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REVIEW

Human African Trypanosomiasis in Non-Endemic Countries (2000–2010)

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Background. Human African trypanosomiasis (HAT) can affect travelers to sub-Saharan Africa, as well as migrants from disease endemic countries (DECs), posing diagnosis challenges to travel health services in non-disease endemic countries (non-DECs).
Methods. Cases reported in journals have been collected through a bibliographic research and complemented by cases reported to the World Health Organization (WHO) during the process to obtain anti-trypanosome drugs. These drugs are distributed to DECs solely by WHO. Drugs are also provided to non-DECs when an HAT case is diagnosed. However, in non-DEC pentamidine can also be purchased in the market due to its indication to treat *Pneumocystis* and *Leishmania* infections. Any request for drugs from non-DECs should be accompanied by epidemiological and clinical data on the patient.
Results. During the period 2000 to 2010, 94 cases of HAT were reported in 19 non-DECs. Seventy-two percent of them corresponded to the Rhodesiense form, whereas 28% corresponded to the Gambiense. Cases of Rhodesiense HAT were mainly diagnosed in tourists after short visits to DECs, usually within a few days of return. The majority of them were in first stage. Initial misdiagnosis with malaria or tick-borne diseases was frequent. Cases of Gambiense HAT were usually diagnosed several months after initial examination and subsequent to a variety of misdiagnoses. The majority were in second stage. Patients affected were expatriates living in DECs for extended periods and refugees or economic migrants from DECs.
Conclusions. The risk of HAT in travelers and migrants, albeit low, cannot be overlooked. In non-DECs, rarity, nonspecific symptoms, and lack of knowledge and awareness in health staff make diagnosis difficult. Misdiagnosis is frequent, thus leading to invasive diagnosis methods, unnecessary treatments, and increased risk of fatality. Centralized distribution of drugs for HAT by WHO enables an HAT surveillance system for non-DECs to be maintained. This system provides valuable information on disease transmission and complements data collected in DECs.

Human African trypanosomiasis (HAT), also known as sleeping sickness, is considered to be endemic in 36 countries of sub-Saharan Africa.[1] HAT could be a concern for traveler services when users are planning to visit or they are returning from known HAT transmission areas in sub-Saharan Africa. In addition, migrants from countries affected by HAT could pose diagnosis challenges to health services in countries where the disease is not endemic.

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Human African trypanosomiasis occurs in focal areas.[1] The geographic distribution of the disease has recently been updated.[2]

Methods

Data collection was performed following a bibliographic research but considering only cases infected in the study period.

This information was complemented by reports to the World Health Organization (WHO) of pharmacy services of non-disease endemic countries (non-DECs) during the process of anti-trypanosome drug request.

Anti-trypanosome drugs are donated to WHO by the producers Sanofi (pentamidine, melarsoprol, and

eflornithine) and Bayer (suramin and nifurtimox) and WHO is the sole distributor of these drugs. Therefore, drugs for the treatment of HAT are not available outside this channel, with the exception of pentamidine that is also produced and distributed by the manufacturer for the treatment of *Pneumocystis carinii* and *Leishmania* infections.

National sleeping sickness control programs and non-governmental organizations in disease endemic countries (DECs) are provided with drugs according to forecasts of usage. In non-DECs, pharmacy services in hospitals diagnosing and treating HAT have to address requests for drugs to WHO. Any request should also be accompanied by epidemiological and clinical data on the patient and contact details of the hospital and medical doctor in charge of the treatment. WHO ensures delivery of drugs between 24 and 48 h. However, to enable prompt initiation of treatment, particularly important for the acute Rhodesiense form of the disease, a few hospitals have requested and have been granted to act as repositories of anti-trypanosome drugs (Table 1). Stocks are placed in these hospitals and consumption and expiration dates are checked twice a year by WHO.

