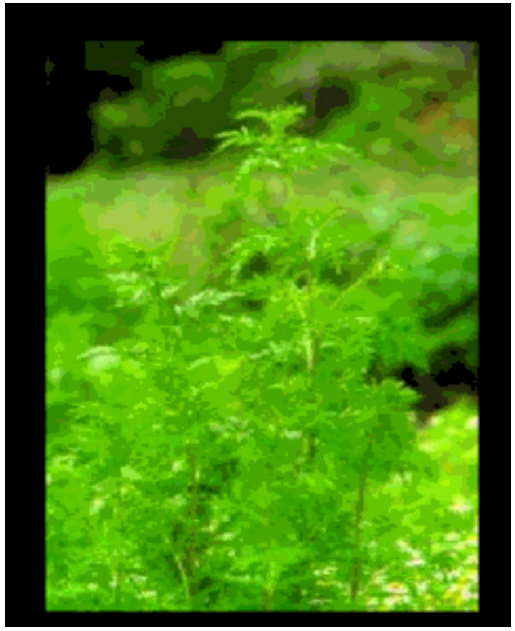
Malaria treatment and the Vietnam War

- During the Vietnam War, parasites became resistant to chloroquine
- US Army developed mefloquine for its troops
- Chinese developed artemisinin for the North Vietnamese



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Artemisinin Combination Therapy

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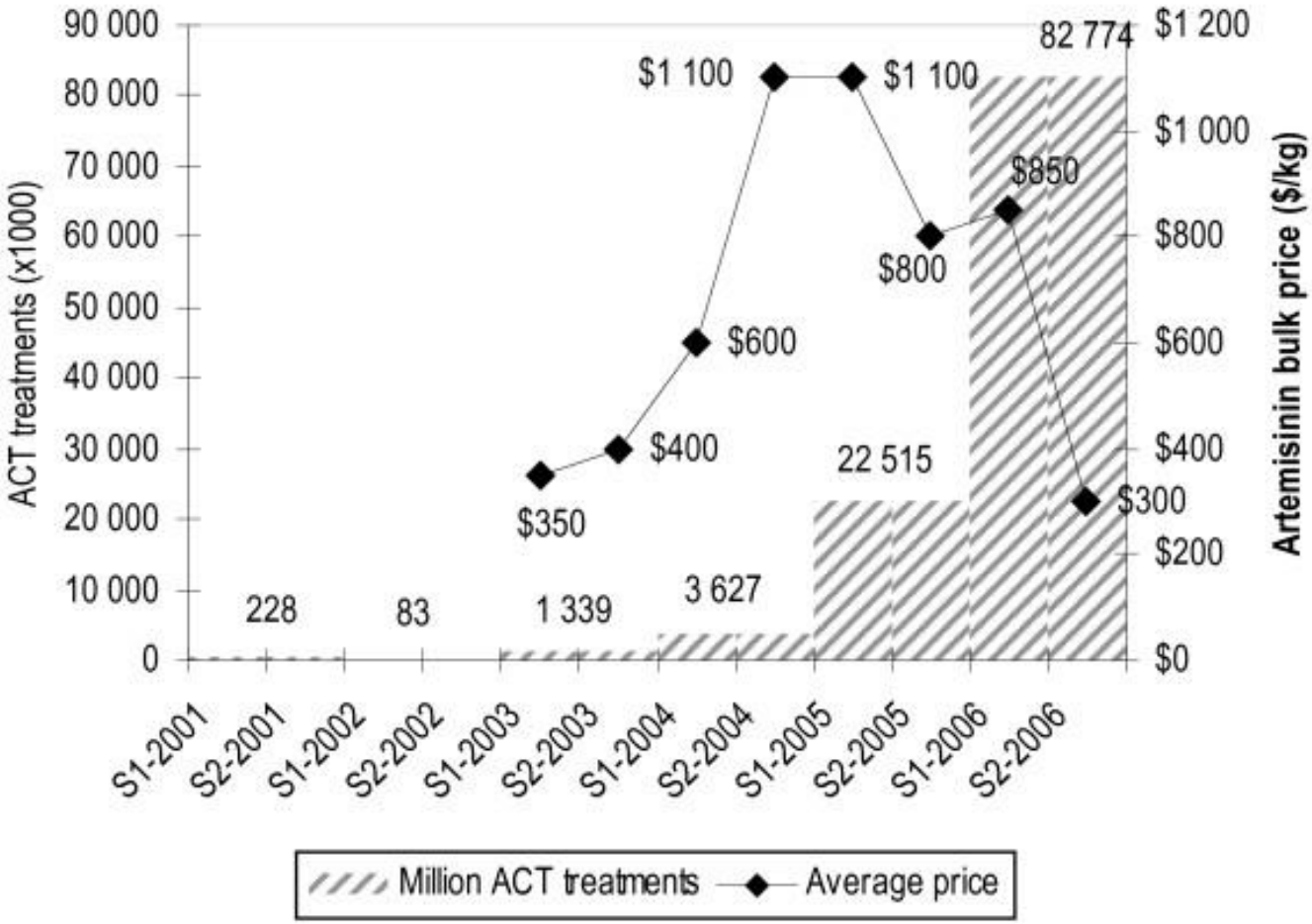
3-Public Private Partnerships

