Who Is a Typical Patient with Visceral Leishmaniasis? Characterizing the Demographic and Nutritional Profile of Patients in Brazil, East Africa, and South Asia

Michael O. Harhay, Piero L. Olliaro,* Michel Vaillant, François Chappuis, María Angeles Lima, Koert Ritmeijer, Carlos Henrique Costa, Dorcas Lamounier Costa, Suman Rijal, Shyam Sundar, and Manica Balasegaram

Graduate Group in Demography, Population Studies Center, University of Pennsylvania, Philadelphia, Pennsylvania; United Nations Children's Fund/United Nations Development Programme/World Bank/World Health Organization Special Programme for Research and Training in Tropical Diseases (TDR), Geneva, Switzerland; Centre for Tropical Medicine, University of Oxford, Oxford, United Kingdom; Clinical Epidemiology and Public Health Unit, Center for Health Studies, Centre de Recherche Publique (CRP-Santé), Luxembourg; Médecins Sans Frontières, Operational Centre Geneva (MSF-OCG), Geneva, Switzerland; Division of International and Humanitarian Medicine, Geneva University Hospitals and University of Geneva, Geneva, Switzerland; Médecins Sans Frontières, Operational Centre Barcelona-Athens (MSF-OCBA), Barcelona, Spain; Médecins Sans Frontières, Operational Centre Amsterdam (MSF-OCA), Amsterdam, The Netherlands; Instituto de Doenças Tropicais Natan Portella, Teresina, Piauí, Brazil; Federal University of Piauí, Piauí, Brazil; Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil; Department of Internal Medicine, B. P. Koirala Institute of Health Sciences, Dharan, Nepal; Institute of Medical Sciences, Banaras Hindu University, Varanasi, India; Drugs for Neglected Diseases Initiative (DNDi), Geneva, Switzerland

Abstract. Drug-dosing recommendations for visceral leishmaniasis (VL) treatment are based on the patients' weight or age. A current lack of demographic and anthropometric data on patients hinders (1) the ability of health providers to properly prepare for patient management, (2) an informed drug procurement for disease control, and (3) the design of clinical trials and development of new drug therapies in the different endemic areas. We present information about the age, gender, weight, and height of 29,570 consecutive VL patients presenting to 20 locations in six geographic endemic regions of Brazil, East Africa, Nepal, and India between 1997 and 2009. Our compilation shows substantial heterogeneity in the types of patients seeking care for VL at the clinics within the different locations. This suggests that drug development, procurement, and perhaps even treatment protocols, such as the use of the potentially teratogenic drug miltefosine, may require distinct strategies in these geographic settings.

INTRODUCTION

Visceral leishmaniasis (VL), caused by *Leishmania donovani* in South Asia and East Africa and *L. infantum* in Latin America (where it is also known as *L. chagasi*) and the Mediterranean basin, kills approximately 51,000 people every year,¹ with an estimated incidence of 500,000 new cases a year.^{2,3} About 90% of all cases worldwide are limited to five countries: India, Nepal, Bangladesh, Sudan, and Brazil.

In the poorest communities of these endemic countries, VL is a leading cause of illness^{4–6} and economic distress to families.^{7–12} VL is often associated with malnutrition, which is also a symptom of more severe infection and a major risk factor for poorer clinical and treatment outcomes.^{13–19} The precise mechanisms of the interaction between VL and malnutrition are not well-understood,^{19,20} partly because of limited epidemiological data on patient populations.²¹ This lack of basic information on VL, particularly demographic and anthropometric data, hinders (1) the ability of health providers to properly prepare for patient management, (2) an informed drug procurement for disease control, and (3) the design of clinical trials and development of new drug therapies in the different endemic areas. When available, data often represents single health clinics or small populations.^{19,20,22–25}

Current treatment options for VL include antimonials (sodium stibogluconate and meglumine antimoniate), Paromomycin (Gland Pharma Limited, Hyderabad, India), amphotericin B deoxycholate, Liposomal amphotericin B (AmBisome® Gilead, Foster City, CA, USA), and Miltefosine (Impavido® Paladin Labs Inc, St Laurent, Québec, Canada).

None of these treatments are ideal. Antimonials, the mainstay of VL treatment for decades, have reduced efficacy in India. AmBisome is expensive (even at the reduced price negotiated between the World Health Organization [WHO] and the manufacturer). Paromomycin requires 3 weeks of injections, and miltefosine is teratogenic in rats and potentially teratogenic in humans, expensive, and requires 4 weeks of oral treatment.^{5,26} Anthropometric and demographic data are also important, because some VL drugs are expensive (liposomal amphotericin B [AmBisome] and miltefosine), come in different dosage strengths (miltefosine), or have risks for some patient groups (e.g., women of reproductive age for miltefosine). Because drug dosing is largely based on either age or bodyweight, population data are needed to help control programs make recommendations.

METHODS

Study objectives. We collected and analyzed basic demographic and anthropometric data to characterize VL patient populations in different endemic regions.

Patient populations. Basic anthropometric data (age, gender, weight, and height) were obtained from 29,750 consecutive VL patients presenting to 20 local clinics in six geographic endemic foci (Figure 1): Teresina, Piauí, Brazil (tertiary referral hospital); Gedaref, Sudan (rural hospitals); Upper Nile/Southern Sudan (primary healthcare centers and rural hospitals); Pokot region of the Uganda–Kenya border (rural hospital); Nepal (tertiary referral hospital); and Bihar, India (primary health care centers, one district hospital, and one private clinic). Data were obtained by the Instituto de Doenças Tropicais Natan Portella, Médecins Sans Frontières (MSF) Operational Centers Amsterdam, Barcelona–Athens, and Geneva, B. P. Koirala Institute of Health Sciences, and Muzaffarpur, Bihar field site of Banaras Hindu University, India.

