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Conflict Leishmaniasis

David M. Claborn

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1. Introduction

Conflict and war can have obvious and profound effects on the transmission and severity of infectious diseases. Although poverty is often listed as the most important external influence on disease rates, the impacts of war and conflict are also important and can lead not only to damaged public health infrastructure, displaced populations and disrupted habitats of zoonotic reservoirs and vectors, but also to the economic perturbations that increase poverty rates within affected populations [1]. Sedentary rural populations are particularly vulnerable to the disruptions of conflict due to their limited ability to adapt after the destruction or confiscation of their crops and arable land [2]. After initial losses, limited access to seeds, tools or draft animals also leads to a vicious cycle of decreasing production, resulting in increased starvation and decreased health status. This is complicated even further by dysfunctional distribution caused by lack of transportation and fuel, damaged roadways, road blocks and local violence. Malnutrition is the inevitable result of these disruptions to the food security of affected populations. Children under the age of five are the most vulnerable to nutritional deficits and thus they frequently suffer disproportionately from the effects of violence and conflict. Pregnant and breast-feeding women are also vulnerable to the effects of disrupted food supplies due to their increased nutritional needs. Increases in malnutrition in turn lead to compromised immune systems, leaving individuals susceptible to many conflict-associated infectious diseases.

Populations that are impacted by violence are often forced or choose to leave their traditional family homes to migrate to a safer environment. Public health workers have known for many years that displaced populations are particularly vulnerable to epidemics of infectious disease [3]. This increased vulnerability can be due to a variety of factors including compromised immune systems as a result of malnutrition, decreased sanitation, insufficient housing or protection from disease vectors, exposure to regional diseases to which immigrants have little or no immunity, and other factors. Thus conflict and poverty are related, and can work

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synergistically to increase disease risks in affected populations, especially those that are displaced.

Conflict can also increase disease risk in populations of warfighters (referred to as "soldiers" here even though it is acknowledged that not all warfighters are soldiers). Soldiers often deploy to regions that are endemic for diseases to which they have no previous exposure. As a result of their lack of exposures, the soldiers are often immunologically naïve to the endemic diseases of the areas to which they deploy, rendering them vulnerable to outbreaks of exotic diseases. Although modern militaries often have sophisticated immunization programs, there are no effective vaccines for many diseases of military importance, including malaria, dengue and leishmaniasis. In such situations, the soldiers must rely on other means of protection including strictly enforced hygiene, anti-vector measures, chemoprophylaxis and personal protection such as mosquito netting and repellents. Disease risk to soldiers is especially high during the initial stages of a conflict when the soldiers may live in rudimentary shelters that provide inadequate protection from vectors, vermin and the elements. Food safety, good water quality, and adequate general hygiene are particularly difficult to maintain during this phase of the conflict. As the conflict ages, the soldiers often acquire better housing and protection from the environmental hazards; however, the protracted stresses associated with war fighting, accompanied by more mundane factors such as boredom and separation from families, can also contribute to immune system dysfunctions and increased disease transmission.

Paradoxically, the impact that conflict-associated diseases have on militaries can improve the success of programs to lower the risk of acquiring those diseases. This observation does not imply in any way that wars are beneficial to public health, but only that the efforts that militaries put toward protecting their troops can improve treatment and prevention of those same diseases in other environments free of conflict or war. For instance, the impact of malaria during WWI and the need to acquire more dependable supplies of the anti-malarial quinine stimulated efforts by the U.S. military to develop cheaper synthetic substitutes like meparene and chloroquine. Similarly, the military's use of insecticidal chemicals such as DDT and BHC served as models for subsequent successful civilian programs to control the disease vectors of malaria and dengue. Also, effective vaccines are often developed initially in response to military need. Finally, one of the most effective repellents used as a personal protective measure against mosquitoes and other vectors, N,N-diethy-meta-toluamide or DEET, was developed by the U.S. Army in large part as a result of its experiences with malaria and other vector-borne diseases during WWII [4]. Such developments are direct results of the attention to the disease during military operations in endemic areas, as well as the medical and scientific expertise and relatively large sums of money available to develop disease interventions for the population of soldiers.

Many of these general conclusions about the impact of conflict on disease rates have particular significance to the disease leishmaniasis. This chapter provides a review of conflict leishmaniasis, especially as related to two events: (a) the civil war in Sudan and, (b) recent conflicts in the Middle East involving the militaries of the U.S. and its allies.

