

## RICKETTSIAL DISEASES: RISK FOR INDONESIA

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### ABSTRAK

#### PENYAKIT RICKETTSIA: RISIKO UNTUK INDONESIA

Penyakit Rickettsia bersifat endemik hampir di seluruh bagian dunia, dan begitu juga di Indonesia. Termasuk dalam penyakit-penyakit rickettsia adalah tifus epidemik, tifus murine, "scrub typhus," dan "spotted fever." Tifus epidemik, yang ditularkan kepada manusia melalui tuma pada tubuh manusia, dan dapat menyebabkan sakit berat dan kematian. Tifus murine (tifus endemik), bersumber pada pinjal hewan, merupakan penyakit yang mirip tifus epidemik, tetapi dengan gejala-gejala yang lebih ringan dan jarang menyebabkan kematian. "Scrub typhus", merupakan penyakit yang dapat ringan sampai berat dan dapat membahayakan hidup, ditularkan kepada manusia melalui gigitan tungau yang belum dewasa yang dikenal sebagai "chigger". "Spotted fever: (demam yang disertai dengan bintik-bintik pada kulit), disebabkan karena terinfeksi oleh salah satu dari berbagai spesies rickettsia dari kelompok "spotted fever", dan ditularkan kepada manusia oleh pejamu (hospes) vertebrata melalui gigitan caplak (tick) yang terinfeksi. Penyakit yang disebabkan oleh organisma yang menyerupai rickettsia (rickettsia-like organism) adalah: "Q fever", yaitu penyakit yang akut atau kronis yang diduga ditularkan secara alamiah akibat terhirup oleh partikel udara yang terinfeksi *Coxiella burnetii* sejenis bakteri yang sangat resisten terhadap upaya menonaktifkannya secara kimiawi dan fisik. Bartonellosis atau penyakit Carrion, ditemukan pada daerah dengan ketinggian sedang di Andes, Amerika Selatan. Penyakit ini ditularkan oleh lalat pasir (sand flies). "Trench fever", mirip dengan tifus epidemik, ditularkan kepada manusia oleh tuma; penyakit ini sembuh sendiri. Penyakit garutan kucing (Cat-scratch disease), disebabkan oleh infeksi *Bartonella henselae* di tempat gigitan atau garutan kucing rumah yang merupakan hospes. Demam sennetsu, merupakan penyakit yang dapat sembuh sendiri dan hanya ditemukan di Jepang dan Malaysia. Pengobatan dengan tetrasiklin atau kloramfenikol untuk penyakit Rickettsia dan penyakit yang menyerupai Rickettsia, serta monositik dan granulositik ehrlichiosis pada manusia, menunjukkan hasil yang baik. Ehrlichiosis pada manusia merupakan penyakit baru yang tidak diketahui penyebarannya di seluruh dunia, sangat mungkin ditularkan oleh "tick". Walaupun umumnya dapat sembuh sendiri, angka kematian ehrlichiosis dilaporkan mencapai 2-10%. Sebagian besar penyakit rickettsia dan penyakit yang menyerupai rickettsia tersebut di atas belum dikaji secara intensif di Asia Tenggara. Walaupun masih terbatas, di Indonesia sudah dilakukan penelitian-penelitian tentang "scrub typhus" dan "murine typhus." Sedangkan penyakit-penyakit yang ada hubungan dengan kutu penyebar Rickettsia seperti "tick typhus" atau "spotted fever", "trench fever", bartonellosis, "Q fever", dan ehrlichiosis masih terabaikan di Indonesia. Tinjauan ini bertujuan untuk memperkenalkan hasil-hasil penelitian tentang penyakit-penyakit rickettsia di Indonesia, dan memperlihatkan beberapa penyakit yang penyebarannya sekarang telah diketahui disebabkan oleh arthropoda.

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## INTRODUCTION

Rickettsiae are gram-negative, obligate intracellular bacteria which are responsible for a large number of arthropod transmitted diseases in man. These diseases include: epidemic (*R. prowazekii*), and murine (*R. typhi*) typhus; Rocky Mountain spotted fever (*R. rickettsii*), Mediterranean spotted fever (*R. conorii*), Siberian tick typhus (*R. sibirica*), rickettsialpox (*R. akari*), and Australian tick typhus (*R. australis*); and 3) scrub typhus (*R. tsutsugamushi*). In addition, other related "rickettsial diseases" associated with man include: 1) trench fever (*Bartonella (Rochalimaea) quintana*); 2) Q fever (*Coxiella burnetii*); ehrlichiosis (*Ehrlichia sennetsu*, *E. chaffeensis*). A list of these diseases and some of their properties are presented in Table 1.

