# Malaria Alert Centre:

# Tracking Antimalarial Resistance in Malawi

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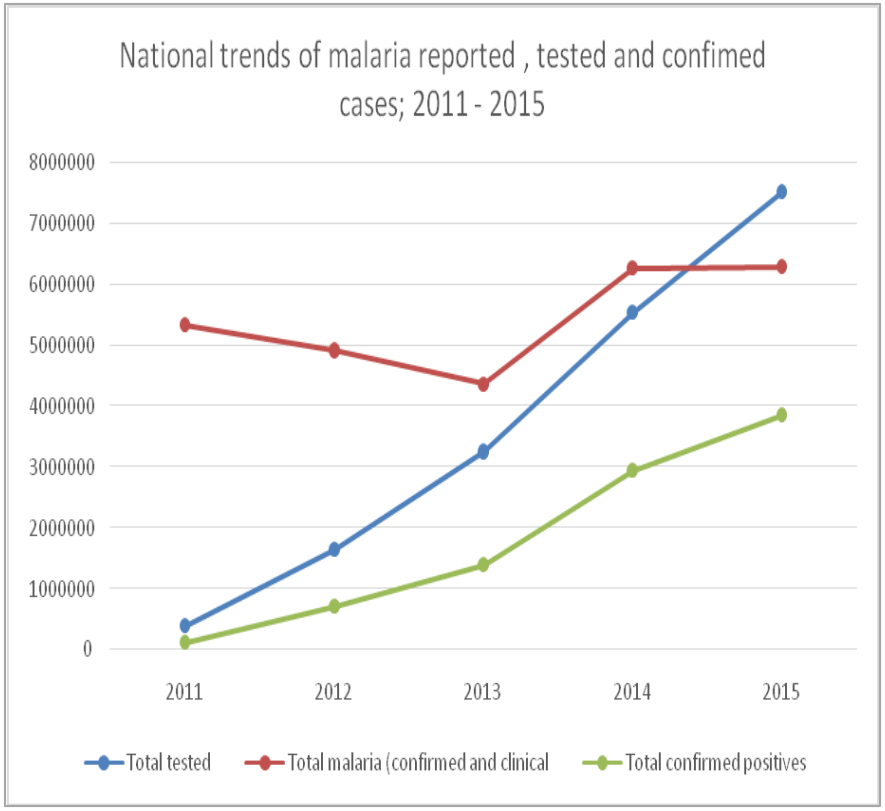
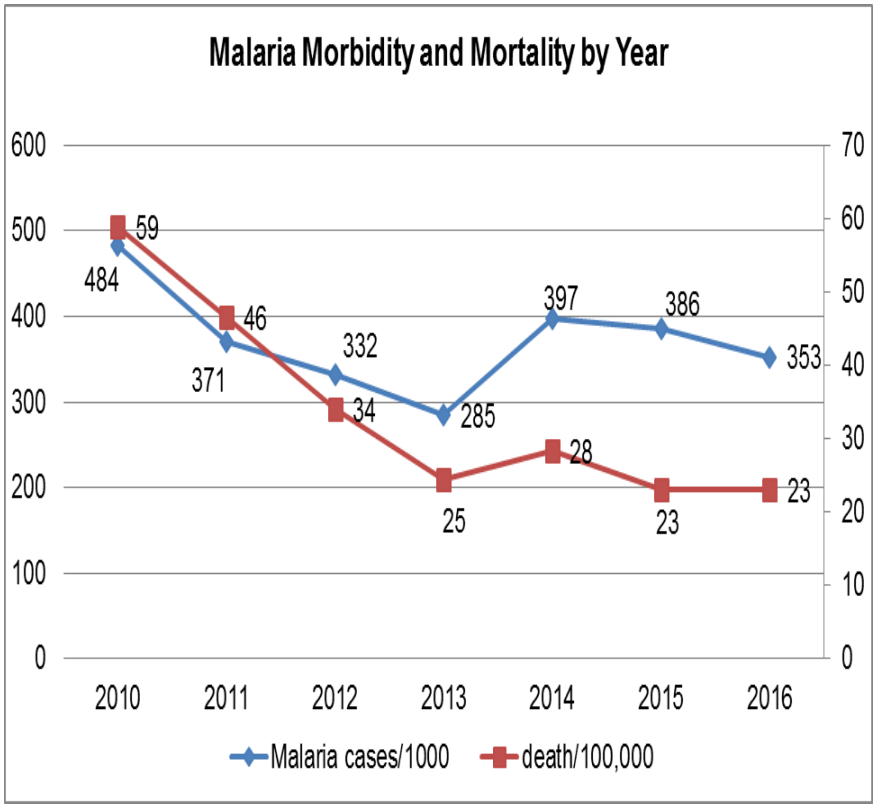
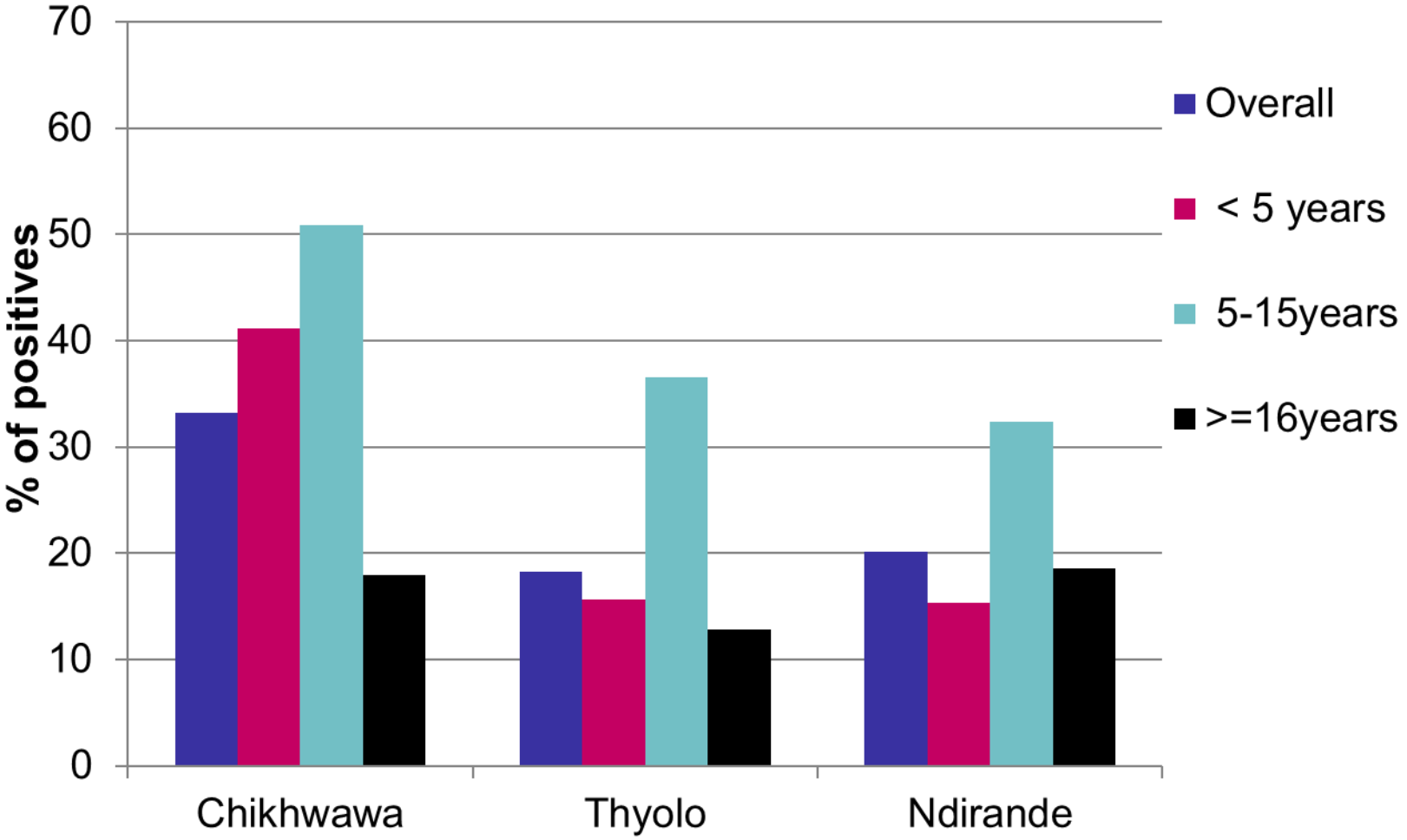
# High burden of malaria - Malawi



