Leishmaniasis in the Eastern Mediterranean Region

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داء الليشمانيات في إقليم شرق المتوسط

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خلاصة يعتبر داء الليشمانيات في بعض الدول الأعضاء بإقليم شرق المتوسط مشكلة مهمة من مشكلات الصحة العمومية ، نظراً لما لهذا الداء من أثر كبير في معدلات المراضة ، ولقُدرته على الانتشار بأبعاد وبائية تلقي أعباء ثقيلة على الخدمات الصحية الوطنية . ويرجع ازدياد معدلات وقوع داء الليشمانيات في بلدان الإقليم إلى أسباب متعددة من بينها تدفق الأفراد غير المنيعين إلى داخل البؤر الطبيعية لانتقال العدوى ، والتغيّرات في إيكولوجية نواقل المرض والمستودع الثوي ، وتناقص استعمال المبيدات الحشرية الثمالية في مكافحة الملاريا ، فضلا عما تحقق من تحسّن في تشخيص الحالات الإيجابية والإبلاغ عنها .

ABSTRACT Leishmaniasis is recognized as an important public health problem in some Member States of the Eastern Mediterranean Region owing to its considerable impact on morbidity and its potential to spread in epidemics, which impose a heavy burden on national health services. The increased incidence of leishmaniasis in countries of the Region is due to several reasons including influx of nonimmune population into natural foci of transmission, changes in ecology of vectors and reservoir host, reduction in the use of residual insecticides for the control of malaria and improvements in diagnosis and reporting of positive cases.

La leishmaniose dans la Région de la Méditerranée orientale

RESUME La leishmaniose est reconnue comme étant un problème important de santé publique dans certains Etats Membres de la Région de la Méditerranée orientale en raison de son impact considérable sur la morbidité, de son potentiel de propagation épidémique qui impose un lourd fardeau sur les services de santé nationaux. L'augmentation de l'incidence de la leishmaniose dans les pays de la Région est due à plusieurs raisons dont notamment l'afflux d'une population non immunisée arrivant dans des foyers naturels de transmission, les changements survenus dans l'écologie des vecteurs et de l'hôte réservoir, le moindre recours aux insecticides à effet rémanent pour la lutte antipaludique et l'amélioration du diagnostic et de la notification des cas positifs.

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Epidemiology

Cutaneous leishmaniasis caused by *Leishmania major* and *L. tropica* is found in most countries of the Region. *Phlebotomus papatasi* is the proven vector of *L. major*, and rodents *Rhombomys opimus*, *Psammomys obesus* and *Meriones* spp. serve as animal reservoir hosts. *Ph. sergenti* is the suspected vector of *L. tropica* in the majority of endemic foci. However, some other species of sandfly are also found as vectors of anthroponotic cutaneous leishmaniasis.

Some countries of the Region have stable endemic foci of zoonotic and anthroponotic cutaneous leishmaniasis, which could cause epidemics among nonimmune populations if they are involved in the transmission cycle. There are also some new foci where leishmaniasis has never before been recorded.

The causative agent of visceral leishmaniasis (also known as kala-azar) in the majority of endemic countries of the Region is *L. infantum*. However, *L. donovani* is responsible for kala-azar cases in Iraq and Sudan and some other countries. The role of dogs as a reservoir of *L. infantum* is well recognized. In some countries wild canines (jackals and foxes) are considered to be reservoirs of visceral leishmaniasis. Several species of sandfly are incriminated as vectors of visceral leishmaniasis. However, further studies are required in this field. There are still important foci where little is known of possible vectors, and new species of vectors are being discovered.

The descriptive epidemiology of leishmaniasis has been strengthened by the biochemical typing of leishmania species, and new zymodemes of leishmania strains have been identified [*1,2*]. The list of reservoir hosts is being expanded [*3*], but still the precise role of some suspected animal hosts is not clear, e.g. *Rattus* spp. More species of sandflies are coming under suspicion as potential vectors of leishmaniasis when new foci of transmission are investigated.

Surveillance

Diagnosis of leishmaniasis is based on clinical, serological and parasitological identifications. Some countries of the Region use improved serodiagnostic procedures for diagnosis of visceral leishmaniasis like the enzyme-linked immunosorbent assay (ELISA), direct agglutination test (DAT) or the polymerase chain reaction (PCR) technique [*4,5*].

