Malaria Transmission in Border Regions of the Western Amazon:

Incorporating watersheds into timeseries analysis to address disease reintroduction and spillover along the Ecuador-Peru border

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The Tigre River in the border region of the Ecuador-Peru Amazon (Amazon Facts, 2020).

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Abstract

Since 2010, Amazon-basin countries have experienced a 600% increase in malaria cases, the most rapid increase compared to any other region of the world. Border regions have been implicated as important hot spots of malaria transmission, particularly in Latin America. This study focuses on the Amazon border between Ecuador and Peru, a region that exhibits a steep gradient of transmission intensity, with Peru having a much higher incidence of malaria than Ecuador. The study provides a framework for incorporating watersheds into timeseries analysis to better predict malaria spatial temporal trends along borders. Results demonstrate that malaria control based on ecologically defined spatial areas could potentially provide more effective disease management than malaria control based on administrative boundaries.

Executive Summary

Since 2010, Amazon-basin countries have experienced a 600% increase in malaria cases, the most rapid increase compared to any other region of the world. Border regions have been implicated as important hot spots of malaria transmission, particularly in the Amazon basin. The two most common types of the Plasmodium parasite that cause malaria are P. vivax and P. falciparum, with P. vivax the predominant type found in Latin America. Given that Anopheles mosquitoes, the vector that transmits malaria, have an average maximum range of around 7 km, human travel and migration are important factors in transmission. If there is a sufficiently large enough vector population in an area, malaria can be introduced through migration from high incidence to low incidence areas.

This study focuses on the Amazon border between Ecuador and Peru, a region that exhibits a steep gradient of transmission intensity, with Peru having a much higher incidence of malaria than Ecuador. The landscape is dominated by secondary and primary tropical forests crisscrossed by large tributaries that flow into the Amazon River. Designated as on track to eliminate malaria by 2020, Ecuador became part of the E-2020 initiative, a cohort of countries seeking to completely eradicate malaria. However, since then, malaria incidence, particularly in the Amazon region along the border with Peru, has seen a steady increase.

Currently, Ecuador and Peru do not coordinate malaria control efforts, making each country vulnerable to outbreaks occurring in the other. This lack of coordination also reflects a failing on the part of the health systems to account for the needs of indigenous communities such as the Achuar, whose traditional territory spans the Peru-Ecuador border. Despite the formal political border, cultural and social ties between the Ecuadorian and Peruvian Achuar remain strong. People frequently travel between the two countries without any bureaucratic formality. Importantly, given the geography of the region, the Achuar mainly travel by boat between communities. One of the greatest priority health concern as reported by Achuar communities to the Peruvian Ministry of Health is the high rate of malaria infection.

Because the current malaria control plans in Ecuador and Peru are based on political administrative boundaries, they fail to capture the cross-border movement of populations such as the Achuar. This limitation in the health system structure related to the malaria transmission in the region results in the exacerbation of health inequities for indigenous communities. Given the historical community ties of the population of the river communities align more closely with natural spatial unit of watersheds, this study aims to demonstrate that by using a watershed unit of analysis, there is greater potential to capture the spatial-temporal patterns of malaria transmission in the region. Specifically, this study aims to (1) identify malaria hotspots in the study area and (2) compare model fit for data aggregated to the watershed vs. district level in an unobserved components (timeseries) analysis.

This report demonstrates that persistent areas of concern for both P.vivax and P. falciparum malaria are found along the border districts of the Ecuador-Peru Amazon, specifically in the districts containing the Achuar communities. Secondly, model comparison done using unobserved components analysis showed better model fit for the watershed unit of analysis compared to data aggregated to the district level for both Ecuador and Peru.

Ultimately, these results demonstrate that malaria control based on ecologically defined spatial areas could potentially provide more effective disease management than malaria control based on administrative boundaries. This project also reinforces the importance of coordinating international malaria control efforts in border regions to prevent disease re-emergence and better protect regional health.

1. Background

1.1 Malaria in the Americas

Despite decades long global health efforts, malaria, a mosquito-borne infectious disease, remains a global threat to human health. In 2019, an estimated 229 million cases of malaria, and 409,000 malaria related deaths occurred worldwide (World Health Organization [WHO], 2020). Affecting mostly tropical regions, malaria has become an increasingly significant health burden in the Americas with 929,947confirmed cases in 2019 (WHO, 2019). Since 2010, Amazon-basin countries have experienced a 600% increase in malaria cases, the most rapid increase compared to any other region of the world (figure 1; WHO, 2018).

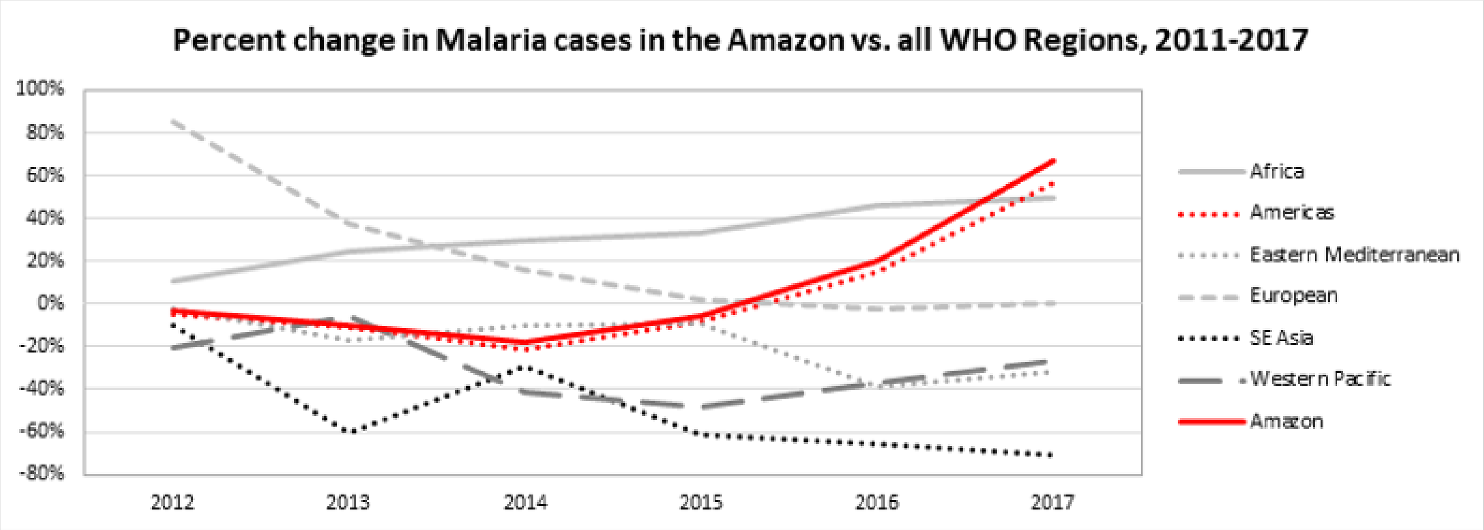


Figure 1: Percent change in malaria has increased most rapidly in the Amazon since 2011 compared to other world regions (WHO, 2018).

1.2 Malaria Transmission

Malaria is spread to humans by the female anopheles mosquitoes infected with the *Plasmodium* parasite. The two most common types of *Plasmodium* which cause malaria are *P. vivax* and *P. falciparum*, with *P. vivax* the predominant parasite found in Latin America (Global Malaria Programma & WHO Global, 2019). *P. falciparum* is considered a more severe form of malaria and is associated with higher mortality rates (Baird et al., 2013). For the *Plasmodium* parasite to complete its lifecycle, it must go through the infection cycle in both humans and mosquitoes (Zerihun et al., 2011).

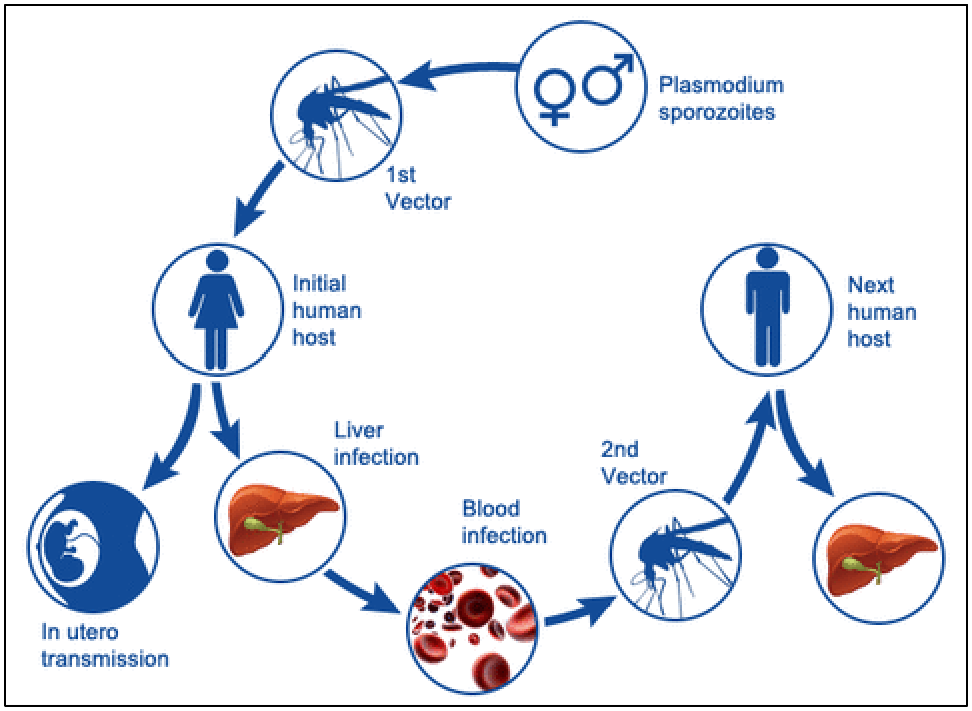


Figure 2: An infectious mosquito feeds on a human being, injecting plasmodium parasites into the blood stream. In humans, the parasite travels to the liver and eventually back to the blood stream, where then a secondary vector becomes infected after feeding on the initial human host (Jenner Institute, 2021).

Given that mosquitoes have a maximum travel range of around 7 km, human travel and migration are important factors in disease spread (Parker et al., 2013; figure 3). If there is a sufficiently large enough vector population in an area, malaria can be introduced through migration (figure 4). Travelers' social networks, their occupations, and common travel destinations influence the distribution of the malaria causing spread across communities (Gunderson, 2021).

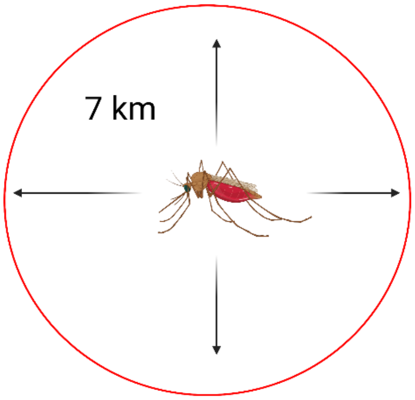


Figure 3: Maximum travel radius of an anopheles mosquito is about 7 km, though typically they stay within 1 km ranges (Verdonschota and Besse, 2014).

