# CHALLENGES AND OPPORTUNITIES FOR PURSUING MALARIA ELIMINATION IN PERU

by

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# Abstract

Recent history suggests that malaria can be eliminated in low-endemic countries, and there is a growing interest among key stakeholders from Peru to plan accordingly and achieve malaria elimination with a comprehensive programmatic goal. In support of this interest, this dissertation integrates a course of studies to inform and support such goal, by accounting for the two most important malaria transmission patterns that currently characterize Peru, the one affecting the Peruvian north coast and the other affecting the Peruvian Amazon basin. The first study will determine the impact of reactive case detection with focal mass drug administration (RCD/FMDA) as compared to passive case detection on reducing the regional annual parasite incidence in Tumbes, Peru (Paper 1). The second study will determine the impact of the malaria elimination program implemented in Tumbes on interrupting the transmission of malaria beyond the intervention area and along the Peruvian north coast (Paper 2). And the third study will determine whether further understanding the patterns of malaria incidence in Loreto, the main human malaria reservoir in Peru, may offer a variety of strategical targets for the malaria elimination program that was launched in Loreto, influencing as well the nearby regions at the Peruvian Amazon basin in 2017 (Paper 3).

It has been observed that the malaria elimination program implemented in Tumbes, which was based on replacing passive case detection with RCD/FMDA strategy, had a significant effect on reducing the regional annual parasite incidence in Tumbes within the intervention areas (2/13 districts) during the first two years of the program (pilot project). When the strategy was scaled up across the entire Tumbes region, malaria transmission was halted with no endogenous cases for the following three years. Additionally, data suggest that the Tumbes intervention indirectly helped to interrupt malaria transmission in the nearby region of Piura. During the intervention in

Tumbes, nearby Piura districts also observed a decrease of their malaria weekly parasite incidence, ultimately reporting zero autogenous malaria symptomatic cases at the end of the study period.

Based on the evidence generated by the two previous studies we explored the pattern of malaria transmission across the Loreto Region through riverine networks where the RCD/FMDA strategy may have a substantial effect on interrupting the transmission of malaria. Our data showed that the distribution of malaria cases does follow the Amazon river tributaries, which are areas competent to sustain the transmission of malaria from one season to the following. Furthermore, we observed that the main predictors of malaria in the region are low altitude and the density of the vegetation and that there are some differences in the distribution of falciparum malaria which seems to be more associated with the density of the vegetation than the distribution of vivax malaria. Among the different riverine networks, we identified some that appear to behave like independent foci of malaria transmission with only select communities demonstrating indices consistent with a year-round transmission, each of them representing potential targets for the RCD/FMDA strategy with a high likelihood to have a substantial effect on interrupting the transmission of malaria.

Based on this information, achieving malaria elimination in Peru therefore appears feasible; however, it will require strongly epidemiological and data-driven approaches to optimize the effect of existing preventing interventions strategies. This will need to target well-characterized human malaria reservoirs in low endemic settings in order to maximize the effect of transmission-blocking drugs and effectively interrupt malaria transmission in limited-connected communities such as those in the Peruvian north coast and in the Peruvian Amazon.

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# Preface

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# List of terms and abbreviations

| | |
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| AIC | Akaike Information Criteria |
| ASTER | Advanced Spaceborne Thermal Emission and Reflection Radiometer |
| GDEM | Global Elevation Model |
| CI | Confidence Intervals |
| DIRESA's | Regional Health Directorates |
| NDVI | Normalized Difference Vegetation Index |
| EVI | Enhanced Vegetation Index |
| FMDA | Focal Mass Drug Administration |
| JHBSPH | Johns Hopkins Bloomberg School of Public Health |
| LRT | Likelihood Ratio Test |
| MERRA | Modern-Era Retrospective analysis for Research and Applications |
| MODIS | Moderate-resolution imaging spectroradiometer |
| MoH | Peruvian Ministry of Health |
| PAMAFRO | Project of malaria control in the borders within the Andean region |
| PCD | Passive Case Detection |
| PMW | Passive microwave sensors |
| QV2M | Specific humidity at 2 m above the displacement height |
| RCD | Reactive Case Detection |
| RCD/FMDA | Reactive case detection with focal mass drug administration |
| RDT | Rapid Diagnostics Test |
| SFMC | Soil moisture content in the top soil layer |

| | |
|---|---|
| TMPA | Multisatellite Precipitation Analysis |
| TRMM | Tropical Rainfall Measuring Mission |
| T2M | Temperature at 2 m above the displacement height |
| WHO | World Health Organization |
| WPI | Weekly Parasite Incidence |

# Chapter 1. Introduction

In the year 2014, the World Malaria Report announced that the number of children who die from malaria each year had fallen more than 50% since 2000 (1). This significant achievement in the fight against one of the leading causes of death for children under five in Africa and Asia was a source or major optimism about the ultimate goal, malaria eradication. And it was right; such achievement showed that when committed towards a common goal, global partners can achieve big goals and overcome the major health disparities that continue to deny millions of children in developing countries a healthy start in life. These partnering efforts included the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), the U.S. President's Malaria Initiative, the UK's Department for International Development, and their strong partnership with many endemic-country governments. However, only three years later, the World Malaria Report 2017 raised concerns about the latest progress in the path towards malaria eradication, which appeared to have stalled. Latest data analyzed showed that many of the countries with ongoing transmission are currently on track for reductions in the burden produced by malaria (2). This a matter of great concern, particularly because the overall progress in the path towards malaria eradication have been halted and several countries and regions are beginning to see reversals in their progress and in the gains achieved (2). As a consequence, the World Health Organization is currently pushing to boost funding for malaria programs, increase access to currently available and effective interventions, and increase investment in the research and development of new intervention tools. Peru has certainly answered the call and, in April 2017, launched a long-term malaria elimination program ("Plan Malaria Cero 2017-2021"), in which the first stage included funding for the first five years of the program. Such a challenge, although accepted, demands a better understanding of the epidemiology of malaria in areas where *P. vivax* is the most prevalent

species. This is particularly important because most of the interventions available were developed focused primarily on controlling malaria in regions where *P. falciparum* is the predominant species.

This dissertation aims to explores the epidemiology of malaria in the main malaria-endemic regions in Peru, the North coast (Tumbes and Piura) and the Amazon basin (Loreto), and to assess the effect of a reactive case detection with focal mass drug administration (RCD/FMDA) based malaria elimination program at and beyond the intervention areas — along the north coast as well as its potential utility at the Amazon basin. In the intervention areas of Tumbes region, we assessed RCD/FMDA effect on interrupting the transmission of malaria and, later on, its potential effect boosting the elimination of malaria across the Tumbes region and beyond, at the Piura region. We hypothesized that the reason why such an intervention would be effective is due to the strong connectivity between the two regions and we can identify some riverine networks with similar characteristics that could be influenced as well in the Loreto region.

## *1.1 Background*

### Malaria eradication as the ultimate goal

Despite extensive efforts made to date, malaria continues to exert a significant burden of disease worldwide (3). To address this public health threat, several local and regional malaria elimination campaigns have been attempted since the last Global Malaria Eradication Program (1955–1969) (4). Following the announcement at the Gates Malaria Forum in October 2007 (5) several key international organizations, including the World Health Organization (WHO) and the Roll Back Malaria, debated the pros and cons of shifting the goal of the malaria control efforts towards malaria eradication. Since then, several malaria elimination programs have been

launched, including countries in southern Africa (6) and Pacific Island states (7). These efforts together with the WHO's Global Malaria Program agenda and field manuals for malaria elimination (8, 9) have pointed out the path towards another global attempt at eradication.

The proportion of the population at risk that now lives in malaria-free areas had increased from 30% to over 50% from 1950 to 2001 (10, 11), contributing to increasing spatial heterogeneity of the malaria distribution worldwide (12, 13). Currently, malaria is affecting primarily the hard to reach populations - often located in the rural and most resource limited regions of each country- , representing an increasing programmatic challenge for the control and later elimination of malaria (14). Furthermore, due to the increasing cost of case detection in the elimination phase and the consequent decrease in programmatic efficiency, funding exhaustion on the part of stakeholders commonly fosters reemergence of malaria in late phases (15). Therefore, there is a need for novel and efficient strategies and tools that can prudently select from currently available interventions to maximize program efficiency (16), but so far these have not been discovered.

**The Peruvian path towards malaria elimination**

In the past, Peru has on two separate occasions progressed to a degree in disease control to demonstrate that malaria elimination is feasible in the country (Figure 1). First, after a peak of over 90,000 cases in 1944, the malaria burden fell to under 1,500 cases (98% reduction) in 1965 and remained at similar levels for approximately two decades (17). Such success was primarily due to the introduction of DDT and other insecticides, capacity building, and the shift of the focus from clinical treatment to transmission control within the National Malaria Service, an effort that was initially sponsored by the Rockefeller Foundation and later by the Interamerican Public Health Service and UNICEF (18). During this period, the two main control measures implemented in the

country were chemical control using DDT (which later was replaced by different families of insecticides, including pyrethroids such as cyfluthrin) for domiciliary residual spraying and spatial fogging with malathion, and source control by community participation on identifying and filling the larval sites. Yet DDT use was halted initially in Loreto in 1988 and then banned in the rest of the country because of its effect on the ecosystem, an event that may explain why malaria started increasing four-fold in Peru and fifty-fold in Loreto in the following decade (17). After peaking in 1998 with 250,000 cases, the malaria burden fell to 87,800 cases in 2005 (65% reduction) and 25,300 cases (90% reduction) in 2011. During years 2006-2010 Peru received funds from the Global Fund to restart the project of malaria control in the borders within the Andean region (PAMAFRO), enhancing passive surveillance, implementing rapid diagnostic tests, insecticide residual spraying, and distributing over 250,000 long-lasting impregnated bed nets in Loreto (19), but in the absence of a control arm we may never know if this project contributed or not to the reduction in malaria cases reported during that period. Currently, the total number of falciparum and vivax malaria cases increased from 3,920 to 12,978 and from 27,324 to 41,328 cases, respectively between 2012 to 2017 (20). Contradictorily, the main contributing factor to this reemergence was the increase of malaria transmission in the Loreto region (Figure 2). The reasons for the increasing burden of malaria in Loreto remains unclear; however, it is believed to be related the overlapping of the latest Dengue outbreak, which apparently, early in the epidemic, forced the local authorities to divert the Public Health budget away from malaria towards urban populations to control dengue (21). Regardless, all these ups and downs have changed the epidemiology of malaria in Peru, to a point where malaria has become a heavily seasonal disease, transmitted by two predominantly peridomiciliary biting vectors - *Anopheles darlingi* and *An. benarrochi* (22), species that primarily affect those who live in rural and isolated regions such as loggers, fishers,

farmers and other laborers who often travel to these areas (23). This epidemiological pattern of transmission of malaria is similar in other endemic Amazonian regions such as San Martin and Ucayali, which vary slightly as compared to Loreto where malaria transmission is more intense and perennial. However, in other malaria-endemic regions such as in Tumbes, Piura, Lambayeque, and La Libertad, all of them located along the Peruvian north coast, malaria occurs with epidemic and sporadic outbreaks, probably related to stochastic factors such as malaria importation and relapses (24). In the north coast malaria cases are largely due to *P. vivax*, with only occasional *P. falciparum* malaria cases reported since 2010. In this region the predominant malaria vector is *An. albimanus* (25) and malaria is highly concentrated within peri-urban communities (26). Across the region, only counted imported malaria cases have been reported since 2014 (27) up to 2017 (20). Accounting for this heterogeneity in the patterns of transmission is highly relevant for malaria control and the prospect of elimination in Peru.

## The challenges towards malaria elimination in Peru

Several interventions could be implemented in the Peruvian Amazon to interrupt malaria transmission and support the current malaria elimination efforts. However, most of these interventions may not be particularly effective in the Amazon region given its specific epidemiological and cultural characteristics. For example, indoor residual spraying (IRS) is an intervention that is effective when the vector has an indoor biting behavior like in African countries, an intervention that has been demonstrated to reduce malaria transmission by up to 50% (28). Though, in the Amazon where vectors (predominantly *An. darlingi*) have both intra and peridomiciliary biting behavior and the household's architecture is predominantly open instead of closed, the vectors often rest outside areas subjected to IRS decreasing its effect and impact.

Similarly, insecticide-treated nets (ITN) have been reported as a highly effective intervention for malaria control globally. Nonetheless, that is not always the case of the Peruvian Amazon where ITNs have been reported to be significantly underused (>60% of households not using any of the distributed LLINs), which is due mostly that ITNs do not fulfill some "basic" architectural and social functions, such as providing privacy and warmth as compared to other traditional non impregnated tocuyo nets provide more adequately (29). Another critical factor to take into consideration when implementing malaria control interventions is the temporal and spatial variability of malaria, which are highly correlated with a variety of climate (precipitation, temperature, humidity, surface pressure, solar radiation, etc.) (30) and land conditions (soil moisture, deforestation, vegetation, and others) indicators (31). However, as recently Feingold et al. reported, there are two parameters that showed the highest correlation, among the many indicators used to characterize the climate and the conditions of the land surrounding the Peruvian Amazon communities: these are precipitation and soil moisture, respectively (32). Finally, the effectiveness of case detection and proper case management interventions also might be different in the Peruvian Amazon, as compared to the Africa scenario, given the high likelihood of relapses due to *P. vivax* (>70% of Peru's malaria burden) (33), the differences in the sensitivity of the surveillance systems as Peru is still microscopy-based, instead of being based on Rapid Diagnostics Test (RDTs) as is done in Africa, and the different first-line therapeutic schemes used in the case of *P. falciparum* (Artesunate/Mefloquine in Peru) (34).

Another important reason why malaria elimination is so difficult to achieve is the key role played by the asymptomatic carriers in its transmission and our inability to diagnose them accurately (35). As a significant fraction of the human malaria reservoir, identifying and treating asymptomatic but infectious carriers rapidly has become one of the cornerstones of the current

malaria eradication campaign (36). In Peru, like in most of the Amazon basin, most malaria cases are due to *P. vivax* (≈80% of all malaria infections), which are predominantly (≈75%) asymptomatic (37, 38). As a consequence, malaria transmission might be largely maintained by relapses from dormant liver parasite stages (i.e., hypnozoites), which are beyond the detection threshold of the diagnostic test currently available (39). In such a scenario, little can be done from the perspective of diagnosing and treating cases approach, so there is an increasing need for better diagnostics and more effective therapies that empower us to interrupt transmission more effectively.

## The opportunities for achieving malaria elimination in Peru

To implement a strategy that accounts for all of the many challenges in the path towards malaria elimination it is particularly relevant to shift the malaria policies from control towards local elimination, as recommended by the current malaria eradication campaign (40). Based on this paradigm, current elimination efforts rely on the hypothesis that by testing, treating, and tracking malaria cases and simultaneously performing vector control through the distribution of insecticide-treated nets and indoor residual spraying, malaria could be controlled and later eliminated (41-43). However, this paradigm has proven to be extremely challenging due several implementational factors or which some of the most relevant includes: 1) the difficulties to locate and target the human malaria reservoir; 2) the operational, technical, and financial challenges of implementing sustainable interventions; and, 3) the lack of cost-effective methods and strategies to detect the asymptomatic malaria cases.

One alternative to overcome these three caveats and accelerate the path towards malaria elimination in the Peruvian Amazon is to implement a strategy based on reactive case detection

instead on the traditional passive case detection. As proposed, reactive case detection, presumptively, is a more effective and sustainable method to target the human malaria reservoir, given that focuses in a very well-defined population subset at an increased risk of parasitemia (largely asymptomatic), instead of searching for malaria in all carriers across the whole population, as in traditional active case detection methods where community-wide sampling is done (44). To do so, under reactive case detection, field teams are deployed to test for malaria in all the members of the households where at least one subject tested malaria positive within the previous six months, considering all of them as the population at high-risk, regardless of the absence of malaria-like symptoms. As a consequence, reactive case detection might represent a more efficient strategy, optimizing the time of the field workers in the field, allowing them to increase the coverage, and contributing to the sustainability and success of each malaria elimination campaigns (45-47). Nevertheless, considering the particular characteristics of the epidemiology of malaria in the Amazon, it is strongly recommended that we first assess the effectiveness of reactive case detection before recommending its broad implementation. This is precisely the reason why I have chosen this topic of interest as the primary aim of this study.

Reactive case detection is different from traditional active case detection methods in that reactive case detection searches for malaria carriers only within a defined sub-population at high-risk instead of among the whole population at risk (47). To do so, field teams first identify the high-risk malaria households by using as a signal the malaria cases that were previously reported within a certain period of time (often within the last malaria season) and then test all the inhabitants of these households under the assumption that it is more likely to detect malaria carriers among them than within the households where no malaria cases were reported during the same period (45). This case detection method has been tested in several countries, including Sri Lanka (48),

Swaziland (49), Zambia (50, 51), Senegal (45), Bhutan (52), Mauritius (53), Peru (37), and Brazil (54, 55), using similar but different operational definitions and diagnostic methods, and as a consequence showing different results. Furthermore, according to a 2013 malaria control program managers survey, reactive case detection has also been implemented in countries like China, Cambodia, Democratic People's Republic of Korea, Indonesia, Malaysia, Nepal, Philippines, Republic of Korea, Solomon Islands, Thailand, Vanuatu, and Vietnam. Sadly, very little is known about the impact of these experiences yet. Experiences from Sri Lanka (48) and Swaziland (49), where reactive case detection was implemented using a 1 km radius from an index case household as the criteria to define the population at risk, although initially reported as successful experiences in time they prove to be very hard sustain given its relatively high cost (47). As an alternative Searle et al. assessed reactive case detection in southern Zambia using a 500 m radius reporting similar results to those achieved with a 1 km radius and identifying 77% of all households with an RDT positive resident and 76% of all RDT positive individuals (46). In the Peruvian Amazon, Branch et al reported that given primarily to the high clustering of malaria carriers screening subjects within 100 m radius around the household of the malaria cases passively detected, using molecular diagnostic methods, allowed them to detect 4.3 and 1.8 more cases of *P. falciparum* and *P. vivax*, respectively, than passive case detection alone (37). According to Stressman et al., in Zambia by screening subjects for subpatent malaria within the household of a malaria case passively detected, they detected a malaria prevalence that was 11 times higher as compared to randomly selected control households (8% vs. 0.7%, respectively) (50). Littrell et al. assessed a similar strategy. In northern Senegal, who reported that even using RDTs and focusing only within the members of a malaria case household they found a 3.2-fold increase in the incidence of malaria as compared to the neighbor households (45). Although each of these experiences used cases

detected through passive case detection (the "index case") to trigger additional case detection activities, there were several key differences in terms of screening inclusion criteria for malaria blood testing (fever, recent history of fever, or none), the criteria used to define the population at risk (1 km, 500 m, 100 m around the malaria cases household, limited to the people living within the household of the index case, or by targeting a specific number of proximate people or households around the household index case) (56). Based on the current understanding of the epidemiology of malaria in the Peruvian Amazon and available infrastructure, I do believe that a reactive case detection strategy that test every member within the household of each of the malaria cases that were detected passively in the previous six months (our proposed criteria to define the high-risk population of malaria), regardless of the absence of symptoms, that uses microscopy as the method for diagnosis, and that them follow them at intervals of two months for six months represent a sustainable and effective alternative to reduce the transmission of malaria in Amazonian riverine communities. This reactive case detection strategy could contribute to optimizing the time, cost, and sustainability of future malaria regional elimination campaigns.

Regardless of the methods used to target the human malaria reservoir we know very little about factors regarding individuals' conceptualization of treatment and factors affecting compliance with antimalarial treatments, which are a matter of great concern because implies treating asymptomatic individuals. Currently, the evidence behind asymptomatic subjects contributing to the transmission of malaria is very consistent, even at submicroscopic parasitemia, so there is an increasing need for a strategy to ensure that a large majority of the individuals identified receive full courses of treatment and achieve parasitologic cure, otherwise these people will constitute a reservoir for reinfection (57). There at least two perspectives to take in consideration when assessing this problem. First, from the patients' perspective, in the absence of

malaria like symptoms, there is any reason why they should seek or complete treatment for malaria when identified by the program. And second, from the healthcare providers' perspective, even when those malaria carriers were tested, we still might fail to diagnose and treat a large fraction of malaria infections due to subpatent infections (infections with parasitemias below microscopy/rapid diagnostic tests threshold of detection) (58). These are two reasons why it is so important to actively search for those cases to effectively reduce transmission (59). Once diagnosed, two activities should be considered as important ones to ameliorate the risk that those human malaria reservoirs continue behaving like a parasite source for vectors and subsequent malaria transmission. These behaviors are: (i) to receive and complete a malaria course treatment, which is highly relevant to prevent secondary cases (60); and, (ii) perceiving themselves at risk (greater than that of others around them) to drive seeking for formal healthcare early at the onset of fever in the future (61). However, in order to be able to enhance these behaviors, we need to understand the decision-making processes behind them. To do so a good initial step might be to identify the main social determinants that influence complete treatment adherence, which has been investigated intensively among symptomatic malaria-infected subjects (62), but not among the asymptomatic malaria cases. So subsequently, explore which are the decision-making processes behind health care seeking behavior in subsequent febrile illnesses.

## The Feasibility of malaria elimination in Peru

In February 2014, a conference was organized in the city of Iquitos, the capital of Loreto, to review the agenda of malaria elimination in Peru. During the meeting, representatives from national and regional organizations, as well as from the Ministry of Health and international partners, in a collaborative effort, outlined the critical policy requirements and knowledge gaps to

achieve control and further elimination of malaria in Peru. After discussing the latest body of evidence and sharing their country-specific experiences, the group resolved that the feasibility of malaria elimination in the Peruvian Amazon was a real possibility, though its success would require a clear financial and political commitment from Peru's government. This is to launch a comprehensive regional plan to guide this initiative, as well as encouraging introducing new tools and strategies to purposely eliminate malaria as they are developed. The consensus highlighted that, in order to prevent early failures, the implementation of these measures should be integrated, culturally appropriate, and politically and economically sustainable; incorporate regional and local authorities (such as provincial governors and local leaders at the city and village levels), to collect adequate reliable data on malaria incidence, and focus on interrupting malaria transmission by targeting the human malaria reservoir.

Decision makers should consider adopting targeted parasite elimination strategies that are appropriate to the region to overcome the limitations of passive case detection and the hard-to-reach populations (either remote communities or sub-populations such loggers and gold miners that spend large amounts of time away from health infrastructures). To do so effectively critical knowledge, currently unavailable, should be developed to allow program officers to decide where to intervene first. During the meeting, some criteria where proposed to select such sites, including: i) have a large population with low incidence of malaria (IPA<1); ii) being cultural and political accessible; ii) being close to each other (either within the same river basin or region); and, iv) have some capacity to implement control measures as a unit so as to respond efficiently to predictable reintroduction events. However, none of these criteria has been backed up with proper analytics or evidence to date.

### The Peruvian malaria elimination program

In April 2017, Peru launched its latest malaria elimination program, under the name of the Zero Malaria Program 2017-2021 ("Plan Malaria Cero 2017-2021") (63), whose overall goal Is to eliminate malaria from Peruvian Amazon using a culturally sensitive community based approach. Such program represents a major opportunity for the country and an excellent challenge for science due to the many knowledge gaps in to fill out to achieve that critical goal. Hence, this study was designed to support this important initiative by identifying the main challenges for the initiative and some key opportunities to overcome them.

## *1.2 Organization of the dissertation*

The dissertation is presented in seven chapters. Chapter 1 introduces the background and specific aims of the research. Chapter 2 provides a review of the current literature on the challenges and opportunities for pursuing malaria elimination in Peru. Chapter 3 provides details on the study area and an overview of the methods for each specific aim. Chapters 4, 5, and 6 describes a course of three substantive research papers, each aligned with one of the above three aims. Chapter 4 focuses on assessing the malaria elimination program that was implemented in Tumbes, which was based on based on RCD/FMDA and compared to PCD. Chapter 5 investigates the impact of this program on interrupting the transmission of malaria beyond the intervention areas and along de Peruvian north coast. Chapter 6 explores whether a further characterization and understanding of the different patterns of the transmission of malaria in Loreto may help to offer a set of strategic targets for the Peruvian malaria elimination program. The final chapter provides a synthesis of the overall conclusions, implications, and suggestions for future research.

The Appendices includes the tools and guides used for data collection, institutional approval letters, and supplementary tables and figures.

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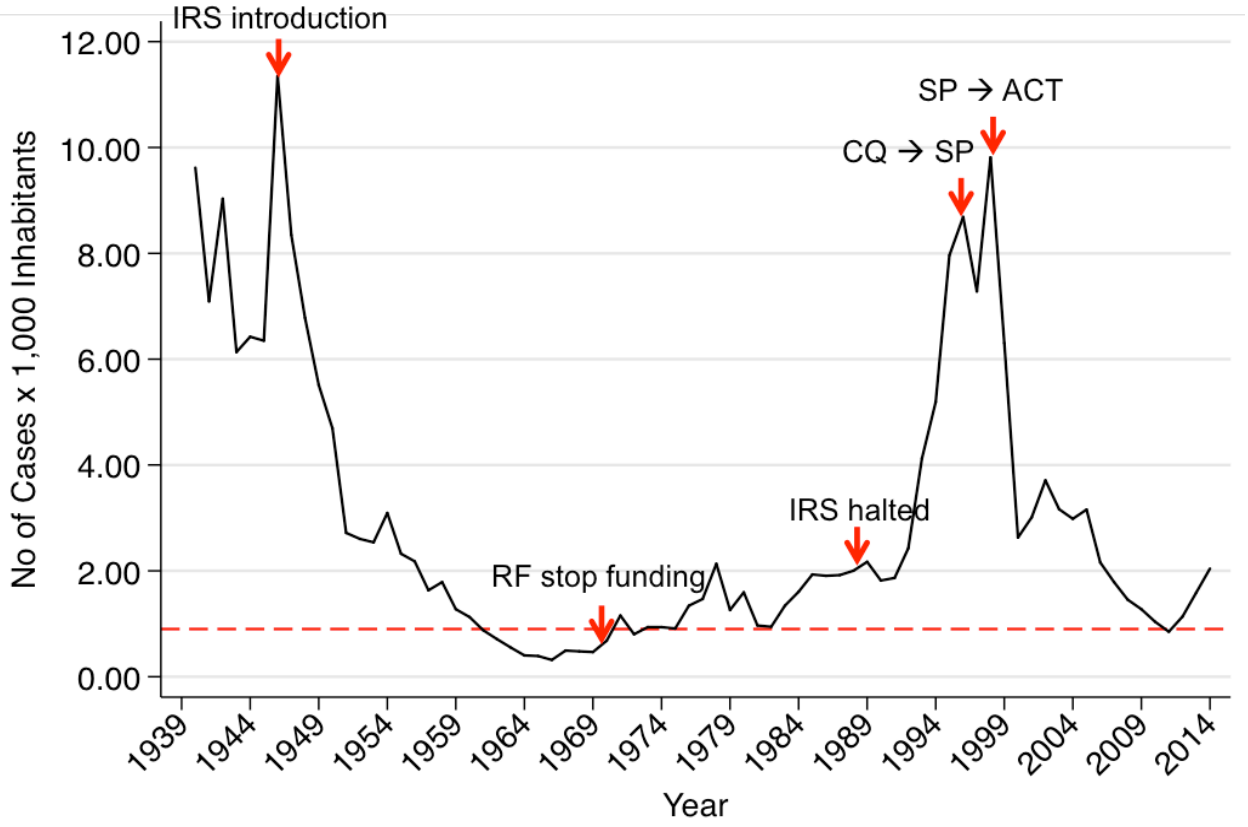
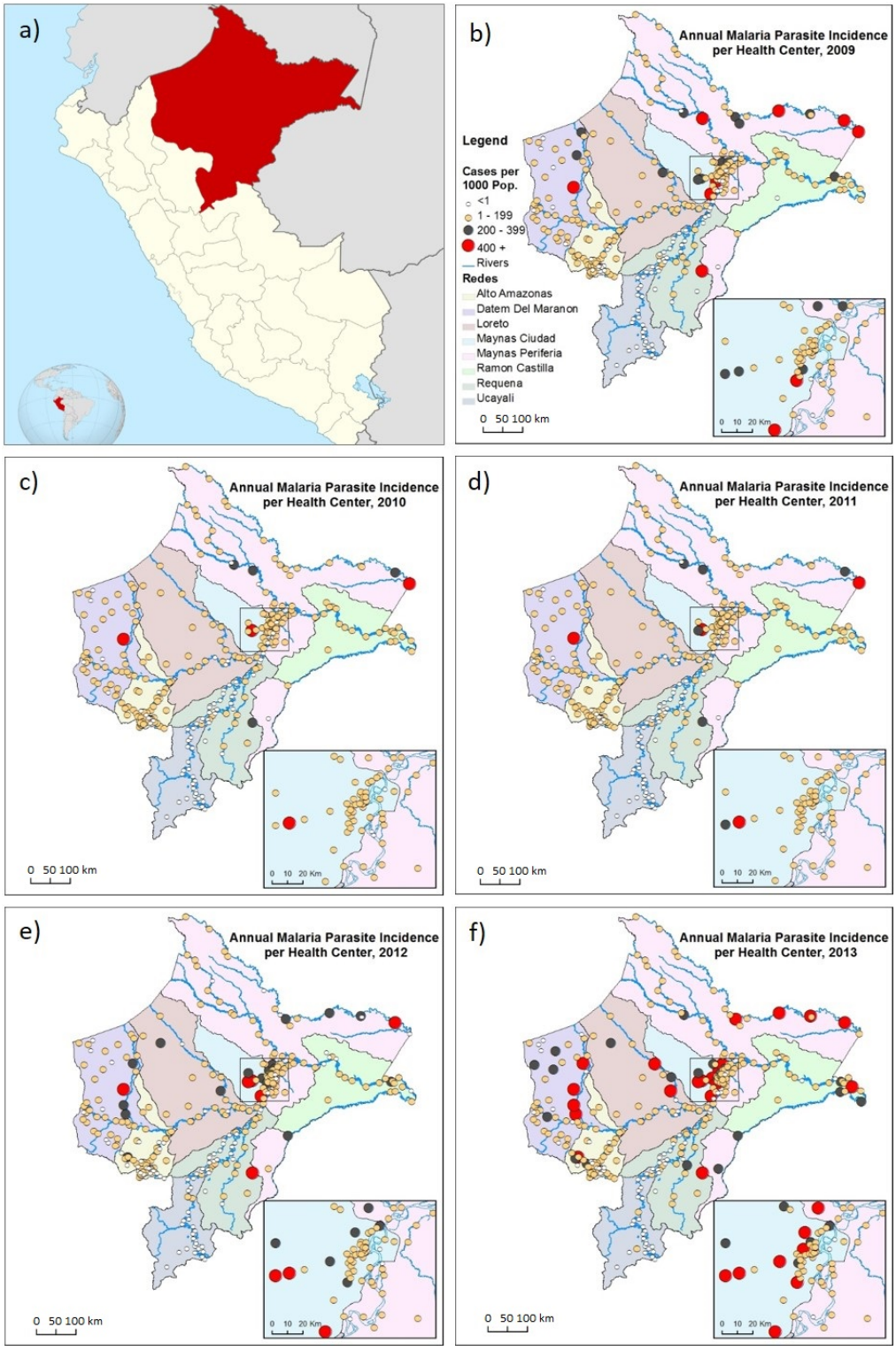
## *1.4 Figures for Chapter 1*

**Figure 1. The historical trend of reported malaria incidence in Peru: 1939-2014**




**Legend:** Annual Parasite Index (total of subjects that tested smear positives to malaria per 1,000 inhabitants per year) in Peru since 1939 to 2014. Here, the red dash shows that the threshold of 1 case per 1,000 inhabitants has been overcome only twice (in the latest 1960's and in the latest 2010's), but malaria is increasing again. During this whole period, several important interventions were introduced in the country. In 1944, the Rockefeller Foundation (RF) sponsored the introduction of Indoor residual spraying (IRS) with dichlorodiphenyltrichloroethane (DDT), but after several years of continuous spraying and malaria-burden decline, such funding ceased in 1970. In 1988, DDT use was halted first in Loreto and later in the rest of the country. In 1996, sulphadoxine–pyrimethamine (SP) replaced chloroquine (CQ) as the first-line treatment of uncomplicated falciparum malaria, but after several clinical trials, Peru decided to adopt artemisinin-based combination therapies (ACTs) to replace SP in 2001, remaining as such to date
**Source:** Quispe, A. M., et al (2016) (64)

**Figure 2.** Annual Parasite Index distribution by surveillance units in Loreto: 2009-2013




**Legend:** (a) Location of Loreto and (b-f) Annual Malaria Parasite Incidence per Health Center for 2009-2013 period.
**Source:** Mousan A et al (2016) (65)

# Chapter 2. Methods

## *2.1 Specific Aims*

### Primary Aim 1

To determine the impact of reactive case detection with focal mass drug administration (RCD/FMDA) as compared to passive case detection (PCD) on reducing the regional annual parasite incidence in Tumbes, Peru. This was a non-randomized community trial designed to test a malaria elimination program based on RCD/FMDA as compared to PCD in Tumbes, Peru.

### Primary Aim 2

To determine the impact of the malaria elimination program implemented in Tumbes on interrupting the transmission of malaria beyond the intervention area and along de Peruvian north coast. This was a time series analysis designed to assess the effect the Tumbes malaria elimination program on interrupting beyond the intervention areas.

### Primary Aim 3

To characterize the different patterns of the malaria incidence in Loreto and offer a set of strategical targets for the Malaria Zero Program. This was a time series analysis designed to characterize the regions of Loreto that exhibits similar or different patterns of malaria incidence, looking for specific communities which are reservoirs for prolonged parasitemia and thus potential priority targets for interrupting transmission

## *2.2 Summary of studies*

**Study 1 (Chapter 3). "Reactive case detection with focal mass drug administration for malaria elimination in northwestern Peru".**

This was a non-randomized community trial that was implemented in Tumbes, Peru. The goal was to determine the impact of reactive case detection with focal mass drug administration (RCD/FMDA) on reducing the regional annual parasite incidence in Tumbes. The effect for both interventions was evaluated as their effect on reducing the mean annual parasite incidence during the pilot study (2009-2010) across the surveillance reporting units from the two intervention districts compared to the surveillance reporting units from the eleven non-intervention districts that utilized passive case detection only. To complement this analysis, we also described the trends of the annual parasite incidences in the department in the five years following the RCD/FMDA scale-up (2011-2015). In both analyses, we used the regional surveillance data and included the reporting units that report at least one malaria case during 2000-2009.

**Study 2 (Chapter 4). "Reactive case detection with targeted mass drug administration: Interrupting malaria transmission and achieving elimination beyond intervention areas in northwestern Peru".**

This was a follow-up study of the non-randomize community trial previously described that aims to assess the impact of malaria elimination program implemented in Tumbes beyond the intervention areas and along the Peruvian north coast. The effect of the intervention was measured by proximity to the districts intervened during the pilot project and across Piura reporting units.

In this analysis we the weekly parasite incidence as the outcome and the regional surveillance data from both regions, Tumbes and Piura.

**Study 3 (Chapter 5). "The patterns of malaria incidence in the Peruvian Amazon and the opportunity of interrupting malaria transmission with focal interventions".**

This study was a Time-Series Cross-Sectional Analysis that explores whether a further characterization and understanding of the different patterns of the transmission of malaria in Loreto may help to offer a set of strategical targets for the Peruvian malaria elimination program. The third study develops the hypothesis that the reactive case detection with focal mass drug administration may have a role in the path towards eliminating malaria from the Peruvian Amazon, particularly in the riverine networks that have some communities that behave like malaria foci that boost the sustainability of malaria transmission from one malaria season to the next one.

## *2.3 Study Population*

The thesis research was conducted in three different regions in Peru, the Tumbes and Piura regions on the north coast, and the Loreto region in the north of the Peruvian Amazon. Study 1 was carried on in the northern region of the Peruvian north coast at the border with Ecuador, while the study 2 was carried on in the nearby region of Piura. Study 3 was carried on in the Loreto region, which is the largest region in the country and is located on the borders with Ecuador, Colombia, and Brazil.

The Peruvian north coast is comprised of four regions (From north to south: Tumbes, Piura, Lambayeque and La Libertad), of which the two northern regions are Tumbes and Piura, both

bordering with Ecuador, and consequently are very important geopolitically, economically and epidemiologically for both countries (Figure 3). Malaria transmission along the north coast has historically progressed from north to south giving tropical weather and greater endemicity in the north (Tumbes and Piura) and the connectivity provided by the Pan-American Highway that connects them to the capital city of Lima. Most malaria cases in northern regions of Peru have been consistently due to *P. vivax*, but occasionally *P. falciparum*. In the year 2000 the north coast regions reported 21,985 malaria cases, with ~20% of those cases secondary to *P. falciparum*; however, in the year 2015, those regions reported only 50 cases (4 in Piura and 46 in La Libertad), with all of those cases secondary to *P. vivax*. The principal malaria vectors in the region are *An. albimanus, An. calderoni,* and *An. pseudopunctapenis* (1), unlike in the Amazon region, where *An. darlingi* mosquitoes predominate (2). The majority of infections are asymptomatic, although we reported several but uncommon severe vivax malaria cases in Piura (3). Malaria along the north coast is strongly seasonal, peaking during the rainy season (February-June) and plunging during the dry season (July-January). Such strong variability might be explained by regional characteristically fluctuations in the climate parameters such as rainfall and temperature, which determine the ability of the environment to support the development of mosquito larvae (4).

Tumbes, the smallest region of the all the four north coast regions, is divided into 13 districts, encompasses roughly 230,000 people, and have a total surface of 4,670 $km^2$. In the late 1990s, malaria was transmitted by both *P. vivax* and *P. falciparum*, but early in the 2000s, the incidence of malaria was drastically reduced due to the introduction of artemisinin-based combination therapy (ACT) in the country. Consequently, the parasite predominance shifted towards *P. vivax*, which have been the most predominant malaria species since then. Except for a well-documented

falciparum malaria outbreak reported in years 2010-2012 due to malaria imported cases from Loreto, the last autochthonous case of *P. falciparum* was reported in the region in 2006 (5).

Peru is divided into 24 regions (Figure 4), of which nine are situated along the Peruvian Amazon basin, including (From north to south): Loreto, Amazonas, San Martin, Ucayali, Huánuco, Pasco, Junin, Madre de Dios y Cusco. Each of these nine regions has been malaria endemic in the past two decades, with a strong seasonal pattern, peaking consistently between March and August. That been said, it is important to highlight that Loreto represents by far the largest human malaria reservoir in the Peruvian Amazon basin, contributing historically to the spread of malaria across the nearby Amazon basin regions. Most malaria cases in Loreto, as in the rest of the country, have been consistently reported as due to *P. vivax*, but the region is currently facing a substantial increment of *P. falciparum* malaria cases. In the year 2010 Loreto reported 25,927 malaria cases, with ~15% of those cases due to *P. falciparum*; however, in the year 2014 Loreto reported 60,566 malaria cases, with ~17% of those cases due to *P. falciparum*. The principal malaria vectors in the region are *An. darlingi* and *An. bennarrochi* (6), the majority of infections are asymptomatic (7), and severe malaria cases are uncommon with very few deaths reported in the literature (8).

## *2.4 Malaria Surveillance data*

### Malaria counts

Malaria is a condition that requires mandatory weekly reporting from all health facilities countrywide according to the surveillance guidelines of the Peruvian Ministry of Health (MoH). Fever cases confirmed microscopically by thick and thin malaria smears are reported to the

Regional Health Directorates (DIRESA's), where their epidemiology units analyze the data and report it to the central government using an Electronic Online Surveillance System named NOTI.

The process of data collection begins with registering every febrile illness that needs to be tested for malaria at each reporting unit by the designated health personnel in charge of the local malaria program. Then the designated personnel proceeds with the notification process by summarizing the data and sending two types of reports: collective cases reported including both fever cases and malaria cases, and the individual cases reports. Once the data is received at each DIRESA, the data is entered into the NOTI system. During the data entry, a monitoring process takes place, checking quality control and optimizing the database. At this point, a weekly surveillance report is generated to allow the local epidemiologist to follow the malaria trend. Once the data entry process and quality control are finished, the NOTI system is collected online at the Peruvian Center of Diseases Control, where the country data is analyzed and examined for indications of outbreaks or other trends. The information is returned to the DIRESA stakeholders as epidemiological bulletins to inform their decision making with a 1-2 weeks delay since the cases are initially documented. Overall the data allows the public health officers to assess the distribution and trends of malaria at the regional scale, but rarely is used to inform decision making at the reporting units scale.

## Population data

The annual population estimates per health center were obtained from the Tumbes, Piura and Loreto's Ministry of Health Directorates. Moreover, the weekly population estimates were calculated based on linear interpolation from the annual population estimates assigned to each health center and the total population estimates of the department for each year.

### Malaria incidence

Malaria incidences were estimated annually and weekly at each health center using the formula for the annual parasite incidence (API), as defined in equation 1, and the weekly parasite incidence (WPI), as defined at the equation 2:

$$\text{Annual Parasite Incidence} = \left( \left( \frac{number\ of\ reported\ cases\ during\ a\ year\ period}{population\ during\ a\ year\ period} \right) * 1000 \right) \quad (1)$$

$$\text{Weekly Parasite Incidence} = \left( \left( \frac{number\ of\ reported\ cases\ during\ a\ week\ period}{population\ during\ a\ week\ period} \right) * 1000 \right) \quad (2)$$

The APIs are reported per region at the Epidemiological Bulletins published by the Epidemiology General Directorate (http://www.dge.gob.pe/portal/). And despite it only depicts a rough picture of the regional malaria trends is commonly used by MoH decision makers as the main metric to guide public health spending and resources allocation. Consequently, those regions with the highest burden receive more budget to manage their malaria cases and those with less malaria cases more budget to fight the most important competitive risks at the moment.

## *2.5 Remote Sensing Data*

The methods used to analyze the remote sensing data and estimate the climate and environmental variables at each health center were described in a separate publication (Table 2) (9). Briefly, as described in the manuscript "temperature, humidity, and surface pressure were calculated based on the outputs from the NASA MERRA (Modern-Era Retrospective analysis for Research and Applications) model; precipitation data from the Tropical Rainfall Measuring

Mission (TRMM) Multisatellite Precipitation Analysis (TMPA); vegetation products from the moderate-resolution imaging spectroradiometer (MODIS) instrument; and elevation data from the Advanced Spaceborne Thermal Emission and Reflection Radiometer (ASTER) Global Elevation Model (GDEM)" (9).

The MERRA model provided us with a historical time series of temperature, humidity, and surface pressure. The model run off since 1979 and incorporates remote sensing observations from different modern satellites providing estimates for other variables also such precipitation, radiation, as well as land surface variables like soil moisture. Data from MERRA products are available hourly with a spatial resolution of 1/2° (latitude) × 2/3° (longitude). For the studies, we obtained from MERRA the following variables: specific humidity at 2 m above the displacement height (QV2M), the temperature at 2 m above the displacement height (T2M), and soil moisture content in the top soil layer (SFMC).

Like MERRA the TRMM TMPA dataset also provides precipitation estimates, but with a higher resolution. To do so, it merges information from multiple satellite sensors and ground-based gauges to produce a more precise one (10). These include several passive microwave sensors (PMW) that are onboard Low Earth Orbit Satellites and sensors that are on board platforms of the Defense Meteorological Satellite Products and NOAA (11). The TMPA product is created by using the PMW rain rates from each sensor through the Goddard Profiling algorithm and is available for the 50°N–S latitude band since 1998 with 0.25° × 0.25° resolution at 3-hourly time steps (12). The TMPA product is available in a real-time version (TMPA 3B42RT) and in gauge-adjusted post real-time research version (TMPA 3B42), which use of rain gauge data for bias adjustment (13). So, to prevent such bias, the studies will use the TMPA 3B42V7, as strongly recommended by Maggioni et al. (14).