1.1. General background on the disease and its vector

Leishmaniasis is a result of a parasitic infection by any of several species of the protozoan *Leishmania.* The parasite genus is somewhat catholic in distribution, infecting up to 12 million people on all continents except Australia and Antarctica [5]. Parasites have been identified in Australia but, to date, have not infected humans, only kangaroos and wallabies [6]. The disease manifests in a variety of pathologies depending on the species of parasite and perhaps other factors, with effects ranging from mild scarring to severe disfiguration to death [7]. Localized cutaneous leishmaniasis usually affects body parts that are typically uncovered such as the face and hands. An initial papule lesion often develops into a circumscribed ulcer that may elicit little pain or itching. However, secondary infections are common. Many smaller lesions of the cutaneous form will self-heal, providing incomplete immunity for the person to further infections with the same parasite species; however, multiple lesions may occur. Diffuse cutaneous leishmaniasis may occur when lesions disseminate and this form of the disease often resembles lepromatous leprosy.

A more severe form of the disease usually associated with infections in the New World is mucocutaneous leishmaniasis. This infection often develops in the nasal septum and can result in severe mutilation of the lip, gums, tonsils, pharynx and palate. Damage may be severe enough to cause death through malnutrition and acute respiratory pneumonia.

The most severe form of the disease is visceral leishmaniasis, or kala-azar. This form is usually fatal if left untreated and most deaths from this disease are due to the visceral form. Victims progress through fevers, malaise, and weight loss that are associated with anemia, hepatome-galy and splenomegaly. Secondary bacterial infections are also common and may lead to tuberculosis, pneumonia or diarrhea; these conditions contribute to the high mortality associated with this form of leishmaniasis.

The *Leishmania* parasites spend part of their development cycles in a variety of reservoirs depending on parasite species. For example, for *L. infantum,* a cause of visceral leishmaniasis, researchers believe the reservoirs are domestic dogs, jackals, foxes and perhaps certain rodents. Conversely, humans are considered to be the reservoir for another parasite associated with visceral leishmaniasis in China, *L. donovani.* [5, 8]. More complete reviews of the various forms of the disease are found in other chapters of this book.

Leishmaniasis is a vector-borne disease and the primary means of transmission from reservoir to host is via the phebotomine sand fly, though there have been reports of transmission by blood transfusion [9]. Common names associated with this insect can be misleading because they are known as 'straw mosquitoes' in some parts of their range even though they are not mosquitoes. Also, non-vector insects, such as certain midges, are sometimes known as sand flies so it is important to understand the difference between this vector and other insects. The phlebotomine sand fly is a small, delicate insect which typically flies in short hops close to the surface of the ground. Knowledge about the larval development sites is incomplete so attempts to control the disease through larval control have been frustrating. The adult sand flies are usually less than 3.5 mm in length and are covered with dense "hairs". When at rest they hold their wings in a characteristic "V" shape over their backs. Only the female sand fly takes a blood

meal as the blood is essential to complete the development of egg batches. Like the male, her primary source of nutrition is carbohydrates from plant juices. The acquisition of the *Leishmania* parasite, then, is incidental to taking blood meals. The sand flies usually feed at night or in the early evening. In the New World, they are mostly encountered near forested environments, often being found near particular types of trees or tree buttresses. However, in the Old World, they are mostly associated with rodent burrows in dry or desert environments. Unlike mosquitoes, the larvae do not develop in water, though they do require a moist, warm environment in which to grow. This explains their association with rodent burrows as this environment provides the organic matter needed for nutrition of the growing larvae as well as a degree of protection from extremes in heat and moisture.

There are no vaccines or chemoprophylactic drugs to prevent leishmaniasis, so any focus on the prevention of the disease is usually associated with preventing the bite of an infective sand fly. Such efforts are obviously impeded when the public health infrastructure is disrupted, including during times of conflict.

2. Literature review

2.1. Civil War in Sudan

The civil war in Sudan that occurred between 1983 and 2005 is often called the Second Sudanese Civil War. It was fought primarily between the central government and a rebel group called the Sudan People's Liberation Army. The causes of the conflict were complex and multiple, having been attributed to ethnic and religious differences between the mostly Moslem north and the non-Moslem south. However, other causes may have also played some role including a long history of internecine strife and colonial reorganization that ignored that history. Whatever, the cause, there is little doubt that nearly two million people died as a result of the war, primarily as a result of violence, famine and disease. The Sudan Civil War had a large impact on civilian populations that were displaced from their traditional homelands and subsequently forced to transit rugged, dangerous environments in search of safer places.