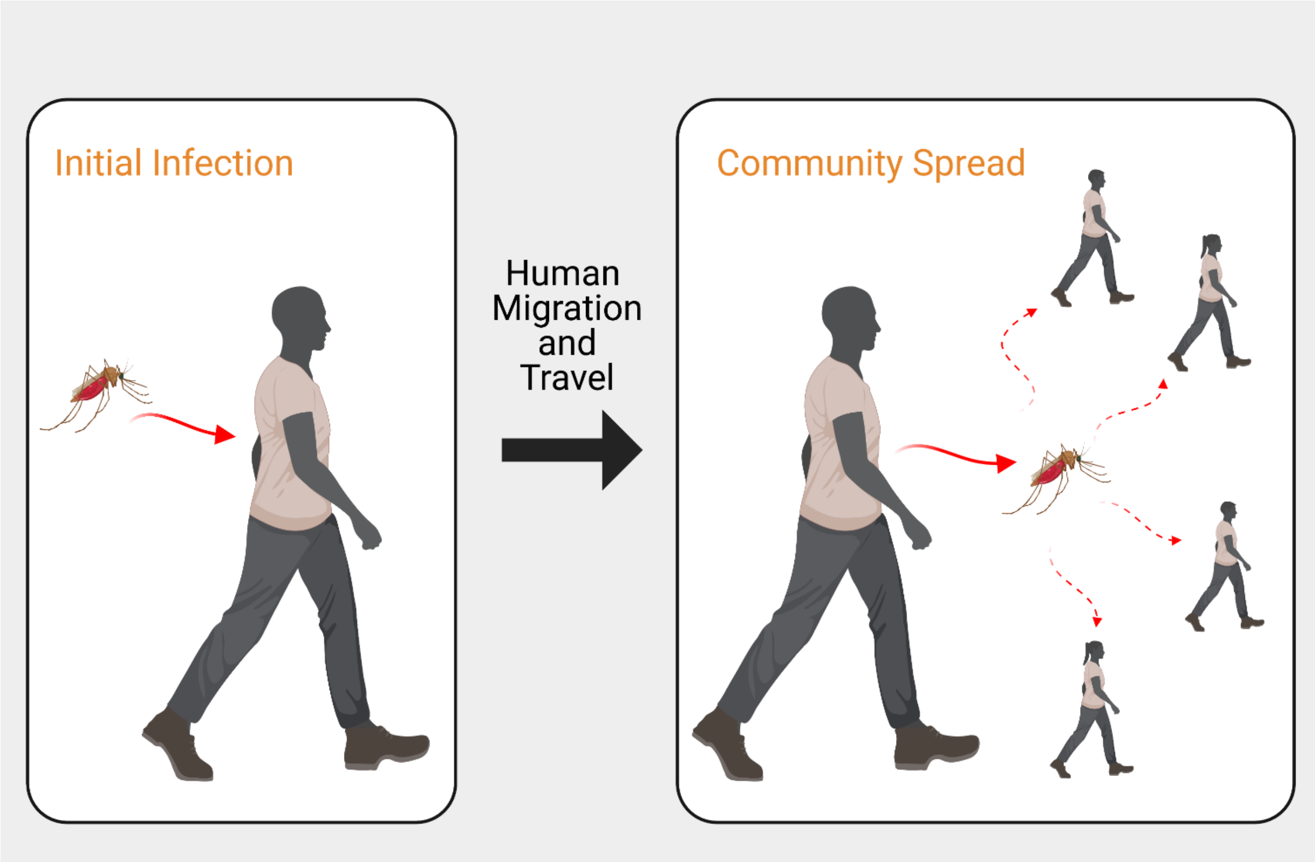


Figure 4: Malaria transmission through human travel starts with an initial host infection followed by secondary spread when that person is bit by a new vector in another location.

1.3 Malaria Transmission Along Border Regions

Drivers of malaria transmission are multifaceted, including public policy, insufficient health care access and funding, and environmental degradation (Janko et al., 2018). However, a critical component related to transmission between countries is human migration (Recht et al., 2017). In Brazil for example, the Ministry of Health reported that 43% of all malaria cases in 2019 occurred in border areas (Ministério da Saúde, 2020). As such, disease spillover along borders between low and high incidence countries remains a major hurdle for total malaria elimination in the region (Gunderson et al., 2020). Even if an individual country begins to lower transmission rates, high regional malaria rates present the possibility of reintroduction by human migration. This spillover effect happens within countries as well: in Brazil there was a 33% increase in malaria cases from 2019 to 2020 in artisanal gold mining areas (Silva et al., 2018). As extractive economic activities in the region continue to support a highly mobile migrant labor force, increased malaria transmission remains a public health threat (Daniels 2018; Conn et al., 2018). Ultimately, malaria transmission and control policies within and between countries influence the malaria burden for the entire region.

2. Introduction

2.1 Setting

This project focuses on malaria incidence in the Amazonian border region of Ecuador and Peru. There are a total of 91 districts within this region: 41 in Ecuador and 50 in Peru (figure 5). Located within the Amazon basin, the climate is tropical with seasonal wet and dry periods (Galapagos Insiders, 2021). The landscape is dominated by secondary and primary tropical forests crisscrossed by large tributaries that flow into the Amazon River (Amazon Waters, 2020).

Figure 5: Map of the study area with cantons/districts numbered. Major rivers labled in red. 1: Tena, 2: Archidona, 3: El Chaco, 4: Quijos, 5: Carlos Julio Arosemena Tola, 6: Pastaza, 7: Mera, 8: Santa Clara, 9: Arajuno, 10: Lago Agrio,11: Gonzalo Pizarro, 12: Putumayo, 13: Shushufindi, 14: Sucumbíos, 15: Cáscales, 16: Cuyabeno, 17: Orellana, 18: Aguarico, 19: La Joya De Los Sachas, 20: Loreto, 21: Morona, 22: Gualaquiza, 23: Limón Indanza, 24: Palora, 25: Santiago, 26: Sucua, 27: Huamboya, 28: San Juan Bosco, 29: Taisha, 30: Logrodo, 31: Pablo Sexto, 32: Tiwintza, 33: Zamora, 34: Chinchipe, 35: Nangaritza, 36: Yacuambi, 37: Yantzaza, 38: El Pangui, 39: Centinela Del Condor, 40: Palanda, 41: Paquisha, 42: Teniente Manuel Clavero, 43: Putumayo, 44: Inahuaya, 45: Torres Causana, 46: Napo, 47: Tigre, 48: Mazan, 49: Alto Nanay, 50: Pebas, 51: Urarinas, 52: Jeberos, 53: PadreMarquez, 54: LasAmazonas, 55:Cahuapanas, 56: Punchana, 57: Indiana, 58: Alto Tapiche, 59: Yavari, 60: Nauta, 61: Parinari, 62:

Saquena, 63: Belen, 64: Iquitos, 65: San Juan Bautista, 66: Fernando Lores, 67: Yaquerana, 68: San Pablo, 69: Barranca, 70: Pastaza, 71: Andoas, 72: Yurimaguas, 73: Contamana, 74: Ramon Castilla, 75: Jenaro Herrera, 76: Requena, 77: Puinahua, 78: Capelo, 79: Santa Cruz, 80: Emilio San Martin, 81: Maquia, 82: Soplin, 83: Tapiche, 84: Teniente Cesar Lopez Rojas, 85: Sarayacu, 86: Vargas Guerra, 87: Pampa Hermosa, 88: Lagunas, 89: Trompeteros, 90: Morona, 91: Balsapuerto (Gunderson et al., 2020)

2.2 Malaria Incidence in Ecuador

In 2015 the World Health Organization classified Ecuador within the pre-elimination stage for malaria, after decreasing the number of cases in the country from above 100,000 to 241 between the years 2000-2014 (WHO, 2016). Designated as on track to eliminate malaria by 2020, Ecuador became part of the E-2020 initiative, a cohort of countries seeking to completely eradicate malaria (WHO, 2019). However, since then, malaria incidence, particularly in the Amazon region, has seen a steady increase (figure 6). This dramatic increase in malaria rates is partially attributed to the withdrawal of international funding and the dissolution of the National Malaria Control Service by the Ecuadorian government in 2016 (WHO, 2019).

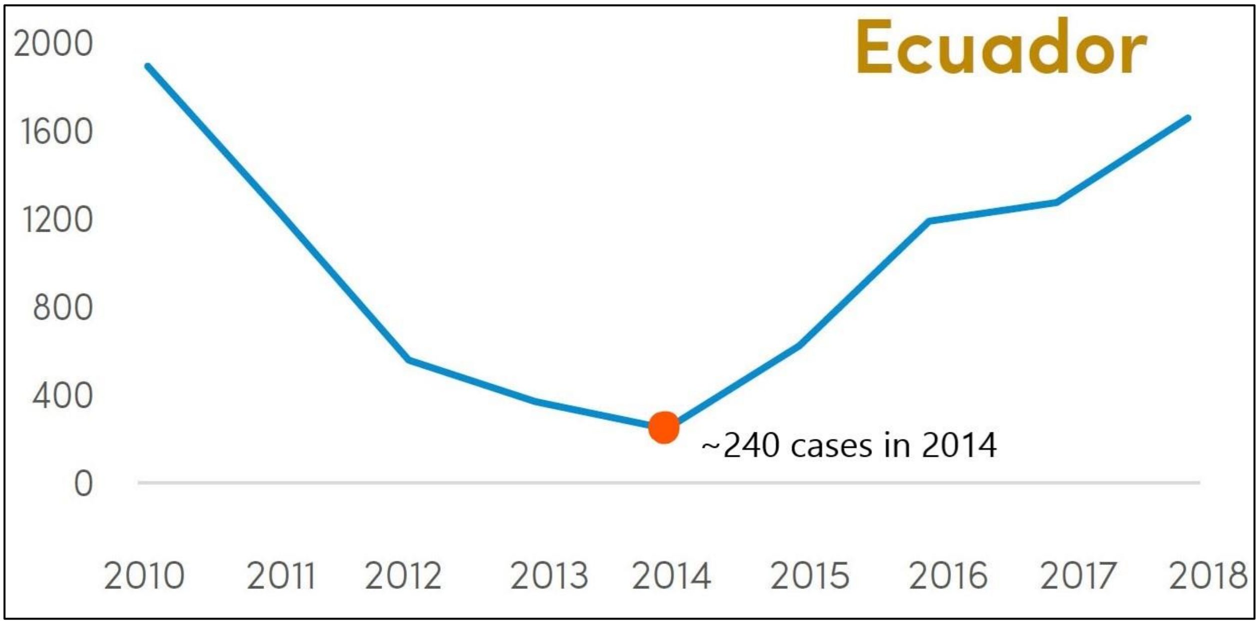


Figure 6: Number of endemic malaria cases from 2010 to 2018 in Ecuador (WHO, 2019).

Of the malaria cases in 2016, 77% came from provinces in the Amazon (Ecuadorian National Direction of Epidemiology [NDE], 2016). These rates indicate continued and prevalent barriers to total eradication of malaria in the country. Studies have demonstrated that vulnerability and disease burden remain higher for indigenous communities in the Ecuadorian Amazon basin as well as for border areas with frequent migration (Pan et al., 2010; Pan American Health Organization [PAHO], 2017; Krisher et al., 2016). While malaria treatment is free and guaranteed by the Ecuadorian Ministry of Health, for indigenous communities in the Amazon, remoteness and isolation result in lack of access to necessary treatment (Peruvian Ministry of Health [PMH], 2006).