Vegetation indices for the studies were obtained from the global 16-day composite of MODIS vegetation indices. Although MODIS produces two indices, the normalized difference vegetation index (NDVI) and the Enhanced Vegetation Index (EVI), for the purpose of the studies the selected index will the NDVI (15). NDVI is available from the MOD13C1 Product at 0.05° x 0.05° resolution (~ 5,6 $km^2$) and is derivate from the reflectance in the near-infrared (N) and red bands (R), using the following formula:

$$\mathrm{NDVI} = \frac{\mathrm{N}-\mathrm{R}}{\mathrm{N}+\mathrm{R}} \qquad (2)$$

Elevation data for the studies was obtained from the ASTER GDEM model, which provides elevation data globally at 30 m resolution. The ASTER instrument produces the ASTER DEMs by using near infrared spectral band and nadir-viewing and backward-viewing telescopes to acquire stereo image data (16). Such data, then is processed automatically and comprehensible by including cloud masking, stacking all cloud-screened DEMs, removing wrong values, and averaging selected data to create final pixel values. The ASTER GDEM is available with a resolution of 1° × 1° tiles for land surface regions between 83° N-S (16).

## *2.6 Surveillance Data Modeling*

To account for the limitations proper of surveillance data as well as for its multilevel structure each of the studies assessed potential confounders using a mixed-effects Poisson regression model. The overall notation for these models is the following:

$$E(y_{ij}) = \mu_{ij} = t_{ij} exp\left[x'_{ij}\beta + z'_{ij}\upsilon_i\right] \qquad (3)$$

$$log(\mu_{ij}) = log(t_{ij}) + \left[x'_{ij}\beta + z'_{ij}\upsilon_i\right] \qquad (4)$$

$$log(\mu_{ij}) - log(t_{ij}) = x'_{ij}\beta + z'_{ij}\upsilon_i \quad (5)$$

$$log(\mu_{ij}/t_{ij}) = x'_{ij}\beta + z'_{ij}\upsilon_i \quad (6)$$

$$log(\mu_{ij}/t_{ij}) = x'_{ij}\beta + z'_{ij}\upsilon_i \quad (7)$$

*Where:* $i = 1, \dots, N\ comunities,\ j = 1, \dots, n_i\ weeks$, and $\upsilon_i \sim N(0, \sigma_\upsilon^2)$

In the study 1, we estimated the adjusted incidence rate ratio (IRR) attributable the RCD/FMDA by fitting a two-level mixed-effects Poisson regression for the weekly malaria incidence adjusting for potential environmental and climate confounders. These variables included temperature, humidity, soil moisture, elevation, precipitation, as well as the normalized difference vegetation index (NDVI) and the enhanced vegetation indexes (EVI).

In the study 2, we used similar approach, but here we focused in the association between the weekly malaria incidence and the road proximity to the intervention districts during the pilot of study 1. Here, we use road distances estimated from each surveillance unit to the Aguas Verdes international bridge over the Zarumilla river, which connects Peru with Ecuador, as a proxy of indirect exposure.

And in the study 3, we use a two-level mixed-effects Poisson regression model to assess the variability of the malaria counts and characterize the different patterns of malaria transmission across the main riverine networks of Loreto. However, giving a large number of zeros in the malaria counts across Loreto, we ultimately fitted a mixed negative binomial regression model to compensate for the over-dispersion of the count data. In all data sets examined, the negative binomial model fitted much better than the Poisson regression model and other alternatives like the zero inflated Poisson regression model, as evaluated by AIC or BIC statistics. Hereby, we

decided to report the negative binomial regression model giving it is a much simpler model to estimate and interpret.

At each study we used the forward selection, the Akaike Information Criteria (AIC) and the likelihood ratio test (LRT) to determine the variables for the multivariate model comparing nested models. And to assess and prevent multicollinearity we used the correspondent Pearson's correlation coefficients for each analysis. All the mixed-effects regression analysis was conducted with Stata/MP 14.0 (Stata Corporation, College Station, TX) using the *"meqrpoisson*" command for the Poisson regression model and the *"membreg*" command for the negative binomial Poisson regression model.

## *2.7 Seasonality component*

There are several alternatives about how to assess or to define malaria seasonality, resulting in a wide range of alternatives reported in the literature. Choosing one is essential to model malaria cases because, like in Peru, malaria distribution in time shows seasonal peaks in most endemic settings. However, it is also important to understand that such choice may vary across settings for optimal malaria control and seasonality characterization. In study 3, we decided to address seasonality by using a trigonometric solution, which is a simple approach to describe and compare the seasonality of malaria across settings (17). To do so, we incorporated sine and cosine terms in our mixed effects regression models. These terms will be included in pairs to satisfy boundary conditions and orthogonality. This is important because the predictions from a regression on sine and cosine terms are automatically identical at the beginning and the end of the interval to deal with the periodicity of each interval without discontinuity. And because an attractive property of the sine and cosine terms is their orthogonality or lack of correlation (Figure 5).

To produce the necessary set of trigonometric predictors we used Stata and *forvalues* loop. Following Cox et al recommendations we set the loop over the integers 1/3 (i.e., 1, 2, and 3) and the counter (strictly, a local macro) "j" to 1, which represents the first time around the loop. Consequently, in Stata we used the following commands:

```
. generate t = week_n / 52
. forvalues j = 1/3 {
.       gen sin`j' = sin(`j' * 2 * _pi * t)
.       gen cos`j' = cos(`j' * 2 * _pi * t)
. }
```

By running the previous coding in Stata, we certainly can describe the seasonal pattern of malaria as two sine and one cosine functions within a regression model, and more importantly, we can adjust our predictor of interest by its main confounders of interest.

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## *2.9 Tables for Chapter 3*

**Table 1**. Annual Parasite Incidences (API) by region during years 2000-2014

| Region | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Loreto** | 26.4 | 37.9 | 58.2 | 52.4 | 47.5 | 59.2 | 45.6 | 39.2 | 26.2 | 26.6 | 11.6 | 11.8 | 25.0 | 42.9 | 57.3 |
| **Tumbes** | 15.3 | 17.5 | 9.8 | 7.8 | 5.3 | 2.1 | 2.2 | 5.5 | 13.0 | 6.8 | 8.2 | 3.0 | 0.4 | 0.0 | 0.0 |
| **Piura** | 9.0 | 8.9 | 6.1 | 1.5 | 0.5 | 0.2 | 0.1 | 0.3 | 2.3 | 1.6 | 1.2 | 0.1 | 0.0 | 0.0 | 0.0 |
| **Madre de Dios** | 5.8 | 4.4 | 9.1 | 6.3 | 21.5 | 50.2 | 45.0 | 41.3 | 39.1 | 18.1 | 25.1 | 14.1 | 5.2 | 2.0 | 0.1 |
| **Ayacucho** | 4.0 | 2.5 | 3.8 | 4.3 | 7.9 | 8.5 | 4.4 | 1.4 | 0.6 | 0.7 | 1.7 | 3.4 | 3.8 | 2.4 | 1.0 |
| **San Martín** | 2.8 | 7.5 | 9.2 | 14.9 | 14.8 | 6.8 | 2.1 | 1.3 | 1.1 | 1.1 | 1.0 | 0.3 | 0.2 | 0.1 | 0.9 |
| **Junín** | 2.1 | 2.1 | 0.1 | 3.8 | 5.1 | 4.6 | 2.3 | 2.7 | 2.0 | 1.5 | 5.6 | 3.5 | 1.4 | 1.7 | 1.5 |
| **Ucayali** | 1.9 | 3.9 | 8.1 | 8.5 | 8.4 | 6.3 | 1.5 | 0.3 | 0.7 | 0.5 | 0.6 | 0.1 | 0.1 | 0.2 | 0.1 |
| **Lambayeque** | 1.8 | 0.4 | 0.5 | 0.9 | 0.2 | 0.3 | 0.0 | 0.1 | 0.1 | 0.3 | 0.1 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Amazonas** | 1.6 | 0.8 | 1.8 | 1.6 | 2.3 | 3.4 | 0.9 | 1.3 | 0.4 | 0.2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.2 |
| **Cusco** | 1.3 | 1.5 | 2.0 | 2.0 | 3.9 | 2.8 | 1.4 | 0.6 | 0.5 | 0.2 | 0.8 | 0.8 | 0.3 | 0.5 | 0.3 |
| **La Libertad** | 1.2 | 1.4 | 0.6 | 0.8 | 0.7 | 0.5 | 0.7 | 0.2 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.0 | 0.0 |
| **Cajamarca** | 1.0 | 0.5 | 0.4 | 0.3 | 0.7 | 0.8 | 0.4 | 0.2 | 0.1 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Ancash** | 0.8 | 0.9 | 0.5 | 0.5 | 0.6 | 0.6 | 0.6 | 0.2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Pasco** | 0.6 | 0.5 | 0.8 | 1.4 | 1.1 | 1.8 | 1.3 | 0.7 | 0.8 | 0.1 | 0.5 | 0.2 | 2.0 | 0.1 | 0.0 |
| **Huancavelica** | 0.5 | 0.1 | 0.2 | 0.1 | 0.3 | 0.1 | 0.2 | 0.1 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Apurímac** | 0.3 | 0.0 | 0.1 | 0.1 | 0.8 | 1.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Huánuco** | 0.1 | 0.1 | 0.2 | 0.1 | 0.2 | 0.1 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Puno** | 0.0 | 0.0 | 0.0 | 0.3 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Loreto** | 26.4 | 37.9 | 58.2 | 52.4 | 47.5 | 59.2 | 45.6 | 39.2 | 26.2 | 26.6 | 11.6 | 11.8 | 25.0 | 42.9 | 57.3 |
| **Tumbes** | 15.3 | 17.5 | 9.8 | 7.8 | 5.3 | 2.1 | 2.2 | 5.5 | 13.0 | 6.8 | 8.2 | 3.0 | 0.4 | 0.0 | 0.0 |
| **Piura** | 9.0 | 8.9 | 6.1 | 1.5 | 0.5 | 0.2 | 0.1 | 0.3 | 2.3 | 1.6 | 1.2 | 0.1 | 0.0 | 0.0 | 0.0 |
| **Madre de Dios** | 5.8 | 4.4 | 9.1 | 6.3 | 21.5 | 50.2 | 45.0 | 41.3 | 39.1 | 18.1 | 25.1 | 14.1 | 5.2 | 2.0 | 0.1 |
| **Ayacucho** | 4.0 | 2.5 | 3.8 | 4.3 | 7.9 | 8.5 | 4.4 | 1.4 | 0.6 | 0.7 | 1.7 | 3.4 | 3.8 | 2.4 | 1.0 |
| **San Martín** | 2.8 | 7.5 | 9.2 | 14.9 | 14.8 | 6.8 | 2.1 | 1.3 | 1.1 | 1.1 | 1.0 | 0.3 | 0.2 | 0.1 | 0.9 |

**Source:** Epidemiology General Directorate (http://www.dge.gob.pe/portal/)

**Table 2.** Malaria counts and weekly parasite incidences (WPI) in Loreto by provinces during years 2010-2017

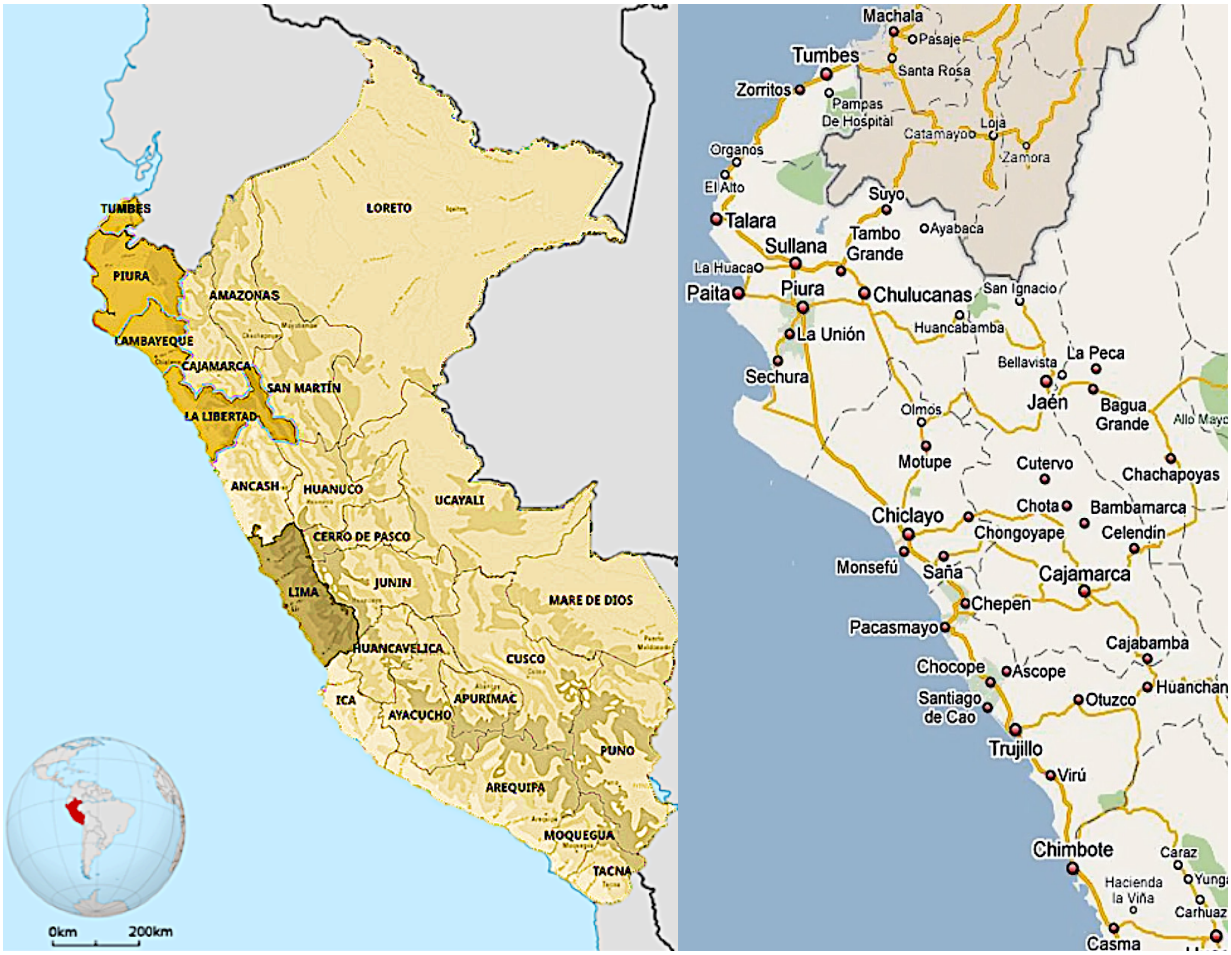
| Region | | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 |
|---|---|---|---|---|---|---|---|---|---|
| Alto Amazonas | Cases | 457 | 508 | 1079 | 1090 | 2286 | 2520 | 2419 | 3739 |
| | Mean WPI | 11 | 17 | 39 | 35 | 65 | 82 | 72 | 111 |
| Datem del Marañon | Cases | 611 | 884 | 1921 | 4955 | 11559 | 11357 | 14925 | 17483 |
| | Mean WPI | 14 | 11 | 28 | 74 | 192 | 325 | 838 | 1171 |
| Loreto | Cases | 1356 | 876 | 2360 | 6359 | 11842 | 12997 | 12756 | 9243 |
| | Mean WPI | 41 | 17 | 53 | 139 | 313 | 369 | 544 | 457 |
| Mariscal Ramon Castilla | Cases | 1735 | 1356 | 7216 | 9380 | 5427 | 8442 | 2565 | 3269 |
| | Mean WPI | 52 | 34 | 140 | 221 | 104 | 185 | 69 | 95 |
| Maynas City | Cases | 3496 | 4152 | 7065 | 13487 | 17810 | 12379 | 11205 | 7616 |
| | Mean WPI | 41 | 71 | 154 | 225 | 228 | 173 | 146 | 125 |
| Maynas Periphery | Cases | 2131 | 3011 | 3524 | 5373 | 6484 | 9117 | 7871 | 9588 |
| | Mean WPI | 43 | 45 | 60 | 101 | 114 | 190 | 161 | 204 |
| Requena | Cases | 796 | 330 | 791 | 1071 | 1069 | 717 | 556 | 414 |
| | Mean WPI | 87 | 29 | 94 | 131 | 113 | 70 | 73 | 52 |
| Ucayali | Cases | 166 | 107 | 59 | 132 | 73 | 132 | 91 | 51 |
| | Mean WPI | 13 | 13 | 8 | 24 | 11 | 20 | 13 | 7 |

**Table 3**. Annual Parasite Incidences (API) by region during years 2000-2014

| Variable | Model | Product | Resolution | Units | Time Range Availability |
|---|---|---|---|---|---|
| Humidity (QV2M) | NASA MERRA model ¨Specific humidity at 2 m above the displacement height" | IAU 2d atmospheric single-level diagnostic (tavg1_2d_slv_Nx) | Daily Average with 2/3° longitude x 1/2° latitude (horizontal resolution) | kg kg-1 | 2000-2015 |
| Temperature (T2M) | NASA MERRA model "Temperature at 2 m above the displacement height" | IAU 2d atmospheric single-level diagnostic (tavg1_2d_slv_Nx) | Daily Average with 2/3° longitude x 1/2° latitude (horizontal resolution) | K | 2000-2015 |
| Pressure (PS) | NASA MERRA Model "Time averaged surface pressure" | IAU 2d atmospheric single-level diagnostic (tavg1_2d_slv_Nx) | Daily Average with 2/3° longitude x 1/2° latitude (horizontal resolution) | Pa | 2000-2015 |
| Soil moisture (SFMC) | Top soil layer soil moisture content (SFMC) | IAU 2d simulated land surface diagnostics (tavg1_2d_mld_Nx) | Daily Average with 2/3° longitude x 1/2° latitude (horizontal resolution) | m3 m-3 | 2000-2015 |
| Vegetation (NDVI) | Normalized Difference Vegetation Index (NDVI) | IAU 2d simulated land surface diagnostics (tavg1_2d_mld_Nx) | 16-day composite of MOD13C1 NDVI with 1/4° longitude x 1/4° latitude (horizontal resolution) | -1.0 to +1.0 | 2000-2015 |
| Precipitation (TMPA 3B42V7) | Tropical Rainfall Measuring Mission (TRMM) Multisatellite Precipitation Analysis (TMPA) | 3-Hour Realtime TRMM Multi-satellite Precipitation Analysis (TMPA 3B42V7) | Daily Average with 0.25° × 0.25° resolution at 3-hourly time steps (horizontal resolution) | kg m-2 s-1 | 2000-2015 |
| Elevation (ASTER GDEM) | Elevation | Elevation (ASTER GDEM) | Elevation estimated with a resolution of 1° × 1° tiles for land surface regions between 83° N-S | m | 2000-2015 |

## *2.10 Figures for Chapter 3*

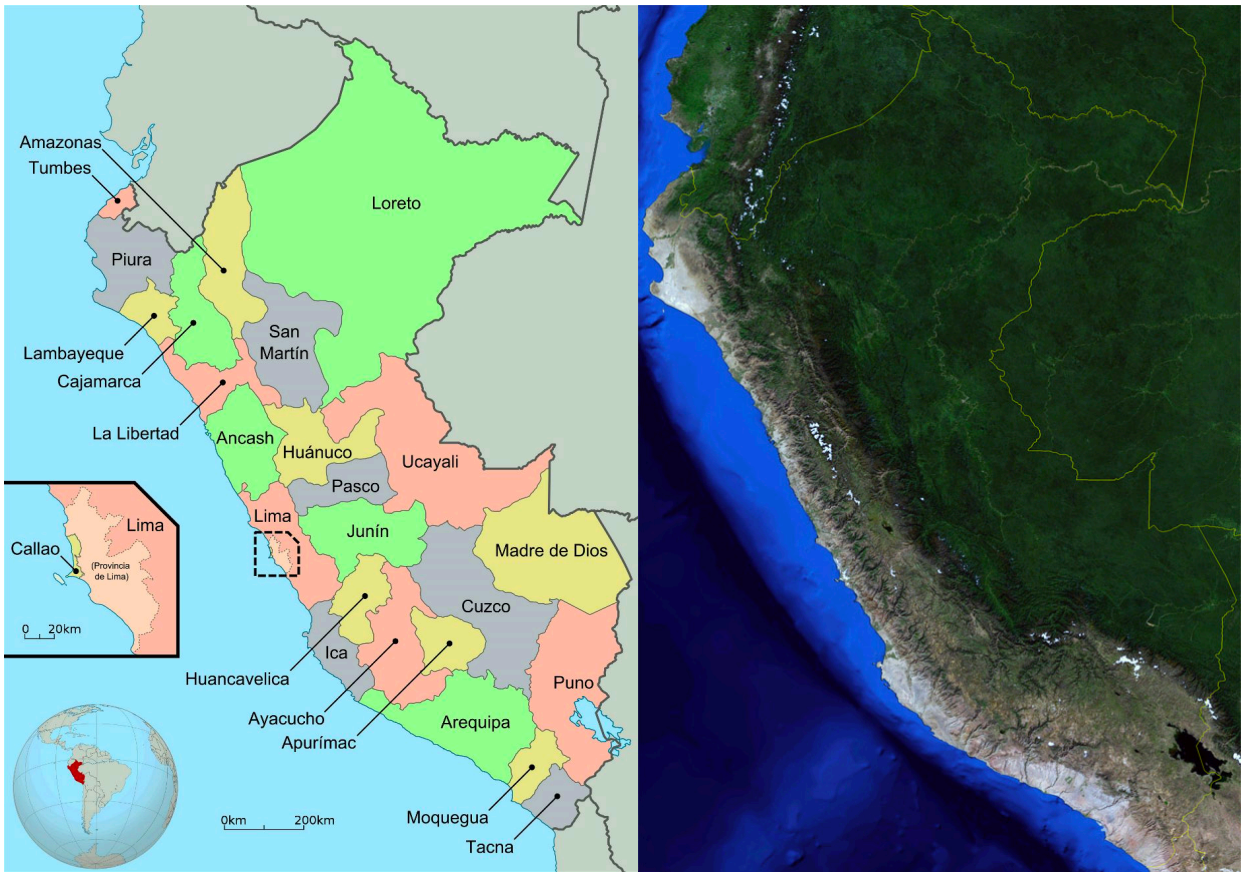
**Figure 3.** Peruvian north coast and its four malaria endemic regions




**Legend:** From north to south: Tumbes, Piura, Lambayeque, and La Libertad

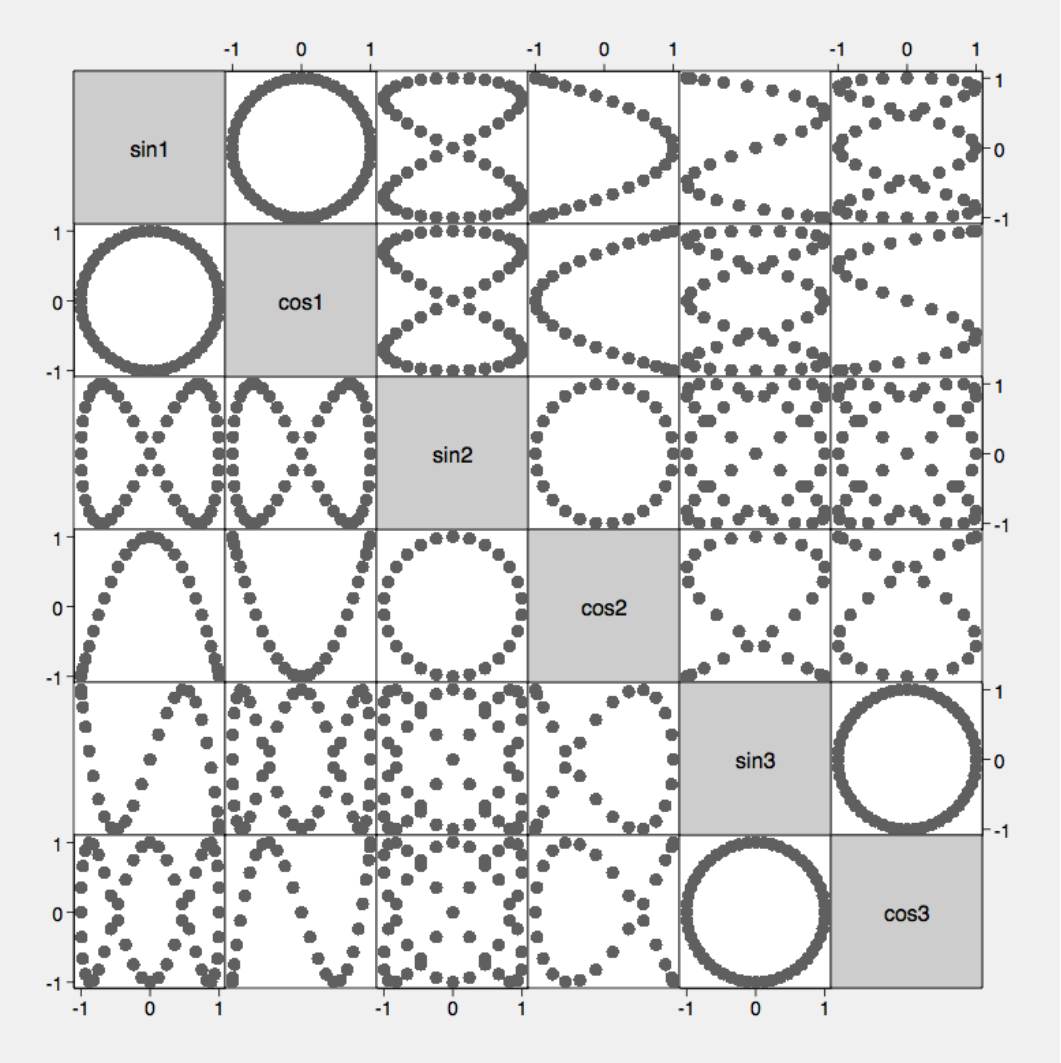
**Source:** Adapted from "https://www.peru.travel/" (left) and "https://www.mapsland.com/" (right)

**Figure 4.** Peruvian Amazon and its elevation variability




**Legend:** Notice that the Peruvian Amazon encompass about two thirds of Peru´s territory including nine administrative regions. Peruvian Amazon basin regions from north to south: Loreto, Amazonas, San Martin, Ucayali, Huánuco, Pasco, Junin, Cusco, and Madre de Dios.
**Source:** Adapted from "https://www.mapsland.com/" (left) and http://www.vidiani.com (right).

**Figure 5.** Scatterplot matrix of the first three pairs of sine and cosine terms




**Legend:** Notice that an attractive property of the sine and cosine terms is their lack of correlation and orthogonality.

# Chapter 3. "Reactive case detection with focal mass drug administration for malaria elimination in northwestern Peru"

## *3.1 Abstract*

Reactive case detection (RCD) with focal mass drug administration (FMDA) represent a novel and efficacious strategy for malaria elimination, although little is known about its effectiveness. In this study, we assessed the effectiveness attributable to the RCD/FMDA strategy as compared to passive case detection (PCD) in reducing the incidence of malaria to zero in Tumbes, Peru. From 2009 to 2010 we piloted a malaria-elimination program based on RCD/FMDA in the two districts with high burden of malaria in Tumbes; then, from 2011 to 2014 we scaled the program up in the other 11 districts in Tumbes. Under RCD each malaria case that was passively detected was followed-up within the first 24 hours by enumerating and treating each of their household contacts, excluding pregnant women, elders (>65 years old), and chronically-ill subjects. Then every eligible subject was treated with oral chloroquine (25mg/kg, total dose) for 72 hours plus oral primaquine (0.5mg/kg) for seven days. The primary study endpoint was a 50% reduction in the annual parasite incidence (API =total malaria cases/1,000 inhabitants) at the surveillance-reporting unit level, and the data were analyzed by the intention to treat method. The Peruvian Ministry of Health sponsored the study, and the Ecuadorian government donated 20,000 vivax malaria treatments. During the pilot study, we treated a total of 8,243 subjects, including 7,376 household contacts. The estimated reduction in the mean API across intervention reporting units was 86% (95% Confidence Interval: 72−100) at 12-months and 98% (93−100) at 24 months and the estimated reduction across non-intervention reporting units was -231% (-39−-66) at 12-

months and -19% (-87− 49) at 24-months, respectively. The reductions in the mean API were statistically significantly higher in the intervention group at both 12-months (p =0.02) and 24-months (p =0.04) compared to baseline. These findings were verified using mixed-methods Poisson regression analysis when adjusting the RCD/FMDA effect by seasonality and climate and environmental parameters of soil moisture, surface pressure, and vegetation. Based on this multilevel multivariate analysis we observed that RCD/FMDA significantly contributed to decreasing the weekly parasite incidence (Beta= -0.53; CI 95%: -0.91, -0.15; IRR=0.59) in the intervention areas as compared to the comparison areas. After scaling up, the API throughout Tumbes dropped to 3.1 and 0.4 in the years 2011 and 2012, with zero cases found in 2013, and one imported case in the year 2014. As a result of this, we concluded that RCD/FMDA represents an effective strategy to support malaria elimination initiatives in regions with high predominance of vivax malaria, strong but limited connectivity between communities, with a long track record using primaquine as is found in northwestern Peru and the Peruvian Amazon.

## *3.2 Introduction*

Malaria control has proven to represent a formidable challenge despite the latest investments and innovations proposed to tackle the burden of such threatening disease (1). Currently, the burden of malaria has steadily declined since 2000, but still represents one of the top ten leading causes of death in children aged 1-59 months worldwide (2). This progress certainly can be attributable to the significant political and financial commitment invested in scaling up of prevention, diagnosis, and treatment during the 2000-2015 period (3). During this period, the increasing trend in malaria incidence was halted and reversed, putting the world on track to achieved target 6C of the 2000 Millennium Development Goals (4). Regardless, such progress

has been somewhat uneven. For example, in 2015 the WHO European Region has reported zero indigenous cases for the first time while in the WHO African region - mainly in Sub Saharan Africa - fifteen countries reported 80% of the malaria cases and 78% of malaria deaths globally (4). Similar uneven progress had been observed within each WHO region and within each country, showing that malaria control efforts must be flexible using macro- and micro-level approaches. One of the reasons for this variability is that the main reservoir of malaria parasites is often over-dispersed (5, 6). As we progress towards malaria elimination, delivering interventions becomes progressively more difficult and expensive, mainly because the malaria map now is concentrated in the hardest to reach populations (7). Furthermore, because antimalarial medication is not free from adverse events and the threat of drugs resistance is not trivial, it is critical to use them wisely (8). In recent years, several new strategies have been proposed to overcome both considerations. Among them, reactive case detection (RCD) with focal mass drug administration (FMDA) appears to be a promising alternative to mass drug administration (9).

RCD is different from traditional active case detection methods in that it searches for malaria carriers, with individuals with asymptomatic parasitemia as the primary target, only within a defined high-risk sub-population instead of treating the whole population (10). First, field teams identify high-risk malaria households, often by identifying and index case detected either passively or previously reported within a specified period (often within the last malaria season). Then, all the inhabitants of these households are tested and treated if testing positive (11). Several countries have used RCD in the past (11-17), including Peru (18) and Brazil (19, 20) in the Americas, using similar but different operational definitions and diagnostic methods, and as a consequence showing different results (21). Focal mass drug administration (FMDA), also known as targeted mass drug administration, is a variant of mass drug administration (MDA) that focuses on treating a defined

high-risk population instead of the whole population at risk, regardless of the presence or absence of malaria-like symptoms and without diagnostic testing. China (22), Greece (23, 24), Tanzania (25), Zambia(26), and Kenya (27) have tested FMDA with relative success, reporting it as a cost-effective alternative to MDA in low malaria-endemic settings (28). By limiting the number of subjects receiving malaria drugs, we can avoid large numbers of unnecessary treatments, limit the risk of severe adverse events and drug resistance, and even with imperfect diagnostics target a more substantial fraction of human malaria reservoir than those covered with screen-and-treat strategies (25). Hence, it is critical to differentiate those that are at high risk of malaria from the rest of the population to correctly implement such a strategy. To do so, researchers have proposed RCD as an alternative to precisely do that. Using RCD, we can detect more malaria by actively screening subjects for malaria within the areas surrounding the households of every symptomatic malaria case that is passively detected (often with parasite densities detectable with microscopy or rapid diagnostic tests [RDT]). Recently China (22) and Greece (23, 24) have reported successful experiences using the RCD/FMDA strategy controlling the burden of malaria in regions where vivax was the predominant species.

In Peru, since the introduction of Artemisinin-based Combination Therapy in 2001-2003 (29), the number of cases of *P. falciparum* has decreased, particularly in the North Coast of Peru. Tumbes, which borders Ecuador, sustained its negative trend until achieving zero local transmission of *P. falciparum* malaria in the year 2005 (30). With the exclusion of an outbreak of *P. falciparum* malaria that occurred within a military base in 2008, nearly all malaria cases reported after the year 2005 were due to *P. vivax*. However, during the same period, *P. vivax* malaria in Tumbes begun to increase, to the point that Tumbes became a significant source of the malaria parasite on both the Ecuadorian border and on the rest of the Peruvian North Coast through the

Pan-American highway. These changes provided a unique opportunity for binational collaboration and to pilot a strategy based on the RCD recently implemented by the regional health directorate in the region and the FMDA experience from Ecuadorian peers (31). In this study, we reported the results of this experience, including initial piloting in two districts and followed by scaling up to the 13 districts in the region of Tumbes Peru.

## *3.3 Methods*

### Study Design

The study design is a non-randomized community trial followed over time. In Tumbes, we piloted an RCD/FMDA strategy at the two most malaria endemic districts − Aguas Verdes (3°28′S 80°14′ W, population ~13,000) and Zarumilla (03°49′S 80°27′W, population ~22,000) −. We selected the remaining eleven districts (population ~167,000) as controls, given that they continue using passive case detection as established by the Peruvian malaria guidelines.

To assess the strategy, we determined the effect on the mean annual parasite incidence across each the reporting units from the two intervention districts compared to the reporting units from the eleven non-intervention (control) districts that utilized passive case detection only. To complement this analysis, we also described trends in annual parasite incidence in the region in the five years following the RCD/FMDA scale-up (2011-2015). In both analyses, we included the reporting units that report at least one malaria case during 2000-2009.

## Study area

Tumbes, one of the 24 regions of Peru, is located in northwestern Peru on the border with Ecuador. The region has a warm climate due to its location nearby the Equator, with beaches considered among the finest in Peru. Despite its small area, the region contains a wide variety of ecosystems. Politically, Tumbes is divided into 13 districts with a total surface of 4,670 $km^2$ and a population of ≈237,685 inhabitants. In the late 1990s, *P. falciparum* was highly endemic in the region (Annual Parasite Incidence >10 x 1,000 inhabitants, with 36% of cases due *P. falciparum* in 1998) (32), but since year 2000 the parasite predominance shifted to *P. vivax* to the point that autochthonous falciparum transmission was reduced to zero in the year 2006. However, during October 2010-June 2012 Tumbes reported an outbreak of *P. falciparum* malaria (n =210 cases). The index case was identified as a military that traveled from Yurimaguas, a small town in the Peruvian Amazon, where *P. falciparum* remains endemic (33). In Tumbes, contrary to the Amazon region where *An. darlingi* is the main vector, the most predominant *Anopheles* species was *Anopheles albimanus*. Malaria endemicity of malaria in Tumbes is low and seasonal, peaking during the rainy season (February–June). Figure 6 displays the map of Tumbes with the distribution of the health centers within each district, the rivers, and roads, as well as the boundaries of the Tumbes regions and its 13 districts. Some health centers are clustered along the Peruvian border with Ecuador, some along the Tumbes River, while other health centers are more dispersed along the Pan-American highway.

## Study Population

For this study, we selected Aguas Verdes and Zarumilla to pilot an RCD/FMDA strategy considering that both represented the two most malaria endemic districts in Tumbes. We used as controls the remaining 11 districts, which continue using PCD as the strategy recommended by the Peruvian National Malaria guideline (34). At the intervention sites, subjects were considered as eligible for FMDA if they: (1) had his/her legal residence registered at their intervention districts; (2) resided at the household of a subject that was diagnosed as malaria positive within the previous 24 hours (index case) or resides outside the index case household but is identified during the census by him/her as a close social contact (either because of work or study in close contact on daily basis); and (3) assented to complete the malaria treatment regardless of the absence of symptoms. Exclusion criteria included children under five years old, elders (65 years of age or older), pregnant women, and chronically ill subjects.

## Study interventions

The study intervention was RCD/FMDA, where every malaria case that was passively detected was immediately followed within the first 24 hours in order to census and treat each of his/her household/social contacts, excluding children under 5 years old, elders (adults 65 years of age or older), pregnant women, and chronically ill subjects (Figure 7). The "control" (or comparison) was PCD, where only the subjects that tested positive for malaria during passive case detection activities received treatment. In both cases, following national guidelines, subjects were treated uniformly and free of charge for uncomplicated *vivax* malaria cases. To ensure that passive surveillance protocols and case management were standardized across regional reporting units, we

collaborated with local authorities to train malaria officers at each of the regional reporting units. We developed a capacity building system (combining in-class active learning methods with Pre-Post assessments) to train the personnel responsible for the malaria program annually, as well as to procure the administrative and laboratory supplies necessary to ensure a continual provision of care.

## Treatment for *Vivax* Malaria

As described in the Peruvian malaria treatment guidelines all patients received treatment uniformly and free of charge at each of the MoH health care facilities (35). Briefly, the treatment of choice for uncomplicated *vivax* malaria cases in adults and children consist in oral chloroquine (10 mg/kg/day) daily for three days, plus primaquine oral (0.5 mg/kg), daily, for seven days. Pregnant women receive chloroquine (10 mg/kg/day) daily for three days and then a weekly dose of 5 mg/kg upon delivery. Immediately after, they receive primaquine phosphate (0.5 mg/kg) daily for seven days. Infants under six months of age were treated with only chloroquine, while the unconscious patients were treated with clindamycin (20 mg base/kg/day) and quinine sulfate (10 mg salt/kg/day) intravenously, three times daily, until they start to tolerate oral standard treatment.

## Study outcomes

As a primary outcome, we assessed and compared the malaria annual parasite incidences at baseline (2008) with the second year (2011) post-intervention between the reporting units from the two intervention districts and the 11 non-intervention districts in the study. As secondary outcomes, we assessed the impact of scaling up the RCD/FMDA strategy to all 13 districts in the

following five years. Annual parasite incidence was calculated by dividing the total count of malaria cases, as reported by the national surveillance system, over the total population as estimated by the Peruvian Ministry of Health, at each of their surveillance reporting units. Those subjects that tested positive and did not report malaria-like symptoms (fever, chills, sweating, headache or any other kind of symptoms that the subject interpreted as indicating malaria) during RCD/FMDA activities were diagnosed with asymptomatic malaria and included in the API calculations.

## Climate and environmental variables

A specific set of climate and environmental variables were obtained for the purpose of adjusting our estimates of the effect of RCD/FMDA by assessing different satellite remote sensing products. These variables included temperature, humidity, soil moisture, elevation, precipitation, as well as the normalized difference vegetation index (NDVI) and the enhanced vegetation indexes (EVI) (Figure 6). Each of these variables was assessed using their weekly averages estimated at the coordinates of each the health centers for the 2008–2014 period. Temperature (T2M or temperature at 2m above the displacement height), humidity (QV2M or specific humidity at 2 m above the displacement height), and soil moisture (SFMC or soil moisture content in the top soil layer) estimates were obtained from the NASA MERRA (Modern-Era Retrospective analysis for Research and Applications) model; elevation data from the Advanced Spaceborne Thermal Emission and Reflection Radiometer (ASTER) Global Elevation Model (GDEM); precipitation data from the Tropical Rainfall Measuring Mission (TRMM) Multisatellite Precipitation Analysis (TMPA); and NDVI and EVI estimates from the Moderate-Resolution Imaging Spectroradiometer (MODIS) instrument. Data was available with different resolution, so each variable was estimated

by averaging their hourly estimates using the standardized protocols for each of the satellite products. MERRA data was available at hourly steps and at 1/2°×2/3° spatial resolution in latitude and longitude; TMPA data was available for the at 3-hourly time steps and 0.25°×0.25° resolution; while MODIS data was available at 0.05° resolution.

## Data Collection

Annual parasite incidence (malaria cases per 1,000 inhabitants) was estimated based on surveillance malaria counts and government population estimates, so we extensively reviewed the regional malaria surveillance registries from each of the reporting units during the study period. For the study, we took advantage of the national surveillance system (implemented in 2001), which provides a confidential and secure database with accurate data recording. All reporting units report their malaria counts on a weekly basis to the regional health directorate, which was in charge of the data entry by using the surveillance software NOTI. The software was designed to minimize data entry errors, such as including field range limits and logic checks, as well as to allow systematic checks for consistency and completeness. The primary data source for each positive malaria cases was the data recorded by the malaria program officers at each reporting unit, complemented by available data from the regional laboratory. We confirmed each case by microscopy at a primary laboratory (located at each reporting unit) and sent a random 10% fraction of these samples to the regional laboratory for quality control purposes.

We maintained the main datasets at a secure computer system, save weekly backups on local hard drives and monthly backups on the Regional Health Directorate computer systems, as prevention to avoid loss of data. All databases were password protected. We maintained confidentiality by storing all forms with personal identifiers (i.e., locator and consent forms) in

locked filing cabinets separate from all other information and limit their access to only the study data managers. Then, we translated the data into CSV files ready to be imported with STATA/MP v14.0 (Stata Corporation, College Station, TX, 2011) for further editing and checks, reviewing the data for consistency and completeness.

## Data Analysis

First, we performed an exploratory analysis to describe and compare the baseline characteristics within and between study arms. Baseline characteristics and primary and secondary outcomes were described with summary statistics, using frequency and percentage for categorical variables and mean and standard deviation for continuous variables. To estimate the effect of the RCD/FMDA during the pilot study we compared the mean API across reporting units between the two study arms, those from the two intervention districts with those from the eleven non-intervention comparison districts, from years 2008 (baseline) to 2010. This and further multivariate analysis were performed by using a mixed-effects Poisson regression model to adjust for potential confounders and to account for the structure of the data. The following variables were assessed as potential confounders: seasonal trend, year, week, precipitation, vegetation, temperature, surface pressure, humidity, and soil moisture. Forward selection was used to determine the variables selection for the multivariate model using the Akaike Information Criteria (AIC) and the likelihood ratio test (LRT) to compare nested models. Pearson's correlation coefficients are also computed for each variable to assess and prevent multicollinearity. All the analyses were conducted with Stata/MP 14.0 (Stata Corporation, College Station, TX) using a significance level of $p<0.05$.

### Ethical considerations

During study planning, the study protocol was presented by the Tumbes Regional Health Directorate authorities to the National Ministry of Health authorities, which approved the study as a pilot demonstrative project of public health relevance. During RCD/FMDA activities eligible subjects were invited to participate, instructed about the study risks and benefits, and only those whom consented received the treatment for vivax malaria. The Regional Health Directorate covered the costs for all the interventions related activities, including the training and retraining of the Ministry of Health personnel and the laboratory and administrative supplies.

## *3.4 Results*

### Malaria cases at baseline

From 2001 to 2008, Tumbes reported a total of 10,146 malaria cases of which 8,168 (81%) were due to *P. vivax*, for a mean API across each of its reporting units of 64 malaria cases per 1,000 inhabitants. During this period, the malaria cases due to *P. falciparum* cases dropped from 902 cases in 2001 down to zero in 2007, without any autochthonous *P. falciparum* malaria cases since 2006. However, an outbreak of 210 *P. falciparum* cases was reported in October 2010 (18 cases in 2010, 156 in 2011, and 36 in 2012) as secondary to an index case (an army recruit of 19 years of age) imported from a small town in the Amazon basin named Yurimaguas. The last case from this outbreak was reported in June 2012, without further *P. falciparum* malaria cases reported to date.

