



Global Health
EDCTP3

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SEMA ReACT

**Severe Malaria treatment with Rectal artesunate and Artemisinin-based
Combination Therapy [in remote settings]**

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Medicines for Malaria Venture



Tropical Diseases
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Background and rationale

Malaria mortality U5 SSAfrica:~483K/year.

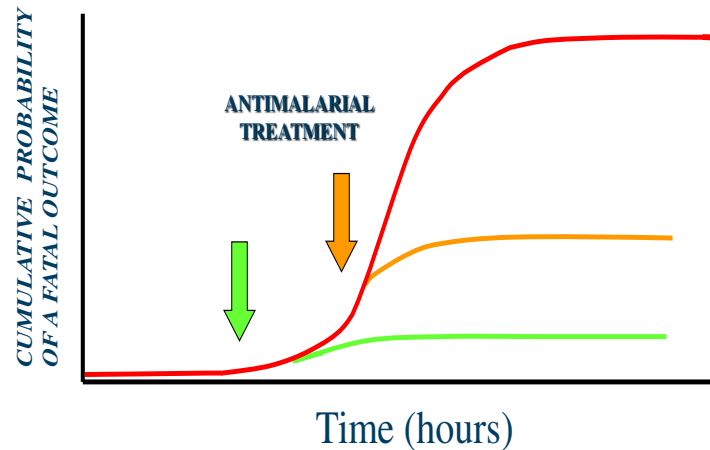
Timely access to effective antimalarial therapies can make a difference between life or death

- Complete treatment with pre-referral rectal artesunate (RAS), followed by injectable artesunate and 3 days treatment with ACTs) leads to an observed 96% reduction in mortality

Though recommended by WHO for years,

- RAS deployment is very limited,
- Roll-out paused following WHO Information Note*
- Moratorium RAS unjustified

Strengthening PHC is beyond remit of national malaria programs (Remote) & socially deprived communities may be without access to higher-level medical facilities
→ timely referral is practically not feasible.



Need to evaluate the accessibility, feasibility and efficacy of alternative treatment modalities for patients in remote settings where referral cannot (or should not) be completed

*in response CARAMAL Results



Hypothesis

Deployment of rectal artesunate (RAS) in the CHW drug kit

- Improves access to formal health care
 - By community members who would have otherwise sought care from elsewhere
- May indicate a decreased mortality at population level

Deployment of amoxicillin in the CHW drug kit

- Improves access to formal healthcare
 - By community members who would have otherwise sought care from elsewhere
 - May indicate a decreased mortality at population level
- for **both malaria** and other diseases!

RAS + ACT

- Can be implemented in remote areas in children 6 months to 5 years
- Is not inferior to RAS + Injectable artesunate + ACT in terms of effectiveness



Implementation: Primary Objective

Primary objective

To evaluate **feasibility of provision of rapid treatment of severe malaria with RAS in children 6 months to 5 years not able to access a referral health facility, by a community health worker or in health facility where there is no injectable artesunate available**

Secondary objectives

1. To assess the **feasibility of referral** in remote areas
2. To determine the **impact of the use of RAS + ACT and /or antibiotics** intervention provided as part of iCCM by CHW on health seeking behaviour
3. To assess **feasibility and acceptability of pre-referral** intervention using RAS+ACT or antibiotic or ORS in children 6 months - \leq 5 years
4. To determine **barriers and facilitators affecting health seeking practice** from initial signs of sickness to first contact for health care
5. To assess **consistency in supply of iCCM commodities** in the community health workers' drug kit

Clinical effectiveness: Primary Objective

Primary objective

To evaluate the **recrudescence rate of RAS plus ACT treatment** for patients 6 months to 5 years in areas where referral for follow-up treatment with injectable artesunate is not feasible, compared to outcomes obtained after full referral is completed.

Main secondary objective

1. To determine the **survival rate at day-28** in patients aged 6 months to 5 years diagnosed with severe malaria initially treated with RAS versus those having been initially treated with injectable artesunate

Secondary objectives

1. To evaluate the **recurrence rate of RAS plus ACT** treatment for patients 6 months to 5 years in areas where referral for follow-up treatment with injectable artesunate is not feasible, compared to outcomes obtained after full referral is completed

2. To **compare the recrudescence rate at day-28** in patients 6 months to 5 years diagnosed with severe malaria initially treated with RAS plus ACTs versus those having been initially treated with RAS and received injectable artesunate (and ACTs) after referral

3. To **compare the impact of RAS with either antibiotic or ORS** treatment on survival, recrudescence and mortality

4. To determine the **genetic diversity, drug resistance and multiplicity of *Plasmodium falciparum*** infections isolated from children with severe malaria at the selected study sites

Study population

Children 6 –59 months of age living in Kapolowe (DRC) & Nchelenge (Zambia)

- With a suspected diagnosis of severe malaria, confirmed by a rapid diagnostic test, or
- Non-severe malaria, confirmed by a rapid diagnostic test severe or
- Non-malaria severe disease

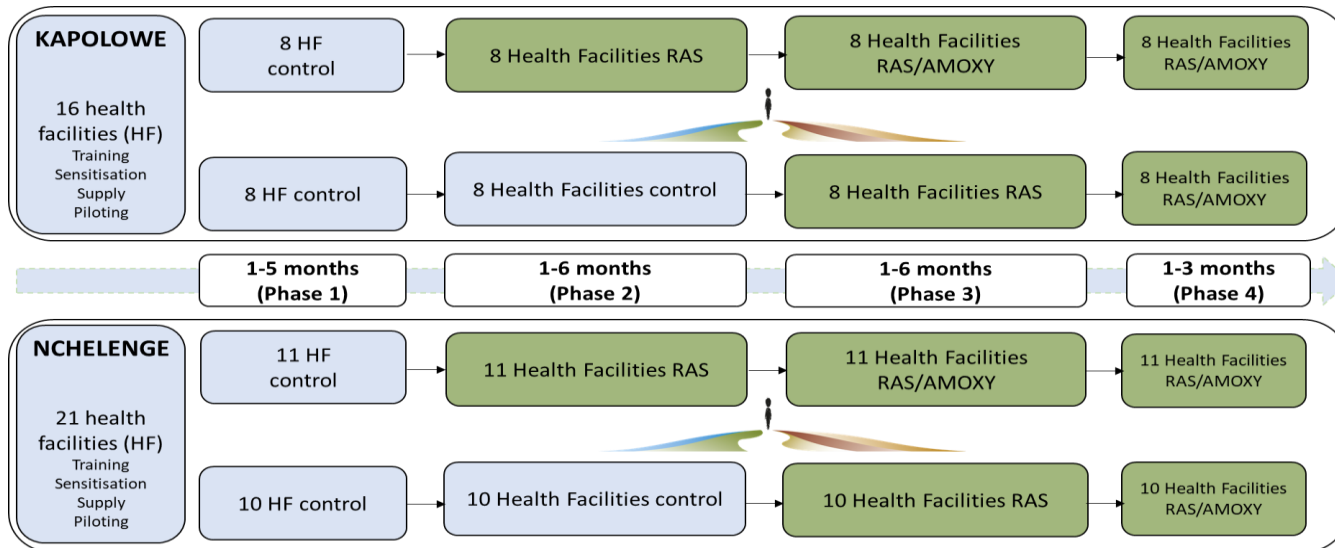
Other target groups include

- Parents of U5 at risk of severe malaria
- WHO's Global Malaria Program, NMCPs, funders and implementers
- Communities and nations where severe malaria deaths in small children continue to occur unabated (in rural regions)