* Address correspondence to Piero L. Olliaro, Special Programme for Research and Training in Tropical Diseases (TDR), World Health Organization, Avenue Appia 20, 1211 Geneva 27, Switzerland. E-mail: olliarop@who.int

FIGURE 1. Data sources.

Patients were diagnosed through clinical suspicion (fever and splenomegaly), and confirmation was made through diagnostic tests, either one or a combination of serology (direct agglutination test or rapid test) and bone marrow/lymph node/spleen aspirate.

Demographics. For each location, we reported the male to female distribution and ratio as well as the percentage of women of reproductive age (15–42 years old) of the total VL patient population. Age, weight, and height were summarized by location and indicated as means with standard deviation (SD) as well as medians and associated interquartile ranges (IQR). We also calculated the percentage of the population < 5 and < 15 years of age to better understand the makeup of the childhood population.

Anthropometric and nutritional analysis. Calculations were done for the following three age groups: children under 5 years, children and adolescents between 5 and 19 years, and adults 19 years and older. For children under 5 years, we used the WHO Child Growth Standards²⁷ derived from the WHO Multicenter Growth Reference Study (MGRS)²⁸ to calculate the percentage of patients within each VL patient population that would be classified as (1) low weight for age (indicative of underweight), (2) low height for age (reflecting stunting and long-term restriction of a child's growth potential), and (3) low weight for height (an indicator of the level of wasting or acute malnutrition). The population health metric for underweight/stunting/wasting is calculated as the percentage of the population with weight for age, height for age, and weight for height more than –2 SD away from the WHO Child Growth Standards median. Severe underweight/stunting/wasting are defined as more than –3 SD away from the WHO Child Growth Standards median.

Growth reference data for assessing children and adolescents between 5 and 19 years of age are also available from the WHO. With these standards, we could calculate weight for age, height for age, and body mass index (BMI) for age. Values that are more than –2 and –3 SD away from the median of the growth reference data define underweight, stunting, and wasting (measured using BMI in this age cohort) and

severe underweight, stunting, and wasting, respectively.²⁹ The standard definition of wasting by the WHO includes all individuals with edema (information that we do not have in our database). For adults 19 years or older, we assessed their nutritional status using international classifications of adult malnutrition according to the WHO Global Database on Body Mass Index.³⁰

Data management and statistical analysis. Deidentified databases were received in the format of Excel spreadsheets. Databases were then cleaned, queried, and merged using STATA/MP version 11 (StataCorp Ltd., College Station, TX). The results of the nutritional status for children under the age of 5 years were computed in SAS system version 9.1.3 (SAS Institute, Cary, NC) using a macro provided free of cost by the WHO.³¹ A similar macro, also from the WHO, was used to assess children and adolescents between 5 and 19 years of age.³² For adults 19 years and older, we used the international classification of adult malnutrition according to BMI calculated in STATA.

Age, weight, height, BMI, and Z score data were compared between geographical locations. Because some of the parameters investigated are skewed, we calculated Z scores to standardize the data with regard to a reference WHO population. The analyses were also repeated using a non-parametric test. The one-way analysis of variance (ANOVA) applied to ranks is equivalent to the Kruskal–Wallis k-sample test, but it generates *F*-test values that are often better than the approximation used by the Kruskal–Wallis test. This test can be extended to other rank scores.³³ Savage scores are powerful for comparing scale differences in exponential distributions or location shifts in extreme value distributions.³⁴ Therefore, savage scores were calculated, and the parametric test was carried out with a general linear model, allowing for a post-hoc comparison of marginal means with a Tukey adjustment for multiplicity. Because results were similar, only Z scores are presented here.

Ethics. Only completely deidentified data were received. The Institutional Review Board at the University of Pennsylvania approved the collection and analysis of the deidentified data described within.

RESULTS

The male to female distribution by location is shown in Table 1. In all locations, there were more males than females, with an overall ratio of 60 to 40. Anthropometric measurements were available for most patients (Table 2), although information about some patients was missing regarding age ($N = 151$), gender ($N = 176$), weight ($N = 506$), or height ($N = 6,539$). The populations' distribution of age (Figure 2 and Table 2), weight (Figure 3 and Table 2), and height (Table 2) differed statistically between locations and within continents.

The percentage of women of reproductive age (15–42 years) of the total VL patient population in each location was 6.2% in Brazil, 9.7% in Gedaref (Sudan), 18.6% in Upper Nile/Southern Sudan, 10.2% in Pokot, 26.3% in Nepal, and 17.2% in Bihar (India).

For consideration of childhood populations that may be relevant to both drug development and procurement, we also present the percentage of each VL patient population under the age of 5 and 15 years, respectively: 47.6% and 59.2% in Brazil, 30.0% and 69.2% in Gedaref, 25.9% and 58.5% in Upper Nile/Southern Sudan, 18.4% and 63.2% in Pokot, 6.4% and 33.5% in Nepal, and 10.2% and 48.5% in Bihar.

