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Assessing the role of multiple mechanisms increasing the age of dengue cases in Thailand

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The mean age of dengue hemorrhagic fever (DHF) cases increased considerably in Thailand from 8.1 to 24.3 y between 1981 and 2017 (mean annual increase of 0.45 y). Alternative proposed explanations for this trend, such as changes in surveillance practices, reduced mosquito–human contact, and shifts in population demographics, have different implications for global dengue epidemiology. To evaluate the contribution of each of these hypothesized mechanisms to the observed data, we developed 20 nested epidemiological models of dengue virus infection, allowing for variation over time in population demographics, infection hazards, and reporting rates. We also quantified the effect of removing or retaining each source of variation in simulations of the age trajectory. Shifts in the age structure of susceptibility explained 58% of the observed change in age. Adding heterogeneous reporting by age and reductions in per-serotype infection hazard to models with shifts in susceptibility explained an additional 42%. Reductions in infection hazards were mostly driven by changes in the number of infectious individuals at any time (another consequence of shifting age demographics) rather than changes in the transmissibility of individual infections. We conclude that the demographic transition drives the overwhelming majority of the observed change as it changes both the age structure of susceptibility and the number of infectious individuals. With the projected Thai population age structure, our results suggest a continuing increase in age of DHF cases, shifting the burden toward individuals with more comorbidity. These insights into dengue epidemiology may be relevant to many regions of the globe currently undergoing comparable changes in population demographics.

dengue epidemiology | Thailand | aging demography | force of infection | infectious disease

A shift of observed dengue cases to older individuals has been observed since the 1980s in Thailand (1, 2), moving the burden from mostly pediatric populations (mean age 8.1 y in 1981) toward adults (mean age 19.5 y in 2010 and 24.3 y in 2017) (Fig. 1). The increase was more pronounced in the later years. Serological studies (3, 4) suggest that an increase in age is seen in the timing of all infections and not only clinically apparent cases, consistent with a decline in the infection hazard, also known as force of infection (FoI). One plausible explanation for the FoI decline is the elevated indirect protection provided by immune individuals to those who are still susceptible to infection as life expectancy in the population increases (5). However, declines in mosquito populations or reductions in human contact with mosquitoes can lead to reductions in FoI as well. In addition to changes in the age at infection, changes in age-specific reporting and clinical presentation may also skew the age of reported cases.

Demographic transition of the human population in Thailand started in the 1800s (6). The life expectancy increased from 40 y pre-1910 to 75 y in 2015. By 2030, 15% of the population is projected to be >65 y. Demographic transitions change replenishment rates of susceptible individuals and the turnover of immunological memory. These changes have previously been shown to change the hazard of infection of dengue as well as other pathogens (5, 7, 8).

Concurrent with the demographic change was urban expansion. Urban infrastructures, such as piped water and waste management systems, reduce breeding sites of mosquitoes. Screens and air-conditioning associated with urban housing and changes in life activities can alter human–mosquito contact. Increases in human population size and/or density, with less than proportional increases in mosquito population sizes (possibly due to vector control) can lead to reductions in hazards of infection due to dilution of potentially infectious bites across the human population (9).

Significance

The age of reported dengue hemorrhagic fever (DHF) cases, the severe form of dengue infections, has been increasing in Thailand for four decades. Factors underlying this shift remain poorly understood, challenging public health planning. Here, we found aging of the population and its effect on the hazard of transmission to be the dominant contributors, with temporal changes in surveillance practices playing a lesser role. With ongoing population aging, we expect a continuing shift of DHF toward older individuals, heightening the chance of clinical complications with comorbidities. With most other highly endemic countries facing similar shifts in age structure, the pattern is expected to appear elsewhere. Awareness is needed to improve diagnosis and treatment.

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Competing interest statement: K.A. is part of the steering committee for Emergent Biosolutions' chikungunya vaccine development program. The remaining authors declare no potential conflict of interest.

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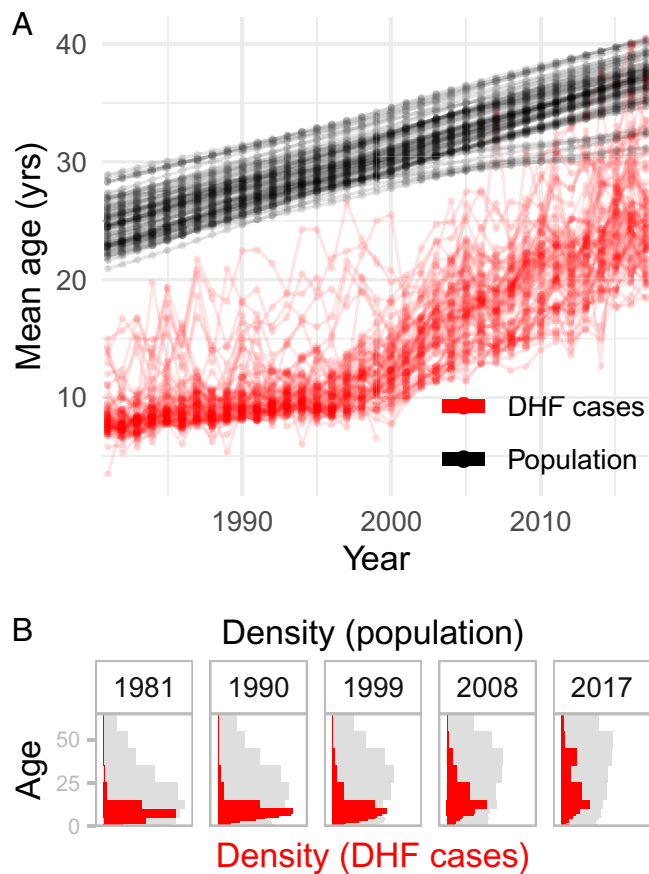


