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Control of leishmaniasis

Report by the Secretariat

BACKGROUND

1.   Leishmaniasis is endemic in 88 countries in the world and 350 million people are considered at risk. An estimated 14 million people are infected, and each year about two million new cases occur. The disease contributes significantly to the propagation of poverty, because treatment is expensive and hence either unaffordable or it imposes a substantial economic burden, including loss of wages.

2.   Leishmaniasis with HIV coinfection is an emerging condition that demands urgent attention. Even when coinfected patients receive proper treatment, they relapse repeatedly and the outcome frequently is fatal.

3.   In resolution WHA43.18 on tropical disease research, the Health Assembly recognized that leishmaniasis, one of the targeted diseases of the then UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, continued to be a major public health problem. In 2006, it remains so.

4.   This report outlines features of the disease that are important in terms of its control. It describes activities in the areas of screening, diagnosis and treatment, and the search for more effective medicines. Further, it discusses the impact on disease-control issues of collaboration between WHO, endemic countries and international networks and partnerships.

CLINICAL FEATURES AND GLOBAL IMPACT

5.   Leishmaniasis is caused by a protozoal parasite of the genus *Leishmania* which multiplies in certain vertebrates that act as reservoirs of the disease. The parasite is transmitted to humans through the bite of sandflies that have previously fed on an infected reservoir.

6.   Expression of the two basic forms of the disease, namely cutaneous and visceral leishmaniasis, depends on the species of *Leishmania* responsible and the immune response to infection. The cutaneous form tends to heal spontaneously leaving scars which, depending on the species of *Leishmania* responsible, may evolve into diffuse cutaneous leishmaniasis, recidivans leishmaniasis, or mucocutaneous leishmaniasis, with disastrous aesthetic consequences for the patient. Visceral leishmaniasis, the most severe form, is fatal in almost all cases if left untreated. It may cause epidemic outbreaks with high mortality. A varying proportion of visceral cases may evolve into a cutaneous form known as post-kala-azar dermal leishmaniasis, which requires lengthy and costly treatment.

7.   Each year, there are some 500 000 cases of visceral leishmaniasis (90% in Bangladesh, Brazil, India, Nepal and Sudan), with an estimated more than 50 000 deaths, and 1 500 000 cases of cutaneous disease (90% in Afghanistan, Algeria, Brazil, Islamic Republic of Iran, Peru, Saudi Arabia and Sudan). The global mortality from visceral leishmaniasis can only be estimated, because in many countries the disease is not notifiable or is frequently undiagnosed, especially where there is no access to medication. In some cases, for cultural reasons and lack of access to treatment, the case-fatality rate is three times higher in women than in men. The disease burden is calculated at 2 090 000 disability-adjusted life years (1 249 000 in men and 840 000 in women), a significantly high rank among communicable diseases.

8.   The number of cases is increasing, mostly because of gradually more transmission in cities, displacement of populations, exposure of people who are not immune, deterioration of social and economic conditions in outlying urban areas, malnutrition (with consequent weakening of the immune system), and coinfection with HIV. In 34 of the 88 countries in which the disease is endemic, cases of coinfection have been reported.

9.   First-line treatment, especially for visceral leishmaniasis, is expensive and needs to be administered, by injection, in hospital. Treatment-cycle costs range from US$ 30 (for generic sodium stibogluconate) to US$ 120 (for meglumine antimonate) or US$ 150 (for sodium stibogluconate). In the case of relapse, patients need to be treated with a far more toxic second-line medicine, such as amphotericin B (US$ 60) or pentamidine (US$ 70). Liposomal amphotericin B has almost no side-effects but is unaffordable in developing countries (US$ 1500 or even more). Paromomycin costs US$ 10. The first oral treatment, miltefosine, costs US$ 150 or more.