We compared the age distribution, using means and SD, in each population and found that age was significantly higher in Bihar and Nepal than in the Pokot region, Sudan, and Brazil ($P < 0.0001$), significantly higher in Nepal than in Bihar ($P < 0.01$), and significantly lower in Gedaref and higher in Upper Nile/Southern Sudan than in Pokot ($P < 0.0001$). We also compared the distribution of weights and found that the weight was significantly higher in Nepal than in Bihar, and both were higher than in Pokot, Sudan, and Brazil ($P < 0.0001$), not different in Pokot and Upper Nile/Southern Sudan from those in Brazil, significantly lower in Gedaref than in Pokot ($P < 0.0001$), and significantly higher in Upper Nile/Southern Sudan than in Gedaref ($P < 0.0001$). Height was not included in the databases from the providers of one site in India (Banaras Hindu University) and the Pokot region. Height was significantly higher in Bihar, Nepal, Gedaref, and Upper Nile/Southern Sudan than in Brazil ($P < 0.0001$), significantly higher in Nepal than in Bihar ($P < 0.0001$), and significantly higher in Upper Nile/Southern Sudan than in Gedaref ($P < 0.0001$).

Nutritional status for the three age categories is presented in Tables 3–5. In a well-nourished population, there are almost no children characterized as more than -3 or -2 SD (Z scores) away from the median. Moderate to severe malnutrition was observed across all locations in our database, although the percentage varied considerably across each VL patient

TABLE 1
Male to female distribution by location

	Male patients	Female patients	Male/female ratio
Brazil	827 (65%)	439 (35%)	1.9
Gedaref, Sudan	4,587 (61%)	2,903 (39%)	1.6
Upper Nile/ Southern Sudan	6,931 (54%)	5,864 (46%)	1.2
Pokot	1,689 (69%)	762 (31%)	2.2
Nepal	748 (57%)	563 (43%)	1.4
Bihar, India	2,381 (57%)	1,700 (41%)	1.4
Total	17,163 (58%)	12,231 (41%)	1.4

Note that values not equal to 100% are because of missing data.

TABLE 2
Distributions of age, weight, and height by location

Location	Cohort	N	Age (years)			Weight (kg)			Height (cm)			Under 5 years (%)	Under 15 years (%)	Women of reproductive age (%)
			Mean $\pm$ SD	Median (25, 75 percentiles)	N	Mean $\pm$ SD	Median (25, 75 percentiles)	N	Mean $\pm$ SD	Median (25, 75 percentiles)	N			
Brazil	Total	1,264	16.2 $\pm$ 18.3	6 (1.5, 29)	1,246	30 $\pm$ 22.4	17.5 (10, 53)	1,031	116 $\pm$ 40.2	101 (77, 160)	1,031	47.6	59.2	6.2
	Males	825	20 $\pm$ 19.3	17 (2, 33)	811	35.5 $\pm$ 23.2	40 (11, 57)	664	125 $\pm$ 41.4	134 (80, 165)	664			
	Females	439	9.2 $\pm$ 13.8	2.5 (1, 9)	435	19.7 $\pm$ 16.7	11.6 (9, 25)	367	99 $\pm$ 32	85 (75, 127)	367			
Gedaref, Sudan	Total	7,493	13.7 $\pm$ 13.5	9 (4, 19)	7,488	27.7 $\pm$ 18.3	21 (12, 44)	7,451	127 $\pm$ 36.4	127 (94.5, 162)	7,451	30.0	69.2	9.7
	Males	4,587	15 $\pm$ 14.3	10 (4, 22)	4,584	29.6 $\pm$ 19	23.5 (13, 47)	4,561	131 $\pm$ 37.4	132 (97, 168)	4,561			
	Females	2,903	11.8 $\pm$ 11.8	8 (4, 15)	2,901	24.8 $\pm$ 16.4	18.5 (11, 39)	2,887	121.5 $\pm$ 34.2	121 (91, 157)	2,887			
Upper Nile/ Southern Sudan	Total	12,844	15.9 $\pm$ 13	12 (5, 25)	12,849	30.1 $\pm$ 16.6	29 (14.7, 45)	11,351	140 $\pm$ 36.4	151 (110, 172)	11,351	25.9	58.5	18.6
	Males	6,915	16.2 $\pm$ 13.4	12 (5, 25)	6,917	31.3 $\pm$ 17.7	29 (15, 48)	6,111	142 $\pm$ 38	149 (110, 177)	6,111			
	Females	5,848	15.6 $\pm$ 12.6	12 (5, 25)	5,853	28.7 $\pm$ 15	30 (14.5, 42)	5,181	138 $\pm$ 34	154 (111, 167)	5,181			
Pokot	Total	2,427	14.8 $\pm$ 10.9	12 (7, 20)	2,436	31.2 $\pm$ 15	29 (18, 45)	No data	No data	No data	No data	18.4	63.2	10.2
	Males	1,680	15.3 $\pm$ 10.7	12 (8, 20)	1,681	32.8 $\pm$ 15	30.5 (19.5, 47)	No data	No data	No data	No data			
	Females	747	13.7 $\pm$ 11.2	10 (5, 20)	755	27.4 $\pm$ 14	23.5 (15, 41)	No data	No data	No data	No data			
Nepal	Total	1,310	24.8 $\pm$ 14.5	23 (13, 35)	1,043	35.7 $\pm$ 13.2	39 (26, 45)	1,042	146 $\pm$ 22.6	153 (138, 161)	1,042	6.4	33.5	26.3
	Males	747	26 $\pm$ 14.8	25 (13, 36)	609	38.8 $\pm$ 13.8	42 (27, 49)	609	149 $\pm$ 23	159 (139, 165)	609			
	Females	563	23.2 $\pm$ 14	20 (13, 32)	434	32.4 $\pm$ 11.5	35 (25, 40)	433	141 $\pm$ 21	149 (135, 154)	433			
Bihar, India	Total	4,081	21 $\pm$ 15.6	16 (8, 30)	4,002	32 $\pm$ 14.5	34 (19, 44)	2,156	138 $\pm$ 25.3	146 (119, 159)	2,156	10.2	48.5	17.2
	Males	2,381	22.4 $\pm$ 16.3	17 (9, 35)	2,324	34.7 $\pm$ 15.4	39 (20, 47)	1,222	143 $\pm$ 26.3	156 (121, 163)	1,222			
	Females	1,699	19 $\pm$ 14.4	14 (8, 28)	1,676	28.3 $\pm$ 12.2	30 (17, 39)	933	131 $\pm$ 22.4	141 (115, 149)	933

