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# Antimicrobial Resistance in Malaria

25 October 2022

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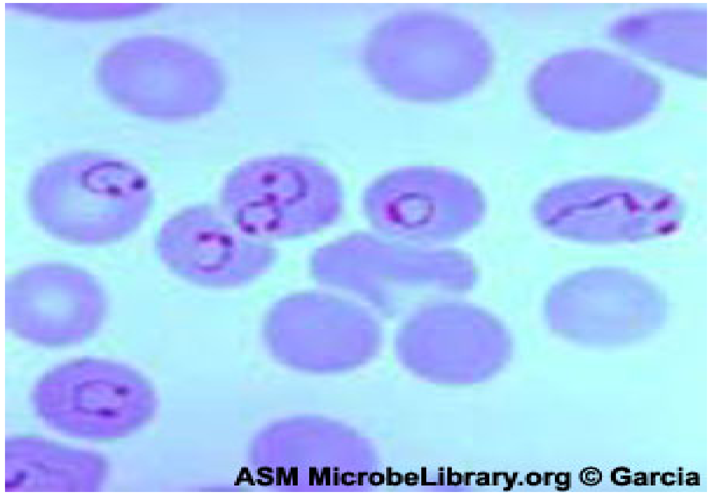
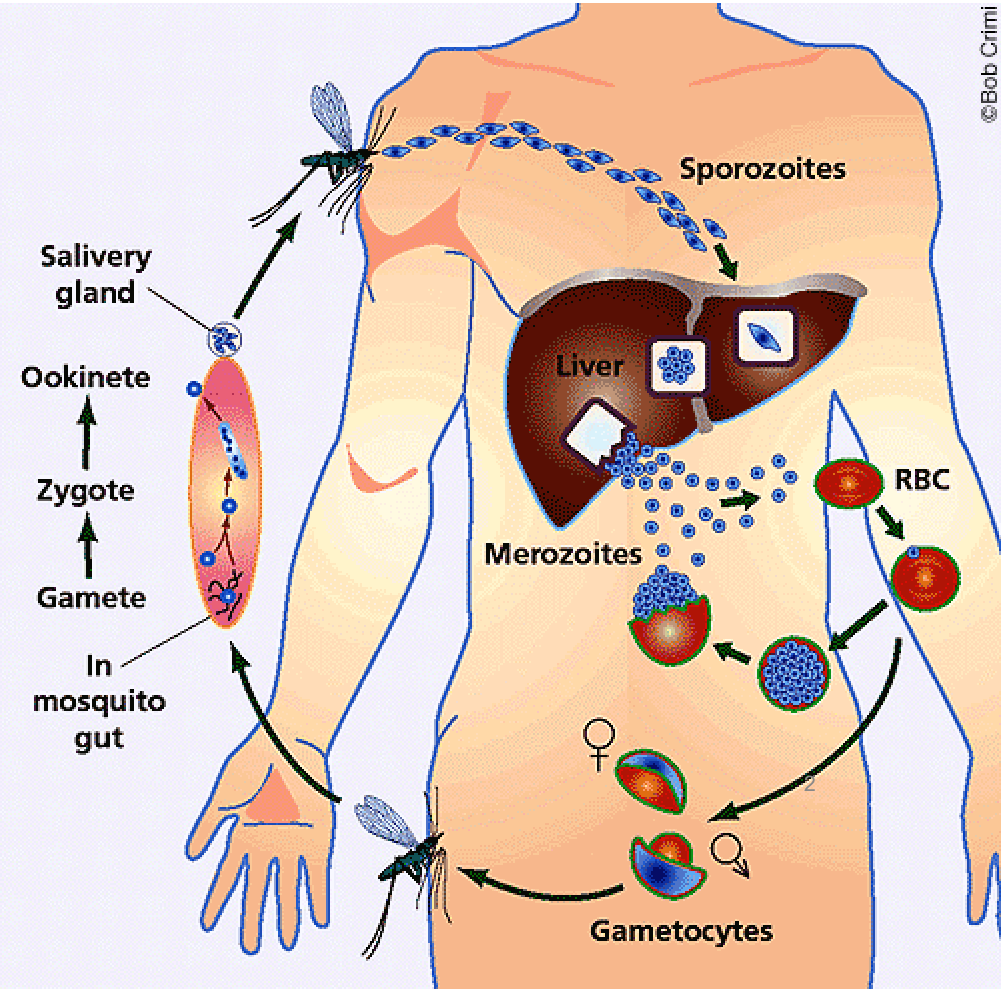
Malaria Genotyping group

