Rural Origin of the Propagation of Dengue, an Urban Disease, in Southeast Asia

Bernard Cazelles

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DENGUE RESEARCH FRAMEWORK FOR RESISTING EPIDEMICS IN EUROPE

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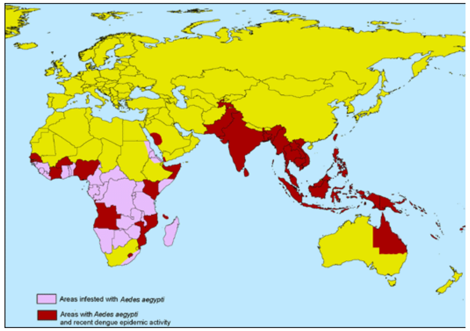
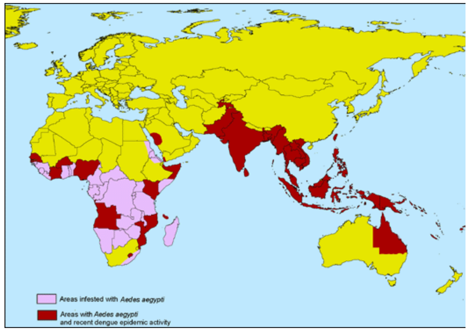
Rural Origin of the Propagation of Dengue



- Dengue is peri urban disease in the tropics and subtropics, cause by an arbovirus transmitted by *Aedes* mosquitoes.
- These mosquitoes are affected by ecological and human drivers but are also influenced by climate, including variability in temperature and moisture.
- Incidence tends to peak during the rainy season
- 40 million symptomatic infections occur annually, over two million may require hospitalization.

Rural Origin of the Propagation of Dengue



- Revealing the dispersal of dengue viruses in time and space is central to understanding dengue transmission in endemic dengue populations
- This is essential to the rational deployment of vector control activities and the design of intervention strategies

Propagation of Dengue: Main Paradigm

- The processes that shape dengue transmission patterns are not well understood
- Particularly the impact of factors such human population movement and urbanization is rarely analyzed deeply
- Urban center seems to have a crucial influence

Propagation of Dengue: Main Paradigm

Dengue in Thailand

Travelling waves in the occurrence of dengue haemorrhagic fever in Thailand

Derek A.T. Cummings[1,2], **Rafael A. Irizarry**[3], **Norden E. Huang**[4], **Timothy P. Endy**[5], **Ananda Nisalak**[6], **Kumnuan Ungchusak**[7] **& Donald S. Burke**[2]

[1] Department of Geography and Environmental Engineering, Johns Hopkins University, Baltimore, Maryland 21218, USA
[2] Department of International Health, and [3] Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland 21205, USA
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[5] Virology Division, United States Army Medical Research Institute in Infectious Disease, Fort Detrick, Maryland 21702, USA
[6] Department of Virology, Armed Forces Research Institute of Medical Sciences, Bangkok 10400, Thailand
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Dengue fever is a mosquito-borne virus that infects 50–100 million people each year[1]. Of these infections, 200,000–500,000 occur as the severe, life-threatening form of the disease, dengue haemorrhagic fever (DHF)[2]. Large, unanticipated epidemics of DHF often overwhelm health systems[3]. An understanding of the spatial–temporal pattern of DHF incidence would aid the

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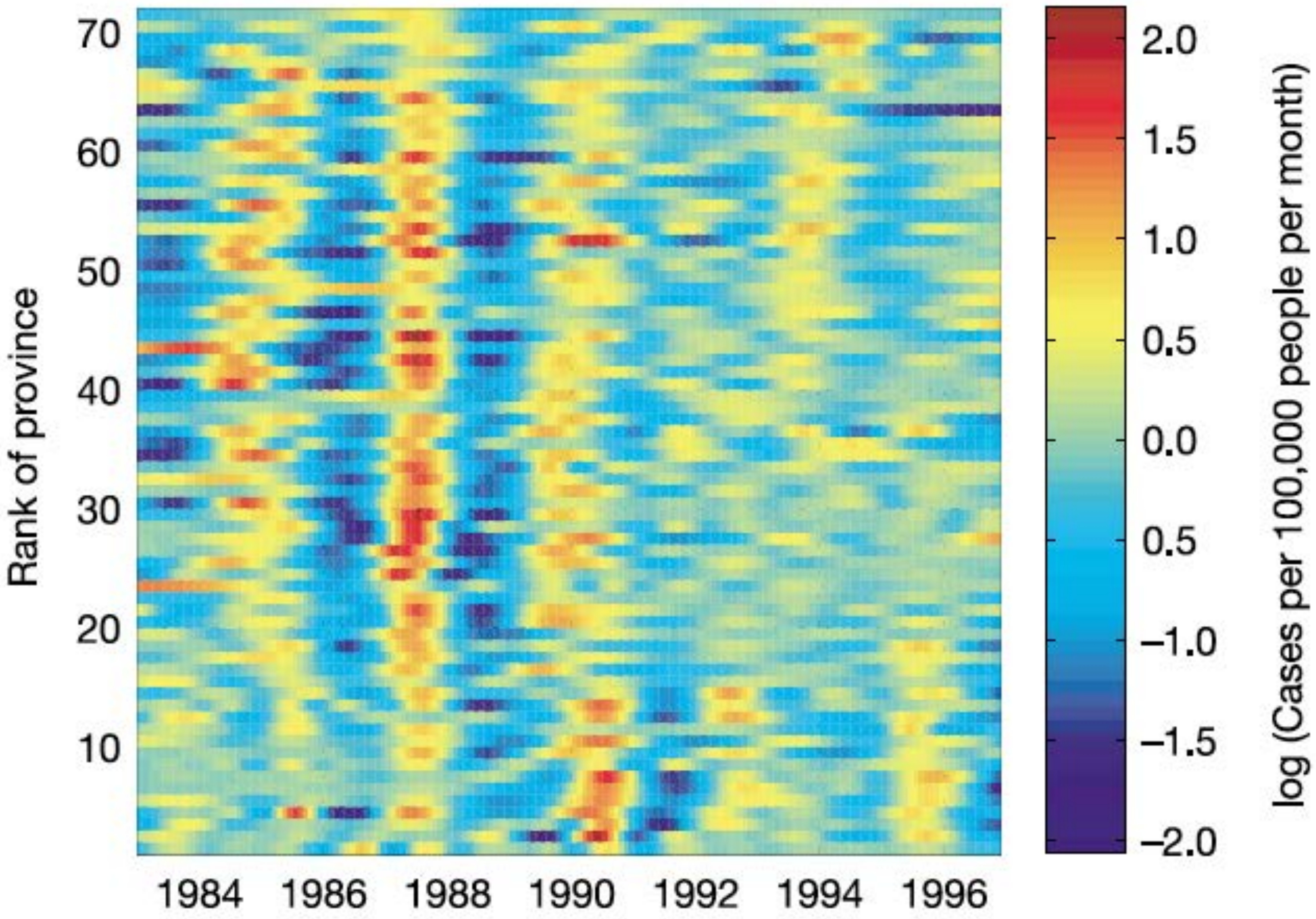
Propagation of Dengue: Main Paradigm

Dengue in Thailand

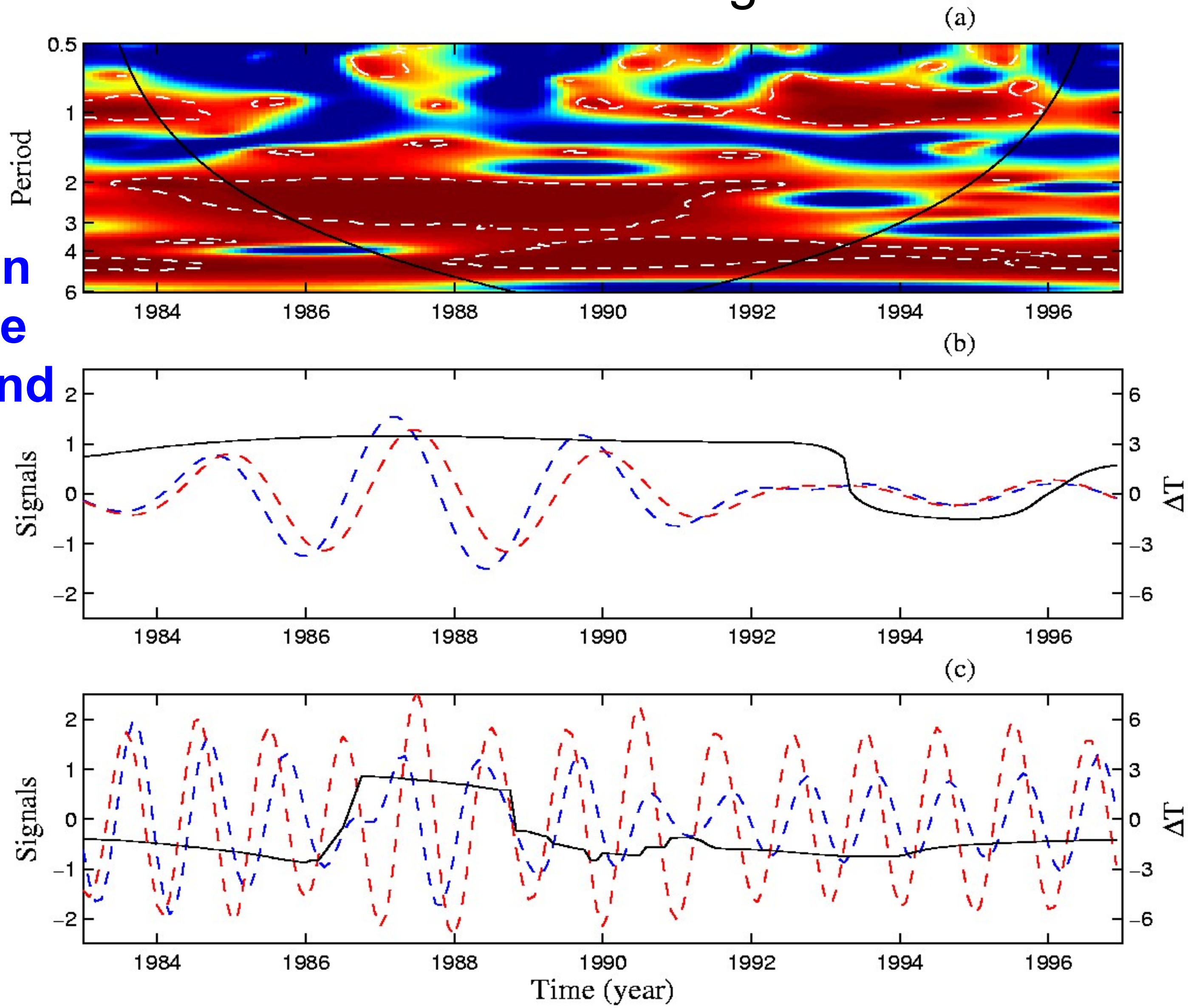


Propagation of Dengue: Main Paradigm

Dengue in Thailand

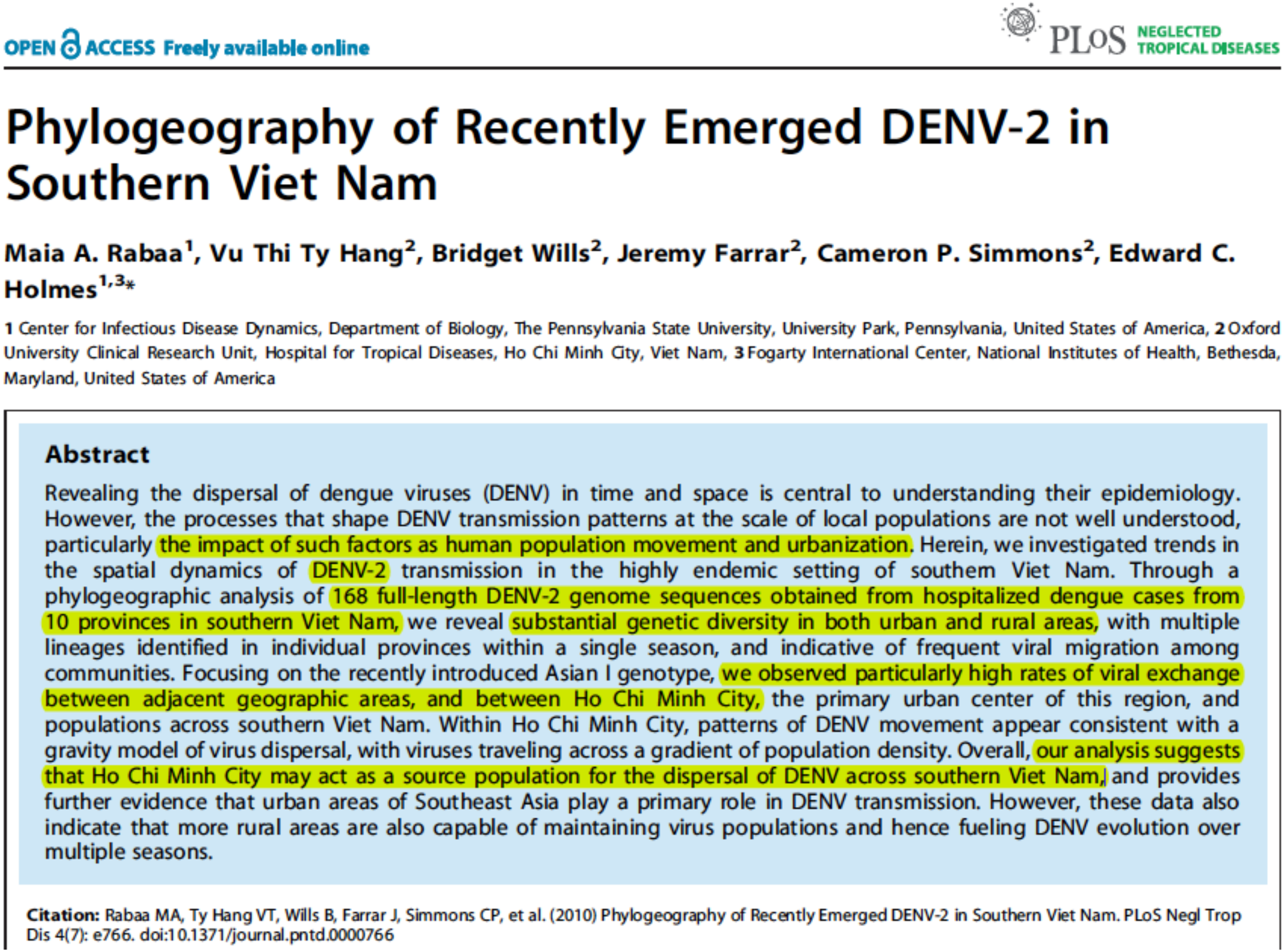
Relation between Bangkok and the remaining Thailand

