

Control of Rickettsial infections: Preliminary observations through obstacles and challenges

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Introduction

Rickettsial illnesses, caused by obligate intracellular gram-negative coccobacilli are re-emerging or newly emerging febrile illnesses where man is an accidental dead-end host. Rickettsial infections are a major cause of non-malarial febrile illnesses among returned travelers to endemic areas.^{1,2} These organisms multiply within eukaryotic cells. The genus of rickettsiae is divided into spotted fever group (SFG), typhus group and scrub typhus. All rickettsioses exist as zoonoses and are found in infected arthropods (ticks, mites, chiggers, fleas or lice) which generally serve as the natural hosts and can transmit the infection vertically to their next generation. These infections can be transmitted from arthropods to wild or domesticated animals such as dogs, cats and cattle.^{3,4}

To date, SFG has nearly 15 pathogenic rickettsioses such as Rocky Mountain spotted fever (RMSF), Rickettsialpox African tick typhus, Mediterranean spotted fever, Israeli spotted fever, Indian tick typhus. Typhus group includes *Rickettsia prowazekii* and *Rickettsia typhi*; Murine (endemic or flea-borne) typhus and Scrub typhus caused by *Orientia tsutsugamushi*, *Orientia chuto*. New or reemerging rickettsioses described in the last few decades, include tickborne lymphadenopathy (TIBOLA) and Dermacentor-borne-necrosis-eschar-lymphadenopathy (DEBONEL) related to *Rickettsia slovaca* infection, as well as lymphangitis-associated rickettsiosis attributed to *Rickettsia sibirica* infection. Furthermore Ehrlichia, Anaplasma and Bartonella species are organisms related to the rickettsiae.^{1,3,4}

Although the clinical presentation of rickettsial infection is similar, the causative species and their illness presentation and severity depends on the region.⁵ Therefore, it is important to recognize both the typical and atypical manifestations of rickettsial infection in each region to promptly diagnose and treat these infections, as delayed diagnosis or undiagnosed illness can be associated with significant morbidity and mortality.

Awareness of rickettsial illness, their prevalence in different geographic regions, availability of confirmatory investigations and treatment modalities are the key to prevent illness related morbidity and mortality. Rickettsioses can result in a significant impact on health economics; in addition to direct economic threats, the association of illness among agriculture and eco-tourism related activities can result in an indirect economic loss.

Similar to other countries in the tsutsugamushi triangle, the documented history of scrub typhus in Sri Lanka dates back to the Second World War.⁶ However, its interest re-emerged during the last several decades due to increasing incidence of illness. During the past decade we experienced patients presenting with serious complications such as encephalitis, myocarditis, pneumonitis, and multi-organ involvement and with various other clinical syndromes.⁷⁻¹³ The incidence of the disease seems to be based on human activity, and ecological and climatic factors. In Sri Lanka, other rickettsial illnesses such as spotted fever group mainly caused by *Rickettsia conorii* (Indian tick typhus) and murine typhus are increasingly documented in many geographical regions.

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In addition to health education towards early recognition, establishment of confirmatory diagnostics, introduction of timely treatment, and attempts at prevention of occurrence of these illnesses is important to reduce disease related morbidity, mortality, and direct and indirect economic losses. To achieve these aims, in local context, we felt the importance of understanding the public awareness of rickettsial illnesses, their potential transmission cycles and in global context, to understand the immunological basis of these illnesses that would help in the invention of effective vaccines against these infections.

Public awareness of rickettsial illness in Sri Lanka

As there was no data on typhus fever awareness in Sri Lanka, community awareness of typhus fevers was assessed in hot-spot locations in four Medical Officer of Health areas of southern province of Sri Lanka using an interviewer-administered questionnaire. A total of 499 participants with mean age 45 years (SD $\pm$ 16) from Tangalle (n=217), Ambalangoda (n=187), Elpitiya (n=46) and Karadeniya (n=49) were assessed. Among the participants, a past diagnosis of typhus was reported by 68 (13.63%). Of those with disease awareness (n=358), 1.2% knew the disease as typhus, 58.7% and 11.8% responded it as peacock-fever and tick-fever, respectively. The causative agent was unknown to 93.6%, but many (70.7%) stated it transmits by an insect bite. Fever (79.9%), eschar (39.4%), headache (27.9%) and myalgia (26.8%) were identified as key symptoms. Disease knowledge was significantly higher among participants with past rickettsioses. None practiced any disease prevention methods. Acquaintances (82.7%) and health personnel (13.7%) were sources of information.¹⁴

