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Spectrum and burden of neglected tropical diseases observed in an infectious and tropical diseases unit in Florence, Italy (2000–2015)

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Abstract Neglected tropical diseases (NTDs) are a diverse group of acute and chronic conditions with distinct characteristics that thrive mainly among the poorest populations, almost exclusively in tropical countries. To evaluate the relevance and impact of NTDs in a temperate area, the number and features of patients diagnosed with NTDs at the Infectious and Tropical Diseases Unit (ITDU), Azienda Ospedaliero-Universitaria Careggi, Florence, Italy between 2000 and 2015 were retrospectively reviewed. Overall 289 NTD cases were diagnosed in 283 subjects accounting for 2.4% of all patients accessing the center: 96 dengue, 62 schistosomiasis, 36 strongyloidiasis, 22 cystic echinococcosis, 19 Chagas disease, 14 leishmaniasis, 11 chikungunya, 10 cysticercosis, 6 soil-transmitted helminthiasis, 6 lymphatic filariasis, 3 trachoma, 2 onchocerciasis, and 2 leprosy. There was one fatal case of disseminated strongyloidiasis. According to the type of exposure, 145 (50.2%) NTDs were diagnosed in immigrants, 121 (41.9%) in travelers, 18 (6.3%) were autochthonous infections, while in 5 cases (1.7%), the type of exposure was unknown. The number of patients seen at the ITDU with a diagnosis of NTD increased over time (from 29 in 2000–2005 to 81 in 2006–2010, to 173 in 2011–2015). Late diagnosis and mismanagement before coming to the center were common features in several cases. Considering the increasing incidence and possible misdiagnosis of NTDs in non-endemic countries, to raise awareness about NTDs among health care providers seems to be of primary concern.

Keywords Neglected tropical diseases · Non-endemic area · Immigrants · Travelers · Mismanagement · Awareness · Italy · Europe

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Introduction

Neglected tropical diseases (NTDs) are a group of diseases defined by the World Health Organization (WHO) as "chronically endemic and epidemic-prone tropical diseases, which have a very significant negative impact on the lives of poor populations and remain critically neglected in the global public health agenda" [1]. When this study was conceived in September 2015, WHO listed 17 NTDs and several other "neglected conditions" (Table 1) [2]. Among the considered diseases, stongyloidiasis has been defined by some authors as the most neglected of NTDs [3].

Table 1 List of neglected tropical diseases according to the World Health Organization, as for September 29, 2015

Class of etiologic agent	Disease
Protozoa	Chagas disease
	Human african trypanosomiasis (sleeping sickness)
	Leishmaniasis
Bacteria	Buruli ulcer
	Leprosy (Hansen disease)
	Trachoma
	Endemic treponematoses (Yaws)
Helminth	Cysticercosis/taeniasis
	Dracunculiasis (guinea-worm disease)
	Echinococcosis
	Foodborne trematodiases
	Lymphatic filariasis
	Onchocerciasis
	Schistosomiasis
	Soil-transmitted helminthiases
Virus	Dengue and Chikungunya
	Rabies

Other neglected conditions: Chronic suppurative otitis media, Mycetoma, Nodding Syndrome, Podoconiosis, Scabies, Snakebite, Strongyloidiasis

NTDs affect nearly 1.5 billion people in the world, most of them living with less than 1.25 $ per day [4]. In 2010, around 128,000 people died from NTDs, and 26.1 million disability-adjusted life years (DALYs) were ascribed to them [5, 6].

NTDs are usually well known and ancient conditions, and they concentrate in poor countries, especially in Sub-Saharan Africa, but some of them are also endemic in Europe and in the USA [7, 8]. Travelling, together with immigration, makes it possible to observe NTDs in non-endemic regions, such as Europe. In 2013, Europe received 563 million of tourists, and was the region of departure for more than half of the international tourists [9]. Europe is among the most important regions in terms of migratory flows, with an estimated 31.9 million non-European Union nationals residing in Europe [10]. Recent reports underlined the possibility of introduction in Europe of certain NTDs for which competent vectors [11, 12] or intermediate hosts are already present in the European territories [13]. Other rising concerns about NTDs are the possibility of transmission during pregnancy, blood transfusion or organ transplantation, and the possible reactivation, in severe or even fatal form, during immunosuppressive conditions [14, 15]. To date, there are very few studies about epidemiological and clinical impacts of imported NTDs in Europe [16]. The aim of this study is to describe the main epidemiological and clinical features of imported and autochthonous NTDs, and to evaluate their relevance and impact in an infectious and tropical diseases unit located in a temperate area.