Fig. 1. The increase in the mean ages of (A) the population (black) and of reported cases with DHF (red) from 1981 to 2017 in the 72 provinces of Thailand calculated using midpoints of the age strata. (B) Country-level age distribution at 9-y intervals; the underlying population is in gray, and DHF cases are in red. Bin widths reflect the age strata reported for the cases at those times. *SI Appendix, Fig. S2* shows the age distribution of all years in the dataset.

The severe forms of dengue, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) (10), have been systematically reported in Thailand since 1972. All four serotypes of the virus (dengue virus 1 [DENV1] to DENV4) have circulated in Bangkok since at least 1962 (11, 12). Serotype-specific surveillance in other parts of Thailand is limited, but all four serotypes were detected in each region from 2005 to 2010, a period for which surveillance is available (2). As the age of infection increased, age-specific probabilities of illness upon infection (13–15) and reporting of illness may have contributed to changes in the age distribution of reported cases.

Infection by DENV is thought to provide long-lasting immunity against strains of the same serotype and short-lived protection against the remaining three serotypes (16). Upon second infections by heterotypic strains, serotype cross-reactive antibodies were shown to prime individuals for severe disease (17). The immunopathological effect was shown to increase with time between the infections (18). Temporal changes in FoI alter these waiting periods, possibly changing the clinical detectabilities of infections over time (19). This could bias the age distribution of the cases captured from second infections as well as third and fourth infections, which were contributing negligibly in the past (20).

We formulated a suite of nested models to test specific hypotheses about the contributions of these possible drivers. These models allow for temporal and age-specific variation in per-serotype

infection hazards, changes in reporting (both in time and age), and changes in the detectability (probability of symptoms) of all four possible infections over time (Fig. 2 and *SI Appendix, Table S2*). The five compartments group individuals by their number of infections acquired: zero to four. Individuals are at risk for each serotype at hazard $\bar{\tau}$. Infection by a serotype progresses individuals from one compartment to the next, where they become protected against their exposed serotypes but remain susceptible to the remaining serotypes (e.g., an individual who had acquired one infection is protected against one serotype and at risk for three serotypes would face a total infection hazard of $3\bar{\tau}$). Our formulation assumes that infections by all serotypes are equally likely and that infection by a serotype induces complete protection against homotypic strains but does not alter the risk of infection against heterotypic strains; hence, order of infection by different serotypes does not matter. The hazard is further scaled by age-specific modifiers to account for risk differences among ages. A fraction of infections becomes symptomatic with probabilities differing across susceptibility states. A portion of the symptomatic infections is captured by the surveillance system. FoI in the population can be derived by averaging the per-serotype infection hazard experienced across all individuals present at a given time.

Testing the suite of nested models against the provincial age-stratified DHF case counts in Thailand (1981 to 2017), we determined which combination of the hypothesized drivers best explains the observed data. We then compared the magnitude of age shift with or without changes in these parameters through simulations to quantify their attributable contributions over time. The drivers of the observed age shift unveiled by this study will help forecast the timescale over which the shift will continue and what role these phenomena might have in the epidemiology of dengue in other settings.

Results

Model Performance Supports Age- and Time-Varying Parameters. The per-province estimates we obtained were evaluated by their expected log predictive density (ELPD), a metric that approximates a leave-one-out cross-validation. Nonoverlapping 95% CIs indicate significant performance differences. The four models with the greatest complexity, which included temporal changes in per-serotype infection hazards $\bar{\tau}(t)$, an age-specific modifier for infection hazards $\kappa(a)$, and temporal and age-specific variations in reporting rates represented in various forms, were the most predictive in 66 of 72 provinces. Of these four models, the variant with clinical detectability $Q(i, t)$ changing over time and reporting variations in age and time being orthogonal, $\phi(t) \times \phi(a)$, had performance equivalent to or greater than the other three models in all 72 provinces (*SI Appendix, Fig. S4*). The greatest number of ties (32 provinces) was with the same combinations (infection hazards varying in age, reporting in age and time varying orthogonally) but without temporally changing clinical detectability. Estimates from both models were highly congruent (*SI Appendix, Fig. S5*). These model comparison results and more detailed comparisons in *SI Appendix, Supplementary Model Evaluations* suggest that reporting differences in age did not substantially change over time. We, therefore, chose to use estimates from the model with variation in infection hazard and reporting, both in time and age, and with temporal changes in clinical detectability but without temporal changes in age-specific reporting for all subsequent analyses.