This survey indicates that many in typhus-prone foci in Southern Sri Lanka were aware of the vector-borne aspect of typhus fevers, but knowledge on preventive measures was nonexistent. Knowledge on clinical features was deficient among those without disease experience. With these findings we concluded that creating public awareness on vector avoidance measures is important in the control of typhus fevers as licensed vaccines are unavailable.

Identification of potential vector species transmitting scrub typhus in Sri Lanka

The control of a vector-borne disease mainly depends on the successful management of vector populations in the environment.^{15,16} Therefore,

information on the existence of vector species and their systematics are very important aspects in designing disease control and management strategies. Chigger mites (Leeuwenhoekiidae, Trombiculidae, and Walchiidae) are parasites of any terrestrial vertebrate¹⁷ and are considered the specific vectors of *Orientia tsutsugamushi*; the bacteria cause scrub typhus.

The descriptions of chigger mites in Sri Lanka have been carried out by few researchers who published their data during 1946 and 1960.¹⁸⁻²¹ These studies have documented one species for the family Leeuwenhoekiidae, in the genus *Whartonia*; 10 species from the family Trombiculidae, in the genera: *Ascotchongastia* (2); *Blankaartia* (1); *Chiroptella* (1); *Ericotrombidium* (1); *Leptotrombidium* (3); and *Microtrombicula* (2); and four species in the family Walchiidae, under *Schoengastiella* (2) and *Walchia* (2) genera. Later, after 43 years, only one study published in 2003 has documented two new species; *C. (N.) kanneliya* and *W. ratnasooriyai*, for the Sri Lankan territory.²² After the work made by Brown et al. (2003)²², there were no other records of vector species for the country. Furthermore, no study has documented a checklist of chigger mites in the country. Here, the present work illustrates an inventory of chigger mites in Sri Lanka for the first time.

Our research involved live trapping of small mammals in surrounding areas of residences and workstations of Scrub Typhus (ST) positive patients. Live captured small mammals were anesthetized and inspected for the presence of chigger mites. Chiggers were collected and stored in 70% alcohol. Permanent slide mounts from these field caught chiggers were prepared and identified using morphological keys already available for other regions of the world. Morphological taxonomic keys were developed to the recorded chigger mites in Sri Lanka as there was no identification key or a proper checklist of chigger mites and their respective hosts that were identified in Sri Lanka.

Entomological surveys were conducted to capture the chigger mites at selected localities in southern and western province. The morphological identification revealed presence of *Leptotrombidium imphalum*, *Scheongastiella punctata*, *Leptotrombidium* sp and *Microtrombicula* sp. A morphological taxonomic key to the Sri Lankan chigger mite species was developed and a checklist for recorded species in Sri Lanka was documented.¹⁵ A reference collection for chigger mites have been created at the Department of Parasitology, Faculty of Medicine, University of Kelaniya, Ragama.

Identification of bactericidal targets of *Rickettsia conorii*; a potential target for vaccine development against rickettsial organisms

Serum antibodies cross-reactive against *Proteus vulgaris* (Weil-Felix reaction) have long been used in the diagnosis of Rickettsial diseases. Weil-Felix antibodies have been shown to be associated with the development of immunity against rickettsial diseases. However, their rickettsial target and contribution to disease pathogenesis are not established. In this study, a transposon for insertional mutagenesis of *Rickettsia conorii* was developed.²³ The resultant variants were defective for replication in cultured cells and in spotted fever pathogenesis. Mutations in the polysaccharide synthesis operon (pso) abolish lipopolysaccharide O-antigen synthesis and Weil-Felix serology and alter outer-membrane protein assembly. Unlike wild-type *R. conorii*, pso mutants cannot elicit bactericidal antibodies that bind O antigen. As the pso operon is conserved among rickettsial pathogens, it was concluded that bactericidal antibodies targeting O antigen may generate universal immunity that could be exploited to develop vaccines against rickettsial diseases.

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