2.3 Malaria Incidence in Peru

In 2015, 62,220 cases of malaria were reported in Peru, accounting for about 15% of total reported malaria cases in the Americas (PAHO, 2016). Increase in cases since 2012 have raised concern for regional control efforts (Angel et al., 2016). Most of the malaria is found within the Amazonian department of Loreto, which reported 95% of the country’s malaria cases in 2015 (PAHO, 2016). Like Ecuador, Amazonian communities in Peru face increased malaria burden along with lack of access to adequate healthcare (PMH, 2006). Negative social determinants of health for indigenous populations in the Peruvian Amazon, including poverty and discrimination, have contributed to a higher risk for malaria and worse long-term outcomes for those populations (United Nations Population Fund [UNPF], 2005).

2.4 Malaria Transmission Along the Ecuador-Peru Amazonian Border

Recent studies in the region have shown that increased case incidence in Peruvian districts that border the Ecuadorian Amazon is associated with increased incidence in Ecuador (Gunderson et al., 2020; figure 7 and 8).

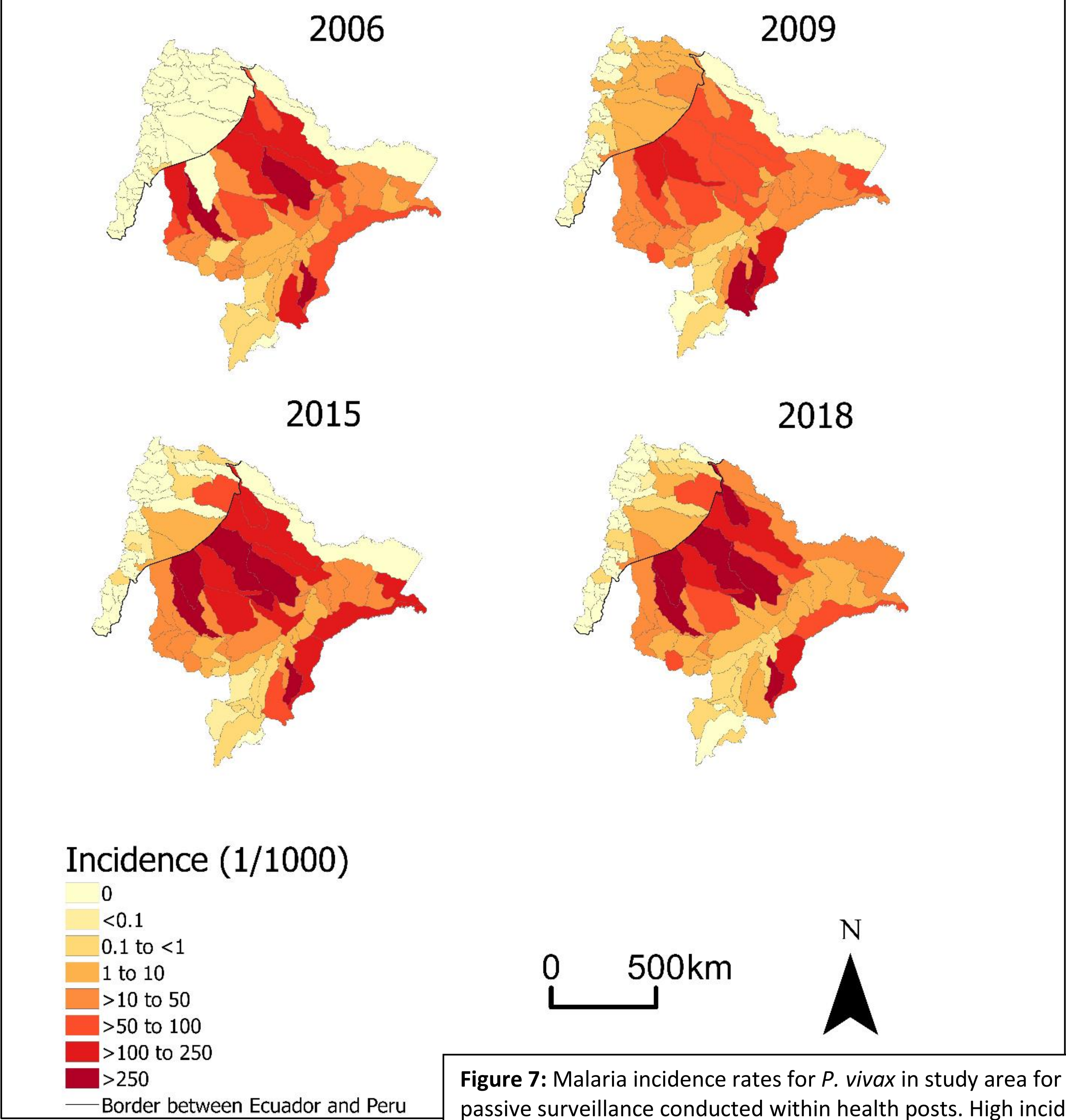


Figure 7: Malaria incidence rates for *P. vivax* in study area for 2006-2018 passive surveillance conducted within health posts. High incidence rates in Peru are a constant source of malaria that can be reintroduced to Ecuador.

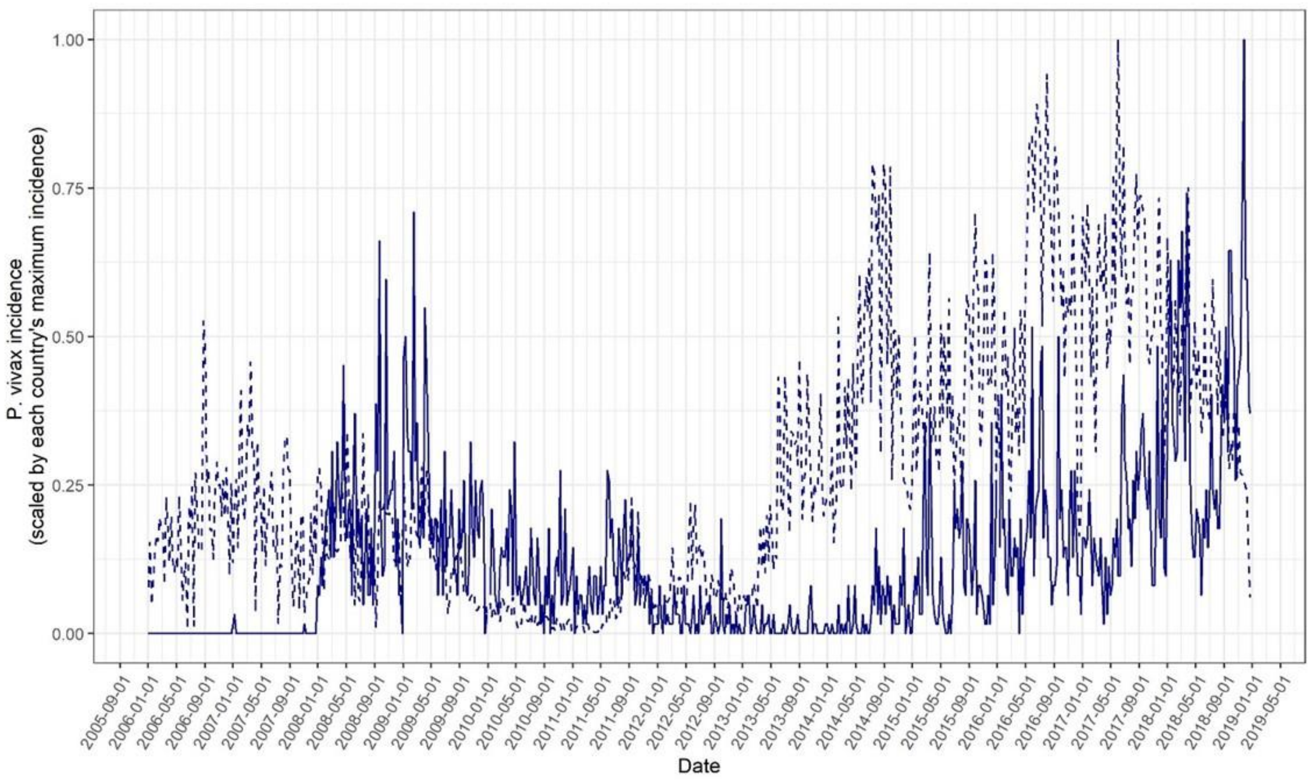


Figure 8: Incidence of *P. vivax* malaria in Loreto districts bordering Ecuador (dotted line) and in Ecuadorian cantons bordering Loreto (solid line) (Gunderson et. al, 2020).

Currently Ecuador and Peru do not coordinate malaria control efforts along the border, making both countries vulnerable to outbreaks spread by migration and travel in the area (Gunderson et. al, 2020). As discussed in the next section, this lack of coordination also reflects a failing on the part of the health systems to account for the needs of the indigenous communities in the region.

2.5 Achuar Communities

The Amazonian region of the Ecuador-Peru border is the native territory of several indigenous peoples including the Achuar. Part of the broader Jivaroana family, the Achuar name comes from joining “Achu”, or the *Aguaje* palm (a staple food for the Achuar), and “Shuar” (person), literally translating to “people of the *aguaje* palm” (Historias, 2016). Largely isolated from other communities by the area’s remote topography, the Achuar have maintained many of their traditional practices (Historias, 2016). They live in small communities typically along the numerous rivers that cover the landscape. Their current territory lies in the Alto Amazonas and Loreto provinces of Peru and the Pastaza district in Ecuador (Etnias, 2018; figure 9).

Figure 9: A close-up of the Ecuador-Peru Amazonian border region showing the location of the current Achuar territory, which overlaps with the Pastaza district on the Ecuadorian side and the Tigre and Trompetero districts on the Peruvian side. **Top photo** features an Achuar community member with their child in Sharamenza, Ecuador; **bottom right photo** features Taish, an Achuar shaman in Wayusentas, Ecuador (Kolirin, 2020).

The 1941 war between Ecuador and Peru led to the division of the Achuar territory by the current international border (James, 1990). Despite the formal political border, cultural and social ties between the Ecuadorian and Peruvian Achuar remain strong. People frequently travel between the two countries without any bureaucratic formality. Importantly, given the geography of the region, the Achuar mainly travel by boat between communities, a practice common throughout the Amazon (Velasco, 2020). Figure 10 shows the interconnectedness of these border communities along rivers and illustrates how social networks are linked by river in the Amazon.

