Resistant humans, mosquitos and parasites in Cambodia

Producing contested evidence for malaria elimination strategies in the margins of a repellent trial

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This thesis aims to contribute to the debate on the validity of knowledge production in global health interventions by exploring how the complex interaction between vector and human behavior, research interventions and disease control policies in the particular context of Cambodia's indigenous population shaped the production of data for malaria elimination research. Presenting the results from mixed methods studies performed within a cluster-randomized controlled trial measuring the impact of topical repellents on malaria transmission among the indigenous slash-and-burn farming population of Ratanakiri province, the author discusses why no such impact was demonstrated at the end of the trial and reflects on research designs that better capture human practices in ways that are useful to public health interventions.

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Samenvatting

Deze doctorale scriptie behandelt de resultaten van twee verschillende malaria onderzoeksprojecten uitgevoerd in de provincie Ratanakiri in Cambodja. Het eerste project bestudeerde sociale factoren die bijdragen tot malaria transmissie op de grens tussen Vietnam en Cambodja. Het tweede project bestond uit een gemeenschapsgerandomiseerde klinische studie die de impact van het gebruik van insectwerende middelen bovenop het gebruik van geïmpregneerde muggennetten op residuele malaria transmissie in Ratanakiri bestudeerde.

De regio waar deze onderzoeksprojecten plaatsvonden wordt bewoond door inheemse volkeren die zich socio-cultureel onderscheiden van de meerderheid Khmer in Cambodja en wordt bovendien gekenmerkt door 'residuele malaria transmissie', wat betekent dat malaria transmissie zich voortzet ondanks de volledige dekking van geïmpregneerde muggennetten en het binnenshuis sproeien van insecticide. Entomologen veronderstellen dat residuele transmissie vooral voorkomt waar malariamuggen in de vroege avond en ochtend actief zijn wanneer mensen niet in hun muggennetten slapen. We bestudeerden de karakteristieken van de relatie tussen mens en vector en vonden een complexe interactie over tijd en plaats, wat vooral te maken had met het vroeg en buiten bijten van malariamuggen, de meervoudige residentie-systemen van de inheemse bevolking, lokale (gedeeltelijk) open huizen, variabiliteit in economische en sociale activiteiten, veranderlijke slaaptijden volgens plaats en seizoen en verscheidenheid in het gebruik van muggennetten door verschillende persoonlijke voorkeuren.

Andere socio-culturele factoren die uniek zijn voor bepaalde sociale subgroepen onder de inheemse bevolking en de Khmer economische migranten die de provincie momenteel onderbrengt, zoals leeftijdsgebonden slaappatronen en structuren, een laag gebruik van preventieve maatregelen en een gebrek aan administratieve registratie op districtsniveau, verhoogden ook hun risico op malaria. Etnografische observaties toonden aan dat de verwachte bescherming van geïmpregneerde muggennetten tegen malaria niet alleen laag was onder inheemse jongeren, maar ook lager dan verwacht onder inheemse en Khmer volwassenen. Alhoewel kwantitatieve surveys een hoog gebruik van muggennetten aantoonden, was het daadwerkelijk gebruik van geïmpregneerde netten veel lager wanneer we rekening hielden met de grote aantallen niet-geïmpregneerde marktnetten die we observeerden in huizen. Door gestructureerde observaties uit te voeren werden deze resultaten niet vertekend door 'response bias' of de vaak onjuiste operationalisatie van het

concept ‘net gebruik’ in gestructureerde vragenlijsten. Door bovendien verschillende structurele vormen van menselijke mobiliteit in Ratanakiri te beschrijven, en de bijhorende risico’s en kwetsbaarheid ten opzichte van malaria, konden we aantonen dat er nood is aan aangepaste preventieve en controle maatregelen voor malaria onder groepen die toch vaak samen gecategoriseerd worden als ‘mobiele populaties’.

De klinische studie rond insectwerende middelen probeerde het gebrek aan bescherming tegen muggenbeten wanneer mensen buiten actief zijn in de avond en vroege ochtend te verhelpen door insectwerende middelen massaal uit te delen aan de lokale bevolking. Alle inwoners werden verwacht om deze middelen twee keer per dag te gebruiken, een keer ‘s ochtends en een keer ‘s avonds, zodat de impact van de potentiële bescherming van het middel op dorpsniveau zou kunnen waargenomen worden. De studie verzekerde de toegang tot insectwerende middelen, het product werd aanvaard door de lokale bevolking en de effectiviteit van de spray om muggenbeten te verminderen werd bewezen. Toch werd er geen vermindering in malaria prevalentie waargenomen op het einde van de klinische studie, een resultaat dat waarschijnlijk vooral aan menselijk gedrag te wijten is. Onze observaties wijzen op een dagelijks gebruik van het product door 8% van de bevolking, een percentage dat ver onder de grens valt van wat er nodig was om een massa effect op de vector populatie te bewerkstelligen en aldus malaria transmissie en prevalentie te verminderen.

Alhoewel menselijk gedrag duidelijk een invloed heeft op de praktijk van gezondheidsinterventies, beschouwen vele wetenschappers dit slechts als een ergernis en een beperking bij het produceren van wetenschappelijke kennis. Het draaiboek van deze klinische studie draaide nochtans anders uit in de realiteit dan verwacht, precies omdat menselijke praktijken de gegevens vertekenden waaruit het primaire resultaat van de klinische studie werd opgebouwd. Context-specifieke factoren, zoals veranderlijk gedrag van studie populatie en studie personeel en de fluide sociale netwerken tussen hen, zorgden ervoor dat het verwachte positieve resultaat van de klinische studie niet behaald kon worden.

Het beschrijven van menselijk gedrag op een manier dat bruikbaar is voor gezondheidsinterventies vraagt om passende onderzoekstechnieken en vernieuwende onderzoeksontwerpen. Ons ontwerp paste zich continu aan aan nieuwe resultaten, combineerde kwalitatieve en kwantitatieve onderzoekstechnieken, leverde wetenschappelijke kennis omtrent de socio-culturele praktijken van de inheemse volkeren in Ratanakiri, verbeterde de epidemiologische data verzameling en resulteerde uiteindelijke in een rigoureuze methodologie die ons in staat stelde om onze resultaten te delen met andere disciplines en antropologische gegevens te vertalen naar een biomedisch gestandardiseerde taal en vorm van kennis productie.

Summary

This PhD-thesis presents results from two malaria research projects conducted in Ratanakiri province, Cambodia. The first research project focused on identifying human factors involved in the maintenance of malaria transmission at the border of Vietnam and Cambodia. The second project concerned a community-randomized trial investigating the impact of mass use of repellents in addition to the use of Long-Lasting Insecticidal Nets (LLIN) on residual malaria transmission in Ratanakiri province.

The region where these research projects took place is inhabited by indigenous people socio-culturally different from the majority Khmer population of Cambodia and is characterized by 'residual malaria transmission', defined as persisting transmission after full coverage of LLIN or Indoor Residual Spraying (IRS) has been achieved. In Ratanakiri, residual transmission is hypothesized to mainly occur by vectors that are active during early evening and morning hours when people are not sleeping in mosquito nets. A close look at the characteristics of the relationship between vector and human behaviour shows a complex interaction over time and place, related to the presence of early and outdoor biting malaria vectors, the indigenous slash-and-burn farmers' multiple residence system, locally used (partially-) open housing structures, variance in labour and social activities, sleeping times according to the place of residence and season, and variance in bed net use depending on related user preferences.

Other socio-cultural factors unique to particular subgroups among the indigenous peoples or among the Khmer labour migrants flooding the province, such as age-specific sleeping patterns and structures, low uptake of preventive measures and lack of administrative registration, also increased their exposure to malaria. Ethnographic observations revealed that the estimated protection from malaria infection by bed nets was not only low among indigenous youth, but also lower than expected among indigenous and Khmer migrant household leaders. While quantitative survey results reported high LLIN use, actual LLIN use was not as high as self-reported data from surveys indicated when taking into account the amount of households where market nets were being used. By carrying out structured observations instead of relying on self-reported use, we avoided response bias and the often sub-optimal operationalization of the concept 'net use' in questionnaires. Moreover, by characterizing the different structural types of human mobility in Ratanakiri, and their differential risk and vulnerability towards malaria exposure, the need for different and adapted malaria prevention and control measures among the groups that are, nevertheless, usually jointly categorized under ‘mobile populations’, is clearly shown.

The repellent trial aimed at filling the protective gap in the evenings and mornings when people are still active outdoors by the mass distribution of topical repellents. During the repellent trial, all inhabitants of the study villages were expected to use topical repellents twice on a daily basis, in the morning and in the evening, with the aim of maximizing the community-wide protective potential of repellents. Access to repellents was assured, acceptance of the product high and efficacy to reduce mosquito bites confirmed. However, no reduction in malaria prevalence could be recorded at the end of the cluster-randomized trial, suggesting that the effectiveness of the intervention mainly depended on human behavior. Our structured observations suggested a daily use by 8% of the study population, far below the minimum required coverage to obtain a mass effect on the vector population and thus on malaria transmission and prevalence.

Although these human practices in turn shape the practice of interventions, many scientists consider them inconvenient challenges and limitations to the production of scientific knowledge. When the protocol of the repellent trial played out into a real life intervention, however, such human practices significantly affected the data upon which the primary outcome of the intervention was built. Due to context-specific factors, variable human behavior of study staff and study population and the shifting social networks in between, the protocol did not work out the way it was intended.

Capturing human behavior and human practices in a way useful to public health interventions requires appropriate research techniques and innovative research designs. A design continually adapted to emerging results, combining qualitative and quantitative research techniques, provided an in-depth understanding of the practices of the indigenous people of Ratanakiri, improved epidemiological data collection and finally resulted in a rigorous methodology that allowed a common mode of communication with other disciplines as well as a translation of anthropological findings to a more bio-medically standardized language and system of knowledge production.

Chapter 1. Introduction

Measuring parasites in the blood of the participants of the repellent trial

This thesis aims to contribute to a debate on the validity of knowledge production that is situated on the margins between an interventionist trial logic and local human practices, both shaping the production of data in global health interventions.

Cambodia: the epicenter of drug resistance and related interventions

Medical intervention trials need human bodies that allow a standardized measurement of certain behavioural or biological parameters in order to produce evidence on the outcome of the intervention. The diversity and variability of human behavior embedded in social contexts, however, is not easily measurable in the standardized way required within the biomedical paradigm. Therefore these ‘human bodies’ often upset the scientific standards that medical research, and more specifically, global health interventions, must adhere to. The problematic variability of unstable human behavior in medical intervention trials has become especially relevant within the geographical context where I undertook my PhD research: a remote province in Cambodia, a country where the emergence of drug-resistant malaria has set the stage for a concentrated investment in the testing of new interventions aimed at the elimination of malaria.

Within the current biomedical paradigm, drug resistance is explained by genetic mutations in malaria parasite populations that are favoured due to repeated exposure to subcurative or substandard doses of antimalarials [1, 2]. Even within this biomedical discourse, scientists agree that a parasite under drug pressure can only evolve to and maintain its resistant form through the use of drugs by people, exposing the social dimension of this biological event [1–3].

Interestingly, Cambodia has witnessed the first emergence of malaria parasite resistance to chloroquine in the late 1950’s and would further provide the stage for the emergence of parasite resistance against the entire line of antimalarials to come until today [4]. According to the more ethnographically inspired discourse of Randall Packard, drug resistance of malaria parasites first emerged along the Thai-Cambodian border area due to a unique convergence of diverse variables – sociocultural, political-economic, ecological and biological [3]. Economic conditions produced by concentrated local mining activities, a consequent mass influx of migrant miners, associated poor living conditions and mass preventive and curative drug intake with subcurative doses led to the first emergence of malaria parasite resistance to chloroquine in the late 1950s. Packard argues that the large workforce in the gem mines of the Thai-Cambodian border region, who often originated from less malarious regions and thus were less immune to the disease, required frequent administrations of chloroquine, both as prophylaxis and as cure, in order to keep the mines productive and their families provided for [3]. They obtained the drugs both from the malaria control program and from the many private practitioners Cambodia is known for [3, 5, 6]. Packard [3] considers that the “value of chloroquine was compromised […] by the immunological status of the mine workers, the method by which the drug was distributed, and the continued influx of new groups of workers” (p. 166-167).

The emergence of drug resistance meant a significant blow to the Cambodian national malaria control program, as it removed an effective and financially reasonable control measure from the limited set of tools available to deal with malaria morbidity and mortality in the country. The program’s need to rely on drugs, and not only on the insecticide DDT as was common practice in the rest of the world during that time [3, 7, 8], was due to the local malaria mosquito species that preferred to stay outdoors instead of resting on the walls inside houses that could be targeted with Indoor Residual Spraying (IRS) [3]. Moreover, the mosquito species had the opportunity to flourish in the many available breeding sites created by the shafts of the gem mines [3]. These socio-economic conditions remained similar throughout the sixties and potentially also contributed to the parasite’s resistance to sulfadoxine-pyremethamine and quinine, the next line of antimalarials, which was first observed in the exact same area in the mid-1960s.

Socio-demographic data from the Cambodian civil war period in the 1970s are difficult to obtain; policy makers and researchers do not know why resistance to mefloquine occurred in the same region in the 1980s [1] (although the refugee camps that were located on the Thai border might have had a role to play). Likewise, it remains yet unclear which divergent forces set the scene for the resistance to artemisinin [9] - and even artemisinin-combination therapies [10] - that developed here again since the turn of the century. However, it is clear that this border zone has always been characterized by constant flows of migrants and the unregulated use of monotherapeutic and/or substandard therapies bought in the private sector [11], which, although usually only mentioned as minor footnotes in the biomedical literature, have been hypothesized as a major contributing factor to resistance [12].

Most literature on drug resistance focuses exclusively on the biological mechanisms underlying the potential genetic mutations of the parasite [1, 4, 9, 13–15]. The importance of the convergence of different socio-economic driving factors that made this historic event possible has only been cited by a few social scientists. Biomedical de-contextualized accounts of resistance to artemisinin-combination therapy, truly the last stronghold in malaria treatment and thus a significant threat to global health, have nonetheless initiated an engagement of scientists worldwide to introduce interventions in the area to contain the spread of drug resistance. These interventions attempt to 'isolate' these parasites from their social and cultural settings in order to produce evidence that global and national health organisations need to scale up countrywide and regional malaria elimination programs [16].

Much of the discussions and decisions about how to manage these Cambodian resistant parasites are taking place outside of the country via the interests and commitments of global health organisations such as the WHO, the Bill and Melinda Gates Foundation, and the Global Fund to fight HIV/AIDS, Tuberculosis and Malaria. The way the Cambodian state translates these decisions to actions on the ground shapes the way people can pursue health in these settings. The ethnographic studies in this thesis show, however, that the people in these remote communities are active participants in malaria control. Through practices of everyday resistance to health policies, including non-adherence to medication and to vector control measures, monotherapeutic or injectionable treatment preferences, agricultural mobility, and alternative uses of malaria preventive measures, they are key actors in the local epidemiology of malaria, and their often hidden practices determine the success or failure of malaria elimination efforts [8].

Cambodian dreams of malaria elimination: a short history

Epidemiologically speaking, this interaction between interventions and people has been relatively fruitful in Cambodia, as malaria prevalence has dropped to very low levels over the last ten years [17, 18]. This low endemicity enables the national malaria control program to orient towards a malaria pre-elimination phase, which is defined as a time point when a country's transmission levels are less than 1 new case per 1000 people at risk every year [19, 20]. Such a state program, building on the ideology of vector control and ultimately aiming to eliminate malaria, is not new, however. When the WHO member states assembled in 1955 to decide on the actions required to control malaria globally, DDT was viewed as the magic bullet after a series of successes in both military personnel during World War II, and among civilians after the war [7]. Spraying DDT on the inside of every house in malaria endemic areas would kill off the vector as soon as it landed on the walls. DDT allowed for malaria to be considered as a 'biological entity' that could be eradicated, and quite cheaply compared to other existing control measures such as drainage and house screening [7, 8]. If implemented fast and on a global scale, the World Health Assembly believed vector control to hold the promise of malaria eradication before the vector could develop further resistance to DDT. This view became embodied in The Malaria Eradication Program in 1955. Although expert committees expressed valid concerns about using only DDT to eradicate malaria instead of a wide array of approaches, the World Health Assembly decided to carry out the eradication strategy anyway, a decision arguably tied to post-war political and economic currents [7]. Although the strategy was partially successful (18 countries achieved eradication by 1970), these were mostly isolated islands or countries with stable economies [3, 8]. Many countries also experienced a decline in malaria morbidity, but as mosquito resistance to DDT began to be observed, national control programs that failed to adopt additional forms of malaria control were undermined [7]. When the eradication program was stopped and control measures abandoned, often due to a belief that malaria was no longer a problem, malaria hit hard and unchecked on a population that had in the meantime lost much of its immunity to the disease. Declining budgets for and interest in sustaining the eradication strategies eventually led to the total abandonment of the eradication ideal by 1969, issuing responsibility back to national control programs for organizing control efforts as part of primary health care infrastructures [8].

The global resurgence of malaria in the context of weakened health systems made scientists and donors realize renewed efforts had to be made. A conference in 1992 came up with a new Global Strategy for Malaria Control, which according to Packard [3] “emphasized the need to shift from highly prescriptive, centralized programs to flexible, cost-effective, and sustainable programs adapted to local conditions and responsive to local need” (p. 217). By 2007, in a context of fast-moving technological innovation underpinning new visions of public health, the WHO and the Bill and Melinda Gates Foundation considered ‘eradication’ to be, once more, a feasible idea [3, 8, 21]. The Global Malaria Action Plan, formulated by the Roll Back Malaria program (RBM), aimed for ‘universal coverage’ of interventions by 2010 and reduction of malaria deaths to near zero by 2015 [8]. Neither of these goals was achieved. Focused on the distribution of control materials to which affected people were expected to comply [3], the importance of local social realities, such as the forced mining and mass treatment conditions along the Thai-Cambodia border that may once have delivered the first resistant parasites, were and are still often viewed in isolation from the epidemiological evidence malaria interventions produce.

The context of malaria elimination interventions

As previously mentioned, to a large extent the scaling-up of control measures was successful in Cambodia [17]. Precisely because malaria prevalence has been drastically reduced, there is now a huge pressure to eliminate the last foci of transmission. Just like during the initial successes of the previous global eradication campaigns, addressing the last few cases and interrupting transmission completely proves much more difficult to achieve. Novel technological measures available within the elimination effort, such as genetically modified mosquitos, topical repellents, spatial repellents, wall-lining, house structure modifications, insecticide-treated products such as hammocks, curtains, blankets, clothes, etc. first require scientific evidence of their effectiveness in order to be adopted and scaled-up by national control programs of endemic countries [22–24]. Many such interventions take place in Cambodia, as finding the strategy that can fully interrupt transmission in the historic and current epicenter of drug resistance may ultimately save the malaria endemic world from spreading resistant parasites.

The production of scientific evidence within the context of a malaria elimination agenda: the case of a topical repellent trial in Ratanakiri, Cambodia

Throughout the next paragraphs and in the chapters that compose this thesis, I will show how the blueprint of guidelines and rules that make 'evidence' valid can in fact limit scientific practice in malaria interventions.

The blueprint of trials

Interventions that want to contribute knowledge to the malaria elimination project usually take the form of 'clinical trials' in order to produce evidence on the effectiveness of a certain tool. 'Trials' are scientific experiments, conducted in field conditions, which follow certain internationally agreed-upon guidelines that, according to Bell [16], allow the production of "simple answers to complex questions" (p. 559).

Although a clinical trial is a scientific experiment grounded in clinical practices [25], when testing a vector control tool's effectivenes the actual clinical part is minimized to the epidemiological measurement of the malaria infection status (i.e. prevalence and/or incidence) of the participants in the trial. Such minimal clinical practices, however, do not exempt vector control interventions from the rules and guidelines of clinical trials, which aim for ethical and scientifically appropriate conduct of research staff while enabling the measurement of a single isolated factor that explains the outcome of the experiment. The discipline of epidemiology, often involved in global health interventions, is intrinsically tangled with these rules of clinical trials. Once epidemiologists aim to produce evidence on the effectiveness of a certain malaria control or preventive tool, they are caught in a system that allows for only one particular kind of evidence to be produced. A commonly neglected methodological implication of this form of research is that it merges ‘research’ with ‘an intervention’: it tests a certain hypothesis by evaluating an intervention that often requires direct implementation within the national public health system of the selected trial country.

Social scientists have laid bare the limitations of clinical trials before [16, 25–31]. For example, Toe showed that the informed consent procedure inherent to clinical trials is in fact ineffective as a participant’s decision to participate in a trial is often made beforehand and based on socio-economic factors [27]. Bell showed that the decision to proceed to implement interventions on a national scale is not always based on the supposed ‘solid’ evidence clinical trials produce: balancing on a heated debate between anti- and pro circumcision scientific and political actors, the strategy of male circumcision could in fact not be scientifically proven to reduce HIV prevalence before national programs went ahead and took it up [16]. Randall shows that the construction of concepts such as ‘household’ - which always need to be measured in health interventions - is often more related to the cultural values of the scientific discipline than the study population, as variations across cultures in the social units composing the household is not usually accounted for in the analyses of survey statisticians [32]. Despite these problems, the kind of evidence produced by epidemiological interventions and trials is still fundamental to producing evidence-based medicine (EBM) and thus its value remains highly regarded in global health practice. The value of doing this kind of science in order to inform national public health programs is therefore not often scrutinized [16].

The protocol of the repellent trial

In 2011, the Unit of Medical Entomology of the Institute of Tropical Medicine (ITM) in Antwerp sent a letter of intent to the Bill and Melinda Gates Foundation (BMGF) to explore their interest in providing a major grant to test whether – as an added control measure to bed nets – the mass use of topical repellents would further reduce malaria transmission in a pre-elimination setting. This vector-based strategy would aim to target the vector by, in addition to killing off mosquitoes landing on long-lasting insecticidal nets (LLIN) while people sleep under them, diverting them with topical repellents prior to LLIN use. The BMGF has had a significant impact on the budget available for such technological innovation today, and was therefore a potential candidate for funding. Specifically in malaria they invest almost $3 billion a year, a significant part of which is allocated to the containment of the Cambodian resistant parasite [21].

The BMGF's emphasis on technological innovation can be understood within the context of the Global Malaria Eradication Programme's failure in the 1950s, which was blamed mostly on external factors, such as insecticide resistance, the environmental problems caused by DDT, and the lack of continued funding to sustain control programs. In the 1990s, with malaria back on the global health agenda, policy makers and malaria researchers seemed convinced that these problems could be tackled with technical innovation and enormous continuous financial investments. Scientists, policy makers and donors believed that the only way to eradicate malaria and therefore stop the continuous funds necessary to control it was to tackle the disease-causing entity and its vector with a breadth of technological innovation [3, 8, 21]. BMGF therefore responded favourably to ITM's letter of intent to explore the potential role of repellents in malaria elimination efforts.

After further negotiations at ITM, medical entomologists and epidemiologists wrote the research protocol "Repellents as added control measure to long lasting insecticidal nets to target the residual transmission in Southeast Asia: a step forwards to malaria elimination". It described an experiment that studied the effect of the additional use of repellents to LLINs on malaria prevalence, a single outcome that would form the 'evidence' this intervention aimed to produce. After successfully going through the necessary ethical committee and institutional review board procedures, and even after officially starting up the project, it still remained undecided whether this intervention in fact constituted a 'clinical trial'. Although it clearly involved 'human subjects', which according the BMGF constitutes the definition of a clinical trial, it involved testing products that were registered as 'biocides', and not medical products. On the other hand, these 'biocides' were being used for medical purposes (the prevention of malaria) and not according to the product specifications for use (the trial aimed for intense and daily application instead of the occasional use the repellent is intended for). After many heated discussions at ITM about the ambiguous nature of the intervention, and especially after the first side-effects of the repellent started being reported by the study population, the departmental heads and the director of ITM decided the intervention must be registered as a clinical trial and comply to Good Clinical Practice (GCP) guidelines.

In the protocol, the principle indicator for the epidemiological efficacy of repellents was the prevalence of ‘parasite carriers’ (the people in whose blood laboratory staff can detect malaria parasites by using a technique called polymerase chain reaction or PCR) in the intervention arm versus the control arm. The measurement of this outcome assumes that the community-wide distribution of the repellent will cause the community-wide use of the repellent. To cover this enormous leap from ‘distribution’ to ‘use’, the epidemiological protocol explains that locally selected distributors will enforce correct use of the repellent with the study population and that leaflet- and poster-based information and education campaigns will make sure they interpret the trial and the use of the repellent correctly. Specific characteristics of the study population that may thwart the measurement of epidemiological efficacy are not mentioned in the epidemiological protocol; the trial designers refer the reader to the independent anthropological study that would be carried out to measure the acceptability of the product. Including such an anthropological workpackage in the trial protocol attempted to include the participants of the trial into the design of the larger interdisciplinary study, without actually including their behavior and practices into the design of the clinical trial itself.

This ‘anthropological work package’ therefore intends to justify ignoring the impact of human behavior and socio-cultural variables on all other levels of the intervention. Applying anthropology in public health interventions is often assumed to legitimize the ‘human factor’ that everybody involved in producing scientific knowledge partly operates with (i.e. related to managing study population) [33]. As the epidemiological approach usually carries more weight in scientific protocols, anthropological insights are often subjugated to the ‘engineering’ of local social processes [34], benefiting the epidemiological outcome of the trial. Brives [25] argues that, within clinical trials, “bodies must be standardized to the greatest extent possible” in order to be able to produce scientifically valid findings (p. 406). Likewise, the epidemiological protocol and intervention seeks to stabilize and standardize human practice by producing both “the results and the objects required to obtain these results” [25] (p. 406). Although the protocol of this anthropological work package delineates the human behavior expected to affect the epidemiological outcome of the trial (mobility patterns, ethnicity, adherence issues with malaria preventive measures), it uses a scientific language meant to render invisible the extent to which factors such as mobility and suboptimal repellent use in everyday life undermine the ability of the trial to measure the epidemiological efficacy of the repellent. Specifically, it aims to measure ‘acceptability’ and 'adherence', concepts that can supposedly be easily integrated in epidemiological data collection and the production of evidence. The anthropological protocol leaves out - consciously - descriptions of the variability of local practices, the fluidity of social processes and networks, and the dynamic and unstable relationship between the study participants and the parasites and vectors that produce the objective parameters in the participants' bodies [25] (i.e. the parasite carriers) the intervention needs to measure. These anthropological concepts do not easily fit with the interventionist logic the protocol needs to adhere to in order to be accepted by institutional review boards, ethics committees and donors. Geissler, a social scientist who has done ethnography in clinical trials, observes that a successful protocol requires some 'inconveniences' to scientific standards to be disguised or hidden from the text. As Geissler [30] argues, "this silence is not usually achieved by suppressing knowledge but through linguistic convention" and indeed, some inconveniences are rather located within the operational and logistical background of the protocol than in the text conceptualizing the science behind the intervention or in the data that shape the final outcome of the trial (p. 13).

Implementation of the protocol: the impact of human behavior on the success of the intervention

Although the technical tools that embody the experiment focus on the vector, the success of the intervention obviously depended entirely on the use of these tools by humans. Therefore, the way the protocol played out in this particular intervention depended largely on the behavior of the study population. Measuring human practice in all its variability and diversity is seen as a challenge by clinical and biomedical researchers who seek to design "good" scientific protocols [35] that describe experimental and technical interventions and allow for 'objective' evidence. A good protocol is meant to convince donors to fund the intervention [35], and donors such as BMGF prefer (bio-)technological innovation [8]. In the case of the repellent trial, biomedical researchers would have to rely on reported repellent use and repellent liquid leftovers as key intervention outcome variables on use, aware that this is not a very 'hard' objective measure. Although the participants in this trial who were meant to use the repellent are in practice just as much part of the experimental design as the repellents and the mosquitos [25], their unstable behavior represents the inconveniences that Geissler describes as 'the unknown knowns' in public health practice [30]. Although scientists involved in global health interventions often are aware of the reality underlying the implementation of their trial, Geissler [30] explains that in fact they "do not know, do not want to know, should not know, or actively unknow them by way of oversight, ignorance, discursive conventions, and alternative terminology" (p. 13).

In the next paragraphs, I will briefly expand on the kind of human behavioural data that is often systematically made 'invisible' in protocols but nevertheless shapes scientific practice and knowledge.

Mobility

Human mobility patterns can be considered one of the main problems in health interventions. Mobility patterns can undermine the scientific methods embodied in the protocol, as data produced in experimental interventions need stability in order to be valid. Brives [25] argues that geographically stable participants are to some extent "objectifiable entities that can be mastered and controlled", which is exactly what clinical trials need in order to produce scientifically valid evidence (p. 406). While some human mobility is driven by factors such as conflict, natural disaster, agricultural development and urbanization, mobility can also be related to other factors such as socio-economic subsistence strategies or traditional residence patterns (i.e. in relation to soil requirements in swidden agriculture) [36]. Given the large sociocultural differences between various types of mobile populations, there is no one standardized way to address the question of mobility in health interventions [36]. As such, human mobility has often been a decisive factor in the failure of health interventions that are initially designed with settled populations in mind or irrespective of potential mobility patterns. Commonly characteristic of state programs [37], interventions implicitly operate on the assumption that individuals and subpopulations are registered and therefore easy to access. Health interventions usually target geographically stable groups, based on the administrative unit of the village or community and associated population census, and consequently fail to reach mobile populations [38, 39]. Moreover, based on the guidelines discussed earlier, clinical trials often have to exclude mobile individuals and mobile ethnic groups as they cannot comply to the treatment during the timeframe of the trial and tend to disappear while the trial is still running. Very few interventions have been successfully conducted among mobile populations, and therefore it remains yet unclear how to deal with this destabilizing factor in public health more generally and in clinical trials in particular. Mobility is one of the key factors that clinical researchers experience as an 'incovenience' [30] and therefore prefer to render invisible in trial designs.

Ethnic relations

The trial that provided the setting for my ethnographic research took place in a remote province in Cambodia mostly inhabited by ethnic minorities [40]. These ethnic minorities, living on both sides of the Cambodia-Vietnam border, have historically been and are still called by different names, such as hill tribes, highlanders, highland people, indigenous people, montagnards, moi (‘savages’), Khmer Leu and Chunchiet [41–43]. Despite internal diversity, these terms represent the highland people as a unitary whole characterized by ‘swidden agriculture’ and ‘animistic beliefs’.

Historically Ratanakiri has been a politically strategic area: the Americans heavily bombarded the area from 1970 till 1973 during the Vietnam war, and afterwards this remote province provided the ideal place for Pol Pot and his Khmer Rouge to base their headquarters. Its remoteness was partly due to the fact that it was populated by these “forest-based highlanders”, who rejected King Sihanouk’s politics because of the active land alienation and the assimilation practices issued by the Khmer government in the 1960s [44, 45]. The indigenous lifestyle that King Sihanouk’s regime wanted to conform to a Khmer lifestyle, however, conveniently provided the Khmer Rouge with the ideal of ‘the peasant’ untouched by the evils of capitalism [45]. The Khmer Rouge Regime, in power between 1975 and 1978 and overthrown by Vietnamese forces in 1979, initially found a large base of supporters among the indigenous peoples of Ratanakiri, as they were promised an “equal” society where they would no longer be subjugated to the Khmer majority [45]. In return for their increased status, however, they had to forcibly give up all cultural practices related to their animistic beliefs and highland livelihood practices [45]. Pol Pot, leader of the Khmer Rouge, collectivized the land, forced them to inhabit the same space, to intermarry, and to practice the same low land agriculture as the Khmers in order for them to truly embody his ideal representation of the ‘peasant’ [41, 44, 46]. The fact that lowland agriculture was completely unsuitable for the highland soils, or that the new husbands and wives did not even speak the same language, was of minor importance to the image he wanted to produce in order to oppose the educated urban population from Phnom Penh. This led to the indigenous peoples’ dissatisfaction with the Khmer Rouge regime. Eventually the brutal killings of non-compliant indigenous peoples led to more than just dissatisfaction and resulted in their mass escape to Laos and Vietnam in 1975 [45]. More recently, the ‘Montagnard’-uprisings in 2002 also caused ethnic fighting along the newly paved road to border gate 19 in Vietnam [43]. During this period, highland ethnic minorities from Vietnam tried to find refuge across the border in Cambodia as their government violently repressed them because of their demonstrations for the return of their lands and the freedom of religion.

During the repellent trial, ethnic relations played out in various ways. In the epidemiological protocol, which included a description of the health information and education campaigns, the local population was not recognized to be culturally or linguistically different from the majority population of Cambodia. During the execution of the intervention, cultural differences with the study population were at the same time highlighted – Khmer staff's conversations being coloured with fear of the enhanced magical powers attributed to the ethnic minorities – and ignored – Khmer staff carrying out all health education and trial information in Khmer instead of a local language. Moreover, this intervention took place in a context of indigenous peoples' motivated distrust towards the Cambodian government on account of land grabbing and displacement issues. The distrust in the national government, and in extension in the public health system, is another factor that the protocol of the repellent trial rendered invisible. Our anthropological studies showed afterwards that this factor did indeed significantly affect the uptake of the intervention.

In summary, the indigenous peoples of Ratanakiri survived several regimes that have tried to wipe out the cultural differences with the ethnic Khmer that inhabit the rest of Cambodia. Contrary to the Khmer Rouge's destructive focus, the contemporary Cambodian state has a vested interest in creating culturally assimilated 'healthy bodies' that can sustain a healthy economic situation. The implementation of specific health programs in local health centres, the control and penalization of private and informal health facilities and NGO sponsored hygiene education in local villages, led by the expertise and knowledge of the National Programs (of malaria, HIV, tuberculosis, etc.), contributes extensively to converting the historically marginalized and non-governed subjects of remote Ratanakiri into controllable, and taxable, citizens.

A defected public health system

In the protocol of the trial, the "unknown knowns" [30] were also expressed by the faith in building the intervention on a national public health system only recently reconstructed after the Khmer Rouge regime's brutal destruction of the medical infrastructure. The current public health system is known to severely lack human resources and materials, hosting a corrupt vertical hierarchy from principal investigators to subcontracted fieldworkers, i.e. a public health system that Feierman describes as being in a constant state of "normal emergency" [47]. The protocol, however, takes for granted a partnership with the Cambodian National Malaria Control Program and its capacity to largely organize and implement the intervention. Such an assumed operational partnership is in fact fictive when considering the very real material inequalities in everyday life (scientific training and equipment, scientific standards, salaries, quality of health care, quality of equipment, freedom of movement, etc.) [30]. These inequalities operate in an unstable landscape between donor's imaginations of scientific practice and ITM's ability to practice science; between the local Cambodian research team's freedom to adhere to scientific standards in practice and the ITM team's requirement to uphold such international standards; between local research teams' and the study population's (historically formed) perception of each other; and between the unequal social status of the majority and the minority groups within the study population.

The logics governing the trial on the one hand, and the public health system in which it operates on the other hand, are not the same [25]. During the trial, there were problems with local salaries and per diems related to corruption in the hierarchical line of the public health system. This influenced the motivation of fieldworkers on the ground, who subsequently did not always make the effort to collect 'real-life' data during the blood collection surveys that constructed the outcome of the trial (i.e. replacing people on the randomized lists with other random people walking around the village; copying answers from previous respondents to fill the lines on the form of the next 10 sampled individuals, etc.). Moreover, incidence rates of the study villages based on the public health system's passive case detection system (malaria cases that have reported at the health centers and were thus registered in national statistics) counted as secondary outcome measures of the trial. Relying on malaria cases recorded in a failing and unreliable passive case detection system proved to be challenging, however, as district malaria staff had not been paid in months to actually write the reports and register the cases in the national surveillance system.

As such, the experiment does not only test whether mass use of repellents may reduce malaria infections in an endemic population; it also trials, in a more covert fashion, whether there is operational capacity for such an experiment, and whether mass distribution efforts can be managed by the 'real-life' public health and program conditions of Cambodia. This is however not seen as an experiment, but assumed as a pre-condition for implementing the trial.

Concluding remarks

The institutional practice of writing a scientifically sound yet attractive protocol requires to not describe 'covert trials' of public health infrastructures, un-generalizable and variable human behavior of study populations and study staff, and material inequalities between researchers absolving the ideals of partnership, as these aspects that shape the practice of science are considered inconvenient challenges and limitations to both the production of scientific knowledge and the acquisition of funds for trials. When the protocol plays out into a real life intervention, however, such practices and inequalities significantly affect the data upon which the primary outcome of the intervention is built. Due to context-specific factors, variable human behavior of study staff and study population and the shifting social networks in between, the repellent protocol did not work out the way it was intended. The practice of science, in the form of the implementation of an intervention in a particular locality, thus exposes a public secret commonly operational in intervention trials [30], discussed informally during dinner at expat restaurants among the different investigators when they exchange their frustrations and challenges in conducting a successful trial, but eventually unspoken of in the official presentation of data and results.

Based on an iterative design of ethnographic and mixed methods research, I have worked within this trial to produce a different kind of evidence, not contingent on single outcome measurements but on the processes underlying them. I have tried throughout the following chapters to show how these 'resistant' events, people and places shaped scientific knowledge, how they challenged the evidence the trial sought and how it led to the reinterpretation of data to comply to international scientific standards of 'evidence'. In this context, 'resistance' refers to the scientific limitations related to contextual variability, issues that are not unique to this particular protocol or intervention trial. Rather than only criticizing the inherent limitations of current scientific practice, however, I recognize these boundaries by proposing broader ways of producing knowledge in collaboration with epidemiologists and other scientists. Iterative processes in scientific practice would allow scientists from different epistemological backgrounds to re-orient the blueprint of scientific practice towards the contextual variability that distorts single isolated measurements.