Rickettsial diseases and diseases due to rickettsial-like bacteria (accept for trench fever and sennetsu ehrlichiosis) are ever present zoonoses which exhibit periodic fluctuations in attack rates due to environmental influences on the vectors and hosts and variations in human (accidental host) activities<sup>1,2</sup>. The resulting disease is associated with the infection of the host's endothelial cells or cells associated with the endothelium, or blood cells<sup>1,2</sup>. The result of rickettsial infection of the endothelium leads to an intense vasculitis in the affected organs (including brain, lungs, kidneys, heart, and liver), which leads to headache, fever, malaise, myalgia and in many cases a macular, maculo-papular or papular rash (rarely in Q fever)<sup>1,4</sup>. Infections involving the cells of the blood system result in bacteremia with fever and headache for infections with bartonellae, and sudden onset of fever, chills, headache, myalgia, arthralgia and anorexia for ehrlichiae<sup>2</sup>. The illnesses are often self-limiting (approximately 15 days of fever), however, depending on the agent involved the mortality rate may be as high

as 60% without proper treatment. The intensity and duration of the maladies are significantly decreased by intervention with antibiotic therapy (e.g., tetracycline or chloramphenicol). Untreated illness may be a source of significant morbidity and mortality<sup>1,3</sup>. There are currently no commercial vaccines available for any of these diseases and indeed specific diagnosis is accomplished only by a few specialized laboratories around the world because of the hazardous nature and fastidious growth characteristics of the organisms involved. Diagnosis is generally by symptomatology and case history with laboratory confirmation done rarely<sup>1,3</sup>. Thus, the base of information on rickettsiosis especially in Indonesia, as an important contributor to acute human febrile disease, is limited<sup>1,4</sup>.

## RICKETTSIAL DISEASES

Rickettsiosis as shown in Table 1 has been divided into three groups based upon the antigenic relatedness of the bacteria causing the diseases. The following is a detailed description of these rickettsial groups as well as diseases due to infection with bacteria related to rickettsiae.

### TYPHUS GROUP

Within the typhus group is epidemic typhus also known as louse-borne or classic typhus. The etiologic agent is *Rickettsia prowazekii* which is passed among man by the human body louse (*Pediculus humanus humanus*), or among flying squirrels and to man by unknown squirrel ectoparasites<sup>1,2,6</sup>. The bacteria are passed to man via the arthropod vector feces rubbed into skin abrasions or the conjunctive or by inhalation of dried infectious feces. Epidemic typhus has world wide