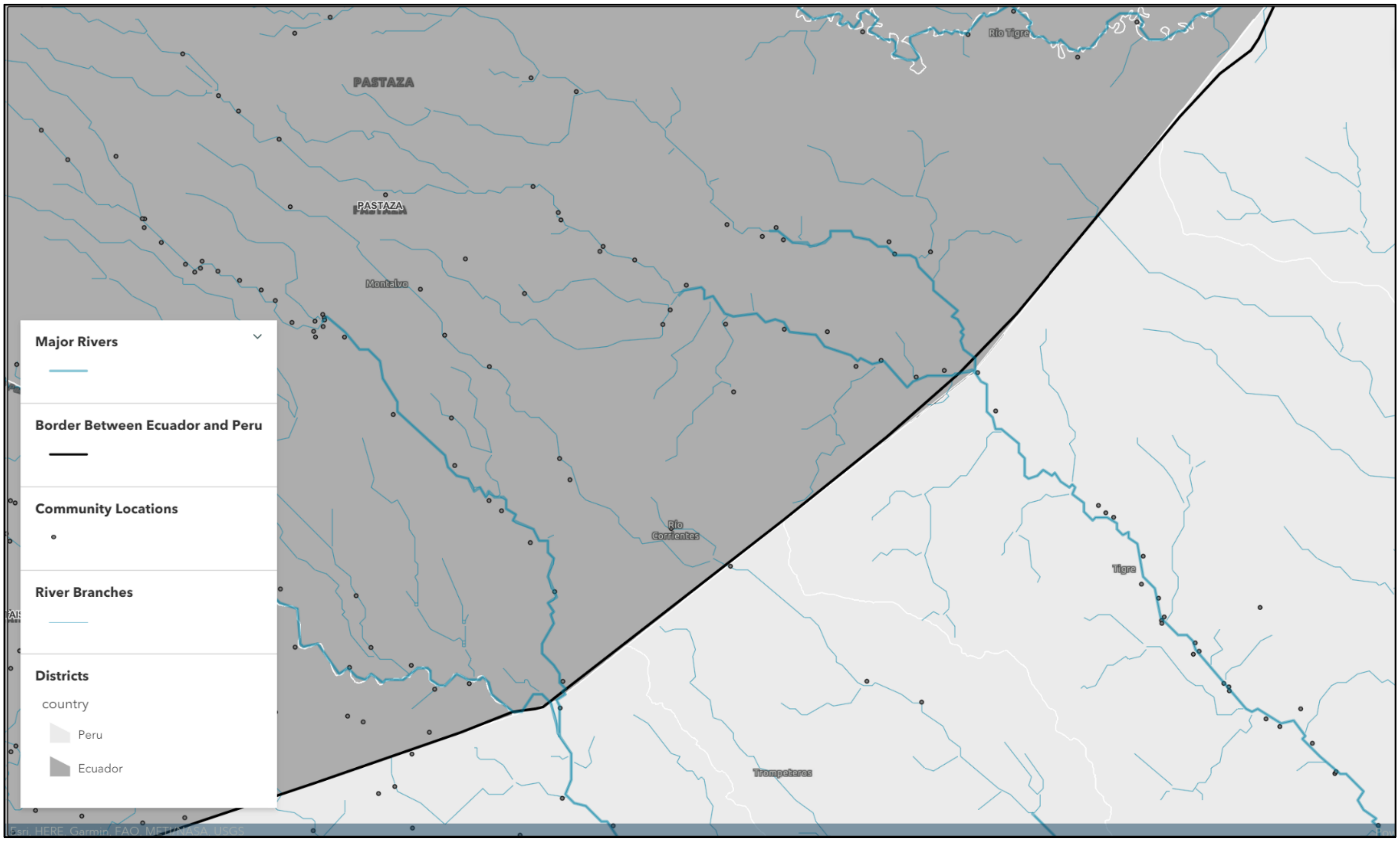


Figure 10: Zoom in of the border illustrating the interconnectedness of communities with the flow of rivers in the region. Thicker blue lines are major waterways, thinner blue lines are their tributaries. Community locations are represented by small gray dots.

When considering public health initiatives in Achuar communities, it is necessary to take into account their unique cosmovision, which understands every part of their self and existence as interconnected with their environment and community (Peruvian Ministry of Culture [PMOC], 2015). According to anthropologist Phillipe Descola, the Achuar have a complex system to diagnose and treat illness (xxx). Their health framework is based on the concept of Shiran Pujustin, "Living Well", which incorporates the status of a person's relationship to both nature and community into the concept of their wellbeing. As documented by Descola, the Achuar classify four categories of sickness: Wáwek, Sugkúr, Mímkau, Yayármau (PHM, 2005). The Peruvian Ministry of Health's report on the *Health of the Achuar People* (2005) described Wáwek illnesses as those that strike quickly, often worsening over a matter of days. Bad spirits or witchcraft are often recognized as the cause of Wáwek sickness. Sugkur illness are considered "strong," but can be cured typically using medicinal plants and traditional healing. Achuar have noted an increase in Sugkur illnesses with greater contact from outsiders. Mimkau and Yayarmau illnesses are also tied to bad spirits or influences (PMH, 2005).

It is also important to note that the Peruvian Ministry of Health has found that increased cultural contact with Western society has introduced new pathogens to Achuar communities, threatening to destabilize their traditional medicinal practices (PMH, 2005). Since the first missionary excursions into the Achuar territory, there now exists a mix of traditional indigenous medical practices with Christian influences (Etnias, 2018). There is also an increasing dependency on pharmaceuticals provided by community health workers that PMH describes as leading to an over dependence on pharmaceuticals to treat minor illnesses (Giovanni, 2015). Health concerns currently effecting Achuar communities include hepatitis, malnutrition, and food and water borne digestion illnesses (PMH, 2005). The greatest priority health concern as reported by Achuar communities is high rates of malaria infection (PMH, 2005).

2.6 Integrated Watershed Management

A holistic approach to conservation that has recently gained traction is integrated watershed management (IWM) (Environmental Protection Agency, 2010). Watersheds are an area of land with its boundaries are defined by where the water flows within it, are naturally formed spatial units that land managers often use to organize conservation efforts. More specifically, integrated watershed management is “the study of the relevant characteristics of a watershed aimed at the sustainable distribution of its resources and the process of creating and implementing plans, programs, and projects to sustain and enhance watershed function that affect the plant, animal, and human communities within a watershed boundary” (California Department of Conservation, 2015).

In the Amazon, integrated watershed management has become increasingly considered vital for conservation efforts given the shear amount of water and various countries involved in land management (Amazon Waters, 2021). Not only would IWM allow for more ecologically sound conservation approaches, but it could also help to increase cross-country collaboration when issues are considered at the watershed versus political administrative level (Epperly, 2018). While less commonly applied to the health sphere, IWM also has possibilities for addressing malaria spillover and disease resurgence in border regions in the Amazon.

3. Study Rationale and Aims

This study seeks to increase understanding related to malaria transmission along the Ecuador-Peru Amazon border. Because the current malaria control plans in Ecuador and Peru are based on political administrative boundaries, they fail to capture the cross-border movement of populations such as the Achuar. This lack of understanding related to the malaria transmission in the region results in the exacerbation of health inequities for indigenous communities (PMH, 2005). Given the historical community ties of the population and their mode of travel by river, their movements align more closely with the natural spatial unit of watersheds than political boundaries, This study aims to demonstrate that by using a watershed unit of analysis, there is greater potential to capture the spatial-temporal patterns of malaria transmission in the region. Specifically, this study aims to (1) identify malaria hotspots in the study area and (2) compare model fit for data aggregated to the watershed vs. district level.

It is expected that for the study area, there will be hotspots in districts directly along the Ecuador-Peru border, likely in the districts where the Achuar communities are located. This information can help demonstrate the need for additional public health research and support for districts identified as areas of concern. For the second aim, it is hypothesized that a timeseries model with malaria data aggregated to the watershed level will better predict malaria spatial temporal trends than models aggregated to the individual district level. Incorporating watersheds as a spatial unit into modeling approaches could help inform control strategy and policy for border regions with human migration along waterways.

4. Materials and Methods

4.1 Administrative Boundaries

Aim one of this study of identifying hot spots includes the entire border Amazonian region of Ecuador and Peru, including all 91 districts or cantons shown in figure 5. For aim two, analysis focused on the Pastaza canton of Ecuador (referred to from here on as a district) and the Tigre and Trompetero districts of Peru (figure 11). These regions contain much of the current Achuar indigenous territory. The Pastaza, Tigre, and Trompeteros districts are interconnected through trade and travel along the Tigre River as described above.

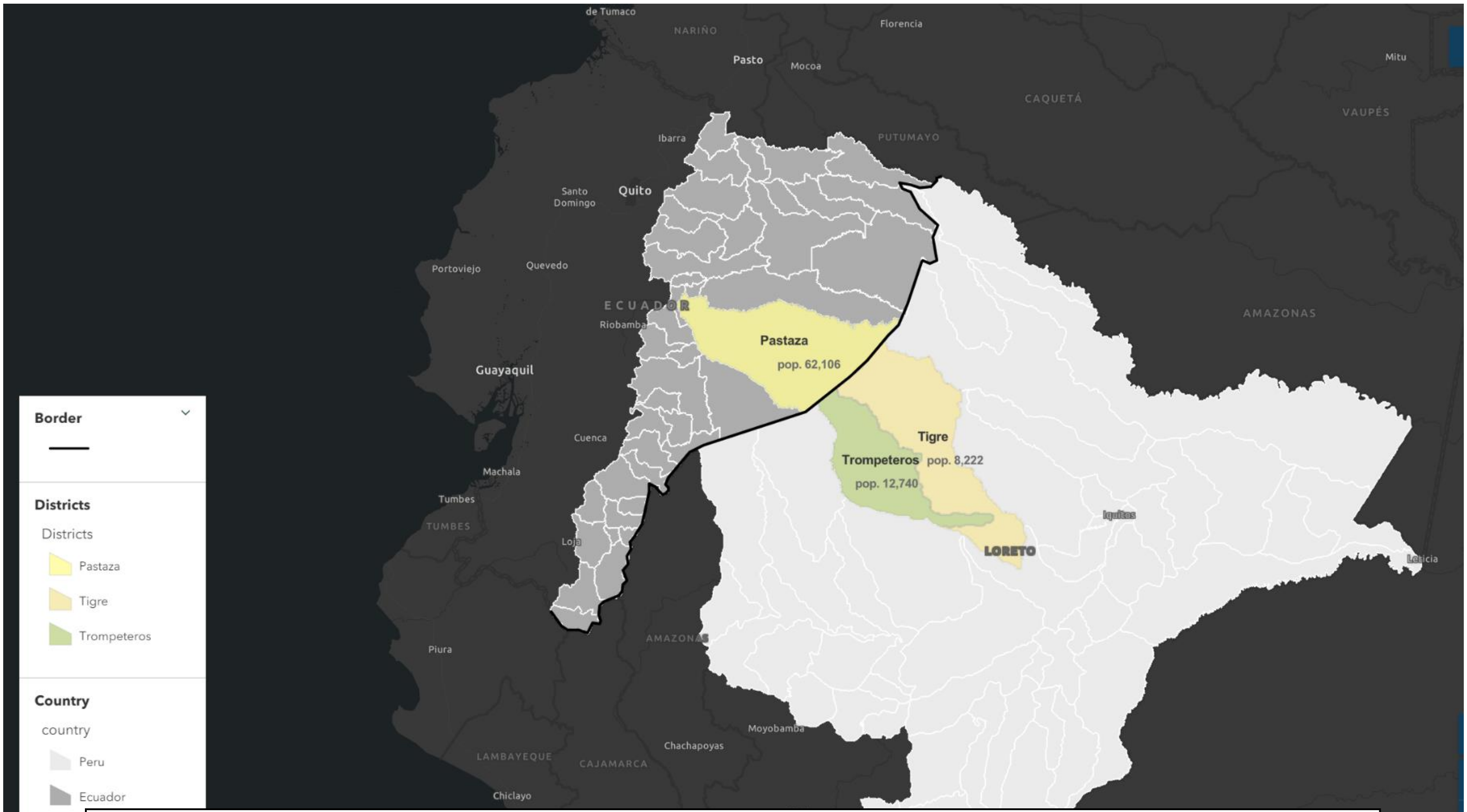


Figure 11: The three districts used in timeseries analysis: Pastaza, Ecuador; Tigre and Trompeteros, Peru.

