The current crisis in Afghanistan has resulted in an influx of Western military personnel, peacekeepers, humanitarian workers, and journalists. At the same time, unprecedented numbers of internally displaced persons and refugees have overwhelmed much of the already fragile infrastructure, setting the stage for outbreaks of infectious diseases among both foreigners and local populations. This review surveys the literature concerning the infectious diseases of Afghanistan and south-central Asia, with particular emphasis on diseases not typically seen in the Western world.

The ongoing crisis in Afghanistan once again draws the Western world’s attention to an obscure area of the globe. The current emergency combines a massive humanitarian crisis with civil war, a situation that has become regrettably common in the late 20th and early 21st centuries. Physicians who travel to Afghanistan as part of US or coalition military forces, or as participants in humanitarian programs, will need to be familiar with the epidemiology, diagnosis, and treatment of the endemic infectious diseases of Afghanistan and the surrounding region. US and European physicians will need to be alert for unusual infections in travelers, military personnel, relief workers, refugees, and others returning from this region.

**BACKGROUND**

Much of Afghanistan, in south-central Asia (figure 1), is mountainous, with windswept high desert plains in the north and southwest. The total area is about the size of Texas (647,500 km²) and supports a population of ~26 million. Two decades of war and civil unrest have led to massive infrastructure destruction and both internal and external population displacements on a vast scale. Infant mortality is high (147 deaths/1000 live births) and life expectancy short (46 years). Fewer than one-third of the total adult population can read and write; women have literacy rates of ~15%. Per capita income is estimated at $800 (in US dollars) per year [1]. The public health infrastructure has been severely disrupted by recent events, leaving ample opportunity for epidemics of infectious disease.

Available data suggest that the Afghan population is greatly affected by infectious diseases, with reports of excess mortality from diarrheal disease (including cholera), respiratory tract infections, and measles [2, 3]. Given the recent population displacement and destruction of infrastructure, it seems likely that the infectious disease situation will worsen before improving. Control of communicable infectious diseases will have to be a top priority of local and relief officials.

Military troops and civilian humanitarian personnel residing in and around Afghanistan will be at risk for a variety of infectious diseases. Although foreign workers will have greater access to safe drinking water, clean food, shelter, and appropriate immunizations, their risks for the endemic infections of the region will be...
considerable. In the past, infectious diseases have produced major disruptions in both military campaigns and humanitarian efforts. The Soviet military had extraordinary annual attack rates of infectious diseases of 53%–69% during their occupancy of Afghanistan, the vast majority caused by viral hepatitis, typhoid, dysentery, and respiratory tract infections [4, 5].

Recent US military efforts elsewhere in the developing world have encountered significant infectious disease morbidity, although not on the scale of the Soviet infectious disease debacle in Afghanistan. The US humanitarian effort in Somalia (1992–1993) was marked by small outbreaks of malaria, dengue, and diarrheal illness [6–8]; febrile diseases accounted for the majority of field hospital admissions in Somalia. During a subsequent US deployment to Haiti (1994), personnel also experienced high rates of febrile illness, at least 30% of which was due to dengue [9]. The Persian Gulf war (1990–1991),
which represented the largest US military operation since the Vietnam war, was fraught with predeployment infectious disease concerns [10], but excellent preventive medicine efforts plus fortuitous weather and geographic factors kept infection rates among the 700,000 deployed troops extremely low [11]. Despite the paucity of infections during the war, the Persian Gulf conflict has spawned a decade of debate regarding the existence of a unique “Gulf War illness,” which some believe may have been caused by infectious agents [12–14].

This review focuses on the endemic diseases of south-central Asia, with emphasis on Afghanistan. For the purposes of this article, central Asia refers to the countries of Afghanistan, Turkmenistan, Uzbekistan, Tajikistan, and Kyrgyzstan. South-central Asia includes the above plus Pakistan. The review is divided into diseases of potential relevance to Western military forces deployed in Afghanistan and other endemic diseases of nonmilitary importance. We hope it will serve as a useful compendium of information for military physicians and humanitarian health workers, as well as civilian physicians in the developed world who see returnees and refugees from the region.

I. ENDEMIC INFECTIOUS DISEASES OF MILITARY IMPORTANCE

Malaria

Forty percent of the world population is at risk of malaria. Malaria remains the most important infectious cause of death worldwide. The World Health Organization (WHO) estimates that there are 300–500 million cases of malaria and as many as 2–3 million deaths per year [15, 16]. In areas of civil unrest or governmental collapse, the risk of malaria increases. In Afghanistan, 500,000 refugees fled to Pakistan after the Communist overthrow of the Kabul government in 1978. A second wave of refugees fled to Pakistan after the Soviet invasion in December 1979. By 1985, at least 3 million refugees were in Pakistan. Mass repatriation followed after the 1992 Najibullah government’s collapse. Subsequent estimates of Afghan refugees living in Pakistan have ranged upward to 3.2 million people, with 75%–80% concentrated in the North West Frontier Province [17–20]. Since that time, continued shifts in population back and forth across the border have occurred. Now refugees are returning to Afghanistan after the success of US Operation Enduring Freedom in the fall of 2001. Consequently, the risk of malaria in Afghanistan is increasing.

Multiple factors have contributed to an increased risk of malaria: collapse of governmental vector control, inadequate shelter, crowding of displaced people, environmental modification leading to increased pools of water from construction of shelters or sanitation efforts, lack of available or affordable antimalarial medications, increased parasite resistance of Plasmodium species to antimalarials and of the vectors to pesticides, and an influx of refugees into previously stable zones of malaria endemicity [17–19].

Civilians are not the only population at risk. Throughout history, malaria has figured in the success or failure of military campaigns and added to the misery of indigenous populations caught up in warfare. During World War II, US Army forces lost 8–9 million sick days and US Navy and Marine forces lost an additional 3 million sick days to malaria. Sick days from malaria far exceeded days lost to bullets and other battle injuries. Malaria was also a major problem for US troops during the Vietnam conflict and resulted in >1 million days lost from malaria and an additional 18,000 cases imported into the United States [21, 22]. At least some of the Vietnam malaria morbidity could have been avoided, because up to 70% of troops failed to take their prophylactic regimens [23]. Similar to prior military campaigns, Soviet military personnel stationed in Afghanistan imported a total of 7683 cases of Plasmodium vivax malaria from Afghanistan into the Soviet Union during 1981–1989. Almost 69% of Soviet patients did not take malaria prophylaxis at all, an additional 19% reported taking chloroquine irregularly, and only 13% completed terminal prophylaxis with primaquine [24]. Malaria developed late in many of the troops, with signs and symptoms of illness appearing in 24% of cases within 1 month of returning to the Soviet Union, 23% after 1–3 months, 20% after 4–6 months, 2% after 1 year, and 0.6% after 2 years [24].

Epidemiology. The epidemiology of malaria is seasonal and hypoendemic in most of Afghanistan and neighboring Pakistan at elevations of <1500–2000 m, which includes the urban areas of Kabul and Jalalabad. In the rice-growing region of eastern Afghanistan, transmission is highest and is mesoendemic [3, 25]. Malarious zones include the eastern provinces and large areas in a crescent shape encompassing the north, west, and south of the country and excluding the central highlands and high mountain ranges of the east [3, 25]. The malaria season is from April through November, with very few cases reported in the winter months. Plasmodium falciparum predominates from September through November, with P. vivax responsible for the majority of cases during the rest of the malaria season.

Rab et al. [26] cited clinic monitoring reports from Health Net International in 1995 indicating >67,000 cases of malaria from 83 clinics and hospitals in 6 eastern provinces in Afghanistan. The rate of positivity of >250,000 examined slides was 19%. Until recently, P. vivax made up ~90% of cases and P. falciparum the remainder. Beginning in 1999, the proportion of malaria due to P. falciparum has been climbing, probably because of the use of chloroquine as the first-line antimalarial [26]. Up to 20% of recent cases are due to P. falciparum, and multiple outbreaks of falciparum malaria have been reported.
since 1999 [3]. In northern Afghanistan, outbreaks have occurred in Faryab, Herat, Baghlan, and Kundus. The scope of the northern outbreaks is unreported except for in Faryab, where a 15% point prevalence was noted. In 1999, point prevalences of 30% and 15%, respectively, in Narang in Kunar Province (23,000 people) and the Nazian region of eastern Afghanistan (8500 people) were found. In all, it is estimated that 2–3 million cases of malaria occurred in Afghanistan in 1999 alone, with 300,000–450,000 being falciparum malaria [3].

In the North West Frontier Province of northern Pakistan, the malaria season is usually April through December. As in Afghanistan, *P. vivax* predominates early in the spring and peaks in July to September, whereas *P. falciparum* predominates toward the end of the season in October through December. Many of the cases of malaria due to *P. vivax* seen in the spring are presumed to be from overwintering of the parasite. In southern Pakistan, the malaria season is year-round and heavily influenced by the July-to-August monsoon season [19, 27–29].

Afghanistan’s northern neighbors have seen a surge in cases of malaria coinciding with the exodus of Afghan refugees. In the 1960s and 1970s, only sporadic cases of *P. vivax* malaria were seen in Tajikistan along the Amu Darya River (Oxus River), which separates the country from Afghanistan. After the Soviet invasion in 1979, a sudden increase in cases was seen, from ≈21 cases per year to 4332 cases in 1995 [30]. Only 2% were due to *P. falciparum*. The remainder were mainly due to *P. vivax*, with scattered cases due to *Plasmodium malariae*. In another study reported by Pitt et al. in 1998 [31], the proportion of *P. falciparum* malaria jumped from 2% to 16%, with 84% due to *P. vivax* and no cases of *P. malariae* or *Plasmodium ovale* malaria. The actual number of cases is estimated to have been higher, perhaps 10,000 [31]. Surveillance by the Health Ministry was severely hampered by the flight of trained epidemiologists (<25 of 200 remain) after Tajikistan achieved independence from the Soviet Union [30]. Compounding the risk of infection from population shifts due to civil strife, climactic conditions at the northern ends of the malaria range (especially malaria due to *P. falciparum*) can produce wide fluctuations in the incidence of disease. High rainfall and above-average temperatures in November and December may intensify and extend the *P. falciparum* malaria season or increase the prevalence of *P. vivax* the following spring [28]. In October 2001, WHO predicted 300,000–400,000 malaria cases per year in Tajikistan [3].

**Resistance.** Under the pressure of chloroquine therapy, resistance patterns in this region have recently mirrored the world trend. Chloroquine resistance was first noted in Pakistan in 1984 [32] and in Afghanistan in 1986 [33] and is now widespread in eastern Afghanistan in the provinces of Kunar, Nangarhar, and Laghman. Resistance is subcategorized as RI, RII, or RIII, from least to most resistant. RI is defined as complete clearance, as in the susceptible condition, but with recrudescence of parasitemia within 28 days. With RII, there is a marked reduction in parasitemia but incomplete clearance. RIII means no significant reduction in asexual parasitemia. Rab et al. [26] found that 55% of *P. falciparum* had RI resistance and 11% had RII or RIII resistance by standard WHO in vivo testing. Published reports of in vivo resistance in Afghanistan are otherwise not available. In the North West Frontier and Balochistan provinces of Pakistan, where high concentrations of Afghan refugees are located, Shah et al. [28] and Rowland et al. [34] have shown that RI resistance to chloroquine was very high for *P. falciparum*, ranging from 30% to 84%, and RII resistance variable, from 2% to 36%. RIII resistance has not been reported; however, recent surveys have not been designed to distinguish RII from RIII resistance [26]. Sulfadoxine-pyrimethamine (Fansidar) is widely believed to be effective [3, 26], although published studies are lacking. In neighboring refugee camps in western Pakistan, resistance to sulfadoxine-pyrimethamine was found in all districts sampled, with a range of 4%–25% (average, 12%) [34].

**Treatment.** The WHO has recently published recommendations for treatment of malaria in residents of Afghanistan and neighboring countries [3]. For uncomplicated *P. falciparum* malaria, sulfadoxine-pyrimethamine, 25 mg/kg (per the sulfa component), is recommended as a single oral dose. For adults, 3 tablets taken as a single oral dose would be sufficient after a confirmed blood smear or dipstick test. For *P. vivax* malaria, chloroquine can be given as a daily dose over 3 days: 10 mg/kg on day 1, 10 mg/kg on day 2, and 5 mg/kg on day 3, for a total of 25 mg/kg.

In Tajikistan, Uzbekistan, and Turkmenistan, the WHO suggests an altruistic 1-time dose of primaquine, 0.75 mg/kg, for gametocyte eradication after *P. falciparum* infection or primaquine, 0.25 mg/kg/day for 14 days, for terminal prophylaxis after *P. vivax* infection [3]. Primaquine is not advocated for residents of Afghanistan, Pakistan, and Iran, given higher transmission rates and possible problems with compliance [3]. Mixed *P. falciparum* and *P. vivax* infections, which are uncommonly reported in Afghanistan and in Afghan refugees in Pakistan, may be treated with chloroquine plus sulfadoxine-pyrimethamine.

If primaquine is used, it must be used cautiously, given the frequency of glucose-6-phosphate dehydrogenase (G6PD) deficiency in the population of Afghanistan and neighboring regions. There is significant variability in the frequency and significance of G6PD deficiency among ethnic groups and tribes. Bouma et al. [35] found that the rates of deficiency among Afghan Pashtun and Pakistani Pashtun were 16% and 7%, respectively. G6PD deficiency among Uzbek refugees was 9%; among Tajik refugees, 3%; among Safi refugees, 16%; and among Turkoman refugees, 2%. Hospital studies have suggested
that the type of deficiency in Pashtuns may be more severe, leading to severe hemolytic crises and death [35]. In light of recognition of the dangers of primaquine and the difficulty of ensuring compliance, the Pakistani government, some non-governmental organizations, and others have previously advocated abbreviated courses of primaquine over 5 days; however, this practice was evaluated by Rowland and Durrani [36] and found to be of no value as terminal prophylaxis.

Alternative therapy for uncomplicated falciparum malaria may include quinine plus either doxycycline, sulfadoxine-pyrimethamine, or clindamycin; mefloquine; artesunate plus mefloquine; atovaquone-proguanil (Malarone); or halofantrine [15, 16, 37–40]. US troops will likely use a quinine-based oral combination regimen. For complicated falciparum malaria, iv quinine-, artesunate-, or im artemeter-based therapies are options [37–40]. Quinidine may be used when iv quinine dihydrochloride is not available but requires close cardiac monitoring for potential QTc prolongation, QRS widening, and a proarrhythmic effect. Chloroquine-resistant \( P. \) \textit{vivax} has not been reported in the area. Treatment for complicated falciparum malaria has been reviewed in depth [15, 37–42].

**Chemoprophylaxis.** Military troops, humanitarian workers, travelers, and other civilians may benefit from chemoprophylaxis during the malaria season. Oral mefloquine is the preferred agent [25, 43] and can be given as weekly dose of 250 mg of salt (1 tablet) beginning 1–2 weeks before entering the malarious zone and continuing for 4 weeks after leaving the area of risk. Children may be given prophylaxis with 5 mg/kg once weekly on the same schedule as adults. An alternative mefloquine dosage of 5 mg/kg daily for 3 days beginning 1 week before departure has been suggested by Boudreau et al. [44] to more rapidly achieve protective steady-state levels. When mefloquine cannot be taken, doxycycline can be substituted. Adults may take 100 mg by mouth daily beginning on the day before travel and continuing for 4 weeks after departure from the region of endemicity. Children >8 years old may take 2 mg/kg oral doxycycline daily on the same schedule [43].

Contraindications to mefloquine include epilepsy, psychosis, depression, and cardiac arrhythmias. Opinion varies as to mefloquine use by aircraft pilots. Mefloquine may cause mild sleep disturbances as well as affect fine motor and spatial discrimination functions [43]. Schlagenhauf et al. [45] found no significant difference in performance by Swissair trainee airline pilots in a comparison of placebo with mefloquine. In the US military, mefloquine is not allowed for those on flight status.

Although not licensed in the United States for prophylaxis, primaquine may be a reasonable choice for prophylaxis if mefloquine or doxycycline cannot be used and the G6PD status is known to be normal (i.e., not deficient). At least 4 studies have shown the agent to be safe and effective [46–49]. When used as a prophylactic agent, it should be given as 30 mg of base/day for adults or 0.5 mg/kg/day for children [43]. Primaquine may be started on entry into a malarious zone or several days before travel to ensure tolerance. It may be stopped 1 week after departure from the area of endemicity.

Atovaquone-proguanil has been recently licensed in the United States. It is highly effective for prophylaxis against \( P. \) \textit{falciparum}, although data on \( P. \) \textit{vivax} are scant. Given that the majority of malaria in the region is due to \( P. \) \textit{vivax}, atovaquone-proguanil probably should be avoided as a prophylactic agent.

