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The Military and Infectious Disease: Rickettsial Disease

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The Military and Infectious Disease: Rickettsial Disease

Since the founding of the United States Army on the fourteenth day of June, in the year 1775, the United States Military has had millions of non-combat related casualties due to preventable illnesses and diseases transmitted through an arthropod vector. U.S. Military operations have been affected from the effects of the smallpox and malaria outbreaks as early as the Continental Army around 1775, as well as the Civil War period in the mid-1860s. In 1898, the U.S. Military was devastated with outbreaks of typhoid fever, yellow fever, and dengue fever during the months of the Spanish-American War (Artenstein et al, 2005). Infectious diseases became common in the U.S. Military, especially during overseas campaigns in tropical areas such as in the Philippines, South America, Vietnam, South Korea, Thailand, Japan, and others.

Infectious diseases such as leishmaniasis, Q fever, malaria, Lyme disease, typhoid fever, and dengue fever (etc.) were all reported to have affected U.S. Military and Department of Defense (DoD) personnel since as far back as the War of 1812, and have continued to be reported in military campaigns such as World War II, The Vietnam War, Operation Desert Storm, and even Operation Iraqi Freedom and Operation Enduring Freedom (Hospenthal, 2005). These infectious diseases require the use of an insect vector for transmission to humans; some infectious diseases, like the malaria causing parasite, Plasmodium species, also complete part of their life cycle inside the insect vector (biological vector). A vector is defined as an arthropod that transmits a pathogen. A vector is broken down into two parts, mechanical and biological: the mechanical vector is the arthropod that physically moves the pathogen without it reproducing; a biological vector is where the pathogen replicates inside the arthropod before transmission

(Service, 2000). Mosquitoes, ticks, fleas, and sand flies are some of the more common insect vectors that we see in the transmission of infectious diseases.

During the Spanish-American War (1898), the U.S. Military encountered cases of yellow fever; an acute viral hemorrhagic disease transmitted to humans by infected *Aedes* mosquitoes. Yellow fever is common amongst tropical regions, such as South America and Sub Saharan Africa; between 1817 and 1900, yellow fever had been an endemic in the U.S. every summer. During the outbreak of the Spanish-American War (1898) in Cuba, more than five thousand U.S. Military personnel died due to disease, and among these deaths, yellow fever was the leading cause. The first records of malaria in history date back to 2700 BC in China, with records of the unique fevers associated with malaria. Hippocrates would go on to describe malaria as a period of tertian, quartan, subtertian and quotidian fevers; malaria was known as the Roman fever during the reign and decline of the Roman Empire (Cater, 2012). The Claude Moore Health Sciences Library (2007) references the events from when the Army Surgeon General George M. Sternberg and Cuban Governor Leonard Wood, with support of Generals Nelson Miles and Theodore Roosevelt, first established the Army medical team to combat the yellow fever outbreak. In the spring of 1900, Sternberg and Wood assigned a team of research scientists known as the Yellow Fever Commission to study the disease, appointing Major (MAJ) Walter Reed as the Officer In Charge (OIC), along with three assistant scientists; each having expertise in bacteriology and pathology, with previous assignments in studying malaria, typhoid fever, dengue, and yellow fever. The research and findings the Yellow Fever Commission lead to the efforts of educating military personnel and the eradication of the disease via the insect vector.

Because of the global demand and presence of U.S. Military Forces in tropical and endemic environments, the U.S. Military's has studied the epidemiologies of many infectious

diseases and continues to study the fight on the front line in the operations to prevent and control infectious diseases, focusing efforts on prevention, control, surveillance, education, research, develop experimental vaccines, therapeutics, and vector control agents. Some of the most renowned doctors and researchers responsible for the medical advancements, treatments and vaccines served in the U.S. Military, or worked closely with the U.S. Military Personnel, in their efforts to find cures and preventive measures. During combat operations, personnel subject to illness (whether military or civilian) reduce the manpower hours needed for mission readiness and thereby reducing mission success rates. Illness within a unit can not only reduce the needed manpower for mission readiness, but also decreases unit morale and, over time, leads to additional manpower and budgeting for medical personnel and medical supplies.

The U.S. Military and DoD Civilian workforce have contributed to the fight against infectious diseases since the formation Continental Army under General George Washington in 1775, where over ten thousand Soldiers of the Continental Army were infected with smallpox; the following year in 1776, General Washington, Commander in Chief, ordered the inoculation of his Soldiers to prevent further outbreaks of smallpox. In 1798, Dr. Edward Jenner M.D., an English physician and scientist, used cowpox to develop a vaccine against smallpox (Artenstein et al, 2005). In the efforts to maintain the fighting strength of the U.S. Military, military doctors and scientists have worked effortless to aide in the fight against infectious diseases (Hospenthal, 2005). The Spanish-American War was one of the first major wars where the Surgeon General realized the need for vaccinations in order to help prevent the spread infectious diseases amongst U.S. and foreign military personnel, and to maintain a strong military force. Over the years, with each new conflict came a new emergence of an infectious disease, which would later lead to a

new experimental vaccine or control measure, all researched and manufactured under the DoD, spearheaded by DoD and U.S. Military physicians and scientists.

Ticks have been categorized as the number one vector of diseases within the United States (Service, 2000). The mortality and morbidity of Rickettsial diseases have had a major impact on military operations for well over two thousand years. The Rickettsial disease typhus was first described and documented as far back as 429 B.C. with the Athenian Army, where it is thought that epidemic typhus and scrub typhus were responsible for the fall of the Athenian General Pericles and led to the downfall of Athens during the Peloponnesian War. Following the 1812 withdrawal from Russia, the Grand Army of Napoleon fell victim to typhus (Bavaro et al, 2005).

