

Region-wide synchrony and traveling waves of dengue across eight countries in Southeast Asia

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Dengue is a mosquito-transmitted virus infection that causes epidemics of febrile illness and hemorrhagic fever across the tropics and subtropics worldwide. Annual epidemics are commonly observed, but there is substantial spatiotemporal heterogeneity in intensity. A better understanding of this heterogeneity in dengue transmission could lead to improved epidemic prediction and disease control. Time series decomposition methods enable the isolation and study of temporal epidemic dynamics with a specific periodicity (e.g., annual cycles related to climatic drivers and multiannual cycles caused by dynamics in population immunity). We collected and analyzed up to 18 y of monthly dengue surveillance reports on a total of 3.5 million reported dengue cases from 273 provinces in eight countries in Southeast Asia, covering $\sim 10^7$ km². We detected strong patterns of synchronous dengue transmission across the entire region, most markedly during a period of high incidence in 1997–1998, which was followed by a period of extremely low incidence in 2001–2002. This synchrony in dengue incidence coincided with elevated temperatures throughout the region in 1997–1998 and the strongest El Niño episode of the century. Multiannual dengue cycles (2–5 y) were highly coherent with the Oceanic Niño Index, and synchrony of these cycles increased with temperature. We also detected localized traveling waves of multiannual dengue epidemic cycles in Thailand, Laos, and the Philippines that were dependent on temperature. This study reveals forcing mechanisms that drive synchronization of dengue epidemics on a continental scale across Southeast Asia.

dengue | epidemiology | surveillance data | Southeast Asia | dynamics

Dengue virus (DENV) is an arbovirus transmitted by *Aedes* mosquitoes in the tropics and subtropics of the world. The virus causes an estimated 390 million infections per year, resulting in 96 million clinically symptomatic cases (1). DENV has four serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) that each circulate worldwide. The spatial propagation of dengue transmission at short distances by the mosquito vector is well-understood, but the mechanism of long-distance spread has remained unclear. Disease transmission over large geographical distances is difficult to measure directly, but epidemiological coupling of locations revealed by synchrony in population-level disease patterns has been used successfully in the past to infer mechanisms of spread

(2–4). For example, synchrony and its spatial hierarchies indicated that measles in the United Kingdom spread from urban centers to rural areas through a mechanism of fadeout and reintroduction (2). Other studies have suggested that influenza in the United States spreads through workforce commuting (3) and that dengue spreads along a major road in Cambodia (5). Studying epidemic synchrony requires data at high spatiotemporal resolution for a large sample of locations. Data limitations have restricted previous studies on disease spread and synchrony to small geographical areas within country boundaries. Given the increased (cross-border) mobility of populations, strong evidence of global warming, and potential for rapid, global spread of highly pathogenic infectious diseases, a better understanding of the mechanisms of

Significance

Persons living in the tropics and subtropics are at risk for dengue fever and dengue hemorrhagic fever, and large epidemics occur unexpectedly that can overburden healthcare systems. The spatial and temporal dynamics of dengue transmission are poorly understood, limiting disease control efforts. We compiled a large-scale dataset and analyzed continental-scale patterns of dengue in Southeast Asia. Our analysis shows that periods of elevated temperatures can drive the occurrence of synchronous dengue epidemics across the region. This multicountry collaborative study improved insight that may lead to improved prediction of dengue transmission patterns and more effective disease surveillance and control efforts.

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long-distance disease spread and spatial synchrony is becoming essential for global health security.

Some infectious diseases in endemic settings, such as dengue or influenza, occur annually in well-defined cycles that depend on climate factors, such as precipitation. In addition to an annual cycle, significant variability at multiannual periodicities has been observed for dengue (6, 7). This multiannual periodicity is thought to be driven by cycling of immunity in the host population and has been observed to vary over time (6). To better understand the spatiotemporal dynamics of large epidemics, previous studies used various time series decomposition methods to isolate multiannual oscillations from background annual cycles and higher frequency noise. For example, previous work on disease spread focused on the 1.5–3 y cycle for measles (2), the 3.5–4.5 and 5–6 y cycles for pertussis (8), and the 2–3 y (9, 10) and 3–4 y cycles (6) for dengue.

Whereas mechanisms that cause spatial patterns of multiannual cycles of diseases, such as measles and pertussis, are known (2, 4, 11), these mechanisms remain unclear for dengue. Previous studies have suggested that immunity-driven extinction–reintroduction dynamics of DENV serotypes can play a role, particularly around urban centers (6, 12). The role of multiyear climate variation has also been studied but without consistent results (13).

We studied the synchrony of multiannual dengue cycles across a large geographical area of eight countries in Southeast Asia that span 3,500 km east to west by 2,500 km north to south, with a combined population of 320 million in 2010. We used monthly dengue surveillance data that represent ~3.5 million reported cases at the provincial level. High dengue transmission rates across all countries combined with extensive diversity in population density, climate, and geology make this region ideal to investigate the long-

distance spread of major dengue epidemics that occurred in this region during the past decades.

