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Severe dengue is defined by a plasma leak syndrome leading to intravascular volume depletion and shock. The majority of patients with dengue shock recover after a single fluid infusion, however, recurrent shock occurs in approximately 30% and carries a higher risk of poor outcomes. Early Identification of these patients would allow more intensive treatment. The compensatory reserve Index (CRI) is a new physiological parameter that tracks real-time changes in central volume. It is derived from feature analysis of the pulse arterial waveform. Arterial waveform data is processed by an algorithm, giving a CRI value between 1 and 0, where 1 represents normovolaemia and 0 represents decompensated shock (SBP < 80 mm Hg). We investigated the utility of CRI to predict re-shock compared to the current gold standards, including clinical and vital sign parameters in severe dengue. We performed a prospective observational study in the paediatric and adult Intensive Care Units (ICU) at the Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam. Patients were monitored with hourly clinical and vital sign parameters, and continuous recording of the arterial waveform using pulse oximetry. The waveform data was wirelessly transmitted to a laptop where it was synchronized with the patient's clinical data. 90 patients were enrolled, of which 55 had the minimum required dataset for analysis. The median age was 11 years (IQR 8-14 years). CRI had a moderate negative correlation with diastolic and systolic BP. Using logistic regression GEE models, CRI was found to predict shock (defined as PP<20mmHg) up to 5 hours before the event, ranging from the highest risk at 25 minutes prior to shock; OR 1.93, (95% CI 1.49-2.51), P<0.001 and AUC of 0.82, decreasing at 1 hour prior; OR 1.67, (95% CI 1.33-2.11), P<0.001, AUC of 0.77 and at 5 hours prior: OR 1.39, 95% (CI 1.11-2.76), P=0.004 and AUC of 0.68. A CRI cut-off of 0.4 provided the best sensitivity and specificity for predicting shock (0.8 and 0.72 respectively). In summary, CRI is a useful non-invasive method for monitoring intravascular volume status in severe dengue and can predict shock recurrence up to 5 hours before the event.

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UPDATE FROM PAGODAS: PEDIATRIC ASSESSMENT GROUP OF DENGUE AND AEDES SALIVA TO INVESTIGATE VECTOR-BORNE DETERMINANTS OF *AEDES*-TRANSMITTED ARBOVIRAL INFECTIONS IN CAMBODIA

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Dengue virus is a serious public health concern in Cambodia. Defining the burden of dengue disease and the *Aedes aegypti* vector determinants that exacerbate disease transmission are critical for Cambodian public health authorities. In this longitudinal pediatric cohort based in community pagodas, we enrolled 771 healthy Cambodian children aged 2 to 9 years old in July and August 2018 to be followed twice per year (rainy and dry season) for serosurveillance for *Ae. aegypti* salivary gland homogenate antibody intensity determinations as well as dengue seroprevalence through a combination of ELISA and plaque reduction neutralization test (PRNT) assays. Traditional entomological surveys were also performed in 731 houses and 5053 water containers in the community. At baseline, dengue virus seroprevalence was: 19.5% (34/174; 95% CI 13.9-26.2) in 2 – 3 year olds, 22% (45/204; 95% CI 16.6- 28.4) in 4 – 5 year olds, 36.6% (67/183; 95% CI 29.6-44) in 6 – 7 year olds, and 65.8% (n=129/196; 95% CI 58.7-72.4) in 8 – 9 year olds. Full serotyping and PRNT titers will be available by presentation time. As the cohort data collection is still ongoing, initial geospatial analysis will be shown for baseline dengue seroprevalent participants (n=273), asyptomatic dengue cases and acute dengue cases as of October 2019 and their association (or lack thereof) with *Ae. aegypti* anti-saliva antibody intensity at wet and rainy season, mean larval density (from 5053 water containers at 731 houses), and Premises Condition Index (PCI) scoring. Our preliminary findings indicate that: 1) dengue seropositivity increases with age, with most children being seropositive by age 8; and 2) there is spatial overlap between house quality (from PCI), high *Ae. aegypti* salivary responses, and dengue seropositivity.

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PHARMACOKINETICS OF TKM-130803 IN EBOLA VIRUS DISEASE IN SIERRA LEONEAN PATIENTS

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TKM-130803 is a specific anti-ebola virus (EBOV) therapeutic comprising of two small interfering RNAs (siRNA) siLpol-2 and siVP35-2. The pharmacokinetics (PK) of these siRNAs was defined in Ebola virus disease (EVD) patients, with reference to efficacy (ET) and toxicology thresholds (TT). The relationship between PK and patient survival was explored. PK and pharmacodynamic (PD) data were available for seven participants with EVD in Sierra Leone who received 0.3 mg/kg of TKM-130803 by intravenous infusion over 2 hours daily for up to 7 days. Plasma concentration of siRNA was compared to survival at 14 days. PK data were fitted to two-compartment models then Monte Carlo simulated PK profiles were compared to ET (Cmax 0.04-0.57 ng/mL and mean concentration 1.43 ng/mL), and TT (3000 ng/mL). Viral loads (VL) were not significantly different at treatment onset or during treatment (p=0.1) in subjects who survived or died. siRNA was in quantitative excess of virus genomes throughout treatment, but the 95% percentile exceeded TT. Plasma concentration of both siRNAs were higher in subjects who died compared to subjects who survived (p<0.025 both siRNAs). The maximum AUC for which the 95% percentile remained under TT was a continuous infusion of 0.15mg/kg/day. TKM-130803 was circulating at concentrations considered sufficient for efficacy but given extremely high viral loads it seems likely that the patients died because they were physiologically beyond the point of no return. Subjects who died exhibited indications of impaired drug clearance, justifying caution in dosing strategies for such patients. This analysis has given a useful insight into the pharmacokinetics of the siRNA in the disease state and illustrates the value of designing PKPD studies into future clinical trials in epidemic situations.

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HEARING LOSS ASSOCIATED WITH VIRAL HEMORRHAGIC FEVERS

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Hearing loss affects over 1.3 billion people worldwide. Despite well known social, economic, and neurologic consequences, this condition receives little attention. Ebola (EBV) and Lassa Fever (LF) have both been reported to cause hearing loss. However, the true burden of hearing loss secondary to these viruses is likely underestimated due to lack of standardized measurement and reporting. This is a cross-sectional study