Reviewer’s report

Title: From high to low malaria transmission in Zanzibar - challenges and opportunities to achieve elimination

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Reviewer: Siddhartha Mahanty

Reviewer's report:

The authors have conducted a comprehensive analysis of health centre data from two districts of Zanzibar in which interventions to reduce malaria exposure were instituted for a 12 year period. The malaria related indices and metrics are compared periodically over the period of evaluation and show, not unexpectedly, a marked decrease in clinical malaria, childhood morbidity and mortality and transmission-associated entomological indices. The analysis is carefully performed and appears statistically sound (with standard methodology), including microscopy and PCR for parasitaemia. The learning points (for me) from this study are that, 1) intensive exposure control, albeit in a static and somewhat "contained" (island resident) population, can have a significant impact on malaria prevalence and burden; 2) individuals with low, conventionally "undetected" parasitaemia have parasites at low levels, detectable by molecular diagnostics; 3) control of indoor biting mosquitoes uncovers other (outdoors) exposure to malaria transmission. Although the data presented are a cause for optimism for these public health interventions in this specific setting, aspects of the study that need acknowledgement and discussion of the contribution of factors such as changes in socioeconomic status, migration to and from the region, access to health care (changes in level of urbanization), availability of antimalarials from other sources etc., to the decreasing malarial rates. These factors are likely to have significant effects on childhood morbidity and mortality independent of anti-malarial interventions and would be best analysed using techniques such as multifactorial logistic regression, rather than factor-wise (binary) comparisons. The reliance on health centre and community random survey data suffers inherently from biases due to factors such as availability of subjects at the time of surveillance, gender participation differences, and other selection biases. Additional propensity analysis may help in managing such biases.

General comments

* The studies included appear to be a mixture of different sub studies with potentially differing definitions of malaria infections, prevalence, incidence etc. This should be clarified in the manuscript
* A comparison of the malarial indices in adjacent provinces would be helpful in interpreting the effect of migration into the study areas

Specific comments

* Zanzibar is the first region in which the current interventions strategy was used, but where else has this strategy been applied for malaria control? Is there corresponding comparative data to suggest generalizability of the authors' conclusions?

- Cross-sectional survey: only those present at the time of survey were tested - but doesn't this introduce bias - for example working men would be away, and may be more exposed to malaria, etc

* Laboratory methods

- PCR assay - what was the sensitivity of cyan SYBR vs other assays? Was there a significant difference in the sensitivity or specificity of the diagnostic tests at high and lower background rates of malaria?

- ELISA - How was positivity defined?

* Statistical methods

- Fishers tests for association between "risk factors" and infection - What risk factors were considered in this analysis?

* Health facility data

- Rc - needs clearer definition and how was annual reproductive control calculated?

- A definition of "clinical API" should be provided.

* Discussion

- There is insufficient discussion of non-medical, social and environmental factors that could have indirectly influenced malarial indices?

- Sentence on Page 12, Lines 11-12 seems incomplete
What are the denominators in these prevalence rates? Are these from random surveys or targeted populations?

* Table 2 & Figure 2 - how were these surveys performed? What is the denominator for rate calculations? How were subjects selected? Random testing vs symptomatic or self reported?

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If not, please specify what is required in your comments to the authors.

Yes

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Not applicable

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