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What caused the 2012 dengue outbreak in Pucallpa, Peru?

A socio-ecological autopsy

Abstract

Dengue is highly endemic in Peru, with increases in transmission particularly since vector re-infestation of the country in the 1980s. Pucallpa, the second largest city of the Peruvian Amazon, experienced a large outbreak in 2012 that caused more than 10 000 cases and 13 deaths. To date, there has been limited research on dengue in the Peruvian Amazon outside of Iquitos, and no published review or critical analysis of the 2012 Pucallpa dengue outbreak. This study describes incidence, surveillance and control of dengue in Ucayali to understand the factors that contributed to the 2012 Pucallpa outbreak. We employed a socio-ecological autopsy approach to consider distal and proximal contributing factors, drawing on existing literature and interviews with key personnel involved in dengue control, surveillance and treatment in Ucayali. Spatio-temporal analysis showed that relative risk of dengue was higher in the northern districts of Calleria (RR=2.18), Manantay (RR=1.49) and Yarinacocha (RR=1.25) compared to all other districts between 2004 and 2014. The seasonal occurrence of the 2012 outbreak is consistent with typical seasonal patterns for dengue incidence in the region. Our assessment suggests that the outbreak was proximally triggered by the introduction of a new virus serotype (DENV-2 Asian/America) to the region. Increased travel, rapid urbanization, and inadequate water management facilitated the potential for virus spread and transmission, both within Pucallpa and regionally. These triggers occurred within the context of failures in surveillance and control programming, including underfunded and ad hoc vector control. These findings have

implications for future prevention and control of dengue in Ucayali as new diseases such as chikungunya and Zika threaten the region.

Keywords

Dengue, infectious disease outbreak, environmental health, Peru

1.0 Introduction

In 2012, the World Health Organization declared dengue the most rapidly spreading mosquito-borne disease, with a 30-fold increase in global incidence over the past 50 years (WHO, 2012). There is no vaccine or medication yet developed to immunize against or treat dengue. Vector control is thus the only effective approach to prevent epidemics and resurgence of the disease (Bhatt, 2013; Hales et al., 2002). In recent years, dengue has re-emerged in regions where incidence had previously been controlled or eradicated. This is largely attributed to inadequate vector management associated with reduced allocation of funding towards vector control, increased insecticide resistance in mosquitoes, and high costs related to material and wages (J. San Martín & Brathwaite-Dick, 2006a; WHO, 2012). The rise of two newly emergent vector-borne diseases, chikungunya fever and Zika virus – which share vectors, symptoms, and similar transmission patterns with dengue – in Latin America and elsewhere has further heighted concern over the inadequacies of control, and surveillance programs for dengue (Bogoch et al., 2016; Musso et al., 2015).

Peru is one of the most highly endemic countries for dengue, reporting between 4,000 and 29,000 cases annually over the last ten years (DGE, 2015; WHO, 2012). Though eradicated at the national level in 1958, the mosquito vector *Aedes aegypti*'s re-emergence in the 1980s led to renewed dengue transmission, particularly in northern Peru (Chowell et al., 2008; DGE, 2015; Forshey et al., 2009). Since then, there have been several major epidemics throughout the 1990s, with early incidence concentrated in Iquitos, the largest city of the Peruvian Amazon (Chowell et al., 2008). Incidence – and research – has thus largely focused on Iquitos (Hayes et al., 1996; Liebman et al., 2012; Morrison et al., 2010; Phillips et al., 1992). Neighbouring Amazonian city Pucallpa (Ucayali region) has also seen increasing incidence: a large epidemic in Pucallpa in 2012 affected more than 10,000 people and highlighted the continued spread of dengue in the Peruvian Amazon (DGE, 2015). In 2012, cases reported in Pucallpa represented about a third of all cases reported in the entire country, but despite the magnitude of the outbreak, there has been no peer-reviewed literature describing and characterizing this event or the conditions leading to its occurrence (DGE, 2015).

Successful control of dengue and related vector-borne diseases requires an evidence base characterization of existing transmission patterns and critical appraisal of vector control and surveillance programming. We herein address this research gap by critically evaluating the 2012 Pucallpa dengue outbreak, using a socio-ecological autopsy approach to identify both proximal and distal/contextual factors contributing the outbreak. We used a mixed methods approach, drawing on incidence records, key-informant interviews, and a literature review to provide an update on – and critical assessment of – the state of dengue in Ucayali region over the past decade, focusing on the context of the 2012 outbreak in Pucallpa. Specifically, we aimed to: 1) describe dengue incidence in Ucayali for the period 2004-14, 2) identify and assess key contributing factors to the 2012 outbreak in Pucallpa, and 3) characterize surveillance and control programs in the region. We conclude by critically appraising the implications for future dengue incidence and control in Ucayali.

2.0 Materials and Methods

2.1 Study area

Ucayali is one of 25 regions in Peru, located in the central-east of the country. Its population of roughly 400,000 (total Peru: 27 million) is unevenly spread in an area of 101,750km^2, with about half of its population residing in the capital city, Pucallpa (INEI, 2009b). The region is part of the Amazonian drainage basin, and settlement has historically been focused along the Ucayali River, a tributary of the Amazon (Goy & Waltner-Toews, 2005). Pucallpa was connected by a road to the country's capital, Lima, in the 1940s, opening opportunities for exploitation of natural resources and unprecedented increased settlement in the region such that Pucallpa's population tripled over the last three decades (Goy & Waltner-Toews, 2005; INEI, 2009a).

Ucayali is predominantly inhabited by Indigenous populations engaged in floodplain agriculture, fishing, hunting and forest product gathering, with these activities highly dependent on seasonal variations caused by an annual flood cycle (Barham et al., 1999; Sherman et al., 2015). Seasonal flooding is also recognized in the region as a determinant of migration patterns and associated spread of disease. Dengue is a major public health priority in Ucayali, with chronic malnutrition, malaria, respiratory illnesses and diarrhea also causing a significant health burden (Goy & Waltner-Toews, 2005).