Patterns in the Estimates. As expected given the shared climate and health system among many factors, estimates of all parameters

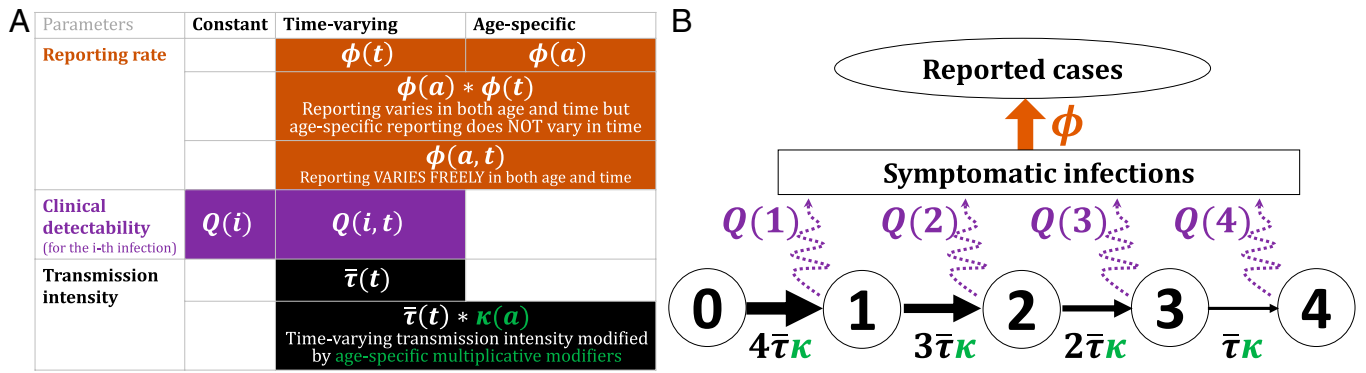


Fig. 2. Hypotheses of factors driving the age increase of DHF cases encoded into (A) model parameters. (B) Diagrammatic representation of the model. Model parameters are grouped according to the hypothesized drivers of changes in age: changes in reporting rate (brown), clinical detectability (purple), and transmission intensity (black and green).

from the selected model were in general positively correlated between the provinces, despite being independently estimated: median pairwise correlations of 0.65 and 0.80 in the temporal and age-specific infection hazard variations, respectively, and

0.49 (temporal) and 0.79 (age specific) in reporting efficiencies (Fig. 3 and *SI Appendix*, Fig. S14). Correlations in estimates of time-varying infection intensity showed notable decay as distance between province pairs decreased but remained above 0.5 even