# Plasmodium cycle

Anopheles gambiae© James Gathany / CDC

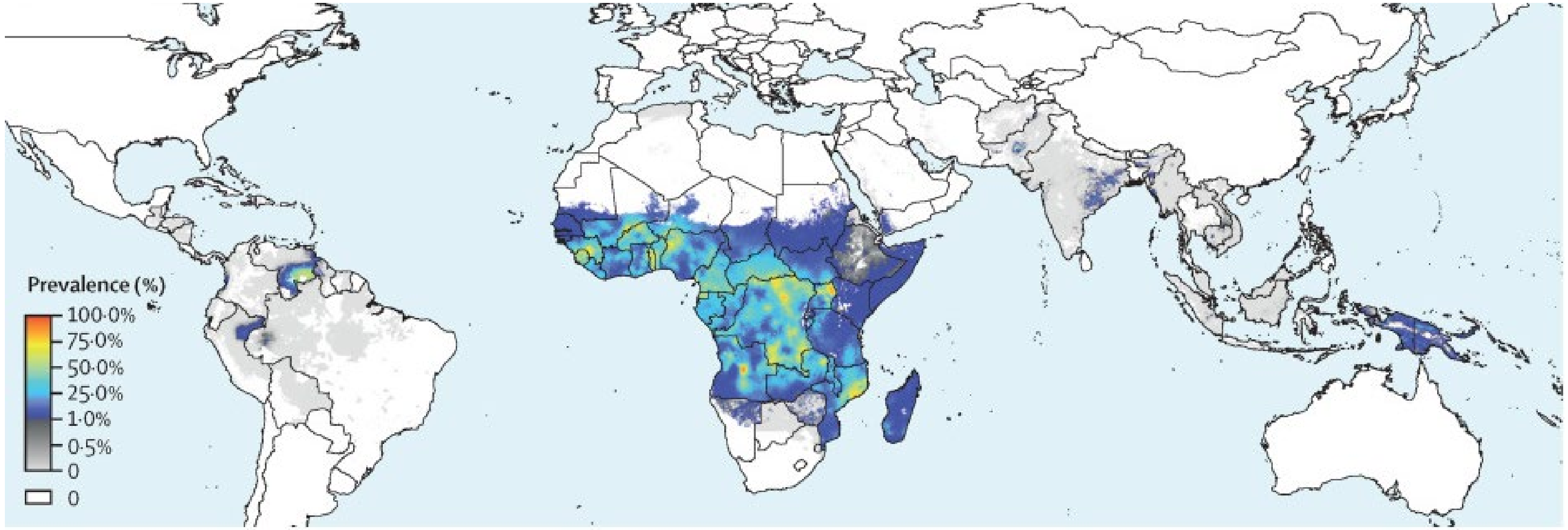


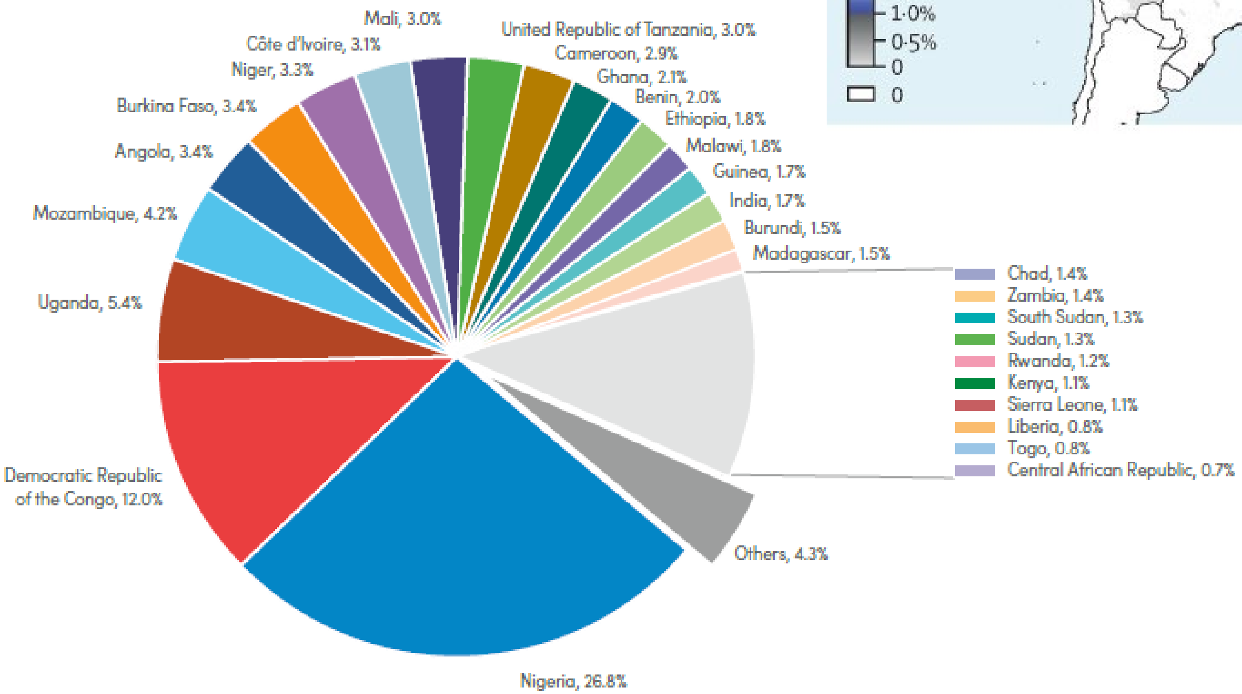

Alan F. Cowman & Brendan S. Crabb. Nature Biotechnology. 2002

- Falciparum
- Vivax
- Ovale
- Malariae
- Knowlesi

# Global malaria distribution




Feachem et al. 2019, Lancet ;394(10203):1056-1112




55% malaria cases from 6 countries:

- Nigeria: 26.8%
- DRC: 12%
- Uganda: 5.4%
- Mozambique: 4.2%
- Angola: 3.4%
- Burkina Faso: 3.4%

WHO. World Malaria Report, WHO, 2021

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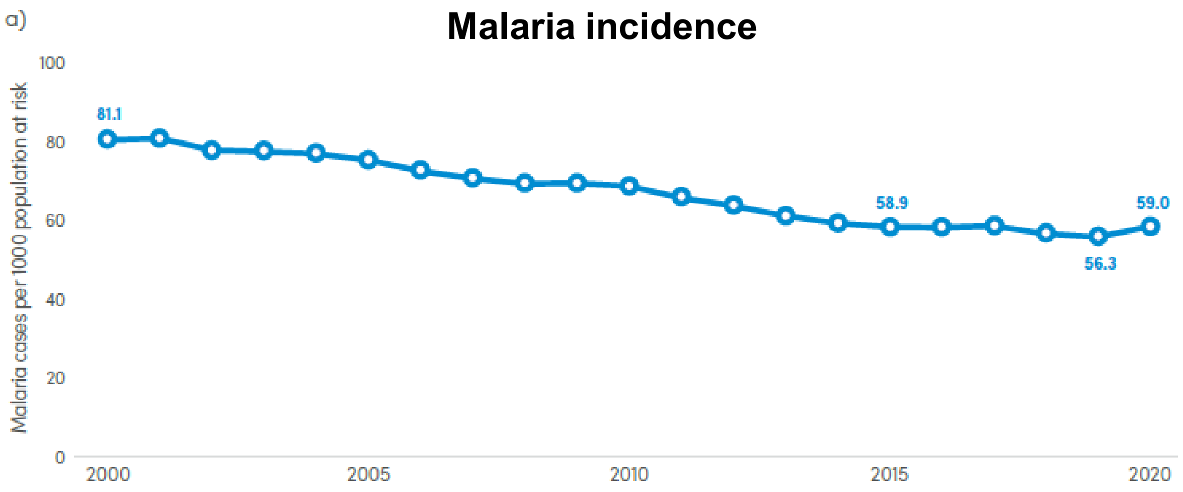
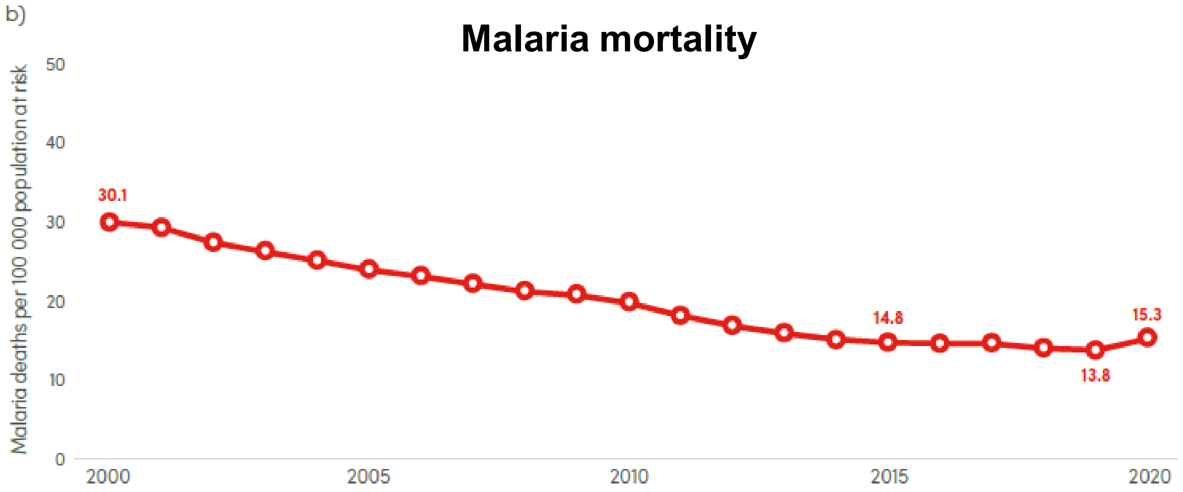
# Epidemiology

- 249 millions cases in 2020 in 85 countries
- Incidence decreased by 27% between 2010 and 2015 and < 2% between 2015 and 2019
- Increase in number of cases in 2019 due to COVID 19 pandemic
- Twenty nine countries accounted for 95% of malaria cases globally
- Global mortality estimated at 627,000 in 2020
- Increase in number of deaths in 2020 due to COVID 19 pandemic (68%), and new method of calculation (32%)
- Mortality decreased by 50% between 2010 and 2019