Both sites are expected to recruit the required number of study participants based on malaria transmission and experience with previous studies



Study design Implementation



Effectiveness-implementation hybrid type III

- Two districts (DRC-Kaplowe and Zambia-Nchelenge) were selected fitting the criteria of hard to reach areas

RAS would be implementable through CHWs participating in iCCM*

- HF's will implement iCCM alone at start

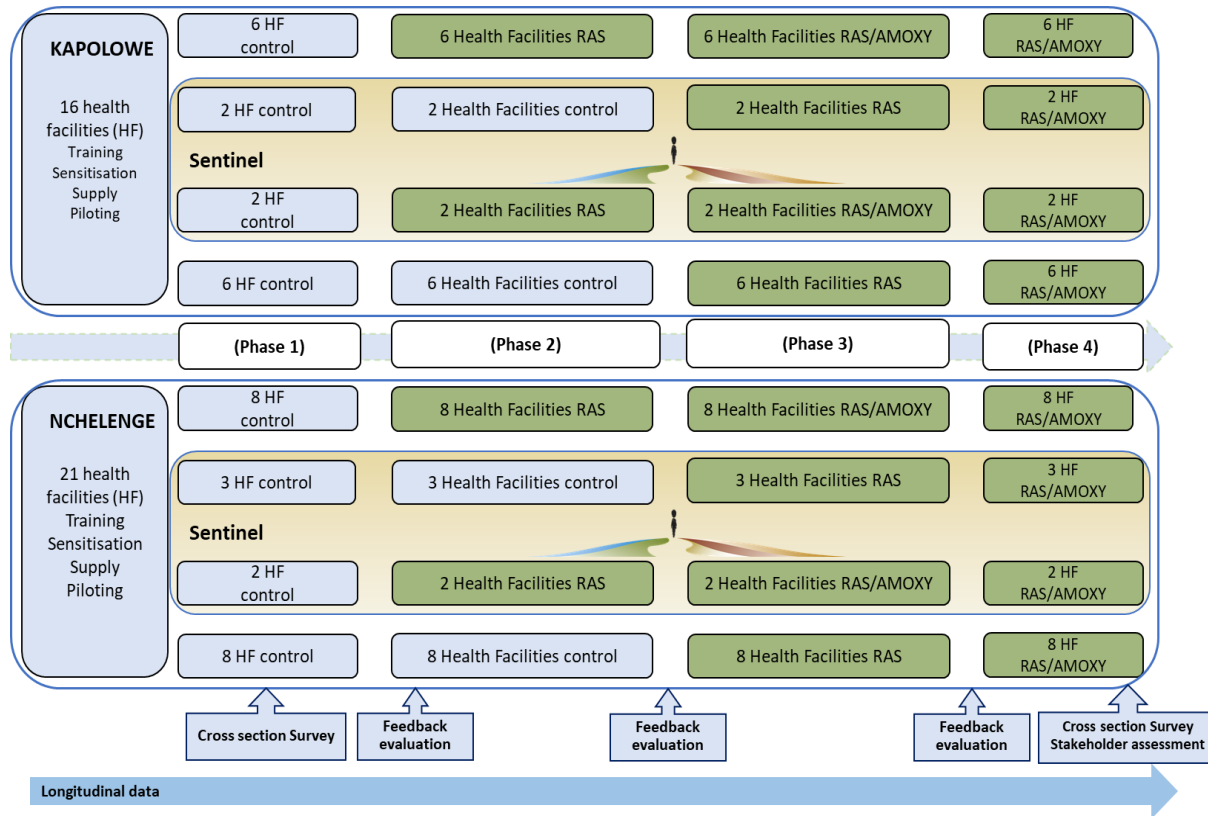
HF be randomized in two groups to implement in a step wedged fashion iCCM with RAS+ACT and later with amoxicillin

Sentinel sites for clinical effectiveness assessment

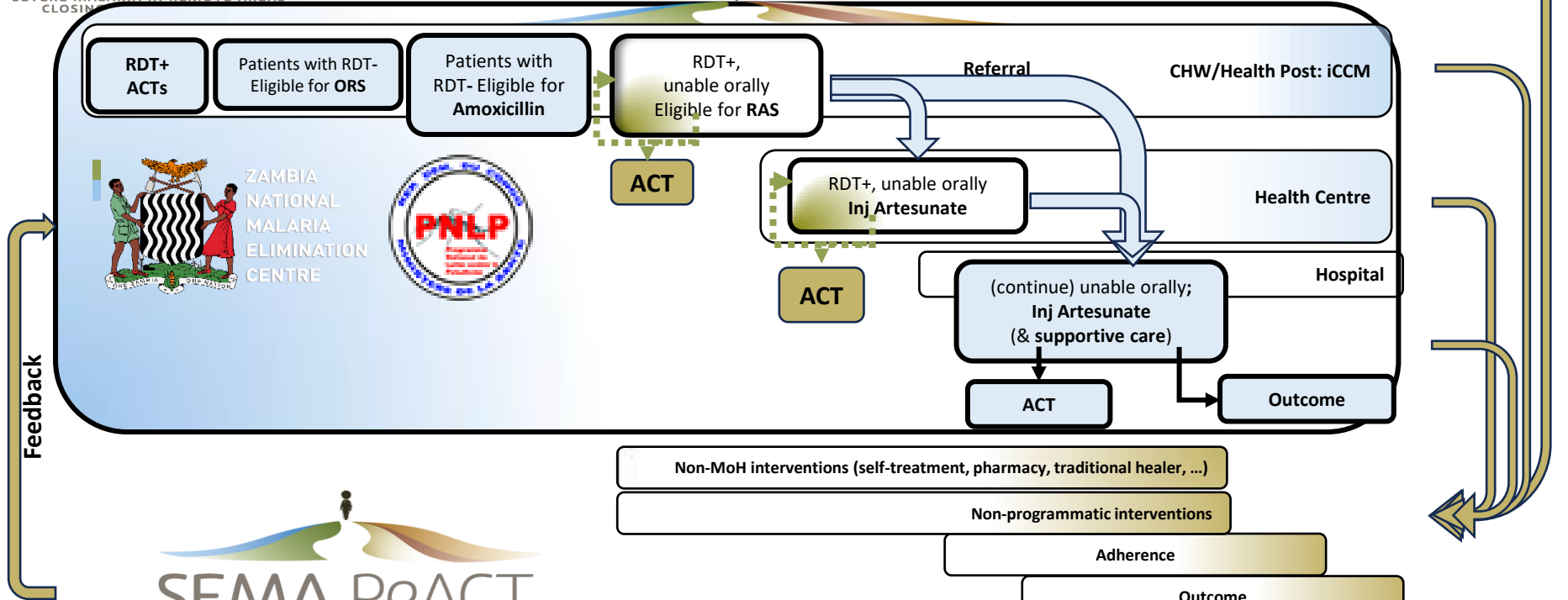
Mixed methods (District levels)

