

Issue Summary
Blood Products Advisory Committee Meeting
December 11, 2003
Gaithersburg, MD

Topic: Potential recommendation on blood donor deferral for Leishmaniasis and exposure to *Leishmania*

Issue: FDA seeks the opinion of the committee on our current thinking on recommending donor deferral for leishmaniasis and exposure to *Leishmania*.

Background:

Leishmaniasis is a disease caused by numerous species of the intracellular protozoan parasite, *Leishmania*. The parasites are found in blood cells of the monocyte/macrophage lineage of the infected host and some are extracellular in the blood as the infection spreads from one macrophage to another. As a group, *Leishmania* cause a spectrum of disease in humans that ranges from self-healing cutaneous lesions to visceral infections that may be fatal if not treated [1]. Treatments are available, but there are significant toxicities, may require i.v. administration for at least 20 days and there is a growing problem with drug resistant strains of the parasite.

The *Leishmania* are primarily endemic to the subtropical and tropical areas of the Middle East, Asia, Africa, Central America and South America and the Mediterranean Coast of Europe [1]. The parasite is transmitted to humans through the bite of a *Leishmania*-infected sand fly. The incubation period can vary from days to years, but clinically evident infections generally appear within months of infection [1]. After the resolution of clinical signs and symptoms, the parasite can remain at a chronic low level, potentially for the patient's lifetime [1].

Less than 15 probable or confirmed transfusion transmitted leishmaniasis cases have been reported [2-8]. In all cases, the species of *Leishmania* identified was either *L. donovani* or *L. infantum*, which cause visceral disease. There is no FDA approved test available to screen donated blood for the presence of *Leishmania* or past exposure to *Leishmania* infection. Therefore, donor deferral is the only protection against *Leishmania* transmission. However, there is no FDA recommendation for the deferral for history of leishmaniasis or potential exposure to *Leishmania* transmission. The endemic areas for leishmaniasis largely overlap with malaria, which is already a deferral, so the most important areas to identify in considering a leishmaniasis deferral policy are those where leishmaniasis, but not malaria is endemic.

The issue of transfusion transmission of leishmaniasis was recently brought to the fore by the stationing of a large U.S. military force as well as associated civilian personnel in Iraq and Afghanistan, endemic areas for the disease. The Department of Defense reports that living conditions in Iraq are ripe for *Leishmania* transmission. DoD reports at least 31* cases of cutaneous leishmaniasis have been diagnosed among the troops [9]. Beginning Oct. 30, 2003, the Armed Services Blood Program Office requires a 1-year deferral of all donors who have traveled to or resided in Iraq in addition to the

* This number, increasing weekly, will be updated in the presentation

existing DoD policy of permanent deferral for a diagnosed case of leishmaniasis. DOD did not extend the donor deferral policy for leishmaniasis to Afghanistan because it is covered under malaria deferral. The AABB released a bulletin advising member organizations to implement a one-year deferral policy focused on Iraq effective Oct. 30, 2003 [10]. After the Gulf war in 1991, DoD and AABB issued advisories recommending deferral for returning soldiers because some were diagnosed with the visceral form of leishmaniasis caused by *L. tropica*, previously thought only to cause cutaneous disease [11]. This policy was rescinded Dec. 30, 1992, because there had been no new reported cases of leishmaniasis.

A draft guidance document would initiate the process for formulation of FDA's recommendation for deferral for leishmaniasis with the intention to make the recommendation applicable to civilian donors, who are exposed to *Leishmania*.

Current thinking:

FDA would like the committee to discuss the scientific merit and public health benefit of donor deferral for exposure to *Leishmania* based on the following current thinking of the agency.

The evidence that an infected individual harbors the parasite for life even after recovery from clinical symptoms [12, 13] is strong enough that FDA would recommend that individuals with diagnosed infections be permanently deferred. Though the documented cases of transfusion transmission have all been due to parasites associated with visceral disease, FDA would recommend the permanent deferral apply to cutaneous disease also. FDA would recommend that the cutaneous form of the disease be included in the deferral; first because there is a theoretical possibility of transmission (parasites have been detected in circulating blood of patients with cutaneous disease and parasites associated with cutaneous disease have been shown to visceralize under certain circumstances [11]); second because the number of individuals with leishmaniasis entering the US is likely quite small, therefore not severely impacting the blood supply. As examples of observed rates of disease, in Operation Desert Storm, 1990-1991, there were 12 visceral and 20 cutaneous cases reported out of 697,000 deployed military personnel [9] and in the current deployments in Iraq and Afghanistan, 31* confirmed cutaneous and no visceral infections [9] out of approximately 150,000 deployed.

