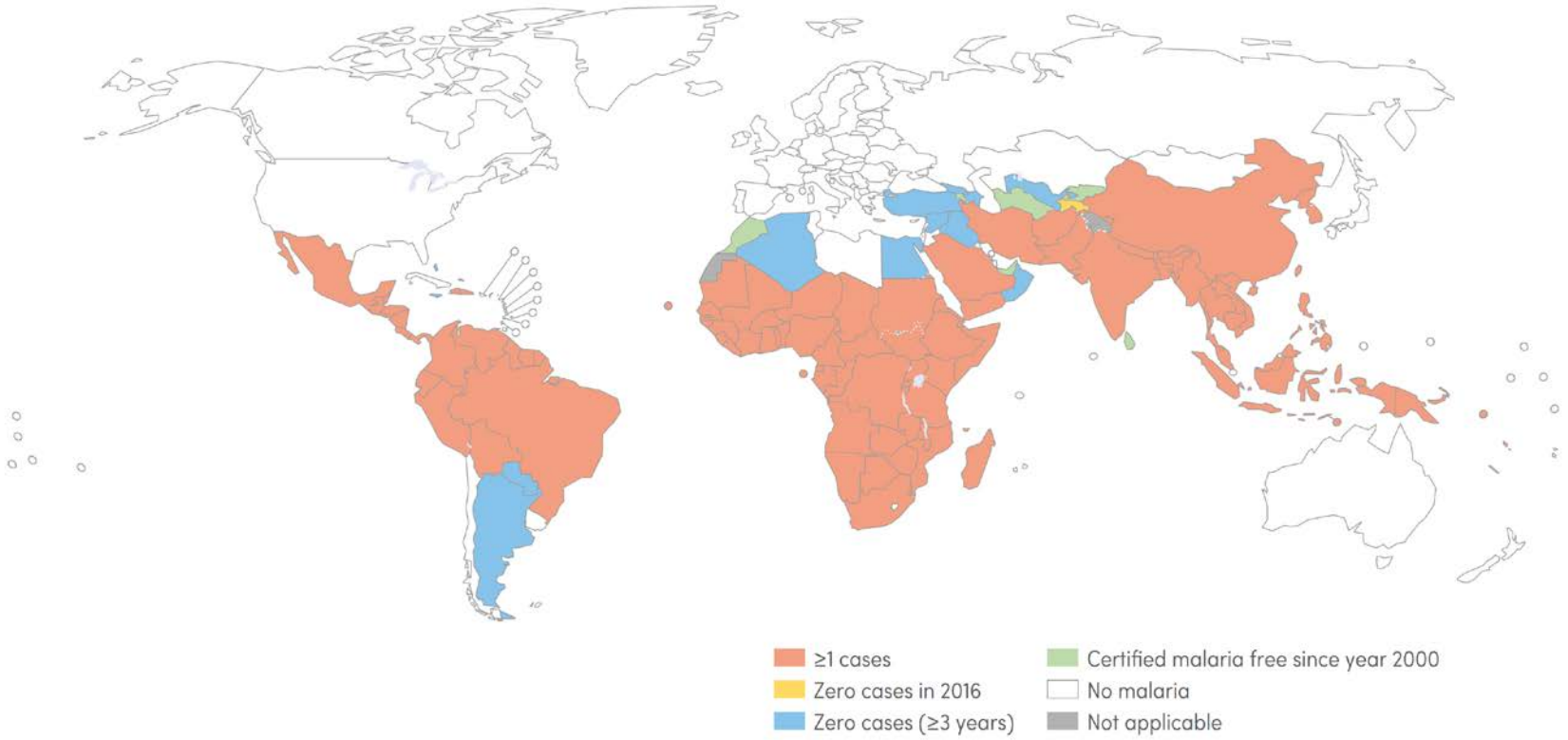
Antimalarial Drug Resistance

Professor PL Chiodini

WHO World Malaria Report 2017

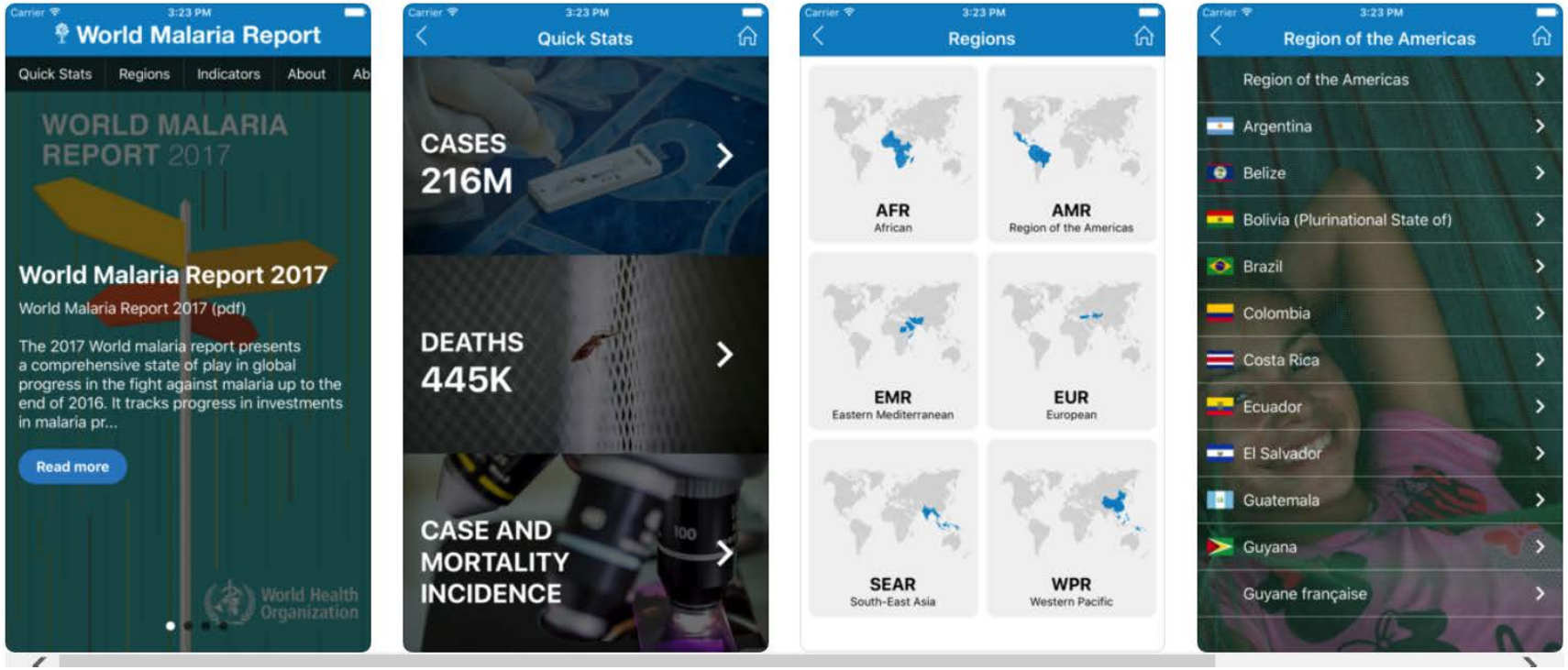


WHO World Malaria Report 2017

- 216 million reported cases in 2016
  - Increased by 5 million from 2015
- 445,000 deaths
- Malaria case incidence has fallen since 2010
  - But rate of decline has stalled/reversed since 2014