Results

Strong Region-Wide Synchrony of Dengue Transmission. We found strong synchrony across the entire region of multiannual dengue cycles and also, for annual cycles and unfiltered incidence rates (IRs) (Figs. 1A and 2). The average power (amplitude) of statistically significant multiannual cycles changed over time and was the highest in 1993–2004 (Fig. S1A). In comparison, the average power of annual cycles was more constant over time but reduced in 1997–2001 (Fig. S1B). We found few statistically significant multiannual cycles in the northern provinces and few annual cycles in the north and the south. Temperatures were too low in the north and too constant in the equatorial south to support cyclical dengue transmission. Synchrony of multiannual cycles changed over time, with the strongest median synchrony of 0.59 (interquartile range = 0.48–0.76) in the 1996–2000 time window (Fig. 3). In comparison, the regional median for annual cycles was consistent over time, ranging between 0.50 and 0.64. The median synchrony of the unfiltered IRs fell between that for the annual and multiannual cycles. Using the average wavelet coherency of dengue cycles as an alternative metric for synchrony over time, we found equivalent patterns (Fig. S1C and D). Using the entire time series, the average synchrony decreased as the distance between province pairs increased up to ~1,000 km. (Fig. S2). Synchrony of multiannual cycles peaked at 0.55 [95% confidence interval (95% CI) = 0.45–0.67] compared with annual cycles at 0.70 (95% CI = 0.64–0.75) at short distances.

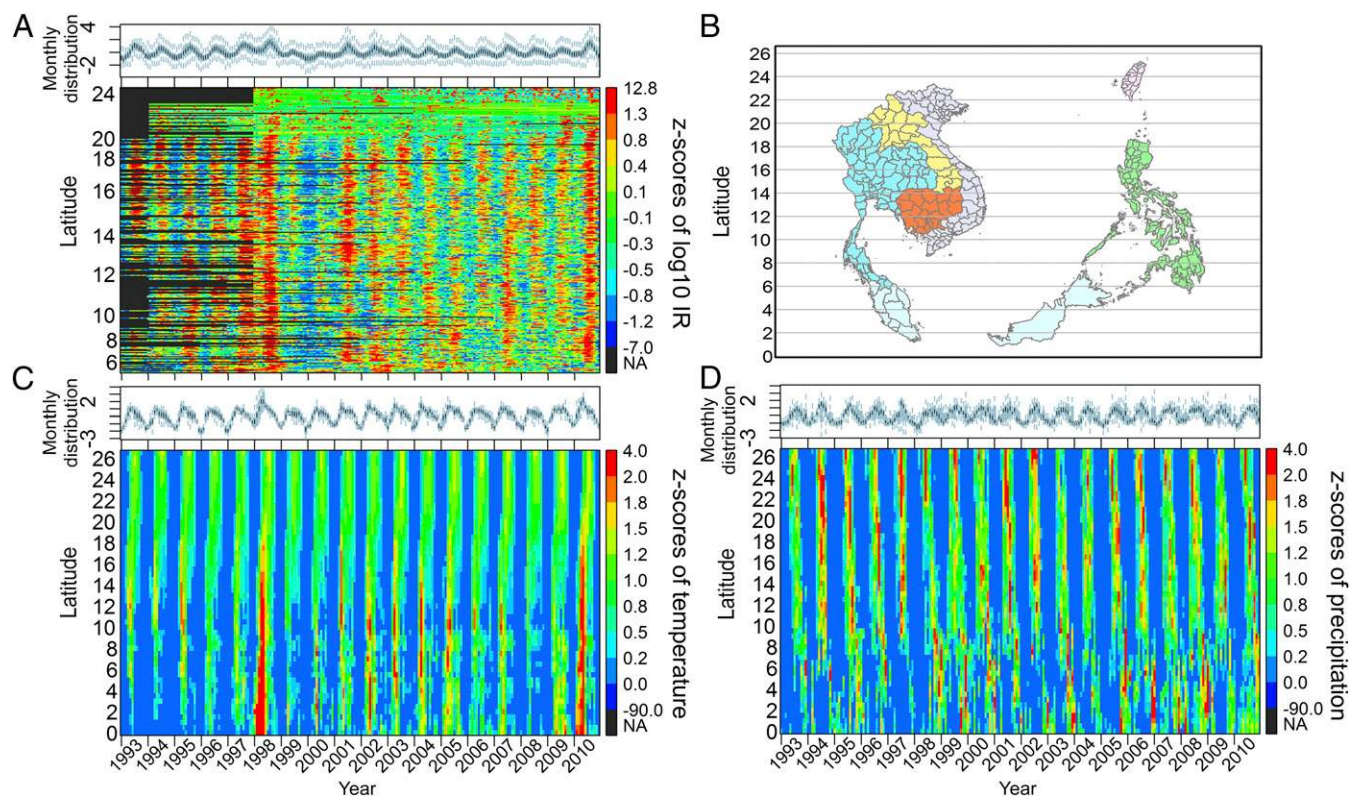


Fig. 1. Monthly dengue IRs (per 100,000 people) and longitudinal climate indicators. Monthly dengue IRs for each province ranked by latitude and monthly climate indicators for corresponding latitudes and time periods. *Upper* shows median values across provinces or latitudes. NA, not available. (A) Monthly dengue IRs per 100,000 people that have been centered and reduced into z scores, \log_{10} -transformed, detrended, and imputed. We imputed missing data by random draws from values of the same months but for different years (Fig. S3). (B) Map of the study provinces by latitude. (C) Average monthly temperature in degrees Celsius from gridded data covering the entire region averaged by latitude and centered and reduced into z scores. (D) The same as C but for total monthly precipitation (millimeters).