Difficulties in clinical and parasitological diagnosis of visceral leishmaniasis still exist. The signs and symptoms of the disease in areas with multiple morbidity may not be sufficiently specific to differentiate visceral leishmaniasis from other diseases. In Sudan, for example, the outbreak of kala-azar in mid-1988 was, by mistake, recognized as an outbreak of typhoid fever [*6*]. Therefore, the majority of countries presently apply serology techniques for diagnosis of visceral leishmaniasis.

Comprehensive information about the distribution of different forms of leishmaniasis in the countries is incomplete and needs further studies. An average annual number of registered leishmaniasis cases in the Region is between 50 000 to 80 000 cases. The majority of registered cases belong to cutaneous forms. However, during an epidemic, as happened in Sudan, the number of visceral leishmaniasis cases can considerably increase (Table 1).

The importance of leishmaniasis in some countries of the Region was recognized after the improvement of registration and information systems. Leishmaniases have been included into the list of notifiable diseases in the majority of the countries with areas of local transmission. Passive case detection

Table 1 **Recorded cases of leishmaniasis in countries of the Eastern Mediterranean Region**

Member State	1988	1989	1990	1991	1992	1993	1994
Afghanistan	5773	11480	8500	12177	16604	13925	16327
Egypt	5	6	2		84	12	
Iran, Islamic Republic of	18953	15757	19772	17326	10566	13069	18777
Iraq	3078	3344	2470	11946	12645	11155	9348
Jordan	145	210	226	114	120	80	207
Kuwait	5				4		
Libyan Arab Jamahiriya	506	316	782	958	798	229	
Morocco	760	255	2615	3661	289	114	56
Oman	11	27	12	3	14	40	29
Saudi Arabia	15184	10950	8198	7902	8415	10019	
Sudan		830	1911	8959	2504	1057	760
Syrian Arab Republic	5831	9814	12561	15034	10991	12310	15900
Tunisia	1137	1365	1204	1399	3480	2723	1708
Republic of Yemen		6	13	14	16	57	37

Source: WHO Regional Office for the Eastern Mediterranean

continues to be the main source of information and depends largely on the awareness of the population about the early symptoms of the disease and the recognition of the need to seek medical assistance. In some endemic foci of cutaneous leishmaniasis, the local people are well aware about the development of lifelong immunity to leishmaniasis after contracting the disease during early childhood and seek medical assistance only in severe clinical forms of the disease. Hence the officially reported data on incidence of cutaneous leishmaniasis may not present the full picture. Active case detection is applied for specific tasks, e.g. for recognition of endemic foci or for research purposes.

Factors affecting the spread of leishmaniasis

There are several reasons behind the increased incidence of leishmaniasis in the Region. The majority of them depend on human activities such as environmental modifications, resettlement of nonimmune populations or development of agroindustrial projects, military activities, urbanization and so on.

Environmental modification, such as construction of dams, can change the temperature and humidity of the soil and vegetation, which may result in changes in the composition and density of sandfly species as well as changes in populations of rodent species. The formation of new settlements with nonimmune populations facilitate the outbreak of leishmaniasis. For example, the outbreak of zoonotic cutaneous leishmaniasis in the central and southern governorates of Tunisia in 1982–83 occurred following the construction of the Sidi Saad Dam [7]. The increase in the incidence of leishmaniasis among nonimmune settlers was observed in water irrigation schemes in the Libyan Arab Jamahiriya, Saudi Arabia, the Syrian Arab Republic and other countries.

An outbreak of zoonotic cutaneous leishmaniasis as a result of man-made changes to the environment has been observed since 1994 in the Kashan region, north of Isfahan in the Islamic Republic of Iran. An incidence of 8–15% was reported among local inhabitants. Available data indicate that the epidemic started after an increase in the number of *Rhombomys opimus*—a rodent reservoir of zoonotic cutaneous leishmaniasis in the area—as a result of planting trees in the region to prevent soil erosion. Since sandfly vectors are present in the area, the active transmission cycle of the leishmania parasite has been formed, thus resulting in an increase of human incidence of leishmaniasis in humans [*8*].

Outbreaks of leishmaniasis are often associated with the movement of people into foci of infection. There have been many examples of such outbreaks in the Region. For example, during the war between the Islamic Republic of Iran and Iraq numerous cutaneous leishmaniasis cases were observed among soldiers stationed in active foci of infection. The outbreak of cutaneous leishmaniasis provoked the Iranians to start mass leishmanization of military personnel as a prophylactic operation. The displaced population of the southern regions of Sudan experienced a severe outbreak of kala-azar. In Pakistan, an outbreak of cutaneous leishmaniasis among soldiers was recorded after military exercises in some endemic foci of Baluchistan. A rise in the incidence of cutaneous leishmaniasis was recorded among personnel of the United Nations peacekeeping forces in east Sinai [*9*].