Methods

This is a retrospective observational study conducted at the Infectious and Tropical Diseases Unit (ITDU), Azienda Ospedaliero-Universitaria Careggi (AOUC), Florence, Italy, which is located in a tertiary hospital. The basic features (number, sex, age, country of birth, and type of access) of all subjects seen in the ITDU, from January 2000 to December 2015, were collected by consulting a database provided by the Unità Operativa Complessa Controllo Direzionale of AOUC. Among all patients who came to the ITDU, only subjects with a laboratory confirmed diagnosis of at least one of the 17 NTDs according the WHO official list plus strongyloidiasis [2] were identified, and included in the study.

Both epidemiological and clinical information concerning the included patients were obtained by consulting the medical records of ITDU, and collected in an anonymized database. There were no exclusion criteria. The ratio between the number of patients diagnosed with a laboratory confirmed NTDs and the total number of patients accessed to the ITDU has been calculated to estimate the burden of NTDs in the clinical practice in the ITDU. Difference in mean age and sex distribution among subjects with diagnosis of NTD vs all subjects accessing the ITDU, travelers with NTD vs immigrants with NTD, travelers with NTD vs subjects with autochthonous NTD, and immigrants with NTD vs subjects with autochthonous NTD was assessed using the Student t test and the Chi-square test, respectively (p values <0.05 were considered significant).

Every patient with at least one NTD was classified as traveler, immigrant, or subject with autochthonous infection according to the most likely modality of infection. An immigrant was defined as any person coming from a different country with the objective of settling in Italy, who probably got the infection in his/her country of origin before settling or while visiting friends and/or relatives (VFRs). A traveler was defined as any non-immigrant person (Italian or foreign born) who probably got the infection during an international travel. A subject with autochthonous infection was defined as a subject who probably got the infection in Italy; in other words, patients without any or significant travel history. Every case of NTD was classified according to the countries, where the infection was probably contracted. Countries were subsequently grouped into 14 regions following the Geosentinel

Table 2 Number of cases of neglected tropical diseases in patients that accessed the Infectious and Tropical Diseases Unit, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy in the period 2000–2015

	2000-2005	2006–2010	2011–2015	2000–2015
Dengue	0	41	55	96
Chikungunya	0	0	11	11
Schistosomiasis	9	13	40	62
Strongyloidiasis	0	12	24	36
Cystic echinococcosis	4	5	13	22
Chagas disease	1	5	13	19
Leishmaniasis	0	1	13	14
Taeniasis/Cysticercosis	6	1	3	10
Lymphatic filariasis	2	0	4	6
Soil-Transmitted Helminthiases	3	1	2	6
Trachoma	3	0	0	3
Onchocerciasis	2	0	0	2
Leprosy	0	2	0	2
All neglected tropical diseases	30	81	178	289

classification [17]. Supplementary Table 1 shows the laboratory tests used for laboratory diagnosis of NTDs.

Results

Accesses to the ITDU

In the study period, 11,528 subjects were seen at the ITDU. Of those, 3405 (29.5%) were evaluated during the period 2000–2005, 3556 (30.8%) during the period 2006–2010, and 4567 during the period 2011–2015 (39.6%). Italian subjects were 9706 (84.2%), foreign born subjects 1430 (12.4%), and for the remaining 392 patients (3.4%), nationality was not known. Out of the 10,111 (87.7%) subjects with known gender, the majority were males (n = 6003, 59.4%) and the mean age was 50.6 years (range 4–101). Outpatient subjects were 4488 (38.9%), whereas 7040 (61.1%) were hospitalized.

Cases of NTDs

Overall, 289 NTDs in 283 subjects were diagnosed at the ITDU, since six subjects were each diagnosed with two NTDs. NTDs were diagnosed in 2.4% (283 out of 11,528) of patients seen at the ITDU. Table 2 shows the number of different NTDs diagnosed per period, and Fig. 1 shows the proportion of patients with an NTD diagnosis among all patients who were seen at the ITDU per period. The majority of subjects were males (n = 183, 64.7%), and the mean age was 39 years (range 9–87), median 35. Among the 244 (86.2%) subjects with known clinical history, 138 (56.5%) were inpatients and 106 (43.4%) outpatients. There was one fatal case due to disseminated strongyloidiasis. Gender distribution was not significantly different between subjects with NTDs and all subjects seen at the ITDU (64.7 vs 59.4% were male), while mean age was significantly lower in the first group (39 years vs 50.6 years) ($p < 0.0001$).