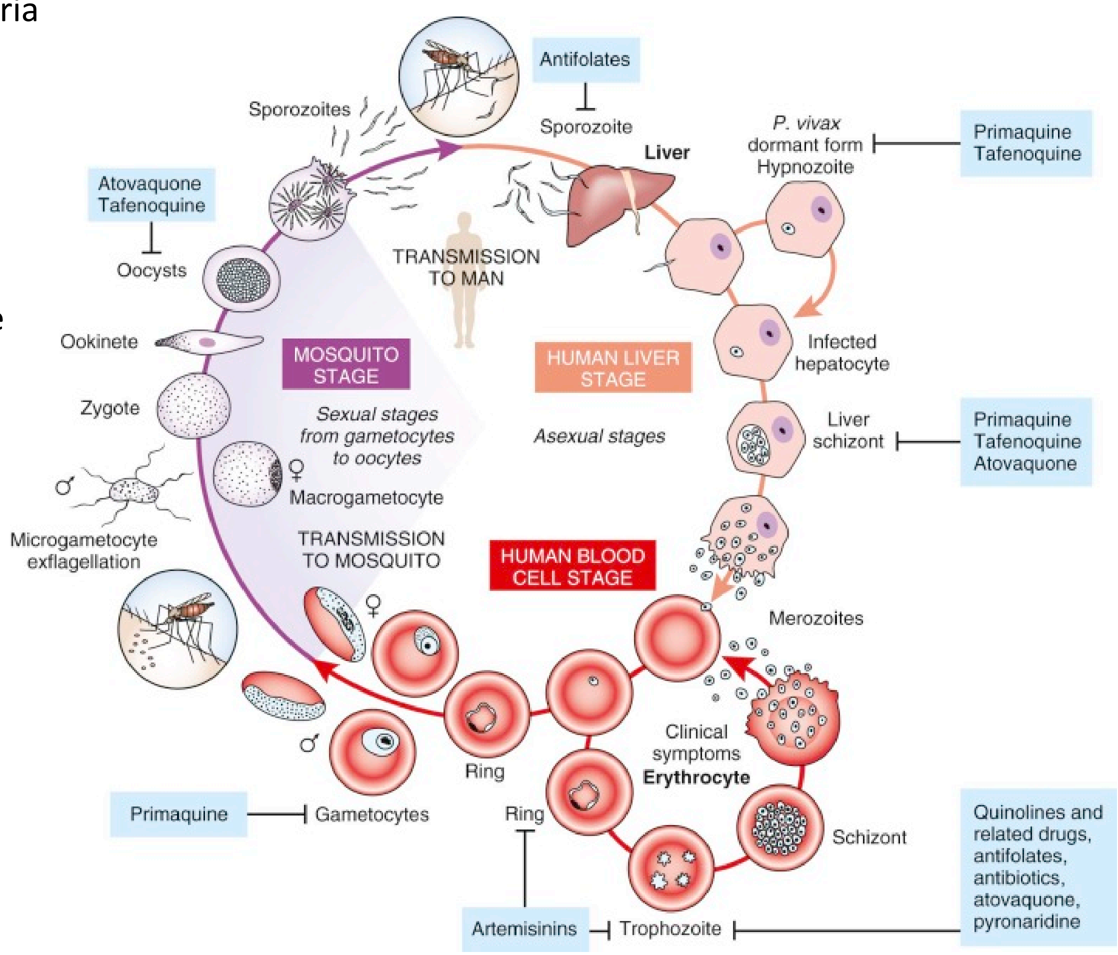


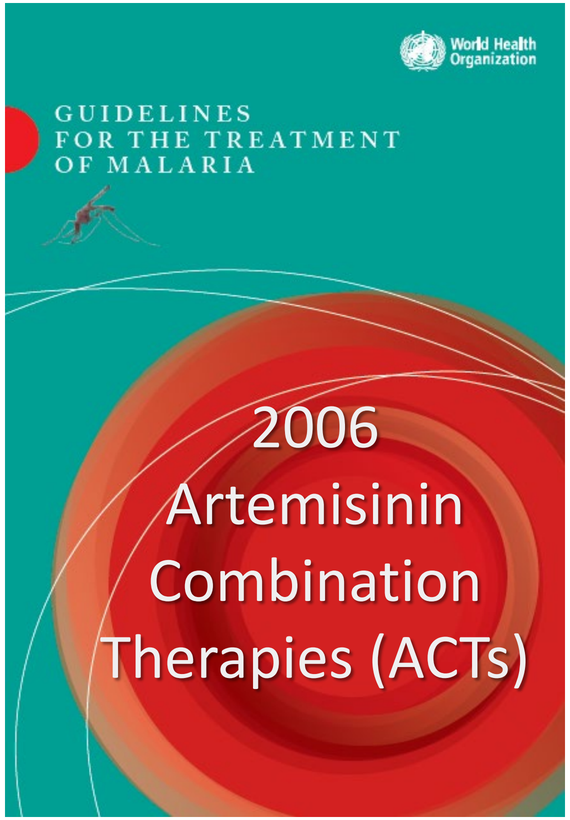

WHO. World Malaria Report, WHO, 2021

# Antimalarial treatments

- Uncomplicated *P. falciparum* malaria
  - Artemether-lumefantrine
  - Artesunate-amodiaquine
  - Artesunate-sulfadoxine - pyrimethamine
  - Artesunate-mefloquine
  - Dihydroartemisinin-piperaquine
  - Artesunate-pyronaridine*
- Severe malaria
  - Injectable artesunate
- Special risk groups
  - Intermittent preventive treatment in pregnant women (IPTp) with SP
  - Perennial and seasonal malaria chemoprevention (PMC and SMC) with SP and SP/AQ respectively




James S. McCarthy, Richard N. Price, in Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases (Eighth Edition), 2015



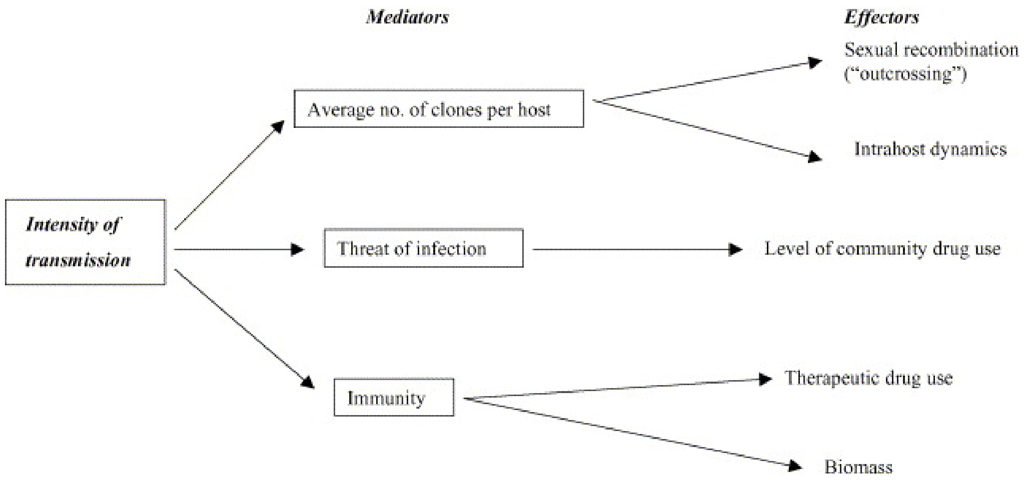
# Antimalarial drug resistance

| Drugs | Introduction | "First" year reported resistance | Difference (years) |
|---|---|---|---|
| Quinine | 1832 | 1910 | 278 |
| Chloroquine | 1945 | 1957 | 12 |
| Proguanil | 1948 | 1949 | 1 |
| Sulfadoxine-pyrimethamine | 1967 | 1967 | <1 |
| Mefloquine | 1977 | 1982 | 5 |
| Atovaquone | 1996 | 1996 | <1 |
| Artemisinin deriv. | 1971 | 2006-2007 | 35 |

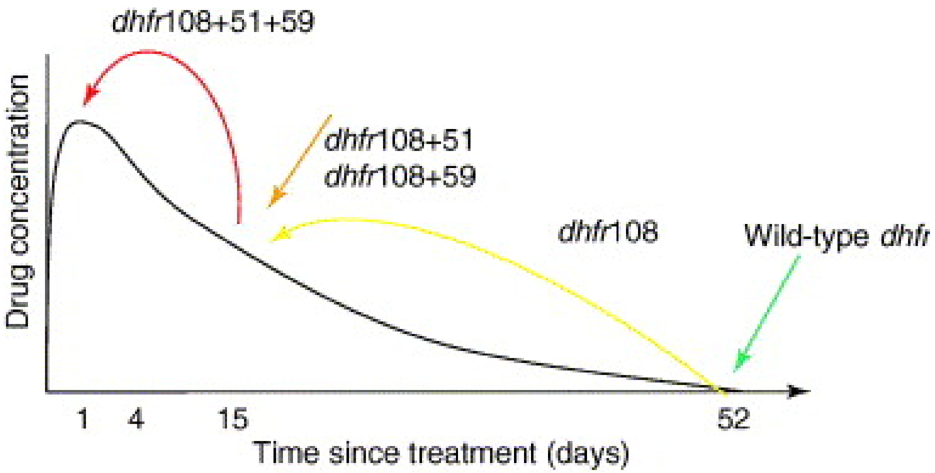
Adapted version of Wongsrichanalai et al. Lancet Infectious Diseases. 2002

# Emergence of antimalarial drug resistance

- De novo mutations arise spontaneously and rarely (1 in $10^{11}$ to < 1 in $10^{18}$)
- De novo mutations highly likely to occur in hyperparasitaemic patients with high parasite biomass (up to $10^{12}$)
- Degree of resistance conferred by the genetic event (mutation, gene copy number)
- Fitness cost of the genetic event leading to resistance
- Drug half life and pharmacodynamics play a major role in selecting resistant parasites
- Emergence also affected by drug levels (under-dosing that selects resistant parasites)
- Selection of resistant parasites by drug pressure
- Emergence and selection of resistant parasite in low transmission settings



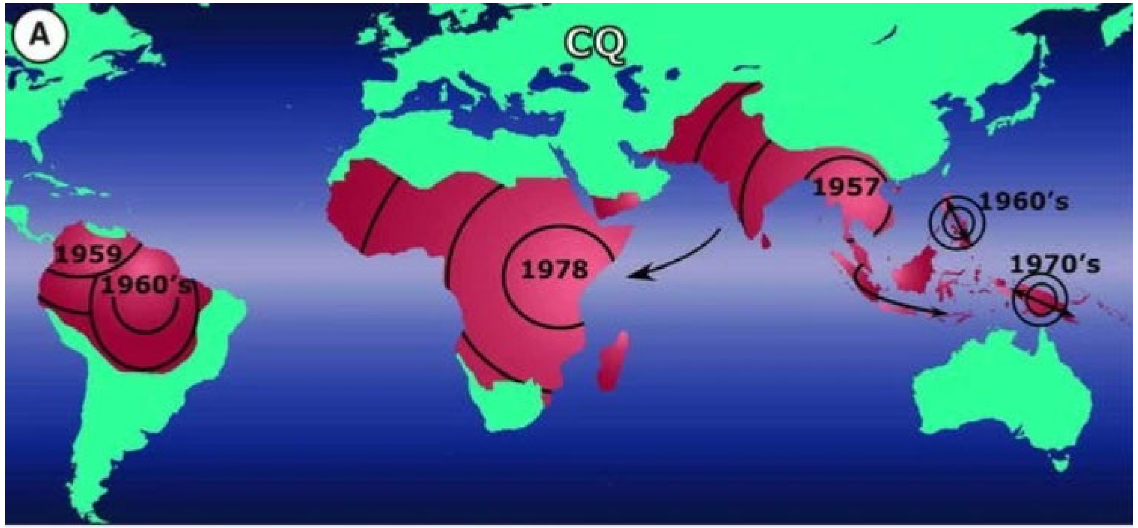

Hastings & Watkins. Acta Trop. 2005 Jun;94(3):218-29.



