# Summary of the Tenth Meeting of the ITFDE (II)
# January 11, 2007

The Tenth Meeting of the International Task Force for Disease Eradication (ITFDE) was convened at The Carter Center from 8:30am to 3:30pm on January 11, 2007. The Task Force reviewed the status of evidence pertaining to the potential eradicability of onchocerciasis (river blindness), five years after the Conference on the Eradicability of Onchocerciasis met at The Carter Center in January 2002.

The Task Force members are Dr. Olusoji Adeyi, The World Bank; Sir George Alleyne, Johns Hopkins University; Dr. Julie Gerberding, Centers for Disease Control and Prevention (CDC); Dr. David Heymann, World Health Organization (WHO); Dr. Donald Hopkins, The Carter Center (Chair); Dr. Adetokunbo Lucas, Harvard University; 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. Pascal Villeneuve, UNICEF; Dr. Dyann Wirth, Harvard School of Public Health, and Dr. Yoichi Yamagata, Japan International Cooperation Agency (JICA). Five of the Task Force members (Hopkins, Lucas, Molyneux, Spencer, Wirth) attended this meeting, and four others were represented by an alternate (Dr. Ousmane Bangoura for Adeyi, Dr. Kayode Oyegbite for Villeneuve, Dr. Lorenzo Savioli for Heymann, Dr. Mike St. Louis for Gerberding).

Presenters at this meeting included Dr. Boakye Boatin of the World Health Organization; Dr. Ousmane Bangoura, The World Bank; Dr. Edward Cupp, Auburn University (retired); Dr. Achim Hoerauf, University Clinic Bonn; Dr. David Molyneux, Liverpool School of Tropical Medicine/ITFDE Member; Dr. Richard Ndyomugyenyi, Ministry of Health/Uganda; Dr. Eric Ottesen, Lymphatic Filariasis Support Center; Dr. Frank Richards, The Carter Center River Blindness Program, and Dr. Mauricio Sauerbrey, Onchocerciasis Elimination Program of the Americas.

## Onchocerciasis

In January 2002, the Conference on the Eradicability of Onchocerciasis concluded that onchocerciasis was not eradicable in Africa, using available tools, but that the disease could be eliminated in the Americas.[1] The conference strongly recommended that everything be done to preserve the gains of the Onchocerciasis Control Program (which closed later that year) and that elimination efforts should be undertaken in Africa in isolated foci where it was technically feasible to do so. The conference also recommended further research into the impact of ivermectin, potential macrofilaricidal drugs, alternative delivery strategies, better diagnostic tools, and mathematical modeling.

Important developments since the previous conference include the realization that up to 37 or 40 million persons may be infected with onchocerciasis compared to the 18 million

[1] Dadzie Y, Neira M and Hopkins D. Final Report of the Conference on the Eradicability of Onchocerciasis. *Filarial Journal* 2003:2

estimated to have been infected earlier, as a result of studies in newly accessed areas of countries such as the Democratic Republic of Congo (DRC). Other notable improvements in the interim include political settlements and much less insecurity in Angola, Liberia, Sierra Leone, and southern Sudan. However, health systems are still very weak in the affected African countries.

The Onchocerciasis Control Program (OCP) ended in December 2002, having protected 40 million persons in 11 West African countries between 1974 and 2002. Vector control by aerial larviciding, and later mass administration of ivermectin (Mectizan®, donated by Merck & Co.) annually to populations in hyper- and meso-endemic villages interrupted transmission in many areas. However, transmission continues in certain Special Intervention Zones in parts of Guinea, Sierra Leone, Ghana, Togo and Benin, where Mectizan® is now being distributed annually or semi-annually, and with ground larviciding in a few of those areas. The current situation is uncertain in Cote d'Ivoire and Guinea Bissau, which have had no interventions since 2002 due to insecurity.

The African Program for Onchocerciasis Control (APOC), which began in 1995, treated 40 million persons with Mectizan® in hyper- and meso-endemic villages in 16 countries in 2005, and aims to treat 90 million persons annually in 19 countries by 2015. Progress is satisfactory in 9 countries, unsatisfactory in 7 countries, and initiation is still delayed in 3 other countries due to insecurity, while the need to make annual drug delivery sustainable by 2015 or before is a big challenge for all. APOC is supporting four vector elimination projects in Uganda, Equatorial Guinea and Tanzania. These vector elimination efforts have been generally successful, especially those in Uganda, in which transmission has apparently been completely eliminated. APOC has also assumed responsibility for oversight and monitoring of former OCP areas, including the Special Intervention Zones, as well as for mass drug administration in Liberia and Sierra Leone, but inadequate surveillance for recrudescence of onchocerciasis is a problem in several key areas outside of the Special Intervention Zones, and surveillance for the emergence of parasite resistance to Mectizan® is limited.

