The Past and Present Threat of Rickettsial Diseases to Military Medicine and International Public Health

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Morbidity and mortality caused by rickettsioses have had a major influence on military activities and public health for >2000 years. The threat posed by the rickettsioses is reviewed, focusing on the impact and epidemiology of those that have adversely influenced wartime operations and the current challenges posed by these diseases. With their uneven worldwide distribution, the discovery of drug-refractory strains of *Orientia tsutsugamushi,* the increased threat of their use in acts of bioterrorism, frequent deployment of troops to regions of endemicity, and exposures due to increased humanitarian missions, these diseases continue to be a threat to military personnel in the field. Effective strategies to reduce the impact of these diseases include development of effective vaccines, enhanced surveillance, and development of new safe, effective, and odorless repellants. The continuation of a proven, highly productive military infectious disease research program is essential for providing solutions to these daunting tasks.

World and military histories are replete with examples of infectious diseases that changed the course of nations. Rickettsial diseases are widely distributed throughout the world. They are generally incapacitating, sometimes fatal, but frequently unrecognized illnesses that cause fevers in susceptible populations. When recognized, they are often easily treated, but the unusual conditions created by war, military operations, or civil unrest often delay or prevent appropriate treatment. Rickettsial diseases are notoriously difficult to diagnose because they share symptoms with many other febrile diseases with similar epidemiology. Thus, the reported historical numbers of cases of infections with rickettsiae are probably not very accurate and are known to be severely underreported. Strategies to ameliorate the military and public health impact of rickettsial and other infectious diseases include medical training and ongoing global surveillance, improved recognition of clinical disease, and the development of novel detection systems, treatments, and approaches to prevention. Our purpose is to review the epidemiology of the rickettsioses, to describe the impact of those rickettsial diseases that have adversely influenced past military deployments and operations, and to outline the current challenges posed by this family of diseases to present military operations and international public health.

The opinions and assertions herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army, the Department of the Navy, the Department of Defense, or the Centers for Disease Control and Prevention.

Financial support: US Army Medical Research and Materiel Command and Naval Medical Research Center (work unit no. 61102AS13JA006).

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Clinical Infectious Diseases 2002; 34(Suppl 4):S145–69

1058-4838/2002/3412S4-0001$03.00

THE RICKETTSIOSES

The rickettsioses, caused by the rickettsiae, members of the order Rickettsiales, which historically included the families Rickettsiaceae, Bartonellaceae, and Anaplasmataceae, were originally defined as obligate intracellular parasites that grow only within eukaryotic host cells [1]. Members of the family Bartonellaceae, however, although highly fastidious, grow slowly on enriched bacteriologic culture media. This latter characteristic, as well as 16S rRNA sequence data, DNA relatedness data, guanine-plus-cytosine content, and other phenotypic characteristics, has resulted in the unification of the genera *Bartonella* and *Rochalimaea* and removal of the family Bartonellaceae from the order Rickettsiales [2]. The rickettsiae are members of the alpha subdivision of the Proteobacteria, short rod-shaped or coccobacillary gram-negative bacteria 1–2 μm $\times$ 0.3–0.5 μm in length and diameter, and divide by transverse binary fission [3, 4]. Although the organisms stain poorly by use of Gram's stain, they are easily observed after Giemsa staining. These groups of bacteria are very difficult to isolate from patient samples, even by experienced specialty laboratories. Different agents are transmitted by specific arthropod vectors, including mites, fleas, flies, ticks, and lice. Except for louseborne epidemic typhus, Carrión's disease, and possibly trench fever, humans are incidental disease hosts. The rickettsial diseases are generally characterized by sudden onset of nonspecific symptoms, including acute sustained high fever, severe headache, myalgia, arthralgia, and malaise. In some diseases, eschars and characteristic skin rashes occur. The bacteriostatic antibiotics chloramphenicol and tetracycline or its derivative doxycycline are normally effective in treating the rickettsioses [3, 5–9]. Table 1 lists the primary rickettsial diseases of military importance along with their causative agents, modes of transmission and distribution, and geographic distribution.

In the past, human rickettsial diseases caused by members of the genus *Rickettsia* were collectively called "typhus fever" and early in the 20th century included even nonrickettsial illnesses such as typhoid fever. Later, the typhus fevers were differentiated primarily by a characteristic lesion (e.g., the eschar of scrub typhus or the tache noire of Mediterranean spotted fever), causative agent, and vector (e.g., louse, flea, tick, mite).

Although all agents cause somewhat similar fevers and rashes, characterization of the causative agents resulted in 3 distinct groups based on their antigenic composition, generally referred to as the spotted fever or tick typhus group (e.g., Rocky Mountain spotted fever), typhus group (louseborne or epidemic typhus, endemic or murine typhus), and scrub typhus group.

Epidemic typhus. Epidemic typhus is primarily a human louse *(Pediculus humanus)*–borne infection caused by *Rickettsia prowazekii.* Transmission of the agent by the human body louse was proven by Nicolle in 1909 [7, 12], and in 1916, Da Rocha-Lima proved that *R. prowazekii* was the etiologic agent [13]. Transmission usually occurs by self-inoculation of rickettsia-laden louse feces by scratching the bite site but can also occur by inhalation of an aerosol containing the dried feces. The louse itself usually dies from the infection. Typically, epidemic typhus occurs in colder climates under conditions of poor hygiene resulting in louse infestation, which are common with conditions of war, famine, and social disruption. Such conditions have occasionally led to massive reemergence of epidemic typhus. Recent outbreaks have occurred in mountainous North and South American regions, including Peru and Mexico, and African countries, including Algeria, Uganda, Rwanda, Ethiopia, Nigeria, Zaire, and Burundi [7, 14, 15]. In Burundi, after the outbreak of civil war in 1993, >760,000 refugees crowded into refugee camps. Starting in August 1995, epidemic typhus had been reported in 76 of 102 patients in N'Gozi prison in northern Burundi, and by September 1997, an estimated 45,000 cases had occurred, most in the higher, colder regions of the country [15]. Although major epidemics of typhus have not occurred in Russia since the 1940s, political unrest and major changes in social conditions have led to increases in body louse infestations and to a small outbreak of epidemic typhus in the winter of 1997–1998 [7, 16]. This disease was purported to be one of several infectious diseases responsible for the massive hospitalization of Soviet troops during the military actions in Afghanistan during the early 1980s [17].

Epidemic typhus is known by several names, including "louseborne typhus," "camp fever," "ship fever," "war fever," "jail fever," *Fleckfieber* (German), *typhus exanthematique* (French), *el tabardillo* (Spanish), and *hassin chifusu* (Japanese). In addition to the typical severe headache and fever that occurs 8–12 days after exposure, epidemic typhus presents with a generalized macular or maculopapular rash that spreads from the trunk to the arms and legs. There is no eschar associated with the inoculation site. When untreated, epidemic typhus has an overall case fatality rate of ~20%, rising to >50% in people >50 years old [12]. A recrudescent, sometimes milder form of the disease, called Brill-Zinsser disease, was originally reported in the late 1890s, when Brill noted typhus-like outbreaks with no vector involvement. Later epidemiological investigations of Zinsser suggested that chronically infected humans were the reservoir of *R. prowazekii* and the source of new epidemics in lousy populations as long as 40 years after their initial infection [12, 18, 19]. Factors such as stress (e.g., wartime), other illness, or immunosuppression may trigger recrudescence of epidemic typhus. Although humans act as the primary reservoir of epidemic typhus, there is also evidence of a flying squirrel/flying squirrel ectoparasite reservoir in the eastern United States that may cause occasional human disease [20].

Murine typhus. Murine (endemic or fleaborne) typhus, caused by incidental infection with *Rickettsia typhi,* is one of the most prevalent of the human rickettsioses, although its

Table 1. Principal causative agents, modes of transmission and distribution of the rickettsial diseases of military importance.

Group, disease	Causative agent	Mode of transmission	Geographic distribution
Typhus			
Epidemic typhus	*Rickettsia prowazekii*	Infected human body louse feces; flying squirrel flea	Worldwide
Brill-Zinsser disease	*R. prowazekii*	Recrudescence of latent *R. prowazekii* infection	Worldwide
Murine (endemic) typhus	*Rickettsia typhi (mooseri)*	Infected rat flea feces	Worldwide
Spotted fever			
Rocky Mountain spotted fever, Brazilian spotted fever	*Rickettsia rickettsii*	Tick bite	North and South America
Boutonneuse fever, Mediterranean spotted fever	*Rickettsia conorii*	Tick bite	Mediterranean littoral to India; Africa
Astrakhan spotted fever	*Rickettsia caspii*	Tick bite	Astrakhan, Russia
North Asian (Siberian) tick typhus	*Rickettsia sibirica*	Tick bite	Siberia, Armenia, Pakistan, northern China
Oriental (Japanese) spotted fever	*Rickettsia japonica*	Tick bite	Southwest Japan
Australian (Queensland) tick typhus	*Rickettsia australis*	Tick bite	Queensland, Australia
African tick bite fever	*Rickettsia africae*	Tick bite	Sub-Saharan Africa
Israeli tick typhus	*Rickettsia sharonii*	Tick bite	Israel
Rickettsialpox	*Rickettsia akari*	Mite bite	USA, Korea, Ukraine, Croatia
Flinders Island tick typhus	*Rickettsia honei*	Tick bite	Flinders Islands, Tasmania
Asian or Thai tick typhus	TT-118	Tick bite	Thailand, Malaysia
Cat flea typhus	*Rickettsia felis*	Cat flea bite (?)	Western and southwestern USA
Scrub typhus	*Orientia tsutsugamushi*[a]	Chigger bite	Afghanistan, Pakistan and India to Siberia, Southwest Pacific Islands, Southeast Asia, northern Australia
Ehrlichioses[b]			
Canine ehrlichiosis; tropical canine pancytopenia	*Ehrlichia canis*	Tick bite	Southeast Asia; southwestern USA, Venezuela
Human monocytic ehrlichiosis	*Ehrlichia chaffeensis*	Tick bite	Americas, Europe, Thailand
Human granulocytic ehrlichiosis	*Anaplasma phagocytophila*	Tick bite	USA, Europe
Sennetsu fever	*Neorickettsia sennetsu*	Unknown	Japan; possibly Malaysia
Q fever	*Coxiella burnetii*	Infectious aerosol, tick bite	Worldwide
Bartonelloses[c]			
Trench fever	*Bartonella quintana*	Infected louse feces into skin; rodent contact (?)	USA, Mexico, Europe, Africa, Middle East, China, Japan, Bolivia
Bartonellosis (Oroya fever, Verruga peruana, Carrion's disease)	Bartonella bacilliformis	Infected sand fly	Andes Mountains of Colombia, Ecuador, Peru, 610–2440 m elevation
Cat scratch disease	*Bartonella henselae*	Cat or dog contact	North America, Europe
Bacillary angiomatosis	*Bartonella* species	Unknown	Worldwide
Rodent bartonelloses	*Bartonella elizabethae, Bartonella* species	*Rattus* or other rodent contact	Worldwide

[a] *Rickettsia tsutsugamushi* was renamed *Orientia tsutsugamushi* because of differences >10% in 16S rRNA and in cell wall structures that lack lipopolysaccharide and peptidoglycan typical of other members of the genus [10].

[b] Molecular phylogenetic analyses with use of 16S rRNA gene and groESL operon nucleic acid data and serological cross-reactions suggest that current species of genus *Ehrlichia* should be distributed into genera of the *Anaplasmataceae,* which are now designated as *Ehrlichia, Anaplasma, Neorickettsia,* and *Wolbachia* [11]. *Ehrlichia sennetsu* is now designated *Neorickettsia sennetsu* [11]).