A few years prior to the beginning of the Sudan Civil War, a series of floods occurred in a large stretch of the Western Upper Nile Province which probably contributed to the subsequent epidemic of visceral leishmaniasis. The floods destroyed a large part of the forest in the region and the regrowth of the forest provided what has been described as optimum habitat for the development of the sand fly vector population, supposedly the larval stage of the insect [10]. This proposed initial cause for the introduction of the disease agent and the subsequent epidemic was likely exacerbated greatly by the civil war which displaced large groups of people, many of whom transited the regrowing acacia forests which sheltered the increased vector populations of *Phlebotomus orientalis*, the presumed vector. DeBeer and co-authors described the impact with the following words:

"The continuous civil war has destabilized the agricultural activities, nomadic movements and health services in this region. Likewise, transportation of food from the north and

implementation of health care measures including control of malaria and VL [visceral leishmaniasis] were interrupted. The implication of those deficiencies was clearly reflected in the severe malnutrition signs in the population studied. The combination of these factors may have also contributed in this VL outbreak. Previous studies have shown that VL can be latent for very long periods, acquiring an overt clinical form after exposure to stresses such as malnutrition." [11].

Analysis of the epidemic at that point indicated that of the patients reporting to clinics for a variety of symptoms, 44% had clinical symptoms of VL. As is usual for this disease, males were more likely to be infected probably due to occupational exposures, but younger children and women also exhibited high rates of infection. Subsequent analysis of the epidemic suggested remarkably high death rates among the population of the western Upper Nile Province. The number of deaths between 1984 and1994 was estimated at 100,000 people, which was about a third of the population in that region [12]. Although *Medicin Sans Frontiers* (MSF) provided a free and effective antimonial treatment, access to the MSF clinics was limited by tribal and military conflict in the region. Eventually, MSF was forced to evacuate due to the threat of attack, greatly reducing the opportunities for local populations to receive effective treatment. Another study of the epidemic estimated the death rate at approximately 38-57% [13]

The Middle East and nearby regions have also experienced mass movement of populations and growth of refugee populations due to military conflict and civil disruptions; these disruptions also appear to have contributed to increased rates of cutaneous leishmaniasis transmission. However, increased disease rates are not always among refugee populations displaced by conflict. For instance, prevalence of cutaneous leishmaniasis, usually *L. major*, among the general civilian population of Israel is estimated at about 3/100,000, but in the population of Israeli soldiers, the rates may be as high as 196/100,000. This remarkable difference is thought to be the result of exposures during exercises in the desert and the soldiers' practice of resting on top of raised animal burrows where both the rodent reservoir and the sand fly vector are abundant [14]. More typically, perhaps, rates of infantile visceral leishmaniasis in the West Bank have reportedly increased due to the re-emergence of the golden jackal as a reservoir in the region.

Leishmaniasis is also endemic to the Khyber Pakhtunkhwa region of Pakistan where a conflict with insurgents has been continuing for several years. Cutaneous leishmaniasis is common among soldiers there, though more common in those from certain regions of the country, especially central Punjab. The reason for the higher rates in these Punjab soldiers is not known, but some have speculated that it is due to the lack of immunity among these soldiers due their lack of exposure in their home district [15].

Conversely, cutaneous leishmaniasis is very much endemic to Syria and the recent civil war in that region appears to have contributed to increased transmission in that country. The number of cases on an annual basis averages about 22,000; however, the conflict appears to be increasing disease transmission in some of the rural areas. Some small towns are reporting infection rates as high as 25%. These rates are being reported in new ways; so-called "doctor-activists" are using social media to document and warn of disease outbreaks in various parts

of Syria. In one case, 125 out of 450 students in a local school were infected as reported through the social media [16]. The reliability of such reports has not, as yet, been documented.

Thus, conflict in regions endemic for leishmaniasis appears to affect disease transmission rates and occurrence. The increase in disease rates can be linked to population displacement, compromised infrastructure like housing, and disruption of healthcare and public health services. Efforts to provide effective treatment of disease victims are often impeded by local violence and lack of transportation.