World Malaria Report app

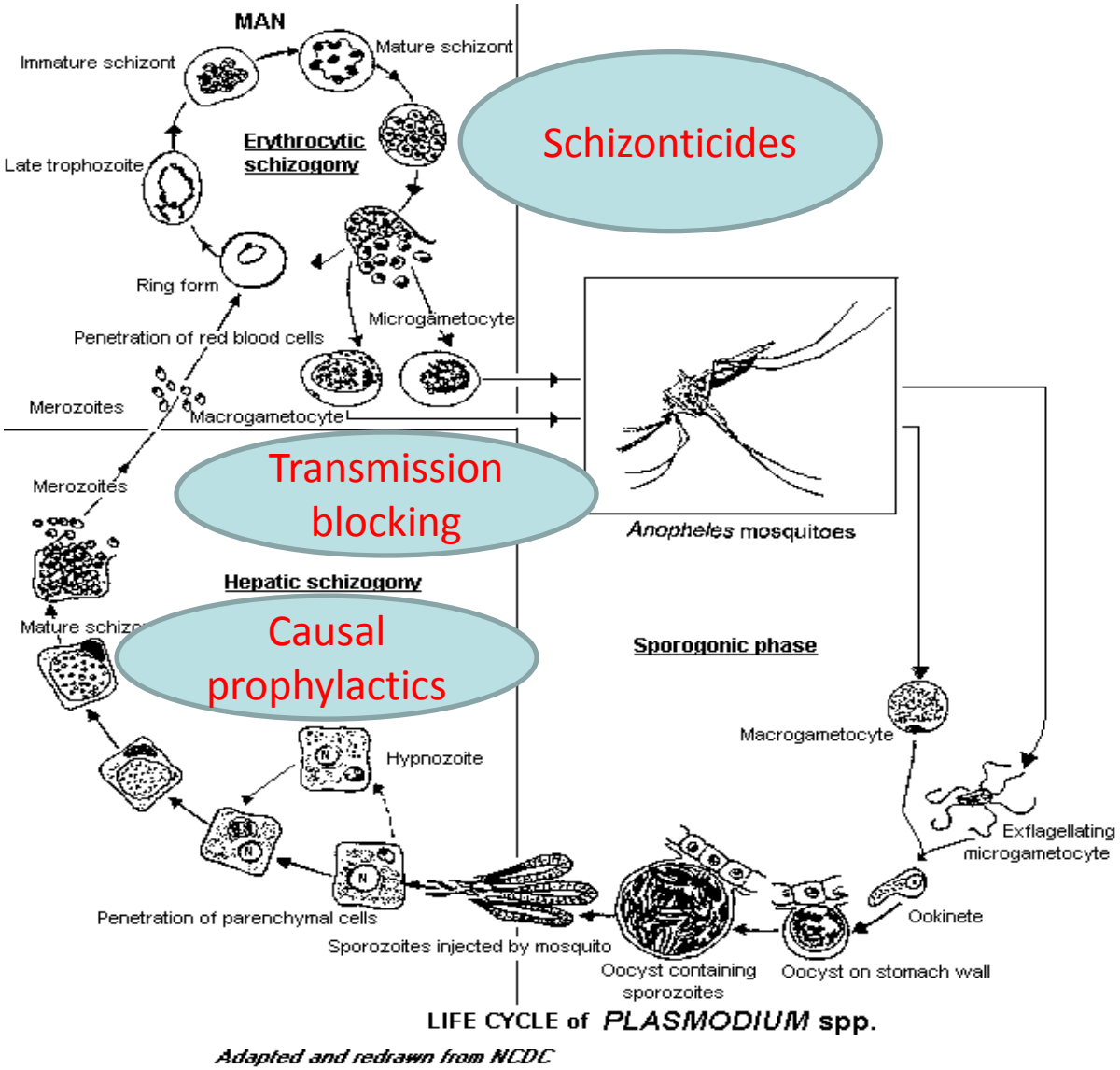
Launched January 2018



Plasmodium spp

Kirchner *et al. Genome Medicine* 2016; 8: 92

- Eukaryotes
- Sexual and asexual reproduction
- Genome
  - 14 linear chromosomes
  - Aggregate size c 22 megabases
  - >5000 protein-encoding genes



Sites of drug action

A brief history of antimalarial chemotherapy

Quinine

- Ancient fever remedy
- Peruvian bark
- To Europe in the mid 17th Century
- Mainstay of Rx until 20th Century

Synthetic antimalarials

- Pamaquine (8-aminoquinoline) 1920s
- Mepacrine [quinacrine] (Atabrine™) 1930s
- **The 4-aminoquinolines**
  - Chloroquine 1930s and 1940s
  - Amodiaquine 1948
- **The antifolates**
  - SP (sulfadoxine-pyrimethamine) 1970s and 1980s

Synthetic antimalarials

- Mefloquine 1970s and 1980s
- Halofantrine 1970s
- Atovaquone-proguanil 2000

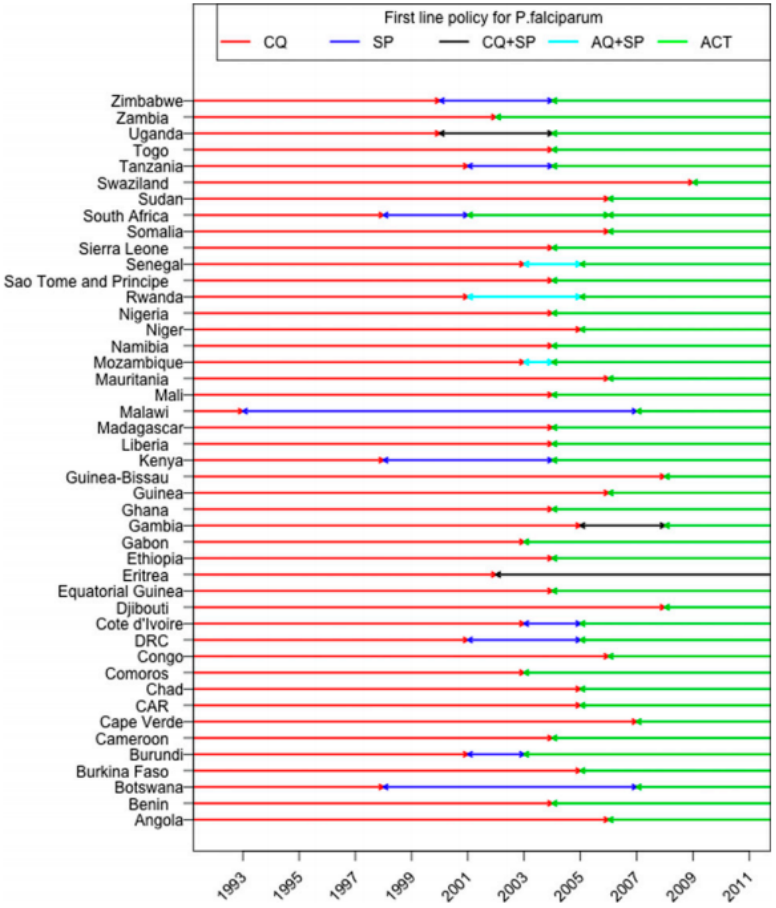
The relentless progression of antimalarial drug resistance