10.   As a rule, patients have to overcome major logistic problems in order to access treatment: long distances to the treatment centre, lack of transport, treatment is unaffordable, or its costs pose a serious financial burden. For these reasons, patients may not comply with treatment (if they began) and drug resistance may emerge. There is a shortage of information on the actual cost of leishmaniasis, although it is known that in some parts of Asia a family in which there is a case of leishmaniasis is three times more likely than an unaffected family to have sold its cow or rice field, plunging it into a vicious circle of disease-poverty-malnutrition-disease.

COMPONENTS OF CONTROL: EPIDEMIOLOGICAL INFORMATION, DIAGNOSIS, TREATMENT AND BEDNETS

11.   Improved control reduces both mortality and morbidity. It also reduces the role of humans as a reservoir in anthroponotic cycles and makes it possible to avert progression of the disease to complicated cutaneous forms. The combination of active case detection and treatment is the key to control. Nevertheless, even that seemingly simple approach faces major obstacles. Although during their initial phases, leishmaniases respond well to treatment, many patients are unaware of the initial symptoms. Furthermore, health systems are frequently either poorly staffed and lack equipment or are non-existent in remote rural areas where contact with sandflies is most common.

12.   Prevalence and incidence data for assessing the full impact of leishmaniasis are unreliable. No objective data are available because: (i) transmission of the disease occurs in remote rural areas; (ii) many cases are not diagnosed because patients do not receive medical care; and (iii) leishmaniasis is notifiable in only 33 of the 88 countries in which it is endemic. As no prospective and broad study has ever been carried out and the overall picture has always been put together from the fragmentary data that exist, the actual prevalence and incidence can only be estimated.

13. Currently, no well-defined model for cost-effective control exists. There is a clear need to strengthen both active case detection of cutaneous and visceral leishmaniasis and diagnostic capacity at peripheral health centres where patients are usually treated on the basis of a presumptive diagnosis. So far, definitive diagnosis has relied on identification of the parasite by microscopy. As most district hospitals, however, do not have the resources to collect and identify parasites in bone marrow aspirates or even to perform skin tests, rapid and easy-to-interpret techniques are needed. At present, three rapid diagnostic methods are available for visceral leishmaniasis that are sensitive and specific: recombinant test k39 dipstick (US$ 1); direct agglutination test with freeze-dried antigen (US$ 3); and latex agglutination test to detect antigen in urine (US$ 1.5).

14. The core problem is access to treatment, as the cost of admission to hospital has to be added to the cost of the medicine (see paragraph 9). The first-line treatments are pentavalent antimonials, which have to be administered intramuscularly or intravenously for four weeks, but they are cardiotoxic and expensive for developing countries. In some areas of India poor use and irregular compliance have resulted in the emergence of drug resistance in 40% to 65% of patients. An alternative medicine is amphotericin B, although its high nephrotoxicity means that patients must be admitted to hospital for the four weeks' duration of treatment; liposomal amphotericin B is unaffordable in developing countries. Miltefosine, the only medicine administered orally, is to date licensed only in Colombia, Germany and India; as the possibility of its being teratogenic has not been excluded, it should be used under direct observation. Also, to avert the emergence of resistance, it should be given in combination.

15. A recent assessment in India of cost and cost-efficiency of interventions, comparing the total cost of treatment (medicine plus hospital stay) with results (cure, relapse, treatment failure, or interruption) showed that the overall figure for successful treatment varied considerably, from US$ 175 for miltefosine as first-line medicine to US$ 467 for amphotericin B as second-line medicine and US$ 1613 for liposomal amphotericin B. If there are 100 000 new cases each year in Bihar State, India, and first-line treatment is with miltefosine and second-line treatment with amphotericin B, the cost of treating those patients would amount to some US$ 11 million.

16. Active case detection in health centres has proved to be cheaper than passive detection: US$ 25/per case and US$ 145/per case, respectively. The cost of preventing one death is US$ 131 by active case detection and US$ 200 by passive case detection – in other words, passive case detection implies the unforeseen death of some patients, hence a greater disease burden. Following an epidemic of visceral leishmaniasis in Africa, it was possible to compare retrospectively excess mortality data, the cost of the control measures and the results obtained. In cost-effectiveness terms, the cost of each disability-adjusted life year saved amounted to US$ 18.40, making treatment a measure of high return on investment. This conclusion should be borne in mind in case of future epidemics.