FIGURE 2. Population pyramids of age and gender by location. Horizontal lines indicate reproductive age (15–42 years).

population. Brazil is distinct, with very low ranges of severe malnutrition for all ages. For example, the percentage of patients severely malnourished under 5 years was 4.6% compared with 19.5% in Gedaref, 39.3% in the Upper Nile region in Southern Sudan, 27.9% in Nepal, and 14.9% in Bihar.

For children under the age of 5 years (Table 3), the weight for height (the main indicator for this age group representing acute wasting) and height for age (representing non-optimal or stunted growth) were significantly lower ($P < 0.01$) in Bihar, Nepal, Gedaref, and Upper Nile/Southern Sudan than in Brazil and significantly lower in Upper Nile/Southern Sudan than in Gedaref ($P < 0.0001$). The weight for age was significantly lower in Bihar, Nepal, Pokot, Gedaref, and Upper Nile/Southern Sudan than in Brazil ($P < 0.0001$). The weight for age Z score was not different between Gedaref, Upper Nile/Southern Sudan, and the Pokot region. For children and adolescents aged between 5 and 19 years (Table 4), we found the same trends for weight for age ($P < 0.0001$) and height for age ($P < 0.0001$). BMI for age, the main indicator of health status for this age group, followed the same general trend. The BMI for age was significantly lower in Bihar, Nepal, Gedaref, and Upper Nile/Southern Sudan than in Brazil ($P < 0.0001$), significantly lower in Nepal than in Bihar ($P < 0.01$), and significantly higher in Upper Nile/Southern Sudan than in Gedaref ($P < 0.0001$). Adult nutritional status (> 19 years of age) assessed by BMI followed a similar trend (Table 5). BMI was significantly lower in Bihar, Nepal, Gedaref, and Upper Nile/Southern Sudan than in Brazil ($P < 0.0001$), significantly lower in Nepal than in Bihar ($P < 0.01$), and significantly higher in Upper Nile/Southern Sudan than in Gedaref ($P < 0.01$).

DISCUSSION

This information is useful for designing and developing drugs and drug formulations as well as for optimizing their use. In malaria, demographic and anthropometric information

has been used to calculate the optimal tablet strengths for artesunate-amodiaquine fixed-dose coformulation³⁵ and inform dosing recommendations by the WHO.³⁶ However, although there are clearly important differences between geographically different populations of patients, in any one area, the cross-section defined may change over time with the stage of the outbreak, distribution of care, and influence of drugs on the parasite.

A methodological challenge emerges in the calculation and interpretation of our findings, particularly around nutritional status. First, these calculations represent a cross-sectional analysis of patient data across varying time periods from 1997 to 2009. As such, the nutritional status of the different VL patient populations may vary according to seasonal and/or other external factors such as conflict or famine. Perhaps, the most central challenge is the lack of appropriate locally tailored reference populations from which we are able to compare our VL patient populations to truly know if our patients differ substantially. In our search of the literature for statistical models to adjust for this limitation, we found articles that draw into question the WHO standards for overweight populations in Asia.³⁷ However, we only found one paper that proposed a statistical model to develop regional- or national-growth distributions from mixed data sources and countries in less-developed settings, where VL is endemic, that could be used to assess malnutrition/stunting/wasting.³⁸ This study, however, used a mixture of public and private data and was only limited to Asian countries. The data to develop the reference distributions to compare our African and Brazilian VL patient populations are not readily available. The use of Demographic Health Survey data is also limited, because the Sudanese patient population would remain incomparable. As such, although we recognize that the WHO standards are not fully optimal to assess all VL patient populations (such as the Nilotic population in the southern part of Sudan), we are limited by data availability to develop better standards. Because the surveys necessary to develop locally tailored data are not

FIGURE 3. (A–C) Smoothed frequency distributions of bodyweight (in kg). This figure shows the population distributions of body weight for each patient population combined (A) and by gender, (B) males and (C) females.

readily available, we use the WHO standards in our analysis. A further limitation is that there are many patients for whom we are missing data for height. Although this tended to be site- or clinic-specific, there is a possibility that there is a structure or pattern in the missing height data that, if available, may result in different nutritional breakdowns.

The countries contributing to this study constitute about 90% of the world's burden of VL, but they are not represented in the database according to their relative disease burdens. For instance, Southern Sudan, with 12,795 patients in the

database, corresponds to 43% of the total, whereas India only contributes 14% but actually represents approximately 2.5% and 66% of the total number of VL cases occurring yearly, respectively.³ Nonetheless, this database represents a cross-sectional picture of a number of VL patient populations in these settings; it is large, uses routine data, and is without the selection bias of patients enrolled in clinical trials.

