

ENDEMIC INFECTIOUS DISEASES AND BIOLOGICAL WARFARE DURING THE GULF WAR: A DECADE OF ANALYSIS AND FINAL CONCERNS

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Abstract. Infectious diseases were one of the first health threats confronted by Coalition troops deployed to the Arabian desert in August 1990. On the basis of experiences in World War II, the major endemic infectious disease risks were thought to be sandfly fever, cutaneous leishmaniasis, diarrheal disease, and malaria. Although there was active surveillance, no case of sandfly fever and few other endemic infectious diseases were identified among over 500,000 U.S., British, and Canadian ground troops. In addition, there was no diagnosis of biological warfare (BW) exposure, and BW agents were not detected in clinical, environmental, or veterinary samples. The most common infectious disease problems were those associated with crowding (acute upper respiratory infections) and reduced levels of sanitation (travelers-type diarrhea). Only one endemic infectious disease has been confirmed as causing chronic health problems: visceral *Leishmania tropica* infection (viscerotropic leishmaniasis). However, this protozoan infection was diagnosed in only 12 U.S. veterans, and no new cases have been identified during the last 8 years. Infectious diseases were not a serious problem for Gulf War troops because of extensive preventive medicine efforts and favorable weather and geographic factors. Moreover, it is unlikely that an endemic infectious disease or a BW agent could cause chronic health problems and remain undetected over a 10-year period.

INTRODUCTION

The United States began deploying troops to the Arabian Gulf on August 7, 1990, just 5 days after Iraq's invasion of Kuwait.¹ Troops from > 40 Coalition countries subsequently were rushed into the theater of operations in order to counter an Iraqi combat force that had already mobilized and conducted a successful military campaign. All activity was focused on preparing to fight a war with a country that had > 1 million men in uniform.² The abrupt and hurried character of the initial deployment never changed. Even after 5 months of buildup and the establishment of an overwhelming offensive capability, Coalition troops continued to pour into the theater of operations during the air and ground war. After hostilities ended, Coalition forces were as quickly sent back home. Most of the 700,000 American troops had returned to the United States by May 1991, 9 months after the invasion.³

In such a short deployment of large numbers of troops, infectious disease outbreaks could have been a major problem. Furthermore, foreign troops were vulnerable to several infectious diseases that are endemic to this semitropical and desert region.⁴ Adding to the difficulties, Western military personnel had had relatively little recent experience dealing with infectious disease threats in the Arabian Gulf. Although Allied forces had been stationed in this region during World War II and the British had helped defend Kuwait from Iraqi aggression in 1961,⁵ the relevance of these experiences was unclear because Gulf countries had sustained rapid modernization, with substantial improvements in medical care, sanitation, and public health. More current health risk information was obtained from oil companies,⁶ which provide for large numbers of guest workers and their families, and from U.S. Navy assets in Bahrain and in Cairo, Egypt.^{7,8}

The first Coalition troops to arrive in the Arabian Gulf encountered an inhospitable desert environment with daily temperatures well over 100°F (53.9°C).^{3,9} Neither water nor sanitation facilities were readily available in the open desert where most troops were encamped. Particularly at the be-

ginning of the campaign, preventive medicine and health care were guided by established procedures designed to function during international deployments.¹⁰ Troops had to depend on what they had brought with them because there were few accessible commercial centers and secure food supply sources had yet to be established. Potable water was less of a problem because U.S. and British military personnel deploy with reverse-osmosis water purification equipment.¹¹ In contrast to the initial deployment, by the time the war began, an immense supply system and a health care system had been established to provide for 1 million ground and shipboard personnel and the possibility of massive numbers of combat casualties.¹²