WHO keeps an emergency stock of drugs at its headquarters in Geneva, whereas for regular distribution to major DECs in need of large amounts, WHO has the collaboration of *Médecins Sans Frontières Logistique* (Bordeaux, France), which provides storage facilities and shipment services. Drugs are shipped either by express courier, by air or boat depending on the urgency and circumstances.

Table 1 Institutions keeping anti-trypanosome drugs

Institution	Location
Liverpool University Hospital, Royal Liverpool & Broadgreen NHS Foundation Trust	Prescot Street, Liverpool L7 88XP, United Kingdom *For the North of England, Scotland, and N. Ireland*
University College London Hospital NHS Foundation Trust	Mortimer Market Centre off Capper Street, London WC1E 6JB, United Kingdom
FMH Innere Medizin und Tropen- und Reisemedizin, Schweizerisches Tropen- und Public Health Institut	Socinstrasse 57, CH 4002 Basel, Switzerland
Hôpitaux Universitaires de Genève, Service de Medicine International et Humaine	Rue Gabrielle-Perret-Gentil 4, 1211 Genève 14, Switzerland
Centers for Disease Control and Prevention	1600 Clifton Road, Mailstop D-09, Atlanta, GA 30333, USA *For US ONLY*
University of Tokyo, Institute of Medical Science, Division of Infectious Diseases	4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan
Universitair Ziekenhuis Antwerpen	Wilrijkstraat, 10, 2650 Edegem, Belgium
Erasmus Medical Center	Dr Molewaterplein 40, Rotterdam 3015, The Netherlands
Netcare Milpark Hospital	9 Guild Road, Parktown West, Johannesburg 2193, South Africa

Results

Form and Stage of the Disease

During the period 2000 to 2010, 94 HAT cases diagnosed in non-DECs were reported. Seventy-two percent of them corresponded to the Rhodesiense form of the disease (Table 2), whereas 28% corresponded to the Gambiense form (Table 3).

Among Rhodesiense HAT cases, 82% were diagnosed in first stage and 18% were diagnosed in second stage.

Among Gambiense HAT cases, 23% cases were diagnosed in first stage, while 77% were diagnosed in second stage.

Occupation

Ninety-three percent of the HAT Rhodesiense cases diagnosed were foreigners traveling to endemic areas for a short period of time. This category includes tourists (60) and soldiers (2). Rangers working in wildlife areas make up the remaining 7%.

Forty-two percent of the HAT Gambiense cases diagnosed were expatriates living in endemic countries for extended periods, mostly for business, including forest activities (9), but also as staff of the United Nations (1) or as religious missionaries (1). Fifty-eight percent were nationals from DECs, living in the non-DEC of diagnosis for political reasons [ie, refugees from Democratic Republic of Congo (DRC) and from Sudan although based in Uganda (5)] or for economic reasons [ie, migrants from DRC (3), Cameroon (3), Angola (2), and Equatorial Guinea (2)].

Country of diagnosis

HAT cases were diagnosed in non-DECs in the five continents (Figure 1). Forty-three percent of the cases were diagnosed in Europe and 23% in North America.

South Africa is the non-DEC diagnosing the highest number of Rhodesiense HAT imported cases, 37% of the total. This is probably due to its proximity to DECs with famed protected areas and game reserves (GR), but also because it often represents the first step in health care seeking for acute health problems in south and east African countries. In the second line are countries that hold historical or economic links with DECs and whose citizens travel more often to DECs for tourism. These include the United States (25% of cases) and the UK (15% of cases). Other European countries account for 18% of cases [The Netherlands (5), Belgium (2), Italy (2), Sweden (1), Norway (1), Germany (1), Poland (1)]. Finally, 5% of the remaining cases were diagnosed in India, Brazil, and Israel.