- Cluster randomized surveys
 - Qualitative research
- Methods to get insight into the behaviour of stakeholders when having a severely ill child at community level

(families - health-seeking behaviour, healthcare providers, traditional practitioners, opinion leaders, etc.)



Suspected malaria



Sample Size

Cluster randomised surveys and qualitative assessment (District level: Implementation & Impact)

- 900 (30-by-*30) /study site. to achieve a $\alpha < 0.05$ for any estimated prevalence.

Qualitative assessment (FGDs, semi-structured interviews) (District & Sentinel sites)

- will be conducted until saturation of information is reached

Implementation assessment: % < 24hours (Sentinel sites)

- Treatment-seeking proportion of 90.5% before the intervention (RAS) and 98.4% after. (Hussey and Hughes, 2013)
- intra-cluster correlation (ICC) of 0.1 and a cluster auto-correlation (CAC) of 0.1, 80% power, two-tailed test with $\alpha=0.05$
- → 864 severe malaria cases needed/site

Clinical effectiveness assessment: 28-day PCR-corrected cure rate (sentinel sites)

- 8,713 patients will be screened → 697 (8%) RAS eligible
- 80% power; $\alpha=0.05$; margin of inferiority at 5%; 8% RDT+ are RAS eligible; equivalent 97% cure rate.
- → 209 and 450 in RAS+ACT arm and RAS-injectable artesunate+ACT arm, respectively
- Calculating backwards in the algorithm, → **697 participants on RAS** → 8713 positive RDT.

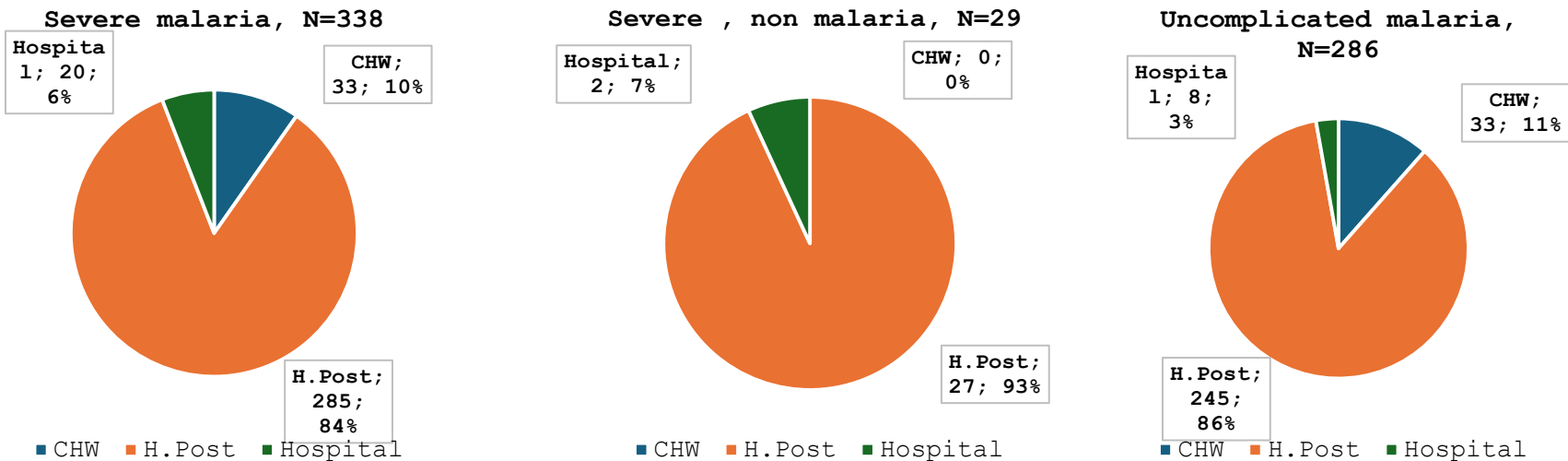
For each severe malaria case, one non-severe malaria case will be recruited (~8% of cases)
Severe cases eligible & treated with amoxicillin will be recruited. (~ #severe malaria cases)



LONGITUDINAL STUDY- PHASE 1 RESULTS- KAPOLOWE DISTRICT



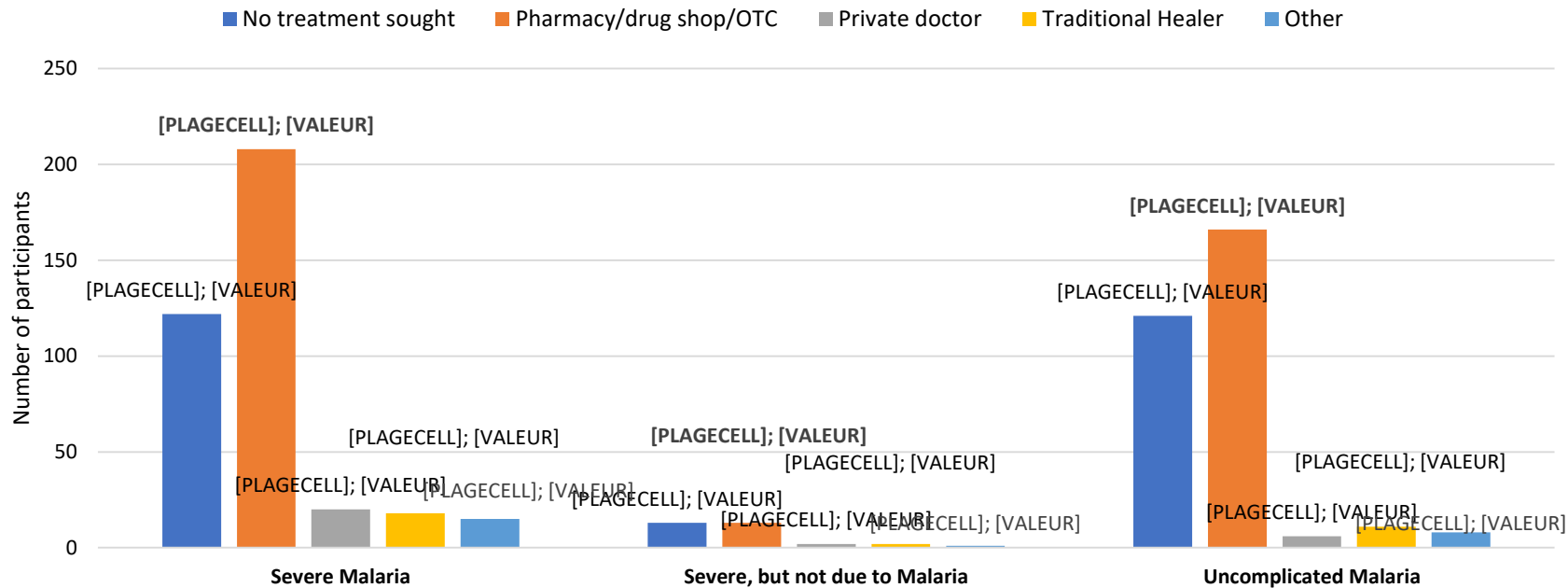
Recruited Participants in Phase 1 (11 March to 1 July) 4 sentinel sites- Kapolowe, DRC