2.2 Dengue governance and reporting in Ucayali

The *Dirección Regional de Salud* (DIRESA) is the regional branch of the national Ministry of Health in Pucallpa, coordinating public health and healthcare activities throughout the

Ucayali region. DIRESA's epidemiology department is responsible for receiving and monitoring case information from hospitals and clinics in the region. Dengue control and surveillance in Peru employs a vertical approach to governance, with the Ministry of Health (MINSA) overseeing regional authorities, which themselves direct sub-regional organizations and municipal agencies. Vector surveillance and control operations are managed by the *Dirección de Salud Ambiental* (DESA). Communication between DESA and DIRESA through regular meetings of the Dengue Committee is intended to facilitate rapid response and intervention when outbreaks are detected. Involvement of the municipality for dengue prevention includes targeted garbage collections, planned in collaboration with the DIRESA.

Patients in Ucayali with dengue-like symptoms are provided with a preliminary diagnosis at their local health centre or hospital. Cases are either ruled out based on laboratory testing or categorized as dengue with or without warning signs (MINSA, 2011). Samples from probable cases are tested at the public health reference laboratory in Pucallpa and samples (both positive and negative) are sent by air to Lima for analysis at the national referential laboratory for confirmatory testing by PCR. A confirmed dengue case in Pucallpa is defined by either: the detection of the antigen NS1, a positive RT-PCR assay result, by virus isolation within the first four days of beginning of symptoms, or by the detection of IgM and/or IgG antibodies using the ELISA diagnostic kits five days after the start of symptoms (MINSA, 2011). Health centres and hospitals record the diagnosis and report that information periodically to DIRESA's epidemiology department, which aggregates information in the format of weekly epidemiological bulletins. These bulletins serve as updates for public health oriented government agencies such as DESA at the regional level and *Ministerio de Salud* (MINSA) at the national level.

2.3 Theoretical framework

Our analysis was guided by health geography and ecohealth as core theoretical foundations, seeking to address dengue as a transdisciplinary health problem and not only as a sum of individual risk factors. Health geography is a discipline that is concerned with a holistic understanding of health and well-being, not only at the individual but also at the societal level (Susser & Susser, 1996). Issues of scale have driven the field of health geography to recognize that population-level influences on health often mediate individual-level risk factors, and that individual health risks are embedded within complex social and environmental system dynamics (Koopman, 1996; McMichael, 1999). This is reflected in Rose's suggestion that health practitioners seek to ask "Why did *this* patient get *this* disease at *this* time?" (Rose, 1985). An ecosystem approaches to human health framework (ecohealth) implies recognizing that the disease emerges from a set of specific environmental, social, economic and political conditions (Díaz et al., 2009). Health geography and ecohealth are characterized by methodological pluralism (Sechrest & Sidani, 1995). The complexity of public health problems and the non-linearity nature of causality in health require multidisciplinary approaches for successful understanding of a health related issue (McLaren & Hawe, 2005). A mixed method approach allows a researcher to explore a topic from a variety of perspectives. Qualitative and quantitative methods are often complementary as they tend to answer different aspects of a given research question, promoting triangulation of results and insights. By combining these styles of investigation, we sought to overcome some of the limitations inherent to cognitive biases that result from a single analytical point of view (Sechrest & Sidani, 1995).

We identified and assessed determinants of the 2012 dengue outbreak in Pucallpa, following a socio-ecological autopsy approach as per Ali (2004). Consistent with health geography and ecohealth theory — and emerging from ecosystem health and political ecologies of disease theory — the socio-ecological autopsy approach calls for transdisciplinary methods to study environmental health problems (Ali, 2004). The approach draws from organizational sociology, sociology of disasters, and disease ecology, to achieve an integrated investigation of the socio-ecological conditions associated with disease outbreaks and emergence. It traces back to individual, corporate and government actions that have shaped the disease ecology of a particular region, and how these may have contributed to the incubation of an environmental health disaster (Ali, 2004; Mayer, 2000). Ultimately, this framework aims to generate context-relevant and effective policies. We used Ali's 'socio-ecological' matrix as a guide, and thus conceptualized proximal and distal determinants across both temporal and spatial dimensions, guided by the question: Why did this outbreak occur *in this place* (Pucallpa) *at this time* (November 2012)?

2.4 Analysis of dengue incidence

Dengue incidence data for the Ucayali region were acquired for the years 2004-14. These dates were selected to provide temporal context for dengue transmission within Ucayali in the years preceding and following 2012. In total, 20,082 potential dengue cases were reported in the region between 2004 and 2014. Of these, 2,330 were ruled out following laboratory testing, and 716 were unconfirmed, leaving 17,036 confirmed dengue cases for the study period.

We conducted a spatio-temporal analysis of dengue incidence from 2004-14. Analyses were guided by the following key question: How did the spatial and temporal distribution of dengue incidence vary across districts in Ucayali over the entire study period and specifically during the 2012 outbreak? Time series graphs were developed to illustrate the number of dengue cases and meteorological variables varying through time in the region. Risk ratios as well as incidence rates per 100,000 population were mapped at the district-level for the Ucayali region for the entire study period. Yearly estimates for district-level population were accessed through *Instituto Nacional de Estadistica e Informatica* (INEI)'s online database (INEI, 2009b). Daily temperature and precipitation records for the years 2004-2014 from climate stations within Ucayali were provided by Peru's meteorological and hydrological institution, *Servicio Nacional de Meteorología e Hidrología* (SENAMHI). Analyses were conducted in Microsoft Excel v.2013 (Microsoft Corp., USA), STATA v.13 (Stata Corp., USA) and ArcGIS v.10.1 (ESRI, USA).

INEI's population estimates for 2009 (mid-period) were used when calculating relative risk for 2004-2014 and estimates for 2012 were used to calculate relative risk during the outbreak year. Incidence rates (cases per 100,000) were obtained by dividing the total count of cases by district by the mid-period population. In addition, a population density layer using mid-period population was generated to illustrate the geographic distribution of population in relation to dengue incidence.

2.5 Analysis of key drivers, surveillance and control

To critically evaluate the social and environmental context of the 2012 outbreak, we drew on dengue incidence data, meteorological data, key-informant interviews and existing literature on risk factors for dengue transmission. Our analysis was guided by a socio-ecological autopsy approach as per Ali (2004).

We undertook a peer-reviewed and grey literature review in 2 key areas: 1) historical and current trends in dengue incidence and control in Peru and worldwide, and 2) environmental and demographic determinants of changing dengue incidence, focusing on literature specific to Latin America. We also considered literature focusing on the evolution of land use in the Peruvian Amazon, more specifically in relation to urbanization. This allowed us to unpack the contextual historical processes that may have contributed to the incubation of the 2012 dengue outbreak in Pucallpa. The literature review provided further context for the quantitative data and key informant interviews.

