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Distribution of rickettsioses in Oceania: Past patterns and implications for the future

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ABSTRACT

Rickettsioses present a threat to human health worldwide, but relatively little is known on their epidemiology and ecology in Oceania. These bacteria are the cause of potentially fatal febrile illnesses in humans (categorized into scrub typhus, typhus group and spotted fever group rickettsioses). They are transmitted by arthropod vectors such as ticks, mites, fleas and lice, which are associated with vertebrate host animals including rodents and companion animals. We conducted a search in the scientific and grey literature of *Rickettsia* spp. and *Orientia tsutsugamushi* within the Oceania region. Human case reports, human serosurveys and PCR-based testing of vectors and host animals reviewed here highlight the widespread distribution of these pathogens in the region, with the majority of human serological and vector surveys reporting positive results. These findings suggest that rickettsioses may have a significantly higher burden of disease in Oceania than is currently appreciated due to diagnostic challenges. Furthermore, consideration of the ecology and risk factors for rickettsioses reported for Oceania suggests that their importance as a cause of undifferentiated acute febrile illness may grow in the future: environmental and social changes driven by predicted climate change and population growth have the potential to lead to the emergence of rickettsioses as a significant public health problem in Oceania.

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1. Introduction

Rickettsia is a genus of bacteria causing febrile illness in humans and other mammals. Belonging to the Class Alphproteobacteria, *Rickettsia* are small, obligate intracellular endosymbionts or parasites of eukaryotic cells (Weinert et al., 2009). To date, at least 16 of 25 known *Rickettsia* species are recognized human pathogens (Fournier and Raoult, 2009), with ticks, fleas, lice and mites acting as vectors and also reservoirs. Historically, *Rickettsia* species were serologically classified into typhus, spotted fever and the scrub typhus groups (Weinert et al., 2009). Formerly known as *Rickettsia tsutsugamushi*, the causative agent of scrub typhus has been reclassified into the *Orientia* genus (also a member of the Rickettsiaceae family) (Weinert et al., 2009). Other causative agents of rickettsioses include *Anaplasma* spp. and *Ehrlichia* spp. of the Anaplasmataceae family (Order Rickettsiales), and Q fever, caused by the morphologically similar but genetically and ecologically distinct bacterium *Coxiella burneti*.

In this review, we focus on illness caused by species of the *Rickettsia* and *Orientia* genera within Oceania, and summarise reports of rickettsia and rickettiosis that have been identified using the diagnostic tools available at the time of the study, but acknowledge that misidentification and misdiagnosis are possible. Prior to the 1990s, identification of rickettsial species relied on morphological, metabolic and antigenic characteristics, resulting in highly unreliable phylogenies (Fournier and Raoult, 2009). Conventional serological identification of rickettsial isolates has generally been limited to reference laboratories since it requires a laboratory equipped for the culture of rickettsia and a large panel of specific antisera (La Scola and Raoult, 1997). Serological methods may be limited by factors such as the cross-reactivity of human sera with *Rickettsia* spp. within and between biogroups, and also with other bacteria such as *Legionella* and *Proteus* spp. Cross-absorption reactivity will vary depending on the technique used. Even microimmunofluoresence assays, the current reference method for rickettsial serodiagnosis, do not provide conclusive evidence that a patient's illness was caused by the rickettsial species used as the antigen in the assay (Parola et al., 2013). Over the past three decades, new identification techniques, particularly molecular methods and DNA sequencing, have enabled rapid, convenient, sensitive and more accurate identification of rickettsial species, their intricate taxonomic relationships (La Scola and Raoult, 1997) and also that of their arthropod host/vectors (Latrofa et al., 2013). Due to serological cross-reactivity, only isolation and molecular identification of the etiologic agents allows for the unequivcocal recognition of rickettsial diseases in regions where they were not previously identified, or for the delineation of a new species (La Scola and Raoult, 1997).