At baseline (2008) a total of 2,479 malaria cases, all *P. vivax*, were reported in Tumbes. The average age of the malaria positive cases was 29±17 years of age, being most of the cases men (69%). That year 43% of the annual cases were reported from Aguas Verdes (population, 17,635) and Zarumilla (population, 22,280), the two most malaria endemic districts in the region. At these two districts, the mean API across their reporting units was significantly higher than among reporting units from the eleven non-intervention districts (42±44 cases per 1,000 inhabitants vs. 7±9 cases per 1,000 inhabitants; $p$=0.001).

## Pilot study

From 2009 to 2010 we treated a total of 8,243 subjects, including 867 malaria cases and 7,376 contacts (1:8.5 cases/contact ratio). During the pilot study, we estimate a mean API reduction across intervention units of 86% (95%CI: 72−100) at 12-months and 98% (93−100) at 24-mo, respectively. Moreover, across non-intervention reporting units, we estimated a mean API reduction of -231% (95%CI: -395−-66) at 12-months and -19% (-87−49) at 24-mo, respectively (Table 1). The reductions in the mean API were statistically significantly higher in the intervention group at both 12-months ($p$=0.02) and 24-months ($p$=0.04).

During the pilot study the variability of the climate and environmental conditions across the Tumbes region was low (coefficient of variation [CV]: <100%) for variables like pressure (CV=0.02), temperature (CV=0.07), humidity (CV=0.14), soil moisture (CV=0.38), and vegetation (CV=0.42), and high (CV >1.00) for precipitation (CV=2.94). Table 2 summarized the estimates for each of the climate and environmental variables of interest of our study at years 2009-

2010 but lagged 10 weeks to reflect better represent the malaria seasonality, including the wet months (November to April) and the dry months (May to October).

## Scale-up study

During scaling up, the APIs dropped to from 7.4 (95%CI: 3.6−11.2) cases per 1,000 inhabitants in the year 2010 to 1.5 (95%CI: 0.6−-2.4) in the year 2011, to 0.23 (95%CI: 0.04−0.42) in the year 2012, and to zero autochthonous cases in years 2013/2016 (Figure 7). In 2014, Tumbes reported one malaria case imported from Iquitos; in 2015, three malaria imported cases, one from Ecuador, one from Iquitos, and one from Amazonas; and 2016, two malaria imported cases, one from Amazonas and one from Iquitos.

## Adverse events

During both study phases participants did not report any antimalarial adverse events, and despite our specific protocol, the Tumbes hospital did not state any case of antimalarial adverse events neither. Also, during both study phases, Tumbes did not report any fatal malaria case.

## Bivariate analysis

The results of the correlation analysis between our variables of interest are summarized in Table 3. Based on the estimates of the Pearson's correlation coefficients we concluded that temperature was highly correlated ($r$>0.5000) with pressure ($r$=-0.6328; $p$<0.0001); that soil moisture was highly correlated with humidity ($r$=0.8087; $p$<0.0001); that precipitation was

moderately correlated with humidity ($r$=0.4233; $p$<0.0001) and soil moisture ($r$=0.4547; $p$<0.0001); and that vegetation (NDVI) was moderately correlated with humidity ($r$=0.3575; $p$<0.0001) and soil moisture ($r$=0.3291; $p$<0.0001).

**Mixed-effects Poisson Regression Analysis for the Weekly Parasite Incidence during the pilot period**

The results from the mixed-effects Poisson regression analysis of the weekly parasite incidences of *P. vivax* cases across the 37 surveillance units from the Tumbes region are summarized in the Tables 4 and 5. First, a basic two-level model was fixed to account for the distribution of the data and the effect of our intervention of interest (RCD/FMDA). Second, a series of models were fixed to adjust for potential environmental and climate confounders. To do so, the predictors were selected using the forward method and the AIC to decide which variables entered the model first. Table 4 summarizes the rationale behind the variable selection, while table 5 summarizes the final model, which includes the following covariables as predictors of the malaria vivax counts: RCD/FMDA, season's trend, soil moisture, pressure, and vegetation. Based on this model we can conclude that the RCD/FMDA significantly contributed to decreasing the weekly parasite incidence, with a risk reduction of ~41% (Beta=-0.53; CI 95%: -0.9172, -0.1478; IRR=0.5866).

## *3.5 Discussion*

We reported the first successful malaria elimination initiative based on RCD with FMDA in a region with a high predominance of vivax malaria worldwide. By using such strategy, we were

able to reverse malaria incidences among the intervention districts when malaria actually was increasing across the Tumbes region. Such a particular scenario powered the pilot study to detect differences, despite the small sample size of reporting units (9 vs. 23) included in the study. Additionally, we found high acceptability within the population at risk been able to treat 8 to 9 contacts per each index case detected passively, which included in nearly every case 1 to 3 social contacts, predominantly co-workers and classmates of the index case. And last but not least through this experience we learned that regardless of the report of a small *P. falciparum* outbreak during the second year of the pilot study malaria could be achieved without significant adverse events.

In our study, we found that ~90% of the total impact attributable to the RCD/FMDA at 24-months of the pilot study occurred during the first year. This finding was of high interest because it was surprisingly high as compared with our initial expectation of reducing it by 50% after the first year. One explanation that may help to understand such high impact is that Tumbes is a small and very well-connected region with good roads such as the Pan-American Highway connecting the intervention districts. So is plausible that the impact of the RCD/FMDA strategy in one the nearby intervention and non-intervention district has had a synergic or indirect or effect over the other respectively. Another plausible explanation is that given that both intervention districts were the two most malaria endemic in the region that allowed to distribute more doses of primaquine, a moderate transmission blocking antimalarial, covering a significant fraction of the human malaria reservoir (including both symptomatic and asymptomatic malaria cases) and hence interrupting transmission more effectively.

Another essential reflection about the findings of our study is that by using RCD, we were able to target more asymptomatic carriers that were initially estimated because we expanded the

scope of traditional RCD methods and also included the social contacts (mostly co-workers and classmates of the index case) that voluntary agree to complete the malaria treatment. Based on previous reports it was estimated that through RCD, we could identify ~4-5 additional secondary infected subjects among the people living near the index case and people who share the same occupational risk factor. Common occupational risk in the area includes driving taxis (including cars and three wheeled motorcycle taxis), micro commerce (bodegas, small markets stores, and street vendors), selling gas and farmers. Moreover, through FMDA, it was described that we could effectively clear a significant fraction of the human malaria reservoir that lives near the index case (24). However, both assumptions seem to vary with a wide range depending on a variety of factors. In example, RCD although it was a case detection method tested in several countries, including Sri Lanka (12), Swaziland (13), Zambia (14, 15), Senegal (11), Bhutan (17), Mauritius (16), Peru (18), and Brazil (19, 20), is a method that has been implemented using similar but different operational definitions and diagnostic methods, and as a consequence showing different results (Table 2). Furthermore, according to a 2013 malaria control program managers survey, reactive case detection has also been implemented in countries like China, Cambodia, Democratic People's Republic of Korea, Indonesia, Malaysia, Nepal, Philippines, Republic of Korea, Solomon Islands, Thailand, Vanuatu, and Vietnam (21). Sadly, very little is known about the impact of these experiences yet. Experiences from Sri Lanka (12) and Swaziland (13), where reactive case detection was implemented using a 1 km radius from an index case household as the criteria to define the population at risk, although initially reported as successful experiences in time they prove to be very hard sustain given its relatively high cost (10). As an alternative Searle et al. assessed reactive case detection in southern Zambia using a 500 m radius reporting similar results to those achieved with a 1 km radius and identifying 77% of all households with an RDT positive

resident and 76% of all RDT positive individuals (36). In the Peruvian Amazon, Branch et al reported that given primarily to the high clustering of malaria carriers screening subjects within 100 m radius around the household of the malaria cases passively detected, using molecular diagnostic methods, allowed to detect 4.3 and 1.8 times more cases of *P. falciparum* and *P. vivax*, respectively, than passive case detection alone (18). Now, according to Stressman et al., in Zambia by screening subjects for subpatent malaria within the household of a malaria case passively detected, they detected a malaria prevalence that was 11 times higher as compared to randomly selected control households (8% vs. 0.7%, respectively) (15). Littrell et al. assessed similar strategy in northern Senegal, who reported that even using RDTs and focusing only within the members of a malaria case household they found a 3.2 fold increase in the incidence of malaria as compared to the neighbor households (11) Although each of these experiences used cases detected through passive case detection (the "index case") to trigger additional case detection activities, there were several fundamental differences in terms of screening inclusion criteria for malaria blood testing (fever, recent history of fever, or none), the criteria used to define the population at risk (1 km, 500 m, 100 m around the malaria cases household, limited to the people living within the household of the index case, or by targeting a specific number of proximate people or households around the household index case) (37).

Regarding the FMDA of our strategy it is important to mention that local officers were not concerned with G6PD deficiency related adverse events because through the years thousands of primaquine were delivery in the region without major adverse events so it was considered safe in Tumbes, which might not be the case in other malaria-endemic regions with *P. vivax* predominance. Another important aspect to be considered when implementing FMDA initiatives is how to properly operationalize who among the population at risk should it be considered as at

the high-risk (Table 3). In our experience, we do it by using RCD methods under the assumption that inhabitants of the household of any malaria case that is passively detected (often with parasite densities detectable with microscopy or RDTs) significantly represent the subpopulation at the high-risk. However, in Tumbes, such strategy might work so effectively mainly because of Tumbes it a low endemic region a high-risk population adequately identified as near each index case. Such condition might vary significantly in most rural settings and not necessarily is the case of the Amazon basin in an example. As a consequence, we considered as very important to pilot every proposed malaria elimination strategy before scaling up and if possible, perform formative research to adapt the strategy and maximize its likelihood to succeed properly.

Similar strategies to the one we tested in Tumbes have been reported in vivax endemic regions from China and Greece with relative success. In the Kiangsu province in China, after failing to achieve coverage rates of over 50% with large-scale MDA, several different RCD/FMDA strategies were implemented in various vivax-predominant malaria settings (22). During years 2000-2006 an RCD/FMDA strategy was applied at the villages with malaria incidences <1% by treating the families of every malaria case detected within the previous two years at the Sihong and Xuyi counties. In 2007, this strategy was expanded to address also the immediate neighbors surrounding the index case households, but in 2008 the index case was redefined as every malaria case detected in the previous year instead of in the last two years. Finally, in the year 2009, when malaria cases were rare, the RCD/FMDA strategy was limited to the villages with over 2-3 cases reported yearly. Overall, treatment (chloroquine 400 mg × 3d + primaquine 22.5 mg × 8d) compliance at the intervention villages ranged from 60% to 99% and the median number of individuals who completed FMDA by each index case was 16 (range 5 to 39) in Sihong and 10 (range 4 to 2) in Xury. Although the peak incidences were low at baseline,

0.79 and 0.29 per 1,000 inhabitants in Sihong and Xuyi, respectively, annual percent changes in Sihong ranged from -36% to -17% in Sihong and from -2% to -67% in Xuyi. Similar results were reported in the municipality of Evrotas, in Greece, where most malaria cases were imported (~62% in the year 2012) and due to *P. vivax* (24). In the year 2013, an RCD/FMDA strategy was implemented defining as the population at high-risk every family of migrants from malaria-endemic countries that resided in Evrotas. From 972 eligible subjects, 93.1% migrants initiated the treatment course, while 1.8% did not initiate it due primaquine contraindications (such as positivity for severe G6PD deficiency), 4.8% abandoned the study before starting the treatment, and 0.3% (3 cases) refused the treatment. Among those that started the treatment, 95.2% completed the treatment, 4.6% cases were lost to follow up, and 0.2% (2 cases) stopped the treatment due to severe side effects (one due to rash and one due to hemolytic anemia) but recover eventually. Although malaria baseline incidence was low (1.5 malaria cases per 1,000 inhabitants) after the intervention malaria cases drop down to zero with only one imported case reported in early 2015. Both experiences are technically and financially different from our strategy but certainly add to the body of knowledge that supports its value as a tool to implement malaria elimination initiatives in settings with *P. vivax* malaria predominance. Other experiences with FMDA such as the ones collected in Tanzania (25), Zambia (26), and Kenya (27), although of high value as antecedents cannot be used to contrast our results due they were deployed in settings with *P. falciparum* malaria predominance. Regardless it is important to highlight that these studies suggest that the RCD/FMDA strategy might not be the most effective strategy for falciparum malaria as it might be for vivax malaria.

In summary, RCD/FMDA represent an effective strategy to support malaria elimination initiatives in regions with low endemicity, a high predominance of vivax malaria, and long-term

history of using primaquine without severe adverse events due to G6PD deficiency. Further studies will be required to scale-up the RCD/FMDA program to areas with a long-term history of using primaquine, without severe adverse events due to G6PD deficiency, and significant endemicity of *P. falciparum*, and moderate to high endemicity. In the specific case of Peru, we recommend adopting the RCD/FMDA strategy, within the national malaria control guideline, to sustain malaria elimination by containing imported cases along the north coast.

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## *3.7 Tables for Chapter 4*

**Table 4. Annual parasite incidence by year and districts**

| District | Population * | Annual Parasite Incidence ** (95% CI) | | | | |
|---|---|---|---|---|---|---|
| | | 2008 | 2009 | 2010 | 2011 | 2012 |
| **Intervention** | 36,231 | 32.1 (-0.8 - 65.0) | 13.4 (2.5 - 24.4) | 4.2 (0.6 - 7.9) | 0.8 (-0.9 - 2.6) | 0.3 (-0.4 - 0.9) |
| Aguas Verdes | 17,636 | 44.9 (-5.6 - 95.5) | 18.9 (3.5 - 34.4) | 1.9 (-0.8 - 4.6) | 0.1 (0.0 - 0.2) | 0.0 (0.0 - 0.1) |
| Zarumilla | 18,595 | 26.7 (NA) | 17.7 (NA) | 1.4 (NA) | 0.2 (NA) | 0.2 (NA) |
| **Non-intervention** | 163,984 | 8.2 (3.6 - 12.8) | 2.3 (0.7 - 3.9) | 8.7 (3.5 - 13.8) | 1.8 (0.6 - 2.9) | 0.2 (0.1 - 0.3) |
| Tumbes | 101,734 | 4.5 (-0.2 - 9.2) | 2.8 (0.7 - 5.0) | 6.1 (0.4 - 11.7) | 2.5 (-0.4 - 5.3) | 0.4 (0.0 - 0.8) |
| Corrales | 22,053 | 9.3 (-5.1 - 23.8) | 3.4 (-2.6 - 9.4) | 12.6 (-4.9 - 30.0) | 2.1 (-1.4 - 5.7) | 0.5 (-0.6 - 1.6) |
| Papayal | 5,047 | 18.8 (0.1 - 37.6) | 2.3 (1.2 - 3.4) | 18.0 (-7.8 - 43.9) | 0.0 (0.0 - 0.0) | 0.1 (-0.2 - 0.4) |
| Zorritos | 9,334 | 0.2 (-0.6 - 1.0) | 0.1 (-1.0 - 1.1) | 0.0 (0.0 - 0.0) | 0.2 (-1.8 - 2.1) | 0.0 (0.0 - 0.0) |
| La Cruz | 8,807 | 0.7 (NA) | 0.7 (NA) | 1.3 (NA) | 0.9 (NA) | 0.0 (NA) |
| Pampas de Hospital | 4,751 | 1.7 (-0.1 - 3.4) | 0.8 (-2.7 - 4.2) | 13.9 (-127 - 155) | 8.0 (-24.5 - 40.6) | 0.0 (0.0 - 0.0) |
| San Juan de la Virgen | 3,976 | 6.5 (-12.5 - 25.4) | 2.4 (-1.0 - 5.9) | 8.9 (-3.3 - 21.1) | 2.4 (-6.9 - 11.8) | 0.9 (-2.9 - 4.7) |
| San Jacinto | 8,282 | 3.4 (-3.6 - 10.3) | 0.1 (-0.2 - 0.5) | 3.4 (-0.9 - 7.6) | 1.3 (-0.9 - 3.6) | 0.2 (-0.2 - 0.6) |

***** Population estimated at baseline (year 2008); ** Annual Parasite Incidence = Total malaria cases/ 1,000 inhabitants; 95% CI = 95% Confidence Interval; NA = Not applicable.

**Table 5.** Weekly Means ± SD (95% CI) of the Environmental and Climate Parameters during the Pilot Study by Districts*

| Districts | Pressure (kPa) | Humidity (kg vapor * $kg^{-1}$ air * $10^3$) | Temperature (°C) | Moisture ($m^3*m^{-3}$) | Precipitation (mm $*m^{-2}$) | Vegetation (NDVI) |
|---|---|---|---|---|---|---|
| **All** | 99.6 ± 1.8<br>(99.5 - 99.6) | 13.6 ± 1.9<br>(13.5 - 13.6) | 25.9 ± 1.8<br>(25.8 - 25.9) | 0.125 ± 0.047<br>(0.123 - 0.126) | 10.1 ± 29.6<br>(9.1 - 11.1) | 0.4 ± 0.2<br>(0.4 - 0.4) |
| **Intervention** | 99.5 ± 1.8<br>(99.3 - 99.6) | 13.5 ± 1.9<br>(13.4 - 13.6) | 25.9 ± 1.8<br>(25.8 - 26.1) | 0.125 ± 0.001<br>(0.122 - 0.128) | 9.9 ± 30.0<br>(7.8 - 12.0) | 0.4 ± 0.2<br>(0.4 - 0.4) |
| Aguas Verdes | 99.4 ± 2.0<br>(99.3 - 99.6) | 13.6 ± 1.9<br>(13.4 - 13.8) | 25.9 ± 1.9<br>(25.7 - 26.0) | 0.124 ± 0.047<br>(0.120 - 0.127) | 9.9 ± 30.0<br>(7.3 - 12.5) | 0.4 ± 0.2<br>(0.4 - 0.4) |
| Zarumilla | 100.9 ± 0.1<br>(100.9 - 100.9) | 13.9 ± 1.6<br>(13.7 - 14.1) | 24.9 ± 1.5<br>(24.7 - 25.1) | 0.122 ± 0.039<br>(0.122 - 0.133) | 11.0 ± 33.4<br>(6.4 - 15.6) | 0.5 ± 0.1<br>(0.5 - 0.5) |
| **Non-intervention** | 99.6 ± 2.0<br>(99.5 - 99.6) | 13.5 ± 1.8<br>(13.5 - 13.6) | 25.6 ± 1.8<br>(25.8 - 25.9) | 0.125 ± 0.045<br>(0.123 - 0.127) | 10.1 ± 30.6<br>(9.0 - 11.2) | 0.4 ± 0.2<br>(0.4 - 0.5) |
| Tumbes | 99.7 ± 2.0<br>(99.6 - 99.8) | 13.7 ± 1.8<br>(13.6 - 13.8) | 25.6 ± 1.8<br>(25.5 - 25.7) | 0.125 ± 0.045<br>(0.122 - 0.128) | 10.5 ± 30.6<br>(8.6 - 12.3) | 0.5 ± 0.2<br>(0.5 - 0.5) |
| Corrales | 98.9 ± 1.9<br>(98.8 - 99.1) | 13.3 ± 2.0<br>(13.2 - 13.5) | 26.4 ± 1.8<br>(26.2 - 26.5) | 0.123 ± 0.051<br>(0.119 - 0.128) | 10.2 ± 28.9<br>(7.7 - 12.7) | 0.4 ± 0.2<br>(0.4 - 0.5) |
| Papayal | 97.8 ± 1.1<br>(97.7 - 97.9) | 12.9 ± 2.1<br>(12.7 - 13.1) | 27.4 ± 1.2<br>(27.3 - 27.5) | 0.121 ± 0.059<br>(0.115 - 0.126) | 7.9 ± 21.9<br>(5.8 - 10.1) | 0.3 ± 0.2<br>(0.3 - 0.4) |
| Zorritos | 100.9 ± 0.1<br>(100.9 - 100.9) | 13.9 ± 1.6<br>(13.6 - 14.2) | 24.9 ± 1.5<br>(24.6 - 25.1) | 0.128 ± 0.039<br>(0.120 - 0.136) | 8.9 ± 28.5<br>(3.3 - 14.4) | 0.5 ± 0.2<br>(0.4 - 0.5) |
| Pampas de Hospital | 100.9 ± 0.1<br>(100.9 - 100.9) | 13.9 ± 1.6<br>(13.7 - 14.1) | 24.9 ± 1.5<br>(24.7 - 25.1) | 0.128 ± 0.039<br>(0.122 - 0.133) | 11.0 ± 33.4<br>(6.4 - 15.6) | 0.5 ± 0.2<br>(0.4 - 0.5) |
| San Juan de la Virgen | 99.7 ± 1.3<br>(99.5 - 99.8) | 13.3 ± 1.9<br>(13.0 - 13.5) | 26.1 ± 1.8<br>(25.9 - 26.4) | 0.125 ± 0.051<br>(0.118 - 0.132) | 10.1 ± 27.0<br>(6.4 - 13.7) | 0.6 ± 0.1<br>(0.5 - 0.6) |
| San Jacinto | 100.9 ± 0.1<br>(100.9 - 100.9) | 13.9 ± 1.6<br>(13.6 - 14.2) | 24.9 ± 1.5<br>(24.6 - 25.1) | 0.128 ± 0.039<br>(0.120 - 0.136) | 11.0 ± 33.5<br>(4.5 - 17.5) | 0.5 ± 0.2<br>(0.4 - 0.5) |
| Canoas de Punta Sal | 100.9 ± 0.1<br>(100.9 - 100.9) | 13.9 ± 1.6<br>(13.6 - 14.2) | 24.9 ± 1.5<br>(24.6 - 25.1) | 0.128 ± 0.039<br>(0.120 - 0.135) | 11.0 ± 33.5<br>(4.5 - 17.5) | 0.5 ± 0.2<br>(0.5 - 0.6) |

***** Weekly estimates averaged at year 2009-2010; SD, Standard deviation; 95% CI = 95% Confidence Interval; Pressure (kPa), kilopascals of pressure estimated per $km^2$ averaged per week; Humidity (kg vapor * $kg^{-1}$ air * $10^3$), $10^3$ kg of water vapor per kg of air measured

daily at 2 m above the displacement height; Temperature (°C), degree Celsius of temperature at 2 m above the displacement height; Soil moisture ($m^3*m^{-3}$), cubic meters of water per square meter of soil; Precipitation (mm * $m^{-2}$), mm of rain per square meter per hour; Vegetation (NDVI), normalized difference vegetation index.

**Table 6.** Correlation Matrix of variables used in the multivariate analysis for the *P. vivax*-weekly parasite counts model

| | | WPI* | RCD/FMDA | Pressure | Humidity | Temp. | Moisture | Precip. |
|---|---|---|---|---|---|---|---|---|
| **RCD/FMDA** | Pearson (*r*) | 0.0062* | | 1.0000 | | | | |
| | *p* value | 0.7154 | | | | | | |
| **Pressure** | Pearson (*r*) | 0.1094* | 0.1310* | 1.0000 | | | | |
| | *p* value | <0.0001 | <0.0001 | | | | | |
| **Humidity** | Pearson (*r*) | 0.0885* | 0.0480* | 0.1260* | 1.0000 | | | |
| | *p* value | <0.0001 | 0.0049 | <0.0001 | | | | |
| **Temperature** | Pearson (*r*) | -0.0464* | -0.1117* | -0.6328* | 0.0424* | 1.0000 | | |
| | *p* value | 0.0065 | <0.0001 | 0.0000 | 0.0131 | | | |
| **Moisture** | Pearson (*r*) | 0.1007* | 0.0119 | 0.0757* | 0.8087* | 0.0582* | 1.0000 | |
| | *p* value | <0.0001 | 0.4849 | <0.0001 | <0.0001 | 0.0006 | | |
| **Precipitation** | Pearson (*r*) | 0.0289 | -0.0006 | -0.0174 | 0.4233* | 0.0728* | 0.4547* | 1.0000 |
| | *p* value | 0.0909 | 0.9717 | 0.3085 | <0.0001 | <0.0001 | <0.0001 | |
| **Vegetation** | Pearson (*r*) | 0.0601* | -0.0709* | -0.1173* | 0.3575* | 0.1113* | 0.3291* | 0.1462* |
| | *p* value | 0.0004 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

* Weekly Parasite Incidence (WPI)= Total malaria cases per week/ 1,000 inhabitants; RCD/FMDA = Reactive case Detection with Focal Mass Drug Administration

**Table 7.** Forward selection of variables for the Mixed-Effects Poisson Regression Model

| Models | AIC |
|---|---|
| **I. Setting the basic model** | |
| Empty Model | 2980.1 |
| Empty Model + RCD/FMDA | 2949.3 |
| Empty Model + RCD/FMDA + Week | 2951.1 |
| Empty Model + RCD/FMDA + Season's year | 2949.5 |
| **Empty Model + RCD/FMDA + Season' trend** | **2927.1** |
| Empty Model + RCD/FMDA + Season' trend + Year | 2927.3 |
| Empty Model + RCD/FMDA + Season' trend + Week | 2925.7 |
| **II. Modeling the effect of RCD/FMDA** | |
| Basic model | 2925.7 |
| Basic model + Precipitation | 2927.3 |
| Basic model + Vegetation | 2912.9 |
| Basic model + Temperature | 2901.7 |
| Basic model + Pressure | 2788.6 |
| Basic model + Humidity | 2879.4 |
| **Basic model + Moisture** | **2879.3** |
| Basic model + Moisture + Vegetation | 2879.6 |
| Basic model + Moisture + Precipitation | 2879.8 |
| Basic model + Moisture + Humidity | 2879.4 |
| Basic model + Moisture + Temperature | 2838.6 |
| **Basic model + Moisture + Pressure** | **2755.6** |
| Basic model + Moisture + Pressure + Precipitation | 2757.0 |
| Basic model + Moisture + Pressure + Temperature | 2756.0 |
| Basic model + Moisture + Pressure + Humidity | 2755.6 |
| **Basic model + Moisture + Pressure + Vegetation *** | **2741.6** |
| Basic model + Moisture + Pressure + Vegetation + Precipitation | 2743.0 |
| Basic model + Moisture + Pressure + Vegetation + Humidity | 2741.6 |
| Basic model + Moisture + Pressure + Vegetation + Temperature | 2741.2 |

* Final model; AIC = Akaike's information criterion; RCD/FMDA = Reactive case Detection with Focal Mass Drug Administration

**Table 8.** Mixed-Effects Poisson Regression Model for the *P. vivax* weekly Parasite Incidence

| | **Estimate** | **95% CI** | **IRR-Fixed Effects** | **95% CI** |
|---|---|---|---|---|
| Constant | -49.7878 | -58.786, -40.790 | 2.38E-21 | 2.95E-26, 1.93E-18 |
| RCD/FMDA | -0.5325 | -0.9172, -0.1478 | 0.5871 | 0.3996, 0.8626 |
| Season's trend [a] | -0.3587 | -0.5663, -0.1512 | 0.6986 | 0.5676, 0.8597 |
| Soil moisture [b] | 0.1237 | 0.0603, 0.1871 | 1.1317 | 1.0622, 1.2057 |
| Pressure [c] | 0.4602 | 0.3707, 0.5497 | 1.5843 | 1.4487, 1.7327 |
| Vegetation [d] | 1.1582 | 0.5880, 1.7284 | 3.1842 | 1.8004, 5.6316 |
| RE (Network) | 0.4886 | 0.1111, 2.1489 | | |

* IRR = Incidence-Rate Ratio; AIC = Akaike's information criterion; 95% IC = 95% Interval of Confidence; RE = Random effects; RCD/FMDA = Reactive case Detection with Focal Mass Drug Administration (positive/negative); a, Season´s trend with a value of zero for wet season and a value of one for the dry season; cubic meters of water per square meter of soil (units of soil moisture); c, kilopascals (units of surface pressure); d, NDVI or normalized difference vegetation index (units of vegetation)

**Table 9.** Activities carried on during reactive case detection activities in different contexts

| Activities | MAU (1) | BRA (2) | SRI (3) | PER (4) | SWA (5) | ZAM (6) | BHU (7) | SEN (8) | BRA (9) | ZAM (10) |
|---|---|---|---|---|---|---|---|---|---|---|
| Included within national guidelines | | | ✓ | | ✓ | | ✓ | | | |
| Year of implementation | 1998 | 1998 | 2003 | 2003 | 2009 | 2009 | 2010 | 2012 | 2013 | 2014 |
| Named RCD | ✓ | | | | ✓ | | | ✓ | ✓ | ✓ |
| Trigger by index cases (PCD) | ✓ | | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ |
| Screening around index case | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ |
| Test for asymptomatic malaria | | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ |
| Use microscopy | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | | ✓ | |
| Use RDTs | | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Use PCR | | | | | | ✓ | | | ✓ | |
| Includes follow up | | ✓ | | ✓ | | | ✓ | | | |
| Use GPS | | | | | ✓ | ✓ | | | ✓ | ✓ |
| Focus on *P. vivax* malaria also | | ✓ | ✓ | ✓ | | | ✓ | | ✓ | |

* MAU, Mauritius; BRA, Brazil; SRI, Sri Lanka; PER, Peru; SWA, Swaziland; ZAM, Zambia; BHU, Bhutan; SEN, Senegal; PCR, polymerase chain reaction; RDT, Rapid diagnostic tests; GPS, Global Positioning System.

**Table 10.** Activities carried on during target or focal mass drug administration in different contexts

| Activities | CHI (11) | GRE (12) | TAN (13) | PER | ZAM (14) | KEN (15) |
|---|---|---|---|---|---|---|
| Included within national guidelines | ✓ | ✓ | | | | |
| Year of implementation | **2000-9** | **2013** | **(Simulation)** | **2009** | **2013-4** | **2011-12** |
| Named explicitly as targeted or FMDA | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Focused on *P. vivax* malaria only | ✓ | ✓ | | ✓ | | |
| Trigger by incident cases | | ✓ | ✓ | ✓ | ✓ | ✓ |
| Trigger by prevalent cases (PCD) | ✓ | | | | | |
| Excluded infants, pregnant women, & chronically ill subjects | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Included DOT with primaquine | ✓ | ✓ | ✓ | ✓ | | ✓ |
| Included G6PD testing | ✓ | ✓ | ✓ | ✓ | | ✓ |
| Included adverse events surveillance | ✓ | ✓ | ✓ | ✓ | | |

* CHI, China; GRE, Greece; TAN, Tanzania; PER, Peru; FMDA, focal mass drug administration; MDA, mass drug administration; PCD, Passive case detection; DOT, Direct observation treatment; G6PD; glucose-6-phosphate dehydrogenase.


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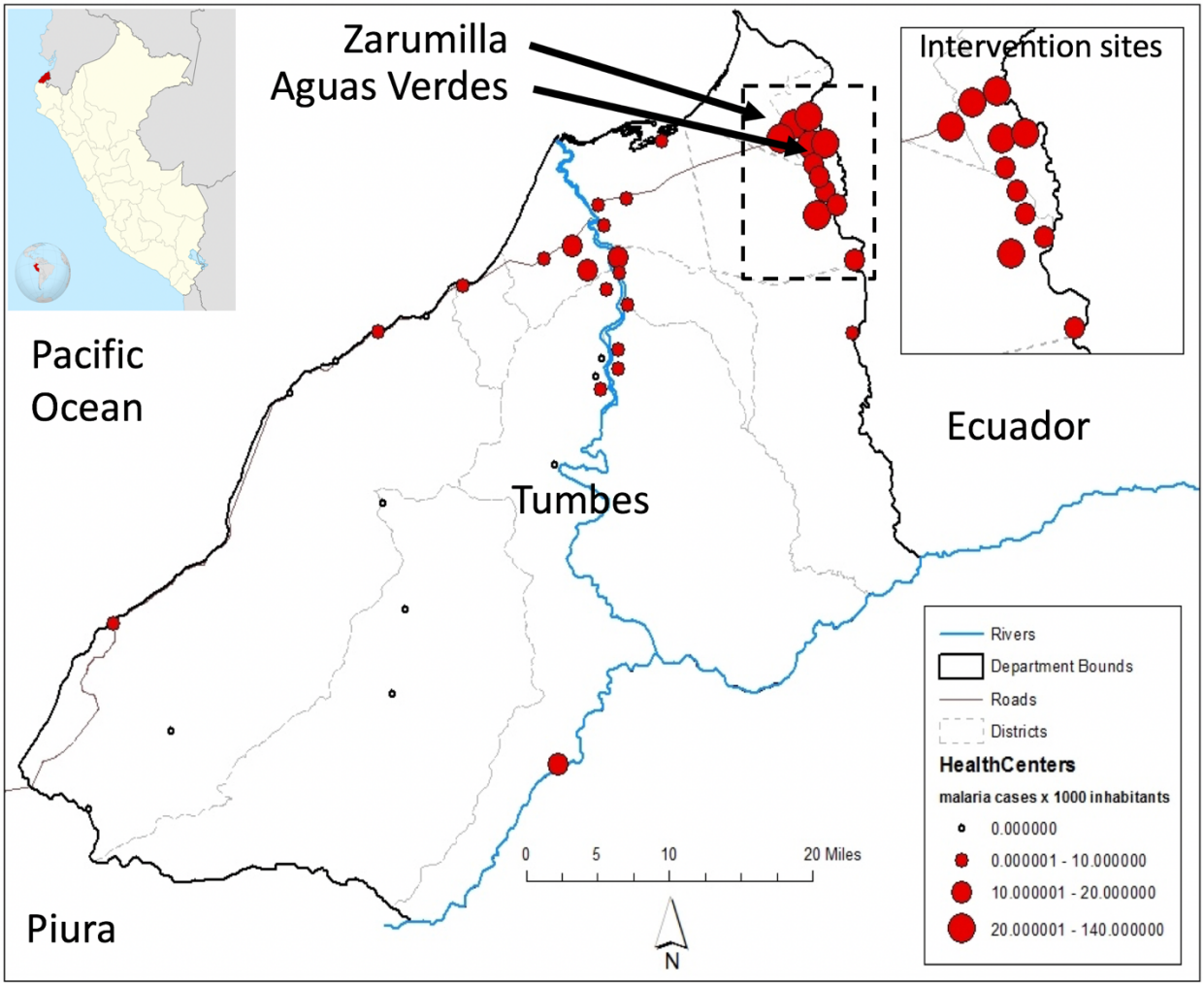
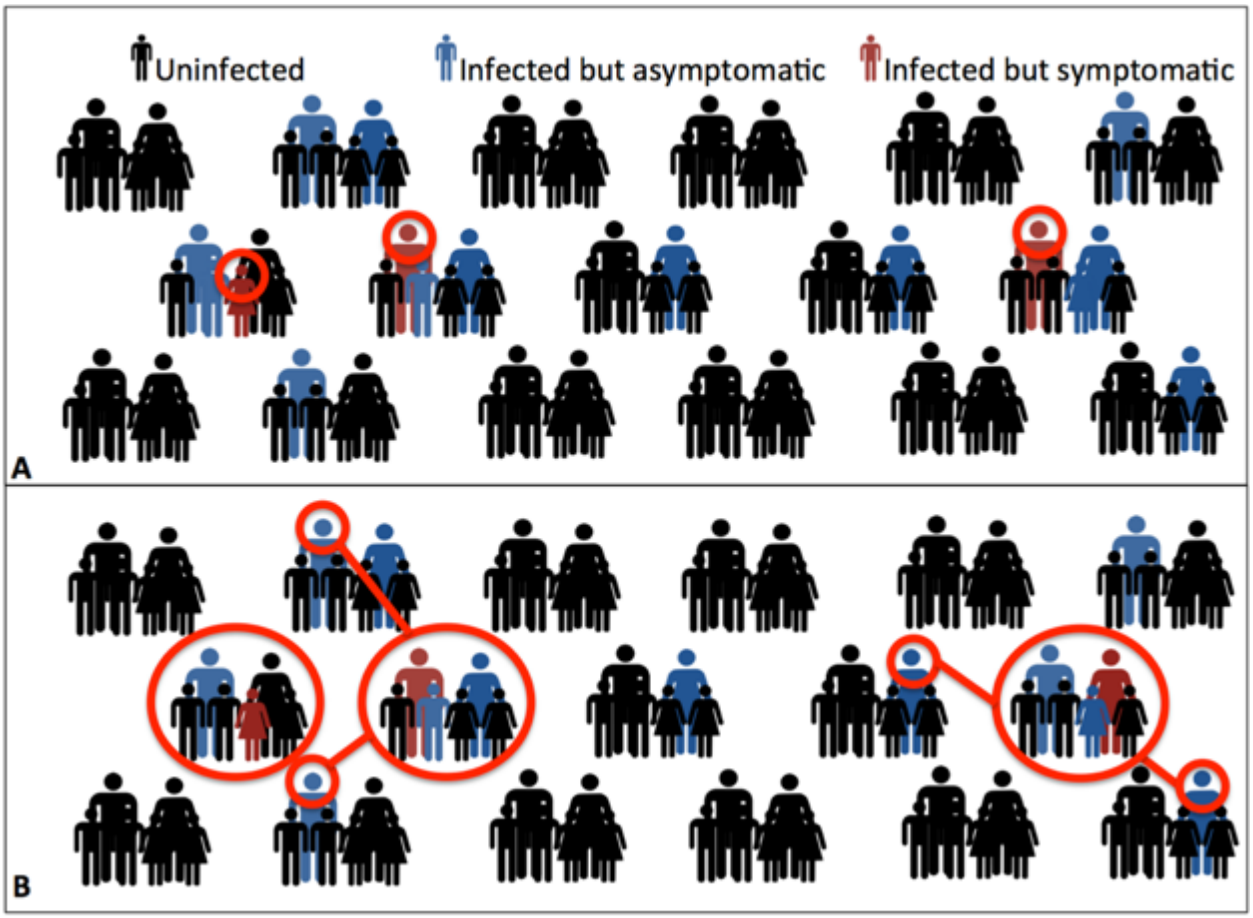
## *3.8 Figures for Chapter 4*

**Figure 6.** Tumbes malaria surveillance reporting units in northwestern Peru



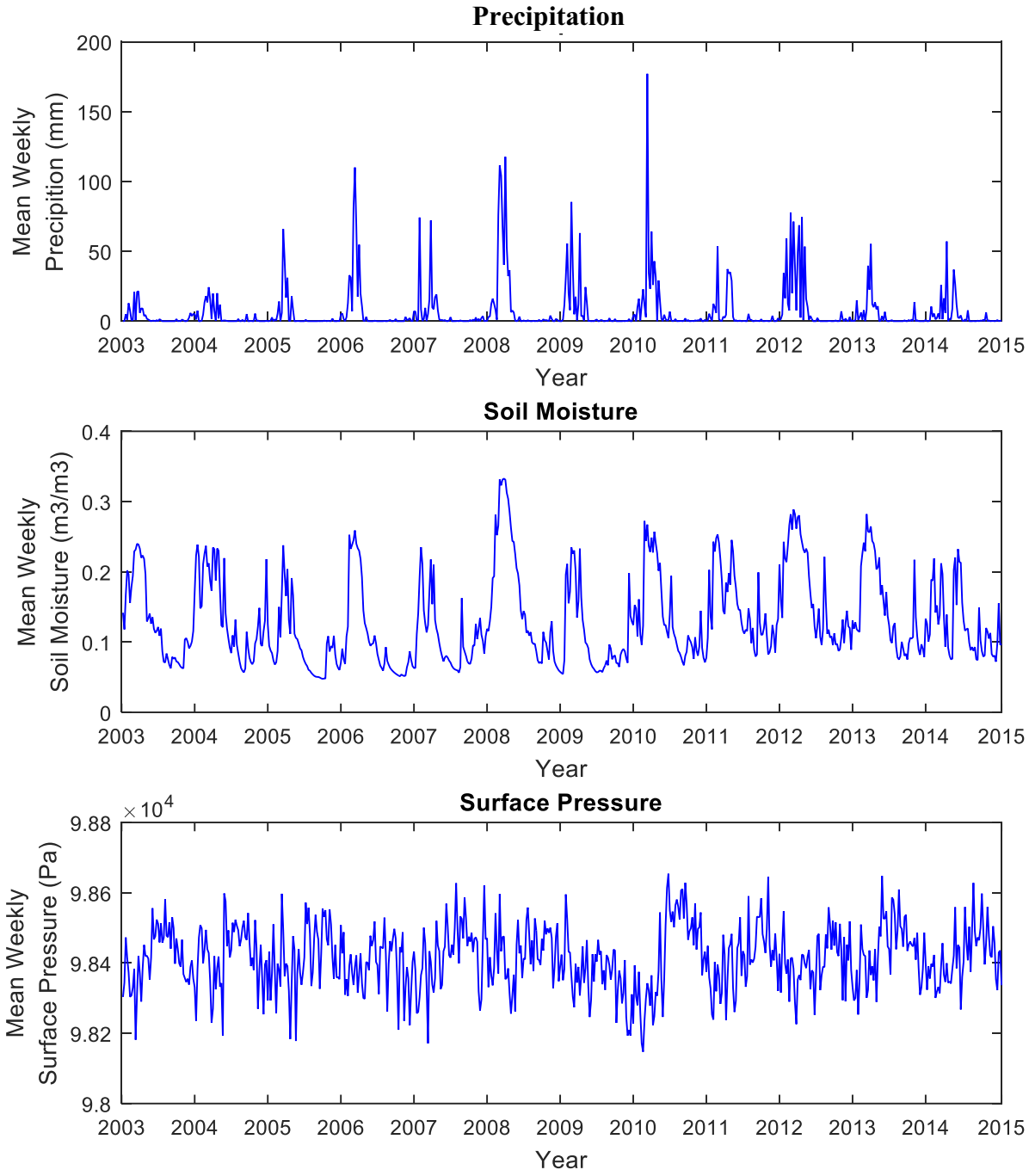

* Red circles mark the location of each surveillance unit across the Tumbes region with both intervened districts of Zarumilla and Aguas Verdes selected at the top right magnified square.

