Yale SCHOOL OF PUBLIC HEALTH

Epidemiology of Microbial Diseases

Optimizing malaria treatment and prevention to maximize efficacy and…. limit resistance

Kainomyx Frontiers Seminar

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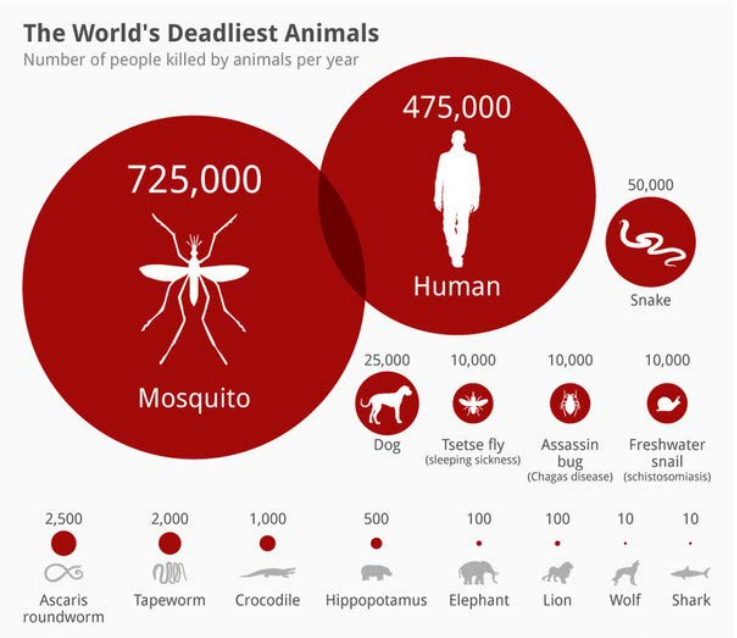
Why study malaria?

Vector-borne diseases exact a huge toll on humans globally



Malaria is responsible for a large % of DALYs in Africa (purple)

	1	2	3	4	5	6	7	8	9	10
Sub-Saharan Africa	HIV/AIDS	Malaria	LRI	Diarrhoea	NN preterm	PEM	NN enceph	Congenital	TB	Road inj
Central sub-Saharan Africa	LRI	Diarrhoea	Malaria	PEM	HIV/AIDS	NN preterm	Congenital	TB	NN enceph	Meningitis
Angola	LRI	Diarrhoea	HIV/AIDS	Malaria	Congenital	PEM	NN preterm	TB	NN enceph	Road inj
Central African Republic	HIV/AIDS	LRI	Diarrhoea	Malaria	TB	NN preterm	PEM	STD	Meningitis	NN enceph
Congo	HIV/AIDS	LRI	Malaria	Congenital	Stroke	Diarrhoea	NN preterm	NN enceph	Measles	TB
Democratic Republic of the Congo	Diarrhoea	LRI	Malaria	PEM	NN preterm	HIV/AIDS	Congenital	TB	NN enceph	Iron
Equatorial Guinea	HIV/AIDS	LRI	Malaria	Congenital	Road inj	Diarrhoea	Stroke	NN preterm	PEM	NN enceph
Gabon	HIV/AIDS	LRI	Malaria	Stroke	Road inj	Congenital	TB	Diarrhoea	IHD	NN enceph
Eastern sub-Saharan Africa	HIV/AIDS	LRI	Malaria	Diarrhoea	TB	NN preterm	NN enceph	PEM	NN sepsis	Congenital
Burundi	Malaria	LRI	Diarrhoea	TB	HIV/AIDS	NN preterm	PEM	NN enceph	NN sepsis	Congenital
Comoros	LRI	Diarrhoea	TB	NN preterm	Malaria	NN enceph	Stroke	NN sepsis	Road inj	Congenital
Djibouti	HIV/AIDS	LRI	Malaria	Diarrhoea	TB	Stroke	NN enceph	Depression	PEM	Congenital
Eritrea	Diarrhoea	LRI	TB	HIV/AIDS	Malaria	Iron	NN preterm	PEM	Depression	Meningitis
Ethiopia	LRI	Diarrhoea	HIV/AIDS	TB	NN preterm	NN enceph	Malaria	NN sepsis	Congenital	Meningitis
Kenya	HIV/AIDS	LRI	Diarrhoea	TB	NN preterm	Malaria	NN enceph	Congenital	PEM	NN sepsis
Madagascar	LRI	Diarrhoea	Stroke	NN preterm	PEM	Malaria	STD	Iron	Depression	Congenital
Malawi	HIV/AIDS	LRI	Diarrhoea	PEM	Malaria	TB	NN preterm	Congenital	NN enceph	Meningitis
Mauritius	Diabetes	IHD	Stroke	CKD	Back & neck	Sense	COPD	Road inj	Depression	LRI
Mozambique	HIV/AIDS	Malaria	LRI	Diarrhoea	TB	NN sepsis	NN enceph	NN preterm	STD	Road inj
Rwanda	HIV/AIDS	LRI	Malaria	Diarrhoea	NN preterm	War	NN enceph	Road inj	TB	NN sepsis
Seychelles	IHD	Stroke	LRI	Diabetes	Back & neck	HTN HD	Sense	COPD	Road inj	Depression
Somalia	Diarrhoea	LRI	Malaria	TB	PEM	Meningitis	NN preterm	NN enceph	Tetanus	Other NN
South Sudan	LRI	Diarrhoea	HIV/AIDS	TB	PEM	Meningitis	Malaria	STD	NN preterm	NN enceph
Tanzania	HIV/AIDS	LRI	Malaria	Diarrhoea	TB	Congenital	PEM	NN enceph	STD	NN preterm
Uganda	HIV/AIDS	Malaria	LRI	Diarrhoea	NN preterm	NN enceph	TB	NN sepsis	PEM	Road inj
Zambia	HIV/AIDS	Malaria	LRI	Diarrhoea	PEM	TB	NN enceph	Congenital	NN sepsis	Meningitis
Southern sub-Saharan Africa	HIV/AIDS	LRI	Diarrhoea	TB	Back & neck	Violence	NN preterm	Stroke	Diabetes	Road inj
Botswana	HIV/AIDS	TB	LRI	Diarrhoea	Back & neck	NN preterm	Road inj	Depression	Other NN	Self-harm
Lesotho	HIV/AIDS	TB	Diarrhoea	LRI	NN preterm	Violence	Other NN	NN enceph	Road inj	Self-harm
Namibia	HIV/AIDS	TB	LRI	Diarrhoea	Stroke	Self-harm	Road inj	NN preterm	Other NN	Back & neck
South Africa	HIV/AIDS	LRI	TB	Diarrhoea	Back & neck	Diabetes	Violence	Stroke	COPD	Road inj
Swaziland	HIV/AIDS	LRI	TB	Diarrhoea	Road inj	NN preterm	Other NN	Violence	Self-harm	Stroke
Zimbabwe	HIV/AIDS	LRI	Diarrhoea	TB	NN preterm	NN enceph	Stroke	PEM	Malaria	Road inj
Western sub-Saharan Africa	Malaria	LRI	HIV/AIDS	Diarrhoea	NN preterm	NN enceph	Haemog	Road inj	PEM	NN sepsis
Benin	Malaria	LRI	HIV/AIDS	Diarrhoea	NN preterm	NN enceph	Congenital	Iron	Road inj	NN sepsis
Burkina Faso	Malaria	LRI	Diarrhoea	NN preterm	Congenital	Meningitis	NN enceph	Road inj	HIV/AIDS	NN sepsis
Cameroon	HIV/AIDS	Malaria	LRI	Diarrhoea	Road inj	NN preterm	NN enceph	Congenital	PEM	NN sepsis
Cape Verde	Stroke	Back & neck	Depression	Congenital	IHD	LRI	Iron	COPD	Sense	Skin
Chad	Diarrhoea	LRI	Malaria	HIV/AIDS	PEM	NN preterm	Meningitis	NN enceph	Iron	Congenital
Côte d'Ivoire	LRI	HIV/AIDS	Malaria	Diarrhoea	NN preterm	NN enceph	Road inj	NN sepsis	Congenital	PEM
Ghana	Malaria	LRI	HIV/AIDS	NN sepsis	NN preterm	PEM	NN enceph	Stroke	Road inj	Iron
Guinea	Malaria	LRI	Diarrhoea	HIV/AIDS	NN preterm	NN enceph	PEM	NN sepsis	Meningitis	Road inj
Guinea-Bissau	Malaria	HIV/AIDS	LRI	Diarrhoea	NN preterm	PEM	NN enceph	Meningitis	Road inj	Congenital
Liberia	Malaria	LRI	Diarrhoea	HIV/AIDS	NN preterm	NN enceph	PEM	TB	NN sepsis	Congenital
Mali	Malaria	Diarrhoea	LRI	PEM	NN preterm	NN enceph	Iron	Meningitis	NN sepsis	Congenital
Mauritania	LRI	Malaria	Diarrhoea	NN enceph	NN preterm	Road inj	Congenital	Iron	NN sepsis	Stroke
Niger	Malaria	Diarrhoea	LRI	PEM	NN preterm	Meningitis	Iron	Congenital	NN enceph	NN sepsis