Overview of the following chapters

In **Chapter two**, I will describe the interdisciplinary research projects I was involved in from design to analysis. These projects allowed me to research the social factors that contributed to malaria transmission, prevention, control and vulnerability in Ratanakiri, eventually leading to the following chapters presented in this thesis.

Chapter three reports on the health seeking behavior with regards to malaria of the indigenous peoples inhabiting the region where the trial took place, explaining how this medically pluralistic site informs and shapes flexible therapeutic itineraries based on a local system of "lay empiricism". Adherence to effective malaria medication is extremely important in the context of Cambodia's elimination targets and drug resistance containment. Although the public sector health facilities are accessible to the indigenous people, their illness itineraries often lead them to private pharmacies selling "cocktails" and artemether injections, or to local diviners prescribing animal sacrifices to appease the spirits. Three broad options for malaria treatment were identified: i) the public sector; ii) the private sector; iii) traditional treatment based on divination and ceremonial sacrifice. Treatment choice was influenced by the availability of treatment and provider, perceived side effects and efficacy of treatments, perceived etiology of symptoms, and patient-health provider encounters. Moreover, treatment paths proved to be highly flexible, changing mostly in relation to the perceived efficacy of a chosen treatment. Despite good availability of anti-malarial treatment in the public health sector, attendance remained low due to both structural and human behavioral factors. The common use and under-dosage of anti-malaria monotherapy in the private sector (single-dose injections, single-day drug cocktails) represents a threat not only for individual case management, but also for the regional plan of drug resistance containment and malaria elimination.

Chapter four will show how this border region between Cambodia and Vietnam presents a challenge for both countries' malaria elimination targets, illustrated by the socio-cultural practices of the at-risk sub group of 'youth' among the Jarai indigenous people inhabiting the border zone in Ratanakiri province, Cambodia and Gia Lai province, Vietnam respectively. Malaria control along the Vietnam-Cambodia border presents a challenge for both countries' malaria elimination targets as the region is forested and potentially characterized by early and outdoor malaria transmission. A mixed-methods study assessed the vulnerability to malaria among the Jarai population living on both sides of the border in the provinces of Ratanakiri (Cambodia) and Gia Lai (Vietnam). A qualitative study generated preliminary hypotheses that were quantified in two surveys, one targeting youth and the other household leaders. Jarai male youth, especially in Cambodia, had lower uptake of preventive measures and more often stayed overnight in the deep forest compared to the female youth and the adult population. Among male youth, a high-risk subgroup was identified that regularly slept at friends' homes or outdoors, who had fewer bed nets that were torn more often than those who slept at home. The vulnerability of Jarai youth to malaria could be attributed to the transitional character of youth itself, implying less fixed sleeping arrangements in non-permanent spaces or non-bed sites. Additional tools such as long-lasting hammock nets could be suitable as they are in line with current practices.

Chapter five explores the mobility patterns of different populations in the study region and the potential impact on malaria vulnerability. Human population movements currently challenge malaria elimination in low transmission foci in the Greater Mekong Subregion. Using a mixed-methods design, combining ethnography, malariometric data and population surveys, malaria vulnerability among different types of mobile populations was researched in Ratanakiri, Cambodia. Different structural types of human mobility were identified, showing differential risk and vulnerability. Among local indigenous populations, access to malaria testing and treatment through the VMW-system and LLIN coverage was high but control strategies failed to account for forest farmers' prolonged stays at forest farms/fields, increasing their exposure. The Khmer migrants, with low acquired immunity, active on plantations and mines, represented a fundamentally different group not reached by LLIN-distribution campaigns since they were largely unregistered and unaware of the local VMW-system due to poor social integration. Khmer migrants therefore require control strategies including active detection, registration and immediate access to malaria prevention and control tools from which they are currently excluded. In conclusion, different types of mobility require different malaria elimination strategies. Targeting mobility without an in-depth understanding of malaria risk in each group challenges further progress towards elimination.

Chapter six explains how local vulnerability to malaria is shaped by a convergence of human practices and local vector behavior. Malaria vector populations in Ratanakiri have developed a propensity to feed early and outdoors, limiting the effectiveness of long-lasting insecticide-treated nets (LLIN) and indoor residual spraying (IRS). The interplay between heterogeneous human, as well as mosquito behaviour, radically challenges malaria control in such residual transmission contexts. This chapter examines human behavioural patterns in relation to the vector behavior, using a sequential mixed-methods study design in which quantitative survey research methods were used to complement findings from qualitative ethnographic research. For the entomological research, indoor and outdoor human landing collections were performed. Variability in human behaviour resulted in variable exposure to outdoor and early biting vectors: (i) indigenous people were found to commute between farms in the forest, where malaria exposure is higher, and village homes; (ii) the indoor/outdoor biting distinction was less clear in forest housing often completely or partly open to the outside; (iii) reported sleeping times varied according to the context of economic activities, impacting on the proportion of infections that could be accounted for by early or nighttime biting; (iv) protection by LLINs may not be as high as self-reported survey data indicate, as observations showed around 40% (non-treated) market net use while (v) unprotected evening resting and deep forest activities impacted further on the suboptimal use of LLINs. The heterogeneity of human behaviour and the variation of vector densities and biting behaviours may lead to a considerable proportion of exposure occurring during times that people are assumed to be protected by the distributed LLINs. Additional efforts in improving LLIN use during times when people are resting in the evening and during the night might therefore still have an impact on further reducing malaria transmission in Cambodia.

Chapter seven describes the use of repellents by the target population in the context of the community-based trial described earlier. As part of a cluster-randomized trial on the effectiveness of topical repellents in controlling malaria infections at community level, a mixed-methods study assessed user rates and determinants of use. Repellents were made widely available and Picaridin repellent reduced 97% of mosquito bites when used properly. However, despite high acceptability, daily use was observed to be low (8%) and did not correspond to the reported use in surveys (around 70%). The levels of use aimed for by the trial were never reached as the population used it variably across place (forest, farms and villages) and time (seasons), or in alternative applications (spraying on insects, on bed nets, etc.). These findings show the key role of human behavior in the effectiveness of malaria preventive measures, questioning whether malaria in low endemic settings can be reduced substantially by introducing preventive measures without researching and optimizing community involvement strategies.

Chapter eight will conclude the thesis, contextualizing the final outcome of the repellent trial in the practice of science as it occurred during the repellent intervention. It further makes recommendations on how we can proceed to improve trial designs.

Between the chapters, short ethnographic **intermezzos** will provide some contextual background, drawing from fieldwork experiences and literature about the study area, and aim to add different shades of meaning to the data presented in the published article that follows.

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Chapter 2. The Projects

Trial staff admiring the first stock of repellents stored at the provincial health department in Banlung, Ratanakiri

A short overview

The results presented throughout the chapters stem from two malaria research projects in Ratanakiri province, Cambodia. The first project (henceforth border malaria project) focused on identifying social factors involved in the maintenance of malaria transmission at the border of Vietnam and Cambodia. The Vietnam-Cambodia border includes five Vietnamese and two Cambodian provinces representing among the most endemic malaria areas in both countries. The border malaria project aimed to assess the effectiveness of national control strategies on both sides of the border. It assumed that differences and gaps between the respective control strategies (for example, difference in the Village Malaria Worker systems and bed net distribution) and mobility (i.e. malaria infected individuals crossing the border), contribute to maintaining a parasite reservoir that constantly supplies new strains across the border.

The second project concerned a community-randomized trial investigating the impact of mass use of repellents in addition to the use of Long-Lasting Insecticidal Nets (LLIN) on residual malaria transmission in Ratanakiri province, Cambodia (henceforth repellent project), and embodies the majority of the research undertaken for this thesis. The repellent project aimed to raise evidence on the effectiveness of the mass use of topical repellents in addition to insecticide impregnated bed nets in controlling malaria infections. This additional tool was meant to address outdoor and early biting transmission, which is essential for achieving the Cambodian government's objective of eliminating malaria by 2025. By using a multidisciplinary approach to cover all potential aspects related to residual malaria transmission (i.e. all transmission which occurs after full coverage of LLIN or IRS has been achieved), this project included three main objectives, each related to a different scientific discipline: epidemiology, entomology, and anthropology. The epidemiological study aimed at assessing the impact of the topical repellent on the prevalence of malaria carriers and malaria incidence, while the entomological study evaluated the entomological efficacy and persistence of the topical repellent on malaria vectors. The anthropological study, that I and the rest of the anthropological team conducted as part of but independently of the trial, aimed to (i) identify factors contributing to the adherence, acceptability and adequacy of these repellents, (ii) assess the use and acceptance of existing control measures, (iii) understand the human behavior related to residual malaria transmission and (iv) investigate the health seeking behaviour of local communities when dealing with malaria.

The respective anthropological work packages in both multidisciplinary studies were conceptualized within the epistemological framework of medical anthropology. Medical anthropology, using the definition of the Society for Medical Anthropology, can be defined as "a subfield of anthropology that draws upon social, cultural, biological, and linguistic anthropology to better understand those factors which influence health and well-being (broadly defined), the experience and distribution of illness, the prevention and treatment of sickness, healing processes, the social relations of therapy management, and the cultural importance and utilization of pluralistic medical systems" [1].

A common thread running through these studies and the following chapters is the research strategy we chose to use: a mixed-method iterative design that combines both qualitative and quantitative research techniques. Methodological triangulation enhances the strengths of the respective methods and allows for qualitative and quantitative data to complement each other during the research process. According to Morse's original notation, the design was [QUAL –> QUAN] [2, 3], indicating qualitatively driven research that informs a sequential second quantitative strand of the research. Before defining questions and survey methodology for the second QUAN strand, the first qualitative strand researched the context that is presumed unknown, and did this by moving from specific observations to broader generalizations and theory (i.e. inductive approach). The detected patterns and generalizations then lead to tentative hypotheses that are further explored both during the QUAL as during the QUAN strand of the study. In addition to the methodological complementarity of qualitative and quantitative methods, such a design allows the combination of self-reporting data collection (surveys and interviews) with respondent independent techniques (participant observation), limiting the expected reporting bias to questions related to the adherence of public health interventions.

Rationale for the research projects

To understand the role of the local malaria epidemiology in Cambodia in justifying the research projects this thesis builds on, a brief explanation of the disease 'malaria' is in order.

Malaria: an interaction between parasites, vectors and humans

Malaria is an ancient disease with references found in Chinese texts dating back as early as 2700 BC. For thousands of year, malaria was believed to be a sickness caused by miasma's and foul air ('mal aria') rising from swamps. It was only in the 1880's, after the emergence of germ theory and the invention of microscopes, that Charles Laveran first discovered this 'swamp fever' to be related to parasites [4, 5]. Four main *Plasmodium* parasite species were found to infect the red blood cells of humans: *Plasmodium Falciparum, Plasmodium Vivax, Plasmodium malariae* and *Plasmodium ovale*. In some forested regions in Southeast Asia, a few human cases of *Plasmodium knowlesi* have also been reported [6], although this species occurs mostly in monkeys. The first symptoms of malaria in humans are usually fever, chills, headache and vomiting. In case of the *falciparum* parasite, the disease may quickly deteriorate and cause death if not treated within 24 hours from the onset of the symptoms. While presenting milder symptoms, clinical relapses are known to occur for both *vivax* and *ovale*, even months after the primary infection [7].

In 1897, Ronald Ross ascertained the mosquito as the vector of the parasite. He found that all *Plasmodium* parasites were transmitted to humans by the bites of female *Anopheles* mosquitos [5]. There are 20 different kinds of *Anopheles* mosquitos and malaria-endemic regions are inhabited by different species of *Anopheles*, exhibiting behaviours particular to the species and locale. In female *Anopheles* mosquitos, the malaria parasite develops into stages that are infectious to humans. The infective form of the parasite, called 'sporozoite', can be transmitted to human hosts through infectious bites. In the human host, the sporozoites travel to liver cells where they multiply and produce merozoites. In the form of hypnozoites, they can also remain dormant in the liver, until a relapse occurs in the case of a *vivax* or *ovale* infection. Merozoites then infect the red blood cells of the human host, where they multiply so successfully that the blood cell bursts, producing the symptoms in the human host characteristic of malaria. Merozoites also develop into gametocytes, which can infect a female *Anopheles* mosquito while it bites a malaria-infected human. In the female mosquito, they eventually transform into the sporozoites that, through the salivary glands of the mosquito, can infect a new human host when the mosquito bites again. Although all *Anopheles* bite at night, in some regions they have been shown to also bite in the early evening and morning. Other characteristics that differ between the *Anopheles* species are whether they prefer to bite humans and/or animals (anthropophagy), whether they prefer to rest indoors or outdoors (exophagy and endophily), whether they live and bite in the forest (sylvatic), and what kind of breeding sites they prefer (shallow puddles, rice fields, etc.). Moreover, *Anopheles* mosquitos have been shown to be able to adapt their behavior in response to environmental impulses, such as reduction of forest habitat, the wide-scale use of insecticides, or the disappearance of a preferred blood meal [8].

Malaria infections are estimated to still cause more than 600,000 deaths each year, despite the myriad of costly interventions that have been implemented worldwide in the past and present to control and eventually interrupt the transmission of the disease 10]. As mosquitos are the primary host of malaria parasites, interventions to reduce malaria transmission often target mosquitos in order to prevent infectious bites. 'Vector control' usually exists of a standardized set of interventions, among which Indoor Residual Spraying (IRS) of insecticide on the inside walls of homes where mosquitos rest and insecticide-treated mosquito nets (ITN) in which people sleep in their homes have been implemented most widely and successfully [7, 11]. Other ways to prevent malaria include prophylaxis, referring to medication that may be taken before and/or while staying in a malaria endemic area. A range of antimalarial drugs exists to treat the disease, use of which depends mostly on the type of malaria parasite the patient is infected with and the severity of the symptoms. Due to the parasite's reduced sensitivity to the single malaria drugs chloroquine, sulfadoxine, quinuine, mefloquine and artemisinin, the most effective treatment currently consists of a combination of artemisinin and another antimalarial drug, known as artemisinin-combination therapies (ACTs) [7].

Malaria is, however, not only a disease of vectors and parasites, but it occurs in and affects specific human populations [4]. Although anyone could biologically be infected by a mosquito bite, the disease has always been more prevalent among economically disadvantaged people, who live in tropical settings, do not have proper housing, live closer to marshes, have unstable incomes or migrant occupations, or have less access to health care [4]. As such, the disease is historically, politically, economically and socially embedded.

Malaria epidemiology in Southeast Asia: a justification for interventions

Malaria is endemic in the Greater Mekong Subregion (GMS) in Southeast Asia, which comprises Cambodia, Laos, Myanmar, Thailand, Vietnam and China's Yunnan province [12]. Malaria control efforts in the GMS face some challenges particular to this region. The epidemiology of malaria is very heterogeneous, shaped by differences in the geographical distribution of malaria, differences in prevalence of the malaria parasite species, a huge biodiversity of *Anopheles* mosquitos with different capacities for transmitting the parasite, and different patterns of human behavior shaping the human-vector contact that enables transmission [12, 6]. Human behavior, for example people (not) using insecticide treated nets or (not) taking combination therapies when confronted with malaria, also influences the biology of the parasite and the mosquito, which in turn shapes the control measures and 'technological innovation' a certain area is assumed to require [13, 14]. Therefore, in order to address this differential behavior both from humans and mosquitos, malaria control programs need innovative measures in addition to the core intervention of LLINs.

Study site and population

The site

The two research projects were situated in Ratanakiri province, which borders Laos to the north and Vietnam to the east. This border province at the fringes of the state has a population of about 150.000, which makes up only 1% of Cambodia's total population [15]. It is one of the least developed provinces in the country; its infrastructure is bad and its people poor. The health indicators in Ratanakiri are poor compared to the rest of Cambodia, as they are governed by endemic diseases such as malaria, typhoid, diarrhea, cholera and Japanese encephalitis [16].

The main *Anopheles* species occurring in the region are *Anopheles minimus* and *Anopheles dirus*, whose behavioural characteristics include (i) a preference for biting humans, (ii) a tendency to bite early in the evening and morning, and (iii) a tendency to bite outdoors. Although their behavior varies among different localities, these common characteristics reduce the effectiveness of the vector control measures usually implemented by malaria control programs. As mosquitos do not rest indoors on the walls of houses, IRS proves to be largely ineffective, while the early and outdoor biting behavior of the mosquitos reduces contact with the insecticide of the mosquito nets used by humans during sleeping times. Secondly, although ACTs are considered to be the most effective treatment for malaria, this region hosts parasites that show resistance to both single drug regimens (chloroquine, artemisinin) and certain combination therapies (artesunate – mefloquine) [17].

Figure 1. Administrative map of Cambodia [18]

The population

Most of my ethnographic research took place in five villages spread throughout Ratanakiri province: two Jarai villages close to the Vietnam border (Phi and Lom), two Tompuon villages along the Tonle San river (Kachon Kraom and Kachon Leu), and one Tompuon village located further south in the province near the Sre Pok river (Sayos). In addition to a small minority of Khmer, Ratanakiri is inhabited by the following indigenous groups: Jarai, Tompuon, Kreung, Lon, Prov, Kavet, Kachok and Lao. These ethnic groups often come from different geographic and linguistic stocks; Jarai, for example, are of Malayo-Polynesian descent, and Tompuon of Môn Khmer descent. Nonetheless, socio-culturally they are often closely related and as neighbours they do interact and intermarry to the extent that it would be wrong to view each ethnic group as a separate entity from the larger social system and ecological niche they share [19]. One of the main characteristics of these indigenous groups are their agricultural activities, as most of them practice subsistence slash-and-burn farming, and are skilled at swidden cultivation. They grow dry rice ("upland rice" in contrast to the irrigated rice paddies common in the rest of the Cambodia) and various vegetables such as eggplant, gourd, corn, cucumber, sesame, and yam [19]. They are skilled at assessing what resources can be harvested from their natural environment, what time is appropriate for the exploitation of the land, and evaluating when the environment's limits have been met [16]. Both Jarai and Tompuon are matrilineal and matrilocal; the oldest daughters inherit the mother's possessions such as domestic animals, house and objects and when they marry, daughters stay (for a while at least) in the parental village house with their husbands and children. Agricultural lands are not inheritable, however, as each nuclear family is responsible for finding new plots to clear in the forest. Farming plots are thus cleared and owned by nuclear families; however, planting and harvesting is still a communal happening as there is a system of labour force exchange with multiple functions. Not only is every family assured of having assistance to their planting in exchange for their given assistance, the interaction by the teenagers working on the field make it the ideal site for young people to meet and explore the interest of potential partners.

Slash and burn fields (including dry rice fields) are sometimes combined with one or more irrigated rice fields (a practice only recently imported by low land Khmer migrants), and people usually live where they work. Most Jarai and Tompuon have several residences: at the rice fields, at the farms, and in the village center. These 'fixed' mobility patterns occur in a definite space appropriated by a particular village [19]. The social environment of a village extends beyond the village dwellings, into the agricultural fields and cleared lands, the waterpoints and the deep forest space inhabited by spirits [19]. Each village has its own forest territory, where mostly nuclear families work agricultural plots [16]. In the dry season, the agricultural 'low' season, most families live in their village house. Although this is no longer common practice in all villages, the elders, parents and the daughters traditionally live together in the village with their husbands and children in a 'long house'. The dry season, a time for relaxing and celebrations in the village, is nowadays often spent harvesting cash crops such as cassava.

People start clearing plots in the forest around February or March and then the land is burned for fertilization. The crops are planted around April and May; the first rice is sown after the first rains of the rainy season. October and November are the months for harvesting the vegetables, the dry rice and subsequently, the irrigated low land rice. During the planting and harvest most indigenous people live at their farmhouse. The time they spend on their farms differs from village to village, depending on the distance of the farms to the village center.

As many people have sold their land to outside investors, they are forced to go deeper into the forest to find more lands for clearing, extending the time they spend on farms which occasionally end up as new village clusters. Some families who have sold agricultural land in the forest start appropriating the limited land directly surrounding the village, which also changes their residency patterns as they return to the village every night after working their fields. Although forest farm plots are traditionally rotated every few years, the return to once cleared lands that were abandoned does not often occur anymore due to the lack of available land.

Figure 2. Slash-and-burn farm plots in the forest of Ratanakiri

Ethnographic vignette

Walking around a village of the Jarai, one of the largest groups of indigenous peoples in Ratanakiri, I wondered at first why I saw only six-year-olds taking care of three-year-olds while tending to cattle and cooking rice. Following the narrow paths through the dense, green jungle in the village's backyard, I soon realized where the rest of the village was. Large open patches in the forest with little field houses and black burned trunks, smoke still rising from them, revealed entire families working under the extremely harsh sun and in the – to me - unbearable humidity. Drenched in sweat with their winter hats and gloves to preserve their skin from the sun's effects, women were collecting plants in the surrounding forest, cooking rice for lunch or breastfeeding infants. The men and older children were clearing the forest, weeding, planting or making traps for late-night hunting. In all these activities there seemed to be a constant interaction with the forest, represented by the fearsome gaze of the deep jungle behind their plots, harbouring vindictive spirits, wild pigs, illegal logging operations, and malaria mosquitoes. In contrast to the danger exerting from the forest, the village seems a place for relaxing, where the safety of numbers, ancestors and house spirits provides a space to wind down and feast after the harvest – or so the elders tell me used to be the case. Now, however, the village seems a place of motorbikes, VCDs (video players), TVs, Khmer candy shops, chain saws and agricultural machinery, indicating that subsistence is no longer their sole concern. An American ethnographer who has worked in another Jarai village for a long time told me that before the 1990s, they have had little to no contact with the cash economy. Things seem to be rapidly changing then, as I observed many families to have shifted to cultivating cash crops such as cashews and cassava. I can see the ancient system of swidden agriculture is no longer omnipresent. This must have an effect on the land because cash crops intensify land use and the forest has no chance to grow back. However, the large-scale rubber plantations cause much more visible changes to the landscape. During my relatively short time here, I have directly observed the rapid changes this province undergoes. Sadness fills me to see the rich forests and fertile lands transform into profitable cash crop plantations for low land Khmer businessmen and government officials from Phnom Penh, without bringing any benefits to the people who live on and from these lands.

Methodology

Project #1: Border malaria between Cambodia & Vietnam: an anthropological approach to improve control strategies

The border malaria study was financed by the Belgian Directorate-General for Development Cooperation (DGD), the federal agency in charge of development aid in Belgium. Since 1998 collaboration between DGD and ITM has been operating through a 'Framework Agreement', a multiyear agreement through which DGD commits to financially support ITM's research, training and capacity building activities in a selection of low-income countries. Two of the partner countries included in the Framework Agreement are Cambodia and Vietnam, and since 1998 ITM has carried out various malaria projects in collaboration with the National Center for Parasitology Entomology and Malaria Control (CNM) in Phnom Penh, and the National Institute of Malariology, Parasitology and Entomology (NIMPE) in Hanoi.

Both Cambodia and Vietnam are engaged in malaria elimination efforts in the face of mounting artemisinin resistance. In line with their national strategies, they aim to target border areas in the malaria elimination effort, as engaging previously identified risk groups for local transmission and for cross-border transmission is considered crucial for the success of interventions. To encourage collaboration between the two partner institutions and partner countries, ITM took the lead - under supervision of epidemiologist Dr. Annette Erhart - in conducting an epidemiological baseline household survey, an anthropological study and a final epidemiological cross-sectional survey on both sides of the border. Between 2008 and 2010, Prof. Koen Peeters Grietens conducted ethnographic fieldwork and took me on as a research assistant towards the end of the project. The three months of fieldwork I conducted for this project between April and July 2010 resulted in ethnographic material I used for my Master's dissertation in Medical Anthropology, and further served as a comprehensive background for the fieldwork I would start in 2012 for the repellent project (cfr. infra).

As some of the results presented in the following chapters stem directly from research undertaken in 2010, and not only from the repellent project which forms the core of this thesis, I also include a description of the methodology used during this research project.

The epidemiological surveys

In Ratanakiri province, Cambodia, two study villages (Phi, Lom) were selected and in Gia Lai province, Vietnam, three study villages (Bi, Lang Nu, Lang Son) were selected based on socio-demographic (ethnic minority populations and size of the village), geographical (short distance to the border), malariological (malaria cases present throughout the year) and anthropological criteria (presence of ethnic minorities sharing cross border relations). In order to collect socio-demographic and malariometric data before and after the anthropological study, two surveys were carried out in these villages in 2008 and in 2010. The first baseline survey screened each household in the study villages for malaria parasites by RDT and blood smear for microscopic examination, malaria antibody detection and genotyping. During the final survey, a random sample of the population was taken based on the expected malaria prevalence from the baseline survey, as well as the expected differences in exposed and non-exposed groups to the main risk factors analysed.

Dr. Annette Erhart, at the time acting head of the Unit of Malaria Control and Epidemiology at ITM, was principal investigator of the overall study and in charge of conducting the epidemiological surveys. The fieldwork in Cambodia was conducted by staff from the Entomology Department at CNM, and in Vietnam by staff from the Epidemiology Department at NIMPE.

The anthropological study

Objectives

In order to socially, culturally and economically contextualize the malaria epidemiology on both sides of the border, this study aimed at (i) assessing the use of border territory among local ethnic minorities and social relations across the border; (ii) mapping the local territories in which social relations take place; (iii) assessing local access to health care and health seeking behaviour on both sides of the border; and (iv) quantifying in a cross sectional survey the effect of anthropologically suspected risk factors on malaria infection.

Data collection

Qualitative strand

The following qualitative research techniques were used throughout the anthropological study: (i) in-depth interviews and (ii) participant observation. The selection of informants was purposive, based on certain characteristics that were relevant to the research questions posed. Access to respondents was usually granted through snowball-sampling techniques, where certain key-informants introduced the researcher to selected participants. I carried out a total of 126 interviews with various respondents from different social, ethnic, professional and economic categories, with the help of Dr. Sambunny Uk, public health specialist from CNM, who translated and assisted me in the research. She also transcribed all recorded interviews. When a conversation was of a more informal nature, or when we decided it was inappropriate to record the interview or the interviewee refused recording, I took notes immediately after the interview. As such, I included an additional 32 unrecorded informal interviews in the final analysis.

I only conducted fieldwork on the Cambodian side of the border. Although I assisted in the analysis of the data, the fieldwork for the qualitative study on the Vietnamese side of the border was conducted exclusively by Dr. Xa Xuan Nguyen from NIMPE, as ITM staff never received permission from the Vietnamese authorities to stay in the selected villages.

Quantitative strand

After the qualitative strand of the study, two quantitative surveys were carried out in 2010. During a household survey, a structured questionnaire on the use of malaria preventive measures and types of mobility was administered to household leaders on both sides of the border. The same questionnaire was administered face-to-face to youth in all the study villages. The interviewers directly observed the type and status of bed nets that respondents were using (for a more detailed description of the data collection process and sampling strategy, see chapter 4). An additional non-response form was used to measure possible systematic self-selection bias. On the Cambodian side of the border, Dr. Sambunny Uk administered the questionnaire to household leaders independently, while I joined her in administering the questionnaire to the adolescent respondents. On the Vietnamese side of the border Dr. Nguyen Xuan Xa administered the questionnaire to both youth and household leaders.

Data analysis

For the preparation of the study, we used the PASS Health Seeking Behaviour Model [21] (see Figure 3). Briefly, this model presents various elements that guide health seeking behaviour and access to care and, as such, can be adapted to different research contexts.

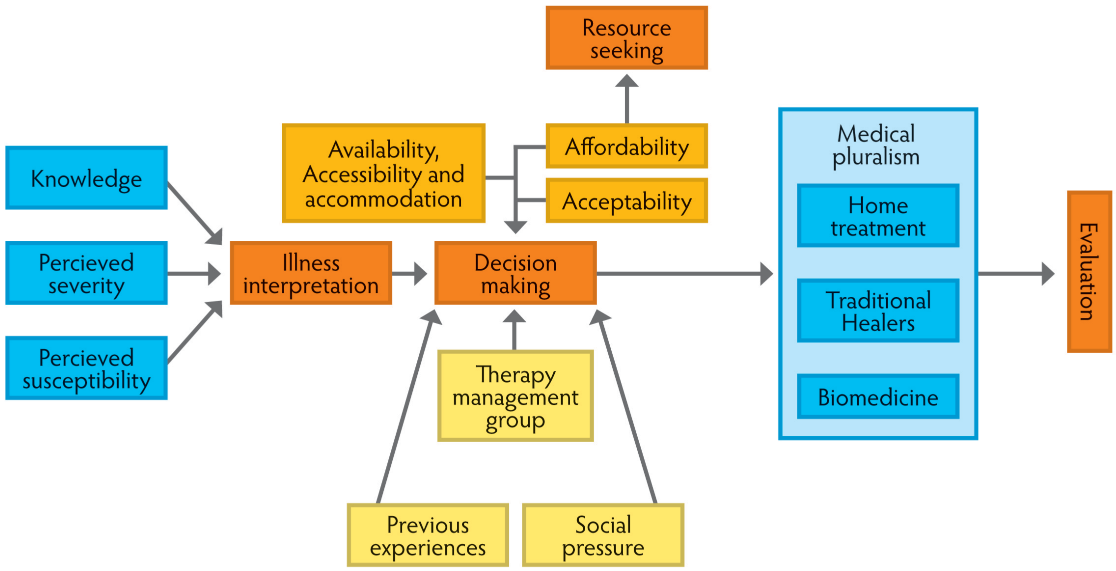

Figure 3. PASS Health Seeking Behaviour Model [21]

When fieldwork for the project started, thematic analysis was continuously carried out as part of the iterative process, after which emerging results and hypotheses were tested in the field until saturation was reached. I carried out the analysis of all qualitative data in NVivo 9 Qualitative Analysis Software through analytic induction, a process involving the iterative testing of theoretical ideas, which refined and categorized themes grounded in the data.

Quantitative survey data were entered and cleaned in Epi Info 6.04 for Vietnam and in MS Excel for Cambodia by data entry clerks from CNM and NIMPE. Data from both surveys were merged in a single database. With the help of Dr. Annette Erhart, the data were analyzed in Stata 13 using the "svy" command to allow for the clustering effect at village level. Descriptive statistics were computed to summarize the main variables from both surveys and separately for Vietnam and Cambodia in SPSS 19.

Project #2. Repellents as added control measure to LLINs in South East Asia: a step forward to malaria elimination

The Bill and Melinda Gates Foundation funded this project. A major grant was conceded to Prof. Marc Coosemans, head of the Unit of Medical Entomology at ITM, to conduct a community-randomized controlled trial that tested whether topical repellents in addition to LLINs could reduce malaria prevalence in a Southeast Asian setting. Though ITM managed the grant, most of its funds were transferred to CNM, ITM's main partner in Cambodia. The allocated budget provided a substantial boost to the country's malaria elimination efforts, as targeting the last foci of malaria transmission with innovative and additional control measures to LLIN was already on the agenda of the national malaria control program. Although initially planned to be conducted in Pursat province, the epicenter of artemisinin resistance, the area was saturated with other elimination projects and it was decided to conduct this large-scale trial in 114 villages in the endemic province of Ratanakiri.

The part of the grant that stayed at ITM was mostly used for salary and travel costs of ITM staff on the project. It also allowed for a PhD-student to be hired for a 3-year period under the supervision of ITM's anthropologist Prof. Koen Peeters Grietens. Due to my previous experience in the area, I was contracted to carry out the anthropological workpackage of this trial. The fieldwork I conducted within the period of this contract resulted in most of the upcoming chapters, and thus this trial serves as the core of the argument of this thesis.

In order to situate the anthropological study within the context of this trial, I will first give an overview of its epidemiological and entomological work packages before expanding on the design of the anthropological study.

Epidemiological study

The overall aim of the epidemiological workpackage was to assess the epidemiological efficacy of repellents on prevalence of malaria carriers and malaria incidence. A community-randomized trial design, rather than individual or household based randomization, was adopted in order to have a more uniform impact on the malaria transmission, and thus on the incidence of malaria infection, by inducing a mass effect on malaria transmission. The community based trial had two arms: one control arm with a large coverage of LLINs provided by the National Malaria Control Program (1 net per 1 person) to control the indoor biting vectors during sleeping time, and a second arm with a similar coverage of LLINs combined with the massive use of the topical repellent KBR3023 to cover the malaria transmission before, during and after sleeping time. A spray formulation with 20% picaridin was provided to adults (>12 years old) and a cream formulation with 10% picaridin to children from 2 to 12 years old. In the control arm, no placebo repellent was considered necessary because randomization is carried out on community level and this in contrast with a household design where a placebo would be essential. The purpose is to measure the additional effect of repellents on the use of ITNs and not the effect of the repellent on its own.

98 communities were selected in the high endemic province of Ratanakiri based on the data of malaria incidence reported by the village Malaria Health workers in 2010-2011. During a

first pilot survey, a stratified randomized sample of 65 persons was selected per community and checked for malaria infection. Based on prevalence of malaria infection, communities were randomly allocated to one of both arms. LLIN distribution in both arms was assured by the National Malaria Control Program (1 net per 2 persons) prior to the start of the trial and selected volunteering village distributors assured repellent distribution on a two-weekly basis in the intervention arm. The principal indicator of the effectiveness of the repellent is the prevalence of parasite carriers measured by PCR techniques. The difference in prevalence between the two arms is then to be attributed to the residual transmission avoided by the use of repellents.

Data collection for the principal indicator occurred during two blood collection surveys per year: one constituting the baseline survey at the start of the rainy season (April) and the other the follow-up survey at the end of the transmission season (October). Each survey consisted of a two-day sampling period per village cluster, with the goal of reaching 65 randomly selected participants per community. In case of a low response rate from initially selected participants after the first survey day, an additional list of 15 randomly selected individuals was used until reaching a minimum number of 50 participants.

Entomological study

In addition to the individual protection that repellents might offer, the entomologists in the trial also expected to see a community protection against residual malaria transmission if high adherence to the use of repellents could be achieved - an observation similar to the effect of ITNs. Therefore, entomological studies were planned to evaluate the mass effect of repellents on residual malaria transmission. In a selection of four endemic communities, 5 to 10 entomological collecting points (local houses) per community were selected for outdoor human landing collections during 10 consecutive nights per survey. In total, four entomological surveys were conducted per intervention year in April, June, August and October to cover the transmission season, with collectors who were not treated with repellents.

A performance study was also conducted, which evaluated the individual protective efficacy of the repellent used for the trial. Two collection sites outside of the study area with a known presence of *Anopheles dirus* and *Anopheles minimus* were selected. 5 treatments (2 negative controls, 1 positive control or standard (20% DEET) and 2 concentrations of the topical repellent used in the trial (10% and 20% icaridin)) were tested on 5 test individuals sitting in

5 collection sites on 5 consecutive days doing human landing collections between 17.00 and 22.00.

All specimens collected in both entomological studies were identified at species level on morphological characteristics. ‘Parity rates’ (rate of pregnant mosquitos) were estimated by analyzing the abdomens of the samples and were used to calculate survival rates of vector populations and ‘vector capacity’ (the capacity of a vector population to transmit malaria). The head and the thorax of all the collected mosquitos were further analyzed by the ELISA method to see if the circumsporozoite proteins that indicate malaria were present. Concrete vector and parasite identification of all positive samples was done by PCR.

Anthropological study

Objectives

In the context of measuring the effectiveness of the epidemiological trial, the main aim of the anthropological study was to assess the acceptability, adherence and adequacy of topical repellents as an additional measure for malaria control. Specific objectives of the study included: (i) To assess local acceptability of the trial topical repellents in the study sites and user’s adherence to the product; (ii) To evaluate repellent use by specific social groups (including age groups, gender, profession, socio-economic status); (iii) To assess the perceived risks, inconveniences (ex. adverse effects) and perceived benefits of the repellent; (iv) To assess local populations’ perceptions of the community based trial; (v) To quantify the reported use and acceptance of the repellent; (vi) To assess the acceptance of and adherence to existing control measures in the study communities (especially bed nets); (vii) To identify human behavioural factors involved in the maintenance of residual malaria transmission; (viii) To examine local access to health care and health seeking behaviour and itineraries; and (ix) To determine a socially acceptable price on the market for the repellent after the trial.

Qualitative study

Data collection

In selected villages in the districts of Voen Sai, Oyadao, Borkeo and Lumphat in Ratanakiri province, Cambodia, the anthropological team collected ethnographic data during intermittent fieldwork periods of two months between January 2012 and December 2013, and during an additional one-month visit in August 2014. Qualitative data collection was initially prioritized to assess the overall cultural context and social setting and to gain an in-depth understanding of those factors that influence people's acceptance of and adherence to topical repellents and control measures in general, health seeking behaviour and behaviour related to residual malaria transmission. I collected all data with the instrumental help of 1 Khmer female researcher (Dr. Sambunny Uk) and 3 Khmer male researchers contracted by CNM (Sokha Suon, Srun Set, Pisen Phoeuk), who were all trained in the social sciences (anthropology and/or sociology). The following qualitative research techniques, often described as inherent to the discipline of anthropology, were used during our study:

Participant Observation. The observation of people's behaviour in its natural setting is a fundamental part of qualitative research as employed in public health research. It is important to critically contrast people's ideas and proclaimed behaviour with their actual actions. This implied that the Khmer researchers and I stayed intermittently for several weeks in the study villages, as well as conducted observation sessions at health centers, during normal consultation hours but also during Village Malaria Workers Meetings and repellent distributor monthly meetings. Informal conversations with people in the villages and at the health centers during our stays in the villages constituted the most important part of our data collection process. Both informal conversations and observations were transcribed in fieldnotes, and each single observation and conversation constituted a separate data document entered in the final database.