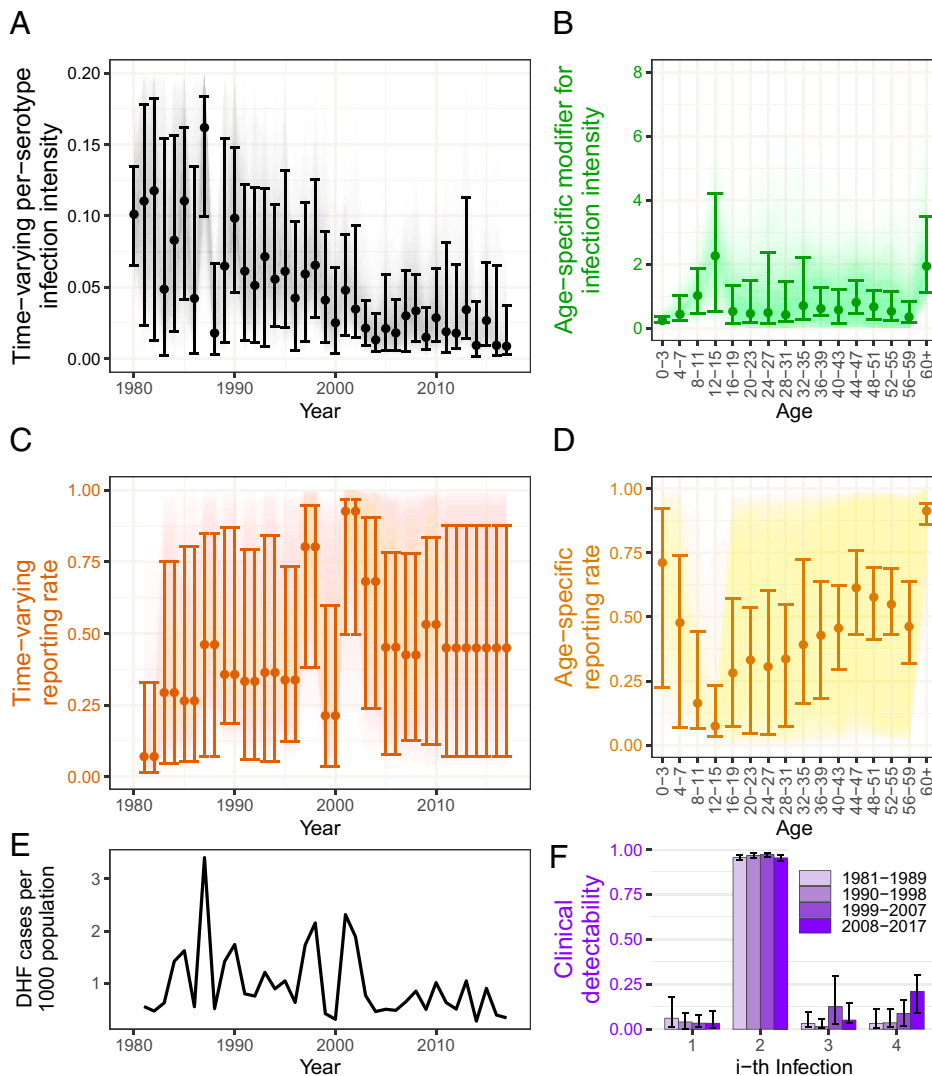


Fig. 3. Parameter estimates of the country-wide best-fitting model. The model includes (A) time-varying per-serotype infection hazards, $\bar{\tau}(t)$; (B) age-specific multiplicative modifiers for infection hazards, $\kappa(a)$; (C) time-varying reporting rates, $\phi(t)$; (D) age-specific reporting rates, $\phi(a)$; and (F) time-varying clinical detectability of infections $Q(i, t)$ shown in colors matching the model diagram in Fig. 2B. Shades represent provincial 95% credible intervals, points are medians of provincial medians, and whiskers are 95% IQRs of the medians. The piecewise constant time-varying reporting rates are shown in repeats across the ranges within their bins. The estimates are compared against (E) the time series of reported country-level DHF case counts per 1,000 population.

for pairs of provinces farthest apart (~1,500 km). The decay was modest for other parameters. Integrated over the uncertainties of all other parameters, reporting was nonuniform in both time and age.

Reporting generally increased over time, although spikes were observed in 1997 to 1998 and in 2001 to 2002, years with large increases in dengue throughout the country. Reporting rates by age were high in the early years of life and declined to a trough (country-level median of 0.07; 95% interquartile range [IQR]: 0.04 to 0.23) at age 12 to 15, after which the rate could only be estimated with low precision within provinces, but their averages across provinces consistently suggest a gradual increase. By age 50, the reporting was 1.8-fold that of age 20.

In terms of infection, the per-serotype hazards declined over time. The nonuniform estimates of age-specific modifiers for infection hazards suggested that the infection risks were structured by age. A peak was seen at ages 12 to 15 (2.4 times the hazard at ages 8 to 11), an inverse of what was seen in the age-specific reporting efficiencies. The hazard heightened again after age 60.

Events Shifting Age of Cases. To quantify the effects of variations in infection intensity and reporting in age and time, we reconstructed the infection histories in the population through simulations using point estimates of the parameters. From the reconstruction, mean age of reported DHF cases increased 0.48 y annually overall with two apparent epochs (Fig. 4A): per year increases of 0.20 (95% CI: 0.18 to 0.23) prior to 2000 and 0.70 (95% CI: 0.66 to 0.73) thereafter. To quantify the contributions that variations in each model component had on the observed age shift, we simulated the age-specific case counts where each of the variations was replaced, in turn, by its mean value. When only variations in the demographic structure were present (Fig. 4B), the mean age increased by 0.28 y per year (95% CI: 0.27 to 0.28), 58% of the actual inferred increase. We performed a simulation study to illustrate how demographic structure alone, without changes in per-serotype

infection intensity, could lead to increased mean age of cases (*SI Appendix, Supplementary Mechanistic Simulation and Fig. S15D*).

We contrasted the mean age simulated with each of the components solely changing against when none were changing (Fig. 4D). Age-specific modifiers for infection hazards slightly decreased the mean age of reported DHF cases (95% CI: 0.06 to 0.07) per year. Temporal changes in per-serotype infection hazards annually decreased the mean age in the early years by 0.09 (95% CI: 0.09 to 0.10) but led to annual increases of 0.19 (95% CI: 0.19 to 0.20) in the later years (2000 to 2017). Age-specific reporting differences alone led to a modest increase of 0.06 to 0.08 y annually. Time-varying reporting efficiencies equally scaled the case counts across all ages in the year, leaving no effect on age.

We further investigated reciprocal setups where changes were removed from each component and contrasted that against when they were all changing (Fig. 4C). Only reciprocal simulations of temporal per-serotype infection hazard inverted the relative trends. In the presence of all changes but age-specific modifiers for infection hazards, the relatively lower increase was still observed. The presence of changes in all other components except age-specific reporting rates only inverted the subtle relative incline observed when it was present alone to a subtle decline in the early periods. From 2000 on, it led to mean age increases that were lower (0.32 per year; 95% CI: 0.30 to 0.34) than when all changes were allowed. Including temporal changes in per-serotype infection intensity and variations in age-specific reporting recovered the remaining 42% of age increase unexplained by demography alone.