ACT use and cost



Kindermans *et al*. *Malaria Journal* 2007 **6**:125

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Conclusions

- Human malarias originated as zoonoses continues to jump from primates to man
- Drug resistance occurs in 3 steps
  1. Mutation
  2. Selection
  3. Spread
- Ways to combat resistance include
  1. A robust pipeline of new drugs
  2. Combination chemotherapy
  3. Public Private Partnerships

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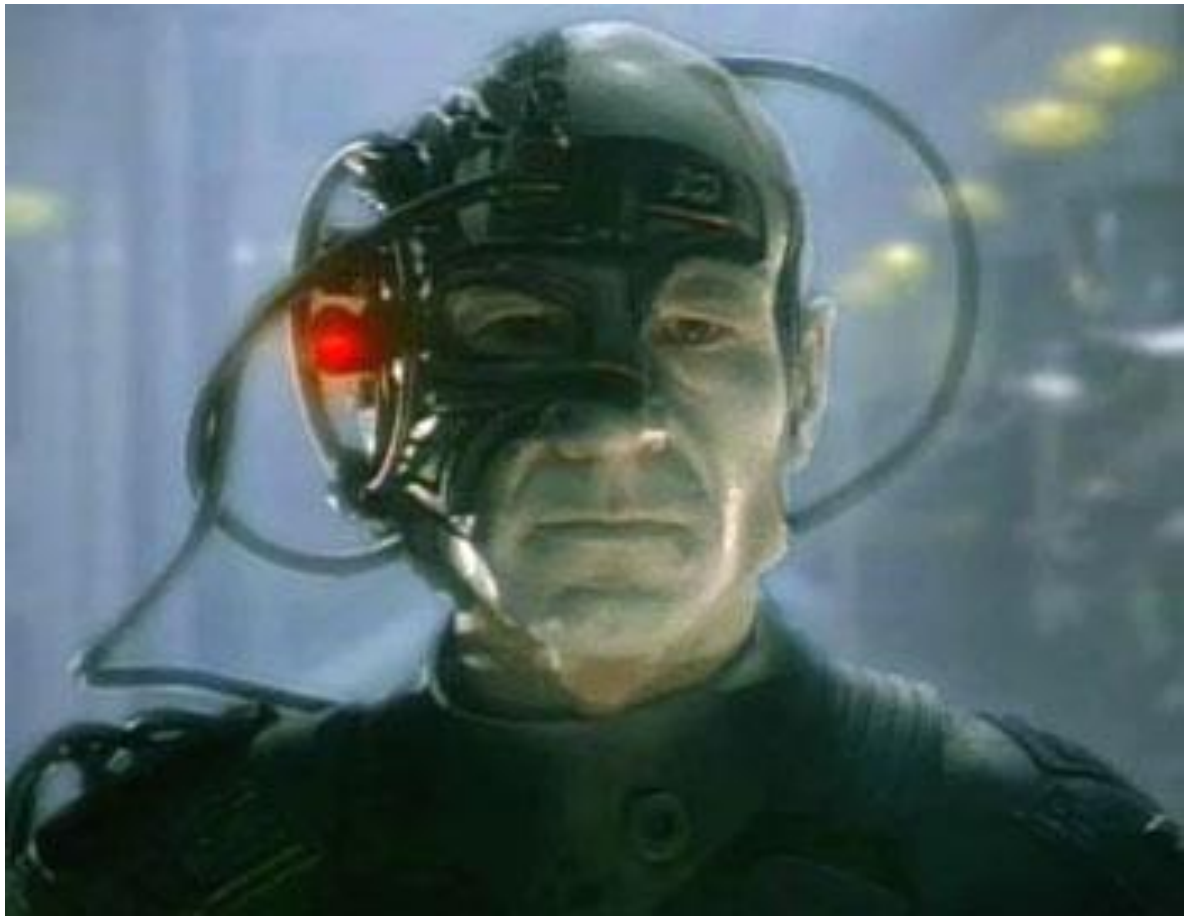
RESISTANCE IS FUTILE!



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