We successfully recruited a total of 653 participants during Phase One. By case category, **H.posts recruited > 84% of all cases, while CHW recruited about 10% of severe and non severe malaria cases.**



Site where treatment was sought before Facility Visit



More than 70% of participants regardless of disease stage / type had first sought treatment at a pharmacy / drug shop or over the counter (OTC) before seeking care at a health care facility.

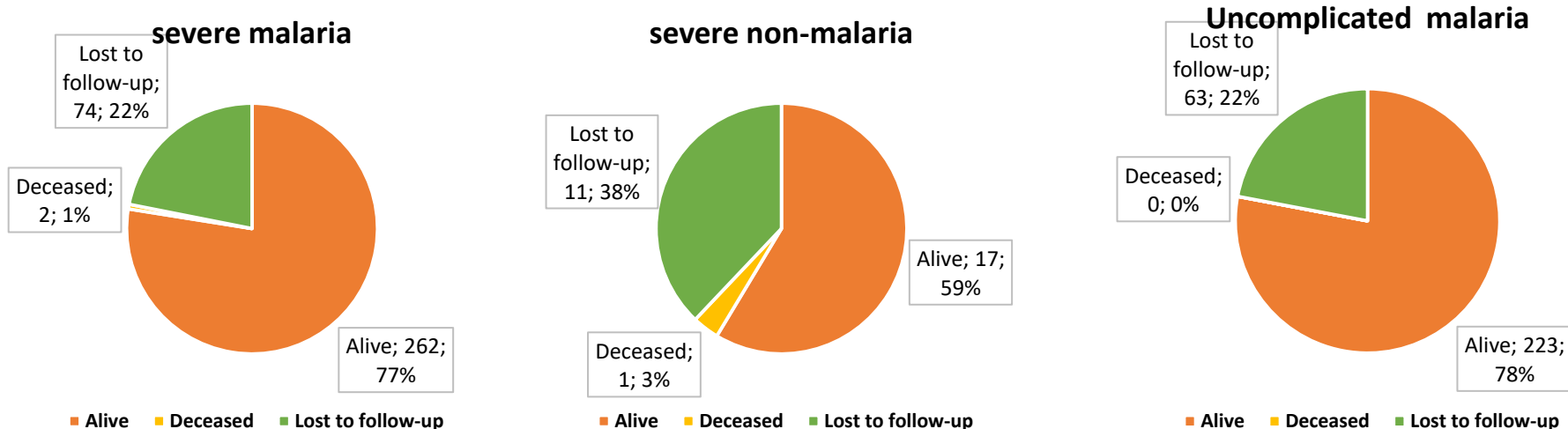


Timelines to seeking care and treatment on arrival

Severe malaria	Median	Q1-Q3
Median number of days taken before seeking care	3	2-4
Median time in minutes between:		
arrival and first treatment at CHW	10	7-14.3
arrival and first treatment at Health Post	10	5-20
arrival and first treatment at Hospital	15	12-17
Severe non malaria		
Median number of days taken before seeking care	3	3-7
Median time in minutes between:		
arrival and first treatment at CHW		
arrival and first treatment at Health Post	15	5-30
arrival and first treatment at Hospital	20	15-35
Uncomplicated malaria		
Median number of days taken before seeking care	3	2-4
Median time in minutes between:		
arrival and first treatment at CHW	18.5	7-41
arrival and first treatment at Health Post	10	5-20
arrival and first treatment at Hospital	12.5	10-30



