Factors Associated With *P. falciparum* Gametocyte Carriage

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Introduction

- Malaria control programs are often based on identifying those individuals most likely to transmit malaria
- Gametocyte carrying humans are necessary for malaria transmission to occur
- Strategy of avoiding identifiable risk factors for gametocytaemia

Background

- Gametocytes are the sexual forms of P. falciparum
- Male and female meet in mosquito gut after ingestion and fuse to form zygotes from which sporozoites arise
- Gametocytes develop over a period of approximately 10 days; peak occurs about 7 to 10 days after peak of asexual parasitaemia

WHO TDR/ Wellcome collaboration

- Individual trials are under powered to answer many questions and are not often designed to do so
- Main objectives of this initiative was to determine the main factors i) affecting cure rates, ii) determining gametocyte carriage, iii) contributing to anaemia, and iv) determining time to recrudescence

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Gametocyte data

- Continuous gametocyte count data were expressed as per microlitre (/µl)
- Gametocytaemia on day 0 or day 1 was considered ‘on admission’
- Also collected on days 2, 3, 7, 14, 21, 28, 35, 42, 49, 56, and 63

Covariates

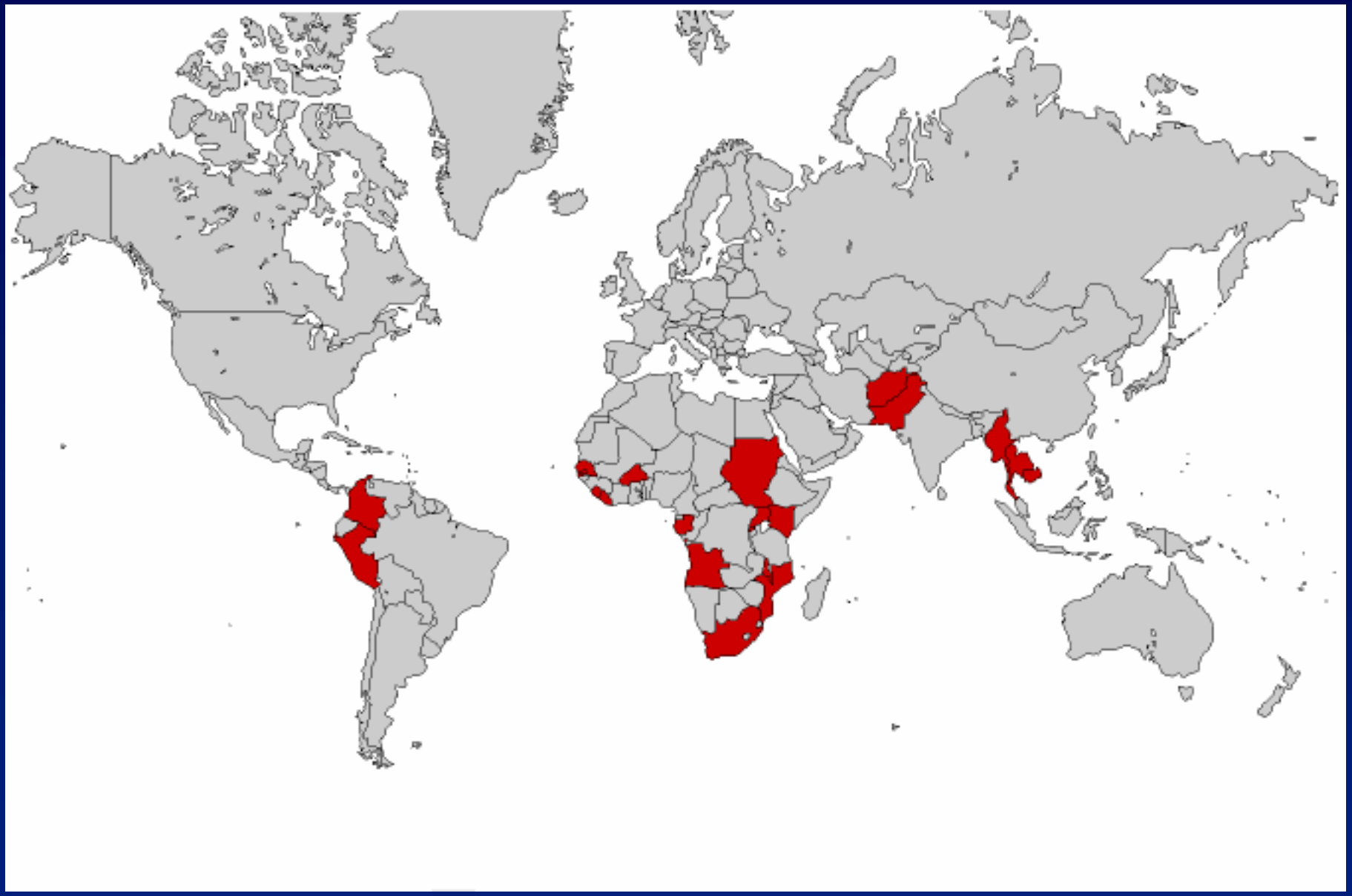
- Age
- Sex
- Fever
- Symptoms
- Log parasitaemia
- Mixed infection
- (Adjusted) haematocrit
- 4 treatment groups: ACT without SP, ART plus SP, any SP, all other treatments
- Failure (defined as ETF, recrudescence, or severe)