SURVEILLANCE ACTIVITIES

More extensive medical surveillance information was collected on U.S. troops during the Gulf War than in previous large-scale conflicts. A comprehensive, state-of-the-art infectious diseases diagnostic laboratory was established in Saudi Arabia by the U.S. Navy at the beginning of the deployment.¹³ In addition, a real-time surveillance system was instituted among 40,000 U.S. Marine Corps ground troops.^{8,14} Outpatient morbidity data for this population were collected on special report forms and analyzed weekly. Additional health monitoring systems were in operation among U.S. and British forces.¹¹

Surveillance of ground troops indicated that most health problems were due to training- and sports-related accidents, diarrheal disease, and acute upper respiratory infections.^{8,11,14} Also, surveillance data demonstrated that morbidity rates were highest during initial periods of crowded deployment and that health complaints declined steadily as troops dispersed and adapted to desert conditions. Approximately 6% of ground troops were treated each week for illness or injury, which compares favorably with troops training in the continental United States.⁸ With the initiation of active hostilities, disease and injury rates did not increase substantially.¹⁴

Overall, morbidity rates were lower in this military campaign than in previous wars involving U.S. troops.^{14,15} During the entire deployment, there was just one death due to an infectious disease among U.S. forces, which resulted from meningococcal meningitis.¹⁶

ENDEMIC INFECTIOUS DISEASES

On the basis of the experience of Allied troops during World War II, the major endemic infectious disease threats were thought to be sandfly fever, cutaneous leishmaniasis, diarrheal disease, and malaria.^{4,5} Sandfly fever was considered to be the most serious threat to the combat effectiveness of ground troops. During World War II, up to 20% of some military units were briefly debilitated by this viral infection.¹⁷ Other potential endemic disease risks were Q fever, brucellosis, viral hemorrhagic fever, and hepatitis A and E.⁴

Although there was an active search for outbreaks of febrile disease and 37 acutely febrile troops were tested for arthropod-borne infections, no case of sandfly fever was diagnosed during the deployment.^{8,18} In addition, a serosurvey of 883 ground troops, which utilized serum samples collected just before and after deployment to the Arabian Gulf, did not find evidence of rickettsial or arboviral infections, including sandfly fever.¹⁹ For the other sandfly-transmitted disease threat, 20 cases of cutaneous leishmaniasis due to *Leishmania major* infection were diagnosed after the war among 500,000 U.S. ground troops.²⁰ Few additional endemic infectious diseases were diagnosed among U.S. troops: one acute case of West Nile fever; 7 cases of malaria; and 3 soldiers who may have contracted Q fever.¹⁴ There were no reported cases of brucellosis or outbreaks of viral hepatitis; hepatitis E was not diagnosed among any U.S. troops.

Military personnel were at increased risk of acute diarrheal and respiratory infections, which were associated with crowding and camping in the field, where it is difficult to maintain high levels of hygiene without running water and modern sanitation facilities. At the onset of the deployment, there were numerous outbreaks of diarrhea due predominantly to enterotoxigenic *Escherichia coli*, which causes common travelers-type diarrhea, and *Shigella sonnei*.¹⁴ Up to 60% of U.S. ground troops experienced at least one episode of acute diarrhea, as demonstrated by 2 surveys: one conducted among 2,000 troops during the early stages of the deployment, and another among 900 troops deployed later during the winter months.^{21,22} Laboratory testing of > 400 stool samples from a broad selection of ground troops with acute diarrhea did not identify potentially more serious outbreaks of enteric disease due to typhoid, cholera, giardiasis, or amebic dysentery.²¹ Also, in an analysis of 422 stool specimens obtained just after the war from asymptomatic U.S. troops, chronic parasitic infections were not found except for 3 samples with *Giardia* cysts.²³

Upper respiratory symptoms and common cold-type illnesses were frequent during periods of crowding.^{14,24} Additionally, there was concern about the health effects of blowing sand, which was a frequent occurrence in this desert environment. However, a survey of 2,600 ground troops indicated that upper respiratory complaints were less of a problem among military personnel living outdoors in tents than among the minority of troops billeted in air-conditioned

buildings, where respiratory infections were more readily transmitted.²⁵

Sexually transmitted diseases historically have been a problem among deployed military forces. But in contrast to previous wars, sexually transmitted diseases were reported at low rates during the Gulf deployment because there was little contact with local populations and limited privacy among deployed military forces.^{11,26,27}