- Chloroquine resistance
  - Arose in Thailand 1957; Colombia 1959
  - Spread through SE Asia and India
  - Reached East Africa from Asia 1978
  - Almost all falciparum areas by end of the 1980s

The relentless progression of antimalarial drug resistance

- SP resistance
  - Triple mutation in dihydrofolate reductase gene
    - 51, 59 and 108
  - Also arose and spread from South East Asia
  - Dihydropteroate synthetase
    - 540 E correlates with trends in SP efficacy

Flegg *et al*. *Am J Trop Med Hyg*. 2013; 89 (5): 857-865



Flegg *et al*. *Am J Trop Med Hyg*. 2013; 89 (5): 857-865

Countries recommending SP for which SP usage estimates are available, year of policy changes, and estimated *dhps*540E prevalence*

	National policy change to SP			National policy change to ACT		
Country	Year	SP use (estimated %)	*dhps*540E prevalence (estimated %)	Year	SP use (estimated %)	*dhps*540E prevalence (estimated %)
Malawi	1993	58	46	2007	13	96
Kenya	1998	41	31	2004	9	91
Zimbabwe	2000	< 1	14	2004	1	26
Burundi	2001	2	41	2003	2	68
DRC	2001	< 1	10	2005	2	33
Tanzania	2001	52	30	2004	23	71
Cote d'Ivoire	2003	2	2	2005	2	3

*The year of policy change to sulphadoxine-pyrimethamine (SP) and later to artemisinin combination therapy (ACT) are both given, along with the estimated SP usage and *dhps*540E prevalence in each of these years. The countries are listed in order of the year of policy change to SP. DRC refers to the Democratic Republic of Congo.

Quinine resistance

Blasco *et al*. *Nature Medicine* 2017; 23(8): 917-928

- Still only partial
  - pfcrt
  - pfmdr1
  - Possibly also protein ubiquitination pathway

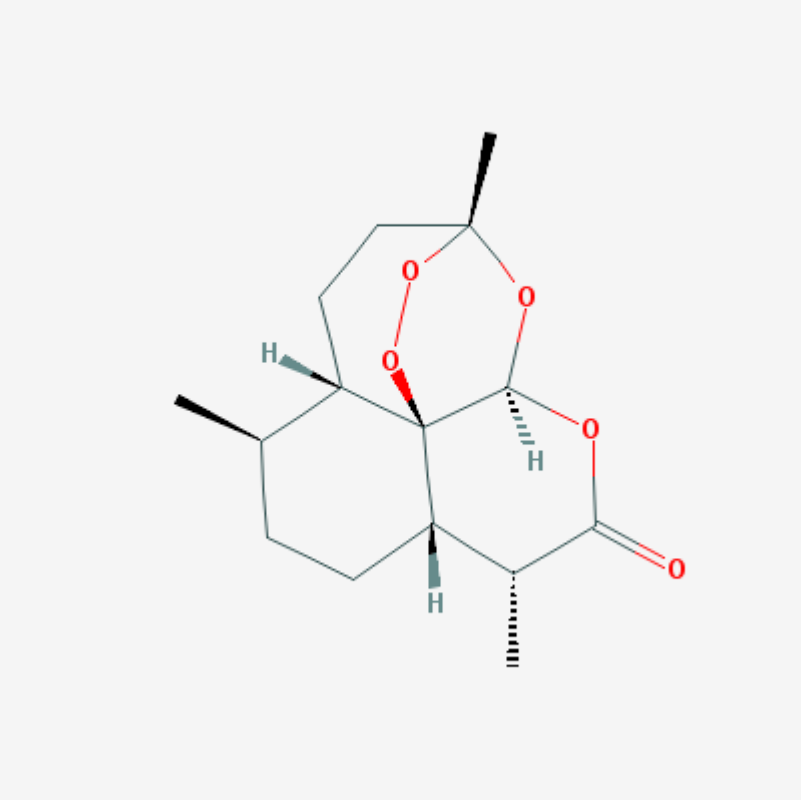
Artemisia annua

(qinghao or sweet wormwood)

in Oxford Botanic Garden ©

Artemisinin (a sesquiterpene lactone)

https://pubchem.ncbi.nlm.nih.gov/compound/artemisinin#section=Top



The power of the artemisinins

- Reduce parasite load by a factor of ~ 10,000 per asexual cycle

  White *et al. Clin Pharmacokinet* 1999; 37: 105-25

- Factor is 100 to 1,000 fold for most other antimalarials

  WHO 2006

See Kokwaro (2009) *Malaria Journal* 2009; 8: (Suppl 1):S2 for discussion

ACT (artemisinin combination therapy)

- Introduced in the mid 1990s
- WHO treatment of choice for uncomplicated falciparum malaria since 2006

ACT (artemisinin combination therapy)