4.2 Watershed Delineation

The watershed delineation for this project was taken from hydrological analysis done by Amazon Waters- an initiative to protect Amazonian waterways founded by the Wildlife Conservation Society (Amazon Waters, 2020). Their spatially uniform GIS database contains multi-scale watershed levels analogous to the hydrological units (HUCs) used by the United States Geological Survey. Their delineation process includes digital elevation model analysis for the region, drainage network development, and the development of a basin hierarchy, as shown in figure 12. (Venticinque et al., 2016).

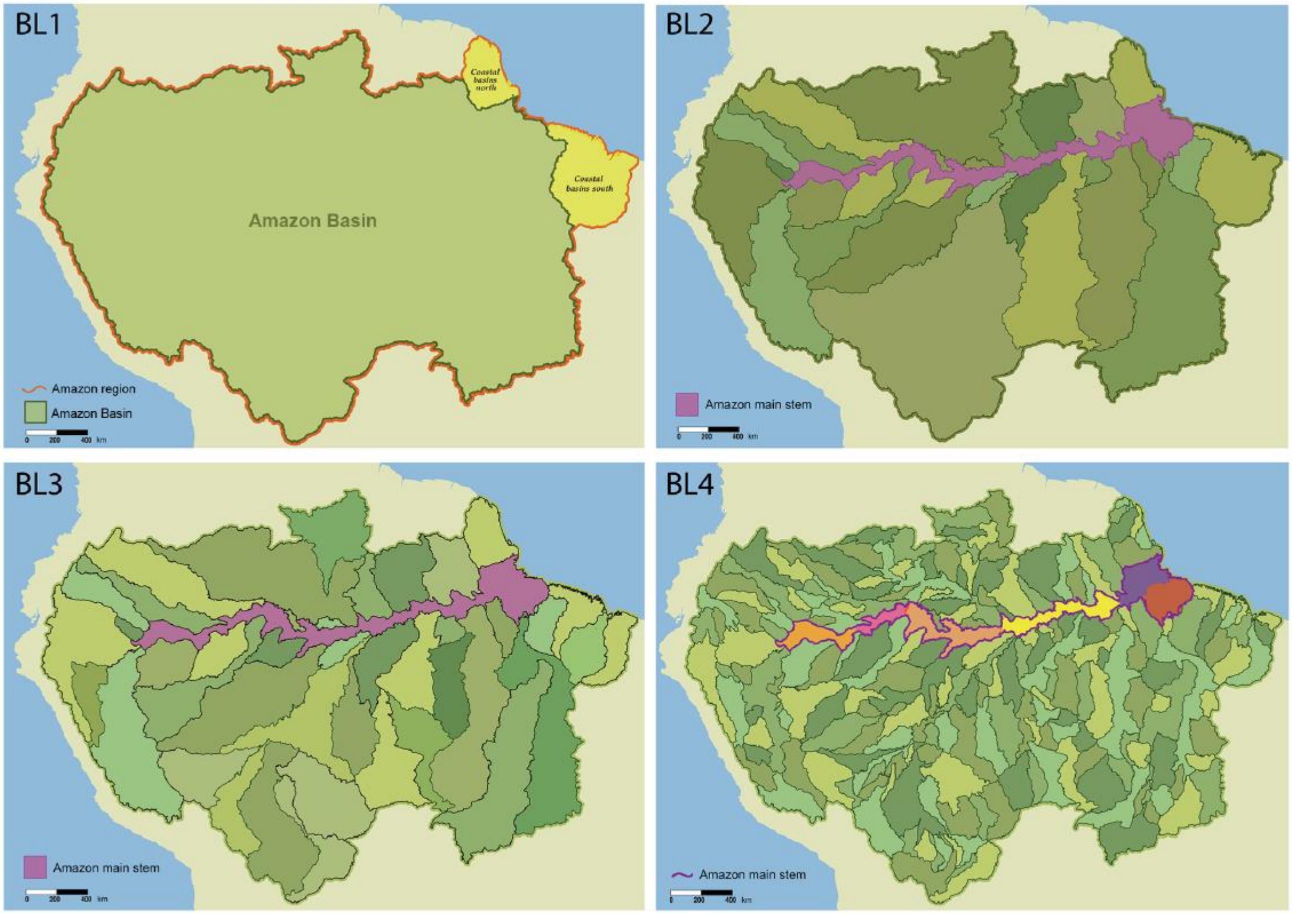


Figure 12: First four levels of water basins as delineated by Venticinque et al., 2016. This project used basin level 4 in its analysis.

This study used basin level 4, minor tributary basins, which “delimits all tributary basins greater than 10 000 km^2 and less than 100 000 km^2. Floodplain drainages include all tributaries with basins less than 10 000 km^2 flowing toward the floodplain at high water” (Venticinque et al., 2016). The final Tigre River watershed used in the analysis is shown in figure 13. Importantly, it cuts across the all the Ecuador-Peru border and covers part of all three of the political districts used in the statistical analysis.

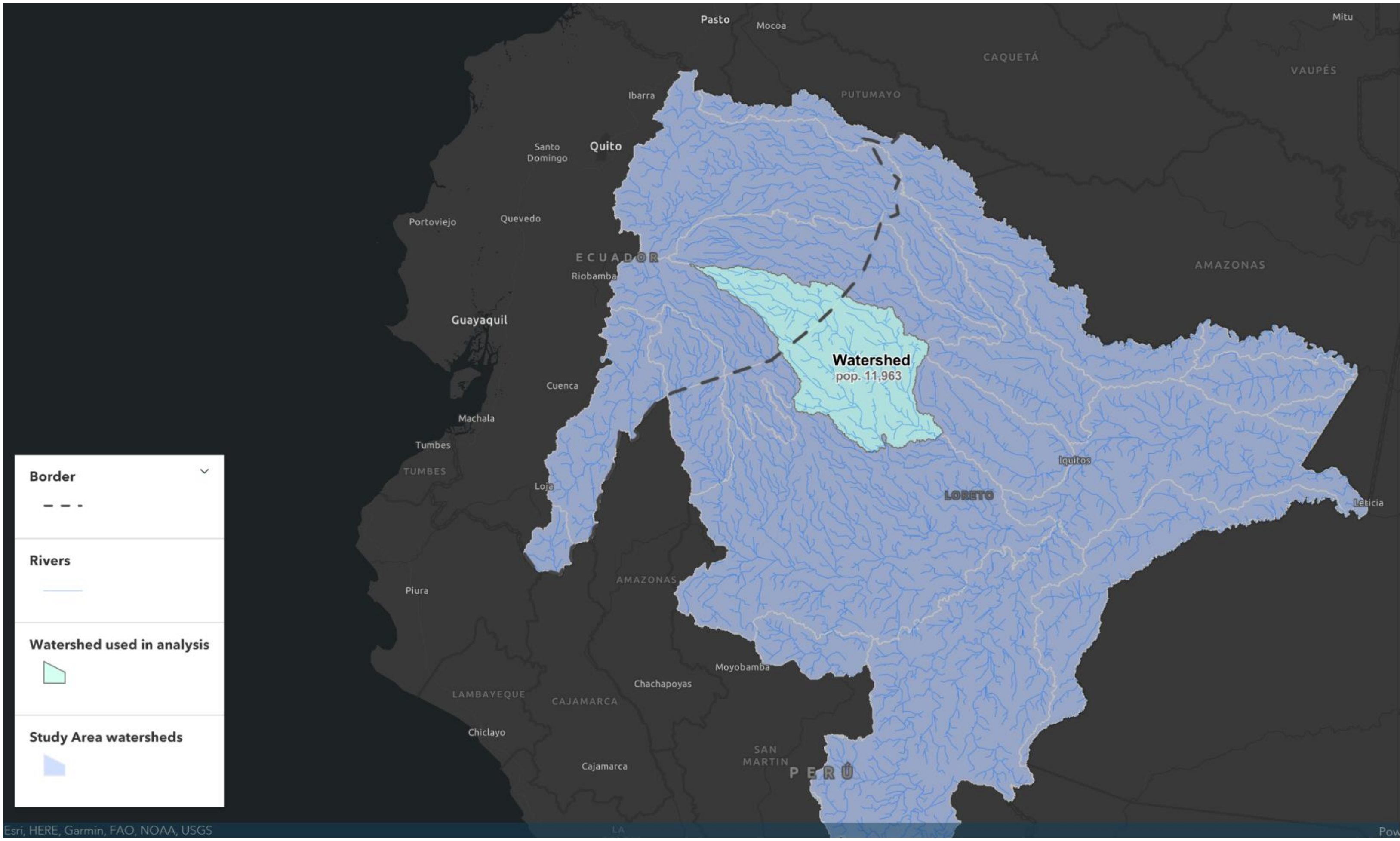


Figure 13: Tigre River watershed (light blue) used for malaria data aggregation in timeseries models.

4.3 Malaria Surveillance Data

Malaria data for Ecuador and Peru was provided by the respective national health ministries. In both Peru and Ecuador, the Ministry of Health collect and report individual cases of malaria across the country collected from local health posts. From the health post level, microscopy-confirmed *P. falciparum* and *P. vivax* cases were compiled by canton (Ecuador) or district (Peru) for each epidemiological week from 2007 to 2016. Similarly, for the watershed