Malaria primarily affects the young, but risk continues lifelong

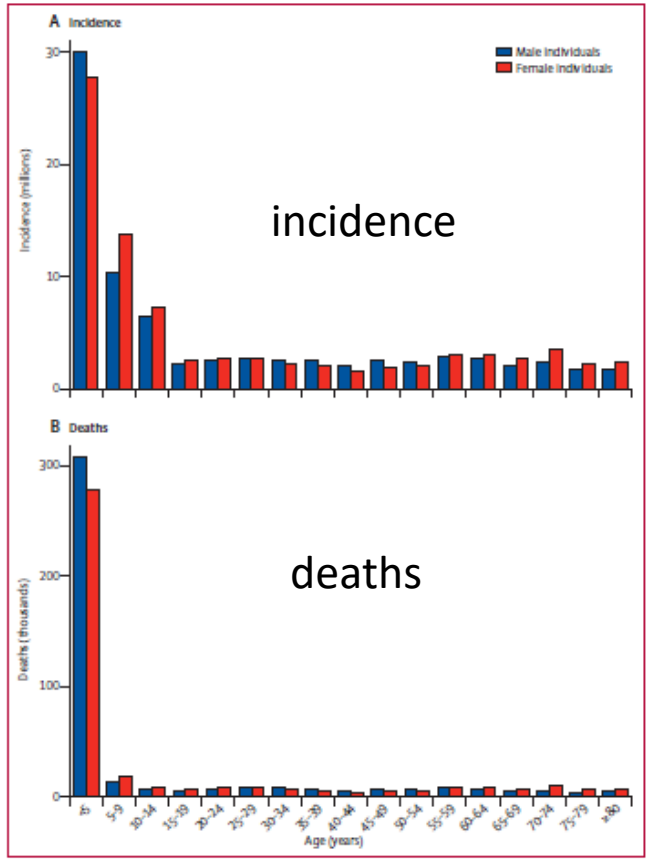
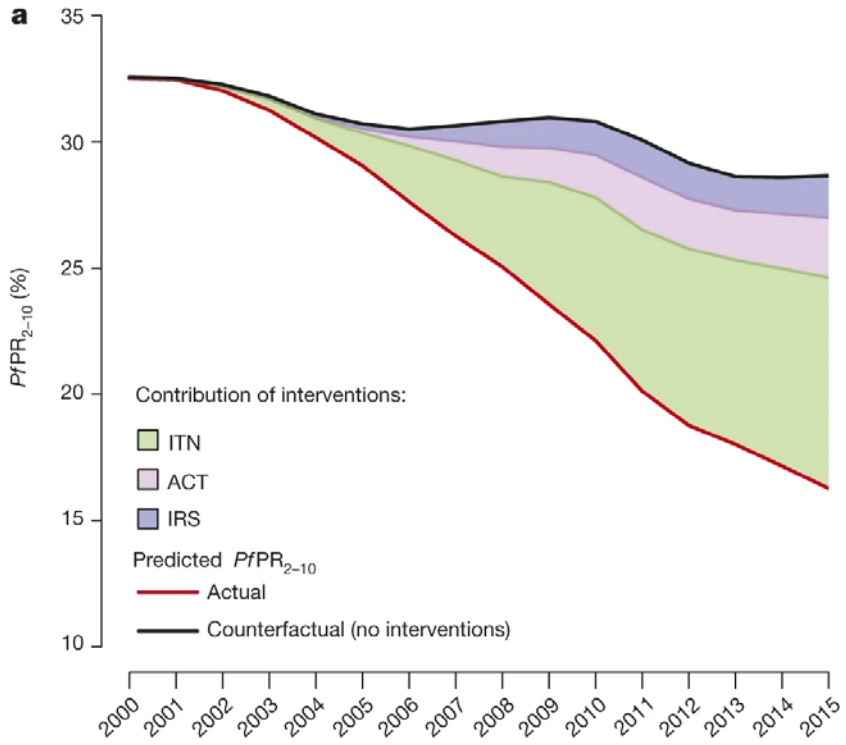
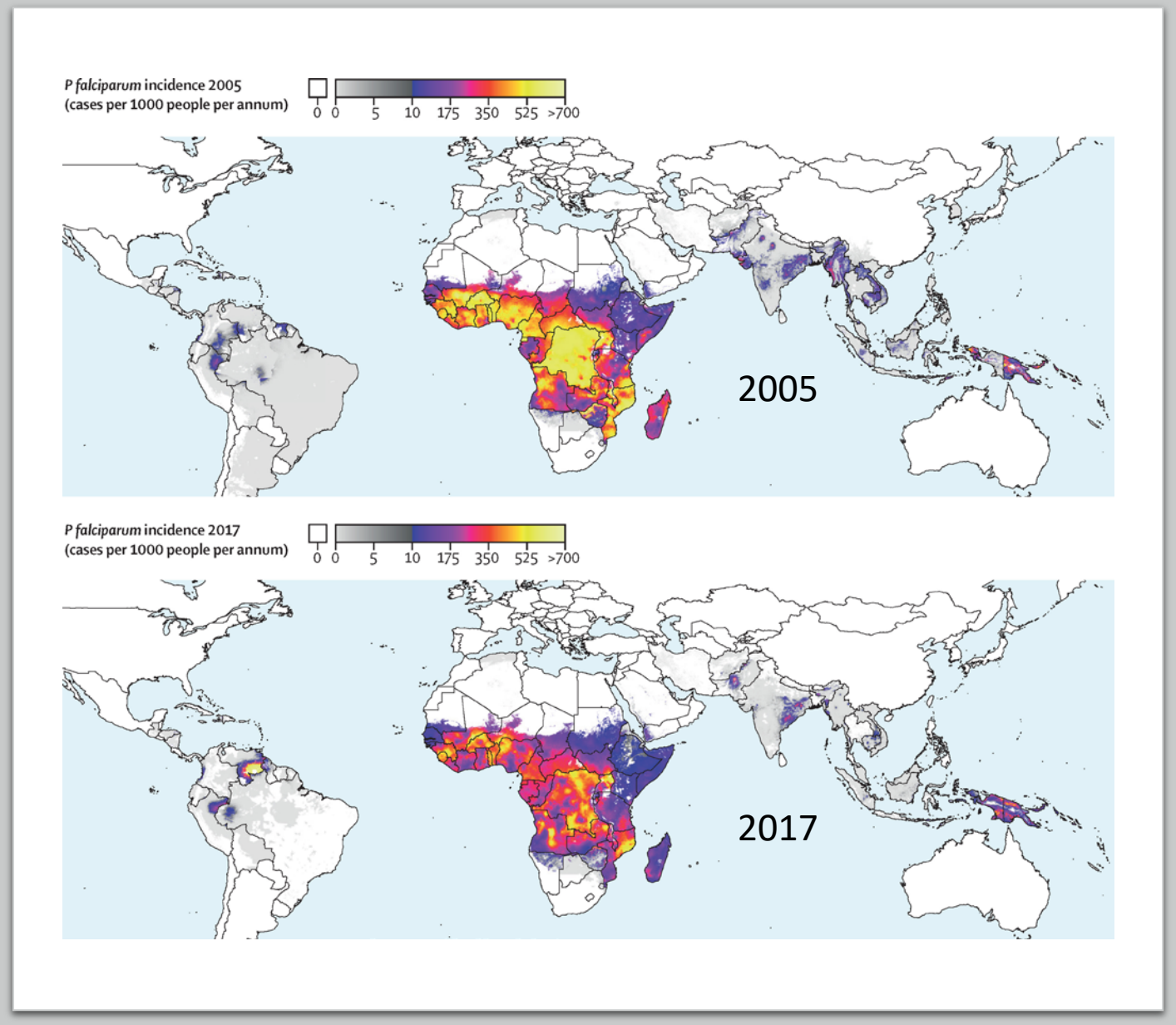


Figure 17: Global age-sex distribution of malaria incidence (A) and deaths (B) in 2013

Global Burden of Disease: Murray CJL, et al. *Lancet* 2013, 2014, and 2015

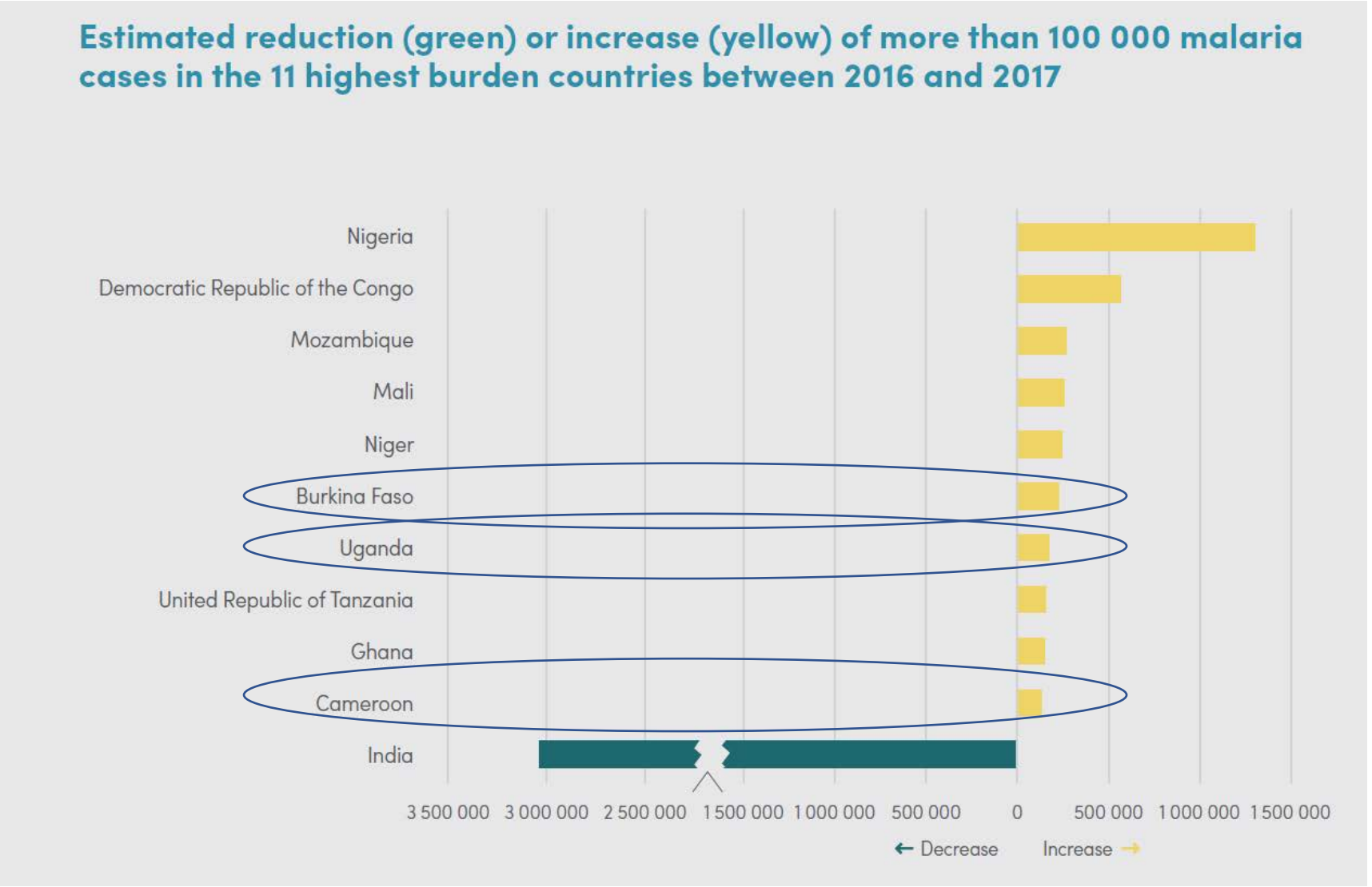
Substantial progress has been made in the past few decades





Bhatt S, et al. *Nature* 2015; Weiss DJ, et al. *Lancet* 2019

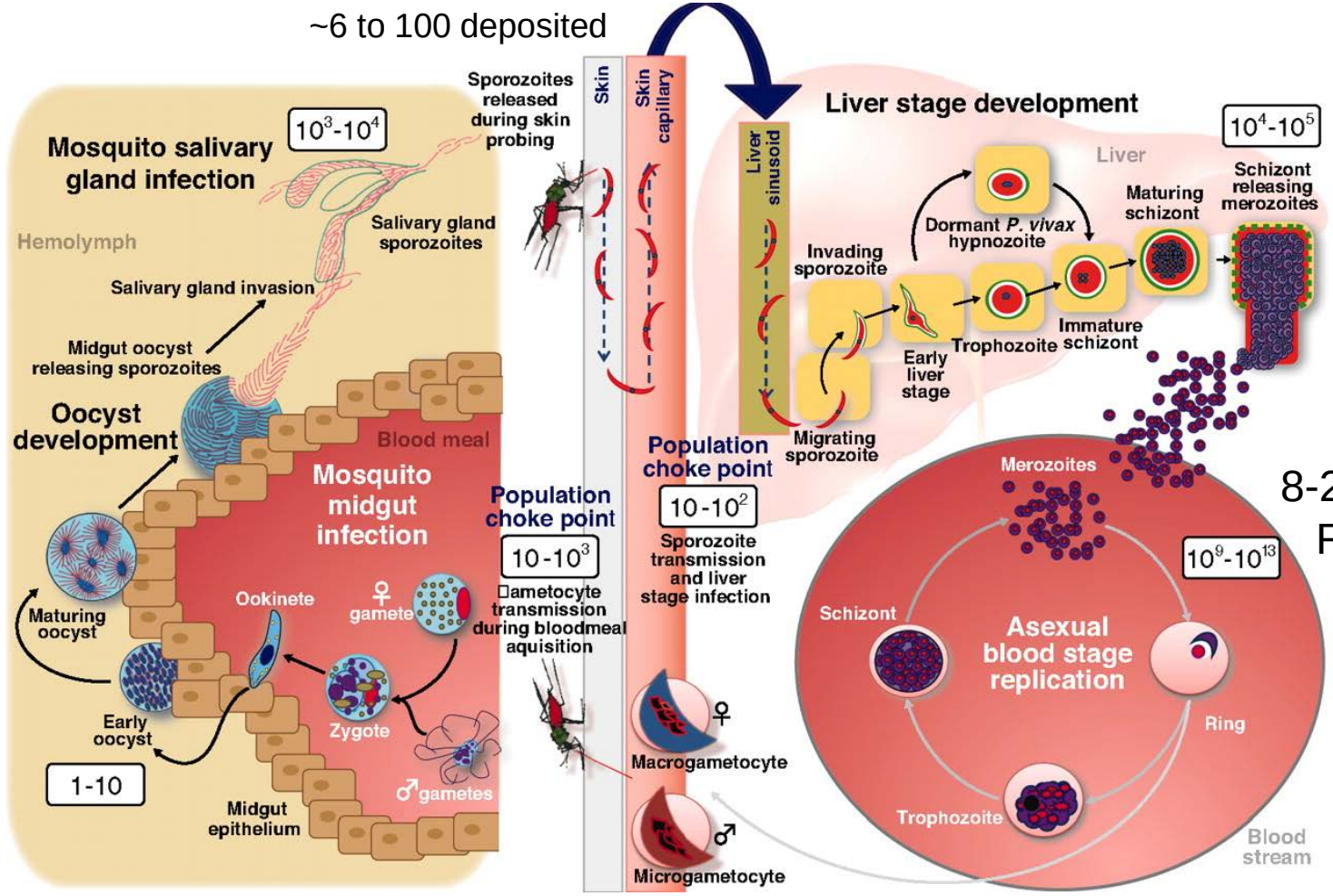
We work in 3 of the 10 highest burden countries, and which are spread across sub-Saharan Africa



WHO, “High Burden to High Impact: a Targeted Malaria Response” 2018

Tackling malaria is also a numbers game

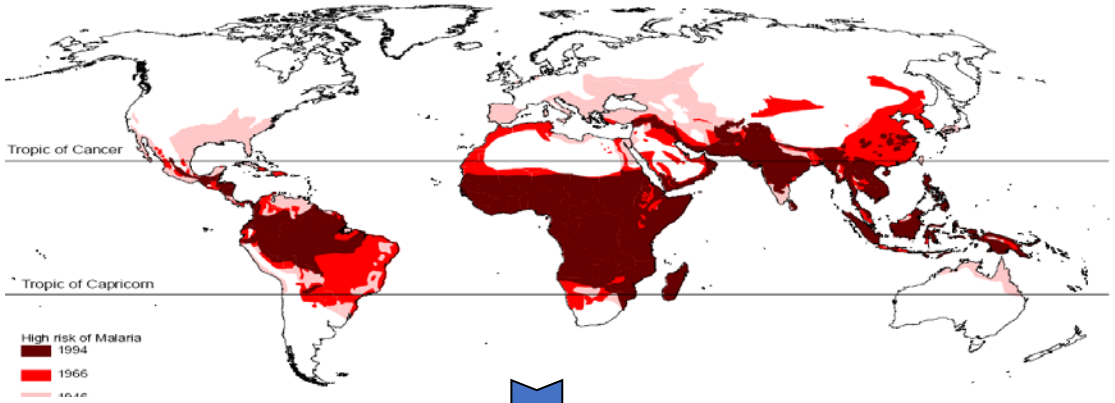
100 or more per oocyst



8-24 per RBC

Kappe S, et al. *Science* 2010

How does malaria manifest itself in 2021?