# Outpatient RDT positivity by site & age group



# Main interventions in malaria control

1. Insecticide-treated mosquito nets (ITNs)
2. Indoor residual spraying (IRS)
3. **Intermittent preventive treatment in pregnant women (IPTp)**
4. **Case management (treatment) of malaria** with effective drugs **(artemesinin-based combination therapy (ACT)**

# Background of MAC

- Established in 2001 by COM and BMGF.

- Main agenda: *To build capacity in malaria control.*
  - *Operational Research*
  - *Monitoring & Evaluation*
  - *Surveillance*
  - *Training*

- Semi-autonomous unit within College of Medicine.

# Tracking resistance in treatment drugs

# Factors Contributing to Antimalarial Drug Resistance

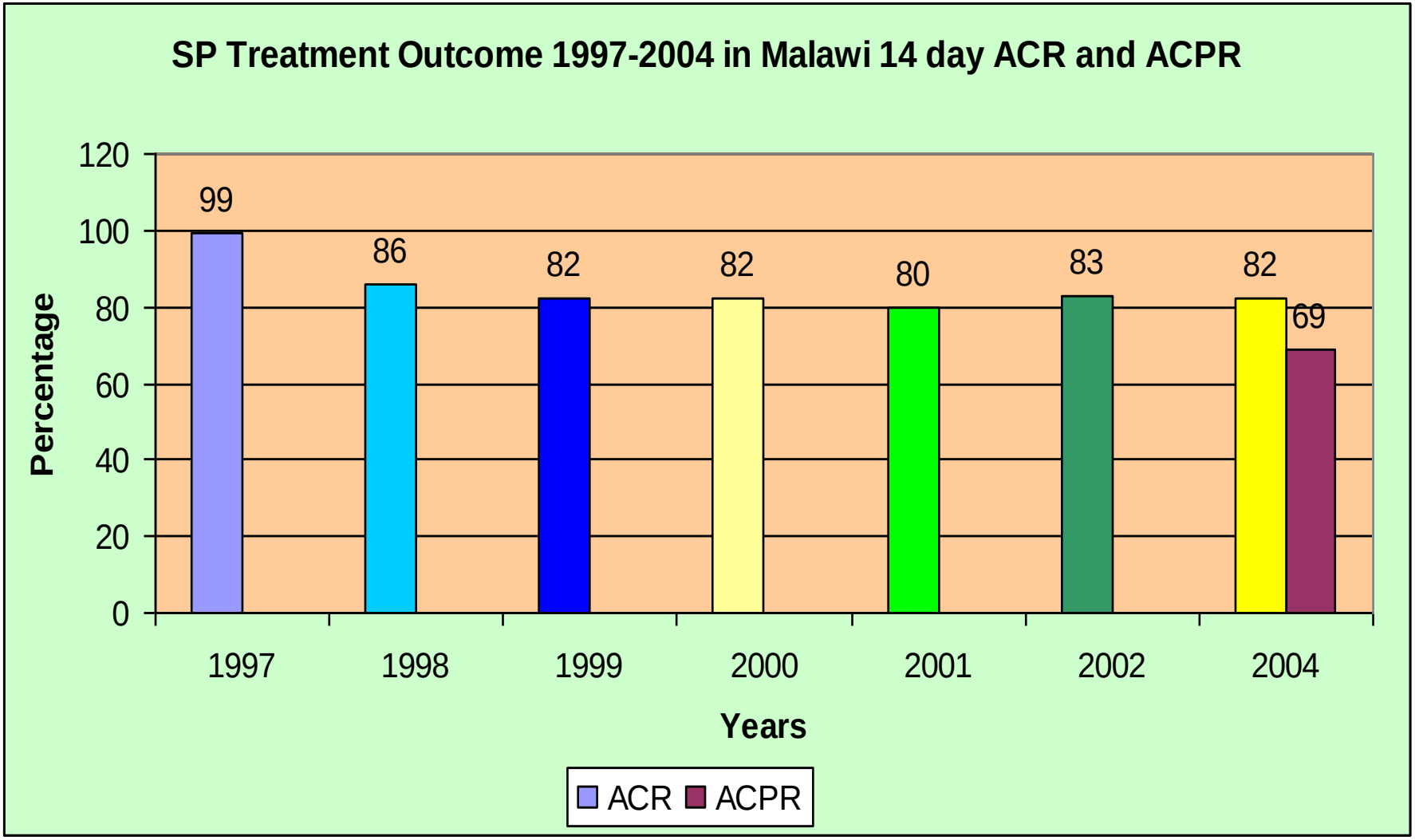
**Drug issues**

- Factors affecting clearance of parasites
- Related antimalarials

**Programmatic issues**

- Drug pressure
  - MDA
  - Presumptive treatment
- Poor compliance
- Drug combination

