

PhD defence Heng Somony

Impact of the National Malaria Control Program and an Interventional trial with topical repellents on the burden of malaria disease in Ratanakiri Province, Cambodia

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Dit is de omschrijving

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Summary:

Background

Cambodia had reduced malaria incidence by more than 75% between 2000 and 2015, a target of the Millennium Development Goal 6. The Cambodian government aims to eliminate all forms of malaria by 2025. Today, after more than a decade of active control, malaria distribution appears patchy and hotspots are continuous sources of infection. Moreover, residual malaria transmission due to early and outdoor biting vectors is a great challenge faced by the malaria elimination strategy today. Although use of Long Lasting Insecticidal Nets (LLINs) and Indoor Residual Spraying (IRS) successfully reduced the malaria burden, they cannot prevent the residual malaria transmission. However, these methods combined with additional vector control tools such as topical mosquito repellents could have a synergic effect on malaria prevention. The public health value of a vector control tool does not depend on its effectiveness on malaria infection only, but also on its ease of implementation and achieved coverage. While community distribution of these tools is proposed as an additional malaria control intervention, its safety at the population level should be ensured. Responding to this a randomized community based trial (MalaResT project) was implemented in Ratanakiri Province, Cambodia to assess the effectiveness of mass-use of effective and safe repellents in addition to LLIN in controlling malaria infections and incidence of the disease.

Objectives

The objectives of this thesis were:

1. To estimate the impact of the National Malaria Control Program on malaria incidence and the spatial heterogeneity of malaria cases in the province of Ratanakiri.
2. To explore the implications of malaria heterogeneity for adapting the current intervention strategies to achieve malaria elimination.
3. To evaluate the effectiveness of mass use of effective topical mosquito repellents in addition to insecticide treated bed nets on the burden of malaria in low transmission areas.

Methods

The Malaria Information System (MIS) of Cambodia National Malaria Program (CNM) collects through passive case detection by Village Malaria Workers (VMWs) and Health Facilities (HFs) the malaria cases in the whole country. Data from 2010-2014 of the Province of Ratanakiri were used to calculate annual malaria incidence rates by *Plasmodium* species at province and commune levels. The communal incidences and the number of cases by village were mapped per *Plasmodium* species and per year. Spatial clustering analysis of village malaria cases by *Plasmodium* species was done by year. SaTScan was used to determine species-specific areas of elevated risk for malaria cases.

A spatial clustering analysis was performed using data from a pre-trial survey of MalaResT project (2012) of 5,793 randomly selected individuals living in 117 villages.

This survey collected malariometric data of each participant using a standard questionnaire. A two-step PCR allowed for species-specific detection of malaria parasites. SaTScan was used to determine species-specific areas of elevated risk to infection, and univariate and multivariate risk analyses were carried out.

In the repellent distribution scheme of MalaResT, 135 individuals from 57 villages were appointed to be repellent distributors. A 2-weekly bottle exchange program was organized. Distributors recorded information regarding the amount of bottles exchanged, repellent leftover, perceived side effects and reasons for not complying in household data sheets. Information on individual adverse events, reported by the village distributors, was obtained through home visits. In order to assess the determinants for accessibility and consumption of topical mosquito repellents, distributor-household contact rates and average 2-weekly consumption of repellent were calculated. Regression models were used to explore associations between contact and consumption rates and determinants such as socio-economic status. The safety of mass-distribution of the repellent (picaridin) was described.

In order to evaluate the effectiveness of mass-use of topical mosquito repellent in addition to LLINs, besides PCR malaria prevalence, incidence of malaria cases through routine passive case detection data was estimated for each of the 98 clusters (113 villages) in 2012 and 2013. Incidence per 1000 person-months was calculated as the episodes per person per month at risk. Comparison of treatment groups was done with linear mixed models, taking into account the clustered nature of the study design and the appropriate error distribution based on a Poisson model.

Results

Overall malaria annual incidence rates per 1000 inhabitants decreased from 73.76 (2010) to 25.25 (2014). *Falciparum* cases decreased more rapidly than *vivax* ones. There were 10 to 16 different significant spatial clusters each year. Big clusters tended to extend along the Cambodian-Vietnamese border and along the Sesan River. Three clusters appeared throughout all years 2010-2014: one with 21 villages among the others appeared each year, one was shrinking progressively from 2012 to 2014 and one was split into two smaller clusters in 2013 and 2014.

MalaResT's pre-trial data showed clusters for *P. falciparum*, *P. vivax* and *P. ovale* infections appearing along the Sesan River, while a cluster for *P. malariae* malaria was situated elsewhere. The main risk factor associated with malaria infection was overnight stay in the plot hut, a human behavior associated with indigenous farming.

During the two years of the randomized community trial, distributor-household contact rates increased by four in 2013 compared to 2012 (median2012 = 20 %, median2013 = 88.9 %). Consumption rate tripled over the 2-year study period (median2012 = 20 %, median2013 = 57.89 %). Contact rates were found to be associated with district, commune and knowing the distributor, while consumption was associated with district and household head occupation. Of the 41 adverse events notified by phone by the village distributors, there were 22 adverse reactions, 11 cases of repellent abuse (6 accidental, 5 suicide attempts) and 8 non-related events. All adverse reactions were mild and occurred in the first few months of use of the first year. Skin reactions were the most common. Of the 11 cases of abuse, two were moderate and two life-threatening. All cases with adverse reactions and repellent abuse recovered completely. Twenty percent of the families reported perceived side effects, mainly itching, headache, dizziness and bad smell, but few discontinued repellent use.

Annual incidence rates for all *Plasmodium* species combined, or separately for confirmed *P. falciparum* or *P. vivax* cases did not differ between treatment groups, neither in 2012 nor in 2013.

Conclusions

The decline of malaria burden can be attributed to intensive malaria control activities implemented in the area: one LLIN per person distribution and early diagnosis and prompt treatment. Primaquine was not used for radical treatment of *P. vivax* which would explain the slow decrease of this species due to relapse cases. Future malaria programs in the province should implement additional specific interventions targeting households in the stable clusters appearing over time and people staying overnight at their farms outside the village, in addition to migrants and forest workers.

After the existing public health system was reinforced with programmatic and logistic support, an intense 2-weekly distribution scheme of a vector control tool over a 2-year period was operated successfully in the field. Lack of associations with socio-economic status suggested that the free distribution strategy resulted in equitable access to repellents. Adverse reactions and abuse during mass use of picaridin were uncommon and generally mild, supporting the safety of the picaridin repellent for malaria control.

Adding mass-use of picaridin to LLIN had no community efficacy in controlling malaria incidence and this despite the high efficacy of the repellent against vector bites, and an excellent accessibility through the implemented distribution system. However, daily compliance of correct skin application remained too low to synergize the impact of LLINs on malaria reduction. Suboptimal compliance might be related to disliking the smell, fear of side effect, and the lack of motivation for daily applications.