According to the category of subjects, 145 NTDs (50.2%) were diagnosed in immigrants, 121 (41.9%) in travelers, 18 (6.2%) were autochthonous infections, while in 5 cases (1.7%), the type of exposure was unknown.

Out of the 121 (100.0%) travelers with known gender, the majority were males (n = 76, 62.8%) and the mean age was 42.3 years (range 11–79). Out of the 136 (93.8%) immigrants with known gender, the majority were males (n = 92, 67.6%) and the mean age was 34.8 years (range 14–75). Out of the 16 (88.9%) autochthonous people with known gender, the majority were males (n = 11, 68.8%) and the mean age was 58.9 years (range 34–87). The difference in mean age among the three groups was statistically significant ($p < 0.0001$), while sex distribution was not.

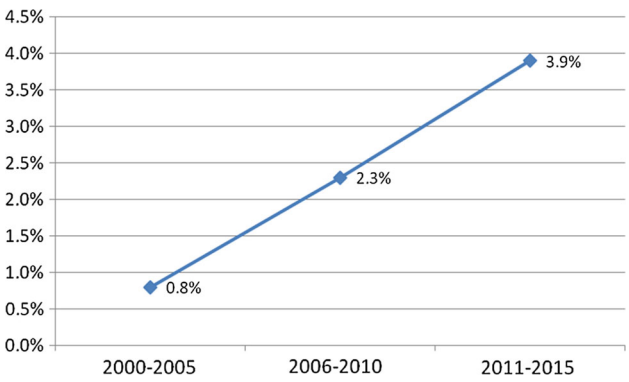

Fig. 1 Proportion, in percentage, of patients with neglected tropical diseases among all patients that accessed the Infectious and Tropical Diseases Unit, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy in the period 2000–2015

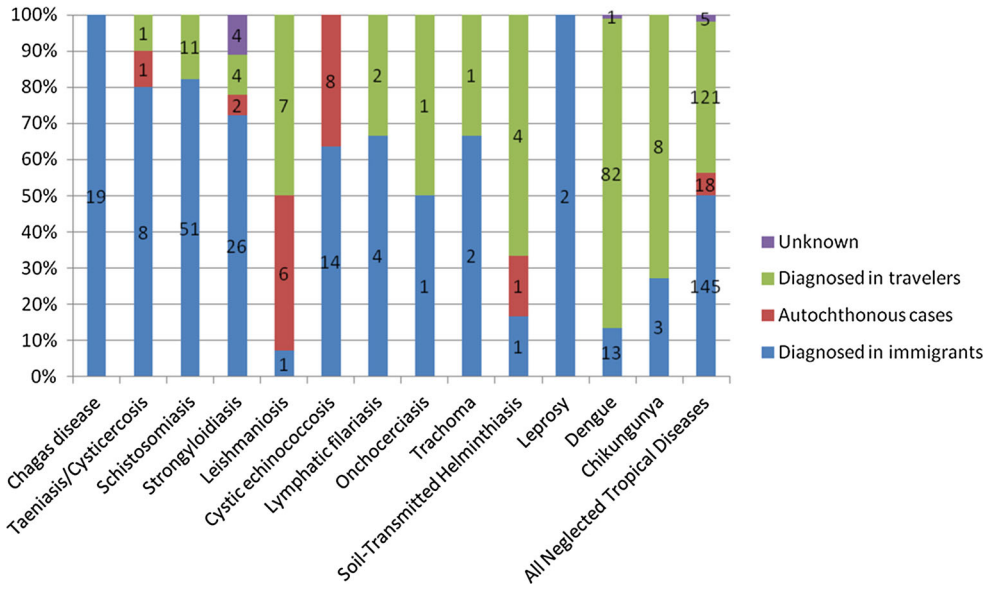

Fig. 2 Cases of different neglected tropical diseases diagnosed at the Infectious and Tropical Diseases Unit, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy in the period 2000–2015, sorted by category of subjects

Figure 2 shows cases of different NTDs according to the category of subjects: travelers, immigrants, and subjects with autochthonous infections. Table 3 shows cases of different NTDs sorted by the Geosentinel Region of most likely infection.