Analysis: on admission

- Univariate analysis: by EIR, outcome as dichotomous
- Multivariate: negative binomial, random effects model, with EIR as covariate, any significant covariates from univariate (examined for interaction), and outcome as continuous
- All adjusted for differences by study and site

Analysis: after treatment

- Included only those with no gametocytes on admission
- Outcome = gametocytes within 28 days (y/n)
- Significant covariates from univariate analysis included in a random effects logistic regression model for each EIR, adjusted for study and site



Pooled dataset

- 85 clinical trials on malaria conducted in 25 countries
- 31,709 patients with slide confirmed P. falciparum malaria
- Follow-up ranged from 14 to 63 days
- Conducted between 1991 to 2005

Study population

- 15,415 male and 15,840 female
- Median age was 7 years (range 1 month – 88 yrs)
- Children younger than 5 years old were the largest age group (39.2%); 5 to 14 year olds (29.3%) and 15 years and older (31.6%)

Gametocyte characteristics

- 27,539 for analysis
- 19,869 with count data
- Median 0 (range 0 to 67,870/µl)

EIR	patent (%)	0 counts* (%)	geometric mean, µl (95% CI)
Low	1,340 (8.0)	13,944/15115 (92.3)	99.3 (90.5, 109.0)
Moderate	574 (9.5)	2,474/2,764 (89.5)	25.1 (20.0, 31.5)
High	802 (16.9)	1,777/1,990 (89.3)	30.6 (25.4, 36.9)
Total	2,716 (9.9%)	18,195 (91.6)	67.4 (61.9, 73.2)

Risk factors on admission

	IRR (95% CI)	p-value
Age	0.99 (0.98, 1.0)	<0.001
Parasitaemia	0.64 (0.60, 0.69)	<0.001

	Low	Moderate	High	
Fever	1.25 (1.04, 1.50)	0.55 (0.44, 0.70)	0.71 (0.50, 1.01)	0.02, <0.001, 0.06
Symptoms	2.33 (1.98, 2.75)	0.04 (0.01, 0.26)	0.44 (0.30, 0.65)	<0.001, 0.001, <0.001
(Adj.) HCT	0.87 (0.86, 0.88)	0.89 (0.87, 0.91)	0.96 (0.94, 0.99)	<0.001, <0.001, 0.01
EIR*	1 -	65.14 (9.57, 443.36)	5.24 (3.48, 7.88)	- , <0.001, <0.001

**for patients without symptoms or fever and mean (adj.) haematocrit, i.e., 33.2%, at presentation*

After treatment

EIR	presented without gametocytes (%)	produced gametocytes (%)*	no counts recorded to d28 (%)
Low	15,385 (62.0)	1,615 (10.7)	282 (1.8%)
Moderate	5,477 (22.1)	671 (18.2)	1,780 (32.5%)
High	3,961 (16.0)	602 (15.4)	42 (1.1%)
Total	24,823 (100)	2,888 (12.7)	2,104 (8.5)

** percentages calculated excludes those missing all values after d0*

Effect of treatment: ART, no SP as baseline group

EIR & Tx grp	odds ratio (95% CI)	p-value	adjusted for…
low			
ART + SP	1.01 (0.44, 2.29)	0.990	mixed, log parasitaemia, (adj) HCT, age, weight
SP + other	22.46 (13.89, 36.30)	<0.001	
all other	5.34 (4.24, 6.71)	<0.001	
moderate			
ART + SP	0.46 (0.26, 0.82)	0.008	(adj.) HCT
SP + other	2.62 (1.64, 4.20)	<0.001	
all other	1.04 (0.69, 1.57)	0.855	
high			
ART + SP	0.73 (0.36, 1.49)	0.394	fever, (adj.) HCT
SP + other	2.57 (1.45, 4.54)	0.001	
all other	1.32 (0.95, 1.82)	0.093	

Summary of findings (1)

- Younger age, lower asexual parasitaemia, presenting without fever, having no symptoms, and lower HCT associated with patent gametocytaemia on admission in moderate and high EIR areas
- In contrast, fever and symptoms on admission were positively associated with patent gametocytaemia in low EIR areas

Summary of findings (2)

- Artemisinin derivatives have been shown to reduce gametocyte carriage, thereby reducing patient infectivity
- Patients who received artemisinin based treatments were less likely to produce gametocytes in the follow-up period

Current/Future research

- Length of gametocyte carriage
- Maximum gametocyte density
- Infectiousness to mosquitoes

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