**Prevention and control measures.** The mosquitoes associated with malaria transmission in Afghanistan are \textit{Anopheles superpictus} (main vector), \textit{Anopheles stephensi}, \textit{Anopheles culicifacies}, \textit{Anopheles pulcherrimus}, \textit{Anopheles annularis}, \textit{Anopheles nigerrimus}, \textit{Anopheles fluviatilis}, \textit{Anopheles splendensis}, \textit{Anopheles subpictus}, and others [3, 18, 50]. Unlike the vectors in sub-Saharan Africa, which are primarily anthropophilic (e.g., \textit{Anopheles gambiae}), the anopheline vectors in south-central Asia are highly zoophilic [18]. Zooprophylaxis, the practice of keeping domesticated animals near human habitation, has thus been suggested as a method to distract feeding mosquitoes from their incidental human hosts. At least 2 studies suggest that in Afghan refugee camps in Pakistan, incidental biting was actually increased because of the hordes of mosquitoes attracted to the courtyards and alongside the refugee compounds where cattle were kept [50, 51]. That is, cattle acted as attractants rather than as distracters of anopheline biting. Rowland [18] was able to decrease zoophilic malaria transmission by treating cattle with pyrethroid insecticide. The cost was less than that of insecticide-treated nets or tents and was looked on favorably by refugees because of control of cattle ectoparasites.

Insecticide spraying with lambda cyhalothrin and malathion has been used extensively in a variety of experimental and public health measures in the Afghan refugee camps in Pakistan and in nonrefugee sites in Pakistan. Highly effective control of \( P. \) \textit{vivax} and \( P. \) \textit{falciparum} can be achieved with spraying but requires organized, well-timed, and seasonal campaigns by local governments or sponsoring agencies. The effectiveness of spraying has been variable, but 1 series of studies showed up to 37%–44% protective efficacy for \( P. \) \textit{vivax} and 49%–56% for \( P. \) \textit{falciparum} in the refugee camps of the North West Frontier Province [19, 52]. Rowland et al. [27] have suggested that malathion may be less useful now (vs. lambda cyhalothrin) than in the past because of widespread resistance in \textit{A. stephensi} and increasing resistance in \textit{A. subpictus} and other species.

Residual spraying within tents and compounds has likewise been found to be effective. Bouma et al. [53] reduced the risk of falciparum malaria in nomadic Afghan refugee children from 50% to 16% by applying 0.5% emulsion of permethrin to the fly-sheetsed ridgepole tents supplied to refugees by the United Nations High Commissioner for Refugees. Permethrin impregnation of bednets, \textit{chaddars} (Islamic cloth wraps used as
veils and for sleeping), top sheets, cloth window screens, and other clothing have yielded excellent results, with a reduction in rate of malaria of up to 40%–65% [18–20, 29, 53–56]. Hewitt et al. [54] in 1996 evaluated multiple self-protective antimalarial measures in 6 experimental huts in the Azakhel refugee camp near Peshawar in the West Frontier Province of Pakistan. The total numbers of catches of blood-fed A. stephensi mosquitoes, the most prevalent vectors at this site, were measured against a variety of control measures. Use of an electric fan, pyrethrum coils, untreated curtains, pyrethroid-vaporizing mats, and permethrin-impregnated curtains reduced the catches of blood-fed mosquitoes by 27%, 36%, 47%, 56%, and 65%, respectively [54].

Insect repellants are widely used by individual travelers and military personnel but are not practical for indigenous people, given the cost and need for reapplication after several hours [57]. The US military uses 35% diethyltoluamide (DEET), and this is currently recommended for short-term travelers to areas of endemicity [57–59] during the hours between dusk and dawn. DEET can also be effectively used on clothing either alone or in combination with permethrin. The slow release, polymer-based 35% DEET preparation used by the US military is available through Amway. Lesser-strength long-acting preparations are also available [60].

**Diarrheal Diseases**

*Etiology of diarrheal diseases.* Ongoing war and population displacement in Afghanistan have led to high morbidity and mortality from enteric disease [61]. In northern Afghanistan, the Amu Darya River, which has been contaminated by sewage, must also serve as the water source for large numbers of internally displaced persons [62]. In many other areas of Afghanistan, dilapidated water and sewage systems are frequently implicated as the cause of enteric outbreaks. Economic downturn and upheaval after the breakup of the Soviet Union has led to plumbing and infrastructure neglect throughout central Asia [63, 64].

Lack of potable water is cited as a primary reason Soviet soldiers experienced high enteric infectious disease rates during their Afghan war of the 1980s. Fifty-eight percent of Soviet troops had major gastrointestinal infections [65]. Bacillary and amoebic dysentery and agents of other waterborne diseases (hepatitis A, typhoid) were major problems, because the Soviet personnel drank untreated local water, either by choice or by necessity [4].

*Cholera.* Cholera is not typically the major cause of diarrhea among residents of south-central Asia. For example, from 1990 to 1995, only 8% of pediatric patients with diarrhea in a Karachi hospital had confirmed cholera [66]. However, cholera can cause epidemic diseases throughout the region. The 7th pandemic of cholera was caused by the El Tor biotype of *Vibrio cholerae* serogroup O1. It arose in Indonesia in 1961 and spread across Asia and Africa, reaching Pakistan, Afghanistan, and Uzbekistan in 1965 [67–69]. El Tor replaced the classical cholera biotype in India and Bangladesh but caused only sporadic small clusters of cases in south-central Asia after 1970. Historically, cholera outbreaks in the region appear to originate in travel and trade from Bangladesh to Pakistan and then spread throughout south-central Asia. There were few cases west of India during periods of restricted contact between Pakistan and Bangladesh [67, 70, 71].

The only strain of *V. cholerae* now routinely isolated in south-central Asia is O1, El Tor, serotype Ogawa [68, 72]. Epidemic cholera reemerged in Pakistan and Afghanistan in 1988 and has remained a significant cause of morbidity and mortality ever since [73, 74]. Cases occurred throughout Pakistan, including the mountainous North West Frontier Province, and Azad, Kashmir. The city of Samarkand, Uzbekistan, suffered outbreaks of El Tor cholera in 1985 and 1990 [75].

In 1993, a newly emerged *V. cholerae* serogroup, designated O139, reached Pakistan from the Bay of Bengal. It carries the same toxin cluster and causes symptoms identical to those caused by *V. cholerae* O1 El Tor but has a different surface antigenic structure. After a few seasons of predominance, *V. cholerae* O139 virtually disappeared from the Karachi, Pakistan, region by 1996, and this strain has probably not yet spread west of Pakistan [66, 73, 76].

Since 1998, better reporting methods indicate that cholera and cholera-like illness have been intermittently widespread in Afghanistan and the Pakistan-Afghan border areas [77–79]. The Afghan cities of Mazar-e-Sharif, Bamiyan, Badakhshan, and Herat all have had significant outbreaks of serious diarrhea, but the largest was in Kabul [72]. El Tor *V. cholerae* was isolated in several of these locations. More than 14,000 cases of cholera-like illness were reported in 6 weeks of 1999, with more than half in Kabul [80]. Cholera continued to occur in 2000–2001, but reporting was irregular in Afghanistan in large part because of escalating civil war [81]. For the entire country, 4350 cases and 198 deaths were reported to WHO in 2000 [3]. In June 2001, the Samangan and Baghlan provinces of Afghanistan had 4499 reported cases and 114 deaths [62]. Given the current upheaval in Afghanistan, epidemic cholera remains a grave concern for local authorities and humanitarian groups.

*Noncholera bacterial agents.* The most significant reported bacillary etiologies of enteric disease are *Salmonella*, *Shigella*, and *Vibrio* species, but in the vast majority of diarrheal cases, no etiologic agent is established. Soviet occupation troops in Afghanistan were greatly affected by *Shigella*, which was reportedly responsible for 14% of all infectious diseases seen by Soviet medical personnel [4]. Some Soviet troops became ex-
tremely ill with combined cholera-shigellosis because of a severe lack of clean water [82]. Not surprisingly, *Shigella* infections were also common in Uzbekistan and Tajikistan [64, 83] when Soviet troops were conducting operations in Afghanistan.

Although the etiologies of diarrhea in Afghanistan remain largely unknown, the causes of noncholera diarrhea are well described in Pakistan. Numerous investigations were conducted before the 1988 resurgence of cholera [70, 84–87]. Many of these were studies of hospitalized children, a group that resembles immunologically naive Western troops and aid workers. The bacterial etiology of diarrhea has been similar throughout Pakistan. Enterotoxigenic *Escherichia coli* (ETEC) and *Shigella, Salmonella,* and *Campylobacter* species were typically isolated everywhere. Multiple serogroups of enteropathogenic *E. coli* were detected in several studies. More recently, *E. coli* O157:H7, a potent Shiga-like toxin producer, has been isolated [88]. Shigellosis was usually caused by the more virulent *Shigella flexneri* and *Shigella dysenteriae* species [84, 89, 90]. Rotavirus and enteric adenovirus were commonly found in Pakistani children with diarrhea [85–87, 91]. Studies in Tajikistan have found that rotavirus accounts for 26% of childhood and 11% of adult gastroenteritis [92].

US military personnel in Saudi Arabia during the Gulf War buildup had large outbreaks of diarrhea due to ETEC and *Shigella sonnei,* both typical agents of travelers’ diarrhea in the eastern Mediterranean and North Africa [93]. The supplementation of the troops’ diet with regionally acquired produce was at least partly responsible, and the number of cases fell when this was restricted. During Operation Restore Hope in Somalia, there was essentially no US military contact with local food. As a result, diarrhea cases were generally limited to *Shigella* species and ETEC, with filth flies as the likely vector [7]. In both the Gulf War and in Somalia, Norwalk virus was recognized as a cause of self-limited vomiting and diarrhea [7, 93].

*Parasites.* A review of several studies in Pakistan dating from 1964 to 1985 found protozoan agents (especially En*ta-moeba histolytica* and *Giardia lamblia*) to be more prevalent in the southern coastal part of the country, whereas helminths (*Ascaris lumbricoides,* hookworms, *Taenia* species, *Hymenolepis nana*) dominated in the north [94]. Either *E. histolytica* or *G. lamblia* was identified in <2% of hospitalized children in Lahore, Pakistan [95]. The authors speculated that the ova of helminths survive the cooler climates better than do protozoan cysts. *Cryptosporidium parvum* was reported in 10% of children in Rawalpindi, Pakistan [96], and has been found to be a major gastrointestinal pathogen in Turkmenistan as well [97]. *Cyclospora* may also be present, because it was found in Irish travelers to Nepal and Pakistan [98].

**Treatment of diarrheal disease.** Effective treatment of diarrheal disease has the potential to substantially lower morbidity and mortality in Afghanistan. Reduction of mortality from diarrheal disease is primarily related to effective management of dehydration [3]. Cholera is usually treated by oral (or if severe, iv) rehydration. Antibiotics are a useful adjunct [99, 100]. However, in Pakistan, *V. cholerae* O1 strains have become resistant to tetracycline, ampicillin, and erythromycin but not chloramphenicol or nalidixic acid [66, 76]. Isolates of *V. cholerae* O139 were resistant to trimethoprim-sulfamethoxazole but susceptible to tetracycline [76]. In Pakistan and Afghanistan, trimethoprim-sulfamethoxazole is the most commonly prescribed antimicrobial in cholera-like illnesses [101]. Nalidixic acid is the local drug of choice for *Shigella,* because resistance to most nonquinolone agents is very high [89, 90]. Treatment with oral ciprofloxacin for 1–3 days or another fluoroquinolone would be the primary choice for cases of dysentery in military personnel or foreign aid workers; if quinolone-resistant *Campylobacter* species is isolated, daily oral azithromycin (500 mg) might prove a useful alternative [102].

**Immunization.** A case of cholera due to *V. cholerae* O1 provides partial immunity for a few years; however, it does not protect against cholera due to *V. cholerae* O139. As a result, cholera due to *V. cholerae* O139 struck all ages when it first appeared, and the mean age of these patients was much higher than that of patients with cholera due to O1 strains [76]. US military personnel would be naive to both strains. Persons with blood serogroup O tend to have more severe clinical disease. Although it was hypothesized that infection with the very common ETEC heat-labile toxin might offer cross-protection because of its structural similarity with cholera toxin, the O139 experience indicates that O antigen is a more important protective factor.

Ryan and Calderwood [103] recently reviewed the current status of cholera vaccines. The currently available parenteral vaccine against *V. cholerae* O1 is not recommended because of low protective efficacy and the high risk of adverse reactions. Two promising oral *V. cholerae* O1 vaccines are not yet licensed in the United States. These include a killed whole cell with a recombinant B (binding) subunit of the cholera toxin (called WC-rBS) and a live cell vaccine with the gene for the A (active enzymatic toxin) toxin subunit deleted (CVD 103-HgR) [103]. The live vaccine has a mercury resistance gene added to monitor the presence of the organism in the environment. In field studies (including Bangladesh), the WC-rBS has shown protective efficacy of 80%–85% for at least 6 months, whereas the CVD-HgR has demonstrated 62%–100% protection for the same period. Neither vaccine protects against the O139 strain. Cholera is rare in Western travelers to areas of endemicity and has not been a problem for the US military in recent deployments. US military personnel will not receive cholera vaccine. No vaccine exists for other diarrheal agents, although several are in
development. The WC-rBS vaccine offers 50% protection against ETEC infection, but the CVD-HgR does not.

Typhoid Fever

Typhoid fever is a major public health concern in south-central Asia and can be expected to complicate ongoing humanitarian relief efforts. Although typhoid fever has not been a significant problem for the US military since the early 20th century [104], it was a huge burden for the Soviet military during its Afghanistan campaign, causing >30,000 hospitalizations [4] and disrupting military operations.

Epidemiology. Typhoid fever is endemic throughout south-central Asia. Outbreaks occur frequently, as exemplified by the 8900 cases (1% of the city’s population) that occurred during the first 6 months of 1997 in Dushanbe, Tajikistan [105]. The Tajikistan epidemic, like most others, was found to have been caused by contaminated public water supplies.

Clinical findings. After a typical incubation period of 8–14 days, typhoid fever begins insidiously with malaise, fever, chills, headache, and myalgia. Either diarrhea or constipation may occur, but many patients report no change in bowel habits. Cough may be the predominant symptom in some cases, and neuropsychiatric presentations also occur. Physical findings may be helpful in diagnosis, especially if a relative bradycardia or rose spots are noted, but most patients lack these classic findings. Gastrointestinal bleeding, bowel perforation, or a typhoidal state of profound debility may occur in advanced cases [106]. If the disease is untreated, mortality is 10%–30%, whereas appropriate, timely therapy lowers the mortality to ~1%. The differential diagnosis of typhoid in south-central Asia includes tuberculosis, brucellosis, intra-abdominal abscess, endocarditis, rickettsial infections, malaria, and West Nile fever.

Diagnosis. Definitive diagnosis of typhoid fever depends on the isolation of Salmonella typhi from blood, bone marrow, or rose spot snips. Culture of blood yields positive results for 80%–90% of patients during the first week of illness, with diminishing yields as the disease progresses. Culture of bone marrow often yields positive results if blood culture results are negative or if antibiotic treatment was begun before blood was obtained [107]. Rose spot skin snips may be diagnostic, but only a minority of patients have these typical lesions. Stool culture yields positive results for about half of patients with typhoid fever [106], but its diagnostic value is limited among residents of areas of endemicity for typhoid fever, because it may be difficult to distinguish acute infection from S. typhi stool carriage. Widal’s serology is of essentially no value in testing the typhoid-immunized patient and has marginal utility among the unimmunized local population [108, 109].

Treatment. Traditional therapy for typhoid fever has relied on 3 inexpensive antimicrobials: ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole. Multiresistant strains (resistant to all 3 traditional agents) were first noted in the Middle East and south-central Asia in the late 1980s and are now widespread. Ninety-three percent of tested strains for the Tajikistan outbreak were multiresistant [105]. In view of the proliferation of multidrug-resistant typhoid, oral fluoroquinolones and parenteral third-generation cephalosporins have become the standard initial typhoid therapies pending susceptibility testing. Both are highly effective, but quinolones are associated with fewer clinical failures and a more rapid response [110].

Complicating the use of quinolones for multidrug-resistant typhoid has been the recent emergence of quinolone-resistant S. typhi. Such strains have been reported in south-central Asia [111], the United Kingdom [112], Southeast Asia [113], and Tajikistan [114]. The optimal treatment of quinolone-resistant or -unresponsive S. typhi infection is unclear. A parenteral third-generation cephalosporin, such as ceftriaxone, would be a reasonable choice, and oral third-generation cephalosporins, such as cefixime, may offer a convenient option for the less seriously ill [115]. Azithromycin is a novel approach for multidrug-resistant typhoid and appears to have success rates comparable to ciprofloxacin and ceftriaxone [116, 117].

Pending susceptibility data, it would seem prudent to initiate therapy for typhoid in patients in south-central Asia with an oral quinolone, changing to either a third-generation cephalosporin or azithromycin if clinical failure occurs or quinolone resistance is documented. Standard doses would be ciprofloxacin, 500 mg orally b.i.d. for 10 days, ceftriaxone, 2 g iv q.d. for 14 days, or azithromycin as a 1-g loading dose followed by 500 mg q.d. for 6 days; azithromycin may be given orally or iv. Dexamethasone may be a valuable adjunct for patients with severe typhoid (altered mental status, hypotension). The definitive study that established the value of steroids used extremely high doses (3 mg/kg) of dexamethasone initially, followed by doses of 1 mg/kg at 6-h intervals [118]; the utility of lower steroid doses is unproven.