# Therapeutic Efficacy Testing in Malawi



# Efficacy of AL vs ASAQ

**Table 2: Participant response to treatment over 28-day follow-up among participants in a thearapeutic efficacy study in Machinga, Nkhotakota, and Karonga Districts in Malawi, 2016**

| | AL | | | | ASAQ |
|---|---|---|---|---|---|
| | | Site | | | |
| Estimate | Total (n=338) | Machinga (n=112) | Nkhotakota (n=113) | Karonga (n=113) | Total (n=114) |
| Participants lost to follow-up, n (%) | 35 (10.4) | 14 (12.5) | 15 (13.3) | 6 (5.3) | 16 (14) |
| Treatment failure, n (%) | | | | | |
| Early | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Late | 72 (23.8) | 22 (22.5) | 31 (31.6) | 19 (17.8) | 3 (3.1) |
| Day of failure, median (range) | 21 (14, 28) | 24.5 (14, 28) | 21 (14, 28) | 21 (14, 28) | 14 (14, 21) |
| Reinfection* | 70 (23.1) | 22 (22.5) | 31 (31.6) | 17 (15.9) | 2 (2) |
| Recrudesence | 2 (0.66) | 0 (0) | 0 (0) | 2 (1.9) | 1 (1) |
| Day 3 clearance†, % (95% CI) | 99.7 (98.3–100) | 99.1 (94.5–100) | 100 (96.7–100) | 100 (96.7–100) | 100 (96.7–100) |
| ACPR, % (95% CI) ‡ | | | | | |
| Uncorrected | 76.2 (71–80.9) | 77.6 (68–83.4) | 68.4 (58.2–77.4) | 82.2 (73.7–89) | 96.9 (91.3–99.4) |
| PCR-corrected | **99.3 (97.6–99.9)** | **100 (96.3–100)** | **100 (96.3–100)** | **98.1 (93.4–100)** | **99 (94.5–100)** |
| Kaplan-Meier survival rate on Day 28, % (95% CI) § | | | | | |
| Uncorrected | 76.8 (72.1–81.5) | 78.2 (70.2–86.3) | 69 (59.9–78.1) | 82.5 (75.4–89.7) | 97.1 (93.9–100) |
| PCR-corrected | 99.3 (98.3–100) | 100¶ | 100¶ | 98.0 (95.3–100) | 99.0 (97.2–100) |

* Significant difference between study sites ($p<0.05$)

† Percent Day 3 clearance was estimated only among participants still enrolled in the study on Day 3.

‡ Adequate clinical and parasitologic response (ACPR) was estimated only among participants who reached a valid study endpoint.

§ The Kaplan-Meier survival rate estimate included all study participants who contributed person-days during the 28-day follow-up

¶ For Kaplan-Meier survival rates of 100%, confidence intervals were not estimated.

**Efficacy of artemether lumefantrine (AL) compared to amodiaquine artesunate (AA), dihydroartemesinin-piperaquine(DP) in the treatment of uncomplicated *pf* in malawi**

**Aim:** To assess the efficacy of AL, ASAQ and DHA-P

**Method:** Three arm, randomized into AL, ASAQ and DHA-P

# Resistance of SP in IPTp

# IPTp using a failing drug

- IPTp-SP currently recommended for HIV-negative women in areas of stable/high malaria transmission.
  - Thought to have both prophylactic and treatment effects

- The efficacy of SP for IPTp is threatened by rising resistance of *Pf* to SP.

*Gutman J, Kalilani L, Taylor S, et al. The A581G mutation in the gene encoding Plasmodium falciparum dihydropteroate synthetase reduces the effectiveness of sulfadoxine–pyrimethamine preventive therapy in Malawian pregnant women. J Infect Dis 2015; 211: 1997–2005.*

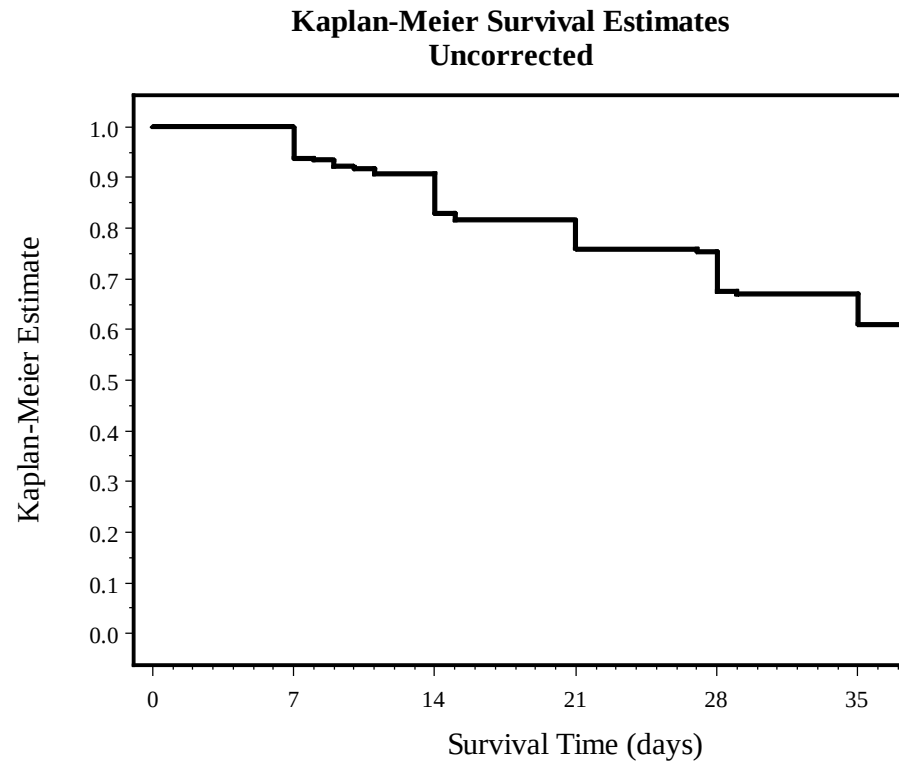
Chico RM, Cano J, Ariti C, et al. Influence of malaria transmission intensity and the 581G mutation on the efficacy of intermittent preventive treatment in pregnancy: systematic review and metaanalysis. *Trop Med Int Health 2015; published online Sept 1.*