A recommended deferral of one year from the last date of departure from Iraq for travelers is warranted at this time because of the large number of potential U.S. donors deployed there, the unique living conditions of potential U.S. blood donors in the country, such as lack of permanent housing, which increase the risk of *Leishmania* transmission [14], and the previous demonstration that *Leishmania* species in that area associated with cutaneous disease can visceralize [11]. FDA would recommend that one year is an adequate length of time for deferral because symptoms of infection usually appear within months of being bitten [1]. Individuals who develop symptoms will be permanently deferred, while the individuals who don't develop symptoms can reenter the donor pool. We recognize that this deferral period will not prevent donations by rare, asymptomatic, chronic carriers, although scientific evidence of such carriers among travelers not previously exposed to *Leishmania* is equivocal.

FDA is not recommending deferral for travel to or immigration from other endemic countries nor immigration from Iraq at this time because the impact on the blood supply would be greater than the current level of risk of transfusion transmission. A preliminary estimate suggests that the blood supply might be reduced by approximately 4% if such a deferral were recommended, while the benefit of risk reduction might be minimal. The main evidence that the risk is low is the absence of reported cases of transfusion transmission of *Leishmania* in the U.S. while there has been recommended deferral for only a brief period after Operation Desert Storm. Additionally, the number of deferrals would exceed the risk because active transmission primarily occurs in limited areas of the endemic countries, such as the eastern part of India or along the Mediterranean coast of Spain and France. A recommendation restricting the deferral to certain areas, as opposed to entire countries, is not supportable at this time because it would be difficult to implement, spatial distribution of the endemic areas is poorly documented and can change over time. The impact of a leishmaniasis deferral would be lessened somewhat because the endemic countries largely overlap with malaria areas. Of the 88 countries that the WHO identifies as endemic for leishmaniasis, all but approximately 20 are also endemic for malaria. Currently travelers to malaria areas are deferred for one year and immigrants 3 years. However, the malaria deferral is for travel to areas considered endemic for the disease meaning that individuals are allowed to donate who have traveled to a country that is endemic for malaria, if they have not entered the areas where malaria transmission occurs [15]. Therefore, some of the travelers to malaria endemic countries would also need to be considered separately for leishmaniasis, if there were a leishmaniasis deferral, making implementation difficult. Finally, the impact on the blood supply of a one-year recommended deferral applied to all leishmaniasis endemic countries depends on the number of travelers and immigrants from those 20 or more countries. Estimates of this impact are high enough that the increase in blood safety from a leishmaniasis deferral recommendation is not considered justified unless the recommended deferral can be focused on specific high-risk areas.

The FDA in consultation with the Centers for Disease Control and Prevention will consider further modifications to the deferral recommendations if there are major changes in the rate of transmission of the disease or changes in the number of potential U.S. donors that are exposed in other endemic countries. Implementation of a standing deferral recommendation could be possible if there were a resource, directly available to the blood collectors, giving current information on the specific areas with a high rate of transmission of *Leishmania*. If funds were invested in a web-based resource recommending that deferral to be restricted to only those areas with the highest risk of transmission, the number of deferrals could be kept low enough to balance the impact on the blood supply with the estimated risk of disease transmission.

Questions for the Committee

1. *Does the committee agree that a recommendation for lifetime deferral for history of any type of leishmaniasis is appropriate?*
2. *Does the committee agree that a one-year deferral recommendation for travel to Iraq is appropriate at this time?*

3. Does the committee agree that a recommendation for donor deferral for travel to *Leishmania* endemic areas other than Iraq is not appropriate at this time?
4. Does the committee agree that a recommendation for donor deferral for immigration from any *Leishmania* endemic area is not appropriate at this time?

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