Importance of non-stationarity



Propagation of Dengue: Main Paradigm

Dengue in Southern Vietnam



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PLoS NEGLECTED TROPICAL DISEASES

Phylogeography of Recently Emerged DENV-2 in Southern Viet Nam

Maia A. Rabaa[1], Vu Thi Ty Hang[2], Bridget Wills[2], Jeremy Farrar[2], Cameron P. Simmons[2], Edward C. Holmes[1,3]*

1 Center for Infectious Disease Dynamics, Department of Biology, The Pennsylvania State University, University Park, Pennsylvania, United States of America, **2** Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Ho Chi Minh City, Viet Nam, **3** Fogarty International Center, National Institutes of Health, Bethesda, Maryland, United States of America

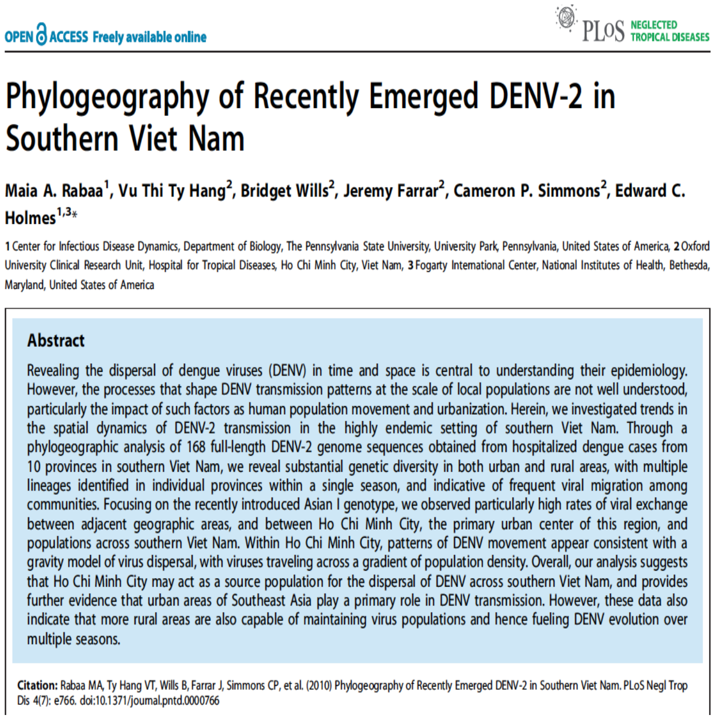
Abstract

Revealing the dispersal of dengue viruses (DENV) in time and space is central to understanding their epidemiology. However, the processes that shape DENV transmission patterns at the scale of local populations are not well understood, particularly the impact of such factors as human population movement and urbanization. Herein, we investigated trends in the spatial dynamics of DENV-2 transmission in the highly endemic setting of southern Viet Nam. Through a phylogeographic analysis of 168 full-length DENV-2 genome sequences obtained from hospitalized dengue cases from 10 provinces in southern Viet Nam, we reveal substantial genetic diversity in both urban and rural areas, with multiple lineages identified in individual provinces within a single season, and indicative of frequent viral migration among communities. Focusing on the recently introduced Asian I genotype, we observed particularly high rates of viral exchange between adjacent geographic areas, and between Ho Chi Minh City, the primary urban center of this region, and populations across southern Viet Nam. Within Ho Chi Minh City, patterns of DENV movement appear consistent with a gravity model of virus dispersal, with viruses traveling across a gradient of population density. Overall, our analysis suggests that Ho Chi Minh City may act as a source population for the dispersal of DENV across southern Viet Nam, and provides further evidence that urban areas of Southeast Asia play a primary role in DENV transmission. However, these data also indicate that more rural areas are also capable of maintaining virus populations and hence fueling DENV evolution over multiple seasons.

Citation: Rabaa MA, Ty Hang VT, Wills B, Farrar J, Simmons CP, et al. (2010) Phylogeography of Recently Emerged DENV-2 in Southern Viet Nam. PLoS Negl Trop Dis 4(7): e766. doi:10.1371/journal.pntd.0000766

Propagation of Dengue: Main Paradigm

Dengue in Southern Vietnam



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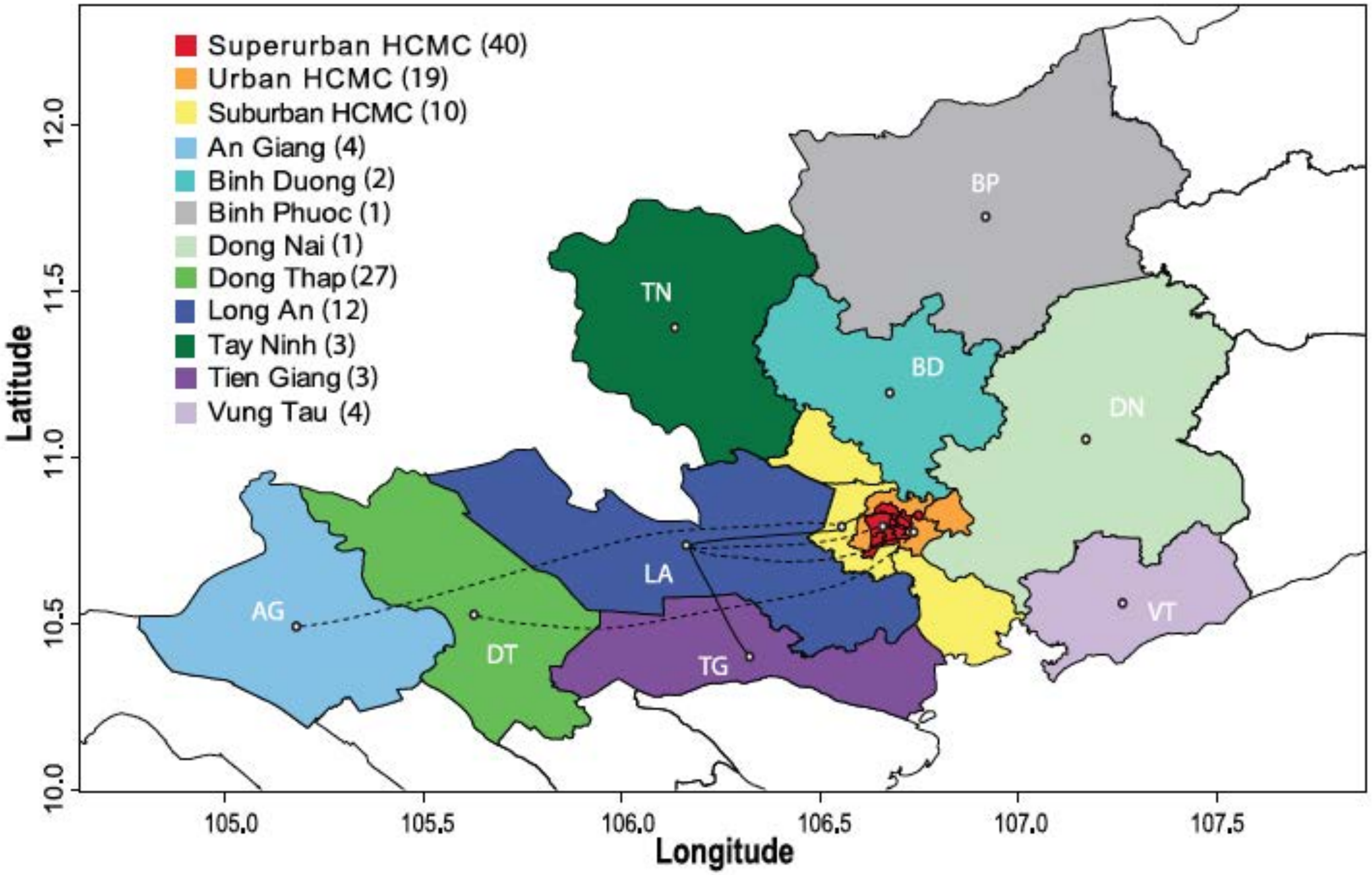
- DENV-2 genome sequences were obtained from dengue patients enrolled into a clinical and virological study at the Hospital for Tropical Diseases in Ho Chi Minh City.
- 168 sequences were analyzed.
- Sequences were sampled from 2001 to 2008.
- These sequences were from hospitalized dengue cases from HCMC and from 9 additional provinces in southern Viet Nam.
- The analysis has been done with the BEAST package.