The Rickettsial diseases consist largely of the spotted fever group, the typhus group, and ehrlichiosis and anaplasmosis. While infections in humans continue to be reported in mild to high rates, humans are not always the designated hosts for much of these infectious diseases but are considered an accidental host. Rickettsial diseases are transmitted primarily by ticks, with some exceptions being the flea (Siphonaptera), louse (order Phthiraptera), and mite (order Trombidiformes). Rickettsial diseases in brief are acute and potentially severe zoonotic infections caused by obligate, intracellular, gram-negative (-) bacteria, associated with arthropods and requiring eukaryotic cells for growth (Jensenius and Parola, 2009). A zoonotic disease is a disease of animals that can be transmitted to humans (Service, 2000). The Rickettsial diseases are under the order Rickettsiales, family Rickettsiaceae, and genus *Rickettsia*. The genus *Rickettsia* is gram-negative, non-motile, non-spore forming, pleomorphic bacteria that can present as cocci, coccobacilli, or rods when viewed under a microscope. The survival of the

Rickettsia species is dependent upon entry into the cytoplasm of the host eukaryotic cell (usually an endothelial cell), where growth and replication occurs (Civen and Ngo, 2008).

Organism	Disease or Presentation	Geographic Location
<i>Rickettsia rickettsii</i>	Rocky Mountain spotted fever	North, Central and South America
<i>Rickettsia conorii</i>	Mediterranean spotted fever, boutonneuse fever, Israeli spotted fever, Astrakhan fever, Indian tick typhus	Europe, Asia, Africa, India, Israel, Sicily, Russia
<i>Rickettsia akari</i>	Rickettsialpox	Worldwide
<i>Rickettsia sibirica</i>	Siberian tick typhus, North Asian tick typhus	Siberia, People's Republic of China, Mongolia, Europe
<i>Rickettsia australis</i>	Queensland tick typhus	Australia
<i>Rickettsia honei</i>	Flinders Island spotted fever, Thai tick typhus	Australia, South Eastern Asia
<i>Rickettsia africae</i>	African tick-bite fever	Sub Saharan Africa, Caribbean
<i>Rickettsia japonica</i>	Japanese or Oriental spotted fever	Japan
<i>Rickettsia felis</i>	Cat flea rickettsiosis, flea borne typhus	Worldwide
<i>Rickettsia slovaca</i>	Necrosis, erythema, lymphadenopathy	Europe
<i>Rickettsia heilongjiangensis</i>	Mild spotted fever	China, Asian Region of Russia
<i>Rickettsia parkeri</i>	Mild spotted fever	USA

Figure 1: A table of the spotted fever groups that are zoonotic to humans (WikiDoc.org, n.d.).

Ticks are not categorized as insects, but are arthropods under categorized under arachnids. Unlike insects, which have three pairs of legs (six total), ticks have four pairs of legs (eight total). Ticks are arthropods belonging to the class Arachnida, and of the order Ixodida, suborder Parasitiformes, which is broken up into three families; Argasidae, the soft bodied ticks, Ixodidae, the hard bodied ticks, and Nuttalliellidae, a single South African species (*Nuttalliella namaqua*) (Samlaska, 1994). The family Argasidae contains roughly one hundred eight-five species, with the family Ixodidae containing roughly six hundred eighty-five species. Ticks are

ectoparasites, parasites that live on the outside of the host, and are vectors for a number of infectious diseases where both animals and humans are infected (Hickman et al, 2003). Ticks are considered obligate haematophages, meaning they require the blood of other animals to move through their life cycle, and they obtain that blood by feeding on mammals, birds, reptiles and amphibians (Service, 2000). Hard ticks will attach to their host and feed for extended periods of time, with a single blood meal lasting anywhere from a few days to a few weeks, and typically take longer to mature (up to three years). When feeding, the cuticle of the hard tick will grow from two to six hundred times its unfed body weight to accommodate the blood consumed (Sonenshine, 1991). Soft ticks tend to feed in shorter intervals, anywhere from several minutes to a few days at a time. When feeding, the cuticle of the soft tick will grow from five to ten times its unfed body weight to accommodate the blood consumed (Vredevoe, n.d.).

Ticks can be identified by their six-segmented legs, idiosoma (main body of tick), and capitulum (mouth and feeding parts). Ticks undergo a hemimetabolous life cycle (incomplete metamorphosis), and can lay up to eight hundred eggs, and will undergo three primary stages of development, the larva, the nymph, and the adult stages. The female tick can lay eggs thousands of eggs at a time, with the eggs hatching within two weeks. With both the soft bodied (Argasidae) and hard bodied (Ixodidae) ticks, the larvae will hatch with six legs and resemble a smaller adult (Sonenshine, 1991). Hard ticks generally take one blood meal per stage before molting, while soft ticks can take multiple blood meals in between molting; the larva will take a blood meal to moly to the nymph stage. The nymph has eight legs like the adult, but is smaller and, depending on the family, will undergo one or more instars before molting to an adult. Hard ticks have only one nymph instar, requiring only one blood meal before reaching the adult stage; where soft ticks will typically under two to eight instars, with each requiring a blood meal before

molting, before they reach their adult stage. The life stages for a nymph to reach the adult stage can take up to a year; for the soft tick, the nymph will cycle between one to multiple hosts throughout the year, molting after each blood meal (Hickman et al, 2003).

The mouthpart of a tick consists of three main structures, hypostome, the chelicerae, and the palp; there is a pair of chelicerae, two highly mobile jointed palps, and one needle shaped structure hypostome. The chelicerae are knifelike projections attached to the hypostome that cut openings in the skin while the hypostome is the barbed long needlelike projection that pierces the skin and sucks the blood; during feeding, the palps will move laterally and will not enter the skin of the host. Both hard and soft ticks contain these mouthparts, with equal function. The hypostome is designed where the barbs are pointed back as to provide a sturdy attachment and making it difficult to remove the tick without damaging the skin of the host. Some ticks will secrete a cement like substance through produced by the salivary for additional adhesiveness to the host, increasing the difficulty of removal from the host; this substance will dissolve once the tick has finished feeding. The tick's saliva also secretes an anticoagulant to prevent clotting in the host's blood (Vredevoe, n.d.).

