MACEPA PATH
Malaria Control and Elimination Partnership in Africa

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Government of the Republic of Zambia

First year results from the Community-led Responses for Elimination (CoRE) trial assessing the effectiveness of reactive focal drug administration compared to reactive focal test and treat in reducing *Plasmodium falciparum* infection prevalence and incidence in an elimination setting in Southern Province, Zambia

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Background

As countries have experienced great progress in controlling malaria, case numbers can be reduced to a point where it is feasible to reactively seek and treat all infections in the index case and neighboring households. We are evaluating two alternative approaches in a two-year Community-led Responses for Elimination (CoRE) trial consisting of two arms. The first (control) is Reactive Focal Test and Treat (RFTAT; the current standard practice) where households in a 140m radius of the index case are tested with a rapid diagnostic test (RDT) and, if positive, treated with artemether-lumefantrine. The second (intervention) is Reactive Focal Drug Administration (RFDA) where all individuals living in the 140m radius from the index are presumptively treated with the longer acting dihydroartemsinin-piperaquine (Figure 2).

Methods

Sixteen health facility catchment areas (HFCAs) in four districts in Southern Province, Zambia (Figure 1), were selected for CoRE enrolment. Reactive case detection (RFTAT or RFDA) was performed by community health workers (CHWs) within seven days with follow-up on day 3 to look for adverse events and drug adherence. A subset were also visited on days 30 and 90 (Figure 3). Dried blood spots were collected from this cohort and tested for *P. falciparum* by polymerase chain reaction (PCR).

Figure 1. Map of the health facility catchment areas enrolled in the CoRE study in Southern Province, Zambia

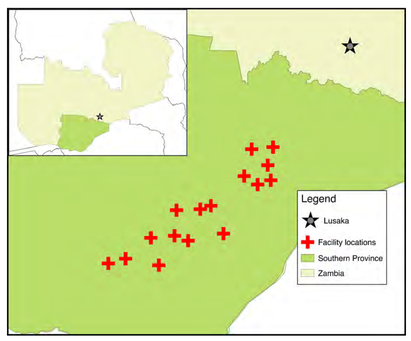


Table 1. PCR results by household type

Index household?	PCR result	
	Negative	Positive
No	46.97% (635)	3.91% (5)
Yes	50.03% (717)	96.09% (123)

Figure 2. RFTAT with AL versus RFDA with DHAP schematic

Individuals are tested and treated (A) or presumptively treated (B). RFTAT fails to treat the sub-patent reservoir (C) enabling onward transmission (E), whereas all individuals are treated with RFDA (D) and protected from reinfection (F) for the duration of the drug. Individuals are shown as infected (red), uninfected (black) or uninfected with chemoprophylactic cover (blue), and as patent (seated) or sub-patent (standing) infections.

