Title of dissertation				
Genetic Analysis of Dengue Virus in Severe and Non-Severe Cases in Dhaka, Bangladesh, in 2018–2022				
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Dengue virus (DENV) infection is characterized by a wide clinical spectrum, ranging from asymptomatic or mild febrile illness to life-threatening severe disease manifestations. The unpredictable outcomes of infection are influenced by a variety of factors, including host immunity, viral virulence, and importantly, the genetic diversity of circulating dengue virus strains. Previous studies have suggested that replacement of DENV serotypes and genotypes in a given region may contribute to shifts in disease severity and the magnitude of outbreaks. To investigate this association in Bangladesh, we conducted a study at Evercare Hospital Dhaka (previously Apollo Hospital Dhaka) between 2018 and 2022, with the aim of describing the clinical characteristics of patients alongside the genetic diversity of circulating DENV strains.

A total of 3759 patients were evaluated for DENV from 2018 to 2022 at our hospital and 839 cases were identified as dengue positive. Samples with a dengue PCR Ct value <34 were used for the serotype determination study. Out of a total of 674 positive dengue cases, 495 serotype positive cases were identified. We performed sequencing of the dengue virus envelope region for a total of 179 cases in five consecutive years. The temporal distribution of serotypes revealed dynamic changes in DENV circulation over the study period. While DENV2 predominated in 2017 and 2018, a clear shift occurred in 2019 with DENV3 emerging as the dominant serotype. From 2019 through 2022, DENV3 remained the only serotype detected, suggesting near-complete replacement of other serotypes in the population.

Analysis of DENV2 sequences from 2017 showed co-circulation of clades B and C of the cosmopolitan genotype. However, by 2018 only clade C viruses were found, and shortly thereafter, all DENV2 strains disappeared from circulation. In contrast, DENV3 genotype I was first introduced into Bangladesh in 2017 and gradually expanded its presence. By 2019, DENV3 genotype I had become the exclusive circulating lineage and continued to dominate until 2022.

This viral turnover coincided with notable epidemiological consequences. Severe cases were commonly associated with fever, pleural effusion, breathing difficulty, thrombocytopenia, hemoconcentration, hypoalbuminemia, and elevated liver enzymes, consistent with dengue-related complications reported elsewhere. In 2019, Bangladesh experienced an exceptionally large dengue outbreak accompanied by a surge in severe cases. Our data showed that the high incidence of severe disease corresponded with the period when DENV3 genotype I became the sole circulating strain. Phylogenetic analysis further revealed that severe cases were not confined to a single lineage but were distributed across several different

subclades of DENV3 genotype I, indicating that severe disease was linked to multiple independent viral clusters rather than a single highly virulent variant.

Taken together, our findings demonstrate that shifts in both serotype and genotype circulation were closely associated with patterns of dengue outbreaks and disease severity in Bangladesh. The replacement of DENV2 by DENV3, and the sustained dominance of DENV3 genotype I from 2019 to 2022, provide a plausible explanation for the heightened disease burden observed during this period. Our study highlights the importance of continuous molecular surveillance of DENV to better predict outbreak dynamics and to understand the virological drivers underlying severe dengue epidemics. These findings underscore the importance of timely monitoring of serotype and genotype changes to anticipate outbreak severity, improve preparedness, and guide public health responses. Whole-genome sequencing will be essential in future studies to identify viral determinants of pathogenicity and the drivers of large-scale transmission of DENV3 in Bangladesh.

Photos

With Professor Tatsuo Shioda and Associate Professor Emi E. Nakayama at The University of Osaka

Presenting the summary of my research at The University of Osaka