In-depth Interviews. Open-ended in-depth interviews were held face-to-face, guided by a continuously adapted interview guide in line with an iterative design. Informants were classified according to relevant variables such as gender, age, subsistence strategies, locality, etc. to allow for internal variation and comparison. All interviews were either carried out in English by me and translated to Khmer by one of the Khmer researchers, or were independently conducted by a Khmer researcher using question guides.

A total of 320 interviews were audio-recorded, transcribed and translated to English, including both short informal conversations and more in-depth individual interviews. In the final analysis, I also included 759 informal conversations and 336 observations recorded in field notes. Both the Khmer researchers and I kept additional reflexive field notes throughout the research process, which I included in the final analysis in the form of memos.

Sampling of informants for the qualitative strand of the study was theoretical, which means they were purposively selected based on preliminary results in order to refine emerging categories and ideas [22]. We continuously selected new participants based on criteria such as gender, age, social position, reported repellent access and use, professional and economic strategies (including agricultural and forest activities) and approached participants face-to-face for social interaction. Access to respondents was often granted through snowball-sampling techniques, where certain key-informants introduced us to other potential participants. We visited many informants several times as an additional way of building confidence between researcher and respondent.

Data analysis

Data analysis was concurrent to data collection. For the preparation of the research, the PASS Health Seeking Behaviour Model was used to design preliminary question guides and as a tool for analysis during preliminary field visits (see Bordermalaria study for a brief description) [21]. Question guides were nevertheless open in order to allow for the emergence of unknown factors. In the initial phase of research, I coded raw data inductively. When preliminary results started emerging, I kept detailed notes of new hypotheses and theories that were forming in discussion with other project members, and adapted the question guides accordingly. These new hypotheses were then further tested in the field until theoretical saturation was reached. NVivo 10 Qualitative Analysis Software was used for all data management and analysis. After all data was collected and entered, the Khmer researchers and I coded all data deductively in Nvivo. I constructed a final coding tree based on the results of the analytic process during fieldwork and performed coding queries to test relationships between codes or between codes and attributes of respondents.

Quantitative study

Data collection

Based on preliminary results from the qualitative strand in 2012, the anthropology team systematically gathered quantitative data using two surveys. A first cross-sectional survey was conducted from August until December 2012 using a close-ended structured questionnaire for both the control and intervention arm of the trial. The questionnaire focused on gathering quantifiable data on the multiple residence system, repellent use, net ownership and use, evening social activities, use of malaria preventive measures other than nets, mosquito nuisance and malaria treatment (see chapter 5, 6 and 7 for a more detailed description of the data collection process and the sampling strategy).

In a second quantitative phase in 2013, the Khmer researchers of the anthropology team carried out a 'structured observation survey' under my supervision, which combined structurally observing variables under study across households and a structured close-ended questionnaire with household members (see chapter 6 and 7 for a more detailed description of the data collection process and the sampling strategy; see chapter 7 for a flowchart of the design and timeline of the anthropological study).

Data analysis

The Khmer researchers of the anthropology team double entered the quantitative data in Epi Info 7, after which I analyzed it in SPSS (IBM SPSS Statistics 19). I performed descriptive statistics on the data and tested the significance of relationships between variables using chi^2-tests. Supported by Dr. Vincent Sluydts (trial coordinator), the effect of age, sex, village, location of interview and month of interview on repellent use was tested with multivariate analyses. With the help of ITM epidemiologist Melanie Bannister-Tyrrell, the variation in observed repellent used between households was explored in an empty random effects model with only household entered as an intercept.

Follow-up study

In August 2014, I went back to the study sites with the same Khmer researchers in order to conduct follow-up research. The Bill and Melinda Gates Foundation no longer funded this research and it was therefore no longer officially part of the repellent trial. The Framework Agreement between ITM and CNM, financed by the Belgian Development Cooperation, further funded the fieldwork.

During the Structured Observation Survey carried out in 2013 in the framework of the repellent trial, two subgroups at risk for malaria were identified that (i) do not use bed nets, and (ii) use bed nets less because they were using repellents. Additionally, repellent distribution data from the epidemiological workpackage of the trial showed (iii) another subgroup that had never picked up or used any repellent during the trial. The aim of the follow-up research in 2014 was therefore to characterize these contexts and conditions of 'non-use' further. Semi-structured interviews were conducted with all household leaders from the non-bed net using households (n=29), from the less-bed net users sub-group (n=60) and the non-repellent using households (n=62).

Preliminary results from this follow-up study were integrated in the intermezzos between the chapters, but are not presented in a separate chapter in this thesis.

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Ethnographic Intermezzo I

When I first arrived in this remote province of Cambodia in 2010 to explore social factors contributing to ‘border malaria’ between Cambodia and Vietnam, the first thing I noticed was the wide array of available malaria treatment in the private pharmacies along the roads, in the villages at the Village Malaria Worker’s house, in the health centers and health posts in the district and commune centers.

After a couple of months of ethnographic ‘immersion’ in the villages, however, my informants finally revealed that ‘modern medicine’ was often being combined with spiritual healing practices, which many indigenous people were not keen on admitting to. In most indigenous villages in Ratanakiri, the world of forest spirits, water spirits, mountain gods and ancestors has a central place in social life. Major events in life, such as clearing a new field or building a new house, as well as misfortune, such as illness or natural disasters, are intrinsically tied to the quality of the relationship between humans and the spiritual realm. With appropriate ceremonies that include sacrifices of domestic animals, the spirits must be compensated for what villagers have received from their lands in order to ensure bountiful harvests in the year to come [1].

Figure 1. Village ceremony with traditional gongs

In case of illness, the indigenous peoples of Ratanakiri combine 'modern medicine' with consultations with a diviner, who usually prescribes a treatment of buffalo, pig, or chicken sacrifice (depending on the severity of the illness) to the spirit or ancestor that the patient has upset. Under certain conditions, this is also the case when people are confronted with malaria. Before contextualizing the different treatment options for malaria in Ratanakiri in the next chapter, I will give a brief overview of the different forms of spiritual afflictions and healing that ethnographic observations uncovered during fieldwork with different indigenous groups.

Spirits or *Arak* live in the big mountains, in stones, big trees, streams, crevasses or parts of the forest. *Arak* can make the villagers sick or kill them if they are disturbed by for example the cutting of spirit trees. *Arak* can also become angry and inflict illness when they are hungry, and then they ask the villagers for food. **God** is a good-natured spirit and takes care of the villagers and the village by assuring successful harvests. God is different for each ethnicity. For example, for the Kreung ethnic group, God refers to the rice spirit and gatekeeper of the village. For Kachok people, God refers to a protective spirit that protects the village from bad *Arak* entering. For the Jarai, God refers to a general spirit that takes care of the villagers but can never be seen. Gods of all ethnic groups require annual ceremonies lest they too inflict illness on the villagers. **Ancestor spirits** are close relatives that have passed away but that still take care of the relatives that remain in the house of the family. When members of a family quarrel or behave violently towards each other, the ancestor spirit can inflict illness on the family members, who are then required to apologize to the ancestor by means of a ceremony. **Ghosts** are villagers that have died a 'natural' or accidental death. They can haunt the other villagers, make them sick and beg them for something to eat. Ghosts are perceived to live close to cemetery areas or in the forest.

These spiritual beings are closely tied to the different healers that exist in indigenous communities. These healers have a special connection to the spirit world that regular villagers do not have, thereby claiming therapeutic expertise otherwise unavailable in the indigenous villages. Traditionally, the most important healer is the **diviner** or the *Kru Arak.* This person is able to communicate with spirits, ghosts, ancestors and God and can often be recognized by particular bracelets or necklaces he or she is wearing. Divination is often done with eggs that reflect the candlelight showing what spirit is harming the patient. Sometimes they make the patient wear particular bracelets or necklaces that touching enables the diviner to dream about the spirit inflicting illness on the patient during sleep. After the diviner recognizes which spirit is inflicting illness and why, he instructs the patient's family on how to make appropriate offerings (usually animal sacrifice) to the spirit during a ceremony. It is the patient's family that is responsible for preparing this ceremony; the diviner is not involved in this. During a ceremony, or for some ethnicities the days after the ceremony, other people are not allowed to enter the house of the patient's family.

The main ethnic group in Cambodia, the Khmer, now increasingly inhabits the area where the indigenous groups live. Reflecting this diversity, Khmer **traditional healers** or *Kru Khmer* also exist in indigenous people's villages. The *Kru Khmer* treats people with herbs, tree roots, tree bark and magic spells and sets bones. Slightly different from a *Kru Khmer*, a *Kru* is not able to directly communicate with spirits but is able to treat people's symptoms with herbs and magic. They can cure as well as inflict illness if they have bad intentions towards a certain villager. The *Kru* can take out the magical object that has been placed in the patient's body by another *Kru*, using bamboo tubes to extract them from the body and spit them out in bowls that contain rice wine. The patient has to stay at the *Kru*'s house for a week to get the treatment. *Kru* are usually more expensive than other types of healers, requiring large monetary payments or gifts of cow or buffalo.

Finally, **witches and sorcerers** can also terrorize people in the indigenous villages. They are often jealous creatures that can aggravate illnesses through magic spells. Although they resemble the *Kru*, their services are not for sale and are not used for therapeutic purposes.

In some Jarai villages along the Vietnamese border, **Christianity** is taking root and dismissing spiritual afflictions and related healing practices. In Lom village for example, one of the main research sites, more than half of the village has converted to Christianity, which has significantly changed the fabric of their society, reflected in the clustering of Christian residences in the part of Lom called Lom Thmei, or 'new Lom'. They no longer 'fear the spirits', so their consequent treatment seeking behaviour has changed drastically.

As one of the Jarai farmers in Lom explained:

> "It is better for my life since I became a Christian person because it can reduce the cost to kill domestic animals to be sacrificed to the God when somebody in my family gets ill. In contrast, now we don't need to kill the animals anymore because the belief in the Jesus God helps us to protect from other spirits. We just buy medicines to cure patients when they have an illness. [...] That's why I think Jesus Christ is better than the other gods because Jesus doesn't allow us to offer animals to any spirits or god, so that we can save money, otherwise we will lose a lot. If we get severe illness, we will

> be informed to sacrifice a big amount, like kill a cow or buffalo to the spirits or God, while others just offer less by killing chickens or a pig. I think Jesus is better than the others. Some people have been told to kill cow or buffalo even though they just have a headache alone." (Jarai farmer, Lom village)

The local priest and other Christians explained to me that the Christian God forbids you to make a large monetary sacrifice through animals, but does require you to show your faith in him and your denunciation of 'backward' ways by buying only modern medicine when illness strikes, rather than combining modern treatments with offerings as is usually the case for the non-Christian villagers. Although the spirits have not disappeared from the forests for these Christian Jarai, the moral justification for not offering to them lies in a God that protects them from these spirits in return for their acceptance of 'modern' ways.

Figure 2. Christian church in 'new Lom' village

In the following chapter, I will expand on the different treatment options and treatment itineraries of the indigenous people of Ratanakiri in relation to malaria.

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Chapter 3. Injections, Cocktails and Diviners: Therapeutic Flexibility in the Context of Malaria Elimination and Drug Resistance in Northeast Cambodia

Local pharmacy selling antimalarials along the road to an indigenous village

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Introduction

By scaling up malaria interventions and containing artemisinin resistance in the country, the Cambodian Government is currently trying to move towards phased elimination of malaria by 2025 [1]. The interest of donors, such as the Global Fund to fight AIDS, Tuberculosis and Malaria, the Bill and Melinda Gates Foundation and the Clinton Foundation, to invest in Cambodia has been largely fueled by events occurring along the Thai-Cambodian border, where *P. falciparum* antimalarial drug resistance first emerged [2]. The large-scale mining activities and the influx of migrant workers, combined with mass prophylactic monotherapy and/or substandard drugs sales of non-curative doses probably contributed to the emergence of chloroquine resistance in the town of Pailin almost half a century ago [2]. Recently, reduced sensitivity of *P. falciparum* to artemisinin – the last stronghold in malaria treatment – has been observed in the same area [3; 4].

Effective malaria treatment is the cornerstone of successful malaria control, and artemisinin-based combination therapies (ACTs) are currently the most efficacious therapeutic option available. In Cambodia, ACTs are mainly available through community health centers (HCs) and volunteer Village Malaria Workers (VMWs) after diagnosis by Rapid Diagnostic Tests (RDTs). Therefore, good quality antimalarial treatment should be easily accessible. Nevertheless, poor treatment adherence could seriously hamper malaria elimination efforts as incomplete treatment would fail to clear infection and favor the spread of drug resistant parasites [5; 6; 7]. Therefore, the effectiveness of ACTs strongly depends on human behaviour [7], which is influenced by contextual factors and by people's practical reasoning. In a context of malaria pre-elimination, these factors become increasingly important as each untreated or mistreated case could contribute to maintaining transmission [8; 9]. This is even more relevant where malaria transmission occurs in remote forested areas due to the sylvatic and highly anthropophylic nature of the main vector *Anopheles dirus* [10; 11], as is the case in Southeast Asia. These areas are often inhabited by poor and vulnerable ethnic minorities living off slash and burn agriculture, with substantial population movements within and across international borders. They often escape standard malaria control measures as these have been conceived for the largest section of the population and not for ethnic minorities with specific socio-cultural characteristics.

In Cambodia, there is a preference for private healthcare and therefore the potential for an incorrect use of antimalarials [12]. In this context, 'drug cocktails' – provider-composed bags of mixed drugs – are extremely popular but hamper malaria elimination efforts by providing incomplete, substandard or inappropriate (monotherapy) treatment that can also be harmful [13; 14; 15]. It is therefore important to understand this phenomenon so that targeted control measures for elimination goals and the confinement of parasite resistance could be adjusted to this specific context.

Methods

Study site and population

Population. The study was carried out in the Cambodian province of Ratanakiri, which in 2008 had a population of 150,000 inhabitants (1% of the total Cambodian population) [16]. The study villages were home to 10 indigenous ethnic groups [17], the Jarai, the Tompuon and the Kreung being the largest of them. Most ethnic minorities practice slash and burn agriculture at forest fields and collect various forest products (hunting and gathering). They often live where they are working, and as such may have several residences spread over the village, rice field or forest farm. Animistic beliefs require agricultural activities to be performed in cooperation with the spirits and ancestors that pervade the trees, rocks and rivers of the village territory [18; 19; 20].

Malaria transmission. Malaria transmission is perennial with two peaks, June-July and October-November, the rainy season lasting from May to October. The main malaria vector is *Anopheles dirus,* an anthropophylic, outdoor and sylvatic species [10; 11]. *P. falciparum* and *P. vivax* prevalence is similar and in 2010 the overall incidence of clinical malaria was 49/1000 population [21]. Given the high number of Long Lasting Insecticidal Nets (LLINs) distributed by the National Malaria Control Program (1 net per 2 persons since 2008 and 1 net per person since 2011), malaria transmission is assumed to occur mostly outdoors, and before or after sleeping time, when people are not protected by bed nets [11; 22].

Malaria treatment guidelines. In the public sector, malaria control measures are implemented through VMWs at community level, health posts at commune level, health centres at district level and referral hospitals usually in the provincial capital. At the time of this study, the first-line treatment was prepackaged (blister pack) mefloquine-artesunate for *P. falciparum* and chloroquine for *P. vivax* - both taken over three days. Mefloquine-artesunate, provided under the brand name A+M, is officially available free of charge at the commune health posts, district health centers and the provincial hospital. For severe malaria, the recommended treatment was either artemether or quinine injections, available at the provincial referral hospital and certain district health centers.

In remote villages, VMWs, after confirmation by an RDT, can administer A+M free of charge [15; 23; 24]. They are supposed to keep detailed records of both RDT results and treatments given and are supervised by the district health centre staff that check the records and replenish their stock.

The private sector in Cambodia is officially organized in four levels of recognized practitioners: (i) private clinics run by medical doctors, (ii) pharmacies with a registered pharmacist, (iii) 'Depot A' pharmacies run by assistant pharmacists and (iii) 'Depot B' pharmacies operated by nurses or midwifes [25]. In terms of antimalarial treatment, Population Services International (PSI) provides Malarine™ blisterpacks (mefloquine-artesunate) to the private sector, which is sold at highly subsidized prizes. Nevertheless, in addition, private practitioners or pharmacists can assemble "cocktails" for their clients [13; 15]. One cocktail consists of a one-day treatment dose combining pills cut off from a blister pack strip or taken from a jar, and provided in a little plastic bag (see Figure 1).

Fig 1. Local anti-malaria cocktail

In addition, the ethnic minority groups in Ratanakiri consult diviners, i.e. traditional healers able to spiritually divine the cause of an illness. Research on home treatment such as coin massages and the use of herbs is outside the scope of this study and was not further explored.

Research strategy

The research was based on a triangulation design, combining qualitative and quantitative data collection techniques in order to strengthen the validity of the data and to achieve complementarity, allowing the quantification of treatment options and treatment choice.

In a first phase of research, a mixed methods study design, consisting of qualitative ethnographic research and a household survey, was carried out in the Oyadao health district, a sub-setting of the study area. This represented an in-depth exploratory case study, aiming at gaining an in-depth understanding of the research questions and at testing preliminary hypotheses about the use of anti-malaria treatment. In a second research phase, complementary quantitative data were gathered from a large-scale cross-sectional survey.

Qualitative study

Data collection. Fieldwork was conducted between April and July in 2010 in Oyadao district, mostly in the border villages of Lom and Phi. For participant observation, the research team participated actively in and observed the daily life of the study population. Continuous informal conversations and interviews with respondents built up confidence for the discussions on more sensitive issues such as adherence to treatment obtained from public facilities. Frequent overnight stays in the two study villages, multiple visits to 11 private sector establishments (including pharmacies and private practitioners) along the main road in Oyadao district, and observation sessions at the health center and health post during consultation hours and monthly VMW meetings, were used to collect information on people's behavior and to compare it with the information given by interviewees. This was an essential step to uncover response bias.

A total of 126 interviews were carried out with various respondents from different social, ethnic, professional and economic categories. These interviews were recorded and transcribed. When a conversation was of a more informal nature, or when the interviewer decided it was inappropriate to record the interview or the interviewee refused recording, notes were taken immediately after the interview. An additional 32 unrecorded informal conversations were included in the analysis.

Sampling. Respondents were theoretically selected, referring to the purposive, gradual and continuous inclusion of respondents based on emerging results during the research process. Access to respondents was usually granted through snowball-sampling techniques, where certain key-informants introduce the researcher to selected participants. Many informants were visited several times as an additional way of building confidence between researcher and respondent, hence reducing bias.

Quantitative study

Data collection. After the qualitative strand of the study, two surveys were carried out. In the household survey a structured questionnaire was administered to all household leaders of the two villages involved in the qualitative study. Questions focused on the different providers of antimalarial treatment and on the choice for their last malaria episode (health centre, private practitioners, VMWs, traditional healers, etc.), including the reason for the choice. The other survey, a large scale cross-sectional survey, focused exclusively on treatment choice.

Sampling. For the household survey, all households in the two study villages for the qualitative study (Phi and Lom) were sampled. For the cross-sectional survey, 900 individuals were randomly selected from the census of the villages included in the research project “Repellents as an Added Control Measure to Long-lasting Insecticidal Nets in Southeast Asia”, a community-based trial implemented in 113 villages of Ratanakiri province. The sample size was calculated based on the expected difference between study arms in the main outcome variable of the overall study, which was repellent use in villages and at farms. In total, 824 people from 109 different villages answered the structured questionnaire. An additional non-response form was used to measure possible systematic self-selection bias.

Data analysis

Qualitative data. Thematic analysis was continuously carried out, after which emerging results and hypotheses were tested in the field until saturation was reached. For the preparation of the study and for analytical purposes, the PASS Health Seeking Behaviour Model was used [26]. Briefly, this model presents various elements that guide health seeking behaviour and access to care and, as such, can be adapted to different research contexts. The final analysis of all qualitative data was carried out in NVivo 9 Qualitative Analysis Software.

Quantitative data. Preliminary analysis of the qualitative data was used to build the standardized questionnaires for the two quantitative surveys. Quantitative data were entered in Excel and analysed in SPSS (IBM SPSS Statistics 19). Frequency tables for the main outcome variables were produced, i.e. perceived VMW treatment availability, availability during last visit to VMW, treatment taken during last malaria episode, provider visited during last malaria episode. Data on the perceived performance of the VMWs were elicited only in the household survey (real life, non-trial setting).

Ethical considerations

The study protocol was approved by the National Ethics Committee for Health Research in Cambodia and The Institutional Review Board of ITM, Antwerp. The interviewers followed the Code of Ethics of the American Anthropological Association (AAA). As proposed by the AAA, all interviewees were informed before the start of the interview about project goals, the topic and type of questions, the intended use of results for scientific publications as well as their right to reject being interviewed, to interrupt the conversation at any time, and to withdraw any given information during or after the interview. Anonymity was guaranteed and confidentiality of interviewees assured by assigning a unique code number to each informant. The interviewers sought oral consent from all interviewees. Oral consent was preferable, since the act of signing one's name when providing certain information can be considered a potential reason for mistrust. Both ethics committees approved the verbal consent procedure.

Results

Choice of public or private health providers

Village Malaria Workers. More than half (55.7%) of all household survey participants reported having ever visited their VMW, and 54.0% of those who had had malaria in the past reported having received treatment from the VMW for their last malaria episode (Table 1). However, qualitative interviews with villagers and VMWs revealed the general perception that the VMW's ran out of stock (RDTs/treatments) rapidly during the rainy season, either due to the difficulty to replenish their stock (heavy workload in the fields, inaccessibility) or due to a higher demand. Indeed, in the household survey, 50.8% of all survey respondents perceived the VMW did not always have medication, 60.6% did not think the VMW would have the required test available, and 48% reported that the VMW was not always available when visited by patients. When asked about their last visit to the VMW, 30.7% of the respondents answered that the VMW did not have a test available, and 36.5% that there was treatment stock out (Table 1).

Table 1. Household survey in Phi and Lom villages

General perception of VMW treatment (n=246)	**N**	**%**
Ever visited the VMW when suspected to have malaria:		
- *Never suspected to have malaria*	76	30,9
- *Ever visited the VMW*	137	55,7
- *Never visited the VMW*	32	13,0
Perception of VMW treatment availability:		
- *VMW does not always have enough tests available*	149	60,6
- *VMW does not always have enough medication available*	125	50,8
- *VMW is not always available*	118	48,0
Treatment options during last malaria episode (n=161)	**N**	**%**
Where did you buy treatment?		
- *Health center*	15	9,3
- *Hospital*	2	1,2
- *Pharmacy*	26	16,1
- *Private doctor*	12	7,5
- *VMW*	86	54,0
- *Market*	17	10,6
- *Other*	1	0,6
- *Missing*	2	1,2
Type of treatment taken during last malaria episode?		
- *Pills - cocktails*	22	13,7
- *Pills - blisterpacks*	126	78,3
- *Injections*	10	6,2
Treatment availability during last visit to the VMW (n=137)	**N**	**%**
Test was not available	42	30,7
Medication was not available	50	36,5
VMW was not available	21	15,3

Health centres, health posts and hospitals. Only 9.3% of respondents in the household survey had attended the health centre during their last suspected malaria episode, and 1.2% had attended the provincial referral hospital (Table 1). Qualitative data consistently showed that only severe cases attended or were referred to the hospital by health centre staff or VMWs.

Private sector. The following categories of private health providers were identified through observation and in-depth interviews with villagers, health staff and private practitioners: (i) *medical cabinets*, referring to private practitioners, not necessarily with any official medical training, working in a medical cabinet; (ii) *pharmacies*: practitioners (sometimes nurses from the health center, sometimes people without any medical training or untrained pharmacists) owning pharmacies and providing treatment; (iii) *mobile private practitioners*: practitioners visiting villages when called upon by patients; (iv) *informal drug selling* (grocery shops or individuals). In the household survey, 34.2% of respondents reported having attended one of private sector options during their last malaria episode (private practitioners, pharmacies, market) (Table 1).

Public-private overlap. Despite the general distinction between public and private sectors, qualitative data clearly showed that this distinction is not so clear-cut. Indeed, each of the health center staff interviewed or observed owned his/her own private pharmacy at home, which was usually located near the health center. During informal conversations at health centers, informants reported that the medical staff often 'advised' people to buy the medication at their private pharmacy before being treated at the health centre, particularly when the type of medication desired was not available at the health center (e.g. artemether injections).

Choice of public or private sector treatment (Figure 2)

Blister packs. Observations and interviews indicate that blister packs were common in both public and private sectors. In both the household and cross-sectional surveys, more than 75% of the respondents claimed to have bought pills in blister packs during the last malaria episode (Table 1 and 2).

Table 2. Cross-sectional survey

Treatment taken during last malaria episode of a household member (n=711)	**N**	**%**
No treatment taken	4	0,5
Treatments separate		
- *Injections*	229	32,2
- *Infusions*	188	26,4
- *Pills - Blisterpack*	555	78,1
- *Pills - Cocktails*	185	26,0
- *Animal sacrifice*	265	37,3
- *Herbal treatment*	103	14,5
- *Coin massage*	285	40,1
Treatments combined		
- *Substandard biomedical treatment exclusively (injections, infusions, cocktails)*	59	8,3
- *Standard biomedical treatment exclusively (blisterpacks)*	141	19,8
- *Traditional treatment exclusively (sacrifice, herbal, coin massage)*	1	0,1
- *Substandard, standard and traditional treatment combined*	119	16,7
- *Standard and traditional treatment combined*	232	32,6
- *Substandard and traditional treatment combined*	92	12,9
- *Standard and substandard treatment combined*	63	8,9
Number of treatments combined		
- *1*	157	22,1
- *2*	217	30,5

- *3*	180	25,3
- *4*	98	13,8
- *5*	40	5,6
- *6*	11	1,5
- *7*	3	0,4

Cocktails. Following repeated observations at private facilities as well as respondents' homes, a cocktail to treat malaria contained one or several antipyretic/analgesics (paracetamol), one antibiotic, vitamins, and one kind of antimalarial monotherapy (either chloroquine or artesunate) (Figure 1). Informants reported to buy one cocktail for around 0.25US$, and usually bought as many as they could afford. 13.7% of respondents in the household survey reported having bought cocktails for their last malaria episode, while this percentage was 26.0% in the cross-sectional survey (Table 1 and 2).

Injections. Observations in pharmacies and interviews with informants indicate that artemether injections (intra-muscular), both European and Asian brands, were for sale in most of the private sector establishments, and were usually administered by the private practitioner or, in order to reduce the cost, were bought as 'take-away' for self-administration. Private practitioners reported the latter option to be the most popular since patients could often not afford to buy a full-dose 5-day injection treatment**.** In the household survey, 6.2% of household leaders reported having bought injections during their last malaria infection (Table 1), while this was 32.2% in the cross-sectional survey (Table 2).

Infusions. Although generally not perceived as a malaria treatment, respondents in the qualitative study often reported intravenous infusions (glucose/vitamins) to be necessary to relieve symptoms and 'strengthen' the patient during a malaria episode. According to the cross-sectional survey, 26.4% of the respondents stated to have bought infusions during the last malaria episode for one of their household members.

Choice of traditional health providers and treatment (Figure 2)

Diviners. In the qualitative study area, we identified two diviners (specialized villagers that can divine the causes of illness and discomforts for a small fee). Informants from those villages stated that it was common for each village to have at least one diviner. Interviews with both villagers and diviners showed that illness etiologies pointed out by diviners referred to the transgression of social norms by the patient, and sacrificial actions to restore health. The diagnosed transgressions usually involved a social disruption (familial disputes, failure to perform ceremonies). Treatments of patients mostly consisted of a ceremony (a social event involving the drinking of rice wine) and sacrifice of a costly buffalo, pig or chicken to the involved spirit, ancestor or witch, depending on the nature of the transgression and the financial situation of the family. In the cross-sectional survey, 37.3% of respondents claimed to have performed a ceremonial animal sacrifice during the last malaria episode of one of the household's members, although most of them combined this treatment with "modern medicine" (blister pack, injections or cocktails).

	PRIVATE	PUBLIC	TRADITIONAL
Providers	Pharmacies	VMW	Diviners
	Private practioners	Pharmacies	
	Drug vendors	Health center/post	
		Hospital	
Diagnosis	Symptoms	Microscopy	Treatment failure
	Rapid test	Rapid test	Divination
Treatment	Cocktails	ACT 'A+M'	Animal sacrifice
	Monotherapy		Ceremony
	Injections		
	ACT 'Malarine'		

Figure 2. Model for treatment options

Determinants for treatment choice

While the household survey showed that the large majority of respondents turned to the VMW for suspected malaria, the qualitative research revealed a preference for general treatment outside the public health sector for the following reasons.

Availability of treatment. According to interviews and informal conversations with villagers, the VMW is usually the first option for suspected malaria but if he is not available or does not have treatment or diagnostic tests, people are reluctant to travel to the health centre.

Perceived side effects. Both A+M and Malarine™ were perceived to cause strong side effects, i.e. dizziness and vomiting, and were therefore avoided whenever possible, as illustrated by the following quote: "*My husband also got medication from the VMW. He took it for three days, but it had very strong side effects. He almost committed suicide!*" (Jarai farmer, Phi). The mentioned side effects were one of the factors leading people to seek treatment in the private sector, either to buy antimalarial cocktails or injections, or to reduce the adverse effects of the public sector treatment with infusions, cocktails or injections. Some patients report to 'preventively' get an infusion at the private practitioner to counteract the expected side effects of the first-line ACT they would get from the VMW or HC staff. Although most pharmacies advertised for Malarine™, private health providers often reported that patients able to afford artemether injections chose for this more expensive but better tolerated option.

Perceived efficacy of the drug. Despite the official indication for hospital use only, qualitative research showed that artemether injections were available in pharmacies without medical prescription. Reasons for their popularity were the quick relief provided which, together with the absence of side effects, allowed patients to rapidly return to their fields, where the workload is the highest during the malaria (rainy) season. Injections were also preferred because they would avoid swallowing of pills by an already weak patient, an often disliked act.

Expected costs. Villagers reported prices ranging from 0.35 to 5 US$ for a consultation at the HC. Prices were similar for private practitioners but without the long waiting period, an appealing option that reduced the loss of productivity. Given the affordable price of cocktails compared to injections (0.25$ versus 2.5$), the former were quite popular and patients were usually able to buy 2-3 single-dose bags.

Health provider - patient encounter. Patients' reluctance to consult the local HC was not only related to the long waiting hours, but also by the fact that HC staff did not have the time to attend the numerous patients waiting for treatment. Informants often reported on the 'unfriendly' reception by the HC personnel, stressing the inherent hierarchy between doctor and patient, and sometimes between Khmer and ethnic minority. Conversely, private practitioners were reported to 'take better care' of their patients, taking more time, and delivering instant care with rapid tests and the client's choice of medication.

Perceived etiology. Despite the overall good knowledge of the "cause-symptoms-treatment" relations of malaria in the study area, the same symptoms could also be perceived as having a "supernatural" etiology, as illustrated by the following quote: *"My children took malaria medication and recovered. But for me it was necessary to make an offer. I took the medication for only one day, and almost died. [So] I have a different problem: with the spirits. After one day of medication I offered a pig to the spirits. Before we go to the VMW, we go to meet the diviner and we follow the diviner"* (Jarai farmer, Phi village). Thus, it was not uncommon that villagers experiencing symptoms such as fever, chills and headaches, consulted immediately the local diviner before considering biomedical treatment options.

Moreover, although illnesses of natural origin and those of supernatural origin were not seen as directly related, they could interact and aggravate the patient's situation as illustrated hereafter: *"The witch makes sure you don't get hungry, you become skinny, or she makes you have pain all over your body. If this is combined with malaria, you die even sooner"* (Jarai farmer, Phi village).

Flexibility of treatment paths (Figure 3)

Although many patients first consult the VMW or private sector to find "modern medicine", it was, however, not uncommon that people perceived that the medication did not work well. When patients did not feel cured after taking anti-malarials, alternative options were explored, including the diviners. Similarly, the diviner's knowledge was not considered flawless either, leading to a highly flexible treatment path in which treatment choice was adjusted according to the need of the patient, its economic situation, and the perceived efficacy of the treatment. This is illustrated by the following quote: *"Last time I got ill, I went to the private practitioner to get an injection or infusion, then I left to Ban Lung for more treatment, and then I went to Vietnam, but I still did not recover. So after visiting three places I was still not better, so then I came back to the village and asked the diviner. The diviner said that I had to sacrifice a buffalo. So I bought the buffalo [...] and after that I did recover"* (Jarai farmer, Phi Village). This flexibility implies that the perceived etiology is related to the perceived efficacy of the first or prior treatment(s), making the latter a form of diagnosis based on lay empiricism. As the results from the cross-sectional survey indicate, treating exclusively with one type of treatment is not common: 77,1% combined two or more treatments during the last malaria episode of a household member.

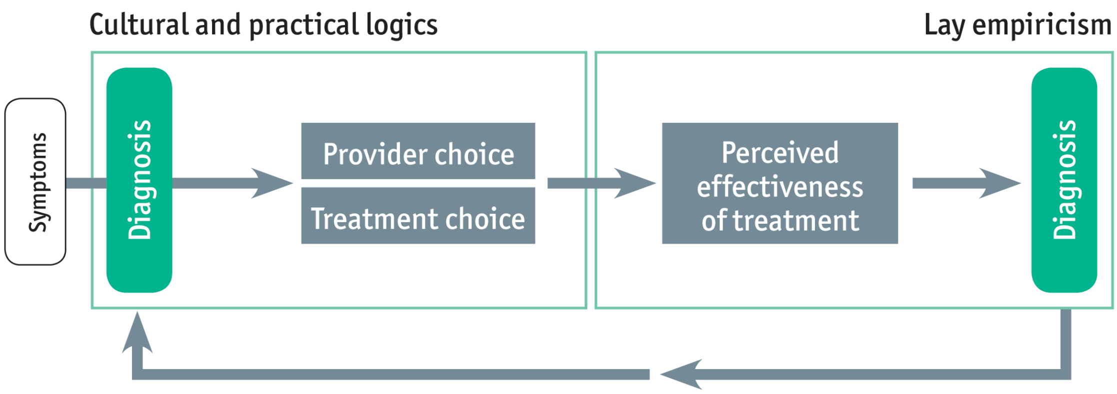

Figure 3. Model for therapeutic flexibility

Discussion

Despite good accessibility of public health facilities, the latter were not always the preferred treatment choice for malaria in rural and remote Ratanakiri. Although each village had a VMW, who was often the first step on the treatment pathway, the community perception that the VMW was not readily available, especially during the malaria season, was one of the reasons why people turned to the private sector and/or traditional treatment. An additional factor driving patients to the private health care providers was the perceived side effects of the first line treatment A+M (or Malarine™). ACT with mefloquine as partner drug is well known to be associated with stronger side effects (acute nausea, vomiting, anorexia and dizziness) compared to other ACTs or artemisinin-derived monotherapies [27], providing evidence for people's fear of A+M's side effects and their preference for artemether injections and cocktails.

Despite the methodological differences as well as different variables being measured between the household and cross-sectional surveys, both of them estimated that approximately one third of the respondents chose private sector treatments. The use of private sector treatment alternatives - injections and cocktails - has economic consequences since families may spend their savings on several suboptimal treatments, while they might have been cured by one complete ACT course. Although cocktails are a cheap option, they are not economically sound as several doses must be bought over time or additional and different medication has to be purchased at a later stage. This finding was also confirmed for Cambodia by Trankell and Ovesen [13]: "one unfortunate effect of this cultural expectation is that the small amount of money most customers have at their disposal will be spread over many non-essential products" (p. 45). Moreover, the perceived treatment failure and the recurrence of symptoms can be related to such systematic under-dosage of anti-malaria monotherapy in the private sector (single-dose injections, single-day drug cocktails). This is even more worrying when knowing sub-standard and fake drugs are widely circulating on local markets in Southeast Asia [6; 28].

A consequence of the perceived lack of efficacy and treatment failure of 'modern medicine' - be it cocktails, injections or blisterpacks - is that people turn to traditional medical systems. This has been shown in Tanzania, where witchcraft interpretations of illness are logical in the context of biomedical treatment failure and the overemphasis of the infallibility of biomedical treatment by educational health messages [29]. The perceived treatment failure encourages people to search for supernatural explanations for their illnesses. As such, the empirical evaluation of the efficacy of the treatment leads patients to search for a different cause of their symptoms, in other words the perceived treatment failure becomes a diagnostic tool [30].

The mentioned therapeutic pathways clearly show the interaction between and the complementarity of the different treatments, indicating highly flexible itineraries instead of a static sequence of health-seeking actions. This variation and flexibility is based on a form of lay empiricism rooted in local cultural logics and perceived treatment efficacy. First, previous experience provides the basis for the rationale (or practical reasoning) of the treatment choice (for example, being able to go back to work after taking a cocktail) while perceived treatment efficacy provides a diagnostic tool for further therapeutic guidance.