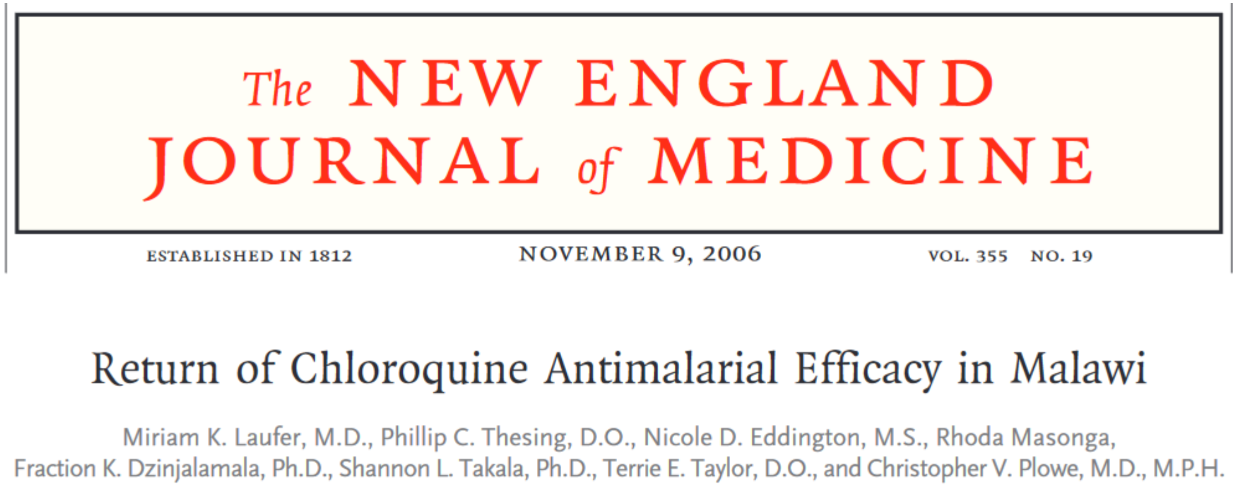

Hastings & Watkins. Trends Parasitol. 2006;22(2):71-7

# Spread of antimalarial drug resistance

- Spread from low to high transmission settings
- Emergence of low grade resistance in high transmission settings
- Intrahost competition plays an important role in high transmission settings




Hayton & Su. Curr Genet. 2008 Nov;54(5):223-39.


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 9, 2006 VOL. 355 NO. 19

Return of Chloroquine Antimalarial Efficacy in Malawi

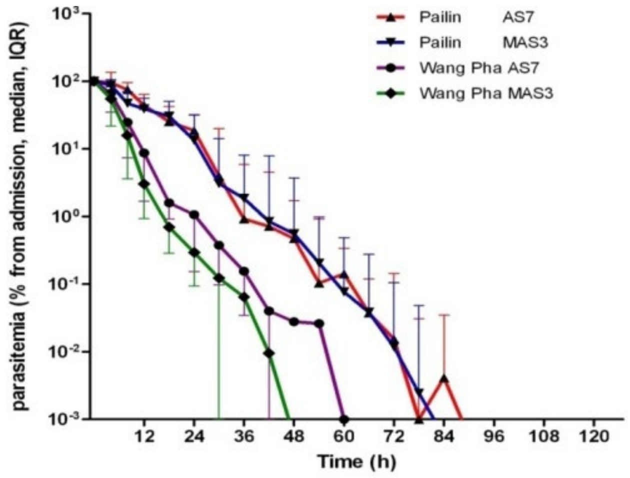
Miriam K. Laufer, M.D., Phillip C. Thesing, D.O., Nicole D. Eddington, M.S., Rhoda Masonga, Fraction K. Dzinjalamala, Ph.D., Shannon L. Takala, Ph.D., Terrie E. Taylor, D.O., and Christopher V. Plowe, M.D., M.P.H.

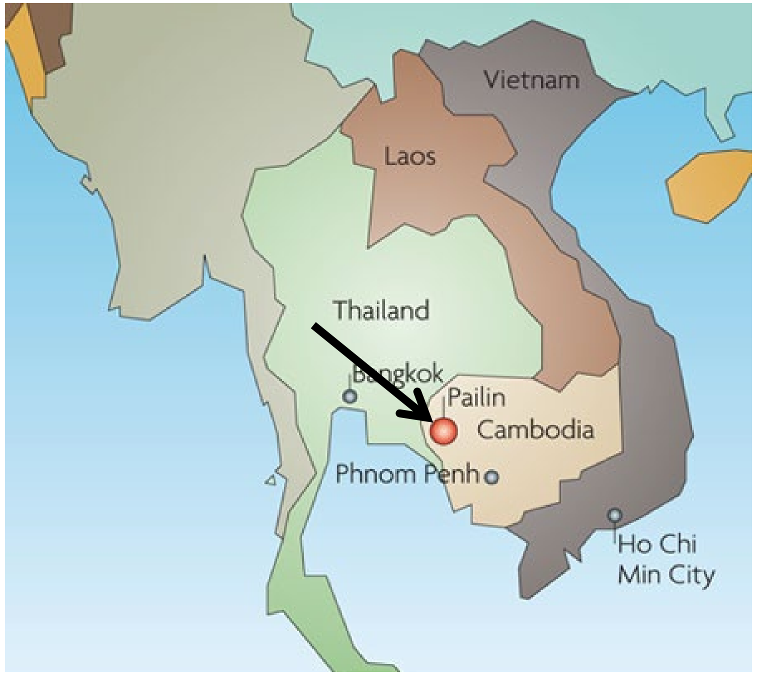
# Emergence of artemisinin resistance

*The* NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

## Artemisinin Resistance in *Plasmodium falciparum* Malaria




Dondorp et al., N Engl J Med. 2009;361(5):455-67

**nature**

Published: 18 December 2013

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


Frédéric Ariey, Benoit Witkowski, Chanaki Amaratunga, Johann Beghain, Anne-Claire Langlois, Nimol Khim, Saorin Kim, Valentine Duru, Christiane Bouchier, Laurence Ma, Pharath Lim, Rithea Leang, Socheat Duong, Sokunthea Sreng, Seila Suon, Char Meng Chuor, Denis Mey Bout, Sandie Ménard, William O. Rogers, Blaise Genton, Thierry Fandeur, Olivo Miotto, Pascal Ringwald, Jacques Le Bras, ... Didier Ménard


Current list of validated and candidate or associated *PfK13* mutations

| Validated | | Candidate or associated | |
|---|---|---|---|
| F446I | P553L | P441L | N537I/D |
| N458Y | R561H | G449A | G538V |
| M476I | P574L | C469F/Y | V568G |
| Y493H | C580Y | A481V | R622I |
| R539T | | R515K | A675V |
| I543T | | P527H | |