> 3.3 billion people live in areas with ongoing malaria transmission

Asymptomatic Parasitemia

Uncomplicated Malaria

~219 million

Severe Malaria

Death

~400,000 deaths

Case presentation: 13-month-old boy, malnourished, living in rural eastern Uganda

July 1st
- Fever 101.2 and parasite density of 14,080 parasites/µL
- Treated with 3 days observed AL dosing and given a new insecticide-treated bed net

July 26th
- 25 days later had temp of 99 and reported fever at home with 9,280 parasites/µL
- Treated with AL again, as per standard of care; observed a.m. doses

August 20th
- 25 days later had fever at clinic with 7,600 parasites/µL
- Treated with AL again, as per standard of care; observed a.m. doses

October 1st
- 42 days later had fever at clinic with 14,200 parasites/µL
- Treated with AL again → October 28th had 23,280 parasites/µL but no fever

November 19th
- 50 days since last treatment, had fever at clinic with 1,100 parasites/µL
- Treated with AL again → responded → December 12th had 48,640 parasites/µL!!!

5 episodes during 5 months

What are some of the key points/questions raised by this child's case?

- Are each of these infections from the same strain, or new strains? Are they multiclonal?
- This is a young malnourished child…are we dosing him properly?
- Is drug resistance an issue? If so, is it "resistance" to the artemisinin or partner drug?
- Are we doing anything to interrupt onward transmission from this child?
- In high endemic areas, do we have to consider treatment of the current infection, as well as prevention of the next one?

And, clearly,

…immunity takes a long time to develop (and is not sterilizing)

…good drugs and bed nets are not sufficient in high transmission settings

Life cycle of the Parikh Lab

Individual and cluster-randomized controlled trials

Drug Resistance – surveillance, emergence, transmission

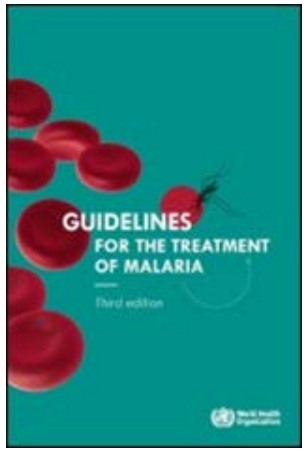
Mathematical modeling and simulations

Focus on populations most at-risk (children, pregnancy, HIV)

Treatment and Prevention of Malaria (Parikh lab)

Novel drugs for transmission reduction (endectocides)

PK/PD studies in the field

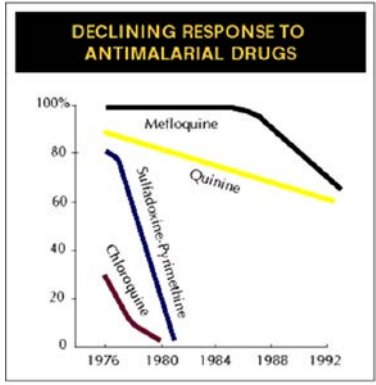


AIDSinfo

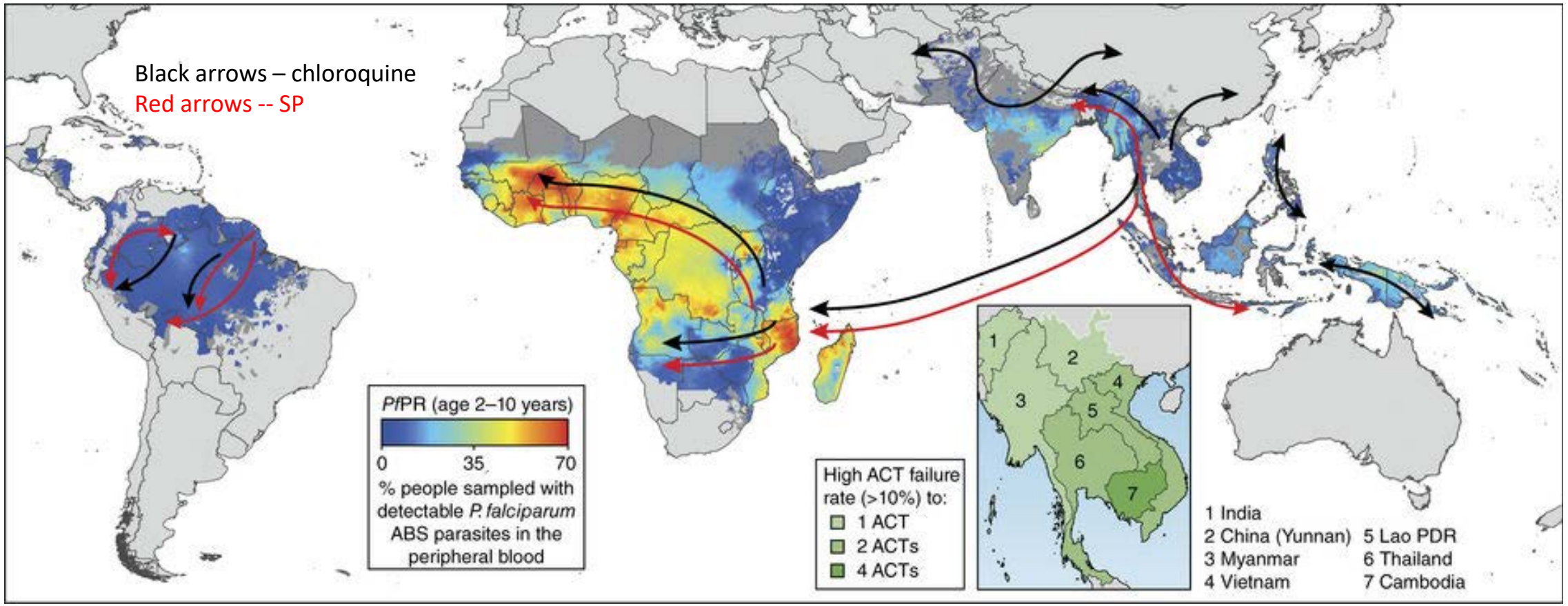
Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children

Novel tools for diagnosis

Antimalarial therapy before and after the introduction of ACTs



The Southeast Journal of Tropical Medicine and Public Health, Mekong Malaria, Volume 30, Supplement 4, p 68, 1995

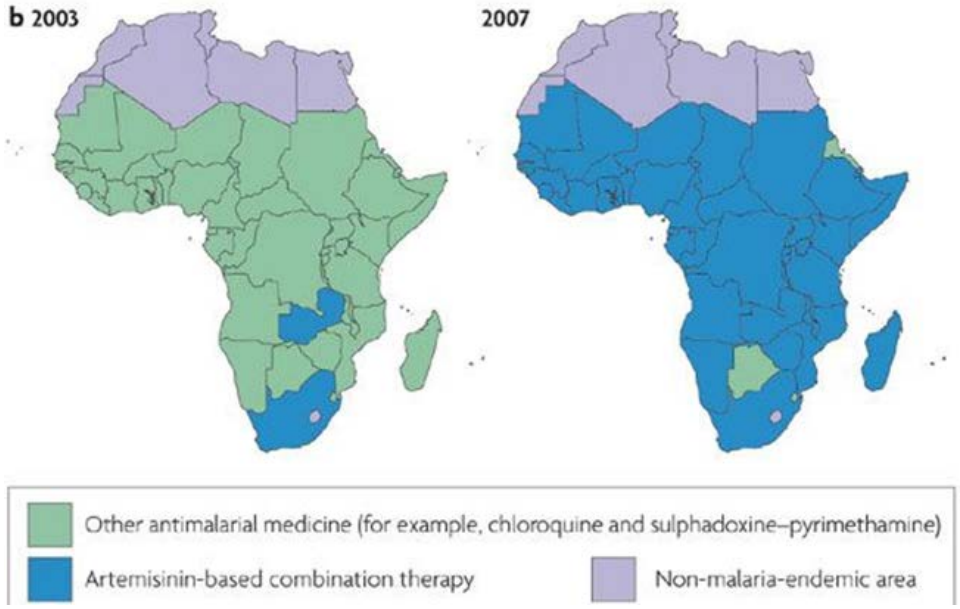


Note that the current recommendation by the WHO is to switch treatment if the "true" failure rate is ≥ 10%

Blasco L, *Nature Medicine* 2017; WHO Artemisinin and ACT Resistance Status Update 2017

How do we treat uncomplicated *P. falciparum* malaria in 2021?

Artemisinin Derivative	Partner Drug
Artemether	Lumefantrine
Artesunate	Amodiaquine
Dihydroartemisinin	Piperaquine
Artesunate	Mefloquine
Artesunate	Pyronaridine
Artesunate	*Sulfadoxine-Pyrimethamine*

