

Summary of the Sixth Meeting of the ITFDE (II) **March 24, 2004**

This sixth meeting of the International Task Force for Disease Eradication (ITFDE) was convened at The Carter Center from 9 a.m. to 3:30 p.m. on March 24, 2004. The Task Force reviewed the status of efforts to control visceral leishmaniasis (kala azar) and hookworm disease.

The Task Force members are: Sir George Alleyne, Pan American Health Organization (PAHO); Dr. Pascal Villeneuve, UNICEF; Dr. Robert Hecht, The World Bank; Dr. Julie Gerberding, Centers for Disease Control and Prevention (CDC); Dr. David Heymann, World Health Organization (WHO); Dr. Donald Hopkins, The Carter Center; Dr. Adetokunbo Lucas, Nigeria; Professor David Molyneux, Liverpool School of Tropical Medicine; Dr. Mark Rosenberg, Task Force for Child Survival and Development; Dr. Harrison Spencer, Association of Schools of Public Health; Dr. Dyann Wirth, Harvard School of Public Health, and Dr. Yoichi Yamagata, Japan International Cooperation Agency (JICA). Four of the Task Force members (Heymann, Hopkins, Lucas, Yamagata) attended this meeting, and two others were represented by alternates (Dr. Richard Jackson for Gerberding, and Dr. Jean-Marie Okwo-Bele for Villeneuve). Resource persons attending this meeting were Dr. James Maguire of CDC, and Dr. Arif Munir of the Ministry of Health of Pakistan.

Visceral Leishmaniasis (kala azar)

The presentations on visceral leishmaniasis were given by Dr. Philippe Desjeux of the World Health Organization and Dr. Caryn Bern of the Centers for Disease Control and Prevention.

Visceral leishmaniasis (VL, kala azar) is caused by infection with the parasite *Leishmaniasis donovani* or *L. infantum*, which are transmitted by bites of sand flies. Ninety percent of all cases are found in only five countries: Brazil, Sudan, India, Nepal and Bangladesh. An entirely anthroponotic form (AVL), which is the origin of the most deadly epidemics, and for which humans are the only reservoir host, occurs mostly in Bangladesh, India, Nepal and Sudan. The more common zoonotic form (ZVL), for which dogs are the most important animal reservoir, is most endemic in Brazil. About 62 countries in Africa, Asia and Latin America are endemic for one or both forms of the disease. Some 200 million persons are at risk of the infection, and an estimated 500,000 persons acquire the disease annually. Migration, urbanization, malnutrition and poverty are among the increasing risk factors for this disease. The disease is a major economic burden on affected households.

Visceral leishmaniasis is typically manifest in humans by weight loss, enlarged spleen, liver and lymph nodes, and anemia, progressing to death if untreated. Post kala-azar

dermal leishmaniasis (PKDL) may occur following treatment; PKDL patients are very infective to sand fly vectors. Another increasing complication is co-infection with HIV, wherein both infections exacerbate each other. Until recently, diagnosis and treatment of visceral leishmaniasis were very difficult. Some resistance to drugs commonly used for treatment is being experienced, especially among patients in India. Resistance is believed to be uncommon elsewhere, but systematic surveillance for drug resistance is lacking. Residual insecticide spraying of homes has been an important intervention. Just as dramatic reductions in this infection followed extensive spraying inside homes to combat malaria in former years, cessation of such spraying has led to equally dramatic epidemics of kala azar more recently.

There have been several important developments pertaining to control of visceral leishmaniasis since the earlier International Task Force for Disease Eradication reviewed this disease a decade ago. The most important negative development is the widespread emergence of HIV infections and their adverse interaction with VL in co-infected individuals. Recognition of the serious synergy of anemia from VL with anemia caused by malaria, hookworm and/or HIV infection has also come to prominence in the interim. Among the positive developments are the availability of a convenient dipstick field diagnostic test, recent availability of the first oral treatment (miltefosine, given over four weeks, currently in phase IV trials; the completion of phase III clinical trials for paramomycin) for VL, and promotion of impregnated bed nets for prevention of malaria, which also prevent sand fly bites.

The Government of India has recently committed to “eliminate” AVL in India by 2010, although adequate baseline data about the extent and prevalence of the infection in India are not yet available.

Conclusions and Recommendations

1. Anthroponotic visceral leishmaniasis (AVL) might in theory be eradicable, but eradication is not assured because parasites are thought to remain after clinical cure, the parasitic infection interacts with HIV co-infections, and because post-kala azar dermal leishmaniasis (PKDL) patients can act as a parasite reservoir in inter-epidemic periods. The zoonotic form of the disease is not eradicable.
2. Among the important needs to improve control of this disease: are improved surveillance systems for disease and for drug resistance, better drug supply and delivery systems, better understanding of risk factors for transmission of the disease, and more knowledge about breeding sites of the sand fly vectors and the potential for control measures targeting the larval stage.
3. Further refinement of improved diagnostic tests and tools for better case management are needed.
4. Well-documented demonstrations of the impact of application of existing control measures, including active VL and PKDL case detection, rapid diagnosis and effective case management, focused vector control (taking advantage of overlap with

malaria control measures where possible) and systematic health education are also indicated.