The pattern of infectious diseases changed when the weather became cooler in November and December 1990. Diarrheal disease decreased in frequency, but outbreaks of acute vomiting due to Norwalk virus infection became common.^{21,22} During the winter months in this region, temperatures range between 45°F (7.2°C) at night to 65°F (18.3°C) in the day.³ Although the popular image is of troops drinking bottled water to prevent heatstroke, in reality, ground troops were trying to stay warm by wearing coats and using tent heaters when hostilities began in January 1991. Because the level of insect activity decreased precipitously with the onset of cold weather, insecticides and repellents were less often used during combat operations at the height of the military buildup.

BIOLOGICAL WARFARE

Biological warfare (BW) was a recognized health threat during the Gulf War because Iraq was known to have a BW program.¹⁵ United Nations inspections after the war found evidence that Iraq was developing weapons that used anthrax spores, botulinum toxin, and aflatoxin.²⁰ To detect BW agents, both rapid detection and traditional laboratory tests were available in the theater, with confirmatory backup in the United States and at the Chemical Biologic Defense Establishment in Porton Down, United Kingdom.¹³ In addition, Coalition medical personnel were intent on diagnosing any effects of biological or chemical warfare exposure to provide effective medical care and to avoid becoming casualties themselves from secondary exposure to contaminated patients.

Despite these efforts, no case of BW exposure was diagnosed during the air or ground war. Moreover, no BW agent was detected in analyzed clinical, air, and water samples.⁸ Over the last decade, several expert review panels have evaluated this issue; none concluded that Coalition troops were exposed to BW agents during the Gulf War.^{3,15,20,28,29}

The presence of dead sheep, goats, and camels on the battlefield has been considered to be possible evidence that either chemical warfare or BW agents were used during the Gulf War. Dead animals, however, were found > 5 months before the war began, at the start of the deployment in August 1990.^{14,30,31} Dead animals—which customarily are left in piles by local herders—were heavily sprayed with pesticides by military entomologist because they were considered to be potential breeding grounds of insect-borne diseases, which may explain later reports of dead flies on animal carcasses. Analysis of tissue samples from 7 dead goats showed no evidence of anthrax or other BW exposure.^{13,20}

AFTER THE GULF WAR

During the 10 years since the Gulf War, numerous causes for the health problems experienced by veterans have been

evaluated, including infectious diseases.³² Large-scale epidemiological studies of Gulf War veterans have not shown an increased rate of hospitalizations or mortality due to infectious diseases.^{33,34} The absence of long-term morbidity may be because most infectious diseases encountered by Gulf War troops do not cause chronic infections but are limited to acute illness. For example, the sandfly fever virus and the major causes of diarrheal and respiratory infections do not persist after symptoms resolve. Just one novel infectious disease, viscerotropic leishmaniasis, has been determined to be a potential cause of delayed illness among 12 U.S. Gulf War veterans.^{35,36}

Viscerotropic leishmaniasis is a comparatively mild form of visceral leishmania infection caused by *Leishmania tropica*, a protozoan parasite that usually causes cutaneous and not systemic disease. Leishmaniasis is transmitted by the bite of an infected sandfly and not by casual contact.³⁷ Gulf War veterans with viscerotropic leishmaniasis have presented with fever, hepatosplenomegaly, lymphadenopathy, mild anemia, and modest aminotransferase elevations. Patients have not had cutaneous manifestations, and unlike classic visceral leishmaniasis (kala-azar), have not had pancytopenia or hypergammaglobulinemia. All but one of the 12 cases of systemic *L. tropica* infection had readily discernible pathology.³⁵