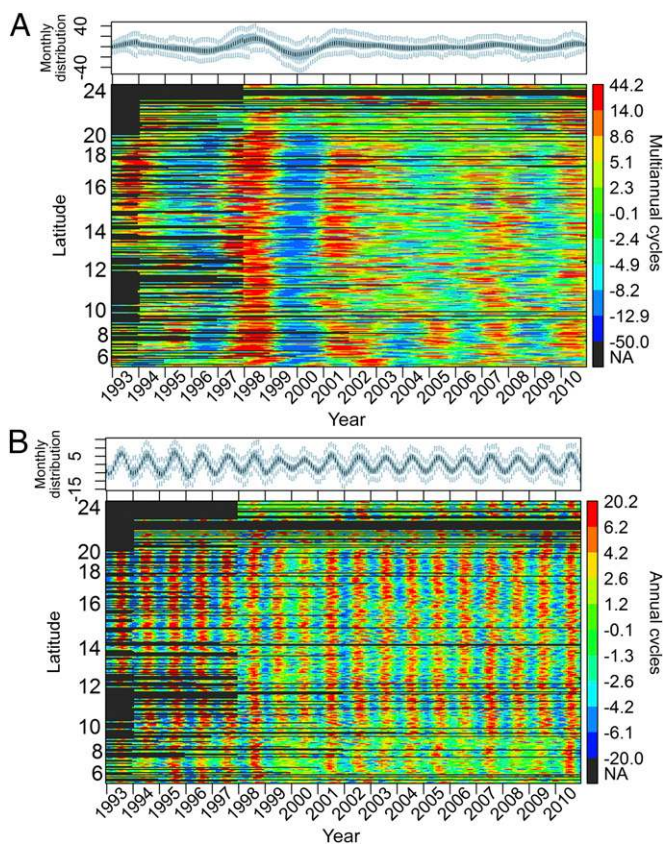


Fig. 2. Wavelet transforms. Reconstructed periodic cycles of monthly dengue IRs for provinces ranked by latitude. *Upper* shows monthly distributions across provinces. NA, not available. (A) Reconstructed multiannual cycles. (B) Reconstructed annual cycles.

Climate Forcing of Synchrony. The strong synchronization of multiannual dengue cycles in 1997–2001 coincided with high temperatures across most latitudes (Fig. 1C) but not with an anomaly in precipitation (Fig. 1D). High temperatures in these years were related to the strongest El Niño episode of the past century (14, 15). We measured a strong wavelet coherency (>0.8) between multiannual dengue cycles and the Oceanic Niño Index (ONI) during 1993–2002 and during 2009–2010 for almost all provinces (Fig. 4). Wavelet coherency for the latter period should be interpreted with caution, because it is at the end of the time series and subject to edge effects. Synchrony of multiannual dengue cycles in the 1997–2001 time window was reduced in a corridor running from Laos to eastern Cambodia (Fig. 3B and Fig. S44). This area is characterized by high altitude and low temperatures and includes the Annamite Mountain Range (Fig. S4). When studying synchrony between each of 12 major cities in the region and all other provinces, we found two clusters of cities: one cluster consisting of Bangkok, Singapore, Zamboanga (the Philippines), Davao, Cebu, and Taipei, that was synchronous with the Annamite corridor, and a second cluster consisting of Phnom Penh, Vientiane, Hanoi, and Kuala Lumpur, that was synchronous with the Annamite corridor (Fig. S4). These clusters of different synchrony suggest at least two separate networks of epidemiologically connected areas in this region, possibly determined by temperature. Indeed, using a linear regression, we found that synchrony of multiannual cycles was stronger at higher temperatures: synchrony increased with 0.029 for each 1 °C increase in temperature (95% CI = 0.026–0.031) (Table S1). For annual cycles, this coefficient was much lower at 0.004 (95% CI = 0.002–0.005). These results suggest that temperature plays a significant role in the spread of

major dengue epidemics. Interestingly, we also found a negative association between population density and synchrony for both annual ($\beta = -0.088/\log_{10}$ population density per km^2) and multiannual ($\beta = -0.037/\log_{10}$ population density per km^2) cycles. This association suggests that more densely populated areas may be able to determine their own nonsynchronous dynamics as independent “pacemakers” instead of phase-locking dynamics with other areas.