To characterize the social context of disease prevention and control programming, we conducted in-person interviews (n=15) with key informants involved in dengue control and surveillance, primarily in Pucallpa but also in Lima. Recruitment of participants was based on individuals' relevance to dengue control and monitoring in Ucayali, and via referral from participants. Interviewees included those working with governmental institutions (predominantly in the health and environmental sectors), academic institutions and non-governmental organizations focused on disaster-relief. All interviews were conducted in Spanish and followed a semi-structured approach. Questions focused on characterizing dengue programming related to prevention, monitoring, diagnosis, and treatment; identifying challenges and barriers to vector control; and, perceived drivers of dengue outbreaks in Ucayali. We sought written and oral informed consent, including permission to audio-record interviews, from all participants.

We considered both distal (upstream) and proximal contributing factors in the 2012 outbreak in Pucallpa. In this context, we assessed factors that permitted the outbreak to occur, as well as those that contributed to the source of the outbreak (Ali, 2004). Based on existing knowledge and literature assessing the key population-level ecological and social determinants of dengue incidence, we evaluated the following thematic factors: meteorological conditions, urbanization and urban water management, dengue serotype introduction, travel and migration, and control and surveillance programming.

2.6 Ethical approval

Ethics approval for this research was received from the [removed for review] Research Ethics Board and is consistent with the [removed for review] requirements for the Ethical Conduct of Research Involving Human Subjects.

3.0 Results

3.1 Past and current dengue incidence in Ucayali, 2004-2014

In Ucayali, dengue incidence has been increasing since the early 2000s, with a major outbreak recorded in 2012 that caused more than 10 000 cases and 13 deaths (WHO, 2013). The majority (95%) of all cases reported in Ucayali in the 2004-2014 period originated from the northern, most densely populated province of Coronel Portillo (Figure 1). Just over three quarters (78%) of all confirmed dengue cases that were reported in Ucayali between 2004 and 2014 were diagnosed within the city of Pucallpa, which is consistent with recognition of dengue as an urban disease.

[INSERT FIGURE 1 HERE]

Between 2004 and 2014, relative risk of dengue was higher in Calleria (RR=2.18), Manantay (RR=1.49) and Yarinacocha (RR=1.25), the three districts comprising the city of Pucallpa, compared to the entire region. During the 2012 outbreak, risk of dengue was also highest in Calleria (RR=2.39), Manantay (RR=1.80) and Yarinacocha (RR=1.11). Age- and sex-adjusted incidence rates were consistent with those observed elsewhere, showing higher incidence among the young (15-24 yrs) and no significant differences by sex (data not shown) (Koh et al., 2008; J. San Martín et al., 2010; Teixeira et al., 2002).

3.2 Factors at play in the 2012 outbreak in Pucallpa

3.2.1 Meteorological conditions

Dengue outbreaks have frequently been associated with meteorological events such as El Niño, and annual cycles of dengue incidence are often affected by weather and seasonality (Morin et al., 2013; Naish et al., 2014). Higher temperatures are typically associated with increased dengue transmission and incidence due to higher mosquito biting rates, accelerated vector development, and shorter extrinsic incubation period in the vector (Hales et al., 1999). The seasonal occurrence of the outbreak in November is consistent with typical seasonal patterns for dengue incidence in the region, as corroborated by key informants (n=5): "*The rainy season is critical. The six critical months are between October and March. When there is intense heat and little rain, the containers [breeding habitats] dry up*" (KI#2). Various studies conducted throughout Asia and Latin America noted a time lag between peak precipitation and dengue outbreaks (Arcari et al., 2007; Colon-Gonzalez et al., 2011; Johansson et al., 2009). This is hypothesized to be due partly to water storage resilience strategies, which increase breeding habitat for *Ae. aegypti* (Arcari et al., 2007; Colón-González et al., 2011).

Inter-annual patterns in dengue have also been associated with meteorological variation. In South America, studies have found that post-El Niño years yielded higher than normal dengue incidence (Eastin et al., 2014; Stewart-Ibarra & Lowe, 2013). The year 2012, though, followed a La Niña episode that is generally characterized by drier and colder conditions in South America (NOAA, 2015) (Figs 3a & b). However, the localized impacts of La Niña in the Peruvian Amazon region are distinct, including maintained monsoon flux and humidity as well as heavy rainfall (Espinoza et al., 2012; Marengo & Espinoza, 2016). Marengo & Espinoza (2016) note that the 2012 flooding in the Amazonia region was one of the worst flooding episodes in history. In this context, and despite typical expectations, the exceptional ENSO event (in this case La Niña phase) may have contributed to the occurrence of the dengue outbreak in 2012.

[INSERT FIGURE 2 HERE]

[INSERT FIGURE 3 HERE]

3.2.2 Urbanization and urban water management

Consistent with the urban habitat preference of the *Ae. aegypti* vector, key informants reported that urbanization has contributed to increased dengue incidence over past decades. Larger population size and proximity to an urban center were found to be significantly linked to increased odds of *Ae aegypti*'s establishment in communities adjacent to Iquitos (also within the Peruvian Amazon) (S. A. Guagliardo et al., 2014). Land use and economic development in the Peruvian Amazon region have largely been driven by extractive industries (including rubber, palm oil, and timber). The Pucallpa-Lima highway was a key development that spurred resource extraction in the region, especially timber, and new economic opportunities have resulted in exponential population growth, especially along the highway and in Pucallpa (Goy & Waltner-Toews, 2005; Hecht et al., 2014). Pucallpa's population grew more than six-fold between 1961 and 1993 (Santos-Granero & Barclay, 2000) and now more than half the population lives in informal or squatter settlements with limited access to basic urban services (Hecht et al., 2014; INEI, 2009a; Padoch et al., 2008). In other tropical environments that have experienced similarly rapid and unorganized growth, increases in vector breeding environments have been attributed to new habitats created by standing water resulting from inadequate provision of water and sewage services (Arcari et al., 2007; Descloux et al., 2012; Eastin et al., 2014). In parallel, key informants mentioned that not only an increase in population, but also in consumption of goods, has led to higher levels of waste (particularly plastics and tires) in Pucallpa, creating receptacles for water to accumulate and for vector reproduction: "*wealthier people produce more waste, that's exactly why there is dengue in urban centers*" (KI#1). Guagliardo et al. (2014) found that plastic containers and water storage tanks were highly productive mosquito breeding environment in Iquitos. There is no published evidence to validate reports of a positive relationship between wealth and plastic containers density. Given population inflow into the Pucallpa urban area, increases in, and comparatively higher levels of, consumption disposable goods are, however, conceptually feasible.