Although the preference for these biomedically 'irrational' practices is indeed logical within this social context, the situation nonetheless may have serious consequences for malaria elimination goals, as these mistreated (private sector) or non-treated (traditional treatment) cases result in a parasite reservoir that can maintain transmission, even where the malaria burden is decreased substantially thanks to the large scale implementation of control interventions. Moreover, the popularity of cocktails and the private sector's potential to deliver these in the form of single-day doses of monotherapies can have a disastrous effect as it would increase the selective drug pressure and favor the spread of resistant parasites [31]. The situation observed in Ratanakiri occurs in other parts of Cambodia [14] and probably in other areas of the Greater Mekong Sub-region. This is why it is plausible that, although a program for the containment of artemisinin resistance is implemented on the Thai-Cambodian border, other foci of artemisinin resistance may appear elsewhere. Indeed, delayed parasite clearance has been reported in the Vietnamese border provinces of Binh Phuoc and, more recently, Quang Nam [32; 33].

Conclusion

The use and/or under-dosage of anti-malaria monotherapy in the private sector (injections, drug cocktails) represents a threat, not only for the individual patient (i.e. recurrences and aggravation of symptoms) but also for the community as the resulting drug pressure can favor the spread of resistant parasites [31]. This is an even greater concern when considering that sub-standard and fake drugs are widely available in local private establishments in Cambodia [6; 28]. Local behavioral and contextual factors need to be taken into account when designing interventions aiming at containing artemisinin resistance and decreasing the malaria burden in ethnic minorities living at the edges of mainstream society. Determinants for treatment choice, such as perceived etiology, perceived side effects, perceived efficacy of the drug, expected costs, attitudes and behaviors of the health staff should receive increased attention when engaging health and non-health sectors to reach high-risk populations. This paper advocates for an inclusion of such socio-cultural determinants into the regional framework for action of the emergency response to artemisinin resistance in the Greater Mekong subregion [34].

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Author contributions

KPG, AE, MC, LD, VS, DM, CG conceived of the study. AE was the PI of the bordermalaria study. MC was the PI of the MalaResT study. KPG and CG designed the experiments. KPG, CG, SU collected the data. US, HS, TS facilitated the fieldwork. AE, MC, LD, VS, KPG supervised the fieldwork. CG did the qualitative and quantitative data analysis. RG, KPG, JMR, SHM contributed to the analysis of the qualitative data and conceptual design of the manuscript. CG wrote the manuscript. US, EA, RG, VS, LD, JMR, SHM, DM, HS, TS, UDA, MC, KPG reviewed the manuscript.

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Ethnographic Intermezzo II

Colonial and post-colonial borders have often ignored spatial clustering of ethnic groups, resulting in ethnic groups being divided across different states by borders that collide with cultural, linguistic and kinship ties.

Horstmann [1] argues “there is no place in the nation state where the contradictions of representation of bounded collectivities could be clearer. In fact, the very nature of international borders has produced […] ethnic minorities which have been forced into marginal positions on the frontier of the nation-sate” (p. 2-3). James Scott [2] explains how many national border areas across Southeast Asia are inhabited by people that are culturally different from the populations inhabiting the “state cores”, spilling “promiscuously across national frontiers”, and thus “generating multiple identities” (p. 11). Being both separated by a border and far removed from the respective Cambodian and Vietnamese state cores, Jarai indigenous people living in villages situated along the border between Cambodia and Vietnam sustain practices that elude their division and enable some level of common cultural identity.

Jarai clearly consider the border culturally artificial, as some elder informants told me of Jarai origin mythologies that state Jarai people were once centered around eight different sibling ancestors and spread out into different villages around a mountain in Pleiku (now in Gia Lai province in Vietnam). For these people, the physical boundary between Cambodia and Vietnam is detached from cultural beliefs and values, and becomes practice through ‘permission slips’ – documents issued by commune chiefs and government officials stationed at official and informal border gates – which give Cambodian Jarai the official permission to enter Vietnam for one or a couple of days in order to sell products, visit relatives or attend health care facilities. Although the border is a site of contestation between Vietnam and Cambodia causing both Vietnamese and Cambodian military to guard it closely and violently, Jarai easily crosscut this contested line with their mobility skills and knowledge of the terrain. For some Jarai, travelling through the official border gate requires extra travel and effort, making it a cumbersome activity when having to cross it frequently, so they opt for the undocumented roads through the forest and thereby evade some level of state control. For other Jarai, the absence of asphalt on these undocumented roads is a liability for transporting goods, making the official border gate a more efficient option.

> "Some have relatives there and stay 1 or 2 days, but we do not need the permission paper. If it is just to sell products, we just enter, sell, then come back quickly and take another product, then enter again without any paper." (Jarai NGO-worker, Banlung)

As this quote explains, Cambodian Jarai visit their Vietnamese Jarai relatives frequently, sell or buy products at Vietnamese markets, or seek Vietnamese health care, which is assumed to be of better quality and cheaper than the care available in the Cambodian public health system. As such, Jarai relatives do not only experience the border through permission slips, but also feel the socio-economic differences between the Cambodian and the Vietnamese fringe populations, including differences in business opportunities and access to health care. Vietnamese markets are 'good for business', as products are cheaper and there is more variety, but for those Vietnamese Jarai who do not cave under the assimilation pressure and comply to living in the government-built road-side settlements, overall living conditions are worse than for Cambodian Jarai. The forests in Vietnam have nearly disappeared and those that remain are illegal to access, complicating business opportunities and subsistence practices. Although health care is generally better organized and more accessible for Jarai in Vietnam, the village malaria workers are not permitted to provide malaria treatment to patients, therefore barring access to free malaria medication *in* the community like in Cambodia. The distance to the public health centers where they *can* collect treatment is often long and roads difficult in the rainy season.

Just as borders often fail to control people's movements, they also fail to control the movement of parasites and mosquitos. This triple mobility – of people, parasites and mosquitos – poses a huge challenge to malaria control and elimination efforts. Malaria morbidity and mortality are known to be enhanced at international borders throughout the Mekong region [3-6], which are usually forested, remote, and inhabited by ethnic minorities. The Vietnam-Cambodia border includes five Vietnamese and two Cambodian provinces representing among the most endemic malaria areas in both countries. Beside the complex eco-epidemiology of forest malaria and the challenges to control it, the presence of an international border creates an artificial situation with several implications: first, commercial opportunities and kinship relations produce uncontrolled cross border movements, which may enhance malaria transmission by exposing people to malaria during their unprotected travels or by their lack of access to malaria preventive measures and treatment on the other side of the border. Second, malaria transmission is controlled differently in method and intensity on both sides of the border. The effectiveness of control strategies in these areas therefore does not merely depend on the efforts of the national control programs themselves but also on the evasion opportunities malaria parasites have due to the differences and gaps between the respective control strategies, i.e. malaria infected individuals crossing the border evade the control efforts on one side and participate in transmission on the other side of the border. Control efforts that are differently applied on both sides of the border may create interacting ‘Vietnamese’ and ‘Cambodian’ malaria epidemiologies, shaped by the way people interact with the vector and parasite and the way the control programs interact with the people.

Certain socio-cultural practices among Jarai, such as age-related sleeping patterns, are much more successful at maintaining consistency across borders than the respective national malaria control strategies. The following chapter will show how the border region between Cambodia and Vietnam presents a challenge for both countries’ malaria elimination targets, illustrated by the socio-cultural practices of the at-risk sub group of ‘youth’ among Jarai indigenous people inhabiting Ratanakiri province, Cambodia and Gia Lai province, Vietnam respectively.

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Chapter 4. High Mobility and Low Use of Malaria Preventive Measures among the Jarai Male Youth along the Cambodian-Vietnamese Border

Young teenagers hanging out before spending the night outside in hammocks

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Introduction

There is increasing evidence that minority groups and settings are key to malaria elimination as malaria risk is unequally distributed among populations [7–12] leading to notable heterogeneity of burden within small areas. The factors contributing to the micro-epidemiology of malaria, including the substantial variation in malaria risk between neighboring villages [13, 14] or even households [15] are still not fully understood but include variation in distance from the nearest mosquito breeding site, wind direction and human genetic factors [16, 17]. In addition, the potential underlying human behavioral factors have seldom been investigated and include local preferences for housing construction, [18–21] uptake of preventive measures, [8–10] human mobility, [4, 22] and the presence of specific socially vulnerable or marginalized groups.[6] For countries with decreased transmission moving toward elimination, these pockets of transmission (or *"hotspots"*) and their multifactorial determinants have become increasingly important to understand and tackle. [15, 16, 23, 24] Standard approaches such as Indoor Residual Spraying (IRS) and Long-Lasting Insecticidal Nets (LLIN) are less likely to be as effective in some of these specific settings due to both human (mobility, housing structures, low uptake of preventive measures) and mosquito behavior (early and outdoor transmission). [6, 14, 25, 26]

In Southeast Asia, despite improved malaria control, a major challenge for malaria elimination is the high mobility of populations in specific settings such as border regions, which are often inhabited by impoverished ethnic minorities largely dependent on the forest for subsistence, as is the case in the Vietnamese and Cambodian highlands.[22, 27–33] Moreover, the presence of *Anopheles dirus,* the main vector in these forested areas, challenges the effectiveness of standard control measures such as LLINs and IRS due to its outdoor and early biting behavior [8, 22, 34–41]. In addition, the presence of an international border creates an artificial situation where commercial opportunities and kinship relations foster uncontrolled cross-border population movements that may influence malaria transmission. Considering that Cambodia and Vietnam are engaged in malaria elimination in the face of mounting artemisinin resistance, identifying potential risk groups for local transmission and those that may additionally carry these parasites across borders is all the more relevant.

The present mixed-methods study aimed at understanding socio-cultural factors related to malaria infection along the Vietnamese-Cambodian border. The research was part of a bi-national Border Malaria Project launched in 2008 investigating cross-border malaria transmission between Ratanakiri (Cambodia) and Gia Lai (Vietnam) provinces.

Methods

Study site and population

The study was carried out along the Vietnam-Cambodia border, namely in the villages of Phi, Old Lom and New Lom in the district of Oyadao in Ratanakiri Province (Cambodia), and in the villages of Bi, Nu and Son belonging to Duc Co district in Gia Lai province (Vietnam). The selection of the study sites was based on their proximity to the border, the presence of ethnic minorities potentially crossing the border and engaging in forest activities, and malaria endemicity. All study villages on both sides of the border belonged to Jarai territory, and as such all participants were of Jarai ethnicity. The Jarai are traditionally dedicated to slash-and-burn farming in the forest. However, the region is undergoing rapid socio-economic changes due to the newly constructed road connecting Pleiku city (Gia Lai, Vietnam) to Banlung city (Ratanakiri, Cambodia), and the designation of Ratanakiri and Gia Lai provinces as a special economic border zone by the Cambodia-Laos-Vietnam Development Triangle master plan.[42]

Malaria transmission in the study area is perennial, with peaks in June-July and October-November. The main malaria vector is *Anopheles dirus sensu stricto*, a sylvatic and highly efficient vector.[14, 40] Malaria prevalence by light microscopy was estimated at about 3% in the Vietnamese villages and about 6% in the Cambodian villages, of which the majority was infected with *Plasmodium falciparum* (Annette Erhart, personal communication). In Vietnam, at the time of the study, conventional insecticide-treated nets (ITNs) were provided free-of-charge by the National Malaria Control Program (NMCP), while in Cambodia, the NMCP provided free-of-charge LLINs. In both settings, Village Malaria Workers from the community provide rapid diagnostic tests free-of-charge. In Ratanakiri, they also provide antimalarial treatment free of charge after a positive test, while in Gia Lai positive cases are referred to the commune health center.

Research design

The research consisted of a mixed method sequential design (in standard annotation [QUAL → quan])[43] in which quantitative survey data were collected to confirm and quantify results from prior qualitative ethnographic research. During a first strand, ethnographic data were collected in local communities to acquire an in-depth understanding of malaria exposure in the study setting and population. The consecutive quantitative strand included two separate surveys, one targeting the Jarai youth (hereafter the "Youth Survey") and the other, adult (married) household leaders (hereafter "Household Survey"). The objective of these surveys was to evaluate the following two hypotheses based on preliminary qualitative data: (i) Jarai youth use preventive measures less often than other age groups; and (ii) male Jarai youth constitutes a potentially high risk group for malaria infection due to their sleeping patterns, including spending nights outside of their families' homes while using little to no preventive measures.

Data collection and sampling

Qualitative data collection. Ethnography was carried out in all six study villages over a total period of 5 months between 2008 and 2010, including participant observation and in-depth interviewing and was concomitantly complemented with additional interviews in Pak Touch village in the Oyadao health district and in the commercial center of Oyadao district, as these were located along the road to the study villages and central places for local commercial activities. A total of 257 interviews were recorded and transcribed, focusing on aspects such as the local housing system, mobility patterns, risk factors for malaria and the use of preventive measures, and more specifically, on the Jarai youth social context. Participant observation consisted of daily life observations and reiterated informal conversations during field stays in the study villages. This technique was used to detect unforeseen variables and to contrast stated opinions with actual behaviour, constituting a respondent independent data collection tool.

Sampling. Following the principle of gradual selection, informants were theoretically selected (in accordance with emerging results/theory) and categorized in relation to relevant criteria (such as gender, age, locality, forest activities, previous malaria experience, use of preventive measures, etc.). In order to increase confidentiality with respondents and consequent reliability of the data, "snowball" sampling techniques - sampling using participants to identify additional respondents - were used.

Analysis. Qualitative data analysis was an iterative process performed concurrently with data collection. Preliminary data were intermittently analyzed in the field, and preliminary results were then translated into the question guides for follow-up interviews. Continuous validity checks were used to confirm or refute initial results until saturation was reached and the data could be theoretically supported. Analytic induction involved the iterative testing of theoretical ideas, which was used to refine and categorize themes grounded in the data while emerging themes were evaluated in dialogue with existing social science theory. This resulted in an analytical framework that was then systematically applied in the data analysis. Data were entered, managed and analyzed in NVivo 8 Qualitative Data Analysis software (QSR International Pty Ltd. Cardigan UK).

Quantitative data

Data collection. In Cambodia, the Youth Survey was carried out in 2010 with all youth identified first based on the 2008 population census and consequently through systematic house-by-house visits in all the study villages. In Vietnam, the Youth Survey was carried out in 2010 with all youth identified using the 2008 population census. Youth was defined as any non-married individual, male or female, aged 10 to 25.

For the Household Survey in Cambodia, all households in the villages that were listed in the population census were visited, after which the list was updated with all non-registered households. In Vietnam, the households were selected from the population census. During this survey, all household leaders -defined as the adult married men, constituting the family head- were interviewed.

The same closed-ended questionnaire on the use of preventive measures and types of mobility was administered face-to-face to both Youth and Household leaders, and the type and status of bed nets that respondents were using was directly observed by the interviewers.

Sampling. In Cambodia, all 246 households living in the three study villages were included in the Household Survey in 2011 (4 households were re-visited 3 times, but household members not found and therefore excluded). The Household Survey in Vietnam did not include all households due to logistical constraints; therefore a random sample of 203 (70%) households among the total 291 living in the three study villages was selected from the census.

Analysis. Quantitative survey data were entered and cleaned in Epi Info 6.04 (CDC, Atlanta; WHO Geneva, 1996) for Vietnam and in MS Excel for Cambodia. Data from both surveys were merged in a single database and analyzed in Stata 13 (StataCorp LP, College Station, Texas USA) using the “svy” command to allow for the clustering effect at village level. Descriptive statistics were computed to summarize the main variables from both surveys and presented separately for Vietnam and Cambodia. Five different subgroups were compared: (i) household leaders, (ii) male adolescents, (iii) female adolescents, (iv) male adolescents sleeping outside of the parental home and (v) male adolescents not sleeping outside of the parental home. Differences between household leaders and adolescents, between male and female adolescents, and between males sleeping or not sleeping outside their parents' house were tested for each country separately using svy-chi-square test.

Case definitions. The social category of 'youth' was defined as the transitional phase between a parent-dependent, non-reproductive childhood and full integration into adult society through marriage, aligning with local understandings of youth and adulthood. Household leaders were defined as the married men constituting the head of the family. Qualitative data initially showed that adolescents from the age of 10 and upwards start undergoing a process of gradual independence from their parents, manifest in many aspects including the tendency to sleep outside their parental houses.

Bed net protection was defined in three categories (Optimal; Partial; No protection) by different combinations of the following four variables: (i) Having a bed net (Yes/No), (ii) Bed net use (Always, Sometimes, Never), (iii) Net type (LLIN, ITN, or non-treated nets (NTN)); and (iv) Net status (Intact, Torn). Individuals were defined as having "Optimal Protection" if they met all of the following three conditions: (i) had a net; and (ii) always used the net; and (iii) used an LLIN or an ITN that was intact. The 'No Protection' category included all participants who either (i) did not have a net or (ii) never used a net; (i) had a net and (iii) always or sometimes used a torn NTN. All other individuals fell under the "Partial protection"-category.

Ethical considerations

The study protocol was approved by the Ethical Committees of the Institute of Tropical medicine, Antwerp and the University of Antwerp, the Ministry of Health Cambodia and the National Institute of Malariology, Parasitology and Entomology, Hanoi. The interviewers followed the Code of Ethics of the American Anthropological Association (AAA).[44] All interviewees were informed before the start of the interview about project goals, the topic and type of questions, the intended use of results for scientific publications as well as their right to reject being interviewed, to interrupt the conversation at any time, and to withdraw any given information during or after the interview. Anonymity was guaranteed and confidentiality of interviewees assured by assigning a unique code number to each informant. As proposed by the AAA, the interviewers sought oral rather than written consent from all interviewees since the act of signing one's name when providing certain information can be considered a potential reason for mistrust and may stigmatize illiterate informants.

Results

Survey participants

In Cambodia, 300 Jarai youth participated in the Youth survey, with slightly more males (n=162) than females (n=138), and a median age of 15 years [IQR 13-17]. All 246 male household leaders were included in the Household survey. In Vietnam, 198 youth participated in the Youth survey, with more males (n=111) than females (n=87), and a median age of 14 [IQR 12-16]. All 203 household leaders from the 70% sampled households participated in the Household Survey.

Jarai housing structures and mobility

Based on the ethnographic study, Jarai families combine sleeping in village homes (traditionally longhouses or *sang*) with sleeping at one or several homes at their forest farms or rice fields (*tông*). Houses located in the Cambodian villages can either be wooden stilted longhouses inhabited by Jarai extended family or a stilted house occupied by only one nuclear family. Homes located at forest farm plots, and/or on farmers' wet-rice fields, are well-constructed stilted bamboo/wooden houses, usually intended for only one nuclear family. The village home is mostly used during the dry season when work on the fields is completed, farmers rest and have their annual ceremonies, celebrations and planned visits. The rainy season is the most work-intensive period for Jarai farmers, often leading to increased sleeping at forest farms and rice fields. On the Vietnamese side of the border, though the same housing tradition existed originally, residence patterns have changed following the government policy encouraging habitation in modern houses and the incorporation of the Jarai in government-owned plantations. Therefore, most Jarai houses on the Vietnamese border are currently made of concrete without stilts; however the stilted bamboo/wooden plot huts at farms and fields still exist, and are usually more rudimentary than in Cambodia.

General sleeping patterns

Cambodia. About half of Jarai household leaders reported sleeping at forest fields during the malaria transmission season (Table 1), and a vast majority of (79.3%) reported engaging in deep forest activities (hunting, fishing and logging), with about one fourth staying overnight in the forest. Among Jarai youth, sleeping at forest fields during the malaria season was less common (37.0%) while deep forest activities were very common (84.7%) both in boys and girls. However, the proportion of male youths sleeping outside the village during deep forest activities was significantly higher than females (35.8% *versus* 2.9%; p=0.002) (Table 2).

Vietnam. Reported sleeping arrangements were similar in Vietnam. Deep forest activities and staying overnight in deep forest was less common than in Cambodia among adults and youth (Supplementary table 1).

Table 1. Youth and Household leader surveys in Cambodia

	Youth Survey (N=300)	Household Survey (N=246)	p-value
	n (%)	n (%)	
Mobility patterns			
Sleeps at forest fields during malaria season	111 (37.0)	106 (51.4)	0.23
Sleeps outside parents' house (always or sometimes)	121 (40.3)	NA	NA
Goes often to deep forest	254 (84.7)	195 (79.3)	0.42
Spends night in deep forest (always or sometimes)	62 (20.7)	73 (24.8)	0.13
Spends nights across the border in Vietnam	89 (29.7)	114 (46.3)	0.02
Sleeping materials			
Net ownership			0.0003
- *Owns a bed net*	166 (55.3)	234 (95.1)	
- *Does not own a bed net*	134 (44.7)	11 (4.5)	
- *Missing*	0	1 (0.4)	
Net use among net owners			0.04
- *Never uses BN*	3 (1.8)	12 (5.1)	
- *Sometimes uses BN*	23 (13.9)	5 (2.1)	
- *Always uses BN*	140 (84.3)	217 (92.7)	
Net type among net users			0.08
- *Uses non-treated net*	115 (70.6)	130 (58.6)	
- *Uses treated net*	48 (29.4)	88 (39.6)	
- *Missing*		4 (1.8)	
State of net among net users			0.18
- *Intact (or repaired)*	81 (49.7)	135 (60.8)	
- *Broken (or repaired and broken again)*	82 (50.3)	75 (33.8)	
- *Missing*		12 (5.4)	
Hammock ownership for personal use			0.29
- *Owns a hammock*	103 (34.3)	110 (44.7)	
- *Does not own a hammock*	197 (65.7)	135 (54.9)	
- *Missing*		1 (0.4)	
Hammock use for sleeping at night among			0.002

hammock owners			
- *Never*	17 (16.5)	92 (83.6)	
- *Sometimes*	50 (48.5)	15 (13.6)	
- *Always*	36 (35.0)	3 (2.7)	
Has a hammock net to use while sleeping in hammock	27 (26.2)	10 (9.1)	0.01
Perceived protection of net among net owners			
Mosquitos enter the net			0.19
- *Yes*	79 (47.6)	77 (32.9)	
- *No*	97 (52.4)	157 (67.1)	
Categories of protection			0.002
Unprotected	186 (62.0)	60 (24.4)	
Partially protected	99 (33.0)	127 (51.6)	
Optimally protected	15 (5.0)	42 (17.1)	
Missing	0	17 (6.9)	

Sleeping outside of the parental home

Based on the ethnographic study, young Jarai people are expected to become gradually independent and self-sufficient, and therefore they sleep outside their parents' house, spending the night at friends' homes, or in hammocks hung between the stilted houses.

Cambodia. Overall, 40% of the youth was sleeping outside their parents' home (Table 2), and this tended to be more common in boys than girls (51.2% *versus* 27.5%; p=0.06) (Table 2). Indeed, traditional cultural imperatives indicate that it is less appropriate for girls to sleep outside their parents' homes before marriage. Therefore, among hammock owners, there was a significant difference in hammock use between youth who used them either occasionally (58.5%) or always (35.0%) compared to a majority of male household leaders (83.6%) who almost never used them. However, there was a significant difference in hammock use between boys and girls (p=0.02) since almost all of the former would report using hammocks (occasionally or regularly, 88.6%), while this was the case for only about half of the girls (53.3%). But compared to adults (2.7%), a substantial proportion of male (36.4%) and female (26.7%) youth reported always sleeping in hammocks, and a similar pattern was observed regarding the use of hammock nets (Table 2).

Vietnam. Sleeping outside of the parental home was even more common in Vietnam, for both male (64.0%) and female youth (39.1%). However, differences in hammock use were less pronounced between youth and adults, as less than two thirds of the youth (63.8%) and more than one third of household leaders (37.1%) were using them always or sometimes at night. Male youth reported more often than females to always use hammocks at night (31.9% *versus* 13.6%); however, this difference was not significant (Supplementary table 1 and 2).

Table 2. Youth Survey by gender in Cambodia

	Male (N=162)	Female (N=138)	p-value
	n (%)	n (%)	
Mobility patterns			
Sleeps at forest fields during malaria season	65 (40.1)	46 (33.3)	0.44
Sleeps outside parents' house (always or sometimes)	83 (51.2)	38 (27.5)	0.06
Goes often to deep forest	139 (85.8)	115 (83.3)	0.66
Spends night in deep forest (always or sometimes)	58 (35.8)	4 (2.9)	0.002
Spends nights across the border in Vietnam	50 (30.9)	39 (28.3)	0.65
Sleeping materials			
Bed net ownership			0.07
- *Has a bed net*	69 (42.6)	97 (70.3)	
- *Does not have a bed net*	93 (57.4)	41 (29.7)	
Net use among net owners			0.006
- *Never uses BN*	2 (2.9)	1 (1.0)	
- *Sometimes uses BN*	15 (21.7)	8 (8.2)	
- *Always uses BN*	52 (75.4)	88 (90.7)	
Net type among net users			
- *Uses non-treated net*	39 (58.2)	76 (79.2)	0.006
- *Uses treated net*	28 (41.8)	20 (20.8)	
State of net among net users			
- *Intact (or repaired)*	26 (38.8)	55 (57.3)	0.03
- *Broken (or repaired and broken again)*	41 (61.2)	41 (42.7)	
Hammock ownership			0.009
- *Has a hammock*	88 (54.3)	15 (10.9)	
- *Does not have a hammock*	74 (45.7)	123 (89.1)	
Hammock use for sleeping at night among hammock owners			0.02
- Never uses hammock	10 (11.4)	7 (46.7)	
- Sometimes uses hammock	46 (52.3)	4 (26.7)	
- Always uses hammock	32 (36.4)	4 (26.7)	
Has a hammock net to use among hammock owners	23 (26.1)	4 (26.7)	
Perceived protection of net among net owners			
Mosquitos enter the net			0.06
- *Yes*	39 (56.5)	40 (41.2)	
- *No*	30 (43.5)	57 (58.8)	
Categories of protection			0.05
Unprotected	117 (72.2)	69 (50.0)	
Partially protected	36 (22.2)	63 (45.7)	
Optimally protected	9 (5.6)	6 (4.3)	

Cross-border mobility

Cambodia. Of the Cambodian Jarai youth, 29.7% regularly spent the night across the border for commercial opportunities such as selling vegetables, or for visiting relatives (Table 1). This figure was significantly higher among household leaders (46.3%; p=0.02) corresponding to age-related economic responsibilities. Overall there was no gender difference among youth spending nights across borders (Table 2).

Vietnam. Substantially less border crossings were reported among Vietnamese Jarai youth (15.2%), as well as among the adults (30.0%) compared to Cambodia (Supplementary table 1).

Protection with bed nets

Net ownership, use, type and state

Cambodia. Although most household leaders reported having a net (95.1%), this number was much lower among youth (55.3%). There was weak statistical evidence that significantly more girls than boys had nets to use (42.6% vs 70.3%; p=0.07; Table 2). Reported ideal net use among net owners was also significantly lower among Jarai youth than among household leaders (84.3% *versus* 92.7%; Table 1), and again significantly lower among boys than girls (75.4% *versus* 90.7%; Table 2). The majority of nets being used were untreated nets bought from the local market both among youth (70.6%) and household leaders (58.6%). Moreover, the majority of nets used by youth were torn, while these represented 34% of nets used by household leaders (Table 1). Among youth, significantly more boys than girls used torn nets (61.2% *versus* 42.7%; Table 2). Youth tended more than adults to perceive that mosquitoes were entering their bed nets (Table 1) and this trend was also seen between boys and girls (Table 2). It was mostly users of intact LLIN or ITN that perceived mosquitos to be able to enter the net, compared to intact or torn NTN users (data not show in tables). Qualitative data indicated the large mesh size of the distributed brand of LLIN influenced the perception that insects could enter despite the insecticide.

Vietnam. Having a bed net among youth was more common in Vietnam (80.3%) than in Cambodia, especially among male youth (73.9%). In contrast to Cambodia, most household leaders (90.4%) and youth (86.5%) reported using ITNs or LLINs that were mostly intact (Supplementary table 1 and 2).

Categories of protection

Cambodia. When combining the above-mentioned variables following the case definition for protection, only a minority of household leaders and youth slept optimally protected (respectively, 17.1% and 5.0%; Table 1), youth being significantly less protected compared to adults. A significantly higher proportion of boys than girls were defined as 'unprotected' (72.2% versus 50.0%; Table 2).

Vietnam. Optimal protection was remarkably higher for Vietnamese Jarai household leaders (77.8%) and youth (41.4%), but the difference between youth and adults remained significant as in Cambodia. Similarly, more male youth (53.2%) than female (17.2%) slept unprotected although significance was not reached (Supplementary table 2).

High-risk group: young males sleeping outside

While Jarai youth generally exhibited lower bed net protection, qualitative data indicated the existence of a high-risk subgroup of male youth sleeping outside of parental homes. Young men are given the least priority in the household when designating who requires net protection. Infants and small children along with their mothers have first priority to use nets, followed by adolescent girls, and last the parents and/or adolescent boys. Older children will tend to sleep on separate beds or mats elsewhere in the household, and when space and/or nets become scarce, Jarai youth, particularly males, are expected to seek sleeping arrangements elsewhere, which frequently translates into them sleeping in non-permanent non-bed spaces often located outside of the parental home. In addition, cultural sleeping arrangements define who can share the same bed: while two sisters and also an older sister with her younger, pre-pubescent brother can share a bed net, older brothers are not allowed to share the same sleeping space with sisters the same age or younger. As a result, the adolescent boy is one of the first to sleep unprotected when there are not enough bed nets available.

In Cambodia, compared to the other male Jarai youth, male 'outside sleepers' owned significantly fewer bed nets that were more often torn, and stayed overnight in the deep forest and at forest fields more often. As this group required materials for sleeping at night outside the house, they owned significantly more hammocks for individual use (66.3%) compared to other male youths (41.8%; Table 3). Although in Vietnam these differences were less apparent and non-significant (except for hammock use at night), there is still a considerable difference in the levels of protection that characterize male outside sleepers and male non-outside sleepers (Supplementary table 3).

Table 3. Youth survey by males sleeping or not sleeping outside their parental home in Cambodia

	Male non-outside sleepers (N=79)	**Male outside sleepers (N=83)**	**p-value**
	n (%)	n (%)	
Mobility patterns			
Sleeps at forest fields during malaria season	23 (29.1)	42 (50.6)	0.01
Goes often to deep forest	62 (78.5)	77 (92.8)	0.06
Spends nights in deep forest	12 (15.2)	46 (55.4)	0.001
Spends nights across the border in Vietnam	31 (37.3)	19 (24.1)	0.06
Sleeping materials			
Net ownership			0.06
- *Has a bed net*	42 (53.2)	27 (32.5)	
- *Does not have a bed net*	37 (46.8)	56 (67.5)	
Net use among net owners			0.42
- *Never uses BN*	2 (4.8)	0	
- *Sometimes uses BN*	6 (14.3)	9 (33.3)	
- *Always uses BN*	34 (81.0)	18 (66.7)	
Net type among net users			0.40
- *Uses non-treated net*	22 (55.0)	17 (63.0)	
- *Uses treated net*	18 (45.0)	10 (37.0)	
State of net among net users			0.01
- *Intact (or repaired)*	20 (50.0)	6 (22.2)	
- *Broken (or repaired and broken again)*	20 (50.0)	21 (77.8)	
Hammock ownership			0.05
- *Has a hammock*	33 (41.8)	55 (66.3)	
- *Does not have a hammock*	46 (58.2)	28 (33.7)	
Hammock use for sleeping at night			0.15
- Never uses hammock	4 (12.1)	6 (10.9)	
- Sometimes uses hammock	12 (36.4)	34 (61.8)	
- Always uses hammock	17 (51.5)	15 (27.3)	
Has a hammock net to use among hammock owners	10 (30.3)	13 (23.6)	0.59
Perceived protection of net among net owners			
Mosquitos enter the net			0.001
- *Yes*	18 (22.8)	21 (25.3)	
- *No*	24 (30.4)	6 (7.2)	
Categories of protection			
Unprotected	49 (62.0)	68 (81.9)	0.09
Partially protected	22 (27.8)	14 (16.9)	
Optimally protected	8 (10.1)	1 (1.2)	

Discussion

With growing interest in malaria pre-elimination contexts, there is a need to identify and effectively target 'hot spots' and similarly 'hot populations'.[11, 16, 17] Along the Vietnam-Cambodia border, factors unique to the Jarai youth, males in particular, such as age-specific sleeping patterns and structures, low uptake of preventive measures and cross-border mobility, increases this subgroup's exposure to malaria. This lack of protection among the young men is due to a combination of factors. They often sleep in non-permanent sleeping spaces inside and outside of the home and, when spending the night in their household, they are given least priority to use the available bed nets, leading to an increased vulnerability to malaria. Furthermore, when sleeping outside their parents' houses, young men are not expected to take a bed net from their parents' house while, at the host family, young visitors are not often granted a bed net.

What explains this behavior in youth more structurally is their status as *youth* and can only be understood as embedded in the sociocultural structures that define youth among the Jarai. Due to the transitional character of their social youth status - no longer considered children but not yet adults - fixed and long-term sleeping arrangements are not usually foreseen.[45] Their mobility, moreover, increases the 'flexibility' (and fleetingness) of their sleeping arrangements and, potentially, the likelihood of sleeping unprotected. The relationship between sleeping in *ad hoc* sleeping spaces and the lower likelihood of using bed nets and the consequent vulnerability of being exposed to malaria in this age group has also been shown across settings in Africa.[46–48] The Jarai youth's mobility is all the more relevant given the prevalence of the main malaria vector *Anopheles dirus* in the study region, which is sylvatic and bites early and outdoors[40]. As illustrated by the low levels of protection among Jarai youth and the comparatively higher mobility of Jarai male youth in both Vietnam and Cambodia, both countries may benefit from adopting similar alternative strategies to address malaria risk in social and/or cultural subgroups that cross-cut borders. While promoting bed net use may be suitable for risk groups such as forest farmers sleeping at their farms, and might still have some impact among Jarai youth generally, especially in Cambodia, the male Jarai outside-sleeping subgroup requires supplementary measures. Long-lasting insecticidal hammocks (LLIHs), for example, could serve as an effective tool in providing additional protection[49–53] given the already present high use of hammocks among these groups. LLIHs are practical for individuals who are highly mobile, including, but not limited to, Jarai youth and male outside sleepers, who frequently move between houses within the village and between forest and village homes, who carry out activities requiring overnight stays in the deep forest, and who often cross the border. Furthermore, easily transportable and manageable preventive measures, such as LLIHs, could prove attractive for such groups as they would not necessarily require a significant adaptation of established patterns of behavior.

Our results revealed that the estimated protection from malaria infection by bed nets was not only low among Jarai youth, but in fact also lower than expected among Cambodian Jarai household leaders. This difference could be attributed to the methodology used, as most surveys do not inquire about the kind of nets used and whether the net is still intact, and do not include direct observation of these variables, having to rely solely on self-reported data that are often biased so as to meet public health expectations. While there is a need to identify risk groups, it is unlikely that this can be achieved by regular surveillance activities (i.e. mobile populations) or standardized surveys alone.

Limitations of the study

Although directly observing the state of nets is less biased than self-reported state of net, measuring the size and the amount of holes in nets was outside of the scope of the study. Whenever holes were big enough to be observed by the interviewer at first glance, people themselves stated the nets were torn and mosquitoes entered, and the net was not impregnated, we assumed mosquitos would indeed be able to enter. The main study limitation was the lack of malariometric data of the identified high-risk subgroups, which did not allow for the epidemiological confirmation that they are indeed more at risk for malaria infection than other subgroups. The strength of the study lies exactly in the increased understanding of this social heterogeneity or the existence of differential risk factors and in the identification of one specific bottleneck for the further reduction of malaria in this border setting. In addition, it shows how this risk is an integrated part of the culturally constructed category of youth and that it cannot be understood nor targeted in isolation from this context.

Conclusion

Standard malaria control tools and strategies developed and directed at majority populations can have a limited impact in contexts where transmission is chiefly restricted to specific areas and/or vulnerable settings and populations. Moreover, specific subgroups display different kinds of vulnerability to malaria and therefore require different approaches in order to further reduce malaria. The key to capturing this diversity lies in using mixed methods approaches, which allow for in-depth understanding of different socio-cultural contexts in relation to malaria exposure, leading to more effective control strategies by tailoring them to specific sub-groups at risk.