Because of concerns that leishmaniasis could be transmitted via blood transfusions, Gulf War veterans were excluded from donating blood between November 1991 and January 1993.³⁸ The ban was lifted because new cases of leishmaniasis were not being diagnosed, there was no evidence of transmission via blood products, and routine screening of blood donors for current health problems would detect the characteristic clinical presentation of this disease.³⁹ The last veteran diagnosed with viscerotropic leishmaniasis presented within 2 years of returning from the Gulf War, and none of the other 40 Coalition countries have reported cases of visceral leishmaniasis.⁴⁰

Available data indicate that Gulf War ground troops were at low risk of leishmania infection. There has been a total of just 32 reported cases of cutaneous and visceral leishmaniasis among > 500,000 Western ground troops.²⁰ The absence of sandfly fever further suggests that sandfly-transmitted diseases were not prevalent during the deployment, and entomological surveys conducted during and after the war rarely found sandflies in the barren desert areas where most troops were stationed.^{18,41} Last, viscerotropic leishmaniasis is probably a rare disease in northern Saudi Arabia and Kuwait where Coalition troops operated because it has not been described in local inhabitants, guest workers, or Allied troops who served in this region during World War II.^{5,6} To date, there have been only a few case reports of viscerotropic leishmaniasis in localized areas of Africa and the Middle East.^{36,42}

There still is concern that some veterans may continue to harbor *L. tropica* infection. These infections could eventually cause clinical disease, particularly in the setting of immunosuppression.⁴³ The problem has been that there is no accurate and noninvasive screening test for this infection. Diagnosis requires painful, often multiple biopsies of bone marrow and lymph nodes, along with highly specialized laboratory techniques to visualize and culture the parasite.⁴⁴

And once the diagnosis is confirmed, parenteral drug treatment—with pentavalent antimony compounds and amphotericin B—is prolonged and sometimes toxic.⁴⁵ Treatment therefore is not recommended for asymptomatic infection.

In addition to the possibility of chronic leishmanial infection, there have been 2 unconfirmed hypotheses that chronic bacterial infections are the cause of long-term health problems among Gulf War veterans. One hypothesis involves infection with *Mycoplasma* sp., either as a natural infection (possibly facilitated by crowding), a vaccine contaminant, or a genetically engineered BW agent.^{20,46,47} This hypothesis was developed by a well-known cancer researcher who had a family member develop an unexplained illness after returning from military service in the Gulf War.⁴⁸ There also have been reports by individual veterans that their chronic, unexplained symptoms improve with tetracycline or doxycycline therapy. But in one published study of this hypothesis, no association was found between *Mycoplasma fermentans* infection and either deployment to the Arabian Gulf or postwar symptoms.⁴⁹ Another study is in progress to determine if proposed diagnostic tests for *Mycoplasma* infection, which utilize polymerase chain reaction (PCR), can identify Gulf War veterans with chronic unexplained illness.⁵⁰

The other hypothesis being studied involves the possibility of a chronic, systemic gram-positive coccidial infection among Gulf War veterans. The postulated bacterial pathogen cannot be cultured from blood samples but can be identified by observing cocci and shells of dead cocci (“explodeds”) in specially evaluated samples of urine sediment.^{51,52} This hypothesis originated from pre-Gulf War observations of a clinician who noted that patients with chronic unexplained illnesses, such as chronic fatigue syndrome, responded to antibiotic therapy.^{20,52} It is noteworthy that this same hypothesis was first proposed in 1915 to explain chronic debility among military personnel.⁵³ One attempt to confirm the finding of abnormal bacteria in urine samples from Gulf War veterans was unsuccessful.⁵¹

VACCINE ISSUES

In addition to chronic infectious diseases, the vaccinations given to Gulf War troops have been hypothesized to be the cause of chronic unexplained illnesses. The U.S. military administered routine booster doses of childhood and adult vaccines, including tetanus-diphtheria, polio, measles-mumps-rubella, typhoid, yellow fever, and influenza. Immune globulin was given to U.S. troops for hepatitis A prophylaxis. Some troops also were vaccinated with the meningococcal and hepatitis B vaccines.