During the American Revolutionary War (1775 – 1783) the U.S. Military experienced the first (documented) encounter with Rickettsial diseases, where nearly a third of the New York Army became ill with typhus in 1776. During World War I, epidemic typhus was of major concern to the public and the U.S. Military, where cases were reported in Russia and Eastern Europe. Millions of civilians and military personnel were infected with epidemic typhus and the fatalities toll was reported to be in the thousands; fewer cases were reported in the U.S. Military personnel (forty-seven), with only a few reported fatalities among the ranks from typhus (Coates et al, 1961). With the recognition that U.S. Military personnel would become affected again with

typhus, on 22 October 1942, during the start of World War II, under the recommendation of the Surgeon General (Dr. Thomas Parran, Jr., M.D.), and supervision Colonel James S. Simmons, MC, the Joint U.S. Typhus Commission was initiated by the Secretary of War (Henry L. Stimson), and later established by Executive Order No. 9285 under President Roosevelt on 24 December 1942. The Joint U.S. Typhus Commission consisted of Army, Navy, and Public Health Service personnel (Armfield et al, 1963).

The purpose of the Joint U.S. Typhus Commission, under the direction of the Secretary of War, was to serve side by side with the U.S. Army to help with the prevention and control measures of typhus fever wherever any new threats would arise. The Joint U.S. Typhus Commission began research on the disease; through the aide of other U.S. Government agencies, field sites were established overseas in efforts to provide adequate research personnel and research laboratories under U.S. Government guidance (Armfield et al, 1963). The medical doctors under the Joint U.S. Typhus Commission all consisted of U.S. Military doctors serving in the Army and Navy, as well as U.S. Public Health Services doctors and doctors from the Rockefeller Foundation. By 1944, the Joint U.S. Typhus Commission had expanded to Cairo, Korea, Naples, Europe, Africa, China, Japan, and India, with collaborations from the surrounding foreign military forces. The Joint U.S. Typhus Commission was effective in establishing protocols for the prevention and control of epidemic typhus in the civilian population and during the 1945 – 1945 assignment in Cairo, Egypt, the Joint U.S. Typhus Commission successfully controlled the typhus outbreak utilizing these protocols (Bavaro et al, 2005). The collaboration with the Egyptian Ministry of Health led to the establishment of what is known now as the Naval Medical Research Unit 3 (NAMRU-3) located in Cairo, Egypt.

During the Korean Conflict (1950 to 1953) there were over thirty thousand cases of epidemic typhus reported amongst the South Korean soldiers and civilian population, the fatality rate was reported to be around six thousand; only a single case of infection among U.S. Military was reported. The U.S. Army implemented the same prevention and control measures as established by the Joint U.S. Typhus Commission; U.S. Troops dusted with dichlorodiphenyltrichloroethane (DDT) and U.S. Military doctors administered the Cox-type vaccine (Angeloni, 1994). DDT is an odorless, tasteless, and colorless organochloride used as widely by the U.S. Military as a pesticide agent (and later other government agencies to include foreign governments). The Cox-type vaccine is a live attenuated vaccine developed in the 1938 by Dr. H. R. Cox, a bacteriologist in the U.S. Public Health Services (Bavaro et al, 2005).

Epidemic (louse-borne) typhus is an infection of the bacterium *Rickettsia prowazekii*, transmitted the the body louse, *Pediculus humanus humanus* (family Pediculidae, order Phthiraptera). Like the tick, the louse is hemimetabolous and feeds on blood for survival. Epidemic typhus typically occurs in colder climates, where conditions of poor hygiene will result in infestations; this includes areas of with recent experience of war, poverty stricken areas, or the aftermath of a recent disaster where large crowds are gathered (Kelly et al, 2002). Epidemic typhus has been documented in the mountainous regions of North America, regions of South America to include Mexico and Peru, and regions of Africa to include Burundi, Ethiopia, Rwanda, Uganda, Nigeria, and Algeria. Humans get the bacterium *Rickettsia prowazekii* after being fed on by a louse. *Rickettsia prowazekii* matures in the gut of the louse and, as the louse feeds, is excreted in the feces and can remain virulent for several days; the bacteria will eventually kill the louse (Sultana, n.d.). The bite wound will be itchy which will illicit the natural

response of scratching; as the bite site is scrayched, the feces are rubbed into the bite wound (self-inoculation) and the bacterium is introduced to it's new host and thus initiates the infection.

The incubation period for epidemic typhus is between 1 – 2 weeks before signs and symptoms of infection begin to surface. The symptoms of epidemic typhus can resemble other infections (such as influenza), so diagnosis is often difficult as typhus is not always the first indicator; it is important to get a good medical history in order to rule out possible infections. Symptoms of epidemic typhus include severe headache, cough, rash, chills, severe muscle pain, sensitivity to light, falling blood pressure, a sustainedhigh fever, fatigue, delirium, stupor, and can ultimately lead to fatalities if left untreated, if treatment is too late in the infection, or if symptoms worsen (Cuomo et al, n.d.). Diagnosis is usually by serology testing (Immunoflouorescence Assay (IFA): using fluorescent dyes to identify antibodies bound to antigens), a biopsy, or polymerase chain reaction (PCR: the amplification of a single DNA copy into thousands of copies) (Angeloni, 1994). The infection is best treated with antibiotics such as doxycycline, cholramphenicol, or ciprofloxacin; doxycycline is the drug of choice while ciprofloxacin is taken for those unable to take doxycycline. Preventive measures for epidemic typhus include delousing via pesticides such as permethrin and malathion, or other chemicals such as lindane (shampoo) (Jensenius and Parola, 1994).

