

## ABSTRACT

### Viral Haemorrhagic Fevers (VHFs) in Barbados: Clinical Investigations of Dengue and Hantavirus infections

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This dissertation examines viral haemorrhagic fevers (VHFs) in Barbados specifically dengue virus (DENV) and hantavirus clinical infections from 2008 to 2016 and 2008-2018 respectively. A summary of epidemiological features of dengue and hantavirus infections in Barbados from 2008 to 2016 are reported. Dengue epidemics occurred at 3-year intervals including 2010, 2013 and likely 2016. DENV-1 strains sequenced from 2013 outbreak year exhibited two distinct genetic lineages one South East Asian and the other Caribbean and South American lineages. Hantavirus epidemiological data are presented for the first time in the Caribbean with notable findings including higher incidence in younger persons, a 2010 epidemic and a female bias (nearly twice as likely as males) in hantavirus infection. Co-detection of dengue- and hantavirus-specific IgM was reported in patients during 2008-2018 including pregnant women for the first time in the Caribbean and worldwide respectively. Pregnant mothers who were DENV-specific IgM positive and hantavirus-specific IgM ELISA positive during pregnancy in Barbados were reviewed and some complications including preterm birth, hypertension and liver damage/injury were observed. Elevated serum endotoxin or lipopolysaccharide (LPS) levels and disease severity were observed in both dengue- and hantavirus-infected patient sera and significant associations with dengue and hantavirus disease severity. Serum endotoxin and its association with hantavirus infection and disease severity represents the first report worldwide. Unknown clinical infections among febrile patients with dengue-like illness including jaundice, myalgia, headaches and mortality were investigated using unbiased next generation sequencing (NGS) techniques for the first time in the English-speaking Caribbean to reveal the causative agent(s) present. Several pathogens were observed among these patients including enterovirus A, enterovirus C, DENV, methicillin resistant *Staphylococcus aureus* (MRSA), *Rickettsia felis*, GBV-C virus and human herpesvirus 6 (HHPV-6). Comparison of three different serological testing methods IFA, ELISA and ICG assays revealed varying assay sensitivities and specificities. The detection of arenavirus-specific antibodies in rodents (*Mus musculus* and *Rattus norvegicus*; IgG) and acute febrile patients (IgM) is reported for the first time in the English-speaking Caribbean.

**Keywords:** Kirk Osmond Douglas; dengue; hantavirus; arenavirus; infectious disease; viral haemorrhagic fever; VHF; next generation sequencing; endotoxin; LPS; epidemiology; NGS; pregnancy; ELISA;