Dengue

Subjects diagnosed with Dengue were 96, accounting for 33.9% of patients with NTDs. Sixty-three (65.6%) were male, and the mean age was 40 years. Sixty-one of these cases have been previously reported [19]. Forty-nine cases (51%) were admitted to the hospital. Secondary Dengue infections, diagnosed on the basis of positivity of IgG and NS1 antigen in the same acute serum sample, were 30 (31.2%). Among the 74 subjects (77.1%) with known symptoms, the most common clinical features were fever (n = 73, 98.6%), arthralgia/myalgia (n = 49, 66.2%), headache (n = 32, 43.2%), gastrointestinal symptoms (n = 26, 35.1%), and cutaneous rash (n = 41, 55.4%). Among the 75 subjects (78.1%) with known blood sample results, the most common laboratory findings were thrombocytopenia (n = 55, 73.3%) and leucopenia (n = 58, 77.3%). Six patients (8.1%) presented warning signs according to the 2009 WHO classification [18]. Neither autochthonous nor severe cases of Dengue were diagnosed.

Chikungunya

Subjects diagnosed with Chikungunya were 11, accounting for 3.9% of patients with NTDs. Eight (72.7%) were female, and the mean age was 45 years. One case has been previously reported [19]. Only one patient (9.1%) was admitted to the hospital. Among the eight subjects (72.7%) with known symptoms, the most common clinical features were arthralgia/myalgia (n = 6, 75%), backache (n = 4, 50%), and cutaneous rash (n = 5, 62.5%).

Schistosomiasis

Subjects with diagnosis of schistosomiasis were 62 representing 21.9% of patients diagnosed with NTDs. Fifty-three (85.5%) were male, and the mean age was 32 years. Of note, there were five travelers who were infected after bathing in the Cavu river in Corsica, France. These cases have been previously reported, together with cases diagnosed in two other Italian centers [14, 20]. Out of the 60 subjects (96.8%) with known clinical history, 8 (13.3%) subjects presented Katayama syndrome, 34 (56.7%) urinary signs or symptoms, 3 (5%) hepato-intestinal signs or symptoms, and 15 (25%) were asymptomatic. Out of the 42 subjects (67.7%) with known comorbidities, 5 (11.9%) presented chronic coinfection with B or C hepatitis viruses. The mean eosinophil cell count was 677/μL, and the median eosinophil cell count was 430. Out of 33 subjects (53.2%) with known urine analysis results, hematuria (n = 21, 63.6%), proteinuria (n = 18, 54.5%), and leucocituria (n = 18, 54.5%) were the most common laboratory findings. Out of the 12 subjects (19.4%) with known IgE value, the mean value was 611 kU/L and the median value was 212 kU/L (normal value <80 kU/L). There were only seven (11.3%) parasitologically confirmed cases, all of them due to *Schistosoma haematobium.* In two cases, the

Table 3 Cases of neglected tropical diseases diagnosed at the Infectious and Tropical Diseases Unit, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy in the period 2000–2015, sorted by most likely place of infection (Geosentinel classification [17])

	Western Europe	Eastern Europe	North Africa	Sub-Saharian Africa	Middle East	South Central Asia	North East Asia	South East Asia	Oceania	Australia and New Zeland	North America	Central America	Caribbean	South America	Unknown	Total
Dengue	0	0	0	5	0	20	0	33	2	0	0	5	9	8	14	96
Chikungunya	0	0	0	0	0	1	0	0	0	0	0	1	5	4	0	11
Schistosomiasis	5	0	12	34	0	0	0	0	0	0	0	0	0	0	11	62
Strongyloidiasis	2	1	1	10	0	2	0	1	0	0	0	0	0	8	11	36
Cystic echinococcosis	8	10	1	0	0	1	0	0	0	0	0	0	0	2	0	22
Chagas disease	0	0	0	0	0	0	0	0	0	0	0	0	0	19	0	19
Leishmaniasis	6	1	1	2	1	0	1	0	0	0	0	0	0	2	0	14
Taeniasis/ Cysticercosis	1	0	0	0	0	0	0	0	0	0	0	1	0	8	0	10
Lymphatic filariasis	0	0	0	5	0	1	0	0	0	0	0	0	0	0	0	6
Onchocerciasis	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Trachoma	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	3
Soil-Transmitted Helminthiases	0	0	0	2	0	0	1	0	0	0	0	0	0	0	3	6
Leprosy	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	2
All neglected tropical diseases	22	12	16	63	1	25	2	35	2	0	0	7	14	51	39	289