Traveling Waves of Multiannual Cycles. We detected traveling waves of multiannual dengue cycles in various parts of the region. We used the phase difference θ to determine the difference (in months) in epidemic timing between provinces. A province could have either a positive- or negative θ compared with another province. A positive θ indicated that a province was timed earlier (leading ahead) vs. the other, and a negative θ indicated that a province was timed later (lagging behind). Outgoing traveling waves can emerge from a province with epidemic dynamics timed ahead of others. In contrast, a province with epidemics lagging behind others could experience an incoming traveling wave. For each province separately, we tested for the presence of local incoming or outgoing traveling waves. For provinces that were lagging behind ($\theta < 0$), we defined an incoming traveling wave as a decreasing lag time with decreasing distance. For provinces that were leading ahead ($\theta > 0$), we defined an outgoing traveling wave as an increasing lag time with increasing distance; 28 provinces had statistically significant incoming traveling waves of multiannual dengue cycles, and 33 had outgoing traveling waves (Fig. 5). Provinces with outgoing traveling waves were located in west Thailand and the Bangkok area, central Laos (Savannakhét and Khammouan), and southern Philippines (Bohol). We found fewer incoming traveling waves for annual cycles concentrated in the northern Philippines ($n = 8$) and central-eastern Thailand ($n = 21$). The presence of multiannual waves but not annual waves was statistically significantly associated with temperature and precipitation. Provinces with outgoing multiannual waves had an average of 1.5 °C higher temperature (95% CI = 1.0–2.1 °C) and 53.1 mm (95% CI = 39.7–66.6 mm) lower precipitation compared to provinces without waves. Provinces with incoming multiannual waves had an average of 39.5 mm (95% CI = 22.4–56.5 mm) lower precipitation, but no significant temperature difference compared to other provinces.

Discussion

This analysis of large-scale surveillance data revealed strong region-wide synchrony in multiannual dengue cycles. We used a “synoptic epidemiology” approach that spans a large geographical scale but includes granular detail, providing an instantaneous picture of region-wide and local disease dynamics. Synchrony of multiannual cycles changed over time, with a maximal region-wide synchronization occurring during 1997–2001, whereas synchrony of the annual cycles was consistent over time. Synchrony of multiannual dengue cycles during this period coincided with the highest temperatures of the study period across most latitudes and the strongest El Niño event of the century (14, 15). We measured strong wavelet coherency between multiannual dengue cycles and the ONI across most provinces during 1993–2002, but this coherency decreased afterward. A previous study found identical nonstationary wavelet coherency during this period between multiannual dengue cycles and El Niño Southern Oscillation indices for one province in Vietnam (Binh Thuan) (9). The transient nature of this association over time suggests a threshold effect, where the spread of major DENV epidemics may be facilitated by abnormally high temperatures or high temperatures for an abnormally long period. Indeed, we found that synchrony of multiannual cycles increased as temperature increased. Throughout 1997 and 1998, high temperatures across the region could have sustained high levels of dengue transmission, leading to a depletion of susceptibles and low transmission in the following years (Fig. 1A). This hypothesis is consistent