- Artesunate-mefloquine
- Artesunate-sulfadoxine-pyrimethamine
- Artesunate-amodiaquine
- Artemether-lumefantrine
- Dihydroartemisinin-piperaquine
- Artesunate-pyronaridine

ACTs (artemisinin combination therapy)

But……

- From 2006 onwards
  - Reports of declining efficacy of artesunate monotherapy and also ACT in western Cambodia

Dondorp *et al. NEJM* 2009; 361: 455-467

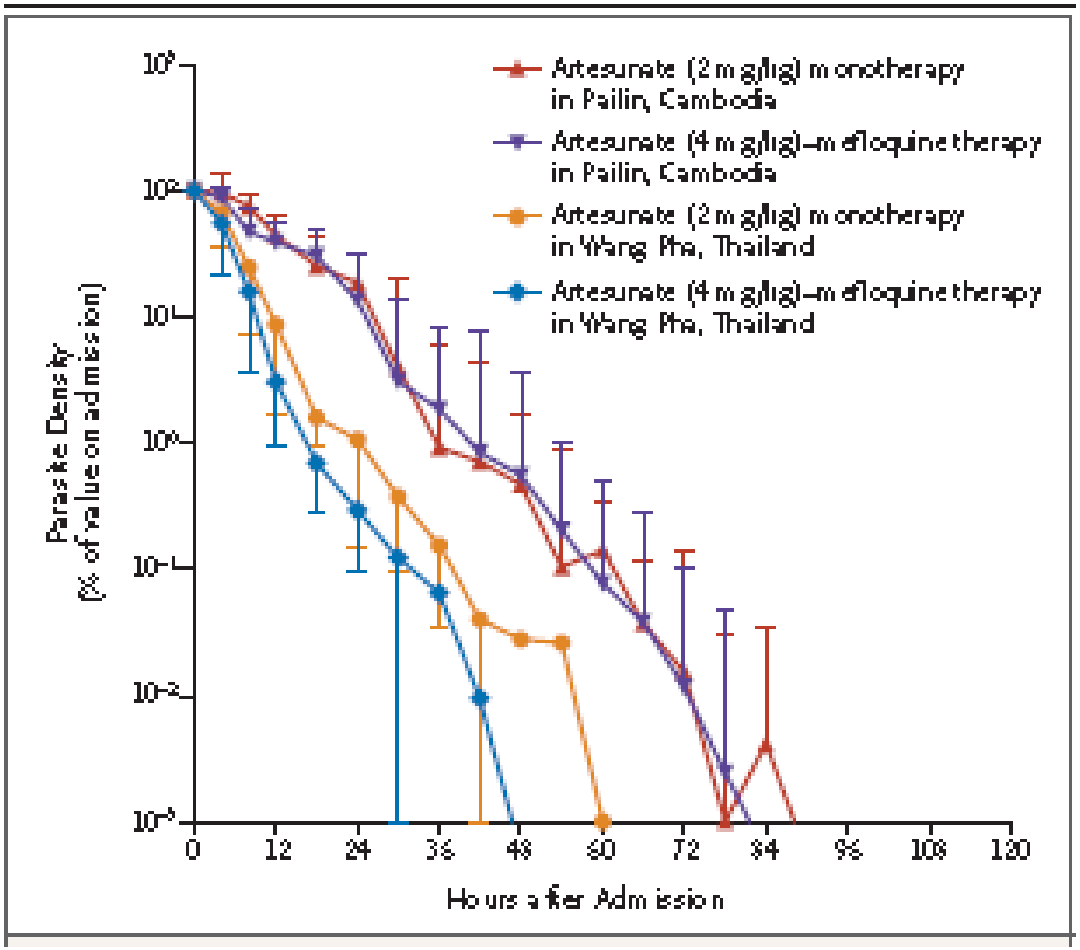
- Pailin, western Cambodia

  Artemisinins in use >30 years

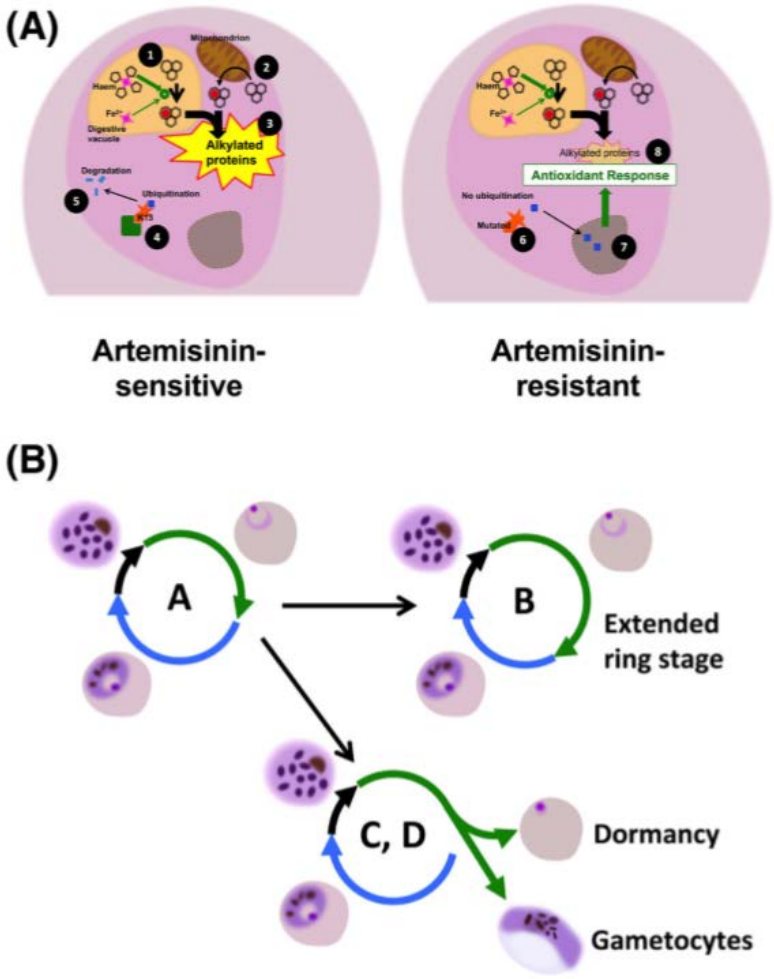
- Wang Pha, northwestern Thailand

  ACT in use since 1994

Dondorp *et al. NEJM* 2009; 361: 455-467



Woodrow & White. *FEMS Microbiology Reviews* 2017; 41: 34-48

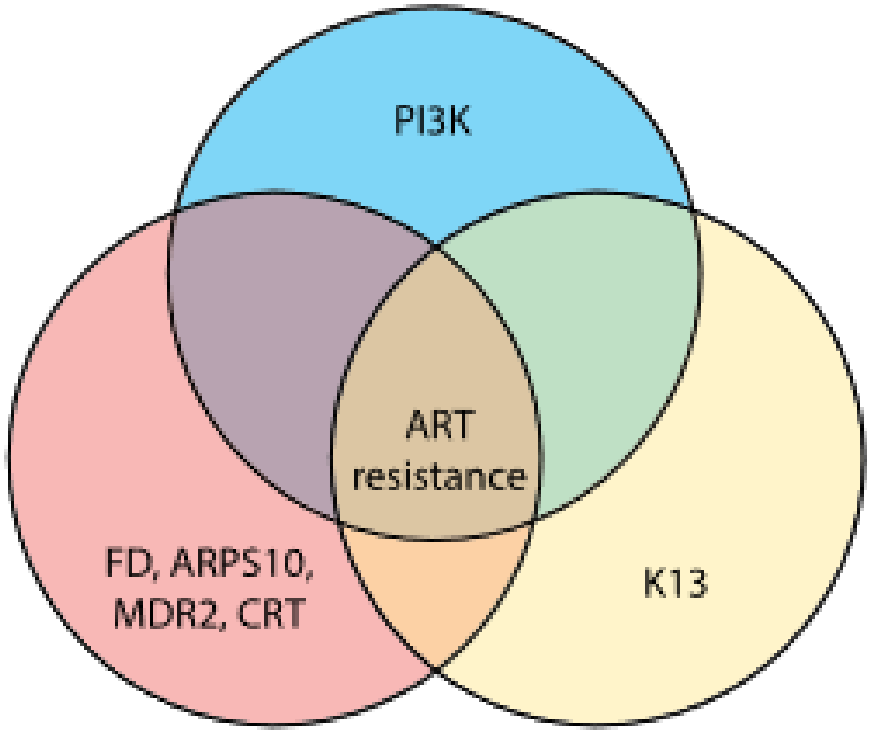


Artemisinin resistance

- Associated with mutation in the Kelch-like protein K13
  - Strong association between parasite clearance half-life >5h and single point mutations in K13
  - Multiple mutants, but C580Y mutation predominant
  - Likely due to improved fitness over other mutants

Kirchner *et al*. *Genome Medicine* 2016; 8:92

Genetic factors contributing to ART resistance



Possible promoters of artemisinin resistance in SE Asia

Woodrow & White. *FEMS Microbiology Reviews* 2017; 41: 34-48

- Drugs
  - Monotherapy
  - Fake or substandard
  - Incomplete course
  - Dosing regimen (either component)
- The parasite
  - Resistant to partner drug
  - Hyperparasitaemia
  - Genetic background
- Low transmission
  - Lower immunity
  - Single clone infections
  - Higher proportion symptomatic
- Host factors
  - Nutritional state
  - Immunosuppression

Partner drugs

- Increasing prevalence of K13 mutants means more and more parasites are exposed to the partner drug acting alone
- Partner drug resistance and treatment failure will select for higher levels of artemisinin resistance