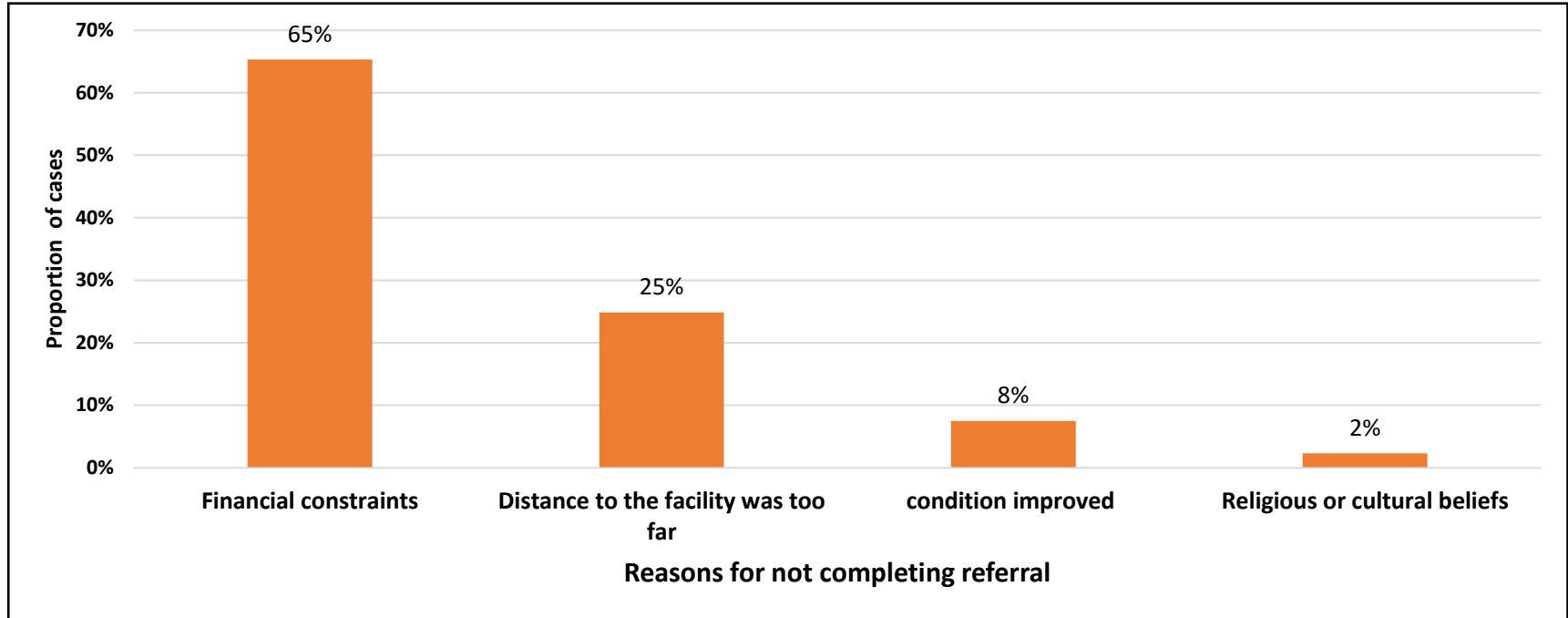
Follow-up period: Day 14 status



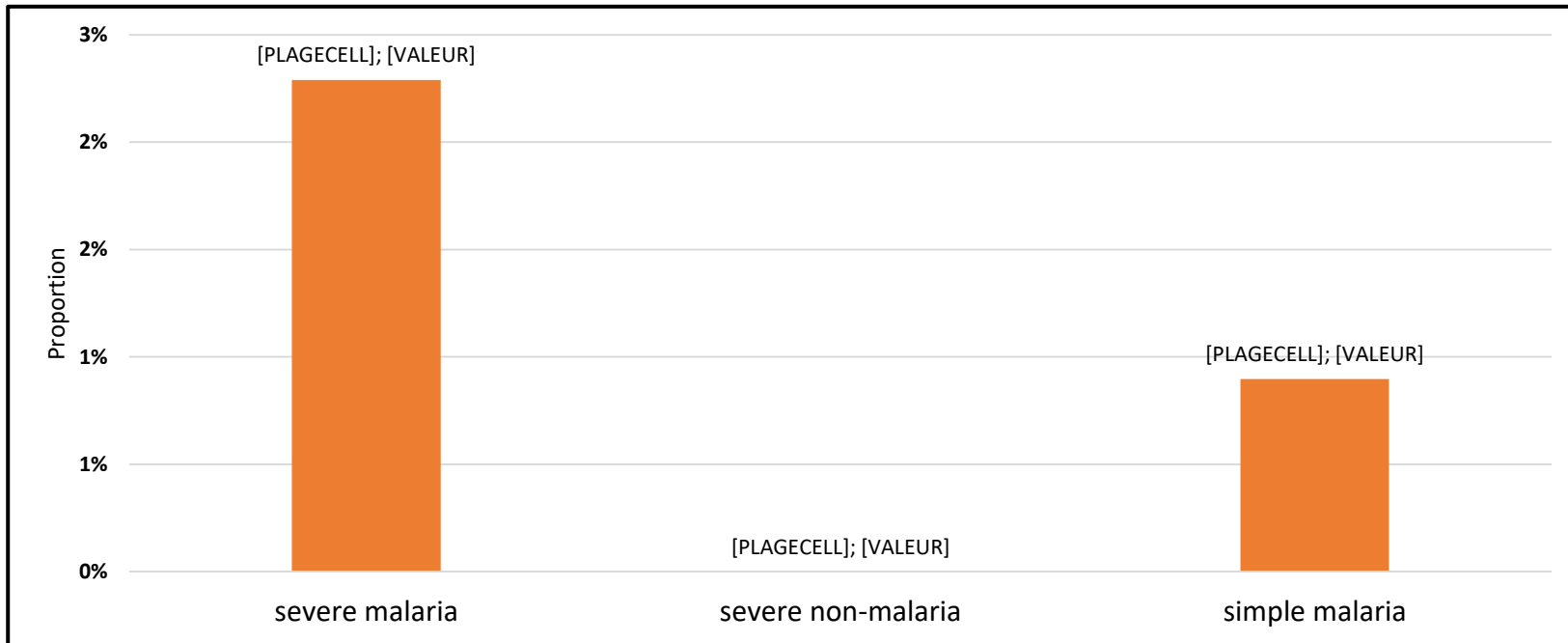
Out of the 653 participants, 77% (502) were alive at the Day 14 visit, 0.5% (3) were deceased, and 23% (148) were lost to follow-up. 8 (2%) of alive participants were still in bad condition at day 14.

Referral execution in remote areas

Out of 262 children alive on Day 14, 241 were referred to higher facilities. **Only 6 (2%) completed the referral trip.** The following are the main reasons for non compliant to referral:



Recurrence of malaria since initial treatment

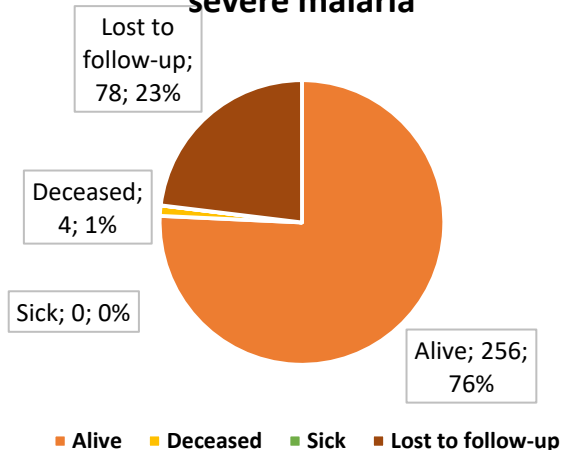


At Day 14, 6 children initially diagnosed with severe malaria experienced a recurrence, compared to only 2 children initially diagnosed with simple malaria

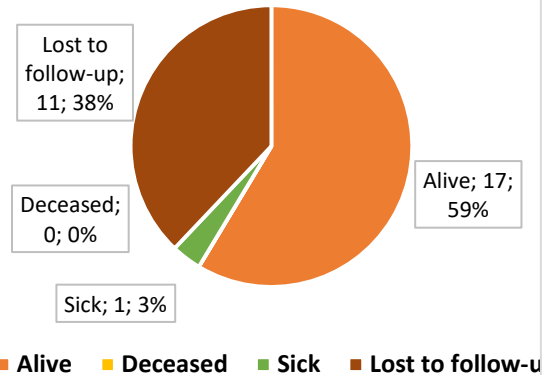


Follow-up period: Day 28 status

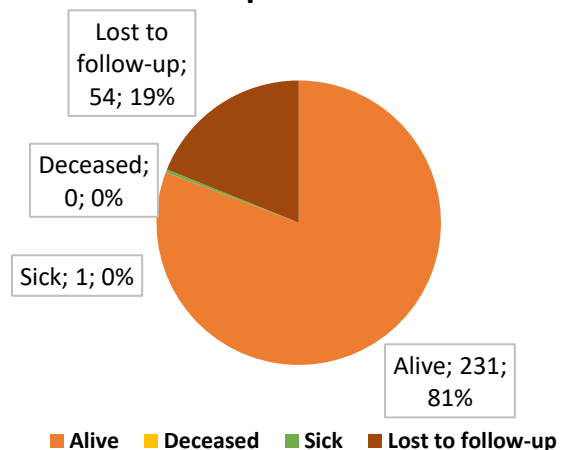
severe malaria



severe non-malaria



Uncomplicated malaria



At the Day 28 visit, out of the 653 participants, 77% (504) were alive, 0.6% (4) were deceased, 0.3% (2) were sick, and 22% (143) were lost to follow-up.



