Higher-Dose, More Frequent Treatment of Wuchereria bancrofti

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(See the article by Dembele et al, on pages 1229–1235.)

In 1997, the World Health Assembly resolved that human infection with the lymphatic filarial parasite Wuchereria bancrofti—a nematode parasite transmitted by mosquitoes, which causes elephantiasis, disfigurement of the male genitalia, and acute adenolymphangitis in tropical and subtropical Africa, South Asia, the Pacific, and Latin America—could be eradicated using available public health interventions. In response to this resolution, the Global Program for the Elimination of Lymphatic Filariasis was organized by the World Health Organization in 2000. The rationale and proposed strategy for geographic local elimination and, ultimately, global eradication of lymphatic filariasis are compelling and straightforward: annual mass administration of single-dose antifilarial drugs aimed at decreasing the reservoir of blood-borne microfilariae in populations in which the parasite is endemic to a level below that necessary for continuing transmission of infective larvae by the local mosquito vectors. On the basis of mathematical models that simulate local parasite, human host, and mosquito vector variables and interactions [1, 2], the linchpins for the success of this strategy are predicted to be the participation of a high proportion of populations in which the parasite is endemic in mass drug administration programs during the (unknown) period necessary to reach this hypothetical microfilarial threshold (estimated to be ~70% or greater population compliance during 5–7 annual treatments) and the use of effective, safe, and affordable antifilarial drugs. In 2008, the Global Program to Eliminate Lymphatic Filariasis estimated that 695 million people were targeted to participate in mass drug administration efforts, and nearly 500 million people received antifilarial medications [3]. In countries with a strong public health infrastructure, such as Egypt, elimination may be near or may have already been achieved [4].

Three anthelmintic drugs are currently recommended by the World Health Organization for mass drug administration to eliminate lymphatic filariasis: diethylcarbamazine, ivermectin, and albendazole [5]. All 3 drugs are affordable: diethylcarbamazine costs less than 1 cent per dose, and ivermectin and albendazole are donated by Merck and GlaxoSmithKline, respectively. In areas of W. bancrofti endemcity where Onchocerca volvulus coexists, which includes most of sub-Saharan Africa except for areas of Kenya and Tanzania near the Indian Ocean, the antifilarial drug combination that is most effective in killing both microfilariae and adult female worms that produce microfilariae before their release into the bloodstream, diethylcarbamazine plus albendazole, cannot be used because of an increased risk of severe posttreatment reactions that result from rapid killing and consequent inflammatory responses to O. volvulus microfilaria localized to the skin and eye. An article by Dembele et al [6] in this issue of Clinical Infectious Diseases addresses whether the effectiveness of the currently recommended standard 2-drug regimen for lymphatic filariasis elimination in sub-Saharan Africa, annual treatment with single-dose albendazole (400 mg regardless of weight) plus ivermectin (150 µg/kg), could be improved by biannual treatment with 800 mg of albendazole plus 400 µg/kg of ivermectin. The study was conducted in Mali, where O. volvulus is co-endemic with W. bancrofti. The results were striking. The high-dose, high-frequency regimen resulted in the complete clearance of microfilaremia at 12, 18, and 24 months, compared with microfilaria-positive rates of 57%, 32%, and 28% during the same interval in the comparator group, given the standard annual regimen. There were no differences in the frequency or severity of adverse events in the 2 groups. Interestingly, the
superior effect of the high-dose, high-frequency regimen appeared to be unrelated to greater killing of adult worms, because the level of filarial antigenemia (an indirect measure of adult worm burden) was reduced equally in both groups and no differences in motile worm nests detectable by ultrasonography were observed for the high-dose versus standard-dose arm (ivermectin given at these doses is not active against adult *W. bancrofti* worms, so any difference between the high-dose and standard-dose groups would presumably be due to albendazole) [7, 8].

The clinical trial reported by Dembele et al [6] sets the stage for additional studies to evaluate how currently recommended drug regimens for lymphatic filariasis elimination can be improved. As exemplified by the Mali trial, it will be important to use a study design that has practical implications for potential implementation in mass drug administration programs conducted in real-life settings, where lymphatic filariasis is endemic. For example, such trials should take into account whether a regimen can be sustained in national programs that have limited financial and human resources and evaluate whether the level of population compliance might be increased and cost of drug distribution reduced by administering antifilarial drugs twice per year for 3 years versus once per year for 5–7 years [9]. It will also be important to conduct follow-up examinations beyond 2 years (the last time of follow-up in the current report), because delayed drug effects on adult worm viability and fecundity may not be apparent until later. Finally, it will be useful to determine whether the superior effect of this or other high-dose regimens of albendazole and ivermectin are related to the increased dose or frequency of either anthelmintic (increased doses of both albendazole and ivermectin were given in the biannual high arm relative to the standard annual regimen).

Perhaps of greatest significance, however, is the notion that the study by Dembele et al [6] reflects increasing awareness of the possibility that global lymphatic filariasis eradication strategies and national mass drug administration programs remain flexible and open to research that has as its goal more rapid and cost-effective achievement of permanent transmission cessation [10]. In addition to evaluating increased doses and frequencies of administration of currently recommended antifilarial drugs, future trials might include, for example, the testing of novel, single-dose antibiotics that target *Wolbachia*, endosymbionts that reduce the fecundity and viability of adult female *W. bancrofti*, in combination with existing anthelmintics [11, 12], and newer anthelmintics that show promise in animal models of filariasis.

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**References**