Potentially life-threatening complications from treatment with Mectizan® in persons with heavy concurrent *Loa loa* infections have posed problems in Cameroon and the Democratic Republic of Congo especially, and are a serious constraint on mass drug administration for onchocerciasis in several other countries where loiasis is co-endemic. All of the APOC and former OCP countries are also co-endemic for lymphatic filariasis (LF), which has been the target of an elimination program since 2000, in which about 28 million persons in 11 African countries received annual mass treatment with Mectizan® and albendazole in 2005. The estimated number of persons at risk for LF in the WHO (AFRO) region is 212.4 million.[2] In some areas, the LF program is administering both drugs in onchocerciasis communities, including those that are hypo-endemic for onchocerciasis and thus were not receiving drug treatment under APOC. The LF program is similarly (if not more severely) hampered by co-endemic *Loa loa*.

[2] World Health Organization, 2005. Global Programme to Eliminate Lymphatic Filariasis: Progress report for 2004. *Weekly Epidemiological Report* 80(23): 201-212.

Since 1993, the Onchocericasis Elimination Program of the Americas (OEPA) has coordinated and helped support semi-annual mass administration of Mectizan® in 13 foci of 6 countries (Brazil, Colombia, Ecuador, Guatemala, Mexico, and Venezuela). As of 2006, it appears that new cases of blindness caused by onchocerciasis are no longer occurring and 8 of the 13 foci are believed to have interrupted transmission of *Onchocerca volvulus*, and one (Guatemala's Santa Rosa focus) has eliminated the parasite and will become the first to halt mass treatments in 2007. Others, including Colombia's single focus in Naiciona, may follow the Santa Rosa example in 2007 or 2008. In foci where transmission continues, the focus in southern Venezuela achieved >85% coverage for the first time, thus becoming the last of the foci to achieve that important milestone (the 12 other foci each have had 7-11 treatment rounds >85%). The South Chiapas focus in Mexico has administered Mectizan® four times per year in 50 of its highest endemic communities since 2003, as part of a trial aimed at hastening interruption of transmission by killing adult worms. The Rio Cayapas sector of the Ecuadorian focus, where *Simulium exigium* is similarly as efficient as a vector as *S. damnosum* in Africa, began with annual mass treatments but switched to semi-annual mass treatments in 1998, and now appears close to interrupting transmission.

A review of the macrofilaricidal effects of Mectizan® on *Onchocerca volvulus*, based on re-analysis of peer-reviewed literature describing results from Africa and Latin America, noted the importance of measuring Mectizan® macrofilaricidal impact in the settings where transmission generally is interrupted (a 'closed system'). The evidence suggests that Mectizan®, 150ug/kg twice per year would eliminate adult female worms in 6.5 years, and four times per year treatment would eliminate the adult female worms in about 5 years. It thus appears that multiple mass treatments each year accelerate the deaths of adult male and female *O.volvulus* in comparison with their natural rates of death when vector control eliminates new infections. WHO/TDR is also investigating the impact of treatment with Mectizan® given annually, semi-annually or at 3 month intervals without concomitant vector control, for 16 years in three foci in Senegal and Mali (former OCP areas). These studies have shown dramatic impact on prevalence of infection in humans and vectors. Data analysis is ongoing with particular interest in ascertaining whether mass treatment can be stopped in these foci without resumption of transmission in the coming one to two years.

Research is also ongoing on other potential macrofilaricides. Daily doxycycline (200 mg/dose) given orally for 6 weeks leads to a complete sterilization of adult *O.volvulus* female worms, and most recent data suggest that it also kills up to 70% after 27 months. The mode of action is by killing endosymbiont *Wolbachia* bacteria. Six weeks of treatment with doxycycline and Mectizan® (ivermectin) is superior to treatment with Mectizan alone in reducing microfilariae over a 21 month period. Moxidectin, an avermectin in the same class as ivermectin but with a longer half life, is now in Phase II trials, with community trials expected to be completed by 2011. It is hoped that it may have a more sustained microfilaricidal effect compared to ivermectin, or that it may even show macrofilaricidal affects. The Bill & Melinda Gates Foundation is funding research at WHO and via the Liverpool School of Tropical Medicine to screen and develop other potentially macrofilaricidal drugs.

Existing diagnostic tests include skin snip PCR to detect parasite DNA, detection of serum antibodies against species-specific antigen (OV-16) to identify past or current exposure to *O.volvulus* infection, and PCR to detect parasite DNA in pools of blackflies as a tool for assessing transmission. None of these is being produced commercially or readily available in laboratories, but if they were (especially the OV-16 antibody test), it would greatly facilitate monitoring of the transmission-interruption efforts. Mr. John Moores, Sr. is supporting research by the new WIRM initiative at the Scripps Institute in San Diego to develop a simple reliable test for detecting living adult *O.volvulus* in humans.