[c] 16S rRNA sequence data, DNA relatedness data, guanine-plus-cytosine content, and other phenotypic characteristics have resulted in unification of genera *Bartonella* and *Rochalimaea,* and proposed removal of family *Bartonellaceae* from order *Rickettsiales* [2].

primary cycle is with rodents, which act as reservoirs, and the vector fleas *(Xenopsylla cheopis)*. Murine typhus has a worldwide distribution and occurs in a variety of environments, from hot and humid to semiarid and mountainous, and often is found in international port cities and coastal regions where rodents are common [21, 22]. In recent years, it has been reported in the United States, Australia, China, Thailand, Kuwait, Indonesia, Vietnam, and Greece [9, 22]. It shares symptoms with many other febrile illnesses, including epidemic typhus and scrub typhus, and is frequently misdiagnosed. As a result, its incidence is probably grossly underestimated [22]. Although likely an ancient disease, murine typhus was first differentiated from epidemic typhus by Maxcy [18] in the mid-1920s in the United States and from scrub or "rural" typhus by Fletcher at the Malaysian Institute for Medical Research [23]. In contrast to the severity of epidemic typhus, murine typhus, although requiring hospitalization in ~10% of cases, is usually a relatively mild febrile illness with an incubation period of 6–10 days followed by a fever of 9–15 days' duration [9, 24]. The rash is primarily found on the trunk and is usually less pronounced than that of epidemic typhus. It is often uncomplicated, is generally self-limiting, and has an overall case fatality rate of ~4% [24]. The rat flea, the principal vector involved in human infection, does not die from the rickettsial infection and remains infectious throughout life [22]. Like epidemic typhus, human infection is primarily caused by scratching the bite site and self-inoculating the rickettsia-laden feces, although *R. typhi* can also be transmitted directly by flea bite [22]. Murine typhus, sometimes known as "urban" or "shop" typhus, is often confused clinically with scrub typhus, but it is generally urban-acquired and lacks the pathognomonic eschar indicative of scrub typhus.

Tick typhus or the spotted fevers. As recently as 1989, only 6 spotted fever group rickettsioses had been described [25]. Now, at least 13 human diseases are recognized to be caused by the spotted fever group rickettsiae, only a few of which are widely distributed on >1 continent because of their specific vector associations (table 1). Humans are incidental hosts that become infected through the bite of infected ticks or mites.

Rocky Mountain spotted fever, caused by *Rickettsia rickettsii,* is transmitted by the bite of ticks, including *Dermacentor* species in North America and *Amblyomma cajennense* in Central and South America. It is the most severe of the spotted fever group rickettsial diseases and is the most commonly fatal tickborne disease in the United States. Case fatality rates up to 30% were reported in the preantibiotic era, but rates have remained between 2% and 10% since the 1950s [26, 27]. Risk factors associated with death include older age and delayed or no antibiotic treatment. There were 242 cases of Rocky Mountain spotted fever in the United States between 1981 and 1992, 4% of which were fatal. However, in a recent Brazilian outbreak, 66% of cases were fatal [28]. Rocky Mountain spotted fever has been reported in Canada, Mexico, Costa Rica, Panama, Colombia, and Brazil [25]. Only about half of confirmed cases of Rocky Mountain spotted fever have the classic triad of rash, fever, and headache. The incubation period is 2–14 days (mean, 7 days), and ~20% of patients have a small primary lesion at the site of tick bite [26, 27]. This disease is characterized by fever, malaise, severe headache, myalgia, rash, nausea, vomiting, and abdominal pain. The rash, which appears on about day 3 of the illness, is characterized as pink and maculopapular, appearing on the forearms, palms, soles, and legs.

Mediterranean spotted fever is caused by *Rickettsia conorii* and is transmitted by *Rhipicephalus sanguineus* ticks. Also known as "boutonneuse fever," "Indian tick typhus," "Marseilles fever," and "Kenya tick typhus," Mediterranean spotted fever is endemic in southern Europe, North and West Africa, India, Pakistan, Israel, Russia, Georgia, and the Ukraine [8]. The frequency of rash is nearly 100%, and an initial cutaneous lesion with necrotic center ("tache noire") is often present at the site of tick bite. Severe Mediterranean spotted fever has been reported in ~6% of cases, with mortality rates as high as 2.5%, including antibiotic-treated cases [29, 30].

South African tick bite fever was initially named by Nuttall in 1911 [31]. The agent, *Rickettsia africae,* was first isolated in Ethiopia from an *Amblyomma variegatum* tick [8]. The disease has been recently described in patients in Zimbabwe [8, 32], Botswana [33], and central Kenya [34] and in a neonate in South Africa [35]. This rickettsiosis is characterized by a pathognomonic lesion at the site of tick bite and regional lymphadenopathy, frequently without rash. It is generally a mild disease of 3–4 days' duration, although severe forms lasting 10–12 days and sometimes resulting in death have been described [31, 33, 34]. Very high attack rates of *R. africae* infections transmitted by *Amblyomma* ticks have been reported in southern Africa [33, 36].

Siberian tick typhus, caused by *Rickettsia sibirica* and transmitted to humans by *Dermacentor, Hyalomma,* and *Haemaphysalis* ticks, was first described in 1943 in central Siberia [31]. This disease has been reported across central Asia and the former Soviet Union, Mongolia, what was then Czechoslovakia, and Pakistan [8, 25, 31].

Rickettsialpox *(Rickettsia akari)* is the 1 known miteborne spotted fever group rickettsiosis. It is caused by bite of blood-sucking infected mites *(Allodermanyssus sanguineus)* that normally feed on a variety of small mammals [37, 38]. It was first reported in New York City in 1946 and has since been reported in Ukraine and Croatia and more recently in South Africa [38].

In addition to these long-established spotted fever group rickettsioses, a series of well-characterized, newly recognized illnesses have been documented in patients on several continents in the past 18 years (table 1). In Japan, several cases of

a spotted fever group agent–caused illness were detected in 1984 by use of the Weil-Felix reaction [39] and confirmed by means of the more specific indirect immunoperoxidase test [40], and in 1985, *Rickettsia japonica,* agent of Japanese or Oriental spotted fever, was isolated from a febrile, exanthematous patient [41]. Two relatively mild spotted fever group rickettsioses are known to occur in Australia: Queensland tick typhus, caused by *Rickettsia australis* and first reported during World War II [31, 42], and Flinders Island spotted fever, caused by *Rickettsia honei.* The latter illness, although identified as a spotted fever group rickettsiosis in 1991, had been recognized years earlier by a local physician as a distinct but milder illness [43]. Unlike the case in Queensland tick typhus, an eschar is an uncommon finding in Flinders Island spotted fever [8]. Also in 1991, an *R. conorii*–like agent named *Rickettsia caspii* was isolated from a patient with "eruptive summer disease" in Astrakhan on the Caspian Sea [44]. The agent is thought to be transmitted by the *Rhipicephalus pumilio* tick [45]. The agent of Israeli tick typhus, *Rickettsia sharonii,* is closely related to but distinct from *R. conorii.* This agent has recently been associated with human disease in Portugal and in Sicily in addition to Israel [45]. The disease is typically more severe than Mediterranean spotted fever, and the eschar is frequently absent.

More recently, *Rickettsia mongolotimonae, Rickettsia slovaca,* and *Rickettsia helvetica* have been identified as causes of human rickettsioses in Europe. Since 1996, a rickettsial agent originally isolated from *Hyalomma asiaticum* ticks in Mongolia has been detected in several patients in southern France [45]. The agent with the proposed name *R. mongolotimonae* is associated with *Hyalomma* species ticks in sub-Saharan Africa [30]. In 1996, Raoult et al. [46] reported on a new febrile human disease transmitted by a *Dermacentor marginatus* tick in the Pyrenees mountains. Western blot analysis indicated specific *R. slovaca* reactivity, and that agent was isolated from the attached tick. In 1999, *R. helvetica,* transmitted by the bite of *Ixodes ricinus* ticks, was implicated as the cause of a human rickettsiosis in eastern France [47]. In addition, serum samples collected from 35 (9.2%) of 379 forest workers in that region were specifically reactive to *R. helvetica* antigens. Those reports suggest neurological syndromes associated with *R. slovaca* and *R. helvetica. Rickettsia amblyommii* has been serologically implicated as causing a mild spotted fever group rickettsiosis, but there have been no isolates from humans yet [48–50].

A rickettsial agent first detected in 1990 in California in cat fleas *(Ctenocephalides felis)* was subsequently identified in a patient in Texas [51]. The rickettsia, then named the ELB agent, was later detected in the blood of 3 additional patients from Texas and Mexico by use of PCR [52]. Specific serological testing also showed reactivity of the agent to serum from patients in France and Brazil. Although the California flea typhus agent was initially considered a typhus group rickettsia, molecular characterization of the agent tentatively named *Rickettsia felis* places it in the spotted fever group [8, 30, 53]. In addition to the spotted fever group rickettsial agents described here, many strains or species have not yet been shown to be human pathogens [25, 30].

Scrub typhus. Scrub typhus, also known as chiggerborne rickettsiosis, tsutsugamushi disease, or tropical or rural typhus, is caused by infection with *Orientia tsutsugamushi* 6–21 days after the bite of infected *Leptotrombidium* mites. Because of significant differences in 16S rRNAs and in cell wall structures, which lack lipopolysaccharide and peptidoglycan typical of other members of the genus, the organism was removed from the genus *Rickettsia* and moved to the new genus [10]. The mites act as both reservoir and vector. Whereas most stages in their life cycle are free-living, the parasitic larval chigger stage feeds on humans and rodents. Geographic distribution of the disease occurs within an area of ~13,000,000 km^2 and includes eastern and southern Asia, including Pakistan and Afghanistan, northern Australia, and the islands of the southwestern Pacific [6, 54]. There is no typical ecology for this disease. It has been acquired wherever the vector mites are found, from sea level to the mountainous heights >2135 m in Borneo and India, under alpine and subarctic conditions as high as 3050 m, and in Pakistan seashores, disturbed rain forests, plantations, riverbanks, semiarid deserts, and terrain undergoing secondary vegetative growth [21, 55]. It has been found more recently in urban settings and even in rice paddies [6, 56, 57].

Scrub typhus is an acute febrile illness that can be mild to fatal depending on the *Orientia* strain. It typically presents with maculopapular rash, eschar (although the otherwise pathognomonic lesion may not be present), a dramatic response to tetracycline, headache, lymphadenopathy, and frequently CNS involvement [6]. Accurate diagnosis is very important, because without appropriate antibiotic treatment, a fatal course is possible, especially if complicated by disseminated intravascular coagulation [58]. Before the age of antibiotic therapy, patients with scrub typhus had high mortality rates, up to 50%–60%, with a clinical course ranging from 10 to 28 days and a protracted convalescence of up to 4 months [6, 59, 60]. It often occurs in conjunction with malaria, leptospirosis, and amebiasis. Although ~25%–50% of scrub typhus cases occur in children, most cases occur through agricultural exposure, such as in rice field workers of Thailand, Japan, or Korea and oil palm and rubber plantation workers of Malaysia [6]. The growing popularity of "ecotourism"—camping, trekking, and rafting in areas of endemicity—has resulted in this disease being increasingly reported in European and American tourists returning home [6]. Although clear descriptions of scrub typhus are found in Chinese texts of 313 A.D., scrub (miteborne) typhus was first described in the modern literature in Japan in 1810. It appeared in the Western literature in 1878 as a disease in river valleys that affected farmers

working during July and August [59, 61]. Because of this association, it is also known in Japan as *tsutsugamushi* ("noxious" or "dangerous mite") disease, *Kedani* ("hairy mite") river fever, or "Japanese river fever." Identification of the causative agent was attributed to Norio Ogata (among others) in the late 1920s [62]. Outside Japan, Lewthwaite and Savoor, working at the Malaysian Institute for Medical Research in 1940, established the etiologic agent of scrub typhus as the same as that causing disease in Japan [23, 63].