**Table 1. Rickettsial Diseases of Human Importance**

| <u>DISEASE</u>                  | <u>SPECIES</u>                   | <u>VECTOR</u>                                    | <u>HOST</u>                          | <u>Endemic to Indonesia</u> |
|---------------------------------|----------------------------------|--|--------------------------------------|-----------------------------|
| <b>Typhus Group</b>             |                                  |  |                                      |                             |
| Epidemic Typhus                 | <i>Rickettsia prowazekii</i>     | Human body louse<br>Squirrel ectoparasites       | Human<br>Flying squirrel             | Unknown                     |
| Brill-Zinsser's Disease         | <i>R. prowazekii</i>             | Recrudescence of latent epidemic typhus          | Human                                | Unknown                     |
| Murine Typhus                   | <i>R. typhi</i>                  | Rat Flea   | Rodents                              | Yes                         |
| <b>Scrub Typhus Group</b>       |                                  |  |                                      |                             |
| Scrub Typhus                    | <i>R. tsutsugamushi</i>          | Trombiculid mites                                | Rodents                              | Yes                         |
| <b>Spotted Fever Group</b>      |                                  |  |                                      |                             |
| Rocky Mountain Spotted Fever    | <i>R. rickettsii</i>             | Ixodid ticks                                     | Rodents, Dogs,<br>Foxes              | Unknown                     |
| Mediterranean Spotted Fever     | <i>R. conorii</i>                | Ixodid ticks                                     | Dogs, Rodents                        | Unknown                     |
| Siberian Tick Typhus            | <i>R. sibirica</i>               | Ixodid ticks                                     | Rodents                              | Unknown                     |
| Australian Tick Typhus          | <i>R. australis</i>              | Ixodid ticks                                     | Rodents,<br>Marsupials               | Unknown                     |
| Rickettsialpox                  | <i>R. akari</i>                  | Hematophagous mites                              | House mouse, other commensal rodents | Unknown                     |
| Oriental Spotted Fever          | <i>R. japonica</i>               | Ticks?   | Rodents?                             | Unknown                     |
| <b>Others</b>                   |                                  |  |                                      |                             |
| Q Fever                         | <i>Coxiella burnetii</i>         | Ticks?   | Rodents, Sheep,<br>Cattle, Goats     | Yes                         |
| <b>Bartonella Group</b>         |                                  |  |                                      |                             |
| Bartonellosis Disease           | <i>Bartonella bacilliformis</i>  | Sandfly  | Rodents                              | Unknown                     |
| Trench Fever                    | <i>B. (Rochalimaea) quintana</i> | Lice   | Human                                | Unknown                     |
| Cat Scratch Disease             | <i>B. henselae</i>               | Ticks/fleas?                                     | Cats                                 | Unknown                     |
| <b>Ehrlichia Group</b>          |                                  |  |                                      |                             |
| Sennetsu Ehrlichiosis           | <i>Ehrlichia sennetsu</i>        | Unknown  | Human                                | Unknown                     |
| Human Monocytic Ehrlichiosis    | <i>E. chaffeensis</i>            | <i>Amblyomma</i> sp.?<br><i>Dermacentor</i> sp.? | Deer?<br>Dog?                        | Unknown                     |
| Human Granulocytic Ehrlichiosis | Unknown                          | <i>Ixodes</i> sp.?<br><i>Dermacentor</i> sp.?    | Deer?<br>Dog?                        | Unknown                     |

distribution and has been involved in determining man's destiny especially during times of war<sup>1</sup>. The symptoms follow an incubation period of 1-2 weeks. They include an abrupt onset of fever, chills, headache and myalgia. Macular rash of upper trunk and axillary folds occurs around day five. The maculopapular rash spreads over the entire body except for the face, palms and soles. Death may occur in the third week, with stupor, peripheral vascular collapse and renal failure. Diagnosis is usually based on clinical suspicion plus reaction to the *Proteus vulgaris* antigens OX19 + OX2 v and no reaction to the *P. mirabilis* Kingsbury strain OXK antigen in the nonspecific Weil-Felix serological test<sup>4,7</sup>. There are also some rickettsial antigen specific noncommercial enzyme immuno- assays (EIA) that are used in a few reference laboratories. In even fewer laboratories there are the capabilities to culture clinical specimens (blood) for rickettsial isolation<sup>4</sup>. Recently, the polymerase chain reaction has allowed the identification of bacteria in blood of acute ill patients<sup>8</sup>. This procedure is very sensitive, but is also technically difficult. The treatment for epidemic typhus is tetracycline (doxycycline) or chloramphenicol<sup>1,2,4</sup>.

Brill-Zinsser disease has been determined to be a recrudescence of epidemic typhus. The reemerging agent, *R. prowazekii*, produces a similar but much milder illness than during the primary disease<sup>1,2</sup>. Diagnosis is usually based upon a history of epidemic typhus. The Weil-Felix reaction and EIA results are usually unreliable. Culture of *R. prowazekii* is possible and PCR has been proven successful with specific primers<sup>9</sup>. Treatment involves use of either tetracycline or chloramphenicol. Brill-Zinsser disease is also distributed world-wide<sup>1,2</sup>.