The increased incidence of zoonotic cutaneous leishmaniasis in Morocco was related to the movement of the rodent reservoir host *Meriones shawi grandis* close to human settlements. This host appeared to adapt to synanthropic behaviour by modification of its nutritional requirements. It became coprophagous and detritivorous, living in peridomestic areas near garbage tips. This is another example of how man-made environmental modification can effect the transmission intensity and subsequently the incidence of leishmaniasis.

A few outbreaks have originated from the introduction of the parasite into areas of potential transmission. This applies to the outbreak of visceral leishmaniasis in Western Upper Nile State in Sudan, where it was unknown until 1984. Because the disease was introduced by the troops from an endemic area on the Sudan–Ethiopia border to a nonimmune population, and because of the breakdown of health services and the famine that resulted from the war in the southern states, a severe epidemic hit the Western Upper Nile State, claiming thousands of lives [*10*]. The disease has spread to the Misarya tribe, nomadic cattle owners from southern Kordofan, where local transmission has not been previously recorded. The Misarya acquired visceral leishmaniasis in their annual trek to Western Upper Nile State during the dry season in search of water and grazing for their cattle [*11*].

The outbreak of leishmaniasis in existing foci may be linked to the existence of concomitant malnutrition and other infectious diseases resulting in the aggravation of asymptomatic infectious and subclinical forms of the disease. Such conditions are often observed among displaced populations or in areas stricken with famine due to drought and destabilized agricultural activities as a result of continuous war [*12*].

Favourable conditions for the increased number of cases of anthroponotic cutaneous leishmaniasis can be found overcrowded cities due to massive rural-to-urban migration, e.g. in Kabul or Aleppo [*13*]. A broad description of the epidemiological dynamics of the infection in Kabul in 1990 showed that it had retained the characteristics of a newly arrived epidemic over a period of almost 20 years. The age distribution of infection did not change, and an increase in the number of cases was observed despite insecticide application in houses and intensive detection and treatment of cases. It has been suggested that the epidemic of anthroponotic cutaneous leishmaniasis in Kabul persisted because of a rapid turnover of people in the city [*14*].

The re-emergence of leishmaniasis in some foci may be the result of interruption of previously applied methods of control, e.g. insecticide spraying or early diagnosis and treatment of positive cases. It is believed that reduction in insecticide spraying for malaria control contributes to the increase in the population of synanthropic sandflies and results in the outbreak of the disease in some endemic foci of cutaneous and visceral leishmaniasis [*15*].

A shortage of specific drugs for the treatment of leishmaniasis can potentially contribute to the intensity of transmission in the foci of anthroponotic forms of the disease, and subsequently to an increase in the morbidity and even mortality among populations at risk of infection. Generally all humans serve as reservoir hosts during epidemics of anthroponotic forms of infection; and if untreated, the severity of the disease will increase and prove fatal in case of a kala-azar epidemic. The lack of diagnostic facilities and drugs for treatment have been among the possible contributing factors to the epidemic of kala-azar in Sudan between 1988 and 1993, and the outbreak of kala-azar and anthroponotic cutaneous leishmaniasis in Iraq after the Gulf War and subsequent economic embargo imposed in 1991. A fourfold to sixfold rise in the number of cases in 1991 compared to 1990 was observed in Iraq, namely 576 cases of visceral leishmaniasis and 1799 cases cutaneous leishmaniasis in 1990 and 3713 cases of visceral leishmaniasis and 8233 cases of cutaneous leishmaniasis in 1991. However, other factors such as population movement and the destruction of health and vector-control facilities during the war contributed to the outbreak of leishmaniasis in Iraq and the Islamic Republic of Iran.

The role of the climate in the emergence and re-emergence of human infectious diseases and particularly vector-borne diseases is well recognized [*16*]. Some outbreaks of leishmaniasis in the Region have been linked to climatic changes. For example, it is believed that heavy rains in Sudan in 1985 and 1986 created ideal breeding conditions for the sandfly and resulted in an outbreak of cutaneous leishmaniasis in Khartoum with more than 10 000 cases [2]. Furthermore, there was a massive migration of population from endemic regions in the west of the country to the nonendemic Nile region north of Khartoum in 1984–85 following the drought in the west during this time [*15*].