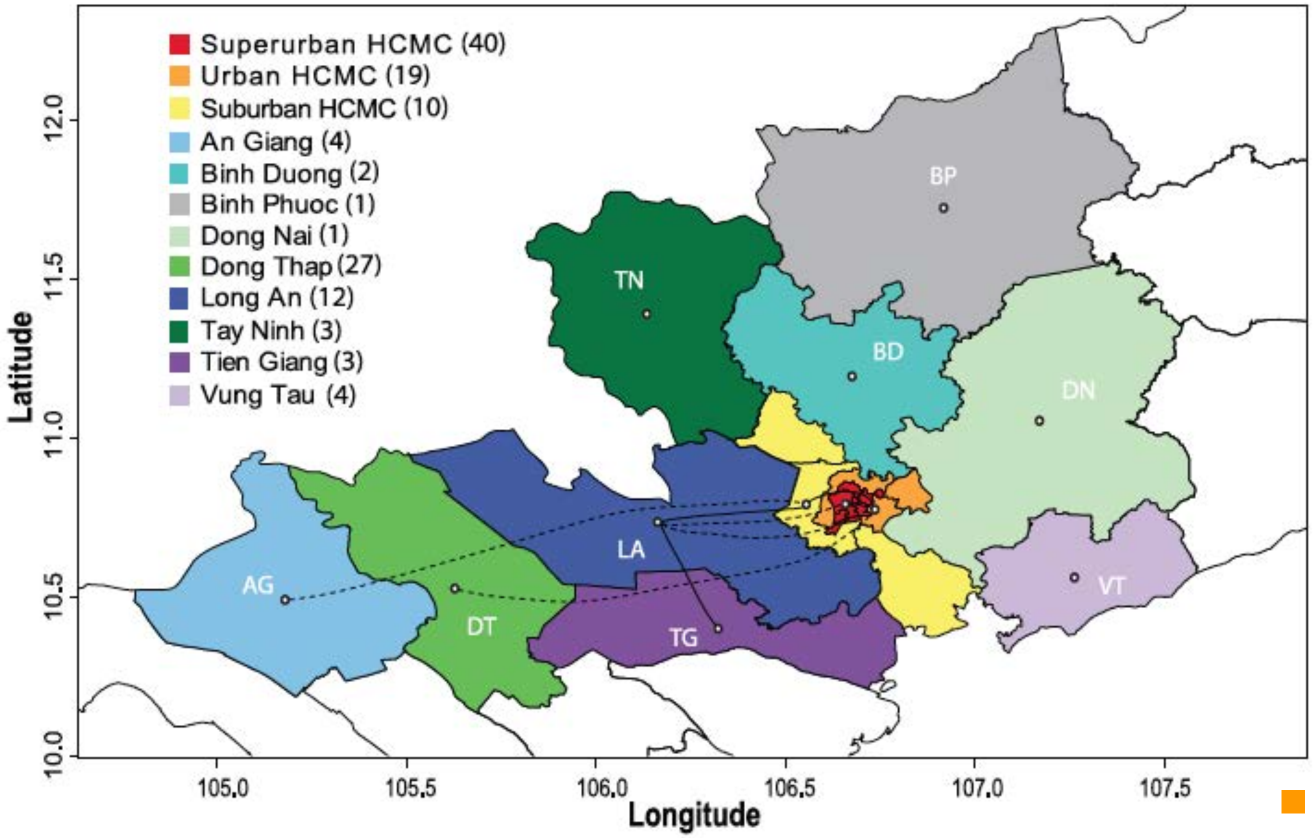
Propagation of Dengue: Main Paradigm

Dengue in Southern Vietnam



Propagation of Dengue: Main Paradigm

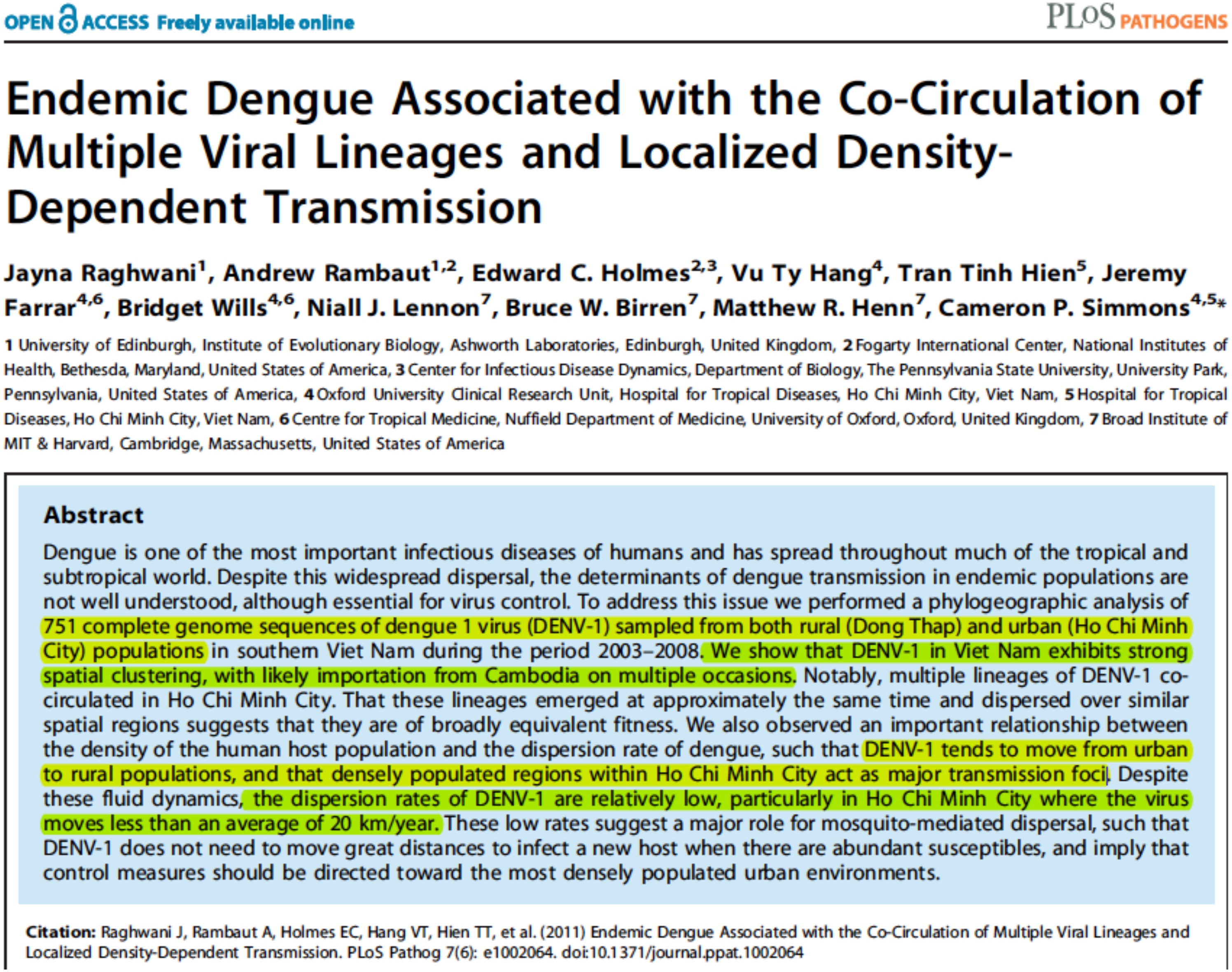
Dengue in Southern Vietnam



- HCMC acts as a driver of viral diffusion
- A major influence of anthropogenic factors

Propagation of Dengue: Main Paradigm

Dengue in Southern Vietnam



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Endemic Dengue Associated with the Co-Circulation of Multiple Viral Lineages and Localized Density-Dependent Transmission

Jayna Raghwani[1], Andrew Rambaut[1,2], Edward C. Holmes[2,3], Vu Ty Hang[4], Tran Tinh Hien[5], Jeremy Farrar[4,6], Bridget Wills[4,6], Niall J. Lennon[7], Bruce W. Birren[7], Matthew R. Henn[7], Cameron P. Simmons[4,5]*

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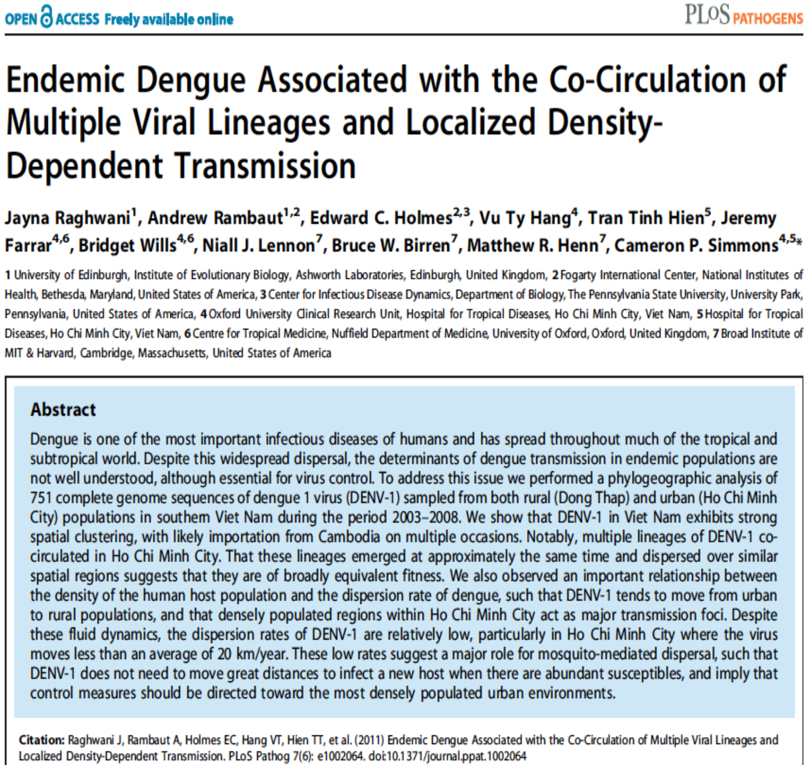
Abstract

Dengue is one of the most important infectious diseases of humans and has spread throughout much of the tropical and subtropical world. Despite this widespread dispersal, the determinants of dengue transmission in endemic populations are not well understood, although essential for virus control. To address this issue we performed a phylogeographic analysis of 751 complete genome sequences of dengue 1 virus (DENV-1) sampled from both rural (Dong Thap) and urban (Ho Chi Minh City) populations in southern Viet Nam during the period 2003–2008. We show that DENV-1 in Viet Nam exhibits strong spatial clustering, with likely importation from Cambodia on multiple occasions. Notably, multiple lineages of DENV-1 co-circulated in Ho Chi Minh City. That these lineages emerged at approximately the same time and dispersed over similar spatial regions suggests that they are of broadly equivalent fitness. We also observed an important relationship between the density of the human host population and the dispersion rate of dengue, such that DENV-1 tends to move from urban to rural populations, and that densely populated regions within Ho Chi Minh City act as major transmission foci. Despite these fluid dynamics, the dispersion rates of DENV-1 are relatively low, particularly in Ho Chi Minh City where the virus moves less than an average of 20 km/year. These low rates suggest a major role for mosquito-mediated dispersal, such that DENV-1 does not need to move great distances to infect a new host when there are abundant susceptibles, and imply that control measures should be directed toward the most densely populated urban environments.

Citation: Raghwani J, Rambaut A, Holmes EC, Hang VT, Hien TT, et al. (2011) Endemic Dengue Associated with the Co-Circulation of Multiple Viral Lineages and Localized Density-Dependent Transmission. PLoS Pathog 7(6): e1002064. doi:10.1371/journal.ppat.1002064

Propagation of Dengue: Main Paradigm

Dengue in Southern Vietnam



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PLoS PATHOGENS

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- Phylogeographic analysis of 751 complete genome sequences of DENV-1 sampled from both rural and urban
- The dengue patients from two prospective studies at the Hospital for Tropical Diseases in Ho Chi Minh City or at Dong Thap Hospital
- Whole genome sequences of DENV-1 sampled over a period of six years (2003–2008).
- The phylogeography analysis was executed with BEAST.

Propagation of Dengue: Main Paradigm

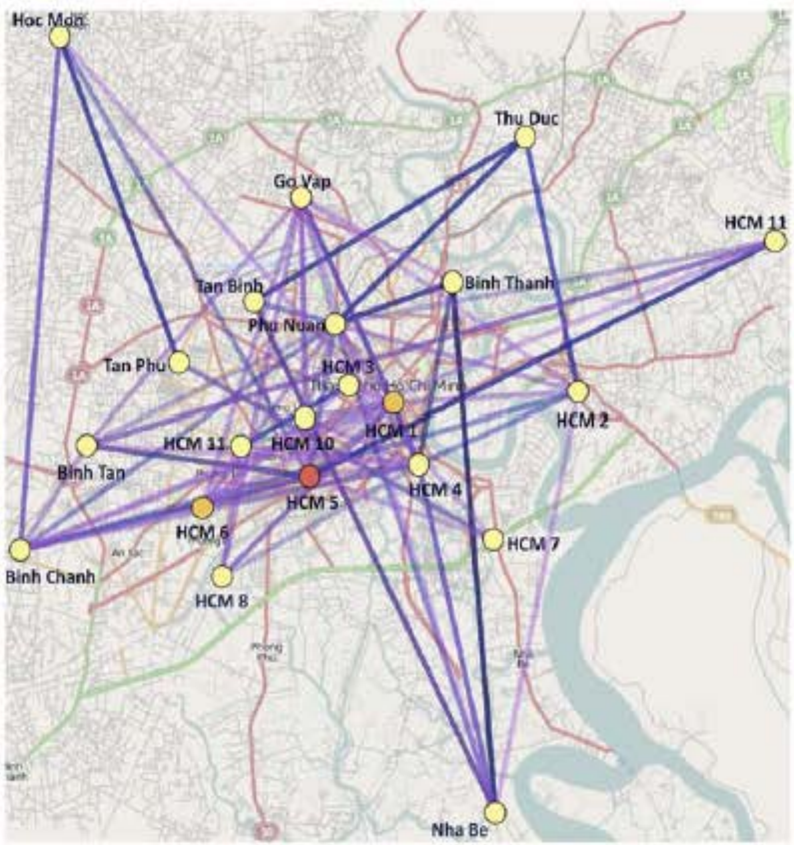
Dengue in Southern Vietnam

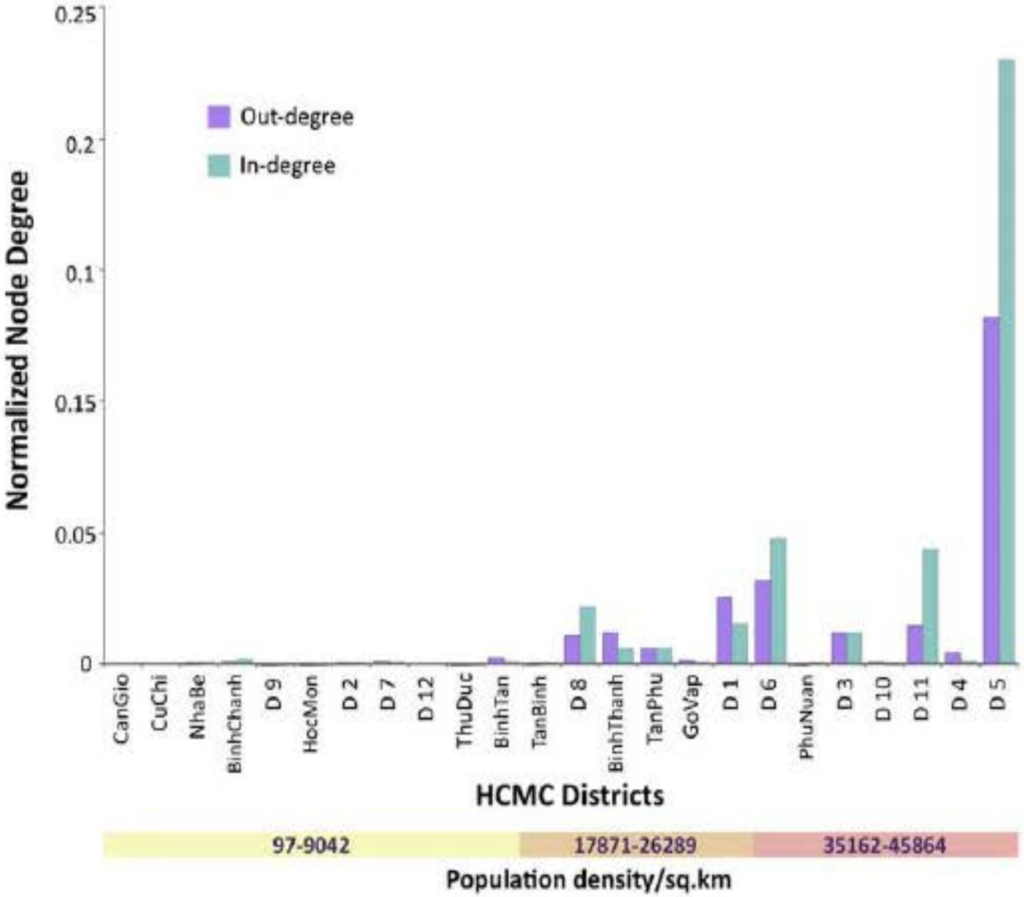
- In four of the five clades, HCMC was the most likely viral source with viruses exported to the rural area. (The exception was clade 1, which was dominated by Dong Thap viruses).
- DENV-1 tends to move from urban to rural populations, and that densely populated regions within Ho Chi Minh City act as major transmission foci.
- However, there was no clear association between genetic diversity, incidence, and dispersion rate observed in the urban environment.

- Phylogeographic evidences of importation of virus from Cambodia then Cambodia may acting as the major source of Vietnamese DENV-1.

Propagation of Dengue: Main Paradigm

Dengue in Southern Vietnam





Propagation of Dengue: Main Paradigm

- Major urban areas of Southeast Asia have been proposed to play central roles in dengue epidemics
- Large viral genetic diversity of the dengue virus and population sizes sufficiently large
- This allows to sustain outbreaks that may subsequently spread to more rural areas, and potentially acting as harbingers of epidemics

- But clearly the analysis of genome sequences is biased toward those of large urban centres.