Ehrlichioses. The *Ehrlichia* species are currently placed in the order Rickettsiales. Recent molecular phylogenetic analyses with use of the 16S rRNA gene and *gro*ESL operon nucleic acid data and serological cross-reactions suggest that current species of the genus *Ehrlichia* should be distributed into distinct clades that are now designated as *Ehrlichia, Anaplasma, Neorickettsia,* and *Wolbachia* [11]. The ehrlichiae are obligate intracellular gram-negative bacteria that grow within cytoplasmic vacuoles [64]. They are found in humans and animals throughout the world. Four forms of human ehrlichiosis have been identified. The first reported human ehrlichiosis, caused by *Neorickettsia sennetsu* (table 1) [11], was identified in 1954 in Japan and may cause a mononucleosis-like illness elsewhere in Asia [23]. It is a self-limiting disease and the vector remains unknown. Forty-six isolate-positive cases were reported in Japan between 1953 and 1978 [65]. In the United States, human ehrlichiosis was first recognized in 1986 near Gurdon, Arkansas, after diagnosis in a 51-year-old man who became ill after tick attachment. The illness presented similarly to Rocky Mountain spotted fever and was characterized by headache, fever, malaise, leukopenia, anemia, thrombocytopenia, kidney failure, presence of cytoplasmic inclusion bodies in the patient's leukocytes, and antibodies reactive to *Ehrlichia canis* but not spotted fever group rickettsiae. The causative agent was subsequently identified as a previously unreported agent, *Ehrlichia chaffeensis. E. chaffeensis,* the agent of human monocytic ehrlichiosis, is associated with a history of tick bite *(Amblyomma americanum)* and has a geographic distribution within the south-central and southeastern United States. This disease was also referred to as the "spotless" Rocky Mountain spotted fever because of the lack of rash. Human granulocytic ehrlichiosis, caused by *Ehrlichia phagocytophila/Ehrlichia equi* subgroup ehrlichiae (renamed *Anaplasma phagocytophila;* table 1 [11]), was first reported in the upper midwestern United States in 1994 [66, 67]. Human monocytic ehrlichiosis and human granulocytic ehrlichiosis present as flulike illnesses after exposure to vector ticks. These can range from severe respiratory illness or death to asymptomatic or self-limiting diseases [65, 66, 68]. The agent of human monocytic ehrlichiosis is closely related to the veterinary pathogen *E. canis,* the cause of canine ehrlichiosis, which was first documented in the mid-1930s [65]. By the mid-1960s, it was globally recognized as a veterinary pathogen and was identified as the cause of tropical canine pancytopenia in military working dogs during the Vietnam conflict [69, 70]. Infection with an *E. canis*–like agent in 1 patient from Venezuela has been reported [71]. Recently a newly recognized agent of human ehrlichiosis has been reported. The agent, *Ehrlichia ewingii,* is closely related to *E. canis* and *E. chaffeensis* but resides in human granulocytes rather than monocytes [72].

Q fever. Q fever is found worldwide and is a zoonotic disease caused by the rickettsia *Coxiella burnetii,* a pleomorphic coccobacillus [73]. Because of its small size (0.2–0.7 μm), its high infectivity for humans by aerosol, and the stability and resistance of the small cell variant to heat, pressure, and desiccation, *Coxiella* has some ideal attributes for a biological weapon. Q fever was first described in 1935 by Edward Derrick at the Brisbane, Australia, health department as a new disease in Brisbane abattoir workers [74]. At about the same time that Burnet and Freeman [75] described *Coxiella* as the etiologic agent of Q fever, an identical agent was isolated from *Dermacentor andersoni* ticks in western Montana.

After an incubation period of $\leqslant$15 days, Q fever generally presents as a self-limiting acute systemic disease with sudden onset of chills, malaise, myalgia, fever of 7–24 days' duration, hepatitis, pneumonia (variable), and severe headache, but no rash, and has a reported 1% mortality rate. It is transmitted primarily by inhalation of aerosols from infected animal tissues or by tick bite. The chronic disease form is infrequent, but the consequent endocarditis is often fatal. Q fever is normally found in abattoir or dairy workers, and livestock, especially goats, are the primary reservoirs. A recent example of incidental risks from exposures to infected flocks occurred among British soldiers who contracted Q fever while burying animals with foot-and-mouth disease in Northumberland, United Kingdom [76].

Bartonelloses. *Bartonella* species are small (0.6–1.0 μm) oxidase-negative, often slightly curved rods that, unlike the other rickettsiae, can be cultured in axenic media [77]. Trench fever, caused by *Bartonella quintana,* was first identified during World War I. It is endemic in Poland, the former Soviet Union, Germany, Austria, France, Tunisia and North Africa, Eritrea, Ethiopia, Burundi, Mexico, Bolivia, China, Japan, and the United States [7, 15, 78, 79]. Although *B. quintana* grows in the human body louse gut, as does *R. prowazekii,* it differs in that *B. quintana* does not kill the infected louse. Similar to epidemic typhus, the mode of transmission is thought to be inoculation of infected feces into abraded skin. After an incubation of 14–30 days, patients experience headache and a low-grade fever that suddenly rises to up to 40.5°C, persisting for up to 6 days. Fever can recur up to 8 times in 5- to 6-day intervals, but mortality is rare.

Diseases caused by *Bartonella henselae* and *B. quintana* have been isolated in the 1990s from both immunocompromised and immunocompetent patients and have been identified as causes

of bacillary angiomatosis, parenchymal bacillary peliosis, and cat scratch disease. Although these diseases are important public health concerns, they are not considered militarily significant [7, 79, 80]. Similarly, louseborne febrile disease has been reported in homeless persons or persons with alcoholism, so-called "urban trench fever," which may be associated with endocarditis [79]. Infected rodents, notably *Rattus* species, may also be a source of rodent-transmitted disease caused by *Bartonella elizabethae* and possibly other *Bartonella* species [81, 82].

Bartonellosis, also known as Carrión's disease, is caused by *Bartonella bacilliformis* and is endemic to the Andes of South America between elevations of 610 and 2440 m, where the sand fly vector is found. Bartonellosis may present as an acute febrile anemia, Oroya fever, or as a chronic illness with benign dermal eruptions, Verruga peruana. The clinical manifestations of Verruga peruana may be preceded by Oroya fever or an asymptomatic infection. In addition, asymptomatic carriers of *B. bacilliformis* are known to exist. Oroya fever may pose a significant risk to military operations and public health because of its explosive outbreaks and high level of mortality (up to 90% case fatality rates) in untreated infections (unpublished data).

Although many of the rickettsioses described above have had a significant impact on military forces, some, including human monocytic ehrlichiosis, human granulocytic ehrlichiosis, African tick bite fever, and other spotted fevers, have just been recognized as human diseases. Other diseases, such as sennetsu fever and rickettsialpox, are not and are not likely to be military medical problems except as rare individual cases. As surveillance capabilities improve, including monitoring for bioterrorism agents, and access to new non–culture-intensive methods evolve, new agents will likely be discovered, some of which may also pose significant military problems.

MILITARY HISTORY OF THE RICKETTSIOSES

Since ancient times, epidemic typhus has had the greatest effect on military operations of all the rickettsioses, because it probably caused more deaths than all injuries from wars in history [83]. The oldest recorded epidemic thought possibly to be typhus was the "plague of Athens," ~429 B.C., as described by Thucydides. The disease killed the Athenian general Pericles, decimated the civilian population during the Peloponnesian War, and was a factor in the downfall of the Athenian state [83, 84]. The earliest clear military report concerning typhus described 17,000 deaths in the Spanish army during the siege of Grenada in 1489 [12, 83]. The Thirty Years' War was dominated by typhus epidemics, and in 1 major episode in 1632, typhus and scurvy killed 18,000 soldiers of the armies of Gustavus Adolphus and Wallenstein near Nuremberg, forcing both armies to march away [83]. Multiple outbreaks affected the armies of Napoleon and his enemies throughout the Napoleonic Wars, but one example stands out. In June 1812, the *Grande Armée* of 500,000 men crossed the Nieman River into Poland to attack Russia. Within days, soldiers, who had been in close contact with louse-infested civilians, began to develop fevers and rashes. The outmanned Russian Army of the Czar retreated before Napoleon's forces, giving up land but setting fires to everything behind it and drawing the French forces deeper into Russia. One month into the campaign, Napoleon had lost 80,000 soldiers to typhus and dysentery, and by August he had lost 105,000 men. One month after seizing Moscow, with his remaining 100,000 tired men, Napoleon ordered a withdrawal from the typhus-ravaged city. By December, the *Grande Armée* had again crossed the Nieman River, but with <40,000 louse-infested soldiers. These stragglers and the advancing Russian Army spread typhus throughout Eastern Europe. Although Napoleon blamed the decimation of his troops on the Russian winter, this military disaster illustrates the incredible power of infectious disease epidemics under the right conditions [84].

A rickettsial disease likely played a role in the American Revolution. In August and September, 1776, Major General Nathaniel Greene, Commander-in-Chief of General Washington's ground forces, had one-third of his 8528 New York soldiers become ill before a major battle with British forces. The epidemic was probably caused by typhus [85]. There was little typhus reported in the American Civil War, but the disease next drew the attention of military medical leaders at the outset of the Spanish-American War. Rapid mobilization, poorly prepared encampments, and the assembly of large numbers of men at the beginning of the Spanish-American War found the United States initially unprepared to face the medical challenge of tropical diseases such as typhus, typhoid, and malaria [86]. It was in this situation that such notable medical officers as Major Walter Reed and his coworkers visited encampments to investigate epidemics. To help sort out these problems, the first diagnostic medical field laboratory was established. Typhus reappeared in World War I, especially in Eastern Europe. In 1915 in Serbia, typhus killed 150,000 people, including 50,000 prisoners of war and one-third of the country's physicians [9, 87]. At the height of the epidemic, mortality was 60%–70%, with an estimated 2500 admissions per day to the Serbian military hospitals. The Soviet Union was purported to have lost as many as 3 million men to typhus during the war [88]. Despite this epidemic, there was no typhus on either side of the western front, probably because of the effectiveness of delousing measures, such as heating clothing to kill lice and eggs and mandatory bathing of troops. Worldwide there were 47 cases and 3 deaths due to epidemic typhus in American troops during the "Great War" [89]. Nevertheless, between 1917 and 1923 there were an estimated 30 million cases of typhus in Europe, with up to 25 million in Russia alone, and ~20% of the Ukrain-

ian population contracted the disease [90]. Conditions were such that despite knowledge of the role of the body louse in disease transmission, public health professionals were particularly ravaged by the disease. From 1918 to 1920 alone, one-third of 3500 Red Army doctors got typhus and 20% died from the disease.

Trench fever had not been recognized as a separate disease until it made its appearance during World War I in 1915 among British troops on the western front and in Salonika [89]. This disease occurred in Russia, England, France, Italy, Germany, and Austria [78] and was spread to Mesopotamia by British troops [7]. Trench fever was second only to influenza as a cause of lost man-days during the war. It was reported to be the cause of up to one-third of all illness in the British Army and up to 20% of illness in the Central Powers, with at least 1,000,000 men affected and unfit for duty for up to 70 days [78, 87]. In the US Army, there were 798 hospital admissions due to trench fever, all but 12 occurring in Europe. Later in the war, trench fever was controlled by the same effective louse control measures used to control typhus.