Day 14 and Day 28 follow-up status

Day 14 Follow-up status	Day 28 Follow-up status		Total
	Yes	No	
Yes	468	37	505
No	42	106	148
Total	510	143	653

Out of the 653 participants, 77% (505) were followed-up at Day 14, and 78% (510) were followed up at Day 28.

Among these, 72% (468 out of 653) completed follow-up at both Day 14 and Day 28.



Severe cases in DHIS2 vs SEMAReACT

	Severe malaria cases		Uncomplicated malaria cases	
	SEMAReACT	DHIS2	SEMAReACT	DHIS2
Kapolowe Gare	38	21	28	249
Koni 1	88	7	65	739
Koni 2	53	104	49	377
Kyembe 2	159	145	144	552
Total	338	277	286	1917

Overall, DHIS2 recorded 453 severe malaria cases across the entire Kapolowe District, while SEMAReACT recruited 338 severe cases from its 4 sentinel sites within the district.

There is a need to examine the difference in severe cases recording on the two systems



Preliminary qualitative results from phase 1 - KAPOLOWE DISTRICT



Results: Qualitative assessment day 14

These results are based on the three-delay model:

- **Decision to Seek Treatment:** Participants reported that waiting between 3 and 7 days before seeking treatment is a common practice within the community.
- **Access to Healthcare Facilities:** The availability of transportation, poor road conditions, and the cost of transport were identified as significant barriers.
- **At the Health Facility:** Issues include inadequate infrastructure, the high cost of care, and frequent shortages of medical supplies.



Results: Qualitative assessment day 14

Acceptability from RAS:

- With regard to knowledge of RAS, almost all of the households surveyed were unaware of it.
- Despite their initial lack of awareness about RAS, participants expressed a strong willingness to accept it.



CROSS SECTIONAL SURVEY RESULTS- KAPOLOWE DISTRICT



KAPOLOWE, DRC.



The district is situated approximately 100 kilometres from Lubumbashi, the provincial capital.

The population of Kapolowe primarily engages in agriculture, fishing, and artisanal mining as their main occupations.



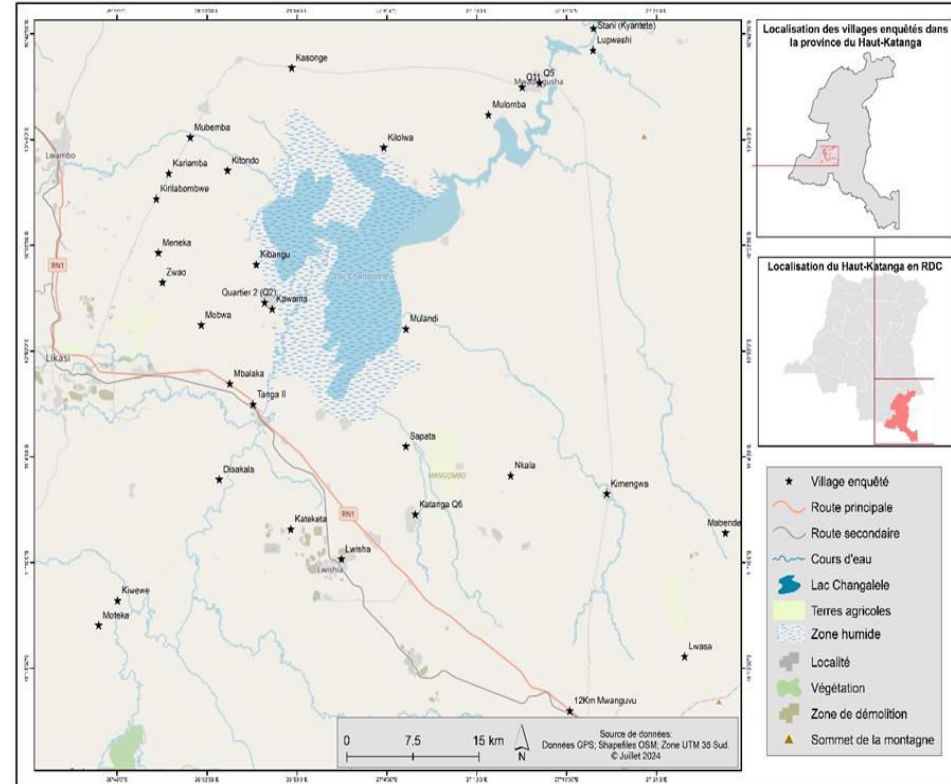
SURVEY METHODOLOGY

The survey aimed to collect data from 900 households across Kapolowe district, adhering to a 30-by-30 cluster randomized survey design. [Oxfam Practical Health guide (*Jaspars and Khogali 2001*)]

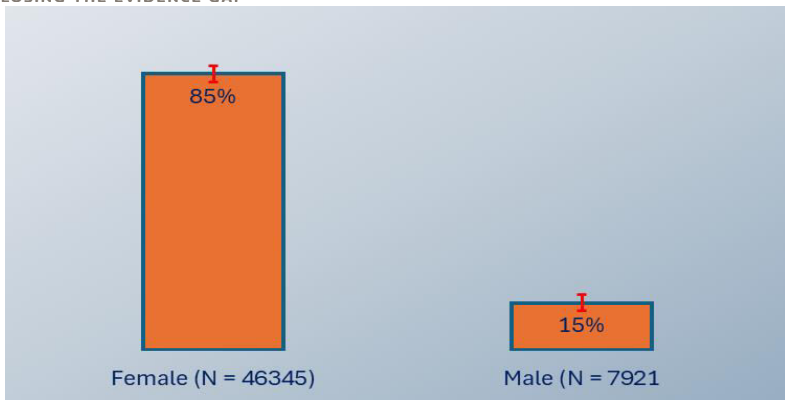
Thirty villages were selected from 181 villages across 16 health areas within 5 distinct Axes in Kapolowe.

