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Epidemiology and direct medical costs of human Leishmaniasis in Italy

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Key words

Human Leishmaniasis • Italy • Epidemiology • Medical costs

Summary

Introduction. *In the last decades, visceral Leishmaniasis infection rate has increased in Western Mediterranean areas. Epidemiological data show that in Italy, especially in some regions, the prevalence of canine form is high. The aim of this study is to evaluate the epidemiological setting of Leishmaniasis in Italy, according to age groups and geographical areas, and to estimate the associated direct medical costs.*

Methods. *The study examined the ordinary and day-hospital discharges and the respective mean of hospital length of stay for Leishmaniasis and visceral Leishmaniasis in Italy, during the period 1999-2003. Moreover, we collected data about notifications of Leishmaniasis, from 1993 to 2004, and mortality due to this infectious disease, from 1993 to 1998.*

We evaluated the prevalence rates of discharges, the visceral and cutaneous Leishmaniasis notifications incidence rates and the mortality rates from disease, per 1,000,000 residents.

Costs analysis was performed getting DRG number 423 rate, which corresponds to "other diagnosis related to infectious and parasitary diseases".

Results. *Ordinary discharges decreased in the study period, while day-hospital discharges increased. Sicilia, Campania and Lazio regions showed the highest number of ordinary hospital discharges for Leishmaniasis (prevalence rates were respectively 16.29, 15.02 and 12.83 per 1,000,000 residents, in 2003). Campania and Sicilia showed also the highest prevalence rates of day-hospital discharges (respectively 17.29 and 35.39 per 1,000,000 residents in 2003).*

The analysis of incidence rates of notifications showed a cyclic trend of the visceral form of the disease, with the highest rates observed in the group aged 0-14 years (incidence rates per 1,000,000: 7.46 in 1996 and 8.59 in 2000).

The highest mortality rates were observed in the group aged over 65 years; low but constant mortality rates for Leishmaniasis were seen in the age group 25-64 years.

Direct costs for both ordinary and day-hospital admissions were: 1,561,218.46 € in 1999; 1,637,256.44 € in 2000; 1,459,892.92 € in 2001, 1,468,983.58 € in 2002 and 1,370,227.80 € in 2003.

Discussion. *Discharges for Leishmaniasis showed non-homogeneous trend in Italy, especially in coastal Regions. Leishmaniasis notifications have slowly increased after 1993 and a high number of notifications was observed in the 0-14 years old group.*

The highest mortality rates were reported in the extreme age-groups: mortality was relevant for patients over 65 years.

Moreover, cost analysis showed that health care of human Leishmaniasis requires long time of hospitalization with consequent high costs.

Conclusion. *Preventive measures have to be turned to extreme age groups. For future studies issues such as high costs of treating disease, cost-effectiveness evaluation of the current therapeutic approach compared to preventive interventions on dogs and vector insects would be of interest.*

Introduction

Human Leishmaniasis represents a serious public health concern in Mediterranean countries [1]. In Italy, the canine form of this infectious disease is highly prevalent and is endemic in many areas, especially in Central-Southern regions where the prevalence of canine Leishmaniasis ranges from 1,7% to 48,4% [2]. In recent years active foci of canine Leishmaniasis have been even identified in Northern regions which were considered free from this concern until 1983 [3, 4].

Since 1993, the prevalence of the human form of the disease has increased [5] and the World Health Organization (WHO) has identified visceral Leishmaniasis as an emerging zoonosis in Southern Europe [3]. The disease is endemic in 88 countries; 90% of visceral Leishmaniasis occurs in Bangladesh, Brazil, India, Sudan and Nepal, while 90% of cutaneous form occurs in Afghanistan, Algeria, Brazil, Iran, Peru, Saudi Arabia and Syria. Globally speaking, there are 12 million cases worldwide and over 350 million people are at risk of infection [6]. The incidence rate of Leishmaniasis is of 1.5-2 million of cases per year worldwide, but the disease is greatly under-reported, as notification is compulsory in only 32 of 88 endemic countries. So, about 50% of new cases are recorded each year [6, 7]. In 2001, WHO estimated 60,000 deaths due to Leishmaniasis [5].

Dogs represent the main cause of disease spreading, since they are the only domestic reservoir of the infection [2, 3, 8]. Epidemiologically, we distinguish two different patterns of transmission: the zoonotic form of the disease (in the Mediterranean countries), with the dog as the main source of infection, and the

anthroponotic one (in East Africa, Bangladesh, India, Nepal), with man to man transmission [9].
Epidemiological data showed that treating this disease has been a challenge in some Italian regions such as Campania, Sicilia and Lazio, as the prevalence of canine Leishmaniasis in these regions is higher than in others [10].
In Italy, there are two forms of Leishmaniasis: visceral and cutaneous. The visceral form can affect people of any age, mainly children, and it is characterized by irregular fever, weight loss, swelling of liver and spleen and anaemia; it can be mortal if untreated [11, 12]. The cutaneous form is characterized by single self-solving lesion or multiple lesions and tends to become chronic [11, 12].
Children age, poor nutrition and professional status could predispose individuals to symptomatic Leishmaniasis [12]. The severity of symptoms is strictly connected with the host immunological state, as well as the timeliness of diagnosis and treatment which improves disease prognosis.
The prevention of human Leishmaniasis cannot exclude interventions of veterinary surgeons [11], as the canine form is endemic in many areas.
In Italy, timely epidemiological studies have been carried out in single areas [13-15]. Sicilia represents a high risk geographic area and disease cases are increasing among people as well as among dogs [13, 16]. Many studies focused on the role of phlebotomists and their distribution in Italy [17]. After the Second World War the incidence rates of the disease were stable (10-20 cases per person-year), but, in recent years, Leishmaniasis seems to be re-emerged [5]; in 2000, the incident cases were 200 [6]. The spreading of the disease in Italy can be related to the setting of surveillance programs in some regions such as Campania, Sicilia and Lazio, to the diffusion of new foci of canine Leishmaniasis and to the HIV/Leishmaniasis co-infection in humans.
In Italy, Leishmaniasis affects mainly immunological-compromised subjects, especially intra-venous drug users [6]. HIV/Leishmaniasis co-infection is highly represented in South-Western Europe: about 85% of the first cases notified to WHO until 1998, have been reported in these area [18]. Italy, France, Portugal and Spain are countries with the highest number of HIV/Leishmaniasis co-infections [19].
While HIV/Leishmaniasis co-infection is increasing in Eastern Africa and the Indian subcontinent, due to the simultaneous spread and geographical overlap of both diseases, cases of co-infection are expected to reduce in South-Western Europe, as treatment (HAART) is easily available. However, the number reported to WHO continues to rise and it is maybe due to the increased awareness and better case definition of disease [9].
Moreover, recent studies show that the co-infection Leishmaniasis-HIV could be mortal [20-22] and this could represent a further public health problem.