WHO. Global Malaria Programme.2020

# ACT resistance

**Artesunate-sulfadoxine -pyrimethamine**

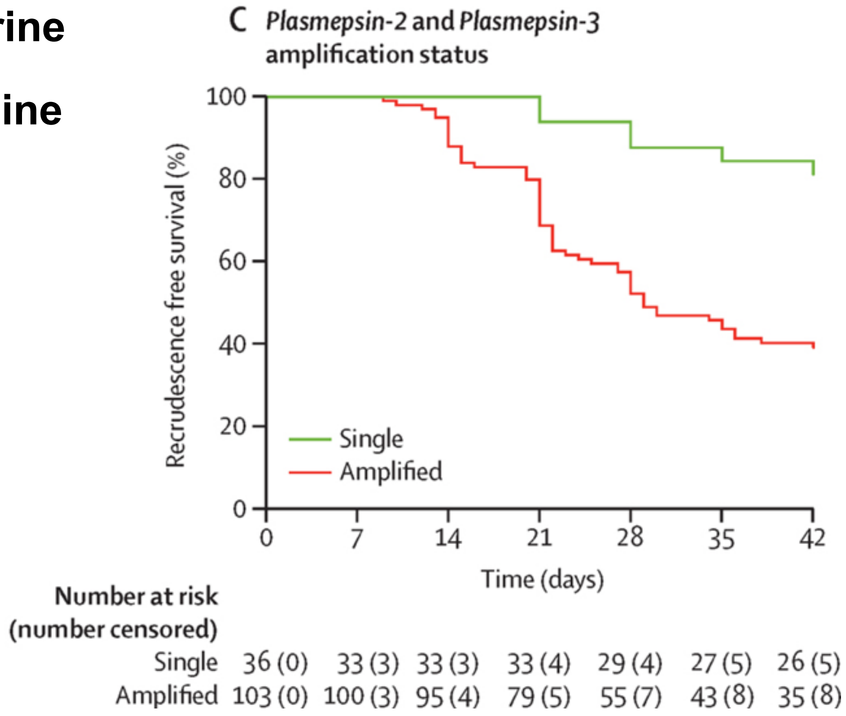
**Artesunate-amodiaquine**

**Artesunate-mefloquine**

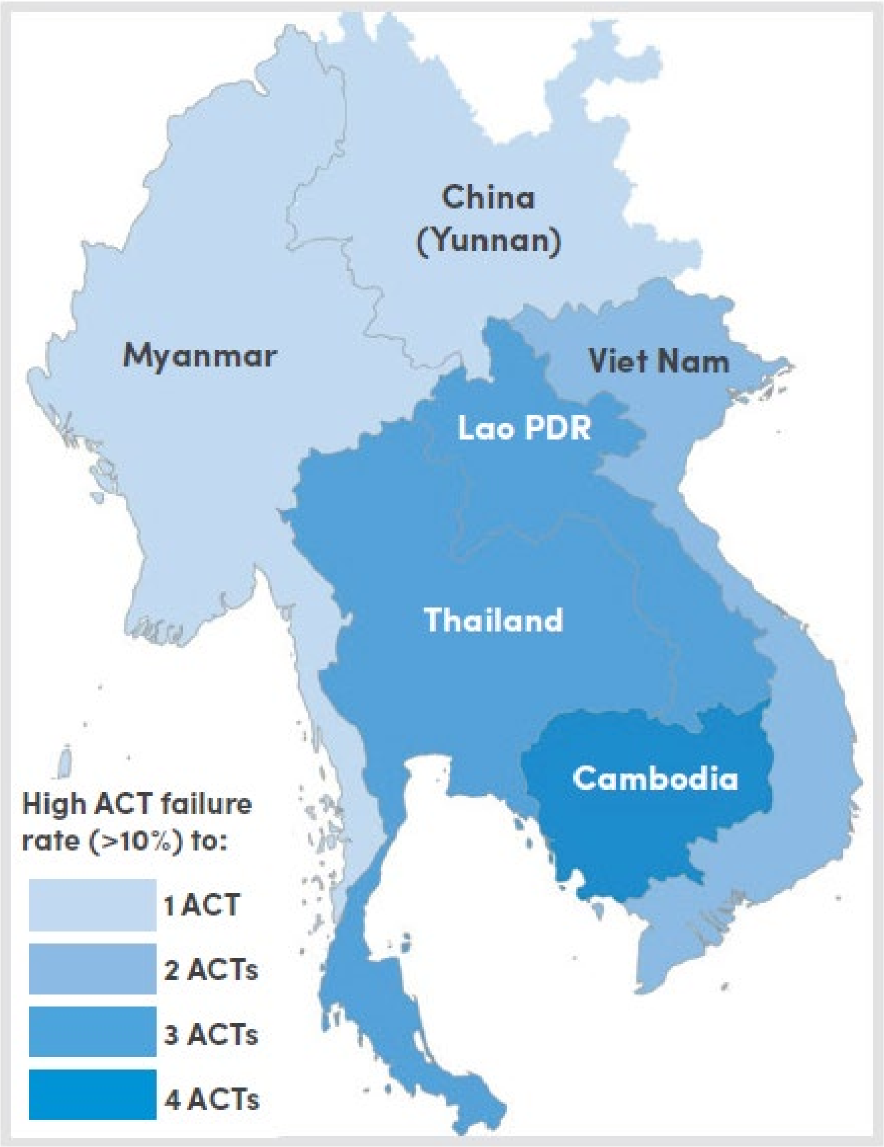
**Dihydroartemisinin-piperaquine**

**Artemether-lumefantrine**

**Artesunate-pyronaridine**

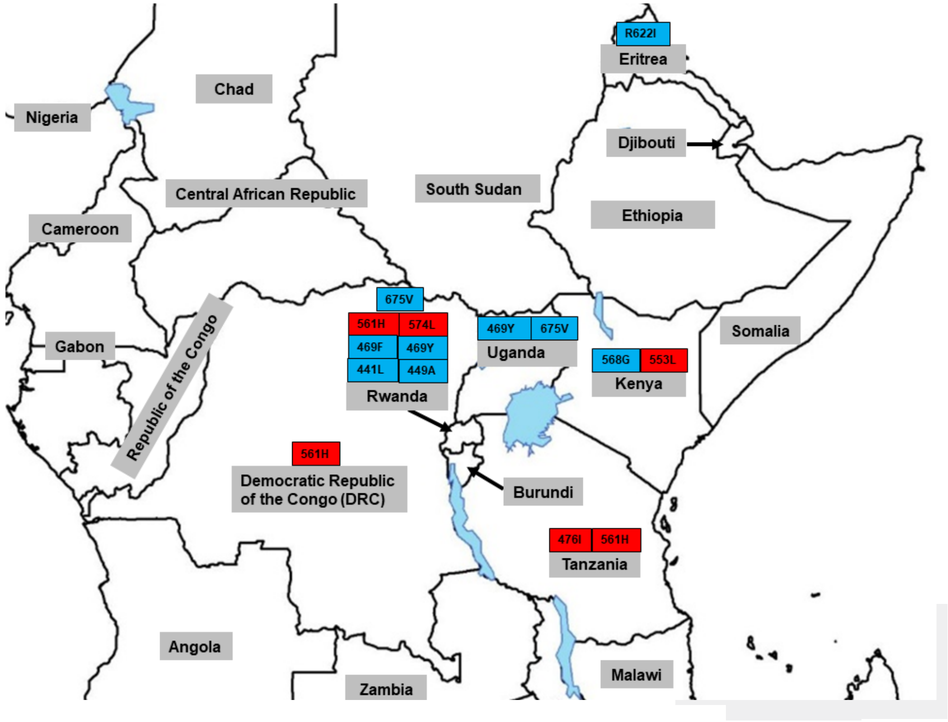



Van der Pluijm et al. Lancet Infect Dis. 2019;19(9):952-961

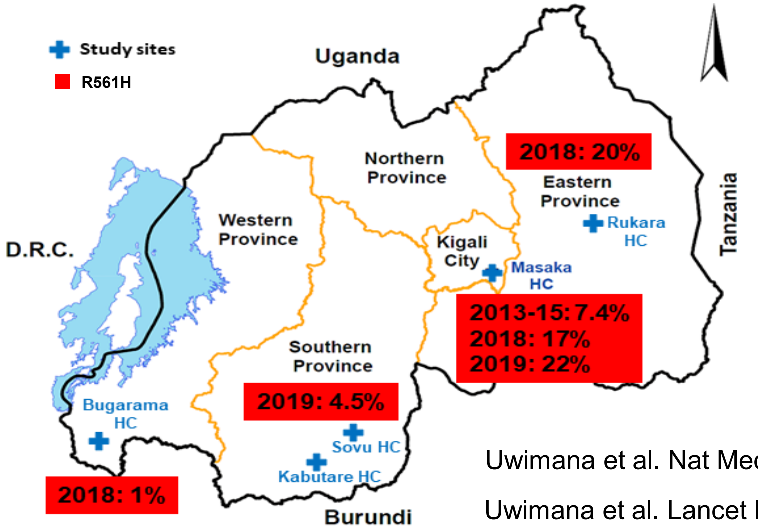



WHO. Global Malaria Programme. 2018

# Confirmed artemisinin resistance in Africa

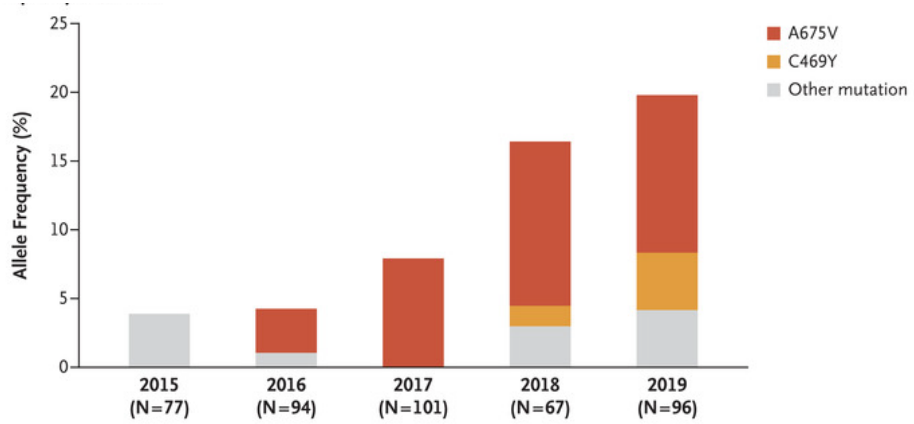



Nsanzabana. Malar J. 2021;20(1):401.




