GULF WAR and HEALTH

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INFECTIOUS DISEASES

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Committee on Gulf War and Health: Infectious Diseases

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SUMMARY

Thousands of US veterans of the Persian Gulf War have reported an array of unexplained illnesses since the war ended in 1991. Many veterans have believed that the illnesses were associated with their military service in southwest Asia during the war. In response, the US Congress legislated in 1998 that the Department of Veterans Affairs (VA) use a specific procedure to determine the illnesses that warrant presumption of a connection to Gulf War service (Public Law [PL] 105-277, Persian Gulf War Veterans Act). Moreover, VA must financially compensate Gulf War veterans in whom the determined illnesses are diagnosed (PL 105-368, Veterans Programs Enhancement Act). To reach those determinations, the law states, VA must obtain independent evaluations of the scientific evidence of associations between illnesses and exposures to various chemical, physical, and biologic substances connected to military service in southwest Asia during the war. The law instructs VA to obtain the scientific evaluations from the National Academy of Sciences (NAS). NAS assigned the task of evaluating the associations to the Institute of Medicine (IOM).

This report is the fifth volume produced by IOM for VA in response to the congressional mandate.[1] A committee of nationally recognized experts in infectious diseases was appointed and charged with evaluating the scientific and medical literature on long-term adverse human health outcomes associated with selected infectious diseases pertinent to Gulf War veterans. The conclusions herein characterize the long-term adverse health outcomes associated with infection by the following pathogens: *Brucella* species (spp.), the cause of brucellosis; *Campylobacter* spp., nontyphoidal *Salmonella* spp. and *Shigella* spp., which cause diarrheal disease; *Coxiella burnetii*, the cause of Q fever; *Leishmania* spp., the cause of leishmaniasis; *Mycobacterium tuberculosis*, which causes tuberculosis; *Plasmodium* spp., the cause of malaria; and West Nile virus, the cause of West Nile fever. The committee identified those pathogens through the process outlined below. The committee then developed conclusions by studying the relevant published evidence, deliberating to reach consensus, and responding to a formal process of peer review.[2]

METHODOLOGY

IOM appointed the Committee on Gulf War and Health: Infectious Diseases in January 2005. The committee considered infections that US troops might have contracted in southwest Asia during the Persian Gulf War. At VA's request, the committee also examined infections that might have afflicted US military personnel deployed to south-central and southwest Asia for Operation Enduring Freedom (OEF)[3] and Operation Iraqi Freedom (OIF).[4] Thus, the committee's deliberations covered infectious diseases known to occur in Saudi Arabia, Kuwait, Iraq, Afghanistan, and most countries along their borders (Yemen, Oman, United Arab Emirates,

[1] Earlier IOM reports in this series present conclusions about long-term adverse health outcomes associated with exposure to depleted uranium, pyridostigmine bromide, sarin, vaccines, insecticides, solvents, propellants, combustion products, and fuels.

[2] A detailed description of how IOM studies are conducted appears at www.iom.edu/?id=32248.

[3] OEF began on October 7, 2001, in Afghanistan.

[4] OIF began on March 19, 2003.

Qatar, Bahrain, Jordan, Israel, Lebanon, Syria, Iran, Turkmenistan, Uzbekistan, Tajikistan, Kyrgyzstan, and Pakistan).

Identifying the Pathogens to Study

The committee first identified about 100 naturally occurring pathogens that could potentially have infected US troops during their service in the Gulf War, OEF, or OIF. The identified pathogens comprise viruses, bacteria, helminths, and protozoa that have been reported in southwest and south-central Asia, have historically caused outbreaks of illness in military populations, or have generated particular concern among US veterans of the Persian Gulf War. As required by PL 105-277 and PL 105-368, the pathogens include *Escherichia coli*, *Shigella* spp., *Leishmania* spp., and the *Phlebovirus* pathogens that cause sand fly fever.