Objective

The aim of our study was to analyse the epidemiological setting of Leishmaniasis in Italy, according to geographical areas and age groups.
We evaluated the number and the prevalence rates of ordinary and day-hospital discharges for Leishmaniasis and Visceral Leishmaniasis, according to geographical areas; we considered the mean length of stay in hospital for the disease and we studied the mortality for human Leishmaniasis in Italy, according to age.
In order to have a full view of this concern, we also analysed the number of official notifications.
Moreover, we calculated direct hospitals costs, in order to assess the economic weight of the human form of the disease.

Methods

Using the Ministry of Health's website [23], we accessed hospital discharge data and the mean length of stay, due to Leishmaniasis (code ICD9–CM*: 085), in Italian hospitals and health care structures, from 1999 to 2003. We evaluated discharge data from both ordinary hospitalizations and day-hospitals and stratified our data by region of residence. We also evaluated the same data for visceral Leishmaniasis only (code ICD9–CM*: 0850), according to region of residence and age groups (0-14; 15-24; 25-64; > 65). We based the number of disease cases on discharge data.
The number of cutaneous and visceral Leishmaniasis notifications was obtained from the Ministry of Health's website [24], for the period 1993-2004. Resident population was estimated using data from Demo-Istat [25] (at 1st of January for each year) during the same period. We obtained population data both for region of residence and age groups (0-14; 15-24; 25-64; ≥ 65). Mortality data were derived from the "Archive of mortality for every single cause" of Epicentro website [26], from 1993 to 1998; we considered deaths from visceral and undetermined Leishmaniasis.
We evaluated the prevalence rates of Leishmaniasis cases (ICD9: 085) and we calculated the percentage and the prevalence rates of visceral forms (ICD9: 0850). The prevalence rates were calculated dividing the number of cases (based on discharge data) by resident population.
We estimated the incidence rates of visceral and cutaneous Leishmaniasis notifications and the mortality rates from Leishmaniasis. The incidence rates were computed as described for prevalence rates; the prevalence and the incidence rates were calculated for 1,000,000 residents.
Costs analysis was performed getting the DRG rates of ordinary hospitalization and one day/daily hospitalization for "Other diagnosis related to infectious and parasitary diseases" (DRG 423); from the Ministerial decree 30 June 1997 [27], they resulted 3,343.54 € and 329.50 € respectively for ordinary and day-hospital di-

* International Classification of Diseases 9th revison - Clinical Modification

Tab. I. Distribution of discharges (cases) for Leishmaniasis and mean days of stay in hospital (in days) in Italian Regions from 1999 to 2003.

Years	1999				2000				2001				2002				2003			
Type of Hospitalisation	OH		DH		OH		DH		OH		DH		OH		DH		OH		DH	
Regions	cases	Mean days*	cases	Mean days*	cases	Mean days*	cases	Mean days*	cases	Mean days*	cases	Mean days*	cases	Mean days*	cases	Mean days*	cases	Mean days*	cases	Mean days*
Piemonte	8	11.13	5	1.4	11	14.91	10	4.71	15	12.34	9	5.89	5	16.81	4	10	5	16.61	8	4.5
Lombardia	29	12.66	12	9.17	25	10.68	30	3.3	15	9.74	35	4.98	23	16.7	32	6.63	15	13	19	3.69
P.A. Bolzano	1	1	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
P.A. Trento	3	8	N.A.	N.A.	N.A.	N.A.	2	1	3	9.34	1	14	1	43	N.A.	N.A.	4	14.5	2	5
Veneto	5	13.2	3	3	13	11	3	18.34	6	14.84	3	4.67	6	10.84	5	12.81	7	15.15	6	8.17
Friuli V.G.	1	1	N.A.	N.A.	1	28	N.A.	N.A.	1	24	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
Liguria	12	7.42	3	12	8	14.63	6	3	19	10.48	11	4.1	10	9.7	3	3	18	10.06	9	2.45
Emilia Romagna	7	18.15	6	8.5	7	7.72	8	14.63	2	21.5	12	7.59	5	13.2	8	6.5	13	15.47	15	10.87
Toscana	13	14.93	7	4.86	14	7.93	10	7.5	9	11.56	6	12.17	21	13.77	6	12.17	20	11.31	7	6.29
Umbria	1	5	N.A.	N.A.	3	11	N.A.	N.A.	3	28.67	1	5	1	11	1	3	N.A.	N.A.	1	14
Marche	2	14	1	1	1	70	N.A.	N.A.	N.A.	N.A.	1	1	N.A.	N.A.	1	1	2	18.5	N.A.	N.A.
Lazio	48	14.42	14	4.08	71	13.54	24	4.38	62	11.96	23	3	37	11.14	15	3.8	66	10.11	32	4.57
Abruzzo	5	15.41	2	1	5	18.2	3	2	5	16.61	1	12	5	31.81	N.A.	N.A.	4	20.5	4	2.25
Molise	3	7	N.A.	N.A.	1	1	N.A.	N.A.	1	11	N.A.	N.A.	3	11	N.A.	N.A.	1	9	N.A.	N.A.
Campania	107	8.88	41	1.88	153	9.54	57	2.6	109	8.82	98	2.74	119	8.81	49	2.33	86	7.48	99	1.66
Puglia	30	16.4	3	5.67	35	12.43	12	3.34	41	14.1	12	2.5	29	13.42	6	2	25	17.88	5	3
Calabria	15	14.2	9	2.12	12	10.17	9	4.12	13	9.93	9	2.67	18	7	15	2.74	10	6.21	10	1.61
Sicilia	135	8.58	64	8.25	72	12.28	97	4.5	79	8.71	155	4.84	104	9.75	223	4.24	81	14.23	176	4.17
Sardegna	24	13.05	12	2.67	25	17.72	20	3.15	14	20.86	13	1.47	11	18.82	10	2.8	12	15.5	8	3.25
Basilicata	N.A.	N.A.	N.A.	N.A.	4	12.25	N.A.	N.A.	1	18	N.A.	N.A.	4	24.5	1	4	1	5	3	2
Valle d'Aosta	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	2	8.5	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
Total	449	10.76	182	4.68	461	15.72	291	5.47	398	14.58	392	5.71	402	15.96	379	5.13	370	12.97	404	4.84

OH = ordinary hospital; DH = day hospital; N.A. = Not Available; * = Mean days of hospital stay

scharges. We multiplied the rate values of ordinary and day-hospital hospitalizations for the respective number of discharges and we added the ordinary hospital costs to day-hospital ones to estimate total direct medical costs.