Interviewees reported that the hour-based water provision in the city has led to water-storage habits that promote the creation of habitats for vector reproduction. A key informant explained that the water provision system in Pucallpa emerged in the context of scarce potable water resources in relation to a rapid urban growth. Another informant stated: "*Water is not available at good quality, quantity or continuity*" (KI#2). Interviewees specified that Pucallpa residents fill water tanks at given locations to provide their homes with potable water on a daily basis. When they proceed to fill their water tank, citizens are also provided with a small amount of larvicide colloquially known by its brand name '*Abate*' (BASF). Key informants reported that the use of larvicide is not yet common practice among the Pucallpa population as many people fear the use of chemicals in the water they consume, despite the World Health Organization's approval of the active ingredient, Temephos, for addition to drinking water. For this reason, a key informant qualified the water tanks as "*dengue breeders*" (KI#2). Successfully communicating the benefits and safe nature of the larvicide to the public appears to have important public health implications since large water tanks — typically stored in close proximity to the household — were found to significantly increase the probability of *Ae. aegypti* presence in neighboring city Iquitos (S. A. Guagliardo et al., 2014). While urbanization and water storage habits may contribute to long-term increases in dengue risk, they do not directly explain the dramatic transmission increase in 2012.

3.2.3 Introduction of new dengue serotype

Key informants reported the introduction of a new serotype, the DENV-2 American/Asian type, to the Ucayali region as a critical factor preceding the outbreak. Though the genotype responsible for the 2012 outbreak in Ucayali remains officially undocumented in published literature, key informants reported that the serotype had been identified by the regional reference laboratory in Pucallpa, and confirmed it to be the dominant virus strain responsible for the outbreak. This is consistent with detection of the Asian/American genotype in the neighbouring Loreto region in the early 2000s (Cruz et al., 2013; Mamani et al., 2011). Among some key informants, new serotype introduction into the non-immune population was perceived as the main cause for the 2012 outbreak, as cited from one interview: "*there would have been no outbreak if there was no new serotype*" (KI#12).

The introduction of the American/Asian genotype to the Americas is held responsible for the displacement of the native (less virulent) strains of the DENV-2 American genotype and for the onset of major epidemics with increased pathogenicity on the continent (Drumond et al., 2013; Rico-Hesse et al., 1997). In 2001, Peru reported the first case of dengue hemorrhagic fever (DHF), and this event was consistent with a general increase in severity of cases that resulted from the emergence of the American/Asian DENV-2 genotype for other countries in the Americas (Cruz et al., 2013; Dick et al., 2012; Mamani et al., 2011; Schneider & Droll, 2012).

3.2.4 Travel and migration

Movements of infected people not only increase the range of disease spread, but also change the dynamic of appearance and severity of the disease in previously uninfected zones (Adams & Kapan, 2009). Post-infection immunity to dengue is type-specific and secondary infection by heterologous serotypes is often more serious (Rico-Hesse et al., 1997). Migration and travel can affect herd immunity and serotype prevalence, which in turn moderate dengue infection and morbidity (Eastin et al., 2014). While travelling, infected individuals can act as reservoirs for a specific virus strain; travel of the disease vector by boat and motorized vehicles can similarly induce virus spread. A study looking at patterns of geographic expansion of *Aedes aegypti* in the Peruvian Amazon region found higher prevalence of the mosquito vector in houses in proximity to a highway (S. A.

Guagliardo et al., 2014). Another recent study has also found that boats travelling along the Amazon River likely served as significant contributors to the dengue vector's geographical expansion (Sarah Anne Guagliardo et al., 2015).

Increased travel to and from Pucallpa over recent years was noted by key informants as a source for dengue and serotype propagation: "*Before, there was only one flight [to Pucallpa]. Now, there are up to five or six flights a day*" (KI#6). The expansion of global air and seaborne travel has been observed as a determinant for dengue spread in China, allowing vectors and pathogens to travel large distances in a short time (Lai et al., 2015). According to key informant interviews, travel is perceived as a condition that enables dengue to be a constant threat in the region: "*there is always dengue because our doors are open to transit*" (KI#2).

Travel and migration likely played an important role in propagating the spread of the DENV-2 American/Asian genotype associated with the 2012 Pucallpa outbreak. A lineage of the DENV-2 American/Asian genotype was first detected on the northern coast of Peru and it dispersed through the country in the early 2000s. A different lineage of the same genotype was detected in Iquitos in 2010, and this specific lineage was associated with a severe dengue outbreak in 2010-2011 (Cruz et al., 2013). This lineage was also shown to be related to DENV-2 isolates that circulated in Brazil during 2007-2008, a period during which severe dengue cases and death occurred (Mamani et al., 2011). This was supported by a key informant: "*the virus of the 2012 outbreak came from Brazil and Loreto*" (KI#1). Plausible mechanisms for this introduction include humans or vectors transported overland by boat, by road, or by air (Figure 4).

[INSERT FIGURE 4 HERE]

3.3 Control and surveillance programs in Ucayali

Following the 1960 continent-wide DDT campaign, many countries in the Americas have vertically structured their control and surveillance programmes, opting for decentralization (J. L. San Martín & Brathwaite-Dick, 2006b). While initially successful, this approach has been retrospectively criticized given the re-infestation of vectors a few decades later. A core challenge has been the disconnect between the centralized control of resources and the allocation of responsibility to sub-regions (J. L. San Martín & Brathwaite-Dick, 2006b). In Ucayali, this translates into an overall dependency of the regional operations on a national budget: "*When outbreaks are declared, (…) the budget is assigned at the national level. We cannot directly purchase materials [for the laboratory], it has to come from MINSA*" (KI#6). Thus, while vector control activities are considered regional responsibilities, the resources necessary to do adequate control and surveillance are determined at the national level. One interviewee noted that the prevention plan for dengue was financed "*90% by the ministry of health and 10% by the region*", therefore "*decision-making takes a long time*" (KI#5) due to centralization of economic resources and power. Decisions to increase funding for dengue only take place in "*extreme conditions*" (KI#5), after deaths were reported. Key informants reported that there is a national preference for disaster-relief interventions rather than prevention: "*Additional funds are requested when there is an outbreak. This is not sustainable*" (KI#14). Informants from various governmental organizations noted that the capacity of their unit to work efficiently is often limited by lack of funding towards the end of the fiscal year (which parallels the rainy season and outbreaks). For example, fumigations and surveillance activities are often suspended during the months of June-August due to depleted budgets, as reported by a key-informant: "*there is no work happening in July, August, and September because there are no workers*" (KI#8). Asking for additional funding was perceived by key informants as time and resource consuming, with resulting delays in intervention.

