

What's in a name? Drug resistance in helminth parasites

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For more on **WHO and monitoring of drug efficacy** see http://www.who.int/neglected_diseases/preventive_chemotherapy/anthelmintic_drug_efficacy/en/index.html

For more on **WHO and the control of neglected tropical diseases** see http://www.who.int/neglected_diseases/en/

In October, the US Agency for International Development will host a meeting in Washington, DC, to plan for the 2009 launch of US President George Bush's 5-year, US\$350 million initiative to combat neglected tropical diseases. Six of the seven targeted diseases—lymphatic filariasis, schistosomiasis, onchocerciasis, and three soil-transmitted diseases (hookworm, roundworm, and whipworm)—are caused by helminth parasites.

Health authorities are increasingly relying upon mass drug administration programmes to control these parasites. They are aware, however, that drug resistance might emerge as a result and are thus planning for that possibility. However, they are struggling with an unexpected problem: what actually is drug resistance in helminth parasites? Since the arsenal of effective anti-parasitic drugs is limited, and because few replacements are being developed, authorities need to know whether reduced drug efficacy is caused by drug resistance rather than other, more readily corrected, problems. WHO, in collaboration with the World Bank, is trying to find the answer.

The effort began in Washington, DC, late last year with a meeting of public-health authorities and researchers to discuss drug efficacy in large-scale treatment programmes in human helminthiasis. Attendees established four working groups—soil-transmitted helminthiasis, onchocerciasis/lymphatic filariasis, schistosomiasis, and pharma-

cology—to study various aspects of the problem. The ultimate goal is to issue guidance for anthelmintic drug efficacy monitoring by mid-2009.

Donald Bundy (Department of Human Development, World Bank, Washington, DC, USA) said resistance is a probable consequence of mass drug administration programmes. "In the veterinary area, it was clear that drug resistance had developed", Bundy said. "In human beings, there are often claims of reduced drug efficacy, but not demonstrated resistance...The bottom line is that we do not have—for any of these helminth infections—a definition of resistance. Nor do we have an agreed way of measuring resistance."

The existence of drug resistance is unquestioned in some parasitic diseases, such as malaria, leishmaniasis, and trypanosomiasis. But for others, especially those caused by helminth worms, reduced drug efficacy might be caused by other factors. Ian Hastings (Liverpool School of Tropical Medicine, UK) says apparent treatment failure could stem from drug resistance or from a patient's inability to metabolise the drug effectively. New infections, he said, are difficult to distinguish from resistant infections.

Dirk Engels (Department of Control of Neglected Tropical Diseases, WHO, Geneva, Switzerland) suggested other reasons why drug efficacy is difficult to monitor and resistance difficult to define: insensitive diagnostic methods, use of inappropriate measures of resistance, improper administration of drugs, and lack of standard procedures for monitoring drug efficacy and detecting potential resistance. However, these difficulties might not be sufficient explanation for the challenges in defining resistance.

"Drug resistance in veterinary parasites is accepted by everyone", said Roger Prichard (McGill University, Ste Anne de Bellevue, QC, Canada). "We are at an earlier stage in the process in human parasites and some people

are still in denial that drug resistance is occurring. But it is, unfortunately. This denial can hamper efforts to combat the spread of the resistant parasites, putting people at risk of increased morbidity". Eradicating the denial is made difficult by lack of agreement on how to measure resistance. The complexity of helminth life cycles, the typical life span of the parasites, and the difficulty in distinguishing new infections from potentially resistant ones further complicate the matter.

For parasites that shed eggs in faeces, for example, egg counts are typically used to test treatment efficacy, said Lorenzo Savioli (WHO, Geneva, Switzerland). He added that egg counts are quite variable, and that worms are rarely completely eliminated. "To kill all the worms, you would need to treat the patient two, three, or four times. But that's not really necessary. When you reduce the worm load, you stop the symptoms and prevent long-term consequences."

Prichard said the key to defining resistance is to better understand parasite response to commonly used drugs. If response to the drugs is lower than normal, and if host characteristics or drug quality can be ruled out as a cause, resistance is likely. Nevertheless, Prichard and others are working to develop genetic techniques to detect mutations that confer resistance.

So far, the soil-transmitted helminthiasis and onchocerciasis/filariasis groups have recommended methods for monitoring drug effectiveness and detecting resistance and are undertaking field studies to test the recommendations. They are also investigating ways to improve and prolong the effectiveness of current drugs while new drugs are under development. WHO expects this work will yield results in early 2009, in time for the start of Bush's neglected tropical diseases initiative.

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The effects of drug resistance in helminth parasites on resource-poor countries could be catastrophic