Results

Table I shows the number of ordinary and day-hospital discharged patients with the main diagnosis of Leishmaniasis and the mean length of stay in hospital (in days) for the disease, in different Italian Regions, from 1999 to 2003. The percentage of discharged patients with diagnosis of visceral Leishmaniasis and respective mean length of stay in hospital are shown in Table II. Discharges data were lacking for a lot of regions and were not reported for Trentino-Alto Adige.
Total ordinary hospital discharges were 449 in 1999 and 370 in 2003, while day-hospital discharges were 182 in 1999 and 404 in 2003.
The mean length of stay in hospital (in ordinary hospitalization) was 10.76 days in 1999 and 12.97 in 2003. The number of mean accesses to day-hospital was 4.68 in 1999 and 4.84 in 2003 but it reached higher values within the study period (5.71 in 2001). In this period there was a decrease of the mean length of stay in hospital (in ordinary hospital) in Toscana, Lazio and Calabria, while in Sardegna, Sicilia and Piemonte there was an important increase.
In the studied quinquennium, Sicilia, Campania and Lazio presented the highest number of ordinary hospital discharges for Leishmaniasis (prevalence rates were respectively 16.29, 15.02 and 12.83 for 1,000,000 residents, in 2003) (Tab. III). Moreover Campania and Sicilia showed also the highest prevalence rates of day-hospital discharges (17.29 and 35.39 for 1,000,000 residents in 2003). Regions with climate conditions which support vectors' survival and replication showed differences in Leishmaniasis discharges and prevalence data: i.e. Emilia Romagna presented low discharges prevalence rates, while Lazio, a region with similar climate of Emilia Romagna, showed higher values.
In Table IV the distribution of visceral Leishmaniasis discharges and corresponding mean length of stay in hospital is shown, stratified by age and gender. It is possible to note that the most affected groups were children from 1 to 4 years and adults from 25 to 64 years.
From 1993 to 2004, the temporal trend of Leishmaniasis notifications incidence rates was analysed, both for total population and stratified for age groups (Fig. 1). The analysis showed a cyclic trend of the Visceral form of the disease, with inter-epidemic periods of about 5 years, with peaks in the years 1995/1996, 2000 and 2004, for all age groups. The highest incidence rates were observed for the group aged 0-14 years (incidence rates for 1,000,000: 7.46 in 1996; 8.59 in 2000; 7.45 in 2004); people ≥ 65 years were less affected. Incidence rates for cutaneous Leishmaniasis notifications were higher in the age group from 0 to 14 years; incidence rates increased in all age groups in more recent years.
Leishmaniasis mortality rates stratified by age groups, in the years 1993-1998, showed that the group presenting the highest values was the oldest one (≥ 65 years old), and the highest rates were observed in 1993 and 1994 (0.33 dead individuals for 1,000,000 residents), followed by the age group 0-14 years which presented the highest rate in 1996 (0.12 dead individuals for 1.000.000 residents). The age group 25-64 years showed low, but constant, mortality rates through the years.
Direct hospitalizations costs, used as a proxy of the economic weight of Leishmaniasis (both the visceral and the cutaneous form) resulted higher in Sicilia, Campania and Lazio (Tab. V) than in other regions; this was confirmed both for ordinary admissions and day-hospital ones. In the studied quinquennium, total direct medical costs were respectively: 1,561,218.46 € in 1999; 1,637,256.44 € in 2000; 1,459,892.92 € in 2001, 1,468,983.58 € in 2002 and 1,370,227.80 € in 2003.

Discussion

Our study shows that the number of cases of Leishmaniasis presents non-homogeneous trend in Italy, especially in coastal regions, through the study period.
The prevalence rates, based on discharges data, were higher in Central-Southern regions and in Islands (endemic area) than in other areas, where only sporadic cases were reported from 1999 to 2003. Probably such a phenomenon was not due to different climate conditions, because some areas present similar conditions, such as Emilia Romagna and Lazio, showed different prevalence rates.
Ordinary admissions decreased through the considered period, while day-hospital ones increased significantly. This suggests a better employ of resources, but it also demonstrates a constant and high health care need for this infectious disease.
Campania and Sicilia showed the highest number of cases, both for day-hospital and ordinary hospitalization. However, we have to consider that these regions have set disease surveillance programs in recent years [3].
Visceral Leishmaniasis was responsible of about 60-70% of disease cases. The mean hospital stay did not increase through the whole period. From 1999 to 2003, the most affected age-groups were children from 1 to 4 years and adults from 25 to 64 of age. This fact was confirmed by the high number of notifications of visceral Leishmaniasis in the 0-14 age group, followed by the 25-64 age group, in the same period. The high number of notifications in the age-group from 25 to 64 can be related, in the most struck areas, with professional risk factors for Leishmaniasis or self-immunity diseases [28, 29], while the high number of cases among 0-14 years old individuals can be related to outdoor activities of children and adolescents.
Our study confirms that human Leishmaniasis and, in particular, visceral Leishmaniasis, is re-emerging. In fact, notifications of the disease have slowly increased after 1993; there is a new disease spreading in Italy, as observed from other Authors [5]. This can be explained

Tab. II. Percentage of Visceral Leishmaniasis discharges (VL cases/Leishmaniasis total discharges) and mean days of hospital stay for Visceral Leishmaniasis. (OH = ordinary hospital; DH = day hospital).