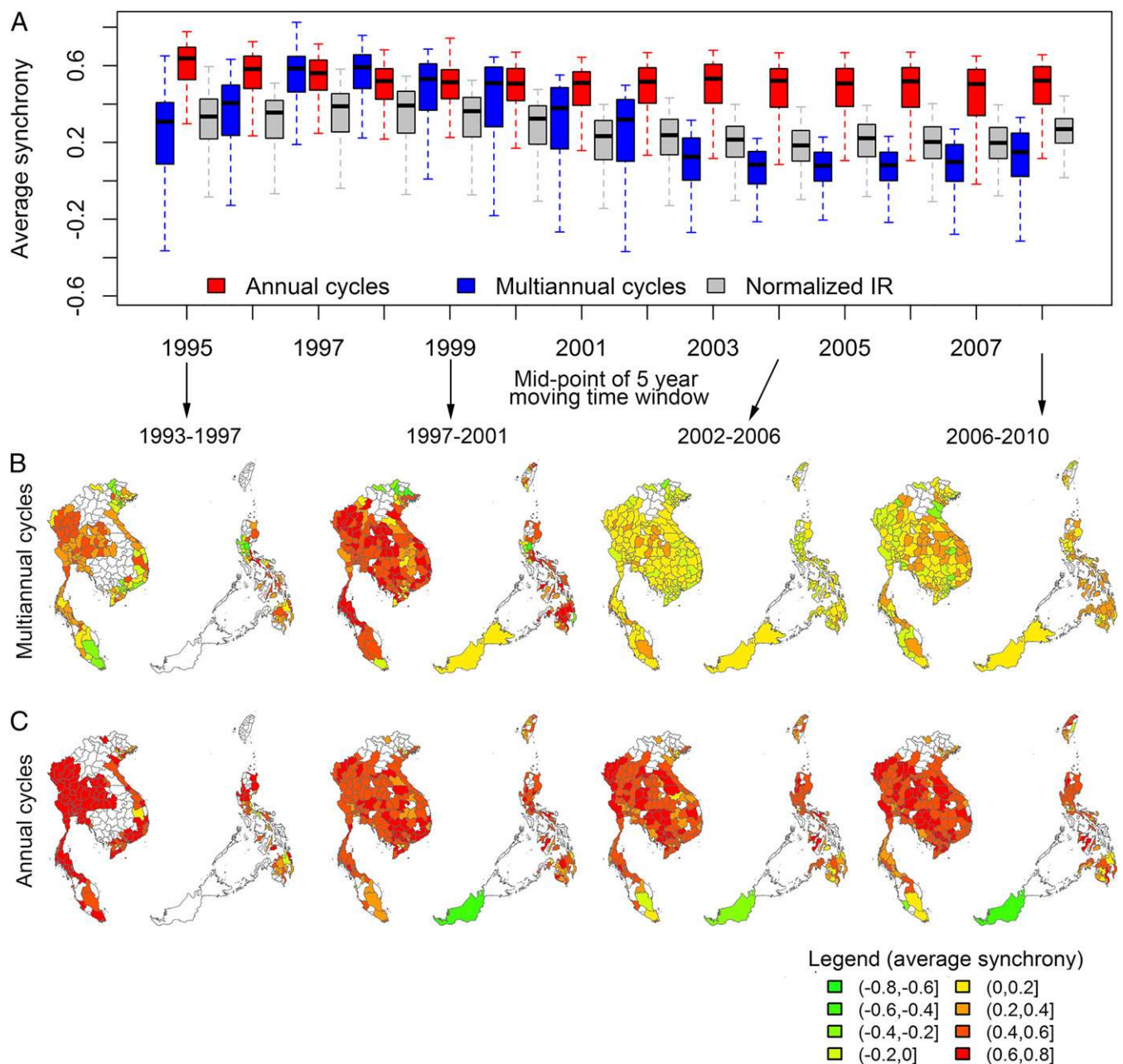


Fig. 3. Synchrony of dengue cycles over time. We computed the average synchrony for moving, overlapping 5-y windows to detect changes over time. (A) Distributions of average synchrony per province per time window plotted at the midyear of each window for multiannual and annual cycles and unfiltered IRs. (B) The average synchrony of multiannual dengue cycles per province for four time windows. (C) The same as B but for annual cycles.

with the biology of the *Aedes aegypti* vector, which reproduces faster and transmits DENV more efficiently at higher temperatures (16, 17). Also, in 1998, a new DENV-2 strain (Cosmopolitan genotype) emerged in Asia (18). High temperatures across a sufficiently large geographical area combined with a large pool of susceptibles could enable the spread of major synchronous dengue epidemics when new DENV types emerge. Indeed, we found a 1.5 °C higher temperature in provinces with outgoing multiannual traveling waves compared to provinces without these waves.

Synchrony of multiannual as well as annual cycles was inversely associated with population density. This association could suggest an extinction–reinvansion mechanism, where synchronous cycles emerge in areas of low population density after a period of low transmission. Densely populated areas are less prone to such

“fade-outs,” because they supply a constant pool of susceptibles that can sustain ongoing transmission of all four DENV serotypes. These urban centers could act as independent pacemakers of epidemic dengue cycles into the surrounding areas (6, 12). This mechanism is consistent with the two clusters of synchrony among major cities in the region: one synchronous with the Annamite Mountain Range and the other synchronous with the west-central Thailand area. These areas are also the two main areas for which we detected outgoing traveling waves for multiannual cycles, suggesting that forcing mechanisms, such as temperature, act independently in each of these areas.

The role of human movement in the spread of disease epidemics has been a strong focus of recent research, greatly facilitated by the emergence of novel data sources, such as mobile phone and flight

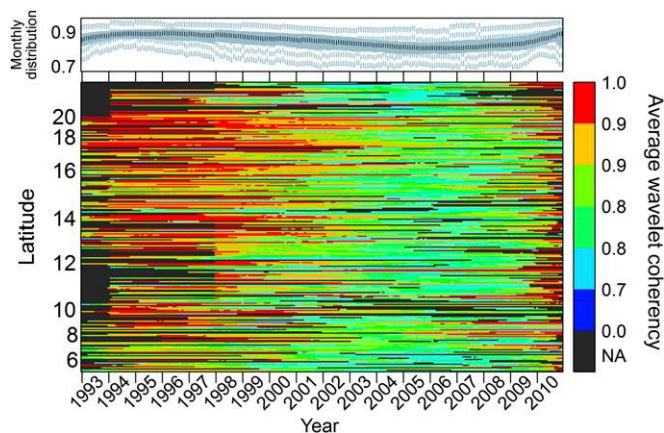


Fig. 4. Wavelet coherence between the ONI and multiannual DENV cycles. The monthly average statistically significant wavelet coherence between ONI and multiannual DENV cycles across (Lower) the multiannual periodicity band for each province ranked by latitude. Upper shows the distributions (medians and interquartile ranges) of province average wavelet coherence per month. NA, not available.