Countries diagnosing Gambiense HAT are mainly those with historical or economic links with DECs, namely France (6), Spain (2), Portugal (2), Germany

Table 2 Cases of Rhodesiense sleeping sickness diagnosed in non-endemic countries (2000–2010)

Year	Place of diagnosis	Place of infection	Sex/age	Activity	Diagnosis	Stage	Chancre	Treatment	Reference
2000									
n/a	Johannesburg South Africa	Kasungu Malawi	M 45	Tourist	Blood smear	First	n/a	Suramin	
April	Massachusetts USA	Serengeti Tanzania	M 37	Tourist	Blood smear	First	Yes	Suramin	3
October	London UK	S. Luangwa Zambia	M 51	Tourist	Blood smear	First	Yes	Suramin	4,5
October	London UK	Serengeti Tanzania	M 30	Tourist	Blood smear	First	Yes	Suramin	4,5
November	Salem Ohio, USA	Mayowasi Tanzania	M 47	Tourist	Blood smear	First	n/a	Suramin	
2001									
February	Verona Italy	Serengeti Tanzania	M 33	Tourist	Blood smear	First	Yes	Suramin	6,7
February	Bergamo Italy	Serengeti Tanzania	M 32	Tourist	Blood smear	First	Yes	Pentamidine	6,7
February	Bradford UK	Serengeti Tanzania	F 44	Tourist	Blood smear	First	Yes	Suramin	6
March	Stockholm Sweden	Serengeti Tanzania	M 41	Tourist	Blood smear	First	Yes	Suramin	6
March	Johannesburg South Africa	Serengeti Tanzania	M 68	Tourist	Blood smear	Second	Yes	Melarsoprol	6
March	Oslo Norway	Serengeti Tanzania	M 27	Tourist	Blood smear	First	Yes	Suramin	6,8
March	Amsterdam The Netherlands	Tarangire Tanzania	M 57	Tourist	Blood smear	First	No	Suramin	6,9
March	Chester New York, USA	Serengeti Tanzania	M 56	Tourist	Blood smear	Second	Yes	Melarsoprol	
April	Amsterdam The Netherlands	Tarangire Tanzania	F 55	Tourist	Blood smear	First	Yes	Suramin	6,9
May	Florida USA	Serengeti Tanzania	M 71	Tourist	Blood smear	First	n/a	Suramin	
June	Amsterdam The Netherlands	Serengeti Tanzania	F 52	Tourist	Blood smear	Second	Yes	Suramin Melarsoprol	6,9
June	Johannesburg South Africa	Serengeti Tanzania	F 34	Tourist	Blood smear	First	n/a	Suramin	10
July	Wyoming USA	Serengeti Tanzania	F 50	Tourist	Blood smear	First	Yes	Pentamidine	
July	Salem North Carolina, USA	Serengeti Tanzania	M 18	Tourist	Blood smear	First	No	Suramin	
August	USA	Serengeti, Tanzania	F 57	Tourist	Blood smear	First	n/a	Suramin	
August	Johannesburg South Africa	Serengeti Tanzania	M 29	Tourist	Blood smear	First	n/a	Suramin	10
August	Johannesburg South Africa	Mayowasi Tanzania	M 40	Tourist	Blood smear	Second	n/a	Pentamidine Melarsoprol	10
October	Leuven Belgium	Serengeti Tanzania	M 28	Tourist	Blood smear	First	No	Suramin	11
October	Antwerp Belgium	Serengeti Tanzania	M 32	Tourist	Blood smear	First	Yes	Suramin	
2002									
April	London UK	L. Zambezi Zambia	M n/a	Ranger	Blood smear	First	n/a	Suramin	
May	Chennai India	Serengeti Tanzania	M 40	Tourist	Blood smear	First	Yes	Suramin	12
August	Louisville Kentucky, USA	Serengeti Tanzania	M 40	Tourist	Blood smear	Second	No	Melarsoprol	
2003									
August	London UK	Serengeti Tanzania	M 9	Tourist	Fluid chancre	First	Yes	Suramin	13
August	London UK	Serengeti Tanzania	M 14	Tourist	Fluid chancre	First	Yes	Suramin	13

Table 2 (*Continued*)