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Supplementary tables

Supplementary Table 1. Youth and Household leader surveys in Vietnam

	Youth Survey (N=198)	Household Survey (N=203)	p-value
	n (%)	n (%)	
Mobility patterns			
Sleeps at forest fields during malaria season	73 (36.9)	125 (61.6)	0.08
Sleeps outside parents' house (always or sometimes)	105 (53.0)	NA	NA
Goes often to deep forest	121 (61.1)	106 (52.2)	0.54
Spends night in deep forest (always or sometimes)	21 (10.6)	21 (10.3)	0.61
Spends nights across the border in Cambodia	30 (15.2)	61 (30.0)	0.42
Sleeping materials			
Net ownership			0.07
- *Has a bed net*	159 (80.3)	203 (100.0)	
- *Does not have a bed net*	39 (19.7)	0	
Net use among net owners			0.07
- *Never*	33 (20.8)	6 (3.0)	
- *Sometimes*	13 (8.2)	5 (2.5)	
- *Always*	113 (71.1)	192 (94.6)	
Net type among net users			0.24
- *Uses non-treated net*	17 (13.5)	12 (6.1)	
- *Uses treated net*	109 (86.5)	178 (90.4)	
- *Missing*	0	7 (3.6)	
State of net among net users			0.18
- *Intact (or repaired)*	107 (84.9)	177 (89.8)	
- *Broken (or repaired and broken again)*	19 (15.1)	20 (10.2)	
Has hammock for personal use			0.75
- *Has a hammock*	69 (34.8)	54 (26.6)	
- *Does not have a hammock*	128 (64.6)	149 (73.4)	
- *Missing*	1 (0.5)	0	
Hammock use for sleeping at night among hammock owners			0.19
- *Never*	25 (36.2)	34 (63.0)	
- *Sometimes*	26 (37.7)	17 (31.5)	
- *Always*	18 (26.1)	3 (5.6)	
Has a hammock net to use while sleeping in hammock	9 (13.0)	2 (3.7)	0.75
Perceived protection of net among net owners			
Mosquitos enter the net			0.54
- *Yes*	73 (45.9)	112 (55.2)	
- *No*	86 (54.1)	91 (44.8)	
Categories of protection			0.03
Unprotected	74 (37.4)	6 (3.0)	
Partially protected	42 (21.2)	32 (15.8)	
Optimally protected	82 (41.4)	158 (77.8)	

Missing	0	7	

Supplementary Table 2. Youth Survey by gender in Vietnam

	Male (N=111)	Female (N=87)	p-value
	n (%)	n (%)	
Mobility patterns			
Sleeps at forest fields during malaria season	52 (46.8)	21 (24.1)	0.03
Sleeps outside parents' house (always or sometimes)	71 (64.0)	34 (39.1)	0.09
Goes often to deep forest	75 (67.6)	46 (52.9)	0.28
Spends night in deep forest (always or sometimes)	18 (16.2)	3 (3.4)	0.25
Spends nights across the border in Cambodia	16 (14.4)	14 (16.1)	0.52
Sleeping materials			
Bed net ownership			0.32
- *Has a bed net*	82 (73.9)	77 (88.5)	
- *Does not have a bed net*	29 (26.1)	10 (11.5)	
- *Missing*			
Net use among net owners			0.006
- *Never*	29 (35.4)	4 (5.2)	
- *Sometimes*	9 (11.0)	4 (5.2)	
- *Always*	44 (53.7)	69 (89.6)	
Net type among net users			0.26
- *Uses non-treated net*	4 (7.5)	13 (17.8)	
- *Uses treated net*	49 (92.5)	60 (82.2)	
State of net among net users			0.99
- *Intact (or repaired)*	45 (84.9)	62 (84.9)	
- *Broken (or repaired and broken again)*	8 (15.1)	11 (15.1)	
Hammock ownership			0.12
- *Has a hammock*	47 (42.3)	22 (25.3)	
- *Does not have a hammock*	64 (57.7)	64 (73.6)	
- *Missing*	0	1 (1.1)	
Hammock use for sleeping at night among hammock owners			0.13
- Never	12 (25.5)	13 (59.1)	
- Sometimes	20 (42.6)	6 (27.3)	
- Always	15 (31.9)	3 (13.6)	
Has a hammock net to use among hammock owners	6 (12.8)	3 (13.6)	0.28
Perceived protection of net among net owners			
Mosquitos enter the net			0.78
- *Yes*	36 (43.9)	37 (42.5)	
- *No*	46 (56.1)	40 (46.0)	
Categories of protection			0.15
Unprotected	59 (53.2)	15 (17.2)	
Partially protected	17 (15.3)	25 (28.7)	
Optimally protected	35 (31.5)	47 (54.0)	

Supplementary Table 3. Youth survey by males sleeping or not sleeping outside their parental home in Vietnam

	Male non-outside sleepers (N=40)	Male outside sleepers (N=71)	p-value
Mobility patterns			
Sleeps at forest fields during malaria season	16 (40.0)	36 (50.7)	0.13
Goes often to deep forest	26 (65.0)	49 (69.0)	0.55
Spends nights in deep forest	4 (10.0)	14 (19.7)	0.43
Spends nights across the border in Cambodia	7 (17.5)	9 (12.7)	0.70
Sleeping materials			
Net ownership			0.18
- *Has a bed net*	32 (80.0)	50 (70.4)	
- *Does not have a bed net*	8 (20.0)	21 (29.6)	
Net use among net owners			0.11
- *Never*	10 (31.3)	19 (38.0)	
- *Sometimes*	2 (6.3)	7 (14.0)	
- *Always*	20 (62.5)	24 (48.0)	
Net type among net users			0.65
- *Uses non-treated net*	1 (4.5)	3 (9.7)	
- *Uses treated net*	21 (95.5)	28 (90.3)	
State of net among net users			0.46
- *Intact (or repaired)*	18 (81.8)	27 (87.1)	
- *Broken (or repaired and broken again)*	4 (18.2)	4 (12.9)	
Hammock ownership			0.30
- *Has a hammock*	15 (37.5)	32 (45.1)	
- *Does not have a hammock*	25 (62.5)	39 (54.9)	
Hammock use for sleeping at night			0.02
- Never	5 (33.3)	7 (21.9)	
- Sometimes	3 (20.0)	17 (53.1)	
- Always	7 (46.7)	8 (25.0)	
Has a hammock net to use among hammock owners	2 (13.3)	4 (12.5)	0.71
Perceived protection of net among net owners			
Mosquitos enter the net			0.35
- *Yes*	17 (42.5)	19 (26.8)	
- *No*	15 (37.5)	31 (43.7)	
- *Missing*	8 (20.0)	21 (29.6)	
Categories of protection			0.34
Unprotected	18 (45.0)	41 (57.7)	
Partially protected	6 (15.0)	11 (15.5)	
Optimally protected	16 (40.0)	19 (26.8)	

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Author contributions

KPG, AE, UDA, MC conceived the study. KPG and CG designed the experiments. KPG, CG, SU, XNX performed the fieldwork. AE and KPG supervised the fieldwork. SU, TS and XNX facilitated the fieldwork. CG and KPG did the qualitative data analysis. CG, SD, MBT, ST, AE did the quantitative data analysis. CG and KPG wrote the manuscript. SD, SU, XNX, MBT, ST, JMR, SHM, RG, UDA, TS, MC, AE reviewed and edited the manuscript.

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Ethnographic intermezzo III

The indigenous people in Ratanakiri have been heavily affected by historical and recent geopolitical conflicts in the region, the most recent one being land grabbing and timber exploitation. Land grabbing by richer Khmer business and political elites has changed the social fabric of indigenous societies, implied land-use changes and impacted on livelihoods and ecosystems [1].

Precipitating the chain of events that led to contemporary land grabbing was the destruction of all evidence of private land ownership by the Khmer Rouge regime. Even in later years after the regime was overthrown, long-standing Cambodian socialist ideals still prevented land to be privately owned. Although the Khmer Rouge's destruction of landownership records facilitated unofficial land grabbing, the Cambodian government also wanted 'officially' owned land, as the rich resources of Ratanakiri needed to finance the modern state building project in the 1990s [1]. There is no legal framework in place in Cambodia that defends territorial ethnic minority rights to claim non-allocated lands - in contrast to the individual ownership of land. This tension between the marginalization of this province and its people on the one hand, as it is too far removed from the center, and on its exploitation on the other hand, is made visible today by the uncontrolled land stealing which happens alongside the official return of land ownership to indigenous families, turning them into potential and effective land sellers [2].

The government also has a vested interest in the Triangle Development Program, in reference to Laos, Cambodia and Vietnam. This project of economic development can be interpreted as a project of "internal colonialism", which, as Scott describes [3], "involves absorption […] of the previous inhabitants", as well as "botanical colonization - in which the landscape was transformed, by deforestation, drainage, irrigation, and levees - to accommodate crops, settlement-patterns, and systems of administration familiar to the state and to the colonists" (p. 12). Plans by national and international investors to appropriate lands and livelihoods, however, are being executed in the name of "sustainable development", which Bourdier [4] refers to as "long-term profit-making economic development" (p. 3). As these lands offer rich resources, the people that inhabit them are considered a nuisance in the run for 'economic development' [4]. The state is challenged by the farming-related mobility patterns of the indigenous peoples, as Scott [3] argues it is easier to "replace open common-property land tenure with closed common-property", "seize timber and mineral resources", and "encourage cash, mono-cropping, plantation-style agriculture in place of the more bio-diverse forms of cultivation" with people who settle permanently in villages along easily accessible roads (p. 5). Although their multiple residence patterns and mobile agriculture are a nuisance to the government, which to some extent allows them to evade state control, state officials simultaneously rely on indigenous people's mobility skills to access the lucrative precious woods in the forest, exacerbating the tension between their marginalization on the one hand and exploitation on the other hand.

Many indigenous people speak of times when everybody used to have plenty of land for subsistence farming, and are not happy that previously available land in the forest for clearing is now increasingly hard to find because of the land concessions issued by the government (i.e. rubber plantations). However, it is not only 'the state' they have issues with: it is just as easy for well-off individual Khmer businessmen to speculate on and buy up land in the area in order to tune into the fashionable rubber market of today, without consulting the communities living on these lands. Although indigenous farmers are now trying to counter these exploitative attacks by engaging with the legal system in Cambodia, they report the system to be incapable of helping them, as many of these Khmer businessmen are the same people as the government officials primarily involved in illegal land deals.

Figure 1. On the left side of the road: vast lands cleared for rubber plantations. On the right side: forest waiting to be cleared.

This land grabbing narrative converges with the "Khmerization" of social structures among the indigenous peoples, resulting in (or stemming from) an increase in the growing of wet rice. Rice irrigation practices assume private landownership in contrast to the temporary use of land implied in land-clearing and swidden cultivation typical for the indigenous peoples [5]. Nowadays, many indigenous people farm both shifting plots of land in the forest as well as fixed land holdings for cash crops and irrigated rice. However, for some people even farming is not an option anymore: many are now (forcibly) selling lands, both shifting forest lands as fixed cash crop lands, either because they believe they must integrate themselves into the cash economy, or out of fear that their land will be taken anyway and they will get nothing in return if they do not sell it soon.

Land grabbing and selling has also brought other social changes, as distinctions between 'poor' and 'rich' become more outspoken, initiating a trend of individualization in otherwise collective communities. As one Jarai farmer expressed:

> "Rich people are now better than poor people: poor families' situation is looking rather bad in the present because they don't have money to support their families. In contrast, before, poor farmers could make the effort to find some meat in the forests for supporting their families, not like now." (Jarai farmer, Lom village)

The next chapter will look at the mobility patterns of the Khmer migrants working on the rubber plantations versus the indigenous population in the study region and their potential impact on malaria vulnerability.

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Chapter 5. Characterizing Types of Human Mobility to Inform Differential and Targeted Malaria Elimination Strategies in Northeast Cambodia

Housing of the Khmer migrant workers along the road towards a rubber plantation in Borkeo district

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Introduction

Despite increasing understanding of the importance of 'hot spots' for malaria control and elimination [1], comparatively less attention is being given to populations subgroups ('hot pops') that are vulnerable to malaria but cannot be easily located in a geographically confined area due to their mobility [2]. While human mobility has been addressed more extensively in relation to neglected tropical disease elimination [3], immunization campaigns [4] and HIV prevention [5], it has, until recently, been largely neglected in malaria control and elimination [3, 6, 7]. Nevertheless, human mobility affects malaria transmission in several ways. Population movements expose individuals to a variety of health hazards to which sedentary populations are not exposed [8] and it is often harder for those individuals to cope with the consequences of disease due, for instance, to language difficulties or a lack of familiarity with local health care. Moreover, the type of work highly mobile populations perform and the generally poorer working conditions can result in higher exposure to malaria vectors [6, 9, 10], as has been reported on rubber plantations or in slash-and burn-agriculture [11, 12]. Population movements may also result in non-immune individuals arriving in endemic areas or infected individuals seeking care in malaria-free regions, increasing difficulties in diagnostics and treatment [13–18].

The importance of human mobility for malaria elimination was evident in previous elimination attempts where malaria re-emerged due to surveillance systems that failed to account for the movements of human populations [16, 19]. Standard malaria control interventions implicitly operate on the assumption that individuals and subpopulations are registered and therefore easy to access. Current malaria control efforts typically target geographically stable groups: village malaria workers are assigned to highly endemic villages based on the administrative unit of the village/community; the distribution of long lasting insecticidal nets (LLIN) relies on intermittently updated census data and also indoor residual spraying (IRS) focuses on stable administrative villages; all of which consequently fail to account for mobile populations [10, 17, 20, 21]. Moreover, in biomedical and clinical research, mobile individuals and mobile ethnic groups (such as e.g. nomadic Fula herders in SSA) are often purposefully excluded so as to minimize poor compliance to treatment or losses to follow-up. As a result, little is known about the effectiveness of standard interventions among these mobile populations. In the context of current malaria elimination targets, human mobility represents a major challenge for national control programs to further decrease malaria transmission [9, 10, 19]. Given the large sociocultural differences between various types of mobile populations, it can be expected that there is no standard way to address mobility in malaria control. In this sense, targeting pastoral nomads (i.e. pastoral herders in SSA) will require a radically different approach as compared to targeting national or international migrants, or commercial itinerant workers (i.e. street vendors and traders in border regions).

Several countries in the Greater Mekong Subregion are aiming to achieve malaria elimination within the next few decades [22]. However, residual transmission foci persist in forested areas such as the North-Eastern Cambodian province of Ratanakiri, that are largely populated by ethnic minority communities, often located at international borders and on the fringes of society, with increasing rural to rural migration to exploit new economic opportunities such as rubber plantations, gem mining and agriculture [23]. The aim of this study was therefore to characterize the different mobile groups in one such context and related those to vulnerability to malaria.

Methods

Study site and population

The study was conducted in the Cambodian province of Ratanakiri, traditionally populated by indigenous groups such as the Jarai, Kreung and Tompuon, also referred to as 'ethnic minorities', in contrast to the majority Khmer population that populates the rest of Cambodia. Indigenous subsistence strategies usually combine slash-and-burn agriculture with hunting, fishing, gathering forest products and small-scale trade. As distances between forest farms, rice fields and villages can be substantial (i.e. at several hours walking distance), most families maintain residences at each location and rotate from one place to another according to the agricultural cycle [24]. In addition to the indigenous populations, the rich resources of the province (forest, farmland, gems, etc.) have recently attracted many national and international investors mainly for large-scale rubber plantations. The latter require a large work force of mainly migrant workers from Cambodia's rural and impoverished lowland provinces. In addition to plantation work, these rural-to-rural migrant Khmer farmers also seek irregular job opportunities on private farms or in construction and gem or gold mining in the area.

Malaria incidence in Ratanakiri is currently decreasing following intensified control measures, improved access to health care, socio-economic development and changes in the landscape, characterized by the replacement of the primary forests with rubber plantations, potentially impacting on vector populations [25]. Malaria transmission in Ratanakiri is perennial with two peaks, June-July and October-November, and the main vector is *Anopheles dirus* [25, 26].

In the public sector, malaria control measures (LLIN distribution, early diagnosis with RDT and treatment) are implemented through village malaria workers (VMWs) at community level. At the time of the study (2008 – 2012), the first line treatment was mefloquine-artesunate (A+M) for *Plasmodium falciparum* and chloroquine for *P. vivax*. In the private sector, Malarine™ branded blisterpacks of mefloquine-artesunate were sold alongside various drug cocktails (small plastic bags containing a variety of drugs such as antimalarials and antibiotics) and artemether injections [27]. Local indigenous groups traditionally consult diviners (traditional healers) to identify the cause of an illness, often in combination with various treatments from the public or private sectors [27].

Research strategy

A parallel mixed-methods study design was chosen, using qualitative ethnographic research and quantitative survey research methods for complementarity (in standard annotation [QUAL + QUAN]) [28]. Qualitative ethnographic data were collected in local communities and selected plantations to acquire an in-depth understanding of mobility patterns, living and working conditions, access to and use of malaria preventive measures and health care services of (i) Khmer migrant plantation workers and gem miners and (ii) local indigenous populations. Three additional surveys were aimed at quantifying the ethnographically assessed variables among these different populations. The ethnographic study and three surveys are described below and summarized in Table 1 and Figure 1.

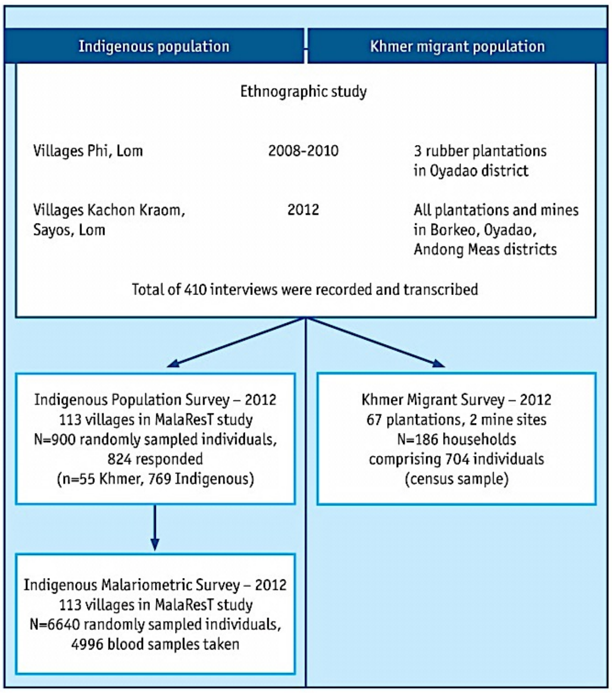

Figure 1. Flowchart of research strategy

Qualitative ethnographic study

The qualitative study was carried out in two phases: (i) A first exploratory qualitative phase was carried out between 2008 and 2010 in the villages of Phi and Lom (Oyado district), inhabited by the indigenous Jarai, and in three adjacent rubber plantations; (ii) In 2012, in-depth qualitative research was conducted in three villages included in a larger cluster randomized trial on the effectiveness of topical repellents as an added control measure to long-lasting insecticidal nets [25] (NCT01663831, hereafter "MalaResT"). The Tompuon villages of Kachon Kraom (Voen Sai district) and Sayos (Lumphat district) and the Jarai village of Lom (Oyadao district) were selected. In addition, in Borkeo, Oyadao and Andong Meas districts, all identifiable plantations and gem mining sites were visited.

Data collection. Participant observation and in-depth interviewing were carried out. The former consisted of observations and reiterated informal conversations. Participant observation was primarily used as respondent-independent data collection tool to detect unforeseen variables and to contrast stated opinions with actual behavior.

Sampling. Multiple purposive sampling techniques were used. Following the principle of gradual selection, informants were theoretically selected (in accordance with emerging results/theory) and categorized in relation to relevant criteria (such as gender, age, locality, forest activities, previous experience with malaria, use of preventive measures, etc) [29]. In order to increase confidentiality with respondents and consequent reliability of the data, snowball sampling techniques (i.e. sampling using participants to identify additional cases) were used.

Data analysis. Qualitative data collection and analysis were performed concurrently and data analysis was an iterative process. Preliminary data were intermittently analyzed in the field, and preliminary results were then translated into the question guides for follow-up interviews. Analytic induction involved the iterative testing of theoretical ideas, which was used to refine and categorize themes grounded in the data [29]. This resulted in an analytical framework that was then systematically applied in the data analysis. Data were entered, managed, and analyzed in NVivo 9 Qualitative Data Analysis software (QSR International Pty Ltd. Cardigan UK).

Khmer Migrant Survey

Three different risk groups –identified in the ethnographic study- were targeted: (i) rural to rural migrants working on rubber plantations; (ii) rural to rural migrants working in self-exploited (gold/gem) mines; and (iii) migrants having initially worked in plantations, but currently working in other informal jobs within the same general location (i.e. working on fields, etc). All work sites with migrant mobile populations in the districts of Oyadao, Andong Meas and Borkeo were identified and included in the study.

Data collection and sampling. In each study site, all Khmer working households (HH) that could be located on the plantation were invited to participate in the survey. After oral consent, first all participating household leaders were asked questions about their expected duration of residence, land ownership, administrative registration, income and use and access to malaria prevention tools. Secondly, the sleeping arrangements (use, type and condition of bed net or hammock net, sleeping surface) of all members of each household were observed and recorded.

*Data analysis***.** Data was entered in Epi Info 7 (CDC, Atlanta, GA, USA) and analysed in SPSS (IBM SPSS Statistics 19). Frequency tables for the main descriptive variables were produced.

Indigenous Population Survey

Data collection and sampling. A random sample of 900 individuals from different households were selected from the population census of the 113 villages included in the MalaResT study in 2012 and invited to participate in the survey. After oral consent, all participants were interviewed on the number of different settlements accessed by the individual's household (village homes, homes on slash and burn farms, homes on rice fields), the time spent in each location by household members, and their use of malaria prevention measures.

Data analysis. Data was entered in Epi Info 7 (CDC, Atlanta, GA, USA) and analyzed in SPSS (IBM SPSS Statistics 19). Descriptive statistics were performed for the main outcome variables.

Indigenous Malariometric Survey

Data collection and sampling. In addition to the *Indigenous Population Survey*, a malariometric survey was conducted during the MalaResT study in October 2012 to determine malaria prevalence and related risk factors. A total of 6,640 individuals across the 113 study villages were randomly selected from the census file and invited to participate in the survey. Participants were interviewed on use of preventive measures and overnight stays at the farm plot hut, clinically examined, and blood sampled for microscopy and molecular detection of malaria parasites [25, 26].

Data analysis. Data was entered in MS Access and analyzed in SPSS (IBM SPSS Statistics 19) and R (R version 3.1.1, The R Foundation for Statistical Computing). Frequency tables for the main outcome variables were produced. Two-level logistic regression with a random intercept fitted to adjust for clustering at village level was used to calculate the odds ratio for the association between spending nights in the forest in the past month and malaria infection, adjusted for age and sex.

Ethical considerations

The study protocol was approved by the Institutional Review Board of the Institute of Tropical Medicine in Antwerp (ITM) and the Ministry of Health, Cambodia. The interviewers followed the Code of Ethics of the American Anthropological Association (AAA). All interviewees were informed before the start of the interview about project goals, the topic and type of questions, the intended use of results for scientific publications as well as their right to refuse being interviewed, interrupt the conversation at any time or withdraw any given information during or after the interview. Anonymity was guaranteed and confidentiality of interviewees assured by assigning a unique code number to each informant. The interviewers sought oral consent from all interviewees. Oral consent was preferred because the act of signing one's name when providing certain information can generate mistrust. The quantitative and malariometric surveys obtained additional ethical clearance from ethical committee of the University Hospital of Antwerp and the National Ethics Committee for Health Research in Cambodia. For the surveys, the study objectives and methodology were first explained to each family in Khmer and individual written informed consent was given by each participant, or by parents/guardians of children below 18 years of age. All methods were carried out in accordance with the approved guidelines

Results

Study participants

Qualitative study. In total, 410 interviews, including formal and informal conversations, were recorded and transcribed.

Indigenous Population Survey. Among the 900 randomly sampled individuals, 824 (91.6%) were reached and interviewed, among which 55 individuals were Khmer (6.7%) that had migrated to a local village. All other respondents were indigenous people, including the ethnicities Jarai, Kreung, Tompuon, Kachok, Kavet, Lao, Lon and Prov.

Khmer Migrant Survey. Among the 67 plantations and 2 gem-mining sites included in the survey, 186 Khmer household leaders were interviewed. Of these 186 households, 704 household members' sleeping arrangements were recorded.

Indigenous Malariometric Survey. Among the 6,640 individuals selected from the census file, 4,996 (75%) participants were reached.

Table 1. Methods used

Qualitative methods		
	Population	
Ethnographic Study	Indigenous populations and Khmer migrant workers	
Quantitative methods	*Population*	*N*
Khmer Migrant Survey	Khmer migrants in rubber plantation, gem/gold miners, or other informal activities	n=186
Indigenous Malariometric Survey	Indigenous populations	n=6,640
Indigenous Population Survey	Indigenous populations	n=824

Types of mobility

During the first phase of the ethnographic study, the following types of mobile groups were identified (Table 1): first, Khmer rural-to-rural migrants, including *(i) Permanent national rural to rural migration,* which describes Khmer farmers leaving their rural communities in lowland provinces of Cambodia to settle permanently in highland Ratanakiri and work on large-scale plantations or smaller farms; and *(ii) Seasonal/temporal national rural to rural migration*, referring to Khmer farmers temporarily working on plantations in Ratanakiri and then returning to their villages at the end of their contract. Secondly, indigenous population movements were identified that included mobility due to *(iii) indigenous multiple residence systems.* This translates into local indigenous population movements driven by subsistence requirements (e.g. sleeping at farms in the forest) and economic activities (e.g. spending nights in the forest for hunting). Indigenous population movement also included *(iv) cross-border mobility*, meaning movement of indigenous people across the Cambodian/Vietnamese border for economic (buying or selling products across the border) and/or social (visiting relatives) reasons.

Vulnerability of Khmer rural to rural migrants to malaria infection

Mobility. More than half (56.5%) of the Khmer households working on plantations, all households working in gem-mining sites and most households (70.6%) headed by independently working Khmer migrants were categorized as "permanent rural to rural migration", reportedly having come to Ratanakiri to work for an indefinite period of time (Table 2). Among the Khmer plantation workers, 43.5% could be categorized as seasonal rural to rural migrants, with a median working time of 5 months (IQR 16, range 1 to 108 months); a figure that went up to 48 months among miners (IQR 54, range 1 to 240 months). Traditionally, the Khmer New Year (April) marked the time point at which the Khmer migrant plantation workers returned home and new migrants came to replace them.

Table 2. Khmer Migrant Survey – Household leaders (N=186)

	Plantation (N=115)	**Mines (N=37)**	**Other (N=34)**	**Total (N=186)**
	n (%)	n (%)	n (%)	n (%)
Duration of stay				
Indefinite	65 (56.5)	37 (100)	24 (70.6)	126 (67.7)
Definite	50 (43.5)	0 (0)	10 (29.4)	60 (32.3)
Median stay (months)	5	48	24	12
Land ownership				
HH° owns land in Ratanakiri	5 (4.3)	3 (8.1)	5 (14.7)	13 (7.0)
HH owns land in home province	60 (52.2)	3 (8.1)	13 (38.2)	76 (40.9)
HH does not own land at all	51 (44.3)	31 (83.8)	17 (50.0)	99 (53.2)
Administrative registration				
Registered locally	21 (18.3)	25 (67.6)	19 (55.9)	65 (34.9)
Not registered locally	91 (79.1)	11 (29.7)	15 (44.1)	117 (62.9)
Don't know	3 (2.6)	1 (2.7)	0	4 (2.2)
Amongst those not registered:	*N=91*	*N=11*	*N=15*	*N=117*
Registered in home village	77 (84.6)	6 (54.5)	13 (86.7)	77 (81.9)
Income				
Median monthly income (riel)	300.000R	200.000R	300.000R	250.000R
Not able to save any money	47 (40.9)	28 (75.7)	17 (50.0)	92 (49.5)
Manager deducts cost of food from salary	35 (30.4)	1 (2.7)	2 (5.9)	38 (20.4)
VMW				
Knows local VMW	3 (2.6)	1 (2.7)	1 (2.9)	5 (2.7)
Knows of existence VMW	7 (6.1)	1 (2.7)	2 (5.9)	10 (5.4)
Did not know of existence	108 (93.9)	36 (97.3)	32 (94.1)	176 (94.6)
Bed nets				
Never received program net in home province	76 (66.1)	28 (75.7)	20 (58.8)	142 (76.3)
Never received program net in visiting province	105 (91.3)	18 (48.6)	19 (55.9)	124 (66.7)

Owned bed nets upon arrival	99 (86.1)	36 (97.3)	31 (91.2)	186 (89.2)
Amongst those who owned nets upon arrival	*N=99*	*N=36*	*N=31*	*N=186*
Considered bed nets owned upon arrival to be sufficient	67 (67.7)	29 (80.6)	23 (72.2)	119 (71.7)

°HH= household leaders

*Includes Khmer workers who initially worked on plantations but now work other informal jobs in the same area, such as labourers on private farms.

Socio-economic vulnerability. Overall, only 7.0% of all Khmer migrant households owned some land for small subsistence farming in Ratanakiri, while the majority did not own land at all (53.2%), especially among the miners (83.8%). Miners also seldom owned land in their home province (8.1%) compared to plantation or other workers (respectively, 52.2% and 38.2%; Table 2). On plantations, the majority of Khmer workers (79.1%) were not officially registered in Ratanakiri; though most of them (84.6%) reported being registered in their home villages. Local official registration was higher among Khmer migrants working independently on private farms (55.9%) and on mining sites (67.6%). The Khmer migrant households' monthly income ranged between 0 and 800.000 riel (200 USD) with a median of 250.000 riel (62.5 USD) (Table 2). and half of households reported not being able to save any of this money.

Access to health care and malaria prevention. Only 5.4% of Khmer migrant respondents knew about the existence of VMW's in the nearby indigenous villages, (Table 2); and only 2.7% knew the actual VMW of the village where their plantation/mine was located. The lack of administrative registration among the majority of Khmer migrants resulted in the majority of households never having received a bed net from the NMCP in Ratanakiri (66.7%), especially those households working on plantations (91.3%). Moreover, a majority (76.3%) of Khmer migrants reported never having received a bed net from the NMCP in their home province. Nevertheless, the majority of the households did bring bed nets (both treated and non-treated) to their new work locations (89.2%), and most of them considered the number of bed nets they brought themselves sufficient to protect all household members (71.7%) (Table 2).

When considering individual malaria prevention among household members of the migrant households, almost all (91.1%) respondents reported to use a bed net, usually while sleeping on mats, or on rare occasions, in hammocks (Table 3). Bednets were usually non-treated and bought from the market (74.7%) and over half of the respondents were sleeping under nets that were observed to be torn (i.e. defined as nets with rips and tears).

Table 3. Khmer Migrant Survey: All Household Members (N=704)

	Plantation *N=374*	**Mines** *N=159*	**Other** *N=171*	**Total** *N=704*
	n (%)	n (%)	n (%)	n (%)
Sleeping habits				
Sleeps on mat	356 (95.2)	159 (100)	163 (95.3)	678 (96.3)
Sleeps in hammock	15 (4.0)	0	6 (3.5)	21 (3.0)
Missing	3 (0.8)	0	2 (1.2)	5 (0.7)
Uses a bed net	325 (86.9)	157 (98.7)	159 (93.0)	641 (91.1)
Amongst bed net users:	*N=325*	*N=157*	*N=159*	*N=641*
Net type				
NTN	269 (82.8)	92 (58.6)	118 (74.2)	479 (74.7)
ITN/LLIN	55 (16.9)	65 (41.4)	40 (25.2)	160 (25.0)
Missing	1 (0.3)	0	1 (0.6)	2 (0.3)
Net status				
Intact net	88 (27.2)	95 (60.5)	104 (65.4)	287 (44.8)
Torn net	237 (72.9)	62 (39.5)	54 (34.0)	353 (55.1)
Missing	0	0	1 (0.6)	1 (0.2)

Indigenous population in-country mobility

Mobility. Mobility among the indigenous population is linked to the tradition of slash-and-burn agriculture. According to the ethnographic study, indigenous families combine sleeping in village homes (traditionally longhouses) with one or several homes at their farms or rice fields in the forest. According to the Indigenous Population Survey (Table 4), most respondents (93.2%) had one or more forest farms, as well as a house on the farm(s) (82.5%). The rainy season, especially during the harvest months, is the most work intensive season for indigenous farmers, often requiring them to sleep in plot huts at their farms in the forest. Indeed, 61.2% reported sleeping at their farms during the malaria season (rainy season which extends into harvest months). In addition to forest farms, 44.1% of respondents reported having a wet rice field, and of those, the majority (67.5%) had built a house on that rice field where they would also be sleeping during the malaria season (53.2%).

Table 4. Indigenous Population Survey (N=824)

	n (%)
Forest farms	
Has forest farm(s)	768 (93.2
Amongst those who have farm(s)	*N=768*
Has a house on farm(s)	633 (82.5)
Sleeps at farm during malaria season	470 (61.2)
Amongst those who have a house on farm(s)	*N=633*
Has a bed net to use at farm	464 (73.3)
Brings back net back and forth from village	96 (15.2)
Keeps bed nets at farm	368 (58.1)
Transportation to farm *(multiple responses possible)*	
On foot	677 (88.2)
By motorbike	346 (45.1)
By boat	44 (5.7)
By bicycle	25 (3.3)
Other	7 (0.9)
Wet Rice Fields	
Has wet rice field(s)	363 (44.1)
Amongst those who have wet rice field(s)	*N=363*
Has a house on field(s)	245 (67.5)
Sleeps at field during malaria season	193 (53.2)
Amongst those who have a house on rice field(s)	*N=245*
Has a bed net to use at field	190 (77.6)
Brings back net back and forth from village	66 (27.0)
Keeps bed nets at field	124 (50.6)
Transportation to field *(multiple responses possible)*	
On foot	323 (89.0)
By motorbike	121 (33.3)
By boat	23 (6.3)
By bicycle	4 (1.1)
Other	6 (1.7)

Village	
Has a village house	755 (91.6)
Amongst those who have village house	*N=755*
Always sleeps in village during dry season	597 (72.5)
Always sleeps in village during rainy season	273 (33.1)
Mobility between farms – fields - village	
Moves between farms and/or fields without stopping in the village	529 (74.8)
Amongst those who move between farms and/or fields	*N=529*
Moves often between farm(s)-field(s) (1-7 times/ week)	281 (53.1)
Moves sometimes between farm(s)-field(s) (1-15 time/month)	115 (21.7)
Never moves between farm(s)-field(s)	116 (21.9)
Missing	17 (3.2)
Items carried between farm-field-village (multiple responses possible):	
Bed nets	69 (8.4)
Hammock nets	38 (4.6)
Sleeping mats	62 (7.5)
Blanket	74 (9.0)
Food	466 (56.6)
Water	116 (14.1)
Cooking material	185 (22.5)
Hunting / fishing material	21 (2.5)
Logging material	259 (31.4)
Farming material	356 (43.2)
Forest activities	
Goes to deep forest	554 (67.2)
Amongst those who go to deep forest	*N=554*
Stays overnight at forest	131 (23.6)
Goes hunting or fishing in forest	288 (52.0)
Gathers forest products (fruits, vegetables, firewood, honey, etc)	477 (86.1)
Goes logging in forest	151 (27.3)
VMW accessibility and treatment	
Never visited the VMW before	188 (22.8)
Have visited the VMW before	631 (76.6)
Missing	5 (0.6)

Amongst those who have ever visited the VMW before	*N=631*
VMW not available during last visit	28 (3.4)
RDT was not available during last visit to VMW	108 (13.1)
RDT was available during last visit to VMW	495 (60.1)
Amongst those who had an RDT during last visit to VMW	*N=495*
Negative test during last visit	141 (28.5)
Positive test during last visit	354 (71.5)
Amongst those who had a positive RDT during last visit to VMW	*N=354*
Received treatment from VMW	289 (81.6)
Received treatment from public sector (HC, hospital)	45 (12.7)
Received treatment from private sector	13 (3.7)
Received treatment from other	7 (2.0)

The village home is mostly used during the dry season when the most labor-intensive work at the field is over and when farmers rest and have their annual ceremonies and celebrations in the village home. Accordingly, only 33.1% of all respondents reported always sleeping in the village during the rainy season, as opposed to the 72.5% that always sleep in the village during the dry season.

Forest farms are usually reached by foot, and can be located as far as 10 kilometers from the village, making it difficult to transport the necessary materials, such as food, water, mats, and bed nets, back and forth between village and farm (Table 4). The majority (74.8%) of respondents reported moving between farms and fields without stopping over in the village, making it even more difficult to carry around sufficient bed nets or hammock nets to protect all family members who go on the journey. However, due to the recent national malaria control policy (since 2011) of distributing one bed net per person, the largely officially registered indigenous families seem to have sufficient bed nets from the NMCP in combination with non-impregnated nets bought from the market to spread them out over several locations, as multiple family members sleep under one net at different sleeping places. Over half of respondents therefore report to permanently keep some bed nets at their farms (58.1%) and rice fields (50.6%), and the majority reports to usually have a bed net to use at farms (73.3%) and rice fields (77.6%) (Table 4).

Deep forest activities. 67.2% of the indigenous population engaged in deep forest activities. These consist of hunting, gathering forest products such as bamboo or wood and other activities in the uncleared forest where people potentially sleep in an improvised way (e.g. in hammocks). 23.6% reported spending nights in the deep forest (Table 4). The malariometric survey indicated a significant relationship between spending nights at the plot hut on the forest farm in the last month and increased odds of malaria infection (OR 1.66, 95% CI 1.20-2.28, p=0.002). There was a trend towards increased odds of malaria associated with spending nights in the deep forest in the last month, though there was only weak statistical evidence for this association (OR 1.35, 95% CI 0.94-1.98, p=0.10) (Table 5).

Table 5. Association between plot hut (farm or field) and forest overnight stays in the last month and malaria infection (all species)

	Total	Total malaria infected (PCR)	Malaria prevalence %	OR*	95% C.I.	p-value
Plot hut overnight stay in last month						
Yes	2727	166	6.0	1.66	[1.21; 2.28]	0.002
No	2238	77	3.0	Ref.	-	
Forest overnight stay in last month						
Yes	800	59	7.0	1.36	[0.94; 1.98]	0.10
No	4165	184	4.0	Ref.	-	

*Adjusted for age and sex, and clustering by village

Access to health care and malaria prevention. Unlike the Khmer migrants, most local indigenous villagers knew the local VMW since he/she was chosen from the indigenous community; only 22.8% of indigenous respondents had never visited the VMW (Table 4). Of those who had visited the VMW for a RDT, 71.5% reported the test to have been positive for malaria, and most of those positive cases (81.6%) received treatment from the VMW.