Prevention. The prevention of typhoid depends primarily on the provision of uncontaminated water and effective sewage disposal. Vaccines lower the risk of infection by ~70% but may be “overwhelmed” by large inocula [119]. Two vaccines are in popular use in the United States and Europe: the inactivated intramuscular Vi vaccine and the oral, attenuated Ty21a strain. Because US military personnel in south-central Asia will have received either of these vaccines and have access to safe drinking water, they are at very low risk of typhoid fever. All visitors to Afghanistan should receive a typhoid vaccine. Despite the high risk of multidrug-resistant typhoid, local populations are not routinely vaccinated. Considerable data support the use of typhoid vaccine in preventing or stemming typhoid epidemics, causing some authorities to recommend more widespread use of typhoid vaccines in south-central Asia [119, 120].
Viral Hepatitis

Viral hepatitis is a significant health risk for US troops, coalition peacekeepers, and humanitarian workers deployed to Afghanistan and neighboring countries. Historically, hepatitis A and B have been major infectious disease threats for military forces [121, 122]. More recently, there has been concern about hepatitis C because a high prevalence of hepatitis C virus (HCV) infection has been found in some populations of US military veterans [123, 124].

Importantly, viral hepatitis was a serious problem for Russian troops during the Soviet Union’s incursion into Afghanistan in the 1980s [4, 5, 125–127] and remains a major health threat to the local population. More than 115,000 cases of acute viral hepatitis were reported in a population of 620,000 Soviet troops who served in Afghanistan [4]. Morbidity rates were so high that viral hepatitis was thought to have directly compromised Soviet military operations. For instance, the 5th Motorized Rifle Division was reportedly rendered ineffective for combat by an outbreak of >3000 cases of acute hepatitis in late 1981 [4].

Hepatitis A is highly endemic in south-central Asia where US troops have been deployed [128]. Hepatitis A virus (HAV) is readily transmitted by the fecal-oral route and is a universal infection among the resident population, with >90% of 5-year-olds infected [128]. The risk of HAV transmission among non-immune personnel is elevated during combat and humanitarian operations because of crowded living conditions and the difficulty of maintaining a high level of cleanliness while camping in the field. Ninety-five percent of cases of acute hepatitis among the Soviet troops deployed to Afghanistan were attributed to HAV infection, which was thought to have resulted from poor personal hygiene, a lack of clean drinking water, and the failure of cooks to wash their hands [4, 5, 125–127]. Because of the collapse of sanitation systems in war-ravaged Afghanistan, hepatitis A again poses a health threat for combat troops and peacekeepers.

Hepatitis B is also endemic in Afghanistan and surrounding countries [129]. In a study in nearby Pakistan, hepatitis B was the cause of 42% of cases of acute hepatitis [129]. Among adults, hepatitis B virus (HBV) is transmitted by sexual and parenteral exposure. For military forces and peacekeepers, HBV infection could be contracted from the transfusion of contaminated blood that may have been inadequately screened in an emergency [130]. Sexual contact and illicit drug use also are potential routes of HBV infection.

Like the other major types of viral hepatitis, hepatitis C is prevalent in south-central Asia [131]. Serological evidence of infection has been found in 16%–24% of general populations surveyed in Pakistan [131]. Hepatitis C virus infection is most readily transmitted by parenteral exposure to contaminated blood. Sexual contact is not an efficient mode of transmission [132]. HCV has been considered a potential health threat for military troops and veterans from illicit drug use, blood transfusions (before reliable screening of blood products became possible in 1993), and contact with the blood of battlefield casualties [123, 124]. Troops injured in Afghanistan could be infected with HCV if unscreened blood donors were used in an emergency [130].

Hepatitis E virus (HEV), which is transmitted via the fecal-oral route, is a potential infectious disease problem in developing countries from consumption of contaminated water and food. HEV infection is highly endemic in south-central Asia, where one-third of the population may experience infection [133–135]. Some of the largest epidemics of hepatitis E have occurred in Pakistan and India [136, 137], causing substantial morbidity and some mortality, especially in pregnancy. The general breakdown in sanitary measures in Afghanistan could potentially lead to HEV infections among deployed military personnel, peacekeepers, and humanitarian workers.

As noted, all of the major types of viral hepatitis are prevalent in Afghanistan and surrounding countries. Given the diverse routes of transmission, the risk of viral hepatitis cannot be completely eliminated among deployed troops and peacekeepers. Nevertheless, in the near term, viral hepatitis probably will not be a major cause of morbidity for currently deployed US military forces.

Studies of US military populations have shown that viral hepatitis has become much less of a problem. Analysis of Department of Defense hospital records indicate that over the last 25 years there has been a steady decline in the incidence of viral hepatitis, whether transmitted by parenteral, sexual, or fecal-oral routes [138–140]. Epidemiological studies of US military populations also indicate a low risk of viral hepatitis except in certain high-risk groups [139, 141]. Hepatitis A is a concern during deployments to developing countries [142]. The risk of hepatitis B is low except among patients with sexually transmitted diseases [142, 143]. For hepatitis C, current military forces have been found to be at low risk of infection. In a recent study of 10,000 active duty US troops, 0.5% had been infected with HCV, which is much lower than the 2.6% prevalence observed in the civilian adult population [144, 145].

Although HEV has the potential to cause epidemic disease in military populations [146], hepatitis E has not been a problem for the US military. In fact, there has never been a documented outbreak of hepatitis E among US forces. Hepatitis E also is relatively rare among Western travelers, even though it is one of the most common types of viral hepatitis in developing countries [147]. One reason for the low risk of hepatitis E may be the fact that HEV infection requires a relatively large dose of infectious agent, usually from grossly contaminated drinking water [148].

Recent military deployments to southwest Asia and Africa further illustrate the low risk of viral hepatitis for US forces
deployed to Afghanistan. Only a few cases of hepatitis A and B were observed among the 700,000 US troops deployed to southwest Asia during the war with Iraq in 1991 [149]. Likewise, viral hepatitis was not a problem for US troops sent to Somalia in 1992, even though hepatitis E virus was a common cause of acute sporadic hepatitis in Somalia during this period [150].

Several factors are responsible for the low risk of viral hepatitis among today's military forces. For one, the US military places strong emphasis on both personal hygiene and camp sanitation, even during combat operations. As a recent example, preventive medicine personnel were deployed with US troops at the start of the ground offensive in Afghanistan to set up hand-washing and waste disposal facilities [151–153]. In addition, the US military can airlift bottled water and fresh food to combat troops and can generate large quantities of potable water by use of portable reverse-osmosis units. Because of these preventive measures, diseases transmitted by the fecal-oral route, such as hepatitis A and E, should not be a major problem.

The US military's emphasis on maintaining a drug-free environment also contributes to a reduced risk of viral hepatitis. During the last 20 years, illicit iv drug use has been nearly eliminated in the US military by routine, random drug testing at induction and throughout military service [154, 155]. As a result, hospitalizations for hepatitis B and C, which are efficiently transmitted by injection drug abuse, have decreased markedly in the US military [139, 140].

The risk of viral hepatitis has been diminished further by the development of the hepatitis B vaccine and, more recently, the hepatitis A vaccine. At present, military medical personnel and troops diagnosed with a sexually transmitted disease are vaccinated against hepatitis B. Also, the hepatitis B vaccine is recommended for US military members assigned for extended periods of time to embassy guard duty and to countries with high rates of hepatitis B [156]. The hepatitis B vaccine has not been given routinely to all incoming US recruits, but young men and women are now entering military service with pre-existing immunity to hepatitis B because of national recommendations for adolescent immunization [157].

In 1995, the hepatitis A vaccine was introduced. This vaccine is being given to incoming US military recruits, to all deployable military members currently on active duty, and to other troops before deployment to developing countries. Because of the effectiveness of the hepatitis A vaccine, immunoglobulin is no longer used on a routine basis for prophylaxis against hepatitis A [156]. Both hepatitis A and hepatitis B vaccines are recommended for anyone working in Afghanistan for an extended time.

Although there is no vaccine for hepatitis C, the risk of HCV infection has been substantially reduced because of the identification of HCV in 1989 and the development of sensitive and specific serological tests. HCV is virtually never transmitted from the routine transfusion of blood products that are screened before use [158]. Moreover, HCV is not transmitted by casual contact, is not readily transmitted by sexual contact, and would not be transmitted from contact between infected blood and intact skin [159]. In prior studies, HCV infection has not been associated with military deployments or the use of im immunoglobulin [141, 142, 160]. High rates of HCV infection among military populations have generally been restricted to veterans of the Vietnam War era [161, 162]. HCV infection has been found infrequently among non–Vietnam era veterans who recently have left active military service or among military veterans randomly selected from the general population [145].

As is the case with hepatitis C, there is no commercially available vaccine for hepatitis E. Prevention of hepatitis E rests on the provision of clean drinking water. Protection of the local populace from this and other waterborne illnesses will require a major rebuilding of water and sanitation infrastructure.

Both hepatitis delta virus and hepatitis G virus infection are found in south-central Asia [163, 164]. The same measures that are effective in preventing hepatitis B are effective against delta hepatitis. Hepatitis G virus is similar in genomic structure to HCV but has not been shown to be pathogenic [165]. During diagnosis of acute cases of hepatitis among combat troops and peacekeepers, leptospirosis must be ruled out because this bacterial infection is a treatable cause of acute jaundice in this region of the world [166].

Acute viral hepatitis due to any of the major causes presents with similar symptoms, principally malaise, nausea, vomiting, abdominal pain, dark urine, light-colored stools, and jaundice. The incubation period for acute viral hepatitis ranges between 3 and ≥12 weeks. Therefore, symptoms can begin months after exposure. There is no accepted therapy for any of the major kinds of acute viral hepatitis, but there have been recent advances in the treatment of chronic hepatitis B and C [167].

Viral hepatitis should not be a major problem for recently deployed US forces. Only in the event of a major breakdown in sanitation would hepatitis E pose a threat for combat troops. The most serious problems may arise after combat operations end, when large numbers of peacekeepers and groups involved in humanitarian relief and reconstruction take up residence in Afghanistan. As occurred among Soviet troops, viral hepatitis will become a problem whenever preventive health measures are not maintained [126].

**Leishmaniasis**

Leishmaniasis is a zoonotic protozoan infection that is endemic throughout south-central Asia. It is most prevalent in Turkmenistan, Uzbekistan, Afghanistan, and Pakistan [168]. Currently, leishmaniasis is epidemic in areas of Afghanistan, including the capital, Kabul. It results in a broad spectrum of
clinical disease, with both visceral leishmaniasis (kala-azar) and cutaneous leishmaniasis occurring in south-central Asia.

Cutaneous leishmaniasis is the most common form in south-central Asia, with visceral leishmaniasis rarely reported. Cutaneous leishmaniasis can cause significant morbidity, leading to disfigurement and disability [169], and may result in medical evacuation, requiring costly and toxic treatment. It has previously affected 20 of 700,000 US troops deployed to Operation Desert Storm [170] as well as Russian troops deployed to south-central Asia [171]. Leishmania tropica and Leishmania major are the etiologic agents of cutaneous disease in this region [168]. Leishmania donovani has been identified as the regional causative agent of visceral leishmaniasis. During Operation Desert Storm, a viscerotropic form of disease caused by Leishmania tropica was identified and diagnosed in 12 US soldiers but no other coalition military personnel [170].

**Life cycle.** Dogs and humans are the usual reservoirs of L. tropica, the common cause of “urban” leishmaniasis in Afghanistan. In south-central Asia, the great gerbils (Rhombomys opimus) are the vertebrate hosts that maintain L. major in nature, and the distribution of L. major is considered coincident to that of R. opimus [168]. Cutaneous leishmaniasis is less common in Kazakhstan, because the great gerbil population is more limited farther north, where the gerbils have only 1 reproductive cycle per year [168].

Sandflies of the genus Phlebotomus are the vectors that transmit the Leishmania species among mammalian hosts and are also the vector for transmission of sandfly fever. Phlebotomus papatasi is the vector that transmits Leishmania major throughout most of the Middle East and is present in south-central Asia [168]. Phlebotomus sergenti has recently been identified as the vector for L. tropica in Afghanistan [172, 173]. They are small (2–3 mm long and <1 mm wide) nocturnal biting midges and may be associated with human habitation [10]. Sandflies are weak and noiseless flyers that travel in short hops at low levels. They rarely travel >100 m from their resting and breeding places, which are humid microenvironments with organic debris [10]. Only the female ingests blood, usually at night, but may feed until late morning inside dwellings. The bite leaves a tiny hemorrhagic spot at the site, which develops into an inflamed, sometimes vesicular, papule at 1–2 weeks. Highly sensitized persons may develop urticaria. Clusters of lesions may occur because infected flies have difficulty feeding [10].

The size of the Phlebotomus population strongly correlates with rainfall in the previous winter [174]. The proportion of L. major in the host population increases during the transmission season of May to September [10]. Although the sandfly population fluctuates by season, clinical leishmaniasis occurs throughout the year in Afghanistan, including Kabul.

**Epidemiology.** Leishmaniasis is endemic in Africa, the Middle East, and south-central Asia [172], with similar strains occurring from Iran to Pakistan [168]. Cutaneous leishmaniasis was first reported in Afghanistan in 1964, and the country has recently been enduring a severe and prolonged epidemic [174]. Cutaneous leishmaniasis has been reported from most provinces of Afghanistan and can be presumed to be ubiquitous, with endemic foci reported from Herat in the east, Kandahar in the south, and Mazar-e-Sharif in the north [175]. Cutaneous leishmaniasis due to L. tropica infection has been defined as an emerging disease in parts of northeast Afghanistan and northwest Pakistan [169]. Kabul is currently experiencing a major epidemic. Only 31 cases were identified in 1964, but that number had swelled to 8500 cases by 1990. In 1996, it was estimated that 270,000 people of a total population of 2 million in Kabul were infected [176].

Outbreaks in refugee camps indicate that cutaneous leishmaniasis caused by L. tropica may be carried by refugees into areas previously unaffected by the disease [175]. Cross-border movement is common and thought to enhance outbreaks around refugee camps. In 1 Afghan refugee camp in Pakistan, 38% of 9200 inhabitants had active lesions, and another 13% bore the scars of past infection [175].

In general, the age distribution of the Leishmania-infected reflects that of the Afghan population [174]. Sandflies exist both inside and outside the home [175], but most transmission takes place in the home [176], thus explaining why women are infected slightly more often than men [175]. Research in 1997 revealed that living in the lower 2 stories of 5-story apartment buildings carried the greatest risk, suggesting limited vertical movement of the vector [176]. High household occupancy is also a risk factor, and cases may be clustered within households [174]. This may be of significance to military troops bivouacked in close quarters. Although the current epidemic is limited to cutaneous leishmaniasis, endemic foci of visceral leishmaniasis have been reported from Kabul and Badghis provinces [177, 178].

Endemic foci of leishmaniasis have been reported in Uzbekistan and Turkmenistan [179]. In the delta plains and oases of Turkmenistan, cutaneous leishmaniasis is endemic. Serological tests for visceral leishmaniasis indicated that it is endemic in the sandy deserts in the interfluval areas of southeastern Turkmenistan [179]. Tajikistan has reported locally acquired leishmaniasis from its southern desert regions, although most cases are imported from southern Uzbekistan or Turkmenistan, or in border regions where sandflies from Afghanistan are carried by dust storms and strong winds [171].

**Clinical findings: cutaneous leishmaniasis.** The incubation period is 2–8 weeks, although rarely it can be as long as 12–18 months. The lesion begins as an erythematous nodule at the site of the bite and slowly enlarges over several months. It eventually ulcerates, having a firm raised border with a crusted center [10]. One or two lesions are present in 80%,
with most lesions occurring on the head (45%), the hand or wrist (26%), or the lower arm, ankle, or foot (19%). Multiple lesions are infrequent but are more common at the extremes of age and tend to be located on the arms and legs rather than the head. Clustering of lesions is due to multiple bites from a single infected sand fly [174]. The mean size of the lesions is 2–3 cm [168]. Dissemination is rare. Proximal subcutaneous nodules were noted in 10% of patients in a study in Saudi Arabia [10].

The mean duration of active lesions is ~5 months and usually not longer than 12 months [10]. Healing results in scar formation and generally gives life-long immunity [10, 175]. One report suggests that cutaneous leishmaniasis can be more frequent and severe in travelers from areas where the disease is not endemic [172].

Clinical findings: visceral leishmaniasis. Although there are no recent reports of visceral leishmaniasis in Afghanistan, foci of endemic disease exist in south-central Asia. Visceral leishmaniasis (kala-azar) is a chronic systemic disease with a prolonged incubation period of 2–8 months; rare patients have an incubation period of up to 2 years. Onset is gradual and consists of fever, weakness, weight loss, lymphadenopathy, pancytopenia, and hepatosplenomegaly. Untreated, visceral leishmaniasis progresses to severe pancytopenia and may lead to death from hemorrhage or superinfection [180].

A nonlethal, viscerotropic form of leishmaniasis caused by L. tropica was reported in 12 US personnel deployed during Operation Desert Storm. Clinical findings in these patients included fever, fatigue, abdominal pain, mild splenomegaly, adenopathy, and mild anemia. No skin lesions were found, and 1 patient was asymptomatic. Diagnosis was made on culture of bone marrow [170]. No subsequent cases have been identified in the Middle East, and no cases have been noted in Central Asia.