Year	1999				2000				2001				2002				2003			
Type of	OH		DH		OH		DH		OH		DH		OH		DH		OH		DH	
Hospitalization Regions	cases VL	Mean days*	cases VL°	Mean days*	cases VL°	Mean days*	cases VL°	Mean days*	cases VL°	Mean days*	cases VL°	Mean days*	cases VL°	Mean days*	cases VL°	Mean days*	cases VL°	Mean days*	cases VL°	Mean days*
Piemonte	62.5	7	60	1.7	72.7	12.4	80	4.4	73.3	14.4	66.7	5.8	100.0	16.8	75	13	100	16.6	75	5.17
Lombardia	55.2	15.8	50	6.2	76	12.2	70	3.6	86.7	10.1	57.1	4.8	69.6	19.6	62.5	7.8	26.7	23.3	26.3	3
P.A. Bolzano	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.
P.A. Trento	100	8	N.C.	N.A.	N.C.	N.A.	0	N.A.	66.7	8.5	100	14	100	43	N.C.	N.A.	50	15	50	5
Veneto	60	9.3	66.7	4	46.2	14.5	66.7	24	16.7	29	66.7	4.5	50	12	60	18	100	15.2	83.3	5.41
Friuli V.G.	N.C	N.A	N.C.	N.A.	100	28	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.
Liguria	58.3	7.7	100	12	87.5	13.9	66.7	2.8	78.9	10.7	81.8	4.7	100	9.7	100	3	94.4	10.6	66.7	2
Emilia Romagna	71.4	22.8	50	7.3	42.9	9.7	50	23.5	100	21.5	41.7	6.6	100	13.2	75	4.2	69.2	15.1	53.3	8
Toscana	38.5	30	28.6	3.5	57.1	9.9	60	10.3	88.9	12.8	100	12.2	76.2	15.3	100	12.2	90	12.2	85.7	6.84
Umbria	N.C.	N.A.	N.C.	N.A.	33.3	24	N.C.	N.A.	66.7	34.5	100	5	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.
Marche	50	23	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.
Lazio	75	15.9	50	5	73.2	15.6	41.7	6	61.3	11.8	65.2	3.1	62.2	10.7	60	4.3	51.5	14.4	53.1	4.71
Abruzzo	100	15.4	100	1	100	18.2	66.7	2.5	100	16.6	N.C	N.A	80	37.8	N.C	N.A	100	20.5	75	2.34
Molise	100	7	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	100	11	N.C.	N.A.	100	11	N.C.	N.A.	100	9	N.C.	N.A.
Campania	79.4	9.3	82.9	2	85	9.7	86	2.7	67.9	10	85.7	2.7	74.8	8.7	79.6	2.4	89.5	7.6	91.9	1.65
Puglia	86.7	15.2	66.7	8	68.6	12	50	4.3	80.5	16.3	66.7	2.6	62.1	16.1	50	1	68	13.6	60	3.67
Calabria	73.3	15.1	77.8	2.2	41.7	8.8	77.8	3.2	69.2	11.9	44.4	1.5	61.1	8.4	46.7	3	60	6.2	20	1
Sicilia	86.7	8.7	42.2	14.7	77.8	13.7	29.9	6.2	73.4	10.1	28.4	5.8	64.4	11.7	25.6	4	69.1	11.8	24.4	3.33
Sardegna	87.5	13.8	91.7	2.8	88	19.1	100	3.2	85.7	20.5	92.3	1.5	81.8	19	60	3	91.7	15.7	87.5	3.43
Basilicata	N.C.	N.A.	N.C.	N.A.	25	35	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	75	26.7	100	4	N.C.	N.A.	33.3	2
Valle d'Aosta	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.	N.C.	N.A.
Total	62.3	14	61.9	5.4	61.8	16	60.4	7.4	67.5	15.6	58.6	5.4	73.9	17.5	59.6	6.1	68.2	13.8	53.3	3.5

VL = Visceral Leishmaniasis; N.A. = Not Available; N.C. = Not Computable; * = Mean days of hospital stay

Tab. III. Prevalence rates (per 1.000.000 residents) of ordinary hospitalization and day-hospital for Leishmaniasis, stratified by Regions, from 1999 to 2003.

Regions	1999		2000		2001		2002		2003	
	OH prev. rates	DH prev. rates	OH prev. rates	DH prev. rates	OH prev. rates	DH prev. rates	OH prev. rates	DH prev. rates	OH prev. rates	DH prev. rates
Piemonte	1.89	1.18	2.60	2.37	3.55	2.13	1.19	0.95	1.18	1.89
Lombardia	3.24	1.34	2.79	3.34	1.67	3.89	2.55	3.54	1.65	2.09
P.A. Bolzano	2.19	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
P.A. Trento	6.42	N.A.	N.A.	4.25	6.32	2.11	2.09	N.A.	8.28	4.14
Veneto	1.12	0.67	2.90	0.67	1.33	0.67	1.32	1.10	1.53	1.31
Friuli V.G.	0.85	N.A.	0.85	N.A.	0.85	N.A.	N.A.	N.A.	N.A.	N.A.
Liguria	7.51	1.88	5.04	3.78	12.03	6.97	6.37	1.91	11.45	5.72
Emilia Romagna	1.78	1.53	1.77	2.03	0.50	3.03	1.25	2.01	3.23	3.72
Toscana	3.72	2.01	4.01	2.86	2.58	1.72	6.01	1.72	5.69	1.99
Umbria	1.22	N.A.	3.65	N.A.	3.64	1.21	1.21	1.21	N.A.	1.20
Marche	1.38	0.69	0.69	N.A.	N.A.	0.68	N.A.	0.68	1.35	N.A.
Lazio	9.37	2.73	13.88	4.69	12.12	4.50	7.23	2.93	12.83	6.22
Abruzzo	3.97	1.59	3.96	2.38	3.96	0.79	3.96	N.A.	3.14	3.14
Molise	9.26	N.A.	3.10	N.A.	3.11	N.A.	9.36	N.A.	3.11	N.A.
Campania	18.70	7.16	26.76	9.97	19.10	17.17	20.87	8.59	15.02	17.29
Puglia	7.42	0.74	8.68	2.97	10.18	2.98	7.21	1.49	6.21	1.24
Calabria	7.35	4.41	5.92	4.44	6.44	4.46	8.96	7.46	4.98	4.98
Sicilia	26.98	12.79	14.42	19.43	15.87	31.14	20.94	44.91	16.29	35.40
Sardegna	14.62	7.31	15.26	12.21	8.56	7.95	6.74	6.13	7.33	4.89
Basilicata	N.A.	N.A.	6.65	N.A.	1.67	N.A.	6.69	1.67	1.68	5.03
Valle d'Aosta	N.A.	N.A.	N.A.	N.A.	N.A.	16.77	N.A.	N.A.	N.A.	N.A.
Total	7.89	3.20	8.10	5.11	6.99	6.88	7.05	6.65	6.45	7.05