Indigenous population cross-border mobility

Mobility. According to the ethnographic study, in the three Jarai villages at the border area, the indigenous territory consists of communities spread over both sides of the border. Short-term cross-border human population movements occurred frequently as the Vietnamese and Cambodian Jarai living within the border communes are allowed to cross the border without permits for one-day stays. It was primarily Cambodian Jarai that crossed the border into Vietnam to pursue economic activities, namely to sell agricultural products and/or to buy products at local Vietnamese stores and markets to take back to Cambodia for resale in small privately owned shops. Longer stays, for which community-level permits and justifications are needed, were generally driven by wanting to seek care in Vietnamese health centers (also for malaria treatment), to visit relatives, and to attend ceremonies. Given the greater economic growth in Vietnam, few Vietnamese Jarai venture into Cambodia for business, but do cross the border for celebrations and other family obligations, as well as to cultivate land in the forest for slash and burn agriculture unavailable in Vietnam.

Malaria prevention. When visiting relatives or other relations across the border, it is not usual to take bed nets when spending nights at hosts' houses across the border. The host family often do not have enough nets to share and rules of hospitality do not require the host to provide bed nets to visitors. However, families that visit once or twice a year and only for ceremonies do so mostly during the dry season.

Discussion

Our study characterized the different structural types of human mobility in Ratanakiri, and their differential risk and vulnerability towards malaria exposure, clearly showing the need for different and adapted malaria prevention and control measures among the groups that are, nevertheless, usually jointly categorized under "mobile populations". Among the local indigenous population, in contrast to the Khmer migrants, LLIN coverage was very high. However, this LLIN distribution was based solely on the administrative village setting, thereby failing to take into account local forest farmers' multiple residence system which entails prolonged stays in the forest farms/fields and increases their exposure to the known early outdoor biting behavior of sylvatic *An. dirus* [12, 21]. Control measures targeting the forest farms, such as additional LLINs and/or other innovative tools, such as spatial repellents or toxic sugar bait traps, can be expected to have a further impact on malaria [30, 31]. Types of human population movements, taking place on a relatively local level, easily go undetected, as illustrated by the multiple residence system among the indigenous Jarai. They could, however, be key to malaria elimination due to the mentioned exposure and in relation to difficulties with uptake of elimination strategies such as MDA, where these populations may easily be missed. More irregular and individual mobility related to the family visits, trade, the exploitation of forest products, including logging, require different tools and strategies, examples of which could be long-lasting insecticidal hammocks [32–36], topical repellents or insecticide treated clothing [37, 38].

With regard to cross-border mobility, while the current borders of the nation-states divide traditional indigenous territory, their social and economic networks require cross-border movements. These cross-border movements can increase local populations' vulnerability to malaria as no bed nets are transported during these visits and hosts generally do not offer them to their guests. In addition, the differential application, in method and intensity, of malaria control activities on either side of nations' borders has been shown to potentially lead to the maintenance of the parasite reservoir by a constant supply of new strains [39].

Additional difficulties for malaria control among indigenous populations include language barriers, historically complicated inter-ethnic relations, the power imbalance observed between local communities and large companies that are currently converting traditional territories into plantations. All of these factors can be hypothesized to compel the most vulnerable groups among indigenous populations, in terms of socio-economic status and social integration, to retreat deeper into remote forested areas, further increasing their exposure/risk and decreasing their accessibility to health services.

The Khmer rural-to-rural migrant group, mostly active on rubber plantations and in mines, represents a fundamentally different social group that increasingly develops as a parallel "social territory" to that of the indigenous populations. The continuous influx of these lowland Khmer constitutes a new potential risk group for malaria. These migrants are often moving from lowland non-endemic provinces, and are therefore more vulnerable to malaria infection due to their limited awareness of malaria prevention and treatment as well as low acquired immunity, in contrast to the indigenous populations, that have good access to malaria diagnostic and treatment through the VMW system and have a higher level of immunity. Khmer migrants were seldom reached by LLIN-distribution campaigns since they remained largely unregistered, and were also unaware of the local VMW-system due to poor social integration locally. Moreover, most plantation workers and miners purchased non-treated nets, the majority of which were already damaged at the time of study, providing less protection against mosquito bites.

The temporal migration from high to low-endemic areas, as large numbers of Khmer migrants return to their home provinces after their work has ended, can result in imported infections [16] or re-introduce malaria where transmission had ceased, which is especially the case in areas of high receptivity (i.e. the historical potential for vector transmission that determines the severity of local onward transmission) [16]. Khmer temporal migrants therefore require different malaria control strategies than local indigenous populations, such as the active detection and registration of those workers and immediate access to malaria prevention and control tools from which they are currently excluded.

The strength of this study lies in its mixed-methods design that allowed the integration of qualitative and quantitative data, producing consistent and complementary findings across different datasets. The triangulation design reduced the risk of bias as it allows the validation of different findings observed across different methods. An additional strength was the interdisciplinarity, which enabled linking different types of local mobility patterns to malaria risk as measured by malariometric data. The ethnographic data collection provided richer contextual data than would have been possible to obtain through standard questionnaires during malariometric surveys. Furthermore, the ethnographic component explicitly informed the development of the malariometric survey by a prior identification of all possible local risk factors/behaviors. The main limitation of the study was the lack of malariometric data on migrant workers in rubber plantations and gem mines that could have assessed the relevance of their exposure in relation to malaria risk. This should be further assessed in population-based studies including the different groups at risk. In addition, due to the rapid economic changes in the region and the continuous exploitation of new plantations, some plantations may have been missed. We do not expect, however, that including additional plantations would have changed the presented results.

Conclusion

Different types of mobility require different malaria control and, ultimately, elimination strategies (Figure 2). In addition, targeting mobility without an in-depth understanding of malaria risk in each group can lead to wasted efforts and resources. Further studies should be systematically embedded into national malaria control and elimination programs in order to identify the different type(s) of mobile populations at stake and enable the development of a theoretical framework for optimizing the delivery of effective malaria control measures to those most in need.

Populations	Mobility	Strategies	Tools
Indigenous highland populations	Multiple Residence System	Focusing on forest fields for control	Additional LLINs
	Cross-border mobility	Additional personal protection tools Health center/post	Repellents
	Individual irregular forest activities		LLIHs
Lowland Khmer migrants	Rural to rural migration	Active case detection	LLINs
		Administrative registration	Repellents
			LLIHs

Figure 2. Malaria vulnerability by type of mobility

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Additional information

The authors declare no competing financial interests.

Author contributions

KPG, AE, UDA and MC conceived of the study. KPG and CG designed the experiments. KPG, CG, SU, PP, SS, SrS performed the anthropological fieldwork. VS performed and supervised the malariometric survey. KPG and CG performed the qualitative data analysis. CG, SD, VS did the quantitative analysis. KPG and CG wrote the manuscript. AE, MC, UDA, SHM, RG, JM, MBT, SH, SD, ST, SU, PP, SS, SrS, LD, VS and TS edited and reviewed the manuscript.

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Ethnographic Intermezzo IV

Bhatt and colleagues estimate that malaria interventions have averted 663 million clinical malaria cases in Sub-Saharan Africa since 2000, of which 68% can be accredited to Insecticide-treated mosquito nets (ITNs) and/or long-lasting insecticidal nets (LLINs) [1]. As these figures indicate, malaria control worldwide still largely depends on the use of mosquito nets. Besides the public health utility this object obviously holds, its social aspects are however seldom of concern for malaria control programs. Social factors such as local net preferences, unstable sleeping arrangements and lack of net adequacy to the local environment and housing structures may be important contributors to persisting malaria transmission after full coverage of nets has been achieved.

Since 2007, the WHO recommends all malaria control programs to assure "universal access" to either ITNs or LLINs [2]. Universal access is defined as the availability of 1 impregnated net for every 2 people at risk for malaria, irrespective of the context. Assessing universal access is done with indicators that build on data gathered with standardized household questionnaires during so-called Malaria Indicator Surveys (MIS), developed by The Roll Back Malaria program (RBM) [3]. There are indicators for household ownership of at least 1 ITN, ownership of sufficient ITNs within a household to cover all members (assumed to be 1 impregnated net per 2 household members), and an indicator for net use, operationalized by the question whether they have slept in the ITN the night prior to the interview [2]. These indicators aim to enable experts to estimate the coverage rates of ITNs or LLINs, depending on the national program.

As previous research has shown in Tanzania [3], and the following chapter will show for Ratanakiri, these indicators cannot provide a realistic evaluation of what is happening in villages targeted by such indicator surveys. First of all, accurately measuring use proves to be more complicated than asking whether someone has slept in an ITN the previous night (see chapter 6 for an elaboration on measuring use). Secondly, measuring only use of ITNs, as is done with these standardized questionnaires, assumes that the ITNs distributed by the national program are indeed the only nets that are used by local populations, an assumption which our observations in Ratanakiri cannot support.

The WHO provides recommendations to national control programs for selecting the proper ITNs to distribute, criteria mostly based on bio-assay tests and net durability tests. However, the situation in Ratanakiri shows that the potential successes of ITN distributions are more related to local net preferences and the adequacy of the nets in relation to domestic spatial organization, than to the government's adherence to WHO recommendations. Ethnographic observations show that households in Ratanakiri often protect themselves from insects with non-treated market nets.

Figure 1. Typical local sleeping space with colourful sheets and pink market nets

People in Ratanakiri find the LLINs distributed by the Cambodian malaria program qualitatively inferior, so they are less often used than assumed and more often stored for later or for guests, ultimately preventing less new malaria cases than intended. This difference in acceptability leads to differences in use between the "program nets" and the colourful untreated nets for sale at local markets and by travelling salesmen.

When considering local net preferences, we must take into account that nets do not only prevent malaria as a public health tool, but are social items that upset domestic sleeping arrangements, housing structures, the spatial organisation within a house, and behaviour from visiting friends and relatives. This social impact of nets is seldom considered when decisions are made on which net to distribute, or when measuring 'ownership', 'coverage' and 'use' of nets to evaluate the effectiveness of a malaria control program. Global and national policies have the implicit assumption that sleeping arrangements are universally the same and stable, and that if everybody is given a net, they will be able to use it. Sleeping or living arrangements in Ratanakiri are not always stable, however. Net use and net preference are in fact deeply rooted in socio-cultural patterns, such as sleeping arrangements within the household and agricultural mobility, and cannot be measured by indicators that measure individual parameters, such as personal preference for a certain colour, alone [4]. Ethnographic observations in Ratanakiri show that the use of natural resources (slash and burn farming and forest activities) require families to stay in dwellings other than their village house due to factors such as distance to the village house, spiritual relations with the cleared lands, and the necessity to protect crops from wild animals and roaming cattle at night and during the day. Livelihood practices are therefore intimately interwoven with sleeping arrangements. Moreover, during my ethnographic studies I observed families constantly changing composition in farm- and village houses: teenagers are often sent back to the village for a couple of days to pick up salt and monosodium glutamate (MSG) to flavor the bland foods available on the farm; children sometimes stay behind in the villages with grandmothers to attend school when the Khmer teachers occasionally show up; and sometimes adult men come back for a night or two to participate in social events such as funerals or spirit ceremonies whilst consuming large amounts of rice wine. These sleeping patterns imply diverse and changing sleeping spaces for different mobile individuals, and not simply a rotation of mobile individuals in one sleeping space. However, the national distribution of one net per one person aims to cover a fixed set of individuals in a fixed sleeping space, and does not consider the fluid reality of varying sleeping spaces among mobile individuals. A consequence is that, when families are divided throughout several residences, the mobile household member finds it cumbersome to carry around an LLIN from sleeping space to sleeping space. Ethnographic observations show that there is always some ceremonial event going on in the village, some far away field to attend to, and some child staying in the village, and therefore there is always some part of the population not adhering to a fixed sleeping space and not using a bed net. Indicators derived from questions that assume a stable pattern or straightforward answer cannot capture such sleeping patterns and irregular bed net use. The perception of the stability and certainty of numbers sits uncomfortably with the constant flux of the phenomena that numbers seek to fix and quantify in this setting. Moreover, researchers have not yet looked at how irregular net use at individual and group level may impact on the assumed community protective effect of a full coverage of LLINs [5].

Likewise, real-life net durability in local houses and circumstances, are often also not properly measured. This may lead to measures of “non-compliance” to nets that actually refer to a lack of access to *good* and *intact* nets [4]. My informants in Ratanakiri tell me that their nets tear quickly because their children urinate on nets (in the absence of diapers) and they have to wash them almost weekly, or because the chickens keep picking at nets and rodents keep eating them in the house. Moreover, they report the material of distributed LLINs to be of inferior quality (harsh fabric, large meshsizes, small overall size, etc.), so they often stop using them fairly quickly after distribution. Some people have told me – jokingly - that they perceive the low quality of nets to reflect the low social status the state (i.e. control program) affords them.

These local practices impact not only on measurements of ITN ownership and use, but also relate to the difficulty of measuring ITN ownership and use *in households*. Randall et al have scrutinized how the concept of “household” in household sample surveys is treated as a “fact of life”, regardless of the different meanings “household” can have in different contexts [6]. Such diversity in social units can impact directly on the analysis of survey data that treat the household as a universal fact. Fieldworkers in our repellent project were often confused as to how to treat questions concerning the household, as extended families lived in ‘longhouses’, or siblings’ families lived together in the same house in the village but were spread over different farmhouses. Reflecting similar complexity, nuclear families formally lived together in a house but variably commuted between several residences at rice fields, farm plots and the village. Determining and measuring how many LLINs a ‘household’ owned, could therefore vary greatly across fieldworkers, and result in very different measurements of ‘household ownership of LLINs’.

In Ratanakiri, malaria indicator surveys aim to measure a ‘universal access’ to and ‘optimal coverage’ of LLINs. In theory, all requirements to eliminate malaria are indeed met: LLINs are distributed so there is no need for cumbersome re-treatment of ITNs with insecticides; LLINS are distributed free of charge so there are no financial barriers; LLINs are distributed one net per one person so every single household members has access to an LLIN; and, effective distribution rounds occur once every couple of years, assuring continued access to LLIN even after net deterioration according to product specifications. However, epidemiological and ethnographic observations show that malaria transmission continues, as LLIN use is *not* optimal despite the assured universal access. Entomological measurements further show that mosquitos may bite early in the evening and outdoors, escaping contact with the LLINs that *are* being used. In addition, measurement problems when defining ‘ownership’, ‘use’ or even ‘household’ leads to skewed findings unable to reflect and explain the continuing malaria transmission.

In the following chapter, I highlight how people in Ratanakiri relate to LLINs and thus determine the continuously evolving relationship they have with malaria vectors. I hypothesize that this interaction between man and mosquito shapes the local malaria epidemiology of outdoor and early malaria transmission. Trying to overcome the inability of malaria indicator survey questions to capture actual net use, I have tried to operationalize this concept with questions embedded in the social reality of net practices in Ratanakiri.

Figures 2-11. Various alternative uses of the LLINs distributed by the national program across indigenous villages in Ratanakiri

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Chapter 6. Re-imagining Malaria: Heterogeneity of Human and Mosquito Behavior in Relation to Residual Malaria Transmission in Cambodia

Nighttime Human Landing Collections of mosquitos by a volunteering villager

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Introduction

The effectiveness of existing malaria control measures has led to new radical challenges in settings where malaria has successfully been reduced. Residual transmission, defined as persisting transmission after full coverage of long-lasting insectical nets (LLIN) or indoor residual spraying (IRS) has been achieved, challenges malaria elimination [1, 2]. Standard control programmes and measures seldom consider human heterogeneity such as local sociocultural variability, examples of which are mobility [3], the lower than expected uptake of preventive measures in certain vulnerable populations [4,5] and difficulties achieving optimal adherence to anti-malarial treatment [6-8]. Low malaria transmission in pre-elimination contexts might additionally cause a decreasing perception of risk, potentially leading to a lower use of malaria preventive measures [9, 10]. In addition, vector behaviour has proven to be equally heterogeneous, as it can adapt to and thus challenge standard vector control tools [1, 11, 12]. After the scaling-up of LLINs in Southeast Asia, remaining vector populations developed a propensity to predominantly feed early and/or outdoors, as well as rest outdoors after feeding, fundamentally limiting the effectiveness of LLIN and IRS [13, 14].

These challenges invoke memories of the Global Malaria Eradication Programme embarked upon in 1955 [2, 15, 16]. Despite significant local successes, in many regions malaria resurged after the abandonment of control programmes, hitting hard on populations that had lost much of their immunity against the disease [16]. After the success of vector control with DDT, which transformed endemic areas into settings with a “manageable proportion” of infective cases – a situation comparable to the current low transmission context of Southeast Asia – interventions that successfully interrupted transmission were still lacking [15, 16]. These failures strongly related to the application of a centrally defined and standardized plan to locally diverse epidemiological, entomological and socio-cultural contexts. The importance of this local heterogeneity, including social and cultural barriers and vector behaviour, which prevented success in the past, must not be forgotten as this is once again key to reaching the current goal of elimination [15-17].

Due to the changing malaria epidemiology, outdoor transmission is becoming an important focus for malaria control strategies today. In the Greater Mekong Region, malaria is now mainly reduced to forested regions, populated by ethnic minorities [4, 9, 11, 18], where residual transmission is hypothesized to mainly occur by vectors that are active during early evening and morning hours when people are not sleeping in mosquito nets. In addition, the high diversity of potential vector species together with highly heterogeneous malaria vector behaviour both between and within vector species, complicates the malaria epidemiology [1, 11]. The same vectors can behave differently in different villages in the same region, which is due to vector biology, ecology, human behaviour and the presence of vector control [12, 13].

The evolving interplay of vector and human behaviour in Southeast Asia's remaining transmission foci (i.e. forested areas) challenges elimination goals [19], echoing problems encountered during the first eradication campaign. Starting from the premise that, in order to target residual transmission in these low transmission settings, a clear understanding is needed of when and how humans and vectors meet, the focus of this research was on the sociocultural heterogeneity in Ratanakiri province, Cambodia, representing a transmission zone in a country otherwise well on its way towards a pre-elimination phase. This paper presents the results from an anthropological study and an entomological study, which were ancillary to an epidemiological trial investigating the effectiveness of the mass use of topical repellents in addition to the use of LLINs in controlling malaria infections.

Methods

Study site and population

Population. Cambodia is inhabited by approximately 90% ethnic Khmer. However, there is a small ethnic minority population located mostly in the northeast, in Ratanakiri and Mondulkiri provinces. These populations are part of a larger cultural area that extends from Laos in the north through the central highlands of Vietnam in the east and finally Ratanakiri and Mondulkiri in the south [20]. The largest ethnic groups in Ratanakiri are the Jarai, the Tompuon and the Kreung, each with a distinct language and cultural system in terms of kinship and political organization [21]. A characteristic shared by these ethnic groups is that they usually combine slash-and-burn agriculture with hunting, fishing and gathering various forest products. As distances between farms in the forest, rice fields and villages can be substantial, many families maintain residences at each location, and move from one place to another according to the agricultural cycle and the forest farm or rice field's requirements [8, 21].

Malaria. Malaria transmission is perennial with two peaks, June-July and October-November, the rainy season lasting from May to October. At the end of the malaria season of 2012, the overall PCR prevalence in Ratanakiri, as recorded by the MalaResT study (cfr. Infra), was estimated at 4.9% [22]. Species-specific areas with elevated risk of infection have been detected for all *Plasmodium* species. The clusters for falciparum, vivax and ovale malaria appear in the north of the province along the main river, while the cluster for Malariae is situated in the south of the province [23]. The primary vectors in Ratanakiri are *Anopheles minimus* and *Anopheles dirus*, and many secondary vectors are present. These vectors are generally exophagic and exophilic, and their densities and behaviour vary extensively per village [13]. Early biting proportion (EBP), which is calculated as the biting activity before 22.00 (i.e. assumed human sleeping time), was observed to be around 50% in Ratanakiri in 2005, the proportion of infectious bites before 22.00 was 29% [13].

Study context

This study took place in the framework of an intervention trial (MalaResT), which aimed to raise evidence on the effectiveness of the mass use of topical repellents in addition to LLINs to reduce malaria infections. In this intervention trial, 113 of the most endemic villages in Ratanakiri were randomly assigned to a control arm, in which every household received one LLIN per one person, or to an intervention arm, where in addition to LLINs topical repellents were distributed biweekly to every household one bottle per one person. For the epidemiological trial, sample size calculations were based on an expected outcome of 40% difference in malaria prevalence between intervention and control arm. During each of the four malariometric surveys organized in the trial, the aim was to collect blood samples of 65 randomly selected participants within each community. Blood samples were analysed using PCR detection in a mobile laboratory, allowing for a sensitive and rapid malaria diagnostic strategy in the field [22], alongside a small questionnaire on overnight stays at different locations in the month prior to the survey.

Research strategy

The research used a sequential mixed methods study design in which qualitative ethnographic research and quantitative survey research methods were used to complement the qualitative findings (in standard annotation [QUAL -> quan]) [24]. Qualitative ethnographic data were collected in local communities to acquire an in-depth understanding of the study setting and population while a cross-sectional and a structured observation survey aimed at quantifying relevant variables from the qualitative study. In addition, a malariometric survey was performed, thus enabling to link previously determined relevant variables to malaria infection, and entomological surveys were performed in selected villages.

Qualitative study

Data collection

The exploratory and in-depth ethnographic research was done in 2012 in a selection of villages included in repellent study mentioned above, more specifically in the intervention villages (with repellents and LLINs) of Kachon Kraom, Lom and Sayos in respectively Voen Sai, Oyadao and Lumphat district, as well as during shorter visits in other communities around these villages, including some control villages (with only LLINs).

Participant observation and in-depth interviewing were carried out within the qualitative strand of the study. Participant observation consisted of observations and reiterated informal conversations and was especially used as an exploratory technique to detect unforeseen variables and to contrast stated opinions with actual behaviour, as it constitutes a respondent independent data collection tool. In 2012, 153 in-depth interviews were recorded and transcribed.

Multiple purposive sampling techniques were used, where informants were selected in relation to emerging preliminary results. In order to increase confidentiality with respondents and consequent reliability of the data, snowball sampling techniques - participants introducing us to other participants - were also used.

Quantitative study

Data collection

For the quantitative strand, two surveys were carried out. From August till November 2012, a cross-sectional survey was performed with a close-ended structured questionnaire based on relevant variables emerging from the ethnographic strand. It explored the following topics: mobility between farms, fields and villages, repellent use, bed net ownership and use, evening social activities, use of malaria preventive measures other than bed nets, perceived mosquito density and nuisance and malaria treatment.

From May until November in 2013, a structured observation survey was carried out. A first visit, in the evenings between 19.00 and 21.00 depending on the availability of the household, consisted of the observation of housing structures, people's resting behaviour, bed net characteristics and topical repellent use of all household members. As actual bed net use at night could not be directly observed, bed nets that were suspended in the evenings before bedtime with at least two corners were considered ready for use. Holes in bed nets were observed but not systematically measured or counted. The next morning, a follow-up questionnaire was administered, exploring socio-economic status, seasonal sleeping spaces, perceived insect and mosquito protection, (alternative) use of nets, child care system, (alternative) repellent use, perceived mosquito nuisance, and previous malaria episodes was carried out with the household leader. Results regarding repellent use are not elicited in this paper.

Sampling

For the cross-sectional survey, 900 individuals were randomly selected from the MalaResT study population. In total, 393 individuals from 56 intervention villages and 431 from 57 control villages were located and answered the structured questionnaire.

For the structured observation survey in 2013, ten intervention villages and four control villages were purposively selected based on the criteria of malaria incidence. In each village, half of all households were randomly selected from the population census. Although there was no prior information available on which household had a farm or not, based on exploratory qualitative research, it was assumed that the majority of households did have a farm and commuted between farm- and village house, favouring the farmhouse during the rainy season and the village house during the dry season. As such, each selected household was assigned either to a farm list (meaning this household had to be observed and interviewed on their farm or rice field, if they had any) or to a village list (the interviewer had to observe and interview this household in their village house, if they had one) to explore potential differences between locations. A total of 653 households were randomly selected for the farm lists, of which 472 households were eligible (meaning they had a farm house where they stayed overnight); and 260 of those households were reached. A total of 655 households were randomly selected for the village lists, of which 555 were eligible (meaning they had a house in the village where they stayed overnight); and 291 households were reached. The main reason for not reaching households was because the selected family was not staying overnight at the respective location within the timeframe of the survey. Finally, a total of 431 households from the intervention arm and 120 households from the control were observed and interviewed.

For both surveys, an additional non-response form – recording reasons for not reaching the household - was used to measure possible systematic self-selection bias.

The possible correlation between malaria infection and overnight stays at different locations was additionally tested in a malariometric survey in October 2012, on a sample of 6,640 individuals selected randomly out of the population censuses of the 113 villages included in the MalaResT study. Out of the list of 6,640 selected individuals, 4,996 individuals were reached.

Entomological collections

To estimate human exposure to malaria vectors, pooled data of different entomological surveys conducted in Ratanakiri province are presented here. Prior to the MalaResT project, indoor and outdoor human landing collections were carried out in two villages (Phi and Lom) during four surveys of five to eight days in July-August 2009, July-November 2010, and July-August 2011. Human landing collections lasted from 18.00 until 06.00. Three collection points were chosen in each village, with paired indoor and outdoor collections per collection point. Within the MalaResT study only outdoor human landing collections were carried out in two intervention (Koy, Chrung) and two control (Kreh, Klis) villages selected out of 113 villages included in the project based on their malaria incidence, their accessibility and the availability of mosquito collectors. In every village, eight entomological surveys of ten successive nights were organized every two months between April and October of 2012 and 2013. Human landing collections lasted from 17.00 until 22.00 and from 17.00 until 08.00. Seven collection points were chosen per village in front of houses across the village, making a collection effort of 70 man-nights per village per survey. The same collection points were maintained throughout both studies. A rotation of collectors was ensured. Mosquitoes were identified and processed according to procedures described in Durnez *et al.* [13]. Mosquito collections were pooled per collection context and per collection hour for data visualisation. Results regarding changing mosquito behaviour in relation to repellent use are not elicited in this paper as they are subject of a separate paper.

Data analysis

Anthropological data

Qualitative data. Qualitative data collection and analysis were performed concurrently and data analysis was an iterative process. Preliminary data were intermittently analysed in the field, and preliminary results were then translated into the question guides for follow-up interviews. Initial results were continuously confirmed or refuted in the field, until saturation was reached. Data were analysed in NVivo 9 Qualitative Data Analysis software (QSR International Pty Ltd. Cardigan UK) by refining and categorizing themes grounded in the data.

Quantitative data. Preliminary analysis of the qualitative data was used to build the standardized questionnaires for the quantitative survey. The quantitative data was entered in Epi Info 7. The dataset was analysed in SPSS (IBM SPSS Statistics 19). Frequency tables for the main outcome variables were produced. Odds ratios and p-values for the association between overnight stays at the plot hut or in the forest and malaria infection were calculated using logistic regression models with a random intercept to adjust for clustering at village level.

Entomological data

Mosquito collections were registered on standardized data collection forms, and data were entered in an Access database. Mosquito collections were pooled per collection context and per collection hour for data visualization. Boxplots indicating median biting times and 25 and 75 percentiles were constructed in R [25]. Exophagy was calculated as the proportion of mosquitoes biting outdoors as follows: $O_{18\rightarrow06hrs}/(I_{18\rightarrow06hrs} + O_{18\rightarrow06hrs})$.

Human exposure to malaria vectors was estimated by the analysis of the following data: the weighting of the mean indoor and outdoor biting rates throughout the mosquito collection period by the proportion of humans that are typically indoors or outdoors at each time period, and this in the scenario of (i) no protective measures, and (ii) the observed use of protective measures. Each type of observed net being used was assigned a level of protection from exposure based on the levels of protection observed by Lines et al in experimental hut trials of (i) untreated intact nets, (ii) untreated holed nets, (iii) intact permethrin-treated nets and (iv) holed permethrin-treated nets [26]. The proportion of indoor and outdoor mosquito bites averted by the use of protective measures was then calculated.

Ethical considerations

The study protocol, including the anthropological, entomological and epidemiological parts, was approved by the National Ethics Committee for Health Research in Cambodia, the Ethics Committee of the University Hospital of Antwerp, and the Institutional Review Board of the Institute of Tropical Medicine of Antwerp. For the anthropological part, the interviewers followed the Code of Ethics of the American Anthropological Association (AAA). As proposed by the AAA, all interviewees were informed before the start of the interview about project goals, the topic and type of questions, the intended use of results for scientific publications as well as their right to reject being interviewed, to interrupt the conversation at any time, and to withdraw any given information during or after the interview. Anonymity was guaranteed and confidentiality of interviewees assured by assigning a unique code number to each informant. The interviewers sought oral consent from all interviewees. Oral consent was preferable, since the act of signing one's name when providing certain information can be considered a potential reason for mistrust. Moreover, oral consent avoided the stress associated with potential illiteracy.

Regarding the entomological study, the mosquito collectors were informed about the objectives, process and procedures of the study and written informed consent was sought from them. Collector candidates were invited among the adult village population and if individuals wanted to withdraw they were allowed to do so at any time without negative consequences. Access to malaria diagnosis and treatment was guaranteed throughout the study. For the epidemiological study, survey participants or his/her parents or guardian provided informed written consent for individual participation.

Results

Variance in sleeping behaviour and bednet use in relation to vector biting times

Vector biting times. Human landing collection performed from 18.00 to 06.00 in 2009-2011 show that median biting times differ slightly between the known malaria vectors in Cambodia (*Anopheles dirus s.l., Anopheles minimus s.l., Anopheles maculatus s.l., Anopheles barbirostris s.l.*), and between outdoor and indoor collections (Figure 1A). *Anopheles dirus s.l.* has a median biting time of 22.00 - 23.00 outdoors and 23.00 - 00.00 indoors. The other vectors have a median biting time of 21.00 - 22.00 indoors and outdoors, except for *Anopheles maculatus s.l.* with an indoor median biting time of 22.00 - 23.00. Outdoor mosquito collections organized only in the evening (17.00 - 22.00) and morning (05.00 - 08.00) in 2012-2013 showed that vectors can start biting from 05.00 onwards and continue to bite up to 08.00, although at very low biting rates (Figure 1B).

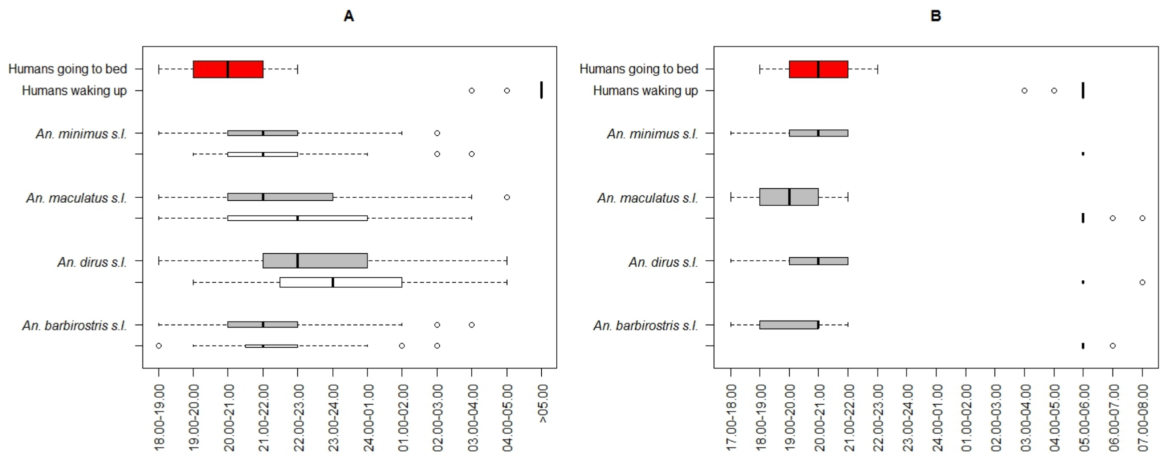

Figure 1: Local human sleeping and waking times (red box plots) compared to collection times of mosquitoes by human landing collections A. outdoors (grey boxplots) and indoors (white boxplots) in 2009-2011, and B. outdoors only during evening (17.00-22.00) and morning hours (05.00-08.00) in 2012-2013. No indoor or whole night collections were performed in 2012-2013. For both A and B, the size of the boxplot is proportional to the observed man biting rates in the respective study settings.

Human sleeping places and times. The place where people live and sleep varies seasonally. Throughout the year families alternate between sleeping in village homes (traditionally longhouses) and one or several homes at their farms in the forest, where dry rice and vegetables are grown (Table 1). The rainy season, which coincides with the malaria transmission season, is the most work intensive season for farmers, often leading to the preference to sleep at their forest farms (61.2 %), while the dry season is usually spent in the village. This leads to variability in sleeping places directly related to malaria transmission, as spending the night at farms in the forest is a risk factor for malaria infection (OR 1.53, 95% CI 1.12 – 2.10, p<0.01) (Table 2). Most respondents do report to keep separate bed nets at the farms (78.3%), however, rather than bringing nets back and forth from the village (20.4%) (Table 1). Observations during ethnographic research confirm that at farms, most people go to bed not long after sunset, exhausted from a long day's field labour and with only minimal access to electricity. Around one quarter of respondents indicated they go to sleep before 19.00 when they are staying at their farms; about 70% of respondents do so between 19.00 and 21.00 and less than 10% after 21.00 (Table 3) (Figures 1A and 2). In villages, sleeping times are later than at forest farms and rice fields, as 31.9% of respondents reported to go to sleep after 21.00. In the mornings, around half of the respondents wake up before 06.00, both at farms and villages, when the main vectors are still active (Figure 1A).

Table 1. Reported multiple residence system (Cross-sectional survey 2012)

	N	%
Has farm(s)	768	93.2
Has a house on farm(s)	633	82.5
Sleeps at farm during malaria season	470	61.2
Has a bed net to use at farm	464	98.7
Brings back net back and forth from village	96	20.4
Keeps bed nets at farm	368	78.3
Has village house	755	91.6
Always sleeps in village during dry season	597	72.5
Always sleeps in village during rainy season	273	33.1

Table 2. Association between overnight stays at plot hut or forest in past month and malaria infection

	Total	Positive	Malaria infection (all species)	OR	95% C.I.	p-value
Plot hut overnight stay last month						
- Yes	2727	166	0.06	1.53	[1.12; 2.10]	<0.01
- No	2238	77	0.03			
Forest overnight stay last month						
- Yes	800	59	0.07	1.35	[0.97; 1.90]	0.08
- No	4165	184	0.04			

Table 3. Reported sleeping and waking times at the village and farm (Cross-sectional survey 2012)

	Village (n=755)		Farm (n=470)	
	N	%	N	%
Sleeping times				
- Before 19.00	77	10.2	94	20.0
- Between 19.00 and 20.59	421	55.8	326	69.4
- At or after 21.00	241	31.9	44	9.4
- Missing	16	2.1	6	1.3
Waking times				
- Before 06.00	354	46.9	211	44.9
- At or after 6.00	384	50.9	254	54.0
- Missing	17	2.3	5	1.1

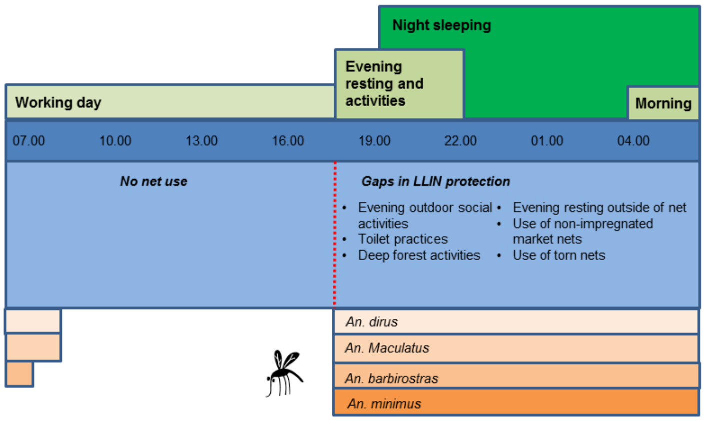

Figure 2: Suboptimal net use during vector biting times.

Use, state and perceived protection of different types of nets. Most respondents reported having a LLIN distributed by the national malaria control programme (98.5%) and sleeping in one (79.1%) (Table 4). 40.0% owned a bed net bought from the market, half of which reported to sleep in one. When observing households, in 5.3% of cases there were no indications of any net use; 45.4% were observed to be using (an) intact LLIN(s) and 23.2% intact non-impregnated market nets. In 24.7% of households (a) holed LLIN(s) was being used and in 16.5% (a) holed market net(s) (Table 5). The majority of household leaders stated mosquitoes (57.7%) and other small insects (64.1%) were able to enter the LLINs (Table 4). Only 14.8% of those household leaders thought the mosquito died from the insecticide after coming into contact with the LLIN. In contrast to LLINs, only a minority reported mosquitoes (17.0%) and small insects (20.0%) to be able to enter their market nets.