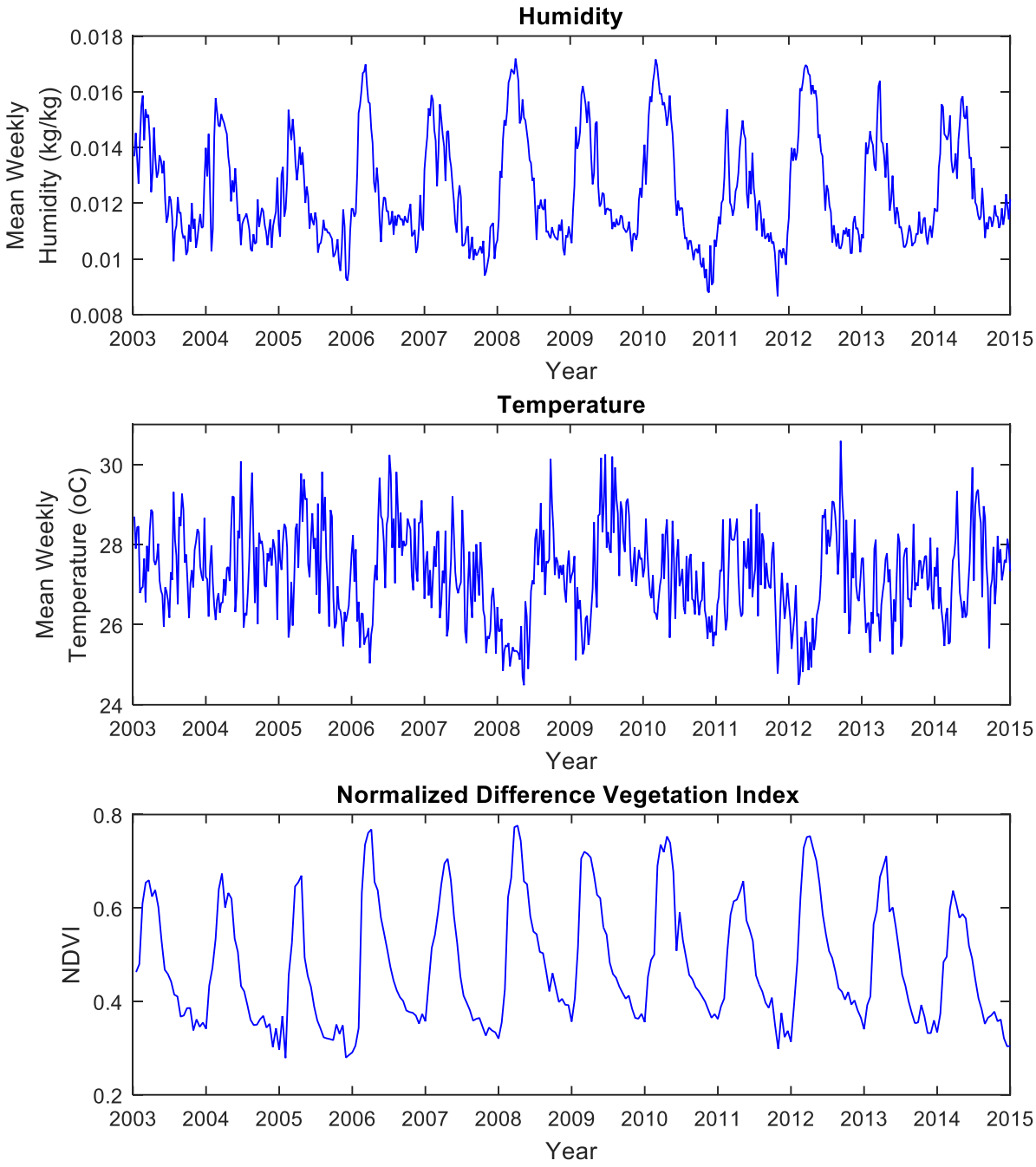
**Figure 7.** Passive case detection vs. Reactive case detection




**Legend:** A) Passive case detection, where only the infected but symptomatic cases have the chance to access antimalarial drugs when voluntary visit the near health facility and tested positive for malaria; B) Reactive case detection with target mass drug administration, where additional to the cases passively detected their households' cohabitants and their immediate coworkers/student peers also were treated for malaria in the absence of symptoms.

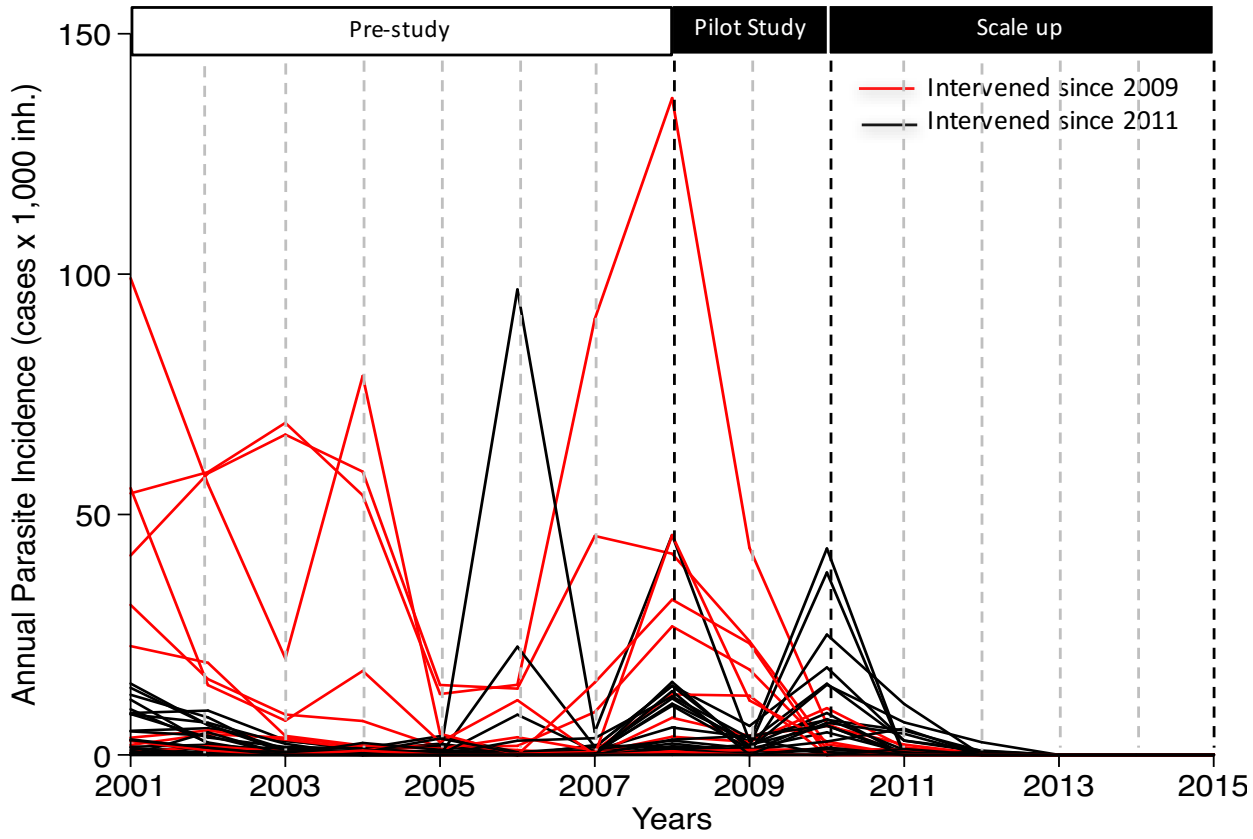
**Figure 8.** Weather parameters on a weekly level during the period 2003-2015 in Tumbes Peru.





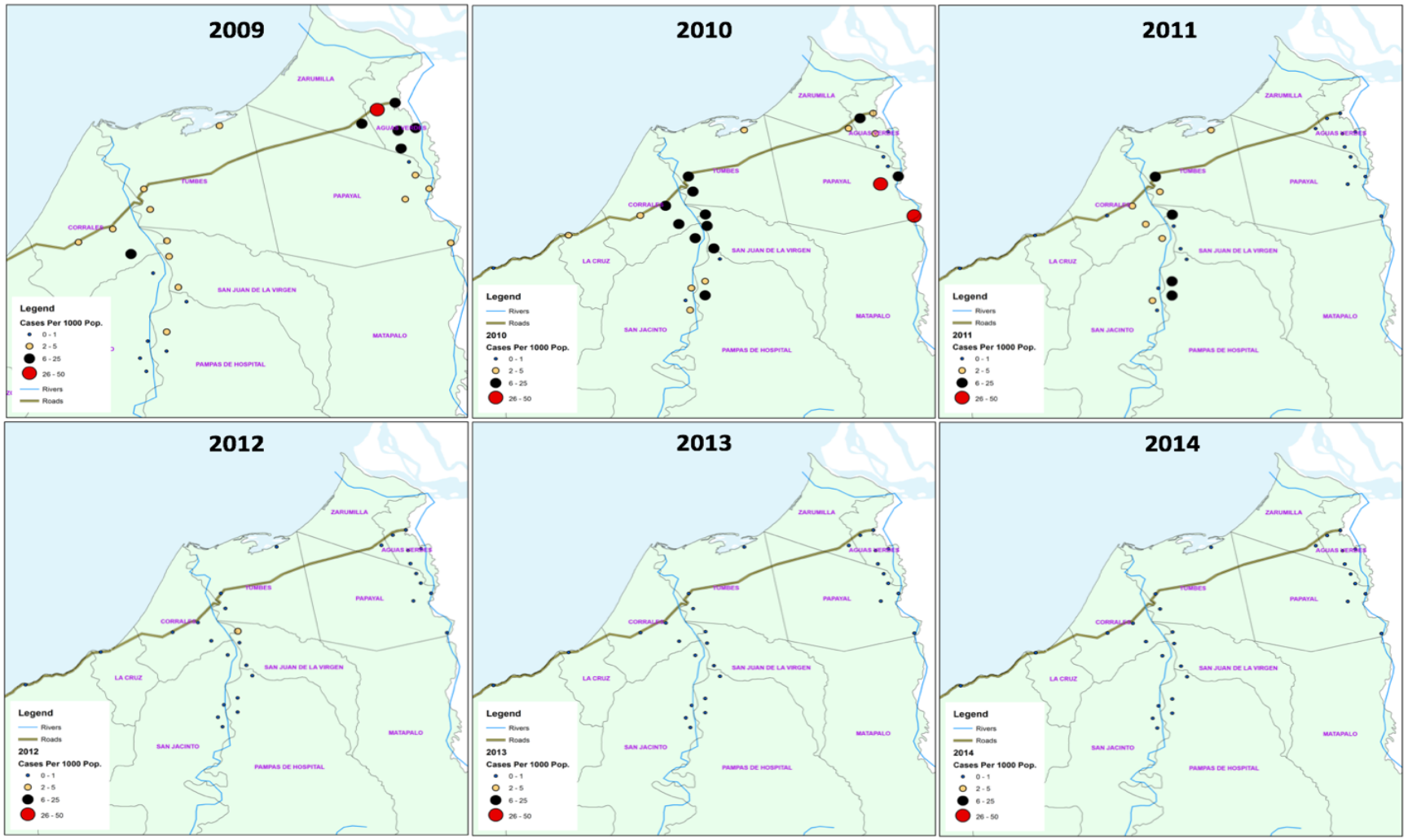

* The precipitation value in mm is referring to the amount of rain per square meter per hour averaged per week; the soil moisture value of $m^3/m^{-3}$ is referring to the mean quantity of cubic meters of water per square meter of soil averaged per week; the precipitation value in kPa is referring to the number of kilopascals of pressure estimated per $km^2$ averaged per week; the humidity value in kg/kg is referring to the number of kg of water vapor per kg of air measured daily at 2 m above the displacement height; the temperature value in degrees centigrade is referring to the temperature at 2 m above the displacement height averaged per week; and, NDVI is referring to the normalized difference vegetation index averaged per week.

**Figure 9.** APIs at each of the surveillance reporting units from Tumbes, 2001-2015




**Legend:** Annual parasite incidences (APIs) were calculated by dividing the total count of malaria cases, as reported by the national surveillance system, over the total population at each surveillance reporting units, as estimated by the Peruvian Ministry of Health

**Figure 10.** APIs across the surveillance reporting units from Tumbes during the study period (2009-2014)




**Legend:** During the pilot study (2009-2010), the mean APIs across the intervention surveillance reporting units reduced by 98% (93−100), while increased by 19% (-49−87) at the non-intervention surveillance reporting units. During scaling up, malaria cases dropped down to zero autochthonous cases since year 2013 up to date.

# Chapter 4. "Reactive case detection with targeted mass drug administration: Interrupting malaria transmission and achieving elimination beyond intervention areas in northwestern Peru"

## *4.1 Abstract*

Reactive case detection (RCD) with focal mass drug administration (FMDA) was previously reported as an effective strategy to support malaria elimination initiatives in Tumbes Peru, a region with a strong predominance of vivax malaria. We assessed the effect of RCD/FMDA beyond the intervention areas in Tumbes along the nearby region of Piura, assuming an "spillover effect" of the treatment beyond the focal area. Briefly, a pilot malaria elimination program based on RCD/FMDA was rolled out from 2009-2010 in the two districts with the highest annual parasite incidence of malaria in Tumbes. And then, due its apparent success, from 2011-2014, the intervention was scaled up to the other 11 Tumbes districts. In this study we focus on evaluating the effect of such intervention in the non-intervention communities in Piura during the 2011-2016 period. The primary study endpoint was a temporo-spatial reduction in weekly parasite incidence (WPI = total malaria cases per week/ 1,000 inhabitants) across all the surveillance units, analyzed by proximity to the intervention areas from Tumbes during the pilot project. During the pilot program we estimated a mean reduction in WPI across the Tumbes intervention areas of 99% (97−100) and 85% (77−94) at 12 and 24 months (m), respectively; and a reduction in the non-intervention areas of 34% (27−40) and 86% (76−93) at 12m and 24m, respectively. During the same period, we estimated a mean reduction in WPI at the near, mid and far range Piura districts

of 63%, -73%, and -420% at 12m, and 91%, -126% and 91% at 24m, respectively. After scale-up, we found a similar association between the mean WPI reduction and proximity to intervention area across the Piura districts, at both 24m ($p=0.04$) and 48m ($p<0.01$). The closer to Tumbes the greater the reduction in the WPI among the Piura districts. During years 2015 and 2016, neither Tumbes nor Piura reported any autochthonous malaria cases. Thus, the RCD/FMDA strategy may represent the main reason why malaria was eliminated from the region of Piura and, consequently, represents a valuable intervention to support malaria elimination initiatives in other settings with a high predominance of vivax malaria with a similar epidemiology.

## *4.2 Introduction*

The world has experienced major progress towards malaria eradication in the last 15 years. Malaria mortality has plunged by 48% between 2000 and 2015 with an estimate of over 6.2 million lives saved, most of them children under five years of age (1). Regardless, malaria continues to represent a major cause of global morbidity and mortality with more than 3 billion people at risk (1). More worrisome, such progress appeared to have stalled in the recent years, with 2016 being the first year since 2000 were there were reports of an increase in the global morbidity, with five million malaria cases in the previous year (2). This scenario has raised a significant concern about why many countries are beginning to shift their negative trends and reversing the gains achieved. While more countries are assuming the challenge of shifting their national policies from control towards elimination, new approaches are needed to supplement existing tools (3). One of these approaches that has gained popularity in recent years is embracing the heterogeneous nature of malaria transmission at the community level and implementing malaria control interventions targeting malaria 'hotspots', which may lead to a more sustainable reduction in malaria burden (4).

Hotspots are theoretically defined as those areas where estimates exceed those from other areas and may fuel transmission to surrounding areas (5). However, operationally hotspots have many different definitions with some commonalities like using the malaria burden as a proxy for transmission, and many differences like using various metrics to assess its size, location, and stability (6, 7). Regardless of the chosen definition, the detection of malaria hotspots has become increasingly relevant for planning national policies and pursuing local malaria elimination initiatives (8-12). However, the questions about how to target them remain controversial. Options range from mass diagnosis and treatment to mass drug administration strategies, from single to packages of combined interventions, and from one time visit to more regular ones, each with their own strengths and limitations (13). Among all these options, one that is gaining support due its proven impact on reducing malaria transmission in low endemic settings is the combination of reactive case detection (RCD) with focused mass drug administration (FMDA) (14). The RCD/FMDA strategy is commonly described as complementing the treating of every subject that tests positive for malaria with all his/her household members, irrespective of each person's result obtained by diagnostic testing (15).

Previous experiences with RCD/FMDA have documented that this strategy may help to overcome the limitation of currently available diagnostics to detect subpatent asymptomatic malaria infections, which are a large fraction of the human malaria reservoir and consequently is less expensive and more effective than the standard mass diagnose and treatment strategies (14). Due to its potential, a large trial is currently underway in Zambia, with promising short-term results in what is a low endemic malaria setting with a high predominance of *P. falciparum* malaria (15, 16). Furthermore, in the study 1 of this thesis we are reporting that the RCD/FMDA may also represent an effective strategy to pursue malaria elimination on low endemic malaria settings with

high predominance of *P. vivax*, if we use primaquine as the drug for interrupting malaria transmission and take advantage of the long-term history of using it without adverse events due glucose-6-phosphate dehydrogenase (G6PD) deficiency (17). Furthermore, during this experience, we observed a possible "spillover effect" of the RCD/FMDA intervention beyond the intervention areas. So, in this follow up study, we aim to determine the impact of the malaria elimination program implemented in Tumbes on interrupting the transmission of malaria beyond the intervention area along the Peruvian north coast.

## *4.3 Methods*

### Study Design

The study design corresponds with the follow up of a non-randomize community trial. In Tumbes, after piloted an RCD/FMDA strategy in the districts of Aguas Verdes (3°28´S 80°14´ W, population ~13,000) and Zarumilla (03°49´S 80°27´W, population ~18,000) in years 2009 and 2010 the intervention was scaled up during the years 2011-2015 to the remaining eleven districts (population ~167,000), while the nearby region of Piura continued to use passive case detection (PCD) as established by the Peruvian malaria guidelines. To assess the "spillover effect" of the intervention to the surrounding non-intervention areas, we determined the effect of the RCD/FMDA intervention on the mean weekly parasite incidence across the reporting units from Piura using road distances to the Aguas Verdes international bridge over the Zarumilla River that connects Peru with Ecuador as a proxy of indirect exposure.

## Study area

Tumbes and Piura are northwestern regions located along the border with Ecuador. Both regions are known for their warm beaches and tropical climate due to its location in proximity to the Equator. The coast is divided by the Peruvian subtropical desert of Sechura on the south and the savanna-like scrub dry forests on the center and north of the region. Politically, Piura is divided into eight provinces and 64 districts, has a total surface of 35,892 $km^2$ and an estimated population of ≈1,844,000 inhabitants; Tumbes is divided into 13 districts, has a total surface of 4,670 $km^2$ and an estimated population of ≈238,000 inhabitants. The Pan-American highway connects both regions from north to south, which favors the propagation of anopheline vectors (primarily *An. albimanus*) as well as human migration for labor-intense agricultural activities (18). The region typically has hot and humid summers with moderate rains that intensify from December to March and cold and dry winters from April to November. However, this seasonal climate pattern can change drastically due to the El Niño phenomenon, which manifests with torrential rains and strong winds that often are associated with major flooding and landslides. Such events have been associated with different malaria outbreaks in the past (e.g., the malaria epidemic in 1997–1998), while its counterpart, La Niña phenomenon, have behaves as a protective factor against malaria as it draws strong dry weather (19). Malaria endemicity of malaria in Tumbes and Piura is low and seasonal, peaking during the rainy season (February–June). Figure 10 displays the map of Tumbes and Piura with the distribution of the health centers within each district, the rivers and roads, as well as the boundaries of both regions and its districts. Some health centers are clustered along the Peruvian border with Ecuador, some along the Tumbes River, while other health centers are more dispersed along the Pan-American Highway.

## Study Population

For this study, we analyzed the totality of surveillance reporting units in Tumbes and Piura using the road proximity to the communities that were intervened during the pilot RCD/FMDA strategy in Tumbes as a proxy for exposure intensity. Considering that the RCD-FMDA pilot ran off during years 2009-1010 and the scale-up during the years 2011-2015, we hypothesized that Piura reporting units nearby Tumbes experimented an "spillover effect" of the intervention in Tumbes, that could be detected by progressively decreasing their WPI.

In Tumbes, communities that were exposed to the RCD/FMDA intervention were subjects, with the exception of children under five years old, elders (65 years of age or older), pregnant women, and chronically ill subjects, were considered eligible if they: (1) has his/her legal residence registered at their intervention districts; (2) resided in the household of a subject that was diagnosed as malaria positive within the previous 24 hours; and (3) assented to complete the malaria treatment regardless of the absence of symptoms. In Piura, the Ministry of Health continued providing subjects health care using the PCD as recommended by the Peruvian National Malaria guideline (20).

## Study interventions

The interventions were the same as previously described. Briefly, (1) under PCD, only the subjects that tested positive for malaria received treatment. Alternatively, (2) under RCD/FMDA, every malaria case detected under PCD was immediately followed within the first 24 hours to census and treat each of his/her household contacts (excluding children under 5 years old, adults 65 years of age or older, pregnant women, and chronically ill subjects). In both cases, following

national guidelines, subjects were treated uniformly and for free for uncomplicated *P. vivax* malaria cases. In Tumbes the care surveillance protocols and case management were standardized across regional reporting units, so we collaborated with local authorities to train malaria officers at each regional reporting units, trained the personnel responsible for the malaria program annually, and procured the administrative and laboratory supplies necessary to ensure a continual provision of care. In Piura, PCD was provided under normal circumstances without further interventions from the researchers.

## Treatment for *Vivax* Malaria

As previously reported and according to the Peruvian malaria treatment guidelines every malaria cases received treatment uniformly and for free (21). The treatment of choice for uncomplicated *vivax* malaria cases in adults and children was oral chloroquine (10 mg/kg/day) daily for three days, plus oral primaquine (0.5 mg/kg), daily, for seven days. In the case of pregnant women, the treatment of choice was oral chloroquine (10 mg/kg/day) daily for three days followed by a weekly dose of 5 mg/kg until delivery, and then primaquine phosphate (0.5 mg/kg) daily for seven days, while in the case of Infants under six months of age the treatment was chloroquine only. For unconscious patients, the treatment of choice was intravenously clindamycin (20 mg base/kg/day) and quinine sulfate (10 mg salt/kg/day) three times daily until subjects can initiate standard oral treatment.

## Study outcomes

As a primary outcome, we assessed and compared the variability of the malaria weekly parasite incidences at each of the Piura reporting units according to their proximity to the two intervention districts initially intervened in Tumbes before the intervention was scaled up across the Tumbes reporting units. Road distances were estimated from each surveillance unit to the Aguas Verdes international bridge (the bridge that which connects Peru with Ecuador over the Zarumilla River), as a proxy of indirect exposure. Weekly parasite incidence was calculated by dividing the total weekly count of malaria cases, as reported by the national surveillance system, over the total population as estimated by the Peruvian Ministry of Health at each surveillance reporting unit.

In order to assess FMDA safety, we implemented a surveillance protocol for severe adverse events by training malaria officers to derivate patients to the Regional Hospital if any study subject present with at least one symptom compatible with a potential severe adverse event. Once admitted patients were subject of clinical assessment by the study coordinator to confirm whether such symptoms correspond without any of the severe adverse events under surveillance. The chloroquine severe adverse events under surveillance included retinopathy (as diplopia or bilateral loss of vision), cardiotoxicity (as breathlessness with exertion or even at rest, syncope or swelling of the legs, ankles and feet), myopathy (as symmetric weakness affecting proximal muscles of the legs and arms), and neurotoxicity (as seizures, insomnia or paresthesia). The primaquine severe adverse events under surveillance included hemolysis (as dark urine) and severe anemia (weakness/malaise)

## Climate and environmental variables

A specific set of climate and environmental variables were assessed as potential confounders of the effect of RCD/FMDA. As previously described these variables included temperature (MERRA-T2M), humidity (MERRA-QV2M), soil moisture (MERRA-SFMC), elevation (ASTER-GDEM), precipitation (TRMM-TMPA), and NDVI **(**MODIS) (Figure 11). Each of these variables was assessed using their weekly averages estimated at the coordinates of each of the reporting units for the 2011–2014 period. Due to the different resolution, each variable was estimated by averaging their hourly estimates using the standardized protocols for each of the satellite products. In the case of the MERRA products data was available at hourly steps and with a 1/2°×2/3° resolution, TMPA data was available at 3-hourly time steps and with a 0.25°×0.25° resolution; while the MODIS data was available at 0.05° resolution.

## Data Collection

Weekly parasite incidence (malaria cases per 1,000 inhabitants) was estimated based on surveillance malaria counts and government population estimates, so we extensively reviewed the regional malaria surveillance registries from each of the reporting units during the study period. Data was provided by the Regional Health Directorates as reported to the national surveillance system (implemented in 2001), which provides a confidential, and secure database with quality-controlled data entry. Briefly, each surveillance reporting unit reports their malaria counts on a weekly basis to the regional health directorate, which managed the data entry and data quality control by using the surveillance software NOTI. For this study, the data was downloaded from the NOTI system without identifiers in the password protected CSV files for the study analysis. We maintained the main datasets in a secure computer system as prevention to maintain

confidentiality and avoid loss of data. Then, we directly analyzed the CSV files using STATA/MP v14.0 (Stata Corporation, College Station, TX, 2011) with the Excel import command for data management, including further checks and reviewed for consistency and completeness.

## Data Analysis

First, we performed an exploratory analysis to describe and compare the baseline characteristics within and between reporting units by region. Baseline characteristics and outcomes were described with summary statistics, using frequency and percentage for categorical variables and mean and standard deviation for continuous variables. To estimate the effect of the RCD/FMDA strategy on interrupting malaria transmission in Piura, we first estimated the fit of a bivariate model with the WPI as a function of the road proximity to the closest intervention district during the pilot study. Then, we fit a multivariate model using a mixed-effects Poisson regression model to adjust for the climate and weather variables as potential confounders and to account for the structure of the data. The forward selection was used to determine the variables for the multivariate model using the Akaike Information Criteria (AIC) and the likelihood ratio test (LRT) to compare nested models. Pearson's correlation coefficients were also computed for each variable to assess and prevent multicollinearity. All the analyses were conducted with Stata/MP 14.0 (Stata Corporation, College Station, TX) using a significance level of $p<0.05$.

## Ethical considerations

During study planning, the study protocol was approved by the Tumbes and Piura Regional Health Directorate authorities, which approved the study as a project of public health relevance

for their regions. Both regions designated a leading epidemiologist to collaborate during data collection. Both Regional Health Directorate epidemiologists participated actively in all the interventions related activities, so they have broad knowledge about the quality and limitations of the data, and where the first recipients of the study results for local decision-making purposes.

## *4.4 Results*

### Malaria cases before and at baseline

From 2000 to 2008, Piura and Tumbes reported a total of 62,893 malaria cases of which 46,073 (73%) were due to *P. vivax*. During this period Tumbes and Piura reported a mean API of 8.74 and 3.21 malaria cases per 1,000 inhabitants, respectively. The average age of the malaria positive cases was 31±7 years of age, with most of the cases adults (71%) or men (65%). During this period, malaria cases due to *P. falciparum* cases dropped from 4,752 cases in 2000 to zero in 2008 in Tumbes, and from 4675 down to zero in Piura, without any autochthonous *P. falciparum* malaria cases reported in the year 2007 and 2008.

At study baseline (2008), Tumbes reported 2,479 *P. vivax* malaria cases and Piura reported 4,016 cases, all *P. vivax*. During that year, the mean weekly parasite incidence (WPI) estimated across surveillance reporting units in Tumbes was 28±93 malaria cases per 100,000 inhabitants and in Piura was 1±11 malaria cases per 100,000 inhabitants. At the two districts that were selected to pilot the RCD/FMDA intervention the mean WPI estimated across their reporting units was significantly higher than among reporting units from the other eleven non-intervention districts from Tumbes (81±167 cases per 100,000 inhabitants vs. 13±46 cases per 100,000 inhabitants;

($p<0.001$), as well as compared to the 64 districts from Piura (81±167 cases per 100,000 inhabitants vs. 1±11 cases per 100,000 inhabitants; $p<0.001$).

## Malaria cases during Pilot study

During pilot study (2009-2010) a total of 8,243 subjects, including 867 malaria cases and 7,376 contacts (1:8.5 cases/contact ratio) were treated in Tumbes. During the second year of the intervention, the mean WPIs dropped to 14.51 malaria cased per 100,000 inhabitants in Tumbes but increased to 3.83 malaria cases per 100,000 inhabitants in Piura.

We estimated that comparing the baseline (2008) and the second year of the pilot study (2010), the Tumbes intervention sites registered a mean WPIs reduction of 95% (95%CI: 74−100), the Tumbes non-intervention sites a mean WPIs reduction of -39% (-75%−-3%), while across the Piura non-intervention sites the mean WPIs reduction was of -260% (-325%−-195%) (Table 11). Such reductions were statistically significant when comparing the intervention sites from Tumbes against the non-intervention sites from Tumbes ($p<0.001$) and Piura ($p<0.001$).

During the pilot study the variability of the climate and environmental conditions across the Tumbes region was low (coefficient of variation [CV]: <100%) for variables like pressure ($CV<0.01$), temperature ($CV=0.04$), humidity ($CV=0.11$), soil moisture ($CV=0.27$), vegetation ($CV=0.16$) and surface sea temperature ($CV=0.10$), and high ($CV>1.00$) for precipitation ($CV=1.81$). Table 12 summarizes the estimates for each of the climate and environmental variables of interest of our study in 2009-2010 but lagged 10 weeks to better represent the malaria seasonality, including the wet months (November to April) and the dry months (May to October) along the Peruvian north coast.

## Malaria cases during the scale-up study

During scale-up, the WPIs dropped from 6.11 (95%CI: 5.30–6.43) cases per 100,000 inhabitants in the year 2010 to 0.02 (95%CI: -0.00−0.05) in the year 2014 across Tumbes and Piura (Table 11). In 2015, Tumbes reported only three malaria imported cases, one from Ecuador, one from Iquitos, and one from Amazonas; and in 2016, two malaria imported cases were reported, one from Amazonas and one from Iquitos.

## Adverse events

During both study phases health centers did not report any severe antimalarial adverse events (severe anemia, hemolysis, retinopathy, cardiomyopathy, myopathy, and neuromyopathy), and despite our specific protocol, the Tumbes hospital did not report any case of severe antimalarial adverse events neither. Also, during both study phases, Tumbes did not report any fatal malaria case.

## Bivariate analysis

The results of the correlation analysis between our variables of interest are summarized in Table 3. Based on the estimates of the Pearson's correlation coefficients we concluded that temperature was highly correlated ($r$>0.5000) with pressure ($r$=-0.6328; $p$<0.0001); that soil moisture was highly correlated with humidity ($r$=0.8087; $p$<0.0001); that precipitation was moderately correlated with humidity ($r$=0.4233; $p$<0.0001) and soil moisture ($r$=0.4547; $p$<0.0001); and that vegetation (NDVI) was moderately correlated with humidity ($r$=0.3575; $p$<0.0001) and soil moisture ($r$=0.3291; $p$<0.0001).

**Mixed-effects Poisson Regression Analysis for the Weekly Parasite Incidence during the pilot period**

The results from the mixed-effects Poisson regression analysis of the weekly parasite incidences of *P. vivax* cases across the 37 surveillance units from the Tumbes region are summarized in the Tables 14 and 15. First, a basic two-level model was fixed to account for the distribution of the data and the effect of our intervention of interest (RCD/FMDA). Second, a series of models were fixed to adjust for potential environmental and climate confounders. To do so, the predictors were selected using the forward method and the AIC to decide which variables entered the model first. The Table 14 summarizes the rationale behind the variable selection, while the table 15 summarizes the final model, which includes the following covariables as predictors of the malaria vivax counts: RCD/FMDA, season's trend, soil moisture, pressure, and vegetation. Based on this model we can conclude that the RCD/FMDA significantly contributed to decrease the weekly parasite incidence (Beta= -0.53; CI 95%: -0.9172, -0.1478; IRR=0.5866).

## *4.5 Discussion*

Focalized interventions such as the RCD/FMDA represents an effective strategy to support malaria elimination initiatives in low endemic malaria regions such as the Peruvian north coast, a region with a predominance of vivax malaria. In this study, we find evidence that suggest that the RCD/FMDA strategy besides contributed to control and later the elimination of malaria within the intervention areas of Tumbes; it further contributed to control and later elimination of malaria beyond the intervention areas in the nearby region of Piura. This finding is, to our knowledge, one

of the first reports of the value of the "spillover effect" in the scope of malaria elimination initiatives.

The "spillover effect" (also known as "contamination") is an often non-desired but well-documented effect in clinical trials. Is not desired because when the "spillover effect" is present it leads to the dilution of the treatment effect and an increase risk of a type II error (22). As a consequence a truly effective intervention might be found ineffective because the observed effect size was neither statistically nor clinically significant due to an "spillover effect" (23). Although there are several methods recommended to avoid and control for the "spillover effect", in the case of a malaria elimination initiative the "spillover effect" is a desired rather than an undesired effect.

In the previous chapter we described that during the pilot study we estimated a mean reduction in WPI across Tumbes intervention areas of 99% (97−100) and 85% (77−94) at 12 and 24 months (m), respectively; and non-intervention areas of 34% (27−40) and 86% (76−93) at 12m and 24m, respectively. During the same period, we estimated a mean reduction in WPI at the near, mid and far range Piura districts of 63%, -73%, and -420% at 12m, and 91%, -126% and 91% at 24m, respectively. After scaling-up the intervention to each of the 13 Tumbes districts, we found a negative association between the mean WPI reduction and proximity to intervention area across the Piura districts, at both 24m ($p$=0.04) and 48m ($p$<0.01). Furthermore, during the following two years (2015 and 2016), the interruption of the transmission of malaria across Tumbes and Piura was reported as successful, without any autochthonous malaria cases reported.

According to our study results the RCD/FMDA strategy represented an effective intervention to interrupt the transmission malaria along the north coast, but also is an intervention with a very valuable "spillover effect" in the Piura region and may support malaria elimination initiatives in other settings with a high predominance of vivax malaria.

In the study 1 we found that ~90% of the total impact attributable to the RCD/FMDA at 24-months of the pilot study occurred during the first year in the region of Tumbes. Also, we observed that there were strong signals of an "spillover effect" from the intervention areas to the nearby non-intervention areas, both during the pilot study in Tumbes as well as during the scale up study in the nearby districts of Piura. This observation might be explained in the case of Tumbes because of the relatively small territory as well as its strong road-connectivity due the Pan-American Highway. So, it was plausible that the impact of the RCD/FMDA strategy in Tumbes was extended to Piura by an "spillover effect". Hence in this second study we tested that hypothesis finding that in fact, such might be the case.

The study two results suggest that we can enhance the effect of a malaria elimination program selecting the proper intervention and by selecting the proper targets. As for the intervention the RCD/FMDA was previously found to represent an effective strategy to support malaria elimination initiatives in Tumbes Peru, a region with a predominance of vivax malaria, while taking advantage of a clear understanding of the patterns of incidence of malaria at each site. And as for the target's selection, the intervention sites were first selected strategically among the most endemic regions based on a clear understanding of the patterns of incidence across the region. By doing so, the intervention also produced a clear "spillover effect" that may have helped to interrupt the transmission of malaria along the Pan-American highway, which is the main road that connects both regions. Additionally, several factors contributed to the success of the program, including the strong seasonality that characterize the pattern of the incidence of malaria along the Peruvian north coast, the lack of a vector with high vectorial capacity in the region, the sustainability of the Tumbes malaria elimination program, as the single road connectivity between both regions and also drives the economy of both regions.

During pilot study (2009-2010) a total of 8,243 subjects, of which around ~90% were asymptomatic subjects without any symptoms or signs of malaria received a complete course of antimalarials for *P. vivax* malaria. Such numbers may be a sign that a significant fraction of the population at risk was treated for asymptomatic malaria and also receive a treatment a transmission-blocking drug such as primaquine. During this second year of the pilot study (2010), the Tumbes intervention sites registered a mean WPIs reduction of 95% (95%CI: 74−100), the Tumbes non-intervention sites a mean WPIs reduction of -39% (-75%−-3%), while across the Piura non-intervention sites the mean WPIs reduction was of -260% (-325%−-195%). Such reductions were statistically significant when comparing the intervention sites from Tumbes against the non-intervention sites from Tumbes ($p$<0.001) and Piura ($p$<0.001). However, during the scale-up study, the WPIs dropped from 6.11 (95%CI: 5.30–6.43) cases per 100,000 inhabitants in the year 2010 to 0.53 (95%CI: -0.08−1.14) in the year 2014 across Tumbes and Piura. And since 2015, Tumbes and Piura have reported only imported malaria cases, either from Ecuador or from the Peruvian Amazon.

During both study phases participants did not report any antimalarial adverse events, and the regional hospitals from Piura and Tumbes did not state any case of antimalarial adverse events neither nor any fatal malaria case.

## *4.6 References*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## *4.7 Tables for Chapter 5*

**Table 11.** Mean weekly parasite Incidence by year and proximity to the intervention districts

| District | Population | Mean Weekly Parasite Incidence ** (95% CI) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Baseline | Pilot Study Period | | | Scale-Up Study Period | | |
| | | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 |
| **Overall** | | 6.86 (5.83 – 7.89) | 5.63 (4.85 – 6.43) | 6.11 (5.30 – 6.43) | 0.81 (0.64 – 0.99) | 0. 12 (0.06 – 0.18) | 0.02 (-0.00 – 0.04) | 0.02 (-0.00 – 0.05) |
| **By Intervention** | | | | | | | | |
| Intervention | 42,922 | 81.00 (63.74 – 98.26) | 36.15 (25.84 – 46.45) | 3.34 (1.60 – 5.09) | 0.13 (0.03 – 0.24) | 0.09 (0.01 – 0.18) | 0.00 (0.00 – 0.00) | 0.00 (0.00 – 0.00) |
| Non-intervention | 1,078,783 | 3.10 (2.59 – 3.61) | 4.09 (3.46 – 4.72) | 6.25 (5.40 – 7.10) | 0.85 (0.67 – 1.03) | 0.12 (0.06 – 0.19) | 0.02 (-0.00 – 0.04) | 0.02 (-0.00 – 0.05) |
| **By proximity** | | | | | | | | |
| <100 Km | 188,773 | 29.11 (24.40 – 33.82) | 11.05 (8.43 – 13.67) | 14.99 (11.90 – 18.09) | 2.53 (1.81 – 3.25) | 0.39 (0.13 – 0.66) | 0.00 (0.00 – 0.00) | 0.00 (0.00 – 0.00) |
| 100-199 Km | 54,174 | 0.25 (-0.12 – 0.63) | 0.07 (-0.01 – 0.17) | 0.17 (-0.17 – 0.52) | 0.02 (-0.02 – 0.08) | 0.02 (-0.02 – 0.08) | 0.00 (0.00 – 0.00) | 0.00 (0.00 – 0.00) |
| 200-299 Km | 182,329 | 1.97 (1.13 – 2.81) | 14.75 (12.24 – 17.27) | 13.52 (10.92 – 16.12) | 1.19 (0.79 – 1.59) | 0.12 (0.02 – 0.21) | 0.10 (-0.03 – 0.23) | 0.14 (-0.04 – 0.32) |
| 300-399 Km | 629,074 | 0.99 (0.60 – 1.37) | 2.15 (1.26 – 3.05) | 1.63 (1.08 – 2.19) | 0.19 (0.08 – 0.30) | 0.05 (0.01 – 0.09) | 0.01 (-0.01 – 0.02) | 0.00 (0.00 – 0.00) |
| 400-499 Km | 40,353 | 0.39 (0.12 – 0.68) | 0.98 (0.41 – 1.55) | 1.34 (0.58 – 2.11) | 0.13 (-0.13 – 0.40) | 0.00 (0.00 – 0.00) | 0.00 (0.00 – 0.00) | 0.00 (0.00 – 0.00) |
| >500 Km | 27,002 | 0.95 (-0.04 – 1.93) | 0.05 (-0.02 – 0.12) | 1.00 (-0.48 – 2.47) | 0.10 (-0.09 – 0.29) | 0.00 (0.00 – 0.00) | 0.00 (0.00 – 0.00) | 0.00 (0.00 – 0.00) |

***** Population estimated at baseline (year 2008); ** Weekly Parasite Incidence = Total malaria cases per week/ 100,000 inhabitants; 95% CI = 95% Confidence Interval.

**Table 12.** Weekly means ±SD (95% CI) of the environmental and climate parameters during the scale-up study *

| District | Pressure (kPa)[a] | Humidity (kg vapor * $kg^{-1}$ air * $10^3$) | Temperature (°C) | Moisture ($m^3$*$m^{-3}$) | Precipitation (mm water * $m^{-2}$) | Vegetation (NDVI) | Sea Temperature (°C) |
|---|---|---|---|---|---|---|---|
| **All** | 94.4 ± 6.9 (94.3 - 94.5) | 14.3 ± 4.9 (14.3 - 14.4) | 24.2 ± 5.1 (24.2 - 24.3) | 0.174 ± 0.127 (0.172 - 0.176) | 5.1 ± 13.2 (4.9 - 5.2) | 0.41 ± 0.23 (0.41 - 0.42) | 19.1 ± 3.1 (19.0 - 19.1) |
| **By Intervention** | | | | | | | |
| Intervention | 94.9 ± 2.3 (94.8 - 95.1) | 14.8 ± 3.8 (14.6 - 15.0) | 25.8 ± 2.2 (25.7 - 25.9) | 0.184 ± 0.088 (0.179 - 0.189) | 7.4 ± 16.8 (6.5 - 8.3) | 0.46 ± 0.25 (0.44 - 0.47) | 22.6 ± 1.7 (22.5 - 22.7) |
| Non-intervention | 94.4 ± 7.1 (94.3 - 94.5) | 14.3 ± 4.9 (14.2 - 14.4) | 24.1 ± 5.2 (24.0 - 24.2) | 0.174 ± 0.129 (0.172 - 0.175) | 5.0 ± 13.2 (4.9 - 5.2) | 0.41 ± 0.23 (0.41 - 0.42) | 18.9 ± 3.1 (18.8 - 19.0) |
| **By proximity** | | | | | | | |
| <100 Km | 98.8 ± 2.8 (98.7 - 98.9) | 15.6 ± 4.9 (15.5 - 15.7) | 26.0 ± 3.0 (25.9 - 26.1) | 0.212 ± 0.178 (0.207 - 0.217) | 6.8 ± 16.3 (6.4 - 7.2) | 0.4 ± 0.2 (0.4 - 0.5) | 22.6 ± 1.7 (22.5 - 22.6) |
| 100-199 Km | 93.5 ± 8.6 (92.8 - 94.2) | 14.4 ± 4.6 (14.1 - 14.8) | 23.0 ± 5.8 (22.5 - 23.4) | 0.171 ± 0.084 (0.170 - 0.181) | 5.6 ± 11.6 (4.7 - 6.5) | 0.3 ± 0.2 (0.2 - 0.3) | 19.6 ± 3.2 (19.4 - 19.9) |
| 200-299 Km | 96.6 ± 4.4 (96.4 - 96.7) | 14.3 ± 5.4 (14.2 - 14.5) | 25.4 ± 4.4 (25.2 - 25.5) | 0.153 ± 0.104 (0.150 - 0.156) | 4.0 ± 11.9 (3.6 - 4.3) | 0.4 ± 0.2 (0.4 - 0.4) | 18.1 ± 2.7 (18.0 - 18.2) |
| 300-399 Km | 93.3 ± 7.1 (93.1 - 93.4) | 14.0 ± 4.8 (13.9 - 14.1) | 23.9 ± 5.4 (23.8 - 24.0) | 0.164 ± 0.113 (0.162 - 0.165) | 4.4 ± 12.0 (4.2 - 4.6) | 0.4 ± 0.2 (0.4 - 0.4) | 18.1 ± 2.7 (18.0 - 18.2) |
| 400-499 Km | 91.6 ± 7.5 (91.4 - 91.8) | 13.8 ± 4.4 (13.7 - 13.9) | 23.0 ± 5.5 (22.8 - 23.2) | 0.167 ± 0.113 (0.164 - 0.170) | 5.5 ± 13.0 (5.1 - 5.8) | 0.4 ± 0.3 (0.4 - 0.4) | 18.1 ± 2.7 (18.1 - 18.2) |
| >500 Km | 83.6 ± 5.2 (83.3 - 83.9) | 13.2 ± 2.8 (13.0 - 13.4) | 18.6 ± 4.4 (18.3 - 18.8) | 0.194 ± 0.077 (0.190 - 0.199) | 8.2 ± 14.0 (7.3 - 9.0) | 0.4 ± 0.3 (0.4 - 0.4) | 18.1 ± 2.7 (18.0 - 18.2) |

***** Weekly estimates averaged at year 2009-2010; SD, Standard deviation; 95% CI = 95% Confidence Interval; Pressure (kPa), kilopascals of pressure estimated per $km^2$; Humidity (kg vapor * $kg^{-1}$ air * $10^3$), $10^3$ kg of water vapor per kg of air measured daily at 2 m above the displacement height; Temperature (°C), degree Celsius of temperature at 2 m above the displacement height; Soil moisture ($m^3$*$m^{-3}$), cubic meters of water per square meter of soil; Precipitation (mm water * $m^{-2}$), mm of rain per square meter per hour; Vegetation (NDVI), normalized difference vegetation index.