diagnosis was made after histopatological examination of biopsy samples of obtained with cystoscopy performed for a suspect bladder neoplasm. All patients underwent to at least one abdominal ultrasound scan, and were treated with oral praziquantel 40 mg/kg per day in two divided doses for 1–3 days.

Strongyloidiasis

Subjects diagnosed with strongyloidiasis were 36, accounting for 12.7% of patients with NTDs. Twenty-three (63.9%) were male, and the mean age was 43 years. There were 2 (5.6%) parasitologically confirmed cases, while the other cases were diagnosed on the basis of positive serology. Stool culture for *Strongyloides stercoralis* was not available in ITDU up to 2014. Out of the 18 subjects (50%) with known blood sample results, the most common laboratory finding was eosinophilia (n = 7, 38.9%) and the mean number of blood eosinophil cells was 1010/μL. Out of the 23 subjects (63.9%) with known symptoms, 11 (47.8%) were asymptomatic, 5 (21.7%) presented skin manifestations, and 5 (21.7%) presented change in bowel habits. One patient (4.3%) with *S. stercoralis* and HTLV-1 coinfection (previously reported) presented with recurrent episodes of meningitis due to intestinal bacteria [21]. There was one case of fatal disseminated strongyloidiasis (4.3%): it was an adult Ivorian patient who suffered from T-cell undifferentiated lymphoma treated with chemotherapy, who developed fever and acute respiratory failure. The diagnosis was based on direct detection of larvae in several biological samples (stool, urine, blood, bronchoalveolar lavage, and gastric aspiration). He was treated with combined oral and subcutaneous ivermectin leading to parasitological eradication of the worm, but he died due to multiorgan failure. All other patients were treated with oral ivermectin 200 mcg/kg per day for 1–4 days.

Cystic echinococcosis

Subjects diagnosed with cystic echinococcosis (CE) were 22 accounting for 7.8% of all NTD patients. Fifteen (68.2%) were male, and the mean age was 46 years. There were 13 subjects diagnosed with hepatic localization only, 3 patients had pulmonary localization, 2 bone localization, one cardiac and renal localization, 1 both hepatic and pulmonary localization, 1 spleen localization, and 1 muscular localization (already reported [22]). Ten subjects (45.4%) were asymptomatic, and 12 (54.5%) suffered symptoms due to the compression effect of the cysts. One subject developed anaphylactic shock caused by fissuring of a hepatic cyst. Among the 15 subjects (68.2%) with known blood sample results, eosinophilia was the most common laboratory finding (n = 8, 53.3%) with a mean value of 1003/mcL. Five patients (5.4%) had a definitive diagnosis based on histopathological examination of cyst samples and PCR on cystic liquid. The other 17 cases were diagnosed on the basis of compatible radiological image and positive serology. Among the 15 subjects (68.2%) with known clinical history, 9 (60%) were surgically treated, 1 was treated with Puncture–Aspirarion–Injection–Respiration (PAIR) technique, and 5 (33.33%) only with albendazole (400 mg two times per day for different periods based on treatment response and localization). Patients treated with surgery underwent to pre-operative treatment with albendazole for 1 week to 1 month before and for at least 1 month after the operation.

