Rickettsia and Orientia represent the genera of causative microorganisms of some of the most covert re-emerging diseases of the present times. These genera are morphologically and biochemically similar to other Gram-negative bacteria. The fastidious bacterial organisms are obligate intracellular parasites. Although rickettsial species are arthropod-associated bacteria, they are also frequently capable of infecting vertebrates, including humans, usually as accidental hosts. The genus Rickettsia is classically separated into the typhus group (TG) and the spotted fever group (SFG) based on the presence of distinct group lipopolysaccharide (LPS) antigens. The typhus group includes two human pathogens, R. prowazekii and R. typhi. SFG contains more than 30 diverse genotypes, which cause at least 13 different diseases or pathological syndromes in humans. Orientia tsutsugamushi is the aetiological agent of scrub typhus, also known as tsutsugamushi disease. It is a single species that comprises of many antigenic and genotypic variants. Looking back, we find examples of rickettsial diseases killed more people than the actual war.

Rickettsial diseases are widely distributed throughout the world and many recent reports suggest to their continued presence in several parts of the Indian subcontinent, particularly that of scrub typhus. Rickettsial diseases are generally incapacitating notoriously difficult to diagnose, and untreated cases can have fatality rates as high as 30-35 per cent. Thus, the reported historical numbers of cases of infections with rickettsiae are probably not very accurate and are known to be severely underreported. When diagnosed properly, they are often easily treated but, lack of definitive diagnostic tools and the hazards of handling these microorganisms aggravate the difficulties of diagnosis and treatment.

The article by Kamarasu and colleagues in this issue provides sufficient information on the existence of rickettsial infections in Tamil Nadu. As there are not many community-based studies on rickettsial infections in our country, the present study is meaningful. It is also true that the specific gold standard techniques like the immunofluorescence antibody test (IFA), the indirect immunoperoxidase (IP) test, ELISA are not available in our country and the isolation of the organisms in animals or cell culture is limited by the lack of containment facility as well as the lack of expertise in handling these high risk group pathogens.

To date, the diagnosis of a rickettsial illness has most often been confirmed by serologic testing. Serologic evidence of infection occurs no earlier than the second week of illness for any of the rickettsial diseases; thus, a specific diagnosis may not be available until after the patient has recovered or died. Higher mortality rates are also correlated with delays in consulting a physician and delays in the administration of appropriate antibiotic therapy. Many of the recent reports of scrub typhus and other rickettsial diseases from the Indian sub-continent are based on clinical findings and the relatively non-specific Weil-Felix test including the study by Kamarasu and co-workers. Using this test, a high occurrence of rickettsial infections was observed in Tamil Nadu. The earlier work undertaken in the laboratory of investigators showed reasonably high specificity but a low sensitivity associated with this Weil-Felix test. The poor sensitivity of the Weil-Felix test is now well demonstrated for the diagnosis of Rocky mountain spotted fever (RMSF), murine typhus, epidemic typhus and scrub typhus. Although a good correlation between the results of the Weil-Felix test and detection of IgM antibodies by an IFA is often observed, with the development of techniques that are used to grow rickettsiae, this test should be used only as a first line of testing in rudimentary hospital laboratories. In spite of all the drawbacks associated
with it, the Weil Felix test still serves as a useful and cheapest available tool for the laboratory diagnosis of rickettsial diseases. A four-fold rise in agglutinin titres in paired sera is diagnostic for infection with these febrile agents. However, with a single serum sample available, the test is suggestive of infection only at a high cut-off titre (>1:320) at which the positive predictive value and the specificity is reliable. Kamarasu et al used antibody titres of 80 or more from single serum sample to indicate either spotted fever or scrub typhus infection. The positive predictive value and the specificity at this threshold titre may not be very high, even then may indicate possibility of infection.

Different serological assays like plate ELISA, dot blot, lateral flow formats have been attempted by several workers employing immunodominant antigens and have shown good promise in terms of sensitivity and specificity (either IgM or IgG or both) in patients infected with *O. tsutsugamushi*. Recently, commercial rapid detection kits like Dip-S-Ticks, Scrub typhus RCT and Scrub typhus IgM and IgG Rapid Immunochromatographic Assay (PanBio, Brisbane, Australia) and Multitest Dip-S-Ticks Scrub Recombinant Assay (Integrated Diagnostics, Baltimore, Maryland, USA) have appeared in the market but are still far from the reach of most of the developing countries due to their high cost. Also, due to antigenic diversity observed in *O. tsutsugamushi* strains, local strains should be included in the antigen pool for effective disease diagnosis.

The development of PCR based diagnostic techniques have offered increased flexibility in choices available for detection of a specific pathogen with the added advantage that it directly detects the DNA of the pathogen rather than detecting antibodies to it. Detection of the organism or its DNA seems more logical to antibody detection because it indicates active disease. This is particularly valid when used in the endemic area of infection, where the background antibodies often interfere with the interpretation of antibody assays. The gene sequence of the 56 kDa major outer membrane protein has been recently used to develop a nested PCR for the detection of *O. tsutsugamushi* from infected clinical materials and has also been extensively used for the specific diagnosis of scrub typhus. A quantitative real time PCR assay has been described recently by Jiang and co-workers, in which primers based on conserved regions of the 47 kDa outer membrane protein (OMP) antigen gene detected *O. tsutsugamushi* DNA from patients’ blood and sera samples at a concentration as low as three to ten copies per reaction and has been reported to be even more sensitive in detecting the presence of *O. tsutsugamushi* than mouse inoculation.

The varied presentation of clinical manifestations warrants an increased awareness among doctors and general public to consider these clinical features for suspecting rickettsial infections. Although much advancement regarding research on this organism, its epidemiology, pathogenesis and the development of novel detection systems, is being carried out by countries like Japan, China, Korea, Thailand, Malaysia, etc., the pace at which our country has progressed in addressing the problems related to this infectious agent has been grossly inadequate. We should aim towards identifying specific genes and proteins, which would aid in better diagnosis, and perhaps, candidate vaccine.

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