During World War II, there over seven hundred cases of murine typhus reported with fifteen fatalities. Just uder five hundred of the reported cases occurred in the contenental United States (CONUS) with a few in the China and India operation area. During the Vietnam War, murine typhus was reported among several serological tests as the cause of fevers of unknown origin, since at the time the disease was not as popular and thus U.S. Military doctors were not actively testing for it in their differential diagnosis (Artenstein et al, 2005). U.S. Military doctors

and scientists stationed at both the Walter Reed Army Institute of Research (WRAIR) and the Naval Medical Research Institute (NMRI) provided the first differentiation of *Rickettsia typhi* from *Rickettsia prowazekii* through protein testing and were able to identify the antigens responsible for their immunogenicity (Bavaro et al, 2005). While the two species were differentiated from one another, they share many attributes, enough so that the diagnostic testing and experimental vaccines could be used for both diseases. WRAIR and NMRI worked together to develop dipstick tests and enzyme-linked immunosorbent assays based on purified typhus antigens; these diagnostic tests have been used in the surveillance of the Rickettsial diseases across the world.

Murine typhus is a flea-borne typhus caused by the bacterium *Rickettsia typhi*, and is primarily transmitted by the oriental rat flea *Xenopsylla cheopis* (family Pulicidae); *Rickettsia felis*, the bacterium found in the cat flea and the opossum flea, has also been known to cause murine typhus. During a blood meal or by contamination of the respiratory tract through inhalation of infected flea feces; self-inoculation by scratching the bite wound is also possible (Gillespie et al, 2008). The flea is about 2.5 mm in length and has long legs that are designed for long distance jumping. Like ticks, fleas undergo incomplete metamorphosis (hemimetabolous) with stages of their life cycle, egg, larva, pupae and adult. The female flea is capable of laying up to fifty eggs per day (five thousand or more in their lifetime). Murine typhus has a worldwide distribution and occurs in environments from hot and humid to mountainous; murine typhus can also be found in coastal regions and port cities where rodents are common (Kelly et al, 2002). Cases of murine typhus have been reported in China, Australia, Kuwait, Vietnam, Indonesia, Greece, Thailand, and the United States. Murine typhus is similar to epidemic typhus on the

genetic scale, and shares many of the clinical manifestations of scrub typhus and epidemic typhus but can be differentiated with proper serological testing.

The incubation period for murine typhus is 6 – 14 days, with clinical symptoms manifesting as fever, headache, fatigue, rash, joint pain, nausea, vomiting, and muscle pain. In some patients, neurological symptoms such as stupor, seizures, confusion, and imbalance have been observed, as well as leukocytosis (increased white blood cells) or mild leukopenia (decrease in white blood cells) in some cases; renal abnormalities are not uncommon, and anemia is often present (severe with G6PD deficient patients) (Civen and Ngo, 2008). The treatment for murine typhus is similar to epidemic typhus, antibiotics such as doxycycline, chloramphenicol, or ciprofloxacin, with doxycycline being the primary drug of choice. Preventive measures for murine typhus include the use of hygiene and insect repellents such as N,N-Diethyl-metoluamide (DEET) and permethrin treated bed nets.

Scrub typhus is a mite-borne typhus caused by the bacterium *Orientia tsutsugamushi*, transmitted by the mites (genus *Leptotrombidium*, family Trombiculidae, order Trombidiformes) through the bite of an infected larva (Azad and Beard, 1998). The geographical distribution of scrub typhus includes Southern and Eastern Asia (including Pakistan, Japan, Malaysia, Korea, Thailand and Afghanistan), the islands of the Southwestern Pacific, and Northern Australia. The bacterium that causes scrub typhus, *Orientia tsutsugamushi*, has a significant difference in the 16S rRNAs and a cell wall that lacks lipopolysaccharides; these genetic differences have removed scrub typhus from the genus *Rickettsia*, and have categorized it under its own genus, *Orientia* (Gillespie et al, 2008). A disease with clinical presentations of scrub typhus was described in Japan in 1810 and first appeared in medical literature in 1878. British forces documented scrub typhus among military personnel in 1932, and again in 1934, along with Japanese military

personnel stationed in Japan. During World War II, there were reported cases of over seven thousand among the U.S. Military, with over three hundred fatalities: the Japanese suffered over twenty thousand cases, with over sixteen thousand cases reported in the Allied Troops. The Joint U.S. Typhus Commission stepped in to implement protocols for preventive measures and control (clearing brushes near the U.S. camps, repellent laced uniforms), and effectively reduced the number of outbreaks towards the end of World War II.

From 1946 to 1948, the number of cases reached the hundreds with reports of U.S. Military personnel stationed at Camp Fuji becoming ill; the incident occurred again in 1953, where hundreds of U.S. Military were treated with febrile illness. These infections continued from 1959 to 1982, infecting Japanese ground forces, and U.S. Marines from 1981 to 1983 and again from 2000 to 2001. Scrub typhus was first reported in 1962 during the Vietnam War, but was quickly controlled through antibiotic prophylaxis and preventive measures. During the Korean Conflict, only eight cases of scrub typhus were reported among U.S. and United Nations Military personnel, while the civilian population began to experience symptoms. In the U.S. efforts to combat this illness, an overseas laboratory of the WRAIR was established in Seoul, Korea (from 1990 to 1993) and named U.S. Army Medical Research Unit (USAMRU).

The U.S. Army research institute, WRAIR, teamed up with the Armed Forces Epidemiology Board and the Malaysian Institute of Medical Research to conduct clinical trials of an recently developed antibiotic, chloramphenicol, manufactured by Parke-Davis (a pharmaceutical company under Pfizer, located in Detroit, Michigan). The trials began in Malaya in 1948, and not only developed treatment for scrub typhus, but for murine typhus as well; this is where the first successful antibiotic treatments of scrub typhus and murine typhus. The trials and treatments were successful, and the U.S. Military and Malaysian forces continued

to utilize the antibiotics developed through the institutes (Bavaro et al, 2008). Studies continued with collaborations with the U.S. Army, U.S. Air Force, and U.S. Navy, with institutional assistance from Walter Reed Army Medical Center (WRAMC), WRAIR, Naval Medical Research Center (NMRC), and the Armed Forces Research Institute of Medical Sciences (AFRIMS). Scrub typhus had the greatest impact of the Rickettsial diseases during World War II, the U.S. Military partnered with multiple institutes, foreign and domestic, to control the spread of this infectious disease and ultimately developed antibiotic prophylaxis and initiated control measures to minimize the infection rate.