Interviewees reported that vector control was constrained by limited employment stability due to sporadic and contract-based allocation of resources. Attributed to this was a lack of systematic entomological control and limited comprehensive data on mosquito densities, a phenomenon that is a limitation for vector control programs worldwide (Chowell et al., 2008). According to a key informant, the environmental health branch of the regional government is understaffed during most of the year, and additional workers are recruited only if there is a critical need for fumigations following an outbreak alert: "*Fumigations occur depending on the number of cases, not on the Aedes index. But everything also depends on how many workers are available*" (KI#8). A systematic literature review of dengue control programs worldwide similarly found that the tight budgets allocated to vector control programs limit staffing levels and access to technical expertise, and reduce the possibility of capacity building in all countries (Horstick et al., 2010). In support of improved surveillance efforts, georeferencing of Pucallpa has recently been completed by staff working at the DESA, with the potential to aid in strategizing vector control and surveillance in the context of limited resources.

High personnel turnover can be considered both a source and consequence of the emergency-oriented nature of control and surveillance activities in Ucayali. Interviewees noted that constant labour force renewal does not allow for institutional memory to establish and for prevention campaigns for short and long terms: "*There is no employment stability, we always have to train people. Change is so frequent because of politics, for example when the mayor changes, we need to start everything all over again.*" (KI#6) Interviewees also revealed that employment instability among the health promotion and communication departments of the DIRESA resulted in few or irregularly planned educational activities tailored for the general population to understand how to eliminate vector breeding sites.

Key informants noted that public communication of dengue risks and prevention remains a challenge for vector surveillance and disease control. Informants reported that many citizens do not trust home inspectors and fumigators, and often refuse to let the workers enter their homes to eliminate vector habitats. Among the reasons suggested by key informants for this lack of trust was concern that thieves may burglarize homes while residents are absent during fumigation: thieves were reported to have "*entered houses dressed in ministry uniforms to steal*" (KI#6). Key informants also reported "*attempts of sexual assaults*" (KI#3) on fumigators by residents. Informants explained that fumigators were now requesting home visits in teams of two, and that these safety measures combined with unadjusted staffing levels has resulted in "*everything [being] done a lot more slowly.*" (KI#3).

4.0 Discussion

Dengue incidence in Ucayali has been increasing since the early 2000s. Our results illustrate that distal processes such as urbanization, increased connectivity, in the context of under-resourced surveillance and control may have acted as contributing factors for this increase in disease incidence, but do not proximally explain the outbreak that took place in Pucallpa in 2012. Introduction of a new, more virulent, dengue serotype into an immunologically naïve population, combined with exceptional weather following La Niña phenomenon, appear to be the most plausible triggers for the 2012 outbreak. These findings are consistent with other studies from the Americas and Asia demonstrating that introduction of a new dengue serotype in an endemic zone often results in outbreaks, and in the case of the Asian/American genotype, more severe health outcomes (Dick et al., 2012; Gubler, 2002; Horstick et al., 2010; Mamani et al., 2011). While the introduction of the new serotype in Ucayali is the presumed trigger for the 2012 outbreak, distal and proximal determinants of the outbreak are not dissociated. Predisposing conditions of inadequate water management, suitable weather for vector reproduction, fast urbanization, and under-funding of control and surveillance activities facilitated the introduction of the new serotype and enabled it to establish undetected and uncontrolled in local vector populations, eventually leading to a large outbreak in Ucayali. Ali (2004) uses the term 'incubation phase' of a disaster (from organizational sociology), in reference to these distal processes and factors that 'inadvertently permit a disaster to occur' by accumulating unnoticed until disaster onset. We identified key triggers for the 2012 Pucallpa dengue outbreak, yet spatial diffusion of that specific dengue genotype is in part a result of random spatial diffusion patterns that emerge where transportation is readily available, making it difficult to fully explain the exact timing for outbreak onset (Mayer, 2000).

[INSERT TABLE 1 HERE]

Our findings highlight several implications for future dengue and other vector-borne disease management and control in Peru. First, limited resources for control and surveillance outside outbreak periods do not allow for timely control responses. Relying on emergency as the basis for intervention is unsuited to vector-driven epidemics (Horstick et al., 2015; Pinheiro & Corber, 1997). In a systematic literature review looking at the gaps in dengue vector-control services worldwide, Horstick et al. (2010), identified related challenges to adequate control, including lack of specialized personnel, insufficient budgets, inadequate geographical coverage, and absence of capacity building, monitoring, and evaluation (p.379). While these are common problems for vector-borne disease prevention worldwide, there are direct health and financial benefits to maintaining a constant surveillance agenda. A recent study looking at the impact of delayed control responses to dengue epidemics in Queensland, Australia, showed for example that costs incurred by surveillance programs are substantially lower overall than those needed to respond to dengue introduction (following halted mosquito surveillance) (Vazquez-Prokopec et al., 2010).