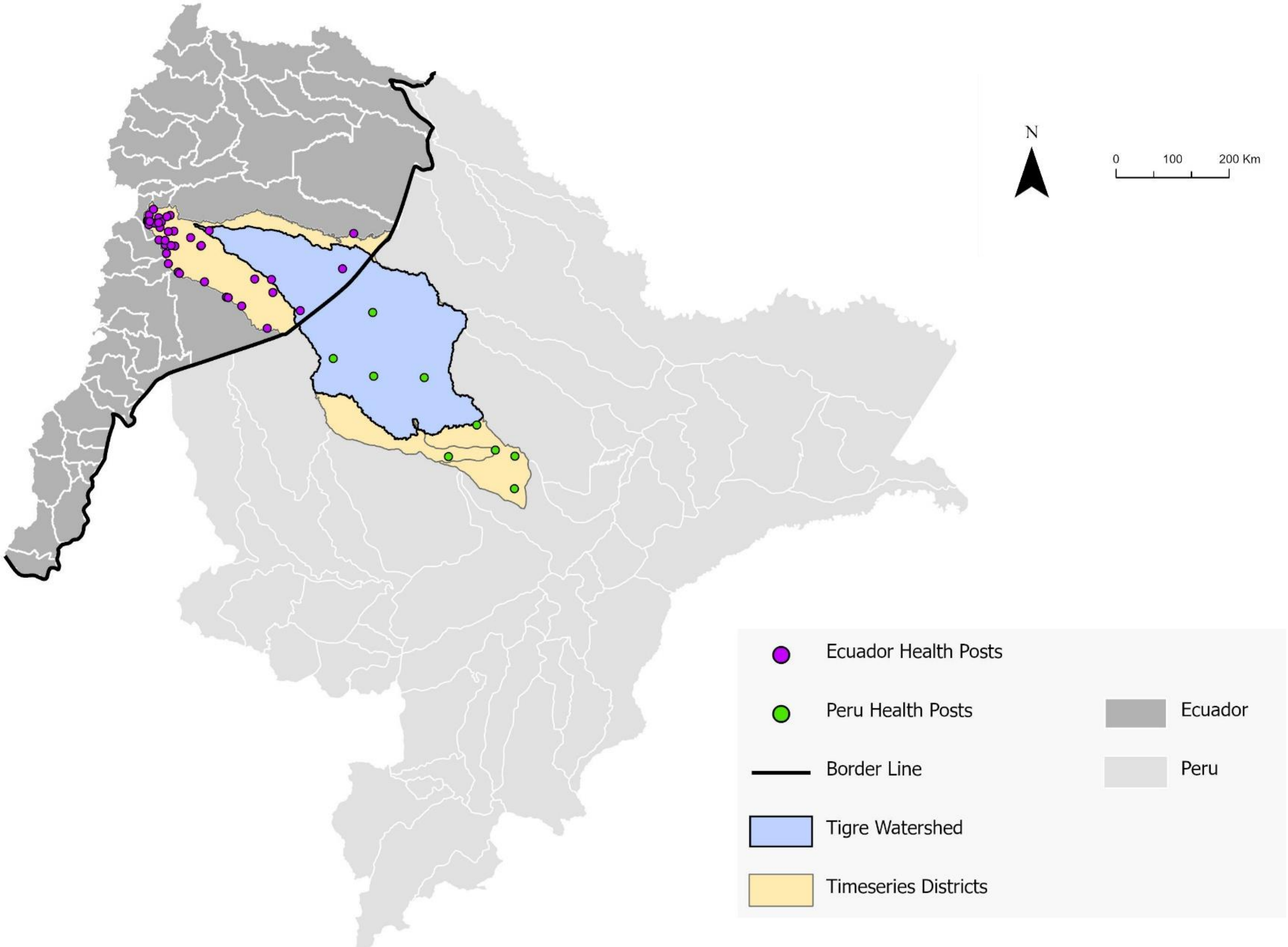


Figure 14: Study area showing the Ecuador (purple) and Peru (green) health posts used in analysis. For each model, data was either aggregated to the watershed level (blue) or district (yellow, partially covered by the watershed).

used in the analysis I complied case counts for health posts located within the watershed for 2007 to 2016 (figure 14).

4.4 Population Estimation and Incidence Rate Calculation

For the three administrative units of analysis (Pastaza, Tigre, and Trompeteros) population estimates were taken from national census data: 2010 for Ecuador and 2007 for Peru. The watershed population on the Ecuadorian side was estimated to be the sum of population counts reported at the health post level for 2010. Because health post population data was not available for the Peruvian section of the watershed, population was estimated using district population density from the 2007 census multiplied by the amount area (km^2) for each district in the watershed. Total area of each Peruvian district within the watershed was calculated in ArcGIS Pro 2.6.3.

District populations and the estimated watershed population were used to calculate incidence rates for *P. vivax* and *P. falciparum* with the formula: # of cases/ population *1000 (scalar).

4.5 Hot Spot Analysis

4.5.1 Space Time Cube

Spatial-temporal hot spot analysis was conducted in ArcGIS Pro 2.6.3. The 2007-2016 epidemiological week malaria data for the Ecuador-Peru study area was joined to the administrative shapefiles publicly available from the Ecuador and Peru governments (Center for Humanitarian Data, 2020). Administrative level 3 (cantons) was used for Ecuador, while administrative level 2 (districts) was used for Peru. Once the spatial layers from each country were combined with the malaria dataset, the shapefile was projected to WGS 1984 UTM Zone 18S using the Project tool.

The Create Space Time Cube from Defined Locations tool was used to produce a netCDF for the study area. Figure 14 illustrates how the tool analyzes patterns in the data over both space and time. The input features were with district polygons with either mean *P. vivax* or mean *P. falciparum* as the analyzed variable. For all analyses Temporal Aggregation was selected. Time steps of 1 month, 2 months, 3 months, and 1 year were run for both *P. vivax* and *P. falciparum*. For all analyses, the Time Step Alignment was set as "end time" which aligns the analysis time step to the last time event and then aggregates back in time.

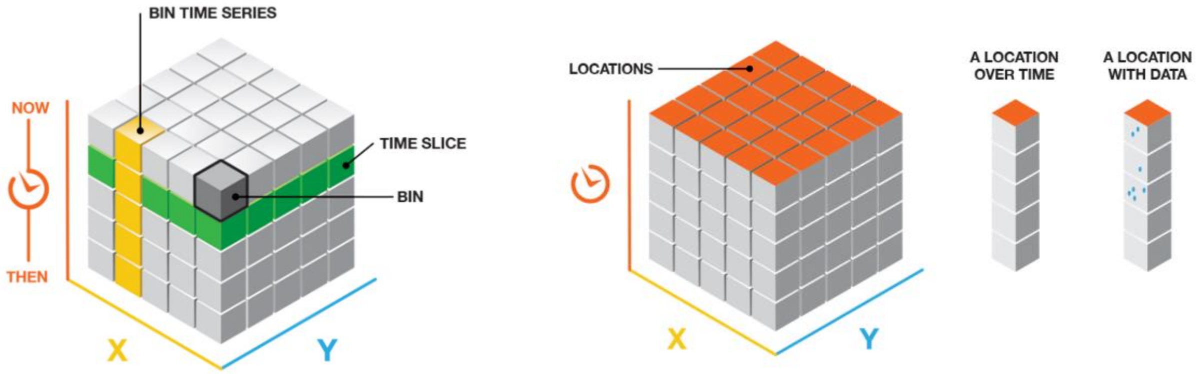


Figure 15: Illustration of Space Time Cube from Defined locations tool. The three dimensional analysis looks for patterns over space and time in longitudinal data.

4.5.2 Emerging Hot Spot Analysis

To visualize the Space Time Cube netCDF output, I used the Emerging Hot Spot Analysis tool. This tool can detect eight specific hot or cold spot trends: new, consecutive, intensifying, persistent, diminishing, sporadic, oscillating, and historical. To measure the intensity of feature clustering, this tool uses a space-time implementation of the Getis-Ord Gi* statistic, which considers the value for each bin within the context of the values for neighboring bins. For this analysis, I selected the spatial relationship to be contiguity edges corners (Queen's Case), meaning that districts that share an edge or a corner were compared to each other over time.

4.6 Unobserved Components Model

Data management and analysis were done using R 3.6.2 (R Core Team, 2019), the xts (v0.12.1; Ryan & Ulrich, 2020), TSstudio (v0.1.6; Krispin, 2020), and rucm (v0.6; Chodhury, 2015) packages. Descriptive data of malaria incidence were tabulated for the three districts and the watershed. Separate unobserved components models were used to evaluate the relationship between the malaria incidence for the three districts and the watershed for both *P.vivax* and *P. falciparum*.

Temporal variables available in the UCM model were selected through backwards stepwise regression and univariate analysis in which variables where $p < 0.05$ could be included in the timeseries model. Model fit was assessed through likelihood-ratio test and comparing Akaike information criterion (AIC) values.

20% of the original malaria data was withheld to calculate root mean square error for final models. Model comparison between the areas was done through ranking of this calculated root mean square error (Chai and Drexler, 2014).

5. Results

5.1 Malaria Trends in Modeled Districts and Watershed

All modeled districts and the Tigre watershed had an increasing trend both in change in mean *P.vivax* and mean *P.falciparum* from 2011 onward (figure 15 and 16). The Pastaza district had the lowest rates of both *P.vivax* and *P.falciparum* staying below an incidence rate of 2 cases/1000/week for all years. The Tigre district in Peru had the highest rates of both types of

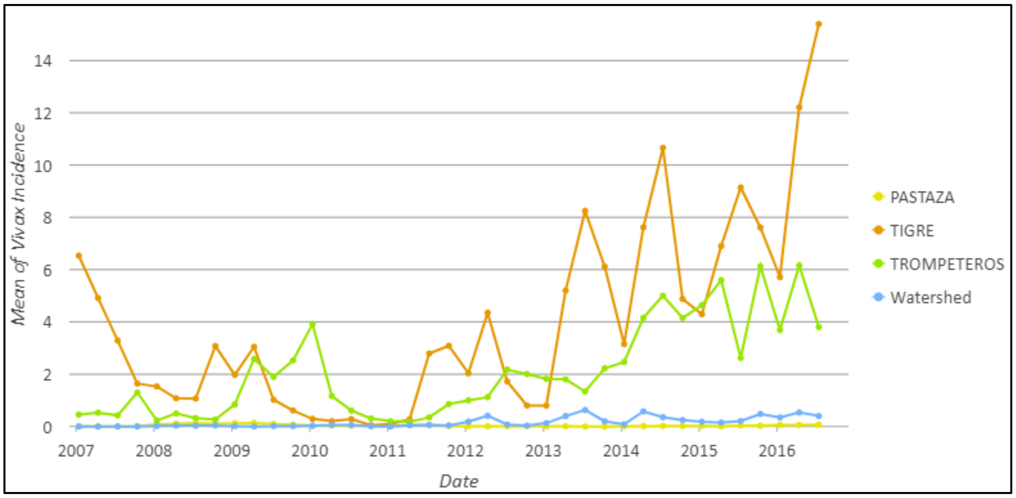


Figure 15: Change in mean *P.vivax* incidence for model districts and watershed from 2007-2016.

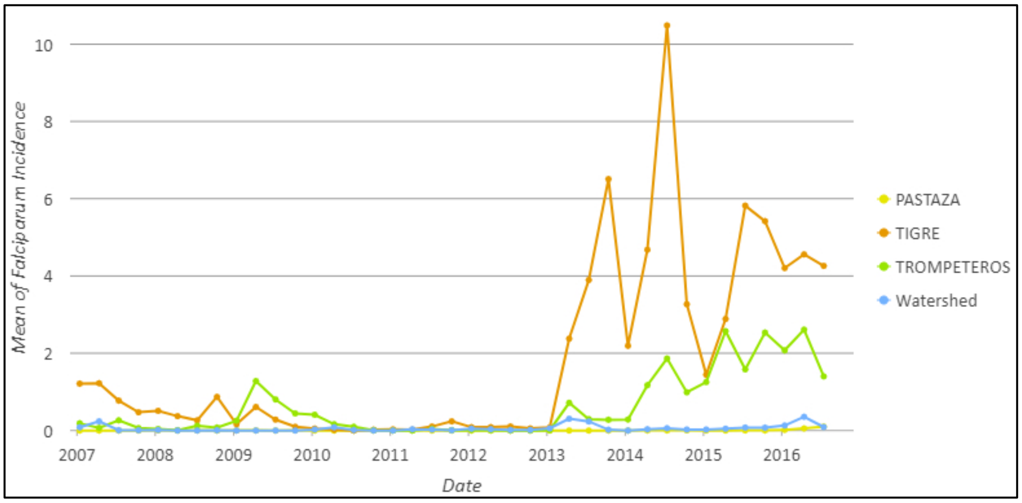


Figure 16: Change in mean *P.falciparum* incidence for model districts and watershed from 2007-2016.

malaria, with incidence rates exceeding 14 cases/1000/week in 2016. Table 1 shows the estimated population for each spatial unit modeled.

