**Title:** Epidemiology and outcomes of patients hospitalized with Dengue: Protocol for a prospective public health surveillance study

**Study investigators**

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**Background:**

The WHO estimates that 390 million dengue infections occur annually with close to 100 million clinical infections. (1,2) 70% of this burden is in Asia. In the Critical Care Asia Africa (CCAA) registry network, (3) there have been 2700 dengue admissions from January 2019 to May 2023 with an ICU mortality of 10% (unpublished data- personal communication). Despite this burden, care is supportive and based on expert opinion, and very little progress has been made in terms of therapeutics. There is an urgent need for trials evaluating a spectrum of interventions, from supportive care (type and volume of fluids, blood transfusions) to specific therapeutics (antivirals and immunomodulators). Because of the burden of disease and ease of diagnosis in most settings, dengue is a suitable disease to be studied in a platform trial.

An essential prerequisite to launching such a trial is a comprehensive understanding of Dengue clinical epidemiology in the hospital. While there are several cohort studies that describe outcomes from severe Dengue, they are often single center or single-country studies with few patients (4,5) and do not provide a comprehensive overview, in a range of settings where a future trial might be conducted, of the clinical presentation, illness severity, biochemical and hematological abnormalities, viral serotype, treatments received and outcomes. In addition, the information collected is not harmonized across studies, precluding meta-analytic estimates. It is also important to note that the epidemiology of dengue itself is changing (6,7) and there is thus a need for an understanding of disease evolution. This understanding is essential to plan future interventional trials, which will need data on outcomes for sample size calculations, prioritization of interventions, the diversity of standards of care, identification of biomarkers for predictive or prognostic enrollment, and resources used to care for these patients. In addition, the information accruing from an international collaboration will shine the spotlight on the burden of Dengue in these countries to the respective Ministries of Health and other public health organizations.

**Research questions:**

1. For patients hospitalized with Dengue, what are the patterns of clinical presentation, illness severity, treatments received, and outcomes?
2. What are the patient and treatment-related predictors of hospital mortality for the cohort of severe dengue patients admitted to ICUs?

**Objectives:**

1. To describe the clinical presentation, demographics, including socio-economic determinants, illness severity, biochemical and hematological abnormalities, treatments received (fluids, vasopressors, organ support strategies, antiviral and anti-inflammatory medications) and outcomes for all dengue patients admitted to participating hospitals and ICUs over a 6-month period.
2. To evaluate treatment-related predictors of mortality for the cohort of severe dengue patients admitted to ICUs using modern causal inference approaches.

**Methods and Measurements:**

Study design: Prospective public health surveillance protocol

Inclusion criteria: Patients diagnosed with suspected or confirmed dengue (based on laboratory confirmation or per WHO or respective Ministry of Health diagnostic criteria). and admitted to a participating hospital.

Exclusion criteria: The only exclusion criteria would be lack of informed consent in jurisdictions that mandate the need for consent.

The study will be conducted across hospitals and ICUs that are part of the Critical Care Asia Africa (CCAA) and the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) networks. We have developed a standardized case report form (CRF) for dengue along the lines of the COVID-19 CRF designed by ISARIC.(8) (appendix) Participation will be open to all research centres with interest and capacity to participate, including but not limited to any hospital that is part of a related network (e.g., Drugs for Neglected disease initiative [DNDi], the Brazilian Research in Intensive Care Network [BRICNET]). The standardized CRF is openly available for use by any site collecting data on Dengue.

The CRF has domains related to demographics, clinical presentation, illness severity, laboratory parameters, treatments received and outcomes. Multiple versions of the CRF with varying amounts of data collection (i.e., core CRF and extended CRF) will be made available to participating sites.

Outcome measures:

Our aim is to describe the clinical presentation (duration of illness, symptoms), demographics including socio-economic determinants, co-morbidities, illness severity (clinical, biochemical, laboratory, need for organ support), treatments received (IV fluids [type, volume, duration], blood and blood product transfusions, organ support provided during hospital stay, experimental therapies [corticosteroids, plasma exchange, IV immunoglobulins etc.], and outcomes [survival, ICU and hospital length of stay). Where feasible, we will also collect information on viral serotype/genotype. We will also evaluate treatment-related predictors of survival for the cohort of severe dengue patients using modern causal inference methods such as target trial emulation with a specific focus on steroids, plasma exchange and IVIg.

The data from this study will inform the design of an adaptive multicenter platform trial evaluating a range of interventions for dengue and severe dengue.

Workflow:

To address our objectives, we have developed a standardized case report form (CRF) in collaboration with the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC). The CRF has already been pilot tested at sites in Vietnam, India and Pakistan. At sites contributing to registries such as the Critical Care Asia network, the CRF has been embedded onto the registry platform. Sites that are not part of registries can collect data using the standardized CRF on to the ISARIC REDCAP platform. Support to establish site-hosted data collection systems is also available from ISARIC.

The peak period for Dengue cases is typically following the monsoon season across Asia (i.e., after September and lasting well into Spring or early summer). We plan to collect data across sites over a period of 6 months. Data cleaning and analysis will potentially take 3 months to complete.