17. Vector control using indoor spraying of insecticides is always determined by the behaviour of the species of sandfly present in each area: whether it is endophilic or exophilic and endophagous or exophagous. Whatever the case, logistics and costs limit the sustainability of periodic spraying of walls. Combined campaigns targeting *Anopheles* mosquitoes and sandflies, however, are more cost-effective. A suitable alternative, at an estimated cost of US$ 5 per unit, is the use of bednets impregnated with long-lasting insecticide; on average, the nets last for five years.

PROSPECT FOR CONTROL

18. Specific leishmaniasis-control initiatives are being taken by different public and private organizations, and interagency collaboration is engaging the private sector, although to an extent that

has yet to attain the level for other neglected tropical diseases. Noteworthy examples include: (i) the Spanish Government's initiative to contribute, with WHO, to the control of visceral leishmaniasis in Ethiopia and Sudan; (ii) the clinical trials platform being organized by the Drugs for Neglected Diseases Initiative in the Horn of Africa; (iii) the draft agreement between the Bill & Melinda Gates Foundation and the not-profit-making company OneWorld Health to carry out phase III/IV trials of paromomycin in India; (iv) specific programmes carried out by the nongovernmental organizations Médecins Sans Frontières and HealthNet International; and (v) activities to control the current cutaneous leishmaniasis epidemic in Kabul, supported by the Governments of Afghanistan and Belgium, WHO, the Foundation La Caixa, HealthNet International and the Massoud Foundation. Some pharmaceutical companies have agreed to reduce the prices of their medicines.

19. WHO has provided most endemic countries with specialized training in field work and helped to organize national control programmes, although these require further coordination. Action should be intensified to support teams that provide care in the most remote areas. Control programmes should be extended to those affected countries where none exist, through the establishment in areas with major foci of disease of a decentralized structure, increasing the number of WHO collaborating centres and giving them a greater role, and reliance on initiatives taken by the various parties referred to in the preceding paragraph.

20. Intensified collaboration between countries is essential in order to establish sentinel surveillance sites, map foci and prevalence on the basis of epidemiological assessments, train technical staff, investigate treatment failures, and set up computerized systems for data collection and analysis.

21. Wherever possible, conducting more surveys in countries is particularly important in order to obtain more accurate data on prevalence. All previous such surveys have always revealed higher levels of prevalence than previously assumed.

THE SEARCH FOR BETTER TOOLS

22. Leishmaniasis is one of the most neglected tropical diseases, in terms of the few tools available for control and the lack of clear criteria for methods of control. WHO has focused research priorities on control of leishmaniasis, and consequently, recent strategic research has led to the development of rapid and reliable non-invasive diagnostic techniques, new medicines, such as orally-administered miltefosine (now in phase IV trials) or injectable paromomycin (now in phase III/IV trials), drug combinations that reduce the risk of resistance, and immunochemotherapy. Moreover, basic research has resulted in the complete mapping of the genome of *Leishmania major* thanks to the *Leishmania* Genome Network. Mapping of the genomes of *L. braziliensis* and *L. infantum* is under way.

23. The most pressing research needs for leishmaniasis control are the search for alternative and cheap medicines for oral, parenteral or topical administration in shorter treatment cycles, and identification of mechanisms to facilitate access to existing control measures, including health-sector reform in some developing countries.

24. The above report was considered by the Executive Board at its 118th session. [1]

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[1] See document EBSS–EB118/2006/REC/1, summary record of the second meeting of the 118th session, section 3, and summary record of the fourth meeting, section 2.

ACTION BY THE HEALTH ASSEMBLY

25.   The Health Assembly is invited to consider the draft resolution contained in resolution EB118.R3.

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