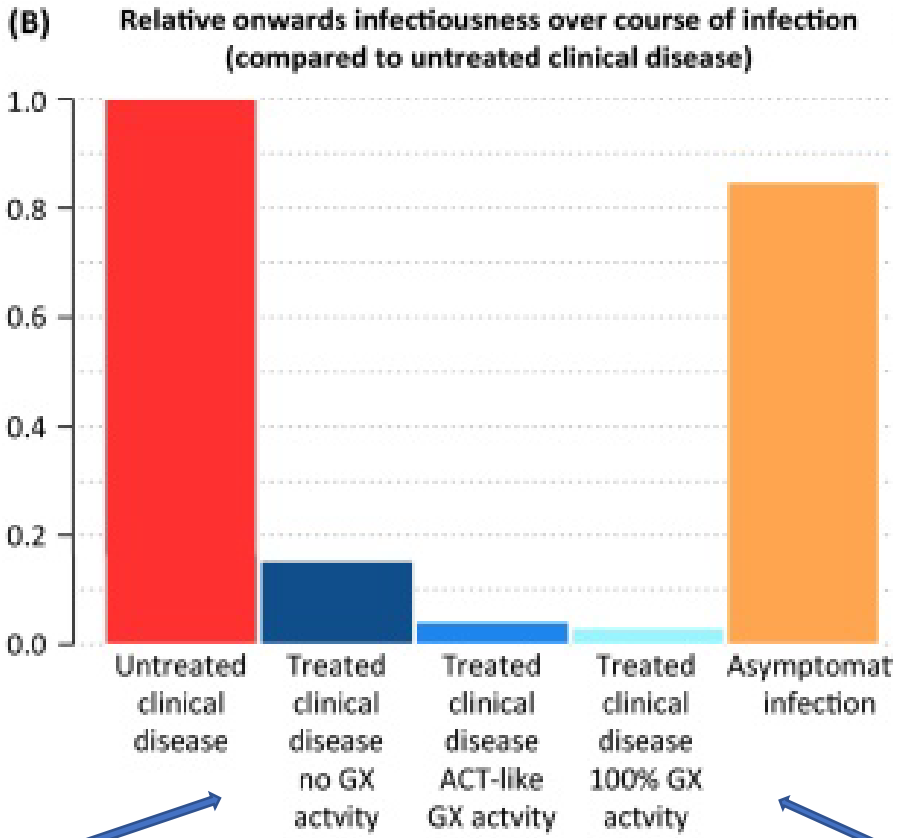


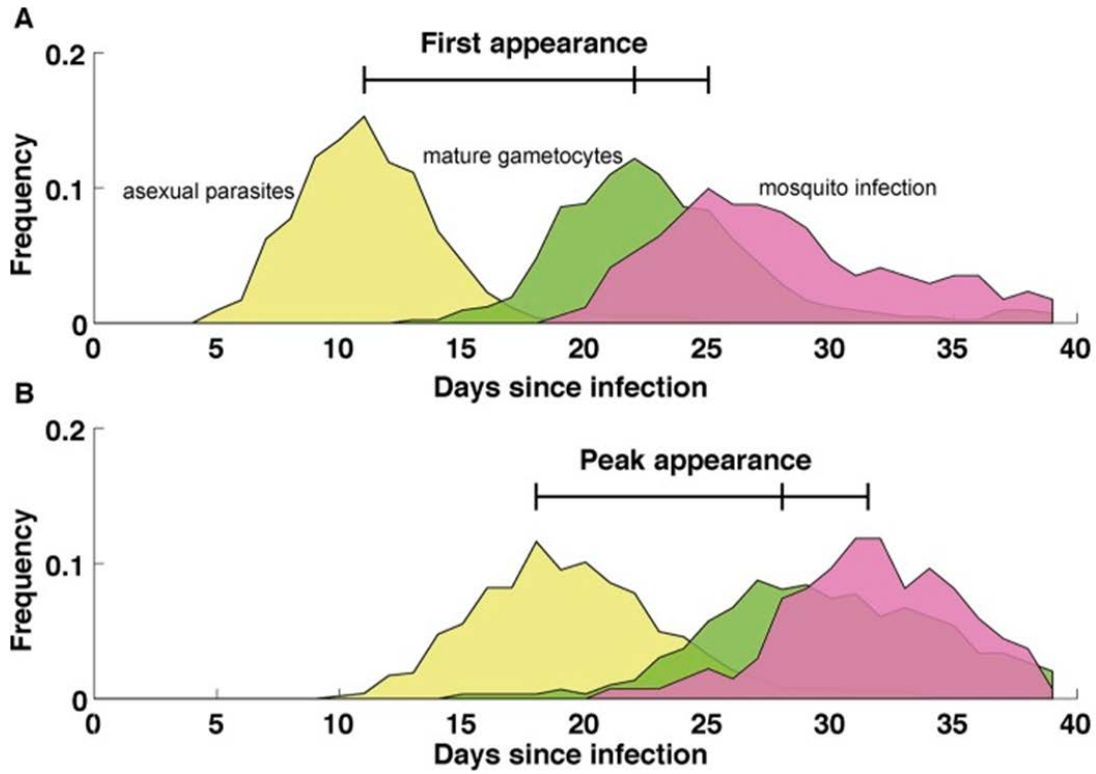
In low transmission areas

- Add single dose 0.25 mg/kg **primaquine** to reduce transmission

World Health Organization, *Treatment Guidelines for Malaria*, 3rd Edition, 2015

Why add a gametocyte-active drug?





Infectious for ~20-50 days

Infectious for ~10-20 days

Infectious for ~0-10 days

Slater HC, et al. *Trends Parasitology* 2015; Nilsson et al. *PloS Pathogens* 2015

Back to our case….First question:

Are these new infections or true failures (recrudescent)?

July 1st	• 6 distinct strains at initial presentation
July 26th	• 3 strains, all new infections
August 20th	• 1 new strain, 1 recrudescent
October 1st	• 5 strains, all new infections
November 19th	• 5 strains, all new infections

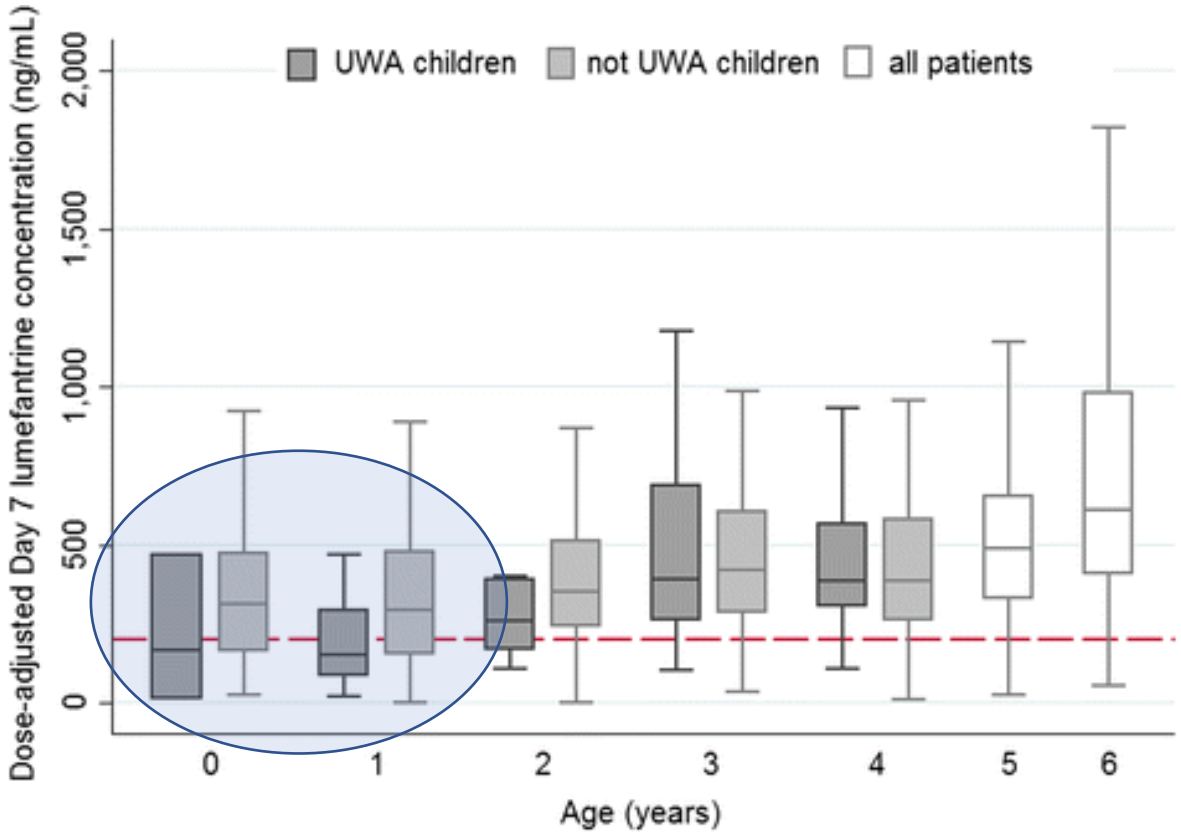
Our second question:
Are we dosing these kids properly?

- Most drugs dosages in children are derived by scaling down by age or weight, ignoring changes in organ development and metabolism

- How can we do pharmacokinetic studies in rural settings?
  - *We combine Intensive and Population pharmacokinetic study designs.*
    - ***Population PK*** is the study of the sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug of interest – uses non-linear mixed effects modeling
  - Allows for flexibility in the number of samples and timing of sampling in each individual
  - Small volume sampling strategies using as little as 100uL of capillary blood
  - LC/MS/MS with LLOQs under 1 ng/mL for most analytes

Answer: Unfortunately, we are not…

Artemether-lumefantrine



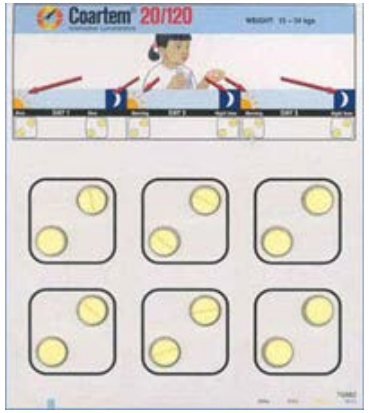
Dihydroartemisinin-piperaquine

Age Group	Actual % attaining target PQ concentration	Simulation % attaining target PQ concentration		
		Reference Dose*	1.5x Reference Dose	2x Reference Dose
6-12 months	28.9	37.9	67.5	83.4
1-2 year, wt <10.5 kg	22.1	19.0	44.5	66.9
1-2 year, wt ≥10.5 kg	25.0	28.3	58.5	76.9

Worldwide Antimalarial Resistance Network Lumefantrine PK/PD Study Group, BMC Medicine 2015; Sambol NC, et al. , et al. *Clin Pharm Therapeutics*

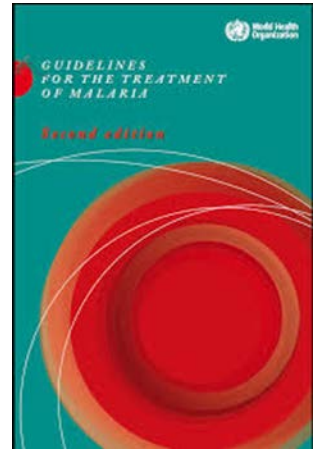
Okay, so lets just change the dose…Not so fast

What questions needed to be answered?



1. Just what is the “right” dose?
2. What is the data that is needed to convince policy makers?

   Do we wait for data or be proactive with modeling?
3. How is the drug currently formulated? Will the manufacturer go along with it?
4. How easy is the “new” regimen to follow?
5. Will this undermine trust in WHO or national guidelines?
6. How will you implement the change at the international, national, local, and CHW scale?



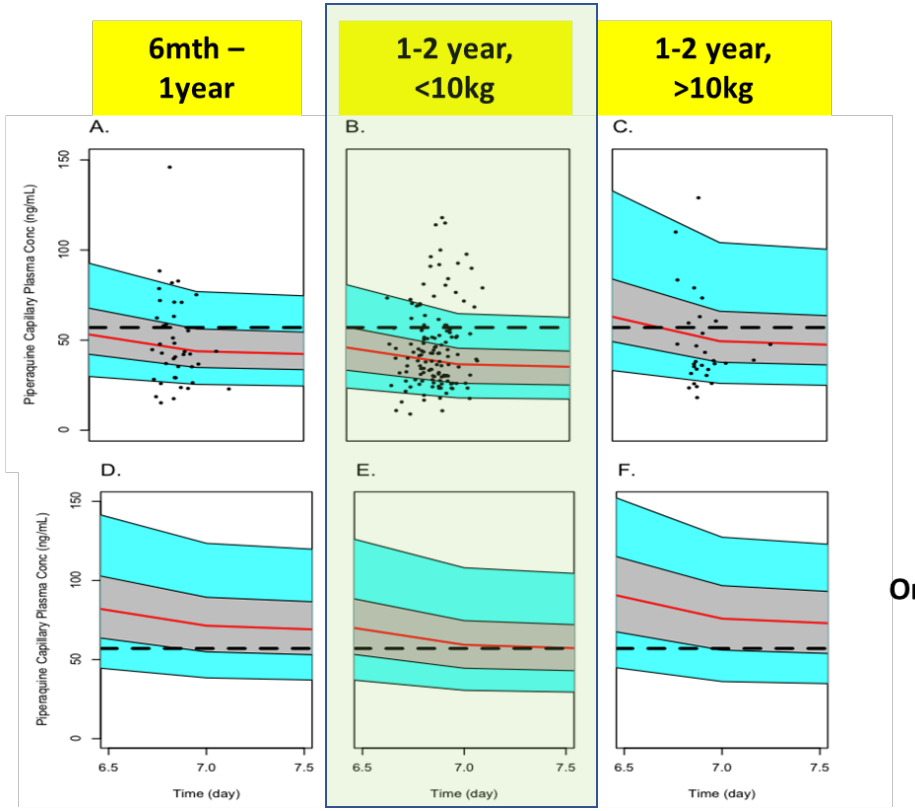
In the case of DP, we used field-based PK/PD studies, coupled with modeling