Murine typhus, also known as endemic, flea-borne, shop, or urban typhus, is endemic

throughout the world<sup>9,10</sup>. The disease is due to an infection with *R. typhi* (*R. mooseri*). This agent is passed to man by the rat flea (*Xenopsylla cheopis*) or possibly other arthropod vectors. The infection is started when either the flea feces is rubbed into bite or other wound, or the host inhales dried feces<sup>1,2,9,10</sup>. Symptoms are similar to epidemic typhus, but milder. There is a gradual onset of disease with non-productive cough, fever, headache, myalgia, nausea, vomiting and in about 50% of the cases a macular or maculopapular rash<sup>4</sup>. The illness maybe debilitating, especially with neurologic or nephrotic changes, fatalities are rare<sup>11</sup>. For diagnosis the nonspecific Weil-Felix reaction generally gives the following results: OX19 + OX2 v OXK -<sup>2,4</sup>. If a reference laboratory is available serologies, in which a four fold rise in titer is diagnostic, and PCR with specific primers, can be performed<sup>1,2,11,12</sup>. Clinical specimens can be cultured for *R. typhi*, but this is difficult and hazardous to laboratory personnel. Treatment as with other rickettsial diseases incorporates use of one of the tetracyclines or chloramphenicol<sup>1,2,11</sup>.

In Indonesia, endemicity of epidemic typhus and Brill-Zinsser diseases is unknown<sup>4</sup>, whereas, it is known that murine typhus is endemic throughout the archipelago<sup>4,13-17</sup>. Nevertheless, murine typhus is rarely diagnosed or is misdiagnosed during acute illness, due to its mild, nonspecific clinical manifestations<sup>9-11</sup>. Therefore, little is known of the actual prevalence of this disease, but only of the prevalence of antibodies to *R. typhi*<sup>4,13-17</sup>. In Java, *R. typhi* has been isolated from rodent hosts and arthropod vectors<sup>13</sup> and the presence of rickettsial nucleic acid in *X. cheopis* fleas has been detected by PCR (Rusidy AF, Richards AL, Soeatmadji DW, Church, et al unpublished observation) utilizing a procedure describe previously<sup>12</sup>. Enteric fever, is also endemic to Indonesia and often presents with clinical manifestations similar to those of rickettsiosis,

i.e., fever, headache, malaise and in 30-50% of cases of typhoid fever, rose spots<sup>18</sup>. Unfortunately, many enteric fevers, like rickettsial fevers, are difficult to diagnose by laboratory methods available in Indonesia<sup>19</sup>. The commonly used Weil-Felix and Widal serological tests are nonspecific tests for rickettsial diseases and typhoid fever, respectively, and require assessing both acute and convalescent serum samples for diagnosis<sup>7,20</sup>. In addition, the isolation and culture of the causative agents are often difficult and require specialized equipment which are not routinely found in the clinical laboratories of Indonesia<sup>19</sup>. Thus, illnesses characterized by fever and headache in Indonesia are often clinically diagnosed as "tifus," which may include many enteric fevers as well as other infectious diseases including rickettsial fevers. "Tifus" is one of the leading reported causes of hospital admission in Jakarta<sup>21</sup>.

## SCRUB TYPHUS GROUP

Scrub typhus is a zoonosis that causes human disease commonly seen in Asia<sup>1,2,4,5,15,16,22-24</sup>. The etiologic agent, *R. (Orientia) tsutsugamushi*, the only species in the SCRUB TYPHUS GROUP, is acquired following the feeding of an infected chigger, the six legged larval stage of trombiculid mites, on skin tissue fluids of a human host. The subsequent rickettsial infection is characterized by first a local then a systemic vasculitis. A cutaneous lesion or eschar begins at the site of the chigger bite, and the vascular inflammation spreads throughout the blood vessels of the body involving various organs<sup>1,25</sup>. Though scrub typhus has been known since the late 1800's its notoriety did not emerge until World War II, where in the Pacific theater, it was feared by military personnel more than malaria<sup>22,25</sup>. This was due in part to the high mortality rate, where

up to 50% of patients died because of lack of a known treatment at that time<sup>22</sup>. Today, the treatment of choice for scrub typhus is tetracycline or chloramphenicol which generally produces a rapid clinical improvement in the patient with defervescence of clinical symptoms usually seen within two days<sup>1,2,24</sup>. However, there have been recent reports of drug resistant scrub typhus described both in Thailand and India<sup>26</sup>. *Kuzhanthi D. personal communication*.