Definition of Long-Term Adverse Health Outcome

The committee then developed a set of criteria for determining which infectious diseases to evaluate for strength of association with specific long-term adverse health outcomes. Long-term adverse health outcomes include secondary diseases or conditions (sequelae) caused by primary diseases, reactivation or recrudescence of diseases, and delayed presentation of diseases. A long-term adverse health outcome, the committee agreed, should have one or more of the following characteristics:

- Significant interruption of normal physical and mental function outside the timeframe of acute infection.
- Persistent organ dysfunction or damage.
- Reproductive effects in military personnel, including birth defects in their offspring.

In addition, a long-term adverse health outcome could be reversible, related to secondary transmission,[5] or both.

Development of Inclusion Criteria

Given that definition, the committee identified about 90 infectious diseases that have long-term adverse health outcomes and that were any of the following:

- Endemic in southwest or south-central Asia during the period in question.
- Diagnosed in US troops during the three deployments under study.
- Of special concern to Gulf War, OIF, or OEF veterans.
- Historically reported among military populations.

Many of the diseases have never been reported in US military personnel in close temporal relationship to deployment to southwest or south-central Asia for the Gulf War, OEF, or OIF. Even so, the committee could not rule out the possibility that one or more people contracted an unreported disease during deployment. Consequently, the committee created a tabular summary of such diseases' acute and long-term characteristics.

[5] In this context, secondary transmission means the spread of a pathogen directly from a primary human host to one or more other humans.

The committee further defined its infections of focus according to the likelihood that the primary infection would be subacute or the infected person would be asymptomatic for days to years, and the adverse health outcome would begin months to years after infection. In such cases, diagnosis of the long-term adverse health outcome during military service in Asia would be unlikely, and such infections were candidates for in-depth review and conclusions. In contrast, military medical personnel would probably diagnose adverse health outcomes that are manifest during the acute illness or shortly after a person's deployment.

Finally, the committee examined the likelihood that the candidate infections would have occurred specifically during military deployment to southwest and south-central Asia during the three operations in question. The risk of contracting the disease in the theater of operations must have been equal to or greater than the risk of contracting it in the United States. Moreover, given the natural history of the disease or infection, it must have been diagnosed in US troops in appropriate temporal relationship to deployment.

By applying those criteria to the dozens of infectious diseases recognized initially, the committee identified the group that required in-depth evaluation and conclusions: brucellosis, *Campylobacter* infection, leishmaniasis, malaria, Q fever, salmonellosis, and shigellosis. Two other diseases did not meet all the criteria but still merited in-depth evaluation: tuberculosis and West Nile virus infection.

Tuberculosis (TB) could cause long-term adverse health outcomes in US troops and veterans deployed to southwest and south-central Asia, where TB is highly endemic. TB has a long history of activation and transmission in military settings. Moreover, about 2.5% of military personnel deployed to OEF and OIF and given predeployment and postdeployment skin tests for TB converted from negative to positive; that is, these troops acquired new TB infections during deployment.[6] Therefore, although the committee found no published reports of active TB cases among the troops in question, conclusions about the long-term adverse health outcomes of TB infection are quite pertinent.

Unlike TB, West Nile virus (WNV) has been reported in troops deployed to southwest and south-central Asia, where the virus is endemic. The long-term adverse health outcomes associated with WNV infection are usually manifest during the acute illness—a characteristic that disqualified other diseases from comprehensive evaluation in this report. Nevertheless, dramatic changes in the epidemiology of WNV since the mid-1990s led the committee to make an exception for WNV and to review it in depth.

In addition, a small set of biologic agents, infections, and diseases that failed to meet the committee's inclusion criteria nevertheless raised serious questions that merited discussion: Al Eskan disease, biowarfare agents, idiopathic acute eosinophilic pneumonia, mycoplasmal infection, and wound infection (including wound infection caused by *Acinetobacter baumanii*, the most notable pathogenic colonizer of wounds during OEF and OIF).

Development of Conclusions

Identifying the Literature to Review and Evaluate

Conducting extensive searches of the biomedical and epidemiologic peer-reviewed literature on the diseases identified for study yielded about 20,000 potentially relevant

[6] Kilpatrick ME. 2005. Presentation to IOM Committee on Gulf War and Health: Infectious Diseases. Washington, DC.

references. On closer examination, some 1,200 references appeared to provide the requisite types and quality of scientific evidence for this study.