Treatment

Prevention

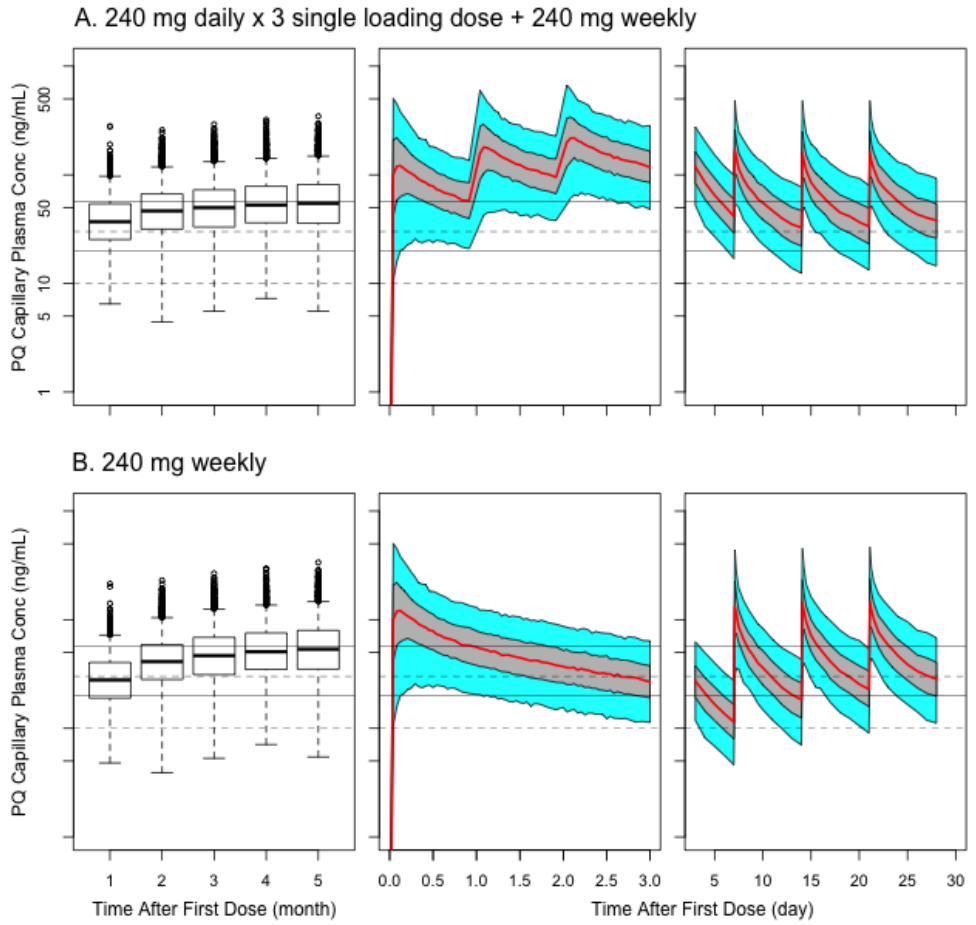
Current Dosing

Age-based dosing



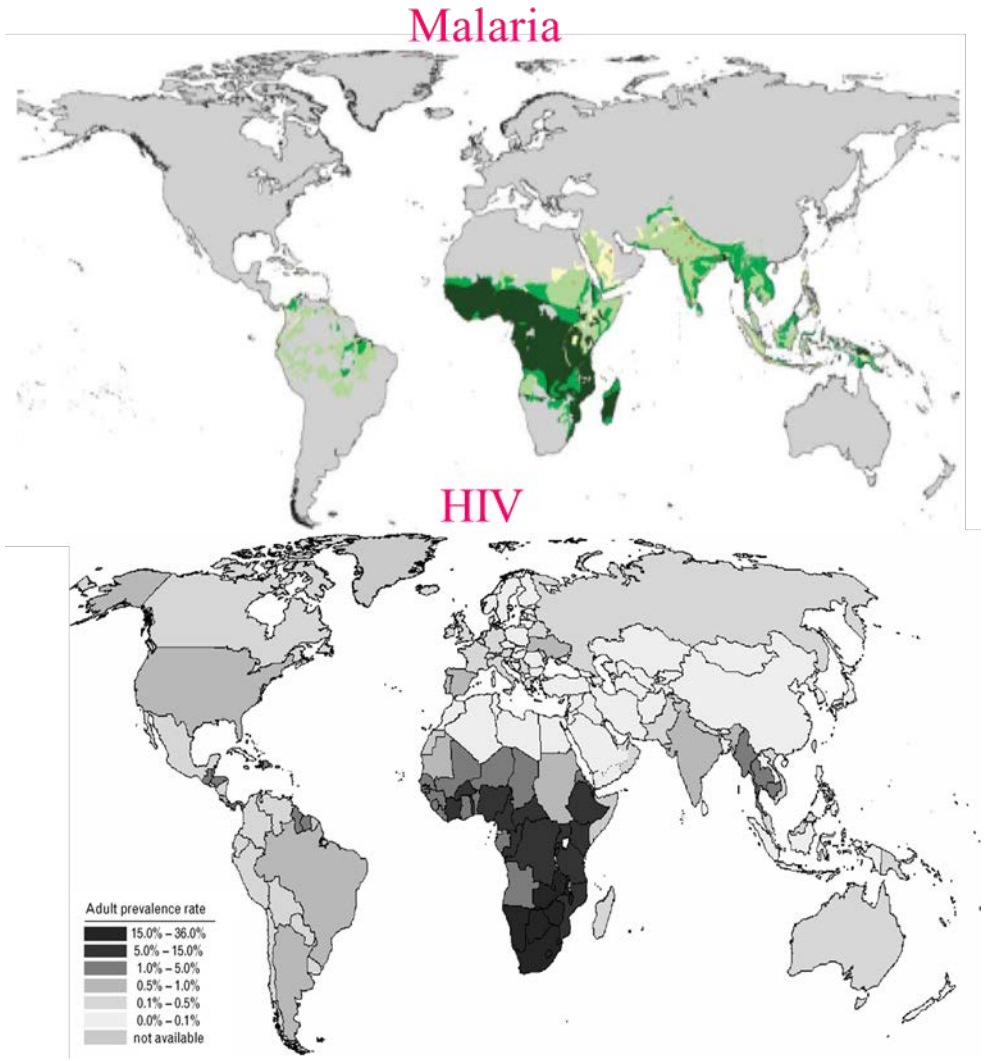
Nearly 65% below target

Only 25% below target

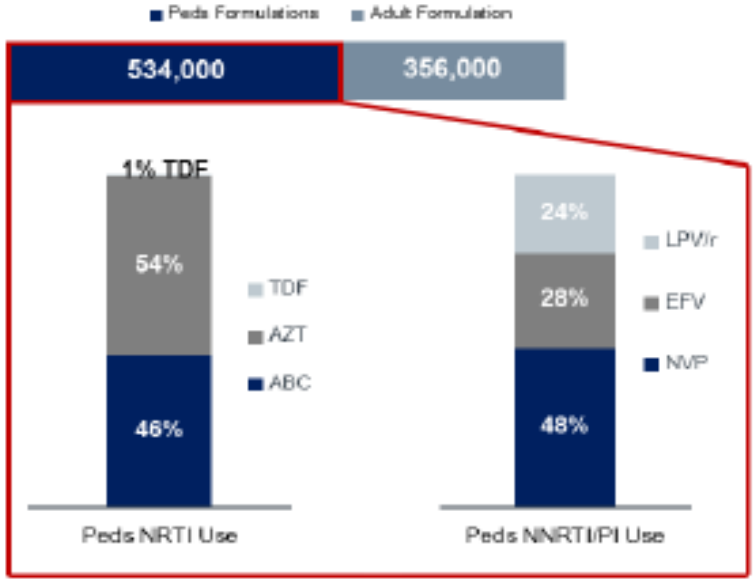


Sambol N, et al. *PLoS One 2016; Journal of Infectious Diseases 2016*

HIV and malaria co-infection: an interesting PK/PD side story

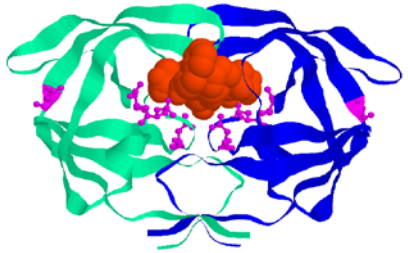


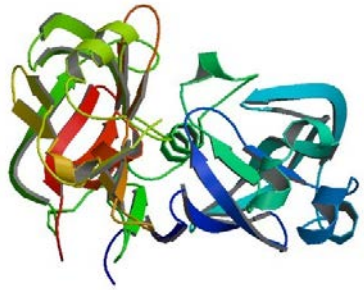
Breakdown of major ARV formulations in pediatrics in LMICs

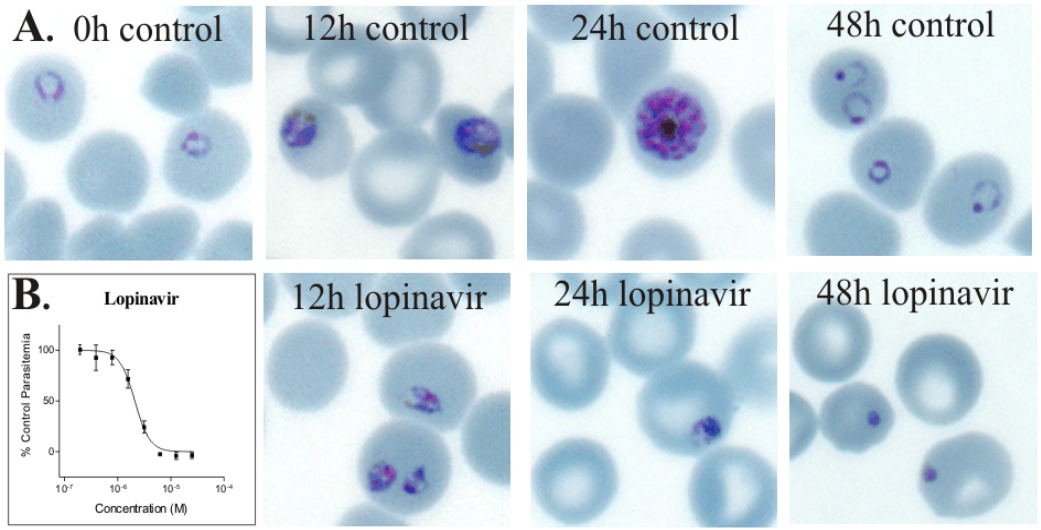


HIV Market Report – Clinton Health Access Initiative, Sept 2018

HIV and malaria both contain critical aspartic proteases







HIV Protease Inhibitor in clinical usage	*P. falciparum* IC_{50} (μM)				Serum concentration with standard dosing (μM)		Serum concentration with boosted dosing (μM)	
	HB3	D6	Dd2	W2	C_{max}	C_{min}	C_{max}	C_{min}
Saquinavir	5.6	4.8	4.3	1.1	3.7	0.3	5.5	0.6
Ritonavir	4.7	7.9	6.9	1.2	15.5	5.1	NA	NA
Indinavir	5.8	15.6	31.2	4.1	10.3	0.3	17.2	0.4
Nelfinavir	15.2	23.0	19.1	6.5	6.0	3.3	NA	NA
Lopinavir	1.4	2.0	2.1	0.9	NA	NA	15.6	8.8
Atazanavir	6.8	11.6	7.1	2.5	3.3	0.2	8.7	1.7

Parikh S, *Antimicrobial Agents and Chemotherapy*. 2005 July;49(7):2983-85

HIV PIs are active throughout the erythrocytic stages, but their mechanism remains unclear

12-hour blocks during 48-hour life cycle

0-12	12-24	24-36	36-48	Percent Inhibition	SD
				2	20
				93	6
				101	4
				104	10
				91	10
				94	9
				106	6
				103	4
				90	11
				83	5

(yellow is the period of the life cycle where drug was present in the *in vitro* culture system