Scrub typhus causes an acute febrile illness caused by the *Orientia tsutsugamushi*. The incubation period is typically 7 – 10 days after being bitten. The common symptoms include a painless maculopapular rash on extremities, fatigue, chills, headache, fevers, conjunctival suffusion, cough, tachypnea, pulmonary infiltrates, gastrointestinal symptoms, regional lymphadenopathy, and often acute hearing loss in less than half of the cases; an eschar (dead tissue) is frequently produced at the bite site, and if untreated, the mortality rates can be above fifty percent (Cuomo et al, n.d.). Treatment for scrub typhus would be the antibiotic doxycycline; if resistance is present in the bacterium (*Orientia tsutsugamushi*), azithromycin or rifampin are optional. Preventive measures include uniforms treated with repellents, surveillance of known habitats, permethrin treated bed nets, topical repellents for clothing, an educational background on tick habitats, permethrin treated bed nets, and a weekly prophylaxis of doxycycline (Coates et al, 1961).

By 1989, around six spotted fever group Rickettsial diseases had been described, today that number has doubled with thirteen spotted fever group Rickettsial diseases. The spotted fever group include some of the more common tick-borne illnesses such as Rocky Mountain spotted

fever, Mediterranean spotted fever, African tick bite fever, Siberian tick typhus, Rickettsialpox, Japanese spotted fever and Queensland tick typhus. With the exception of two, the spotted fever group is transmitted by ticks. Very few of the spotted fever groups are distributed on the same continent, this is likely due to their specific vector association. Humans are incidental hosts (harbour the parasite, but do not play a major role in the life cycle), and are infected through the bite of infected ticks (and in some cases, mites or fleas). All of the ticks responsible for transmitting the spotted fever group Rickettsial diseases belong to the hard tick family, Ixodidae.

Rocky Mountain spotted fever is the disease caused by the bacterium *Rickettsia rickettsii*, and is transmitted through the bite of the brown dog tick, *Rhipicephalus sanguineus* (also a vector for canine babesiosis and canine ehrlichiosis), and *Dermacentor* tick species in the United States and the Cayenne tick, *Amblyomma cajennense*, in both Central and South America; the American dog tick, *Dermacentor variabilis*, is found primarily in the eastern half of the United States, with the Rocky Mountain wood tick, *Dermacentor andersoni*, occupying the western half. Rocky Mountain spotted fever is the most common and the most severe of the spotted fever group Rickettsial diseases and is reported as having the most fatalities of all the tick-borne diseases within the United States (Kelly et al, 2002). The bacterium *Rickettsia rickettsii* is considered the most virulent of the spotted fever group Rickettsial, and is classically presented with the rash, fever, and headache triad.

While there has not been a documented epidemic within the U.S. Military where Rocky Mountain spotted fever was known to be the causative agent of the infection, the U.S. Military is ever so cautious of the hazards that this infectious disease can bring. U.S. Soldiers typically conduct training in field environments within woody and grassy areas, these training environments are the ideal breeding ground for ticks to wait for their host; this behavior is known

as questing, where the tick will climb and perch on stems waiting for an unsuspecting host to pass by to attach and feed. There have been multiple cases of Soldiers returning with ticks on them after a field training exercise, or a Soldier becoming ill from an expected tick bite after a field training exercise, however the prevention and control measures established by the Joint U.S. Typhus Commission under the Surgeon General and Secretary of War have continued to be implemented at the unit level through the command group and has helped to prevent the spread of infections.

The attachment time required for the feeding tick to transmit Rocky Mountain spotted fever is minimum, about 4 – 6 hours, with an incubation time usually between 2 – 14 days. The clinical manifestations include the maculopapular rash on extremities, headache, vomiting, loss of appetite, abdominal pain, fatigue, conjunctival injection (redness of eyes), muscle pain, nausea, and fever; the maculopapular rash will typically start peripherally and expand centrally, often involving the palms and soles, and can progress to petechial rash usually after the sixth day; a petechial rash is a rash consisting of several 1 – 2 mm red or purple spots clustered together on skin forming a rash, these spots are due to internal bleeding from broken capillary vessels (Letizia and Blaylock, 2015). Since Rocky Mountain spotted fever can easily resemble other illnesses and infections, it is essential for health care providers to obtain a travel history and background for possible indicators; early detection and treatment is crucial to accommodate the infected individuals and prevent long-term health problems as fatality occurs early within the first eight days (CDC, 2013).

Similarly to the other Rickettsial diseases, *Rickettsia rickettsii* infects the endothelial cells that line the blood vessels, however, it does not circulate the blood in large numbers unless the patient is in a severe stage of the disease, making detection difficult. Any diagnostic testing is

generally performed on the rash via biopsy (PCR, immunohistochemical staining), serological testing via immunofluorescence assay is possible even as early as the first week of symptoms. Treatment for Rocky Mountain spotted fever is doxycycline. The CDC (2013) recommends doxycycline as the first and last resort for treatment, however, if the patient is allergic to doxycycline the antibiotic chloramphenicol may be considered. Proper use of topical insect repellents (such as DEET) can help deter ticks from attaching. After outdoor activities of expected tick environments, a thorough search can be conducted to remove any ticks that may have attached.