Assessing the Strength of the Evidence

By evaluating the evidence in the published scientific literature, the committee determined the relationships between each of the nine diseases of interest and specific adverse health outcomes that might appear weeks to years after the primary infection. Those relationships are conceived in terms of the strength of association between the primary infection and a specific long-term adverse health outcome.

The committee framed its conclusions in categories, described below, that qualitatively rank the strength of the evidence of an association. Used by many previous IOM committees, including those in the *Gulf War and Health* series, this five-tier framework was adapted from the system used by the International Agency for Research on Cancer to evaluate evidence of the carcinogenicity of various agents.

SUMMARY OF CONCLUSIONS

Sufficient Evidence of a Causal Relationship

> The evidence is sufficient to conclude that there is a causal relationship between exposure to a specific agent and a specific health outcome in humans. The evidence is supported by experimental data and fulfills the guidelines for sufficient evidence of an association (defined below). The evidence must be biologically plausible and must satisfy several of the guidelines used to assess causality, such as strength of association, a dose–response relationship, consistency of association, and a temporal relationship.

The committee concludes that there is sufficient evidence of a causal relationship between

- *Coxiella burnettii* infection (Q fever) and osteomyelitis.
- Malarial infection and
    - Ophthalmologic manifestations, particularly retinal hemorrhage and scarring, recognized for the first time months or years after the infection.
    - Hematologic manifestations weeks or months later, particularly anemia after falciparum malaria and splenic rupture after vivax malaria.
    - Renal disease, especially the nephrotic syndrome that may occur weeks to months after acute infection.
    - Late presentation of disease (*Plasmodium malariae*) or relapse of disease (*Plasmodium ovale or Plasmodium vivax*) months to years after acute infection.
- *Mycobacterium tuberculosis* infection and occurrence of active TB months to decades after infection.

Sufficient Evidence of an Association

> The evidence from available studies is sufficient to conclude that there is an association. A consistent association has been observed between exposure to a specific agent and a specific health outcome in human studies in which chance and bias, including confounding, could be ruled out with reasonable confidence. For example, several high-quality studies report consistent associations and are sufficiently free of bias, including adequate control for confounding.

The committee concludes that there is sufficient evidence of an association between

- Brucellosis and
    - Arthritis and spondylitis; arthritis usually is manifest within 12 months of the acute illness, and spondylitis might be manifest later.
    - Hepatic abnormalities, including granulomatous hepatitis.
    - Chronic meningitis and meningoencephalitis.
    - Uveitis.
    - Orchioepididymitis and infections of the genitourinary system.
    - Cardiovascular, nervous, and respiratory system infections.
- *Campylobacter jejuni* infection and Guillain-Barré syndrome (GBS) if GBS is manifest within 2 months of the infection.
- C*ampylobacter* infection and reactive arthritis (ReA) if ReA is manifest within 3 months of the infection; most cases of ReA are manifest within 1 month of the infection.
- *Coxiella burnetii* infection (Q fever) and
    - Endocarditis years after primary infection.
    - Vascular infection years after primary infection.
    - Chronic hepatitis years after primary infection.
- *Plasmodium malariae* infection and manifestation of immune-complex glomerulonephritis years to decades later.
- *Plasmodium falciparum* infection and recrudescence weeks to months after the primary infection, but only in the case of inadequate therapy.
- Nontyphoid *Salmonella* infection and ReA if ReA is manifest within 3 months of the infection.
- *Shigella* infection and
    - Hemolytic-uremic syndrome (HUS) if HUS is manifest within 1 month of the infection; most cases of HUS are manifest within 10 days of the infection.
    - ReA if ReA is manifest within 3 months of the infection; most cases of ReA are manifest within 1 month of the infection.
- Active TB and long-term adverse health outcomes due to irreversible tissue damage from severe forms of pulmonary and extrapulmonary TB.
- Visceral leishmaniasis (kala-azar) and
    - Delayed presentation of the acute clinical syndrome.
    - Reactivation of visceral leishmaniasis in the context of future immunosuppression.
    - Post-kala-azar dermal leishmaniasis (PKDL) if PKDL occurs generally within 2 years of the initial infection.