Trends in Susceptibility, Infections, and FoI. Although we have estimated temporal per-serotype infection intensities, individuals in the population experience differing infection hazards depending on their susceptibility status and age. To derive the FoI experienced by the population overall, we first reconstructed the time series of end of year susceptibility statuses from point estimates of the annual parameters. Seronaive proportions increased, while

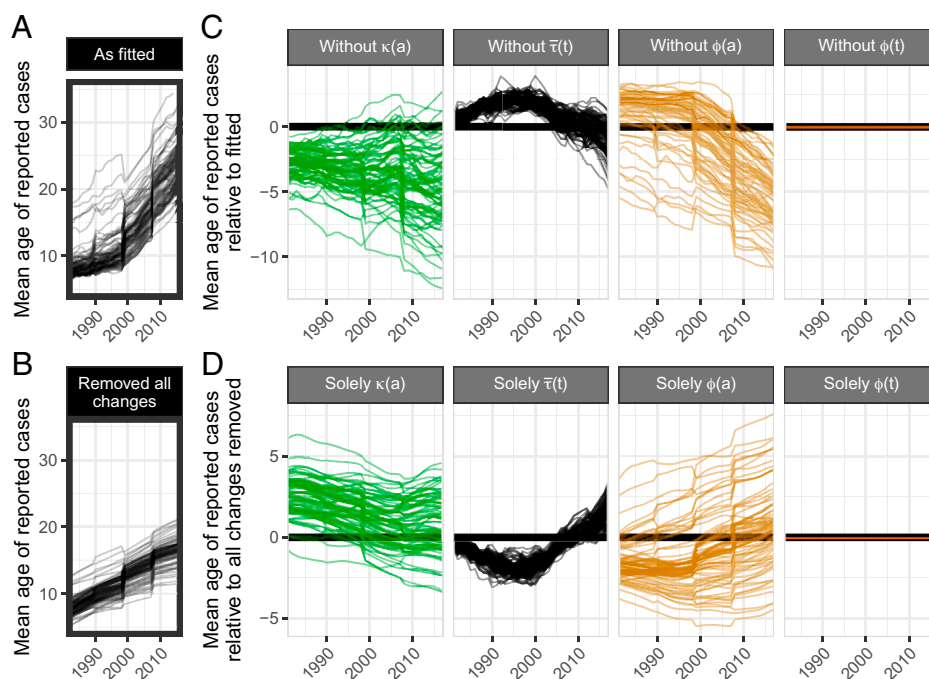


Fig. 4. Provincial mean age of simulated cases when (A) parameters were kept as fitted and when (B) all variations, whether in age or time, were removed. (C) The mean age difference between when variations in each of the component estimates were removed (by replacing with its mean) relative to when all variations were retained as fitted. (D) The mean age difference between when only a single component retains variations relative to when variations in all components were removed.