Table 1: Estimated population of modeled districts and watershed

	Watershed	**Pastaza**	**Tigre**	**Trompeteros**
Estimated Population	11,963	62,106	8,222	12,740

5.2 Aim 1: Hot Spot Analysis

5.2.1 *P. vivax Hot Spot Results*

Figure 17 shows maps of identified hot spots in the broader study area. For a one-month timestep aggregation, sporadic hot spots were found in the region of the Tigre watershed, including Pastaza, Tigre, and Trompeteros. For the following two timesteps, two and three months, the districts of Trompeteros and Andoas in Peru, as well as the Pastaza and Taisha districts in Ecuador, were identified as consecutive hot spots, meaning those locations had a single uninterrupted run of statistically significant hot spot bins in the final time-step intervals. As such the locations had never been a statistically significant hot spot prior to the final hot spot run and less than ninety percent of all bins were statistically significant hot spots. When using a one-year timestep, the Peruvian districts of Yaqueran and Soplin, which border the Brazilian Amazon, were identified as persistent hot spots meaning they were identified as locations that have been a statistically significant hot spot for ninety percent of the time-step intervals with no discernible trend indicating an increase or decrease in the intensity of clustering over time.

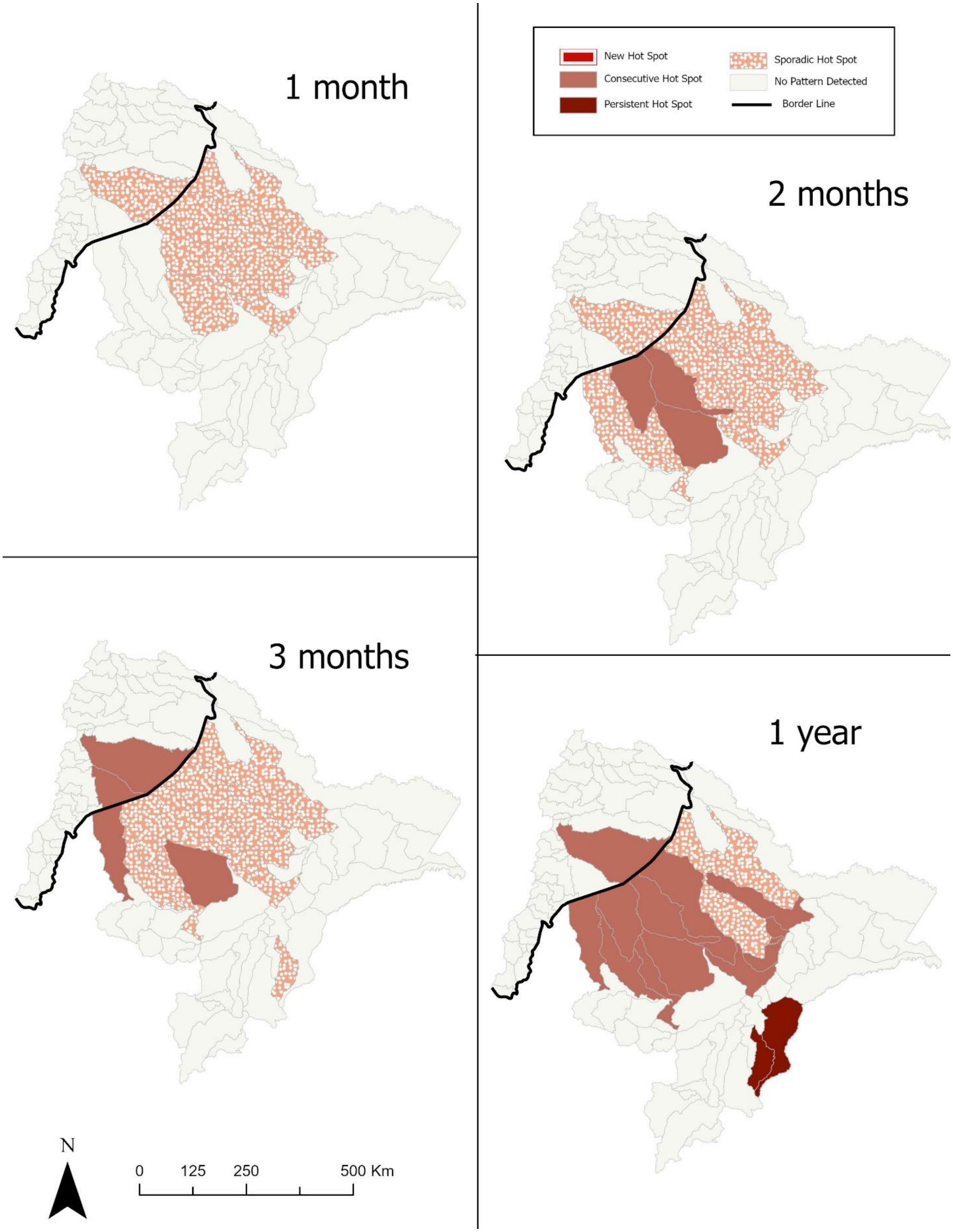


Figure 17: Emerging hot spot analysis results for mean *P.vivax* at one, two, three month and one year timestep intervals.

5.2.2 *P. falciparum Hot Spot Results*

Figure 18 shows final output maps of identified hot spots for *P. falciparum* in the broader study area. For a one-month timestep interval, sporadic and consecutive hot spots were found only in the Peruvian districts directly along the border. For the following two timesteps, two and three months, the Ecuadorian districts of Pastaza and Taisha districts were identified as consecutive and sporadic hot spots respectively with no change between the two time steps. For the one-year time step interval, Taisha, Ecuador and Barranca, Peru were identified as new hot spots meaning they were locations that were a statistically significant hot spot for the final time step and had never been a statistically significant hot spot before.

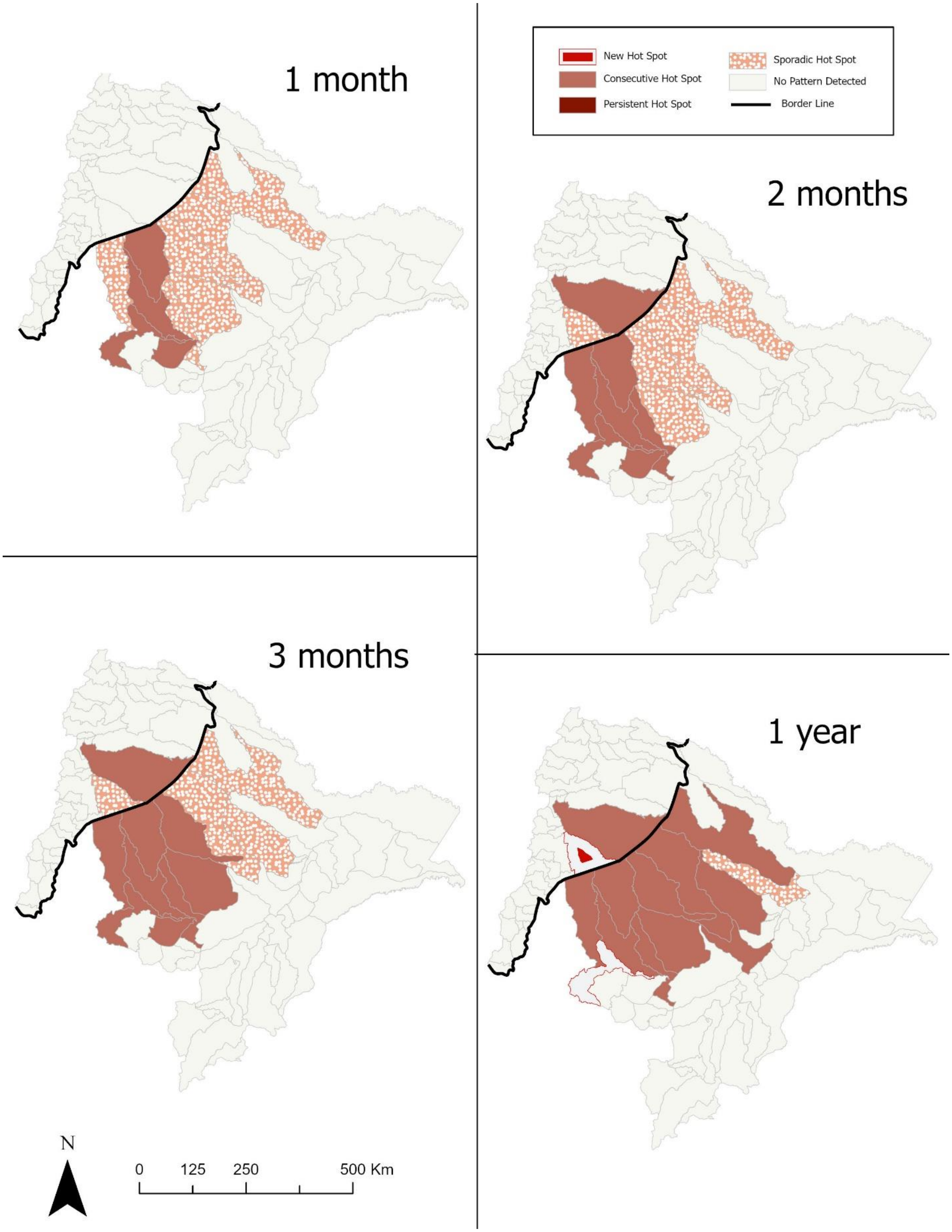


Figure 18: Emerging hot spot analysis results for mean *P. falciparum* at one, two, three month and one-year time step intervals.

5.2 Aim 2: Unobserved Components Model Comparison

5.2.1 *P. vivax* UCM Results

For the unobserved component model variables for *P.vivax* models, the best-fit model was selected through comparison of AIC values. Possible parameters included the irregular component, slope, level, season, and cycle. Ultimately, slope was excluded from the final models. Final estimates of the free parameters used in the models are listed in Table 2. The results from timeseries model indicate the Pastaza district model and the watershed model outperformed models the Tigre and Trompeteros models. Table 3 shows the comparison of root mean square prediction error (RMSPE) for all models. Figures 19-22 show the final model trend lines for each region analyzed.

Table 2: Final estimates of the free parameters for *P.vivax* UCMs

Model	Irregular Error Variance Estimate	Level Error Variance Estimate	Season Error Variance Estimate	Cycle Error Variance Estimate
Watershed	0.0504	0.0010	2.127 E -8	0.0004
Pastaza	0.0019	0.0001	3.143 E -6	1.000 E -7
Tigre	3.3522	0.6764	4.019 E -6	0.0453
Trompeteros	0.9899	0.2881	0.0013	3.2041 E -6

Table 3: Root Mean Square Prediction Error for *P. vivax* unobserved components models. Pastaza (red) had the lowest RMSPE, 0.053, followed by the Watershed model (yellow).