Uwimana et al. Nat Med. 2020;26(10):1602-1608.

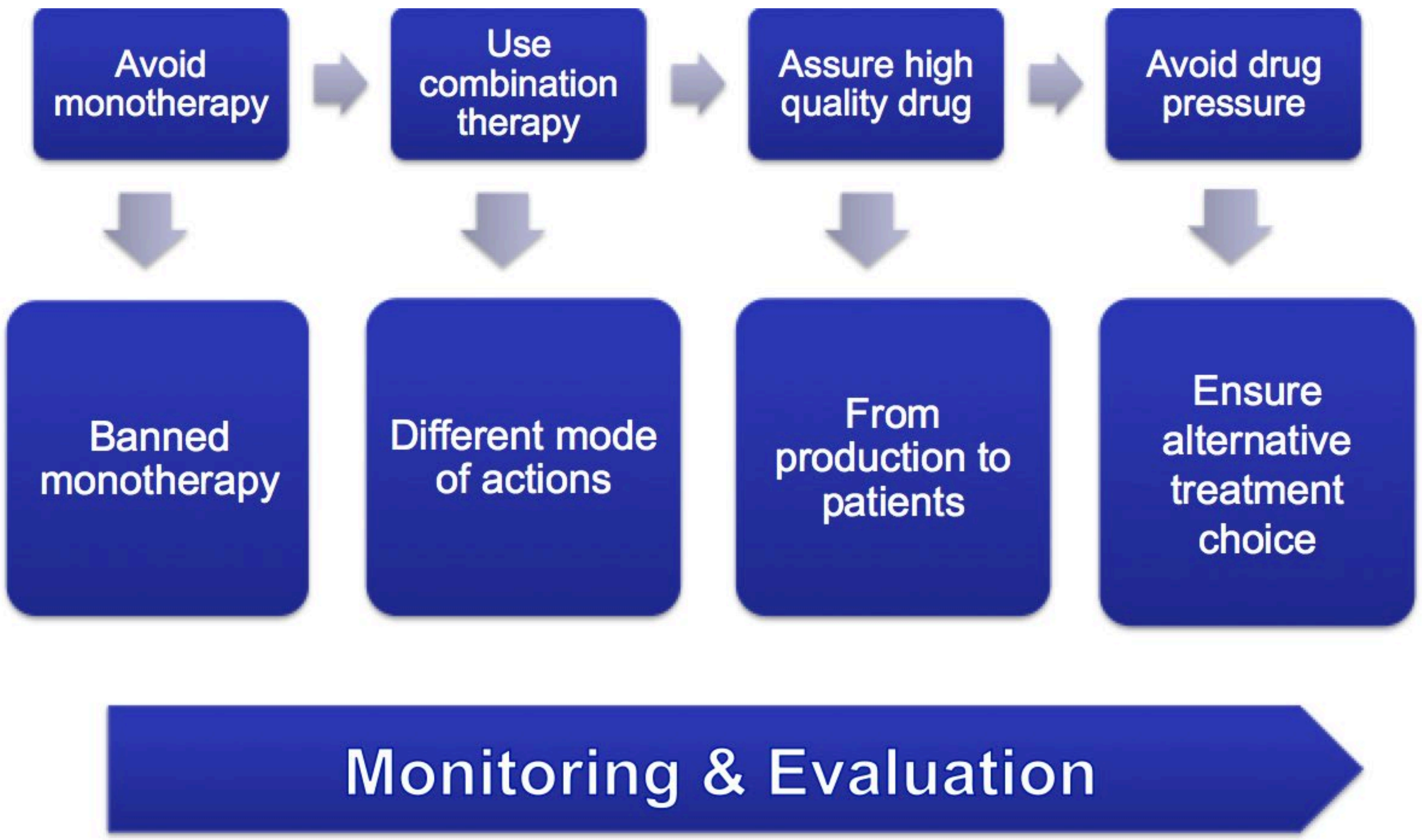
Uwimana et al. Lancet Infect Dis. 2021;21(8):1120-1128.




Balikagala et al. N Engl J Med. 2021;385(13):1163-1171

- Local emergence of Artemisinin resistant parasites in Rwanda and Uganda
- Molecular markers (*Pfk13* mutations) associated with delayed parasite clearance
- Artemisinin resistance was not associated with ACT treatment failure

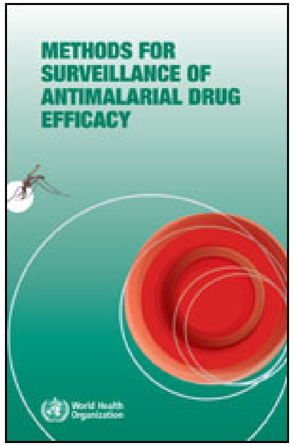
# How to prevent/slow antimalarial drug resistance



# Antimalarial drug efficacy monitoring

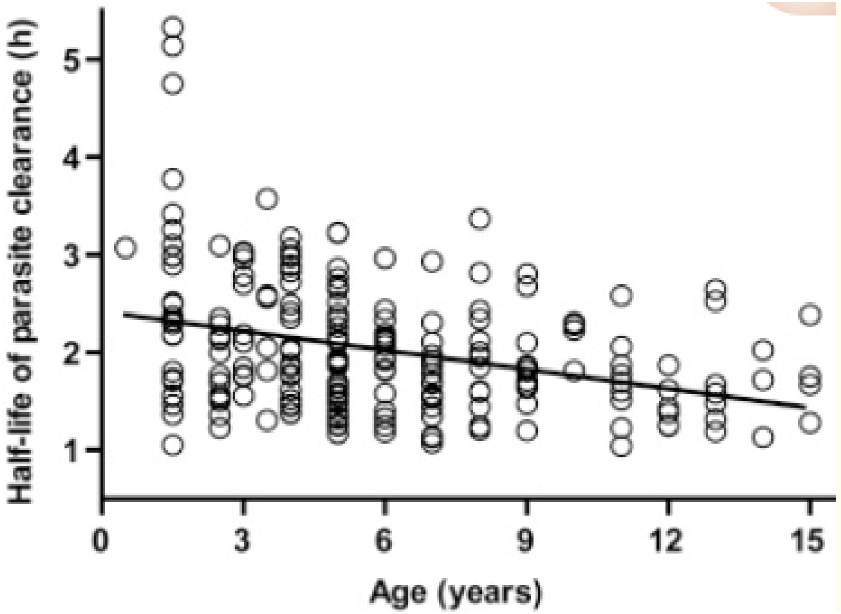
**Gold standard**

| | In vivo trials | In vitro/ex vivo assays | Molecular markers |
|---|---|---|---|
| **Advantages** | • The gold standard for measuring clinical efficacy<br>• No technical expertise needed<br>• No special equipment or expensive reagents required<br>• Guiding treatment policy change<br>• Availability of WHO standardized protocols | • Reflecting true or intrinsic resistance<br>• Not affected by host confounding factors, including immunity<br>• Not affected by drug pharmacokinetics<br>• Valuable for investigating candidate drugs<br>• Helpful for characterizing resistance | • Detecting resistance before becoming clinically evident<br>• Suitable for surveillance purposes<br>• Not affected by host confounding factors, including immunity<br>• Not affected by drug pharmacokinetics<br>• Easy collection, storage and transport of blood samples on filter papers |
| **Drawbacks** | • Misclassification of recurrent parasitemia<br>• Effect of immunity and drug pharmacokinetics on outcome<br>• Difficulties in selecting the suitable cohort of patients<br>• Need for correction by genotyping | • Not always correlated with in vivo results<br>• High technicality and expertise required<br>• Labor-intensive and requiring culture-sensitive conditions<br>• Hazardous in case of isotopic assays<br>• Lack of standardization and reproducibility | • Not always correlated with in vivo results<br>• High technicality and expertise required<br>• Lack of standardization |