In cases where a village had fewer than 50 households, the village was combined with the nearest neighbouring village and treated as a single unit for the survey.

Households were included in the survey if they had children aged 5 years or younger.

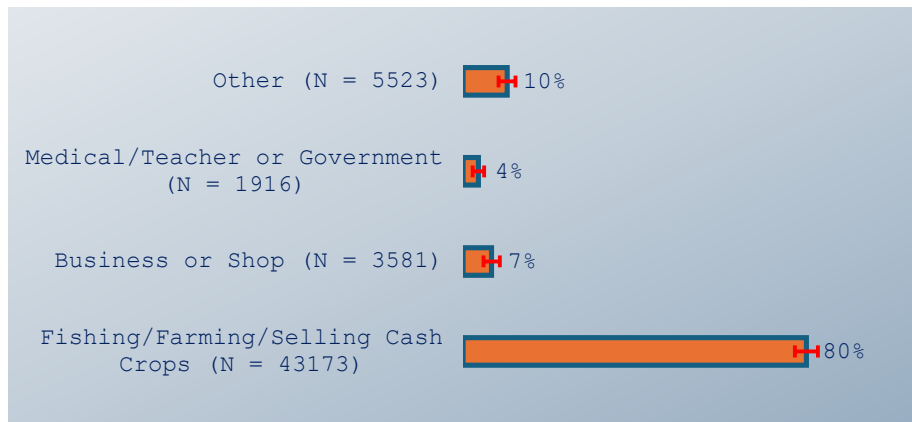
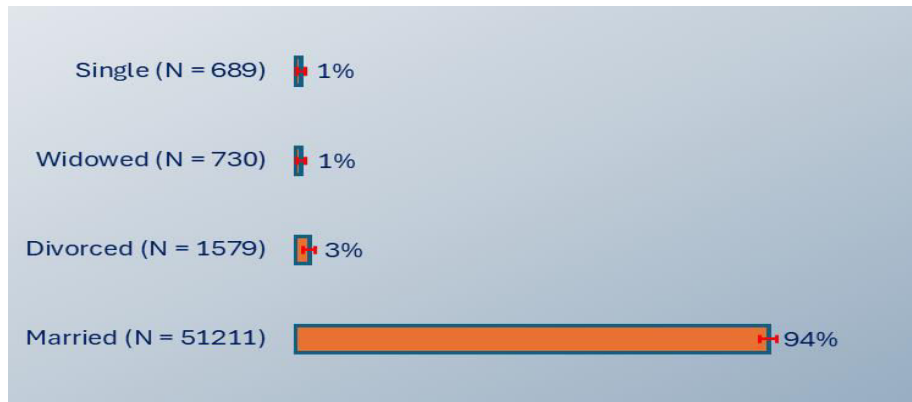


RESULTS: Demographics

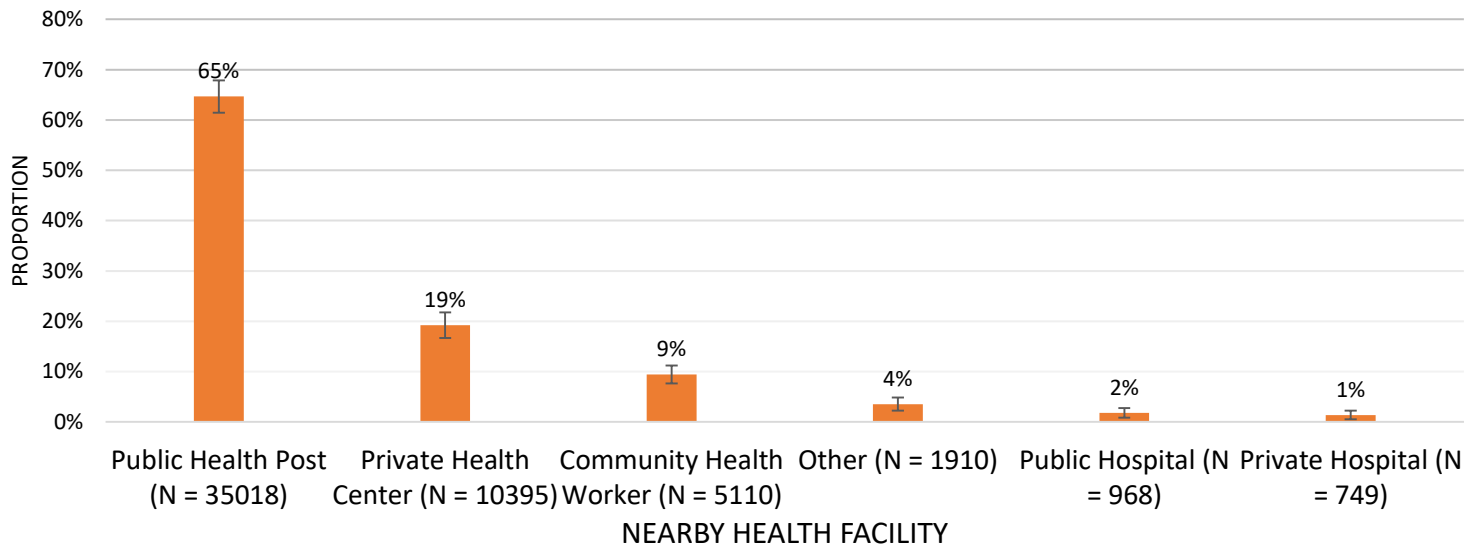


	%	95% CI
No education (N = 10638)	20%	17% - 22%
Primary education (N = 26880)	50%	46% - 53%
Secondary education (N = 13199)	24%	21% - 27%
Diploma/Degree (N = 3312)	6%	4% - 8%

Female respondent 85%, >75% literate, >80% involved on fishing/ farming/ cash crops. Average Household size was 6 individuals