Table 4. Reported bed net coverage and use

Cross-sectional survey 2012 (n=824)	N	%
Owns LLIN	812	98.5
Sleeps in LLIN	652	79.1
Owns market net	330	40.0
Sleeps in market net	162	19.7
Structured observation survey 2013 (n=551)	**N**	**%**
Mosquitoes enter LLIN	318	57.7
Mosquitoes die when entering LLIN	47	14.8
Small insects enter LLIN	353	64.1
Small insects die when entering LLIN	75	21.2
Mosquitoes enter market net	45	17.0
Small insects enter market net	53	20.0
Which net do you use in the village? (n=489)*		
- programme	343	70.1

- bought	136	27.8
- have no BN in village	10	2.0
Which net do you use at the farm? (n=416)*		
- programme	336	80.8
- bought	65	15.6
- have no BN in farm	15	3.6
Children sleep without net while parents are still awake (n=370)	244	65.9

* only those who report to also sleep at their farm / village house

Table 5. Observed bed net coverage and use (Structured Observation Survey 2013)

	Village		Farm		Total	
	n	%	n	%	n	%
Observation bed nets						
HH observed not using nets	15	5.2	14	5.4	29	5.3
HH observed using LLIN(s)	187	67.8	176	71.5	363	69.5
HH observed using market nets	118	42.8	84	34.1	202	38.7
HH observed using intact LLIN(s)	138	47.4	112	43.1	250	45.4
HH observed using intact market nets	77	26.5	51	19.6	128	23.2
HH observed using torn LLINs	60	20.6	76	29.2	136	24.7
HH observed using torn market nets	53	18.2	38	14.6	91	16.5
HH observed having intact LLINs ready for use	129	44.3	106	40.8	235	42.6
HH observed having intact market nets ready for use	75	25.8	51	19.6	126	22.9
HH observed having torn LLINs ready for use	57	19.6	74	28.5	131	23.8
HH observed having torn market nets ready for use	53	18.2	37	14.2	90	16.3
Observation evening resting						
HH where children were observed sleeping	102	35.1	143	55.0	245	44.5
- Without net	76	74.5	105	73.4	181	73.9
- With net	26	25.5	38	26.6	64	26.1
HH where adolescents were observed sleeping	31	10.7	30	11.5	61	11.1
- Without net	24	77.4	22	73.3	46	75.4
- With net	7	22.6	8	26.7	15	24.6
HH where adults were observed sleeping	42	14.4	44	16.9	86	15.6
- Without net	30	71.4	36	81.8	66	76.7
- With net	12	28.6	8	18.2	20	23.3
HH where elderly were observed sleeping	26	8.9	18	6.9	44	8.0
- Without net	18	69.2	14	77.8	32	72.7
- With net	8	69.2	4	22.2	12	27.3
HH where somebody was observed sleeping (all age categories combined)	133	45.7	161	61.9	294	53.4
- Without net	107	80.5	130	80.7	237	80.6
- With net	26	19.5	31	19.3	57	19.4

Net preference. Qualitative research showed that many people prefer market nets over LLINs, which are reported to be made of coarse fabric, considered too small to hold a large family, easy to break and to have such a big mesh size that mosquitoes and other insects can enter despite the insecticide. Moreover, the insecticide is perceived to stop working after a couple of weeks to one year. Consequently, many people own and use the colourful, soft and big nets that are bought non-impregnated from the market. The main perceived advantages of these market nets are the large size, accommodating larger families and preventing the net from creeping up, the colourful designs, and the small mesh size perceived to better prevent mosquitoes/insects from entering. The qualitative study indicated families to prefer to sleep together in the large-sized market nets when staying in their larger village homes; while the smaller LLINs were preferred for small farmhouses or bamboo constructions at the farm or rice field. When quantifying this variable during the structured observation survey, 24.6% reported to prefer market nets to the distributed LLINs (Table 4) (Figure 3).

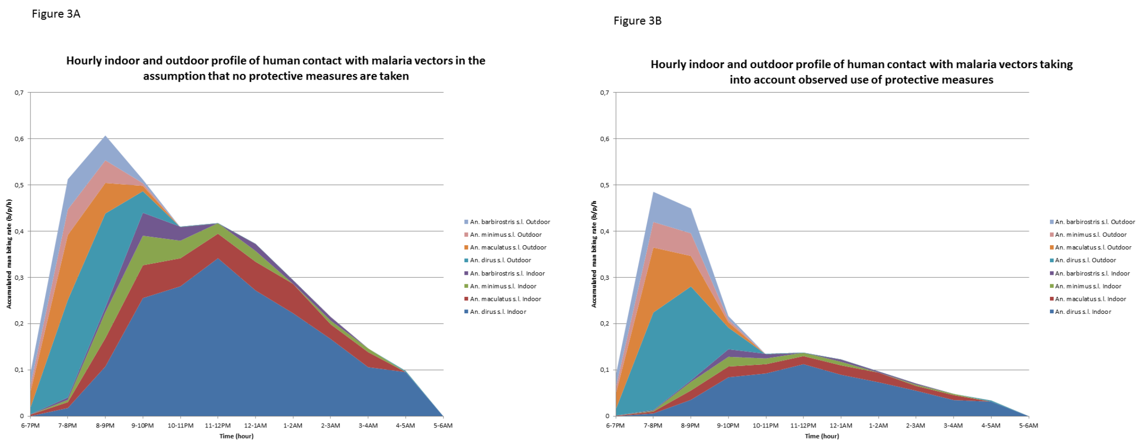

Figure 3: The hourly indoor and outdoor profile of human contact with malaria vectors in Ratanakiri province, Cambodia based on entomological data collected during 2009-2011 and human behaviour data collected during 2012-2013. The stacked line graph presents estimates of accumulated indoor and outdoor human contact rates with the four most common malaria vectors collected in the study area (Anopheles dirus s.l., Anopheles minimus s.l., Anopheles maculatus s.l., and Anopheles barbirostris s.l.). The movement pattern of people was taken into account by weighting the vector biting rates throughout the night by the proportion of humans that are typically indoors or outdoors at each time period. (A) No weighting by use of vector control tools; (B) Weighting by observed use of vector control tools.

Variance in evening and outdoor activities in relation to vector biting places

Vector biting place. Between 2009 and 2011, the majority of malaria vectors were collected outdoors, which was 70% of all mosquito species collected. Slight differences in exophagy rates were observed between vector species (80% for *Anopheles barbirostris s.l.*, 70% for *Anopheles dirus s.l.*, 68% for *Anopheles maculatus s.l.*, and 66% for *Anopheles minimus s.l.)*. For *Anopheles dirus s.l.* and *Anopheles maculatus s.l.*, the median outdoor biting time was one hour earlier as compared to the median indoor biting time (Figure 1A).

Open housing structures. Completely or partially open houses (i.e. without exterior walls) and bamboo-thatched plot huts only provide minimal protection from insects during evening activities. More open and/or thatched roof houses were located at forest farms as compared to the villages (Table 6). Entomological data suggests that people are still exposed to 'outdoor' mosquito biting in the evenings while sitting inside their open houses (though less than outside) (Figure 1), and anthropological data indicates this is especially the case at farmhouses located in the forest where the malaria risk is higher.

Table 6. Observed housing characteristics per location (Structured observation survey 2013)

	Village (n=291)		Farm (n=260)	
	N	%	N	%
Stilted house	252	86.6	211	81.2
Roof				
- thatch	35	12.0	104	40.0
- tin	247	84.9	150	57.7
- tile	7	2.4	0	0
- plastic	2	0.7	6	2.3
Walls				
- plastic sheeting walls	37	12.7	75	28.8
- no walls or only partly walled	98	33.7	130	50.0
Permanently open windows	179	61.5	201	77.3

Social evening activities. During evening hours when vectors are active, many people engage in various in-house and outside activities (basket weaving, collecting water and firewood, tending to cattle, watching television, etc.). These activities vary according to the location (Table 7) due to differences in the availability of electricity. At the forest farms and rice fields, only a small number of families have a battery or a generator, allowing them to show movies on DVD in the evening, attracting mostly children from across other forest farms. In villages, more than half of the respondents reported to have some form of power to use in the evenings, resulting in considerably more people engaging in social activities in the evening, such as watching television (Table 8).

Table 7. Reported evening activities at farms (Cross-sectional survey 2012)

	N	%
Evening activities at farms (n=470)		
Housework related activities (handicraft, cleaning, cooking, etc.)	318	67.7
Tending cattle	27	5.7
Nothing/chatting	181	38.5
Forest activities (gathering firewood, fishing, hunting, etc.)	48	10.2
Multimedia (tv)	43	9.1
Other (reading, bathing, having dinner)	33	7.0

Table 8. Access to electricity in the village (Cross-sectional survey 2012)

	N	%
Household's access to power (n=824)	511	62.0
Personal generator	175	21.2
Battery	352	42.7
Solar power	35	4.2
Large village generator	42	5.1
Power grid	1	0.1

People use smoke from fires or from cigarettes outdoors during these evening biting hours to decrease mosquito nuisance, especially when at farms or in the deep forest where mosquito nuisance is reportedly higher (Table 9). Although the majority of respondents reports to also protect themselves from mosquito biting by wearing long clothes, observation in villages shows that children usually have either lower or upper bodies completely exposed, and adults' clothes are only partially covering the body (due to large rips or men wearing only long trousers).

Table 9. Reported mosquito bite protective measures at different locations (Cross-sectional survey 2012)

	Village (n=773)		Farm (n=759)		Deep forest (n=550)	
Smoke from fire	337	43.6	476	62.7	112	20.4
Smoke from cigarettes	171	22.1	199	26.2	184	33.5
Coils	44	5.7	33	4.3	13	2.4
Clothes with long sleeves/pants	523	67.7	676	89.1	513	93.4
Insecticide sprays	36	4.7	27	3.6	3	0.5
Traditional methods (herbs, etc.)	2	0.3	2	0.3	3	0.5

Evening resting. Qualitative research showed that, more than adults, children often rest (and fall asleep) on the floor in the house or on bamboo beds or hammocks outside, and more so at forest farms than in the village (Figure 2). Such 'resting behaviour' is not considered the onset of the night's sleep, and is mostly done without bed net protection, despite often occurring in 'sleeping places' and during prime vector biting time (Figures 1A and 2). It is only later in the evening, when all members of the household go to sleep and actual 'night time' sets in, that children are put inside the bed net with their parents. During the structured observation survey, at forest farms 55.0% of observed households had children taking a nap before actual sleeping time and doing so without bed nets in 73.4% of cases (for resting behaviour of other age categories, see table 5). The majority of household leaders (65.9%) also report to let their children sleep unprotected while parents are still awake in the evening.

When looking at all age categories combined, people were observed sleeping in the evenings in 53.4% of households, and doing so unprotected in 80.6% of cases (Table 5).

Deep forest economic activities. Most of the indigenous population (67.2%) engaged in economic forest activities (Table 10), of which 23.1% reported to also spend nights in the forests (Figure 2). Moreover, 52.0% of the forest-goers are engaged in fishing and hunting, which often happens during the night. There was a trend towards increased odds of malaria infection associated with spending a night in the deep forest in the last month, however, there was limited statistical evidence for this association (OR 1.35, 95% CI 0.97 – 1.90, p=0.08) (Table 2).

Table 10. Reported outdoor deep forest economic activities (Cross-sectional survey 201

	N	%
Performs deep forest activities	554	67.2
Hunting	165	29.8
Fishing	236	42.6
Logging	151	27.3
Collecting forest products (bamboo shoots, fruit, honey, firewood, etc.)	477	86.1
Other	43	7.8
Stays overnight in the deep forest:		
- Never	418	75.5
- Often	3	0.5
- Sometimes	128	23.1

Toilet practices. Qualitative research showed that people urinate and defecate in the forest surrounding the village or the farm, and even call this “going to the forest” (Figure 2). There are few, if any, latrines, toilets or other sanitary constructions in the villages, and none at the forest farms and rice fields. People report to be very bothered by mosquito bites while going to the toilet, as usually several parts of the body become exposed. As people also go to the toilet during evening, night and morning hours, this activity potentially constitutes a risk for malaria infection.

Exposure to malaria vector bites in relation to the use of vector control tools

After adjusting for the typical movement of people, and not taking into account the use of vector control tools, the greatest part of potential vector exposure still occurs indoors (73%) (Figure 3A). When taking into account the observed use of intact LLINs and market nets (assuming an 85% efficacy), holed market nets (assuming a 24% efficacy), and holed LLINs (assuming a 71% efficacy) [23] in the village only (entomological data from farms not available), the portion of indoor vector exposure still consisted of 47% of the total exposure

(Figure 3B). Taking into account protection levels of LLINs and market nets being used and local sleeping times, in the study context, the observed use of all nets is estimated to decrease indoor exposure by 67%.

Discussion

In low transmission settings, finding appropriate strategies to prevent residual malaria transmission, including transmission due to early and outdoor biting, is currently one of the major challenges in Southeast Asia [27, 28]. A close look at the characteristics of the relationship between vector and human behaviour shows a complex interaction over time and place. The resulting heterogeneity is related to the presence of early and outdoor biting malaria vectors, the slash-and-burn farmers' multiple residence system, locally used (partially-) open housing structures, variance in labour and social activities, sleeping times according to the place of residence and season, and variance in bed net use depending on related user preferences.

Although heterogeneity of human and mosquito behaviour is of general importance to malaria control, and as such transcends contextual particularities, in-depth socio-cultural research is needed to explore the way local communities shape this heterogeneity. In the current study context, focusing on ethnic minorities socio-culturally different from the larger Khmer society in Cambodia, more transmission occurs at forest farms than in the villages, which has also been shown in similar Southeast Asian contexts where ethnic minorities rely on the forest for farming [9, 18]. In addition, the indoor/outdoor distinction is less clear at forest farms as housing here is often completely or partly open and differs from corresponding village homes. As such, the malaria vectors, which in this context preferably bite outdoor, will not be entirely prevented from biting people inside these open houses, challenging the current conceptualization of outdoor transmission. Moreover, the fact that people commute between these different houses with different levels of exposure to indoor and outdoor mosquito biting, results in a constantly varying vulnerability to malaria. Reported sleeping times also vary according to the context. People at fields go to bed earlier than in the villages and earlier than expected as entomological early man biting proportions, (EBP) calculated in similar contexts in Southeast Asia, often take 22.00 as cut-off times for people going to sleep [13, 27]. However, these calculations could be more accurate using locally researched sleeping times as this directly impacts on the proportion of infections that can be accounted for by early or nighttime biting.

In a previous study conducted in Vietnam, also approximately half (52%) of respondents were asleep by 19.00, only 24.5% were still awake after 20.00, and by 21.00 almost everybody (92%) was asleep. Here, sleeping times at farms, where most transmission occurred, were also consistently earlier than in villages and earlier than used for calculating EBP [9]. The same applies to the social evening activities varying according to the place and time of the year. Outdoor evening activities during early vector biting hours occur less during the agricultural peak season (which coincides with the malaria season), especially at those residences in the more forested areas where farmers are tired after an exhausting day's work and the lack of electricity limits social activities. Although malaria vectors start biting outdoors as early as 17.00 and that they continue to do so until 08.00, for the majority of people that sleep under bed nets, the window for outdoor and early transmission was shorter than expected. These earlier than expected sleeping times in settings with a high bed net coverage could be responsible for further driving the selection of early-biting mosquitoes. Conversely, the small percentage of people going to sleep under bed nets after 21.00 or the people that do not use any bed nets or only torn market nets, could disproportionately contribute to malaria transmission. Without LLINs, exposure does indeed still occur largely indoors.

One of the defining elements of residual transmission is based on the premise of total LLIN coverage [1]. While survey results report high LLIN use, due to response bias and the often suboptimal operationalization of the concept 'net use' in questionnaires, actual LLIN use may not be as high as self-reported data from surveys indicate [29]. This is also suggested by the direct observation of the amount of households where market nets were being used, which corresponded to the percentage of people reporting *to own a market net* and not to the reported percentage of market net *use*, which was about 20% lower. In addition, many of these non-treated market nets were holed, offering only very limited protection [26], which, in turn would result in lower than expected community-level protection of non-users [30].

In addition to 30% of households not using LLINs, various gaps in protection were identified during vector biting times, which related, among others, to children and adults resting outside or inside in sleeping spaces in the evening before their reported sleeping times and, at night, when using non-treated torn nets while sleeping in often open housing. Additional gaps in night protection, however, cannot be addressed with LLIN, such as outdoor economic forest activities and toilet practices. Moreover, entomological data confirms that without LLIN, and not considering the potential protective mass-effect of LLIN in a village, a considerable proportion of exposure does indeed occur indoors. Considering all these factors, the contribution of night transmission may still be underestimated.

It has been hypothesized that controlling malaria with LLINs has certain fundamental limitations in regions characterized by early and outdoor biting, thus improving coverage of LLINs alone might not achieve malaria elimination [1]. It is clear that additional interventions aiming for personal protection during evening and night activities are essential. However, based on the current evidence, additional efforts in improving LLIN use during times when people are resting in the evening and during the night may still have an impact on further reducing malaria transmission in Cambodia.

Re-imagining malaria interventions by focusing not only on the heterogeneity in malaria transmission, but more specifically on the connection between heterogeneous human and vector behavior, is crucial when evaluating what works, what is still missing, and how to accelerate the progress in malaria control towards elimination.

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KPG, LD, MC, TS conceived of the study. KPG, CG and LD designed the experiments. CG, SU, PP, SS and SrS performed the anthropological fieldwork. KPG and RG supervised the anthropological fieldwork. LD performed and supervised the entomological collections. VS, SH and TS facilitated the fieldwork. CG analysed the qualitative and quantitative anthropological data. LD analysed the entomological data. MC and LD designed the entomological figures. CG wrote the manuscript. LD, RG, VS, SU, PP, SS, SrS, SH, TS, MC and KPG reviewed and edited the manuscript.

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Ethnographic intermezzo V

During a formal meeting where national and international partners involved in the artemisinin resistance containment effort gathered in Cambodia to discuss their progress in the framework of a research project on improving malaria case detection in resistant zones, a most worrisome realization dawned on my ITM supervisor. Although many different interventionist terms were being thrown back and forth, such as ‘community participation’, ‘reactive case detection’, ‘effective registration of subpatent infections’, all past, ongoing and planned interventions to contain the spread of artemisinin resistance seemed in fact based on the complete and single reliance on the work of a few selected farmers of the malaria endemic Cambodian countryside, i.e. the volunteering Village Malaria Workers. Each intervention tests different strategies, like improving logistics for rapid tests, providing VMW’s with mobile phones, tablets or bicycles or increasing financial re-imbursements of travel costs, but they can all in fact be traced back to the ‘strengthening’ or ‘scaling up’ of the VMW system. While having worked in the malaria field for many years, both in Asia and in Africa, this was the first time my supervisor actually realized the unfounded trust and pressure the global health community was putting on the backs of local people neither medically trained or paid for their work as malaria diagnostic and treatment dispensers to contain a major global malaria threat. Yes, the Village Malaria Worker system has been applauded for its effectiveness in reducing malaria prevalence, bringing access to malaria treatment close to the affected communities while engaging the members of these communities as active participants in the national malaria control program. However, the researchers and policy makers present during these resistance containment meetings also know that VMWs still maintain day-time jobs or work their often remote agricultural fields while being expected to be available to patients to provide malaria treatment. Without being financially compensated for their time, except through some indirect benefits such as respect from other villagers or incentives such as the re-imbursement of travel costs to monthly meetings that may slightly exceed their actual travel cost, the whole resistance containment effort seemed to be solely relying on the good will of poor farmers.

As my supervisor expressed his bafflement, I realized for the first time the full extent to which the repellent trial also relied on the work of volunteers to implement the intervention. These volunteers were usually the same people as the VMWs of the trial villages in Ratanakiri. As the many forms they have to keep to produce ‘data’ requires Khmer reading and writing skills, which are not widely distributed in Cambodian countryside villages and especially not among ethnic minority populations, the VMWs are the usual suspects for all interventions and state programs.

Figure 1. VMW and repellent distributor loading new stock of repellents during a monthly distributor meeting at the district health center

Not only were the repellent distributors required to pick up and dispense large stocks of repellents and malaria treatments with their own hard-earned motorbikes in exchange for some re-imbursed travel costs to monthly meetings, they were required to keep detailed forms registering all household details, levels of consumption, type of malaria infections, reasons for non-compliance, and other complicated data which were fed into the database of the trial.

The tension between the complete reliance on these few individuals to produce malaria elimination data and the lack of any true community involvement in the design or implementation of this and other trials does not seem to sit uncomfortable in biomedical malaria circles, however. It seems as though community engagement or participation is not viewed as something social or political, as for example having the *right* to decide what distribution system of repellents fits their community best, but as a scientific or medical variable which increases compliance to and thus the effectiveness of the trial. Moreover, it shifts the responsibility to eliminate malaria from the governments that are formally engaged in the malaria elimination effort towards these unsuspecting community members. Whittaker and Smith deftly note that many malaria control programs view community participation as something similar to "patient compliance", ensuring "passive community conformity to programme priorities" [1]. This approach fits within the conceptual framework of malaria control being about prevention and treatment of the disease, which both rely completely on the adherence of local people to preventive measures or antimalarials, rather than addressing the "pragmatic difficulties" in reforming poverty and other underlying structural factors to malaria vulnerability [2].

The practice of local villagers supporting malaria control programs without formal salaries has direct consequences for the data produced by intervention trials. Previous literature has already shown that "misbehaviour of front line staff" (i.e. fieldworkers) can impact on the quality of the data they collect - sometimes even leading to data fabrication [3] – when there is no adequate supervision- or support system in place [4, 5]. Biruk describes how - even with an adequate support system in place - fieldworkers' "potentially unruly or unscripted practices" must be "tamed" by replicable collection methods and standardized guidelines. Fieldworkers negotiate these guidelines within the dynamic social system of a village, however, and therefore social reality, refusing to be represented by forms and numbers, is transformed rather messily into data points [6]. Moreover, fieldworkers may develop their own strategies to distort or fabricate the data if the financial re-imbursements and institutional support do not adequately compensate for the workload or the moral challenges they face working in their own communities [3]. In Ratanakiri, ethnographic observations showed VMW's and repellent distributors sometimes fabricated data on forms, sold antimalarial medication or rapid tests to private practitioners, or were simply 'not available' to do the work the malaria elimination effort required of them, resulting in missing or incorrect data and untreated malaria cases. Actively changing the reality their forms were meant to capture, or making up the reality that their forms do capture, they produce a substantial portion of the data that is internationally exported to researchers, universities, donors and policy makers. In addition, one can wonder in how far such unchecked 'free roaming' of artemisinin-combination therapies actually *contributes* to the parasite resistance such practices are meant to contain.

Figure 2. Repellent distributor working on repellent forms on her desk below the house

To truly engage community members in the design and implementation of interventions, formative research approaches might prove an effective way forward [7-10]. First identifying local cultural, social, economic and structural variables that may influence the understanding and acceptance of health messages and the implementation of the intervention, communication messages are only developed in a second stage, after which they are tested in the community to see which instructions are most likely to motivate participants to cooperate in the intervention. In a last stage, the impact and acceptance of the implemented measures is monitored and evaluated. This means that the first steps of formative research take place *before* an actual intervention or trial is implemented, implying an iterative process of data collection. During the repellent trial, donors considered these methods too time- and budget consuming and were therefore rejected on the basis of ‘operational difficulties’. This rejection already hints at the results that are presented in the following chapter, where I explain why the use of repellents was too low to ignite any significant change in malaria transmission dynamics.

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Chapter 7. Factors influencing the use of topical repellents: implications for the effectiveness of malaria elimination strategies

Repellent bottle attached to hunting gear showing repellents were used during some activities

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Introduction

Although parasites, vectors and humans all play a key role in malaria transmission, human behaviour in all its diversity and variability is not always sufficiently considered in prevention policies [1–4]. This is reflected in the unprecedented decrease in malaria in the Greater Mekong Sub-region over the last 10 years in general but not in minority populations, such as the indigenous people of the Cambodian province Ratanakiri. The province is mainly populated by ethnic minorities[5], socio-culturally and linguistically different from the majority Khmer population of Cambodia [5–8]. In terms of the mosquito population, local vectors have been shown to bite early and outdoors. Even with an optimal coverage of Long Lasting Insecticidal Nets (LLIN) or Indoor Residual Spraying (IRS), malaria transmission may still continue as vectors escape contact with insecticide treated surfaces while their blood meals are still active outdoors [9–11]. The progressive confinement of malaria to specific risk populations such as ethnic minorities and forest workers, and the subsequent complex interplay between human and mosquito behaviour [9], calls for innovative measures adapted to local circumstances [9, 12, 13].

Several additional measures to LLINs have been suggested in light of current elimination goals, such as toxic sugar baits which attract and kill mosquitoes [14], insecticide-treated clothing [15, 16], insecticide-treated hammock nets [2, 17] and spatial repellents [18, 19]. To fill the gap in the evenings and mornings when people are still active outdoors, topical repellents have also been suggested as a potentially useful measure for malaria elimination [11, 20]. Repellents have been shown to offer personal protection against mosquito bites [21–24], as a stand-alone measure [25, 26] or in combination with LLINs [27]. However, topical repellents require daily application by the study population in order to be effective, which is often cited to be a major challenge in repellent interventions [25, 28–30].

In Cambodia, a cluster randomized epidemiological trial was recently conducted to raise evidence on the effectiveness of the mass use of topical repellents at community level in addition to the use of LLINs in controlling malaria infections (hereafter referred to as MalaResT). In contrast to the personal protection envisioned by previous repellent studies, the MalaResT study aimed for *community* protection, meaning that diversion of mosquitos from users to non-users is avoided by the expected effect on vector populations of large-scale effective repellent use [28]. The trial was conducted from April 2012 to December 2013, and consisted of a control arm where LLIN were distributed by the National Malaria Control

Program (NMCP), and an intervention arm where in addition to LLINs topical repellents were distributed. The topical repellent used in this study was Picaridin (KBR3023), which is safe [31] and effective against local vector species [23]. A lotion formulation of 10% was used for children between 2 and 10 years old and a spray formulation of 20% from 11 years old onward. Here results are presented from the anthropological study conducted within but independent of the epidemiological trial, of which the primary objective was to acquire an in-depth understanding of the factors influencing the use or non-use of the distributed repellents. In this paper only results directly related to the use of repellents are presented. Other results stemming from this study are reported elsewhere [1, 5, 9, 32, 33].

Methodology

Study site and population

Study site. The study took place in the malaria endemic province of Ratanakiri in Northeastern Cambodia. The border province is geographically and politically located at the fringes of the nation-state and represents one of the least developed provinces in the country. In remote villages of Ratanakiri, Village Malaria Workers (VMW) are trained to diagnose with rapid diagnostic tests and treat positive malaria cases with antimalarials [1, 34]. The pluralistic medical system in Ratanakiri is composed of public sector health facilities with free-of-charge combination therapies; private pharmacies selling “cocktails”, artemether injections and subsidized combination therapies; and local diviners prescribing animal sacrifices to appease the spirits [1]. LLINs are distributed free of charge at 1 net per 1 person by the NMCP and are currently the main malaria prevention tool in the study area.

Study population. The local population is almost exclusively composed of the following ethnic groups: Jarai, Tompuon, Kreung, Prov, Kachok, Kavet, Lon, Lao and Cham, although more recently an influx of lowland Khmer looking for economic opportunities has been observed [35]. Among these ethnic minority groups, the main revenue is generated by subsistence slash-and-burn farming on plots located near or in the forest and, less frequently, on wet rice fields. People move to live on their farms and fields in the rainy season when the workload is heaviest, coinciding with the malaria peak season. Forest farming exposes them to malaria due to the sylvatic nature of *Anopheles dirus*, the main malaria vector of the region, especially when staying overnight in homes at their farms for extended periods during the rainy season [1, 9, 32, 36, 37]. Even with the current optimal LLIN distribution, effective *use* of LLINs in villages and at farms remains suboptimal and as such constitutes a major bottleneck for effective malaria control [5, 9].

Malaria. Malaria transmission is perennial with two peaks, June-July and October-November, the rainy season lasting from May to October. At the end of the malaria season of 2012, the overall PCR prevalence in Ratanakiri, as recorded by the MalaResT study, was estimated at 4.9% [38]. Sleeping overnight at plot huts at the farm has been identified as a risk factor for malaria [32].

Study design

An anthropological study investigating the acceptance of and adherence to topical repellents and existing measures such as LLINs was part of the MalaResT trial (Figure 1). The anthropological study consisted of a mixed-methods design, combining qualitative and quantitative research methods. Such a design allows the combination of self-reporting data collection (surveys and interviews) and respondent-independent data (participant observation), limiting the expected reporting bias to questions related to the adherence of public health interventions. During the initial phase of the research in 2012, qualitative data gathering was prioritized to gain an in-depth understanding of those factors that influence people's acceptance of and adherence to topical repellents and control measures in general. Based on the qualitative data, a cross-sectional survey using a structured closed questionnaire was designed and conducted from August until November 2012. Due to the expected high response bias, a quantitative structured observation survey was conducted from May through December 2013. Additionally, a short questionnaire was done with individuals participating in the biyearly cross-sectional malariometric surveys designed to assess the additional effect of widespread repellent use on malaria prevalence.

Qualitative study

Data collection

Fieldwork, continuously conducted throughout 2012 and 2013 in ethnic minority villages in the districts of Voen Sai, Oyadao, Borkeo and Lumphat, consisted of participant observation and face-to-face open-ended interviews and informal conversations, guided by an continuously adapted interview guide in line with an emergent theory study design. All interviews, conversations and observations were conducted by the first author (CG) (ITM, Antwerp), 1 Khmer female (US) and 3 Khmer male social scientists (PP, SS and SS) (CNM, Phnom Penh). Sampling of informants was theoretical (i.e. purposively selected based on emerging results). Participants were selected based on criteria such as gender, age, social position, reported repellent access and use, professional and economic strategies (including agricultural and forest activities) and were always approached face-to-face for social interaction. Access to respondents was often granted through snowball-sampling techniques, where certain key-informants introduce the researcher to other potential participants. Many informants were visited several times as an additional way of building confidence between researcher and respondent. A total of 320 interviews were audio-recorded and transcribed, including both short informal conversations and more in-depth individual interviews. Participant observation consisted of the research team actively participating in the everyday life of the study population and observing the study setting in its day-to-day and night-time context, including overnight stays in the study villages and observation sessions at the district health centers where repellent distributor meetings were held. Continuous unrecorded informal conversations with respondents built up the confidence needed to discuss more sensitive issues such as adherence to public health interventions; 759 such informal conversations were carried out and recorded in field notes taken immediately after. Additional reflexive field notes were kept throughout the research process and included in the analysis in the form of memos.

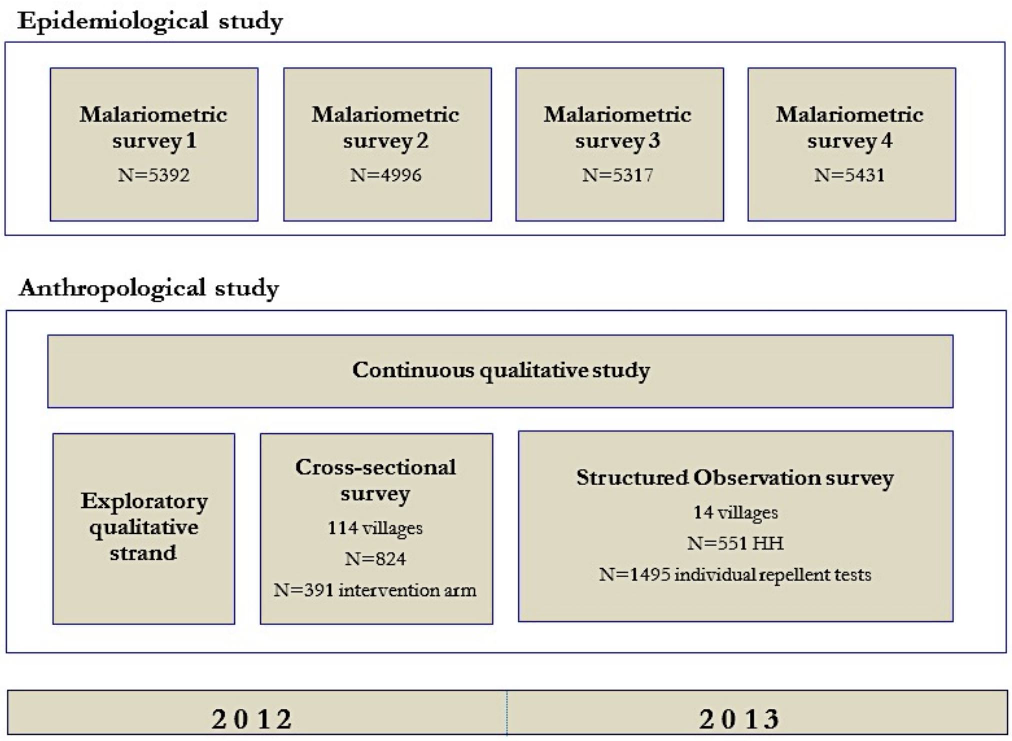

*Figure 1. Flow-chart of the methodology used in the (i) epidemiological trial and (ii) the concurrent anthropological study***.**

Data analysis

Data analysis was concurrent to data collection. In the initial exploratory phase, inductive or open coding of raw data was preferred. When preliminary results started emerging, new hypotheses and theories were formed and tested in the field until saturation was reached. Axial coding was performed to facilitate the analytic process. NVivo 9 Qualitative Analysis Software was used for all data management and analysis.

Quantitative study

Data collection

Based on preliminary results from the qualitative strand in 2012, quantitative data were systematically gathered using two surveys.

Cross-sectional survey. First a cross-sectional survey was carried out focusing on the multiple residence system, repellent use, net ownership and use, evening social activities, use of malaria preventive measures other than nets, mosquito nuisance and malaria treatment. For this survey, 450 individuals from the intervention arm of the epidemiological trial were randomly selected from the census list. A total of 393 people from 56 different intervention villages answered the questionnaire. Of the 57 individuals that were selected but not included in the survey, two were refusals; all other cases were individuals (i) whose names did not exist in the village although they were listed in the census, (ii) were mentally or physically not able to respond due to severe illness, (iii) had moved to another village or province, (iv) could not be located after three visits.

Structured observation survey. In a second quantitative phase, a structured observation survey was carried out. Households were visited unannounced in the evening between 18:30 and 20:30, when according to the guidelines of the trial the repellent should have been applied. The aim was to establish repellent use of all household members through participant observation techniques, administer a short questionnaire on repellent use, and record characteristics of bed nets in the household. The following morning the same household was visited again by the same interviewer for the second part of the structured questionnaire with the household leader, mainly focusing on socio-economic status, seasonal sleeping spaces, (alternative) use of nets, (alternative) repellent use, mosquito nuisance, and previous malaria episodes. For this survey, 10 intervention villages were selected with good access to repellents. In each village, half of all households were randomly selected from the population

census. A rotation system of villages allowed for most of the villages to be visited throughout the rainy season from May until December to account for potential seasonal variation across the data. Based on previous qualitative research, it was known that the majority of households had a farm (and/or rice field) and commuted between farm- and village house, favoring the farmhouse during the rainy season and the village house during the dry season, and that this was a malaria risk factor [32]. Each selected household was thus assigned to either a 'farm list' (i.e. to be observed and interviewed on farm or rice field) or to a 'village list' (i.e. to be observed and interviewed in their village house) to explore potential differences between locations. A total of 517 households were randomly selected for the farm lists, of which 392 households were eligible (i.e. stayed overnight at farm); and 221 were reached. A total of 519 households were randomly selected for the village lists, of which 400 were eligible (i.e. stayed overnight in the village); and 210 were reached. The main reason for not reaching households was because the selected family was not staying overnight at the respective location within the timeframe of the interviewer's stay in the village. Finally, a total of 431 intervention households were observed and interviewed, corresponding to 1495 individuals of whom repellent use was assessed.
The observational technique used consisted of an interviewer spending the evening in a randomly selected household, and -after individual consent- asking permission to smell each household member's arm for traces of repellent in relation to the smell of the repellent. The qualitative strand indicated that perceptions regarding smell were a key factor for use. This approach was used in order to limit response bias and was preferred over directly observing the repellent being used, as the observer's presence was expected to directly influence the decision to use the repellent (often described as the Hawthorne effect, leading to social desirability bias [39]). During the observation, participants who had not used the repellent, were expected to say so when the interviewer tried to smell their arm.

Malariometric survey. In the epidemiological study, malariometric surveys were performed twice a year (baseline at the start of the rainy season and follow-up towards the end), and consisted of a blood prick alongside a short questionnaire assessing net- and repellent use yesterday and last week. For each of the malariometric surveys, 65 individuals per cluster were sampled randomly (Figure 1). An additional list of 15 randomly sampled individuals was used for those clusters where initial response was lacking. Only results from the two follow-up surveys in the intervention arm are shown here.

Data analysis

Preliminary analysis of the qualitative data was used to build the standardized questionnaires used in both quantitative surveys. Quantitative data were entered in Epi Info 7 and analyzed in SPSS (IBM SPSS Statistics 19). Descriptive statistics were performed and significance of relationships between variables tested using chi^2-tests. Multivariate analysis tested the effect of age, sex, village, location of interview and month of interview on repellent use, of which only age was significant. The variation in observed repellent used between households was explored in an empty random effects model with only household entered as an intercept.

Ethical Clearance

The study protocol, including the anthropological work package, was approved by the National Ethics Committee for Health Research in Cambodia, the Ethics Committee of the University Hospital of Antwerp, and the Institutional Review Board of the Institute of Tropical Medicine of Antwerp. For the anthropological part, the interviewers followed the Code of Ethics of the American Anthropological Association (AAA).