**Table 13.** Correlation matrix of the variables used in the multivariate analysis for the *P. vivax*-weekly parasite counts model

| | | WPI[a] | Distance | Pressure | Humidity | Temp. | Moisture | Precip. | Vegetation |
|---|---|---|---|---|---|---|---|---|---|
| **RCD/FMDA** | Pearson (*r*) | -0.0609* | 1.0000 | | | | | | |
| | *p* value | 0.0000 | | | | | | | |
| **Pressure** | Pearson (*r*) | 0.0411* | -0.4258* | 1.0000 | | | | | |
| | *p* value | 0.0000 | 0.0000 | | | | | | |
| **Humidity** | Pearson (*r*) | -0.0144* | -0.1375* | 0.0475* | 1.0000 | | | | |
| | *p* value | 0.0124 | 0.0000 | 0.0000 | | | | | |
| **Temperature** | Pearson (*r*) | 0.0029 | -0.2467* | 0.6980* | 0.2812* | 1.0000 | | | |
| | *p* value | 0.6135 | 0.0000 | 0.0000 | 0.0000 | | | | |
| **Moisture** | Pearson (*r*) | -0.0143* | -0.1122* | -0.3027* | 0.7186* | -0.1666* | 1.0000 | | |
| | *p* value | 0.0128 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | | | |
| **Precipitation** | Pearson (*r*) | 0.0062 | -0.0330* | -0.1234* | 0.0203* | -0.1139* | 0.1270* | 1.0000 | |
| | *p* value | 0.2795 | 0.0000 | 0.0000 | 0.0004 | 0.0000 | 0.0000 | | |
| **Vegetation** | Pearson (*r*) | 0.0029 | -0.0414* | -0.2593* | -0.0502* | -0.2341* | 0.1007* | 0.2548* | 1.0000 |
| | *p* value | 0.6186 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | |
| **Sea Surface** | Pearson (*r*) | 0.0493* | -0.5089* | 0.2161* | -0.3708* | -0.0312* | -0.1121* | 0.1029* | 0.0645* |
| **Temperature** | *p* value | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 |

[a] Weekly Parasite Incidence (WPI)= Total malaria cases per week/ 1,000 inhabitants; [b] RCD/FMDA = Reactive Case Detection with Focal Mass Drug Administration; * p value <0.05

**Table 14.** Forward selection of variables for the Mixed-Effects Poisson Regression Model

| Models | AIC |
|---|---|
| **I. Setting the basic model** | |
| Empty Model | 71468.4 |
| Empty Model + Distance | 69547.5 |
| **II. Modeling the effect of proximity towards the intervention sites** | |
| Basic model | 61411.5 |
| Basic model + Sea Surface Temperature (SST) | 61167.0 |
| Basic model + Precipitation | 61106.7 |
| Basic model + Temperature | 60588.9 |
| Basic model + Pressure | 60550.1 |
| Basic model + Soil Moisture | 60038.2 |
| Basic model + Humidity | 59276.6 |
| Basic model + Dry Season | **57542.9** |
| Basic model + Dry Season + SST | 57494.3 |
| Basic model + Dry Season + Vegetation | 57484.1 |
| Basic model + Dry Season + Precipitation | 57475.7 |
| Basic model + Dry Season + Temperature | 57184.8 |
| Basic model + Dry Season + Pressure | 57010.2 |
| Basic model + Dry Season + Soil Moisture | 56542.0 |
| **Basic model + Dry Season + Humidity** | **56177.9** |
| Basic model + Dry Season + Humidity + Precipitation | 56179.8 |
| Basic model + Dry Season + Humidity + Soil Moisture | 56157.3 |
| Basic model + Dry Season + Humidity + Vegetation | 56152.0 |
| Basic model + Dry Season + Humidity + SST | 56076.6 |
| Basic model + Dry Season + Humidity + Pressure | 55730.1 |
| **Basic model + Dry Season + Humidity + Temperature** | **49936.8** |
| Basic model + Dry Season + Humidity + Temperature + Precipitation | **56168.4** |
| Basic model + Dry Season + Humidity + Temperature + Vegetation | 56136.7 |
| Basic model + Dry Season + Humidity + Temperature + Soil Moisture | 56133.4 |
| Basic model + Dry Season + Humidity + Temperature + SST | 56047.8 |
| **Basic model + Dry Season + Humidity + Temperature + Pressure** | **55560.1** |
| Basic model + Dry Season + Humidity + Temperature + Pressure + Vegetation | 55561.3 |

| Models | AIC |
|---|---|
| Basic model + Dry Season + Humidity + Temperature + Pressure + Soil Moisture | 55495.3 |
| **Basic model + Dry Season + Humidity + Temperature + Pressure + SST** | **55374.1** |
| Basic model + Dry Season + Humidity + Temperature + Pressure + SST + Vegetation | 55374.2 |
| **Basic model + Dry Season + Humidity + Temperature + Pressure + SST + Soil Moisture *** | **55229.4** |
| Basic model + Dry Season + Humidity + Temperature + Pressure + SST + Soil Moisture + Vegetation | 55228.7 |

* Final model; AIC = Akaike's information criterion; RCD/FMDA = Reactive case Detection with Focal Mass Drug Administration

**Table 15.** Mixed-Effects Poisson Regression Model for the *P. vivax* weekly parasite incidence

| | Estimate | 95% CI | IRR-Fixed Effects | 95% CI |
|---|---|---|---|---|
| Constant | -6.0745 | -7.5784 to -4.5706 | 0.0023 | 0.0005 to 0.0104 |
| Distance [a] | -1.0342 | -1.1378 to -0.9307 | 0.3555 | 0.3205 to 0.3943 |
| Dry Season [b] | -1.7065 | -1.7873 to -1.6256 | 0.1815 | 0.1674 to 0.1968 |
| Pressure [c] | 0.1228 | 0.1122 to 0.1335 | 1.1307 | 1.1188 to 1.1428 |
| Temperature [d] | -0.1323 | -0.1460 to -0.1187 | 0.8760 | 0.8641 to 0.8881 |
| Precipitation [e] | -0.0124 | -0.0142 to -0.0106 | 0.9877 | 0.9859 to 0.9895 |
| SST [f] | -0.1447 | -0.1611 to -0.1283 | 0.8653 | 0.8512 to 0.8796 |
| Vegetation [g] | -0.7177 | -0.9041 to -0.5312 | 0.4879 | 0.4049 to 0.5879 |
| Soil Moisture [h] | 0.0016 | 0.0010 to 0.0023 | 1.0016 | 1.0010 to 1.0023 |
| RE (Network) | 7.2098 | 3.8490 to 13.5054 | | |

* IRR = Incidence-Rate Ratio; AIC = Akaike's information criterion; 95% IC = 95% Interval of Confidence; RE = Random effects; a, distance by road to the sites intervened with the Reactive case Detection with Focal Mass Drug Administration strategy (positive/negative); b, dry season or season´s trend with a value of zero for the wet season and a value of one for the dry season; c, pressure (kPa) or kilopascals of surface pressure estimated per $km^2$; d, temperature (°C) or degree Celsius of temperature at 2 m above the displacement height; e, precipitation (mm water * $m^{-2}$) or mm of rain per square meter per hour; f, SST (°C), or degree Celsius of Sea Surface Temperature at the locations' latitude; g, Vegetation or normalized difference vegetation index (NDVI); h, soil moisture ($m^3$*$m^{-3}$) or cubic meters of water per square meter of soil.

## *4.8 Figures for Chapter 5*

**Figure 11.** Annual parasite incidence by surveillance units in Tumbes and Piura.

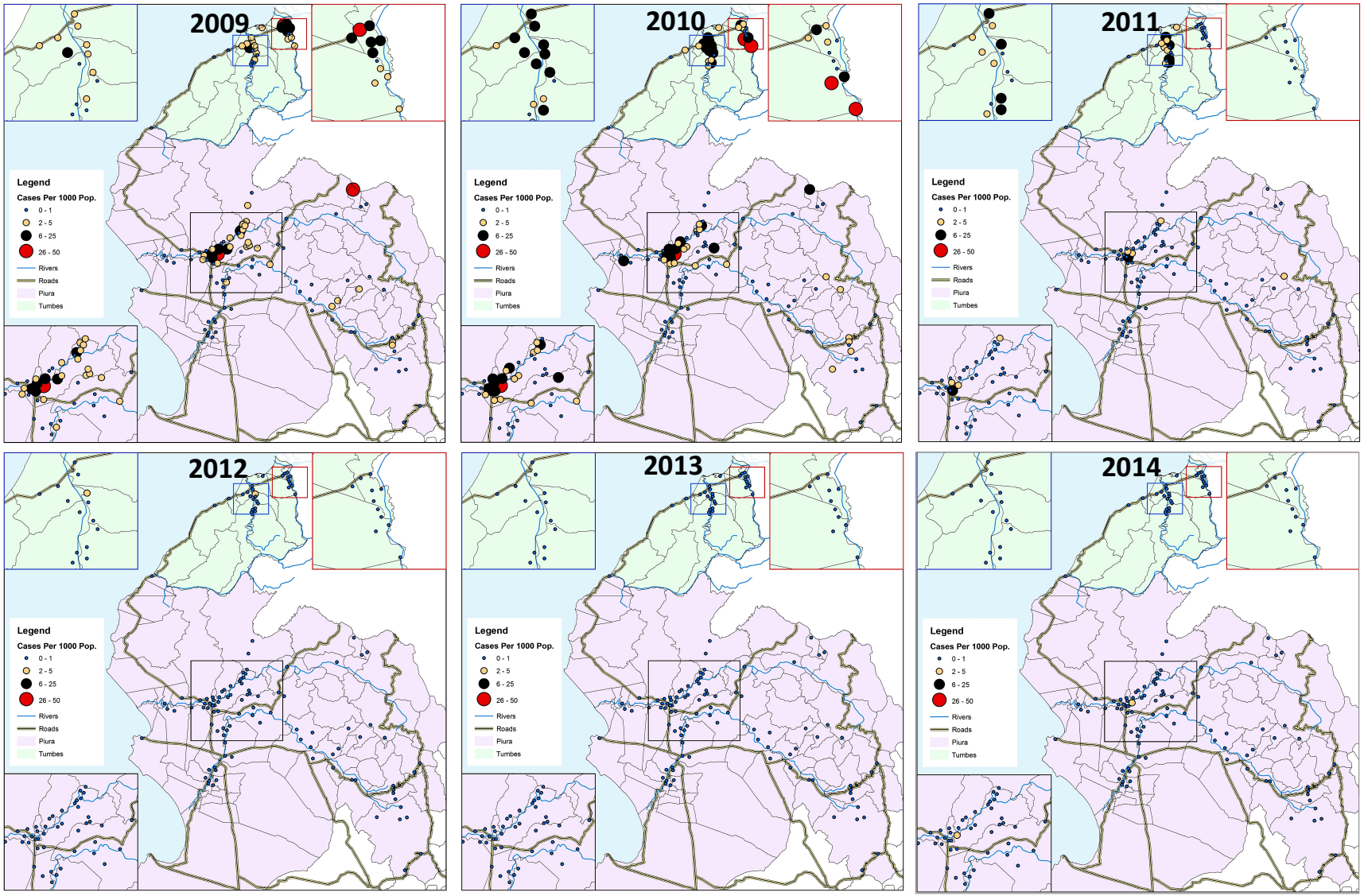
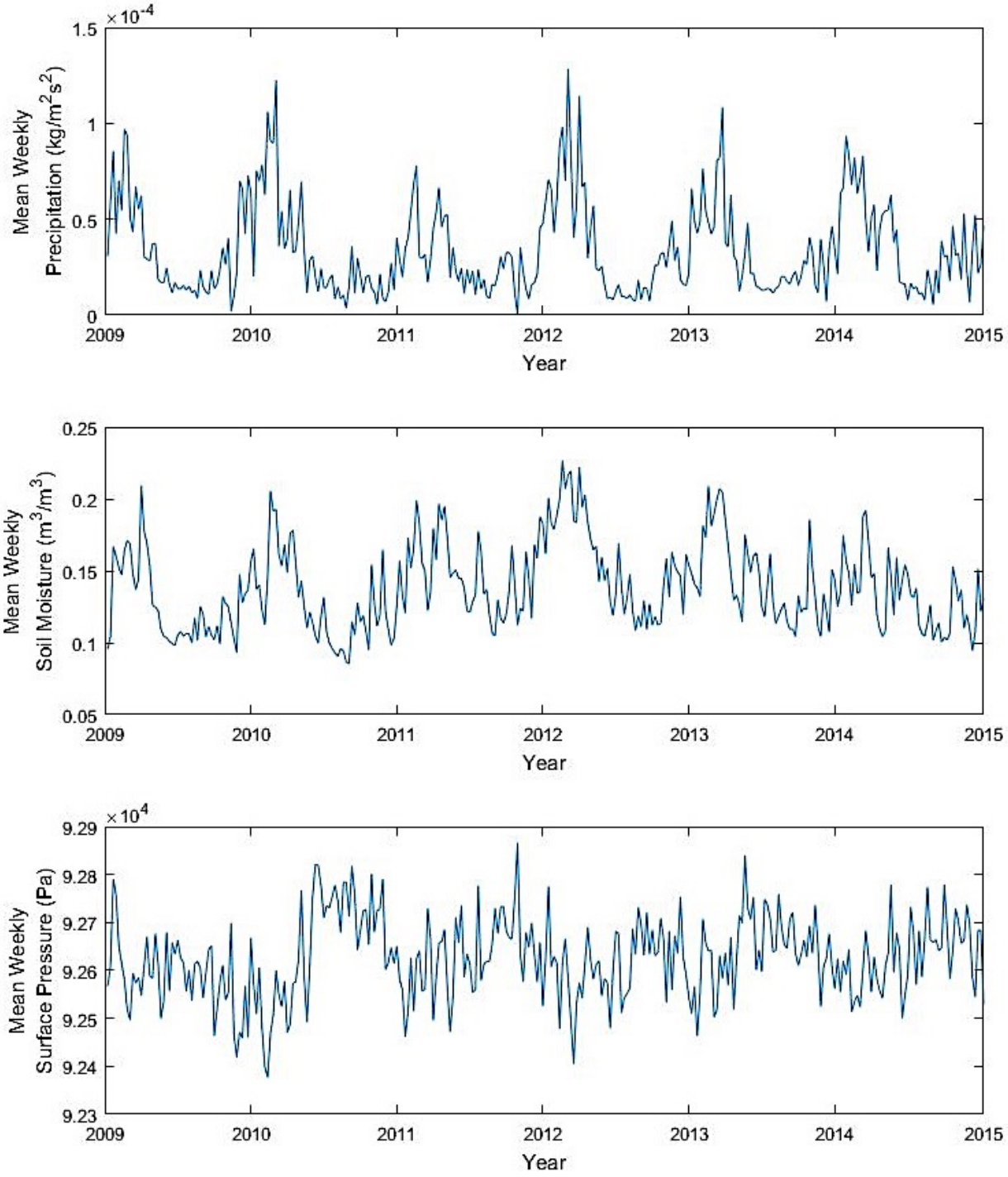
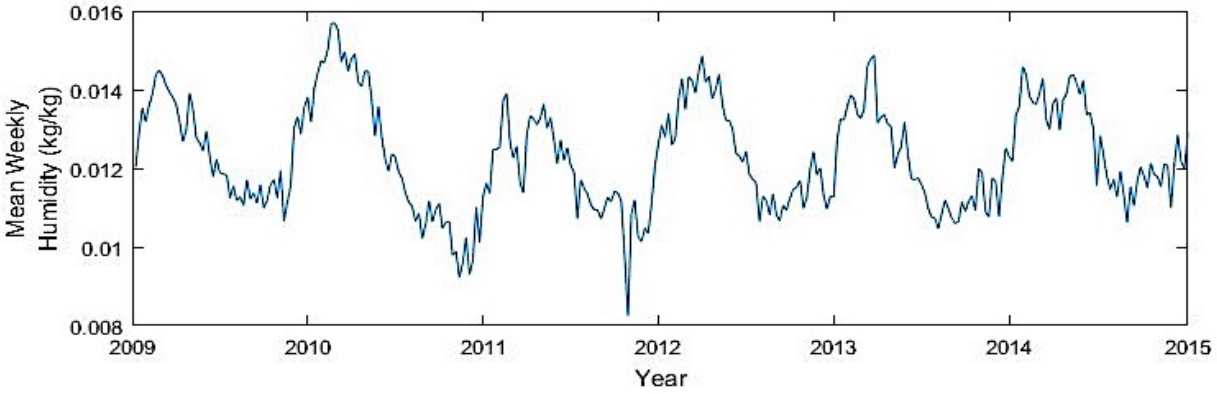
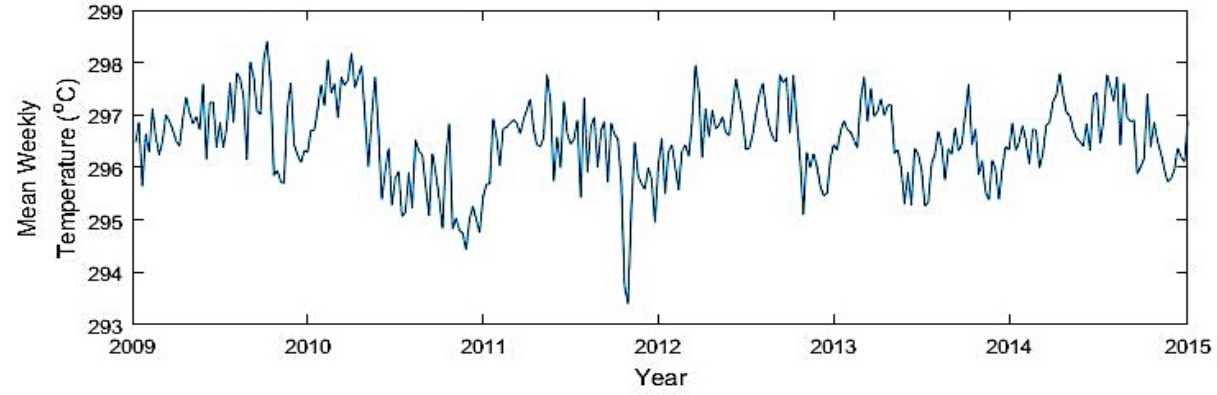
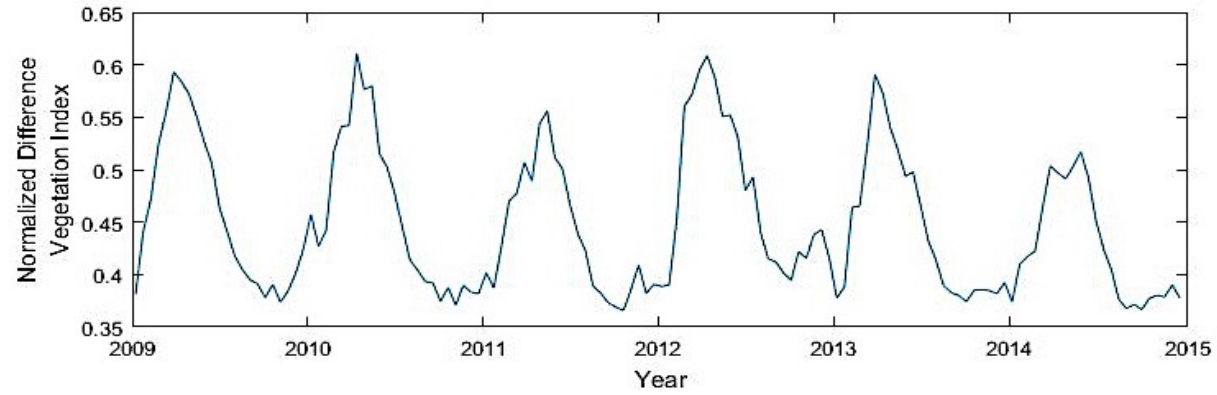


**Figure 12.** Weekly climate and environmental variables at the Tumbes and Piura regions






* The precipitation value in mm is referring to the amount of rain per square meter per hour averaged per week; the soil moisture value of $m^3/m^{-3}$ is referring to the mean quantity of cubic meters of water per square meter of soil averaged per week; the precipitation value in kPa is referring to the number of kilopascals of pressure estimated per $km^2$ averaged per week; the humidity value in kg/kg is referring to the number of kg of water vapor per kg of air measured daily at 2 m above the displacement height; the temperature value in degrees centigrade is referring to the temperature at 2 m above the displacement height averaged per week; and, NDVI is referring to the normalized difference vegetation index averaged per week.

# Chapter 5. "The heterogeneity of patterns of malaria incidence in the Peruvian Amazon and the opportunity of interrupting malaria transmission with focal interventions"

## *5.1 Abstract*

The elimination of malaria demands a clear understanding of the patterns of malaria incidence that characterize each of the settings chosen as intervention targets. Typically, each malaria endemic country presents different regions where malaria transmission is sustainable in time and space. Such foci represent targets for maximizing the effect of current available malaria control intervention. Thus, in this study we aim to characterize the different patterns of incidence of malaria in the Peruvian Amazon to guide the decision making about where, how and which intervention should be chosen to maximize the effect of prospect interventions. Overall, we observed that the distribution of the human malaria reservoir in Loreto follows the natural boundaries of 14 Amazon river navigable tributaries. At each of these rivers we identify a different pattern of malaria incidence, some of which seems to represent a good target to implement focal interventions such as reactive case detection with focal mass drug administration. Across the Loreto region each of these 14 river networks seems to behave like an independent and well interconnected system with a human malaria reservoir larger enough to sustain the transmission of malaria from one season to the following. In this study we tested such hypothesis by fitting a multivariate mixed-effect negative binomial Poisson regression model, with the following covariates: population, time in epidemiological weeks, a sine-cosine function to adjust for

seasonality, traveling distance to the regional hospital, the type of health care offered at each health facility, as well as by altitude, vegetation and precipitation. Although further assessments will be needed to probe such hypothesis, our results indicated that in the Peruvian Amazon there exist several different patterns of malaria incidence, including some (those with few communities carrying larger fractions of the human malaria reservoir) that offered optimal targets for focal interventions while other will other (those with an over dispersed human malaria reservoir) might need more permanent interventions.

## *5.2 Introduction*

The elimination of malaria represents a hard to reach outcome but a necessary global health goal (1). Unfortunately, after a period of substantial gains in global malaria control, progress has slowed and in some regions reversed (2). In this context, the efforts must continue to resolve the major technical, operational and financial challenges that have not yet been addressed in order to achieve the goal of regional elimination. Research continues to be an important driver in the future eradication scenario (3). A key point for malaria elimination is to design strategies to reduce transmission; effective identification and malaria case management may help to reduce the pool of parasites that contribute to further transmission (2). Transmission is a dynamic and variable process with different patterns according to each affected region. It involves many interlinked factors, from natural environmental conditions to man-made disturbances (4). For example, where malaria transmission is seasonal, optimal timing of control becomes particularly crucial regarding planning control strategies. With such information, health officers may plan to maximize the impact of Indoor Residual Spraying (IRS) by prioritizing rounds before the onset of the malaria season (5).

Out of the five Plasmodium species that are capable of infecting humans, *P. falciparum* and *P. vivax* are the most common. Although both species are ubiquitous in tropical and sub-tropical endemic regions around the world, most of the mortality and burden attributable to malaria is due to *P. falciparum* cases from Sub-Saharan Africa where such species is hyperendemic (6). Similar to *P. falciparum*, *P. vivax* has also been occasionally associated with fatal and severe malaria (7). These cases are commonly reported in regions where *P. vivax* represents the dominant malaria species circulating like in the Americas (except in the Dominican Republic, Haiti and Colombia where *P. falciparum* is responsible for most cases) (2). This is a reason of increasing concern given that several countries in the region are registering an increasing number of their severe and non-severe vivax malaria cases (8, 9). Moreover, in some countries such as Venezuela and Peru, the cases of malaria, particularly *P. falciparum* malaria cases, have reemerged since 2010 (10). Such increasing malaria trends may threaten the regional progress was given that the contribute ~50% of malaria cases in the region (10, 11).

Around the world, most malaria endemic settings have "seasonal peaks" of malaria cases, which are described as associated with the rainy months or wet months. However, this varies from year-to-year giving a variety of factors such as the lack of standard definition of seasonality (12) or disrupting effects such as the El Niño–Southern Oscillation (13, 14). For example, in Manhiça (Mozambique) malaria seasons have been classified in different publications as being perennial either with "some" (15), "substantial" (16), or "marked" (17) seasonality, all of which are difficult to measure. As a result, the intensity and seasonality of malaria transmission varies widely within and between countries in sub-Saharan Africa. The same occurs in other regions of the worlds where el Niño–Southern Oscillation have a major impact on the intensity of transmission of malaria both

during the El Niño years intensifying transmission or during La Niña over dispersing malaria transmission across endemic areas (18).

Assessing the distribution of the human malaria reservoir is essential to prioritize interventions and decide on resource allocation. To do so, we can use mathematical models to assess the distribution of the human malaria reservoir across a range of transmission intensities by using the malaria symptomatic cases as its most strong signal. Thus, in Peru, there is a need for models that consider the effects of seasonality, health-care coverage and access, transmission dynamics patters, among other factors, across its distinct epidemiological contexts to guide the choice and timing of control interventions.

This paper aims to assess the variability of patterns of malaria incidence in the Peruvian Amazon and use that information to identify opportunities to interrupt malaria transmission with focal interventions such as reactive case detection and focal mass drug administration.

## *5.3 Methods*

### Study Design

The study design corresponds with a time series study, where we analyze surveillance data routinely collected by the Health Directorate of Loreto covering a total of 342 surveillance reporting units. Such units include 282 health posts, 50 health centers, and 10 clinics/hospitals, distributed along the Amazon river tributaries in the Peruvian Amazon basin.

## Study area

The study was conducted in the Loreto region, which is the largest region in the Peruvian Amazon (Figure 13). Loreto's territory represents almost one-third of the country territory (368,851 km²), but with a population of ~1M inhabitants; it also represents one of the regions with the lowest population density in Peru (2.7 persons per Sq. km). Geographically, Loreto comprises lands that are either at high (between 500 and 1500 meters or "upper jungle") or low (bellow 500 meters or "lower jungle") altitude, which are humid and largely covered with thick vegetation. Loreto is one of the richest regions of Peru in terms of natural, gas and oil resources, but contradictorily, it is also one of the poorest regions in Peru with 70% of its population below the poverty line. Consequently, the MoH represents the main healthcare provider in the region with a small fraction of Loreto inhabitants receiving healthcare from the social security system, the military health care system or private clinics. Politically, Loreto is divided into eight provinces and 53 districts, connected mainly by the Amazon river tributaries. The main Amazon river tributaries are navigable, so they naturally restrict the propagation of anopheline vectors (primarily *An. darlingi*) as well as the human migration for labor or commerce activities (19). The region weather is typical of a humid and warm rainforest, with an average daily high temperature of 31 °C and an average temperature of 28 °C. During the hottest months (December-March), temperatures range typically from 26 °C (79 °F) to 36 °C (97 °F), while coolest months from 17 °C (63 °F) to 20 °C (68 °F). The average humidity level is 84%, with tropical rain all year round.

Malaria in Loreto is over-dispersed and exhibits high heterogeneity with an increasing burden in some regions. Overall, the Loreto region alone counts for over 90% of the burden of malaria in Peru, showing an increasing trend since 2010 (Figures 15 and 16). Symptomatic malaria cases due to *P. vivax* (≈80% of all malaria infections) exceeds malaria cases due to *P. falciparum*

at a ratio of 4:1 with an estimated ratio of symptomatic per asymptomatic malaria cases of 1:4-5 (20, 21). In 2017, Loreto reported an annual parasite incidence of were 57 cases per 1,000 inhabitants, corresponding to 39,372 *P. vivax* malaria cases and 12,905 *P. malaria* cases, respectively, in 2017 (22). The seasonality of malaria across the Loreto regions is marked with perennial malaria cases peaking during the rainy season (February–July), but with high heterogeneity across districts (23).

## Study Population

For this study, we analyzed all surveillance reporting units from Loreto using traveling times by standard boats to the Regional hospital in Iquitos, as a proxy for connectivity across navigable rivers and accessibility to tertiary health-care. Considering that susceptible subjects mainly commute across communities by navigable rivers, we hypothesized that each of the main Amazon rivers behaves as endemic malaria region independent and large enough to sustain malaria transmission from one season to the next season.

The study period was limited to the 2010-2015 period because of three reasons. First, before 2010 the Loreto region was actively exposed to several rounds of malaria control intervention within the scope of the PAMAFRO (malaria control in the border areas of the Andean region) project. Briefly, at intervention areas, the project enhanced community participation with local health workers to implement educational campaigns, passive surveillance, implementing rapid diagnostic tests, and distributing over 250,000 long-lasting impregnated bed nets (24). Second, starting in 2016 the MoH officers raised awareness for malaria elimination due to the imminent implementation of the Peruvian Amazon malaria elimination program (Zero Malaria

Program 2017-2021") (25). Moreover, third, NASA recently released new projects and algorithms to allow continual longitudinal analysis of variables from expired satellite projects like MERRA for example.

## Malaria surveillance

Across Loreto, during the study period surveillance activities continued taking advantage of previous system enhancement either by active case detection (ACD) or passive case detection (PCD). Briefly, under ACD eligible communities were visited to test and treat every subject either using a rapid diagnostic test or microscopy, followed by observed treatment by local health workers or community health workers if testing positive. Under PCD every febrile subject presenting to a health center was tested for malaria using either a rapid diagnostic test or microscopy and treated by local health workers. In both cases, following the Peruvian National Malaria guideline (25), subjects were treated uniformly as uncomplicated *vivax* malaria cases. During the PAMAFRO project surveillance protocols and case management were improved and standardized across regional reporting units and the personnel responsible for the local malaria program were trained to collect and report malaria surveillance in weekly reports. Once collected the data are reported to the health network reference center and from there to the Regional Health Directorate, which entered the data into the Electronic Online Surveillance System (NOTI System) and issuing weekly epidemiological bulletins reporting the malaria incidence together with the counts from other diseases under mandatory surveillance. For this study, the data was downloaded from the NOTI system and provided to us in a password protected CSV files without identifiers.

## Malaria Treatment

As previously reported and according to the Peruvian malaria treatment guidelines, all malaria cases received treatment uniformly and free of charge (26). The treatment of choice for uncomplicated *vivax* malaria cases in adults and children was oral chloroquine (10 mg/kg) over 72 hours, plus oral primaquine (0.5 mg/kg), daily, for seven days. In the case of pregnant women, the treatment of choice was oral chloroquine (10 mg/kg) over 72 hours followed by a weekly dose of 5 mg/kg until delivery, and then primaquine phosphate (0.5 mg/kg) daily for seven days< while in the case of Infants under six months of age the treatment was chloroquine only. And for unconscious patients, the treatment of choice was quinine sulfate (10 mg salt/kg/day) three times daily and intravenously clindamycin (20 mg base/kg/day) until subjects can initiate standard oral treatment. The treatment of choice for uncomplicated *falciparum* malaria cases in adults and children was artesunate + mefloquine (adopted 2001) + primaquine 0.75 mg/kg single dose on last day of ACT (adopted 2015). For complicated falciparum malaria, the treatment of choice was quinine sulfate (10 mg salt/kg/day) three times daily and intravenously clindamycin (10 mg base/kg/day) twice daily until subjects can initiate standard oral treatment. In the case of pregnant women, the treatment of choice was oral quinine (10 mg/kg) three times daily for seven days, + oral clindamycin (10 mg/kg) twice daily for five days starting at the third day of treatment, + oral primaquine 0.75 mg/kg single dose at the third day of treatment.

## Study outcomes

As a primary outcome, we assessed and compared the variability of the malaria weekly parasite incidences reporting units located along at each of the main Amazon river tributaries

separately. Weekly parasite incidence was calculated by dividing the total weekly count of malaria cases, as reported by the national surveillance system, per 1,000 inhabitants of each community as estimated by the Peruvian Ministry of Health at each surveillance reporting unit.

## Climate and environmental variables

For the purpose of characterizing the patterns of transmission, we assessed a set potential climate and environmental associated factors with our outcome of interest. These variables included temperature (MERRA-T2M), humidity (MERRA-QV2M), soil moisture (MERRA-SFMC), elevation (ASTER-GDEM), precipitation (TRMM-TMPA 3B42V7), and NDVI **(**MODIS MOD13C1). Each of these variables was assessed using their weekly averages estimated at the coordinates of each the Loreto surveillance reporting units for the 2010–2015 period. Due to the different resolution, each variable was estimated by averaging their hourly estimates using the protocols standardized by NASA for each of their satellite products. In the case of the MERRA products data was available at hourly steps and with a 1/2°×2/3° resolution, TMPA precipitation estimates were available at 3-hourly time steps and with a 0.25°×0.25° resolution; while the MODIS NDVI estimates were available at 0.05°x 0.05° resolution and the ASTER GDEM was available with a resolution of 1° × 1° tiles for land surface regions between 83° N-S.

## Data Collection

Weekly parasite incidences (malaria cases per 1,000 inhabitants) was estimated at each surveillance reporting unit by dividing their weekly malaria counts over the government estimates of the population coverage by each surveillance reporting unit. We assessed the Loreto

surveillance system to obtain the weekly counts from each of its 342 surveillance reporting units during the 2010-2015 period. Briefly, for each epidemiological week all the surveillance reporting units reported their malaria counts to the regional health directorate, which uses the surveillance software NOTI for data entry and quality control. We maintained the main datasets without identifiers in a secure computer system as prevention to maintain confidentiality and avoid loss of data. Then, we directly analyzed the CSV files using STATA/MP v14.0 (Stata Corporation, College Station, TX, 2011) with the Excel import command for data management, including further checks and reviewing for consistency and completeness.

## Data Analysis

First, we performed an exploratory analysis to describe and compare the baseline characteristics within and between reporting units by region. Baseline characteristics and outcomes were described with summary statistics, using frequency and percentage for categorical variables and mean and standard deviation for continuous variables. To estimate the effect of the RCD/FMDA on interrupting malaria transmission in Piura, we first the fit a bivariate model with the WPI as a function of the road proximity to closer intervention districts during the pilot study. Then we fit a multivariate model using a mixed-effects Poisson regression model to adjust for the climate and weather variables as potential confounders and account for the structure of the data. The forward selection was used to determine the variables for the multivariate model using the Akaike Information Criteria (AIC) and the likelihood ratio test (LRT) to compare nested models. Pearson's correlation coefficients are also computed for each variable to assess and prevent multicollinearity. All the analyses were conducted with Stata/MP 14.0 (Stata Corporation, College Station, TX) using a significance level of $p<0.05$.

### Ethical considerations

During study planning, the study protocol was approved by the Tumbes and Piura Regional Health Directorate authorities, which approved the study as a project of public health relevance for their regions. Both regions designated a lead epidemiologist to collaborate during data collection. Both Regional Health Directorate epidemiologist participated actively in all the interventions related activities, so they had a broad knowledge about the quality and limitations of the data, and were the first recipients of the study results for decision-making purposes.

## *5.4 Results*

### Malaria incidence in Loreto

In 2010 Loreto reported a total of 11,512 malaria cases, including 9,162 cases positive for *P. vivax*, 2,312 for *P. falciparum*, and 55 to both species. With this count, we estimated an annual parasite incidence of 13.3 cases per 1,000 people (95% Confidence Interval [CI]: 13.1 to 13.6 cases per 1,000 people), representing a record low since 1994 (Figure 14). Across surveillance units, we estimated that in 2010 the average weekly parasite incidence (WPI) was about 32.5 cases per 100,000 people (95% CI: 29.2 to 35.7 cases per 100,000 people), with a range of 0 to 10,259 cases per 100,000 people.

## Malaria incidence in Loreto's Health Networks

Loreto showed a high heterogeneity variability of WPI among health networks (Table 15). During the period 2010-2017 (Figure 15-16), the health networks with the high mean WPI were Datem del Marañon with 331.6 cases per 100,000 people (95% CI: 305.5 to 358.1 cases per 100,000 people), Loreto with 241.5 cases per 100,000 people (95% CI: 226.5 to 256.5 cases per 100,000 people), Maynas City with 145.5 cases per 100,000 people (95% CI: 226.5 to 256.5 cases per 100,000 people), Maynas Periphery with 114.8 cases per 100,000 people (95% CI: 109.7 to 120.1 cases per 100,000 people) and Ramon Castilla with 112.4 cases per 100,000 people (95% CI: 102.8 to 122.1 cases per 100,000 people). During the same period the health networks with the lowest WPI were Requena with 81.2 cases per 100,000 people (95% CI: 81.2 to 122.1 cases per 100,000 people), Alto Amazonas with 53.9 cases per 100,000 people (95% CI: 50.0 to 57.8 cases per 100,000 people), and Ucayali with 13.6 cases per 100,000 people (95% CI: 10.5 to 16.7 cases per 100,000 people). Among clinics and hospitals, which do not belong to any health network the mean WPI during 2010-2017 also low compared to most health networks with 17.5 cases per 100,000 people (95% CI: 15.7 to 19.2 cases per 100,000 people).

## Malaria incidence across Amazon river tributaries

For the purpose of testing the hypothesis that each of the main Amazon river tributaries behaves as independent ecosystems large enough to sustain the transmission of malaria from one season to the following, we assessed the patterns of incidence along them. To do so, first, we explore the variability of the WPI among the health networks, which was already disaggregated following the Loreto map using the rivers as the natural boundaries. Second, using guidance from key informants from the Loreto Health Directorate (with over twenty years of experience

managing and directing the malaria program in Loreto) we split the largest health networks into smaller river systems following the path of the main Amazon river tributaries as well as by splitting the Amazon river into as small as possible units but administratively independent sections. Consequently, we started with the eight health networks from the health infrastructure map of Loreto and then decided to disaggregate the Loreto map into 14 riverine systems.

The process started by disaggregating the health network Datem del Marañon, which is crossed by the Marañon river and its two main tributaries, the Pastaza and the Morona rivers (Figure 17). Here the decision was to disaggregate the health network into three river systems allocating all the surveillance units from the Andoas and Pastaza districts to the Pastaza river, the ones from the Manseriche, Barranca and Cahuapanas districts to the Marañon river, and the ones from the Morona district to the Morona river. In doing so we observed significant differences (ANOVA $p$-value $<0.001$) in the mean WPI during the 2010-2017 period among the rivers Marañon ($24.5 \pm 2.1$ malaria cases per 1,000 people), Morona ($54.0 \pm 6.1$ malaria cases per 1,000 people) and Pastaza ($904.3 \pm 38.7$ malaria cases per 1,000 people) both, during the whole period or observations as well as from year to year (Figures 17 and 18).

In the case of the Maynas Periphery and Ramon Castilla health networks, which are two of the largest health networks in Loreto, we allocated all the surveillance units from the Yaquerana district -Maynas Periphery together with ones from the Yavari district – Ramos Castilla, all located along the along the Yavari River (Figure 18). Second, similarly, we allocated all the surveillance units along the Peru-Colombia border, all located along the Putumayo River. Third, we split the Amazon river into three sections, the first allocating the surveillance units from the Belen and Fernando Lores districts (both from Maynas Periphery health network), the second combining those from Indiana and Las Amazonas districts (Maynas Periphery health network), and the third

linking those from Pevas and San Pablo districts (Ramon Castilla health network). Third, we combined all the surveillance units along the Napo River, including the ones located at Torres Causasana, Napo, and Mazan districts (all from the Maynas Periphery health network) (Figure 19). By doing so we observed significant differences (ANOVA $p$-value <0.001) in the mean WPI during the 2010-2017 period among the Putumayo river (53.9 ± 4.2 malaria cases per 1,000 people), Yavari river (279.6 ± 9.4 malaria cases per 1,000 people), Amazonas section Fernando Lores (24.5 ± 2.1 malaria cases per 1,000 people), and Amazonas section Las Amazonas (54.0 ± 6.1 malaria cases per 1,000 people), Amazonas section Ramón Castilla (904.3 ± 38.7 malaria cases per 1,000 people). Such differences varied widely year by year as well (Figures 20 and 21).

In the case of the Loreto health network, we allocated all of the surveillance units from the Tigre district with the Tigre river, while all other surveillance units were allocated to the Marañon River. We observed significant differences ($t$-test $p$-value <0.001) in the mean WPI during the 2010-2017 period for both rivers (339.7 ± 10.9 vs. 148.5 ± 10.6 malaria cases per 1,000 people; $p$-value <0.001). Such differences also varied widely year by year (Figures 20 and 21).

**Modeling the risk of malaria in time and space**

To model the malaria counts in time and space, first we fit a mixed-effects Poisson regression model using health centers as a first level and the rivers system as a second level, and by adjusting the malaria counts by population, seasonality, time, and traveling time to the Loreto Regional Hospital as a surrogate of connectivity. Second, we improved the fit of the model by adding key administrative, weather and climate covariates (Figures 22-28). At the end of the process, the main predictors identified included precipitation (Figure 26), vegetation (Figure 27), altitude (Figure

28), and the level of care offered at each surveillance unit or Health Center type (Tables 19 and 20).

Once the mixed-effects multivariate Poisson regression model was fitted we addressed the issue of the many weekly zero counts, which represent 25.1% of all weekly malaria counts in our dataset. To do so, we fitted a mixed-effect negative binomial Poisson regression model with the same covariates (Table 21). To compare the fit of both models, we used the Likelihood-ratio test and observed that indeed, the mixed-effect negative binomial Poisson regression model fitted the data significantly better than the mixed-effect negative binomial Poisson regression model (p-value <0.0001). That being said, we also observed that precipitation lost its significance as a predictor of the malaria risk, so we ran a new model without precipitation. Comparing both models with the Likelihood-ratio test the one without precipitation fitted malaria counts better.

Table 21 shows the regression coefficients of the final model where it can be seen that the risk of malaria increases with time, traveling distances from Iquitos, and vegetation, but decreases with higher altitude. Also, the model supports the hypothesis that the rivers behaves as independent networks with different patterns of malaria transmission.

**Modeling the risk of vivax and falciparum malaria**

When assessing the predictability of the model by malaria species, we noticed that precipitation seems to compete with traveling distance as a predictor of the risk of malaria. By comparing the coefficients in both models, we observed that the risk of falciparum malaria seems to be more associated with the variability of the river systems than the risk of vivax malaria, as well as more associated with the density of vegetation.

## *5.5 Discussion*

In the path to eliminate and eradicate malaria, there is a clear and urgent need for improvement of the data analysis used to inform decision makers. By doing so, malaria-endemic countries certainly can take the best of their surveillance data to track their human malaria reservoir and characterize its patterns of malaria transmission. In our study, we assessed the surveillance data from the Peruvian Amazon, which a low endemic malaria region, and were able to identify different patterns of malaria incidence across Loreto. In the study region, the distribution of malaria cases seems to follow the Amazon river tributaries, which are areas competent to sustain the transmission of malaria from one season to the following. Furthermore, we observed that the main predictors of malaria in the region are low altitude and the density of the vegetation, which together seems to characterize well the variability of ecosystems across the region. Additionally, we found some differences in the distribution of falciparum malaria which seems to be more associated with the density of the vegetation than the distribution of vivax malaria.

The problem of zero counts of cases of malaria in epidemiological weeks resulted in a major challenge during the analytical process of our study. This is normally addressed by switching from a mixed-effects Poisson regression model to a mixed-effects Zero-Inflated Poisson regression, but mixed-effects negative binomial Poisson regression seems to represent a more appropriate alternative to deal with the over dispersion of the data.

The pattern of incidence of malaria showed a high variability across river systems as well as year by year. While in some regions the incidence of malaria grew rapidly early in the study period, others seem to expand later in the study period. In contrast, while some rivers exhibit some stability in time with a softened seasonality, others exhibited instability and with a strong seasonality effect.

Once characterized the information gathered about the patterns of incidence along the river system can be used to guide focalized intervention that helps to interrupt the transmission of malaria in a more cost-effective manner. A reasonable explanation for these results could be the relative stability of the human malaria reservoir as well as of the mosquitoes breeding sites along each of the river systems in the Amazon basin. However, here we can only be conservative with these findings because of the lack of more rigorous study design and the fact that the signal we analyzed was based on diagnosis obtained by microscopy. This means the human reservoir we are assessing in only the tip of an iceberg of asymptomatic malaria below the limit of detection of microscopy like as previously described (27).