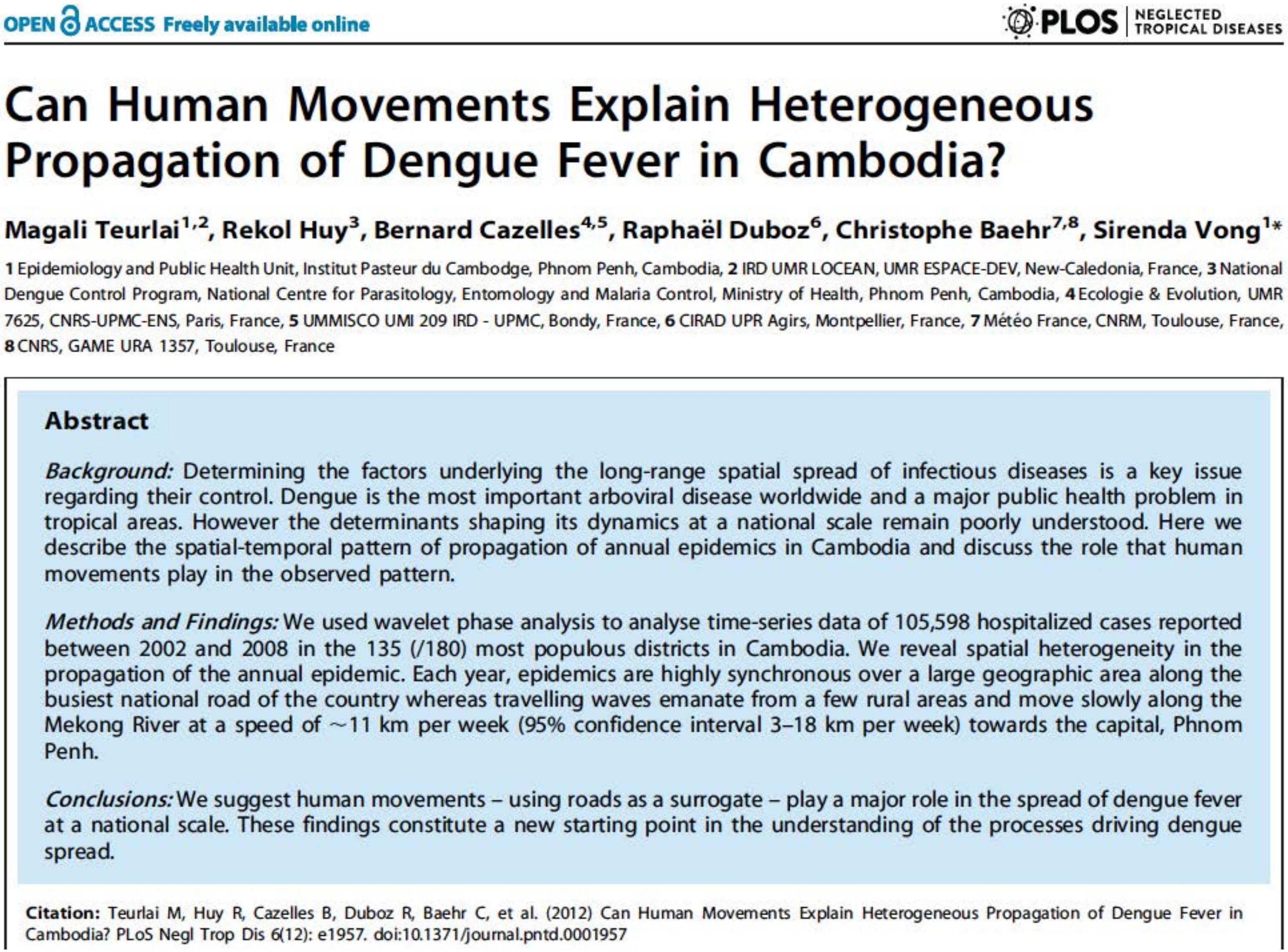
Rural Origin of the Propagation of Dengue

3 examples where the “urban paradigm” failed!

- Dengue epidemics from Cambodia (2008-2010)
- Dengue epidemics in Southern Vietnam (2001-2011)
- Data from Thailand at the province level (1982-2011)

Rural Origin of the Propagation of Dengue

Dengue in Cambodia



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PLOS | NEGLECTED TROPICAL DISEASES

Can Human Movements Explain Heterogeneous Propagation of Dengue Fever in Cambodia?

Magali Teurlai[1,2], Rekol Huy[3], Bernard Cazelles[4,5], Raphaël Duboz[6], Christophe Baehr[7,8], Sirenda Vong[1]*

1 Epidemiology and Public Health Unit, Institut Pasteur du Cambodge, Phnom Penh, Cambodia, **2** IRD UMR LOCEAN, UMR ESPACE-DEV, New-Caledonia, France, **3** National Dengue Control Program, National Centre for Parasitology, Entomology and Malaria Control, Ministry of Health, Phnom Penh, Cambodia, **4** Ecologie & Evolution, UMR 7625, CNRS-UPMC-ENS, Paris, France, **5** UMMISCO UMI 209 IRD - UPMC, Bondy, France, **6** CIRAD UPR Agirs, Montpellier, France, **7** Météo France, CNRM, Toulouse, France, **8** CNRS, GAME URA 1357, Toulouse, France

Abstract

Background: Determining the factors underlying the long-range spatial spread of infectious diseases is a key issue regarding their control. Dengue is the most important arboviral disease worldwide and a major public health problem in tropical areas. However the determinants shaping its dynamics at a national scale remain poorly understood. Here we describe the spatial-temporal pattern of propagation of annual epidemics in Cambodia and discuss the role that human movements play in the observed pattern.

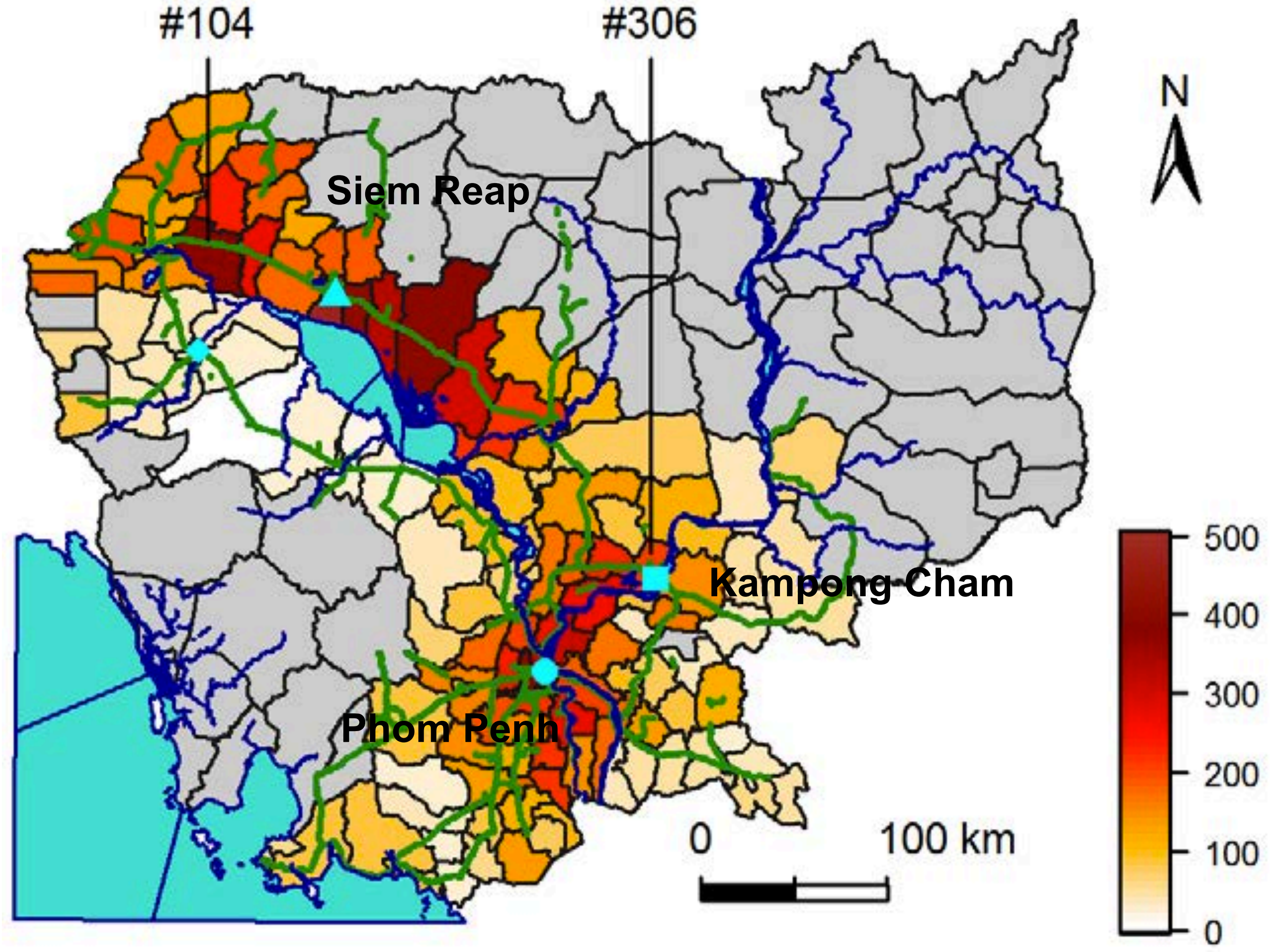
Methods and Findings: We used wavelet phase analysis to analyse time-series data of 105,598 hospitalized cases reported between 2002 and 2008 in the 135 (/180) most populous districts in Cambodia. We reveal spatial heterogeneity in the propagation of the annual epidemic. Each year, epidemics are highly synchronous over a large geographic area along the busiest national road of the country whereas travelling waves emanate from a few rural areas and move slowly along the Mekong River at a speed of ~11 km per week (95% confidence interval 3–18 km per week) towards the capital, Phnom Penh.

Conclusions: We suggest human movements – using roads as a surrogate – play a major role in the spread of dengue fever at a national scale. These findings constitute a new starting point in the understanding of the processes driving dengue spread.

Citation: Teurlai M, Huy R, Cazelles B, Duboz R, Baehr C, et al. (2012) Can Human Movements Explain Heterogeneous Propagation of Dengue Fever in Cambodia? PLoS Negl Trop Dis 6(12): e1957. doi:10.1371/journal.pntd.0001957

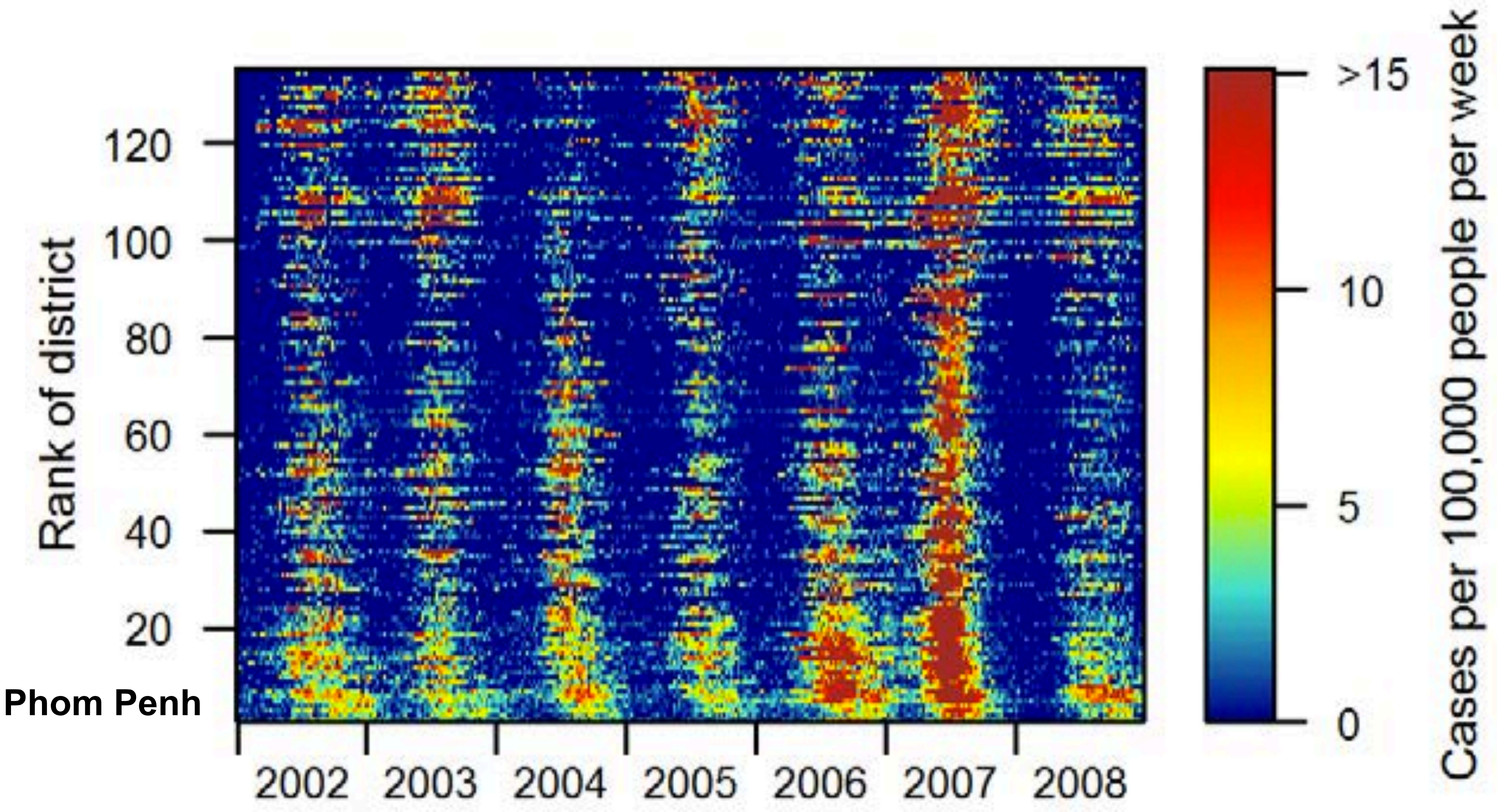
Rural Origin of the Propagation of Dengue