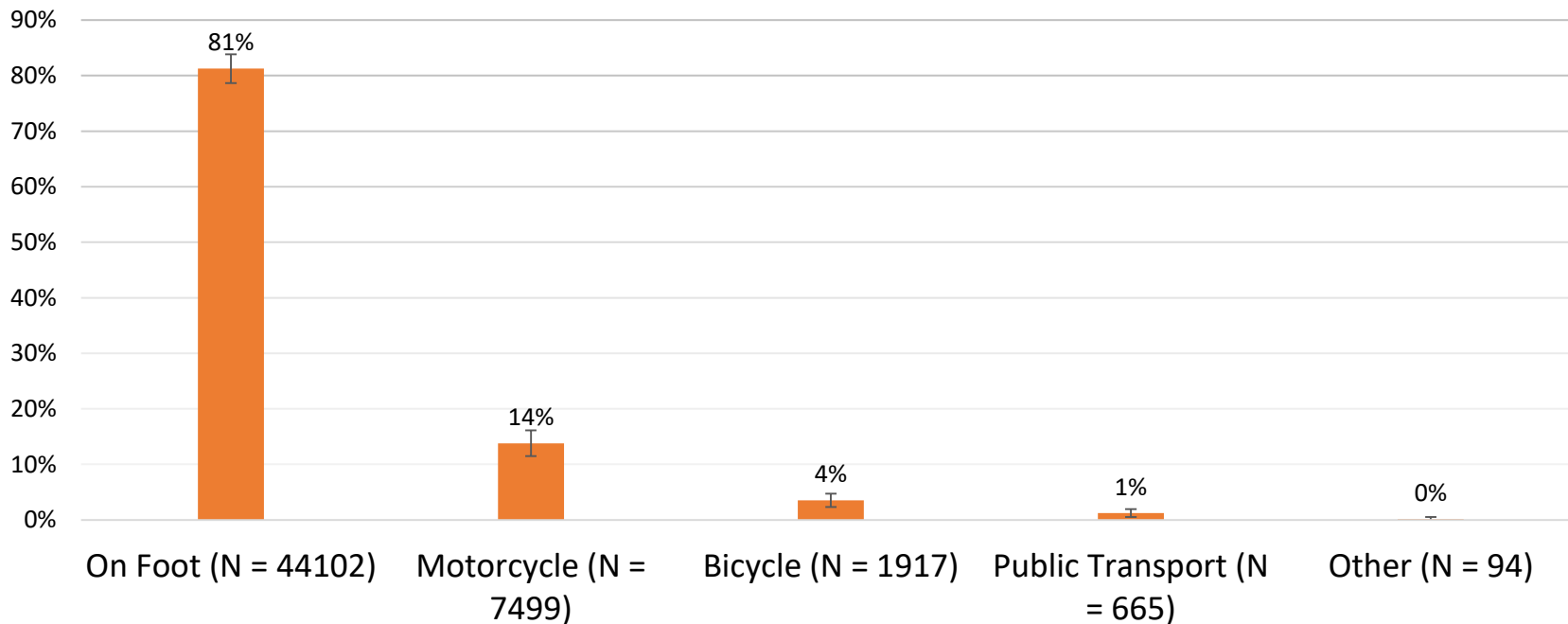
Nearest Health Service to Household Residence



The majority of households, 65% (95% CI: 61% - 68%), identified a public health post as the nearest health service to their residence



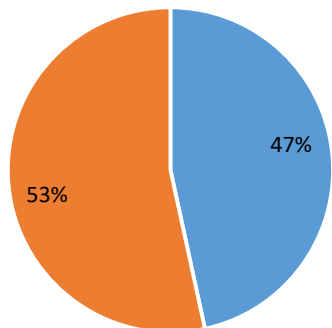
Primary Mode of Transportation to Nearest Health Facility



The majority of respondents, 81% (95% CI: 79% - 84%), reported they travel on foot to the nearest health facility

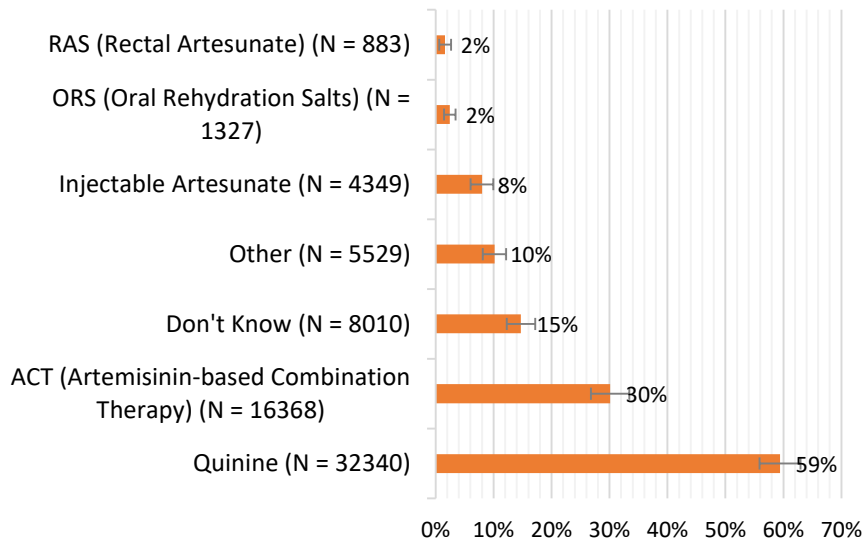
Awareness of malaria messaging, treatment and CHW in the area

Awareness of malaria messaging

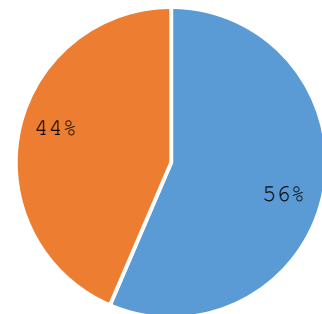


■ No (N = 25284) (95%CI: 43% - 50%)
 ■ Yes (N = 28980) (95%CI: 50% - 57%)

Awareness of malaria treatment drugs



Awareness of CHW in the area



■ No (N = 18042) (95%CI: 54% - 59%)
 ■ Yes (N = 13917) (95%CI: 41% - 46%)

47% had not heard any malaria messaging over the past 6 months, Quinine was the most commonly mentioned (59%) drug as the treatment of malaria. However, in health areas with available CHWs, the majority of respondents (56%) were unaware of any CHW they could contact in case of illness.

Treatment seeking behaviour and timing by malaria and health facilities categories and malaria testing

Treatment-Seeking Behaviour (suspected **Uncomplicated Malaria**) – **78%** caregiver sought treatment

Treatment-Seeking within 24 hours (suspected **Uncomplicated Malaria**) – **36%** caregiver sought treatment in 24hours

Treatment-Seeking Behaviour (suspected **severe Malaria**) – **81%** caregiver sought treatment for their children

Treatment-Seeking within 24 hours (suspected **severe Malaria**) – **35%** caregiver sought treatment in 24hours

Formal HF were the **primary source** of treatment for **uncomplicated malaria** cases, with **61%** of children

Formal HF were the **primary source** of treatment for **severe malaria** cases, with **65%** of children

Among children with symptoms of **uncomplicated malaria** cases, **73%** underwent testing for children

Among children with symptoms of **severe malaria** cases, **81%** underwent testing for children



Other general findings and Mortality reported

CHWs played a minimal role in the treatment of malaria, with only 1% of caregivers reporting CHW involvement in the care of their children.

A total of N = 952: 95% CI: 495 - 1,408 deaths were reported within the past year.

- Of these N = 616: 95% CI: 271 - 961 are suspected to have died due to malaria.


The estimated under-five mortality rate for the district is 12.66 per 1,000 children under five (95% CI: 6.83 - 18.09).





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