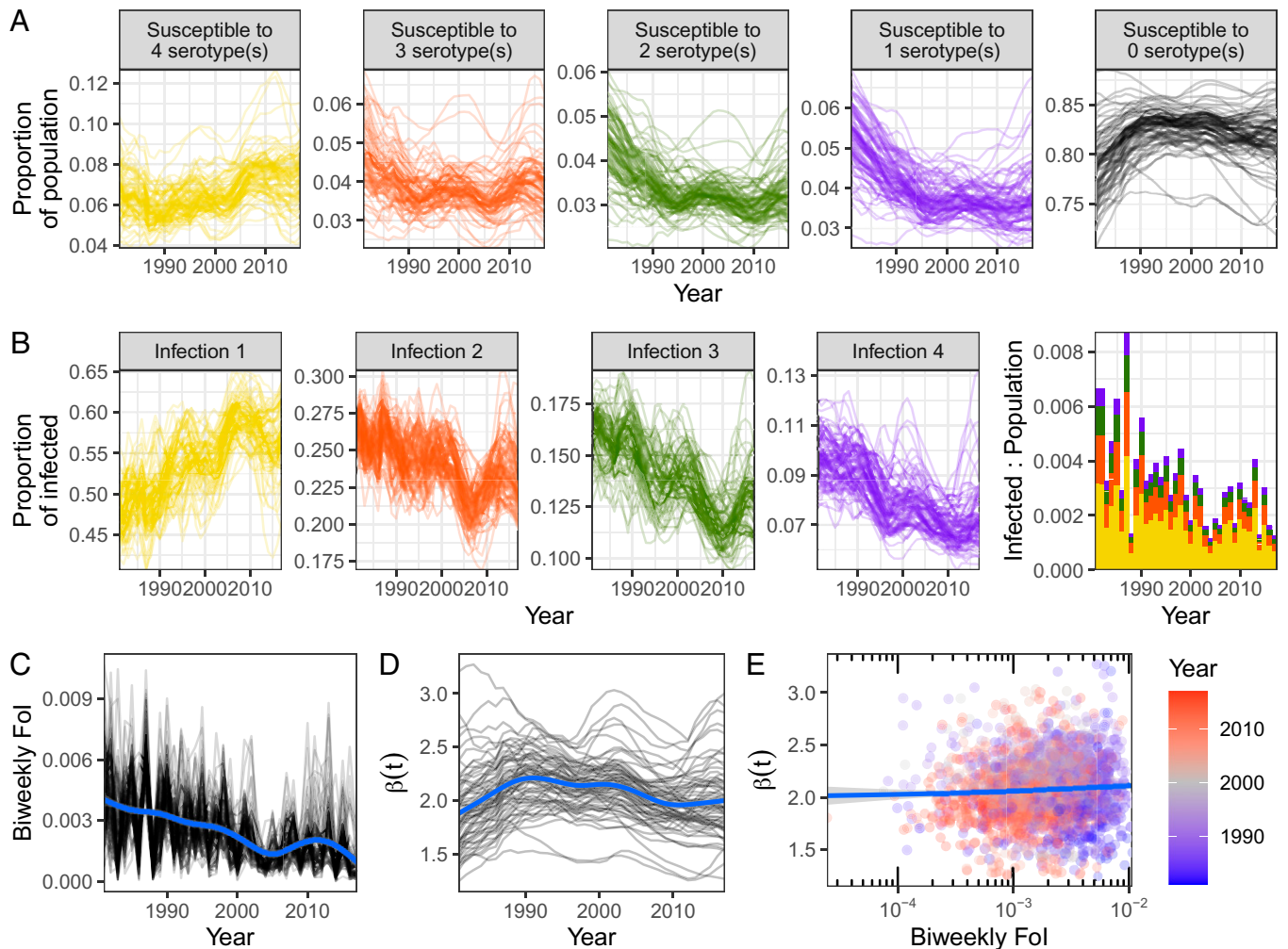


Fig. 5. Biweekly infection histories in the Thai population. (A) Biweekly time series of population susceptibility reconstructed from fitted provincial infection hazards. (B) Proportions of total dengue infections at each point in time that were first, second, third, and fourth infections and the infectious fraction in the population. (C) Biweekly FoI of DENV calculated by averaging age-specific FoI over all individuals in the population accounting for their susceptibility status. (D) Biweekly transmission efficiencies calculated from the FoI and infectious fractions. (E) Relationship between transmission efficiencies and FoI (log scaled).

proportions of individuals who had acquired at least one infection declined (Fig. 5A). Proportions of infections that were first infections tapered around 2009 with the rise of second infections (Fig. 5B). Third and fourth infections exhibited downward trends in their contributions. All infections combined, the decline in infectious proportion in the population seen up to 2004 (Fig. 5B) was observed in 71 of 72 provinces.

Biweekly infection hazards (annual hazards divided by 26) faced by individuals were averaged to reconstruct the biweekly FoI in the population (Fig. 5C and *SI Appendix, Fig. S16*). The FoI fluctuated around a trend that declined until 2005 (median reduction of 0.003 per year across provinces; 95% IQR: 0.001 to 0.004) and flattened thereafter.

Drivers of Changes in FoI. We further sought to describe contributions of processes leading to the changes in FoI. In frequency-dependent transmission models, which reflect the vector availability–limited nature of DENV transmissions (21), the FoI is a product of the transmission efficiency β and the infectious proportion I . With the reconstructed $I(t)$, we solved for the biweekly $\beta(t)$ throughout the study period (Fig. 5D). Linearly regressing values on time, we characterize changes per year as follows. Up to 1990, $\beta(t)$ was increasing countrywide (95% CI: 0.03 to 0.05 each year); 83% of provinces were increasing, 7% were decreasing, and 10% remained unchanged.

Post-1990, 74% of provinces showed significant declines (95% CI: 0.01 to 0.01 countrywide). Averaged over all study years, provinces showed -1.8% (95% IQR: -40.2 to 24.3%) change in $\beta(t)$, which accounted for 2.8% (95% IQR: -51.1 to 55.0%) of the -72.2% (95% IQR: -90.1 to -32.8%) change in FoI (Fig. 5E), while changes in $I(t)$ due to changing population demography accounted for the remainder. Spatial distribution of these changes is shown in *SI Appendix, Fig. S17*. *SI Appendix, Fig. S15B* illustrates how changes in demography in a theoretical population can mechanistically reduce FoI in the absence of changes in $\beta(t)$.

Discussion

We compared the performance of a suite of nested models and found that models that included variation in infection hazards in time and reporting rates that varied in time and age were most consistent with the observed data. Simulating the age-specific reported case counts with different sets of these changes removed revealed that the observed age shift in reported DHF cases in Thailand between 1981 and 2017 could be primarily attributed to the shifting age demography of the population, especially in the early years, followed by the synergistic contributions of declining per-serotype infection hazards in time and the higher reporting rates among older individuals (>60 y). Using infection histories

inferred through the estimates generated by this model, we further derived the provincial FoI time series and found them to be declining country wide at least up until 2005. The decline was primarily attributable to reductions in infections due to changes in host demography, while there were minor (-2.8%) changes in transmission efficiency.