- West Nile virus infection and variable physical, functional, or cognitive disability, which may persist for months or years or be permanent.

Limited or Suggestive Evidence of an Association

> The evidence from available studies suggests an association between exposure to a specific agent and a specific health outcome in human studies, but the body of evidence is limited by the inability to rule out chance and bias, including confounding, with confidence. For example, at least one high-quality study reports an association that is sufficiently free of bias, including adequate control for confounding. Other corroborating studies provide support for the association, but they were not sufficiently free of bias, including confounding. Alternatively, several studies of less quality show consistent associations, and the results are probably not due to bias, including confounding.

The committee concludes that there is limited or suggestive evidence of an association between

- Brucellosis and
    - Myelitis-radiculoneuritis, demyelinating meningovascular syndromes, deafness, sensorineural hearing loss, and GBS.
    - Papilledema, optic neuritis, episcleritis, nummular keratitis, and multifocal choroiditis.
    - Fatigue, inattention, amnesia, and depression.
- *Campylobacter jejuni* infection and development of uveitis if uveitis is manifest within 1 month of infection.
- *Coxiella burnetii* infection and post-Q-fever chronic fatigue syndrome years after the primary infection.
- *Plasmodium falciparum* infection and neurologic disease, neuropsychiatric disease, or both months to years after the acute infection.
- *Plasmodium vivax* and *Plasmodium falciparum* infections and demyelinating polyneuropathy and GBS.

Inadequate or Insufficient Evidence to Determine Whether an Association Exists

> The evidence from available studies is of insufficient quantity, quality, or consistency to permit a conclusion regarding the existence of an association between exposure to a specific agent and a specific health outcome in humans.

For some potential long-term adverse health outcomes of the nine identified diseases, the evidence of an association is inadequate, insufficient, or both. The committee presents these potential long-term adverse health outcomes and their characteristics in tabular form in the body of the report.

Limited or Suggestive Evidence of No Association

> Evidence from well-conducted studies is consistent in not showing an association between exposure to a specific agent and a specific health outcome after exposure of any magnitude. A conclusion of no association is inevitably limited to the conditions, magnitudes of exposure, and length of observation in the available studies. The possibility of a very small increase in risk after exposure cannot be excluded.

For many potential long-term adverse health outcomes of the nine identified diseases, there is no evidence of an association. In this report, the committee focused on identifying positive associations between specific infectious diseases and specific long-term adverse health outcomes and did not present the numerous long-term adverse health outcomes for which there is no association.

DEPARTMENT OF DEFENSE POLICIES ON TUBERCULIN SKIN TESTING AND PREDEPLOYMENT AND POSTDEPLOYMENT SERUM COLLECTION

Each branch of the US military has polices regarding tuberculin skin testing and treatment of latent TB infection (LTBI). The most effective way to mitigate TB transmission and activation is to identify and treat for LTBI. In addition, the only way to determine whether military personnel and reservists have become infected with *M. tuberculosis* during their service is to test all personnel for TB shortly before and after deployment. Such testing would make it possible to trace cases of active TB to periods of military service if that is when infection occurred.

Department of Defense (DOD) policy specifies that predeployment serum specimens for medical examinations will routinely be collected within 1 year of deployment and that postdeployment serum specimens for medical examinations will be collected no later than 30 days after arrival at the demobilization site, home station, or in-patient medical treatment facility. The committee agrees with DOD's overall policy regarding collection and use of serum specimens. However, for banked serum specimens to be most useful for determining whether infectious exposures occurred during deployment, the predeployment specimens need to be collected before travel. Current policy allows for collection of predeployment serum specimens up to 1 year after deployment. If the collection of serum is not done until after deployment, it would be difficult to ascertain whether any signs of infection found in the "predeployment" specimen are due to exposure during the current deployment or before it.