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Human visceral leishmaniasis: A picture from Italy

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Abstract The aim of our study was to describe the distribution of Visceral Leishmaniasis (VL) in Italy, focusing on HIV-infected patients, to estimate the burden of the disease and the public health actions that should be undertaken. A review of official notifications and hospitalization data has been performed. From 2006 to 2008, a total of 289 cases of VL were notified; the overall notification rate was 1.63/1,000,000 (95% CI 1.45—1.83). In total, 1192 VL-associated hospitalizations were detected, with a hospitalization rate of 6.71/1,000,000 (95% CI 6.34—7.10). For the age group ''≤24 years'', a statistically significant increase was detected ($p < 0.05$). A total of 68.9% ($n = 821$) of hospitalizations were detected in HIV-positive patients. The geographic distribution of rates revealed a significant increase in the north-eastern area of the country. Our study confirms that the epidemiological pattern of VL is changing and that, in Italy, control measures and preventive strategies should be based on not only the official notification system but also hospital data. This would lead to the identification of areas of parasite spread and to the creation of awareness campaigns geared toward general practitioners in the affected areas. Easy case detection would allow for timely public health actions and strategies for the implementation of more effective interventions for reservoir control.

Introduction

Leishmaniasis is a major vector-borne infection caused by more than 20 leishmanial protozoa and is transmitted to humans by approximately 30 different species of *Phlebotomine sandflies* [1]. Leishmaniasis is endemic in the Mediterranean basin and in large areas of the tropics and subtropics [2]. The host inflammatory immune response

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regulates the expression and the outcome of the disease [3]. Symptomatic disease is subacute or chronic and diverse in presentation and outcome. Without treatment, visceral leishmaniasis is almost universally fatal [4].

The human disease is present in two different epidemiological and clinical forms: visceral leishmaniasis (VL) and cutaneous leishmaniasis (CL). Dogs are considered to be the major host for these parasites and the main reservoir for human visceral infection [5]. VL is a typical rural and periurban disease and is present in patchy spots along areas of the Tyrrhenian Coast, the low Adriatic Coast and in the Islands, according to the biological characteristics of the vectors. Cases of VL have been reported in many regions of the center-south, but the most affected areas are in Campania and Sicily [2,5]. The mean increase in atmospheric temperature could possibly favor the diffusion of VL and its vectors into regions of northern Italy that, until a few years ago, were untouched, with only sporadic cases of canine leishmaniasis reported. The increase in temperature could also increase the incidence of VL in the regions where it is already endemic [6]. Moreover, co-infection of Leishmania and human immunodeficiency virus (HIV) has emerged as a serious health concern [7—11], and VL promotes the clinical progression of HIV disease [12].

In Italy, VL is a notifiable disease; however, infection reporting is not rigorous in all regions, meaning that VL could be underreported [13].

The aim of our study was to describe the distribution of VL in Italy, with a focus on HIV-infected patients, to assess the burden of the disease and the public health actions that should be undertaken.

Materials and methods

In Italy, VL is a notifiable disease; the number of VL official notifications for the period from 2006 to 2008 was retrieved from the Ministry of Health website. In Italy, the national surveillance system for communicable diseases was revised in 1990. Notifiable diseases were grouped into five categories, defined according to the urgency with which they must be reported and the type of information to be collected. Italy is divided into 20 geographic regions, each of which has a regional health authority responsible for public health activities. Specifically, within each region, there are a number of health facilities known as local health units that, through a department known as the public health service, are responsible for local public health activities. Physicians are required to report

Fig. 1 Distribution of Italian regions by ISTAT geographical areas.

all confirmed and suspected cases of communicable diseases to the public health service of the local health unit. The local health unit then groups the cases and sends them to the Regional Health Authority, which forwards the data to the national level, namely the Ministry of Health, the National Institute of Health (ISS) and the National Institute of Statistics (ISTAT) [14].

The resident population was estimated using data from the Italian National Institute of Statistics (http://demo.istat.it/); population data were obtained according to sex, age groups (<15; 15—24 years; 25—64 years; ≥65 years) and geographical region The Italian regions are follows: North—West (Valle d'Aosta, Piemonte, Liguria, Lombardia); North—East (Trentino Alto Adige, Veneto, Friuli—Venezia—Giulia, Emilia—Romagna); Center (Toscana, Marche, Umbria, Lazio); South (Campania, Abruzzi, Molise, Basilicata, Puglia, Calabria); and the Islands (Sicilia, Sardegna). The distribution of Italian regions by geographical areas is shown in Fig. 1. Data on hospitalizations came from the Italian Ministry of Health; the hospital discharge record is a synthesis of the patient's medical record and is mandatory for both inpatients and outpatients and contains, for each hospital discharge in Italy, the social and demographic data of the patient (i.e. age, gender, place of birth, place of residence) and the clinical data (''principal''

Table 1 Number of Visceral Leishmaniasis (VL) notifications and temporal trend of VL notifications incidence rates (rate between VL notifications and population × 1,000,000), for age groups, from 2006 to 2008, in Italy.