Scrub typhus is considered a rural, tropical disease most commonly found afflicting individuals traversing through or working in terrain encompassing secondary vegetation resulting from previously cleared forest or abandoned agricultural areas<sup>1,22-24</sup>. However, there have been reports of individuals acquiring scrub typhus in urban settings of Hong Kong, Japan<sup>27,28</sup> and while gardening in suburban and urban areas of South Korea<sup>29</sup>. Scrub typhus cases have been reported from the southern section of Jakarta by Gispen et al.<sup>30</sup>. *R. tsutsugamushi* has been isolated from trombiculid mites and three different species of rats collected in North Jakarta<sup>14</sup>. Recently, a case of scrub typhus in an individual residing in central Jakarta has been identified<sup>31</sup>.

The species, *R. tsutsugamushi*, is made up of many distinct strains that vary in virulence<sup>32</sup> and antibiotic resistance<sup>26</sup>. Immunity to homologous strains of scrub typhus rickettsiae may continue for years, however, immunity to the many heterologous strains of *R. tsutsugamushi* may only persist for a few months<sup>33</sup>. Consequently, individuals can become infected more than once with *R. tsutsugamushi*<sup>33,34</sup>. This lack of cross immunity and the previously successful treatment with antibiotics diminished the drive for and the successful completion of the development of an effective vaccine for scrub typhus<sup>35</sup>.

## SPOTTED FEVER GROUP

The spotted fever group is composed of more than 20 antigenically related rickettsial species<sup>1</sup>. Described here are several human diseases associated with the spotted fever group rickettsiae. Rocky Mountain spotted fever (*R. rickettsii*) is found only in the Western Hemisphere. The vectors are the ixodid ticks and the normal hosts include rodents, dogs and foxes. Mediterranean Spotted Fever also known as Boutonneuse fever, Kenya tick typhus, Indian tick typhus and South African tick typhus (*R. conorii*) is also vectored by ixodid ticks. Hosts include dogs and rodents. Mediterranean Spotted Fever distribution includes the Mediterranean, Black and Caspian Sea areas, and in the Middle East, India and Africa. Siberian tick typhus or North Asian tick typhus (*R. sibirica*) is found in Siberia, Armenia, Mongolia, Central Asia & Europe. Ixodid ticks are the vectors and rodents are the usual hosts. Australian or Queensland tick typhus (*R. australis*) was discovered in Queensland, Australia, but has now been reported in other areas of Australia<sup>16</sup>. The vectors are ixodid ticks and the hosts are rodents and marsupials. Rickettsialpox (*R. akari*) has been located mainly in urban areas of North America and Russia, but has also been found in Southern Africa and Korea<sup>1,2</sup>. The vector is the hematophagous mite (*Allodermanyssus sanguineus*). Hosts include the house mouse and other commensal rodents.

Infection with spotted fever group rickettsiae usually involves the bacteria entering the human body through openings or abrasions in the skin due to the tick or mite bite, or by the infection of the conjunctiva by fingers contaminated after crushing the arthropod vectors. The organisms multiply locally at the site of invasion and spread to the endothelial cells of blood vessels. An inflammatory

response develops, causing vasculitis, and the triad of fever, head ache and rash (rash may only occur in 50% of the patients and is more difficult to see in darker pigmented people). The disease often affects multiple organs with manifestations involving the skin, skeletal muscles, central nervous system, myocardium, lungs, liver and kidneys<sup>1,3</sup>. Diagnosis often depends on the history and clinical presentation. The Weil-Felix agglutination reaction is variable for both the OX19 and OX2 antigens and negative for the OXK. A four fold or greater rise in titer for EIA or IFA followed by confirmatory Western blot analysis will provide laboratory diagnosis for spotted fever disease<sup>37,38</sup>. However, for species identification the method of choice is culture of the agent in laboratory animals or tissue culture. In addition, PCR has been shown to detect rickettsial nucleic acid from blot clots of individuals with acute cases of Rocky Mountain spotted fever<sup>39</sup>, and species identification can be ascertained utilizing PCR and restriction fragment length polymorphisms (RFLP) analysis<sup>40,41</sup>. Spotted fever disease may be fatal, but when identified and treated early with tetracycline or chloramphenicol mortality can be reduced significantly<sup>1,3,42</sup>.

Members of the spotted fever group of rickettsiae have not been reported in Indonesia though they are endemic in other Asia countries and Australia<sup>1,2,4,5,22,36</sup>. There has been a lack of seroreactivity found in Indonesian populations that were surveyed utilizing an EIA with *R. conorii* antigen preparation<sup>15</sup>.