Diagnosis. Leishmaniasis, especially if atypical or visceral, can present a diagnostic dilemma. Successful diagnosis is inversely related to the duration of disease: The longer the disease is present, the more likely diagnostic tests will be negative. Diagnostic tests include microscopic examination of smear from the cutaneous lesion (looking for amastigotes), histological punch biopsy, and culture on special media (such as Novy, MacNeal, Nicolle). A smear from the nodular margin of the most active lesions should be obtained with scalpel or syringe and fixed in methanol and stained with Giemsa. PCR is being increasingly used to aid in diagnosis [175]. Serological and skin tests are available but are not helpful in diagnosing acute cutaneous disease.

Regional attempts at diagnosis of leishmaniasis in Afghanistan revealed that 36% of new cases were positive by microscopy, and 48% of slide-negative cases were confirmed by culture. Some cases missed by both standard methods were detected by PCR [175]. All available methods should be used to maximize diagnostic yield. Several skin tests are in development but are not yet available for routine clinical use.

Treatment. Untreated cutaneous lesions usually heal with scarring. Therapy is toxic and should be limited to those with visceral disease or large, multiple, or function-limiting cutaneous lesions. Traditional therapy consists of a pentavalent antimonials agent (meglumine antimoniate or sodium stibogluconate) at a dose of 20 mg/kg/day for 20–28 days by slow iv infusion, but the antimonials are toxic [181]. Considerable data support the use of amphotericin compounds; liposomal amphotericin has been approved for use in visceral leishmaniasis by the US Food and Drug Administration (FDA) [182–184]. Amphotericin B deoxycholate might be effective in complicated cutaneous leishmaniasis, but data are limited [184]. Other potential second-line therapies for visceral disease include pentamidine, miltefosine, and paromomycin [185]. Promising oral options for cutaneous disease include ketoconazole, fluconazole, miltefosine, itraconazole, and dapsone [184, 185], but these are neither widely used in the region nor FDA approved for this indication. Before ulceration of cutaneous lesions, treatment can be attempted with intralesional injections with sodium stibogluconate or with cryotherapy. Optimal treatment of complex or visceral disease usually requires evacuation to a tertiary medical care facility, because available therapies have substantial toxicity.

Prevention. Prevention measures include personal protective measures to limit sandfly bites, rodent control, and residual insecticide spraying. Sandflies can penetrate the mesh of mosquito nets, but application of permethrin enhances efficacy [10]. Fans can also reduce the ability of sandflies to bite. Flies cannot bite through cloth; thus, permethrin-treated uniforms should prove efficacious. DEET should be applied to all exposed skin surfaces, particularly about the face and ears, and especially at night. Indoor spraying is also an effective means of control [176]. Although spraying rodent burrows in south-central Asia has lowered disease transmission, it has not resulted in long-term control [186]. There is little evidence of widespread insecticide resistance, though P. papatasi has been reported to have some resistance to DDT. In previous efforts in Afghanistan, residual spraying reduced disease by 50%, whereas bednets and protective clothing reduced disease by 75% [169]. Both should be used whenever possible.

Arboviral Diseases of Afghanistan

Crimean-Congo hemorrhagic fever. Crimean-Congo hemorrhagic fever (CCHF) is a zoonotic hemorrhagic fever caused by a virus of the bunyavirus family, which also includes hantavirus and Sandfly fever virus. CCHF is distributed widely throughout Asia, Europe, and Africa, and recent outbreaks of CCHF have occurred in Afghanistan and Pakistan. The disease...
is transmitted by ticks, body fluids, and tissues from infected animals. Those with significant outdoor exposure, as well as butchers, abattoir workers, and veterinarians, are at increased risk of disease. Secondary human cases may occur among household members as a result of contact with infected body fluids from ill patients. Nosocomial transmission is well described [187], and health care personnel should use appropriate contact isolation.

**Natural history.** CCHF was described in the Crimea in 1944 during an outbreak of >200 cases and given the name Crimean hemorrhagic fever. A later virus isolate from the Congo was noted to be the same pathogen, resulting in the name Crimean-Congo hemorrhagic fever virus. Ixodid ticks may become infected with the CCHF virus either through transovarial transmission or through taking a blood meal from an infected animal. The CCHF virus can infect a variety of ixodid ticks, but *Hyalomma* species ticks appear to be the most important vectors, and these vectors are present in Afghanistan [188]. Many animal species are infected, but apparently only humans develop illness as a result [189].

**Regional information.** The illness is widespread in Afghanistan. Forty-seven cases of CCHF were identified in the frontier area on the Afghan-Pakistani border in October 2001 [190]. An outbreak in Pakistan in late February of 2002 killed at least 3 people, and the United Nations reported in March 2002 that an outbreak of unknown hemorrhagic fever had killed 28 in eastern Afghanistan [191]. Cases occurred in May to July 2000 in the Gulran district of Afghanistan, with 15 deaths [192]. Quetta, Pakistan, had nosocomial transmission during a 1994 cluster [193]. Cases have been reported in surrounding nations, including Iran [62, 194], Turkmenistan, Russia, the Middle East, Africa, and Eastern Europe. No CCHF has been identified in the New World.

**Epidemiology.** The illness has a predictable seasonality in some locations as a result of seasonal tick activity. In other locations, the illness is transmitted only sporadically [195]. It appears that most humans are infected as a result of tick bite, although direct contact with infected animals or people can occasionally result in infection. It has been assumed that the number of asymptomatic cases is low, on the basis of serological studies from South Africa, where 70% of those with serological evidence of infection reported a history of hospitalization with CCHF. In Russia, however, only 20% of those seropositive for CCHF virus reported significant illness [189]. Whether this represents strain variation or difference in study technique is not clear.

**Clinical findings.** The incubation period following contact with infected blood or tissue is usually 3–6 days, with a maximum of 13 days [189, 196]. The incubation period after the bite of an infected tick is 2–12 days. Symptoms are sudden in onset, with fever, chills, headache, myalgia, dizziness, neck pain and stiffness, and photophobia. Back or leg pain may be severe. Nausea and abdominal pain, possibly with diarrhea, may be present. Behavior changes may occur. Patients may present with flushed facies, conjunctival injection, pharyngeal hyperemia, or palatal petechiae [197]. Hepatomegaly occurs in ~50%. Fever is intermittent, and patients may be afebrile on presentation [198]. Within 3–6 days, patients may develop hemorrhagic signs, such as epistaxis, bleeding gums, melena, hematuria, vaginal bleeding, and petechial or purpuric rash. By the end of the first week, most patients are severely ill, with multiple organ involvement. Encephalopathy, hepatic insufficiency, renal failure, pulmonary edema, and capillary leak syndrome are common in severe cases. The mortality rate from CCHF is ~30% (range, 15%–50%), with deaths occurring between days 5 and 14 from onset of symptoms [197].

**Laboratory findings and diagnosis.** Abnormal laboratory test results that might suggest CCHF include elevated hepatic transaminase levels, thrombocytopenia, lymphopenia, evidence of disseminated intravascular coagulation, and elevated creatinine level. Diagnosis may be achieved by isolation of virus in blood or tissue samples, either by cell culture or by inoculation of a specimen into suckling mouse brain. Virus titers are highest in the first few days of illness, and the virus can be isolated in the first 12 days of illness. Fatal cases have higher and more prolonged viremia, presumably with greater risk of nosocomial transmission. PCR-based methods have recently been used successfully in diagnosis as well. Pathological specimens can be tested by fluorescent antibody staining. Serological assays are available for diagnosis of CCHF and were used in the field in both US Desert Storm and Somalia deployments, but no cases were found. IgM and IgG are demonstrable by days 7–9 of illness. Notably, a measurable antibody response occurred in only 2 of 15 fatal cases in 1 series. ELISA seems to be the most sensitive serological method, followed by reversed passive hemagglutination-inhibition, immunofluorescent antibody assay, and complement fixation [198]. An EIA-based antigen capture test can confirm the diagnosis in half of nonfatal cases and most fatal cases.

**Treatment.** Supportive therapy is the mainstay of therapy in CCHF. Most patients will require monitoring in an intensive care unit for respiratory and hemodynamic support. The antiviral drug ribavirin has been used in treatment of established CCHF, with some published data supporting its use [184]. The appropriate dosage of ribavirin is not well defined, but Centers for Disease Control and Prevention (CDC) recommendations are ribavirin in a volume of 50–100 mL infused over 30–40 min with a loading dose of 30 mg/kg (maximum dose, 2.64 g), followed by 16 mg/kg (maximum dose, 1.28 g) iv q4h for 4 days and then 8 mg/kg (maximum dose, 0.64 g) iv q8h for 6 days (for 10-day treatment) [199]. A proposed oral dose (if the iv formulation was unavailable) is a 2-g loading dose fol-
lowed by 1 g orally q6h for 4 days and then 500 mg q6h for 6 days (total of 10 days). It should be noted that hemolytic
anemia is common with ribavirin therapy, and it is teratogenic
(pregnancy category X) [200].

Convalescent immune serum from previously infected pa-
tients has also been used [201]. Heparin treatment is contro-
versial [197]. Treatment of exposed health care workers with
ribavirin should also be considered [200]. The CDC recom-
pends a prophylactic dose of 500 mg q6h for 7 days.

Prevention. For the individual, use of effective personal
protective measures against tick bites and limiting animal ex-
posure are the best ways to avoid infection. Use of permethrin-
impregnated clothing and gear, tucking trousers into boots or
socks, wearing light-colored clothing to facilitate tick identi-
cation, use of effective DEET insect repellants on exposed skin,
and daily skin inspection for ticks (“buddy checks”) are main-
stays of prevention. Nosocomial spread within the health care
setting is possible, and appropriate universal precautions should
be observed in the patient care areas and the laboratory. A
suspected patient should be placed in a private room, and
negative-pressure respiratory isolation should be considered,
particularly if coughing, vomiting, or other activities generating
large-droplet aerosols occur. Those entering the patient’s room
should wear gloves and gowns, and those approaching within
1 m should wear face shields or surgical masks and eye pro-
tection to prevent contact with blood or other body fluids [202].
The risk of nosocomial spread is greater with severely ill pa-
tients. For large groups of people at risk (such as within a
refugee camp), local application of acaricide could be consid-
ered during seasonal risk (spring to fall). Although experimental
vaccination has been tried on a small scale, it is currently una-
vailable for large-scale human use.

West Nile virus infection. West Nile virus is a member of
the Japanese encephalitis group of flaviviruses and is found
throughout Asia, Europe, the Middle East, and Africa. The virus
has recently become established in the eastern United States,
where it appears to be spreading rapidly. The virus has also
become reestablished in areas where it has not been seen for
many years (e.g., France). The most serious manifestation of
West Nile virus infection is encephalitis. Recent outbreaks of
West Nile encephalitis in humans have occurred in Algeria in
1994, Romania in 1996–1997, the Czech Republic in 1997, the
Democratic Republic of the Congo in 1998, Russia in 1999,

Natural history. West Nile virus was first isolated in the
West Nile District of Uganda in 1937. It is transmitted prin-
cipally by culicine mosquitoes but also can be transmitted by
other genera. A wide variety of animals can be infected. In
humans, the virus usually produces either asymptomatic in-
fec tion or mild flu-like illness. The tempo of epidemics seems
to be increasing worldwide, and degree of morbidity may be
escalating as well [203].

Regional information. The virus is almost certainly present
in Afghanistan. The illness is well described in Pakistan [204,
205], Iran [206], and other neighboring countries. Antibodies
to West Nile virus have been detected in the human population
in Kunduz, Herat, Bamian, and Helmand provinces of Af-
ghanistan [207].

Epidemiology. The virus typically infects young children in
areas of endemicity. The infection is usually asymptomatic or,
at most, causes a mild febrile syndrome. Only rarely are children
affected with a more serious illness. Morbidity and mortality
are generally confined to the elderly. The illness is seasonal in
temperate climates, because of the activity of the mosquito
vector. Summertime is the peak of transmission. Like many
other flavivirus encephalitis agents, the ratio of encephalitic to
nonencephalitic infection is very low (<1%). Life-long immu-
nity is conferred by infection.

Clinical findings. The incubation period for West Nile virus
infection is 3–6 days. Symptomatic disease is usually a febrile,
flu-like illness with abrupt onset and moderate or high fever.
Typical symptoms (in roughly descending order of frequency)
consist of headache, myalgias, arthralgias, maculopapular rash
(in some outbreaks the rash is infrequent), facial flushing, sore
throat, lymphadenopathy (also of variable frequency), conjunc-
tivitis, ocular pain, and/or gastrointestinal symptoms [208].
In some cases, the illness may be biphasic. In a small number
of cases, acute aseptic meningitis or encephalitis can occur,
which is associated with neck stiffness, vomiting, confusion,
disturbed consciousness, somnolence, tremor of extremities,
abnormal reflexes, convulsions, pareses, and coma. Rarely, an-
terior myelitis, hepatosplenomegaly, hepatitis, pancreatitis, and
myocarditis may occur. Recovery is complete in nonfatal cases,
but less rapid in adults than in children, and is often accom-
panied by long-term myalgias and weakness. Permanent se-
queae have not been reported. Most fatal cases have been
recorded in patients >50 years old. Some authors have noted
that the most recent outbreaks have had greater virulence than
past reports [203, 208].

Laboratory findings and diagnosis. There are no specific
routine laboratory findings to suggest West Nile fever. Labo-
atory findings involve a slightly increased sedimentation rate
and a mild leukocytosis; CSF of patients with CNS involvement
shows moderate lymphocytic pleocytosis and elevated protein
levels [208]. MRI can also suggest acute infection [209]. The
virus can be isolated from the blood during the early phases
of the infection, usually by inoculation into cell culture, al-
though inoculation into suckling mouse brain is also sufficient.
The virus can be recovered from the blood of immunocom-
petent febrile patients for up to 10 days and from blood of
immunocompromised patients as late as 22–28 days after in-
fection. Peak viremia occurs 4–8 days after infection. Serological diagnosis is also available, although cross-reactivity with other flaviviruses may occur. The most commonly used test is the IgM capture ELISA, but the reference standard is the plaque reduction neutralization test with acute and convalescent serum [210]. CSF should be sent for IgM ELISA and PCR testing, although PCR yields positive results for only 50%–60% of confirmed cases [211].

Treatme... and prevention. There is no specific treatment for this infection. Supportive care is the mainstay of medical intervention. The primary preventive measure is avoidance of mosquito bites. There is no available vaccine.

Sandfly fever. Sandfly fever viruses are in the Bunyaviridae family, as are CCHF virus and hantavirus, and all are concerns in Afghanistan. The sandfly fever virus complex comprises a large number of species from both the New and Old World. In the Old World, 3 viruses are most notable: Toscana, Naples, and Sicily viruses. The Toscana virus seems to be the most virulent but is limited in distribution to Italy and the Iberian Peninsula. The Naples and Sicily viruses are widely distributed throughout Europe and Asia and cause a self-limited febrile syndrome. This is a disease of military relevance, because debilitating outbreaks have occurred among foreign troops in areas of endemicity, including US and British troops stationed in the Middle East during WWII [212].

Natural history. The sandfly viruses are transmitted via the Phlebotomus sandfly. In central Asia, the sandfly is frequently found in association with burrowing rodents and is a poor flier. Consequently, the illness tends to be focally distributed [213]. The epidemiology is similar to that of leishmaniasis, which is transmitted by the same sandfly vector. The sandfly virus may have a greater attack rate than does Leishmania. Solid immunity is conferred by infection, so patients are protected after recovery. Most inhabitants of regions of endemicity are infected during childhood. The pathogen causes a self-limited illness and does not result in long-term sequelae. However, the introduction of large numbers of naive hosts into areas of endemicity may result in outbreaks of sandfly fever.

Regional information. The Sicily and Naples viruses are both definitely present in Afghanistan [207]. Iran, Pakistan, and the former Soviet republics of central Asia have also documented transmission of these viruses as well [214, 215]. Much of what is known of the epidemiology of these viruses was elucidated during the Soviet occupation, when both Sicilian and Neapolitan sandfly fever were common causes of febrile illness among Soviet troops [216, 217].

Clinical findings. The illness caused by sandfly fever virus is largely a nonspecific flu-like illness, with an incubation period of ~3–6 days. In 17 experimentally infected volunteers, all experienced fever of ~3 days’ duration. Headache, myalgias, and low back pain were common, and photophobia, chills, nausea, and vomiting were noted in some patients [218]. The Soviet literature describes a dengue-like presentation that was sometimes incapacitating for a few days [216, 217].

Laboratory findings and diagnosis. Serological testing is the most practical means of making the diagnosis [219], and the virus can be cultured from blood of acutely ill patients. Leukopenia is a common laboratory abnormality [218].

Treatment and prevention. There is no treatment for sandfly fever, and supportive care is all that is required in this self-limited illness. Sandfly control measures will protect against infection. Because sandflies are not strong fliers, they will land on walls and other surfaces near their blood meals; therefore, contact insecticides can be effective. Personal protective measures, such as wearing long-sleeved clothing impregnated with permethrin and using DEET-containing repellent on exposed skin, will assist in preventing exposure. Mosquito netting must be of fine mesh to be effective. Local fogging with insecticide may assist in controlling sandflies in fixed-area housing, such as encampments. Traditional sandfly control measures in central Asia have involved control of the rodent host, including plugging the rodent burrows [213].