Tick-borne rickettsial agents are transmitted to humans by tick salivary excretions during the process of tick biting. Rare cases of transmission by organ transplant have also been reported (Barrio et al., 2002). Flea and louse borne pathogens are transmitted through contact of broken skin or mucosal surfaces with crushed vectors or their faeces (Azad and Beard, 1998). Flea-borne rickettsioses can also be acquired by inhalation or by inoculation of the conjunctiva with these infectious materials (Eremeeva and Dasch, 2014). Clinical symptoms of rickettsioses commonly appear 1–2 weeks after inoculation and vary between the different pathogens. Clinical presentations are non-specific and rickettsioses are frequently difficult to distinguish clinically from other common etiologies of undifferentiated fever in the Pacific including dengue, leptospirosis, and typhoid fever. Characteristic symptoms and signs include fever, headaches, myalgia, eschars at the inoculation site, rash (petechial, macular, or maculopapular), and lymphadenopathy, and can be accompanied by gastrointestinal, respiratory and occasionally neurological symptoms (Parola and Raoult, 2006). Severity of infection varies significantly between individuals, and ranges from mild self-limiting illness to fatal cases. Treatment with specific antibiotics (usually doxycycline) is highly effective, particularly if initiated early in the clinical course (Parola and Raoult, 2006). However, many first-line antibiotics commonly used for empirical treatment of undifferentiated fever (e.g. penicillins and cephalosporins) are ineffective for rickettsioses. Some cases progress to severe disease and death despite appropriate antibiotic treatment (e.g. Currie et al., 1996; Sexton et al., 1990).

While some rickettsioses, such as epidemic, murine or cat flea typhus, are widespread throughout the world, most are restricted to specific areas of endemicity (Azad and Beard, 1998; Parola and Raoult, 2006). Such variation in distribution reflects that of their respective arthropod vector species, which require particular environmental conditions and the presence of appropriate vertebrate hosts for survival (Azad and Beard, 1998; Parola and Raoult, 2006). Humans are at risk of infection by direct exposure to vectors, which is also a mechanism of indirect exposure when in proximity to or contact with vertebrate hosts. Infection risk is therefore partly determined by living conditions and occupational or recreational exposures. Risk can also vary with life stage of the vector, for example the larval stages of trombiculid mites carrying *Orientia tsutsugamushi* are found on grasses where they wait to attach themselves to a passing vertebrate hosts. The emergence of human rickettsioses thus reflects a potentially complex evolution in disease ecology (Frances, 2011), encompassing changing dynamics between multiple components of exposure pathways (Fig. 1).

The region of Oceania encompasses the Australian continent and island nations and territories within Melanesia, Micronesia and Polynesia. With the exception of New Zealand and the southern portion of Australia, all of these nations and territories fall within the tropics. Oceania hosts a population of 38.5 million people, with Australia (23.1 million), Papua New Guinea (6.4 million) New Zealand (4.4 million) and Hawaii (1.4 million) as the only nations/territories with populations exceeding 1 million (Central Intelligence Agency, 2013). The nations and territories of Oceania represent a broad range of economies and living conditions. Poverty, remoteness and tropical climate all contribute to vulnerability to and significant burden of infectious diseases in this region (Lau, 2014). Worldwide, little is known about the ecological, epidemiological and clinical characteristics of tropical rickettsioses (Parola and Raoult, 2006), and Oceania is no exception (Eldin et al., 2011; Parola et al., 2013). The lack of knowledge is compounded by under-diagnosis, poor medical awareness, non-specific symptoms that overlap with many other tropical infectious diseases, and poor access to advanced laboratory diagnostic facilities in developing countries (Parola and Raoult, 2006). Here, we review scientific and grey literature to summarise reports of rickettsioses caused by *Rickettsia* spp. and *O. tsutsugamushi* within Oceania (see Parola et al., 2013 for a recent, global review of the distribution of tick-borne rickettsioses). We suggest that, like in other tropical regions, rickettsioses are underdiagnosed in Oceania and more widespread than current literature suggests. Alongside dengue, leptospirosis, typhoid, and malaria, rickettsioses may be a significant, serious and emerging cause of undifferentiated, potentially serious, acute febrile illnesses in this region.

2. Methods

Searches of published scientific literature and grey literature reporting the occurrence of rickettsioses caused by *Rickettsia* spp. and *O. tsutsugamushi* within Oceania were conducted using Google and Google Scholar as search engines. Search terms used in addition to 'typhus', 'rickettsia' and 'spotted fever' are listed in Appendix

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