OEPA's Program Coordinating Committee (PCC) has interpreted guidelines for certification of onchocerciasis elimination that were developed by onchocerciasis experts under the auspices of WHO in 2001,[3] in order to adapt those criteria for practical use in the American program, while keeping to the spirit of the original guidelines. The changes include 1) for elimination of ocular morbidity, using only oncho specific punctuate keratitic lesions (A/B) and/or microfilaria prevalence in the anterior segment of the eye. A 95% confidence that rates are <1% is considered elimination of ocular morbidity from onchocerciasis; 2) for infection in blackflies, adopting the 'TDR standard' of L3 in blackflies (<0.05%) and striving to calculate Annual Transmission Potential (ATP) levels (less than 5-20 L3 innoculated per person per year) as a reliable indicator of interruption of transmission, and 3) absence of infection in humans defined as OV-16 antibody prevalence of <0.1% in school children (as the other reliable indicator of interruption of transmission). The affected countries and the PCC will continue to decide when to stop mass drug administration and how to monitor for recrudescence of transmission in the American foci.

The governments of Sudan and Uganda have both decided to try to interrupt transmission of onchocerciasis in isolated foci in their countries where it would appear technically feasible to do so. Sudan's Vice President and the Federal Minister of Health launched its effort to use semi-annual treatment (rather than current annual treatment) with Mectizan® in two isolated foci, Abu Hamed (in Nile State, north of Khartoum) and Sundus (in Gadarif State, southeast of Khartoum) in December 2006. These foci have a combined eligible population of approximately 150,000 persons. The relevant vector is *S. damnosum*. External assistance for this new effort in Sudan is being provided by the Lions-Carter Center SightFirst Initiative and the Mectizan Expert Committee. Heightened surveillance and monitoring and evaluation will accompany this effort.

Uganda has concluded that successful interruption of onchocerciasis transmission mainly by semi-annual mass treatment with Mectizan® for 6-7 years would be more cost effective than indefinite control using annual mass drug administration. Accordingly, the President of Uganda is scheduled to launch that country's new elimination initiative on January 30, 2007. Transmission has already been interrupted in 3 of 13 foci: the Victoria focus (eliminated in the late 1970's) and the APOC supported vector elimination efforts

[3] Anonymous, 2001. Certification of elimination of human Onchocerciasis: criteria, procedures, and guidelines, 2001. World Health Organization, Geneva, WHO/CDS/CPE/CEE/2001.18.b.

in Itwara and Mpamba-Nkusi. Six other foci are now targeted for interruption of transmission using a strategy of semi-annual mass distribution of Mectizan® and/or selective ground-based larviciding. Four foci require further epidemiological investigation. *S. neavei* is the vector in the 6 foci targeted for elimination. External support for this elimination initiative is being provided by The Carter Center, Merck (via the NGDO Group for Onchocerciasis Control), Mr. John Moores, Sr., and the Mectizan Expert Committee. The population targeted for semiannual Mectizan® treatment is about 760,000; overall the population at risk of onchocerciasis in Uganda is estimated at 1.8 million persons.

## Conclusions and Recommendations

1. The Task Force concluded that the eradicability of onchocerciasis in Africa using currently available tools has not yet been proven, and it welcomes the initiatives undertaken by the governments of Senegal, Mali, Equatorial Guinea, Tanzania, Sudan and Uganda to test this concept by eliminating selected onchocerciasis foci, using Mectizan® multiple times per year with or without vector control, in accord with the recommendation of the 2002 Conference.
2. The Task Force strongly encourages continued studies of the efficacy of potential macrofilaricides against adult *Onchocerca volvulus*, studies to develop a convenient and reliable test to detect living adult worms, and the the production and ready availability of currently proven diagnostic tools. A research breakthrough on any of these, especially a macrofilaricide, would greatly increase the potential for eradicating this parasite in Africa.
3. Programs in the Americas, Yemen and in parts of Africa should consider using doxycycline as a macrofilaricide in order to accelerate elimination of adult *O.volvulus* parasites in selected isolated foci. Having a rapid adult worm diagnostic would help target the prolonged treatment to those individuals who are infected.
4. The existence and expansion of the program to potentially eliminate lymphatic filariasis by mass administration of Mectizan® and albendazole is a welcome addition to the barriers against onchocerciasis transmission in Africa. APOC and the affected African countries should seize every opportunity to integrate efforts against these two diseases as well as other compatible interventions. There is no excuse for continuing singular approaches in co-endemic countries where such integration could also increase the sustainability of interventions against onchocerciasis and other diseases.
5. Countries need to consider the potential public health benefits of MDA with Mectizan® to control onchocerciasis, or Mectizan® and albendazole to halt transmission of lymphatic filariasis in areas where loiasis is co-endemic.
6. The Task Force applauds OEPA and CDC's informal efforts to continue to adapt and test the suggested guidelines for certification of interruption of onchocerciasis transmission in Guatemala. Any effort to formally revise the guidelines should await data pending from related initiatives in OEPA, Uganda, Sudan and former OCP areas.

7. The Task Force acknowledged the magnitude of the contribution to onchocerciasis control and elimination by the late Dr. Brian Duke, and requested the chair to convey to his widow its condolences on his recent demise as well as its appreciation and gratitude for his extraordinary work and dedicated commitment to this field.