Dengue in Cambodia



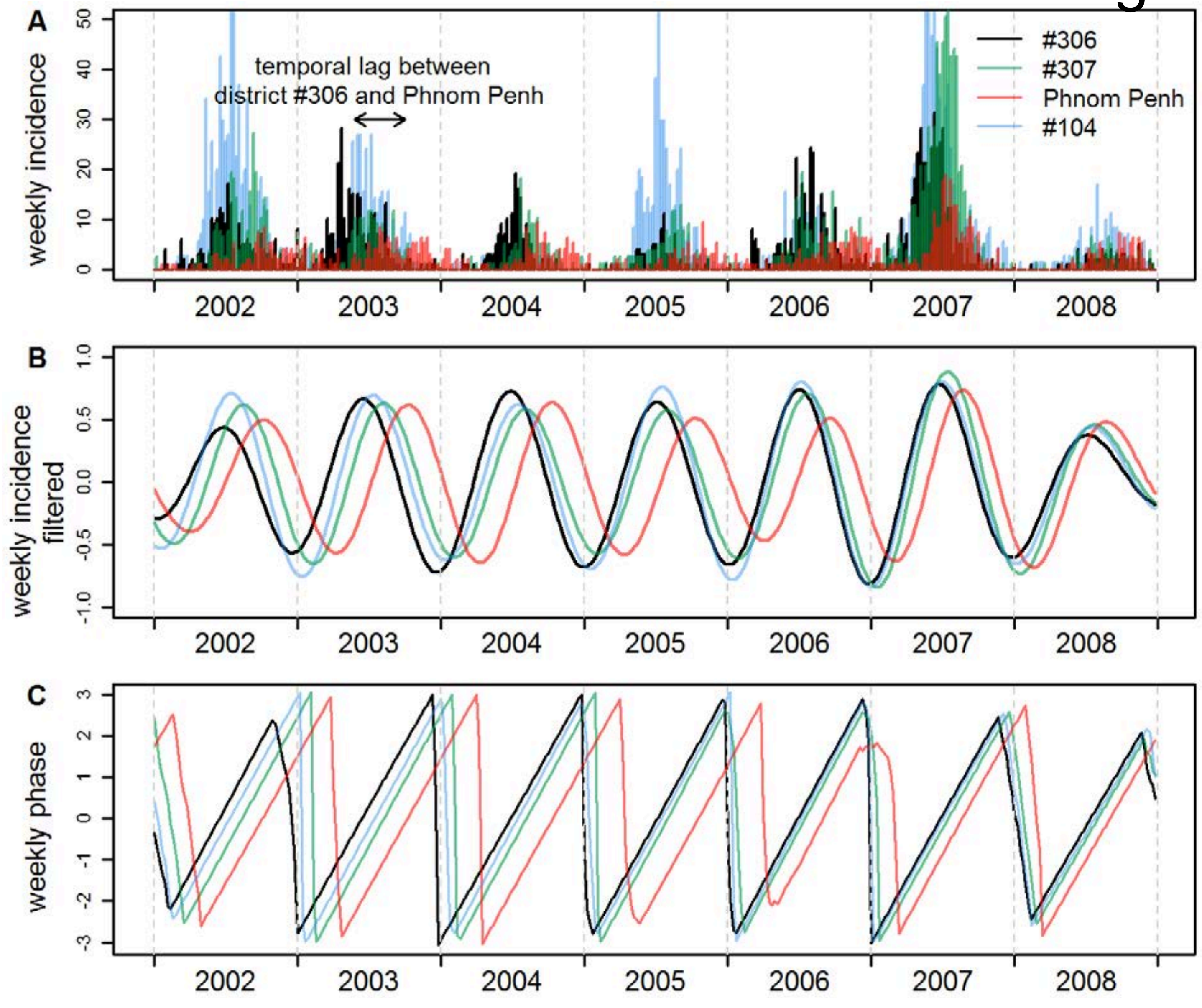
Rural Origin of the Propagation of Dengue

Dengue in Cambodia



Rural Origin of the Propagation of Dengue

Dengue in Cambodia



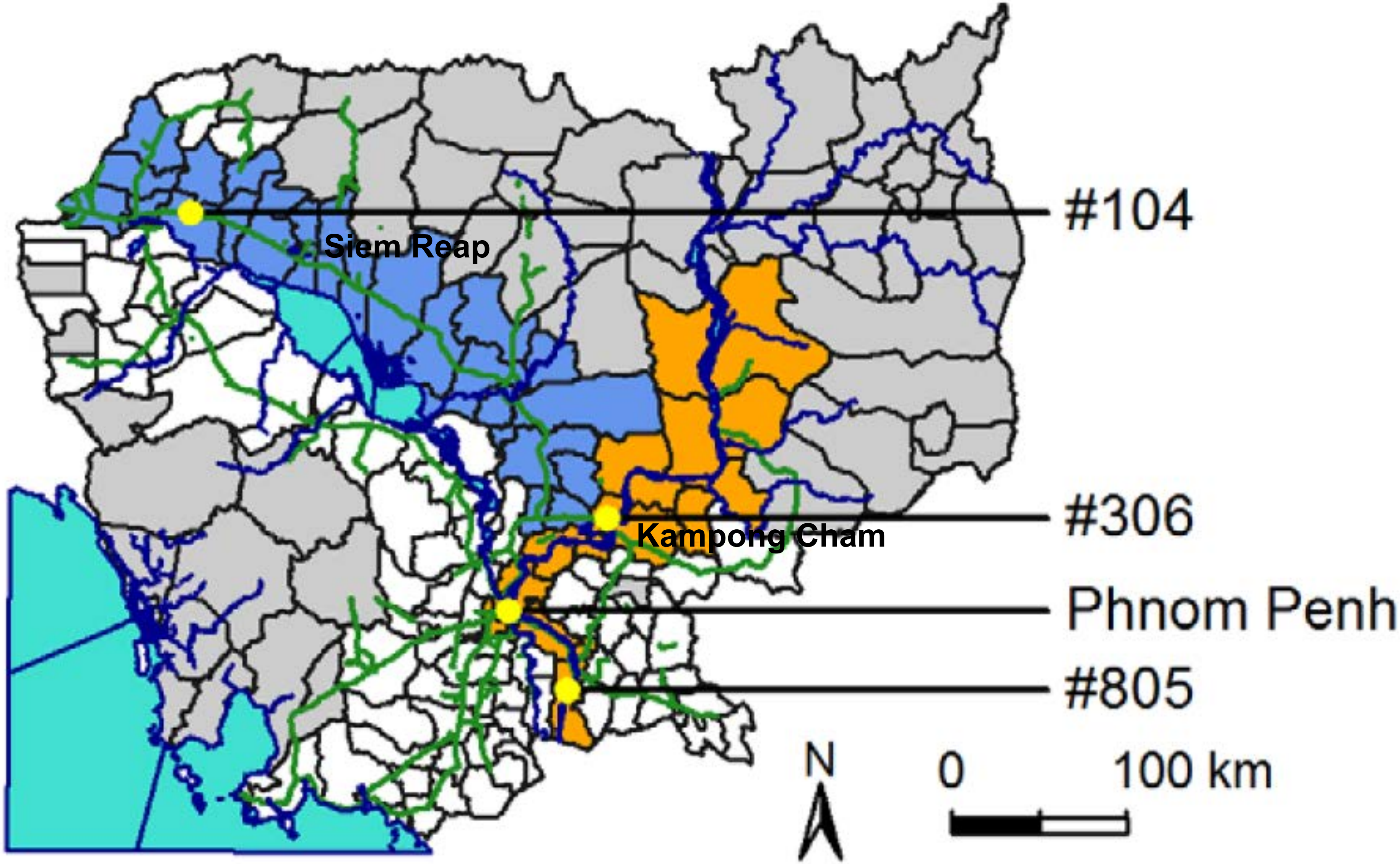
#306: a rural district on the Mekong river near Kampong Cham