	2006		2007		2008		p^a	
	n°	Rate [95% CI]	n°	Rate [95% CI]	n°	Rate [95% CI]		
≤24 years	34	2.37 [1.67–3.27]	23	1.60 [1.04–2.36]	25	1.73 [1.15–2.51]	N.S.	
25–64 years	60	1.83 [1.41–2.34]	64	1.94 [1.51–2.46]	35	1.05 [0.75–1.45]	<0.05	↓
≥65 years	19	1.64 [1.02–2.51]	17	1.44 [0.87–2.26]	12	1.00 [0.55–1.70]	N.S.	
Global	113	1.92 [1.59–2.30]	104	1.76 [1.44–2.12]	72	1.21 [0.95–1.51]	<0.05	

[a] Cochrane–Armitage test for linear trend.

diagnosis and up to five other diagnoses, procedures and outcomes). Diagnoses and procedures are coded using the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9 CM). Data from all over Italy are collected in the National Hospital Discharge Database, available from the Ministry of Health. Hospital discharge data were examined for the 3-year period 2006–2008. A VL-associated hospitalization event was defined as a hospitalization for which the ICD-9-CM code ''085: Visceral Leishmaniasis'' was listed among the discharge diagnosis (one principal and up to five secondary diagnoses). Each hospitalized patient is identified by a single (anonymous) ID code that has allowed us to consider only the first VL-associated hospitalization event; thus, we have the possibility to exclude readmissions for relapses or maintenance of therapy in the same individual. VL-associated hospitalizations were analyzed according to the year of discharge, patient's sex, age groups (≤24 years; 25–64 years; ≥65 years), geographical region of residence, co-infection with HIV and nationality. Hospitalizations relating to HIV-infected patients were identified by searching for the ICD-9-CM code ''042: Human immunodeficiency virus [HIV] disease'' among the discharge diagnosis (one principal and up to five secondary diagnoses). Additionally, in this case, all re-hospitalizations were excluded according to the ID code available for each patient.

All data used in this analysis were released in an anonymous form; therefore, the approval of an Ethics Committee was not required.

The rates of VL notifications and hospitalizations were calculated by dividing the number of notifications by the resident population in each region. All rates were expressed per 1,000,000 people in the resident population. Confidence intervals were calculated using the Poisson approximation. A Cochran–Armitage test for trend [15,16] was used to assess the significance levels of variation of notification and of hospitalization rates over the years in different geographical areas of the country. Under-reporting was estimated, on a regional basis, by calculating the proportion of notified cases over the number of hospitalizations.

Statistical analysis was performed using Stata software package 9.0. [17]. The level of significance was set at 0.05.

Results

Notifications

During 2006–2008, a total of 289 cases of VL were notified in Italy; the overall notification rate was 1.63/1,000,000 (95% CI 1.45–1.83). The notification rate was higher in males (2.24/1,000,000; 95% CI 1.93–2.58) than in females (1.05/1,000,000; 95% CI 0.85–1.28).

The temporal trend of VL notifications rates by age groups was analyzed (Table 1): globally, in Italy, a statistically significant reduction in notification rates was detected ($p < 0.05$). In particular, the decrease was statistically significant for the 25–64-year age group ($p < 0.05$).

Hospitalizations

During the same period, 1192 VL-associated hospitalizations were registered; the global hospitalization rate was 6.71/1,000,000 (95% CI 6.34–7.10). The rate was higher in males (9.33/1,000,000; 95% CI 8.70–10.01) than in females (4.23/1,000,000; 95% CI 3.82–4.68).

The temporal trend of VL-associated hospitalization rates during the years 2006–2008 by age groups is shown in Table 2. Globally, in Italy, an increase in the VL-associated hospitalization was observed,

Table 2 Number of VL hospitalizations and temporal trend of VL hospitalizations incidence rates (rate between VL-associated hospitalizations and population × 1,000,000), for age groups, from 2006 to 2008, in Italy.

