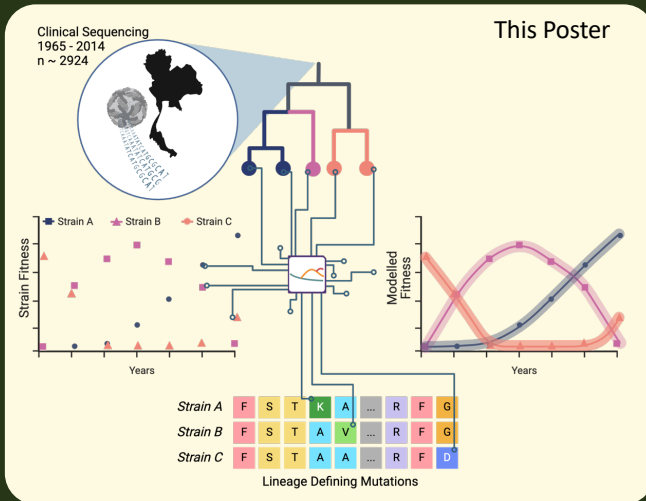


Phylogenetic Fitness Comparisons of Co-circulating Dengue Strains in Thailand (1965-2014)

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Graphical Abstract



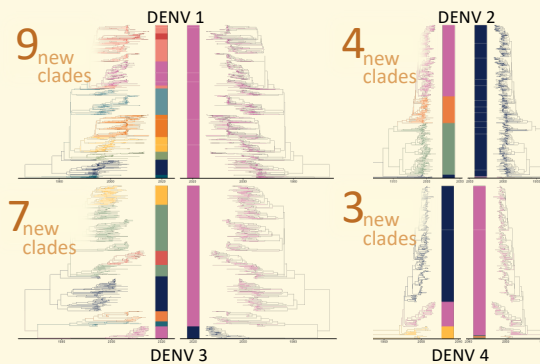
Abstract

- Understanding the drivers of dengue co-circulation is limited by reliance on crude genotype definitions and scant longitudinal sequencing data
- Objective: To characterize DENV lineage dynamics and fitness evolution using a novel phylogenetic framework and a dense, longitudinal dataset from Thailand (n = 2,924 sequences, 1965–2014)
- Developed a phylogenetic model¹ that quantifies fitness at individual tree nodes and identifies lineages based on fitness rather than predefined genotypes.
- Applied this model across DENV serotypes to redefine lineages and assess their relative fitness over time using logistic growth modeling.
- Identified new (and more) fitness-based lineages for DENV1–4. Contrast to few genotypes currently recognized.
- Fitness estimates accurately tracked lineage dynamics
 - Major outbreak years (e.g., 2001–2002 for DENV3, 2005 for DENV4) were associated with shifts in lineage fitness.
- Several lineage-defining nucleotide mutations were identified across all serotypes

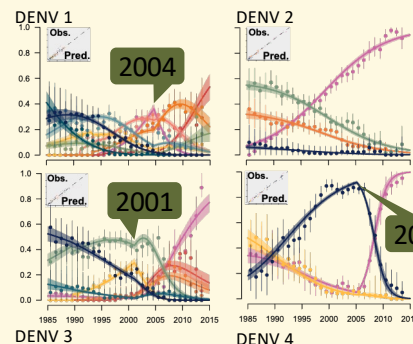
Local Dengue Fitness Dynamics Can Be Modelled & Associated with Key Mutations

- We model fitness dynamics more extensively than previously
- Lineage definitions can inform genotype determinations
- DENV fitness can be modeled and used to detect emerging, fitter lineages in rapid response to an outbreak.
- Future work: explore mechanisms of identified fitness-enhancing mutations

1 Novel Fitness-Based Lineages Identified



2 Model Dynamics Match Suggest Fitness Change-Points in Key Epidemic Years



3 Lineage Defining Mutations Overlap With Prior Research (Only E shown)



Mechanistic Insights:

- D1: I|114|L
 - Internal B-sheet to coil²
- D2 G|228|E & T|226|K
 - Enhances Infectivity in Mosquitos³
- D4: S|227|L
 - Mut. active surface near prM⁴
- D3: S|124|L
 - Thermal Stability defining position⁵
- D3: H|132|Y
 - Implicated in D2 Ab Cross-reactivity⁶



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DAF is a PhD candidate in the NIH Oxford-Cambridge Scholars Program. This work was supported by the Intramural Research Program of NIAID and the ITCCH funding program.