As in other studies (22, 23), we found that second infections were most associated with DHF at all times. Third and fourth infections were more likely to be associated with DHF than first infections. Our results supported changes in clinical detectability of third and fourth infections over time but not first and second infections. We propose three hypotheses driving this change. First, the postponed infections were correlated with greater comorbidities in older age categories. Although this should have been absorbed by age-specific reporting rates in our models, there may remain effects that were dependent on the immunological status of individuals. Second, effects of immunopathogenesis may be exacerbated by longer waiting times between infections. Third, DENV may have evolved sufficiently to escape cross-protection against disease conferred by multiheterotypic immunity.

Age-specific reporting rates were estimated to be higher in older individuals (>60) than other age groups in all provinces, irrespective of time. The high consistency in these independent estimates implies the existence of common influencing factors. Older individuals are associated with more comorbidities, making infections at later ages more severe/detectable (14). Care-seeking tendencies may also be higher in this age class.

Another interesting pattern that emerged from independent estimates across provinces is high infection hazards in individuals aged 12 to 15. This is coupled with low reporting rates for that same age band. This consistent signal across provinces may reflect common age-dependent risks of exposure [e.g., schooling and changes in contact network patterns with age (24)] and/or heightened susceptibility to infection following their first infection (22, 23), as well as other behavioral or physiological changes. The lower reporting rate may have resulted from care-seeking behaviors and/or disease severity. Both infection hazard and reporting rate were estimated to be high at ages over 60. Increased hours spent around homes by older individuals may increase their risk of infection as female *Aedes aegypti* with blood meals were more frequently found indoors than outdoors (25). Immune senescence (26) may also be associated with increased risk.

In attempting to delineate the contributions of factors driving the observed age shift, we found that shifts in the age distribution of susceptibility alone, even without variations in per-serotype infection hazard and reporting, were able to explain 58% of the continuing age increase of DHF cases (0.28 of the 0.48-y annual increase). In fact, they explained all of the increases prior to year 2000. The shift was later exacerbated by delayed occurrence of infections in life and higher reporting tendencies in older individuals. With more partially/fully immune individuals against the four dengue serotypes sustained in the population, the average infection hazard in the population would still be reduced.

Consistent with serological studies (3, 4), we found both per-serotype $[\bar{\tau}(t)]$ and overall infection hazards (FoI) to be declining up to 2005 before plateauing, although neither contributed to the age increase of DHF cases in the early period. Paradoxically, the presence of temporal changes in $\bar{\tau}(t)$ (and demographic structure) but nothing else led to a less prominent increase in this early period than without (Fig. 4D). This contradicts the expectations from simulations where declines in $\bar{\tau}(t)$ were coupled with age increases of cases (SI Appendix, Fig. S15B). Summing the isolated effects of age-varying reporting rates and age-structured infection hazard was insufficient to offset this discrepancy. These findings

imply that the effects were synergistic and cannot be considered in isolation.

In this study, we sought to explain drivers of the age shift where we found the reduction in infection hazard to be part of it, particularly in the later years where the age increase accelerated. Our findings that changes in transmission efficiencies during the study period were variable across provinces, tending the average change toward zero (despite a vast amount of environmental, socioeconomic, and vector control changes over the study period), left most of the reduction in FoI attributable to the decline in infectious proportions. The finding is less consistent with nonimmune-mediated factors, such as reduced mosquito densities and development of housing, and more consistent with elevated shielding of susceptible individuals by immune individuals due to the longer life expectancy. Other immune-mediated factors may include the roles of cross-reactive immunity due to infection by other *Flaviviruses* [such as Zika (27) or Japanese encephalitis (JE)] or due to vaccination [JE (28)]. Regardless of whether these influences exist/persist, with the projected population age structure in Thailand, our theoretical simulations suggest that the age of DHF cases will continue to increase until birth rates of the Thai population reach a new equilibrium (SI Appendix, Fig. S15D). This shift of infections toward older individuals with more prevalence of comorbidities will likely complicate the clinical management of dengue cases (29).

We found consistent trends among provinces, despite parameters being estimated independently. The strength of the evidence can be reduced with spatial dependence between provinces, a correlation structure not accounted for in our analyses. Nonetheless, modest decay in correlation between estimates of all parameters across space [except for temporal infection intensity, which is known to be spatially focal for dengue (30)] suggests limited effects of spatial dependence on our inferences. Our models were formulated to capture effects of factors varying over age or time, modulating either rates at which individuals acquire infections or the detection/reporting of infections. Correlation among coefficients not included in our models may reduce the precision of our parameter estimates.

The predominant and long-standing effect of demographic transition on increases in mean age has implications beyond Thailand. Aging populations are a global phenomenon first experienced in Europe and Japan (31). Africa, Asia, and Latin America, all of which are hyperendemic areas for dengue, are still in a period of transition (32). As such, we anticipate similar observations to emerge in other regions. Awareness of these changes is necessary for clinical preparedness. Further, the declining FoI implies that the timing of infections becomes less synchronous within each birth cohort. This asynchrony could lead to lower predictability of immune status by age and higher variability in the history of strain-specific exposure of individual cohorts. This may, in turn, change the selection landscape and may have implications for vaccines.