Our data show some important points about affected populations in VL-endemic areas. We found significant differences across countries in population structure (as represented by age and sex distribution) and nutritional status. These differences are probably best explained by an interplay of social, economic, demographic (e.g., each country and region is in a different stage of the demographic transition), host, and parasite factors. More male than female patients presented to the clinics at all locations. The male to female ratio varied across sites from 1.2 (Upper Nile/Southern Sudan) to 2.2 (Pokot region). This has been reported previously.^{19,20,22–25} It is unclear whether this is because of factors such as increased exposure, vulnerability, or health-seeking behavior (it is possible that male patients are more likely to present to health centers for care) and how these factors vary in the different epidemiological and cultural settings. Populations were younger in Latin America than in Africa and South Asia. In addition to the population demographics, access to health services, exposure to risk factors, parasite species, and transmission patterns might also play a role in these age, weight, and nutritional profiles. The bimodal distributions that we observe are puzzling; they likely reflect either different exposure level throughout life or different health-seeking behaviors. A better understanding of these parasite, human, and social components is central to developing and targeting interventions for VL.^{20,39}

Women of reproductive age (15–42 years of age) constitute variable proportions of the total VL patient populations (from 6.2% in Brazil to 26.3% in Nepal). This information is important for selecting an appropriate treatment and risk-monitoring strategy to protect this vulnerable and under-researched group. In particular, wide-scale deployment of miltefosine in the Indian subcontinent in the context of the VL elimination program must consider the practicalities, feasibility, and costs of ensuring contraception for a very large proportion of patients. In situations where contraception is not feasible, appropriate alternative regimens must be considered. Therefore, areas with high proportions of women of reproductive age should carefully consider the place of miltefosine-based regimens in their treatment protocols.

Severe malnutrition is frequent not only in South Asia but also in East Africa, but it is uncommon in Brazil. Severe underweight, stunting, and wasting (acute malnutrition) are present across all ages. For instance, severe underweight (low weight for age) was extremely common in Nepalese and Indian children under 5 years (44–46%) but also in Sudan (30–33%). In Nepal, India, and Gedaref, 25–38% children have severe stunting (low height for age). Acute malnutrition (low weight for height) was most common in Southern Sudan (39%) and Nepal (28%). Data on older children, adolescents, and adults follow a similar pattern.

Malnutrition and VL are interconnected health problems. It is difficult to evaluate to what extent malnutrition is either a risk factor or the result of VL. Regardless of the causes of malnutrition (and our inadequate grasp thereof), malnutrition

TABLE 3
Nutritional indicators (< 5 years; 0–60 months)

Indicator	Population location	N	Percentage (95% CI)		Z scores	
			> -3 SD	> -2 SD	Mean	SD
Weight for age	Brazil	603	4.0 (2.3, 5.6)	15.3 (12.3, 18.2)	-0.70	1.28
	Gedaref, Sudan	2,499	32.9 (31.0, 34.8)	60.1 (58.2, 62.1)	-2.36	1.42
	Upper Nile/Southern Sudan	3,259	29.6 (28.0, 31.2)	53.2 (51.5, 54.9)	-2.12	1.46
	Nepal	70	44.3 (31.9, 56.6)	64.3 (52.3, 76.2)	-2.58	1.48
	Bihar, India	416	45.7 (40.8, 50.6)	68.8 (64.2, 73.3)	-2.67	1.25
Height for age	Brazil	528	7.6 (5.2, 9.9)	20.1 (16.6, 23.6)	-0.91	1.43
	Gedaref, Sudan	2,464	26.5 (24.7, 28.3)	50.0 (48.0, 52.0)	-1.98	1.60
	Upper Nile/Southern Sudan	2,916	9.2 (8.1, 10.2)	22.8 (21.2, 24.3)	-0.59	1.88
	Nepal	69	24.6 (13.7, 35.5)	50.7 (38.2, 63.2)	-1.81	1.79
	Bihar, India	191	38.2 (31.1, 45.4)	64.4 (57.3, 71.5)	-2.48	1.64
Weight for height	Brazil	525	4.6 (2.7, 6.5)	13.0 (10.0, 15.9)	-0.32	1.47
	Gedaref, Sudan	2,450	19.5 (17.9, 21.1)	45.2 (43.2, 47.2)	-1.89	1.29
	Upper Nile/Southern Sudan	2,730	39.3 (37.4, 41.1)	65.9 (64.1, 67.7)	-2.51	1.35
	Nepal	61	27.9 (15.8, 39.9)	52.5 (39.1, 65.8)	-2.05	1.68
	Bihar, India	195	14.9 (9.6, 20.1)	33.8 (26.9, 40.7)	-1.37	1.46

has an important effect on patients', outcome and hence, program planning. Therefore, documenting malnutrition is important. Ideally, both preventive nutritional programs for the general population as well as supplementary and therapeutic feeding interventions for VL patients should be in place in VL-endemic areas. Nutritional interventions for VL have long been integrated within the treatment centers of MSF in an effort to improve treatment outcomes. An example of other possible ways to improve integration might include the supplementation of nutritional interventions (e.g., vitamin A) to mass distribution programs of fine-mesh impregnated bed nets against VL.⁴⁰ Nutrition should be adequately addressed in the public sector as well. Also, it cannot be excluded that vulnerability to infection and consequent impact of anthropometrics (nutritional status) may also differ because of parasite differences in each region. This is a hypothesis that deserves further investigation.

Because all current drug therapies are dosed on the basis of bodyweight and may have use restrictions depending on age and gender (e.g., miltefosine in women of reproductive age), the combination of different parasite and population characteristics may lend to different treatment strategies and drug

needs in different locations.^{41,42} Recently, a campaign to eliminate VL in the Indian subcontinent has begun. With increasing access to therapy, local anthropometric data are integral to preparing and sustaining these efforts. These data can inform drug procurement, including direct and indirect costs such as those related to injectable devices and female contraception. At present, the demand for VL drugs is limited, and therefore, production is irregular and can face long delays.⁴³ This patient database allows the calculation of population-tailored drug costs and volumes in addition to more precise estimations of demand (and hence, negotiated prices) at both national and international levels. Such data are integral to preparing and sustaining drug delivery efforts as elimination campaigns evolve.