In addition to commonly used vaccines, up to 150,000 U.S. troops received at least one dose of the U.S. Food and Drug Administration (FDA)-approved anthrax vaccine, and ~ 8,000 forward-deployed U.S. troops received an investigational botulinum toxoid vaccine.²⁰ Because these 2 nonlive vaccines have a long track record of safe use, independent review panels have not concluded that they are a likely cause of chronic health problems.^{15,20,54}

There were some differences in the vaccinations given to Coalition military personnel. British troops were routinely immunized against yellow fever, tetanus, typhoid, and po-

lio.⁵⁵ Some troops were given the cholera vaccine, and medical personnel were immunized against hepatitis B. A small number of troops may also have received the meningococcal vaccine or immune globulin in the theater. In December 1990 and January 1991, an emergency immunization program was initiated to protect British personnel against potential BW agents.⁵⁶ All personnel in the theater were offered immunization against anthrax and plague. In addition, pertussis was given with the anthrax vaccine as an adjuvant. The uptake of the first 2 doses of anthrax vaccine was high but fell off later as the threat of attack with biological agents receded during the Gulf War.

In epidemiological studies conducted after the Gulf War among British veterans, an association was found between self-reported somatic symptoms and multiple vaccinations in the Gulf.^{57,58} Further research is in progress to determine the significance of these findings.⁵⁹ It is noteworthy that a Canadian medical contingent was colocated with a British field hospital during the Gulf War, and these personnel were immunized like British troops. Other Canadian personnel, such as sailors on board ships, were not given the same vaccinations. In an epidemiological study conducted after the war, no difference was found in the prevalence of postdeployment health complaints among groups of Canadian veterans that received different vaccinations.⁶⁰ In addition, previous studies of laboratory workers who received numerous vaccinations over a short period of time, including the anthrax and botulinum vaccine, have not found evidence of long-term sequelae.⁶¹

RESEARCH STUDIES

Numerous clinical and epidemiological studies have been conducted to evaluate the health problems of Gulf War veterans.⁵⁰ There currently are 3 primary areas of infectious diseases research related to Gulf War health questions. One major emphasis has been on the development of reliable and noninvasive diagnostic tests for leishmania infection. The U.S. Department of Defense is funding research to develop FDA-approved skin tests and serological tests to detect parasite antigens and circulating antibody.^{50,62} The skin test antigens, prototype serologic test kits, and PCR assays developed to date will be extensively evaluated in leishmania-endemic populations to determine their sensitivity, specificity, and positive predictive index.⁶³ Although it is not possible currently to screen veterans for visceral *L. tropica* infection, steady progress in diagnosis and treatment of leishmaniasis will lead to improved medical care.⁴⁵

The second primary area of active research involves 2 therapeutic treatment trials in the United States to evaluate whether a systemic bacterial infection is the cause of chronic illnesses among Gulf War veterans. In one study projected to cost \$12 million, a double-blind antibiotic treatment trial has been instituted by the Department of Veterans Affairs as a Multisite Cooperative Study at 30 Veterans Affairs and Department of Defense clinical centers. Either doxycycline or placebo is being given over a 1-year period to ~ 450 veterans who are positive by PCR for *Mycoplasma* sp. genetic material. Study participants are being followed for changes in functional status and various symptoms, including pain, fatigue, and neurocognitive difficulties.⁵⁰ In the oth-

er major treatment trial, which received \$3 million in directed funding from the U.S. Congress, multiple, high-dose antibiotics are being administered to Gulf War veterans with unexplained symptoms who have been found by the study investigator to have characteristic cocci in urine samples.⁵⁰