Abdul-Ghani et al., Acta Trop. 2014;137:44-57

# Antimalarial drug resistance and immunity




Lopera Mesa et al., J. Infect. Dis. 2013;207(11):1655-63


J Infect Dis. 2009 Mar 1; 199(5): 758–765. PMID: 19199542
doi: 10.1086/596741


Author Manuscript

**Decreasing Efficacy of Antimalarial Combination Therapy in Uganda Explained by Decreasing Host Immunity Rather than Increasing Drug Resistance**


Bryan Greenhouse,[1] Madeline Slater,[1] Denise Njama-Meya,[2] Bridget Nzarubara,[2] Catherine Maiteki-Sebuguzi,[2] Tamara D. Clark,[1] Sarah G. Staedke,[3] Moses R. Kamya,[2] Alan Hubbard,[4] Philip J. Rosenthal,[1] and Grant Dorsey[1]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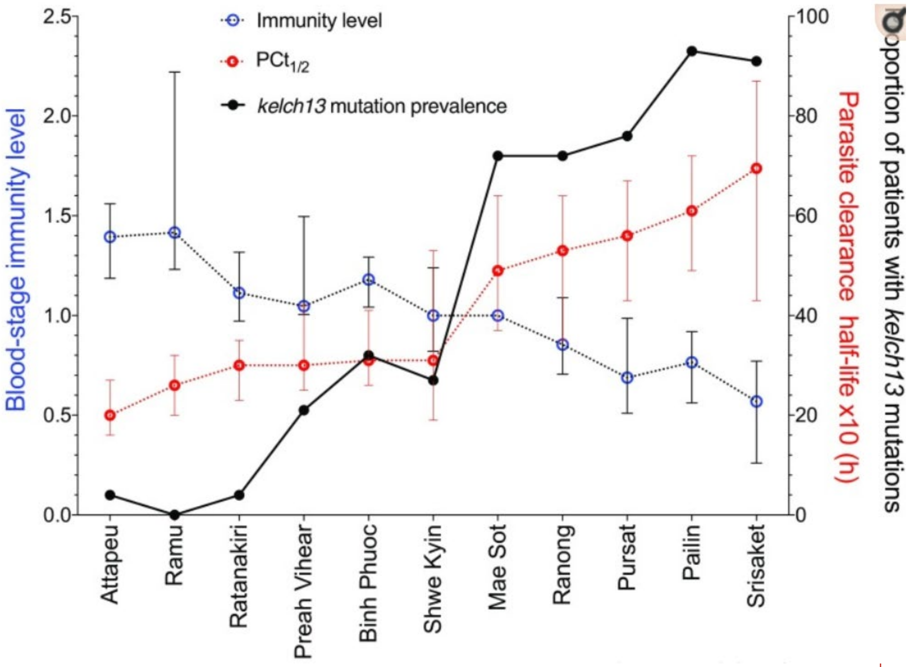
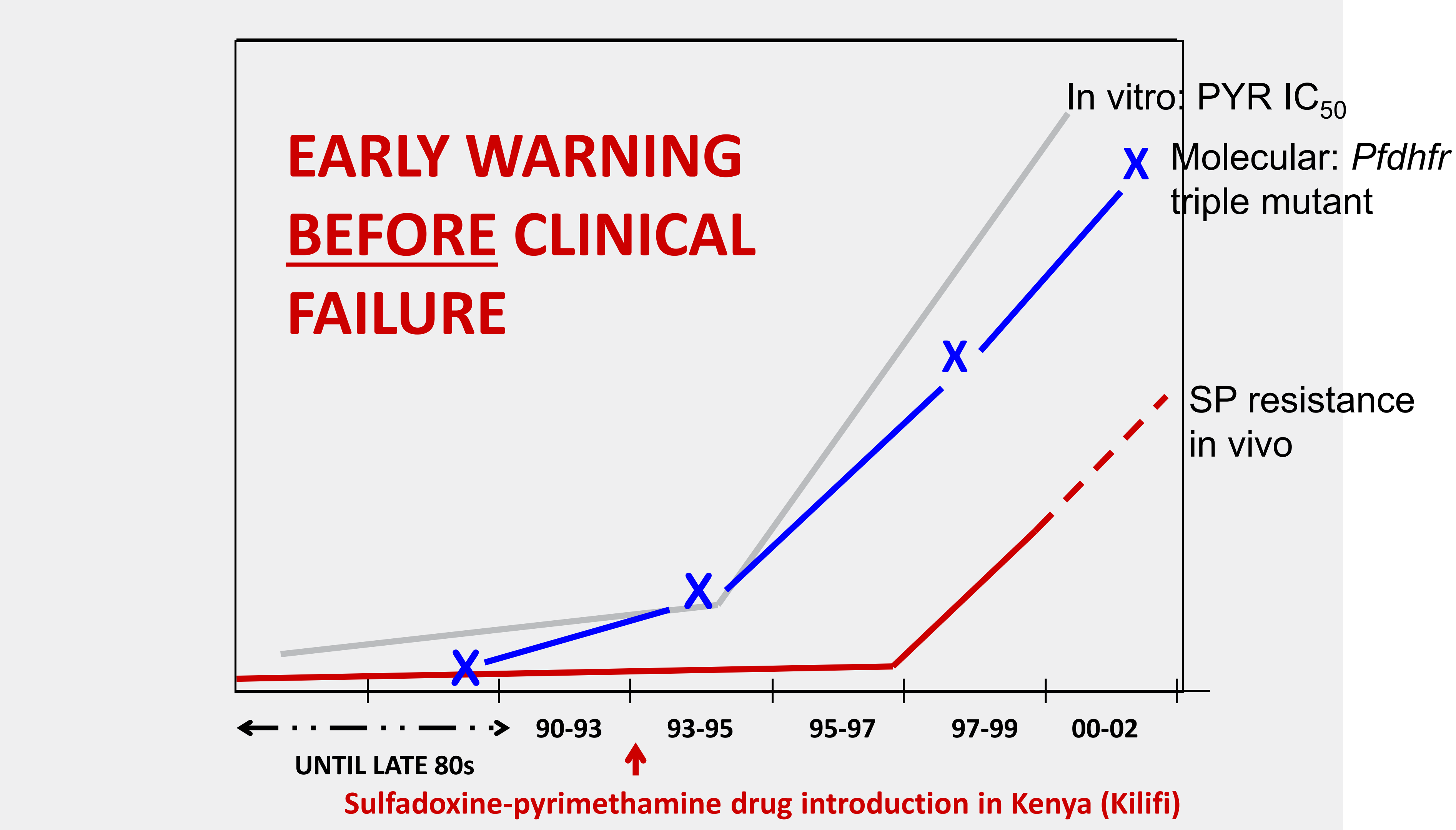



- Decreasing blood stage immunity associated with increasing PC1/2 and increasing prevalence of PfK13 mutations
- Naturally acquired immunity: confounding factor for drug efficacy
- Naturally acquired immunity accelerates parasites clearance after artesunate treatment
- Therapeutic efficacy studies in < 5 years old in high transmission settings