These results should be interpreted in light of the different stages of the demographic transition of these countries, which is more advanced in Brazil, India, and Nepal than in sub-Saharan Africa. In spite of its limitations, this database represents a clear step in the positive direction of systematically collecting and sharing data that can inform both policy makers and drug development initiatives. We eagerly seek to expand this working database to refine our knowledge of these and

TABLE 4
Nutritional indicators (5.0–19 years)

Indicator	Population location	Age group (years)	N	Percentage (95% CI)		Mean	SD
				> -3 SD	> -2 SD		
Weight for age*	Brazil	5–10	106	3.8 (0.0, 7.9)	20.8 (12.6, 28.9)	-1.25	1.03
	Gedaref, Sudan		1,600	18.4 (16.4, 20.3)	45.6 (43.1, 48.0)	-1.93	1.22
	Upper Nile/Southern Sudan		2,371	20.5 (18.8, 22.1)	43.3 (41.3, 45.3)	-1.86	1.36
	Nepal		149	50.3 (42.0, 58.7)	77.2 (70.1, 84.3)	-2.92	1.33
	Bihar, India		1,020	41.6 (38.5, 44.6)	67.6 (64.7, 70.6)	-2.57	1.25
Height for age	Brazil	5–19	152	5.3 (1.4, 9.1)	22.4 (15.4, 29.3)	-1.19	1.05
	Gedaref, Sudan		3,016	5.7 (4.9, 6.5)	20.3 (18.9, 21.8)	-0.95	1.31
	Upper Nile/Southern Sudan		4,386	1.9 (1.5, 2.3)	6.9 (6.1, 7.6)	0.10	1.45
	Nepal		363	17.6 (13.6, 21.7)	44.4 (39.1, 49.6)	-1.86	1.28
	Bihar, India		951	24.6 (21.8, 27.4)	53.5 (50.3, 56.7)	-2.13	1.33
BMI for age	Brazil	5–19	151	4.6 (1.0, 8.3)	12.6 (7.0, 18.2)	-0.83	1.14
	Gedaref, Sudan		3,003	25.5 (24.0, 27.1)	57.5 (55.8, 59.3)	-2.23	1.15
	Upper Nile/Southern Sudan		3,956	58.1 (56.6, 59.7)	83.3 (82.1, 84.5)	-3.11	1.16
	Nepal		351	33.9 (28.8, 39.0)	60.7 (55.4, 65.9)	-2.30	1.36
	Bihar, India		953	14.9 (12.6, 17.2)	40.4 (37.2, 43.6)	-1.78	1.15

*Weight for age not calculated for > 10.0 years of age.

TABLE 5
BMI (kg/m²; age > 19.0 years)

Population location	N	Mean (SD)	Median (25, 75 percentiles)	Severe thinness: BMI < 16.0	Moderate thinness: BMI = 16.0–16.99	Mild thinness: BMI = 17–18.49	Underweight: BMI < 18.50	Normal range: BMI = 18.50–24.99
				% (N)	% (N)	% (N)	% (N)	% (N)
Brazil	351	20.8 (2.8)	21 (18.8, 22.7)	3.7 (13)	3.9 (14)	13.7 (48)	21.4 (75)	78.6 (276)
Gedaref, Sudan	1,857	18.1 (5.6)	17.8 (16.2, 19.4)	21.8 (404)	14.5 (269)	25.7 (477)	61.2 (1,150)	38.2 (709)
Upper Nile/Southern Sudan	3,893	15.9 (6.7)	15.5 (14.3, 16.9)	59.7 (2,325)	17.4 (678)	15.5 (602)	92.6 (3,605)	7.4 (287)
Nepal	603	17.3 (2.4)	17.1 (15.8, 18.8)	29.2 (176)	18.7 (113)	23.4 (141)	71.3 (430)	28.7 (173)
Bihar, India	994	18.2 (2.5)	18 (16.6, 19.4)	15.4 (153)	15.4 (153)	29.2 (290)	60 (596)	40 (398)

other endemic VL populations. As such, we welcome correspondence from any readers regarding collaboration to refine and expand this database and to assist in their own related programs.

Received June 4, 2010. Accepted for publication November 14, 2010.

Acknowledgments: The authors thank Kevin Haynes of the Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine for his assistance with database management. PLO initiated this research. FC, MAL, KR, CHC, DLC, SR, and SS contributed original data. MOH and MV compiled the database and conducted the analyses. All authors were involved in the conception, design, and interpretation of this analysis. MOH, PLO, and MB wrote the manuscript, and all authors participated in multiple rounds of edits and revisions. All authors have seen and approved the final draft submitted for review.

Financial support: MOH is supported by Training Grant T32 AG 000177-21 from the National Institutes on Aging, United States National Institutes of Health (NIH). Although the work of all other authors was funded by their respective institutions, this project was and continues to be orchestrated collaboratively between the United Nations Children's Fund/United Nations Development Programme/World Bank/World Health Organization Special Programme for Research and Training in Tropical Diseases and the Drugs for Neglected Diseases Initiative.

Disclaimer: PLO is a staff member of the World Health Organization (WHO). The authors alone are responsible for the views expressed in this publication, and they do not necessarily represent the decisions, policy, or views of the WHO or NIH.