Prevention and control

A combination of approaches is usually used to control leishmaniasis: early recognition and treatment of cases and, where necessary, control of vectors and reservoir hosts. Health education of the population in endemic foci is the most important element of the control strategy.

Passive case detection followed by treatment and case reporting constitutes the basis of the majority of control programmes in the endemic countries of the Region. The success of such programmes is more significant in areas with anthroponotic forms of leishmaniasis and high awareness among the population of early symptoms of the disease and the importance of early reporting and treatment.

The first-line drugs against leishmaniasis are pentavalent antimonials. They have drawbacks such as serious side effects, long duration of treatment and relatively high cost. Some control programmes are not always able to provide drugs free-of-charge to leishmaniasis patients. Therefore, patients have to look to the market for the drugs, which are costly and often out of reach of patients from the lowest socioeconomic class. The high cost of drugs results in interruption of treatment with the possibility of development of chronic and debilitating forms of the disease [*17*]. International and voluntary organizations greatly support national control programmes with antileishmania drugs, especially in emergencies.

Some countries of the Region have tried paromomycin ointment for the treatment of cutaneous leishmaniasis. However, available results suggest that the formulation of the ointment needs further improvement before this method of treatment can be recommended for field practice [*18–20*].

Several research groups in the Islamic Republic of Iran, Pakistan and Sudan are at present participating in the Phase II and Phase III trials of the killed–*Leishmania major* vaccine developed by the Razi Institute, Teheran. Preliminary results indicate that leishmania vaccines will be an effective control tool in future after completion of clinical trials [*21–23*].

Control of vectors through residual insecticide house-spraying plays a significant role in the reduction of transmission, particularly in foci of anthroponotic cutaneous leishmaniasis. However, the high cost of modern insecticides and increasing concern about their impact on the environment have resulted in a significant reduction in the use of insecticides by national programmes. Trials on the use of insecticide-impregnated bednets in foci of cutaneous and visceral leishmaniasis are going on in the Islamic Republic of Iran, Sudan and the Syrian Arab Republic. The trials are supported by the EMRO/CTD/TDR Small Grants project. The preliminary results from these trials are very encouraging.

Control of reservoir hosts is an important component of the control strategy against zoonotic forms of leishmaniases. Some new approaches to control the transmission of zoonotic cutaneous leishmaniasis through environmental modifications have been studied in Jordan and Tunisia with support of the EMRO/CTD/TDR Small Grants project. The destruction of *Psammomys obesus* burrows by deep ploughing, removal of chenopods and planting of trees in a 2–3 kilometre zone surrounding human settlements has resulted in a significant reduction of the incidence of cutaneous leishmaniasis among the local human population [*24*].

The success of the control measures depends on a basic understanding of the epidemiology of different forms of leishmaniasis and the cultural/social customs of the population. For example, indoor insecticide spraying will not be effective in areas with exophilic vector species, nor will treatment of burrows of *Psammomys obesus* with grain treated with zinc phosphide. If the vector is exophagic and the people in the foci prefer to sleep outside without mosquito nets during the transmission season, then the use of insecticide-impregnated materials will not affect the transmission.

The training of medical personnel in clinical features of leishmaniasis, diagnosis and treatment are essential components of training in countries with endemic foci. Specific training of laboratory technicians in isolation and identification of leishmania strains is needed for the planning of the control strategy. The recording and reporting of leishmaniasis should be particularly strengthened.

Conclusions

Cutaneous and visceral forms of leishmaniasis continued to be an important public health problem in countries of the Eastern Mediterranean Region.

Leishmaniases can be considered as re-emerging diseases in areas with known foci of transmission and as emerging disease in areas without previous history of transmission.

The main factors responsible for the increased incidence of leishmaniasis in some countries of the Eastern Mediterranean Region are the following:

- increased involvement of nonimmune human populations with the transmission cycle of the disease, because of extensive population movements;
- natural and man-made environmental factors facilitating changes in the populations of vectors and reservoir hosts;
- improvement of surveillance systems with better diagnosis and reporting of cases; and
- constraints in the provision of control.

The problem of leishmaniasis in the Region can be solved through the strong political commitment of Member States to control leishmaniasis, the formation of the national reference centres on leishmaniasis in endemic countries, the improved provision of diagnosis, treatment and control facilities and the support of applied research. Some very important steps have been already made by Member States in this direction but there is still room for further action.

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