World War II. Immediately preceding and early in World War II, it became apparent that US troops would soon be exposed to serious diseases such as typhus fever that had not recently been seen in United States medicine. Training in militarily relevant diseases and tropical medicine education in United States medical schools was generally inadequate or absent. To help counter this problem, a series of 8-week tropical medicine courses involving >1800 medical corps officers (of the 55,000 in the US Army at that time) was conducted by the Army Medical Department Research and Graduate School, later named the Walter Reed Army Institute of Research (WRAIR). Actual training began before the attack on Pearl Harbor [86]. Because the potential for decimation of the military by typhus was recognized very early, in late 1942 the Secretary of War, supported by the executive order of President Roosevelt, established the Joint US (Army, Navy, Public Health Service) Typhus Commission [13]. As the war progressed, the seriousness of the threat became apparent. For example, in 1943, in Egypt alone, there were >25,000 epidemic typhus cases in the civilian population, and between 1941 and 1944, 92,000 cases were recorded. In French North Africa, there were >132,000 cases during that same period, and in the European theater, 3500 cases were reported near Hamburg, Germany, among the 61,000 inhabitants of the infamous Bergen-Belsen concentration camp at the time of liberation in 1945. Case fatality rates were not recorded at Bergen-Belsen, but at the Dachau concentration camp, a rate of 9.1% mortality was reported during a 1-month period shortly after the 29 April 1945 liberation [13]. Shortly after the end of the war in the Pacific, Japan and Korea suffered an epidemic of ~26,000 cases with a mortality of 6%–10% in both countries [12, 91]. The Typhus Commission participated in the control of the Naples typhus outbreak during the winter of 1943–1944. Their recommendations resulted in >3,000,000 applications of the newly developed dichlorodiphenyltrichloroethane (DDT) dusting powder in that area. During that epidemic in the Naples region, only 2 of the 1914 reported cases of typhus occurred in US military personnel. The overall epidemic case fatality rate was 22.6%. Through Typhus Commission-directed research, advances were made in diagnostics, therapeutics, louse control methods, and vaccine development [13]. One of the more effective measures was compulsory immunization of soldiers going into areas of endemicity. Although epidemic typhus vaccines made of suspensions of louse feces or of killed infected lice were developed near the end of World War I and soon thereafter, these preparations were not practical for large-scale production [13, 36]. Vaccines consisting of formalin-killed suspensions of centrifugation-purified yolk sac–propagated *R. prowazekii* and later including ether-extracted soluble antigens were both potent and feasible for commercial production. Several million doses of this Cox-type vaccine were widely used by US forces. British troops received a similar vaccine called the Craigie vaccine that included *R. typhi* antigens. In France and Russia, formalin-inactivated mouse lung–propagated rickettsial suspensions purified by differential centrifugation or by ether extraction were used [36]. Thus, an extremely effective militarywide program of preventive measures, including effective applications of DDT, vaccination, and command enforcement of Typhus Commission recommendations, led to the occurrence of only 104 cases and no deaths from epidemic typhus in the US forces for the entire war, despite massive epidemic occurrence in other military and civilian populations [13, 36, 92].

Before 1940, all forms of typhus were reported together, and murine typhus was not listed as a separate disease in US Army statistics. In contrast to the characteristic epidemic potential of epidemic typhus, murine typhus occurred as sporadic cases in troops during World War II [92]. Of the 787 murine typhus cases reported in US troops, 497 were from within the United States, mostly in the southeast, and 34 were in the China-Burma-India (CBI) theater of operations. Fifteen deaths were recorded in the US Army, a fatality rate of 19 per 1000. Fourteen of the fatal cases were contracted overseas. Because there were only 104 epidemic typhus cases and no deaths in American troops, the incidence of fleaborne typhus actually exceeded that of louseborne typhus in the US Army in that war [13, 93].

The wartime problem of epidemic typhus had been anticipated, but the impact of scrub typhus as a militarily important disease was unexpected [94]. It was the most significant rickettsiosis affecting US troops during World War II [95]. Scrub typhus was responsible for numerous casualties, including deaths of American military personnel in the Asia-Pacific region [92]. In some operations it was reported to have disabled more men than

actual combat [95]. The nature of scrub typhus as a serious military problem was shown by mortality rates ranging from 0.5% to 27.5% and by exceedingly high incidence of disease in certain areas of endemicity. In one small unit in New Guinea, there were 6 deaths (37.7%) among 16 cases within a 3-week period [96]. Before that war, the disease was little known outside Japan, but between 1942 and 1945, intensive exposure of immunologically naive Allied troops resulted in >16,000 cases and 639 deaths (4.0%) as well as an estimated 20,000 cases in Japanese troops [95, 97]. By the end of the war, scrub typhus was responsible for thousands of man-days lost and an estimated 7300 cases and 331 deaths (4.5%) in US troops. This had a significant effect on military operations in the South West Pacific (SWPA), South Pacific (SPA), and CBI theaters of operation [95]. The vast majority of these cases resulted from 2 major episodes. The first occurred in the SWPA, where 5718 cases were reported, and the second in the CBI theater [93]. The index case in US troops was reported in northern Queensland, Australia, in March 1942, followed by 8 more cases in September near Port Moresby, as troops began to move into New Guinea. The first real outbreak occurred in Australian forces heavily deployed to that region [93]. The 2 most serious outbreaks affecting US Army troops in the SWPA occurred between June and August 1944, after landings on Owi-Biak and Sansapor beachheads, Shouten Islands, Dutch New Guinea, where there were ~2000 cases. Although mortality was low in these outbreaks (0.5%), prolonged morbidity severely hampered the combat mission, because an estimated 150,000 man-days were lost [93, 95]. Also included in the SWPA are 284 cases in reoccupied Republic of the Philippines in November 1944.

Scrub typhus had been known in Burma since 1932 [97], and the military impact was felt by British forces, who experienced 110 cases in 1934 [98]. By far the greatest regional impact of scrub typhus felt by any Allied forces was the experience of the British forces in the CBI theater [98]. During the Burma campaign in 1944 alone, 5000 cases and 350 deaths (7% case fatality ratio) were reported. At one point, scrub typhus ranked only behind malaria as the most important medical problem. About 1000 cases and a 6% mortality rate were reported in British personnel in operations along the India-Burma border over 2 seasons between October 1943 and January 1945, including 121 cases in a single battalion. Japanese military reports indicated similar experiences in Burma with the disease they called "Burma eruptive fever," which resulted in a case fatality rate of 7.4% [95, 99]. Cases of "CBI fever" in US troops were first reported at the 100th Station Hospital in Delhi, India [93, 97]. Late in 1943, an outbreak occurred in US Army troops in Assam, producing mortality higher than in any other area during the war. This mortality was attributed to concomitant diseases such as malaria and dysentery as well as prolonged stress of continuous combat. In fact, the mortality rate for scrub typhus in the CBI theater, 14.6 per 100,000, was the highest for any infectious disease in any World War II theater of operations [93]. Altogether, 967 cases were reported in the 65,000 US troops deployed in the CBI theater. From November 1943 to September 1945, a combined total of 1098 cases were reported among US and Chinese troops, with an overall case fatality rate of 8.9% [94]. The highest incidence was in northern Burma, where 695 US Army cases and 58 deaths were recorded in 1 outbreak. Most cases occurred during combat operations and reflected field exposure to the mite vectors. Focal but widely distributed "hot spots" of disease occurrence were typical in the CBI theater. There was no seasonal variation in disease incidence, and infected mites were found to persist for >1 year at any given focus. In January 1945, outbreaks were also reported in Ceylon and the Maldives, where >750 cases were reported in British and East African troops [99].

Considerable firsthand information about the nature of scrub typhus was gleaned from clinical and epidemiological studies in the SWPA and CBI under the auspices of the Typhus Commission. Disease incubation times varied from 7 to 17 days, averaging 11 days. The febrile course in untreated patients was ~2 weeks, and typically lymphadenopathy was the most consistent sign (97%, Owi-Biak epidemic), followed by rash (70%–100%) and often but not invariably by 1 or more primary lesions or eschars at the site of chigger bites (11%–85%). The disease course was found to be typically more severe in older troops and in those who had been under strain of combat.

Areas of endemicity for scrub typhus showed extreme variation in ecological types, ranging from both inside and at the margins of rain forests, grassy areas, and abandoned oil palm groves [100], as well as in mountain scrub areas >915 m high. Thus, there was no predictable exposure ecology, because troops often unknowingly moved into infested areas. Disease prevention was difficult, but recommendations by the Typhus Commission suggested that the disease could be controlled by carefully clearing areas or by use of clothing treatments such as spraying or dipping uniforms in liquid repellents [101]. One study involving 223 men in 7 units was conducted after repellent supplies became available. In that study, 23 (15%) of 150 men wearing untreated clothing became infected, whereas none who wore impregnated clothing became infected [101]. The effectiveness of these recommendations was borne out, because most cases occurred before implementation of recommended clothing treatments. Other related studies by US Typhus Commission entomologists provided the first conclusive proof of transovarial transmission of the agent in vector mites. The classic type strain of *O. tsutsugamushi,* Karp, was isolated in Australia by guinea pig inoculation of blood from an American soldier wounded in New Guinea in January 1943. He survived both wound and disease, but the highly virulent strain later killed a laboratory worker trying to develop a vaccine [102].

Tickborne rickettsiosis apparently played a minor role during World War II. However, in August and September 1944, 10 of 12 cases of Queensland tick typhus caused by *R. australis* occurred among soldiers deployed in North Queensland, Australia [42]. A retrospective analysis of a tickborne disease outbreak in Texas suggested that ehrlichiosis was the cause of a World War II–era outbreak at Camp Bullis among >1000 military personnel, where 1 death was attributed to a previously unrecognized febrile illness [103].

Early in the war, Q fever was thought to be a rare disease of little military importance. There are no statistical data on Q fever in the US military during the war, because the disease was usually not recognized and often misdiagnosed as atypical pneumonia. Although there were no reported fatalities, later in the war it became evident that Q fever would become more important [104]. German reports of that period refer to experience with "Balkan grippe" in Bulgaria and Greece in 1941 and 1942 that was likely Q fever. In February 1945, 1 British parachute regiment that had recently returned from Greece to Italy experienced a 30% attack rate of what was later serologically confirmed to be Q fever. There were 7 outbreaks during winter 1944 and spring 1945, including 3 serologically confirmed outbreaks in US troops in northern Italy and in Corsica. *C. burnetii* was isolated in 2 outbreaks by personnel of the 15th Medical General Laboratory. That laboratory unit had been working closely with the British Typhus Research Team and the US Typhus Commission since 1942 [86]. One infantry unit of 900 men deployed in Italy experienced a major outbreak during combat. Four days after moving to the front from the rest area, 269 (30%) of the men became ill and were hospitalized [105]. In the spring of 1945, Q fever was diagnosed at Camp Patrick Henry, Virginia [106]. A group of 1638 of 7500 troops returning to the United States from Grottaglie Air Base in southern Italy at the end of the war in Europe became ill with what was diagnosed as Q fever. Thus, the potential military importance of this disease became apparent [74, 104].

