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Dissertation summary

Studies on rodent-borne zoonotic diseases circulating among small mammals and humans in urban and rural settings in Sri Lanka: hantavirus infection and leptospirosis.

This dissertation consists of three chapters describing the findings on two rodent-borne zoonotic infections circulating among the small mammals and humans in Sri Lanka. Chapter I, presents a small mammal survey carried out to identify the hantavirus species and their reservoir animals in a chronic kidney disease of unknown etiology (CKDu) hotspot in the country. Of the 116 small mammals collected, 40 were seropositive to Thailand orthohantavirus (THAIV) IFA and 6 hantavirus genome positive rodents were also identified. One *Rattus rattus* was carrying a genome similar to THAIV genetic variant Anjzorobe virus (ANJZV), designated as SA108 virus, and 5 *Mus booduga* animals were carrying a genome with the features of a novel orthohantavirus species designated as Lanka virus. The viral genome copy numbers in infected rodent lung tissues were found to be higher than that in kidney tissues. The tanglegram analysis placed *M. booduga*, the Lanka virus host in a different group of host rodents than those of THAIV and ANJZV. This is the first confirmed report of a *Mus* species acting as a hantavirus reservoir host and the first hantavirus genome detection in Sri Lanka. The findings of the study will contribute to the development of specific diagnostic methods to determine the definite hantavirus serotypes in Sri Lankan CKDu communities.

The study presented in the chapter II, was carried out with the objective of determining the serotype of the hantavirus infecting the residents in CKDu endemic regions in Sri Lanka. Herein, the diagnostics were developed to serologically distinguish Lanka virus and SA108 virus infections. Using the virus-infected rodent cDNA samples viral gene sequences were amplified and cloned to use their protein products as antigens to establish specific diagnostic methods. The pseudotype virus-based neutralization assay found to be ineffective to distinguish two infections due to high cross reactivity. Due to this rGP antigens were used as screening IFA antigens to select the serum samples with GP specific IgG antibodies. The use of Gn glycoproteins of two viruses which had different antigenic characters as IFA antigens, successfully distinguished the two viral infections in rodent sera. This assay was then used to serotype the hantavirus infection in Sri Lankan human samples. According to the results, Lanka virus infection was found to be predominant by far, compared to the SA108 virus infection among both CKDu patient and healthy control groups. The analysis of data showed that out of 336 sera serotyped by rGn-IFA, 294 (87.5%) were Lanka virus infected, 2 (0.6%) were SA108 virus infected and 40 (11.9%) were inconclusive. The results of this study demonstrate that Lanka virus had been infecting the humans in several CKDu endemic areas at least for a decade and warrants the need of further in-depth studies to understand the epidemiological link between Lanka virus and CKDu.

In chapter III, circulation of two zoonotic pathogens was assessed in an urban public market in the city of Kandy, Sri Lanka. The small mammals infesting the premises were first screened for *Leptospira* and hantavirus infections. Anti-leptospiral antibodies were detected in 13.8% of tested animals, with three *Leptospira* isolates obtained by animal kidney culture and additional 3 animals were detected with *Leptospira* genes in their kidneys by PCR. All isolates and positive PCR amplicons from animal kidneys were identified as pathogenic species *L. borgpetersenii* and MLST scheme 3 analysis of these samples resulted novel sequence types. IgG antibodies against hantaviruses were detected in 12 animals. The market workers were screened next for these two diseases using their sera. Anti-leptospiral antibodies and anti-hantavirus antibodies were detected by IFA and found that 23.4% and 2.1% were seropositive for *Leptospira* and hantaviruses, respectively. The hantavirus serotype in infected humans were identified by ELISA as THAIV-like while rGn-IFA confirmed it as Lanka virus. The study results show molecular and serological evidence for the presence of two zoonotic pathogens and their infections in animal and human associated to the market. The transmission of these pathogens from infected animals to humans can occur within the market or via the contaminated food, indicating a high public health risk. Therefore, implementation of strict animal control measures is suggested to the authorities to ensure the safe health of market workers and the general public.