Knocking-out DV plasmepsins did not impact activity

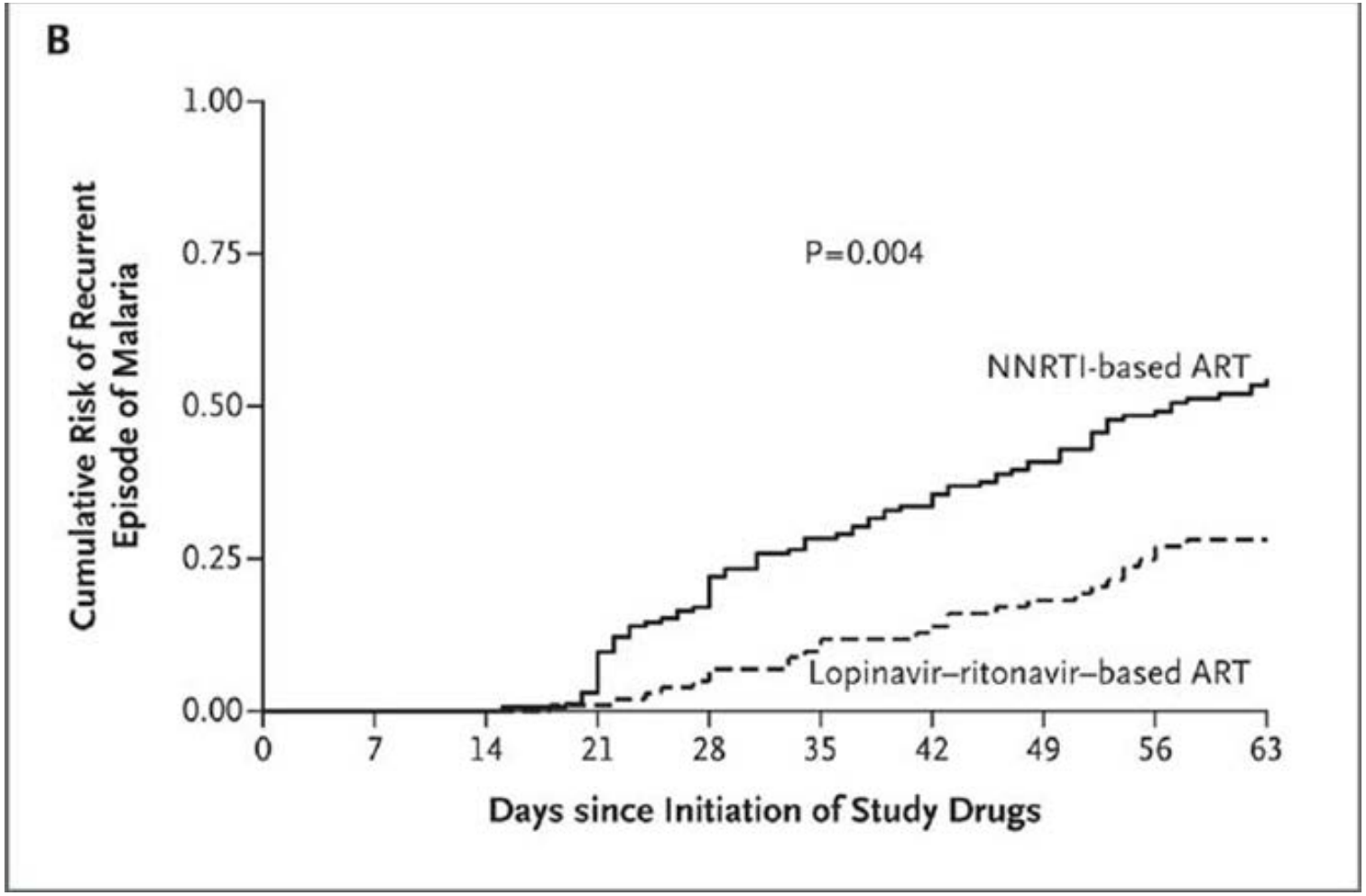
TABLE 1. Activity of HIV-1 protease inhibitors against *P. falciparum* plasmepsin knockout parasites

Drug	IC_{50} (μM) for *P. falciparum*[a]				
	Wild type	PMPI KO	PMPII KO	HAP KO	PMPI/IV KO
Saquinavir	12.2 ± 0.3	11.6 ± 0.6	11.1 ± 0.3	15.1 ± 2.7	13.4 ± 0.7
Ritonavir	12.2 ± 0.4	11.4 ± 1.0	11.7 ± 0.4	14.5 ± 0.5	12.4 ± 0.6
Lopinavir	3.0 ± 0.4	2.4 ± 0.2	2.5 ± 0.1	3.2 ± 0.2	3.9 ± 0.7

[a] IC_{50} data are means ± standard deviations of results from three experiments.
Abbreviations: PMP, plasmepsin; KO, knockout; HAP, histoaspartic protease.

Parikh S, *Antimicrobial Agents and Chemotherapy 2006*

Bench to field: Should HIV PIs be 1st-line for HIV-infected individuals in malaria-endemic regions?



Efavirenz or Nevirapine

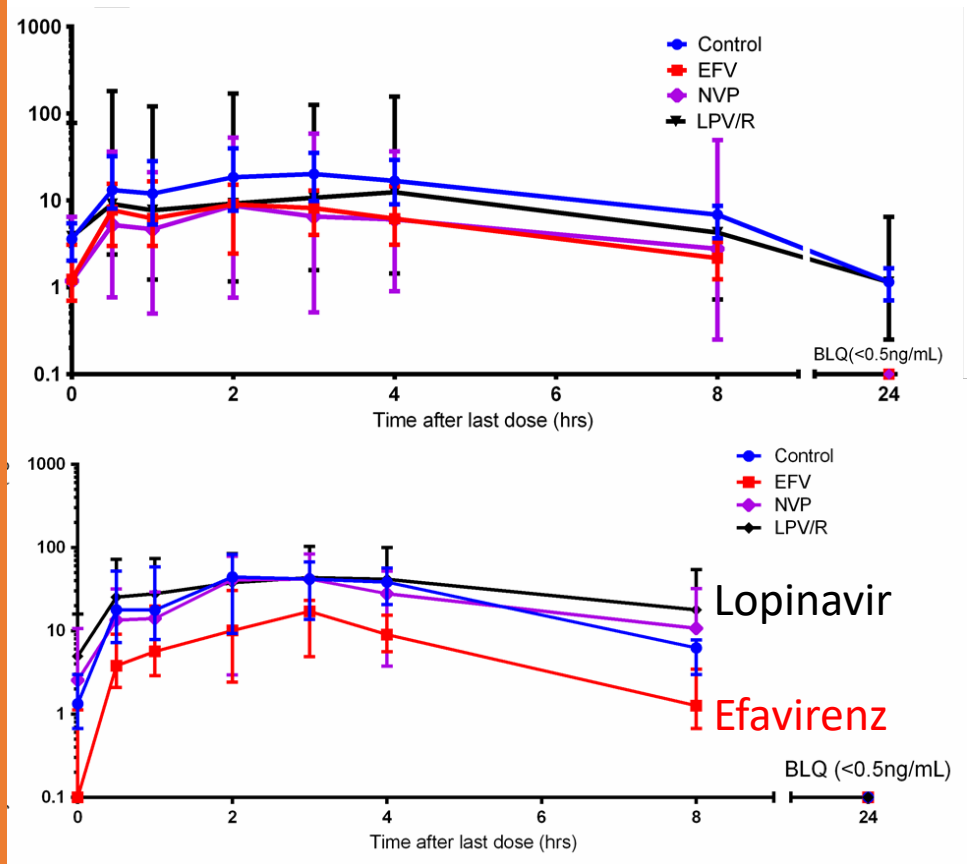
Lopinavir-ritonavir

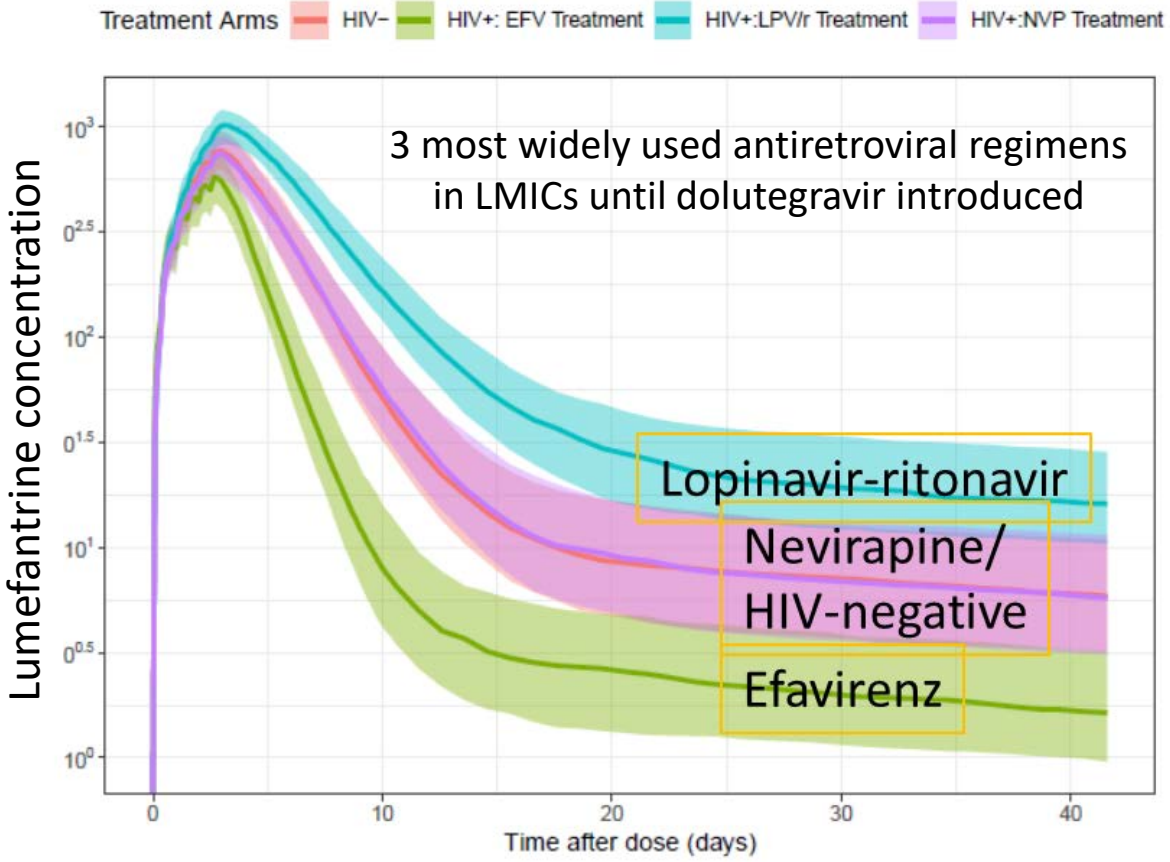
Achan J, et al. *New England Journal of Medicine*, 2012

Is this benefit due to a direct drug effect, a CYP-mediated drug interaction, or both?

Efavirenz lowers the levels of all 3 active components of AL (and LPV/r increases lumefantrine and DHA)

DHA and Artemether concentrations

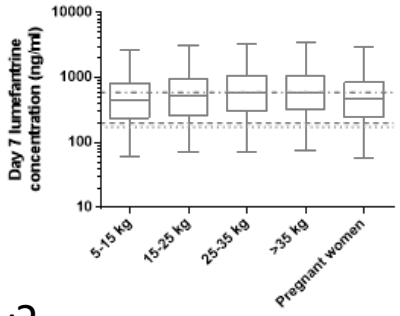




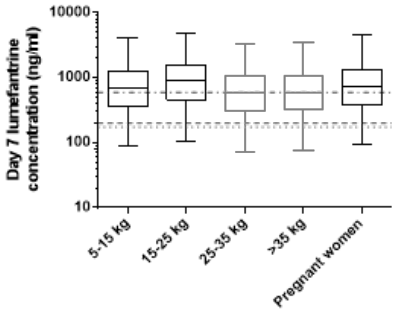
Parikh S, et al. *Clinical Infectious Diseases* 2016; *unpublished*

How can we improve artemether-lumefantrine dosing in children, including those on certain ARVs?