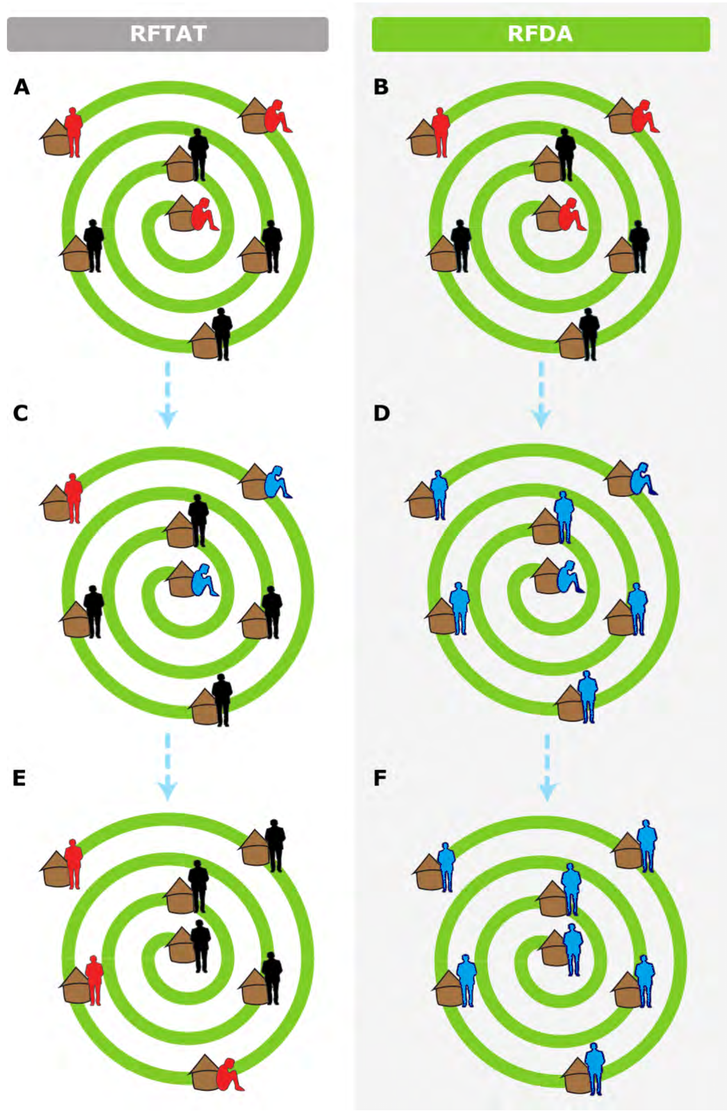
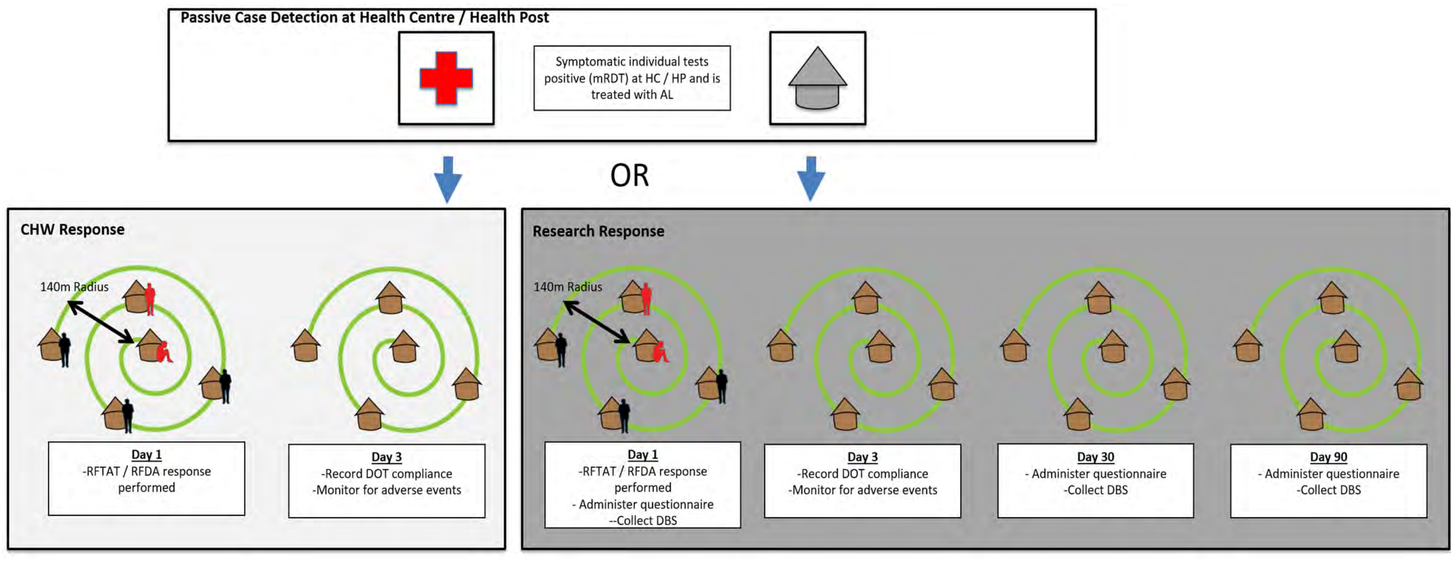


Figure 3. Summary schematic of interactions for participants enrolled in the CoRE study

mRDT: malaria rapid diagnostic test; HC: Health Centre; HP: Health Post; AL: Artemether Lumefantrine; DBS: Dried Blood Spot; DOT: Direct Observed Therapy



Acknowledgements

Thank you to all the participants and district and provincial staff for their involvement in the study.

Table 2. Summary information for the first year of the CoRE trial

Arm	Index cases	House-holds	People	Treated	People per house	Travelled
RFTAT (control)	34	61	394	20	6.5	13
RFDA (intervention)	48	147	840	777	5.7	65

Results

Falling malaria

Historical analysis of the facilities enrolled in CoRE identified significant reduction in adjusted incident rate ratio over time (Table 3). A significant increase in the proportion of confirmed cases reporting travel was also observed (Table 4).

Inter-arm differences

A number of historical differences prior to the initiation of the trial were identified, with the intervention arm showing increased number of cases tested, confirmed cases, and test positivity, while the control arm showed increased outpatient attendance. No statistically significant differences were observed between the two arms.

Table 3. Incident rate ratio of confirmed malaria incidence
N = 937 observations, 16 health centres

Year	Incident rate ratio (95% confidence interval)	P-value
2012	Reference	Reference
2013	1.07 (0.90 – 1.28)	0.446
2014	1.00 (0.83 – 1.21)	0.998
2015	0.82 (0.68 – 0.99)	0.039
2016	0.69 (0.52 – 0.90)	0.006
2017	0.48 (0.31 – 0.74)	0.001

Table 4. Proportion of confirmed malaria cases at health centers reporting travel by year

Year	Number confirmed cases	Confirmed cases reporting travel
2014	475	2.9% (14)
2015	773	15.7% (121)
2016	743	30.0% (743)
2017 (Jan—Apr)	305	38.7% (118)

Conclusions

PCR analysis shows that transmission is highly heterogeneous with almost all (96%) infections identified in the index household (Table 1). Similarly, index cases were almost exclusively the only individuals to test positive by PCR on a day 30 or 90 visit. This may suggest a high-risk lifestyle or a treatment failure. Samples will be genetically analysed for both eventualities.

At the population level, first-year results showed no significant difference between the two arms. It is, however, too early to accept this as the final outcome with one year left.

A significant challenge for CoRE is the scarcity of infection events (both confirmed malaria incidence and malaria parasite prevalence).

When evaluating impact in an elimination setting, sample sizes can become prohibitively large. Thus, the endline survey will determine the primary outcome using serology, a measure of cumulative exposure, to maximise outcome events. It is hoped that CoRE data can be pooled with an ongoing trial in Swaziland to increase sample size.