Regional dependency on national budgets was an important constraint to control and surveillance activities in Pucallpa outside of outbreak years. This was an important contributing factor restricting ongoing prevention prior to the outbreak, timely detection during the early phase, and rapid response following increased transmission. Though government resources are key for dengue control programs to be maintained, more attention and resources could be directed towards capacity-building and involvement of Pucallpa's community —especially regarding the safety and use of larvicides — in order to maintain the institutional capacity to address control and surveillance year round. A study in Mexico found that long-term community participation in dengue control programmes was critical in allowing for sustainable control to occur (Tapia-Conyer et al., 2012). In the same study, Tapia-Conyer et al. (2012) argue that Integrated Vector Management is compatible with sustained social mobilisation for optimal results in dengue prevention and control, and other authors have argued likewise (Gómez-Dantés & Willoquet, 2009; Lopez-Gatell et al., 2015). Nonetheless, engaging communities remains a persistent and pre-existing challenge in this context (Horstick et al., 2010). One key limitation for community involvement in Pucallpa is the current water provision system. Insufficient municipal supply of water, inadequate storage facilities and reluctance of residents to accept the use of larvicides in potable water acted — and still act — as proximal drivers for dengue outbreaks (Gómez-Dantés & Willoquet, 2009). Improving water supply in Pucallpa is a key step in environmental management that would bring benefits to households, including more efficient *Aedes* control methods (Lopez-Gatell et al., 2015). Attempts to provide health education and alter public behavior are challenging in most public health interventions, but represent a "temporary necessity, pending changes in the norms of what is socially acceptable", so that vector control habits such as the use of larvicide in water tanks are no longer perceived as efforts but rather as a norm (Rose, 1985).

In Pucallpa, seasonality is a proximal driver for dengue. While meteorological factors are generally considered key drivers in dengue transmission, there is debate concerning the role that long-term climate conditions will have on dengue incidence worldwide. Changes in climate have been implicated in an upsurge of dengue and other tropical diseases globally (as concluded by the IPCC in April 2007) (J. San Martín et al., 2010). In parallel, non-climatic drivers are typically considered to have greater and more proximal influence on changing transmission of dengue compared to long-term changes in climate. The interaction of proximal socio-economic-demographic determinants with distal trends in climate change remains poorly conceptualized, undertheorized, and methodologically underdeveloped in the context of vector-borne disease epidemiology**.** In this perspective, we demonstrated using the socio-ecological autopsy approach that the 2012 dengue outbreak emerged from a "set of processes that evolved over time and through different geographic scales of involvement at the political-economic, social and biophysical levels" (Ali, 2004)(p.2602).

The absence of sub-spatial data, especially within the city of Pucallpa, is a key limitation for this study. In addition, the quality of dengue surveillance data may vary across time and space, limiting data comparability. Another possible inherent limitation to this study is underreporting. Underreporting is frequent with dengue; but assumptions of constant underreporting across space and time limit this bias.

Pucallpa's rapidly changing human and environmental landscapes are shaping the conditions for dengue to remain a major health threat in the region. A reductionist focus on individual case patterns rather than population-level incidence would be unable to elucidate the regional context within which population-level patterns of incidence are shaped. In the case of dengue, individual risk factors (e.g. sex, age, immunity status) are insufficient to explain the emergence and proliferation of the 2012 Pucallpa outbreak. This socio-ecological approach has thus, as Rose (1985) describes it, led to identifying very different determinants and connected interventions that point to the importance of regional and municipal governance structures in underpinning risk of dengue spread in the Amazon basin in general and Pucallpa in particular.

Dengue is still considered a Neglected Tropical Disease – defined by the insufficient coordinated efforts to control disease spread compared to the burden it imposes internationally – which explains the WHO's efforts to prioritize dengue via its Global Strategy for Dengue Prevention and Control, 2012-2020 (Horstick et al., 2015; WHO, 2012). From this initiative, the 'Integrated Management Strategy Prevention and Control' (IMS-dengue) was approved by the PAHO in the early 2000s, aiming to improve surveillance and control efforts in all areas concerned with the reduction of burden of dengue (Murray et al., 2013). Peru is one of the 19 countries that have implemented the IMS as of 2010 (Dick et al., 2012), yet the 2012 outbreak in Pucallpa and our socio-ecological autopsy herein highlight continued challenges in optimizing control and surveillance efforts in Ucayali. Given the historical reliance on governmental action for control and surveillance activities, there is a need to address fragmented public health programming, as well as focus on increasing community participation to mitigating dengue spread (Lopez-Gatell et al., 2015).

Notably, reduced funding at the local level in endemic regions occurred simultaneously with an increase in dengue research funding worldwide, initiated by the perceived threat of dengue in many areas of the developed world which are currently not endemic (Horstick et al., 2015). This highlights a disconnect in global resource allocation, with emphasis on increased research/ development funding for geographic spread to new areas paralleled by limited government funding for ongoing dengue prevention and control in affected countries, which themselves represent the source of infection for spread.

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Tables and figures

Table 1. Proximal and distal determinants for 2012 dengue outbreak in Pucallpa

Dimensions	Proximal	→	Distal
Temporal	Seasonal trends	Urbanization; Introduction and spread of new dengue serotype throughout Peru	Travel and migration; Climatic phenomena and climate change
Spatial	High population density; Inadequate water provision infrastructure	Increasing urban links and connectivity through travel; Under-resourced surveillance and control	Vertical structure of surveillance and control; Continental serotype spread