Year	Place of diagnosis	Place of infection	Sex/age	Activity	Diagnosis	Stage	Chancre	Treatment	Reference
2004									
August	Johannesburg South Africa	Kasungu Malawi	M 38	Tourist	Blood film	Second	n/a	Suramin Melarsoprol	14
August	Bozeman Montana, USA	Mayowasi Tanzania	M 58	Tourist	Blood smear	First	Yes	Pentamidine Suramin	
October	Johannesburg South Africa	Kasungu Malawi	M n/a	Tourist	Blood smear	Second	n/a	Suramin Melarsoprol	
October	Pretoria South Africa	Serengeti Tanzania	F 52	Tourist	Blood smear	Second	No	Suramin Melarsoprol	15
December	Rochester Minnesota, USA	Serengeti Tanzania	F 61	Tourist	Blood smear	Second	Yes	Pent/Suramin Melarsoprol	16,17
2005									
February	Johannesburg South Africa	Kariba Zimbabwe	M 60	Ranger	Blood smear	First	n/a	Suramin	
June	Bethesda Maryland, USA	Serengeti Tanzania	F n/a	Tourist	Blood smear	First	n/a	Suramin	
November	Des Moines Iowa, USA	Serengeti Tanzania	M 71	Tourist	Blood smear	Second	No	Suramin Melarsoprol	
December	Johannesburg South Africa	Kasungu Malawi	M 26	Soldier	Blood smear	First	Yes	Suramin	18
December	Johannesburg South Africa	Kasungu Malawi	M n/a	Tourist	Blood smear	First	Yes	Suramin	
2006									
May	Johannesburg South Africa	Q. Elizabeth Uganda	F 52	Tourist	Blood smear	First	No	Suramin	
June	Grand Rapids Michigan, USA	Tarangire Tanzania	M 63	Tourist	Blood smear	Second	No	Suramin Melarsoprol	
2007									
January	Johannesburg South Africa	Vwaza Malawi	F 25	Tourist	Blood smear	First	Yes	Suramin	19
January	Johannesburg South Africa	Vwaza Malawi	M 31	Tourist	Blood smear	First	No	Suramin	19
February	Johannesburg South Africa	Kasungu Malawi	M n/a	Tourist	Blood smear	First	No	Suramin	
February	Johannesburg South Africa	Kasungu Malawi	M n/a	Tourist	Blood smear	First	No	Suramin	
September	London UK	S. Luangwa Zambia	M n/a	Tourist	Blood smear	First	No	Suramin	
November	Johannesburg South Africa	Kasungu Malawi	M n/a	Soldier	Blood smear	First	Yes	Suramin	
December	Johannesburg South Africa	Kasungu Malawi	M n/a	Ranger	Blood smear	First	No	Suramin	
2008									
March	Port Elizabeth South Africa	Serengeti Tanzania	M n/a	Tourist	Blood smear	First	Yes	Suramin	
July	London UK	Serengeti Tanzania	F 32	Tourist	Blood smear	First	Yes	Pentamidine Suramin	20
November	Amsterdam The Netherlands	Serengeti Tanzania	F 30	Tourist	Blood smear	First	Yes	Suramin	21
November	Lansing Michigan, USA	Mayowasi Tanzania	M 63	Tourist	Blood smear	First	Yes	Suramin	
2009									
January	Cedar Rapids Iowa, USA	Serengeti Tanzania	M n/a	Tourist	Blood smear	First	Yes	Suramin	
May	Johannesburg South Africa	Serengeti Tanzania	M 69	Tourist	Blood smear	First	Yes	Suramin	
July	Leiden The Netherlands	Serengeti Tanzania	F 25	Tourist	Blood smear	First	Yes	Suramin	
July	Poznan Poland	Q. Elizabeth Uganda	M 61	Tourist	Blood smear	First	Yes	Pentamidine	
August	Tel Aviv Israel	Serengeti Tanzania	F 31	Tourist	Blood smear	First	Yes	Suramin	22