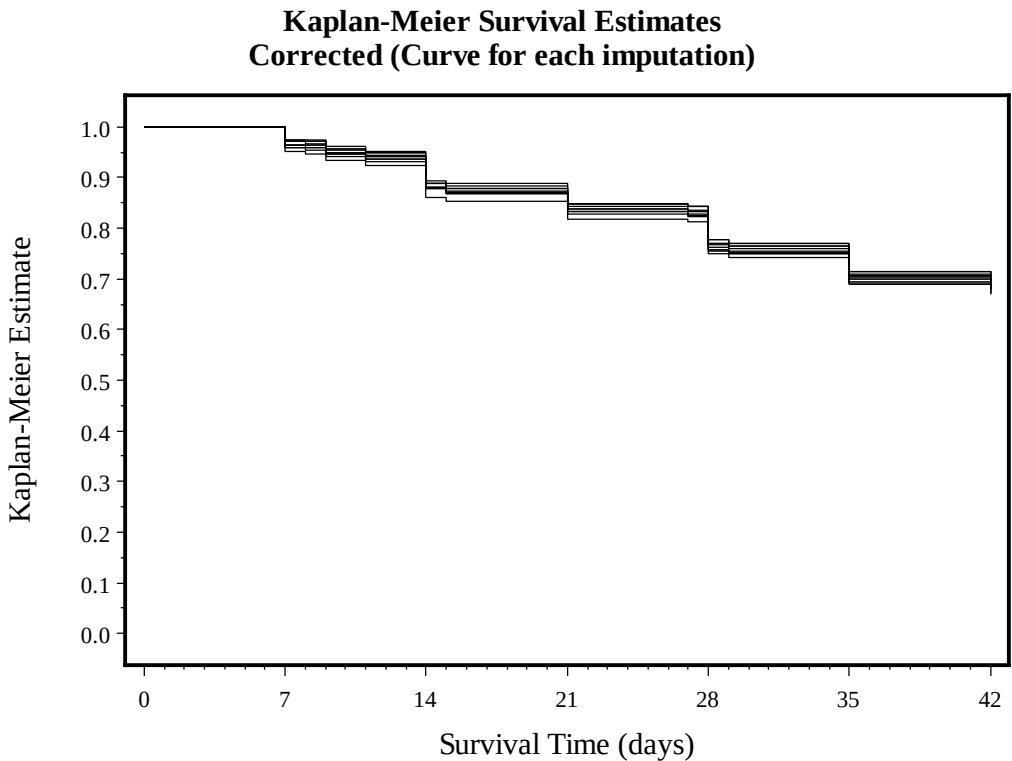
# High rates of quintuple mutants in Malawi

- On day 0 samples from pregnant women in the *in vivo* study were tested for molecular markers of resistance to SP
- 94.5% quintuple mutants (172/182 samples)
- *dhfr* 164 0.95% mutant (2/211)
- *dhps* 518 1.96% mutant (4/204)
- *dhps* 613 1.1% mutant (2/180)