2.2. Western military experience with leishmaniasis in the Middle East

There were thousands of cases of leishmaniasis among American and European soldiers during WWII with most of them originating in the Middle East, so it was no surprise that the disease would become an issue when coalition forces returned to the Arabian peninsula in 1990 for Operations Desert Shield and Desert Storm (aka the Gulf War or the First Gulf War). There were 20 cases of cutaneous leishmaniasis reported among American soldiers, but medical personnel were surprised by the emergence of viscerotropic *L. tropica*, a species of the parasite that usually elicited cutaneous disease. There were 12 cases of viscerotropic leishmaniasis among Americans and this development started a search for new methods of diagnosis and treatment of the disease [5]. It should be noted that the American military actually had quite a bit of experience with leishmaniasis in another setting, that is, Central America; however, the disease ecology, vector biology and the parasite species were very different in that region as compared to those in the Middle East. One of the repercussions of these infections was that veterans of the campaign were barred from donating blood for many months after deployment. However, the extent of the outbreak among American soldiers was limited, due in part to the timing of the operation and the areas in which most of the troops were housed during the buildup stages prior to the short war. In addition, all of the services established extensive preventive medicine programs that utilized topical repellents, clothing treatments, vector control and public education to reduce the risk to military personnel deployed to the region. (Toward full disclosure, the author was a U.S. Navy medical entomologist stationed with a Marine Corps unit in eastern Saudi Arabia during that conflict.)

When the U.S. military returned to the region in large numbers in 2003 for Operation Iraqi Freedom, military units almost immediately experienced an outbreak of cutaneous leishmaniasis. In early 2004, over 500 cases had been diagnosed among American servicemen. Concurrently, two cases of visceral leishmaniasis were diagnosed in Americans deployed to Afghanistan [17]. By late November of the same year, nearly 1200 cases had been reported [18]. The extent of this early outbreak was attributed to high levels of exposure to the vector during the early, mobile stages of the war. Soldiers often slept outside or in relatively primitive housing, mostly tentage. With time, better tents or relatively permanent buildings with insect-excluding screens, even air conditioning, provided much better protection and led directly to decreased disease rates. Also, vector control efforts were increased and improved as units settled into semi-permanent cantonment areas. Particularly important to improvement in the efficacy of vector control was field research on the biology of the local vector and the efficacy of different potential control methods.

Both disease prevention and disease treatment benefited from the increased attention paid to leishmaniasis by military medical authorities as a result of the conflict in Iraq. Early in the conflict, military medical personnel sought to define appropriate treatments and, given the possibility that cutaneous lesions might heal without treatment, to provide standardized guidelines on the decision to treat or not to treat [19]. Treatment of Old World cutaneous leishmaniasis was considered justified if lesions were present on the face, ears or other cosmetically sensitive areas, if the lesions persisted for many months, if the lesions spread over the fingers, the wrist, the elbow or other joints, or if lesions occurred on the hands or feet where the risk of secondary infection was increased. Treatment was also justified if there was evidence of dissemination or if sores occurred on a patient with an impaired immune system. At that stage in the conflict, treatment for Old World cutaneous leishmaniasis included the following:

1. curettage, or removal of all inflamed tissues;

2. cryotherapy using liquid nitrogen;

3. local heat therapy;

4. treatment with topical creams, some including paromomycin or SNAP (S-nitro-N-acetypenicillamine);

5. intralesional injection of pentavalent antimony'

6. various oral medications; and others.

Medical authorities in the U.S. military identified a need for improved treatment of leishmaniasis, noting the "optimal treatment for the localized infection has not been identified." [20]. Noting that the parasite was thermosenstive, the researchers compared a heat therapy technique to a standard treatment of intravenous sodium stibogluconate for treatment of cutaneous *L. major* infections. They noted similar rates of cure between both but also noted the patients treated with thermal treatments exhibited fewer toxic side effects. Many other alternative therapies and short-course treatments were investigated.