5. Research priorities include the need for thorough epidemiologic investigations in endemic areas, studies of sand fly entomology, including molecular biology, systematic investigations of the interfaces of host/parasite/vector, and search for a vaccine, but with emphasis on knowledge that is practical and has the potential to yield near-term benefits.
6. Advocates should use this report and other ammunition to publicize that VL is another important disease of poverty, a risk for fatal epidemics, and a potent threat to human security at personal, familial and community levels.

Hookworm

This presentation was given by Dr. Peter Hotez of The George Washington University and Sabin Vaccine Institute.

Hookworm infections are caused primarily by *Necator americanus* and secondarily by *Ancylostoma duodenale*. These parasites thrive in soil that has been contaminated with feces from infected persons. They penetrate skin that is exposed to the contaminated soil. An estimated 740 million people are infected, with some 10,000 persons dying annually as a result. The burden of this disease and associated anemia falls heavily on children and adults, especially women of reproductive age. Peak hookworm intensity often occurs in adults; in some cases intensity increases with age. Hookworm is now thought to be the most debilitating of the “unholy trinity” of soil-transmitted helminths, which also includes ascariasis and trichuriasis. Anemia due to hookworm infection often overlaps with anemia due to malaria, and anemia facilitates the progression of AIDS/HIV infection. The two existing DALY (Disability Adjusted Life Years) estimates for hookworm infection, both of which are quoted by the WHO, differ markedly (1.8 million and 22 million). This likely reflects the difficulties in assigning disability weights to physical and mental retardation, reduction in school attendance and work efficiency, etc. Other recent revelations are that nursing infants may be infected via breast milk, and that wearing shoes is not an important intervention, as it was long thought to be (because the parasites still penetrate other exposed skin surfaces, and *Ancylostoma* are also infective orally). Humans are the only known reservoir of *Ancylostoma duodenale* and *Necator americanus*.

Currently available interventions include anthelmintic chemotherapy with benzimidazoles (mebendazole, albendazole) and improved sanitation. In certain circumstances, school-based mass de-worming treatments are advocated, but the impact of this disease is also manifest among pre-school children as well as among adults long past school age, and transmission normally occurs in the community, not in the schools. In addition, high rates of post-treatment re-infection occur in areas of high hookworm transmission. Therefore the long-term effects of anthelmintic chemotherapy on hookworm control are uncertain. Annual mass administration of albendazole (with

Mectizan) to entire communities to interrupt transmission of lymphatic filariasis in Africa could be having a significant effect on hookworm morbidity, but this is so far un-assessed.

The Bill & Melinda Gates Foundation is supporting work towards development of a vaccine to prevent hookworm infection and re-infection. Phase 1 trials are expected to begin in the United States by the end of 2004, and Phase 1-2a trials in Brazil in 2005/6.

Conclusions and Recommendations

1. Hookworm disease cannot now be eradicated, given its ubiquity and the interventions that are currently available, but new tools and understanding make better control possible.
2. Operational research is needed to demonstrate the impact of all currently available interventions, including systematic health education, mass chemotherapy, and improved sanitation, at national and regional levels.
3. Research is needed to monitor the impact of mass de-worming activities on the health of target populations and on transmission of the disease.
4. Operational research is also needed to evaluate ways to sustain interventions, particularly periodic de-worming.
5. Monitoring for hookworm resistance to albendazole is needed, especially in Africa.
6. Developing a vaccine to prevent hookworm infection appears to be technically feasible, and a first-generation anti-hookworm vaccine is under development. Such a vaccine could help reduce the disease burden and impact of hookworm, as well as its effects on the economy and on school attendance.

Drs. David Heymann and Donald Hopkins gave brief updates on the latest status of polio eradication and dracunculiasis eradication, respectively.

During the final half-hour of the meeting, members of the Task Force summarized the results of this meeting's deliberations for Dr. David Brandling-Bennett of the Bill & Melinda Gates Foundation, in a conference telephone call. Dr. Brandling-Bennett, who participated in several previous meetings of this Task Force as an alternate for Sir George Alleyne of the Pan American Health Organization, underscored the relationship between the two diseases discussed at this meeting and the poverty and weak primary health systems in many countries. The Gates Foundation is just completing a strategic plan, and it is supporting research on a vaccine against hookworm. The Foundation is seeking to identify technologies on which it can focus, as well as ways to promote more integrated approaches to disease control.