Trench fever had not been seen in epidemic proportions since the end of World War I. Sporadic outbreaks occurred in 1934 and 1938 in Poland, in Russia until the early 1930s, in Beijing in 1931, in Japan during the 1920s and 1930s, and among troops during the Spanish Civil War [107]. Large-scale epidemics appeared in World War II in Yugoslavia and the Ukraine, and several strains were isolated from patients' blood [78]. Cases of relapsed trench fever were reported up to the 1970s among German World War II veterans [107].

Before World War II, there was little interest in research on rickettsial diseases in the United States, because these diseases were not widespread in the American civilian population. Only when significant numbers of American soldiers stationed abroad during World War II contracted rickettsial diseases was research in this area expanded by the military. Although antibiotics were used to curb the spread of other bacterial diseases during World War II, attempts to use penicillin to treat scrub typhus in soldiers proved unsuccessful [97, 108]. Antibiotics that were effective against rickettsial diseases were not available until the mid- to late 1940s. The first clinical trails proving the efficacy of the newly developed antibiotic, chloromycetin, in the treatment of scrub typhus were performed in 1948 near Kuala Lumpur, Malaysia, by US Army doctors working out of WRAIR and the University of Maryland [109–111]. In later trials, they also proved the efficacy of the antibiotic as a chemoprophylaxis [112]. These successful studies conducted in collaboration with the Malaysian Institute for Medical Research led directly to a highly productive 40-year research association of the Malaysian government with the US Army Medical Research Unit-Malaysia at that institute. Consequently, these major advances in control of rickettsial diseases are directly due to research conducted by military medical researchers or collaborators supported directly by military funds.

Korean conflict. Epidemic typhus and scrub typhus occurred infrequently in the US military during the Korean conflict, and no cases of murine typhus or Q fever were reported [93, 113]. Only a single case of louseborne typhus was reported, occurring in a medical team member [113]. However, a very real potential for outbreaks of epidemic typhus existed during the conflict, because famine, poverty, overcrowding, lousiness, and population disruption were commonplace. Typhus controls, including those used effectively during World War II, included DDT treatments, spraying with newer insecticides such as lindane, and administration of >14 million doses of the Cox-type typhus vaccine to South Koreans [113]. These measures were effective to some extent: The average incidence of epidemic typhus among Korean civilians early in 1951 of 3228 cases and 473 deaths per month decreased during the first 6 months of 1952 to 125 cases and 16 deaths per month [114]. The efficacy of DDT, the mainstay of typhus prevention used during World War II, began to wane during the Korean conflict, when many strains of lice became resistant, in both Korea and Japan [7]. For example, during the winter and spring of 1951, DDT delousing of communist prisoners of war failed to control louse infestations [113]. In contrast to the absence of the disease in US forces, a typhus epidemic caused 32,000 cases in South Korean soldiers and civilians, leading to 6000 deaths.

At least 8 cases of scrub typhus were diagnosed in US or United Nations troops during the Korean conflict [93, 113, 115], including 2 soldiers in British Commonwealth forces (June 1951) [116], 1 Australian soldier (October 1953), 1 US Army sergeant (September 1953) [117], and 1 US Marine Corps sergeant (November 1951) [113, 117]. These include the first confirmed report of scrub typhus in Korea [116]. Typically these cases showed fever, rash, eschar, lymphadenopathy, and serological testing yielding positive results to the Weil-Felix OX-

K antigen, and in 2 cases actual rickettsial isolations were obtained. Chloramphenicol, a broad-spectrum antibiotic developed and proven effective against scrub typhus after World War II [110], was administered to scrub typhus patients for the first time in a combat situation. Patients responded rapidly to treatment [115, 117]. Epidemiological studies of indigenous rodents in combat areas confirmed the endemicity of both vector mites and *O. tsutsugamushi* in that 17% of *Apodemus agrarius* rodents, those most frequently collected in the combat areas, were infected, as measured by isolation and demonstration of vector transmission [118].

Vietnam conflict. Scrub typhus was a leading cause of fevers of unknown origin (FUO) among US troops during the Vietnam conflict (table 2) [93, 129–134], and the incidence of scrub typhus in malaria patients was estimated to be ~6% [93]. Malaria was the most common specifically diagnosed febrile illness, but it was also one of the more easily diagnosed febrile diseases [131, 135, 136]. Unexplained FUO, however, was a major clinical problem and was the most common admission diagnosis in 1967 [135]. Between 1966 and 1969, the diagnosis of FUO ranked second only to sexually transmitted diseases, causing an average lost duty time of 4.5 days [136]. From 1967 to 1970, an estimated average of 225,000 man-days per year were lost to FUOs as a group, whereas ~200,000 were lost to malaria [137]. Not surprisingly, FUOs were greater among combat troops who typically had intense jungle environment exposure than among support troops [132]. Soldiers' activity often suggested the cause of the FUO. For example, malaria, scrub typhus, and leptospirosis were more frequently contracted in heavily forested areas where the anopheline mosquito (malaria) and chigger (scrub typhus) vectors were common, whereas the mosquito *Aedes aegypti* (Chikungunya virus and dengue) and flea *X. cheopis* (murine typhus) were typically found in more urban areas [129, 132, 133, 136]. In December 1972, the Armed Forces Epidemiology Board summarized the considerable importance of rickettsial diseases to the military in Vietnam when it reported that when malaria and other identifiable diseases were excluded, 20%–30% of the remaining FUOs were scrub typhus and ~10%–15% were murine typhus [138].

Unlike the fatality rates of up to 9% in US troops seen in the CBI theater during World War II [136], scrub typhus caused no known American deaths during the Vietnam conflict. The disease was first seen in American personnel in 1962 [93], coincidentally following successful treatment for malaria. In many FUO studies, scrub typhus was discovered as a coinfection with malaria, probably because of the similar jungle environment [136]. Although the actual number of cases of rickettsioses in US military personnel in Vietnam is unknown, a series of 5 clinical and laboratory-based FUO studies served to underscore their significance (table 2). In addition, serological data from reports of the 9th Medical Laboratory for 1969, the year of greatest US military troop concentration, showed scrub typhus as the primary cause of FUOs (18%), followed by amebiasis (17%) and murine typhus (15%). The rickettsioses—scrub typhus, murine typhus, and tick typhus—were responsible for more than one-third of FUOs serologically diagnosed that year [136]. An estimated 93% of scrub typhus cases occurred among artillery and infantry personnel rather than their support personnel. Extrapolating from this figure, an estimated 2000 cases of scrub typhus probably occurred during that 1-year period [93].

One military report depicted multiple major outbreaks of scrub typhus in US forces and indigenous units and highlighted the impact of scrub typhus in the Vietnam theater of operations [139]. In deployments of 8–24 November 1966, near the Cambodian border, 16 of 110 indigenous survivors and 1 of 4 surviving Americans incurred the disease. During that same period, 16 cases occurred in a 34-man combat reconnaissance platoon (47% attack rate) deployed in the Mekong River delta. The overall attack rate was 13.4% for all 3 outbreaks. Cases were not recognized until 3 weeks after return to home base, but exposure was determined to have been during deployment. The higher attack rate in the reconnaissance platoon was likely due to intense exposure to a single mite-infested focus while the troops were pinned down and surrounded by enemy soldiers. Because of safety concerns, miticide-impregnated clothing was not used during the Vietnam era. The report suggests that the frequency of occurrence of scrub typhus among US and indigenous forces operating in combat zones in Vietnam was seriously underreported and the significance seriously underestimated because of failure to recognize cases in which the pathognomonic features were absent.

Murine or urban typhus was not generally considered a serious problem in Vietnam [92], although it was second only to malaria as a cause of FUOs in American personnel on bases and in cantonments [22]. It was not noted there until July 1967 in an FUO evaluation, possibly because of the lack of a dependable serological assay. Office of the Surgeon General records show only 19 clinical cases, all in support troops, from 1965 to 1970. However, serological data from the 9th Medical Laboratory from July 1967 through 1968 showed 61 cases demonstrating a 4-fold rise in titer, as determined by the relatively insensitive Weil-Felix reaction [93]. One retrospective study of US Air Force personnel at Cam Ranh Bay suggests a much higher occurrence when 30% of FUOs in which malaria had been excluded were shown to be murine typhus (table 2) [131]. It was generally of urban distribution, and 55% of murine typhus cases in 1 group studied involved support troops.

Canine ehrlichiosis or tropical canine pancytopenia, caused by *E. canis* after the bite of infected ticks, had a severe impact on military working dogs throughout the Vietnam conflict. Epizootics occurred in German shepherds and Labrador retrievers in 20 (91%) of the 22 US Army infantry scout dog

Table 2. Selected incidence, outbreak, and prevalence studies of rickettsial diseases in military personnel.

Study [reference]	Rickettsial disease	Location (habitat)	*n*	No. (%) positive	Study period	Primary military population	Diagnostic test	Comment[a]
Corwin et al., 1999 [119]	Scrub typhus	Laos	127	5 (4)	Jun 1996–Apr 1998	Primarily US military	ELISA	Prospective incidence study
		Vietnam	194	9 (5)				
		Cambodia (work primarily in remote regions)	26	0				
Corwin et al., 1997 [120]	Murine typhus	Rural Indonesia	248	91 (37)	1992–1993	Indonesian Army	ELISA	Prospective prevalence, study
	Scrub typhus			19 (8)				
	Murine typhus	Cambodia		3		Peacekeepers in Cambodia		Prospective incidence study
	Scrub typhus			1				
Smoak et al., 1996 [33]	African tick typhus	Shoshong, Botswana (flat terrain, semiarid)	169	39 (23)	Jan 1992	US Army	IFA, ELISA	Outbreak; 24 seroconversions
Sanchez et al., 1992 [121]	Rocky Mountain spotted fever	Fort Chaffee, AR (wooded hills, low-level brushy areas)	40	15 (38); 2	May–Jun 1989	Maryland Army National Guard	IFA	Retrospective prevalence study and 2-case outbreak
	Human monocytic ehrlichiosis	Fort AP Hill, VA	31	4 (13)				
Eamsila et al., 1996 [122]	Scrub typhus	Throughout Thailand	911	45 (5)	1989–1991	Royal Thai Army, Rangers, Border Patrol	IFA	Prospective incidence study
			1888	195 (10)				Prospective prevalence study
Taylor et al., 1986 [123]	Scrub typhus	Ulu Kinta, north central peninsular Malaysia (rubber plantations, secondary jungle, and scrubby foothills)	699	23 (3)	Mar 1983–Feb 1984	Malaysian Police Field Force	IFA; murine isolations	Prospective FUO study of consecutive patients with fever
Olson and Bourgeois 1977 [124]	Scrub typhus	Pescadores Islands, Republic of China	517	23 (4)	May 1975–Oct 1977	Army, Republic of China (Taiwan)	IFA	Prospective incidence study
Olson et al., 1979 [125]	Scrub typhus	Okinawa, Korea, Philippine Islands, Japan, Taiwan, Indonesia	507	6 (1)	1975–1976	US Marines	IFA	Prospective incidence study

Gale et al., 1974 [126]	Scrub typhus	East coast of Taiwan (clearing abandoned farmland, hill areas 300–500 m)	241	59 (25)	5–11 Oct 1970	Army, Republic of China (Taiwan)	IFA	Retrospective prevalence study and outbreak analysis of patient records; 19 of 21 patients seroconverted, 1 fatality; *Orientia tsutsugamushi* recovered in *Leptotrombidium deliense* mites and rodents
Reisen et al., 1973 [127]	Scrub typhus	Clark Air Base, Luzon, Philippines (training area in foothills of Zambales Mountains)	1000/mo exposed	6	Sep 1969–Aug 1970	US Air Force	Weil-Felix test with OX-K antigen	Outbreak; *O. tsutsugamushi* recovered from rodents and vector mites
Colwell et al., 1969 [128]	Scrub typhus	Dong Tam, Mekong River Delta, Vietnam	76[b]	2 (3)	Jun–Dec 1967	US Army Infantry	IFA, murine inoculation	Prospective FUO study
Berman and Kundin, 1973 [129]	Scrub typhus	Vietnam: 6 Navy-Marine Hospitals, Northern Provinces of South Vietnam	793[b]	108 (14)[c]	Feb 1967–Feb 1969	US Marines	IFA, Weil-Felix test with OX-K antigen; murine inoculation	Retrospective FUO study; *O. tsutsugamushi* isolated from 32 patients
	Murine typhus			4 (0.5)				
Reiley and Russell, 1969 [130]	Scrub typhus	Vietnam, 8th Field Hospital, Nha Trang (semi-mountainous central coastlands)	94[b]	16 (17)[c]	Oct 1966–Feb 1967	US Army	IFA	Prospective FUO study
Deaton, 1969 [131]	Scrub typhus	12th US Air Force Hospital, Cam Ranh Bay	92[b]	3 (3)	Jul 1967–Jun 1968	Primarily US Air Force	Weil-Felix test with OX-K antigen	Retrospective FUO study of clinical records
	Murine typhus			25 (27)				
Deller and Russell, 1967 [132]	Scrub typhus	93rd Evacuation Hospital at Long Binh (lowland areas near Saigon)	110[b]	11 (10)[c,d]	Apr–Aug 1966	US Army	IFA, Weil-Felix test with OX-K antigen	Prospective FUO study

NOTE. FUO, fever of unknown origin; IFA, indirect fluorescent antibody.