Chagas disease

In total, 19 subjects were diagnosed with Chagas disease (6.7% of all patients with NTDs). Twelve (63.2%) were female, and the mean age was 39 years. Three of them have been previously reported [23, 24]. With regard to the modality of diagnosis, 2 female subjects were diagnosed in virtue of a screening test performed during pregnancy, 2 subjects were diagnosed thanks to a screening test before beginning of immunosuppression therapy, 4 were diagnosed as they were relatives (sons) of a positive mother, 2 because of the presence of compatible clinical features of chronic disease, and other subjects (9) came to ITDU requesting to be tested, because they have heard about this disease in their country of origin. Among the 13 subjects (68.4%) with available detailed clinical history, 9 suffered from indeterminate form, 1 had heart involvement, 1 had gastrointestinal involvement, and 2 had both cardiac and intestinal involvement. One was diagnosed with a chagasic megacolon after multiple admissions in several Italian hospitals due to bowel obstruction secondary to fecal impaction, as previously described [24]. Another case (previously described) was diagnosed with a chagasic cardiomyopathy after several months during which she had undergone several pneumological pulmonary tests due to dyspnea [23]. The two pregnant women gave birth to four children (one had three pregnancies), three of whom were followed up to at least 1 year of age and all were negative to parasitological and serological tests for *Trypanosoma cruzi*. Twelve subjects (92.3%) were treated with benznidazole (5 mg/kg per day in two divided doses, up to 300 mg per day). The two pregnant women were treated after pregnancy, at the end of breastfeeding. In three cases (25%), treatment was stopped before completion: one subject developed Drug Reaction (or Rash) with Eosinophilia and Systemic Symptoms (DRESS) syndrome, one subject developed a cutaneous rash refractory to antihistaminic and corticosteroids treatment, and in one subject, affected from a metabolic myopathy, a huge increase of

creatine phosphokinase was observed. One subject underwent implantation of implantable cardioverter defibrillator device due to ventricular dysrhythmias and one subject underwent a left hemicolectomy due to megacolon with refractory constipation [24].

Leishmaniasis

Subjects diagnosed with leishmaniasis were 14 accounting for 4.9% of all patients with NTDs. Nine (64.3%) were male, and the mean age was 46 years. There were 5 cases of visceral leishmaniasis, 8 cases of cutaneous leishmaniasis, and 1 case of visceral leishmaniasis with mucocutaneous lesions. In one subject presenting with fever and multiple hypoechoic splenic lesions, diagnostic splenectomy was performed to rule out splenic lymphoma. The species identification of the causative agent was pursued with PCR only in a case of cutaneous leishmaniasis acquired in Bolivia leading to the identification of a Leishmania subgenus *Viannia*, *Leishmania guyanensis* complex. One subject with autochthonous cutaneous leishmaniasis was immunocompromised due to treatment with oral steroids, etanercept, and methotrexate for the treatment of rheumatoid arthritis.

Immunocompetent subjects with visceral leishmaniasis were treated with liposomal amphotericin B (LAMB) 3 mg/kg per day iv at day 1–5, 14, and 21. Subjects with cutaneous or mucocutaneous leishmaniasis were treated with LAMB 3 mg/kg per day iv for 14 days.

Cysticercosis

In total, ten subjects with cysticercosis were diagnosed accounting for 3.5% of all patients with NTDs. Six (60%) were female, and the mean age was 39 years. These cases have been previously reported, together with cases diagnosed in other centers [25]. All were cases of neurocysticercosis (nine parenchymal and one both parenchymal and intraventricular). According to Del Brutto criteria [22], there were seven definitive cases (70%), one probable case, while two case did not satisfy the Del Brutto criteria for definitive or probable diagnosis, but they were deemed to be a neurocysticercosis case. The most common symptom was generalized seizure with loss of consciousness ($n = 5$, 41.7%).

None of the subjects underwent a surgical operation, and they all were managed with combination of albendazole (400 mg two times a day for 1–3 months), corticosteroids, and anti-epileptic drugs.

Lymphatic filariasis

There were six subjects affected by lymphatic filariasis. Cases diagnosed with filariasis were 2.1% of total NTDs patients. Three (50%) were male, and the mean age was 45 years. All subjects presented typical cutaneous manifestations and positive parasitological and/or serological test.

Soil-transmitted helminthiasis

In total, six subjects were diagnosed with soil-transmitted helminthiasis (STHs). Cases diagnosed with STHs were 2.1% of all patients with NTDs. All STHs cases were due to ascariasis. No trichuriasis or hookworm infections were diagnosed. All patients suffered a change in bowel habit: in three cases, adult parasites were ejected together with feces.

Trachoma

There were three subjects (two immigrants from Somalia and one from Nigeria) affected by trachoma. All were male, and mean age was 33. Trachoma cases represented 1.1% of NTDs.

Onchocerciasis

There were two subjects with onchocerciasis representing 0.7% of total NTD patients. There were one 66-year-old woman and one 49-year-old man. Both subjects presented typical conjunctival and cutaneous manifestations and positive parasitological test.