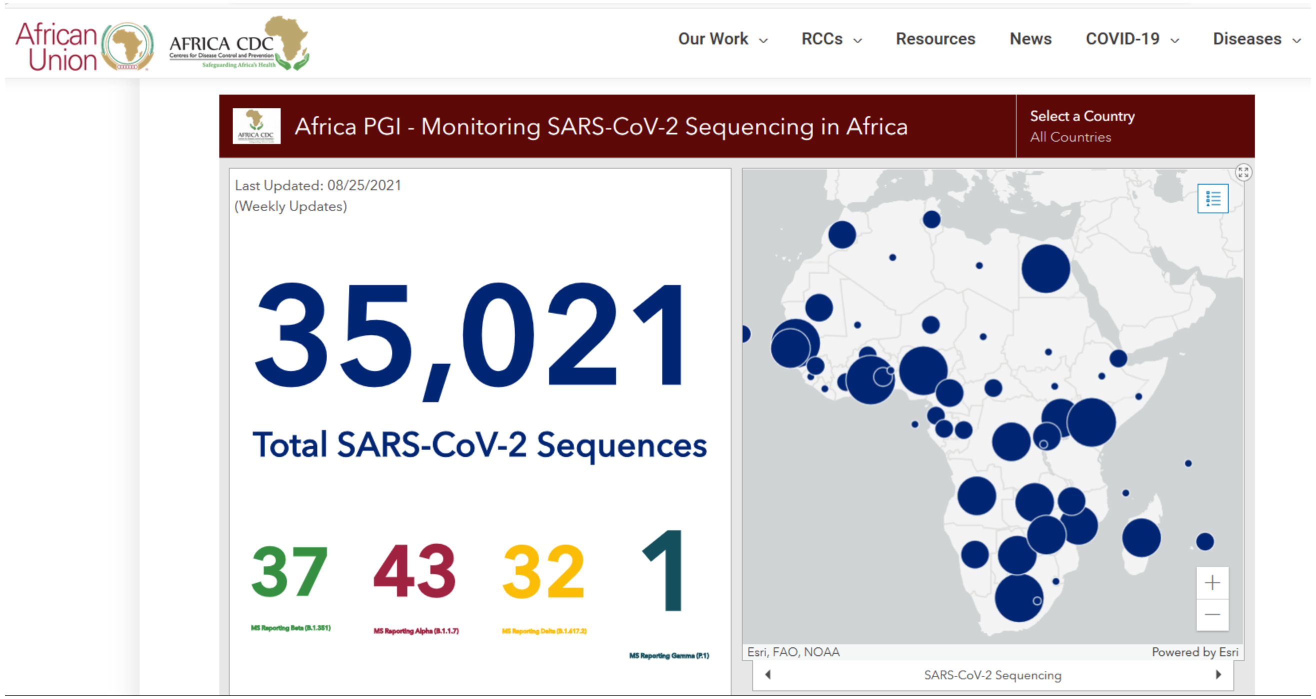
Ataide et al. Proc Natl Acad Sci U S A. 2017; 114(13): 3515–3520

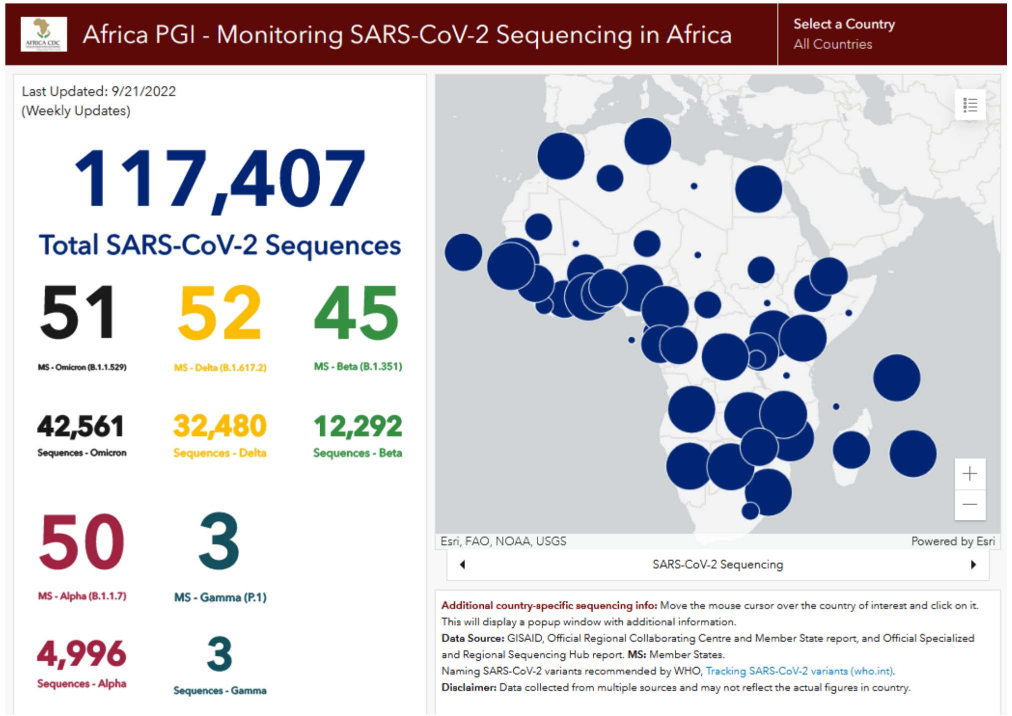
# Use of molecular markers of resistance for surveillance




Data from Alexis Nzila, Edward Mberu Kamau and Carol Sibley

# COVID-19 as an accelerator for molecular surveillance in Africa

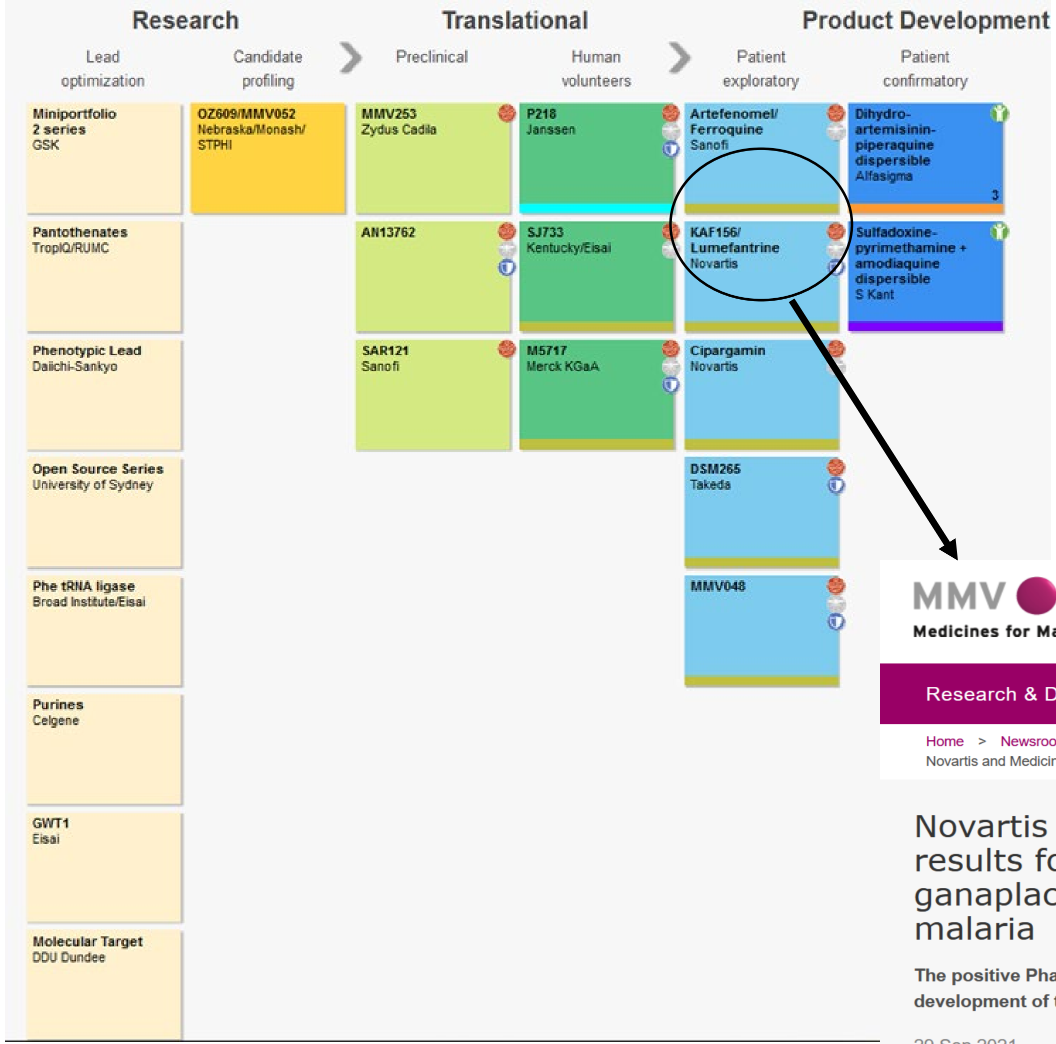



https://africacdc.org/institutes/ipg/ Accessed 31.08.2021

https://africacdc.org/institutes/ipg/ Accessed 26.09.2022

# Antimalarial drugs pipeline

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Novartis and Medicines for Malaria Venture report positive results for Phase IIb study of novel ganaplacide/lumefantrine combination in children with malar

## Novartis and Medicines for Malaria Venture report positive results for Phase IIb study of novel ganaplacide/lumefantrine combination in children with malaria

**The positive Phase IIb results for the next generation antimalarial therapy support continued development of the combination**

29 Sep 2021

https://www.mmv.org/research-development/mmv-supported-projects

# Thanks for your attention!