	2006		2007		2008		p^a	
	n°	Rate [95% CI]	n°	Rate [95% CI]	n°	Rate [95% CI]		
≤24 years	28	1.95 [1.32–2.78]	68	4.73 [4.69–4.77]	194	13.43 [11.64–15.42]	<0.05	↑
25–64 years	314	9.57 [8.56–10.68]	115	3.49 [2.89–4.17]	221	6.65 [5.82–7.57]	<0.05	↓
>65 years	80	6.90 [5.51–8.54]	118	10.01 [8.32–11.94]	54	3.74 [2.78–4.99]	<0.05	↓
Global	422	7.18 [6.52–7.89]	301	5.09 [4.54–5.69]	469	7.87 [7.18–8.60]	N.S.	

although the trend was not statistically significant ($p > 0.05$). There were significant decreases in VL-associated hospitalization for the 25–64-year and ≥65-year age groups ($p < 0.05$), while for the ≤24-year age group, a statistically significant increase was detected ($p < 0.05$).

Among the 1,192 VL-associated hospitalizations, 68.9% ($n = 821$) involved HIV-positive patients, and 70.1% ($n = 576$) of them occurred in male patients ($p < 0.05$).

Fig. 2 reports the distribution of the percentage of notified VL cases with respect to the registered hospitalizations, underlining a quite different distribution of trends, with endemic regions (from certain Southern and Tyrrhenian areas) experiencing higher notification rates, whereas Central (i.e., Toscana) and Northern (i.e., Emilia–Romagna) regions experienced higher levels of underreporting.

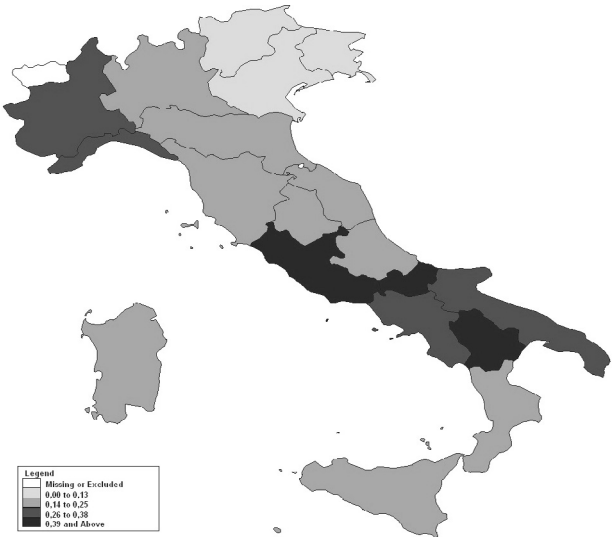

Fig. 2 Under-reporting estimates (proportion of VL notified cases over the number of VL hospitalizations) in different Italian regions, 2006–2008.

In Table 3, the rates of VL-associated hospitalizations for HIV-positive, HIV-negative and all patients are reported according to sex, age group and geographical region. We observed that VL-associated hospitalizations occurred more frequently in men than in women for both categories of patients. The analysis of VL-associated hospitalization rates by age groups highlights that in HIV-positive patients, increases in patients ≤24 years and ≥65 years were identified, while a reduction was noted in the 25–64-year age group. An increase in VL-associated hospitalizations for the ≤24-year age group was noted in HIV-negative patients; no changes were detected over the three-year period for the 25–64-year age group, while a reduction was detected for patients ≥65 years. When considering the geographical region of residence, increasing trends of VL-associated hospitalizations rates were detected ($p < 0.05$) for the North-eastern and North-western regions, while the rates were stable in the Center and South; moreover, a significant reduction was observed in the Islands ($p < 0.05$). The same pattern was observed when both the HIV-positive and HIV-negative patients were considered separately. Among the 821 VL-associated hospitalizations for HIV-positive patients and the 371 hospitalizations for HIV-negative patients, 90.5% and 97.6% were Italians, respectively.

Discussion

Our study highlights a non-homogeneous trend of VL-associated hospitalizations and notifications in Italy that is consistent both with rates detected in a previous Italian study [18] and with globally reported trends. In fact, while the infection is declining according to the official surveillance system based on notifications, the number of hospitalized patients was stable. In particular,

Table 3 VL notifications by HIV status, according to sex, age groups, and region, Italy 2006—2008.