data (19, 20). Strong synchrony and traveling waves of dengue epidemics across Southeast Asia could be driven by (cross-border) population movement. We were unable to formally test this because of limited data on human movement. However, a high degree of population connectivity and spread of DENV across country borders in Southeast Asia has been shown by phylogenetic studies, showing that DENV genotypes circulating in countries, such as

Thailand and the Philippines, were isolated across the entire region (18, 21–23). We found spatial structuring in time lags of dengue cycles across provinces that was consistent with traveling waves of dengue incidence. Outgoing traveling waves were concentrated in central Thailand, the east Mekong, and the southern Philippines. It was also in these countries that dengue was first recognized in the 1950s (24). Provinces with outgoing traveling waves had higher temperatures and lower precipitation compared to other provinces. Local climate, virus, and population conditions in these areas may have ignited the emergence and spread of new DENV types that resulted in region-wide synchronous dynamics through widespread high temperatures during a strong El Niño episode and population movement.

Powerful forcing mechanisms in Southeast Asia, particularly sustained high temperatures, can drive the synchronized spread of major dengue epidemics on a continental scale. This analysis improves opportunities for future studies on the causal mechanisms and for predictive modeling of large-scale dynamics of dengue as well as other infectious diseases. This study also demonstrates the advantages of multicountry collaboration to advance infectious disease surveillance, analysis, and control.

Materials and Methods

Data. Monthly dengue surveillance data and corresponding population (25) and climate data (26–28) at the provincial level (29) were available for 273 provinces in Thailand, Cambodia, Laos, Vietnam, Malaysia, Singapore, the Philippines, and Taiwan (more details on data sources and inclusion are in *SI Materials and Methods*). We computed monthly dengue IRs per 100,000 people for 1993–2010 for provinces in Thailand, Malaysia, and Singapore; 1994–2010 for the Philippines and Vietnam; and 1998–2010 for the other countries (Figs. S3 and S5 and Movie S1). All data are publicly available through Project Tycho (www.tycho.pitt.edu).

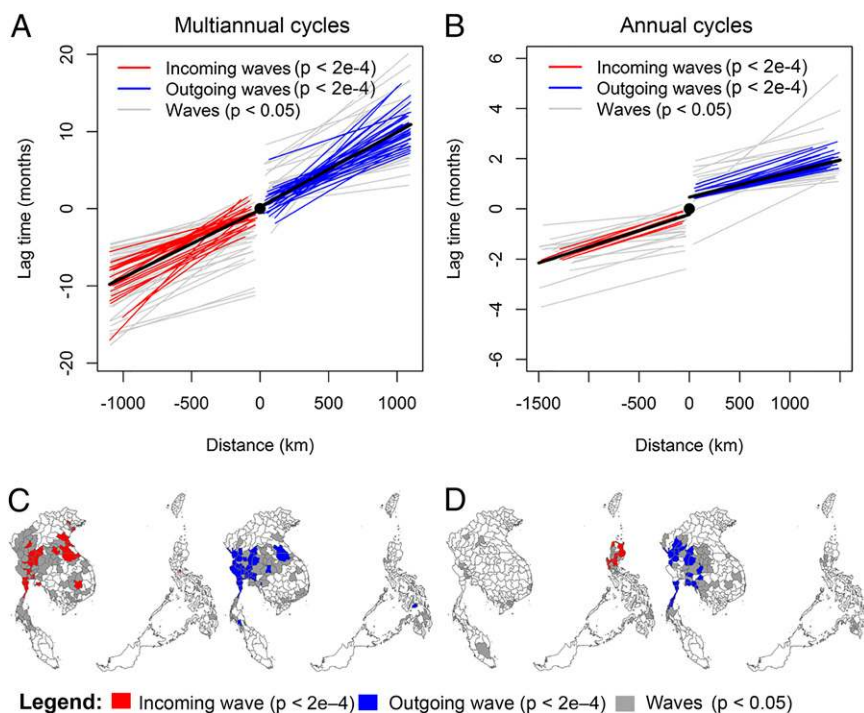


Fig. 5. Traveling waves of synchrony across provinces. For each province, we fitted a linear model of the phase difference θ of multiannual and annual dengue cycles vs. geographical distance (kilometers). A negative θ indicated that a province epidemic cycle was timed later than another province, possibly experiencing an incoming traveling wave (decreasing θ with decreasing distance). A positive θ indicated that a province was timed earlier than another province, possibly experiencing a positive traveling wave (increasing θ with increasing distance). For $\theta < 0$, we inverted the distance for more intuitive displays. (A) Fitted values of linear models of θ for multiannual cycles vs. distance for each province. We fitted models separately for incoming and outgoing waves. Fitted values are only shown for provinces with a statistically significant model coefficient. We used a Bonferroni-corrected significance level ($P < 2e-4$) for each province but also, showed fitted values for models with significant coefficients at the 0.05 level (gray lines). The fitted values for the regional average model are shown as black lines. (B) The same as A but for annual cycles. (C) Provinces with statistically significant incoming (red) and outgoing (blue) waves of multiannual cycles. (D) The same as C but for annual cycles.