If the results of either of these treatment trials indicate a favorable response to therapy, further study will be necessary before antibiotic therapy can be generally recommended for the treatment of Gulf War veterans. First, the results will have to be independently verified. Second, the mechanism of action of antibiotic therapy will have to be determined—that is, to see whether the response is due to the elimination of a specific infectious agent or whether the effect is due to some other action of drug therapy.^{64–66} Should a specific infectious etiology be identified, further research will be necessary to determine the most effective diagnostic and treatment strategy. Last, additional research will be required to determine whether putative *Mycoplasma* sp. and coccal pathogens are a cause of chronic disease in the general, civilian population.⁶⁷

In addition to human research, the availability of U.S. military working dogs provides a third primary area for unique research opportunities because of the animals' potential to serve as sentinels of infectious disease. Military working dogs receive regular examinations and laboratory testing throughout their lives, and a complete postmortem examination is performed upon death, including analysis of tissue samples by the Armed Forces Institute of Pathology, Washington, D.C. There were 118 military working dogs deployed to various locations in the Arabian Gulf between August 1990 and December 1991. The health records of deployed dogs have been evaluated for evidence of zoonotic diseases.⁶⁸ None of these dogs had clinical signs compatible with either cutaneous or visceral leishmaniasis. A case-control study is now being conducted that uses findings from the health records and autopsies. All 118 military working dogs deployed to the war zone will be compared with 472 nondeployed dogs for differences in clinical and pathological findings.

CONCLUSION

Infectious diseases were not a serious problem for Coalition troops during the Gulf War. Several factors were responsible for this favorable outcome. A comprehensive preventive medicine effort reduced morbidity through disease surveillance, monitoring of potable water, routine food inspection, camp sanitation, arthropod vector control, and personal use of insect repellents.^{8,30} Also, a sophisticated diagnostic laboratory and extensive medical care resources provided rapid identification and effective treatment of outbreaks of infectious diseases.¹³

Probably as important in reducing infectious disease morbidity were advantageous weather and geographic factors. Most troops were deployed to the barren desert, where animal hosts of infectious diseases are scarce, and the height of the military buildup occurred during the winter months, when insect vectors of infectious diseases are least active.⁶⁹ Limited contact between deployed troops and local populations further reduced the risk of infectious disease transmission.

The lack of serious infectious disease morbidity during the Gulf War may not apply to future wars, even in the Arabian Gulf. The risk of infectious diseases would have been much higher for Coalition troops had they been stationed in the riverine valleys of southern Iraq during the summer months. In most jungle and tropical regions around the world, insect-borne infectious diseases are a major threat for deployed troops throughout the year. Infectious disease transmission may also be higher in deployments that involve frequent contact with local populations. Importantly, whenever there is crowding or a breakdown in sanitation during chaotic wartime conditions, the potential for respiratory and diarrheal disease outbreaks will be high.

A decade after the Gulf War, endemic infectious diseases and BW agents have not been shown to be a cause of chronic morbidity among Gulf War veterans. In research studies and the systematic clinical examination of > 100,000 U.S., British, and Canadian veterans, common fungal skin infections have been the most frequently diagnosed infectious disease.⁷⁰⁻⁷² In addition, no pattern of infectious diseases has emerged among patients with chronic unexplained symptoms, who have been hypothesized to have a unique "Gulf War syndrome." Nor has a characteristic physical sign or laboratory test abnormality been observed that would indicate a chronic infectious process, including a unique skin rash, lymphadenopathy, hepatosplenomegaly, transaminase elevations, or hematological abnormalities.⁷⁰⁻⁷² The finding in several surveys that most veterans did not develop unexplained symptoms until several months after returning home further suggests that an infectious disease acquired in the Gulf is not a cause of chronic health problems.^{20,70}

Although it is unlikely that infectious diseases endemic to the Arabian Gulf or traditional BW agents could cause long-term health effects and remain undetected over a 10-year period, latent leishmania infection could progress to clinical disease among some veterans. Gulf War veterans with objective signs of this infectious disease should therefore be evaluated.

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