Authors' addresses: Piero L. Olliaro, Special Programme for Research and Training in Tropical Diseases (TDR), World Health Organization, Geneva, Switzerland, E-mail: olliarop@who.int. Michael O. Harhay, Population Studies Center, 239 McNeil Building, 3718 Locust Walk, Philadelphia, PA 19104-6298, E-mail: mharhay@pop.upenn.edu. Michel Vaillant, Competence Centre in Methodology and Statistics, Centre de Recherche Public - Santé, 1a-b rue Thomas Edison, L-1445 Strassen, Luxembourg, E-mail: michel.vaillant@crp-sante.lu. François Chappuis, Division of International and Humanitarian Medicine, Geneva University Hospitals, rue Gabrielle-Perret-Gentil 6, 1211 Geneva 14, E-mail: francois.chappuis@hcuge.ch. María Angeles (Nines) Lima, Médecins Sans Frontières, Medical Department, Operational Centre Barcelona-Athens, Nou de la Rambla 26, Barcelona 08001, Spain, E-mail: nines.lima@barcelona.msf.org. Koert Ritmeijer, Médecins Sans Frontières, P.O. Box 10014, 1001 EA, Amsterdam, The Netherlands, E-mail: koert.ritmeijer@amsterdam.msf.org. Carlos Henrique Costa, Instituto de Doenças Tropicais Natan Portella R. Artur de Vasconcelos 151-Sul 64001-450 Teresina, Piauí, Brazil, E-mail: chncosta@gmail.com. Dorcas Lamounier Costa, Instituto de Doenças Tropicais Natan Portella, Rua. Artur de Vasconcelos 151 Centro, CEP 64 001-450 Teresina, Piauí, Brazil, E-mail: dorcas.lc@gmail.com. Suman Rijal, Department of Internal Medicine, B P Koirala Institute of Health Sciences, Dharan, Nepal, E-mail: suman.rijal2@yahoo.com. Shyam Sundar, Department of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi - 221 005, India, E-mail: drshyamsundar@hotmail.com. Manica Balasegaram, Drugs for Neglected Diseases initiative, 15 Chemin Louis Dunant, 1202, Geneve, Switzerland, E-mail: mbalasegaram@ndi.org.

REFERENCES

- Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL, 2006. *Global Burden of Disease and Risk Factors*. Oxford University Press and The World Bank.
- Desjeux P, 2001. The increase in risk factors for leishmaniasis worldwide. *Trans R Soc Trop Med Hyg* 95: 239–243.
- Desjeux P, 2004. Leishmaniasis: current situation and new perspectives. *Comp Immunol Microbiol Infect Dis* 27: 305–318.
- Bern C, Maguire JH, Alvar J, 2008. Complexities of assessing the disease burden attributable to leishmaniasis. *PLoS Negl Trop Dis* 2: e313.
- van Griensven J, Balasegaram M, Meheus F, Alvar J, Lynen L, Boelaert M, 2010. Combination therapy for visceral leishmaniasis. *Lancet Infect Dis* 10: 184–194.
- Mubayi A, Castillo-Chavez C, Chowell G, Kribs-Zaleta C, Ali Siddiqui N, Kumar N, Das P, 2009. Transmission dynamics and underreporting of Kala-azar in the Indian state of Bihar. *J Theor Biol* 262: 177–185.
- Adhikari SR, Maskay NM, 2003. The economic burden of Kala-azar in households of the Danusha and Mahottari districts of Nepal. *Acta Trop* 88: 1–2.
- Adhikari SR, Maskay NM, Sharma BP, 2009. Paying for hospital-based care of Kala-azar in Nepal: assessing catastrophic, impoverishment and economic consequences. *Health Policy Plan* 24: 129–139.
- Anoopa Sharma D, Bern C, Varghese B, Chowdhury R, Haque R, Ali M, Amann J, Ahluwalia IB, Wagatsuma Y, Breiman RF, Maguire JH, McFarland DA, 2006. The economic impact of visceral leishmaniasis on households in Bangladesh. *Trop Med Int Health* 11: 757–764.
- Boelaert M, Meheus F, Sanchez A, Singh SP, Vanlerberghe V, Picado A, Meessen B, Sundar S, 2009. The poorest of the poor: a poverty appraisal of households affected by visceral leishmaniasis in Bihar, India. *Trop Med Int Health* 14: 639–644.
- Meheus F, Boelaert M, Baltussen R, Sundar S, 2006. Costs of patient management of visceral leishmaniasis in Muzaffarpur, Bihar, India. *Trop Med Int Health* 11: 1715–1724.
- Rijal S, Koirala S, Van der Stuyt P, Boelaert M, 2006. The economic burden of visceral leishmaniasis for households in Nepal. *Trans R Soc Trop Med Hyg* 100: 838–841.
- Anstead GM, Chandrasekar B, Zhao W, Yang J, Perez LE, Melby PC, 2001. Malnutrition alters the innate immune response and increases early visceralization following *Leishmania donovani* infection. *Infect Immun* 69: 4709–4718.
- Cerf BJ, Jones TC, Badaro R, Sampaio D, Teixeira R, Johnson WD Jr, 1987. Malnutrition as a risk factor for severe visceral leishmaniasis. *J Infect Dis* 156: 1030–1033.
- Dye C, Williams BG, 1993. Malnutrition, age and the risk of parasitic disease: visceral leishmaniasis revisited. *Proc Biol Sci* 254: 33–39.
- Harrison LH, Naidu TG, Drew JS, de Alencar JE, Pearson RD, 1986. Reciprocal relationships between undernutrition and the parasitic disease visceral leishmaniasis. *Rev Infect Dis* 8: 447–453.
- Khalil EA, Zijlstra EE, Kager PA, El Hassan AM, 2002. Epidemiology and clinical manifestations of *Leishmania donovani* infection in two villages in an endemic area in eastern Sudan. *Trop Med Int Health* 7: 35–44.