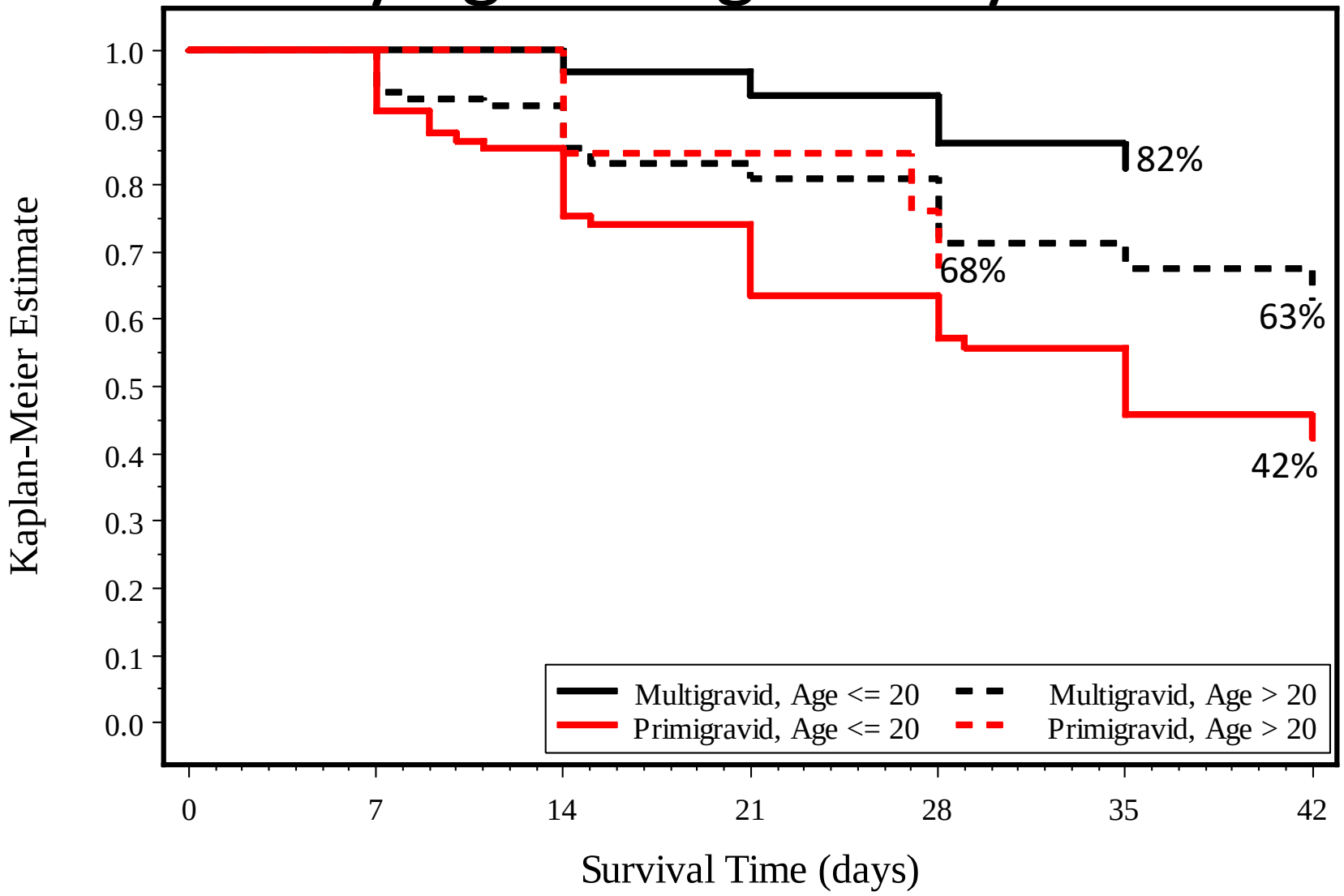
# *in vivo* Survival

| Day of follow-up | Uncorrected | PCR Corrected |
|---|---|---|
| **14** | 83% | 88% |
| **28** | 68% | 76% |
| **35** | 61% | 70% |
| **42** | 58% | 69% |