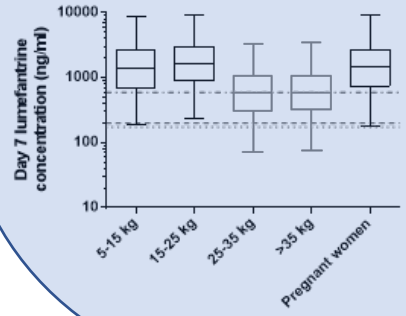
Twice daily dosing
x 3 days



Thrice daily dosing
x 3 days



Twice daily dosing
x 5 days



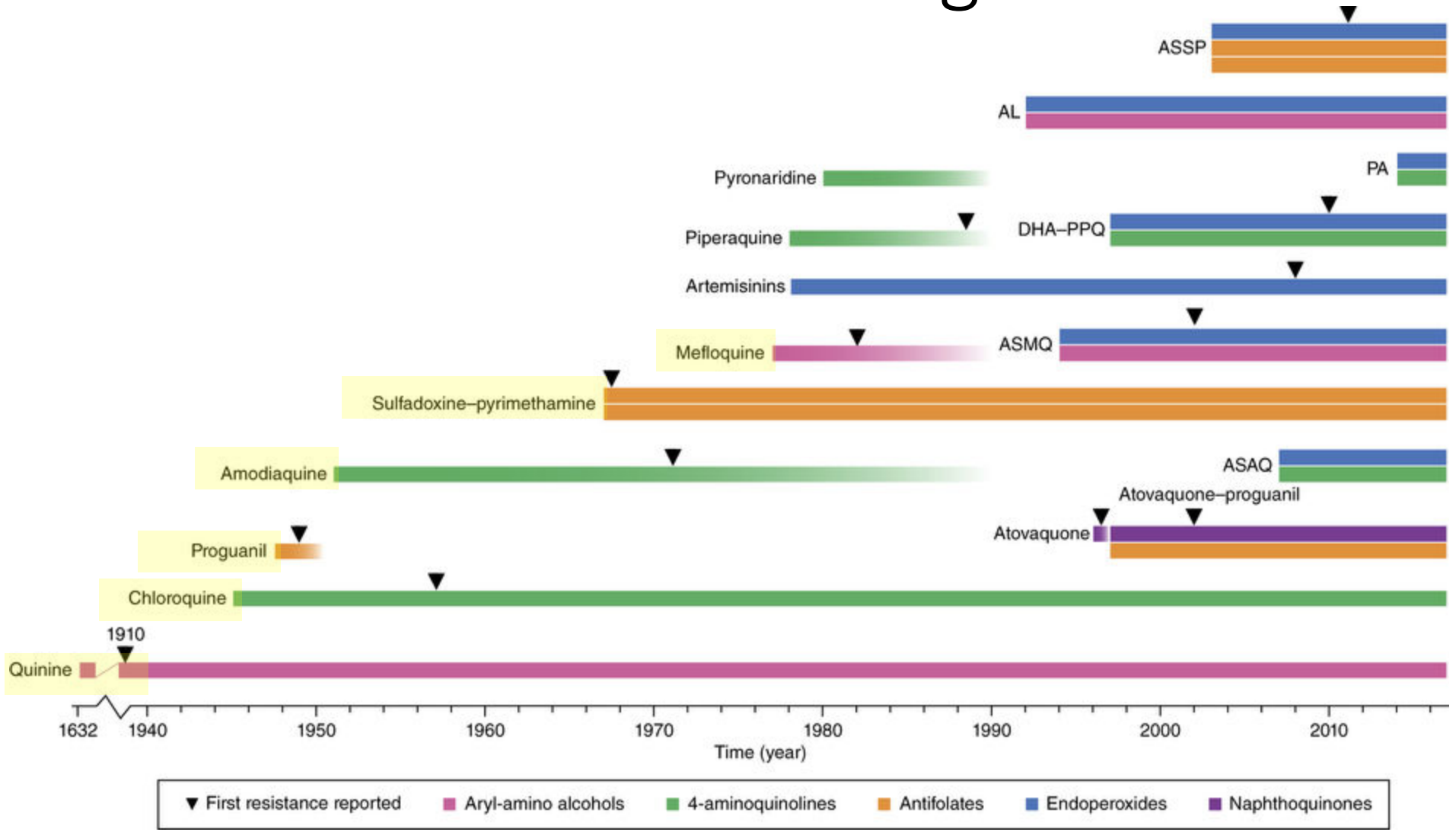
Why?

- Lumefantrine exhibits dose-limited absorption
- Exposes the parasite to an additional 48-hour life cycle and a longer duration of artemisinin

Kloprogge F, et al. *PLoS Medicine* 2018

"Because 3-day courses of artemisinin do not cure infections, even those with so-called artemisinin-sensitive parasites, 3-day artemisinin-based combination regimens depend on a partner drug to achieve a complete cure…In the long term, we must optimize current artemisinin-based combination therapies and investigate potentially increasing the duration of artemisinin administration" Youyou Tu, November 2019

Drug resistance will occur, but will this hasten it along?



Blasco, et al. *Nature Med* 2017

Background: How do we assess for drug resistance

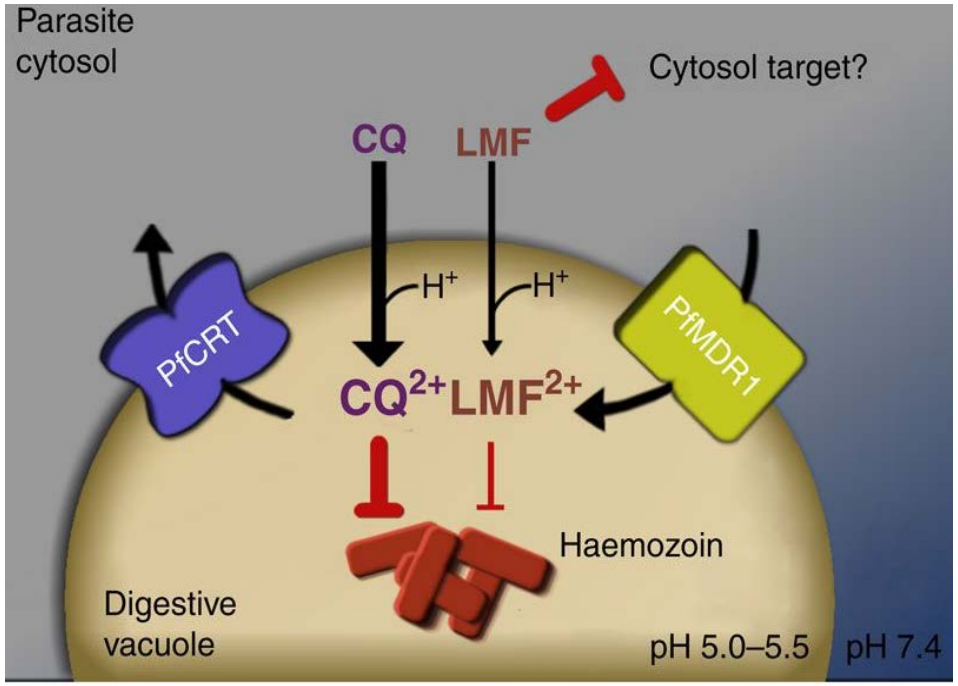
Method	Advantages	Disadvantages
Therapeutic efficacy study	• Easy to standardize • Direct results from patients • Policy based on results • Defines 1st and 2nd line drugs • Safety data obtained • Helps to identify important mutations	• Challenging logistics • High cost • Delay in results • Potential underestimation (PK/PD, immunity)
In vitro testing	• Intrinsic parasite susceptibility	• Difficult to standardize • Infrastructure needs • Not always c/w efficacy
Molecular markers	• If validated, good indicator of clinical resistance • Information on the emergence/spread • Relatively easy to implement • Low cost	• Requires clinical validation • Moderate infrastructure • Not always tightly a/w efficacy

Our next question:

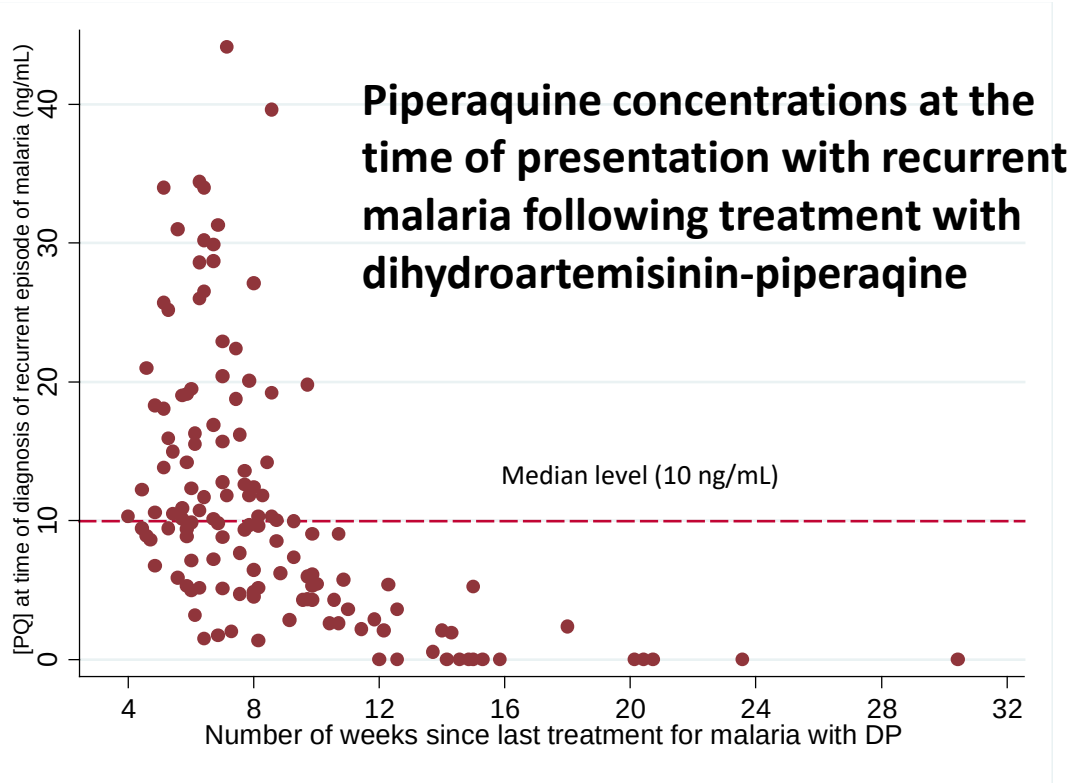
Are we selecting for mutations associated with reduced susceptibility to certain ACTs?

PfMDR1 and PfCRT are transporters which reside on the digestive vacuole and regulate solute flux

N86Y and K76T wild-type are associated with reduced lumefantrine sensitivity (but enhanced amodiaquine sensitivity)



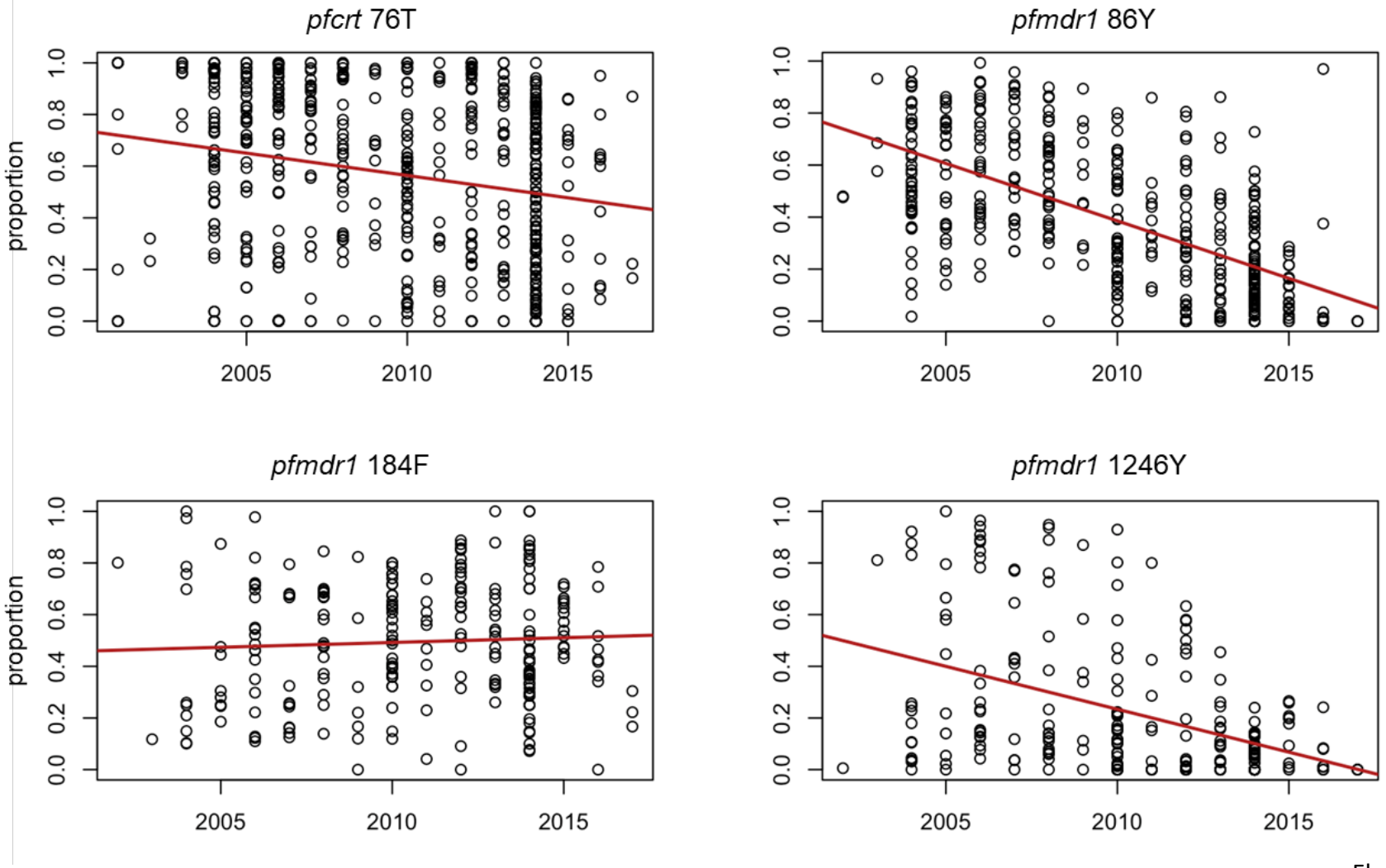
So, we improved exposure, but the benefit appears marginal. Are there other downsides?