Mediterranean spotted fever (also known as Boutonneuse fever, Kenya tick typhus, Indian tick typhus, or Marsheilles fever) is caused by the *Rickettsia conorii* bacterium. Different subspecies (or strains) of *Rickettsia conorii* exist based on their geographical location, each subspecies is genetically different from the next, but not enough to be categorized as its own species. In the Mediterranean regions, South Africa, Kenya, Somalia, etc. (see figure 4) the dog tick, *Rhipicephalus sanguineus*, is the vector and the bacterium strain is *Rickettsia conorii conorii*. Within India and Pakistan, the bacterium strain is *Rickettsia conorii indica*, and is transmitted by the kennel tick, *Rhipicephalus sanguineus*, the southern cattle tick, *Rhipicephalus microplus* (formerly *Boophilus microplus*), and the African dog tick, *Haemaphysalis leachii*. The strains *Rickettsia conorii israelensis* (Israel, Sicily, Portugal) and *Rickettsia conorii caspia* (Astrakhan region, Kosovo, Chad) are both transmitted by the tick *Rhipicephalus sanguineus*, with *Rickettsia conorii caspia* having the additional vector of the tick *Rhipicephalus pumilio*. The Mediterranean spotted fever, *Rickettsia conorii conorii*, is considered the most fatal, with fatalities being around thirty percent of infected persons (Kelly et al, 2002).

There have been no known documented cases of Mediterranean spotted fever within the United States, and the documented cases within the U.S. Military are minimal, with a few subspecies being identified overseas in deployed U.S. Military personnel. Known cases have occurred in peridomestic areas, persons with poor hygiene practice, and the homeless population, with other cases being reported in persons who are around dogs or within buildings where dogs are held; the season at which infections peak is typically mid summer (July) to early fall (September). The incubation period for Mediterranean spotted fever is similar for all subspecies, with a 5 – 7 day incubation time. As with Rocky Mountain spotted fever (and the other Rickettsial diseases), you can expect to see fever, maculopapular rash on the extremities, headache, nausea, fatigue, eschar, and muscle aches; additional clinical signs include tache noire (black macules occurring on the posterior edge of the knees) and adenopathy (inflammation of glands and lymph nodes). Diagnosis is difficult, as the clinical signs are not easy to differentiate from illnesses with the similar symptoms; serological testing as with the other spotted fever groups as well as a biopsy of the eschar would be the best diagnostic testing available (CDC, 2013). Treatment is with doxycycline, with prevention by use of topical insect repellents, permethrin treated bed nets, surveillance of known habitats, and educational background on tick habitats.

Rickettsia	Vector tick	Geographic repartition	Human disease name	Symptoms present, % patients			Fatal forms? (% patients)
				Fever	Inoculation eschar	Rash	
<i>R. conorii conorii</i> , isolates Malish, Moroccan Kenyan	<i>Rhipicephalus</i> sp., <i>Haemaphysalis leachii</i>	Mediterranean area (southern Europe, northern Africa), Croatia, Slovenia, Kenya, Somalia, South Africa, and surrounding the Black Sea (Turkey, Bulgaria, Ukraine, Romania)	Mediterranean spotted fever	91–100	20–87	93–100	Yes (0–18.1)
<i>R. conorii israelensis</i>	<i>Rh. sanguineus</i>	Israel, Portugal, Sicily	Israeli spotted fever	100	0–46	98–100	Yes (0–3.5)
<i>R. conorii caspia</i>	<i>Rh. sanguineus</i> , <i>R. pumilio</i>	Astrakhan region, Chad, Kosovo	Astrakhan spotted fever	100	23	94	No
<i>R. conorii indica</i>	<i>Rh. sanguineus</i> , <i>Boophilus microplus</i> , <i>H. leachii</i>	India, Pakistan	Indian tick typhus	100	Rare	100 (frequently purpuric)	No

Figure 2: Mediterranean spotted fever categorized by name, location, *Rickettsia conorii* strain and tick vector, with common symptoms and fatalities (Letizia and Blaylock, 2015).

South African tick bite fever is transmitted through the bite of the tropical bont tick, *Amblyomma variegatum*, and the South African bont tick, *Amblyomma hebraeum*. The causative agent is the bacterium *Rickettsia africae*, which was first isolated in Ethiopia. *Rickettsia africae* is found predominantly in sub-Saharan Africa, with some cases recorded in the French West Indies. The *Amblyomma variegatum* and *Amblyomma hebraeum* ticks are aggressive when it comes to feeding, where a single host may be attacked by several ticks (Kelly et al, 2002). These ticks will hide out in shaded tall grasses or bush and wait for a host to pass by; once on the skin of the host, the ticks may crawl around for hours before attaching, and will typically feed at the knee, groin, or axilla (thin, moist, and warm areas of the body) (Letizia and Blaylock, 2015). Incidences of South African tick bite fever have increased over the past several years due to increased tourism and has become very common in travels in sub-Saharan Africa returning to Europe and the United States. Most U.S. Military personnel continue to utilize preventive measures to control the disease within the unit, with proper protective equipment (acaricides, repellents, treated uniforms).

The incubation period for *Rickettsia africae* is 5 – 7 days after the tick bite. Clinical manifestations include similar symptoms from the previous spotted fever group Rickettsial diseases, fever, headache, nausea, fatigue, as well as inoculation eschars at the site of the bite(s) (black crusts surrounded by halo ring), and muscle pain (usually more prominent in the neck), except no macupapular rash. Lymphadenitis (inflammation of the lymph nodes) is common, and multiple eschars generally indicate the aggressiveness of the tick vector (i.e. multiple ticks feeding at once). While the infection rate is high, especially amongst European and U.S. tourists, no fatalities have been reported (Letizia and Blaylock, 2015). As with the previous spotted fever group Rickettsial diseases, clinical diagnostic tests are difficult but proper serological testing (immunoflourescent assays, immunohistochemical stains, PCR) and biopsies can be conducted once antigen levels are high enough and eschars are formed. Treatment with doxycycline is the standard for this disease, and typical prevention measures include topical repellents, surveillance of known habitats, permethrin treated bed nets, treated uniforms and cloths, and pemetrhin treated bed nets to sleeping under.