[a] Diagnosed rickettsial disease cases and/or seroconversions (≥4-fold rise in antibody titer).

[b] Diagnosed malaria cases excluded.

[c] Includes cases diagnosed clinically and mixed infections that include a rickettsiosis.

[d] Experimental design excludes rickettsial disease cases diagnosed clinically

platoons, all detachments of 1 military police dog company, and in some US Air Force sentry dog and Marine Corps scout dog units throughout Vietnam, often leaving some military dog units unable to perform their missions [140]. The disease is characterized by hemorrhage, emaciation, pancytopenia, and high mortality. Between July 1968 and December 1970, 220 US military dogs died of this canine ehrlichiosis and many more were euthanized [137]. A program of tetracycline therapy based on recommendations of WRAIR's Saigon laboratory resulted in 50% of infected dogs returning to duty.

Finally, as military personnel returned home after their tours of duty in South Vietnam, a host of tropical diseases, including the rickettsioses, accompanied many. These diseases were thus a public health concern even outside the military medical health care system [135, 141].

Operation Desert Shield/Storm. The incidence of infectious disease during Operation Desert Shield/Storm was much lower than expected, with low occurrence of arthropodborne illness in deployed troops [142]. One retrospective survey of 865 US Marines and support Navy personnel reported that 5.7% and 9.8% were seroreactive to typhus and spotted fever group rickettsiae, respectively, but no diagnostic rises in titer indicative of active disease were found [143]. There were 1 case of Q fever–associated meningoencephalitis, 1 pneumonia case, and 3 seroconversions in soldiers. The latter 4 instances were associated with exposure to sheep, goats, or camels in Saudi Arabia [105]. Overall, unlike past wars, little evidence was seen of illness associated with the rickettsioses, suggesting that preventive measures were effective or potential exposures were low because of the seasonal timing and the very short duration of the ground war [142, 144].

RECENT PEACETIME MILITARY AND PUBLIC HEALTH EXPERIENCE

Camp Fuji, Japan, scrub typhus, 1948–present. Typically, until the World War II outbreaks in the mountains of India and Burma, scrub typhus had been identified primarily with tropical and subtropical climates and ecology. Seasonal occurrence of scrub typhus had been known to be a prominent feature in the temperate climates of Japan for many years, with most cases being reported between July and September, and case fatality rates ranged from 20% to 60% before the antibiotic era [60]. However, a new endemic focus and type of scrub typhus was identified in 1948 outside the classic geographic and ecological areas and in the absence of then-known vectors [21]. This fall/winter scrub typhus is now the dominant type reported in Japan and is associated with novel serotypes [145]. It is clinically different from the classic form of the disease and is transmitted by *Leptotrombidium pallidum* or *Leptotrombidium scutellare* mites rather than *Leptotrombidium akamushi.* The first extensive reported outbreak of the new form occurred near Mount Fuji, Japan, when 27 of 1769 troops of the 8th US Army who had trained at 1000 m were admitted to Army hospitals between 6 October and 13 November with typical signs and symptoms of scrub typhus. The 8th Army troops had also trained in that region in the summer and fall of 1946 and 1947, but no disease became evident from those exposures. A case had been reported in a Japanese field artillery soldier training in that area as early as 1934 [146]. In October 1953, 79 cases of scrub typhus were diagnosed in 2 regiments of the US 3rd Marine Division, Fleet Marine Force, Pacific, who were training on the southwest slope of Mount Fuji [55]. Between 1959 and 1982, 111 cases were reported in the Japanese Ground Self-Defence Force training in the same area [147], even though the training areas were routinely dusted with miticides [148]. Between 1981 and 1983, 56 cases were reported in US Marines, all of whom reported to the battalion aid station between October and November in each outbreak year [147, 149]. In 1996, 6 cases of 800 exposed US Marines were documented, including 1 in which appropriate treatment was delayed for 72 h [150]. Most recently, between October and November 2000, 10 cases of scrub typhus were reported in US Marines having fever, headache, and rash, with 8 showing a typical eschar as well. All demonstrated a rapid response to doxycycline treatment. The outbreak was investigated by the Naval Environmental Preventive Medicine Unit No. 6, Pearl Harbor, Hawaii, and was serologically confirmed by the Naval Medical Research Center, Silver Spring, Maryland. Interestingly, acute serum samples were reported negative by a Japanese laboratory, but 6 of 9 convalescent serum samples tested positive at the Naval Medical Research Center. An overall attack rate of 1% (10/800) was reported [151, 152]. In 2001, 8 presumptive cases were reported in US Marines training at Camp Fuji (K. Marienau, personal communication). Although fall/winter-type scrub typhus is commonly reported in the Camp Fuji training area, diagnosis by military medical personnel is often missed or delayed.

Korea, scrub typhus, 1985–present. Although scrub typhus was reported during the Korean conflict and proven to be endemic in rodents and vector mites, there was little evidence that it was a problem for the civilian population or United Nations troops assigned there. There had been little emphasis on risk assessment or surveillance in support of US military personnel. However, in the 1980s, reports of scrub typhus in civilian populations began to appear, suggesting that it was a growing problem in South Korea, especially in rural areas but also in some urban areas, and therefore of concern to military as well as Korean public health officials [6, 58, 153, 154]. Nationwide surveys indicated that between 1986 and 1993, ~40% of febrile illnesses were scrub typhus, occurring in all regions of South Korea [153]. Although some scrub typhus cases were reported in May, June, and July, 90% of the 8200 cases occurred

in October and November. Depending on the outbreak, untreated cases ranged from inapparent or mild to severe and fatal. Of 137 isolates tested with use of strain-specific monoclonal antibodies, 81% were classified as the highly pathogenic Boryong strain that predominated in the southern part of the country. Other strains, including Karp and Gilliam strains, were reported in the central portion of the country. The only proven *O. tsutsugamushi* vector in South Korea is the *L. pallidum* mite. Between 1985 and 1990, there were 189, mostly civilian, confirmed cases in the Chinhae region of southern coastal South Korea, a newly recognized area of endemicity. Typically, most cases were diagnosed between October and December [58]. On Cheju Island, scrub typhus was shown to be a cause of fever in 9 (53%) of 17 cases in 1987 and 34 (56%) of 64 cases in 1988. Also, specific antibody to scrub typhus was detected in serum samples of 5.5% of 200 rodents tested in that area [155]. During US Air Force Exercise Foal Eagle 1992, there was 1 confirmed case among US forces, and several suspected cases were also treated [156]. A WRAIR overseas laboratory, the US Army Medical Research Unit-Korea, was activated in 1990 in part to investigate the threat of this disease and Korean hemorrhagic fever to personnel in South Korea. They reported that scrub typhus is actually more prevalent in Korea than is Korean hemorrhagic fever [58]. Although the laboratory closed in 1993, cases in US military continue to be diagnosed (D. Strickman, personal communication). As recently as 1995, scrub typhus was reported to be the most prevalent febrile illness in South Korea [153]. As in other countries, in the absence of aggressive public health efforts, US and local military personnel who frequently train or are deployed to rural and, increasingly, urban areas can act as sentinels. Active medical surveillance of these personnel will be helpful in assessing risk to both military and civilians.

In addition to Korea and Japan (above), military forces of several other countries within the region in which scrub typhus is endemic continue to experience episodic outbreaks that affect their readiness. In 1965, the Royal Thai Army experienced an outbreak in northeast Thailand, with an attack rate of >20% (41 cases in 185 soldiers exposed) [157]. Collaborations between the Royal Thai Army and US Army at the Armed Forces Research Institute of Medical Sciences (AFRIMS), Bangkok, resulted in several recent studies documenting the regional vectors of scrub typhus and the continuing risk to deployed troops [122, 158]. These investigations, conducted in 1996 and 1997, documented the distribution of scrub typhus in deployed Thai military personnel not only in the northeast, as previously reported, but also throughout Thailand, including along the Thai-Cambodian border [158] (table 2). It is noteworthy that these findings failed to correlate with past public health statistics for those regions. However, in 1993, >200,000 cases of acute FUO were reported in Thailand by the Ministry of Public Health, 9.6% of which were determined to be scrub typhus [6]. The US Army–Royal Thai Army collaboration at AFRIMS also produced the first reported occurrence of antibiotic-resistant scrub typhus [159]. In neighboring Malaysia, prospective and retrospective studies conducted by investigators from the US Army Medical Research Unit, Malaysia, described both the impact and lack of recognition of scrub typhus in Malaysian, British, and New Zealand soldiers deployed in that country as well as in the indigenous population (table 2) [6, 123, 160–163]. Further south, in Indonesia, investigators at the US Naval Medical Research Unit No. 2, Jakarta, reported on the risk of rickettsioses in that country [164–166], specifically in Indonesian soldiers. These soldiers showed an in-country rickettsial exposure rate of 43% before deployment in United Nations–sponsored peacekeeping operations in Cambodia [120]. As previously noted, rickettsioses, including Q fever, Queensland tick typhus, and scrub typhus, have been reported in Australia, especially during World War II [31, 42]. In addition, a novel spotted fever group illness has recently been reported [43]. Although there are few reliable prevalence and incidence data of rickettsial diseases in Australia [43], recent outbreaks of scrub typhus have been reported in 1996 and 1997 in Australian military personnel training in north Queensland [167]. The impact of scrub typhus on even small units was recently shown when key members of an Australian Special Forces unit in jungle training were adversely affected by the disease (G. Dasch, personal communication). Scrub typhus is considered the most serious of the rickettsial diseases in Australia [43]. In the People's Republic of China, at least 5 rickettsioses have been reported, with scrub typhus being documented by rickettsial isolation from patients in 8 southern and central provinces in mainland China from Tibet to Zhejiang Province [168]. On Hainan Island alone, >10,000 cases of scrub typhus were diagnosed between 1956 and 1985. In Republic of China (Taiwan) military personnel, annual outbreaks of scrub typhus were common, particularly among those training or working in the Pescadores Islands (table 2) [126, 169]. In Hong Kong, between 1979 and 1988, 59 retrospectively diagnosed scrub typhus cases occurred primarily in Nepalese Gurkhas and soldiers from the United Kingdom [170], but during the same period, only 5 indigenous cases were reported to public health authorities. Overall, throughout the vast region in which scrub typhus is endemic, the disease appears to be greatly underdiagnosed, within both the military and the public health communities. It demonstrates diverse and unusual clinical presentations and hence is frequently unrecognized [54].