#307: a rural district on the Mekong river

#104: a rural district or the north on the national road

Rural Origin of the Propagation of Dengue

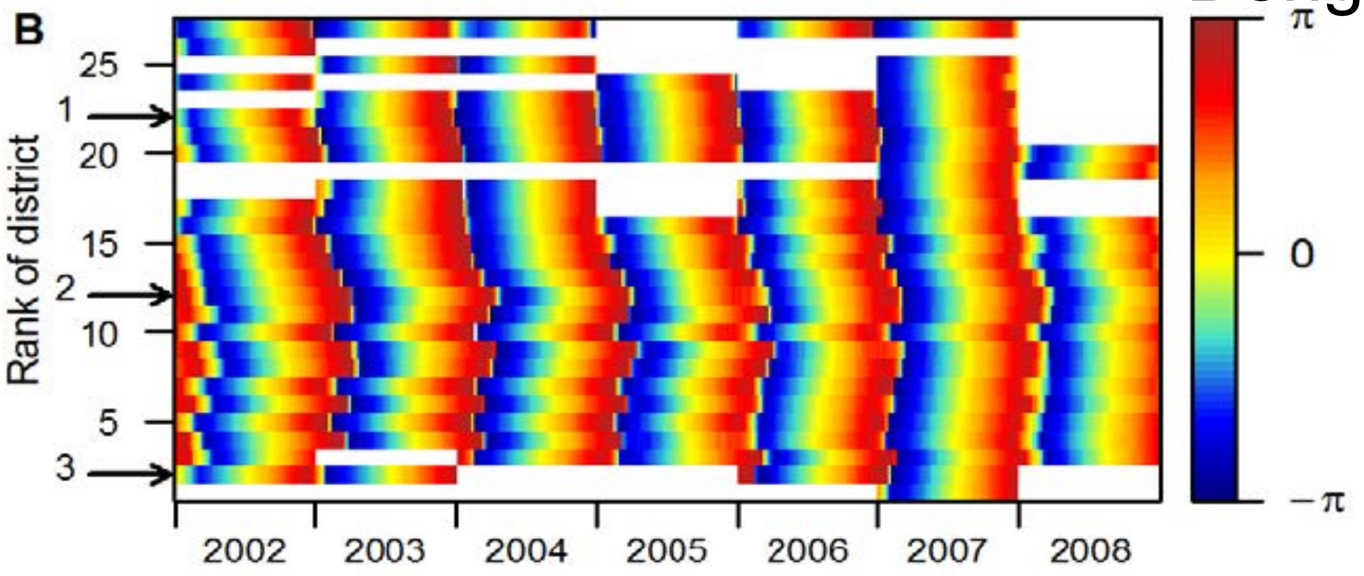
Dengue in Cambodia



Rural Origin of the Propagation of Dengue

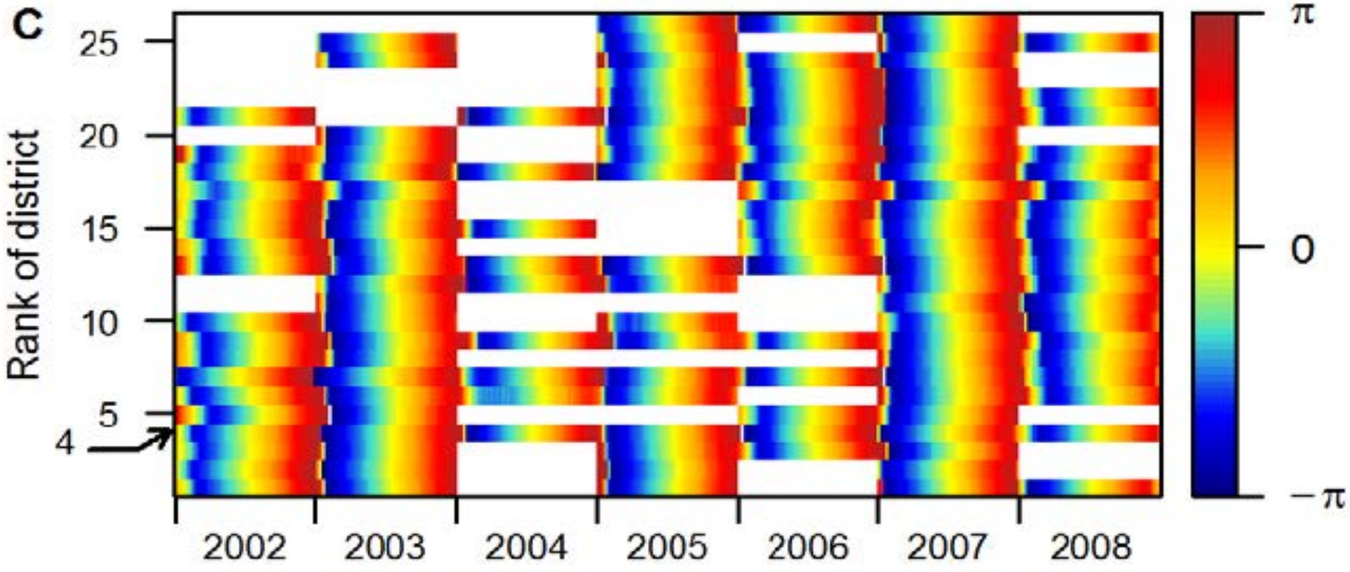
Dengue in Cambodia

B



Districts along the Mekong river: 1: #306; 2: Phnom Penh and 3:#805

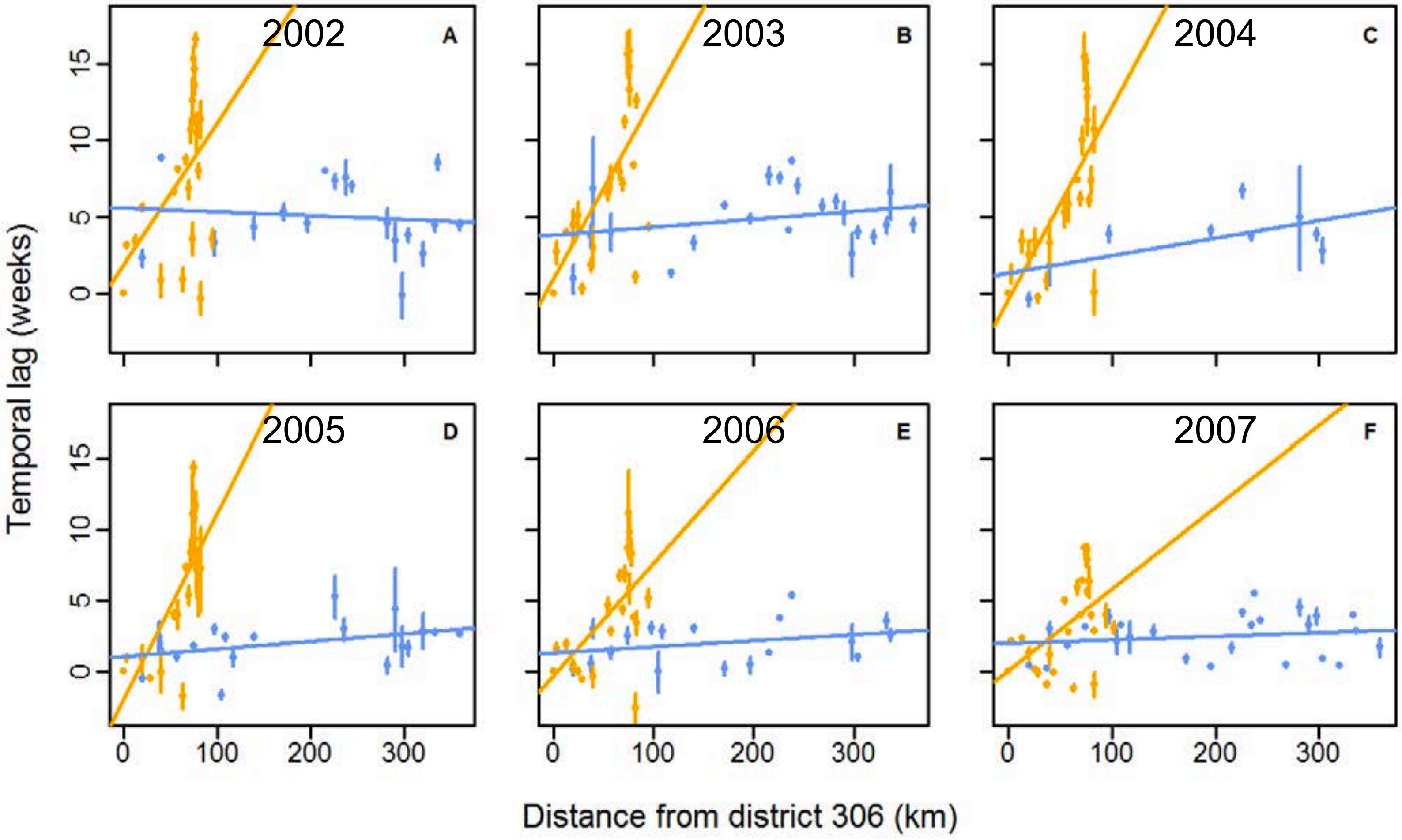
C



Districts along the main national road: 4:#104

Rural Origin of the Propagation of Dengue

Dengue in Cambodia



Rural Origin of the Propagation of Dengue

Dengue in Cambodia

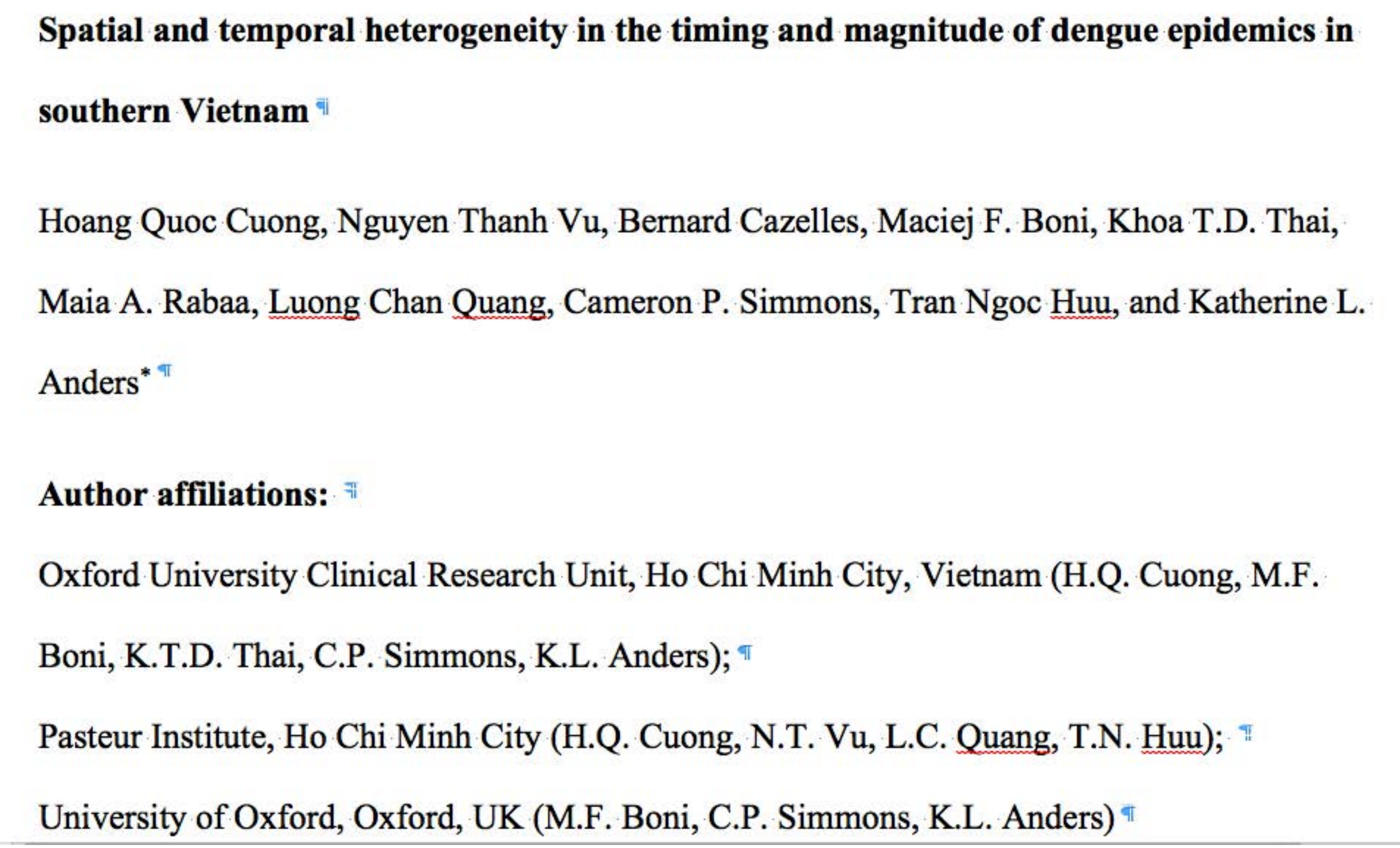
- Our results show that the seasonal epidemic consistently starts in the same three rural districts in Cambodia with a non homogeneous propagation in the country.

- In districts located along the busiest road, dengue epidemics appear simultaneously and early.

- Districts located along the Mekong River get hit by the seasonal epidemic later, with the delay being proportional to the distance to district #306.

Rural Origin of the Propagation of Dengue

Dengue in Southern Vietnam



Spatial and temporal heterogeneity in the timing and magnitude of dengue epidemics in southern Vietnam ¶

Hoang Quoc Cuong, Nguyen Thanh Vu, Bernard Cazelles, Maciej F. Boni, Khoa T.D. Thai, Maia A. Rabaa, Luong Chan Quang, Cameron P. Simmons, Tran Ngoc Huu, and Katherine L. Anders* ¶

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Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam (H.Q. Cuong, M.F. Boni, K.T.D. Thai, C.P. Simmons, K.L. Anders); ¶

Pasteur Institute, Ho Chi Minh City (H.Q. Cuong, N.T. Vu, L.C. Quang, T.N. Huu); ¶

University of Oxford, Oxford, UK (M.F. Boni, C.P. Simmons, K.L. Anders) ¶

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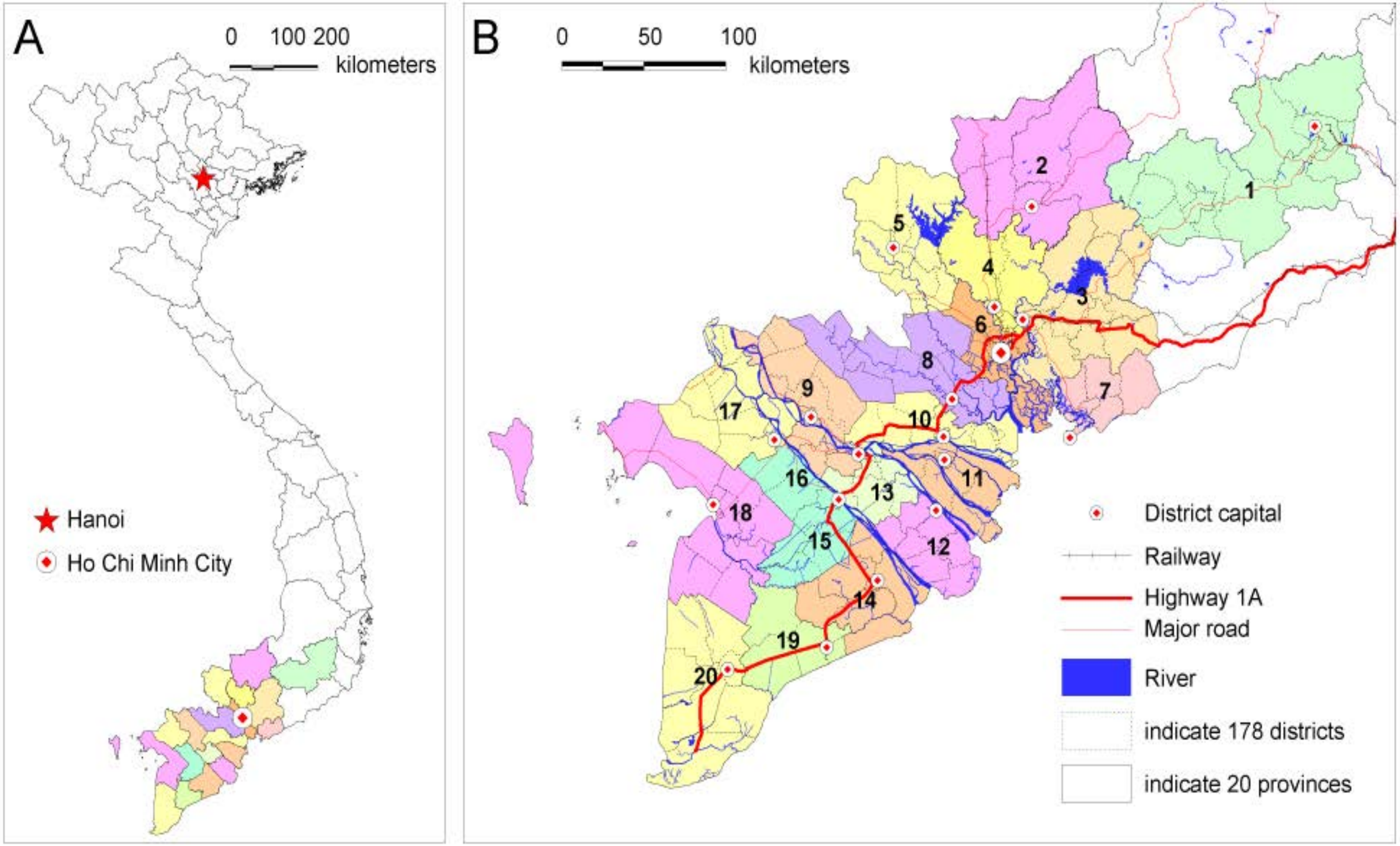
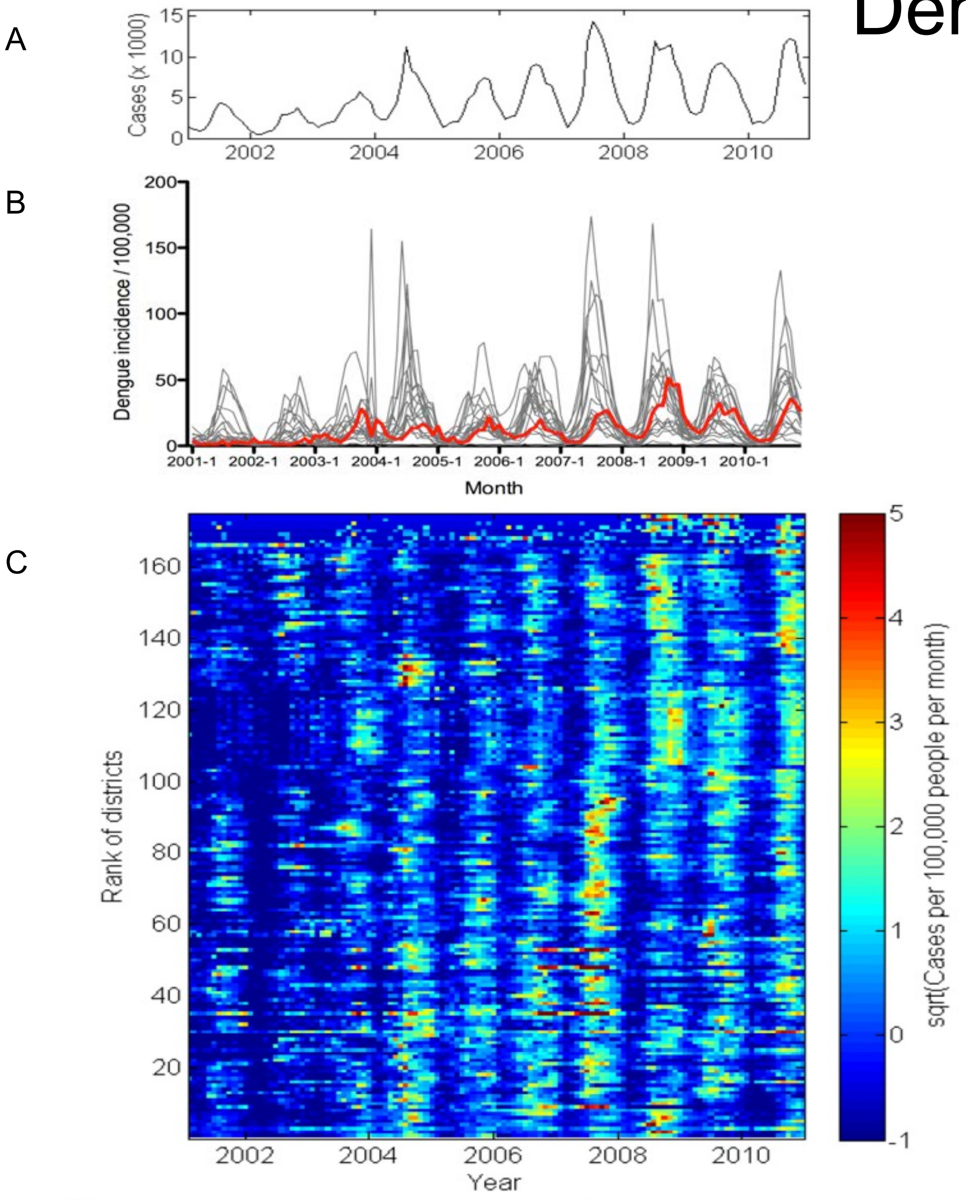
Dengue in Southern Vietnam