The final spotted fever group Rickettsial disease to be discussed is Rickettsialpox. Unlike the previous spotted fever group Rickettsial diseases, Ricketssialpox is transmitted via the house mouse mite (*Liponyssoides sanguineus*, family Dermanyssidae, order Mesostigmata), where the house mouse (*Mus musculus*) is the resevoir host. The causitive agent is the bacterium *Rickettsia akari*, and geographical distribution is worldwide in urban areas, with cases reported from Russia, Canada, Korea, Turkey, Mexico, United States, Asia, and South Africa; domestic cases have been reported since 1950 in Boston, Cleveland, New York, Pittsburgh, and Philidelphia, and first identified in Queens, New York, where it spread. Humans will typically be infected only if the house mouse, or another preferred host, is absent from the mites life cycle. *Rickettsia*

akari is morphologically identical to *Rickettsia rickettsii*, but manifests differently in clinical settings (Letizia and Blaylock, 2015). According to Public Health Agency of Canada (2011), approximately eight hundred total cases have been reported, with the majority of these cases being from 1940s to the 1950s, with zero fatalities reported.

The incubation period for Rickettsialpox is 12 – 15 days, but some reports have shown up to 28 days. Similar to the other spotted fever group Rickettsial diseases, the clinical manifestations include lymphadenopathy, eschars, fever, headache, muscle pains, fatigue, and a papulovesicular rash (a rash consisting of both papules and vesicles) on the body and extremities, which will generally erupt 2 – 3 days after initial symptoms. The papulovesicular rash can mimic chickenpox, smallpox, and cutaneous anthrax; cutaneous anthrax and smallpox are on the CDC's list of Category A biological agents (Letizia and Blaylock, 2015; CDC, 2015). Clinical testing consists of serological tests such as immunofluorescence assay and antigen testing; blood work can be taken as well with laboratory results showing mild leukopenia (decreased white blood cells), thrombocytopenia (decreased platelets), and proteinuria (protein in urine). The standard of care antibiotic for treatment is doxycycline, chloramphenicol can be considered if the patient is allergic to doxycycline. Preventive measures include topical repellents, treated uniforms and cloths, educational guidance to civilian and military personnel, surveillance of known habitats, and permethrin treated bed nets to sleeping under (Letizia and Blaylock, 2015).

Lyme disease is a common tick-borne disease in the United States, Russia, and Europe, with most cases are reported during the spring and summer months. The bacterium *Borrelia burgdorferi* (family Spirochaetaceae, order Spirochaetales) is a spirochete that causes lyme disease in the United States (Letizia and Blaylock, 2015). The vectors for lyme disease in the United States consist of two hard bodied ticks, the deer or black-legged tick, *Ixodes scapularis*,

in the eastern United States, and the bear or tick, *Ixodes pacificus*, in the western United States. In Europe, the disease is vectored by the castor bean tick, *Ixodes ricinus*, and in Eastern Europe and Russia, by the tiaga tick, *Ixodes persulcatus*; in Europe and Russia, the bacteria *Borrelia afzelii* and *Borrelia garinii* are the causative agents of lyme disease (Levin, 2009). The usual hosts are deer (family Cervidae) and the reservoir host is typically the white footed mouse, *Peromyscus leucopus*. Humans are infected through the bite of a nymph of either tick species, where the nymph will feed for several days, the nymph will need to be attached for at least 24 hours before the bacteria can be transmitted (Letizia and Blaylock, 2015).

As with the spotted fever group Rickettsial diseases, lyme disease is seen among the U.S. Military typically after field training with few cases being reported. According to a report conducted by Smith et al (1996), the civilian population, nearly one hundred thousand cases have been reported to the CDC since lyme disease came on the radar as a nationally reportable disease in 1991. The report was conducted at U.S. Army Center for Health Promotion and Preventive Medicine (CHPPM) where an investigation of the DoD research and surveillance activities involving lyme disease and other tick-borne diseases located on Aberdeen Proving Grounds. The report consisted of detailed educational guides and preventive measures for use by U.S. Soldiers and DoD civilians; the report showed tick removal kits and tick cards with speciation and disease association, both of which CHPPM distributes to DoD Health Clinics worldwide. The DoD has a insect repellent system that they advertise as three-prong: permethrin impregnated uniforms (lifetime protection) to help repel ticks, DEET to be used on any exposed areas of the skin, and properly worn uniforms for maximum protection against ticks. On the research side, the U.S. Army has developed field tests such as the PCR test kit, which is a virtual lab within a suitcase sized case. CHPPM also has a mapping system for tick populations where the density

overlays are pinpointed on military maps for risky areas of heavy tick infestation (Smith et al, 1996). The level of commitment from CHPPM and other DoD installations concerning tick-borne diseases is serious as tick-borne disease effect more than just the U.S. Military and DoD civilian populations, but have caused infections on the global scale and continue to put the world at risk for such diseases.

The CDC (2013) lists the incubation period for lyme disease is between 3 – 30 days, where a rash known as erythema migrans, that will gradually expand over several days, is seen in roughly eighty percent of reported cases. The rash will have a central clearing that creates a bullseye appearance (characteristic for diagnosis); with some cases, erythema multiforme lesions on the skin can also appear. The addition of the usual symptoms of fatigue, headache, fever, chills, nausea, and swollen lymph nodes vary depending on case. In late stage infections, encephalomyelitis (inflammation of the brain and spinal cord), carditis (inflammation of the heart), and arthritis are common, where chronic arthritis is possible (Letizia and Blaylock, 2015); these three conditions point out the seriousness of lyme disease if not treated early and appropriately. Laboratory testing with serology and PCR are possible for detection in the later stages, if the bullseye rash isn't characteristic for a diagnosis. Treatment for lyme disease includes doxycycline as well as alternative antibiotics such as amoxicillin or azithromycin, and in cases with encephalomyelitis, doxycycline, ceftriaxone or cefotaxime is recommended (CDC, 2013). Preventive measures include topical repellents (DEET), treated uniforms and cloths, educational guidelines for civilian and military personnel, surveillance of known tick habitats, and pemetrin treated bed nets for sleeping (Letizia and Blaylock, 2015).