Results

Acceptability

Conceptualization of the repellent

More than half of respondents perceived the repellent to be some type of medicine and a similar number conceived the repellent to be some type of poison (Table 1). Qualitative data related these conceptualizations to the strong smell of the repellent. Although the perceived toxicity of the product raised some concerns in the study population, especially for its application on children, it was also considered a required characteristic of the repellent in order to be effective. As such, 37.2% considered the repellent as being both a poison and a medicine.

Table 1. Perceived inconveniences, risks and benefits of the repellent

	n	%
Cross-sectional Survey (N=393)		
Conceptualization of the repellent		
Repellent is poison		

- I don't know	6	1.5
- Never used any repellent	13	3.3
- No	154	39.2
- Yes	219	55.7
- Missing	1	0.3
Repellent is medicine		
- I don't know	3	0.8
- Never used any repellent	13	3.3
- No	141	35.9
- Yes	235	59.8
- Missing	1	0.3
Repellent is both medicine and poison	146	37.2
Perceived effectiveness of the repellent		
Mosquitos still bite after spraying repellent		
- Always	2	0.5
- Never	353	89.8
- Sometimes	14	3.6
- Never used any repellent	17	4.3
- Missing	7	1.8
Insects still bite after spraying repellent		
- Always	2	0.5
- Never	355	90.3
- Sometimes	14	3.6
- Never used any repellent	17	4.3
- Missing	5	1.3
Perceived inconveniences of the repellent		
Skin-related side effects (rash. hot skin. dry skin. etc.)	338	86.0
Flu-like symptoms	128	32.6
Headache	75	19.1
Dizziness	72	18.3
Vomiting	50	12.7
Structured observation survey (N=431 household leaders)		
Alternative uses of the repellent by respondent or family members		
Uses repellent on insects	333	77.3
Uses repellent around body	305	70.8
Uses repellent on bed net	270	62.6
Uses repellent on clothes	248	57.5
Uses repellent on walls	229	53.1
Uses repellent in bed net	197	45.7
Uses repellent around house	131	30.4
Uses repellent on blanket	100	23.2
Uses repellent under bed	91	21.1
Uses repellent on pillow	72	16.7
Uses repellent to cool body	65	15.1
Uses repellent on hair	64	14.8

Uses repellent on grass	20	4.6
Perceived mosquito density second year vs. first year of the trial		
- *Less*	240	55.7
- *Same*	108	25.1
- *More*	75	17.4
- *Don't know*	7	1.6
- *Missing*	1	0.2

Perceived benefits of the repellent

Effectiveness. Almost all respondents reported mosquitos and other insects to stop biting after spraying the repellent. More than half of respondents believed that in the second year of the trial, mosquito densities were reduced because of the repellent (Table 1).

Alternative uses. A high level of reported acceptance of the repellent was predominantly due to the non-prescribed usages of the repellent. The majority of household leaders reported to spray the repellent directly on insects (77.3%), in the air around the body (70.8%), on the outside of the bed net (62.6%), on their clothes (57.5%), on the walls of the house (53.1%), and on the inside of the bed net (45.7%) (see table 1 for more details). Additional alternative uses that were not quantified included its use against hair lice, forest leeches and maggots in animal wounds.

Perceived inconveniences of the repellent

Most respondents stated to have experienced skin-related inconveniences (itchy skin, hot skin, skin rash, dry skin) because of the repellent (86.0%). About a third of respondents complained about getting flu-like symptoms and about a fifth of respondents claimed to get dizzy, to get a headache or even to feel like vomiting when spraying repellent (Table 1).

Use

Use at multiple residences

Accessibility. Although the qualitative study indicated the local repellent distributors experienced difficulties and reluctance to travel to the farms where many villagers reside in the rainy season, in the first year of the trial almost all respondents reported having received repellents the month prior to the survey (Table 2). A large majority (81.7%) considered the amount of repellent distributed enough, although 36.9% of respondents mentioned having run out before the next encounter with the distributor.

Table 2. Reported repellent use

	n	%
Cross-sectional survey (N=393)		
Acces		
Received repellent last month	381	96.9
Ran out repellent before new distribution	145	36.9
Considers amount of repellent distributed:		
- *Enough*	321	81.7
- *Not enough*	37	9.4
- *Too much*	11	2.8
- *Never used any repellent*	18	4.6
- *Missing*	6	1.5
Reported use		
Always use the repellent	247	62.8
Use the repellent 7 days a week	232	59.0
Used the repellent yesterday evening	288	73.3
Used the repellent this morning	183	46.6
All of the above	134	34.1
Reported use per location		
Always use repellent in the evening when in village (N=361) †	204	56.5
Always use repellent in the evening when at farm (N=348) †	190	54.6
Always use repellent in the evening when at rice field (N=155) †	79	51.0
Always use repellent in the evening when in deep forest (N=249) †	180	72.3
Structured observation survey (N=1495 individuals in 431 households)		
Reported use per residence		
Use repellent 7 days a week when in village (N=1315) †	622	47.3
Use repellent 7 days a week when at forest farm (N=1325) †	719	54.3
Use repellent 7 days a week when at rice field (N=729) †	359	49.2
Structured observation survey (N=431 household leaders)		
Reported repellent use in the deep forest		
- *Never go to the deep forest*	112	26.0
- *Always use the repellent in the deep forest*	237	55.0
- *Sometimes use the repellent in the deep forest*	49	11.4
- *Never use the repellent in the deep forest*	25	5.8
- *Don't have repellents*	8	1.9
Median application times per day in the forest	3	

† N excludes respondents that report to never stay at that location

Reported use. (i) During the cross-sectional survey, 73.3% reported to have used the repellent the day prior to the interview (Table 2). Reported daily evening use when checking for each location of residence separately in the same questionnaire was lower (56.5% in village, 54.6% at the farm, 51.0% at rice field). Only 34.1% of respondents answered to use the repellent across the variety of repellent use questions throughout the questionnaire (i.e. yesterday evening, this morning, always, 7 days a week). (ii) Reported daily use during the structured observation survey similarly resulted in a daily use of around 50% across the different locations (Table 2). (iii) According to the malariometric surveys of year 1 and 2, around 70% of respondents reported to have used the repellent the day prior to the survey (Table 3).

Table 3. Reported repellent use Malariometric surveys 2 and 4

	n	%
Malariometric Survey 2 in Year 1 (N=2490 intervention arm)		
Used the repellent yesterday	1786	71.7
Used the repellent in the last week	2056	82.5
Malariometric Survey 4 in Year 2 (N=2730 intervention arm)		
Used the repellent yesterday	1885	69.0
Used the repellent in the last week	2230	81.7

In both intervention years, around 75% of those household leaders that regularly go to the deep forest, reported to always use the repellent there, with a median of 3 applications per day (Table 2).

When cross-checking quantitative results in the qualitative study, indeed a strong preference among men for using the repellent could be observed, especially while performing deep forest activities such as hunting, logging and fishing. Women and children used repellents only sporadically, especially when residing in the village.

Observed use. The observational study, aiming to confirm and refute preliminary results both from the qualitative study and the cross-sectional survey, showed that 7.9% of participants had used the repellent the evening of the visit (Table 4). Among those participants that were observed in the village, 7.1% had used the repellent; among those observed at the farm, 5.9% and at rice fields 15.4%. Age was significantly associated with repellent use: children under 11 years old who use the lotion formulation of the repellent had used it significantly more often than those using the spray formulation of the repellent (Table 4). Of those respondents that had not used the repellent on the evening the survey took place, 87.1% reported to still occasionally use the repellent; 12.9% said to never use the repellent. Although usually not all members of one household had used the repellent (except for households that consisted of only husband and wife), repellent use was significantly clustered by household. The variation between households explained 40% of the total variance (data not shown in tables).

Table 4. Structured Observation Survey: observed repellent use (N=1495 individuals in 431 households)

	n	%
Observed repellent use	118	7.9
Observed repellent use per subgroup location		
Village (N=691) †	49	7.1
Farm (N=577) †	34	5.9
Field (N=227) †	35	15.4
Observed repellent use per subgroup age category *		
Spray users (age 11+) (N=943)	55	5.8
Lotion users (age 2-10) (N=552)	63	11.4

* $p<0.05$

† N refers to the total amount of respondents interviewed at that location

Reported vs. observed use. Among village respondents who reported using the repellent 7 days a week while in the village, only 10.1% were observed to have used the repellent on the evening of the interview (Table 5). Among respondents observed and interviewed at the farm, observed use among those who reported maximal adherence to the repellent when at the farm was 7.9%; at the rice field, observed use was 18.2% among those who reported maximal adherence at this location.

Table 5. Structured Observation Survey: reported versus observed use

	N (%)	N (%)
	Use was observed	**Use was not observed**
Village		
Reported to use 7 days a week (N=316)	32 (10.1%)	284 (89.9%)
Reported to not use or use < 7 days a week (N=375)	17 (4.5%)	358 (95.5%)
Farms		
Reported to use 7 days a week (N=330)	26 (7.9%)	304 (92.1%)
Reported to not use or use < 7 days a week (N=247)	8 (3.2%)	239 (96.8%)
Rice fields		
Reported to use 7 days a week (N=137)	25 (18.2%)	112 (81.8%)
Reported to not use or use < 7 days a week (N=90)	10 (11.1%)	80 (88.8%)

Reasons for use or non-use

Use. In the cross-sectional survey, the large majority of repellent users (75.1%) reported to use the repellent in order to protect themselves from mosquito bites, less so for protection from malaria (28.8%) (Table 6). Although protection from malaria was not reported to be an important reason for using the repellent, 83.0% of respondents stated that they themselves, or one of the household members, had had malaria before. During the structured observation survey, 45.4% reported they or a household member had had malaria in the last year. Substantially more people used the repellent during those months of heavy rain (August, September, October) (data not shown) when almost all respondents perceived greater mosquito- and insect nuisance as compared to drier months (Table 7). Perceived nuisance (from insects but also leeches), moreover, was highest in the forest, corresponding to the high reported repellent use among those working in the forest (74%) (Table 2).

Table 6. Reasons for (non-) repellent use and in relation to other preventive measures

	n	%
Cross-sectional survey (N=395)		
Reasons for using repellent		
Use repellents to protect from insect bites	295	75.1
Use repellent to protect from malaria	113	28.8
Someone in the household has had malaria before	326	83.0
Structured observation survey (N=1495 individuals in 431 households)		
Reason for not using the repellent the evening of the visit (N=1377) †		
- use repellent later in evening	717	52.1
- run out of repellent	178	12.9
- forgot	141	10.2
- don't like because of side effects	77	5.6
- don't like because of smell	69	5.0
- other	43	3.1
- never received any repellent	29	2.1
- repellent not yet distributed	27	2.0
- forgot bottle somewhere	25	1.8
- did not have time	24	1.7
- not interested in repellent	23	1.7
- no mosquitos now	22	1.6
- too hot	1	0.1
- missing	1	0.1
Do you use it sometimes or never?		
- sometimes	1200	87.1
- never	177	12.9
Structured observation survey (N=431 household leaders)		
Repellent use in relation to other preventive measures:		
No longer use repellent when using smoke from fire		
- Yes	49	11.4
- No	292	67.7
- Never make fire	55	12.8

- *Never use repellent*	35	8.1
No longer use repellent when using smoke from cigarettes		
- *Yes*	59	13.7
- *No*	216	50.1
- *Never smoke cigarettes*	121	28.1
- *Never use repellent*	35	8.1
Use bed net less often when using repellents		
- *Yes*	60	13.9
- *No*	336	78.0
- *Never use bed nets*	7	1.6
- *Never use repellent*	27	6.3
- *Missing*	1	0.2
Someone in the household has had malaria in the last year	164	45.4

† N refers only to those who had not used the repellent on the evening of the interview

Table 7. Structured observation survey: reported insect nuisance related to repellent use (N=431 household leaders)

	n	%
Most mosquito nuisance during:		
- *dry season*	26	6.0
- *rainy season*	384	89.1
- *same*	21	4.9
Most insect nuisance during:		
- *dry season*	24	5.6
- *rainy season*	388	90.0
- *same*	19	4.4
Most mosquito nuisance in (multiple options possible):		
Deep forest	143	33.2
Forest around farm	134	31.1
Forest around village	37	8.6
Bamboo forest	34	7.9
Farm	47	10.9
Field	14	3.2
Village	20	4.6

Non-use. About half of respondents that had not used the repellent during the visit reported to use the repellent later in the evening. Other reported reasons were having run out of repellent, forgetting to use the repellent, not liking the smell of the repellent or a fear of side-effects (Table 6). The 12.9% that reported to never use any repellent, did so mainly because of the smell and a fear or previous experience of adverse effects (data not shown in tables).

According to the qualitative strand, the strong smell and the perceived toxicity were the main reasons for women not using the repellent on themselves and their children. This was especially the case for pregnant women who are considered generally more sensitive to strong smells and who were worried about the effects on the pregnancy. Parents also reported to be too busy in the evening with cooking and other household chores to apply the repellent to small children. Observations indicated that most people simply ‘forgot’ to use the repellent as it was not part of their established daily routine.

Repellent use in relation to other preventive measures

The qualitative study showed that people use smoke for warding off mosquitos while they are still active outside. Among those who use repellents and make fires, 14.4% report to no longer use the repellent when already using smoke from fire. Among repellent users and smokers, 21.5% reported no longer using the repellent when smoking cigarettes (Table 6). When looking only at those who use both repellents and bed nets, 15.2% reported to use their bed nets less often when using the repellent. Qualitative data indicated that the repellent could provide the comfort needed to sleep without a bed net during particularly hot nights, when bed nets are taken out for washing, and when bed nets tear beyond repair and new ones are not yet purchased from the market.

Discussion

The trial study population was expected to use topical repellents on a daily basis with the aim of maximizing the community-wide protective potential of repellents. Access to repellents was assured [40] and acceptance of the product high. Moreover, entomological data show that the Picaridin repellent reduces 97% of mosquito bites during five hours in similar settings and this without declining efficacy over time [23]. However, no reduction in malaria prevalence could be recorded at the end of the cluster-randomized trial (M. Coosemans, personal communication), suggesting that the effectiveness of the intervention mainly depended on human behavior, possibly in combination with potential effects of the repellent on vector behavior. Both a systematic review of repellent interventions [30] and mathematical modelling [28] have shown that “user compliance” is indeed one of the most decisive factors for the success of such an intervention. In the MalaResT trial, reported *use yesterday* was 73%, and reported *daily use* about 34%. In contrast, observed daily use was estimated at 8%, far below the minimum required coverage to obtain a mass effect on the vector population and thus on malaria transmission and prevalence [28]. Limited use of repellents was also reported in other repellent studies. One of the study limitations of a repellent intervention in Tanzania [29] was the difficulty of achieving daily repellent application by all household members. Similarly, in a repellent study in Afghanistan, no significant reduction of malaria infections could be shown in adults over 20 years old, presumably because of reluctance among adults to adapt to using the new product daily [25].

Measuring use. In addition to the difficulties involved in achieving a high uptake, measuring "user compliance" is in itself an issue that is not often scrutinized. Assessing 'use' is complex, partly due to the response bias inherent in self-reporting methods for public health interventions [1–3, 41]. In a repellent trial in the Bolivian Amazon [26], self-reporting was recognized to be an unreliable measure of use and this was consequently measured by combining results from monthly questionnaires; records on the liquid left in bottles; and, unannounced evening "sniff checks". In both Tanzania and Laos [29, 41], reported "user compliance" was compared to the amount of repellent liquid used in bottles. In Laos, where "compliance" was measured by comparing self-reported use with the amount of repellent left in returned bottles, this resulted in a 40% bias or "false positive rate" [41]. In this study, an emergent theory mixed-methods design was used in order to target difficulties in measuring and understanding 'use'. This was done by relating data from qualitative and quantitative methods for triangulation and complementarity purposes. Structured observation, less sensitive to social desirability bias, measured a considerably lower daily use than self-reported use recorded in surveys. Although logistically a difficult undertaking, such a respondent-independent technique proved a more suitable method for estimating use as it showed an 82 to 92% difference between people reporting to use the repellent 7 days a week and those observed to use the repellent the evening of the visit in the same location. Farm-respondents' response on whether they used repellents when sleeping in the village was 7 times higher than the observed use among farmers staying in the village, showing that the level of biased response was likely not overestimated. Moreover, as shown by the myriad of alternative uses of the repellent, the repellent's purpose was conceptually redefined by the end users, increasing the difficulty of recording use without qualitative research informing the quantitative surveys. In public health research, the use of malaria preventive tools is often measured by individual indicators that can only detect a homogeneous and constant use while considerable accuracy could be gained from the triangulation with other methods/disciplines, such as the systematic observation across place and time.

Contextualizing use. The context in which this study took place was characterized by a complex interplay of humans and mosquitoes [9]: the local population travelled between different residences located in villages, at farms and/or on rice fields, each of which located in areas of higher- or lower malaria transmission. Repellent use depended on a combination and convergence of location, time (i.e. seasonality and economic and livelihood activities), level of insect nuisance, age and gender (see Figure 2). In order to reflect the existing behavioural heterogeneity, the concept of 'use' was operationalized to include social and cultural factors driving the uptake of malaria preventive measures, rather than reducing it to individual behavioural determinants alone as is often implicit in the term "compliance" [42, 43].

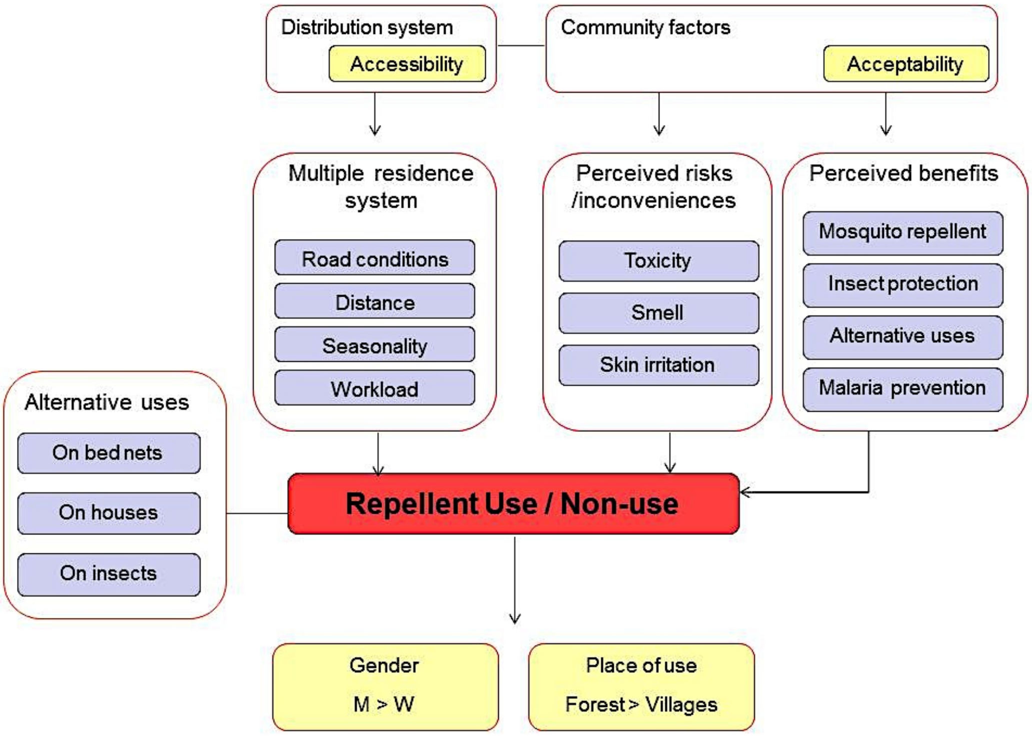

Figure 2. Explanatory model of repellent use showing factors contributing to the use and non-use of repellents in the study setting.

A strong preference for frequent application of the repellent was noted when performing economic and subsistence activities in the forest, mostly by men, and in places where insect nuisance is high. As insect nuisance has been shown to be one of the main stimulants for repellent use also in other contexts [44–46], repellents may prove to be a effective tool for personal protection in the male deep-forest subgroup more so then for families residing at farms, despite their increased epidemiological risk [32, 47, 48]. Moreover, our results show that repellent use was not driven by perceived malaria risk.

Use of repellents in specific risk groups may be optimized by formative research [49, 50] prior and during the intervention of which kind of formula of repellent is preferred (sprays, lotions, different smells); through which channels they should be distributed; which form of community participation and level of ownership fits the local context [51]; offering an alternative and/or additional strategies to information and education campaigns.

Limitations

No post-trial assessment on repellent use was conducted as the trial was not able to reduce residual malaria transmission at community level. While the strength of the study lies in the triangulation of qualitative and quantitative methods, including respondent dependent and independent data collection, limitations were the limited detail of the ethnographic strand on specific locations as information was expected on all study clusters due to the requirements of the large-scale epidemiological trial. The Khmer ethnicity of some of the interviewers and working within a trial context may have impacted on the data quality. Lastly, the direct observation of use was a strength in this study but complete non-reactivity is impossible and we are aware of the limitations in terms of social desirability bias.

Conclusion

While the large-scale distribution of topical repellents may not result in a community protective effect, engaging specific risk groups, potentially contributing disproportionately to malaria transmission, could be more effective. It is, however, questionable that a further substantial reduction in malaria can be achieved by introducing standardized preventive measures without researching how these strategies impact at the local level and without optimizing community involvement strategies and/or targeting specific subgroups. Especially malaria elimination strategies for settings characterized by large percentages of asymptomatic infections [32], such as those moving from high to low endemicity in a short period of time, with decreasing perceived benefits of preventive measures, need to be reconsidered.

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Additional information

The authors declare no competing financial interests.

Author contributions

KPG, MC, LD, SS and ST conceived the study. KPG and CG designed the experiments. CG, SU, PP, SS, SrS performed the fieldwork. KPG, MC, LD, VS, RG supervised the fieldwork. CG and VS performed the quantitative data analysis. CG performed the qualitative data analysis and wrote the manuscript. KPG, MC, LD, SU, PP, SS, SrS, RG, VS, LD, SS, TS, SH edited the manuscript. All authors reviewed and approved the manuscript.

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Chapter 8. Discussion

'Operational difficulties': what to do with the empty bottles of repellents left at the health centers after monthly distributor meetings?

In the previous chapters I have shown that 'resistant' local people, parasites and mosquitos shape an unstable and heterogeneous context that is not easily captured by common scientific research practices. The resistance I refer to relates to parasite resistance in Cambodia undermining malaria control globally; vector resistance to uniform behavior and to insecticides challenging vector control strategies; and human resistance to not only stable behavior but also to being 'tested' in health interventions without any true involvement at community level.

A first factor of human resistance described in this thesis is related to the pluralistic medical system of a region inhabited by indigenous people socio-culturally different from the majority Khmer population of Cambodia. This medical system included divination for spiritual afflictions; a popular informal health sector providing monotherapeutic and 'on demand' mixed medicine bags as well as take-away single artemether injections for malaria; a local Village Malaria Workers challenged by field labour requirements and a 'voluntary' status; and, an unpopular and less than fully functioning public health care system partly overlapping with the private sector (see chapter 3). Therapeutic decisions were made based on a form of 'lay empiricism', whereby perceived effectiveness, side-effects, expected costs, patient-provider relationships and perceived etiologies of the symptoms provided the basis for a decision on where to seek health care first, and where to go to next, when illness symptoms arose and continued.

Second, the indigenous peoples' multiple residence system and their forest-based subsistence, economic and spiritual activities that impact on malaria risk, transmission and on their use of malaria preventive measures can also be considered a form of resistance to the malaria elimination effort. Understanding the socio-cultural system was necessary to capture malaria exposure and risk, as was shown by the various ways the social status of Jarai youth increased contact with the malaria parasite (see chapter 4). Factors unique to Jarai youth, males in particular, such as age-specific sleeping patterns and structures, low uptake of preventive measures and cross-border mobility, increased this subgroup's exposure to malaria. What explains this behavior in youth more structurally is their status as *youth* and this can only be understood as embedded in the sociocultural structures that define youth among Jarai. Due to the transitional character of their social youth status - no longer considered children but not yet adults - fixed and long-term sleeping arrangements are not usually foreseen. Their mobility, moreover, increases the 'flexibility' (and fleetingness) of their sleeping arrangements and, potentially, the likelihood of sleeping unprotected. Jarai youth's mobility is all the more relevant given the prevalence of the main malaria vector *Anopheles dirus* in the region, which is sylvatic and bites early and outdoors.

Indeed, the interaction of socio-cultural variables with heterogeneous vector behavior also 'resists' epidemiological measurements (see chapter 5). Although the high diversity of vector species together with highly heterogeneous vector behavior - both between and within vector species - in itself complicates the malaria epidemiology, the *relationship* between vector and human behavior shows an even more complex interaction over time and place related to the the slash-and-burn farmers' multiple residence system, locally used (partially-) open housing structures, variance in labour and social activities, sleeping times according to the place of residence and season, and variance in bed net use depending on related user preferences. These social patterns resist the assumption that only 'residual malaria transmission' characterizes the region, which is defined as persisting transmission after full coverage of LLIN or IRS has been achieved. In addition to 30% of households not using LLINs at all, chapter 5 identifies various gaps in protection during vector biting times, related to children and adults resting outside or inside in sleeping spaces in the evening before their reported sleeping times and, at night, when using non-treated and torn nets while sleeping in often open housing.

Diversity in human mobility patterns also exposes a differential risk and vulnerability towards malaria exposure, clearly showing the need for different and adapted malaria prevention and control measures among the groups that are, nevertheless, jointly categorized under "mobile populations" (see chapter 6). Among the local indigenous population, LLIN distribution is based solely on the administrative village setting, thereby failing to take into account forest farmers' multiple residence system, which entails prolonged stays on forest farms. Such types of human population movements, taking place on a relatively local level, easily go undetected. The Khmer rural-to-rural migrant group, mostly active on rubber plantations and in mines, represents a fundamentally different social group that increasingly develops as a parallel social territory to that of the indigenous populations. The continuous influx of these lowland Khmer constitutes a new potential risk group for malaria. Moving from lowland non-endemic provinces, they are more vulnerable to malaria infection due to their limited awareness of malaria prevention and treatment as well as low acquired immunity. Khmer migrants were seldom reached by LLIN-distribution campaigns since they remained largely unregistered, and were also unaware of the local VMW-system due to poor social integration locally.

Capturing such human behavior and practices in a way useful to public health interventions, however, requires appropriate research techniques and innovative research designs. An iterative design continually adapting to emerging results, combining qualitative and quantitative research techniques, provided an in-depth understanding of the practices of the indigenous people of Ratanakiri and improved epidemiological data collection, resulting in a rigorous methodology that allowed a common mode of communication with other disciplines and a translation of anthropological findings to a more bio-medically standardized language. However, the practice of developing such a methodology within the repellent trial was characterized by the constant struggle of presenting ‘knowledge’ in a language that touches only on the contours of the findings. Dynamic data related to human mobility, ethnic differences or a failing public health system, none easily captured by single determinants, were still mostly considered to be ‘operational difficulties’ within the logic of the trial and not as results that should be taken into account in the further flow of the trial. The relevance of socio-cultural factors, although recognized, was still considered in isolation from the epidemiological study, as they were ‘contained’ by the anthropological work package. However, these factors were *also* key for the effective implementation and epidemiological measurement of the trial’s main outcome.

When trying to measure the ‘use’ of the repellents and LLIN, a local practice that logically produced all further data the trial built on, this relevance became most apparent. The trial population was expected to use topical repellents on a daily basis, in the morning and in the evening, with the aim of maximizing the community-wide protective potential of repellents. Access to repellents was assured, acceptance of the product high and efficacy to reduce mosquito bites confirmed. However, no reduction in malaria prevalence could be recorded at the end of the cluster-randomized trial, suggesting that the effectiveness of the intervention mainly depended on human behavior. Observed daily use was estimated at 8%, far below the minimum required coverage to obtain a mass effect on the vector population and thus on malaria transmission and prevalence. Assessing ‘use’, however, is complex, partly due to the response bias inherent in self-reporting methods for public health interventions. Observation techniques proved more suitable for estimating use as it showed an 82 to 92% difference between people reporting to use the repellent 7 days a week and those observed to use the repellent on the evening of the visit. Repellent use was found to depend on a combination and convergence of location, time (i.e. seasonality and economic and livelihood activities), level of insect nuisance, age and gender. Moreover, the constant mobility of local people between forest, field and village, made it impractical to appropriate a practice (repellent application) that interfered with the flow of daily life. Poverty directed the many alternative uses of the repellent that *were* taken up, such as its use as a domestic insecticide spray or anti-lice lotion, as trial participants thought the time spent collecting repellents should be made worthwhile.

In order to reflect the existing behavioural heterogeneity, the concept of 'use' was thus operationalized with questions that incorporated social and cultural factors (i.e. variability of seasonal and economic practices in relation to associated repellent use) driving the variable uptake of malaria preventive measures, rather than reducing it to behavioural determinants based on individual parameters alone, as is often implicit in the term "compliance" [1, 2]. Similarly, while survey results reported high LLIN use, due to response bias and the suboptimal operationalization of the concept 'net use' in questionnaires, actual LLIN use was not as high when we directly observed the amount of households where market nets were being used.

Contextualizing the final outcome of the epidemiological intervention

The scientists involved in the repellent trial concluded with the statement that, as there was no significant difference in malaria prevalence between the intervention and the control arm, the repellent cluster-randomized trial was not able to demonstrate that the community-wide distribution of topical repellents reduces residual malaria transmission in this South-east Asian region [3]. Stressing that the protective efficacy of repellents against malaria was only measured at community-level and not on an individual basis, it is now being communicated to donors, steering committees and scientific peers that the results of this trial support the conclusion that community-wide distribution of topical repellents does not provide sufficient additional protection from malaria to justify the investment and thus is of no public health value in a malaria elimination setting. I argue that this conclusion can in fact not be fully supported by the data if taken into account the *practices of science* (i.e. 'operational difficulties' as seen through the lens of the trial) on which the data was built.

First, when one considers the low daily adherence to the use of repellents in the intervention arm, it is impossible to show the impact of the 'mass' use of repellents at community level as this 'mass use' never occurred on a daily basis. Although the epidemiologists of the trial rationalize no statistically valid causal link can be made between human behavior and the outcome of the trial, the results presented throughout the previous chapters illustrate at least *why* this trial population was not as 'compliant' to the desired levels of repellent application as was implicitly expected by the researchers executing the epidemiological study when the trial was set up.

Secondly, increased levels of use of repellents among subgroups working in the forest may have had an effect on the malaria prevalence in specific risk groups. However, it is likely that this subgroup's absence in villages on survey days hindered the ability for malariometric surveys to record any specific effect. Although such human behavior was assumed to be balanced over the control and intervention arm, and therefore would not impact on the final epidemiological outcome, this finding still leaves room for repellents serving a useful public health purpose in specific at-risk subgroups such as forest workers.

Third, the conclusion that repellents have no public health value in any Asian elimination setting, assumes that if the repellents cannot work under the trial conditions set up in this particular setting (i.e. using the Information and Education Campaigns that encouraged daily 'compliance' in the study population), repellents cannot work anywhere as a malaria elimination strategy. Such a conclusion isolates the outcome and the particulars of the trial from the social and historical context in which the study population and staff is embedded and the specific human behavior that stems from it. This is also evident in the choice of secondary outcome measures the trial builds on, as incidence rates that are measured by passive case detection within an indigenous population that tries to avoid public health centers, cannot be considered hard or objective data, and thus invalidates a strategy that operates within a public health system.

Scientific knowledge produced by interdisciplinary collaboration

The primary outcome of the trial is not the only result presented as 'knowledge' produced by the trial. In various publications, most of which included in this thesis, and in an expert comment published alongside the main trial publication [4], the contributions of the anthropological study become more visible and leave room for a broader interpretation of the primary outcome of the trial, encouraging at least a partial exposure of the "public secrets" operational in this intervention [5, 6].

Geissler and Pool [7] argue that public health practitioners often (wrongly) assume that anthropology "holds the key to target populations culture", and as such is able to change the "beliefs, attitudes, and behaviours" of study populations towards better compliance to clinical trials (p. 6). Indeed, the applied anthropological research in this trial made another, more dynamic, aspect of human behavior visible than what the trial researchers expected to find, and which is initially difficult for them to work with in view of peer- and protocol expectations. However, this project shows that medical anthropological research can be used within trials beyond simple measures of “acceptability” or “compliance” that would too easily serve the epidemiological outcome. I have adopted a methodology that could capture the varying and unstable practices of the trial population and transform them into quantitative ‘useful’ outcomes that could be communicated in a language acceptable to all scientific collaborators in the project. I have also pursued a gentle exposure of the “unknown knowns” [5] of the nuisance human behaviour, without upsetting the flows of partnership the intervention needed in order to thrive, or undermining the scientific knowledge other disciplines were pressured to supply to donors and peers.

First, as illuminated throughout the different chapters, the results from the anthropological study itself produced valuable knowledge about the local setting and population and their interaction with local malaria control measures, malaria epidemiology and malaria vectors.

Second, through qualitative research, the “anthropo team” identified potential risk factors for malaria in the local setting, which contributed to the construction of a useful questionnaire during the epidemiological blood collection surveys. As such, we improved the epidemiological knowledge produced in the trial by knowing what questions to ask and how to ask them. Through these blood collection surveys, we were able to link malariometric data of current infections to human behavior and practice. For example, during our qualitative research we identified a multiple residence system and agricultural mobility which clearly presented differential risk locations for malaria. As such, by linking malariometric data to human practices, we were able to show that overnight sleeping at plot huts on forest farms is indeed an epidemiological risk factor for malaria. This was presented as a first result of the trial in Sluydts et al, 2014 [8].

Our anthropological research was able to show that asking standardized WHO questions about bed net use (“Did you sleep in a bed net last night?”) were inadequate in the current setting as people were often using other bed nets than the program provided LLINs they were supposed to be using, and did this variably across place and time. This knowledge was used to construct other questions for the epidemiological questionnaire that was used during blood collection surveys.

Although it was general knowledge among project members, even before the protocol was written, that ethnic minorities socio-culturally different from the ethnic Khmer majority in

Cambodia inhabited the study area and even that they had different sleeping habits and mobility patterns, this was not considered relevant information for the trial initially. As we showed the setting currently knows a high influx of Khmer migrants who portray a different set of behaviors than the indigenous peoples that mostly inhabit the villages the trial was targeting, the trial team decided to include a question on the ethnic identity of the participant in the blood collection survey to explore potential differences between Khmer and indigenous people's risk behaviour.

In the initial design of the trial, repellent consumption rates were to be measured only by the per family left-over repellent during the bi-weekly bottle exchanges with local distributors. Although self-reported measures of compliance are prone to bias, we included in the epidemiological questionnaire (i) self-reported use, for comparison with our structured observations, and (ii) a question on whether the respondent had used the repellent *on the skin,* as we had observed many alternative uses of the repellent (i.e. using the spray as insecticide, anti-lice lotion, etc.) during our qualitative study. As the epidemiological questionnaire was still recording high levels of use, it was mostly our qualitative work that warned for the low daily usage mid-intervention. As a response, the trial team made efforts to develop new health promotion material and intensify health promotion activities during the second year of the trial to increase daily usage of the product.

We also showed that a self-selection bias was potentially being introduced in the sample of the epidemiological surveys, as the use of "extra lists" (instead of the original random sample of 65 respondents per cluster; see description of epidemiological study) was likely consistently excluding people who were not available in the village during the malariometric surveys because they were working on farms or in the forest and who were therefore in fact more at risk for malaria. The 'randomness' of this sample was therefore questioned, and extra efforts were made by trial field teams to search for selected participants working on farms.

Finally, the collected epidemiological data was in itself not able to explain why the mass distribution of repellents could not demonstrate a reduction in malaria prevalence. Our research into the real-life use of repellents helped to understand, although not conclusively, *why* mass distribution of repellents over a two-year timeframe could not reduce malaria prevalence in this particular setting.

Concluding recommendations

Both epidemiological and anthropological research highlighted different layers of knowledge; epidemiological research revealed the malaria prevalence and epidemiology on a large scale, while anthropology made visible why and how this malaria prevalence and epidemiology was distributed in this specific population. Epidemiological research further revealed the need for additional interventions to LLINs within the context of this malaria epidemiology and the consequential epidemiological impact of implementing such an intervention, while anthropological research showed how the use of these vector control tools in the target population could in turn influence the malaria micro-epidemiology of this setting. In this context, although the knowledge produced by each discipline was significant in its own right, it was made *meaningful* with the help of the other.

The practice of knowledge production by clinical trials could progress by including such different layers of knowledge not only during the *execution* of pre-conceived trial designs, in the form of anthropological work packages looking at 'acceptability' or 'adherence', but in the *design* of the trial itself. Inviting anthropologists to think alongside epidemiologists during the phase where the trial procedures and outcomes are conceived may help to write certain 'inconvenient' variables back into the design, producing a form of evidence that is contextualized instead of isolated from the underlying processes that shape it. Moreover, although variables such as youth not sleeping where they are supposed to (see chapter 4), or unregistered migrants leaking in and out of a trial population (see chapter 5) *are* difficult to integrate into a trial design because they are often not initially foreseen to upset the practice of the trial, it could be achieved when working *iteratively,* i.e. by feeding new variables into the trial design during the implementation phase and continuously adapting the intervention accordingly.

In conclusion, through an iterative process where data produced by one discipline constantly feeds the data collection process ongoing in the other discipline, valuable knowledge can be produced which is not tied to isolated measurements alone but incorporates an epidemiologically valid primary outcome, the underlying processes that shape that outcome, and the underlying processes that shape the practice of measuring that outcome.

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