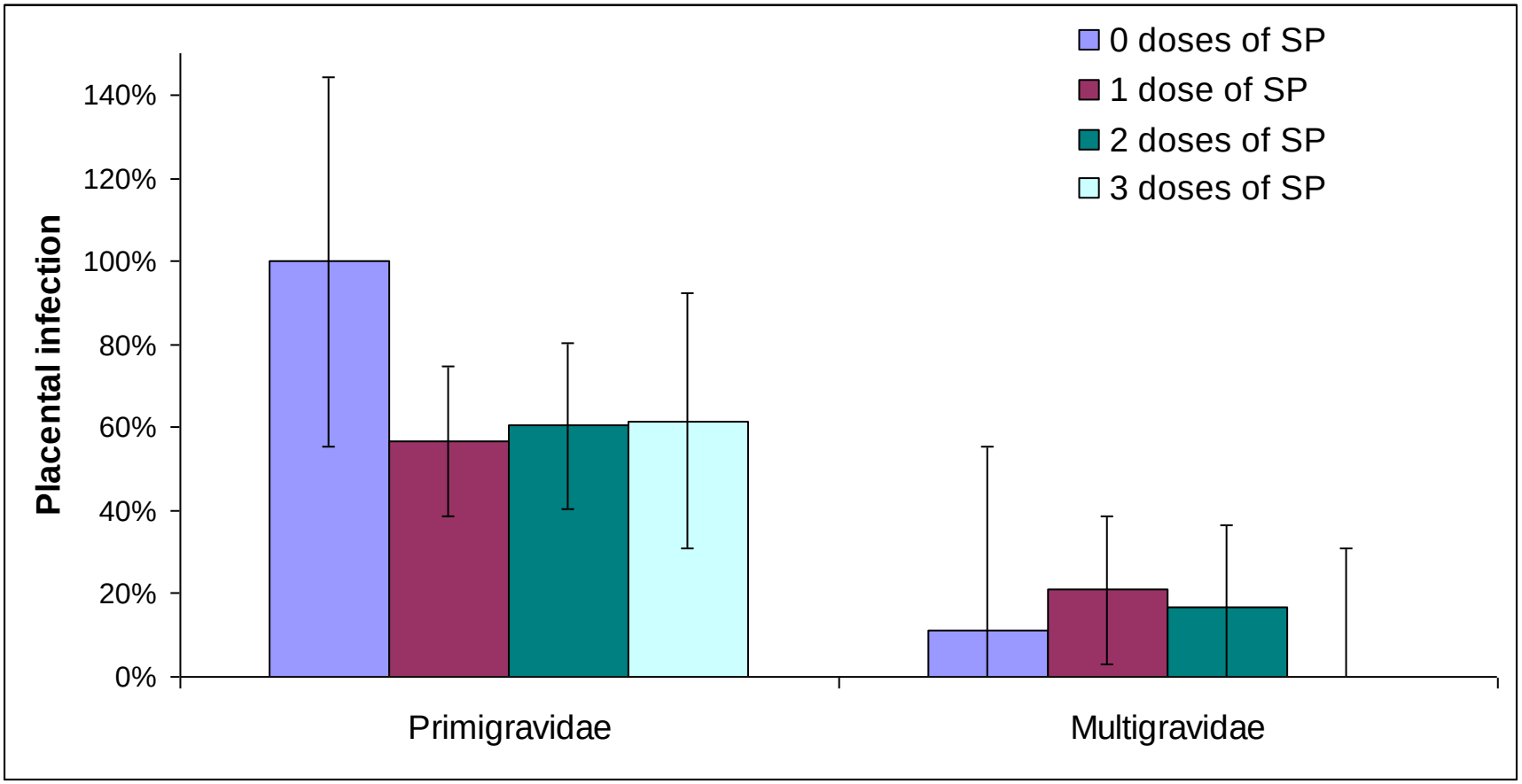


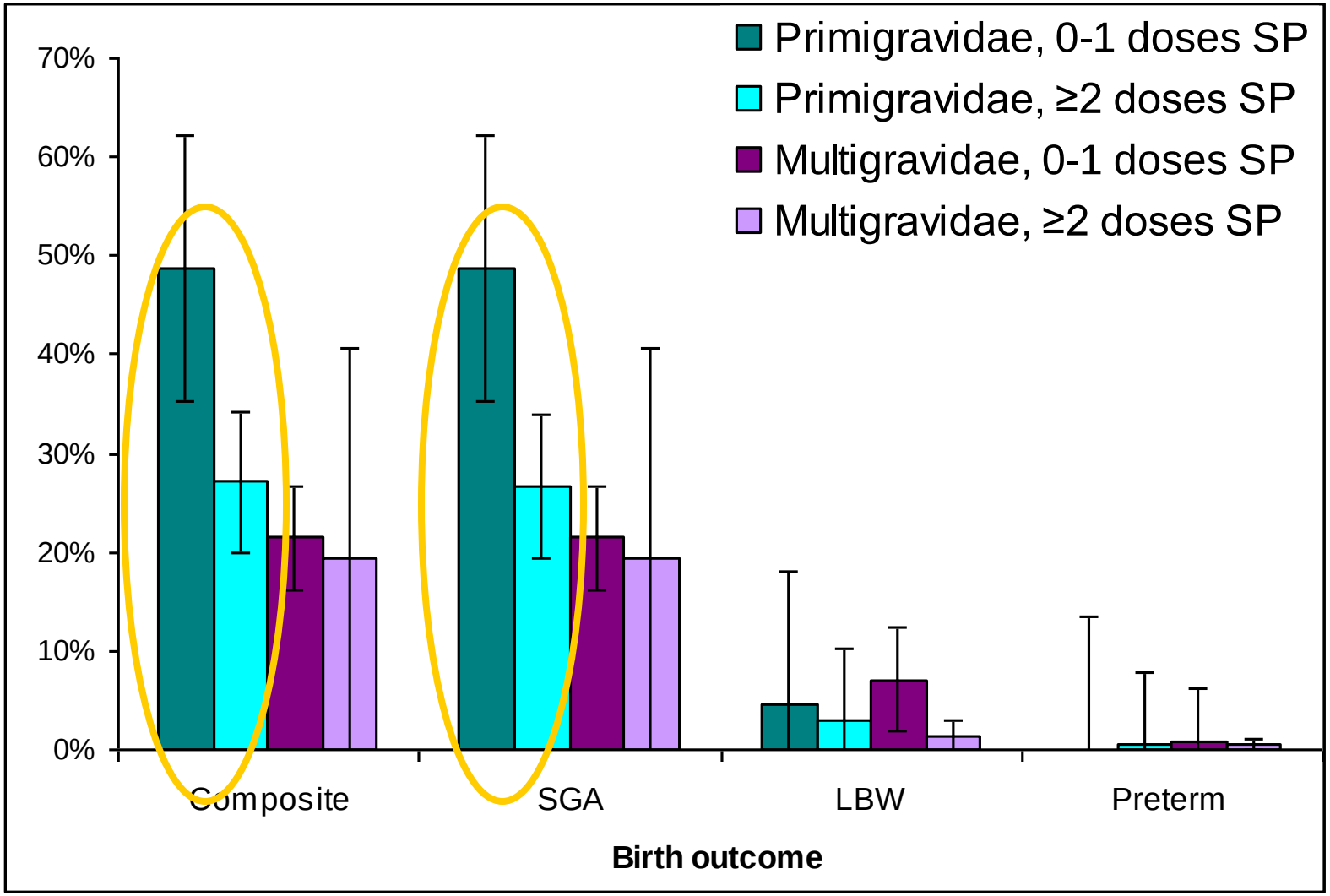
# *In vivo* survival (uncorrected) stratified by age and gravidity



# Effect of increasing number of SP doses on placental infection stratified by gravidity



# Infant outcomes stratified by SP doses and gravidity



# Drug Compliance

# Adherence: 72-hour Follow-up Group

| | Total (N=368) % | <5 years (N=155) % | 5-17 years (N=66) % | ≥18 years (N=165) % |
|---|---|---|---|---|
| **Pill count correct** | 77 | 71 | 77 | 82 |
| **Correct adherence by recall:** | | | | |
| **Number of doses** | 78 | 72 | 82 | 82 |
| **Number of doses and pills/dose** | 76 | 71 | 79 | 81 |
| **Number of doses, pills/dose, and timing** | 68 | 60 | 67 | 76 |
| **Adherent by pill count & recall** | 65 | 57 | 61 | 73 |

# Significant Predictors of Adherence

| | Adjusted odds ratio (95% CI) |
|---|---|
| **Age Group** | |
| **<5 years** | **0.5 (0.3-0.8)** |
| **5-17 years** | **0.6 (0.3-1.2)** |
| **≥18 years** | **Ref** |
| **Migowi health centre** | **2.5 (0.9-6.7)** |
| **Nambazo health centre** | **0.6 (0.2-1.5)** |
| **Phalombe health centre** | **Ref** |
| **First dose given at health centre** | **2.4 (1.3-4.7)** |
| **Medication package used to give instructions** | **2.5 (1.1-5.4)** |
| **Patient prefers LA compared to other antimalarials** | **2.7 (1.5-4.7)** |

# Rapid Diagnostic Tests studies

Chinkhumba *et al. Malaria Journal* 2010, **9**:209
http://www.malariajournal.com/content/9/1/209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## Comparative field performance and adherence to test results of four malaria rapid diagnostic tests among febrile patients more than five years of age in Blantyre, Malawi

Jobiba Chinkhumba[1*], Jacek Skarbinski[2], Ben Chilima[3], Carl Campbell[2,7], Victoria Ewing[4], Miguel San Joaquin[4], John Sande[5], Doreen Ali[5], Don Mathanga[1,6]

# Future work

- New drugs for IPTp – DHA piperaquine
- Monitoring of the current drug regimen
- New RDTs
- Mapping resistance


PRESIDENT'S MALARIA INITIATIVE




# Thank you