DH = day-hospital discharges; OD = ordinary hospital discharges; N.A. = Not Available

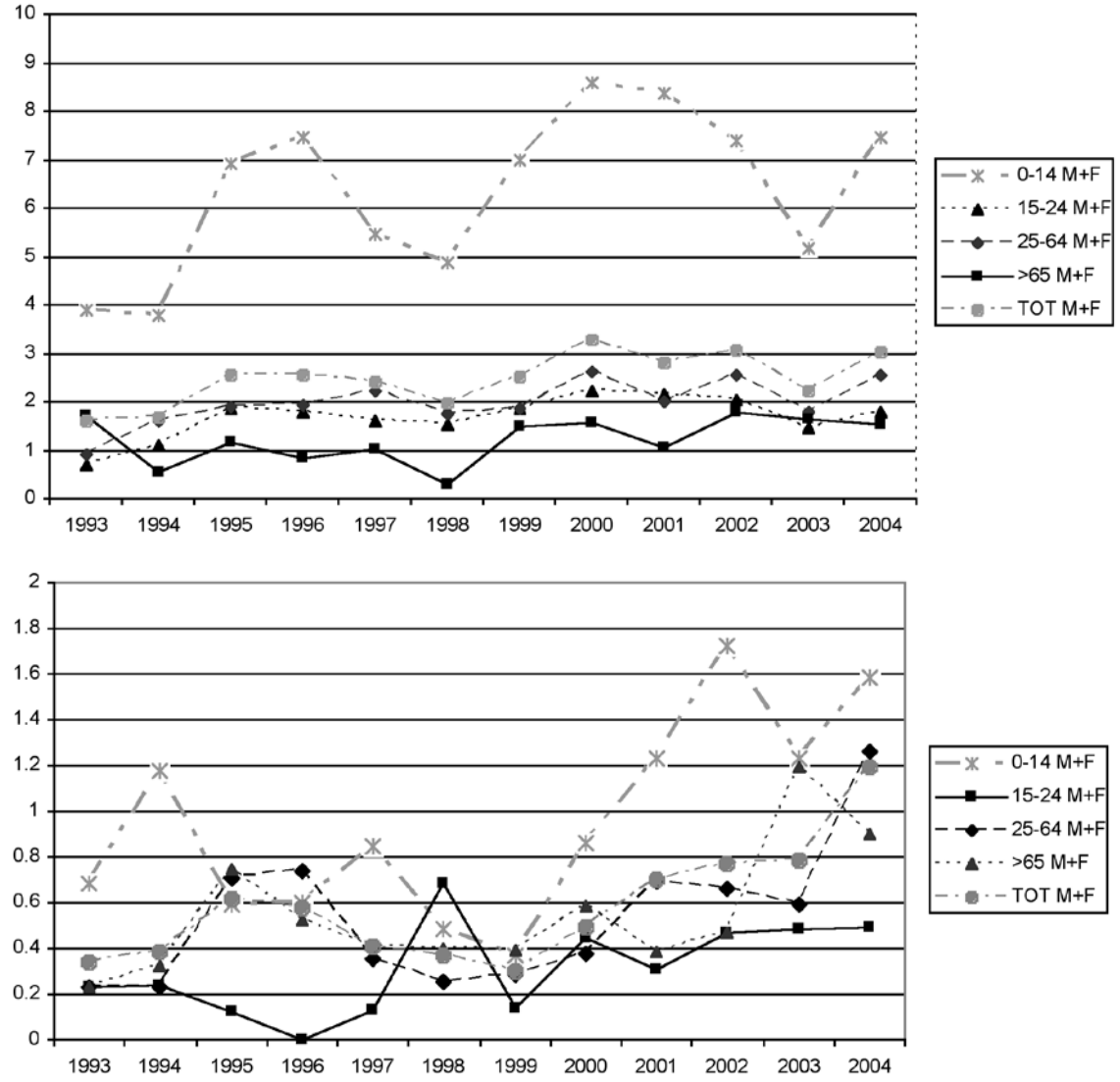
even by the identifications of new active foci of canine Leishmaniasis in Northern regions [3, 4]. Anyway, other concomitant factors could play an important role in the spread of the disease such as the climatic changes in Italy and the changing of human behaviours towards animals.
Death from Leishmaniasis is a rare event and few people died of Leishmaniasis in Italy, from 1993 to 1998. Mortality was not relevant for most of patients, except for the elderly. It is interesting that the highest mortality rates were observed in the extreme age-group: these patients are the less exposed to risk factors, but they are the ones with the heaviest outcomes of the illness, maybe due to late diagnosis. Patients aged 1-14 years reached a top of mortality only in one year, while the group from 15 to 24 years showed a mortality rates equal to zero throughout the considered period. These data suggest that even if death represents a rare outcome of Leishmaniasis, the young and the elderly have to be considered at high risk for death. As the disease is fatal if untreated, priority will be given to early detection of human cases. In fact, several cases are undiagnosed or misdiagnosed, especially when people have difficult access to health services. Early case finding [32] and immediate treatment of infected subjects are two important tools to limit the disease burden. Diagnosis of Leishmaniasis lean on serological tests and on aspirates of spleen, bone marrow or lymph-node. Both these two diagnostic approaches present some limits as the serological tests are too much centralized and parasitological exams are invasive and difficult to decentralise [33].
The diffusion of Leishmaniasis has to be faced through different interventions. It is known that environmental interventions of primary prevention (the struggle against vector insects, the control of canine and human reserves [28, 30]) are efficacious. In Public Health, the control of Leishmaniasis rests on preventive measures. The use of repulsive substances against phlebotomists, early diagnosis through periodical veterinary dogs' checkups and, above all, the engagement and the steadfastness to apply therapeutic protocol [30] as treatment of dogs allow to reduce the parasite-concentration of the animals and to support the cells-mediated immune reply [31].
Moreover first line drugs (Sb5+) are too much expensive and they have to be given systematically for a long time. During recent years a lot of efforts have been made by researchers in human and veterinary medicine to develop new therapeutic protocols to treat Leishmaniasis. Despite of this, anti- Leishmaniasis drugs are still not efficient, cheap, and easy to administer to patients and lacking in side effects.
From our point of view the disease control can be obtained only by establishing a national surveillance system, implementation of already existing surveillance program and inviting physicians to look for the disease in patients with systemic symptoms.