This study showed that the combination of altitude and vegetation predict the risk of malaria in the Loreto region better that other climate and weather predictors such as temperature, precipitation, humidity, soil moisture or pressure. The negative association with altitude could indicate a need for warmer temperatures for malaria transmission, which increases in the lower jungle compared with the high jungle. Furthermore, the combination of altitude and vegetation may better characterize better the conditions necessary for the appearance of mosquitoes breeding sites and guaranteed the Anopheles mosquitoes survival.

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## *5.7 Tables for Chapter 6*

**Table 16.** Malaria mean weekly parasite Incidence by year and health network

| | Mean Weekly Parasite Incidence ** (95% CI) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **2010** | **2011** | **2012** | **2013** | **2014** | **2015** | **2016** | **2017** |
| **Overall** | 32.5 (29.2 - 35.7) | 30.9 (28.5 - 33.3) | 69.6 (64.0 - 75.1) | 111.9 (104.7 - 119.1) | 145.9 (136.3 - 155.5) | 181.7 (170.7 - 192.8) | 247.8 (229.0 - 266.5) | 295.5 (273.4 - 317.6) |
| **Health Network** | | | | | | | | |
| Clinics/Hospitals | 3.8 (1.8 - 5.7) | 1.6 (1.0 - 2.3) | 5.4 (3.6 - 7.2) | 19.5 (14.2 - 24.7) | 32.1 (25.2 - 39.0) | 23.7 (18.6 - 28.8) | 30.8 (23.2 - 38.3) | 22.8 (17.9 - 27.7) |
| Maynas City | 41.4 (35.3 - 47.4) | 70.6 (62.4 - 78.9) | 154.0 (131.5 - 176.5) | 225.5 (206.1 - 244.9) | 228.2 (209.6 - 246.8) | 173.3 (158.7 - 187.9) | 146.0 (133.7 - 158.3) | 125.0 (107.4 - 142.7) |
| Maynas Periphery | 43.0 (32.9 - 53.1) | 45.1 (38.5 - 51.7) | 60.4 (52.9 - 67.8) | 101.4 (90.4 - 112.4) | 114.4 (98.3 - 130.4) | 190.3 (170.0 - 210.6) | 160.6 (143.7 - 177.5) | 203.6 (183.4 - 223.8) |
| Ramon Castilla | 52.1 (38.0 - 66.2) | 34.1 (24.9 - 43.2) | 139.9 (113.8 - 166.0) | 220.6 (163.9 - 277.2) | 104.1 (88.1 - 120.0) | 184.7 (153.5 - 216.0) | 68.9 (54.2 - 83.5) | 95.1 (78.1 - 112.2) |
| Loreto | 40.9 (28.2 - 53.5) | 16.6 (12.4 - 20.9) | 53.0 (41.4 - 64.6) | 138.8 (112.1 - 165.5) | 313.3 (259.5 - 367.1) | 369.0 (325.9 - 412.0) | 543.8 (473.2 - 614.3) | 456.7 (401.8 - 511.5) |
| Requena | 86.7 (62.5 - 111.0) | 29.3 (20.3 - 38.3) | 94.2 (71.6 - 116.8) | 130.8 (100.1 - 161.6) | 113.1 (88.0 - 138.2) | 70.0 (55.6 - 84.5) | 73.2 (55.3 - 91.1) | 51.9 (37.6 - 66.3) |
| Ucayali | 12.6 (3.4 - 21.8) | 13.4 (8.5 - 18.3) | 8.2 (4.3 - 12.0) | 23.9 (10.6 - 37.1) | 10.7 (5.5 - 15.9) | 19.6 (9.8 - 29.5) | 13.0 (-0.3 - 26.3) | 7.5 (4.3 - 10.7) |
| Alto Amazonas | 10.5 (6.9 - 14.1) | 16.9 (11.6 - 22.1) | 38.8 (25.8 - 51.7) | 35.4 (27.4 - 43.4) | 65.1 (52.1 - 78.1) | 82.1 (67.0 - 97.2) | 72.1 (62.6 - 81.5) | 110.6 (96.0 - 125.2) |
| Datem del Marañon | 13.7 (8.9 - 18.5) | 11.2 (8.5 - 14.0) | 27.5 (21.5 - 33.5) | 73.8 (59.5 - 88.1) | 192.2 (152.0 - 232.5) | 325.3 (265.7 - 384.8) | 837.9 (715.8 - 960.0) | 1170.8 (1020.5 - 1321.1) |

***** Population estimated at baseline (year 2008); ** Weekly Parasite Incidence = Total malaria cases per week/ 100,000 inhabitants; 95% CI = 95% Confidence Interval.

**Table 17.** Malaria mean weekly parasite Incidence by year and river system

| River System (Units) | Mean Weekly Parasite Incidence ** (95% CI) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **2010** | **2011** | **2012** | **2013** | **2014** | **2015** | **2016** | **2017** |
| Amazonas 1 | 3.5 | 2.9 | 17.4 | 51.4 | 17.4 | 11.7 | 7.1 | 7.1 |
| (12 Units) | (2.2 - 4.9) | (1.8 - 3.9) | (11.1 - 23.6) | (36.0 - 66.7) | (11.8 - 22.9) | (8.7 - 14.8) | (5.0 - 9.2) | (4.7 - 9.6) |
| Amazonas 2 | 8.5 | 31.2 | 87.6 | 73.1 | 38.8 | 27.3 | 15.4 | 28.1 |
| (11 Units) | (6.0 - 10.9) | (21.6 - 40.8) | (61.8 - 113.4) | (55.4 - 90.7) | (30.2 - 47.3) | (20.7 - 34.0) | (10.5 - 20.2) | (17.0 - 39.3) |
| Amazonas 3 | 11.5 | 9.6 | 71.0 | 148.6 | 40.4 | 150.8 | 61.8 | 52.0 |
| (20 Units) | (8.9 - 14.1) | (7.0 - 12.1) | (48.0 - 94.0) | (79.2 - 217.9) | (33.2 - 47.7) | (113.2 - 188.5) | (43.6 - 80.1) | (37.1 - 66.9) |
| Huallaga | 1.3 | 0.3 | 1.3 | 6.2 | 4.9 | 46.7 | 61.2 | 120.4 |
| (37 Units) | (0.7 - 1.9) | (0.1 - 0.5) | (0.6 - 2.1) | (3.3 - 9.1) | (2.6 - 7.3) | (38.6 - 54.8) | (51.9 - 70.6) | (103.6 - 137.2) |
| Marañon | 13.9 | 1.1 | 7.6 | 28.9 | 116.6 | 115.9 | 161.0 | 220.3 |
| (52 Units) | (8.1 - 19.7) | (0.8 - 1.4) | (5.5 - 9.7) | (19.5 - 38.2) | (82.8 - 150.5) | (99.3 - 132.4) | (126.4 - 195.6) | (170.5 - 270.1) |
| Morona | 1.5 | 0.1 | 2.4 | 19.1 | 49.3 | 24.6 | 17.2 | 82.5 |
| (9 Units) | (0.4 - 2.6) | (-0.1 - 0.3) | (1.2 - 3.6) | (9.8 - 28.3) | (32.2 - 66.5) | (13.6 - 35.6) | (8.6 - 25.8) | (58.8 - 106.2) |
| Nanay | 41.4 | 70.7 | 154.0 | 225.4 | 228.2 | 173.3 | 145.9 | 125.0 |
| (62 Units) | (35.3 - 47.4) | (62.4 - 78.9) | (131.5 - 176.5) | (206.0 - 244.8) | (209.6 - 246.8) | (158.7 - 187.9) | (133.6 - 158.2) | (107.4 - 142.7) |
| Napo | 53.5 | 84.5 | 89.3 | 179.9 | 263.6 | 361.2 | 349.7 | 459.0 |
| (22 Units) | (43.2 - 63.7) | (69.0 - 99.9) | (76.0 - 102.6) | (154.1 - 205.7) | (221.5 - 305.7) | (311.7 - 410.6) | (308.9 - 390.6) | (408.3 - 509.7) |
| Pastaza | 19.5 | 31.4 | 78.2 | 201.3 | 518.0 | 885.2 | 2371.3 | 3130.0 |
| (15 Units) | (14.3 - 24.6) | (23.4 - 39.4) | (60.7 - 95.7) | (160.3 - 242.3) | (401.2 - 634.7) | (713.9 - 1056.4) | (2030.0 - 2712.5) | (2731.4 - 3528.5) |
| Putumayo | 1.4 | 0.0 | 0.0 | 0.0 | 0.1 | 195.3 | 128.7 | 105.3 |
| (10 Units) | (-0.7 - 3.6) | (0.0 - 0.0) | (0.0 - 0.0) | (0.0 - 0.0) | (-0.1 - 0.3) | (151.1 - 239.5) | (91.3 - 166.2) | (81.0 - 129.6) |
| Tigre | 61.4 | 32.9 | 94.1 | 234.8 | 362.7 | 535.1 | 784.6 | 611.7 |
| (18 Units) | (38.6 - 84.1) | (24.3 - 41.5) | (71.1 - 117.0) | (186.7 - 283.0) | (307.6 - 417.7) | (458.8 - 611.3) | (678.4 - 890.7) | (554.2 - 669.3) |
| Ucayali | 62.8 | 24.2 | 66.5 | 96.3 | 80.1 | 53.8 | 53.8 | 37.6 |
| (32 Units) | (46.0 - 79.6) | (17.8 - 30.5) | (51.0 - 81.9) | (74.9 - 117.7) | (62.8 - 97.3) | (43.4 - 64.1) | (40.9 - 66.7) | (27.8 - 47.4) |
| Yavari | 303.1 | 151.2 | 345.3 | 447.0 | 304.8 | 307.3 | 119.0 | 259.4 |
| (8 Units) | (222.4 - 383.8) | (117.0 - 185.5) | (283.8 - 406.9) | (386.3 - 507.7) | (257.6 - 352.1) | (265.7 - 348.8) | (99.7 - 138.3) | (218.0 - 300.9) |
| Yurimaguas | 23.6 | 40.1 | 89.2 | 63.5 | 133.3 | 135.0 | 95.4 | 116.3 |
| (34 Units) | (15.1 - 32.1) | (27.5 - 52.7) | (58.2 - 120.1) | (45.5 - 81.5) | (103.3 - 163.4) | (100.6 - 169.4) | (75.7 - 115.0) | (87.5 - 145.0) |

***** Population estimated at baseline (year 2008); ** Weekly Parasite Incidence = Total malaria cases per week/ 100,000 inhabitants; 95% CI = 95% Confidence Interval.

**Table 18.** Weekly means of the environmental and climate parameters during the scale-up study *

| Location | Mean (95% CI) | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Pressure** (kPa) | **Humidity** (kg vapor * $kg^{1}$ air * $10^3$) | **Temperature** (°C) | **Moisture** ($kg/m^2$) | **Precipitation** ($mm^{-1}$ water * $m^2$) | **Vegetation** (NDVI) | **Altitude** (m) |
| **All** | 99.03 (90.02 - 94.03) | 17.09 (17.07 - 17.10) | 26.01 (26.00 - 26.02) | 0.34 (0.34- 0.34) | 194.8 (193.9 - 195.6) | 0.74 (0.74 - 0.74) | 139.8 (139.6 - 140.0) |
| **By river** | | | | | | | |
| Amazonas1 | 99.81 (99.81 - 99.82) | 19.4 (19.4 - 19.4) | 25.4 (25.4 - 25.5) | 0.40 (0.40 - 0.40) | 252.0 (247.9 - 256.1) | 0.74 (0.74 - 0.74) | 107.8 (107.8 - 107.9) |
| Amazonas2 | 99.52 (99.48 - 99.55) | 18.8 (18.7 - 18.8) | 25.4 (25.3 - 25.4) | 0.39 (0.38 - 0.39) | 252.5 (248.2 - 256.9) | 0.69 (0.69 - 0.70) | 110.2 (109.6 - 110.8) |
| Amazonas3 | 99.91 (99.90 - 99.91) | 19.2 (19.2 - 19.2) | 25.4 (25.4 - 25.4) | 0.40 (0.40 - 0.40) | 299.5 (296.1 - 302.9) | 0.74 (0.74 - 0.74) | 94.5 (94.2 - 94.7) |
| Huallaga | 97.68 (97.65 - 97.70) | 14.9 (14.9 - 15.0) | 26.5 (26.5 - 26.5) | 0.28 (0.28 - 0.29) | 139.0 (136.8 - 141.1) | 0.76 (0.76 - 0.76) | 188.1 (187.4 - 188.7) |
| Marañon | 98.58 (98.56 - 98.60) | 15.9 (15.8 - 15.9) | 26.6 (26.6 - 26.7) | 0.29 (0.29 - 0.29) | 154.0 (152.1 - 155.9) | 0.72 (0.72 - 0.72) | 140.4 (140.0 - 140.8) |
| Morona | 97.70 (97.68 - 97.72) | 15.7 (15.6 - 15.8) | 26.0 (25.9 - 26.1) | 0.29 (0.29 - 0.30) | 164.6 (160.1 - 169.0) | 0.76 (0.76 - 0.76) | 150.0 (150.0 - 150.0) |
| Nanay | 99.78 (99.78 - 99.78) | 19.1 (19.1 - 19.1) | 25.3 (25.3 - 25.3) | 0.39 (0.39 - 0.39) | 243.2 (241.4 - 244.9) | 0.75 (0.74 - 0.75) | 116.7 (116.5 - 116.9) |
| Napo | 99.54 (99.53 - 99.55) | 18.8 (18.8 - 18.8) | 25.0 (25.0 - 25.0) | 0.40 (0.40 - 0.40) | 254.9 (252.0 - 257.8) | 0.75 (0.75 - 0.75) | 169.4 (168.1 - 170.7) |
| Pastaza | 98.60 (98.58 - 98.61) | 16.1 (16.0 - 16.2) | 26.4 (26.3 - 26.5) | 0.32 (0.32 - 0.32) | 165.0 (161.4 - 168.6) | 0.75 (0.75 - 0.76) | 190.4 (189.8 - 191.0) |
| Putumayo | 99.82 (99.81 - 99.83) | 18.7 (18.7 - 18.8) | 24.9 (24.9 - 25.0) | 0.41 (0.41 - 0.41) | 292.1 (287.8 - 296.4) | 0.73 (0.73 - 0.74) | 108.3 (108.0 - 108.6) |
| Tigre | 99.36 (99.35 - 99.37) | 16.9 (16.9 - 17.0) | 26.0 (25.9 - 26.0) | 0.35 (0.35 - 0.36) | 167.6 (164.4 - 170.9) | 0.73 (0.73 - 0.74) | 125.0 (125.0 - 125.0) |
| Ucayali | 99.16 (99.15 - 99.18) | 16.6 (16.5 - 16.6) | 26.2 (26.2 - 26.2) | 0.31 (0.31 - 0.32) | 163.9 (161.5 - 166.4) | 0.75 (0.74 - 0.75) | 120.9 (120.7 - 121.0) |
| Yavari | 99.79 (99.78 - 99.80) | 18.4 (18.4 - 18.5) | 25.5 (25.4 - 25.5) | 0.38 (0.38 - 0.38) | 257.2 (251.3 - 263.0) | 0.74 (0.74 - 0.75) | 88.6 (87.4 - 89.8) |
| Yurimaguas | 98.33 (98.32 - 98.34) | 14.4 (14.4 - 14.5) | 27.4 (27.4 - 27.4) | 0.26 (0.26 - 0.26) | 111.2 (109.3 - 113.2) | 0.75 (0.75 - 0.75) | 178.7 (178.5 - 179.0) |

* Weekly estimates averaged at year 2009-2010; SD, Standard deviation; 95% CI = 95% Confidence Interval; Pressure (kPa), kilopascals of pressure estimated per $km^2$; Humidity (kg vapor * $kg^{-1}$ air * $10^3$), $10^3$ kg of water vapor per kg of air measured daily at 2 m above the displacement height; Temperature (°C), degree Celsius of temperature at 2 m above the displacement height; Soil moisture ($m^3$*$m^{-3}$), cubic meters of water per square meter of soil; Precipitation (mm water * $m^{-2}$), mm of rain per square meter per hour; Vegetation (NDVI), normalized difference vegetation index.

**Table 19.** Correlation Matrix of the variables used in the multivariate analysis for the P. vivax-weekly parasite counts model

| | | WPI[a] | Traveling Time | Pressure | Humidity | Temp. | Moisture | Precip. | Veget. |
|---|---|---|---|---|---|---|---|---|---|
| **Traveling Time** | Pearson (*r*) | 0.0330* | 1.0000 | | | | | | |
| | *p* value | <0.0001 | | | | | | | |
| **Pressure** | Pearson (*r*) | 0.0626* | **-0.5064*** | 1.0000 | | | | | |
| | *p* value | <0.0001 | **<0.0001** | | | | | | |
| **Humidity** | Pearson (*r*) | 0.0163* | -0.4274* | 0.5812* | 1.0000 | | | | |
| | *p* value | <0.0001 | <0.0001 | <0.0001 | | | | | |
| **Temperature** | Pearson (*r*) | -0.0164* | 0.1724* | -0.2564* | **-0.6275*** | 1.0000 | | | |
| | *p* value | <0.0001 | <0.0001 | <0.0001 | **<0.0001** | | | | |
| **Moisture** | Pearson (*r*) | 0.0434* | -0.4005* | **0.6390*** | **0.7848*** | **-0.6409*** | 1.0000 | | |
| | *p* value | <0.0001 | <0.0001 | **<0.0001** | **<0.0001** | **<0.0001** | | | |
| **Precipitation** | Pearson (*r*) | 0.0054 | -0.1778* | 0.3146* | **0.6486*** | **-0.5085*** | **0.5701*** | 1.0000 | |
| | *p* value | <0.0001 | <0.0001 | <0.0001 | **<0.0001** | **<0.0001** | **<0.0001** | | |
| **Vegetation** | Pearson (*r*) | 0.0167* | 0.0735* | -0.0483* | -0.0185* | 0.0113* | 0.0038 | 0.0113* | 1.0000 |
| | *p* value | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0002 | 0.2117 | 0.0002 | |
| **Altitude** | Pearson (*r*) | 0.0518* | 0.4406* | **-0.6548*** | **-0.5089*** | 0.2288* | **-0.5134*** | -0.3068* | 0.0719* |
| | *p* value | <0.0001 | <0.0001 | **<0.0001** | **<0.0001** | <0.0001 | **<0.0001** | <0.0001 | <0.0001 |

[a] Weekly Parasite Incidence (WPI)= Total malaria cases per week/ 1,000 inhabitants; * p value <0.05

**Table 20.** Forward selection of variables for the Mixed-Effects Poisson Regression Model

| Models | AIC |
|---|---|
| **I. Setting the basic model** | |
| Empty Model | 893556.8 |
| Empty Model + Population | 881416.5 |
| Empty Model + Population + Traveling time | 875501.2 |
| Empty Model + Population + Traveling time + Week | 804957.0 |
| Empty Model + Population + Traveling time + Week + Sin1 + Cos1 | 792122.4 |
| Empty Model + Population + Traveling time + Week + Sin1 + Cos1 + Sin2 + Cos2 | 791474.7 |
| **II. Modeling the effect of proximity towards the intervention sites** | |
| Basic model | 791474.7 |
| Basic model + Pressure | Correlated |
| Basic model + Precipitation | NC |
| Basic model + Temperature | NC |
| Basic model + Altitude + Health Center Type | NC |
| Basic model + Vegetation | 791399.8 |
| Basic model + Soil Moisture | 791210.0 |
| Basic model + Humidity | 791169.4 |
| **Basic model + Altitude** | **789304.1** |
| Basic model + Altitude + Humidity | Correlated |
| Basic model + Altitude + Soil Moisture | Correlated |
| Basic model + Altitude + Temperature | NC |
| Basic model + Altitude + Health Center Type | NC |
| Basic model + Altitude + Vegetation | 789257.1 |
| **Basic model + Altitude + Precipitation** | **789208.6** |
| Basic model + Altitude + Precipitation + Health Center Type | NC |
| **Basic model + Altitude + Precipitation + Vegetation** | **786192.7** |
| **Basic model + Altitude + Precipitation + Vegetation + Health Center Type** | **789166.6** |

* Final model; AIC = Akaike's information criterion; RCD/FMDA = Reactive case Detection with Focal Mass Drug Administration; NC, not computable.

**Table 21.** Mixed-Effects Poisson Regression Model for the overall weekly Parasite Incidence

| | Estimate | 95% CI | IRR-Fixed Effects | 95% CI |
|---|---|---|---|---|
| Constant | -0.7826 | -1.3960, -0.1692 | 0.4572 | 0.2476, 0.8443 |
| Population | 0.0000 | 0.0000, 0.0000 | 1.0000 | 1.0000, 1.0000 |
| Time traveling [a] | -0.0070 | -0.0074, -0.0066 | 0.9931 | 0.9927, 0.9935 |
| Time in weeks [b] | 0.0068 | 0.0067, 0.0069 | 1.0068 | 1.0068, 1.0069 |
| Sine 1 [c] | -0.0064 | -0.0145, 0.0017 | 0.9936 | 0.9856, 1.0017 |
| Cosine 1 [c] | -0.3568 | -0.3633, -0.3503 | 0.6999 | 0.6954, 0.7045 |
| Sine 2 [c] | -0.0446 | -0.0508, -0.0384 | 0.9564 | 0.9505, 0.9623 |
| Cosine 2 [c] | 0.0649 | 0.0588, 0.0710 | 1.0671 | 1.0605, 1.0736 |
| Altitude [d] | -0.0050 | -0.0052, -0.0048 | 0.9950 | 0.9948, 0.9952 |
| Precipitation [e] | 0.0003 | 0.0003, 0.0003 | 1.0003 | 1.0003, 1.0003 |
| Vegetation [f] | 0.1142 | 0.0721, 0.1562 | 1.1209 | 1.0748, 1.1690 |
| Center Type | | | | |
| Health Post | Ref. | | Ref. | |
| Health Center | 1.2497 | 1.2401, 1.2594 | 3.4894 | 3.4559, 3.5232 |
| Clinic/Hospital | -0.5551 | -0.5889, -0.5213 | 0.5740 | 0.5549, 0.5937 |
| RE (Network) | 1.3638 | 0.6501, 2.8612 | 1.3638 | 0.6501, 2.8612 |

* IRR = Incidence-Rate Ratio; AIC = Akaike's information criterion; 95% IC = 95% Interval of Confidence; RE = Random effects; a, Traveling time to Iquitos city by river; time in epidemiological weeks; sine and cosine functions to characterize the seasonality of the weekly parasite incidence; d, altitude in meter over the sea level; e, precipitation (mm water * m-2) or mm of rain per square meter per hour; f, vegetation or normalized difference vegetation index (NDVI).

**Table 22.** Mixed-Effects Negative Binomial Regression Model for the Overall Malaria Weekly Parasite Incidence

| | IRR with Precipitation | 95% CI | IRR without Precipitation | 95% CI |
|---|---|---|---|---|
| Constant | 0.7355 | 0.6275, 0.8622 | 0.7355 | 0.4219, 0.5647 |
| Population | 1.0000 | 1.0000, 1.0001 | 1.0000 | 1.0000, 1.0000 |
| Time traveling [a] | 0.9979 | 0.9969, 0.9989 | 1.0028 | 1.0017, 1.0039 |
| Time in weeks [b] | 1.0084 | 1.0082, 1.0086 | 1.0085 | 1.0083, 1.0087 |
| Sine 1 [c] | 1.1089 | 1.0727, 1.1463 | 1.1131 | 1.0831, 1.1441 |
| Cosine 1 [c] | 0.7658 | 0.7452, 0.7870 | 0.7649 | 0.7447, 0.7857 |
| Sine 2 [c] | 1.0174 | 0.9903, 1.0451 | 1.0250 | 0.9978, 1.0529 |
| Cosine 2 [c] | 1.0893 | 1.0607, 1.1186 | 1.0878 | 1.0593, 1.1170 |
| Altitude [d] | 0.9870 | 0.9864, 0.9876 | 0.9882 | 0.9877, 0.9888 |
| Precipitation [e] | 1.0001 | 0.9999, 1.0003 | | |
| Vegetation [f] | 1.2652 | 1.0677, 1.4992 | 1.2149 | 1.0250, 1.4399 |
| Center Type | | | | |
| Health Post | Ref. | | Ref. | |
| Health Center | 3.6913 | 3.5026, 3.8901 | 4.0858 | 3.8755, 4.3075 |
| Clinic/Hospital | 0.1350 | 0.1095, 0.1664 | 0.1378 | 0.1112, 0.1708 |
| Ln(alpha) | 1.9954 | 1.9784, 2.0125 | 2.0040 | 1.9784, 2.0125 |
| RE (Network) | 1.98e+09 | 1.90e+09, 2.06e+09 | 1.66e+09 | 1.60e+09, 1.74e+09 |

* IRR = Incidence-Rate Ratio; AIC = Akaike's information criterion; 95% IC = 95% Interval of Confidence; RE = Random effects; a, Traveling time to Iquitos city by river; time in epidemiological weeks; sine and cosine functions to characterize the seasonality of the weekly parasite incidence; d, altitude in meter over the sea level; e, precipitation (mm water * m-2) or mm of rain per square meter per hour; f, vegetation or normalized difference vegetation index (NDVI).

**Table 23.** Mixed-Effects Negative Binomial Regression Model for the Vivax Malaria Weekly Parasite Incidence

| | IRR with Precipitation | 95% CI | IRR without Precipitation | 95% CI |
|---|---|---|---|---|
| Constant | 0.3394 | 0.2898, 0.3975 | 0.3651 | 0.3160, 0.4219 |
| Population | 1.0000 | 1.0000, 1.0000 | 1.0000 | 1.0000, 1.0000 |
| Time traveling [a] | 1.0010 | 1.0000, 1.0021 | 1.0010 | 1.0000, 1.0021 |
| Time in weeks [b] | 1.0085 | 1.0083, 1.0088 | 1.0085 | 1.0083, 1.0088 |
| Sine 1 [c] | 1.1150 | 1.0789, 1.1523 | 1.1391 | 1.1084, 1.1706 |
| Cosine 1 [c] | 0.7347 | 0.7149, 0.7549 | 0.7393 | 0.7198, 0.7593 |
| Sine 2 [c] | 1.0315 | 1.0042, 1.0596 | 1.0291 | 1.0020, 1.0570 |
| Cosine 2 [c] | 1.0653 | 1.0375, 1.0939 | 1.0647 | 1.0369, 1.0933 |
| Altitude [d] | 0.9898 | 0.9893, 0.9904 | 0.9897 | 0.9891, 0.9902 |
| Precipitation [e] | 1.0002 | 1.0000, 1.0004 | | |
| Vegetation [f] | 1.1119 | 0.9374, 1.3189 | 1.0949 | 0.9238, 1.2976 |
| Center Type | | | | |
| Health Post | Ref. | | Ref. | |
| Health Center | 4.2299 | 4.0135, 4.4581 | 4.2288 | 4.0114, 4.4580 |
| Clinic/Hospital | 0.1366 | 0.1104, 0.1691 | 0.1348 | 0.1089, 0.1669 |
| Ln(alpha) | 1.9546 | 1.9369, 1.9724 | 1.9550 | 1.9372, 1.9727 |
| RE (Network) | 1.55E+07 | 1.48E+09, 1.61E+09 | 1.56e+09 | 1.49e+09, 1.62e+09 |

* IRR = Incidence-Rate Ratio; AIC = Akaike's information criterion; 95% IC = 95% Interval of Confidence; RE = Random effects; a, Traveling time to Iquitos city by river; time in epidemiological weeks; sine and cosine functions to characterize the seasonality of the weekly parasite incidence; d, altitude in meter over the sea level; e, precipitation (mm water * m-2) or mm of rain per square meter per hour; f, vegetation or normalized difference vegetation index (NDVI).

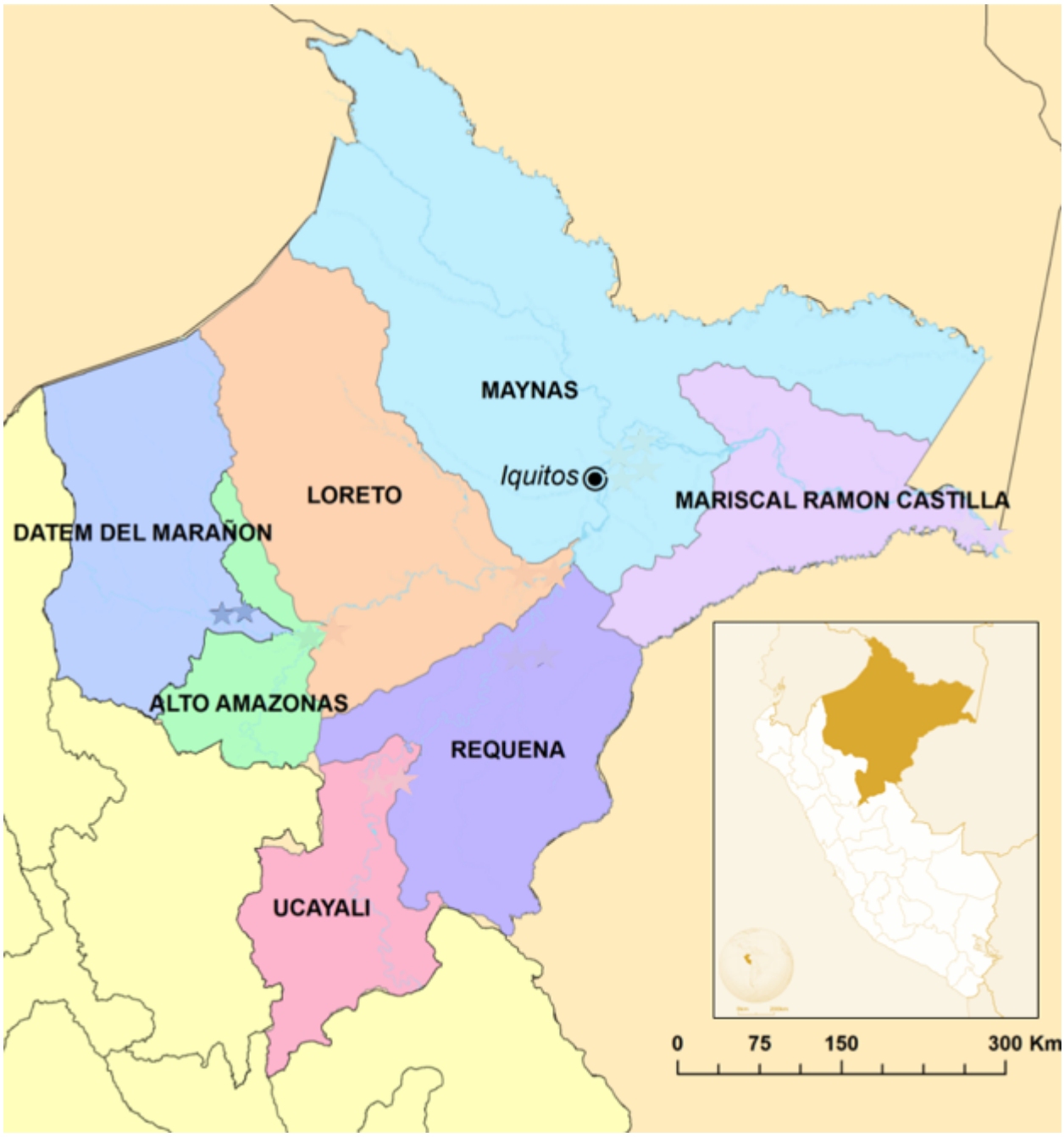
**Table 24.** Mixed-Effects Negative Binomial Regression Model for the Falciparum Malaria Weekly Parasite Incidence

| | IRR with Precipitation | 95% CI | IRR without Precipitation | 95% CI |
|---|---|---|---|---|
| Constant | 0.0370 | 0.0288, 0.0476 | 0.0487 | 0.0385, 0.0617 |
| Population | 1.0000 | 1.0000, 1.0000 | 1.0000 | 1.0000, 1.0000 |
| Time traveling* | 0.9984 | 0.9966, 1.0001 | 0.9972 | 0.9955, 0.9990 |
| Time in weeks[+] | 1.0088 | 1.0084, 1.0092 | 1.0089 | 1.0085, 1.0092 |
| Sine 1 | 0.8336 | 0.7891, 0.8807 | 0.9249 | 0.8847, 0.9669 |
| Cosine 1 | 0.8574 | 0.8200, 0.8965 | 0.8828 | 0.8450, 0.9223 |
| Sine 2 | 0.9464 | 0.9056, 0.9891 | 0.9356 | 0.8953, 0.9777 |
| Cosine 2 | 1.1580 | 1.1089, 1.2093 | 1.1516 | 1.1028, 1.2025 |
| Altitude | 0.9936 | 0.9926, 0.9946 | 0.9932 | 0.9923, 0.9942 |
| Precipitation | 1.0010 | 1.0007, 1.0013 | | |
| Vegetation | 4.1567 | 3.1370, 5.5079 | 4.1300 | 3.1173, 5.4716 |
| Center Type | | | | |
| Health Post | Ref. | | Ref. | |
| Health Center | 4.4154 | 4.0650, 4.7961 | 4.2288 | 4.0114, 4.4580 |
| Clinic/Hospital | 0.3035 | 0.2247, 0.4101 | 0.1348 | 0.1089, 0.1669 |
| lnalpha | 2.8321 | 2.8040, 2.8602 | 2.8353 | 2.8072, 2.8634 |
| RE (Network) | 14.450 | 3.6399, 57.368 | 14.227 | 3.5835, 56.484 |

* IRR = Incidence-Rate Ratio; AIC = Akaike's information criterion; 95% IC = 95% Interval of Confidence; RE = Random effects; a, Traveling time to Iquitos city by river; time in epidemiological weeks; sine and cosine functions to characterize the seasonality of the weekly parasite incidence; d, altitude in meter over the sea level; e, precipitation (mm water * m-2) or mm of rain per square meter per hour; f, vegetation or normalized difference vegetation index (NDVI).

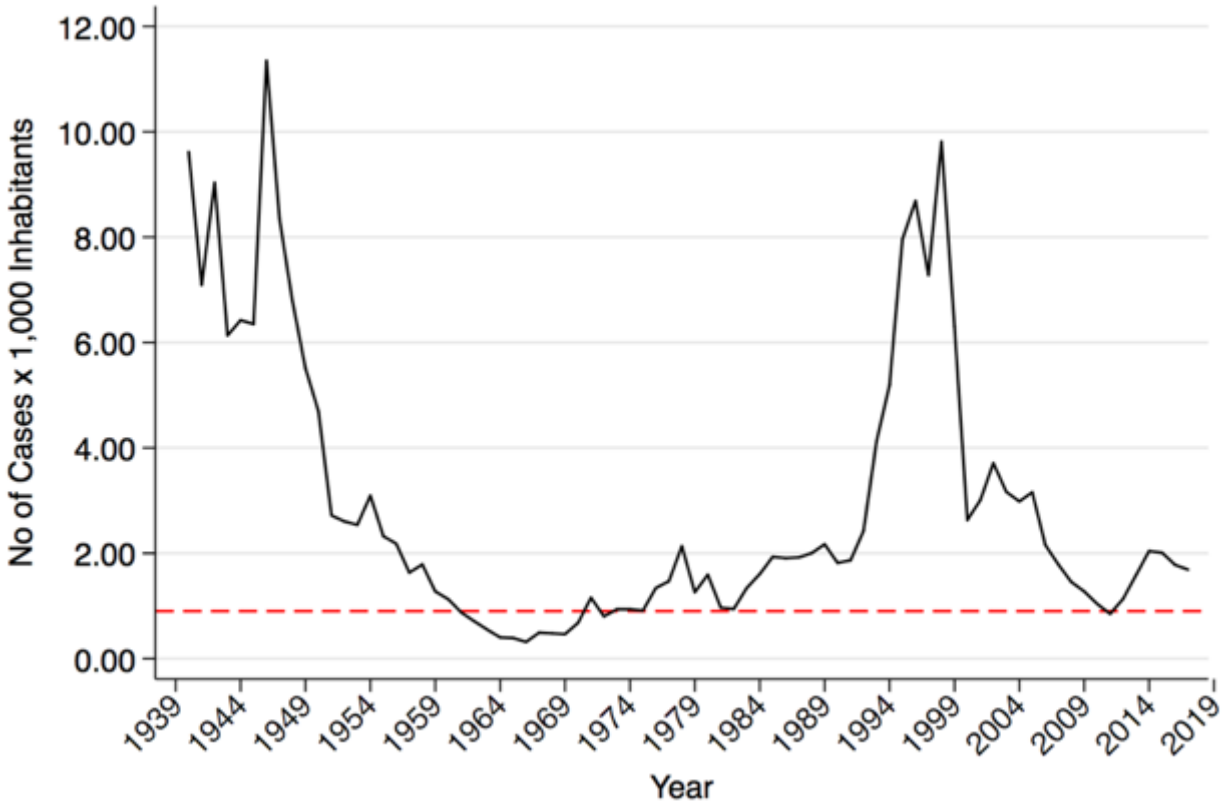
## *5.9 Figures for Chapter 6*

**Figure 13.** Loreto location and provinces



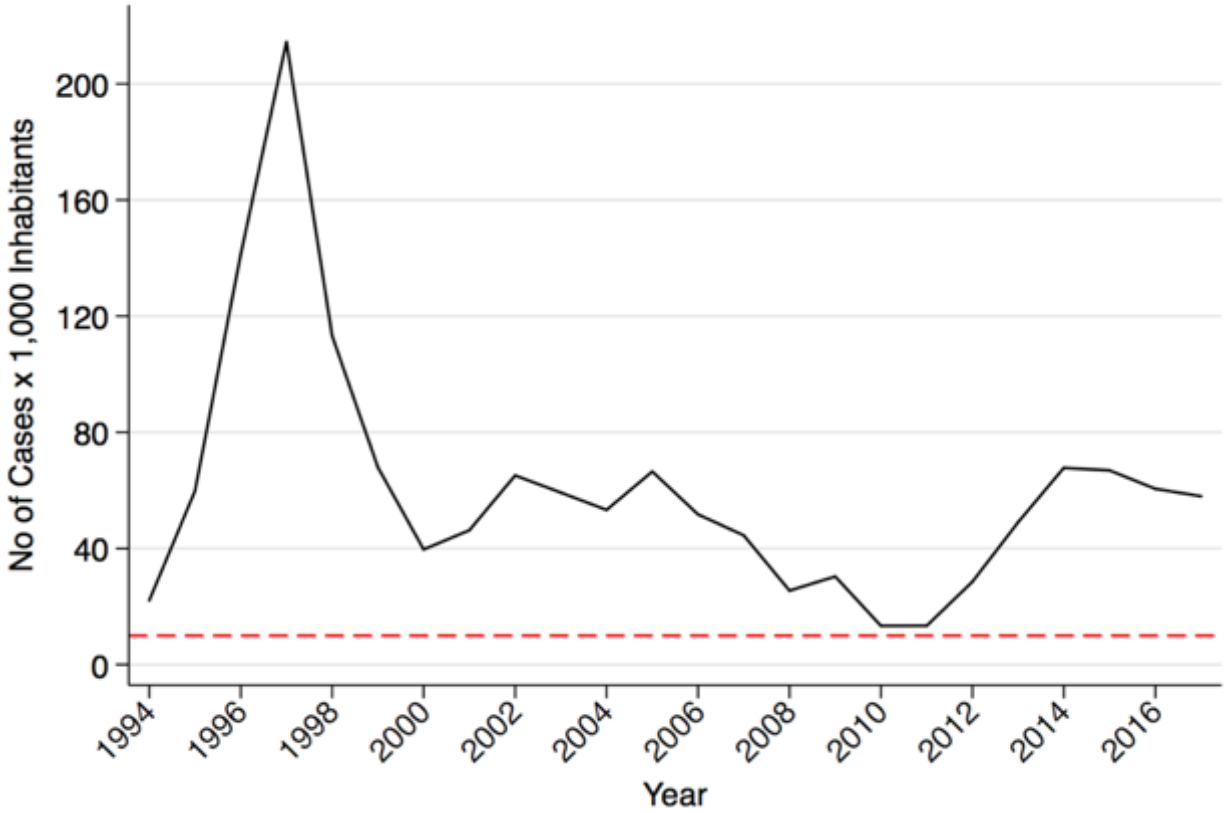

**Source:** Adapted from Ferruci HR, Razuri H, Casapia M, Rahme E, Silva H, Ault S, Blouin B, Mofid LS, Montresor A, Gyorkos TW. Governance, organization, accountability and sustainability of a region-wide school-based deworming program in Loreto, Peru. Acta Trop. 2016; 159: 219-226.

**Figure 14.** Annual Malaria Parasite Incidences in Peru



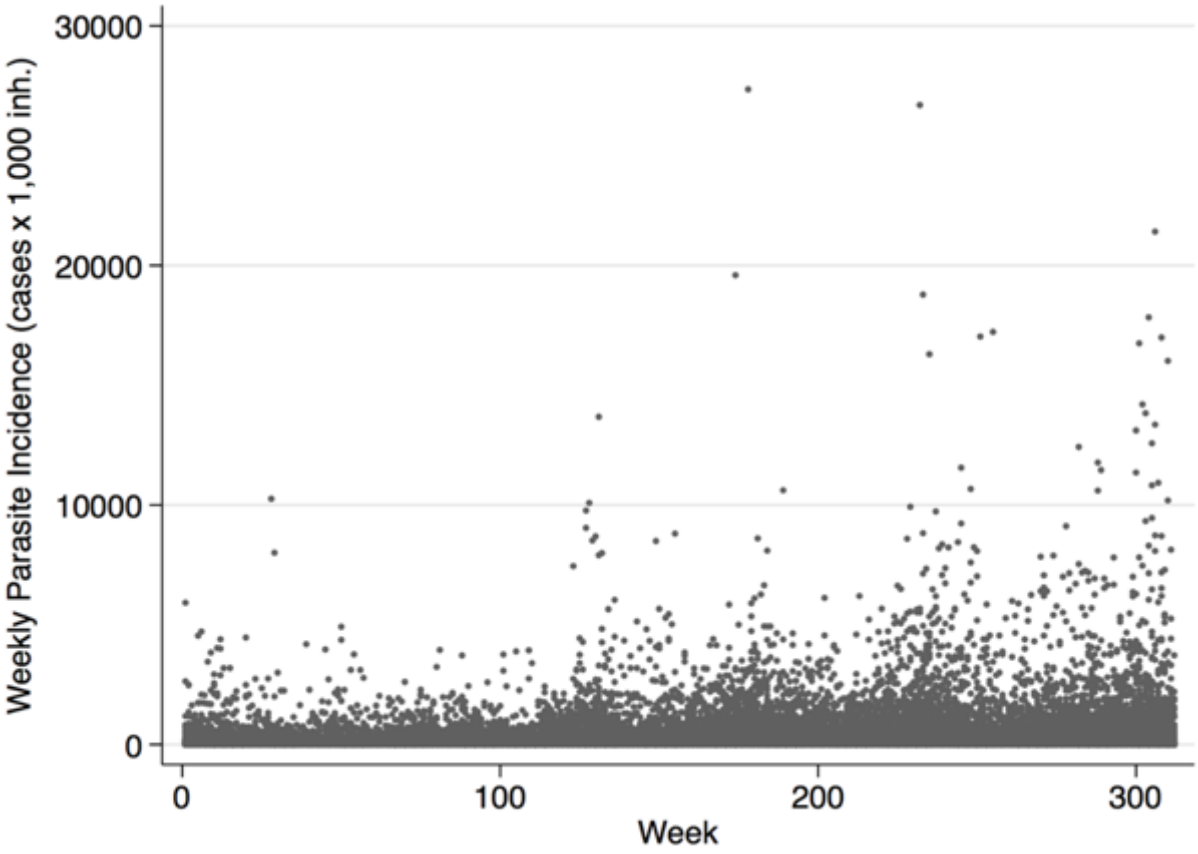

**Legend:** Annual Parasite Index (total of subjects that tested smear positives to malaria per 1,000 inhabitants per year) in Peru since 1939 to 2017. Here, the red dash shows that the threshold of 1 case per 1,000 inhabitants has been overcome only twice (in the latest 1960's and in the latest 2010's), but malaria is increasing again.