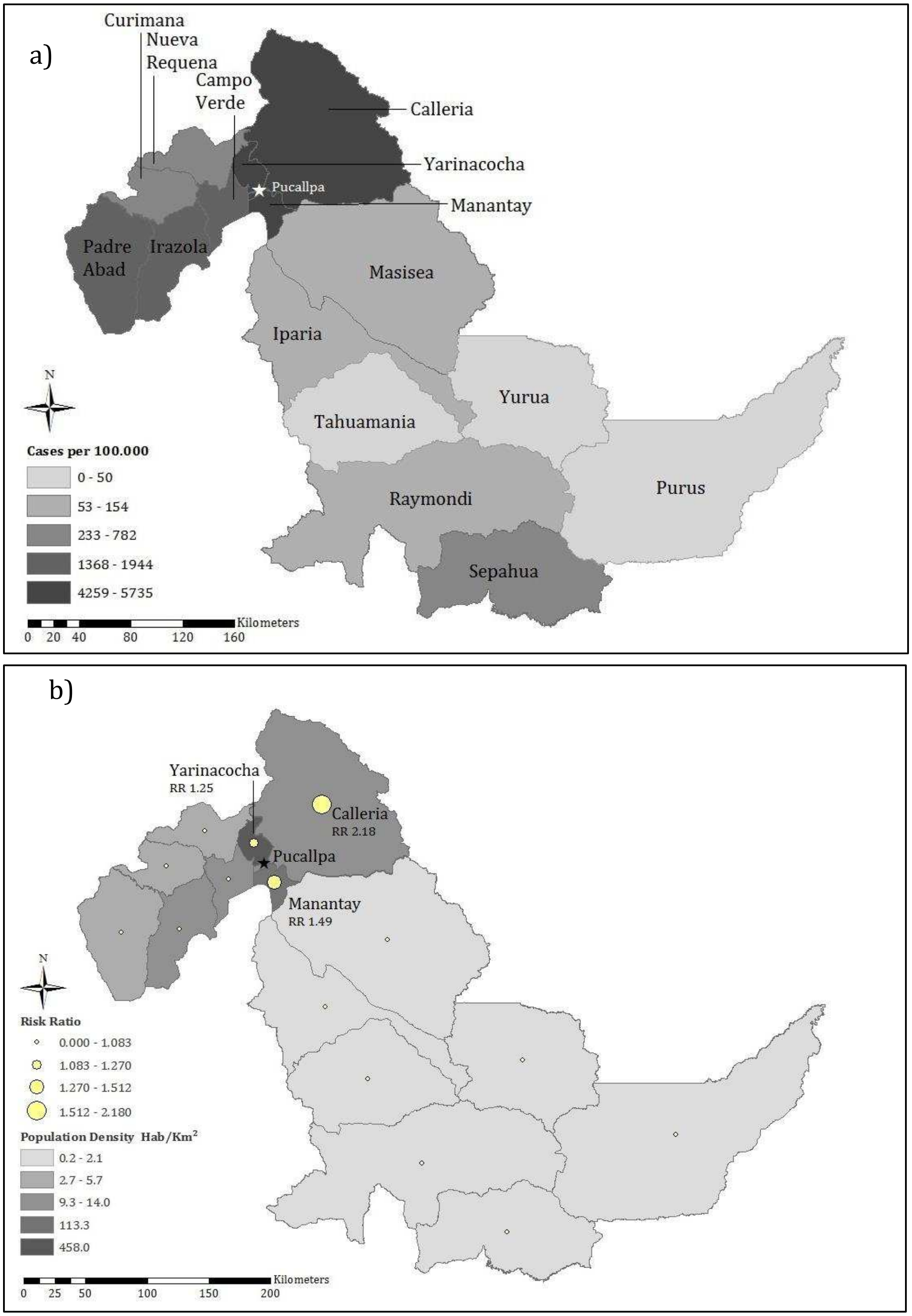

Figure 1: a) Confirmed dengue cases per 100,000, by district (2004-2014), b) Risk ratio for dengue by district (2004-2014), combined with population density layer