Tab. IV. Visceral Leishmaniasis distribution for age-groups (in years) and gender (Male/Female), in five years (1999-2003).

Year		1999				2000				2001				2002				2003			
Type of Hospitalization		OH		DH		OH		DH		OH		DH		OH		DH		OH		DH	
Age Group		M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
< 1 y	Discharges	12.00	15.00	2.00	4.00	18.00	19.00	6.00	12.00	14.00	6.00	7.00	3.00	6.00	9.00	1.00	5.00	9.00	12.00	6.00	7.00
	Mean days*	13.42	9.74	4.50	2.00	11.73	7.48	5.50	2.5	8.86	3.17	2.86	3.34	11.67	9.00	7.00	3.00	11.78	8.42	2.00	3.58
1-4 y	Discharges	29.00	16.00	17.00	16.00	38.00	29.00	24.00	23.00	27.00	19.00	27.00	31.00	23.00	26.00	13.00	17.00	18.00	23.00	32.00	35.00
	Mean days*	8.56	6.88	1.89	1.50	12.29	8.32	2.84	2.22	9.63	8.27	2.12	2.55	6.79	8.58	2.00	3.06	5.39	7.31	1.66	1.83
5-14 y	Discharges	24.00	10.00	11.00	5.00	12.00	5.00	10.00	8.00	13.00	20.00	14.00	13.00	6.00	12.00	6.00	9.00	21.00	7.00	22.00	10.00
	Mean days*	9.50	8.60	5.55	2.40	10.50	13.00	5.71	2.13	8.70	10.31	2.00	2.93	9.17	8.75	2.67	2.45	8.67	6.15	1.82	1.40
15-24 y	Discharges	28.00	12.00	5.00	1.00	32.00	6.00	2.00	1.00	10.00	9.00	4.00	4.00	15.00	9.00	11.00	6.00	12.00	4.00	11.00	0.00
	Mean days*	7.83	7.67	22.61	70.00	13.22	16.17	3.50	1.00	12.70	12.23	7.00	6.50	9.74	11.67	3.37	5.34	7.84	5.25	2.19	0.00
25-44 y	Discharges	81.00	19.00	16.00	6.00	57.00	28.00	28.00	10.00	49.00	20.00	40.00	12.00	59.00	17.00	37.00	12.00	63.00	14.00	23.00	7.00
	Mean days*	12.99	7.95	7.07	14.50	15.86	11.75	7.08	7.91	14.82	18.00	5.13	7.34	13.41	13.06	4.82	8.59	14.16	9.15	5.14	2.29
45-64 y	Discharges	56.00	9.00	15.00	1.00	63.00	16.00	27.00	9.00	45.00	14.00	33.00	14.00	42.00	16.00	24.00	4.00	30.00	14.00	25.00	6.00
	Mean days*	15.45	11.89	5.00	1.00	14.05	11.94	7.38	5.45	15.41	11.86	4.97	4.72	15.93	18.07	8.17	5.25	15.41	17.36	5.05	4.17
65-74 y	Discharges	17.00	7.00	4.00	3.00	15.00	2.00	4.00	1.00	27.00	4.00	7.00	7.00	16.00	14.00	11.00	4.00	13.00	10.00	9.00	8.00
	Mean days*	15.12	15.15	2.75	5.34	11.00	15.00	1.75	2.00	10.04	7.75	7.15	3.58	12.07	13.22	2.00	7.25	14.93	19.00	5.34	5.13
> 75 y	Discharges	5.00	9.00	0.00	3.00	3.00	5.00	2.00	1.00	2.00	5.00	0.00	1.00	9.00	4.00	2.00	1.00	13.00	5.00	3.00	0.00
	Mean days*	9.81	14.12	0.00	15.67	8.34	16.40	6.50	1.00	31.50	7.41	0.00	1.00	15.23	18.75	2.50	1.00	11.85	7.80	2.67	0.00
Total	Discharges	252.00	97.00	70.00	39.00	238.00	110.00	103.00	65.00	187.00	97.00	132.00	85.00	176.00	107.00	105.00	58.00	179.00	89.00	131.00	73.00
	Mean days*	12.22	9.54	5.92	6.80	13.48	10.70	5.66	3.54	12.72	11.20	4.19	3.92	12.60	12.01	4.64	4.75	12.19	10.49	3.28	2.54

OH = ordinary hospital; DH = day hospital; * = Mean days of hospital stay

Fig. 1. Italian temporal trend of Visceral (Fig. 1A) and Cutaneous (Fig. 1B) Leishmaniasis notifications incidence rates (rate between notifications and population *1,000,000), for age-bands, from 1993 to 2004.



The implementation of surveillance system should be different in different areas in relation to the different distribution of disease, the different health services available in the area and different perception of disease [28]. Health education has to be supported in order to increase the level of awareness among exposed population and bring vectors and human resevoir under control trough promotion of control measures [34].

Primary prevention would be turned to reservoir control by using deltamethrin treated collars in dogs; these reduce up to 90% the proportion of sand flies that take a blood meal from dogs [35]. The reservoir control can be obtained only with the engage of veterinaries and Zooprophylactic Institutes. The collaboration between medical and veterinary setting and the exchange of epidemiological data is the most important instrument to determine the priorities in the surveillance system and to control the spread of the disease.

Regarding preventing measures direct to humans, our study shows that these should be turned to extreme age-groups (young and elderly) which represent those at higher risk; further studies would be performed to probe the risk factors to be infected.

Our study has some limitations and some strengths. One of the limits is represented by the possible information bias as the number of the notified cases of Leishmaniasis may be underreported, even if the disease is included in the class two of notification, according to the Ministerial decree 15 December 1990. As disease is also under-diagnosed, so that not all cases have been hospitalized, we can hypothesize that we have underestimated disease burden. Moreover the costs analysis is not complete because we only considered the direct hospitalisation costs.