6: HCMC   2: Binh Phoc   14: Soc Trang   18: Kien Giang

Rural Origin of the Propagation of Dengue

Dengue in Southern Vietnam



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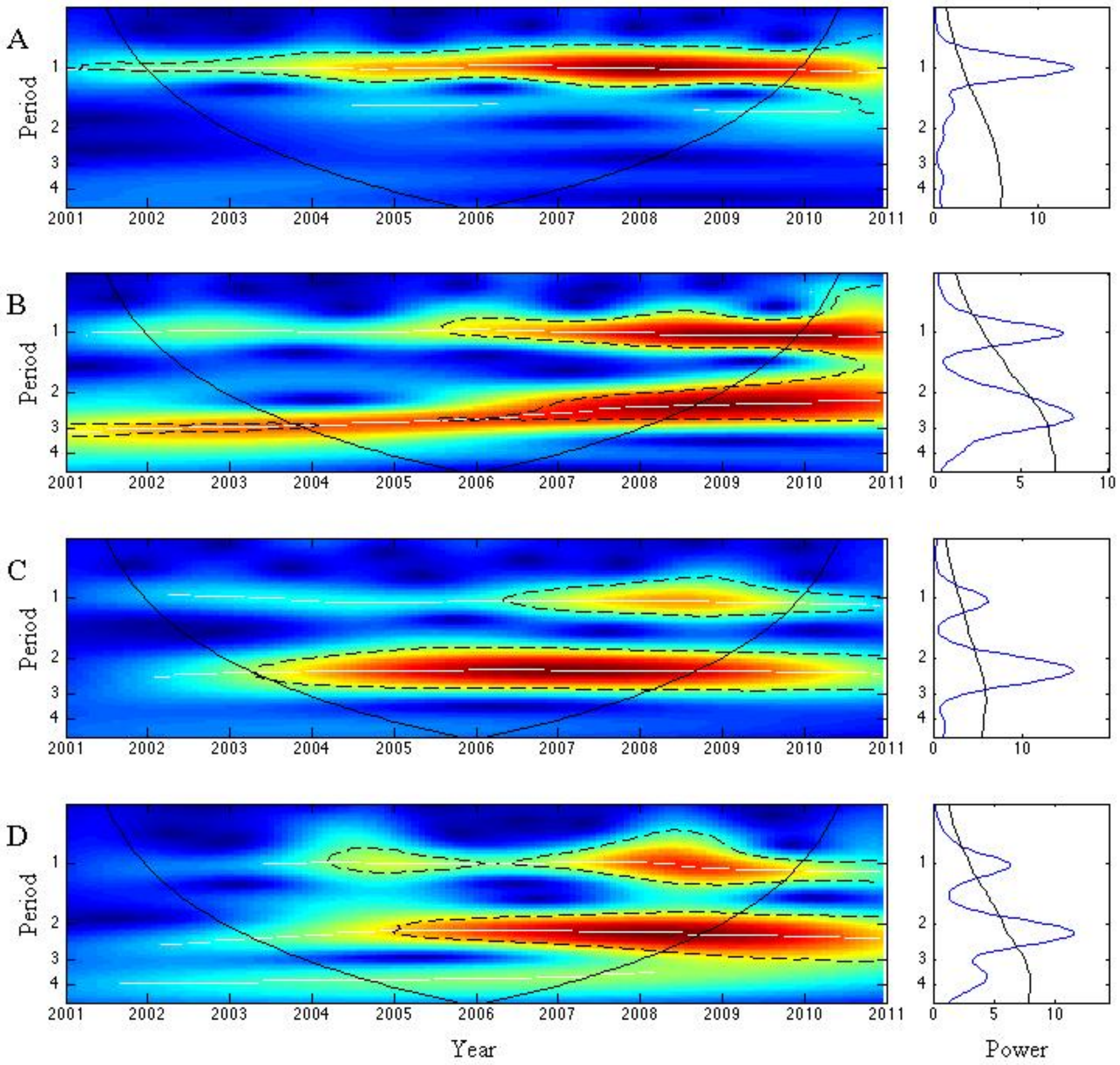


Aggregate

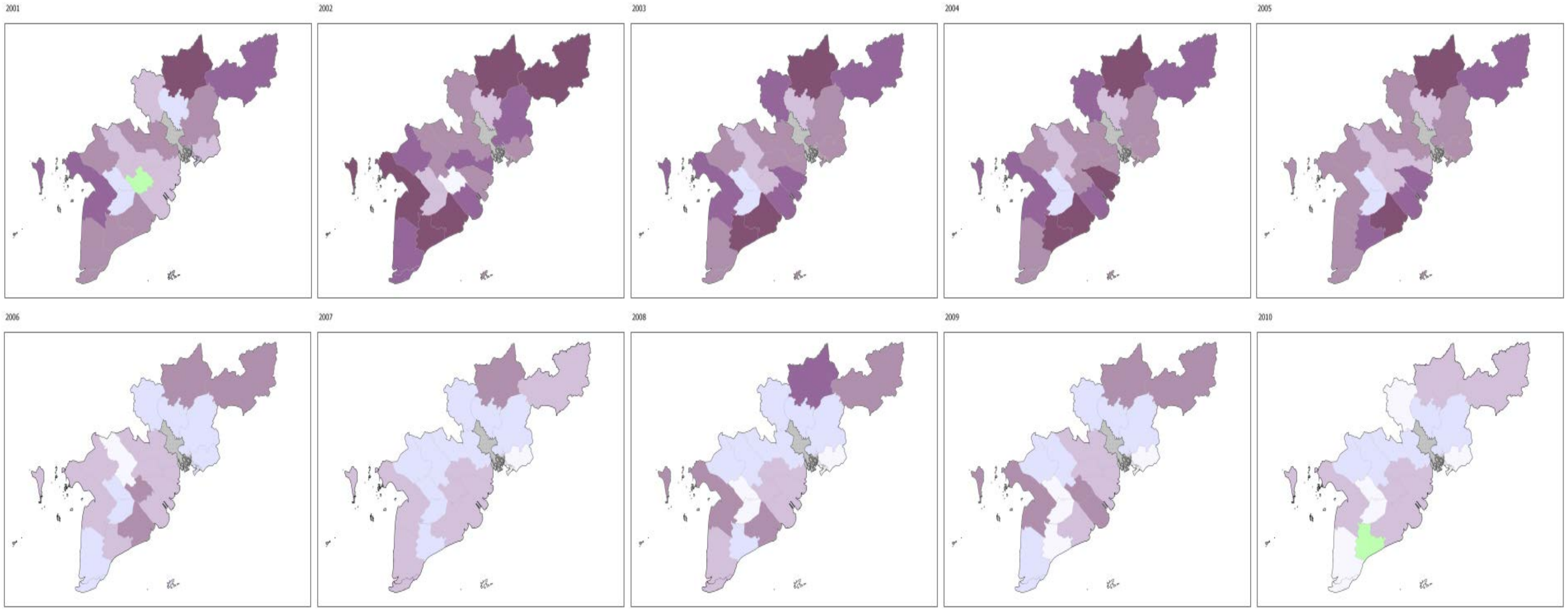
Binh Duong

Bac Lieu

Ca Mau

Rural Origin of the Propagation of Dengue

Dengue in Southern Vietnam



Multi-focus origin mainly: 2: Binh Phoc 14: Soc Trang 18: Kien Giang

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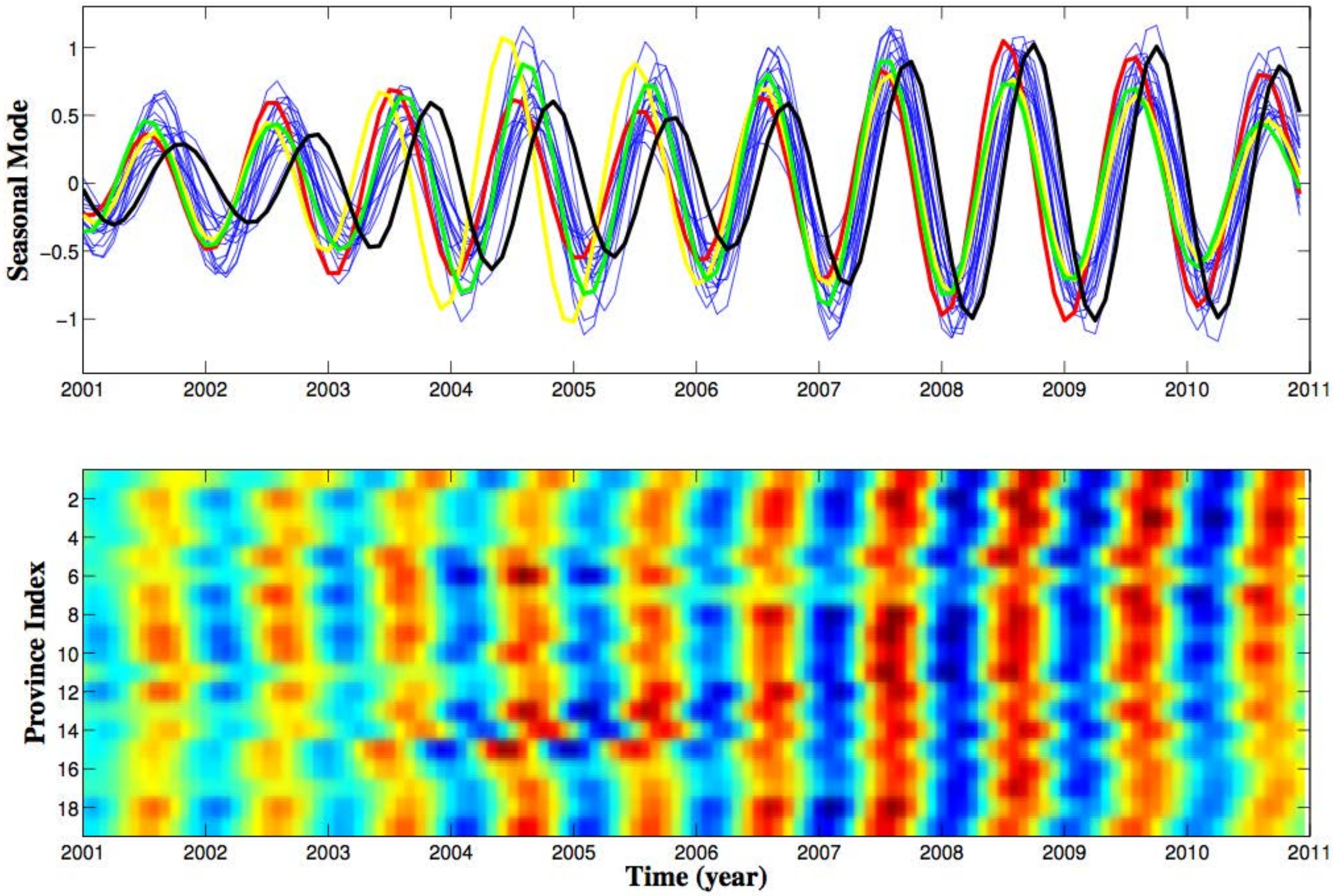
Dengue in Southern Vietnam