Resistance to partner drugs

Blasco *et al*. *Nature Medicine* 2017; 23(8): 917-928

- *pfcrt*
  - Digestive vacuole membrane protein
  - Chloroquine selected for mutants, especially K76T
  - Active H+ dependent CQ efflux from digestive vacuole
  - Other antimalarials also affected via altering local concentration at site of action
  - Cambodian strains have Cam734; CQ resistance with no fitness cost

Resistance to partner drugs

Blasco *et al*. *Nature Medicine* 2017; 23(8): 917-928

- *pfmdr1*
  - An ATP-binding cassette transporter
  - Affects many antimalarials
  - Mefloquine and lumefantrine both select for increased copy number
  - N86Y can augment CQ resistance due to mutant *pfcrt*
  - Many new mutants since ACTs introduced

Chloroquine resistance in non-falciparum malaria

- *Plasmodium malariae*
- *& Plasmodium ovale*
  - AMR currently not a public health problem
    - Siswantoro *et al. AAC* 2011. 55: 197-202

Chloroquine resistance in *Plasmodium vivax* malaria (WWARN)

Other ways to use existing drugs

- Longer courses of ACT?
- Multiple first line therapies?
- Single dose primaquine

Other ways to use existing drugs

- Combination therapy
  - Trials underway for

    Artemether-lumefantrine-amodiaquine

    Dihydroartemisinin-piperaquine-mefloquine

Before it is too late….

Eliminate malaria in artemisinin resistance-affected areas before resistance can become locally more severe or spread further

Elimination Strategy for the Greater Mekong Sub-region

Dondorp *et al. Trends in Parasitology* 2017; 33: 353-363

- Community-based
  - Primary Health Care
    - VMW; VHW; Private Sector
- Surveillance
  - Mobile phones
  - Dried blood spots on filter paper

Elimination Strategy for the Greater Mekong Sub-region

Dondorp *et al. Trends in Parasitology* 2017; 33: 353-363

- Early effective treatment
  - ACTs plus gametocytocidal dose of primaquine
  - Drug rotation but difficult to administer
  - Trials of triple agent ACTs
  - 5 or 7 day ACT regimens
  - Sequential Rx with 2 different ACTs

Elimination Strategy for the Greater Mekong Sub-region

Dondorp *et al. Trends in Parasitology* 2017; 33: 353-363

- Vector control
  - Insecticide-treated bed nets
    - But in GMS 60% of infected bites occur before bed time
  - Indoor residual spraying
    - But outdoor biting
    - Architecture of rural homes

Elimination Strategy for the Greater Mekong Sub-region

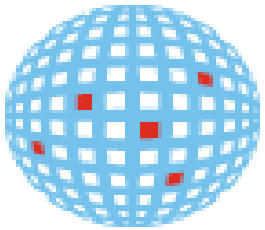
Dondorp *et al. Trends in Parasitology* 2017; 33: 353-363

- Asymptomatic parasite carriers
  - Targeted mass drug administration
    - With the addition of ivermectin?
  - Mass screening and treatment
    - High-throughput LAMP?
    - Ultrasensitive HRP2-based RDT?

Elimination Strategy for the Greater Mekong Sub-region

Dondorp *et al. Trends in Parasitology* 2017; 33: 353-363

- Case and focus investigation and response?
  - Less applicable to GMS
  - Target individuals co-exposed with index case?
- Vaccination?
  - In combination with other measures
- Chemoprophylaxis of high-risk groups?
  - Eg forest workers



WWARN

WorldWide Antimalarial Resistance Network

Clinical Module

Clinical responses of malaria patients treated with various drugs

Pharmacology Module

Precise antimalarial drug concentrations and pharmacokinetic parameters for key target populations

In vitro Module

In vitro drug susceptibility results from malaria parasites collected from infected patients

Molecular Module

Molecular markers for drug resistance in malaria parasites

What is in the pipeline?

https://www.mmv.org/

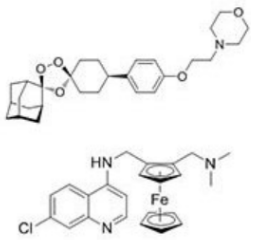
Artefenomel (synthetic peroxide)-Ferroquine (3rd generation 4-AQ)

https://www.mmv.org/

Artefenomel/ FQ

Sanofi

Legend



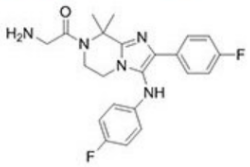
Product vision	• Novel agents in combination for treatment including resistant strains; single-dose potential
MoA	• Artefenomel (OZ439): novel, synthetic trioxolane • Ferroquine (FQ): inhibition of heme detoxification
Key features	Artefenomel • Fast killing of parasites • Active against artemisinin-resistant parasites • 800mg human dose stays above Minimal Parasiticidal Concentration for >8 days • Transmission-blocking activity in a Standard Membrane Feeding Assay Ferroquine • Long duration of plasma exposure • Active against chloroquine, mefloquine and piperaquine-resistant *P. falciparum*
Challenges	• OZ439 food effect/formulation
Status	• Phase IIb combination study ongoing
Next milestone	• Phase IIb study completion in 2019
Previously	• OZ439: discovery partnership with Monash University, University of Nebraska and Swiss Tropical Institute • Ferroquine discovered by CNRS Lille
MMV Project Director	• Dr Florian Wartha (interim)