Wavelet Transforms. We used wavelet methods to decompose reported dengue IRs into multiannual and annual cycles as described previously (2, 8, 9, 30, 31). Wavelet transforms are appropriate to characterize nonstationary signals with multiple periodicities, such as dengue IRs (6). We used a Morlet wavelet with a nondimensional frequency $\omega_0 = 6$ as used previously (8, 30). This wavelet is complex, enabling the extraction of phase angles to study epidemic timing. We explored the influence of the selected value of ω_0 on synchrony in a sensitivity analysis and found that only extreme values influenced study results (Fig. S6). We found that most provinces had statistically significant annual cycles with a periodicity of 6–18 mo and statistically significant multiannual cycles with a periodicity of 19–60 mo (Fig. S7). We analyzed reconstructions of these cycles for provinces with statistically significant cycles in the annual or multiannual periodicity range.

Synchrony. We used pairwise Pearson correlation coefficients of multiannual and annual dengue cycles and unfiltered IRs between provinces to measure synchrony ρ . Pearson correlation indicates similarity in both timing and amplitude of epidemic cycles. We computed the average ρ for a province as the average across all province pairs that included that province weighted by the number of pairs with non-missing data. We computed this average using the entire time series of dengue cycles but also, for moving, overlapping 5-y time windows. We also computed the average wavelet coherency between province pairs in the annual and multiannual periodicity bands as described previously (7, 32) using parameter values for the wavelet transforms as described. Wavelet coherency (ranging from zero to one) describes the phase relationship between two time series localized in a time-periodicity spectrum. For strong wavelet coherency, statistically significant cycles of a specific periodicity need to be phase-locked (positively or negatively). We also used wavelet coherency to assess the association between multiannual dengue cycles and the ONI. The ONI identifies El Niño and La Niña events in the tropical Pacific based on sea surface temperature in the Niño 3.4 Region. To measure the dependency of synchrony on the average level of population density, temperature, and precipitation of province pairs, we used a multivariate linear regression with synchrony as the dependent variable and these covariates as independent variables.

Phase Angles. We used phase angle transforms of multiannual and annual cycles to study epidemic timing as described previously (2, 7, 31, 32). We expressed the pairwise phase difference θ between province pairs in months by assuming a 12-mo periodicity for annual cycles and 39-mo periodicity for multiannual cycles. We defined a traveling wave for a province as a

statistically significantly linear association between θ and geographical distances for that province vs. all others (Fig. S8). A negative θ indicated that a province epidemic cycle was timed later vs. others and that this province could have an incoming traveling wave. A positive θ indicated that a province was timed earlier and could have an outgoing wave. For each province, we tested the presence of “local” incoming traveling waves (decreasing θ with decreasing distance for $\theta < 0$) and local outgoing traveling waves (increasing θ with increasing distance for $\theta > 0$) using a linear regression model:

$$\theta_{p,q} = \begin{cases} C - \beta_p d_{p,q} & \text{for } \theta < 0, \text{ incoming waves} \\ C + \beta_p d_{p,q} & \text{for } \theta > 0, \text{ outgoing waves} \end{cases}$$

where $\theta_{p,q}$ is the lag time between provinces p and q for annual or multiannual cycles, and $d_{p,q}$ is the distance in kilometers between provinces. We inverted the sign of distance for negative lag times for more intuitive displays of incoming waves. We defined local as distances $\leq 1,000$ km (multiannual cycles) or $\leq 1,500$ km (annual cycles). Using a linear model of θ vs. distance including all province pairs, we found that, after these distances, θ did not continue to statistically significantly change with distance. We defined a statistically significant traveling wave as a positive β_p using a Bonferroni-corrected significance level of $2e-4$ for each province, resulting in a combined level of 0.05 across all provinces. We used a logistic regression to estimate the role of population size, temperature, and precipitation (independent variables) on the occurrence of traveling waves (dependent binary variable).

The entire analysis was conducted in the R Statistical Package, version 3.2.1.