Table 2 (*Continued*)

Year	Place of diagnosis	Place of infection	Sex/age	Activity	Diagnosis	Stage	Chancre	Treatment	Reference
August	Johannesburg South Africa	Mana Pools Zimbabwe	F 44	Tourist	Blood smear	First	Yes	Suramin	
October	Atlanta Georgia, USA	Mana Pools Zimbabwe	M 60	Tourist	Blood smear	First	Yes	Suramin	
November	Düsseldorf Germany	S. Luangwa Zambia	M 58	Tourist	Blood smear	First	Yes	Suramin	
December	Johannesburg South Africa	Nkhotakota Malawi	M 54	Ranger	Blood smear	First	Yes	Suramin	
2010									
July	Johannesburg South Africa	S. Luangwa Zambia	M 34	Ranger	Blood smear	First	No	Suramin	
August	Dallas Texas, USA	S. Luangwa Zambia	M n/a	Tourist	Blood smear	First	No	Suramin	
September	London UK	Mana Pools Zimbabwe	F 55	Tourist	Blood smear	Second	No	Suramin Melarsoprol	
October	Liverpool UK	S. Luangwa Zambia	F n/a	Tourist	Blood smear	First	No	Suramin	
November	Sao Paulo Brazil	Mana Pools Zimbabwe	M n/a	Tourist	Blood smear	First	Yes	Pentamidine	
November	Johannesburg South Africa	S. Luangwa Zambia	M n/a	Tourist	Blood smear	First	Yes	Suramin	
November	Pretoria South Africa	Kasungu Malawi	M n/a	Tourist	Blood smear	First	Yes	Suramin	

M = male; F = female.

(2), South Africa (2), and Greece (1), as well as other countries receiving refugees and migrants, namely the United States (3), Italy (3), Australia (2), Canada (2), and The Netherlands (1).

Country of Origin

For exported cases of Rhodesiense HAT, infection is supposed to have been contracted in protected areas such as national parks (NP), wildlife reserves, and GR. The country exporting the majority of cases, ie, 59%, is the United Republic of Tanzania, mainly from Serengeti NP, Tarangire NP, and Mayowasi GR. Other exporting countries are Malawi (19%) mainly from Kasungu NP, Zambia (12%) particularly from South Luangwa Valley NP, Zimbabwe (7%) from Mana Pools NP, and Uganda (3%) from Queen Elizabeth NP.

Countries of origin for Gambiense HAT are mainly DRC and Gabon, each accounting for 23% of cases, followed by Angola (15%), Cameroon (11%), Equatorial Guinea, and Uganda (8% each), Sudan and Central African Republic (4% each), and one case (4%) in a sailor returning from West Africa. In the latter case, the country of infection could not be identified as the patient arrived to the hospital in a coma and died shortly thereafter.

Diagnosis and Misdiagnosis

Rhodesiense HAT was mainly diagnosed by examination of blood smear (97% of cases) and in 3% of cases by fluid chancre examination.

Chancre was present in 57% of Rhodesiense HAT cases diagnosed and it was absent in 25%. For the rest of the cases (18%), this information was not available. Trypanosomal chancre was described in one Gambiense case only.[28]

Foreigners were infected during short visits to DECs (usually for safaris of 1–3 wk duration) and diagnosed between 1 and 3 weeks after exposure. This means that they were usually diagnosed in the week following their return from the trip or even in some cases during the trip. In 17 cases it was referred that the diagnosis was delayed between 1 and 7 days after admission due to misdiagnosis, most notably with malaria or tick-borne diseases.