Anyway, we considered two different, institutional and reliable sources of data and we can so affirm that our study best represents Italian situation. Cost analysis, even if incomplete, shows that efforts would be done to improve and optimize treatment costs and times.

Tab. V. Hospitalizations costs for Leishmaniasis (in euro), stratified by Regions (1999-2003). Ordinary hospitalization (OH), day hospitalization (DH) and total costs (Total = ordinary + day hospitals costs).

	1999			2000			2001			2002			2003		
Regions	DH	OH	Total	DH	OH	Total	DH	OH	Total	DH	OH	Total	DH	OH	Total
Piemonte	1,647.50	26,748.30	28,395.80	3,295.00	36,778.90	40,073.90	2,965.50	50,153.10	53,118.60	1,318.00	16,717.70	18,035.70	2,636.00	16,717.70	19,353.70
Lombardia	3,954.00	96,962.70	100,916.70	9,885.00	83,588.50	93,473.50	11,532.50	50,153.10	61,685.60	10,544.00	76,901.40	87,445.40	6,260.50	50,153.10	56,413.60
P.A. Bolzano	—	3,343.50	3,343.50	—	—	—	—	—	—	—	—	0.00	—	—	—
P.A. Trento	—	10,030.60	10,030.60	659.00	—	659.00	329.50	10,030.60	10,360.10	—	3,343.50	3,343.50	659.00	13,374.20	14,033.20
Veneto	988.50	16,717.70	17,706.20	988.50	43,466.00	44,454.50	988.50	20,061.20	21,049.70	1,647.50	20,061.20	21,708.70	1,977.00	23,404.80	25,381.80
Friuli V.G.	—	3,343.50	3,343.50	—	3,343.50	3,343.50	—	3,343.50	3,343.50	—	—	0.00	—	—	—
Liguria	988.50	40,122.50	41,111.00	1,977.00	26,748.30	28,725.30	3,624.50	63,527.30	67,151.80	988.50	33,435.40	34,423.90	2,965.50	60,183.70	63,149.20
Emilia Romagna	1,977.00	23,404.80	25,381.80	2,636.00	23,404.80	26,040.80	3,954.00	6,687.10	10,641.10	2,636.00	16,717.70	19,353.70	4,942.50	43,466.00	48,408.50
Toscana	2,306.50	43,466.00	45,772.50	3,295.00	46,809.60	50,104.60	1,977.00	30,091.90	32,068.90	1,977.00	70,214.30	72,191.30	2,306.50	66,870.80	69,177.30
Umbria	—	3,343.50	3,343.50	—	10,030.60	10,030.60	329.50	10,030.60	10,360.10	329.50	3,343.50	3,673.00	329.50	—	329.50
Marche	329.50	6,687.10	7,016.60	—	3,343.50	3,343.50	329.50	—	329.50	329.50	—	329.50	—	6,687.10	6,687.10
Lazio	4,613.00	160,489.90	165,102.90	7,908.00	237,391.30	245,299.30	7,578.50	207,299.50	214,878.00	4,942.50	123,711.00	128,653.50	10,544.00	220,673.60	231,217.60
Abruzzo	659.00	16,717.70	17,376.70	988.50	16,717.70	17,706.20	329.50	16,717.70	17,047.20	—	16,717.70	16,717.70	1,318.00	13,374.20	14,692.20
Molise	—	10,030.60	10,030.60	—	3,343.50	3,343.50	—	3,343.50	3,343.50	—	10,030.60	10,030.60	—	3,343.50	3,343.50
Campania	13,509.50	357,758.80	371,268.30	18,781.50	511,561.60	530,343.10	32,291.00	364,445.90	396,736.90	16,145.50	397,881.30	414,026.80	32,620.50	287,544.40	320,164.90
Puglia	988.50	100,306.20	101,294.70	3,954.00	117,023.90	120,977.90	3,954.00	137,085.10	141,039.10	1,977.00	96,962.70	98,939.70	1,647.50	83,588.50	85,236.00
Calabria	2,965.50	50,153.10	53,118.60	2,965.50	40,122.50	43,088.00	2,965.50	43,466.00	46,431.50	4,942.50	60,183.70	65,126.20	3,295.00	33,435.40	36,730.40
Sicilia	21,088.00	451,377.90	472,465.90	31,961.50	240,734.90	272,696.40	51,072.50	264,139.70	315,212.20	73,478.50	347,728.20	421,206.70	57,992.00	270,826.70	328,818.70
Sardegna	3,954.00	80,245.00	84,199.00	6,590.00	83,588.50	90,178.50	4,283.50	46,809.60	51,093.10	3,295.00	36,778.90	40,073.90	2,636.00	40,122.50	42,758.50
Basilicata	—	—	—	—	13,374.20	13,374.20	—	3,343.50	3,343.50	329.50	13,374.20	13,703.70	988.50	3,343.50	4,332.00
Valle d'Aosta	—	—	—	—	—	—	659.00	—	659.00	—	—	—	—	—	—
Total	59,969.00	1,501,249.50	1,561,218.50	95,884.50	1,541,371.90	1,637,256.40	129,164.00	1,330,728.90	1,459,892.90	124,880.50	1,344,103.10	1,468,983.60	133,118.00	1.237.109,80	1,370,227.80

Lack of an effective vaccine against different form of Leishmaniasis and the difficulty to contrast the diffusion of vectors represent the major limits for the control of the disease.

As the high economic weight of the disease, cost-effectiveness evaluation of current therapeutic approach compared to preventive interventions toward dogs and vector insects would be interesting for future studies.

References

[1] Cascio A, Colomba C. *Childhood Mediterranean visceral Leishmaniasis*. Infez Med 2003;11:5-10.

[2] Gradoni L. *The diagnosis of canine Leishmaniasis*. In: *Canine Leishmaniasis: moving towards a solution. Proceedings of the 2nd International Canine. Leishmaniasis International Forum*. Boxmeer, Netherland: ed. Intervet International 2002, pp. 7-14.

[3] Capelli G, Baldelli R, Ferroglio E, Genchi C, Gradoni L, Gramoccia M, et al. *Monitoring of canine Leishmaniasis in northern Italy: an update from a scientific network*. Parassitologia 2004;46:193-7.