Sample size:

We will enrol all consecutive patients admitted with dengue to participating hospitals and ICUs over a 6-month period. From the CCAA data, 1600 patients were admitted in 2022 to the participating sites of the CCAA network. Assuming similar numbers across the sites involved in our study, we hope to collect data on 800 patients over a 6-month period. With this sample size and assuming a 10% mortality (based on CCAA data), we estimate that we should be able to model for 6-8 key co-variates (rule of 10 events per covariate). We will roll out the study during periods of maximum dengue burden in each of the countries, which is typically following the monsoon season (September 2023 to February 2024).

Analysis:

We will describe hospital and ICU-level characteristics. For patient-level data, we will use descriptive statistics to summarize de-identified data pertaining to patient demographics, clinical presentation, illness severity, treatments received and outcomes. We will use logistic regression to evaluate predictors of hospital mortality for the cohort of severe dengue patients and specifically evaluate treatment-related predictors of survival using target trial approaches that establish time zero for eligibility and the start of follow-up. We will publish a formal SAP prior to database lock.

**Data Management and Sharing**:

Data collection:

Clinical, demographic and laboratory data will be collected throughout the acute illness period according to local resources. Identifying information will be stored and protected only at the site where data will be pseudonymised by issue of a study number for each participant. Data and information transmitted outside of the site will contain the study number as the sole identifier, resolvable to an individual participant only by the site.

Data access and sharing:

At all times, sites will retain control and decision-making authority over the data they collect and submit to the central database. Site-based clinical investigators contributing to research will decide how they are recognised in research outputs of the central database.

Fully anonymised data, in aggregate or in limited subsets, will be made openly available in research outputs of this work. Anonymity will be confirmed by statistical disclosure analysis before data are made available. Where anonymity prohibits scientific discovery, pseudonymised data will be shared with public health authorities and other researchers to execute analyses overseen by the contributing sites. De-identification, masking and data minimisation will be executed on all shared data to ensure data privacy.

Data quality:

Several procedures to ensure data quality and protocol standardisation will help to minimise bias. These include:

* A detailed data dictionary and CRF completion guide will define the data to be collected on the case report form;
* Quality checks, with a focus on critical data points, will be built into the data management system to ensure standardization and validity of the data collected;
* Data queries may be generated by the central database to ensure accuracy and completion;
* Site-level or central data monitoring may be conducted, according to available resources.

**Ethics and informed consent:**

This is an observational study which does not involve any additional patient procedures or health risks. As such, inclusion in this study involves only minimal possible risks to privacy and confidentiality. Study processes, training and procedures have been designed to limit these risks in several ways. Staff will be trained in data privacy and will apply strict controls to the data and information collected. Site-level research records will be securely stored, controlled, and destroyed according to local regulations.

This project will be submitted to the institutional committee reviewing human investigations at each of the participating hospitals. In jurisdictions that allow for central ethics approval, we will approach the respective committees.

During the dengue season hundreds or thousands of dengue patients may be seen at participating sites every month. As such, inclusion of patients in this study will be limited if there is a requirement for informed consent. As the project involves collection of low-risk observational data and given that no intervention is involved, we will seek waiver of informed consent in order to strengthen the generalisability and power of the analysis. In addition previous research has demonstrated that mandating consent in low-risk observational research increases the risk of bias.(9,10). Also the Indian Council of Medical Research National Ethical Guidelines for Biomedical and Health Research Involving Human Participants acknowledges the provision of waiver for research involving public health surveillance. (11)

**References:**

1. Available from: <https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue> (accessed on 13th June 2023)
2. Colon-Gonzalez FJ, Sewe MO, Tompkins AM et al. Projecting the risk of mosquito-borne diseases in a warmer and more populated world: a multi-model, multi-scenario,intercomparison modelling study. Lancet Planet Health 2021;5:e404-14
3. Available from: <https://www.tropmedres.ac/news/morus-new-critical-care-asia-network-42-icus-in-9-countries> (accessed on 13th June 2023)
4. Murhekar M, Joshua V, Kanagasabai K, Shete V, Ravi M, Ramachandran R et al. Epidemiology of Dengue fever in India, based on laboratory surveillance data, 2014-2017. Int J Infect Dis 2019;84S:S10-S14
5. Juneja D, Nasa P, Singh O, Javeri Y, Uniyal B, Dang R. Clinical profile, intensive care unit course, and outcomes of patients admitted in intensive care unit with dengue. J Crit Care 2011;26(5):449-52
6. Szente Fonseca SN. Changing epidemiology of dengue fever in children in South America. Curr Opin Pediatr 2023;35(2):147-54
7. Malavige GN, Jeewandara C, Ghouse A, Somathilake G, Tissera H. Changing epidemiology of dengue in Sri Lanka- Challenges for the future. PLoS Negl Trop Dis 2021;15(8):e0009624
8. Available from: <https://isaric.org/research/covid-19-clinical-research-resources/> (accessed on 13th June 2023)
9. Kho ME, Duffett M, Willison DJ, Cook DJ, Brouwers MC. Written informed consent and selection bias in observational studies using medical records: systematic review. BMJ 2009;338:b866
10. Tu JV, Willison DJ, Silver FL, Fang J, Richards JA, Laupacis A et al. Impracticability of Informed Consent in the Registry of the Canadian Stroke Network. N Engl J Med 2004;350:1414-21
11. Available from: <https://ethics.ncdirindia.org/asset/pdf/ICMR_National_Ethical_Guidelines.pdf> (accessed on 27th October 2023)