LV-associated hospitalizations, rate/1,000,000 population [95% CI] by HIV status, region and sex

		HIV-positive				HIV-negative				All				
	Variable	2006	2007	2008	p^a	2006	2007	2008	p^a	2006	2007	2008	p^a	
Sex														
	Male	7.08 (202) [6.15—8.11]	5.4(155) [4.60—6.30]	8.5(246) [7.48—9.61]	<0.05	3.01(86) [2.43—3.70]	1.92(55) [1.46—2.47]	2.11(61) 1.63—2.69	<0.05	10.09(288) [8.96—11.33]	7.32(210) [6.35—8.37]	10.61(307) [9.45—11.85]	NS	
	Female	1.95(59) [1.50—2.50]	1.51(46) [1.12—2.00]	3.68(113) [3.05—4.41]	<0.05	2.48(75) [1.97—3.09]	1.48(45) [1.09—1.96]	1.6(49) 1.20—2.09	<0.05	4.43(134) [3.71—5.25]	2.99(91) [2.4—3.67]	5.28(162) [4.5—6.16]	NS	
Age group, years														
	≤24 years	0 [0.00—0.21]	0.70 (10) [0.36—1.23]	9.90(143) [8.37—11.62]	<0.05	1.95(28) [1.32—2.78]	4.03(58) [3.09—5.18]	3.53(51) 2.66—4.60	<0.05	1.95(28) [1.32—2.78]	4.73(68) [4.69—4.77]	13.43(194) [11.64—15.42]	<0.05	↑
	25—64 years	7.65(251) [6.75—8.64]	2.21(73) [1.75—2.77]	4.88(162) [4.17—5.67]	<0.05	1.92(63) [1.49—2.44]	1.27(42) [0.93—1.70]	1.77(59) 1.36—2.27	NS	9.57(314) [8.56—10.68]	3.49(115) [2.89—4.17]	6.65(221) [5.82—7.57]	<0.05	↓
	≥65 years	0.86(10) [0.44—1.53]	10.01(118) [8.32—11.94]	4.52(54) [3.43—5.85]	<0.05	6.04(70) [4.75—7.58]	0 [0.00—0.25]	0 0.00—0.03	<0.05	6.90(80) [5.51—8.54]	10.01(118) [8.32—11.94]	4.52(54) [3.43—5.85]	<0.05	↑
Region[b]														
	Northwest	4.15(47) [3.63—4.69]	4.36(50) [3.84—4.92]	8.86(99) [8.11—9.64]	<0.05	1.77(20) [1.44—2.14]	2.65(29) [2.24—3.09]	2.15(24) [1.79—2.55]	NS	6.05(67) [5.43—6.71]	7.02(79) [6.35—7.72]	11.01(123) [10.17—11.87]	<0.05	↑
	Northeast	0.69(11) [0.49—0.93]	0.49(8) [0.32—0.70]	5.65(87) [5.05—6.28]	<0.05	0.25(4) [0.13—0.40]	0.13(2) [0.05—0.41]	0.77(12) [0.55—1.01]	<0.05	0.97(15) [0.72—1.25]	0.62(10) [0.43—0.85]	6.42(99) [5.78— 7.09]	<0.05	↑
	Center	6.42(73) [5.77—7.08]	4.49(53) [3.96—5.06]	5.68(65) [5.08—6.31]	NS	2.26(26) [1.89—2.68]	1.80(20) [1.47—2.17]	1.40(16) [1.11—1.73]	NS	8.77(99) [8.02—9.56]	6.29(73) [5.66—7.09]	7.07(81) [6.40— 7.78]	NS	
	South	5.63(76) [5.03—6.27]	4.20(53) [3.69—4.75]	3.47(50) [3.00—3.97]	<0.05	6.45(86) [5.81—7.13]	2.19(33) [1.81—2.59]	2.51(38) [2.11—2.94]	<0.05	11.50(162) [10.64—12.40]	6.39(86) [5.75—7.05]	5.98(88) [5.37—6.63]	<0.05	↓
	Islands	8.39(54) [7.66—9.16]	5.95(37) [5.34— 6.60]	8.38(58) [7.65—9.15]	NS	3.62(25) [3.14—4.13]	2.32(16) [1.94—2.73]	2.91(20) [2.49—3.37]	NS	11.85(79) [10.97—12.70]	8.27(53) [7.55—9.03]	11.30(78) [10.45—12.18]	NS	
Total	Italy	4.44(261) [3.93—5.01]	3.40(201) [2.95—3.89]	6.02(359) [5.42—6.67]	<0.05	2.74(161) [2.34—3.19]	1.69(100) [1.38—2.05]	1.84(110) [1.52—2.21]	<0.05	7.18(422) [6.52—7.89]	5.09(301) [4.54—5.69]	7.86(469) [7.18—8.60]	NS	

[a] Cochrane—Armitage test for linear trend; NS:Not Significant.