Leprosy

Leprosy was diagnosed in two subjects accounting for 0.7% of patients with NTDs. Both patients were male 29 and 49 years, respectively. One subject migrated from the Philippines, and had been treated for 14 years for a suspected cutaneous sarcoidosis, until diagnosis was performed in his own country during a travel to visit relatives and friends. The other is an immigrant from Sudan who suffered from lepromatous leprosy with leonine facies.

NTD coinfections

In total, there were six subjects (2.1%) diagnosed with more than 1 NTD (five immigrants and one traveler). In the group of immigrants, three were diagnosed with strongyloidiasis and schistosomiasis (one was from Somalia, one from Nigeria, and one from Egypt) and two with strongyloidiasis and Chagas disease (one was from Bolivia and one from Brazil). The traveler with NTD polyparasitism was a French hunter who went to Central African Republic: he was diagnosed with schistosomiasis and onchocerciasis, probably acquired during two different travels.

Buruli ulcer, dracunculiasis, foodborne trematodiases, human African tripanosomiasis, rabies, and yaws

No cases were diagnosed in these series.

Discussion

The present study describes a significant burden of NTDs (including strongyloidiasis) on the clinical activities of an Italian infectious and tropical diseases unit. In this study, patients with NTDs accounted for 2.4% of the evaluated subjects. Through the study period, we observed a steadily increase in both the total number of NTDs diagnosed and the proportion of subjects with a NTD diagnosis among all subjects accessing the ITDU. In particular, the total number of NTDs observed increased from 30 to 81 to 178 in the 2000–2005, 2006–2010, and 2011–2015 periods, respectively. Moreover, the proportion patients with NTDs among all patients accessing the ITDU increased from 0.8% to 2.3% to 3.9% in the 2000–2005, 2006–2010, and 2011–2015 periods, respectively. Comparing the 2000–2005 and 2011–2016 periods, there was an increase of 487% of the proportion patients with NTDs among all patients accessing the ITDU. This increase probably reflects the expansion of international travels and migration phenomenon, the enhanced number of patients seen at the ITDU, but also the availability of new specific laboratory test at a local level, suggesting the importance of availability of specific tools for screening, clinical diagnosis, and control activities of NTDs. Indeed, serological tests for Chagas disease, cysticercosis, dengue, schistosomiasis, strongyloidiasis have been available only since 2001, 2002, 2005, 2008, and 2008, respectively, while before samples had to be shipped to other referral laboratories. In the matter of fact, the availability of serology increased the probability of diagnosing some NTDs, such as schistosomiasis, strongyloidiasis, and Chagas disease, since direct parasitological methods have a much lower sensitivity in these cases. The present study suggests that NTDs are candidates to become more relevant in the European scenario. While the most NTD-affected areas in the planet are located outside Europe, and even if one of the common features of NTDs is that they do not spread widely [26], the current economical and socio-political frameworks with the ongoing crises in Africa and in the Middle East [27] are likely to prompt an increasing migrating flow from countries heavily affected to Europe and especially to Italy, given its central position in the Mediterranean sea. In the present study, migrants accounted for about 50.2% of NTD cases observed, and an increased number of diagnoses were observed in certain periods of time in relation to geopolitical events. For example, an increase of schistosomiasis diagnosis was observed after 2011, following the military conflict in Libya, after the arrival of a large number of asylum seekers from Africa in Italy. Europe is also the third most populous continent in the planet [28], it is the preferred world travelers destination [9], and some NTDs (such as leishmaniasis, cystic echinococcosis, and strongyloidiasis) are still endemic in Europe, and especially in Southern Europe and in the Mediterranean basin.