Regional Arboviral Diseases, Possibly in Afghanistan

Tickborne encephalitis. Tickborne encephalitis (TBE) comprises 2 closely related syndromes: central European encephalitis and Russian spring-summer encephalitis. Although the disease has not been specifically reported in Afghanistan, it is conceivable that TBE might occur there. The illness has been historically present in central Russia and many of the former Soviet republics.

The flavivirus of TBE is transmitted in central Asia by the Ixodes persulcatus complex ticks. The virus circulates between the tick vector and rodent and insectivore hosts. Domestic animals, such as sheep and goats, are important in the transmission cycle, however, by increasing tick exposure to humans and possibly by passing viruses to humans in infected milk. People can be infected by tick bite, oral ingestion of virus, or aerosol [210].

The illness is transmitted from May through August in most areas, coincident with feeding activity of the tick vector [213]. Of the TBE complex, the eastern variant (the agent of Russian spring-summer encephalitis) has greater virulence, but both can cause significant morbidity. Those with substantial outdoor exposure are at increased risk. Russian spring-summer encephalitis is widespread throughout Russia, the former Soviet republics, and as far east as Japan. The disease is not known to exist in Afghanistan and, if present, is unlikely to be widespread.

TBE is frequently noted to be biphasic. Symptoms begin after 3–7 days of incubation, with fever, headache, myalgias, and malaise up to 1 week in duration. There are no specific symptoms in this first phase of illness to suggest TBE, and most
persons recover from this point without further illness. A significant percentage relapse with meningitis or meningoencephalitis in the second phase. The virus is cultured from a minority of patients. Serological methods, particularly ELISA, are the most practical and widely used method of diagnosis. Russian spring-summer encephalitis is notable for its significant postinfectious sequelae, particularly decreased motor capacity of the shoulder girdle. The case fatality rate is ~6%–20% [210]. No specific treatment is available for TBE, but there is an effective vaccine. The European vaccine will protect against the eastern variant. The vaccine is not licensed in the United States.

**Hantavirus syndromes.** Korean hemorrhagic fever first gained the attention of the Western world during the Korean War, in the spring of 1951. By the end of United Nations involvement, >3000 cases were reported, occurring even among South Korean troops [220]. The causative agent was identified in 1976, named Hantaan for the river along the 38th parallel between North and South Korea. Since that time, further study has revealed a number of hantaviruses causing renal or pulmonary syndromes. The Puumala virus is associated with the red bank vole and is not likely to be present in Afghanistan. The Hantaan and Seoul viruses are associated with Apodemus mice and Rattus norvegicus, respectively. Seoul virus has been linked to urban outbreaks of hemorrhagic fever with renal syndrome, particularly in Asia but also worldwide. Hantaan virus is predominantly rural. The agent is transmitted to humans through inhalation of rodent excreta [221]. The illness occurs predominantly in adults and in males more frequently than females. Infected children usually experience a mild course. Antibodies to Hantaan virus have been demonstrated in India and Iran [221]. The central Asian former Soviet republics are likely to harbor Puumala and probably Hantaan viruses, but the hantaviruses are not known to occur in Afghanistan. Hemorrhagic fever with renal syndrome is not commonly noted outside of east Asia, despite serological evidence of the infection.

The full hemorrhagic fever with renal syndrome is classically described in 5 stages: febrile, hypotensive, oliguric, diuretic, and convalescent, beginning suddenly with fever, chills, headache, increased thirst, anorexia, and diffuse abdominal pain [220]. In practice, the clinical presentation is variable and difficult to diagnose. Of 26 patients with hemorrhagic fever with renal syndrome, 2 had a septic shock syndrome and died within 6 days, 18 had some variation of renal failure and fever, and 6 had a nonspecific febrile syndrome [222]. Physical clues to the diagnosis were conjunctival injection, pharyngeal erythema, palatal petechiae, periorbital edema, and petechial rash [222]. The syndrome typically causes proteinuria, hematuria, leukocytosis, elevated creatinine and blood urea nitrogen levels, prolonged prothrombin time, and thrombocytopenia. The infection is diagnosed by serological testing; a rise in immunofluorescent antibody over 1 week suggests the diagnosis [221]. The immunofluorescent antibody titer reaches a peak at week 2 of illness and persists for years. Treatment involves both supportive care (including dialysis if needed) and ribavirin [223]. The best means of prevention is avoidance of rodent habitats and protection against inhalation of potentially contaminated dust or aerosols.

**Sindbis fever.** Sindbis fever, or Okelbo fever, has a very wide geographic distribution, including Africa, the Middle East, Europe, Asia, and Australia. Clinical Sindbis virus infection has not been identified in Afghanistan, but seroconversion has been demonstrated in Kunduz and Helmand provinces of Afghanistan [207]. Very little Sindbis virus seroconversion was detected in 1 large serosurvey in Iran [206]. The ecology of the virus is similar to that of West Nile virus, and the 2 have been noted to occur in outbreaks simultaneously in one area. The mosquito vector for both agents is present in Afghanistan.

**Chikungunya virus infection.** This virus has not been isolated from central Asia but is present in Africa, the Middle East, and Thailand. Seroconversion to this virus has been noted in Helmand Province of Afghanistan [207]. The virus causes a dengue-like illness with prominent arthralgias.

**Bhanja virus illness.** This tickborne Bunyavirus is found in India, Pakistan, central Asia, and also Eastern Europe and Africa [224]. The presence of Bhanja virus in countries both immediately north and south of Afghanistan implies its presence within the country. However, the medical significance of this infection is not great. The illness is a self-limited febrile syndrome without notable defining characteristics and would not likely occur in great numbers.

**Issyk-Kul virus infection.** This virus causes a nonspecific viral syndrome in former Soviet republics north of Afghanistan [225]. It has not been documented in Afghanistan and seems to be associated with bats. Like Bhanja virus, it does not have a high rate of transmission to humans and should not be a significant medical concern if present.

**Syrdarya virus infection.** This virus has been identified in Kazakhstan and has been associated with a summertime febrile syndrome [226]. The geographic distribution of this virus is not clear, but it is unlikely to be a significant medical concern.

**Other arbovirus infections.** A large number of arthropod-borne viruses, including Isfahan, Wad Medani, Dera Ghazi Khan, Wanowrie, and other viruses, have been isolated in areas near Afghanistan [227]. To date, the clinical significance of these viruses is unclear, but they are unlikely to have great clinical impact.

Rift Valley fever is not known to occur in Afghanistan, and there is little reason to suspect that it is present. Likewise, neither Kyasanur Forest virus nor Omsk hemorrhagic fever virus are thought to be present, despite areas of endemicity of
Relative proximity. Japanese encephalitis virus is present in India and Pakistan but not thought to be active in Afghanistan. It is possible that cases of infection could occur, and serosurveys have revealed evidence of antibodies to the pathogen in Kunduz and Helmand provinces [207]. Also, dengue is not clinically observed in Afghanistan, but the illness is noted in both India and Pakistan. Seroconversion to dengue virus was noted in Helmand Province of Afghanistan [207].

Respiratory Diseases
Acute respiratory disease is a major cause of morbidity and mortality in Afghanistan and surrounding regions. Overcrowding, inclement weather, mass population movements, and a collapse of vaccination programs all enhance the spread of respiratory tract infections. Recent data from Afghanistan establish lower respiratory tract infections as leading causes of death in children <5 years old [2, 62].

Respiratory diseases have long been recognized as major military health threats, capable of disrupting military operations [228, 229]. Adenoviruses, influenza virus, Staphylococcus pneumoniae, and Bordetella pertussis have traditionally been the major agents. Recent US military outbreaks of influenza [229], pertussis [230], and pneumococcal disease [231] have demonstrated the power of these pathogens to alter military training and deployments.

The Soviet army, during its Afghan campaign, had extraordinary rates of pneumonia and bronchitis. Novozhenov and Gembitskii [232] report that 43% of personnel deployed to Afghanistan contracted acute pneumonia during their first year. Although pulmonary illness affected Soviet personnel year-round, most respiratory disease occurred during the fall and winter seasons. Typhoid fever often presented as a pneumonia among the Soviet troops and should be considered in the local differential diagnosis of cough and fever. Although Russian observers thought that pneumonia among Soviet troops in Afghanistan was generally “more severe” than that usually seen among young adults in Russia, limited diagnostic capabilities left the microbial etiologies largely unknown [232].

Currently, laboratory facilities and disease reporting remain inadequate to define most respiratory infections in Afghanistan. Given low immunization rates and limited public health capabilities, vaccine-preventable diseases, such as measles, influenza, pertussis, diphtheria, and tuberculosis, are likely to be common. Influenza in Afghanistan usually occurs between November and February. Epidemics of both influenza A and B have been reported recently [233]. The WHO investigated an influenza-like illness in the Badakhshan region in early 1999. Poor living and sanitary conditions resulted in rapid spread though 80% of households, and 1%-2% of cases were fatal. The etiology was eventually proven to be influenza A virus [234].

Prevention of respiratory tract infections in the military setting hinges on vaccination against influenza virus and, in some circumstances, pneumococci and adenovirus [227]. A recent US Marine Corps outbreak of pneumococcal pneumonia was interrupted by the use of vaccination and azithromycin prophylaxis [231]. Short-term antibiotic prophylaxis with azithromycin has also been shown to be effective in preventing short-term respiratory infections in selected high-risk situations [235]. Anti-influenza drugs may be useful if antigen drift renders the influenza vaccine less effective and outbreaks occur [229]. Prevention of respiratory disease among the civilian population will involve improvement of the underlying situation of the Afghan people (resettlement of refugees, protection from cold, adequate nutrition), as well as vaccination for measles, diphtheria, pertussis, and possibly influenza. Improved information on the etiologic agents of lower respiratory tract infections in Afghanistan will help clinicians and humanitarian agencies better target the use of both antibiotic treatment and vaccines.

Tuberculosis
The level of Mycobacterium tuberculosis transmission has always been one of the best mirrors of the socioeconomic conditions of a society [236]. Tuberculosis is highly endemic in central Asia and should be considered a serious threat to relief workers and others who are in close contact with the local population. Cases associated with the closely related Mycobacterium bovis, usually an occupational hazard of herdsmen, are commonly attributed to consumption of unpasteurized milk products. Military personnel, peacekeepers, and humanitarian workers should avoid local milk and cheese. As of 1997, overall prevalence of tuberculosis in Afghanistan was 753 cases per 100,000 population, with 35% of the population latently infected. The estimated annual incidence of active tuberculosis in 2001 was 325 per 100,000, 50 times the year 2000 US tuberculosis incidence of 5.8/100,000 [62]. Correspondingly, WHO described the tuberculosis situation in Pakistan in 1997 as “one of the worst in the world.” Villages in northern Pakistan have been found to have a prevalence of smear-positive pulmonary tuberculosis of 554 per 100,000. Nationally, the incidence of new cases in Pakistan was recently estimated at 177 per 100,000. A 1995–1998 study in Rawalpindi found that 52% of isolates were resistant to ≥1 standard therapeutic agent, including ethambutol, isoniazid, and rifampin [237, 238].

Tajikistan is the poorest of the former Soviet republics. National trends showed an increase in reported tuberculosis incidence from 30 per 100,000 in 1995 to 250 per 100,000 in some areas in 1997 (WHO estimates incidence at 105 per 100,000 for the country in 2001). Before the breakup of the Soviet Union, protocol-directed treatment of patients with at least 3 antituberculosis drugs for at least 6 months was standard,
but health personnel now often rely on only 2 drugs: isoniazid and rifampin. With concomitant shortage of chest radiograph material, laboratory supplies, and tuberculin skin tests and breakdown in the local surveillance system, the generation and transmission of multidrug-resistant tuberculosis threatens to overtake drug-susceptible tuberculosis, further stressing an already overburdened population [239].

The Aral Sea, bordered by Kazakhstan, Uzbekistan, and Turkmenistan, is often considered the worst of the worst-man-made environmental disaster. Formerly the fourth largest inland body of water in the world, it has been systematically destroyed by years of poorly conceived centrally planned irrigation projects. With people robbed of their former sea-based livelihood, poverty-related problems, including anemia, malnutrition, and tuberculosis and other infectious diseases, are rampant. The tuberculosis crisis in the Aral Sea area is considered by WHO to be the worst in the former Soviet Union. Tuberculosis incidence in some former Aral Sea fishing ports and spa towns is reportedly 250 per 100,000 per year [240]. In Kazakhstan, studies in 1993 found 66% of isolates to be resistant to streptomycin. Uzbekistan’s tuberculosis incidence is lower, reported as 55 cases per 100,000 in 1998. However, after a declining period in the mid-1980s, morbidity rates from tuberculosis increased dramatically beginning in 1996, doubling among adolescents and young people (age <30) within 5 years. A rise in mortality rates was also noted [241]. An Uzbek case notification rate of 158 new cases per 100,000 was reported in 2000. This represented an estimated 33% rise in incidence between 1995 and 2000 [242]. Rates of multidrug-resistant tuberculosis are currently undefined for lack of capable regional laboratory facilities [243].

Kyrgyzstan’s officially reported incidence of 119 cases per 100,000 population in 1997, which ranked as the highest among countries of the former Soviet Union, increased in parallel with deterioration of the public health infrastructure and paucity of funding [244]. Tests performed between 1985 and 1987 showed high levels of initial and acquired drug resistance in both urban and rural areas. Patients are often not treated with standard regimens, and isoniazid and rifampicin are often alternated to make scarce drugs go further [245].

Given the high rates of resistance to isoniazid and streptomycin among M. tuberculosis strains in south-central Asia, treatment of tuberculosis cases in this region should include isoniazid and rifampin plus at least 1 other drug, all to be given as directly observed therapy. Common choices for the additional drug include pyrazinamide or ethambutol. A 4-drug regimen containing isoniazid, rifampin, ethambutol, and pyrazinamide is optimal pending results of mycobacterial susceptibility testing.

Bacille Calmette-Guérin vaccination may be effective in preventing severe manifestations of tuberculosis in children, such as tuberculosis meningitis. As a regional recommendation, WHO currently advocates bacille Calmette-Guérin vaccination for all newborn children and children up to age 5 who have not received it [3]. US military personnel do not receive bacille Calmette-Guérin.

**Ricketsial Disease**

**Q fever.** Q fever is a worldwide zoonosis consisting of pneumonia, hepatitis, and occasionally meningocerebralitis or endocarditis. Humans are most frequently infected by inhalation of aerosolized infected body fluids from infected animals.

**Natural history.** Coxiella burnetii is the causative pathogen of Q fever. This bacterium was first identified in abattoir workers in Australia and in a tick in the United States. Many animal species can be infected, but sheep, goats, and cattle are the principal reservoirs. Urine, feces, milk, and especially placental tissues are potentially infectious; most cases result from airborne exposure. The infectious dose of C. burnetii is exceptionally low—a single organism can cause illness [246].

**Epidemiology.** The disease is not commonly diagnosed, but outbreaks of Q fever are regularly reported. Parturient animals shedding C. burnetii may be associated with outbreaks, but patients ingesting raw milk products are also at risk. It should be noted, however, that the pattern of clinical illness varies regionally, with a nonspecific febrile syndrome, pneumonia, or hepatitis reported to be the most common presenting features of Q fever in various regions of the world [247]. A significant number of cases are presumably subclinical; in a well-described outbreak in Switzerland, 54% of cases were asymptomatic [248]. Three possible cases of Q fever occurred among the 700,000 US troops participating in the Persian Gulf War [149].

**Regional information.** A serosurvey in domestic animals revealed antibodies to C. burnetii in Balkh, Kunduz, and Baghlan provinces of Afghanistan [207].

**Clinical findings.** Clinical Q fever can be divided into acute and chronic syndromes. The acute illness may be a nonspecific febrile illness, pneumonia, or hepatitis or a combination thereof. The febrile syndrome has no particular identifying features. Rash, the usual hallmark of rickettsial illness, is generally absent. The pneumonia is variable and can present as an “atypical pneumonia” resembling that caused by Mycoplasma or Chlamydia species, or a classic picture of multiple round, segmental opacities can be seen. Pleural-based opacities are common. The lesions tend to resolve slowly with therapy (10–70 days; average, 30 days). Q fever hepatitis may present as a typical mild acute infectious hepatitis, with a small percentage of patients (≤5%) showing jaundice; hepatomegaly or splenomegaly is variably found. Liver function testing yields abnormal results for a majority of Q fever patients, however. In rare cases, Q fever may present as acute or chronic meningitis or encephalitis, with reports of a variety of associated neurological findings

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[247, 249, 250]. Chronic Q fever generally manifests as endocarditis, granulomatous hepatitis, or vertebral osteomyelitis, although other findings have been described [251].

Treatment. The objectives for treatment of acute and chronic Q fever are significantly different. For acute forms, single-agent therapy with doxycycline is usually effective and is preferred to tetracycline [252]. Treatment is generally given for 14 days. Alternative treatments are rifampin or fluoroquinolones. Chronic Q fever requires prolonged antibiotic courses, and valve replacement may be needed.

Diagnosis. Isolation of the pathogen is not advised except in specialized laboratories. Acute Q fever is usually diagnosed by demonstration of a 4-fold rise in antibody titer between acute and convalescent serum. Complement fixation, microimmunofluorescent antibody assay, and ELISA are all used for this purpose [247]. IgM antibody testing is not often done, because antibody can persist for >1 year in a small number of patients and may not reflect acute infection.