- Due to the pharmacokinetic mismatch between artemisinins and partner drugs, there is an extended tail of monotherapy with the long-acting partner drug
- Theoretically, this may provide enhanced selection pressure for the emergence of drug resistance or its spread

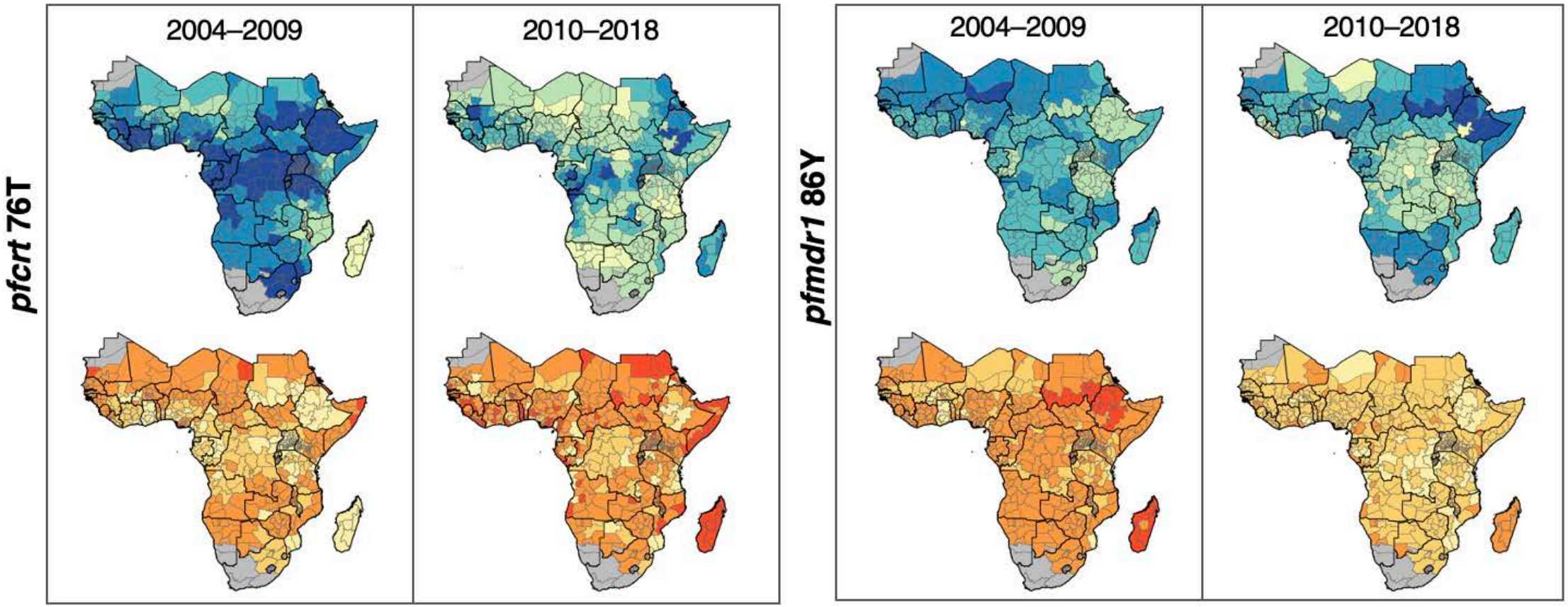
Creek D, et al. *JID* 2015

Molecular markers show a continent-wide trend since the introduction of ACTs (and withdrawal of CQ)



Ehrlich H, et al. *Lancet Microbe* 2020

Molecular markers show a continent-wide trend since the introduction of ACTs



Ehrlich H, et al. *PNAS* in revision

Ivermectin mass drug administration reduced malaria incidence when given every 3 weeks

Malaria episode incidence per child					
	Intervention (95% CI)	Control (95% CI)	Risk ratio (95% CI)	Risk difference (95% CI)	P value
Whole cohort (ITT)	2·00 (n=327)	2·49 (n=263)	0·80 (0·70 to 0·91)	-0·49 (-0·79 to -0·21)	0·0009

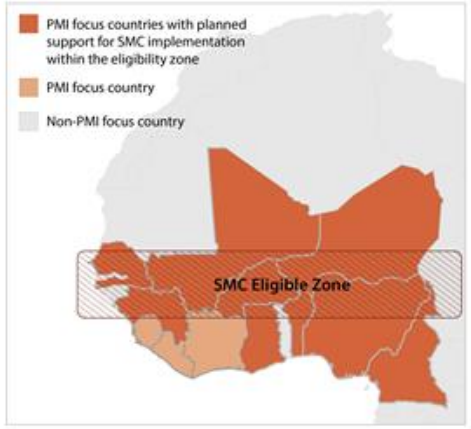
Efficacy and risk of harms of repeat ivermectin mass drug administrations for control of malaria (RIMDAMAL): a cluster-randomised trial

Brian D Foy, Haoues Alout, Jonathan A Seaman, Sangeeta Rao, Tereza Magalhaes, Martina Wade, Sunil Parikh, Dieudonné D Soma, André B Sagna, Florence Fournet, Hannah C Slater, Roland Bougma, François Drabo, Abdoulaye Diabaté, A Gafar V Coulidiaty, Nöel Rouamba, Roch K Dabiré

Foy B, et al, *Lancet* March 2019

RIMDAMAL2- **cluster-randomized trial** in Burkina Faso

to integrate repeated high-dose IVM MDA into the existing monthly SMC delivery platform and distribution of LLINs.

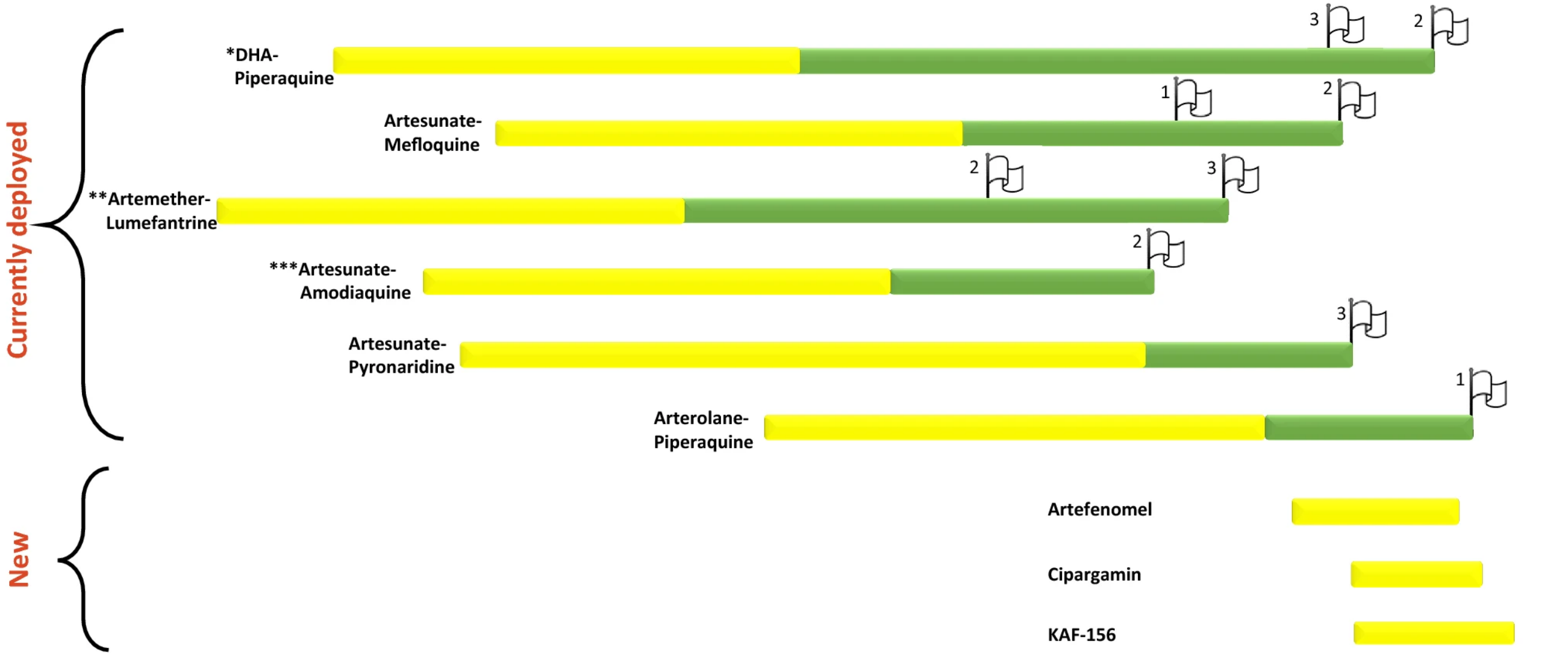


+

seasonal malaria chemoprevention (SMC)
monthly treatment during the rainy season (4 mo; JASO)
sulfadoxine-pyrimethamine (SP) plus amodiaquine (AQ)
3-day oral regimen: 500/25 mg S/P and 153 mg AQ for children 12-59 months; 250/12.5 mg S/P and 76.5 mg AQ for children 3-11 months

ivermectin mass drug administration
monthly treatment during the rainy season (4 mo; JASO)
ivermectin, 3-day oral regimen of 300 µg/kg/day (1-4, 6 mg tablets/day) estimated by height bands
or
placebo, 3-day oral regimen of 1-4 tablets/day per same height bands

Developmental timeline of currently deployed ACTs and leading new compounds



Ashley EA, et al. *Drugs* 2018

Years until end of Phase 2b

Years from end of Phase 2b until approval

1 Country registration
2 WHO pre-qualification
3 Approval by a stringent regulatory authority (e.g. US FDA, EMA)

Summary

- We have to pay attention to antimalarial PK/PD in vulnerable populations
  - DP and AL are under-dosed in children and contributed to higher “failure” rates
  - Population PK/PD modeling allows one to simulate alternative dosing schemes taking other covariates into account such as age, weight, parasite density, etc…
  - Certain HIV drugs have both:
    - potential direct antiparasitic effects (HIV PIs), and
    - Indirect drug-drug interactions with antimalarials (impacts NNRTIs/PIs, and AL/DP/AQ)
  - Performing such studies “after the fact” makes it very difficult to change policy (but it is possible)

Summary

- Drug resistance is likely inevitable, but we need to monitor and understand its evolution and spread better
  - Current surveillance does not capture the geographic heterogeneity and larger patterns in partner drug resistance evolution
- ACTs have revolutionized treatment, but are based on a “fatal flaw”, a PK mismatch in half-lives that leaves a long period of effective monotherapy
  - This leads to a “double-edged sword” with dosing
- ACTs and bed nets are not enough → ivermectin endectocide trial in Burkina Faso