Recent tickborne rickettsioses. Tickborne spotted fever group and ehrlichial rickettsioses are frequently found together. Studies in military populations have documented their recent episodic impact on military training and operations in tick-infested areas [171]. An outbreak of human ehrlichiosis in US

military personnel was retrospectively diagnosed in 9 of 74 US Army reservists from Connecticut who experienced mild to severe clinical illness following a June–July 1985 field training exercise in east-central New Jersey [172]. In 1989, a cluster of tickborne infections due to *R. rickettsii* and/or *Ehrlichia* species occurred on 2 United States–based military installations [121]. Serum samples collected from several of those personnel who had experienced mild spotted fever disease specifically reacted to an unspeciated spotted fever group rickettsial agent, "*R. amblyommii*" [48, 49]. In 1990, an elaborate prospective search by scientists at WRAIR, Washington DC, and the Centers for Disease Control and Prevention, Atlanta, resulted in isolation of the causative agent of human monocytic ehrlichiosis [173]. The etiologic agent, now named *E. chaffeensis,* was recovered from the blood of a febrile soldier who was training at Fort Chaffee, Arkansas. In a related investigation, of 3000 ticks collected during May, August, and November 1990 at Fort Chaffee, 4.8% and 0.3% were positive for spotted fever group rickettsiae and ehrlichiae, respectively [174]. In a more recent study, risk of tickborne rickettsiosis to military personnel was further supported by serological investigations involving the testing of almost 10,000 serum samples drawn from 840,390 personnel on active duty as of December 1997. About 4% of serum samples provided some evidence of seroreactivity to the human granulocytic ehrlichiosis agent, a low but significant result that suggests past infection with the agent among US military personnel [175]. One study suggested that risk was reduced when permethrin-impregnated uniforms were worn [176]. Although the repellent system is available in the supply system and is actively promulgated, compliance is sometimes lacking [50]. During the year 2000, for example, 846 ticks were actually removed from soldiers training at Fort A. P. Hill, Virginia, who had access to repellents. In fact, in addition to a high prevalence rate of the "*R. amblyommii*" spotted fever group agent, 16 of these ticks were positive for *E. chaffeensis.* Clearly, these studies detail the risk of ehrlichial and spotted fever group rickettsial infections to deployed military personnel who are exposed to heavily tick-infested areas.

In January 1992, airborne soldiers based in Vicenza, Italy, deployed to Botswana to train with elements of the Botswana Defense Force. Within 2 days of returning to home base after the 2-week deployment, 30% of the US troops sought medical attention, presenting with symptoms of fever, headache, and regional lymphadenitis. A WRAIR epidemiology team was called in to investigate the outbreak. Thirty-one of 169 (attack rate, 18%) airborne soldiers based at Vicenza were diagnosed with laboratory-confirmed spotted fever rickettsiosis, consistent with African tick bite fever caused by *R. africae* [33]. This same disease had been responsible for several outbreaks in troops on maneuvers in the South African bush veld early in World War II [36]. Also in 1992, during Operation Restore Hope, Mediterranean spotted fever caused by *R. conorii* was diagnosed in a 36-year-old male soldier after deployment to Somalia [177]. Relatively small outbreaks can have unexpected consequences. One recent outbreak has highlighted the potential for spread of rickettsial infections beyond those initially infected, as well as possible threats to our blood supply. In May and June 1997, 8984 National Guard members from 10 states were engaged in annual training at Fort Chaffee, Arkansas. A total of 320 units of blood from 377 National Guard donors were transfused into 129 recipients. Within days after donation, 12 of the donors were determined to have confirmed or probable Rocky Mountain spotted fever and/or monocytic ehrlichiosis. The US Food and Drug Administration (FDA) ordered a recall of the donated blood and blood products that had been distributed over several states [178].

The risk of ehrlichiosis to humans is not limited to the United States or Japan, where scrutiny is most intense. Human monocytic ehrlichiosis has also been reported in Europe, Africa, and South America. A US Army scientist working at the US Army Component, AFRIMS, Bangkok, and Thai colleagues have reported the first evidence of human ehrlichiosis in Thailand [179]. Human ehrlichiosis has also been reported in an active-duty soldier stationed in South Korea [68]. Recently in the United States, ehrlichiosis was reported in a Naval Academy midshipman training in Quantico, Virginia [180], and in May 1999, tickborne human monocytic ehrlichiosis killed a 22-year-old service member who trained at Fort Campbell, Kentucky [181] (M. Salamy, personal communication).

CURRENT CHALLENGES TO MILITARY OPERATIONS AND PUBLIC HEALTH POSTED BY RICKETTSIAL DISEASES

The Department of Defense, the National Institutes of Health, and the World Health Organization have focused their attention and much of the available infectious disease research funding in recent years on a host of well-known diarrheal and mosquito-borne parasitic or viral diseases, such as cholera, malaria, West Nile virus, and dengue. The rickettsial diseases, especially scrub typhus, have received relatively little attention from the civilian research community. Even the present weakly funded military effort to investigate these diseases has come under increasing scrutiny as resources for military infectious disease research have declined and a robust Department of Defense research infrastructure has disappeared. This is ironic, because many advances have been accomplished in the study of the rickettsial diseases, even with the limited resources available. Furthermore, despite the current focus of the public and public resources on the threat posed by newly emerging diseases, the rickettsial diseases have continued to evolve and emerge in unique new guises without the awareness of the public or many in the military community.

As a result, increased funding for research or surveillance has not been forthcoming. Unfortunately, the rickettsial diseases are not perceived to be emerging, even though they exhibit most of the hallmarks of those diseases: underdiagnosed and unrecognized, present in new ecological settings, associated with increased clinical risk often because of associated antibiotic resistance or new clinical presentations, more widespread geographically than previously believed, new genetic types of etiologic agents, and new arthropod vectors.

Precisely because rickettsial infections are not the common and routine focus of attention for medical staffs, they pose significant threats to military operations. Reservoirs of rickettsiae continue to cycle in nature, and military operations will place susceptible persons at risk of infection with these agents. Rickettsial diseases tend to be forgotten by military health officials between major deployments to regions of endemicity. Personal protective measures are effective in reducing exposure, but they require diligent command support to maintain the necessary discipline or they will be ineffective.

It is imperative that the military research community continues to be the primary force in the investigation of rickettsial diseases. Not only are deployed military personnel usually at greater risk than the general population of contracting these diseases, but also the military is uniquely situated for surveillance, documentation, and study of individual exposures, among both deployed military personnel and local civilian populations. Indeed, these military personnel have often been sentinels for detecting widespread illness that has been overlooked by public health authorities in civilian populations. Additionally, a large amount of fundamental work on rickettsial diseases has been done historically by the military, and little knowledge, infrastructure, or interest exists in the civilian community to conduct studies of the types necessary to protect troops deployed to areas of endemicity where many of the etiologic agents are found.

Prevention and vector control measures. The US military currently has limited capability to prevent the rickettsial diseases. There are no FDA–licensed vaccines protective against any of the rickettsioses, although there are military requirements to protect against them [111]. There is evidence that weekly doxycycline prophylaxis can reduce morbidity due to scrub typhus and probably the other rickettsioses, but this has not been proven [9, 161]. Old treatments of ground and vegetation with chlorinated hydrocarbons (lindane, dieldrin, and chlordane) are no longer permitted, and there are no compounds currently registered for chigger control on an area basis. The US military no longer has a viable system for mass delousing of populations. The former system depended on an insecticide (lindane) that is no longer considered safe and on equipment that is no longer maintained [182]. DDT, used so effectively during World War II to control louseborne typhus, is no longer legal to use in the United States. Resistance of lice to DDT was reported during the Korean conflict, and resistance to lindane and malathion has also been reported [7]. The standard Army repellent formulation of *N,N*-diethylmetatoluamide (DEET), when combined with other prevention practices, can effectively reduce risk of chigger-, tick-, and flea-borne transmission of the rickettsiae. The permethrin-treated battle dress uniform offers excellent protection from ticks and should prevent infestation by body lice. Commercial aerosol DEET repellents applied to clothing, especially trousers and boots, helps prevent flea bites. Command emphasis on good personal hygiene practices, such as bathing after contacting lousy people, domestic rodent control with poison baiting and trapping, and field sanitation, can control outbreaks of these and other vectorborne diseases [9]. However, persons provided with personal protective training and aids commonly continue to contract arthropodborne diseases such as leishmaniasis (Operation Desert Shield/Storm), malaria, and Mediterranean spotted fever (Somalia) [177], Rocky Mountain spotted fever [121], African tick typhus [33], and scrub typhus [151].

Diagnosis and state-of-the-art rapid agent detection systems. From the early 1900s, when the rickettsioses were first recognized as distinct diseases and their epidemiology became better understood, clinical diagnosis has been difficult because of their similarity to a host of febrile illnesses. Since the late 1940s, when effective, rapid-acting antibiotic treatment became available, it has been realized that correct diagnosis and early treatment can markedly reduce morbidity and mortality caused by the rickettsioses. Therefore, the need for good diagnostic tools that can aid the medical officer with diagnosis became evident. Since the earlier years of the 20th century, this need has been met with the development of a series of increasingly sensitive and specific serological tests and, later, rapid agent detection systems [183]. These tests include the nonspecific Weil-Felix serological test based on *Proteus* species bacterial antigens. This test was first developed in 1916 for typhus and spotted fever rickettsiae and modified in the mid-1920s for scrub typhus. Although the Weil-Felix test lacks both specificity and sensitivity (66%–80%) [129], the availability of cheap commercial reagents still makes this test popular today, especially in developing countries in which the diseases are endemic. The more accurate rickettsial complement fixation and microagglutination tests were first used in the 1940s–1960s, and the more sensitive and specific indirect fluorescent antibody (IFA) test became widely available in the 1960s–1980s. The IFA test is still used as the reference standard, primarily by research and commercial laboratories that provide confirmatory retrospective diagnosis in disease investigations. In the early 1980s, the indirect immunoperoxidase test, a serological assay closely related to the IFA test, was shown to correlate closely with the IFA when compared for *R. typhi, O. tsutsugamushi,* and *R. conorii* [183]. Because of its ease of use, reduced need for ex-

pensive equipment, and availability of cheap reagents, this test is still widely used in Malaysia and other countries in which scrub typhus is endemic [40] (C. Chan, personal communication). In the 1990s, the development of reliable, sensitive, specific, and commercially available dipstick tests and ELISAs greatly facilitated rapid diagnosis in primitive clinical settings and the retrospective survey of very large numbers of serum samples, respectively. Because commercial interest in this family of diseases was very weak because of the small markets involved, often in underdeveloped countries unable to pay for tests, this new generation of simple, rapid tests was developed in close collaboration with Department of Defense medical research laboratories [184–188]. Although superior to the earlier tests, the new serological tests also generally require paired acute and convalescent patient serum samples and are retrospective, telling the medical officer what the service member or civilian had.