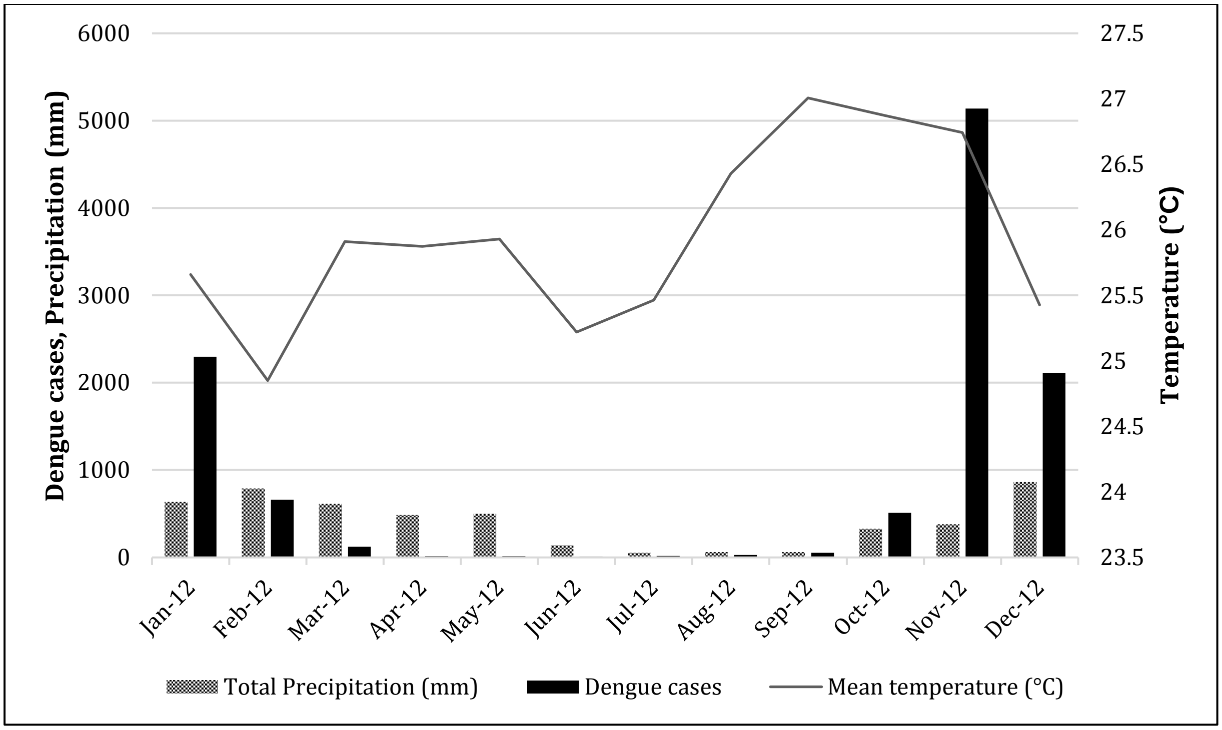

Figure 2. Monthly precipitation and temperature aggregates, Pucallpa 2012

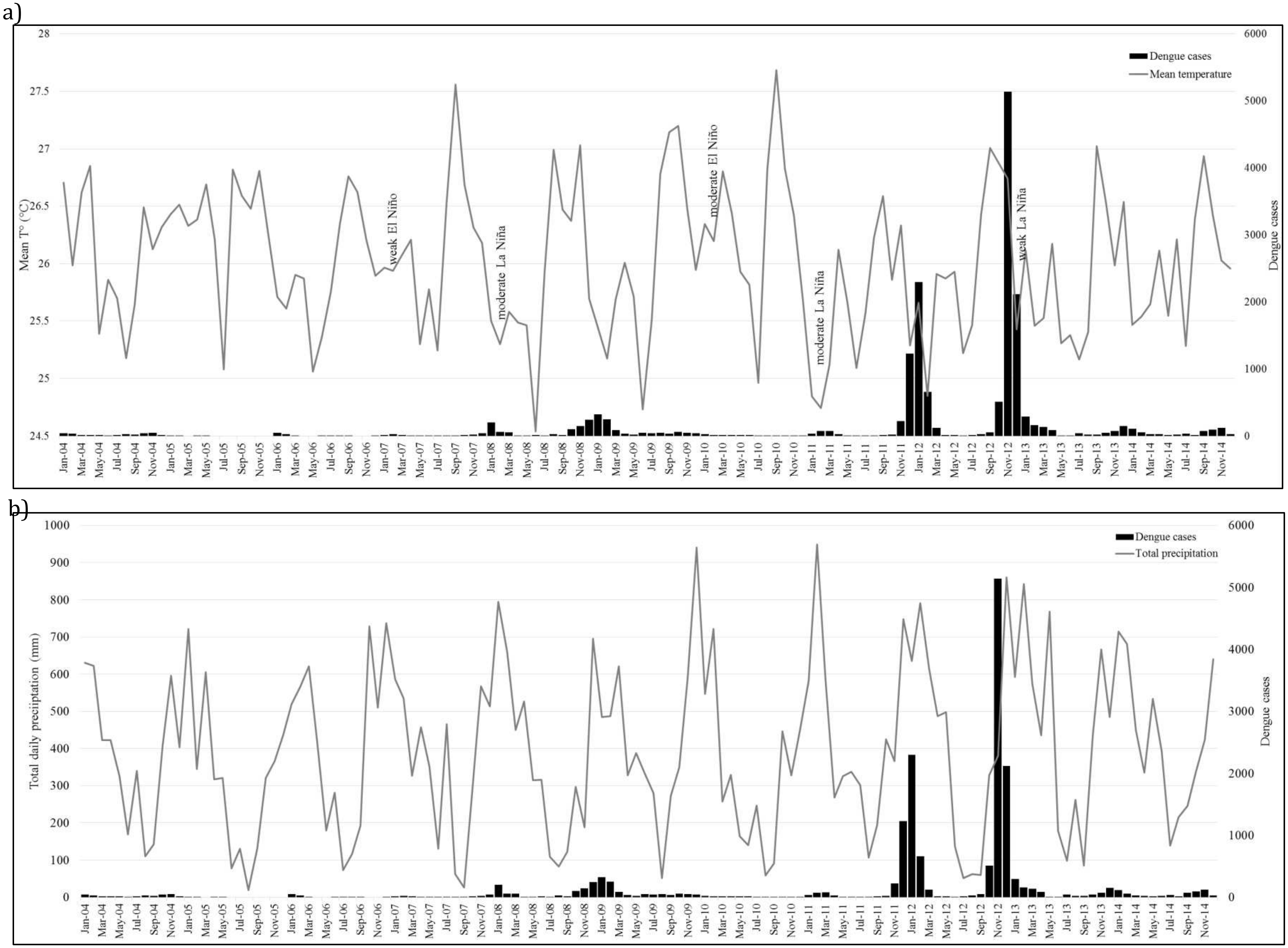

Figure 3: a) Monthly averaged mean daily temperature and dengue cases in Ucayali; b) Monthly averaged total daily precipitation and dengue cases in Ucayali.

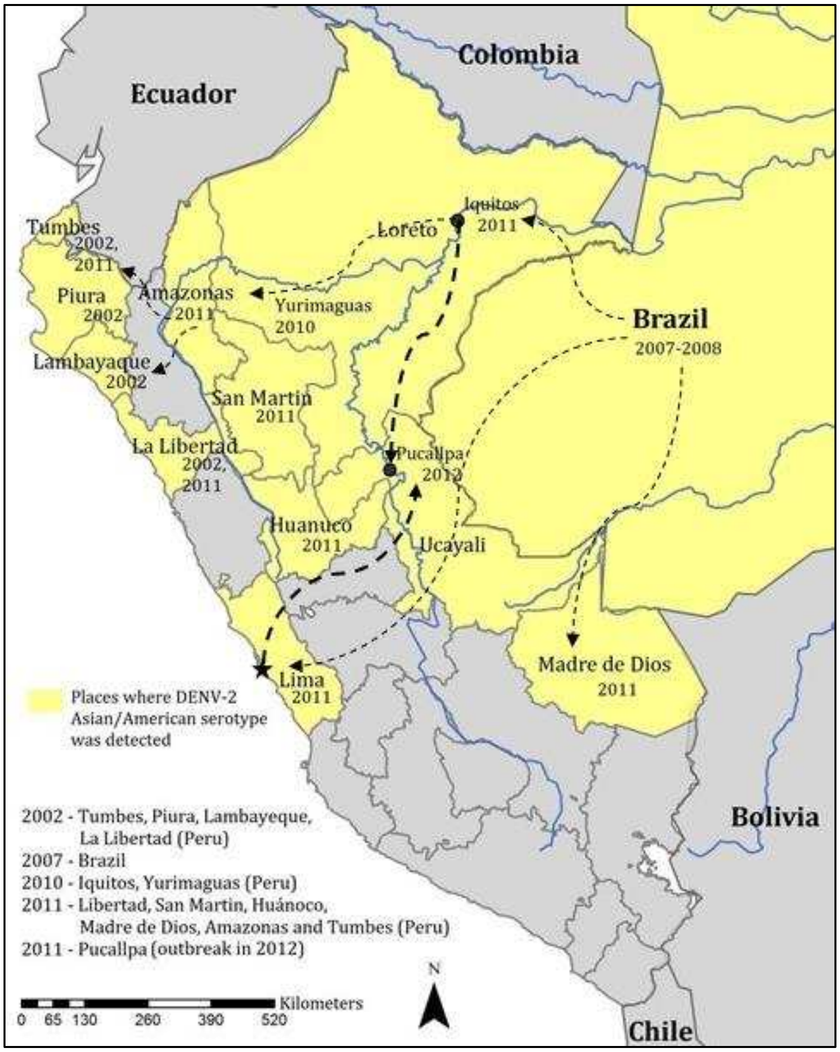

Figure 4. Plausible travel routes and timeline of DENV2-Asian/American serotype spread. Sources: (DGE, 2012; Mamani et al., 2011; Mostorino et al., 2002; Williams et al., 2014)