Prevention. Avoidance of unpasteurized mild and cheese and protection against ticks are effective prevention strategies, but prevention against the aerosolized pathogen is difficult. Foreigners in Afghanistan should not consume unpasteurized milk products because of the risk of Q fever, brucellosis, and M. bovis infection. Most prevention efforts focus on those most at risk, including abattoir workers and researchers. An inactivated vaccine exists for laboratory personnel working with C. burnetii but is not licensed for general use.

Scrub typhus. Scrub typhus has been described since antiquity in both China and Japan. The illness gained attention in Western medicine during World War II, when it had a dramatic impact on allied troops operating in Southeast Asia. The Vietnam War again brought this illness to attention in the United States. The pathogen, Orientia tsutsugamushi, is endemic from Japan, Korea, and nearby Russia through China and Southeast Asia and westward to India and Pakistan [253]. The distribution of the pathogen within this area is notably focal, and it circulates between the various rodent species and Leptotrombidium mites. Humans are infected on entering this cycle, and they develop a typical rickettsial illness as a result, with the exception that lymphadenopathy is more prominent and rash is less common than for most other rickettsial diseases.

Natural history. O. tsutsugamushi is transmitted to humans from the larval stage of the mite. The mite is infected transovarially by feeding on an infected host. Because the mite feeds only once during its life, transovarial transmission is crucial for perpetuation of the organism. The mites have a large number of potential hosts but are frequently found in association with rats and related rodents, which as a rule reside within a relatively small range. Therefore, the nidus in which a person encounters disease is very small, but focal areas may be very densely populated with infected vectors; researchers have described this phenomenon as “mite islands” [213, 254]. When a human enters such a location, infection can result. The nature of the “mite island” is highly variable, depending on the behavior of local vector. For example, in West Pakistan, the vector can be found in semidesert, plains, and high alpine areas up to 3050 m [255–257].

Epidemiology. The scrub typhus pathogen is transmitted year-round in tropical climates and seasonally in temperate areas. Those with outdoor exposure are at greater risk of infection; children, military personnel, and others with occupational exposure are within this group. Importantly, the growing urbanization in Southeast Asia has not decreased the prevalence of this pathogen. Palm plantations and “edge ecozones,” such as that created by clear-cutting a forest section, provide a good habitat for the rodents and mites. Transmission has been noted to occur within urban areas as well (Bangkok) [258]. The mites are extremely small and frequently are not noticed by the host.

Regional information. Serological evidence of scrub typhus has been reported from Kunduz and Badakhshan provinces of Afghanistan, but no clinical cases have been identified [207]. The illness is well described in West Pakistan in ecozones similar to those of Afghanistan [255–257]. Altogether, it is reasonable to expect the disease to exist in Afghanistan, although it is undoubtedly limited in distribution.

Clinical findings. After an incubation period of 6–18 days, the patient may present with sudden onset of fever, headache, myalgias, and arthralgias. Cough, sore throat, diarrhea, or emesis may be found in a minority of patients. Patients may have a wide variety of other respiratory, gastrointestinal, or neurological complaints as well. Signs may include an inoculation eschar (50%–60%), regional (occasionally generalized) lymphadenopathy (85%–90%), hepatomegaly, splenomegaly, conjunctival injection (30%), and macular rash (34%–71%). It is most important to find an eschar in suspected cases; it is located at the site of the mite attachment. The eschar may be located virtually anywhere on the body, appearing as an ulcer, usually with a blackened center and surrounding erythema [254]. The rash is present on a minority of patients and may be difficult to see on dark-skinned patients. When present, it begins as a truncal, macular rash late in the first week of illness and spreads to the extremities.

Laboratory findings and diagnosis. Elevated hepatic transaminase levels, thrombocytopenia, and hyponatremia are possible findings on routine laboratory tests, with evidence of disseminated intravascular coagulation in severe cases. The diagnosis is generally made serologically, by indirect immunofluorescence assay, immunoperoxidase assay, or ELISA. The traditional Weil-Felix test has been largely supplanted in most laboratories but is still used in some countries [254]. About one-half of patients will react to the OX-K antigen by 10–14 days after onset. It should be noted that the Weil-Felix test can
yield false-positive results as a result of leptospirosis, relapsing fever, or urinary tract infection with *Proteus* species.

**Treatment.** The treatment of choice is tetracycline (500 mg q.i.d.) or doxycycline (100 mg b.i.d.) for 7 days. If a therapeutic response has not occurred within 72 h, another diagnosis should be entertained, with exceptions in doxycycline-resistant locations. Chloramphenicol has been a traditional therapy and is also effective. Azithromycin and fluoroquinolones have in vitro activity and have been successfully used for treatment. Of note, some cases of doxycycline- and chloramphenicol-resistant scrub typhus have been identified over the past decade in northern Thailand. A recent study shows that rifampin at 600–900 mg/day was effective and safe, although the authors expressed concern about excessive rifampin use potentially compromising the future use of rifampin-containing regimens for tuberculosis therapy [259].

**Prevention.** The use of doxycycline at doses of 200 mg once a week will prevent scrub typhus infection. Postexposure prophylaxis at the same dose is also effective but should be continued for 6 weeks, because early termination could result in symptomatic illness [254]. Doses of doxycycline (100 mg/day) used for malaria prophylaxis are also effective. Avoidance of mite-infected areas is the best means of prevention. Personal protective measures, such as permethrin-sprayed clothing and application of DEET, will lower attack rates. Rodent control is not helpful, as early researchers noted increased rates of disease in humans after such measures [255].

**Spotted fever rickettsial diseases.** The number of recognized spotted fever group rickettsiae seems to grow every year. The recognized etiologic agents of spotted fever illness in Afghanistan may therefore multiply in the future. Currently, 2 spotted fever illnesses are recognized in the area: Siberian tick typhus and Mediterranean spotted fever. Two other pathogens, *Rickettsia mongolotimonae* and Astrakhan fever rickettsia, have unclear distribution [260]. Another rickettsia, labeled JC 880, has been isolated from Pakistan, but its pathogenic status is as yet not fully known [261]. The 2 recognized pathogens will be discussed together, as they are clinically similar.

**Natural history.** *Rickettsia conorii*, the agent of Mediterranean spotted fever, is widespread, found in Africa, the Mediterranean basin, India, Pakistan, and eastern Russia. The pathogen is transmitted by ixodid ticks of various species, depending on the location. As with scrub typhus and most other spotted fever rickettsiae, the pathogenic lesion is a vasculitis. Siberian tick typhus is found in central Russia, Pakistan, and China. Astrakhan fever has been recognized as a clinical entity since 1983 but only recently found to be caused by a rickettsia similar to *R. conorii*. The region of known transmission borders the Caspian Sea. *R. mongolotimonae* has been identified from Inner Mongolia in China and in the hospital La Timone, Marseilles, France, which explains the name. The illness is not likely to be common, but *R. mongolotimonae* has been isolated from a few patients in China and France [260].

**Regional information.** Siberian tick typhus and Mediterranean spotted fever occur within Afghanistan. Both pathogens have been isolated near the Pakistani-Afghan border [261], and significant numbers of Afghans have seroconverted to a spotted fever rickettsia in a number of locations in the country [207]. The other rickettsiae mentioned have not been isolated in or near Afghanistan but are included as possibilities.

**Clinical findings.** Mediterranean spotted fever is the more serious of the spotted fever illnesses found in the region. The symptoms are typical of a spotted fever illness, with sudden onset of headache, fever, and myalgias. An eschar is frequently present, and a petechial rash may appear. Siberian tick typhus has a similar presentation but is milder and not thought to be fatal. Mediterranean spotted fever can be fatal in 2%–3% of those infected, particularly the elderly or those with underlying illness [260].

**Laboratory findings and diagnosis.** Transaminitis, thrombocytopenia, and hyponatremia are possible findings on routine laboratory tests. Evidence for disseminated intravascular coagulation may be seen in more severe cases. The diagnosis is usually made by detection of spotted fever group antibodies. Routine spotted fever serology does not generally distinguish between spotted fever group rickettsiae, although a research laboratory may be able to do so. Likewise, PCR testing or culture for the acutely ill patient or the tick vector can be performed in a research setting. Clinically, it may be difficult to distinguish isolates in the field setting [260].

**Epidemic typhus.** Epidemic typhus is a historically important disease of populations compromised by war or famine, conditions currently present within Afghanistan.

**Natural history.** The pathogen is transmitted by the bite of the common body louse, for which the infection is fatal. Lice are predictably present in conditions of poor hygiene, overcrowding, and poverty. The spread of typhus is enabled by wintertime conditions, which favor close contact and less-frequent clothing changes.

**Regional information.** The disease is probably present in Afghanistan, with anecdotal reports of cases and documented seroconversion to typhus antigens among the population [207].

**Clinical findings.** After an incubation period of ∼1 week,
illness begins abruptly with fever, chills, headache, and myalgias. The illness becomes more severe, and the patient may be confined to bed, with unremitting fever and rash starting toward the end of the first week. The rash classically begins on the trunk and spreads to the extremities, at first macular, then becoming petechial. Decreased level of consciousness is common. The range of potential complications is large, with CNS, gastrointestinal, and pulmonary complications described. The reported case fatality rate in compromised hosts has been as high as 40% [262].

**Laboratory findings and diagnosis.** The diagnosis is confirmed by serological techniques. Immunofluorescent antibody assay or latex agglutination tests are considered reliable and will yield positive results for nearly all patients after day 15 of illness. Culture of the organism is possible in a specialized laboratory, as is PCR of blood from acutely ill patients. Weil-Felix testing is neither specific nor sensitive and is not recommended. Immunohistochemical staining of tissue (skin biopsy) can provide a rapid diagnosis if reagents are available [262].

**Treatment.** Active agents include tetracycline, doxycycline, and chloramphenicol. A single dose of doxycycline is curative in most cases.

**Prevention.** The best means of prevention is elimination of the louse vector in the population at risk. Delousing with an agent such as DDT, lindane, or malathion has been shown to be effective.

**Endemic typhus.** Endemic, or fleaborne, typhus is significantly milder than epidemic (louseborne) typhus and only occasionally results in death. The disease is distributed worldwide and is also known as murine typhus.

**Natural history.** The classic cycle of transmission is between rats and the oriental rat flea. The cycle may involve the cat flea and opossums in some locations. Humans are a dead-end host, as with other rickettsial infections.

**Regional information.** The disease is thought to be present in Afghanistan. The disease has a worldwide distribution, with seroconversion noted in such diverse countries as Iran, Nepal, and Ethiopia [263]. Seroconversion to typhus antigens has also been noted within the Afghan population [207].

**Clinical findings.** The illness begins after 1–2 weeks of incubation, with fever, chills, headache, and myalgias. Rash may eventually be present in up to 50% of cases and is usually macular or maculopapular. Symptoms and signs similar to epidemic typhus are reported but are generally less severe. The illness is typically mild, with case fatality rates of 1%–4%. The illness is more severe in the compromised host [264].

**Prevention.** Prevention should focus on elimination of the rodent host and the flea vector.

**Relapsing fever.** Relapsing fever is not a rickettsial illness. However, the clinical presentation is similar to those of rickettsial illnesses, and it is present in the area of discussion. Relapsing fever is very widespread throughout Africa, Europe, Asia, and North and South America.

**Natural history.** Tickborne relapsing fever is caused by *Borrelia* species and transmitted by soft ticks (*Ornithodoros*), which are present in a variety of locations in Afghanistan. These ticks’ feeding behavior is different from that of ixodid ticks, and they tend to live in nests or bedding and feed on victims while they sleep. The diseases they transmit tend to be very focal because the ticks tend to remain in the same area, and the foci are long-lasting because the ticks are long-lived. The severity of disease is quite variable. In West Pakistan, severe illness has been reported, but mild illness has been noted in the central Asian countries to the north [265]. The disease is considered more severe than louseborne relapsing fever.

**Regional information.** Relapsing fever disease is present in Afghanistan and its neighboring countries to the north. Soviet physicians diagnosed cases in Kabul and Mazar-e-Sharif in Afghanistan [207].

**Clinical findings.** The incubation period varies by location but is generally ~1 week (2–10 days). Onset of illness is generally sudden, with fever, chills, myalgias, severe headache, nausea, vomiting, and, in a minority of patients, a macular rash. Cough is present in ~60% and may evolve to frank pneumonia. Jaundice and hepatosplenomegaly may be present, as well as hemorrhagic signs. Ocular findings are not uncommon, with conjunctival injection most frequent. The fever may resolve in 3–13 days (average, 4–7) by “crisis,” dropping quickly to normal or below. The crisis may be associated with hypotension or shock. There may not be any further fevers, but frequently after an interval of 5–9 days, the patient will have a relapse. Untreated central Asian relapsing fever has been associated with a large number of relapses, and the case fatality rate is up to 40% [265, 266].

**Diagnosis.** Thrombocytopenia and leukocytosis are common, and CSF pleocytosis is noted in a minority of tickborne relapsing fever. The diagnosis is generally confirmed by the visualization of spirochetes in blood smears of febrile patients. Notably, Weil-Felix testing with the OX-K antigen may yield positive results, as well as serological tests for syphilis in a minority of patients [265, 266].

**Treatment.** Antibiotic therapy with tetracycline or doxycycline, macrolides, penicillin, or chloramphenicol is effective. Tetracycline is the preferred agent, at a dose of 500 mg orally q6h for 5–10 days. Antibiotics should be given iv to seriously ill patients. The Jarisch-Herxheimer reaction, characterized by fever, chills, and hypotension, often occurs within hours of
treatment. In relapsing fever cases, severity of the Jarisch–Herxheimer reaction has been ameliorated by meptazinol [267], an opioid agonist-antagonist, and by anti-TNF antibodies [268].

Prevention. The best means of preventing this infection is avoidance of the rodent-tick cycle, particularly in sleeping areas. It is advisable to separate eating and sleeping locations in areas of endemicity for relapsing fever.

Anthrax

Anthrax (sporadic cases) is endemic in Afghanistan and surrounding regions [3]. The incidence of disease is highest in the spring and summer. A recent outbreak in neighboring Tajikistan occurred in July 2000 in the Khatlon region, with 17 human cases and no deaths. The source was traced to infected cows. [3]. Year-to-year incidence of anthrax is not published; however, according to Wilson [269], 90 cases of anthrax were reported in Afghanistan in 1981. Arya et al. [270] found a total of 5 cases of pediatric cutaneous anthrax between 1979 and 1980 among 26,000 admissions to the Institute of Child Health in Kabul; 1 patient died of upper airway compression. Barnard [271] described 1 patient with cutaneous anthrax of the eyelid in 1989 and 2 earlier cases in 1976 among 4000 consecutive patients seen at the NOOR Eye hospital in Kabul [271]. Multiple outbreaks have been reported by the media and cited in the online emerging infectious disease service, Pro-Med [272], but cannot be easily verified.

In addition to naturally occurring outbreaks, there is special concern about use of anthrax spores as a bioweapon within Afghanistan and surrounding regions and in Western countries. There is evidence of widespread development and past use of anthrax as a biological agent. Cole [273] reported in 1996 that 17 countries were believed to have offensive biological weapons programs. Some of these countries have weaponized anthrax [274–278]. The Germans used anthrax in animal feed against its enemies in World War I [279]. The Japanese Unit 731 in World War II used anthrax, plague, and other agents against prisoners and civilians in China [279]. A plume of anthrax spores was accidentally released near Sverdlovsk from a Soviet bioweapons factory in 1979, killing 68 people and considerable livestock [274, 277–280]. The Japanese cult, Aum Shinrikyo, dispersed aerosols of anthrax and botulinum in Tokyo 8 times. For unknown reasons they were unsuccessful and abandoned their efforts with anthrax, switching to dispersing sarin gas in the Tokyo subway [274]. In 1995, Iraq admitted to having weaponized anthrax during the 1991 Gulf War [275–277, 279, 281]. Finally, high-grade weaponized spores have been spread in the United States in the fall of 2001 by a terrorist or terrorist group by use of a novel method not previously anticipated: the US mail. Although postal deployment of infectious spores is highly inefficient, the damage from primary aerosolization and secondary contamination has caused panic, paralysis of the government and business, economic disaster, and 5 deaths [277, 282–292].

Weaponized, dispersible anthrax spores are well suited as weapons of mass destruction. In 1970, an expert committee of the WHO reported that a 50-kg load of anthrax spores released from a plane over an urban population of 5 million could result in 250,000 casualties and 100,000 deaths. The US Congressional Office of Technology in 1993 estimated that 100 kg released upwind of Washington, D.C., would kill 130,000 people and possibly as many as 3 million depending on the aerosol and environmental conditions [274, 281, 293]. The highly concentrated anthrax in the letters mailed to Senator Daschle has been estimated to have had up to 1 trillion spores/g of powder [294].

Whether spread in nature or by terrorists, there are 3 major forms of the disease that depend on route of entry of the infective spores. About 95% of natural anthrax is cutaneous and caused by contamination of abrasions or other skin lesions. The areas of skin that are uncovered and exposed to infected animals and their products, contaminated mail, or other fomites are most likely to be affected: face, neck, feet, legs, hands, and upper extremities. Gastrointestinal anthrax is rare and usually reported in Africa or Asia from ingestion of infected animals. Inhalational anthrax is also rare but was seen sporadically in wool mills before institution of modern protective practices [274, 277, 293, 295–297]. The inhalational form of the disease spread by aerosolization of spores has the greatest potential for biological terrorism.

