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Editorial: **Drugs for 'neglected diseases': a bitter pill**

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Médecins sans Frontières

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Health is determined by many factors, yet pills remain the key to the cure of many diseases. Provided you can get hold of them, that is. People in poor countries often have no access to essential drugs; this can be a matter of life or death. For some diseases drugs do not exist (e.g. Buruli ulcer); for others, drugs have been withdrawn from the market (such as eflornithine for treating sleeping sickness); or are too expensive (antibiotics, antimalarials, antiretrovirals) (Pécoul *et al*. 1999). Cost is the main obstacle. To put it simply: greed in the West curtails the availability of life-saving drugs for all.

Lack of research

Research and development into tropical diseases have come to a virtual standstill due to low profits. Of 1223 drugs globally licensed between 1975 and 1997, only 13 were for treatment of tropical diseases (Trouiller & Olliaro 1999). Two of these were an outcome of military research (halofantrine, mefloquine), six resulted from veterinary research (albendazole, benznidazole, ivermectin, oxamniquine, praziquantel and nifurtimox) and two were merely modifications of existing drugs (pentamidine and amphotericin B). Thus, over more than 20 years only three drugs were developed specifically for the tropics (artemether, atovaquone and eflornithine). Artemether was a Chinese Academy discovery; the development of atovaquone for malaria would have been endangered had it not turned out that it is effective against AIDS-related opportunistic infections (Hudson *et al*. 1985); and eflornithine is no longer produced. Apparently it is more profitable to develop and market Viagra than to research a new drug to treat patients with visceral leishmaniasis, a fatal disease if left untreated. Such a drug is more likely to be developed through veterinary research if it has economic potential on the pet market.

Patent protection

A wide range of international trade regulations protect market rights of producers through implementation of the World Trade Organization agreement (Aventin & Mathys 2000). Patent protection guarantees income for the industry and stimulates drug research, but patents also increase drug prices world wide and place them out of reach for many. The scenario is extremely bleak for patients suffering from diseases restricted to poor areas, diseases without commercial incentives to invest in solutions. Two typical examples of such neglected diseases are sleeping sickness and visceral leishmaniasis.

Sleeping sickness

Sleeping sickness is rapidly re-emerging in Africa after it had nearly vanished from the continent in the 1960s. It is estimated that 60 million people are at risk and half a million are infected, predominately in war-torn countries such as Sudan, Angola, Democratic Republic Congo and Uganda (Barrett 1999). Therapy of first-stage sleeping sickness is with suramin (developed in the 1920s) for *Trypanosoma brucei rhodesiense* and with pentamidine (developed in the 1940s) for *T. b. gambiense*. These treatments have remained unchanged for more than half a century.

The long-term supply of suramin is by no means secure. The producer, Bayer, planned to stop production on several occasions, and only continued after intervention by WHO. Pentamidine (Aventis) was originally developed for treating sleeping sickness. Once its potential to treat *Pneumocystis carinii pneumoniae* in AIDS patients was established, the price went up. The company donated a limited stock to WHO, which kept the market price low (US$ 3 per vial) for its restricted use in treating sleeping sickness. But the donation has been used up and over the next few years the price of pentamidine will gradually increase to the market price of US$ 14 per vial. Donations are often preferred to dual pricing (for rich and poor customers). Dual price-setting could jeopardise sales of expensive compounds also marketed for nonparasitic indications. Alternative treatment options for first-stage sleeping sickness do not exist.

Therapy for second-stage (cerebral) sleeping sickness relies mainly on the organic arsenicol melarsoprol, introduced in the late 1940s. This drug requires intravenous administration,

and lethal complications occur in a substantial number of patients (Pepin *et al*. 1989a; Veeken *et al*. 1989). Even though melarsoprol is toxic and resistance to it is increasing (Legros *et al*. 1999), we should be glad it is still on the market. Its future production is not guaranteed and can only be secured with commitment from the industry. Due to its specific component arsenic, environmental lobbyists keep putting pressure on the manufacturer to stop production.

Currently we have only one drug for treating relapse sleeping sickness. This drug, eflornithine, was developed through anticancer research, where it performed unsatisfactorily. It was introduced successfully for treating refractory sleeping sickness patients (Van Nieuwenhove *et al*. 1985). In 1995 the manufacturer Hoechst, Marion, Roussel (HMR) stopped the production of eflornithine. The drug was not turning an adequate profit. A last batch of 8000 vials was produced at the end of 1999, enough to treat approximately 1200 patients. At the same time, HMR transferred the license for eflornithine to WHO. This liberates the company from further obligations to manufacture the drug. A new producer for eflornithine remains to be identified.

Nifurtimox is normally used to treat Chagas disease (American trypanosomiasis). It has been used in African sleeping sickness, mostly for second line treatment, with mixed success (Pepin *et al*. 1989b; Van Nieuwenhove S 1992; Doua & Boa Yapo 1993). Its potential use for combination therapy, in first and second stage, is not evaluated yet. It can be administered orally and costs only US$ 10 for a 14-day course. A new drug (benznidazole) has been introduced to treat Chagas disease and the manufacturer (Bayer, Argentina) of nifurtimox stopped its production. The company is willing to produce further batches, but will not take responsibility for commercializing and marketing the drug.

Research and development of new treatments for sleeping sickness has come to a standstill. There are compounds in the preclinical pipeline, such as megazol and diminazene acetate (used in veterinary trypanosomiasis), but due to lack of funds no progress is being made.

Leishmaniasis

Visceral leishmaniasis (kala-azar) is a fatal disease caused by a parasite of the genus *Leishmania*. Half a million people become infected each year world wide (WHO 1996). Organic pentavalent antimonials (e.g. stibogluconate) have been the mainstay of treatment of kala-azar since their discovery in the 1920s (Goodwin 1995). Branded antimonials are expensive, approximately US$ 185 per patient treated, and need to be given daily, intramuscularly, for one month. In this case too, we should be grateful that this old-fashioned drug is still available. The future supply of antimonial drugs is by no means certain, and demand at times exceeds output.

Generic sodium stibogluconate is available for US$ 13 per patient treated, 1/14 of the price of the branded drug (Moore *et al*. 2000). Governments do not license the generic drug simply because it is produced in India. The trial described in this issue (Veeken *et al*. 2000), comparing the efficacy of branded stibogluconate and generic stibogluconate under field conditions, demonstrates that the drugs are equivalent. Hopefully this result will facilitate introduction of cheap, affordable treatment for thousands of kala-azar patients.

Resistance to drugs used for treating kala-azar is increasing, especially in India (Thakur *et al*. 1998). Treatment of relapses requires drugs that kill *Leishmania* parasites through different modes of action. Alternative treatments for kala-azar are few and either expensive (pentamidine or Ambisome®, a lipid amphotericine formulation (Davidson *et al*. 1991)), potentially toxic (amphotericine B) or currently unavailable (aminosidine). With the exception of miltefosine (Jha *et al*. 1999), which has potential as an orally administered drug, no further research is underway.

What should be done?

We cannot accept that the dearth of effective drugs for tropical diseases is simply the consequence of a global market economy. Drugs for neglected diseases do not belong in the free market; they require a centralized, public, nonprofit approach. Drugs are not a consumer commodity. Governments, manufacturers and nongovernmental organizations have a shared responsibility. The public sector must invest in research and development and secure the market. This necessitates centralized estimation of the needs and global distribution. Pharmaceutical companies must be engaged in the sustainable production of life-saving drugs. Registration and legislation should be adapted to overcome barriers of export and import between different countries. The pill should not be that bitter.

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