Ehrlichiosis and anaplasmosis are diseases that have been noted after recent tick exposure and are categorized under the Rickettsial diseases. The geographical distribution and clinical

manifestations are very similar in these two tick-borne diseases. The U.S. distribution includes South Central and Southeastern United States are the primary locations, however cases have been reported in forty-seven states, as well as Europe and Asia. Ehrlichiosis is caused by three bacteria species, *Ehrlichia chaffeensis*, *Ehrlichia ewingii*, and *Anaplasma phagocytophilum* (causes ehrlichiosis and anaplasmosis); *Ehrlichia chaffeensis* is the causative agent of Human Monocytic Ehrlichiosis (invasion of the monocytes and macrophages), which was initially diagnosed in 1987, while Human Granulocytic Anaplasmosis, diagnosed seven years later, invades granulocytes (Letizia and Blaylock, 2015). The vector for these disease in the U.S. is the lone star tick, *Amblyomma americanum*, however, the American dog tick, *Dermacentor variabilis*, western black-legged tick, *Ixodes pacificus*, have also been known to transmit the diseases; for the international infections, the vectors include the deer tick, *Ixodes scapularis*, *Ixodes pacificus*, the castor bean tick, *Ixodes ricinus* (Europe), and the tiaga tick, *Ixodes persulcatus* (Asia).

The first impact on the U.S. Military occurred during the Vietnam War where hundreds of military working dogs were infected with canine ehrlichiosis (*Ehrlichia canis*) with signs of pancytopenia, hemorrhage, and high fatality rates; two hundred twenty U.S. Military working dogs died between 1968 and 1970, with more being euthanized due to the deteriorating infection. Infections among U.S. Military and DoD civilians has occurred in training and deployed environments with tick infested areas; outbreaks occurred in northwest Wisconsin and Minnesota, but the number of reported cases was minimal until 1993, where more than a thousand cases were reported at Camp Bullis (Kelly et al, 2002). Since the Vietnam War, the U.S. Military has collaborated with several U.S. and foreign government agencies to conduct investigational research on ehrlichiosis and anaplasmosis. Research concerning tetracycline

therapy conducted at WRAIR resulted in fifty percent response rate among infected military working dogs. WRAIR continued to conduct research on the etiology and pathology of canine ehrlichiosis and the bacterium responsible *Ehrlichia canis* (Bavaro et al, 2005). Between 2000 and 2007, the number of reported cases increased to three cases per one million persons per year, with a low fatality rate.

The incubation period for ehrlichiosis and anaplasmosis are between 7 – 14 days, with signs and symptoms presented with fever, muscle pain, malaise, chills, nausea, abdominal pain, confusion, headache, vomiting, cough, possible rash (rarely seen, uncommon), and conjunctival injection (red eyes) seen more in ehrlichiosis than in anaplasmosis. Laboratory testing for these diseases have found a decrease in leukocytes (white blood cells) and thrombocytes (platelets), with elevated liver function test (LFT) (Letizia and Blaylock, 2015). As with all of the Rickettsial diseases, the prescribed method of treatment is by use of antibiotic doxycycline, as the use of these antibiotics and other tetracycline drugs has been associated with a higher fatality in patients (CDC, 2013). Prevention is best with the use of treated uniforms and cloths, educational guidelines for civilian and military personnel, surveillance of known tick habitats, and permethrin treated bed nets for sleeping (Letizia and Blaylock, 2015).

Q fever is a tick-borne disease where livestock (cattle, sheep, goats) are the reservoir hosts. The causative agent is *Coxiella burnetii*, and while it can be transmitted via tick bite, it is more commonly transmitted by ingestion or inhalation; isolation from the *Dermacentor andersoni* ticks in western Montana. The bacterium *Coxiella burnetii* is excreted in the milk, urine, and feces of the infected livestock; *Coxiella burnetii* can also be shed in high volumes within the placental and amniotic fluids during birth. Q fever has a worldwide distribution, with fewer cases in the United States, and the majority of cases being reported in the Netherlands .

While Q fever is not a true Rickettsial disease, it is grouped with them due to the similarities in clinical manifestations (Litizia and Blaylock, 2015). Q fever was first described in 1935 in Australia, and is transmitted by inhalation of aerosols from infected animal tissues or byproducts, or by tick bite (Kelly et al, 2002); *Coxiella burnetii* has some ideal characteristics for a good biological weapon due to its highly infectious nature, and it is listed under the NIAID (2009) Category B Priority Pathogens.

The CDC (2013) lists signs and symptoms to include high fever, headache (often severe), malaise, muscle pains, non-productive cough, chills, sweats, vomiting, diarrhea, nausea, abdominal pain, chest pain. Litizia and Blaylock (2015) list the three major clinical presentations to include a self-limiting febrile illness, pneumonia accompanied by fever and retro orbital pain, and hepatitis accompanied by fever and doughnut shaped granulomas; endocarditis (inflammation of inner heart layer), optic neuritis (inflammation of optic nerve), and encephalitis (inflammation of the brain) are a few of the complications that can manifest if early treatment is not provided. Bacterial cultures can be performed to assist with diagnosis; cultures are performed within a Biosafety Level 3 (BSL-3) laboratory due to the highly infectious nature of *Coxiella burnetii*, the CDC and the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) are compatible laboratories capable of culturing *Coxiella burnetii* (Litizia and Blaylock, 2015).

Outbreaks of tick-borne diseases remain common in the temperate and tropical regions of the world and within the United States, and the U.S. Military continues to come into contact with these diseases during overseas deployments and domestic field exercises. The U.S. Military and all the collaborating agencies continue to research and develop ways to prevent further infection from these diseases at the laboratories and other U.S. Military facilities located around the world;

these agencies and organizations continue to take measures in the operation for prevention and control, and the production of possible vaccines and prophylactic drugs. The CHPPM continues to track the tick-borne diseases within the United States and neighboring countries; the surveillance system helps with monitoring, prevention, control, and research efforts for the Rickettsial diseases. The Armed Forces Pest Management Board (AFPMB) and United States Armed Forces Health Surveillance Center (AFHSC) continue to provide annual surveillance on vector-borne diseases, with detailed reports by Service Branch to include active component, National Guard, Reserve units, and other beneficiaries such as DoD civilians and contractors.

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