Imidazolopiperazines:
KAF156 targets liver, asexual blood stages and gametocytes
https://www.mmv.org/

KAF156/ Lumefantrine

Novartis

Legend

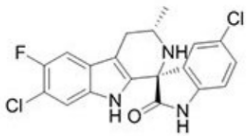


Product vision	• Novel agents in combination for treatment including resistant strains; single-dose potential
MoA	• Not yet determined. Decreased susceptibility to KAF156 is associated with mutations in three *P. falciparum* genes, *CARL* (cyclic amine resistance locus), UDP-galactose and Acetyl-CoA transporters
Key features	KAF156 • Novel mechanism of action – activity against parasites that are resistant to current drugs • Rapid killing of parasites (PCT<48 hours) • 800mg human dose stays above Minimal Parasiticidal Concentration for >8 days Lumefantrine • New once-daily formulation • Transmission-blocking activity in a Standard Membrane Feeding Assay
Status	• Phase IIb combination study ongoing
Next milestone	• Phase IIb study completion in 2019
Previously	• Previous name: GNF156. Discovery partnership with Novartis and STPHI
MMV Project Director	• Dr Florian Wartha (interim)

Spiroindolones: KAE609, Cipargamin
Upsets parasite sodium homeostasis; very rapid clearance
https://www.mmv.org/

Cipargamin
Novartis

Legend



Product vision	• Part of single-exposure radical cure • Potential for use in severe malaria
MoA	• *Pf*ATP4 inhibitor
Key features	• First validated new molecular target in 20 years; very rapid killing of parasites • 75mg human dose stays above Minimal Parasiticidal Concentration for >8 days • Potential for transmission-blocking activitiy in a Standard Membrane Feeding Assay
Challenges	• Safety profile to be further characterized in malaria patient study
Status	• Completed first phase IIa (short-duration monotherapy PoC in patients) • Phase II study in patients started in February 2018
Next milestone	• Phase II study completion in 2019/20
Previously	• Names NITD609, KAE609: discovery partnership with Novartis and STPHI
MMV Project Director	• Dr Wiweka Kaszubska (interim)

Inhibitors of dihydroorotate dehydrogenase in mitochondrion: DSM265 acts against liver and blood stage schizonts

https://www.mmv.org/

DSM265

Takeda

Legend

Product vision	• Part of a single-exposure radical cure • Potential for chemoprotection
MoA	• Plasmodial dihydroorotate dehydrogenase (DHODH) inhibitor
Key features	• Novel mechanism of action • 400mg human dose gives concentrations above Minimal Parasiticidal Concentration for >8 days
Challenges	• Cost of goods for API and formulation • Reduced relative activity against *P. vivax* • Single enzyme target; potential for resistance
Status	• Phase IIa in Peru in patients with *P. falciparum* or *P. vivax* malaria completed • Controlled Human Malaria Infection Study of combination with OZ439 completed
Next milestone	• Confirm suitability of new formulation
Previously	• Discovery partnership with University of Texas Southwestern, Washington University and Monash University
MMV Project Director	• Dr Jörg Möhrle

Inhibitors of *Pf*PI4K (phosphatidylinositol 4-kinase)
https://www.mmv.org/

MMV048

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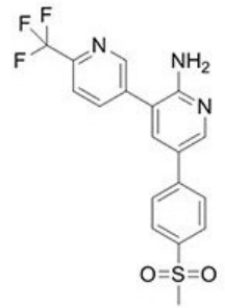

Product vision	• Part of a single-exposure radical cure • Potential for chemoprotection
MoA	• *Pf*PI4K inhibitor
Key features	• 80mg dose predicted to give coverage above Minimal Parasiticidal Concentration for ≥8 days • Good prophylactic activity against *P. cynomolgi*, *in vivo* after single dose • Long half-life in human • Potential for transmission-blocking activity in a Standard Membrane Feeding Assay
Challenges	• Preclinical safety limiting further dose escalation in patients
Status	• Phase I and human volunteer challenge model completed (including with new formulation) • FPFV Phase IIa in Ethiopia (end 2017)
Next milestone	• De-risk safety margin in preclinical species to allow further dose escalation in patients
Previously	• Name MMV390048: Discovery and Phase I partnership with H3D, University of Cape Town
MMV Project Director	• Dr Cristina Donini

“Malaria response at a cross-roads”

“The choice before us is clear. If we continue with a “business as usual” approach – employing the same level of resources and the same interventions – we will face near-certain increases in malaria cases and deaths.”

Dr Tedros Adhanom Ghebreyesus

Director-General, World Health Organization

http://www.thehtd.org/