[4] Ferroglio E, Maroli M, Gastaldo S, Mignone W, Rossi L. *Canine Leishmaniasis, Italy*. Emerg Infect Dis [serial on the Internet] 2005 Oct [date cited]. Available from: http://www.cdc.gov/ncidod/EID/vol11no10/04-0966.htm

[5] Gradoni L, Gramiccia M, Scalone A. *Visceral Leishmaniasis treatment, Italy*. Emerg Infect Dis [serial online] 2003 Dec [date cited]. Available from: http://www.cdc.gov/ncidod/EID/vol9no12/03-0178.htm

[6] Epicentro. Leishmaniosi. Aspetti epidemiologici. Available online at: http://www.epicentro.iss.it/problemi/Leishmaniosi/epid.htm#I_rischi_epidemiologici_della_coinfezione_Hiv/Leishmania

[7] WHO. Leishmaniasis. Magnitude of the problem. Available online at: http://www.who.int/Leishmaniasis/burden/magnitude/burden_magnitude/en/index.html

[8] Gaeta GB, Gradoni L, Gramiccia M, Martino L, Pizzuti R, Pempiello R, et al. *Leishmaniosi viscerale in Italia*. Recenti Progressi in Medicina 1994;85:340-7.

[9] World Health Organization (WHO). Leishmania/HIV coinfection: south-western Europe 1990-1998 (WHO/LEISH/2000.42). Geneva: WHO,2000)

[10] Verso MG, Caracappa S, Vitale F, Vesco G, Picciotto D. *Rilievi epidemiologici della Leishmaniosi nel territorio italiano*. G Ital Med Lav Erg 2003;25:441-3.

[11] WHO. *Leishmaniasis: background information, The disease and its epidemiology*. http://www.who.int/Leishmaniasis/disease_epidemiology/en/index.html

[12] Gramiccia M. *La Leishmaniosi del vecchio mondo*. Ann Ist Super Sanità 1997;33:231-9.

[13] Cascio A, Gradoni L, Scarlata F, Gramoccia M, Giordano S, Russo R, et al. *Epidemiologic surveillance of visceral Leishmaniasis in Sicily, Italy*. Am J Trop Med Hyg 1997;57:75-8.

[14] Gradoni L, Pozio E, Gramiccia M, Maroli M, Bettini S. *Leishmaniasis in Tuscany (Italy): VII, Studies on the role of the black rat, Rattus rattus, in the epidemiology of visceral Leishmaniasis*. Trans R Soc Trop Med Hyg 1983;77:427-31.

[15] Gradoni L, Pizzuti R, di Martino L, Gramoccia M, Pempinello R, Gaeta GB, et al. *The epidemiology and surveillance of visceral Leishmaniasis in the Campania region of Italy. The value of zymodeme typing*. Epidemiol Infect 1993;111:297-306.

[16] Orndorff GR, Cooper BA, Smith W, Ryan JR. *Canine visceral Leishmaniasis in Sicily*. Mil Med 2000;165:29-32.

[17] Maroli M, Bigliocchi F, Khoury C. *Il flebotomo in Italia: osservazioni sulla distribuzione e sui metodi di campionamento*. Parassitologia 1994;36:251-64.

[18] World Health Organization. Leishmania-HIV co-infection. *Epidemiological analysis of 692 retrospective cases*. Wkly Epidemiol Rec. 1997;72:49-54.

[19] Desjeux P, Alvar J. *Leishmania/HIV co-infections: epidemiology in Europe*. Ann Trop Med Parasitol 2003;97(Suppl 1): S3-S15.

[20] Molina R, Gradoni L, Alvar J. *HIV and the transmission of Leishmania*. Ann Trop Med Parasitol 2003;97:29-45.

[21] Russo R, Nigro L, Panarello G, Montineri A. *Clinical survey of Leishmania/HIV co-infection in Catania, Italy: the impact of highly active antiretroviral therapy (HAART)*. Ann trop med Parasitol 2003;97(Suppl 1):149-55.

[22] Tremblay M, Olivier M, Bernier R. *Leishmania and the pathogenesis of HIV infection*. Parasitol Today 1996;12:257-61.

[23] http://www.ministerosalute.it/programmazione/sdo/ric_informazioni/default.jsp

[24] http://www.ministerosalute.it/promozione/malattie/bollettino.jsp

[25] http://www.demo.istat.it

[26] http://www.epicentro.iss.it/morti_index.htm

[27] http://www.ministerosalute.it/programmazione/normativa/sezNormativa.jsp?label = tar

[28] Gradoni L, Gramiccia M, Khoury C, Maroli M. *Linee guida per il controllo del serbatoio canino della leishmaniosi viscerale zoonotica in Italia*. Rapporti ISTISAN 04/12.

[29] Gradoni L, Pizzuti R, Scalone A, Russo M, Gramoccia M, di Martino L, et al. *Recrudescence of visceral Leishmaniasis unrelated to HIV infection in the Campania region of Italy*. Trans R Soc Trop Med Hyg 1996;90:234-5.

[30] Ghinelli F, Libanore M. *Vector-borne diseases, Recent advances in the diagnosis, treatment and prevention*. Recenti Prog Med 2002;93:45-57.

[31] Bongiorno G, Habluetzel A, Khoury C, Maroli M. *Host preferences of phlebotomine sand flies at a hypoendemic focus of canine Leishmaniasis in central Italy*. Acta Trop 2003;88:109-16.

[32] Ryan JR, Smithyman AM, Rajasekariah GH, Hochberg L, Stiteler JM, Martin SK. *Enzyme linked immunosorbent assay based on soluble promastigote antigen detects immunoglobulin, M (IgM) and IgG antibodies in sera from cases of visceral and cutaneous Leishmaniasis*. J Clin Microbiol 2002;40:1037-43.

[33] World Health Organization. Special programme for research and training in tropical disease (TDR). Strategic direction for research: Leishmaniasis. February 2002. Available online at: http://www.who.int/tdr/diseases/leish/files/direction.pdf

[34] Desjeux P. *Leishmaniasis. Public Health Aspects and Control*. Clin Dermat 1996;14:417-23.

[35] Reithinger R, Teodoro U, Davies CR. *Topical insecticide treatments to protect dogs from sand fly vectors of Leishmaniasis*. Emerg Infect Dis 2001;7:872-6.

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