According to Eurostat, in 2012, there were 1196 million trips taken by European citizens. Among them, 47.8% were for tourism, 34.7% to visit relatives and/or friends (VRFs), and 13.3% were for business [29]. Three quarters of these trips were domestic (i.e., in the same country): among the foreign trips, 85.4% remained in Europe (Spain was the most common destination), followed by Asia (4.5%) and Africa (4.1%). In 2011, according to Eurotravnet statistics, out of 5996 sick travelers, 48.5% traveled for tourism, 13% to VRFs, and 10.3% for business [17]. They acquired infections mainly in Sub-Saharan Africa (34.3%) followed by Southeast Asia (15.9%). In the present study, travelers were the second most commonly affected by NTD after immigrants, while autochthonous infections were very few. Despite all that, there are very few studies focusing on the global impact of NTDs in Europe and especially in Italy. A previous similar study carried out in Madrid (Spain), in which only travelers and immigrants were included, reported similar results. In that study, patients with a diagnosis of at least one of the 13 core NTDs accounted for 9.3% (576 out of 6168) of evaluated patients in the period 1989–2007 [16]. A recent study performed in the Emilia-Romagna Region on parasitic diseases (including not only the 17 NTDs, but also several other conditions, such as giardiasis and amoebiasis) showed an overall incidence of 5.7 cases per 10,000 patients admitted, and a higher incidence (18.3 cases per 10,000) in foreign born patients [30]. According to this study, the most common parasitic disease was echinococcosis (27%). The authors concluded that the low incidence of parasitic diseases could be attributed to the "healthy migrant effect" and to the underdiagnosis by health professionals. The experience presented in this study confirms that NTDs may be underestimated in the European setting. Several cases of late diagnosis and/or mismanagement are presented in this study highlighting the need to improve awareness about NTDs among European health care providers. For example, the only fatal case reported in this series could have been easily avoided by screening and treating the patient for strongyloidiasis before starting immunosuppressive treatment. Published literature has confirmed the lack of awareness of NTDs in Europe. For instance, in a systematic review of the literature on cysticercosis managed in Europe, about one-third of neurosurgical operations could have

been avoided if a proper pre-operative diagnosis had been made [31]. Other examples of mismanagement of NTDs in Europe have been reported, for example, a woman returning from Ecuador to Germany was admitted with high fever, abdominal pain, iper hypertransaminasemia, thrombocytopenia, and gallbladder wall thickening, and she was operated in the suspicion of acalculous cholecystitis and secondary sepsis, but she died a few days later because of spontaneous bleeding from the abdominal wound, since she was affected by severe dengue [32]. Faced with the current epidemiological scenario, European health care providers need to extend their "diagnostic panorama" [33] to conditions usually rarely considered in the academic teaching programs. A correct diagnosis of NTDs in Europe is important not only to achieve a correct clinical case management, but also to avoid autochthonous transmission of certain NTDs that are currently not endemic in Europe. Cases of Chagas disease, dengue, and schistosomiasis have been recently acquired in Europe through different routes of transmission, including blood transfusion, mother-to-child transmission, vectorial transmission and thanks to the presence of suitable climatic condition and intermediate host availability [14, 20, 34, 35]. In particular, a timely diagnosis of dengue, Chikungunya, or Zika virus infections in a country, such as Italy, which is heavily infested by a competent dengue virus vector, such as *Aedes albopictus*, also has a public health relevance for the possible vector control activities that might be implemented. Concerning more insidious conditions, such as Chagas disease or strongyloidiasis, which are frequently asymptomatic for years before causing any symptoms, but which may be transmitted through organ transplantation (both Chagas disease and strongyloidiasis), blood transfusion (Chagas disease only) and vertically (Chagas disease only), it is essential that screening protocols targeted at risk population are drawn and implemented. The same recommendation is valid for immunosuppressed patients who may develop severe or even fatal complications in case of undiagnosed strongyloidiasis or Chagas disease.

This study has several limitations, including the retrospective design that may have led to underestimation of the real burden of NTDs. Another limitation is that the study has been performed in one centre only, and cannot not be representative of other sites throughout the country. Moreover, it is a hospital based study, which may not be representative of the burden of NTDs in the general population. An underestimation of the real burden of NTDs in the present study is also due to the availability of diagnostic laboratory tests, which has increased during the years, as mentioned above.

In conclusion, the present study showed that NTDs have their relevance in the clinical practice in Europe. The real importance of NTDs in Europe is probably underestimated, and raising the awareness of clinicians may be of primary concern to avoid underdiagnosis, diagnostic delays, or improper therapies. The struggle against NTDs needs a series of public health measures: health care providers' education, control of reservoirs and vectors, screening in immunocompromised patients, prevention of vertical transmission, control in blood and organ donors, and improvement of the access of immigrants to National Health System, which are still deficient and should be performed on a large scale. A prospective and possibly multi-centre study which considers the health system and the socio-economic burden of NTDs would be useful to understand and objectively determine the relevance of these diseases in Europe and to address policy makers whether to invest in NTDs control activities in Europe.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study formal consent is not required.

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