**Figure 15.** Annual Malaria Parasite Incidences in Loreto, 1994-2017




**Legend:** Annual Parasite Index (total of subjects that tested smear positives to malaria per 1,000 inhabitants per year) in Loreto since 1994 to 2017. Here, the red dash shows that the threshold of 1 case per 1,000 inhabitants has been overcome only once (late in 2010), but malaria increased again.

**Figure 16.** Weekly Malaria Parasite Incidences by epidemiological week in Loreto, 2010-17

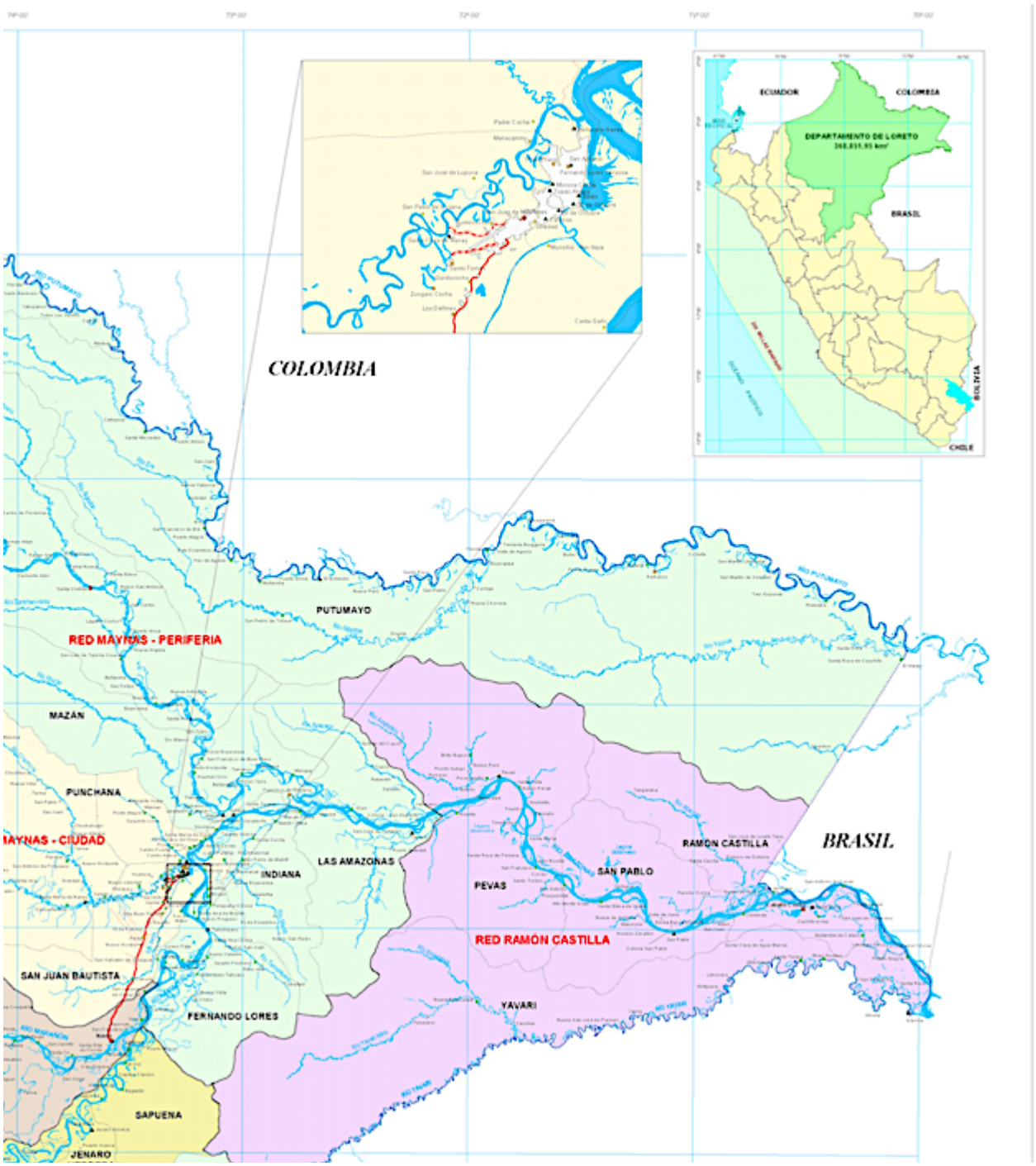



**Legend:** Weekly Parasite Index (total of subjects that tested smear positives to malaria per 1,000 inhabitants per week) in Loreto since 2010 to 2017.

**Figure 17.** Health infrastructure at the Datem del Marañon health networks

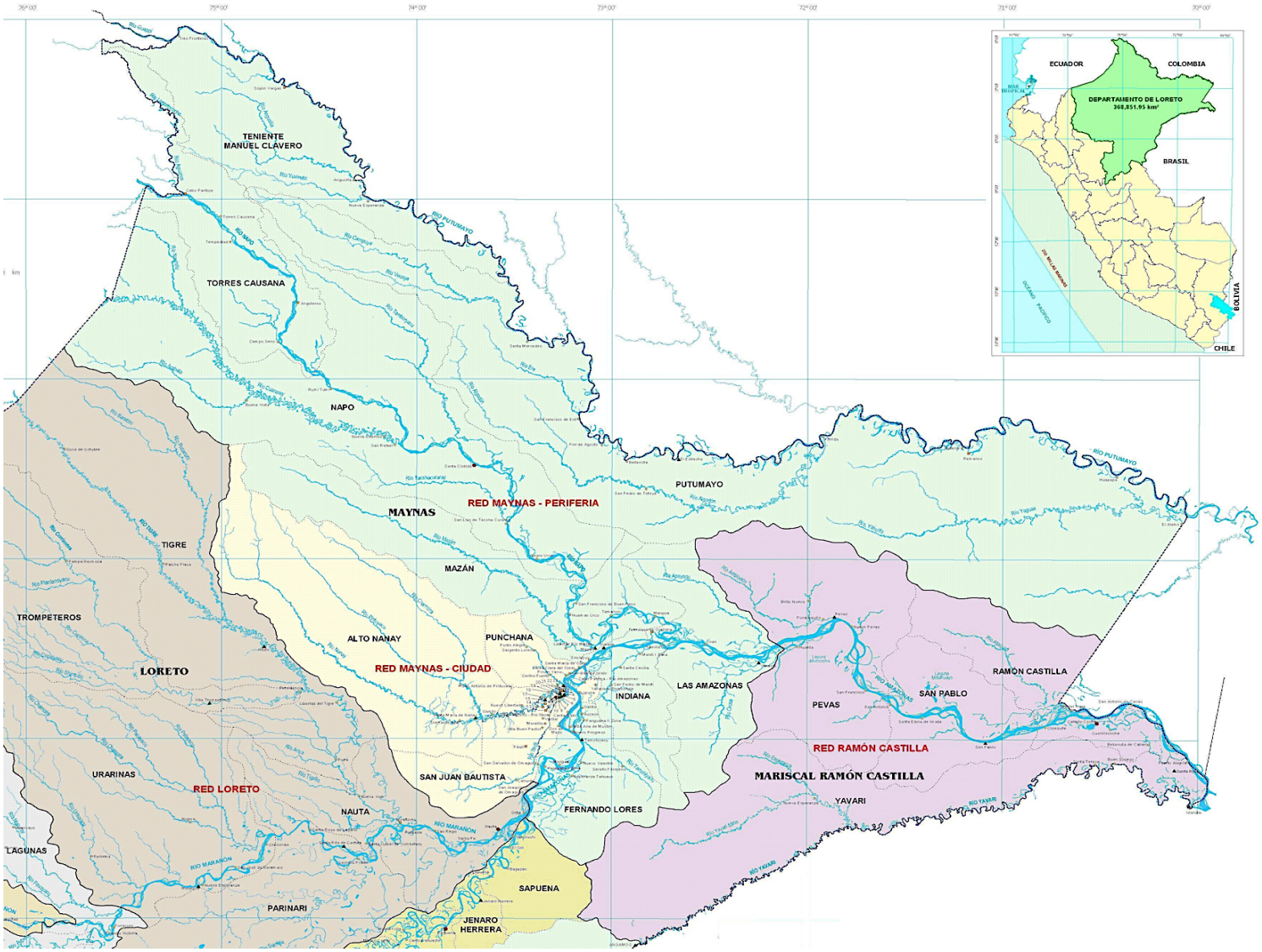

**Legend:** The health networks are highlighted in red and the districts in black.

**Figure 18.** Health infrastructure at the health networks Maynas City, Maynas Periphery and Ramon Castilla



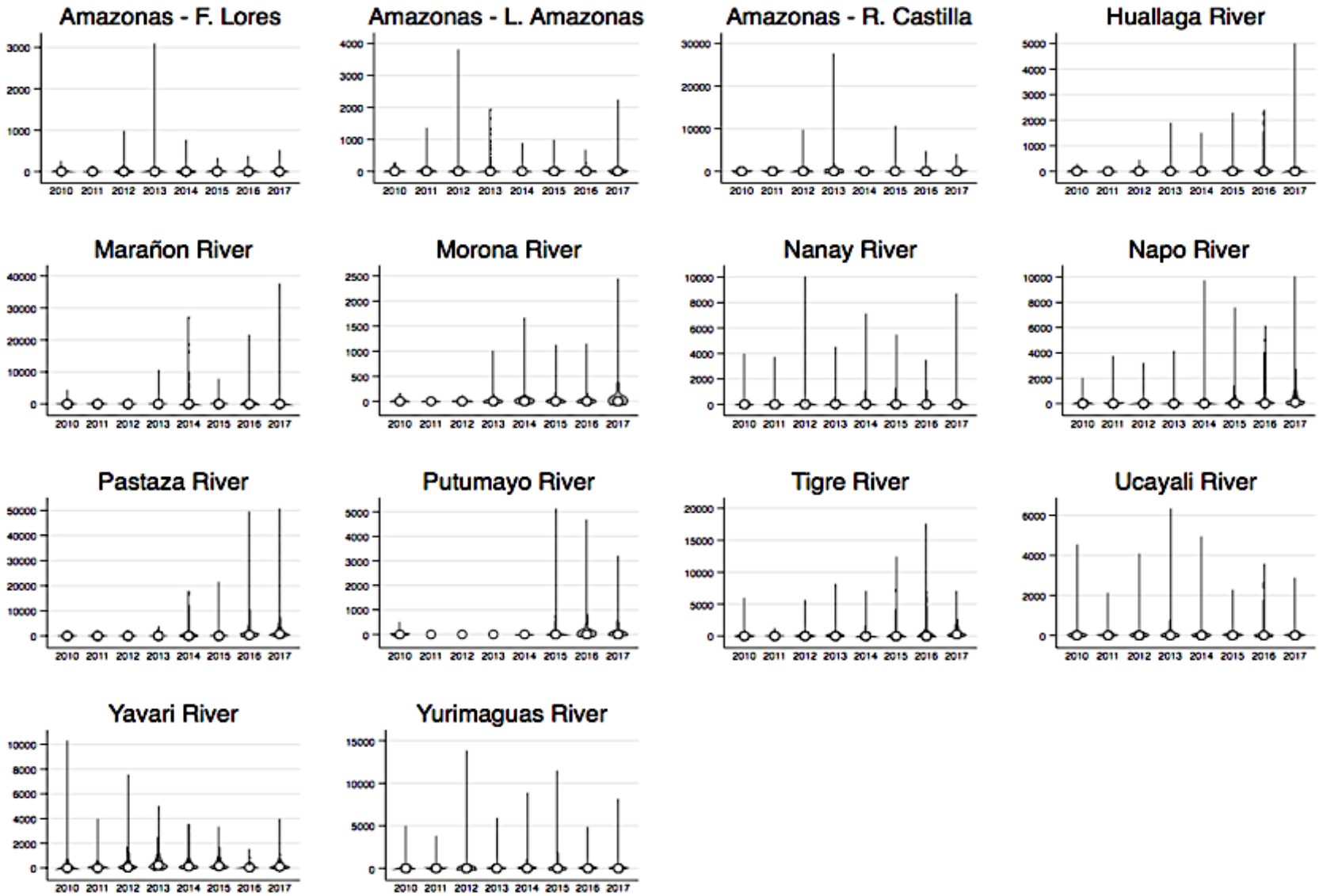

**Legend:** The health networks are highlighted in red and the districts in black.

**Figure 19.** Districts allocated to the river networks Maynas City (*"Ciudad"*), Maynas *("Periferia"*), and Ramon Castilla.



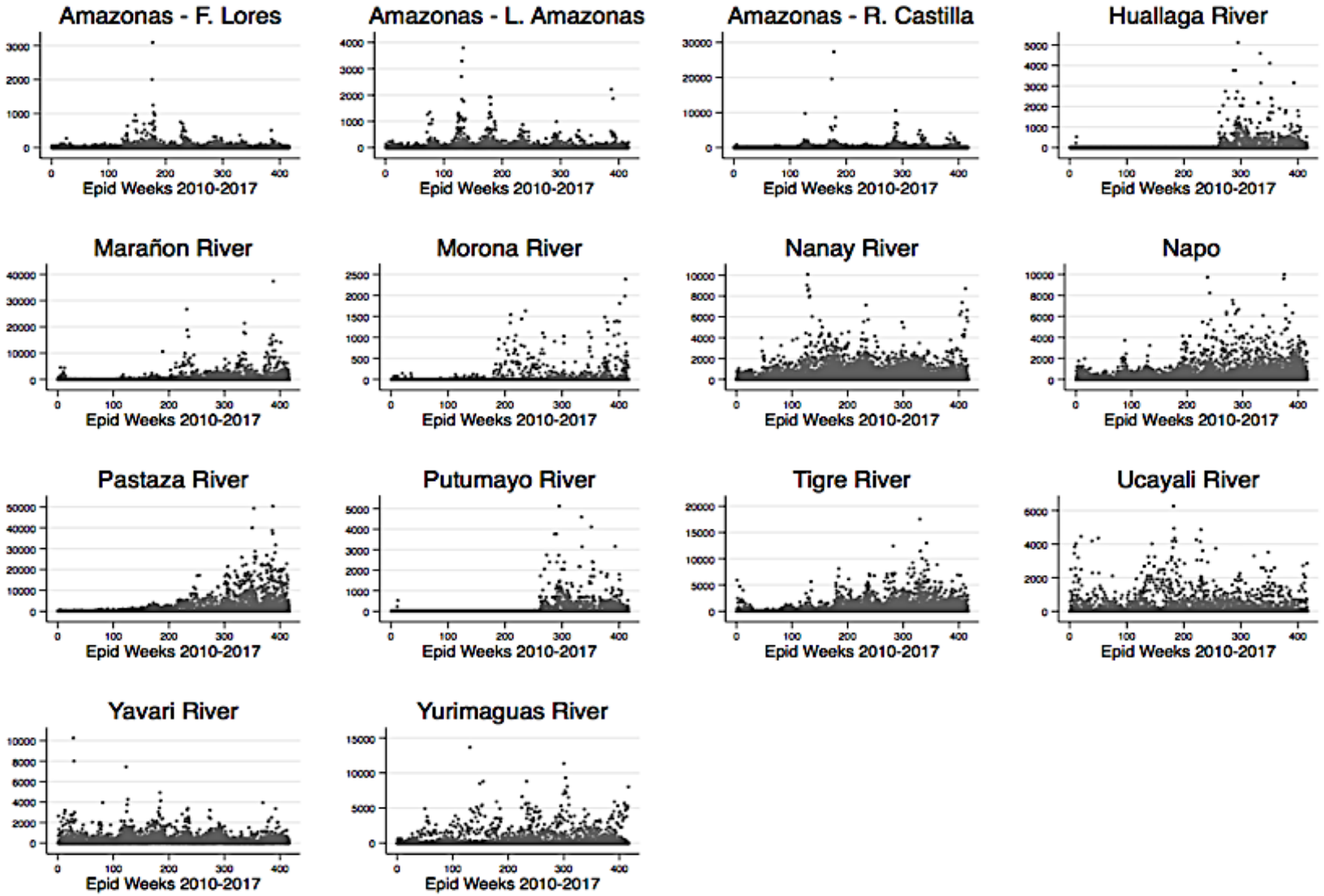

* The health networks are highlighted in red and the districts in black.

**Figure 20.** Mean Weekly Malaria Parasite Incidences among Loreto Surveillance Units by year and River System



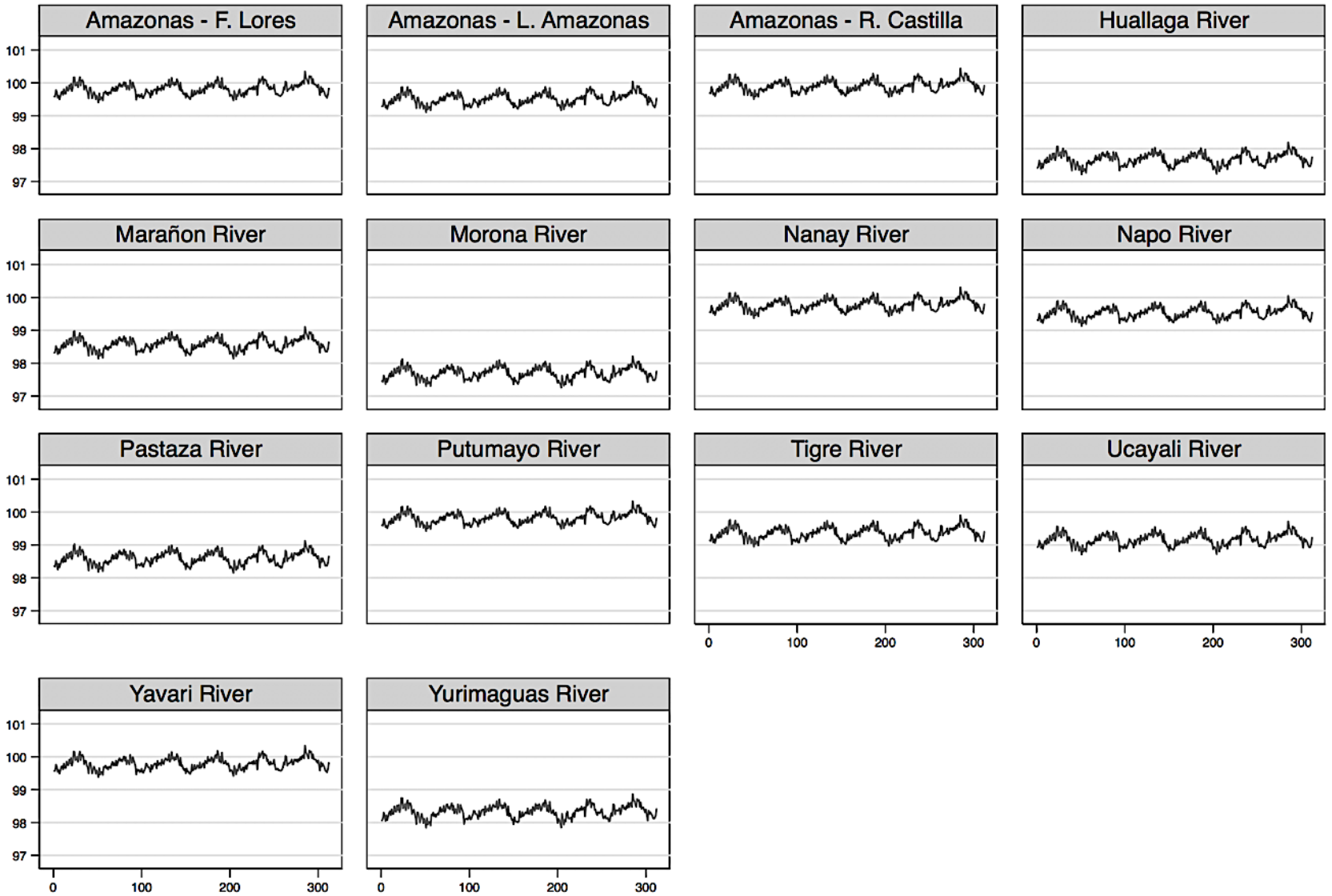

* Y by X Axis: River network's mean weekly parasite incidence (malaria cases x 100,000 inhabitants) by year during 2010-2017

**Figure 21.** Weekly Malaria Parasite Incidences among Loreto Surveillance Units by epidemiological weeks and River Systems



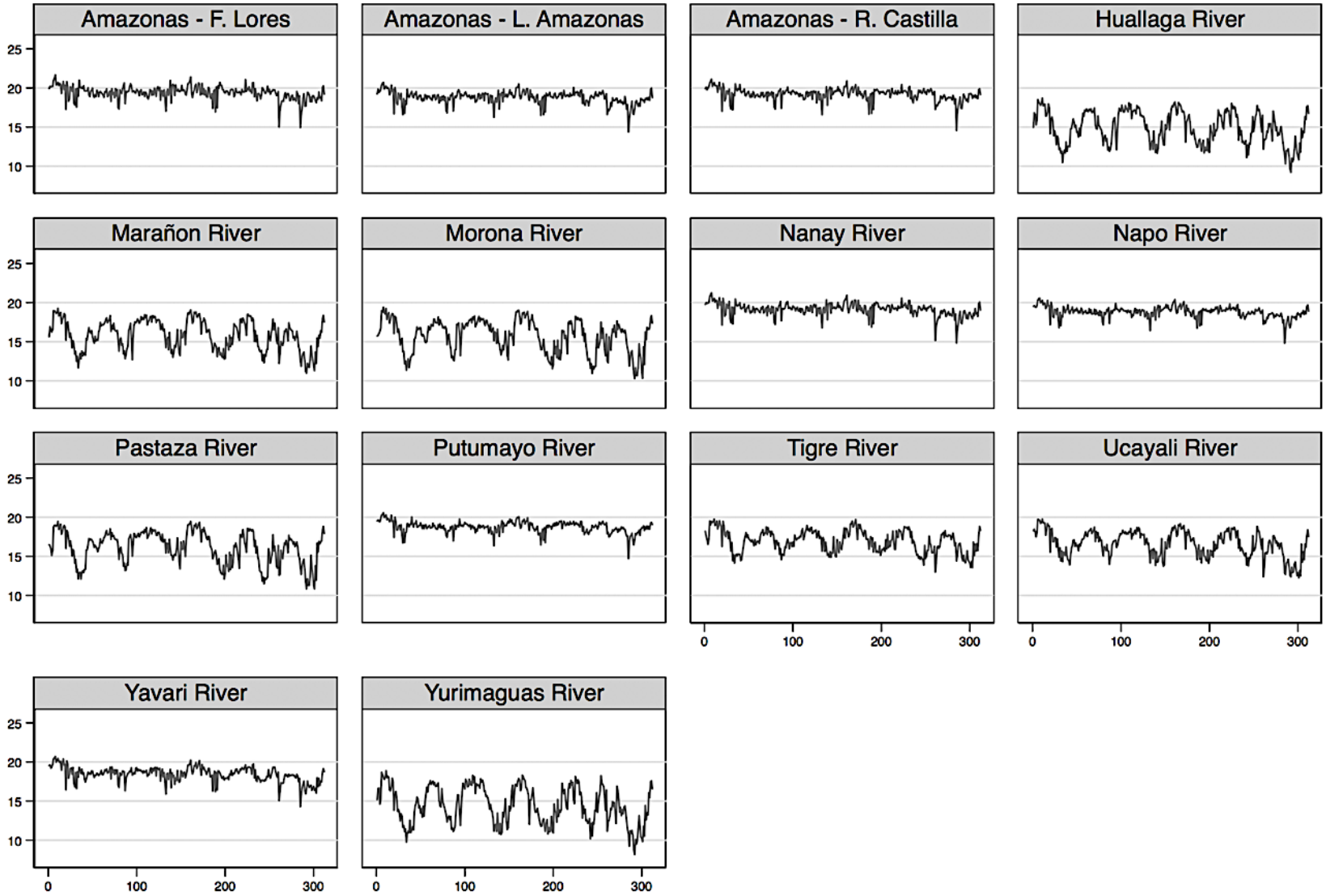

* Y by X Axis: Weekly parasite incidence (malaria cases x 100,000 inhabitants) across Loreto's surveillance units by river network and epidemiological week during 2010-2017

**Figure 22.** Pressure (KPa) among Loreto Surveillance Units by epidemiological weeks and River Systems



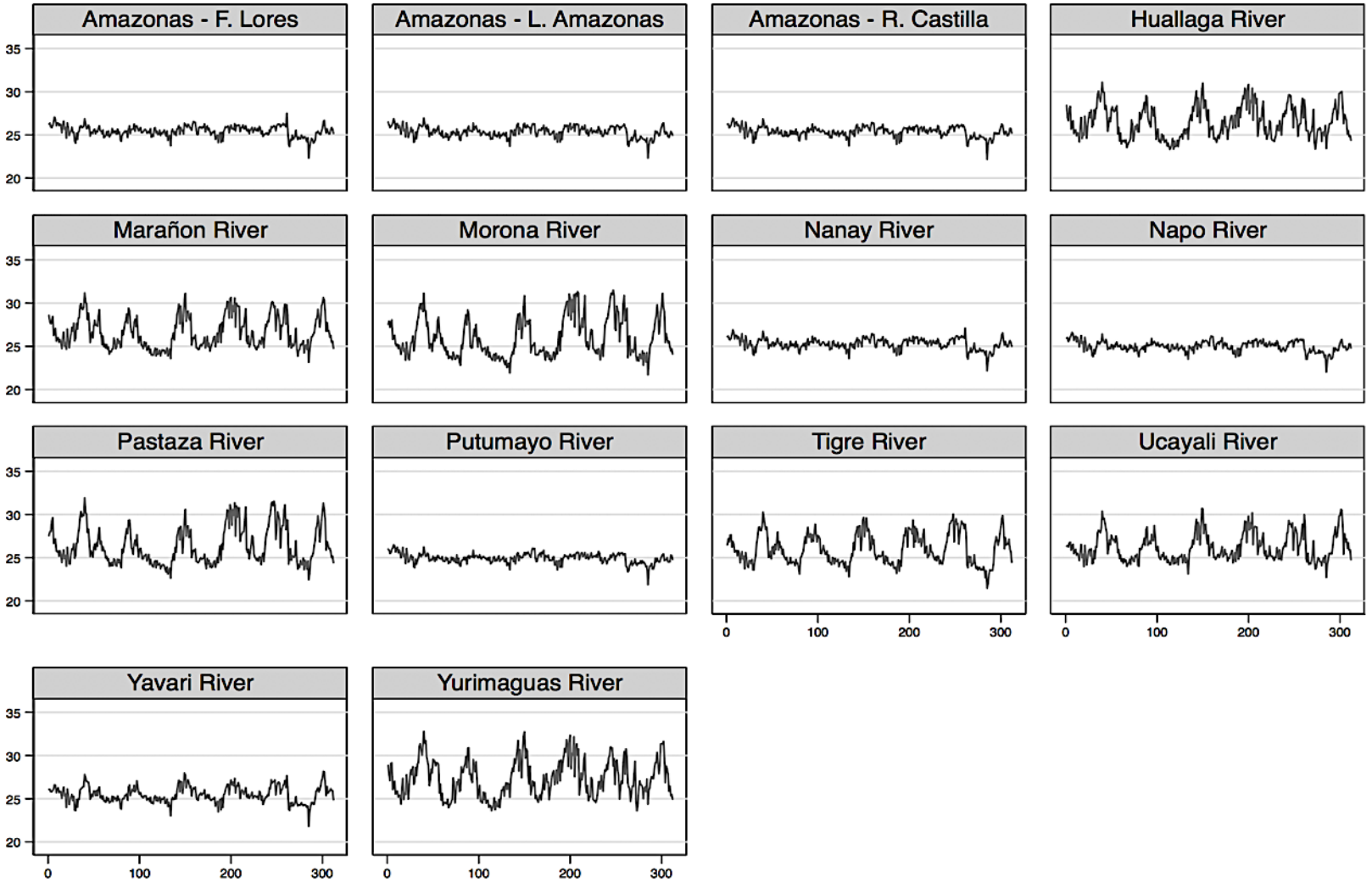

* Y by X Axis: Loreto's temperature estimated mean by epidemiological week during years 2010-2017

**Figure 23.** Humidity (*kg vapor * kg[1] air * 10[3]*) among Loreto Surveillance Units by epidemiological weeks and River Systems



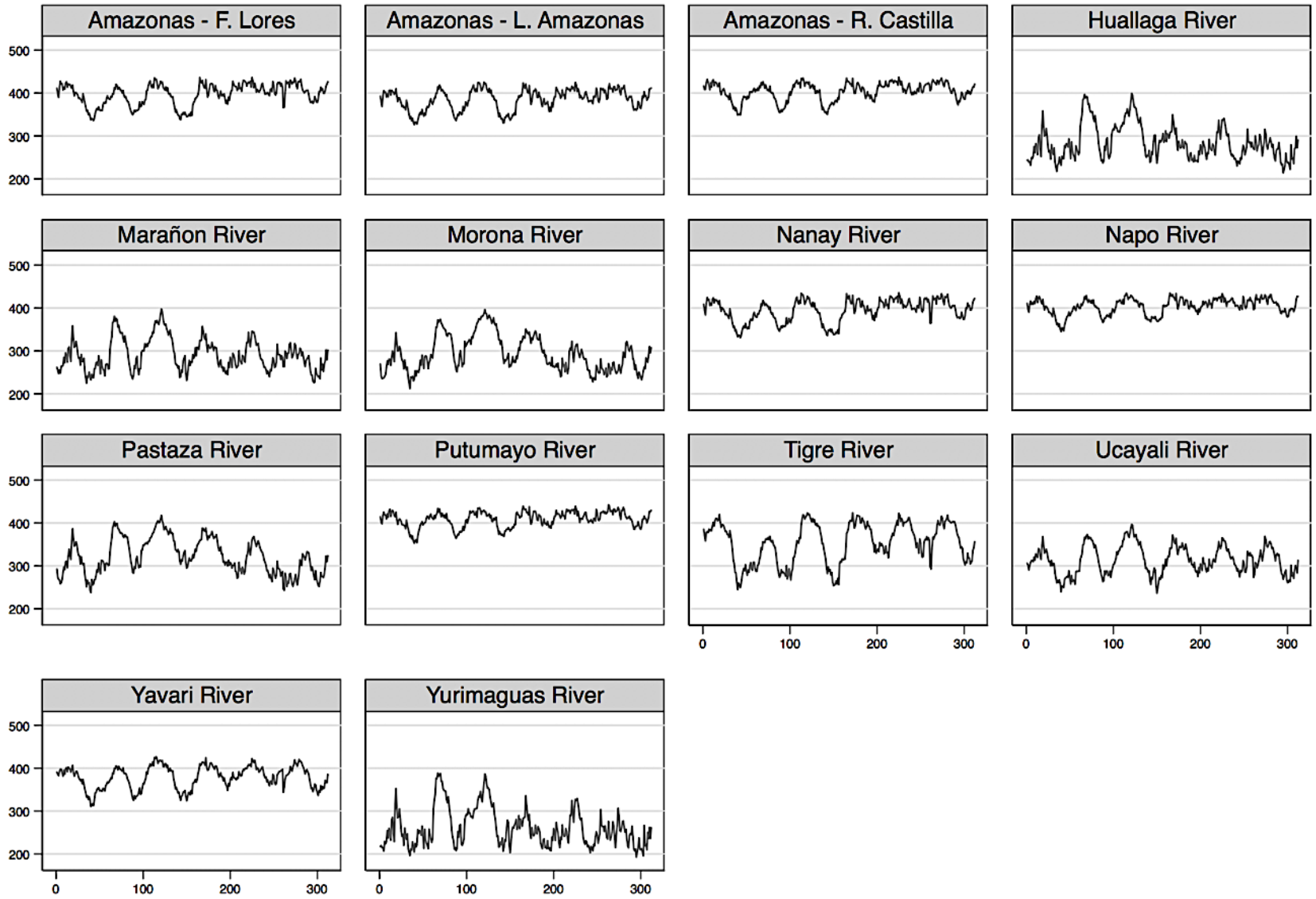

* Y by X Axis: Loreto's humidity estimated mean by epidemiological week during years 2010-2017

**Figure 24.** Temperature (°C) among Loreto Surveillance Units by epidemiological weeks and River Systems



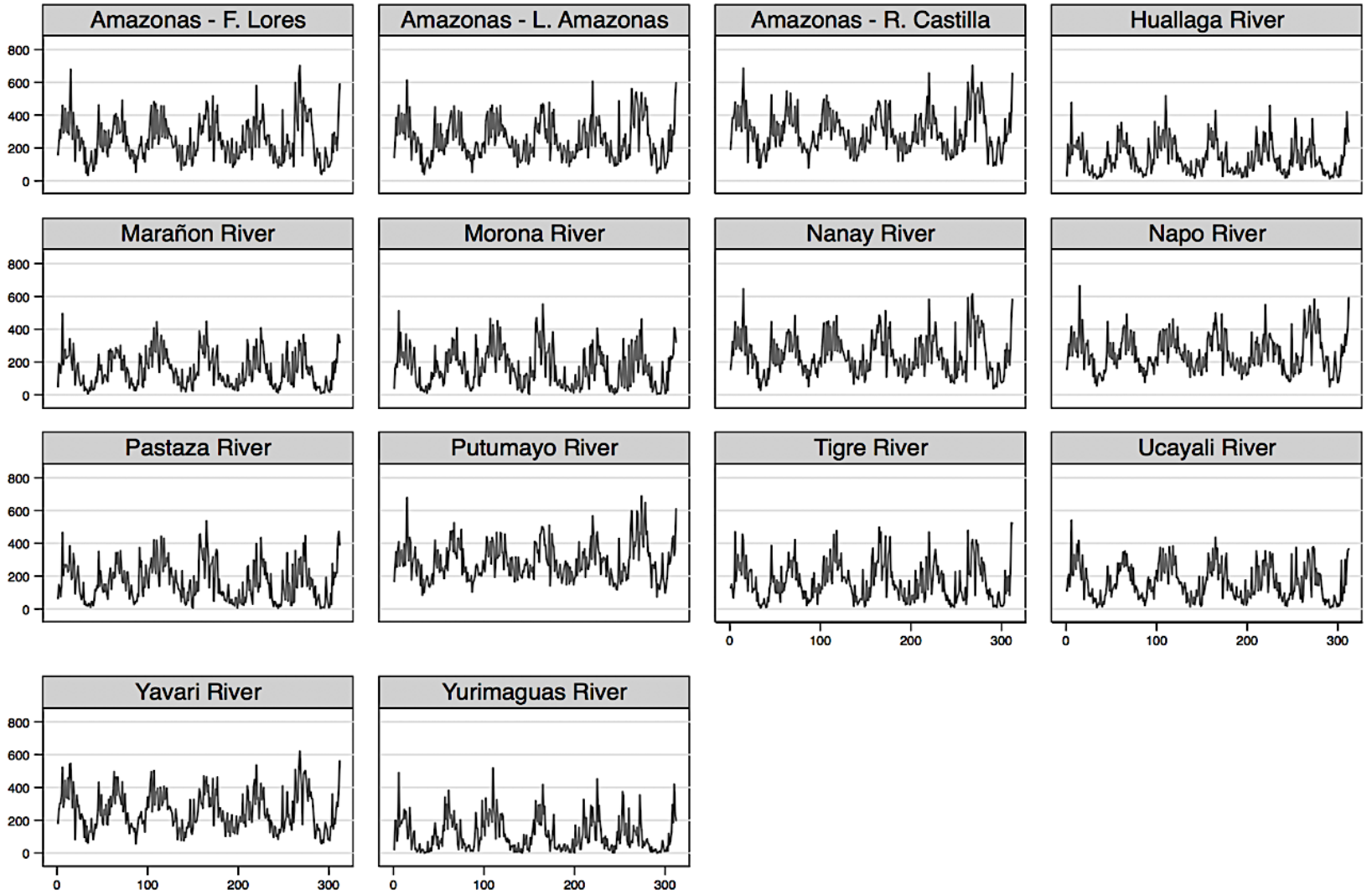

* Y by X Axis: Loreto's temperature estimated mean by epidemiological week during years 2010-2017

**Figure 25.** Soil Moisture (kg/m$^2$) among Loreto Surveillance Units by epidemiological weeks and River Systems



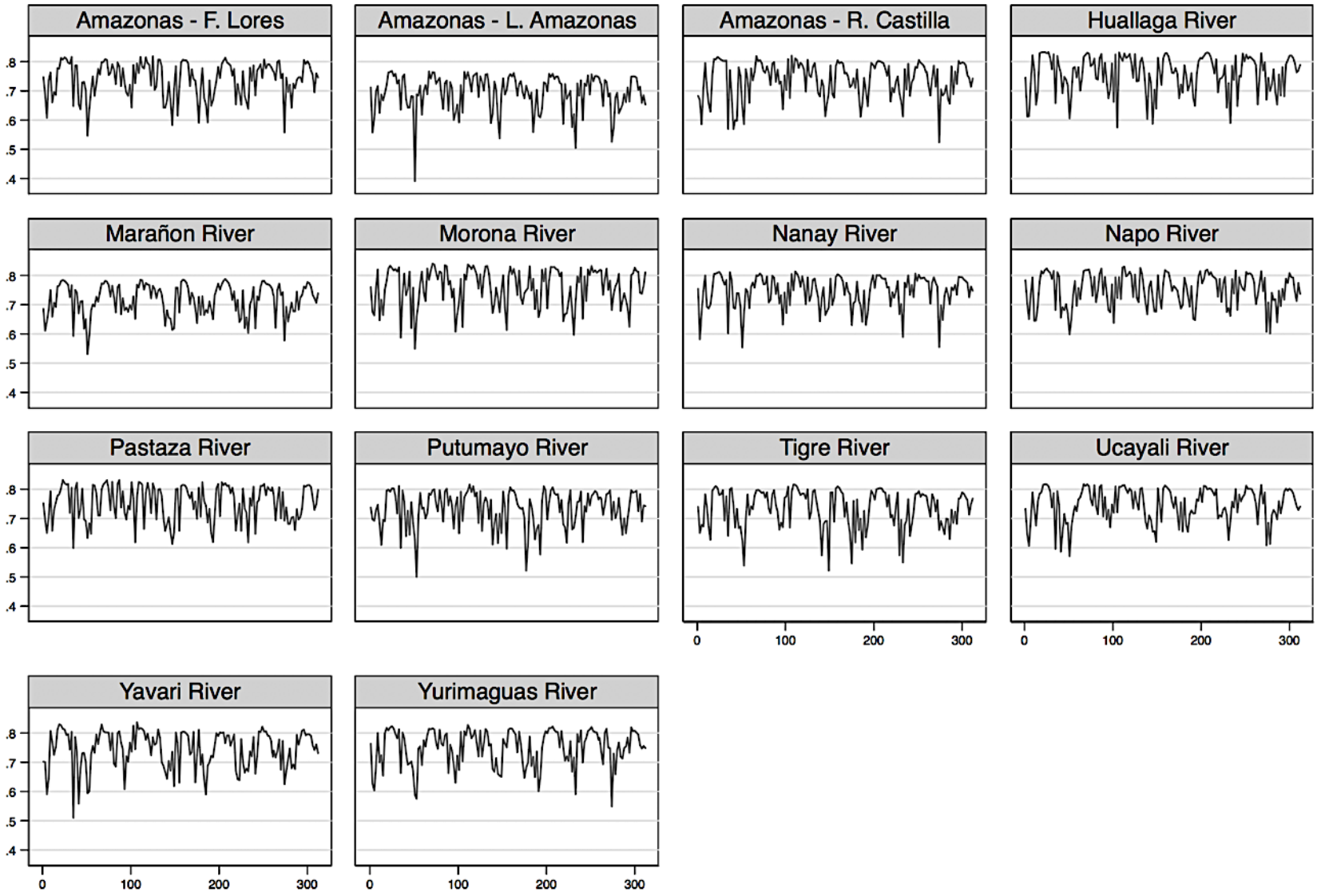

* Y by X Axis: Loreto's soil moisture estimated mean by epidemiological week during years 2010-2017

**Figure 26.** Precipitation ($mm^{-1}$ *water* * $m^2$) among Loreto Surveillance Units by epidemiological weeks and River Systems



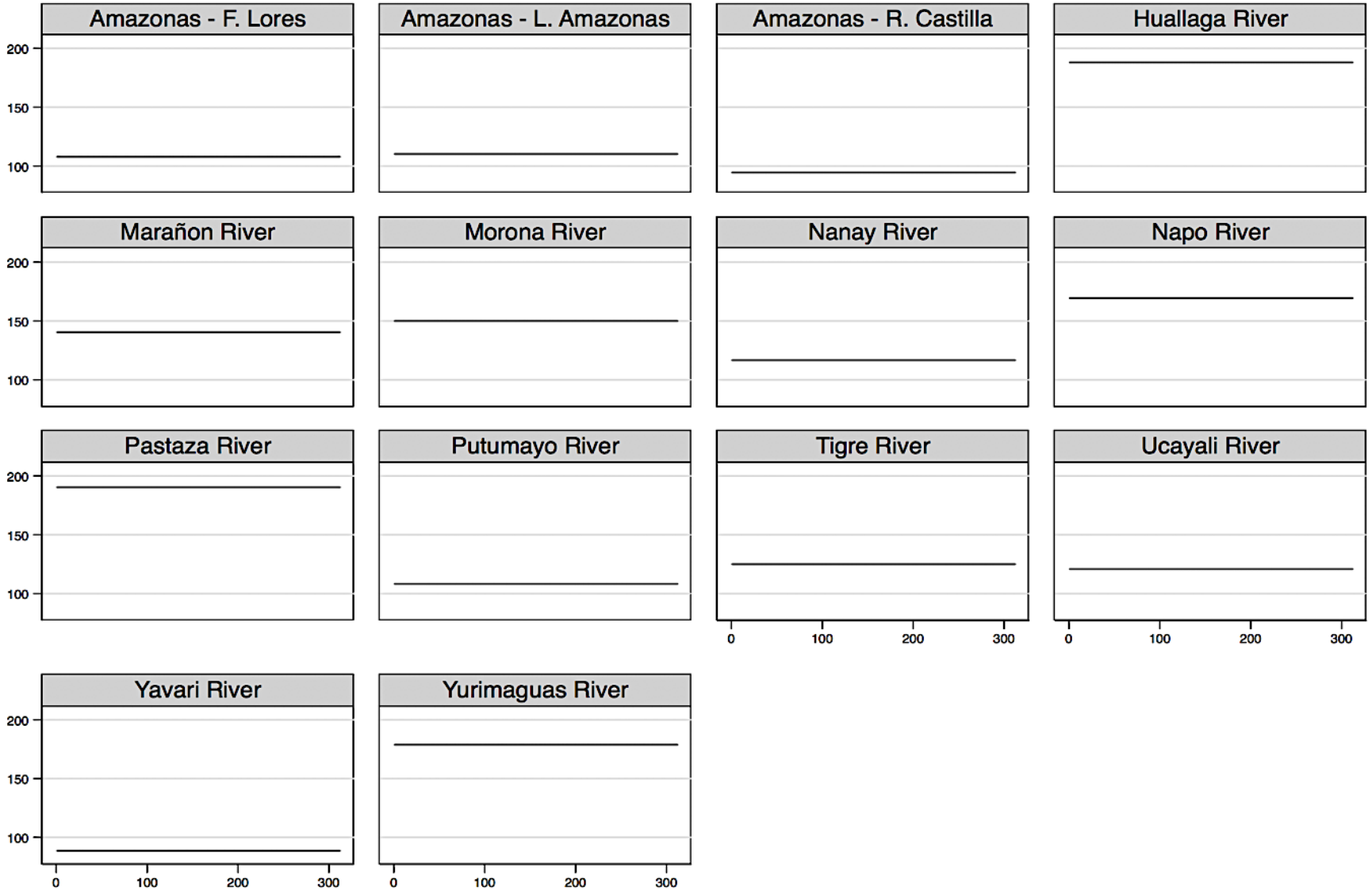

* Y by X Axis: Loreto's precipitation estimated mean by epidemiological week during years 2010-2017

**Figure 27.** Vegetation (*NDVI*) among Loreto Surveillance Units by epidemiological weeks and River Systems




* Y by X Axis: Loreto's NDVI estimated mean by epidemiological week during years 2010-2017

**Figure 28.** Altitude (*m*) among Loreto Surveillance Units by epidemiological weeks and River Systems




* Y by X Axis: Loreto's altitude estimated mean by epidemiological week during years 2010-2017

# Chapter 6. Synthesis and Implications

## *6.1 Introduction*

Malaria eradication is an ambitious but necessary global health goal. In the path towards purposely and permanently reducing the worldwide incidence of malaria to zero (the definition of eradication), each endemic malaria country must first do the same within their borders (which is the definition of elimination) (1). Moreover, as an intermediary step towards elimination, each endemic malaria country must set and achieve the control of malaria by deploying interventions to interrupt its transmission and reduce the malaria incidence to a previously and locally acceptable level (which is the definition of control). So, this is where the "think global but act local" mentality plays a key role in the fight against malaria.