*Bacillus anthracis*, a gram-positive, nonmotile, nonflagellated, spore-forming bacillus, is the etiologic agent of anthrax. It grows well on blood agar at 37°C, producing flat, irregular colonies that may be evident within 18–24 h under aerobic conditions. Anthrax will grow more slowly in an anaerobic environment. Under a dissecting microscope, chains of bacilli may take on the appearance of curled hair or a Medusa head. Anthrax spores are the infective form and measure 1–8 μm in diameter. They may survive harsh environmental conditions for decades in the soil or on animal hides, wool, or other fomites. In an animal host, the spore is transformed into its vegetative form, measuring 1–8 μm × 1–1.5 μm. Growth on laboratory media reveals end-to-end chains of bacilli likened to boxcars or jointed bamboo under the microscope [274, 277, 278, 293–296].

Pathogenicity depends on production of an antiphagocytic capsule and production of 2 binary toxins formed from 3 factors: the protective antigen (primary component of the FDA-approved vaccine), lethal factor, and the edema factor. Lethal toxin consists of protective antigen, a binding protein, and lethal factor, a zinc metalloprotease. Edema toxin is protective antigen bound to edema factor, a calmodulin-dependent adenylate cyclase. Lethal toxin inactivates mitogen-activated protein kinase, inhibits intracellular signaling, stimulates macro-
phages to release TNF-α and IL-1β, and is associated with sudden death. Edema toxin causes local swelling, inhibits neutrophil function, and interferes with monocyte production of TNF-α and IL-6 [274, 278, 293–296].

After spores gain entry into an animal host through the skin, by inhalation, or after ingestion, the bacteria are taken up by macrophages and transported to regional lymph nodes. The spore is transformed into its vegetative, toxin-producing form and exponentially reproduces and disseminates, causing death unless the lethal toxemia is averted [274, 278, 295, 296]. Mortality from cutaneous anthrax is 10%–20% but is reduced to <1% with appropriate and timely antibiotic therapy. Gastrointestinal anthrax mortality has exceeded 50% despite therapy. Inhalational anthrax mortality has been difficult to assess [274, 278, 293, 295–297]. In the United States, 18 cases of inhalational anthrax were reported in the 20th century, with 16 deaths, for a mortality rate of 89% [274]. In the 1979 Sverdlovsk industrial accident, inadvertent release of an aerosol is reported to have caused 79 cases of anthrax, with 68 deaths [274, 293, 295, 297]. Other estimates of the numerator and denominator exist and both are suspect, but 68 of 79 translates into a rough estimate of 86% mortality.

More exact statistics exist from the infamous terrorist attack in the United States after the collapse of the World Trade Center towers. As of 30 December 2001, there were 11 confirmed cases of inhalational anthrax and 5 deaths, for a mortality of 43% [286, 292]. Of the 8 patients who presented in the initial phase of illness, 6 were given expeditious and appropriate multiple antimicrobial therapy—all survived. This suggests that the high mortalities previously reported can be improved on with early recognition and intensive and appropriate therapy [286].

Recognition requires a high index of suspicion and appreciation of the natural epidemiology or the clustering of cases in the unnatural epidemiology of a man-made bioterrorist event (e.g., the mailborne epidemic in the United States in the fall of 2001). Radiographs may allow early evidence of inhaled anthrax. Jernigan et al. [286] reported on the first 10 cases of inhalational anthrax in October and November 2001 in the United States. All 10 patients had abnormal chest radiographs, with 70% showing mediastinal widening, 70% infiltrates or consolidation, and 80% pleural effusions. CT was done for 8 patients and yielded abnormal results for all, with 100% showing pleural effusions, 88% mediastinal lymphadenopathy or widening, and 75% infiltrates or consolidation.

Culture of blood is highly sensitive and generally yields positive results within 24 h, even if previous antibiotics have been given [283–286]. Results of culture of CSF, pleural fluid, vesicular fluid, or swabs of skin ulcers are frequently positive [274, 277, 278, 286, 295, 296]. Examination of the bulky coat of spun blood may yield a rapid presumptive diagnosis for a suspected patient with bacteremia [284, 286]. The CDC recommends that clinical an-

"\[B. anthracis\]

In nature, B. anthracis is almost always susceptible to penicillin, which has been the standard of therapy [274, 277, 278, 293, 295, 296]. In light of recent findings in the United States, however, penicillin should probably be used as a single agent only when treating uncomplicated naturally occurring cutaneous anthrax. Naturally occurring complicated cutaneous, inhalational, or gastrointestinal anthrax may be best treated with combination therapy (which could include penicillin), on the basis of limited data of lower mortality rates compared with historical cases, some of which were treated with penicillin alone [274, 285, 286].

In the event of a known or suspected bioweapon-related illness, penicillin is not recommended, given the possibility of penicillin resistance. For uncomplicated cutaneous disease, the CDC [287] is currently recommending ciprofloxacin (500 mg orally b.i.d.) or doxycycline (100 mg orally b.i.d.) for adults. For uncomplicated cutaneous anthrax in children [287], ciprofloxacin, 10–15 mg/kg q12h (up to 1 g/day) or doxycycline (100 mg orally b.i.d.) for children >45 kg and >8 years of age or 2.2 mg/kg q12h for children <8 years (maximum, 100 mg orally q12h) is recommended. If tests reveal penicillin susceptibility and no penicillinase, amoxicillin may be substituted: 500 mg orally t.i.d. for adults and 80 mg/kg/day in divided doses t.i.d. for children. Therapy for at least 60 days is advocated for illness related to bioterrorism or in other events in which aerosolization may have occurred.

For inhalational, gastrointestinal, or complicated cutaneous anthrax, combination empirical antimicrobial therapy is recommended on the basis of data collected about victims of the terrorism-related anthrax attack in the United States in the fall of 2001 [283–286, 294, 298]. Intravenous ciprofloxacin or doxycycline plus 1 or 2 other antibiotics is advocated. Antibiotics that may be useful in combination include ampicillin, penicillin, clindamycin, clarithromycin, imipenem, vancomycin, rifampin, and chloramphenicol. Other fluoroquinolones are likely to be as effective as ciprofloxacin. Steroids have been recommended by some experts for severe edema or meningitis, but proof of benefit is not available. Clindamycin has been advocated as an adjunctive antibiotic because of the observation of reduced toxin production with serious Streptococcus pyogenes infections and the potential benefit of decreasing toxin production with B. anthracis. After stabilization, therapy can be
Leptospirosis

Leptospirosis comprises a group of zoonotic diseases usually spread by contact with contaminated animal urine. Clinical manifestations are protean, commonly including sudden-onset fever, headache, chills, myalgias, and conjunctival suffusion. In south-central Asia, the majority of infections are probably clinically inapparent or misdiagnosed as meningitis, encephalitis, viral hepatitis, or influenza, although recognized outbreaks of leptospirosis have been described in Kazakhstan [304]. Up to 6% of febrile military patients in Pakistan were found to have leptospirosis in 1989 [305]. On the basis of serological evidence, risk should be considered year-round and include urban areas. Two basic types of foci likely occur: peridomestic or agriculturally associated foci, with rats as the primary reservoir host, and sylvatic foci, with small rodents serving as the primary reservoir host. Animal serological studies in Afghanistan detected antibody titers ≥1:800 in 15% of domestic animals tested. Organisms found included *Leptospira interrogans* serogroups *hebdomadis*, *tarassovi*, *grippotyphosa*, *pomona*, *javanica*, *icterohaemorrhagiae*, *canicola*, *ballum*, *bataviae*, and *pyrogenes*. Antibodies to some serogroups were found in >50% of buffalo and camel, 25% of cattle, and ~2% of sheep, goats, and zebras examined [306]. The close association of tribal people with their infected domestic animals, combined with limited water resources, indicates that leptospirosis will be a problem for displaced persons and relief workers as well.

Diagnosis is by serological test with a panel of locally occurring leptospires. Confirmation relies on rising titers or isolation of the organism from blood (in the first 7 days of acute illness), CSF (days 4–10), or urine (after day 10). Rapid diagnostic tests are available [307]. Effective chemoprophylaxis may be achieved by oral doxycycline, 200 mg administered once weekly [308]. Prevention of leptospirosis and scrub typhus may be an added benefit of using doxycycline for chemoprophylaxis against malaria. A 7-day course of iv penicillin or doxycycline constitutes effective treatment for clinical leptospirosis [309, 310].

Rabies

Rabies is enzootic in foxes, wolves, and jackals in the region, although dogs should be considered the primary source of human exposure. Rabies causes hundreds of human deaths annually in Afghanistan. Packs of wild dogs are common, with essentially no vaccination or public health control. From March to April 2001, >80 people were attacked by rabid dogs in the city of Kabul; WHO estimates 4 human cases daily in the capital city [3]. In 1999, a large epizootic cluster occurred in the Afghan provinces of Kabul and Ghazni. Postexposure human rabies vaccine has typically been unavailable in recent times in Afghanistan.

Long-term travelers to Afghanistan and vicinity should obtain preexposure vaccination. Preexposure prophylaxis may provide protection when there is inapparent or unrecognized exposure to rabies and when postexposure therapy may be delayed. Urgent postexposure treatment, particularly after bites of dog, cat, fox, or jackal, for the unvaccinated should include human rabies immune solution and initiation of a 5-dose series of human diploid cell strain vaccine. US military personnel will likely have ready access to vaccine and rabies immunoglobulin; humanitarian workers and others who may not have such access should receive preexposure vaccination.

Sexually Transmitted Diseases

Sexually transmitted diseases are typically highly endemic in lesser-developed countries with limited resources for treatment, prevention, and education. Although there are almost no data on sexually transmitted diseases from Afghanistan proper, considerable data exist on trends in neighboring states. Since the collapse of the Soviet Union, poverty, migration, and unemployment have put large populations at increased risk. Between 1990 and 1997, up to 175-fold increases in syphilis notifications occurred in eastern European and central Asian countries. In Kazakhstan, incidence increased to 110 per 100,000 in the south to 380 per 100,000 in the north, with rural areas particularly afflicted. Syphilis notifications began declining in 1997 through-
out the former Soviet states, but this decline is considered largely a reflection of reduced intensity of active case finding and changes in reporting completeness. Rising numbers of newborns with congenital syphilis have been reported from most central Asian countries [311]. Health education interventions are inadequate, and even in less turbulent times, many women did not consult a physician until the second or third trimester of pregnancy, if at all [312].

Road transport is the main mechanism of transporting raw materials, goods, and food across Pakistan, and the trucking industry employs a large segment of the labor force. A survey of Pakistani truck drivers found that most were married but stayed away from their wives for up to 2 months at a time; a majority were not aware that condoms are an effective way of preventing HIV transmission and did not consider themselves at risk of acquiring HIV, believing that HIV affected only immoral persons. Condom use was only 3%–6% with any non-marital partner among this cohort. It might be surmised that, as in India and central Africa, truck drivers constitute a highly mobile segment of the work force whose sexual practices place them at high risk of contracting and spreading HIV and other sexually transmitted diseases in the region [313]. Rapid HIV spread has been associated with injecting drug use in the high-risk social and economic environment of Kazakhstan; estimates suggest that between 50% and 90% of new HIV infections are among injecting drug users. The stunning increases in the incidence of syphilis emerged in concert with declines in numerous health and welfare indicators [314]. In Kazakhstan, a total of 1010 HIV-infected persons were recorded as of January 2000, with 29 reported AIDS diagnoses. Tuberculosis was detected in 13% of HIV-infected examinees and 42% of those with AIDS.

The medical literature on chlamydial infection, gonorrhea, herpes, chancroid, and other sexually transmitted infections of south-central Asia remains sparse and woefully noncurrent. Genital Chlamydia trachomatis prevalence in Pakistani women of 15% was reported in a Karachi obstetrical study, as determined by endocervical swab immunofluorescence and iodine stain techniques [315].

Plague

Plague has previously caused 4 pandemics, killing hundreds of millions of people during the last 2 millennia. The first reports of epidemic plague in Afghanistan occurred in the 11th century in the city of Ghazni. In the 12th century, Kandahar and Sheikhdzhum frequently experienced plague. The last suspected plague epidemics in Afghanistan were in 1905, extending from Kabul to the Gelmand Valley, and in Kusan and Badghis in 1912 [207]. Buck et al. [316] reported on serological investigations in rural areas of Afghanistan in 1972 that failed to show any evidence of plague. The WHO indicates that no cases of plague from Afghanistan or Pakistan are currently being reported, but natural foci of plague exist in the central Asian republics of the former Soviet Union [3].

Yersinia pestis is the gram-negative bipolar-staining bacillus responsible for bubonic and pneumonic plague. It is aerobic and grows well on blood agar and is a nonfermenter of lactose on MacConkey agar. It is nonmotile and negative for citrate utilization, urease, and indole [317, 318].

This agent has been identified as one of the potential agents that may be encountered in bioterrorism or biowarfare, presumably from an aerosolized source [280]. In nature, bubonic and secondary pneumonic plague are the most important forms of disease. Primary pneumonic plague should be expected if plague is used as a biowarfare agent. The incubation period for bubonic plague is 1–7 days, with primary pneumonic plague having a shorter range of 1–5 days. Disease is spread from the bite of infected fleas, especially Xenopsylla cheopis, which are associated with rodents [3, 317–319].

Transmission from person to person is rare for bubonic plague, but it can easily be spread via respiratory droplets from those with pneumonic plague [3, 281, 319]. Contact isolation is required for bubonic plague. Strict respiratory isolation and treatment of close contacts with chemoprophylaxis is needed for pneumonic plague [319].

The preferred treatment for plague is streptomycin, 30 mg/kg/day in divided doses q12h for 10 days, or gentamicin, 5 mg/kg/day in divided doses q8h for 10 days. For plague meningitis, chloramphenicol should be administered as a loading dose of 25 mg/kg, followed by 60 mg/kg/day in divided doses q6h for 10 days. Alternative therapy includes doxycycline, 100 mg orally q12h, or tetracycline, 2–4 g in divided doses q6h for 10 days [317–319]. Plague pneumonia is virtually always fatal if antimicrobial therapy is delayed for >24 h after the onset of illness [318].

Contacts of pneumonic plague or suspected victims of intentional bioterrorism aerosol exposure should be given chemoprophylaxis with doxycycline (100 mg orally q12h), tetracycline (15–30 mg/kg in divided doses q6h), or chloramphenicol (30 mg/kg orally in divided doses q6h) for 7 days. Only an experimental vaccine is currently available. This formalin-killed vaccine was effective in preventing bubonic plague but was ineffective in preventing infection from aerosol exposures [281, 319].

II. ENDEMIC INFECTIOUS DISEASES OF NONMILITARY IMPORTANCE

Polio

Polio types 1 and 3 are still endemic in Afghanistan and are responsible for significant disability among the population. Eradication efforts have proceeded despite years of ongoing conflict, and significant progress was made in the last 2 years,
but current events are likely to diminish recent improvements in vaccine coverage. A recent outbreak of polio occurred in Kunduz (both types 1 and 3 poliovirus isolated), and cases have been continuously identified throughout the country [320–322].

**Epidemiology.** Polio is acquired by the ingestion of fecally contaminated water and food. There are no animal reservoirs of polio. Polio national immunization days were suspended in mid-1997 and 1999 in some parts of the country, including Kunduz, which may have contributed to the recent outbreak [320, 321].

**Clinical findings.** Poliovirus infection has an incubation period of 3–35 days (usually 1–3 weeks) and generally results in asymptomatic or inapparent infection. In ∼5% of cases, an acute febrile syndrome may result, typically lasting ∼1 week. Nonparalytic aseptic meningitis, typical of other enteroviruses, occurs in ∼2% of cases and paralytic polio in <2%. The course in paralytic cases may be preceded by a prodrome of nonspecific fever and malaise for ∼1 week, and paralytic symptoms may progress over a few days. There are 3 patterns of paralysis: bulbar, spinal, and bulbospinal. Spinal paralysis is most common, accounting for 80% of cases, with the bulbospinal form accounting for most of the residual and fatal cases [322]. Polio should be considered in any case of acute flaccid paralysis. Many patients do recover completely, but polio remains a major problem in Afghanistan. In 1996, polio was the leading cause of disability among those <15 years of age in Kandahar Province [323].

**Diagnosis.** The preferred method of diagnosis is isolation of virus from stools or a pharyngeal swab. An optimal sample by WHO criteria is 2 specimens collected 24 h apart within 14 days of the onset of acute flaccid paralysis.

**Treatment and prevention.** There is no specific treatment for polio. Polio is prevented by vaccination, and the disease has been eradicated from most of the world. The Indian subcontinent, central Asia, Africa, and the Middle East represent the last areas where polio still circulates.

**Measles**

Measles is one of the most serious disease threats to the local population of Afghanistan. This disease has the capacity, in the setting of overcrowding and malnutrition, to cause epidemics resulting in massive morbidity and mortality. A measles epidemic was most recently reported in April 2000, with at least 1200 fatalities and a case fatality rate of 8%–13% [324]. Most of the deaths were reported from Badakhshan, bordering Tajikistan.