True rapid identification of rickettsioses by testing the blood of a febrile service member or an air sample analysis for biological defense requires sensitive "real-time" agent detection. Nucleic acid– and antigen-based assays to rapidly detect organisms have been developed in parallel with the seroassays. The earliest agent detection procedures used animal inoculations to isolate the cause of the disease, but these methods were very cumbersome and hazardous and required weeks to confirm diagnosis. This past decade has led to the development of a number of DNA assays that lend themselves to rapid disease diagnosis and can be used in biological defense to detect disseminated biological agents. These assays include the PCR, in which agent-specific DNA is amplified in a small temperature-cycling incubator [189]. The resulting amplimer is labeled and measured, and theoretically a single organism can be detected, but this approach requires 2 separate amplification steps because of the very low numbers ($<10^4$ organisms/mL) of rickettsial agents that circulate in the blood. Recent instrumentation resulting from collaboration between the US military and civilian industry uses a modification of the PCR methodology and includes the Idaho Technologies LightCycler. This portable, light, basketball-sized laboratory instrument can test multiple samples and produce results within 30 min in a single amplification step. A second instrument is the Perkin Elmer 7700 (TaqMan), which is capable of rapid real-time agent detection, identification, and quantitation. This is a large desktop instrument suited to advanced clinical laboratories, but these assays can also be used with smaller, field-deployable instrumentation such as the Smart Cycler System from Cepheid. Recent studies have been conducted by means of the real-time PCR reaction with agent-specific fluorescent probes to detect rickettsial nucleic acid [190, 191]. In addition, PCR methodology is currently used to detect infectious rickettsial agents in attached ticks collected from humans [50].

Drug-unresponsive scrub typhus. Aside from resistance to vector control measures, arguably the greatest challenge to the military forces posed by the rickettsial diseases is that of antibiotic resistance in rickettsial agents. The high morbidity and mortality of scrub typhus among the military during World War II and of epidemic typhus and spotted fever among civilians were virtually eliminated by the successful use of the bacteriostatic antibiotic chloramphenicol and later tetracycline, doxycycline, rifampin, and ciprofloxacin. These antibiotics are normally effective in treating the rickettsioses and are still routinely used [9]. Because rapid laboratory tests are still often unavailable and the rash or pathognomonic eschar is often absent in patients, the dramatic clinical response after administration of those antibiotics has often been used to facilitate diagnosis of rickettsioses [110]. Failure to rapidly defervesce renders the diagnosis unlikely, and until recently, few instances of rickettsiae responding poorly to appropriate antibiotics in clinical cases had been recorded [6, 59]. Antibiotic-refractory cases of spotted fever group and murine typhus have been reported, although selection of antibiotic resistance in the laboratory has been demonstrated for *R. prowazekii, R. typhi,* and *C. burnetii* and exists naturally in spotted fever group rickettsiae to rifampin. Strong evidence for the existence of drug-unresponsive scrub typhus was first developed by a US Army physician assigned to AFRIMS, Bangkok, and a Thai colleague working at a local provincial hospital in northern Thailand [159]. They observed very ill patients, 15% of whom died despite administration of oral doxycycline or intravenous chloramphenicol. Later isolation of the agent from patients' blood and serological testing proved that these cases were scrub typhus. The suspicion of antibiotic resistance was supported by in vitro cell culture and animal studies of *Orientia* isolates from those patients [54, 192, 193]. Additional indirect evidence for the existence of antibiotic-resistant *Orientia* species was reported recently when 14 soldiers deployed in Indochina and receiving daily doxycycline prophylaxis for malaria seroconverted to *O. tsutsugamushi* [119]. Three of those soldiers displayed typical signs and symptoms of scrub typhus despite administration of prophylaxis. Recent research has shown that the macrolide azithromycin and rifampin could be useful in some situations in which the disease fails to respond adequately to doxycycline or chloramphenicol [159, 192].

Rickettsial agents as bioterrorist weapons. Some rickettsial agents are cheap and relatively easy to mass-produce, and their deployment can be as easy as releasing them upwind in stabilized aerosol form or releasing infected arthropods. The defeat of Iraq during Operation Desert Shield/Storm and the fall of the Soviet Union have exposed the existence of active biological weapons programs and have given rise to concerns of their possible use by terrorists or aggressive nations willing to use these "poor man's" weapons of mass destruction on

military forces and civilians [194]. Although it is estimated that at least 17 countries have active agent development programs, including 5 implicated as sponsors of international terrorism, biological warfare organisms have never been used against US forces; thus, we have no practical experience with their effects on the battlefield [195]. Early implementation of a proven prophylaxis program would be needed to combat such an attack. *R. prowazekii, R. rickettsii, R. typhi,* and *C. burnetii* could readily be used as biological weapons, and 3 of these agents are on the United States' select agent list, which is intended to regulate access to potential threat agents. The World Health Organization estimates 104,000 casualties, 19,000 dead and 85,000 incapacitated, after hypothetical air deployment of 50 kg of typhus agent. Similar dissemination over a major population center of 50 kg of Q fever agent would result in 500 deaths and 125,000 incapacitated over 20 km downrange, producing casualties at the same rate as anthrax or tularemia [88, 105, 196]. A single organism can cause a fever in humans, and the small cell variant and possibly spore-like form of *C. burnetii* is extremely resistant to heat, pressure, and desiccation, making it an ideal biological weapon. There are no biological weapons in the current arsenal of the United States [196]. Recent military emphasis on biological warfare defense has been on air sample collection, rapid detection of agents, development of FDA-licensed protective vaccines, and immediate prophylactic measures [197]. Therefore, development of FDA-approved vaccines that could provide adequate prophylaxis is needed now. Such development could provide effective deterrence to the deployment of *R. prowazekii, R. rickettsii,* and *C. burnetii* as biological weapon agents by permitting protection of susceptible populations [197].

Risk prediction for military operations and public health. Because of mass exposures of nonimmune persons in areas of endemicity for rickettsial agents, troops are excellent sentinels for their presence [198]. Mass deployments both overseas and within the continental United States have afforded us the opportunity to conduct, both prospectively and retrospectively, ongoing threat assessment (table 2). For example, early in Operation Desert Shield, the US Navy positioned the Navy Forward Laboratory in Saudi Arabia to conduct epidemiological investigations and evaluate infectious disease threats to military personnel deployed in the Persian Gulf [142, 143]. Naval Medical Research Unit No. 2, Jakarta, supported the investigations of Corwin et al. [119] in Indochina that suggest that antibiotic refractory scrub typhus may be found in countries bordering Thailand, where the phenomenon was first reported [159]. Such efforts provide point prevalence data and incidence data on infectious diseases of concern and often detect new agents and disease threats [9, 102, 173]. These efforts are in concert with World Health Organization goals of obtaining reliable data on global prevalence and distribution of these diseases as a first step toward reducing the morbidity and mortality they cause [199]. These observations are essential steps for improving public health where these diseases are endemic and reducing the risk for international travelers and those involved in diverse humanitarian aid efforts in those countries.

Risk to blood supply. As described above, there is a real risk of rickettsial contamination of blood intended for transfusion into service members and the civilian population. Both *O. tsutsugamushi* and *R. rickettsii* have been implicated in cases of transfusion transmission of disease [200]. This concern extends beyond arthropodborne diseases. For example, in July 1997, the British government, because of concern over Jakob-Creutzfeldt disease and acting in response to recommendations of their Spongiform Encephalopathy Advisory Committee, concerned with bovine spongiform encephalopathy ("mad-cow disease"), ordered WBC reduction practices be implemented to reduce risk of infection to transfusion recipients. This is done by removing most WBCs from the blood unit before transfusion. The risks of rickettsial contamination of blood and of the merits of WBC reduction and blood sterilization by photochemical inactivation have been investigated by WRAIR and the Naval Medical Research Center [200–202] and by the Centers for Disease Control and Prevention [203].

EFFECTIVE STRATEGIES TO REDUCE THE HUMAN IMPACT OF RICKETTSIAL DISEASES

Clearly, rickettsial diseases have had a significant impact on civilian populations and military deployments and training throughout history. Efforts early in the last century to "clean up" the soldier led to effective control of body lice, such that epidemic typhus and trench fever were of insignificant consequence on the western front during World War I. Because appropriate sanitation measures were absent in Eastern Europe, however, these diseases had a devastating impact on civilian and military groups. Education and reinforcement of those efforts, combined with introduction of DDT, similarly rendered typhus to be of no strategic significance in the European theater during World War II, whereas scrub typhus was of consequence in the Asia-Pacific theaters of operations. Thanks in part to dedicated military scientists, academic collaborators, and the investigations and recommendations of the Joint US Typhus Commission, scrub typhus was effectively neutralized both late in the war with preventative measures and soon thereafter with the introduction of effective antibiotics treatments, which have immensely benefited civilian populations. Nevertheless, as just described, the effectiveness of our military continues to be impaired by the rickettsioses and their vectors when preventive measures are not implemented and these diseases are not promptly and properly diagnosed.

Of primary concern in the modern military is emerging antibiotic-resistant scrub typhus in regions where the United States not only has historical interests but also currently deploys in training exercises and other humanitarian operations [119]. Development, testing, and certification of an effective scrub typhus vaccine will reduce this risk to our exposed military personnel and offer benefits to indigenous populations. For example, recent evidence of reductions in HIV loads in scrub typhus patients suggests other possible benefits from scrub typhus research [204]. In a clinical study, Watt et al. [204] found the patients' median virus loads to be significantly lower in the scrub typhus group than in HIV-infected patients with other infections. This suggests that HIV-suppressive factors produced during scrub typhus infection, and possibly scrub typhus immunization, might also provide a treatment for HIV patients. The Department of Defense Military Infectious Disease Research Program has recently sponsored development of a scrub typhus recombinant protein that is presently used by the military and civilian sectors in state-of-the-art simple, rapid serological tests. This sponsorship has also led to production of rickettsial antigens according to "good manufacturing practices" standards that are required for human vaccine candidates. Newly emerging technologies can now permit accurate and rapid detection of most of the rickettsial diseases that affect patient care. Compact reliable instrumentation will soon be available at the field hospital and even far forward at the battalion aid station level of medical support. Confirmed diagnosis and prompt, proper treatment will reduce lost soldier-days and save lives. The same technologies will also permit rapid detection of deployed bioterrorism agents to which our troops may be exposed in modern deployments. Disease prevention will require the development of new safe, simple, effective repellants that do not signal their presence. Current military missions that include disaster and humanitarian relief efforts, with medical care of displaced and refugee populations, are likely to place military units at risk of infection [9]. More than 1 billion people in ~13,000,000 km^2 of land in the Asia-Pacific region are exposed to scrub typhus, but disease incidence information is very limited [54]. Ongoing surveillance and threat assessment are essential for protection of our deployed forces as they proceed in harm's way to protect the vital interests of the United State and its allies, for protection of international travelers, and for improvements in indigenous public health. The Department of Defense Infectious Disease Research Program and the Blood Research Programs are evaluating means to increase troop and civilian safety by eliminating infectious agents from blood products needed for transfusion.

As ongoing Department of Defense programs attempt to evaluate the relative significance of infectious diseases of military importance and provide support for research to minimize their impact, it is too easy to forget the painfully gained knowledge of past wars, including that won at high cost by military medicine. We must constantly remind ourselves that the rickettsial diseases have not disappeared and maintain vigorous training and research programs for these diverse challenges.

Acknowledgments

We thank Theodore Woodward for his historical perspective, comments, and manuscript review; Wei-Mei Ching for editorial review; Rich Robbins for assistance in locating obscure documents at the Armed Forces Defense Pest Management Information Analysis Center; Jean Ward for assistance in finding historical resources at the Armed Forces Epidemiology Board; Henry Lewandowski for providing Camp Fuji documents; and Carolyn Kelly for helpful comments and editorial assistance.

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