## DISEASES DUE TO RICKETTSIA-LIKE ORGANISMS

Q fever (*C. burnetii*) is found worldwide and is associated with domestic animals and rodents. Though *C. burnetii* has been found in

several tick species and other arthropod vectors, it is thought to be maintained in nature primarily by aerosol transmission. Humans are believed to be infected by inhalation of the airborne organisms. *C. burnetii*, unlike the rickettsiae, are very resistant to inactivation by chemical and physical treatments. *C. burnetii* is known to survive on wool and other fomites for up to one year<sup>2</sup>. Symptoms of acute Q fever are nonspecific and characterized by fever, headache, chills, myalgia, and malaise. Pneumonitis may occur, however, rash rarely does. Q fever is usually self limiting, though chronic Q fever with hepatitis or endocarditis is not uncommon<sup>1,2</sup>. Diagnosis by reference laboratory usually involves performance of a noncommercial enzyme-linked immunoassay. Recently, PCR with species specific primers have become available. Culture of *C. burnetii*, is risky and so is only performed in a few laboratories world wide. Treatment usually is with one of the tetracyclines, though there maybe resistance<sup>2</sup>, or chloramphenicol.

Q fever is most likely endemic in Indonesia as it is believed to have world wide distribution<sup>1,2</sup>. In addition, a serosurvey conducted by Van Peenen, et al., reported that 25% of human serum tested from throughout the archipelago had evidence of Phase II antibodies against *C. burnetii*<sup>43</sup>. The prevalence of hospital admitted cases of Q fever in Indonesia is currently unknown.

Very recently, the *Rochalimaea* genus has been combined with that of *Bartonella* because of similarity in 16S rRNA, and DNA relatedness. The genus name *Bartonella* was retained because of its nomenclature priority<sup>2</sup> *B. bacilliformis* was identified in 1909 as the erythrocyte-adherent agent of bartonellosis or Carrion's disease. Bartonellosis is found only in the intermediate altitudes of the South American Andes. This is believed to be due to

the limited distribution of the sandfly vector (*Lutzomyia verrucarum*).

Trench fever, discovered among the troops fighting in the trenches during World War I, was originally named *Rickettsia quintana*. However, when it was found to be able to grow on blood agar plates and therefore determined not to be an obligate intracellular parasite (it attaches to the outer membrane of eukaryotic cells<sup>44</sup>) as are the other rickettsiae, it was separated into its own genus *Rochalimaea*<sup>1,2</sup>. *Bartonella (Rochalimaea) quintana* is the only agent described in this review that does not have a host other than humans. The vector, the human body louse (*Pediculus humanus humanus*), transmits the disease from man to man. Humans have been known to be infectious for more than ten years<sup>2</sup>. Distribution is associated with humans, generally living in poor social economic conditions, worldwide.

Identification of the agent associated with cat scratch disease had eluded scientists for some time. It is believed now to be *B. (Rochalimaea) henselae*<sup>45,46</sup>. The natural vector for *B. henselae* is unknown, but may be ticks and/or fleas. This agent is found worldwide and its major host is the domestic cat<sup>47</sup>.

Infections for bartonellae are usually via openings or abrasions in the skin of the human body due to the bite of sandfly, louse, tick or flea, by infection of the conjunctiva by fingers contaminated after crushing vectors or as in cat scratch disease the bite or scratch of the natural host-cat. The organisms multiply locally and spread through the blood vessels (bacteremia). The immediate response to bacteremia includes fever and headache. In Carrion's bartonellosis there are also anemia, adenopathy, thrombocytopenia, severe myalgias and arthralgias, and possible mental status changes. Without antibiotic treatment, fatality rates for

bartonellosis maybe high<sup>2</sup>. Verruga peruana may be a common late-stage manifestation of Carrión's disease. Bacteremia due to *B. quintana* and *B. henselae* are rarely fatal though the illness maybe more severe in the immunocompromised host, e.g., AIDS patients<sup>47</sup>. Cat scratch disease is commonly associated with a cutaneous papule or pustule at the site of the bite or scratch and regional lymphadenopathy. Fever may also accompany this self-limiting disease. Diagnosis of *Bartonella* species by culture of clinical specimens is difficult and thus the laboratory must be instructed about the presumptive diagnosis before submitting the specimen. Warthin-Starry silver technique is used for staining of tissue samples. Fourfold or greater rise in titer for EIA- and IFA-IgG or the presence of species specific IgM is diagnostic. PCR is the most sensitive method for *Bartonella* species identification. Treatment with tetracyclines, erythromycin or chloramphenicol is effective<sup>1</sup>.