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- Bhatt S, et al. (2013) The global distribution and burden of dengue. *Nature* 496(7446):504–507.
- Grenfell BT, Björnstad ON, Kappey J (2001) Travelling waves and spatial hierarchies in measles epidemics. *Nature* 414(6865):716–723.
- Viboud C, et al. (2006) Synchrony, waves, and spatial hierarchies in the spread of influenza. *Science* 312(5772):447–451.
- Rohani P, Earn DJ, Grenfell BT (1999) Opposite patterns of synchrony in sympatric disease metapopulations. *Science* 286(5441):968–971.
- Teurlai M, et al. (2012) Can human movements explain heterogeneous propagation of dengue fever in Cambodia? *PLoS Negl Trop Dis* 6(12):e1957.
- Cummings DAT, et al. (2004) Travelling waves in the occurrence of dengue haemorrhagic fever in Thailand. *Nature* 427(6972):344–347.
- Cazelles B, Chavez M, Magny GC, Guégan J-F, Hales S (2007) Time-dependent spectral analysis of epidemiological time-series with wavelets. *J R Soc Interface* 4(15):625–636.
- Choisy M, Rohani P (2012) Changing spatial epidemiology of pertussis in continental USA. *Proc Biol Sci* 279(1747):4574–4581.
- Thai KTD, et al. (2010) Dengue dynamics in Binh Thuan province, southern Vietnam: Periodicity, synchronicity and climate variability. *PLoS Negl Trop Dis* 4(7):e747.
- Cuong HQ, et al. (2011) Quantifying the emergence of dengue in Hanoi, Vietnam: 1998–2009. *PLoS Negl Trop Dis* 5(9):e1322.
- Magpantay FMG, Rohani P (2015) Dynamics of pertussis transmission in the United States. *Am J Epidemiol* 181(12):921–931.
- Gubler DJ (2004) Cities spawn epidemic dengue viruses. *Nat Med* 10(2):129–130.
- Johansson MA, Cummings DA, Glass GE (2009) Multiyear climate variability and dengue—El Niño southern oscillation, weather, and dengue incidence in Puerto Rico, Mexico, and Thailand: A longitudinal data analysis. *PLoS Med* 6(11):e1000168.
- Slingo JM, Annamalai H (2000) 1997: The El Niño of the century and the response of the Indian summer monsoon. *Mon Weather Rev* 128(6):1778–1797.
- Webster PJ, Palmer TN (1997) The past and the future of El Niño. *Nature* 390(12):562–564.
- Watts DM, Burke DS, Harrison BA, Whitmore RE, Nisalak A (1987) Effect of temperature on the vector efficiency of *Aedes aegypti* for dengue 2 virus. *Am J Trop Med Hyg* 36(1):143–152.
- Brady OJ, et al. (2014) Global temperature constraints on *Aedes aegypti* and *Ae. albopictus* persistence and competence for dengue virus transmission. *Parasit Vectors* 7:338.
- Salda LTD, et al. (2005) Molecular epidemiology of dengue 2 viruses in the Philippines: Genotype shift and local evolution. *Am J Trop Med Hyg* 73(4):796–802.
- Wesolowski A, O’Meara WP, Eagle N, Tatem AJ, Buckee CO (2015) Evaluating spatial interaction models for regional mobility in Sub-Saharan Africa. *PLoS Comput Biol* 11(7):e1004267.
- Colizza V, Barrat A, Barthélemy M, Vespignani A (2006) The role of the airline transportation network in the prediction and predictability of global epidemics. *Proc Natl Acad Sci USA* 103(7):2015–2020.
- Vu TTH, et al. (2010) Emergence of the Asian 1 genotype of dengue virus serotype 2 in viet nam: In vivo fitness advantage and lineage replacement in South-East Asia. *PLoS Negl Trop Dis* 4(7):e757.
- Holmes EC, Tio P-H, Perera D, Muhi J, Cardoso J (2009) Importation and co-circulation of multiple serotypes of dengue virus in Sarawak, Malaysia. *Virus Res* 143(1):1–5.
- Lee K-S, et al. (2012) Dengue virus surveillance in Singapore reveals high viral diversity through multiple introductions and in situ evolution. *Infect Genet Evol* 12(1):77–85.
- Hammon WM, Rudnick A, Sather GE (1960) Viruses associated with epidemic hemorrhagic fevers of the Philippines and Thailand. *Science* 131(3407):1102–1103.
- US Census Bureau (2014) *International Database*. Available at www.census.gov/population/international/data/idb/informationGateway.php. Accessed July 14, 2014.
- Fan Y, van den Dool H (2008) A global monthly land surface air temperature analysis for 1948–present. *J Geophys Res* 113(D1):D01103.
- Becker A, et al. (2013) A description of the global land-surface precipitation data products of the Global Precipitation Climatology Centre with sample applications including centennial (trend) analysis from 1901–present. *Earth Syst Sci Data* 5(1):71–99.
- Center for International Earth Science Information Network (CIESIN), Columbia University; Centro Internacional de Agricultura Tropical (CIAT) (2005) *Gridded Population of the World Version 3 (GPWv3)* [NASA Socioeconomic Data and Applications Center (SEDAC), Palisades, NY].
- GADM (2013) *Database of Global Administrative Areas*. Available at gadm.org/home. Accessed July 21, 2015.
- Torrence C, Compo GP (1998) A practical guide to wavelet analysis. *Bull Am Meteorol Soc* 79(1):61–78.
- Cazelles B, et al. (2008) Wavelet analysis of ecological time series. *Oecologia* 156(2):287–304.
- Grinsted A, Moore JC, Jevrejeva S (2004) Application of the cross wavelet transform and wavelet coherence to geophysical time series. *Nonlinear Process Geophys* 11(5/6):561–566.
- Björnstad ON, Falck W (2001) Nonparametric spatial covariance functions: Estimation and testing. *Environ Ecol Stat* 8(1):53–70.