	Watershed	Pastaza	Tigre	Trompeteros
RMSPE	0.361	0.053	5.81	3.13

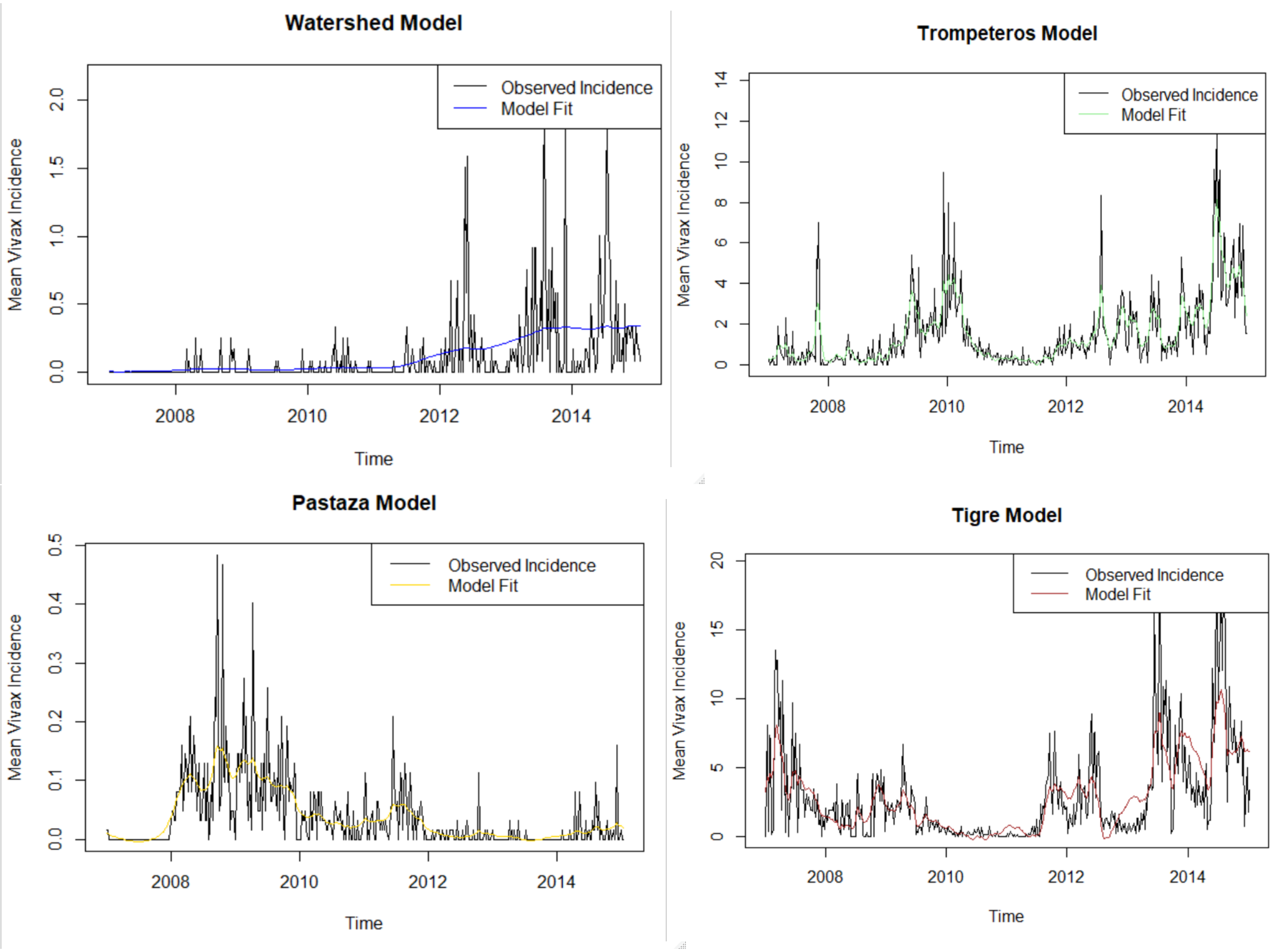


Figure 19-22: Final fitted model trend lines for *P. vivax* UCM analysis.

5.2.2 *P. falciparum* UCM Results

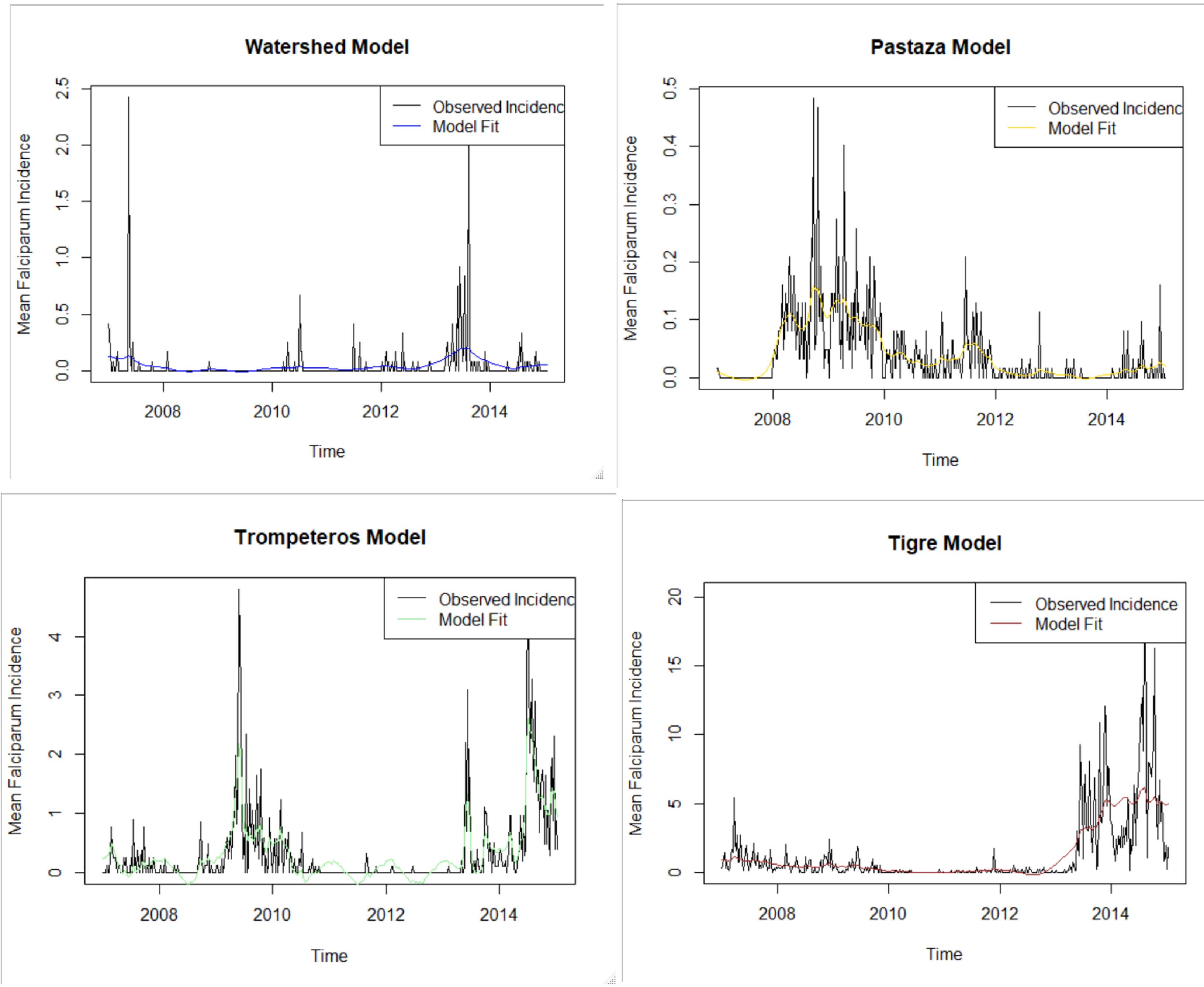
For the unobserved component model variables for *P.vivax* models, the best-fit model was also selected through comparison of AIC values. The possible parameters were the irregular component, slope, level, season, and cycle. Ultimately, the slope component was excluded from the final models. Final estimates of the free parameters used in the models are listed in Table 4. The results from timeseries model indicate the Pastaza district model and the watershed model outperformed the Tigre and Trompeteros models. Table 5 shows the comparison of root mean square prediction error (RMSPE) for all models. Figures 23-25 show the final model trend lines for each region analyzed.

Table 4: Final estimates of the free parameters for *P. falciparum* UCMs

Model	Irregular Error Variance Estimate	Level Error Variance Estimate	Season Error Variance Estimate	Cycle Error Variance Estimate
Watershed	0.02951	0.000199	1.355 E -8	7.835 E -8
Pastaza	0.00193	7.658 E -5	3.796 E -6	1.023 E -9
Tigre	1.6315	0.07922	0.00248	0.1300
Trompeteros	0.12982	0.03889	8.1676 E -9	6.2260 E -10

Table 5: Root Mean Square Prediction Error for *P. falciparum* UCM analysis. Pastaza (red) had the lowest RMSPE, 0.111, followed by the Watershed model (yellow).

	Watershed	Pastaza	Tigre	Trompeteros
RMPSE	0.216	0.111	4.02	1.58



Watershed Model

Pastaza Model

Trompeteros Model

Tigre Model

Figure 23-25: Final fitted model trend lines for *P. falciparum* UCM analysis.

6. Discussion

Districts directly along the border of the Ecuador-Peru Amazon were more likely to be identified as hot spots for both *P. vivax* and *P. falciparum*. Though there were variations in type of hot spot identified, the districts containing the present day Achuar territory were consistently found to have sporadic or consecutive hot spots for all time steps. Identifying the districts along the border as transmission hot spots reinforces the concern of reintroduction of disease by migration from high to low incidence regions (Gunderson et al., 2020). In the case of the Achuar communities, it also highlights the persistent barriers facing indigenous communities in the elimination of malaria (PMH, 2005). The remoteness of the region due to its topography provides less access to preventative measures such as bed nets and residual insecticide spraying, likely exacerbating the transmission (Pizzitutti, 2019).

While there were some location differences per time step between *P.vivax* and *P. falciparum,* both malaria types were identified consistently along the border of interest. One finding of note for the *P. vivax* hot spots was the identification of the Peruvian districts, Yaqueran and Soplin, as persistent hot spots. While not directly along the Ecuador border, these districts do border Brazil, a country with high endemic rates of malaria in the Amazon (Ministério da Saúde, 2020). Further study regarding the transmission dynamics with that shared border should be considered as the hot spot analysis indicates similar border disease spillover might be occurring between Peru and Brazil.

For model outputs, the Pastaza and Watershed UCMs were found to have best fit based on RMSPE, indicating the overall potential for watershed units of analysis to help capture varying disease dynamics between the two countries. A severe limitation of these models is their lack of variables beyond temporal parameters. Future models should include environmental estimators such as temperature, rain fall, and soil moisture content to improve overall model fit. Sociodemographic variables such as age, gender, and education should also be included to potentially target specific population segments that could face higher disease burden. Another limitation of this study is the likely overestimate of population in the watershed unit of analysis. Because the region is so remote, population density measures for the entire district likely overestimate density in the region of the watershed directly on the border. Ultimately though, this study provides a framework of how to begin to incorporate Integrated Watershed Management approaches to public health analyses.

6.2 Implications for policy and practice

This study is the first to attempt to integrate watershed analysis into malaria modeling for this region of the Amazon. Prior research has demonstrated the key role of human migration in malaria transmission in the area (Gunderson, 2021). Of greater concern, higher levels of malaria transmission can increase the risk of spreading resistant *Plasmodium*, undermining current medications and control efforts (Guyant et al., 2015).

This study also highlights the ongoing high disease burden for indigenous communities in the Amazon. For equitable health outcomes, more strategic, community -entered approaches that take into account specific cultural and historical needs of the indigenous population are needed (Krisher et al., 2016). Successful elimination in border regions will require taking these population level dynamics into account and for international cooperation to support indigenous peoples whose traditional territories cross borders (Krisher et al., 2016).

8. Conclusion

Because the current malaria control plans in Ecuador and Peru are based on political administrative boundaries, they fail to capture the cross-border movement of populations in the Amazon. Incorporating watershed analysis into malaria control plans could potentially provide more effective disease management than current strategies. Given how susceptible border regions in the Amazon are to disease reintroduction, targeted coordination in these areas is necessary to reach stated goals of malaria elimination. For malaria control, by taking into account watershed level dynamics, health networks can better protect communities, and ultimately, regional health.

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