[b] Rates by region have been standardized for age.

it is interesting to note that the increase in VL-associated hospitalizations is statistically significant just in those geographical areas in the north of the peninsula, where the disease was not endemic until recently [19,20]. This result is in line with the increasing seroprevalence that was estimated in the canine population of northern Italy in a recent study by Franco et al. [21]. Moreover, the differences detected at the regional level could not be ascribed to local differences in health care systems because the Italian National Healthcare Service is characterized by universal coverage, which entitles all citizens, regardless of their social status, to equal access to essential health care services. Essential health services are provided free of charge or at very low cost (namely ''ticket'') and include general medical and pediatric services, essential drugs and those for chronic diseases, treatments administered during hospitalization, rehabilitation and long-term post-acute inpatient care, instrument and laboratory diagnostics and other specialized services for early diagnosis and prevention. Finally, the National Healthcare Service guarantees that the system is subject to popular democratic control at the national, regional and local levels (participation).

Moreover, by observing the VL-associated hospitalization temporal trends stratified for age groups, we can highlight an increase in the ≤24-year age group and reductions in the other groups. This trend confirms the typical epidemiological pattern of VL in the Mediterranean basin, where it predominantly affects children [2]. The children's nationality information confirms that they were all Italian; thus, all of the hospitalized VL cases were likely locally acquired, although it is not possible to exclude that the disease was acquired during travel abroad. It is not easy to guess the reasons for this sharp increase without a direct analysis of each case; however, we might hypothesize that the increase could be linked to the intensification of travel in endemic areas [22] and migration flows from endemic countries. Moreover, some specific scientific studies have been conducted in Northern areas of Italy whose objectives were to detect VL in children [23,24].

When analyzing the temporal trends by age groups according to the HIV status of the hospitalized patients, among the HIV-positive patients, we observed a statistically significant increase for the VL-associated hospitalization rate in the ≥65-year age group. This finding is consistent with findings from a Portuguese study that reported that VL was traditionally a pediatric disease, but that in the past few years, the number of cases in infants has decreased, with an increase in the number of infections in adults, which are often associated with HIV/AIDS [25]. Moreover, our results highlight that 69.8% of VL-associated hospitalizations are HIV-positive patients, and among these, 70.1% are males; these observations are in accordance with a study conducted in 2005 in Spain, where 83% of HIV-infected patients with VL were male [26].

Early diagnosis and treatment of VL infection is challenging because physicians are not experienced with the disease. The variety of clinical presentations, the long incubation period [27], and patients' unusual travel histories prejudice timely public health actions and effective strategies for the control of VL. It is well known that climatic factors can influence the appearance or reappearance of infectious diseases in a particular area when there are other biological, ecological and socioeconomic factors that are favorable for the event, with concomitant increases in incidence [28].

Underreporting is common in VL [29]; this is partly due to asymptomatic infections and caveats in available data sources [30]. In a study conducted in 1975, it was estimated that for 1 clinical case of VL, there may be 30—100 subclinical infections [31,32]. This phenomenon is particularly worrying considering that the patients are hospitalized for VL; the physicians working in the hospitals have the duty to notify to the Hygiene and Public Health Services of all newly infected patients. In Italy, VL notification is compulsory within 48 h of diagnosis, according to a Ministerial decree of 15 December 1990 [33]. Moreover, the apparent disconnect between hospitalizations and notifications emphasizes the fact that hospital physicians are not aware of the importance of infectious disease notification for public health policy.

Moreover, this underestimate could have severe consequences, especially when blood donors are infected [34,35]. The role of underestimation is highlighted in Fig. 2, emphasizing that underreporting in non-endemic areas could be an indication of the need for specific education of healthcare professionals on the diagnosis and notification of VL to improve preventive strategies.

This study has some limitations: leishmaniasis is transmitted during the summertime, so knowledge of the travel history for each individual patient is essential. The accurate identification of sites of infection is difficult and cannot be derived from an anonymous database analysis. Because the Italian VL notification system does not include clinical guidelines about its diagnosis, the identification of each VL case is based on physicians' expertise and the availability of laboratory facilities with trained staff. Unfortunately, it was not possible to conduct

a detailed analysis of the epidemiology of VL in children <1 year of age because the notification system reports data grouped for all children under 15. Moreover, accurate entomological and canine infection information is very important for mapping risk areas. The estimation of disease burden could be very important for policy makers and funding organizations to establish priorities for research on the prevention, diagnosis and treatment of this neglected infectious disease. In fact, to enhance the efficacy of control strategies, interdisciplinary collaborations that are focused on reservoir control (e.g., vaccines for canine leishmaniasis and deltamethrine-treated collars) and vector control are of paramount importance.

Conflict of interest

We have no conflict of interest to declare.

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