Black: HCMC

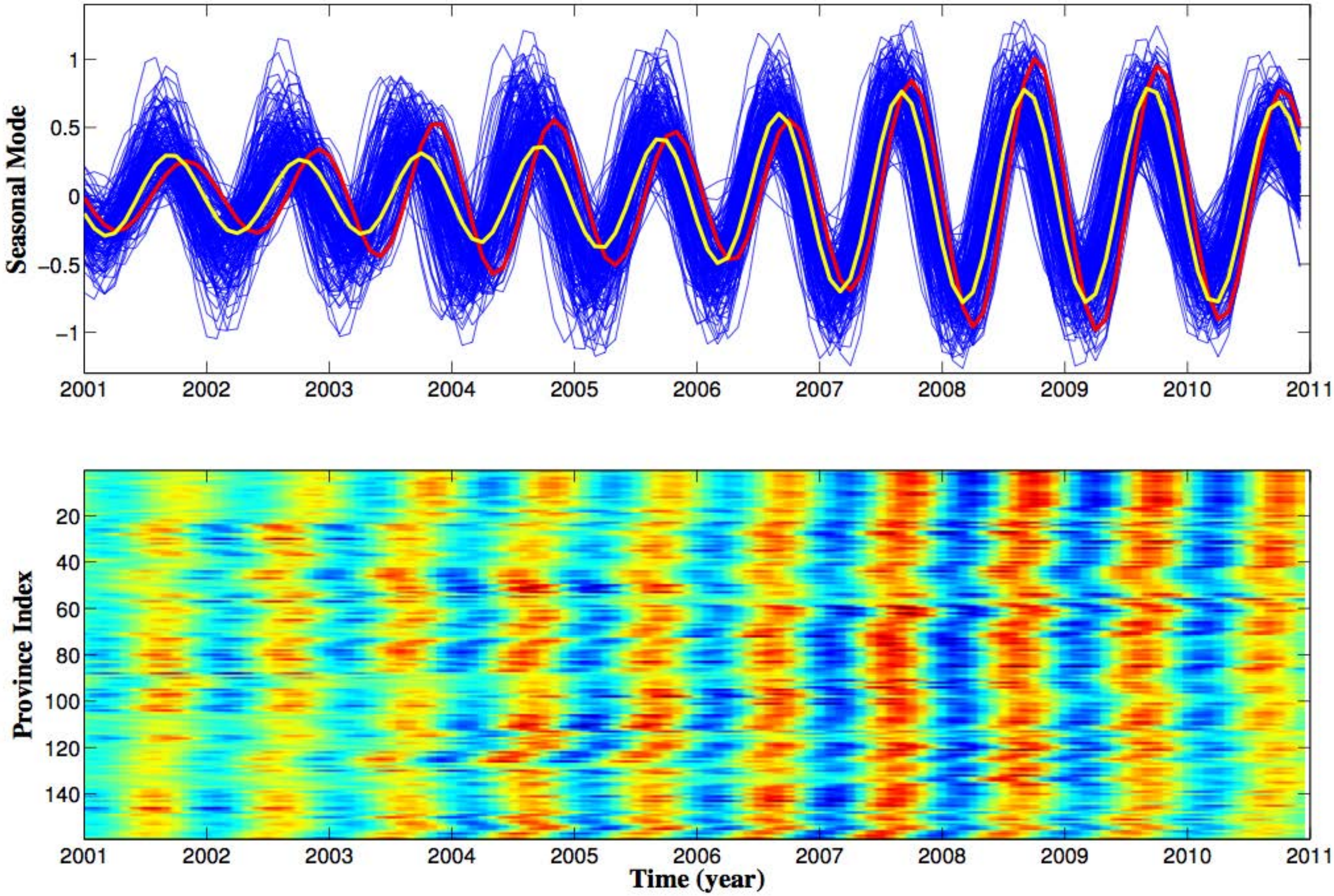
Red:
Binh Phuoc

Green:
Soc Trang

Yellow:
Kien Giang

Rural Origin of the Propagation of Dengue

Dengue in Southern Vietnam



Red:
Super-Urban
HCMC

Yellow:
Peri-Urban
HCMC

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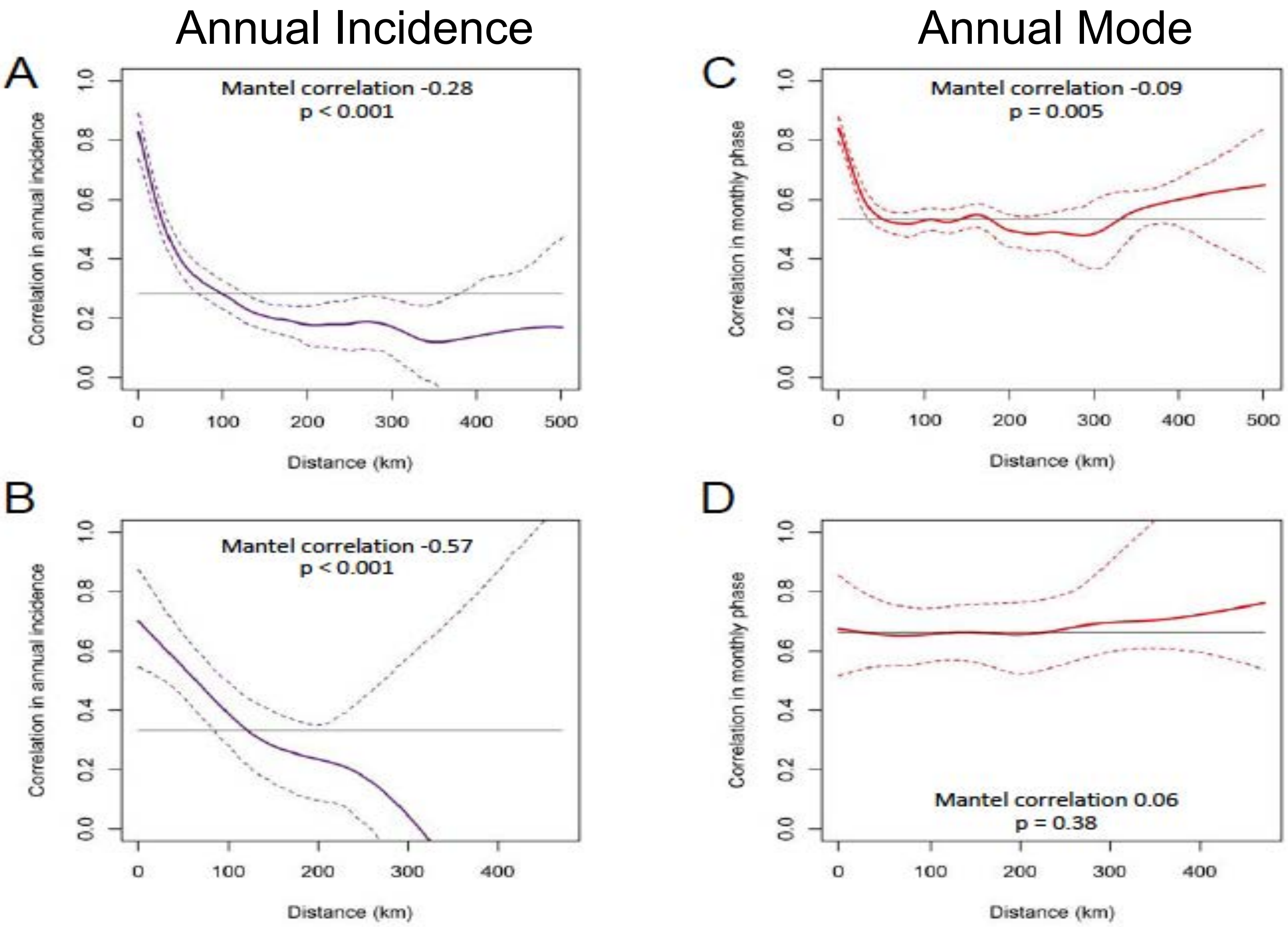
Mantel Correlation



District Data
(n=159)

Province Data
(n=19)

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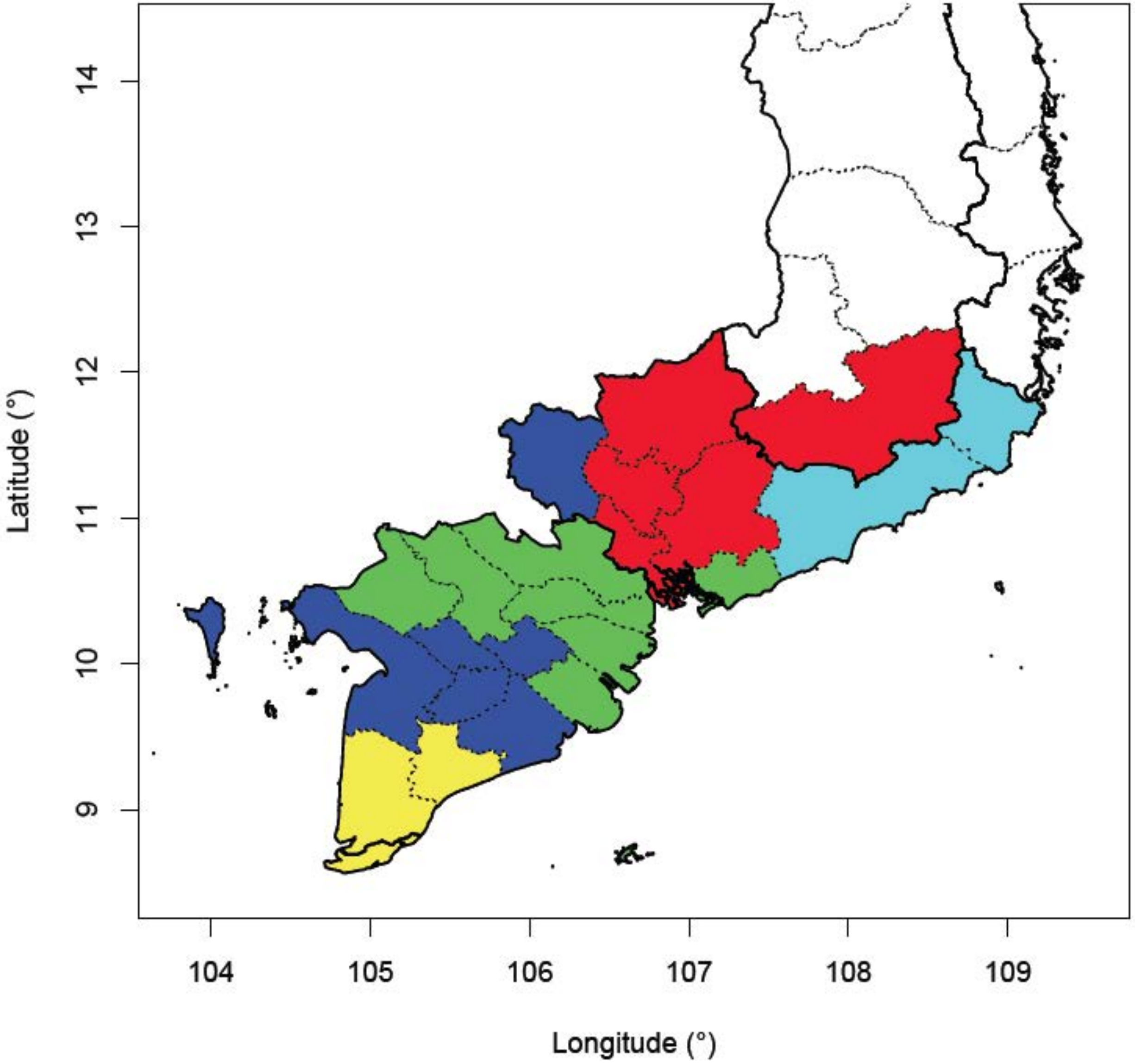

Wavelet Clustering

=>

Geographical pattern

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- In HCMC the incidence was lower than most rural provinces and annual epidemics occurred 1–3 months later than elsewhere.
- HCMC cannot serve as a source population initiating annual dengue epidemics in other provinces.
- But the presence of multiple different locations with early dengue epidemics indicates that there is no consistent geographic source from which dengue epidemics emanate.

- Larger similarity in districts in closer proximity, and this association remains significant out to a distance of 50 to 100 km.
- This suggests an important role for local drivers of dengue transmission operating at the local spatial scale.

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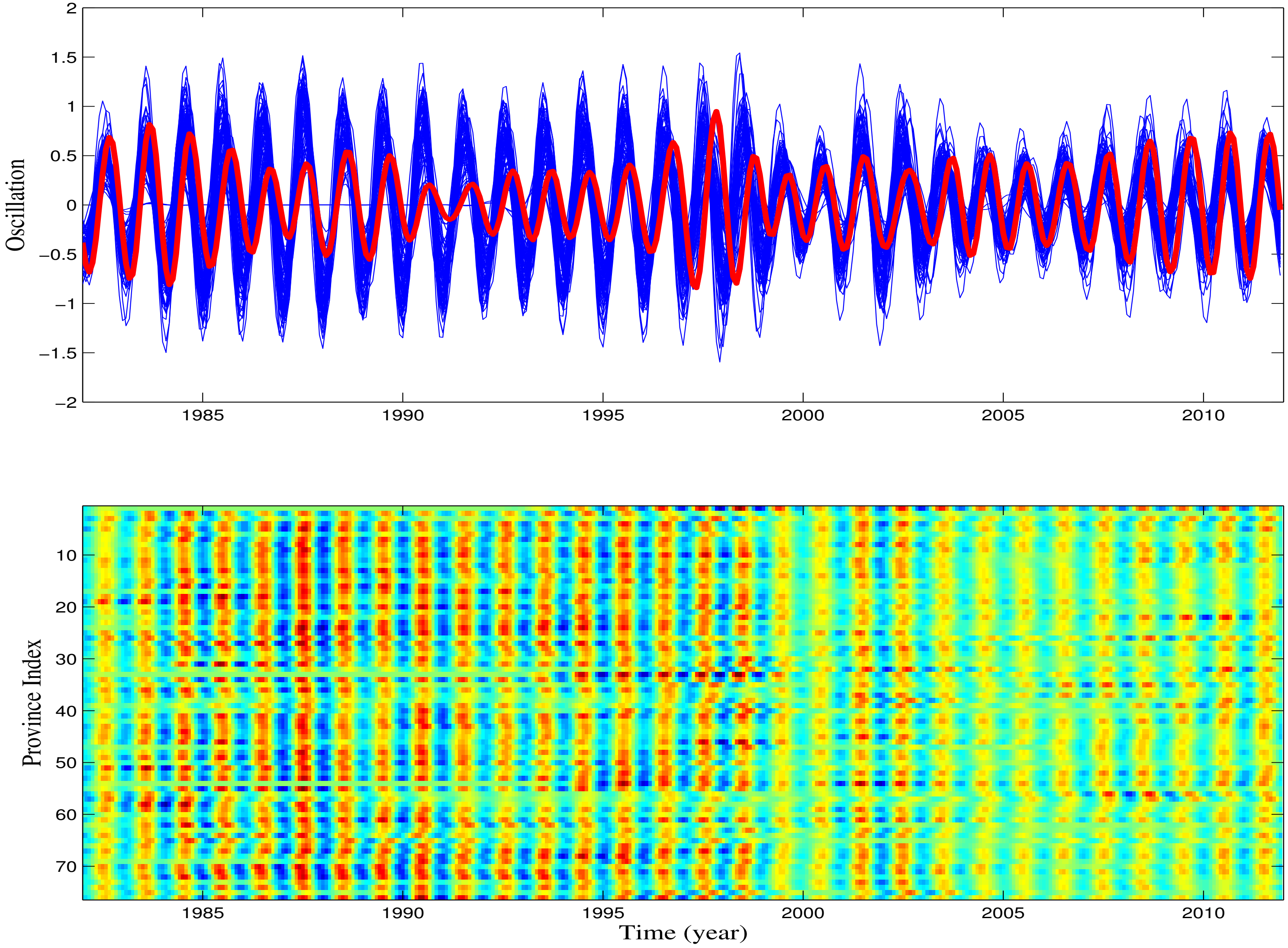
Seasonal Mode

Dengue in Thailand



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Concluding Remarks

- An improved understanding of heterogeneities in dengue transmission may provide insights into biological and ecological drivers.
- Dengue transmission intensity in peri-urban and rural settings often equals or exceeds that in urban centers.
- These findings can aid the targeting of vector-control interventions and the planning for dengue vaccine implementation.

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Concluding Remarks

- A number of factors could also explain the observed spatial dynamics in southeast Asia
  - geographic differences in micro-climate may contribute to differences in the timing of dengue epidemics
  - the ratio of vectors to human hosts, rather than density of vectors or hosts alone
  - a higher median population age in urban center
  - differences in DENV serotype abundance and turnover

Rural Origin of the Propagation of Dengue

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