18. Malafaia G, 2009. Protein-energy malnutrition as a risk factor for visceral leishmaniasis: a review. *Parasite Immunol* 31: 587–596.
19. Mueller Y, Mbulamberi DB, Odermatt P, Hoffmann A, Loutan L, Chappuis F, 2009. Risk factors for in-hospital mortality of visceral leishmaniasis patients in eastern Uganda. *Trop Med Int Health* 14: 910–917.
20. Kolaczinski JH, Reithinger R, Worku DT, Ocheng A, Kasimiro J, Kabatereine N, Brooker S, 2008. Risk factors of visceral leishmaniasis in East Africa: a case-control study in Pokot territory of Kenya and Uganda. *Int J Epidemiol* 37: 344–352.
21. Burki T, 2009. East African countries struggle with visceral leishmaniasis. *Lancet* 374: 371–372.
22. Alvar J, Bashaye S, Argaw D, Cruz I, Aparicio P, Kassa A, Orfanos G, Parreno F, Babaniyi O, Gudeta N, Canavate C, Bern C, 2007. Kala-azar outbreak in Libo Kemkem, Ethiopia: epidemiologic and parasitologic assessment. *Am J Trop Med Hyg* 77: 275–282.
23. Herrero M, Orfanos G, Argaw D, Mulugeta A, Aparicio P, Parreno F, Bernal O, Rubens D, Pedraza J, Lima MA, Flevaud L, Palma PP, Bashaye S, Alvar J, Bern C, 2009. Natural history of a visceral leishmaniasis outbreak in highland Ethiopia. *Am J Trop Med Hyg* 81: 373–377.
24. Raguenaud ME, Jansson A, Vanlerberghe V, Van der Auwera G, Deborggraeve S, Dujardin JC, Orfanos G, Reid T, Boelaert M, 2007. Epidemiology and clinical features of patients with visceral leishmaniasis treated by an MSF clinic in Bakool Region, Somalia, 2004–2006. *PLoS Negl Trop Dis* 1: e85.
25. Rukunuzzaman M, Rahman M, 2008. Epidemiological study of risk factors related to childhood visceral leishmaniasis. *Mymensingh Med J* 17: 46–50.
26. Alvar J, Croft S, Olliaro P, 2006. Chemotherapy in the treatment and control of leishmaniasis. *Adv Parasitol* 61: 223–274.
27. World Health Organization, 2009. *World Health Organization, United Nations Children's Fund. Child Growth Standards and the Identification of Severe Acute Malnutrition in Infants and Children. A Joint Statement by the World Health Organization and the United Nations Children's Fund.* Available at: <http://www.who.int/nutrition/publications/severemalnutrition/9789241598163/en/index.html>. Accessed October 9, 2009.
28. World Health Organization, 2009. *WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: Growth Velocity Based on Weight, Length and Head Circumference. Methods and Development.* Geneva, Switzerland: World Health Organization.
29. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J, 2007. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ* 85: 660–667.
30. World Health Organization, 2009. *BMI Classification. Global Database on Body Mass Index.* Available at: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html. Accessed October 9, 2009.
31. World Health Organization, 2009. *WHO Anthro Software and Macros.* Available at: <http://www.who.int/entity/childgrowth/software/en>. Accessed October 9, 2009.
32. World Health Organization, 2009. *WHO Anthro Software and Macros (5–19 Years).* Available at: <http://www.who.int/growthref/tools/en/>. Accessed October 9, 2009.
33. Quade D, 1966. On analysis of variance for the k-Sample problem. *Ann Math Stat* 37: 1747–1758.
34. Hajek J, 1969. *A Course in Nonparametric Statistics.* San Francisco, CA: Holden-Day.
35. Taylor WR, Terlouw DJ, Olliaro PL, White NJ, Brasseur P, ter Kuile FO, 2006. Use of weight-for-age-data to optimize tablet strength and dosing regimens for a new fixed-dose artesunate-amodiaquine combination for treating falciparum malaria. *Bull World Health Organ* 84: 956–964.
36. World Health Organization, 2010. *Guidelines for the Treatment of Malaria*, 2nd edition. Geneva, Switzerland: World Health Organization.
37. World Health Organization Expert Consultation, 2004. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 363: 157–163.
38. van Buuren S, Hayes DJ, Stasinopoulos DM, Rigby RA, ter Kuile FO, Terlouw DJ, 2009. Estimating regional centile curves from mixed data sources and countries. *Stat Med* 28: 2891–2911.
39. Reithinger R, Brooker S, Kolaczinski JH, 2009. Visceral leishmaniasis: time to better use existing resources. *Lancet* 374: 1330.
40. Ritmeijer K, Davies C, van Zorge R, Wang SJ, Schorscher J, Dongu'du SI, Davidson RN, 2007. Evaluation of a mass distribution programme for fine-mesh impregnated bednets against visceral leishmaniasis in eastern Sudan. *Trop Med Int Health* 12: 404–414.
41. Olliaro P, Darley S, Laxminarayan R, Sundar S, 2009. Cost-effectiveness projections of single and combination therapies for visceral leishmaniasis in Bihar, India. *Trop Med Int Health* 14: 918–925.
42. Olliaro P, Sundar S, 2009. Anthropometrically derived dosing and drug costing calculations for treating visceral leishmaniasis in Bihar, India. *Trop Med Int Health* 14: 88–92.
43. den Boer ML, Alvar J, Davidson RN, Ritmeijer K, Balasegaram M, 2009. Developments in the treatment of visceral leishmaniasis. *Expert Opin Emerg Drugs* 14: 395–410.