Materials and Methods

Data. Dengue has been a notifiable illness in the national surveillance system of Thailand since 1972. Provincial age-stratified case counts are given annually through aggregation of dengue case counts reported to health facilities within its boundaries. Data in 1981 to 2005 were digitized with double data entry for a previous study (5). Data for 2003 to 2017, split by severity, are publicly available from the Department of Disease Control, Thai Ministry of Public Health website (33). The severity levels include dengue fever, DHF, and DSS as per the World Health Organization 1997 guidelines (34). DHF counts were used in this study to maintain consistency across time.

Population age censuses for 1994 to 2017 were acquired from the Department of Provincial Administration, Ministry of the Interior through the Official Statistics Registration Systems (35). The censuses of 1980, 1990, and 2000, taken from the same system, were available from archived data of the previous study (5). Populations in the noncensus years were interpolated using fitted birth cohort population trajectories from census years.

During the study period from 1981 to 2017, 4 of the 72 provinces were segregated, resulting in 76 provinces in later years for both datasets. To account for the segregation, case counts and census data of the segregated provinces were combined to form the original provinces.

Model Parameters and Their Estimation. Following the approach of a previous study (5), $\tau_x(t)$ represents the infection hazard of serotype x in the province at time t . Because case counts in the Thai national surveillance dataset are not serotype specific, only the average hazard of the four cocirculating serotypes at time t could be estimated, denoted $\bar{\tau}(t)$. To capture possible variability of infection hazard by age a , $\bar{\tau}(a, t)$ was estimated as the product of the age-specific time-invariant modifiers $\kappa(a)$ and $\bar{\tau}(t)$ (i.e., the hazards experienced are scaled by age-specific constants). Here, we extend the previous model by allowing the reporting rate, ϕ , to be time varying, $\phi(t)$; age varying, $\phi(a)$; or both. The variations in both time and age were estimated to be either the product of their independent variations $\phi(t) \times \phi(a)$ or freely variable across those two dimensions, $\phi(a, t)$. Furthermore, the observed cases were not presumed to be the result of individuals' second dengue infections. Clinical detectability of the i th infection $Q(i)$, taking values between zero and one, was estimated for the four infection indices $i \in \{1, 2, 3, 4\}$. These fractions aimed to capture the biological symptomatic and care-seeking tendencies of the infections. To assess whether $Q(i)$ was time varying, $Q(i, t)$ was alternatively estimated to be piecewise constant in time. Combining the three model components yielded 20 nested models (SI Appendix, Fig. S3). Parameters $\kappa(a)$, $\phi(t)$, and $\phi(a)$ were each estimated as 16 piecewise constant intervals to keep models utilizing different components comparable. Each $Q(i, t)$ was estimated for four time intervals (16 free parameters). To keep the degrees of freedom df the same as the $\phi(t) \times \phi(a)$ variation, $\phi(a, t)$ was estimated for four time intervals and eight age intervals (32 free parameters). Mathematical formulations of the models and the fitting procedures are detailed in SI Appendix, Supplementary Methods.

Model parameters were estimated from the data of each province using Rstan v2.21.2 (36) with three independent chains, each of length 15,000 (3,000 discarded as warm-up). Posteriors of all chains combined were considered converged when $\hat{R} < 1.1$ and effective sample size > 300 for all parameters. Goodness of fits to the annual age-stratified DHF counts were compared through their ELPD computed from approximate leave-one-out cross-validation by the R package loo (37). Nonoverlapping 95% CIs of the ELPDs (calculated as ± 2 SE from the mean) indicate significant superiority of the model with higher ELPD in predicting unobserved data. Models with ELPD superior to all other models

constitute the best-fitting models of each province. The country-wide best-fitting model was then determined by identifying the model that received the highest sum of votes from provinces (inverse weighted by the number of ties if multiple models performed equivalently). We also evaluated the negative log likelihood, the Bayesian information criterion, and the root-mean-squared error of the case counts in SI Appendix, Supplementary Model Evaluations.

Reconstructing Infection and Transmission Histories. Fractions of individuals in each birth cohort who had experienced i infections ($i \in \{0, 1, 2, 3, 4\}$) at the end of each year were calculated from the estimated infection hazards. These piecewise constant infection hazards reflect the averages within each year. As serial intervals of dengue are approximately 2 wk (38, 39), we converted the estimates to the scale of biweeks by dividing by 26. Biweekly Fols $\lambda(t)$ in the population were computed as weighted averages of hazards across ages and the number of infections that individuals had experienced. The frequency-dependent transmission efficiencies $\beta(t)$ were derived by solving the equation $\lambda(t) = \beta(t) I(t)$, where $I(t)$ is the fraction of individuals who were infectious at time t . Average rates of changes over time for these quantities were summarized by linearly regressing each of the quantities on the year using the glm function in R. Rates were considered increasing/decreasing when the 95% CI of the slope estimates excluded zero.

Data Availability. Data and code for all analyses have been deposited in Zenodo (40).

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