To act local, we need to understand the local patterns of transmission of malaria. This will help to develop the means to interrupt such transmission sustainably. However, that is not an easy task given the many scenarios and combination of factors that interact to sustain the transmission of malaria. In that sense, it is easy to understand why is so important to fit a variety of models and analytical approaches to effectively guide each elimination effort (2).

This dissertation aims to contribute to key pieces of knowledge necessary to support current Peru's malaria elimination program. First, we determined the impact of reactive case detection with focal mass drug administration (RCD/FMDA) as compared to passive case detection on reducing the regional annual parasite incidence in Tumbes, Peru (Chapter 3). Second, we determined the impact of the malaria elimination program implemented in Tumbes on interrupting the transmission of malaria beyond the intervention area and along the Peruvian north coast (Chapter 4). Moreover, third, we assessed the patterns of malaria incidence in Loreto I order to

offer a variety of strategical targets for the malaria elimination program that was recently launched in Loreto (Chapter 5).

## *6.2 Key results*

### Specific Aim 1

We observed that the malaria elimination program implemented in Tumbes, which was based on replacing passive case detection with RCD/FMDA strategy, did have a significant effect on reducing the regional annual parasite incidence within the intervention areas (2/13 districts) during the first two years of the program (pilot project). Furthermore, that strategy most likely contributed to eliminate malaria from the Tumbes region after the strategy was scaled up across each of the 13 districts three years after.

From this study we learned that malaria can be eliminated from low-endemic regions with high predominance of *P. vivax* by using focal interventions if some critical conditions align up to increase its likelihood of success. First, as was the case of Tumbes, the human malaria reservoir should be relatively steady in time and space, meaning that the foci of malaria can be identified and have a predictable pattern of incidence that can be used to inform the selection of both the intervention and the targets for prioritization, with a low chance of error. For this purpose, we must use data driven analytical strategies and take the best of the all the geographical, remote sensing, and administrative data available. Furthermore, another key factor that was took in consideration during this decision-making process was the connectivity between communities and the patterns of human mobility in the region. In the case of Tumbes, it was clear from the beginning that the main way to commute along the north-coast was the Pan-American Highway and that has

become also a major driver of the human mobility due the intense commercial traffic across the Peru-Ecuador border. This knowledge offered Peruvian MoH officers a great advantage to properly select the districts that were targeted during the pilot study, be successful, and later one to take advantage of this successful experience to later on obtain the clearance necessary to scale up the project to the whole region of Tumbes by the central government.

Another important lesson from this study was recognizing the high relevance of accounting for the social structure of the communities when deploying interventions to interrupt malaria transmission. In the case of Tumbes, within the FMDA component of the strategy besides including eligible contacts within the boundaries of the household of the index cases (identified with RCD) the officers also intervened on the contacts who worked or studied with the index case in the previous 24 hours. This key adaptation of the RCD strategy allowed Peruvian officers to expand the effect of the intervention beyond the limits of the index case household without sacrificing the sustainability of the program. Actually, this modification might one of the main reasons for the success of the Tumbes malaria elimination program. That been said, it is important to remember that in most RCD documented experiences the population at risk was delimited by a perimeter distance around the index case household either 1 km like in Sri Lanka (3) and Swaziland (4), 500 m as in southern Zambia (5), or 100 m used in the Peruvian Amazon (6). Consequently, as the perimeter is expanded, the coverage becomes more expensive and less sustainable given the relatively higher cost (7).

Another result of high interest from our study was the fact than the selected intervention included a transmission blocking drug like primaquine, which have huge implications from the stand point of a FMDA strategy. First, there was the risk of severe adverse events due the massive use of primaquine doses in populations with an unknow prevalence of severe glucose-6-phosphate

dehydrogenase deficiency (G6PDd). And second, primaquine is a long-time recognized transmission-blocking drug that can prevent relapses of malaria (8), but such effects varies significantly from region to region and is not exempt of risks. The odds of relapse in the absence of primaquine therapy varies by geographic origin from 1 to 4, being higher in tropical regions like Tumbes (9). Prior to the pilot project the malaria incidence was increasing consistently across Tumbes as well as the number of doses of chloroquine-primaquine used to treat every vivax malaria case, so clearly primaquine was not helping to interrupt the transmission of malaria nor deterring adverse events due the massive use of doses of primaquine. Yet it was a matter of great concern that so many precautions were taken to account for the remote possibility of a severe adverse event due G6PD deficiency, including active surveillance and capacity building. That been said, Peru have a decades of experience using primaquine to treat malaria cases with close to none fatal adverse event cases reported (10) and a very low prevalence (prevalence range: 0-0.7%) of G6PD deficiency reported by a small, historical study (11). Regardless, Peru recently approved the use of primaquine to interrupt falciparum malaria cases in the Peruvian Amazon so primaquine is considered a safe drug in low doses regardless of the G6PD deficiency risk in the country now.

Another finding that deserves mention is the relevance of proper funding, strong political will, community acceptability and a successful pilot experience. In Tumbes, we had each of them from the beginning of the project which was essential for the success of the project. First, the financial aid from Ecuador's government warrantying the availability of 20,000 complete malaria treatments, which were sufficient to pilot and then scale the intervention to the 13 Tumbes districts, was essential for the whole project. This exceptional donation had a major impact in the political will from the regional authorities facilitating the decision making from the beginning. Another probe of the relevance of the political will in our experience was the fact that the MoH authorities

from the central government requested a second year of data to approve the scale up project due the initial and reasonable doubts about the safety and community acceptability of the RCD/FMDA intervention. And last but not least, one observation we cannot neglect was the impact of a successful pilot study in the scope of a long-term, large, labor and resource intensive project. The pilot experience helped a lot in terms of gaining experience, community acceptance and sustainability, all which were validated and reaffirm after the very first year of the scale up study giving the fact that each of the newly intervention districts starting reverting their malaria incidence trends.

To sum up we reported the first successful malaria elimination initiative based on RCD with FMDA in a region with a high predominance of vivax malaria worldwide. Such strategy may be useful to achieve the control and further elimination of malaria without significant adverse events.

**Specific Aim 2**

In our previous study we found that ~90% of the total impact attributable to the RCD/FMDA at 24-months of the pilot study occurred during the first year in the region of Tumbes. Also, we observed that there were strong signals of an "spillover effect" from the intervention communities to the nearby non-intervention communities, both during the pilot study in Tumbes as well as during the scale up study in the nearby districts of Piura. This observation might be explained in the case of Tumbes because of the relatively small geographic area as well as its strong road-connectivity due the Pan-American Highway. So, it was plausible that the impact of the RCD/FMDA strategy in Tumbes was extended to Piura by an "spillover effect". Hence in this second study we tested that hypothesis finding that in fact, such might be the case.

The study two results suggest that we can enhance the effect of a malaria elimination program by both selecting the proper intervention and by selecting the proper targets. As for the intervention the RCD/FMDA was previously found to represent an effective strategy to support malaria elimination initiatives in Tumbes Peru, a region with a predominance of vivax malaria, while taking advantage of a clear understanding of the patterns of incidence of malaria at each site. As for the target's selection, the intervention sites were first selected strategically among the most endemic regions based on a clear understanding of the patterns of incidence across the region. By doing so, the intervention also produced a possible "spillover effect" that could help to interrupt the transmission of malaria along the Pan-American Highway, which is the main road that connects both regions. Additionally, several factors contributed to the success of the program, including the strong seasonality that characterize the pattern of the incidence of malaria along the Peruvian north coast, the lack of a vector with high vectorial capacity in the region, the sustainability of the Tumbes malaria elimination program, and the single road connectivity between both regions that drives the economy of both regions.

During the pilot study (2009-2010) a total of 8,243 subjects, of whom around ~90% where asymptomatic subjects without any symptoms or signs of malaria received a complete course of antimalarials for *P. vivax* malaria. Such numbers may be an indication that a significant fraction of the population at risk was treated for asymptomatic malaria and also received treatment of a transmission-blocking drug such as primaquine. During this second year of the pilot study (2010), the Tumbes intervention sites registered a mean WPIs reduction of 95% (95%CI: 74−100), the Tumbes non-intervention sites a mean WPIs reduction of -39% (-75%−-3%), while across the Piura non-intervention sites the mean WPIs reduction was of -260% (-325%−-195%). Such reductions were statistically significant when comparing the intervention sites from Tumbes

against the non-intervention sites from Tumbes ($p$<0.001) and Piura ($p$<0.001). However, during the scale-up study, the WPIs dropped from 6.11 (95%CI: 5.30–6.43) cases per 100,000 inhabitants in the year 2010 to 0.53 (95%CI: -0.08−1.14) in the year 2014 across Tumbes and Piura. Since 2015, Tumbes and Piura have reported only imported malaria cases, either from Ecuador or from the Peruvian Amazon.

During both study phases participants did not report any antimalarial adverse events, and the regional hospitals from Piura and Tumbes did not state any case of antimalarial adverse events neither nor any fatal malaria case.

## Specific Aim 3

The evidence from this study suggest that there are several different patterns of incidence of malaria across de Loreto Region and that such variability might be explained by the seasonality of malaria, its most important climate predictors, as well as by the connectivity and accessibility to health care. Overall, it seems that the distribution of the human malaria reservoir follows the natural boundaries offered by each of the main Amazon river tributaries. Hence, at each of these river networks we can observe a different pattern of malaria incidence, which represents an great opportunity for deploying focal interventions while taking advantage of the independence of each river system. In our previous two studies we reported that is possible to interrupt the transmission of malaria in systems that are strongly connected by implemented focal strategies such as RCD/FMDA to target the main foci if the system behaves as such while considering the independent well interconnected system by only one main road. In the case of the Peruvian Amazon, we believe that each of these factors that played a key role in the success of the malaria elimination in the north coast applied also to the Loreto region.

Briefly, out third study we found that Loreto is a low endemic area with an over-dispersed distribution of malaria cases and a high predominance of *P. vivax* malaria over P. falciparum malaria (4:1). At the beginning of our study period, 2010, we estimated an annual parasite incidence of 13.3 cases per 1,000 people (95% Confidence Interval [CI]: 13.1 to 13.6 cases per 1,000 people), but when we disaggregated the malaria incidence weekly and by surveillance units we estimated an average WPI of 32.5 cases per 100,000 people (95% CI: 29.2 to 35.7 cases per 100,000 people). By doing so we observed that across surveillance units there was a wide range of WPI (0 to 10,259 cases per 100,000 people). Furthermore, if we assessed the variability of the WPI in times we also observed that the pattern of incidence changed in time.

There are different ways to disaggregate a large region like Loreto, but whatever disaggregation we may attempts may end useless if they are not be functional for the purpose of facilitating the distribution of interventions in a cost-effective manner. In the case of the Loreto region, the main way to commute between communities, is along the Amazon river navigable tributaries. Hence, it makes sense to use that knowledge as well as the administrative and MoH health infrastructure map, to assess the patterns of incidence across the rivers systems to inform the decision making behind a prospect malaria elimination program in Loreto.

In this study we tested the hypothesis of our interest by disaggregating the Peruvian Amazon basin in the main Amazon river navigable tributaries and then explore which ones may behave as independent systems large enough to sustain the transmission of malaria from one season to the next. To do so, first we explored the variability of the WPI among the health networks and then used key informants from the Loreto Health Directorate (each of them with over twenty years of experience managing and directing the malaria program in Loreto) to divide the largest health networks into smaller river systems following the distribution of their MoH surveillance units

along the path of the navigable rivers. Consequently, we started with the eight health networks from the health infrastructure map of Loreto and ended with 14 riverine systems.

## *6.3 Strengths and limitations*

There are several strengths and limitations that should highlighted in this dissertation research. One important limitation we need to mention is that each of the studies uses malaria surveillance data with malaria febrile cases diagnosed trough microscopy. There are important sources of bias, including selection, classification, instrument bias, interpretation, and reporting bias. First, the surveillance of febrile syndrome implies that some fractions of the population will be less likely to be included in the study, including febrile infants, elders and adult young males. Also, there exist a high risk of over sampling communities closer to the surveillance units and those communities or populations that lives in close proximity to the city of Iquitos. On the other hand, febrile indigenous populations and other minorities will less likely to be captured by the surveillance system. Additionally, there is a high risk of misclassification and interpretation of the microscopic images of the malaria parasites due the poor accuracy attributed to microscopy and the high variability of competency among the microscopists (12). In the same direction there was observed a high variability in the models and maintenance of microscopes used for malaria microscopy in Loreto (12), which increase the risk of instrument bias. And lastly, there is a high risk of reporting bias due the remote location of some the surveillance units and the variety of methods (radio, telephone, text, e-mail and physical reports) used for the reporting of the data prior to data entry. All of these biases affect the internal and external validity of our studies, but do not necessarily invalidate them because in malaria research surveillance data is highly informative to assess the pattern of incidence and assess the location of the human malaria reservoir.

Furthermore, in the case of the Loreto region the surveillance system was enhanced in the context of the PAMAFRO project, which invested for over five years on capacity building and improving the quality of the data reporting, quality control and data entry processes. However, we acknowledge that using surveillance data represents a major weakness in our series of studies which may be difficult to overcome.

The aim of the study one was to determine the impact of RCD/FMDA as compared to passive case detection on reducing the regional annual parasite incidence in Tumbes, Peru, but we used a non-randomize community trial. Consequently, the study has a high-risk of selection bias due the lack of randomization and a high-risk of an "spillover effect". To overcome this major limitation, we implemented a variety of measures to mitigate the effect of such bias by including standardized surveillance data with rigorous quality control and a rigorous collection of information on potential confounders including remote sensing data, traveling distances trough accessibility and friction maps, seasonality assessment and accounting for the over dispersion and aggregation of the data by using mixed-effects Poisson regression methods and negative binomial correction when necessary.

## *6.4 Recommendations for future research*

This dissertation reports the first successful malaria elimination initiative based on RCD with FMDA in a region with a high predominance of vivax malaria worldwide. However, there are some limitations related to the quality of the evidence generated by a non-randomized community trial through our first two studies, which demands further assessments to verify our results. So, our first recommendation is to test our hypothesis using a community randomized trial instead. Regardless, we recommend authorities to consider RCD/FMDA as a better alternative to

passive case detection in settings with low malaria endemicity and a transmission pattern similar to the Peruvian north coast. This strategy might be of great value particularly in the Peruvian Amazon where several of the factors that facilitated the success of the RCD/FMDA in the Peruvian north coast also characterize the Peruvian Amazon, including low endemicity, strong seasonality, long-term massive use of doses of primaquine without major adverse events, and high connectivity and clustering of susceptible subject within communities constrained by naturally limited networks with the Amazon river navigable tributaries behaving similar to the Pan-American highway in the Peruvian north coast. That been said, it is unclear how such strategy might work in a region with so much variability in their pattern of incidence of malaria but certainly we believe such a strategy would be a very cost-effective alternative for most of the river networks where the human malaria reservoir behaves as stable foci in space and time.

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reactive case detection strategies for malaria elimination in a region of low transmission in southern Zambia. *Malar J, 15*(1), 412. doi:10.1186/s12936-016-1460-x

Searle, K. M., Shields, T., Hamapumbu, H., Kobayashi, T., Mharakurwa, S., Thuma, P. E., . . . Moss, W. J. (2013). Efficiency of household reactive case detection for malaria in rural Southern Zambia: simulations based on cross-sectional surveys from two epidemiological settings. *PLoS One, 8*(8), e70972. doi:10.1371/journal.pone.0070972

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Sturrock, H. J., Hsiang, M. S., Cohen, J. M., Smith, D. L., Greenhouse, B., Bousema, T., & Gosling, R. D. (2013a). Targeting asymptomatic malaria infections: active surveillance in control and elimination. *PLoS Med, 10*(6), e1001467. doi:10.1371/journal.pmed.1001467

Sturrock, H. J., Novotny, J. M., Kunene, S., Dlamini, S., Zulu, Z., Cohen, J. M., . . . Gosling, R. D. (2013b). Reactive case detection for malaria elimination: real-life experience from an ongoing program in Swaziland. *PLoS One, 8*(5), e63830. doi:10.1371/journal.pone.0063830

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Tietje, K., Hawkins, K., Clerk, C., Ebels, K., McGray, S., Crudder, C., . . . LaBarre, P. (2014). The essential role of infection-detection technologies for malaria elimination and eradication. *Trends Parasitol, 30*(5), 259-266. doi:10.1016/j.pt.2014.03.003

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Tseroni, M., Baka, A., Georgitsou, M., Harvalakou, M., Panoutsakou, M., Psinaki, I., . . . Hadjichristodoulou, C. (2014). *Targeted Mass Drug Administration of antimalarials to control malaria in Lakonia, Greece- transmission period 2013*. Paper presented at the European Scientific Conference on Applied Infectious Diseases Epidemiology, Stockholm,

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Tseroni, M., Baka, A., Kapizioni, C., Snounou, G., Tsiodras, S., Charvalakou, M., . . . Project, M. (2015). Prevention of Malaria Resurgence in Greece through the Association of Mass Drug Administration (MDA) to Immigrants from Malaria-Endemic Regions and Standard Control Measures. *PLoS Negl Trop Dis, 9*(11), e0004215. doi:10.1371/journal.pntd.0004215

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Yangzom, T., Gueye, C. S., Namgay, R., Galappaththy, G. N., Thimasarn, K., Gosling, R., . . . Dev, V. (2012). Malaria control in Bhutan: case study of a country embarking on elimination. *Malar J, 11*, 9. doi:10.1186/1475-2875-11-9

Zhao, Y., Xie, Q., Lu, Y., & Hu, B. (2017). Hydrologic Evaluation of TRMM Multisatellite Precipitation Analysis for Nanliu River Basin in Humid Southwestern China. *Sci Rep, 7*(1), 2470. doi:10.1038/s41598-017-02704-1

# Curriculum Vitae

**ANTONIO M. QUISPE, MD, CPH, MSC, PHD**
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ORCID ID, http://orcid.org/0000-0003-2100-7423
LinkedIn profile, https://pe.linkedin.com/in/antonioquispe

## PERSONAL STATEMENT

I am a physician-researcher, epidemiologist, and statistician that, in the last decade, have successfully contributed to the mission of several national and international organizations, in both the public and the private sectors. Founding my own company, studying, and working overseas, managing local and international grants, and consulting with impactful agencies have been experiences that allowed me to grow professionally and personally. Consequently, my dream and lifetime goal are to take advantage of my training and personal strengths to contribute to the public health by tacking global health problems, as well as to pursue a long, productive life as a senior researcher.

## EDUCATION

**Johns Hopkins Bloomberg School of Public Health (JHBSPH), Maryland, United States 2012-2017**
Program: PhD in Global Disease Epidemiology and Control
Thesis: "Feasibility of malaria elimination in Peru"

**School of Medicine, Universidad Peruana Cayetano Heredia (UPCH), Lima, Peru 2007-2008**
Program: Master in Clinical Epidemiology with Mention in Quantitative Methods
Thesis: "*Plasmodium vivax* hospitalizations in a mono-endemic malaria region: severe vivax malaria?"

**School of Sciences, Universidad Peruana Cayetano Heredia (UPCH), Lima, Peru 2006-2007**
Program: Specialization in Research Statistics
Thesis: "Applicability of pain scales in children questionnaires"

**School of Medicine, Universidad Nacional Mayor de San Marcos (UNMSM), Lima, Peru. 1998-2005**
Degree awarded: Medical Doctor

## WORK EXPERIENCE

**National Maternal Perinatal Institute (INMP), Ministry of Health, Lima, Peru Ago 2018 – Present**
Physician-Researcher, Research Functional Unit
- Design, lead, analyze and publish research studies with and in collaboration with INMP.

**Institute of Evaluation of Health Technologies and Research (IETSI), Lima, Peru May 2017 – Jul 2018**
Physician-Researcher, Directorate of Developing Research in Health
- Design, lead, analyze and publish research studies with and in collaboration with EsSalud.

**Institute of Evaluation of Health Technologies and Research (IETSI), Lima, Peru Nov 2015 – Apr 2017**

Consultant and Medical Evaluator

- Evaluate health technologies and recommend its acquisition by Peru's national insurance system "EsSalud".

**Hospital Militar Central (Peruvian Military Hospital), Lima, Peru Apr–Jul 2015**

Medical Epidemiologist, Chief, Section of Epidemiological Surveillance Department of Health Intelligence

- Three-months contract to implement the Statistics Department and lead the Epidemiological Surveillance Section.
- Write the Stata's and Latex's coding necessary to monitor and analyze the indicators for hospital performance.

**Bill and Melinda Gates Foundation (BMGF), Seattle, Washington, USA Jul–Oct 2013**

Intern, Integrated Development Program

- Interning at the BMGF Quantitative Pharmacology Team and assist the Integrated Development & Malaria Programs.

**U.S. Naval Medical Research Unit No. 6 (NAMRU-6), Lima, Peru Sept 2012 – Dec 2014**

Adjunct Scientist

- Lead, design, conduct, report and publish vector-borne diseases research studies.

**U.S. Naval Medical Research Unit No. 6 (NAMRU-6), Lima, Peru Feb 2009 – Aug 2012**

Head, Epidemiology Section, Department of Parasitology

- Lead the Epidemiology Section, and design, conduct, and report epidemiological research.
- Coordinate the NIH/FIC training grant D43 TW007393, including the Master Program in Epidemiologic Research.

**"San Bartolome" Mother-Child Teaching Hospital, Ministry of Health, Lima, Peru Apr 2008 – Jan 2009**

Physician Research Epidemiologist and Biostatistician

- Provide analytical support as well as lead evaluations and research studies to improve the quality of health care.

**School of Medicine, Peruvian University "Cayetano Heredia" (UPCH), Lima, Peru Sept 2008 – Jun 2009**

Guest Faculty

- Coordinated and taught research methods courses at the Masters in Epidemiology Program.

**School of Medicine, Private University "San Juan Bautista" (UPSJB), Lima, Peru Apr 2008 – Sept 2008**

Guest Faculty and Statistics Instructor

- Faculty at the Basic Statistics Course for medical students.

**Web Med Research E.I.R.L., Lima, Peru Jan 2005 – Present**

Company Founder and Principal Investigator

- Consulting on medical research, data analysis, health technology assessments, program evaluation and training.

**Honors (Received in the last 10 years)**

- April 2018, **Research Scholar,** at the Institute for Disease Modeling (IDM), Seattle, Washington, USA.
- September 2017, Award to the **Second-Best Research Study** awarded by the National Institute of Health (INS), Peru within the framework of the 11th International Scientific Congress of the INS.
- January 2017, **Certified as a Researcher** at the National Registry of Researchers (REGINA) by the National Council on Science, Innovation and Technology (CONCYTEC), Peru.
- December 2016, **Ambassador** at the Bill & Melinda Gates Foundation (BMGF), Seattle, Washington, USA.
- January 2016, **Congress Russell Kirby Travel Award** 2016, to attend the Congress of Epidemiology of the Americas in Miami, Florida.
- December 2014, **Certificate of Appreciation** from the U.S. Embassy in Peru.
- November 2014, **JHBSPH Students Assembly Travel Award 2014** to attend the 63th ASTMH Conference in New Orleans, Georgia
- June 2014, **Full Scholarship** from the Johns Hopkins University to attend the **JHU Teaching Academy**.
- March 2014, **Delta Omega Scholarship 2014**, "Measurement" Category Winner at the Delta Omega Alpha Chapter Scholarship Competition granted by the Delta Omega Honorary Public Health Society, Johns Hopkins University.
- January 2014, **Certificate of Appreciation** from the **US Embassy** in Lima, Peru.
- December 2013, **Travel Award** from JHU Global mHealth Initiative to attend the mHealth Summit at Washington DC.
- October 2013, **Travel Award** from the Johns Hopkins Malaria Research Institute to attend and present at the annual meeting entitled "Malaria: Lessons from the Field".
- March 2012, **Full Scholarship** from Program NIH/FIC D43 TW007393 to receive PhD training at JHBSPH
- May 2011, **NAMRU-6 Extra Mile Award**
- December 2010, **NAMRU-6 Employee of the Year Award**,
- December 2010, **NAMRU-6: LES Employee of the Quarter Award**
- June 2010, **Fogarty Scholarship** from Program NIH/FIC D43 TW007393 to attend the Summer Institute at JHBSPH
- November 2009, **Franklin Award** from Department of State - United States of America
- September 2009, **Full Scholarship** from the David Rockefeller Center for Latin American Studies to attend the III Research Symposium for Spanish and Latin-Americans Researchers at Harvard University

**BOOK CHAPTER**

**Antonio Marty Quispe Gutiérrez**. (2017). Giardiasis Epidemiology, Current Topics in Giardiasis, Dr. Alfonso Rodriguez-Morales (Ed.), InTech, DOI: 10.5772/intechopen.70338.

**PUBLICATIONS (Published in the last 10 years)**

Davila CR, Paucar-Zegarra R, **Quispe AM**. Anemia in Infancy. *Rev Per Inv Mat Per* 2018;7(2) (Accepted for Publication) **(Health Q4)**

Fasanando-Vela R, Meza-Liviapoma J, Toro-Huamanchumo CJ, **Quispe AM**. Undergraduate Research Training: E-learning Experience in Peru. 2017;30(3):258-259 *(Pubmed ID: 29786032)* **I.F. 1.667 (Education Q1)**

Mousam A, Maggioni V, Delamater PL, **Quispe AM**. Using remote sensing and modeling techniques to investigate the annual parasite incidence of malaria in Loreto, Peru. *Advances in Water Resources* 2017;108:423-38 **I.F. 4.349 (Q1, Water Science and Technology)**

Granda AC, Correa-Tineo S, **Quispe AM**. [Hernia repair comparing Lichtenstein and Nyhus techniques for inguinal hernia and its postoperative complications in a Peruvian hospital]. *Acta Med Peru* 2016;33(3):208-16.

Carnero AM, Mayta-Tristan P, Konda KA, Mezones-Holguin E, Bernabe-Ortiz A, Alvarado GF, Canelo-Aybar C, Maguiña JL, Segura ER, **Quispe AM**, Smith ES, Bayer AM, Lescano AG. Plagiarism, cheating and research integrity: Case studies from a Masters' program in Peru. *Sci Eng Ethics*. 2016;23(4):1183-97. **I.F. 1.454 (Health Q2)**

**Quispe AM**, Llanos-Cuentas A, Rodriguez H, Clendenes M, Cabezas C, Leon LM, Chuquiyauri R, Moreno M, Kaslow DC, Grogl M, Herrera S, Magill AJ, Kosek M, Vinetz JM, Lescano AG, Gotuzzo W. Meeting Report. Accelerating to zero: Strategies to eliminate malaria in the Peruvian Amazon. *Am J Trop Med Hyg* 2016;94(6):1200-7 *(PMC ID: PMC4889734)*. **I.F. 2.453 (Medicine Q1)**

Sanchez JF, Halsey ES, Bayer AM, Beltran M, Razuri HR, Velasquez DE, Cama VA, Graf PCF, **Quispe AM**, Maves RC, Montgomery JM, Sanders JW, Lescano AG. Needs, acceptability, and value of humanitarian medical assistance in remote Peruvian Amazon riverine communities. *Am J Trop Med Hyg* 2015;92(6):1090-9 *(Pubmed ID: 25846293)*. **I.F. 2.453 (Medicine Q1)**

**Quispe AM**, Pozo E, Guerrero E, Durand S, Baldeviano GC, Edgel KA, Graf PCF, Lescano AG. Plasmodium vivax hospitalizations in a mono-endemic malaria region: severe vivax malaria? *Am J Trop Med Hyg* 2014;91(1):11-7 *(Pubmed ID: 24752683).* **I.F. 2.453 (Medicine Q1)**

Loza Concha R. **Quispe AM**. [Cost utility of renal transplant vs. hemodialysis in the treatment of end stage chronic kidney failure in a Peruvian hospital] *Rev Per Med Exp Sal Pub* 2011;28(3):432-9 *(Pubmed ID: 22086622)*

**Quispe AM**, Santivañez-Pimentel A, Leyton-Valencia I, Pomasunco D. [Caesarean section among seven public hospitals at Lima: trend analysis during 2001-2008 period]. *Rev Per Med Exp Sal Pub* 2010; 27(1): 45-50 *(Pubmed ID:21072449).*

**Quispe A**, Santivañez-Pimentel A, Leyton-Valencia I, Olivos JC. [Analysis of clavicle fractures tendency in three Lima hospitals]. *Rev Per Gin & Obst* 2009;55:182-186

**Quispe AM**, Segura ER, Salmon-Mulanovich G. [Clinical trials and the accomplishment of CONSORT guidelines in Peru]. *An Fac Med* 2010;71(1):62

Danesi A, **Quispe AM**, Masías-Bustos L. [Correlation and concordance between the main stroke risks scores in patients with non-valvular auricular fibrillation]. *Rev Per Card* 2009;35(1):5-10

**TECHNICAL DOCUMENTS (Published in the last 10 years)**

IETSI-EsSalud. [Safety and efficacy of pembrolizumab in the treatment of patients with malignant melanoma with metastatic or unresectable disease without prior systemic treatment]. Preliminary Health Technology Assessment. N° 062—SDEPFyOTS-DETS-IETSI-2016, Lima, Peru. 2016.

IETSI-EsSalud. [Efficacy and safety of simeprevir in combination with peginterferon alfa and ribavirin in the treatment of patients diagnosed with chronic hepatitis C genotype 1A negative to the Q80K or genotype 1B mutation with significant fibrosis]. Preliminary Health Technology Assessment. N° 060—SDEPFyOTS-DETS-IETSI-2016, Lima, Peru. 2016.

IETSI-EsSalud. [Efficacy and safety of sorafenib in the treatment of patients with differentiated, metastatic, unresectable thyroid carcinoma refractory to treatment with radioactive iodine]. Preliminary Health Technology Assessment. N° 056—SDEPFyOTS-DETS-IETSI-2016, Lima, Peru. 2016.

IETSI-EsSalud. [Efficacy and safety of axitinib in patients with metastatic renal cancer treated with sunitinib]. Preliminary Health Technology Assessment. N° 048—SDEPFyOTS-DETS-IETSI-2016, Lima, Peru. 2016.

IETSI-EsSalud. [Safety and efficacy of bevacizumab in combination with chemotherapies that do not contain platinum in the treatment of patients diagnosed with metastatic ovarian cancer]. Preliminary Health Technology Assessment N° 040—SDEPFyOTS-DETS-IETSI-2016, Lima, Peru. 2016.

IETSI-EsSalud. [Safety and efficacy of bevacizumab in combination with fluoropyrimidine-based chemotherapy in first-line treatment for patients diagnosed with metastatic colorectal cancer]. Preliminary Health Technology Assessment N° 038—SDEPFyOTS-DETS-IETSI-2016, Lima, Peru. 2016.

IETSI-EsSalud. [Torasemide safety and efficacy in treating patients diagnosed with congestive heart failure patients] Preliminary Health Technology Assessment. N° 037—SDEPFyOTS-DETS-IETSI-2016, Lima, Peru. 2016.

IETSI-EsSalud. [Safety and efficacy of safety and efficacy of ipilimumab in treating patients diagnosed with malignant melanoma metastatic or unresectable disease with no prior systemic therapy]. Preliminary Health Technology Assessment N° 035—SDEPFyOTS-DETS-IETSI-2016, Lima, Peru. 2016.

IETSI-EsSalud. [Crizotinib safety and efficacy in treating patients with lung cancer diagnosis of metastatic non-small cell positive ALK fusion gene]. Preliminary Health Technology Assessment N° 019—SDEPFyOTS-DETS-IETSI-2016, Lima, Peru. 2016.

IETSI-EsSalud. [Safety and efficacy of vildagliptin in the treatment of elderly patients diagnosed with diabetes mellitus type 2, with risk of hypoglycemia and limitations for use of insulin (with high degree of dependence), without adequate metabolic control (as HbA1C) despite treatment with metformin and glyburide maximum dose]. Preliminary Health Technology Assessment N° 012—SDEPFYOTS-DETS-IETS1-2016, Lima, Peru. 2016.

IETSI-EsSalud. [Safety and efficacy of metreleptin in the first-line treatment of patients with congenital generalized lipodystrophy]. Preliminary Health Technology Assessment N° 009—SDEPFYOTS-DETS-IETSI-2016, Lima, Peru. 2016.

**ABSTRACTS AT INTERNATIONAL CONFERENCES (Published in the last 10 years)**

**Quispe AM**, Arróspide A, Valladares M, Huapaya C, Acosta J. [Risk of tuberculosis in hospital environments in a country with high endemicity]. Second Place and oral presentation at the XI International Scientific Congress organized by the National Institute of Health, Lima, Peru – November 2017.

**Quispe AM**, Quintana F, Pozo E, Kosek MN, Gotuzzo E. Reactive detection of cases with targeted mass treatment: Interrupting transmission of malaria and achieving its elimination beyond intervened areas in Northwestern Peru. Oral presentation presented at the 65th ASTMH Annual Meeting, Baltimore, MD – November 2017.

**Quispe AM**, Quintana F, Pozo E, Risco R, Hernandez RH, Cabezas C, Esipov S. Spreading of Dengue and Chikungunya in Northwestern Peru: from Waves to Coinfection. Poster presented at the 2016 Epidemiology Congress of the Americas, Miami, FL – June 2016.

Wagner K, Mousam A, Kephart JL, Aquila V, Maggioni V, Cabezas C, **Quispe AM**. El Niño as a threat to regions progressing toward malaria elimination in Peru. Poster at the Epidemiology Congress of the Americas, Miami, FL – June 2016.

**Quispe AM**, Campos J, Cruz R, Fernandez J, Chavez E, Ore, M. Responding to Infectious diseases outbreaks in the Peruvian military: 10-year review using an electronic disease surveillance system. Poster presented at the 64th ASTMH Annual Meeting, Philadelphia – October 2015, and at the International congress at the Peruvian National Health Institute, Lima, Peru – November 2015.

Quintana FA, Mendoza EL, Gonzales RV, Arrasco J, Herrera YO, **Quispe AM**. Reactive case detection with targeted mass drug administration for malaria elimination in northwestern Peru. Poster presented at the 64th ASTMH Annual Meeting, Philadelphia – October 2015, and at the International congress at the Peruvian National Health Institute, Lima, Peru – November 2015.

Mousam A, Maggioni V, Delamater P, Kephart JL, **Quispe AM**. The impact of climate variability on malaria prevalence rates in Loreto, Peru. Poster presented at the 64th ASTMH Annual Meeting, Philadelphia – October 2015, and at the International congress at the Peruvian National Health Institute, Lima, Peru – November 2015.

**Quispe AM**, Khepart JL, Lescano AG, Thields TM, Shiff CJ. A free surveillance app for planning malaria interventions and outbreak responses at the community level in malaria endemic countries. Poster presented at the; at the Malaria World Day, Baltimore, Maryland – April 2014; at the Second Conference in Scientific Research in tropical Medicine and Public Health "Amy C Morrison", Iquitos, Peru – August 2014; and at the Young Investigators Awards at the 63rd ASTMH Annual Meeting, New Orleans – November 2014.

**Quispe AM**, Aquila V, Khepart JL, Lescano AG. Latitude and microclimate associated with malaria incidence at the district level in a low endemic area. Poster presented at the 63rd ASTMH Annual Meeting, New Orleans, Louisiana – November 2014.

Smith-Nuñez ES, Durand S, Baldeviano GC, **Quispe AM**, Jequeiros F, Sihuincha M, Celis JC, Tapia LL, Campos K, Edgel KA, Lescano AG. WHO criteria for severe malaria in identifying severe *vivax* malaria Preliminary data from a study in Iquitos, Peru. Poster presented at the 62th ASTMH Annual Meeting, Washington, DC – November 2013.

Baldeviano GC, Leiva KP, **Quispe AM**, Ventocilla J, Tapia LL, Durand S, Santolalla ML, Ricopa L, Campos K, Sihuincha M, Smith-Nuñez ES, Edgel KA, Lescano AG. Serum markers of severe clinical complications during *Plasmodium vivax* malaria mono-infection in the Peruvian Amazon basin. Poster presented at the 62th ASTMH Annual Meeting, Washington – November 2013.

**Quispe AM**, Santolalla ML, Tapia LL, Maguiña EA, Guerrero E, Pozo E, Baldeviano GC, Graf PCF, Edgel KA, Lescano AG. Malaria risk in a vivax mono-endemic area nearing elimination. Poster presented at the 61th ASTMH Annual Meeting, Atlanta, Georgia – November 2012.

Baldeviano GC, **Quispe AM**, Llacua LA, Santolalla ML, Tapia LL, Maguiña EA, Pozo E, Guerrero E, Palacios AM, Loncarich V, Graf PCF, Edgel KA, Lescano AG. Naturally acquired immunity in an area of low Plasmodium vivax transmission in the North Coast of Peru. Poster presented at the 60th ASTMH Annual Meeting, Washington, DC – December 2011.

**Quispe AM**, Pozo E, Campos P, Guerrero E, Durand S, Jimenez L, Palacios AM, Edgel KA, Graf PCF, Lescano AG. Severe malaria in a nearly exclusive Plasmodium vivax endemic area. Poster presented at the 59th ASTMH Annual Meeting, Atlanta, Georgia – November 2010.

**Quispe AM**, Sanchez JF, Bayer AM, Beltran M, Halsey ES, Gonzaga VE, Razuri HR, Zavaleta C, Maves R, Sanders JW, Montgomery JM, Lescano AG. Self-reported health status and wellbeing in the rural Peruvian rainforest. Oral presentation presented at the 58th ASTMH Annual Meeting, Washington, DC – November 2009.

**Quispe AM**, Santivanez A, Pomasunco D. Clavicle fractures rates among three Peruvian Ministry of Health Hospitals. Oral presentation presented at the 18th Annual Meeting of the International Congress of Gynecology and Obstetrics Peruvian Society, Lima, Peru – February 2009.

## RESEARCH SUPPORT

**CONCYTEC 136-2017-FONDECYT, Beltran (PI), Role: co-PI 11/15/2017 al 11/14/2019**
Validation of panels for the detection of somatic mutations in solid tumors and their prognostic value in the management of lung, colon and melanoma cancers in the Peruvian population
**US$125,000**

- Grant awarded with the objective of validating panels for the detection of somatic mutations and their prognostic value in cancers of the lung, colon and melanoma that affect the Peruvian population.

**Bill and Melinda Gates Foundation OPP1099774, Gotuzzo (PI), Role: Co-PI 10/01/2013 to 03/31/2016**
Accelerating to zero: Strategies to Eliminate Malaria in the Amazon
**US$50,000**

- Conference grant, which aim to convey the goals of a malaria elimination project in the Peruvian Amazon.

**US DoD-AFHSC/GEIS, Quispe (PI), Role: PI 11/01/2010 to 10/30/2012**
Risk factors for severe Plasmodium vivax malaria in Peru
**US$300,000**

- Study that assessed the clinical and epidemiological markers associated with severe malaria secondary to *Plasmodium vivax* in Peru, and the potential role of *Plasmodium falciparum* co-infection and other co-morbidities.

**US DoD-AFHSC/GEIS, Quispe (PI), Role: PI 10/01/2010 to 09/30/2011**
*Plasmodium Vivax* malaria incidence in infants, children and adults in Northwestern Peru. **US$150,000**

- Study that evaluated the incidence of vivax malaria in different age groups in low endemic settings.

**NIH/FIC 2D43 TW007393, Lescano (PI), Role: Coordinator 10/01/2005 to 09/30/2015**
Peru Infectious Diseases Epidemiology Research Training Consortium **$ 961,200**

- This program aims at building sustainable research capacity in Peru for studies on infectious diseases epidemiology

## OTHER EXPERIENCE, PROFESSIONAL MEMBERSHIPS

2018 – Present: **Grants Reviewer**, Research Vice-rectorate, UNMSM, Lima, Peru.
2017 – Present: Associate **Member**, American College of Epidemiology, Albany, NY.
2017 – Present: **Senior Advisor**, National Medicine Students Scientific Society (SOCIMEP), Peru.
2015 – Present: **Member**, Society for Epidemiologic Research, Clearfield, Utah.
2014 – Present: **Certification in Public Health** (No 10442), National Board of Public Health Examiners, Washington, DC

2012 – Present: **Mentor**, GloCal Health Fellowship Program, University of California, Los Angeles, CA.
2012 – Present: **Grant proposal reviewer**, Research Vice-Rectorate, UPCH
2011 – Present: **Advisor**, Medicine Students Scientific Society, UNMSM), Peru.
2010 – Present: **Statistical Reviewer and Member**, Institutional Animal Care and Use Committee, NAMRU-6
2009 – Present: **Member**, American Society of Tropical Medicine and Hygiene, Oakbrook Terrace, IL

## PEER REVIEW

- 2017 – Present: **Reviewer**, Revista CIMEL-Ciencia e Investigación Médica Latinoamericana, Perú. (ISSN 1680-8398)
- 2017 – Present: **Reviewer**, Sky Journal of Journal of Microbiology Research, U.S. (ISSN 2315-876X)
- 2016 – Present: **Board Member**, International Archives of Medicine, U.S. (ISSN: 1755-7682)
- 2016 – Present: **Reviewer**, Peer J, U.S. (ISSN: 2167-8359)
- 2016 – Present: **Reviewer**, American Journal of Tropical Medicine and Hygiene, U.S. (ISSN: 1476-1645)
- 2015 – Present: **Reviewer**, Tropical Diseases, Travel Medicine and Vaccines, U.S. (ISSN: 2055-0936)
- 2014 – Present: **Reviewer**, Journal of Women's Health Care, U.S. (ISSN: 1540-9996)
- 2014 – Present: **Reviewer**, Hemodialysis International, U.S. (ISSN: 1542-4758)
- 2011 – Present: **Reviewer**, Revista Peruana de Medicina Experimental y Salud Publica, Peru (ISSN: 1726-4634)
- 2011 – Present: **Reviewer**, Iranian Red Crescent Medical Journal, Iran (ISSN: 2074-1812)

## LANGUAGES AND COMPUTER SKILLS

**Languages**: Spanish (Native language), English (TOEFL iBT 100), Italian (Basic), and Portuguese (Basic).
**Statistical Analysis Software**: MatLab, STATA, R, ArcGIS, ATLAS.ti, PASS, PS, SPSS, and EpiInfo.
**Reference Manager Software**: EndNote, Bibus, Mendeley, RefWorks, Zotero, and BibDesk (LATEX)
**Survey & Data Management Software:** Surveygizmo, Surveymonkey, RedCap, MySQL, & MS Access

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