Also subsequent to military experience with leishmaniasis was concern regarding the infection of the blood supply with viable parasites. After Operations Desert Shield and Desert Storm, researchers with the Walter Reed Institute of Research investigated the survivability of *Leishmania* parasites under blood bank storage conditions, concluding that *L. tropica* and *L. dovovani* were a risk to the blood supply for at least 25 days post-donation [21]. As a result of these and other findings, military veterans of Desert Shield and Desert Storm were banned from donating blood for several months. The military experience with *Leishmania* parasites, as well as more recent transfusion-associated transmission, have brought greater attention to this issue and have led to more research on methods to detect and eliminate contamination of blood bank products. In Spain, a country endemic for leishmaniasis, it was noted that there was no suitable screening test to identify the parasite in donor blood and that the only preventive measure available to prevent transfusion of viable parasites was the donor selection criteria; however, some research on methods to inactivate the parasites was underway [22].

A great deal of knowledge about preventing leishmaniasis has become available as a result of military experience with the disease. In an exhaustive series of papers on the importance,

biology and control of the vector, Coleman and co-authors identified several issues that were directly applied to control of leishmaniasis in Iraq [23, 24, 25]. Important findings in this series included:

1. Air conditioning reduced the number of sand flies inside a tent by up to 83%;

2. Sand flies in the region were more active in early evening during cooler months, but changed during warmer months to peak activity in the middle of the night;

3. Lights could be used to improve the effectiveness of various traps for surveillance of the vector;

4. PCR techniques could be utilized to identify the probable vector of leishmaniasis for a given region.

These and other practical findings enabled military preventive medicine personnel to establish an effective leishmaniasis control program based on improved housing, targeted use of pesticides, expanded use of repellents, public education and effective vector surveillance. Many elements of this and similar programs have been implemented in the civilian environment and in other militaries, sometimes with mixed effects. One part of the U.S. Army's personal protection regimen that is heavily emphasized is the use of permethrin-treated uniforms. The permethrin serves as a contact irritant and has been shown to be effective against many vectors. In one such study in Iran, soldiers were placed in leishmaniasis-endemic areas either with or without permethrin-treated uniforms and forbidden to use topical repellents. There was not a statistical difference in the rate of disease incidence between the two groups, leading the researchers to conclude that permethrin-treated uniforms were not effective for prevention of cutaneous leishmaniasis [26]. This finding is not surprising given that permethrin is not a spatial repellent and would not be effective in preventing the sand flies from biting on exposed skin. Conversely, Egyptian and U.S. Navy researchers tested commonly used insecticides on cotton duck and vinyl military tent surfaces for efficacy against sand flies, noting that insecticides on vinyl surfaces exhibited lower toxicities to the flies as well as shorter periods of efficacy [27].

The practical findings from the entomological research that was initiated because of the war in Iraq have been applied in endemic areas, especially after disasters and inside refugee camps. These environments resemble those of military campaigns in that large numbers of people are subjected to the elements while residing in emergency housing (tents) that is often less than adequate.

3. Conclusions

Conflicts often result in significant displacements of large populations, both civilian and military. These displacements and the accompanying violence often lead to breakdowns in infection control in medical care facilities, disruption of public health and disease control programs, reduced access to populations in need, and greater exposure to vectors and

environmental hazards [28]. All of these issues have application to the disease leishmaniasis. Public health and clinical workers in endemic areas should be aware of the increased risk of disease in the conflict environment, whether that conflict be a civil war, internecine strife, or a declared international conflict.

Of utmost importance in such environments is the establishment of effective disease surveillance, especially among the vulnerable population of impoverished or displaced persons. Surveillance systems are notoriously weak in conflict environments [28]. As a result, detection and reporting of outbreaks and epidemics are often delayed or even non-existent. This may be due to the absence of laboratory facilities or the lack of expertise required to collect, process and identify specimens. Vector surveillance programs can also be important in identifying locales where disease transmission risk is particularly high, but lack of access to the populations at risk and to the surrounding environment may prevent any meaningful surveillance. The data from such surveillance programs are essential to the allocation of limited resources for control of several diseases associated with disrupted environments, including leishmaniasis, but if such allocation is impossible due to the conflict, the options for disease control are very limited.

It is well-known that many military forces voluntarily implement public health assistance for conflict-affected population. In addition, the militaries may spend a great deal of time researching effective prevention and treatment of disease among their own soldier population. These efforts often have application outside the originally military funding the research. Although certain benefits can be realized from increased awareness of disease effects as a result of foreign military presence in an endemic locale, in most instances it would be difficult to contend that the local populations see benefits in public health and disease control as a result of conflict. These general remarks have particular application to the disease called leishmaniasis.

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