EHRlichIA GROUP is made up of related bacteria species in the genus *Ehrlichia* and the tribe Ehrlichieae in the family Rickettsiaceae<sup>48</sup>. Several species have been related to animal disease and two to human diseases. Sennetsu ehrlichiosis, also known as sennetsu fever, sennetsu rickettsiosis (*E. sennetsu*) was described in Southwest Japan in the late 1800's. However, the agent was not identified until 1953. The vector is currently unknown as is the natural host. The disease has only been identified in Japan and Malaysia<sup>2</sup>. The symptoms include a sudden onset of fever, chills, headache and myalgia, insomnia, diaphoresis, sore throat, and anorexia. General lymphadenopathy is common, hepatomegaly and splenomegaly occur in approximately a third of the cases. The disease is self-limiting, and no serious complications or fatalities have been reported<sup>2</sup>. Successful treatment with

oxytetracycline, doxycycline and chloramphenicol have been reported<sup>2</sup>.

Human ehrlichiosis is a recently described disease whose importance as an arthropod borne-illness continues to grow<sup>5,38,48-52</sup>. Recently this disease has been divided into two similar illnesses that have different causative agents. The original human ehrlichiosis is now known as human monocytic ehrlichiosis (*E. chaffeensis*). The second, is known as human granulocytic ehrlichiosis, the etiological agent is unknown but is very closely related to *E. phagocytophila* and *E. equi*<sup>51</sup>. The tick vectors for the two diseases are believed to be *Amblyomma* and *Dermacentor* species for human monocytic ehrlichiosis and *Ixodes* and *Dermacentor* species for human granulocytic ehrlichiosis. The natural hosts may be deer, dogs or other mammals<sup>52</sup>. Distribution in the United States is wide spread. Other locations throughout the world have not been extensively studied<sup>5</sup>. Though different agents are involved in human monocytic and granulocytic ehrlichiosis, symptoms are similar and include a sudden onset of fever, chills, headache, myalgia, arthralgia, anorexia, nausea, vomiting, pneumonia and rarely rash<sup>52</sup>. The diseases are self-limiting. However, fatality rates of 2-10% have been reported<sup>2,52</sup>. Laboratory diagnosis is by polymerase chain reaction to identify the agent during the acute phase and by serological assays (EIA/IFA/ Western blots) during convalescence<sup>49,50,52</sup>. Attempts of isolation from blood are usually unsuccessful<sup>52</sup>. Recommended treatment is with the tetracyclines (doxycycline). Chloramphenicol may not be effective<sup>52</sup>.

Ehrlichiae are responsible for many animal and human diseases<sup>2,48</sup>. They can be divided into two groups based upon whether they infect monocytes or granulocytes. *E. sennetsu*; *E. chaffeensis*; *E. canis* canine ehrlichiosis,



tropical canine pancytopenia; and *E. risticii* equine monocytic ehrlichiosis, Potomac horse fever; cause monocytic ehrlichiosis. *E. phagocytophila* tick-borne fever of sheep, goat, cows, bison and deer; *E. equi* equine ehrlichiosis; and *E. ewingii* canine granulocytic ehrlichiosis are granulocytic ehrlichiosis. Currently little is known of the presence of any of these agents in Indonesia.

### SUMMARY STATEMENT

Rickettsial diseases and diseases due to rickettsial-like bacteria are endemic throughout the world. This includes Indonesia as well. Scrub typhus and murine typhus have been investigated in Indonesia, however, diseases such as those related to the spotted fever group of rickettsiae, trench fever, bartonellosis, Q fever and ehrlichiosis have been almost completely overlooked. Thus the aim of this review was to promote awareness of diseases associated with rickettsiae and related organisms, and to stimulate rickettsial disease research in Indonesia.

### DISCLOSURE

The opinions and assertions contained herein are the private ones of the authors and are not to be construed as official or as reflecting the views of the U.S. Navy or the Department of Defense, or Departemen Kesehatan RI.

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