**Epidemiology.** Humans are the only species infected by this virus, which causes one of the most communicable diseases known. Natural transmission has been interrupted in the United States and is uncommon in other industrialized countries. The illness is still common in the developing world, where it is responsible for considerable morbidity and mortality. In a recent household survey in the Kohistan district of Afghanistan, measles was 1 of the top 2 causes of death in children <10 years [2]. Measles is also a leading cause of blindness among children. The number of cases peaks in the winter and early spring.

**Clinical findings.** Measles in the developing countries is much more severe than most Western physicians would recognize. Among refugees and those compromised by inadequate nutrition, the case fatality rate can exceed 20%. The illness should be easily diagnosed from the constellation of signs, including the maculopapular rash, starting on the face and proceeding inferiorly and to the extremities. The rash can become petechial or even purpuric in the compromised host. Coryza and conjunctivitis are prominent, and patients may experience significant diarrhea or respiratory complaints. Pneumonia is the most common severe complication, either primary measles pneumonia or superinfecting bacterial pneumonia with streptococci, staphylococci, or *Haemophilus influenzae*. Bacterial lymphadenitis is also a possible complication, as well as croup and otitis media [322]. The neurological sequelae may include encephalitis. Measles can become hemorrhagic in the compromised host and may resemble a hemorrhagic fever. Koplik’s spots should be sought for diagnostic purposes, because they are essentially pathognomonic if found.

**Diagnosis.** The most common means of diagnosis is serology. Detection of IgM antibody by ELISA is the preferred method and is diagnostic of acute measles in a person who has not recently received live attenuated measles vaccine. False-negative testing can occur, particularly if the sample is taken in the first 72 h after rash onset [325]; acute and convalescent IgG can also be diagnostic if a 4-fold increase in titer occurs. Histological demonstration of multinucleated giant cells in sputum or mucosal swab specimens can be a practical means of making the diagnosis in the field.

**Treatment.** There is no specific treatment of measles, but many complications of measles in the malnourished child can be ameliorated by the administration of vitamin A. Two consecutive doses of 200,000 IU orally (100,000 IU in those <1 year) should be given to those with severe symptoms [322]. In the refugee setting, it is prudent to give vitamin A to all with measles.

**Prevention.** The current measles-mumps-rubella vaccine is safe and effective. If given within 72 h of exposure, it can also prevent disease. Immunoglobulin, which is usually given as immune serum globulin, can modify or prevent disease when administered within 6 days of exposure, at a dose of 0.25 mg/kg (immunocompromised, 0.5 mg/kg) up to a maximum dose of 15 mg [322]. It should be noted that immunoglobulin will interfere with the immune response to the measles vaccine, so
administration of the vaccine should be delayed if immunoglobulin has been given. Vaccination of populations at risk before outbreaks of disease is much preferred.

**Diphtheria**

In the 1990s, Russia and all of the newly independent former Soviet republics experienced a diphtheria epidemic, largely in the adult population [326–331]. Absence of routine adult immunization for diphtheria and possibly decreases in pediatric vaccination played a large role in this epidemic, which was eventually controlled by mass vaccination efforts. Movement of refugee populations from Afghanistan, and return of Soviet soldiers from Afghanistan, very likely contributed to the massive epidemic. Diphtheria continues to be an ongoing health concern in Afghanistan.

**Natural history.** Diphtheria is traditionally a disease of children <15 but occurs in any unvaccinated population. The disease is seasonal in temperate climates, with more cases occurring in winter and spring.

**Clinical findings.** The illness can be classified as cutaneous, nasal, pharyngeal/tonsillar, laryngeal, combined, or severe. Cutaneous diphtheria is well described in the tropics and does not generally cause systemic illness. The incidence of this cutaneous disease in Afghanistan is not currently known, but it is not likely to be of great clinical significance.

Nasal diphtheria is a common form of presentation and is generally a mild disease. The patient may note a serosanguineous or mucopurulent nasal discharge, often in conjunction with a white membrane on the nasal septum. Serious illness is uncommon, and patients should recover with appropriate therapy.

Pharyngeal diphtheria is the most common form, with abrupt or gradual onset; symptoms may include malaise, sore throat, and low-grade fever. The time between onset and presentation to a medical facility was 5 days for 50% of patients and up to 1–2 weeks for 11% in the Kyrgyz epidemic [326]. Fever, sore throat, weakness, and odynophagia were most common complaints. The disease is characterized by the formation of a white membrane, which may be a localized patch on the tonsil or extend across most of the soft palate. The color of parts of the membrane may evolve to a green-gray or black. The membrane is adherent to the tissue and bleeds on probing or attempted removal. In more severe cases, significant neck edema or labored respirations may be present, the latter due to membrane obstruction of the airway. The size of the membrane may correlate with the severity of symptoms.

Laryngeal diphtheria can be the site of initial infection or result from extension of the pharyngeal form. Symptoms include hoarseness, dyspnea, stridor, and a barking cough. The membrane and associated edema can lead to airway obstruction of the airway. The airway should be rapidly secured in treating such patients [326].

Toxic complications include myocarditis and neuritis. Myocarditis occurs after the first week of disease and may result in cardiac conduction abnormalities, arrhythmias, or congestive failure. Neuritis may present as a predominantly motor deficit, palatal paralysis, cranial nerve palsies, or, less commonly, proximal extremity or diaphragm involvement with variable severity [322]. The case fatality rate of diphtheria during outbreaks in the Russian and neighboring central Asian countries varied between 4% and 20%.

**Laboratory findings and diagnosis.** The diagnosis should be confirmed by culture of the organism from the location of concern. The medium of choice is tellurite-containing media, such as Tinsdale agar. This is not a routine agar for throat cultures, and the laboratory should be notified if diphtheria is suspected. A simple Gram’s stain can assist in a clinically relevant setting, but other diphtheroids are commonly isolated from pharyngeal areas as well. Any suspicious isolate should be tested for toxin production by a specialized laboratory. Treatment should not be delayed for diagnostic testing [332].

**Treatment.** Therapy for diphtheria requires both antitoxin and antibiotics. The antitoxin should be given as soon as possible, because it neutralizes only toxin that has not yet entered the host cell. The patient should be tested for allergy before antitoxin administration. The dose varies depending on the form of disease: nasal, 10,000–20,000 U; laryngeal, 20,000–40,000 U; pharyngeal, 15,000–25,000 U; combined-delayed, 40,000–60,000 U; and severe, 40,000–100,000 U.

Antibiotic therapy terminates toxin product and clears the organism. Macrolides have been the treatment of choice; traditionally, erythromycin orally or iv (40 mg/kg to 2 g/day in 4 divided doses) has been used. Procaine penicillin in a dose of 300,000 U (for those ≤10 kg) or 600,000 U (>10 kg) per day for 14 days is also effective. Patients should be placed in respiratory isolation, and 2 throat samples should test negative by culture [332] at the completion of therapy.

**Prevention.** Vaccination is the most effective form of prevention. Because all US military personnel are vaccinated, their risk of disease is extremely low. Close contacts of cases should undergo culture, and treatment should be initiated with macrolides for a 7- to 10-day course or with a single dose of benzathine penicillin at 600,000–1,200,000 U.

**Tetanus**

Tetanus occurs as a result of toxin production by Clostridium tetani. Four types of tetanus occur clinically: generalized, localized, cephalic, and neonatal. Several hundred cases of tetanus are reported in Afghanistan every year, which presumably reflects a small percentage of the true number of cases [322].
Neonatal tetanus accounts for a large proportion of the total cases.

**Clinical findings.** Generalized tetanus is the most recognized form, with painful spasms of muscle groups throughout the body. These spasms can result in death from respiratory compromise if the muscles of respiration become involved. Localized tetanus represents involvement of muscle groups near the site of infection and toxin production and tends to resolve spontaneously. Cephalic tetanus is analogous to localized disease but involves the face. Cranial nerve palsies are not uncommon. Neonatal tetanus occurs when the umbilical cord becomes contaminated with *C. tetani*, frequently in the setting of low maternal vaccination rates for tetanus. The infants initially demonstrate failure to thrive and poor feeding, with later onset of spasms and rigidity. The neonatal tetanus case fatality rate is ~90% [322].

**Diagnosis.** Diagnosis is generally based on clinical findings, and there is no definitive laboratory evaluation. Culture of the bacteria from the site does not confirm the diagnosis. Ancillary testing with electromyography may be helpful.

**Treatment.** The principles of therapy are to stabilize the airway and respiration, initiate neuromuscular blockade, provide sedation, minimize effects of autonomic instability, and maximize supportive care. The use of intramuscular human tetanus immunoglobulin has been shown to decrease the duration of disease [333].

**Prevention.** Adequate vaccination with tetanus toxoid is the best means of prevention. For neonatal tetanus, vaccination of the mother before birth and aseptic technique in handling of the umbilicus are important. Passive immunization with tetanus immunoglobulin for high-risk wounds in those who are inadequately immunized may prevent disease.

**Leprosy**

Leprosy remains a serious health problem in many undeveloped countries. India, Brazil, Myanmar, Indonesia, Nepal, and sub-Saharan Africa have the most serious endemic leprosy in terms of prevalence. The disease is endemic in Afghanistan but is not a major health threat, with a reported prevalence of 1 case per 100,000 population [334]. Leprosy is caused by *Mycobacterium leprae*, a slow-growing bacterium preferring cooler parts of the body to grow, including the skin, peripheral nerves, the eye, the respiratory tract, and male genitalia.

**Clinical findings.** Leprosy is a complex disease with variable presentation. The clinical presentation of leprosy depends on the host response. With a vigorous host response, the patient will have tuberculoid leprosy. This is a paucibacillary state with single or few hypopigmented lesions with elevated erythematous margins. Enlarged peripheral nerves, particularly the ulnar and great auricular nerves, may be noted. Lepromatous leprosy occurs with poor host immune response and an overwhelming load of bacilli. The skin is thickened, with frequently symmetrical nodules and plaques, and with particular involvement at cooler areas of the body. The nasal cartilage may be eroded, the testicles may atrophy, and ocular involvement may occur. Many cases have a mixed presentation [335].

**Treatment.** Treatment of leprosy depends on the burden of organisms. For paucibacillary disease, treatment with a 6-month course of oral rifampin (600 mg once a month) and dapsone (100 mg orally q.d.) is recommended. The "ROM" therapy (one-time dose of rifampin, ofloxacin, and minocycline) is used under certain circumstances as well. Multibacillary disease is treated for 12 months with oral rifampin (600 mg once a month) and clofazimine (300 mg once a month), along with daily dapsone (100 mg) and clofazimine (50 mg) [335].

**Echinococcal Infections**

Echinococcal infections in humans are caused by the larval stages of the parasitic helminths (tapeworms) of the genus *Echinococcus*. The 2 species endemic to central Asia are *Echinococcus granulosus*, the cause of cystic hydatid disease of the liver, lung, bone, or brain, and *Echinococcus multilocularis*, the cause of alveolar hydatid disease—solid tumor-like masses that begin in the liver and expand in a highly invasive manner [336].

**Epidemiology.** *Echinococcus* has a worldwide distribution. The definitive hosts of *E. granulosus* are carnivores, mostly dogs, which shed the embryonated eggs. The eggs are scattered in the pasture and ingested by intermediate hosts, usually sheep. Once hatched, the larvae migrate through the intestinal wall and penetrate the animal’s organs, especially the liver and lungs. The life cycle is completed when the carnivore ingests the viscera of the intermediate host. Humans become accidental hosts when they ingest the eggs, which can survive several days but cannot resist desiccation and extreme temperatures. In rural areas, the custom of slaughtering sheep at home, among dogs, is an important dissemination factor. The circumstances of transmission vary according to the country. In eastern Europe and central Asia, the natural life cycle of *E. granulosus* involves dogs as the definitive host and sheep as the intermediate host [337].

Infection rates of the populations of south-central Asia vary substantially, even within the boundaries of specific regions. High levels of disease occur in areas of oases, valleys, and middle mountains, whereas moderate levels occur in the semidesert and alpine regions. Low levels of disease are noted in deserts and salt-marsh regions. The highest risk of disease is among cattle breeders [338].

For reasons that are unclear, echinococcal disease has recently increased dramatically in Kazakhstan and Uzbekistan. Detected cases of echinococcosis in Uzbekistan have increased 4-fold in the past 10 years [339], and surveys indicate that 20%–30% of dogs are infected. Infection in domestic animals was docu-
Cystic hydatid disease is widely distributed in Europe and Asia (Eurasia) than is alveolar hydatid disease [342]. The definitive hosts for *E. multilocularis* (alveolar hydatid disease) are carnivores (predominantly foxes), whereas the intermediate hosts are rodents. It has a wide distribution in the northern hemisphere (North America and northern and central Eurasia). *E. multilocularis* has recently been discovered to have a much wider geographic distribution than was previously known. Growing fox populations, the increasing invasion of urban areas by foxes, and other factors may represent a new public health hazard [336]. Recent surveys in central Europe have extended the known geographic occurrence of *E. multilocularis* from 4 countries at the end of the 1980s to at least 11 countries in 1999, although the annual incidence of disease in humans remains low. It is not known whether these findings reflect a recent extension of the parasite’s range or just better case finding in previously unnoticed areas of endemicity. In central Asia, both forms of echinococcal disease can be considered reemerging diseases. Rates of prevalence of these diseases are likely severely underestimated, and alarming increases of the number of human cases have been reported from Bulgaria, Kazakhstan, and the People's Republic of China [343]. No information is available on the incidence of echinococcal disease in Afghanistan; however, the presence of intermediate and definitive hosts and a high prevalence in surrounding countries make it highly likely that it occurs in Afghanistan.

**Clinical findings.** The initial growth period of primary hydatidosis is frequently asymptomatic, and symptoms may first occur months to years after exposure. In cystic hydatid disease, cysts enlarge slowly over years until they are 1 to >10 cm. Cysts are round and unilocular. They have a thick wall, which may calcify with time, and are most frequently found in the liver and lungs but are also found in bone, brain, and other organs. When signs and symptoms do develop, they are related to cyst size and location. Rupture of cysts can result in anaphylaxis or widespread secondary echinococcosis. Complications include bronchial fistulization, intrapleural rupture (rare but severe), and metastatic hydatidosis resulting from the breaking of a primary cyst into a blood vessel [344]. Human alveolar echinococcosis is often lethal in untreated patients [336]. Without a cyst wall to restrict growth, it spreads aggressively, behaving much like a malignancy.

**Diagnosis.** Diagnosis is suspected when clinical symptoms occur after possible exposure in a region of endemicity. Ultrasonography, CT, and MRI can identify lesions and reveal others not readily apparent by conventional radiography [344].

Laboratory diagnosis complements the clinical picture. In-direct hemagglutination and EIA are the most effective immunologic methods for screening for hydatid disease. These, combined with immunoelectrophoresis, confirm the diagnosis in 80%–94% of hepatic disease and 65% of pulmonary disease. Western blot and PCR may be used for further identification, especially when cysts are calcified [345]. Some have found PCR to be superior to conventional tests used for the immunodiagnosis of echinococcosis and have suggested its use for routine diagnosis [346]. All seropositive patients should undergo further clinical examination and continued follow-up [347].

**Treatment.** Echinococcosis can be treated by medical, surgical, and percutaneous methods. The prognosis has improved recently, but complications occur and operative mortality is still 1%–2% [344]. Most patients require surgery or guided percutaneous drainage, but ~30% will respond to medical therapy alone. Albendazole has largely supplanted mebendazole because of its better absorption. Praziquantel can be used in combination with albendazole and is recommended to reduce the likelihood of secondary cysts if rupture of a primary cyst occurs or is likely to occur [348]. Ultrasound-guided cyst puncture has been used successfully in selected patients, although the risk of anaphylaxis from spillage of cyst contents exists.

Surgery is usually indicated for large cysts with multiple daughter cysts, superficially located single liver cysts, complicated cysts, compression or obstruction, and cysts located in vital organs. However, surgical therapy has significant risks, and medical therapy with or without a guided aspiration procedure may be a more reasonable alternative for uncomplicated cysts and for those at high surgical risk [348].

**Prevention.** Control measures include avoiding contact with dog feces, handwashing, reducing the dog population, treating high-risk dogs with praziquantel, and incinerating infected organs. Despite ongoing efforts through use of anthelmintics and life style changes, few countries have been able to substantially reduce or eradicate these infections. Vaccines are currently being tested successfully in animals and have potential for use in humans [349]. Deployed troops should limit contact with dogs and domestic animals, take care in the handling of infected animals, and dispose of infected organs appropriately.

**CONCLUSION**

The current upheaval in Afghanistan increases the threat of infectious diseases outbreaks among Western military and humanitarian aid workers as well as local populations. As recent US military experiences in the Persian Gulf, Somalia, and Haiti have shown [6–11], US troops can be effectively protected from infectious diseases through careful predeployment preparation, personal protective measures, and rapid evaluation and treatment of acute illnesses. Preventing and treating infections...
among the indigenous population will undoubtedly be more difficult. Nevertheless, efforts to improve the quality of the food and water supply, provide needed vaccinations, and bolster the local public health infrastructure will not only reduce the toll from infectious diseases but also contribute greatly to the overall recovery of Afghanistan.

Acknowledgments

We thank Waine MacAllister and Sylvia Romero for many hours of editing and manuscript preparation, Scott Sherman for his contributions, Peter Melby for his review of the Leishmaniasis section, and Maria Kelchner for Russian translations. The map of Afghanistan was provided by the University of Texas at Austin Library Online. We greatly appreciate it.

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