Forty-six percent of the Gambiense HAT cases reported were diagnosed by examination of cerebrospinal fluid (CSF) only, including one case of brain biopsy. Blood was the body fluid where the parasite was initially found in 39% of the cases requiring concentration methods like capillary centrifugation test; in six of them blood was the sole fluid where the parasite was found, whereas in three cases it was also observed in CSF and in one case in blood, CSF, and bone marrow (BM). In 12% of the cases, the parasite was first found in lymph. Among them, in one case the parasite was found in lymph only and in two cases the parasite was found in lymph as well as in BM. Finally, one single case (3%) was diagnosed by the clinical signs and serological test.

The cases of Gambiense HAT were diagnosed after 3 to 12 months of the first examination, and following several admissions with a variety of misdiagnoses. The list of misdiagnoses reflects the difficulties in diagnosing Gambiense HAT: Hodgkin and non-Hodgkin

Table 3 Cases of Gambiense sleeping sickness diagnosed in non-endemic countries (2000–2010)

Year	Place of diagnosis	Place of infection	Sex/age	Activity	Diagnosis	Stage	Treatment	Reference
2000								
2001								
	Toronto Canada	DRC	M 42	Refugee	CSF, blood, and lymph	Second	Eflornithine	23,24
	New York USA	Angola	M 30	UN staff	CSF	Second	Eflornithine	25
	Atlanta USA	Kajo-Keji Sudan	M 19	Refugee	CSF	Second	Eflornithine	
	Poitiers France	Kinshasa DRC	M 28	Expat business	Lymph node/BM	Second	Eflornithine	26
	Hamburg Germany	Campo Cameroon	M 38	Migrant	Lymph node/BM	First	Suramin	27
2002								
	Paris France	Gabon	M n/a	Expat forest	Blood smear	First	Pentamidine	28
2003								
2004								
	Udine Italy	Komo, Gabon	M 44	Expat forest	CSF	Second	Eflornithine	29
	Verona Italy	CAR	F 54	Expat missionary	Blood CCT and blood smear	First	Pentamidine	29
	Amsterdam The Netherlands	Zaire Angola	F 27	Migrant	CSF	Second	Eflornithine	30,31
2005								
2006								
	Torino Italy	DRC	M 29	Migrant	CSF	Second	Eflornithine	
2007								
	Bordeaux France	Gabon	M 37	Expat forest	Lymph node	First	Pentamidine	32
	Bordeaux France	Gabon	M 72	Expat forest	Blood smear	First	Pentamidine	32
	Berlin Germany	Manfe Cameroon	M n/a	Migrant	CSF	Second	Eflornithine	
	Athens Greece	West Africa	M 65	Sailor	Blood smear	Second	Eflornithine	
	Madrid Spain	Mbini Eq. Guinea	M 55	Migrant	CSF (PCR) + serology	Second	Eflornithine	
2008								
	Perth Australia	Adjumani Uganda	F 19	Refugee	CSF	Second	Eflornithine	33
	Toronto Canada	DRC	M 20	Refugee	Blood smear	Second	Eflornithine	
	Valencia Spain	Mbini Eq. Guinea	M 18	Migrant	CSF	Second	Eflornithine	
2009								
	Sydney Australia	Adjumani Uganda	F 24	Refugee	Brain biopsy	Second	Eflornithine	34
	Castres France	Cocobeach Gabon	M 22	Expat business	Blood smear/BM/CSF	Second	Eflornithine	
	Marseille France	Gabon	M n/a	Expat business	Blood smear	First	Pentamidine	
	Braga Portugal	Catete Angola	M 55	Expat business	Blood/CSF	Second	Eflornithine	
2010								
	Lisbon Portugal	Muxima Angola	F 2	Migrant	Blood/CSF	Second	Eflornithine	
	Washington USA	Kumba Cameroon	M 37	Migrant	Blood CCT	Second	Eflornithine	
	Cape Town South Africa	Bandundu DRC	M n/a	Migrant	Blood CCT	Second	Eflornithine	
	Cape Town South Africa	Kikwit DRC	M 25	Migrant	CSF	Second	Eflornithine	

M = male; F = female; CSF = cerebrospinal fluid; CCT = capillary centrifugation test; BM = bone marrow.

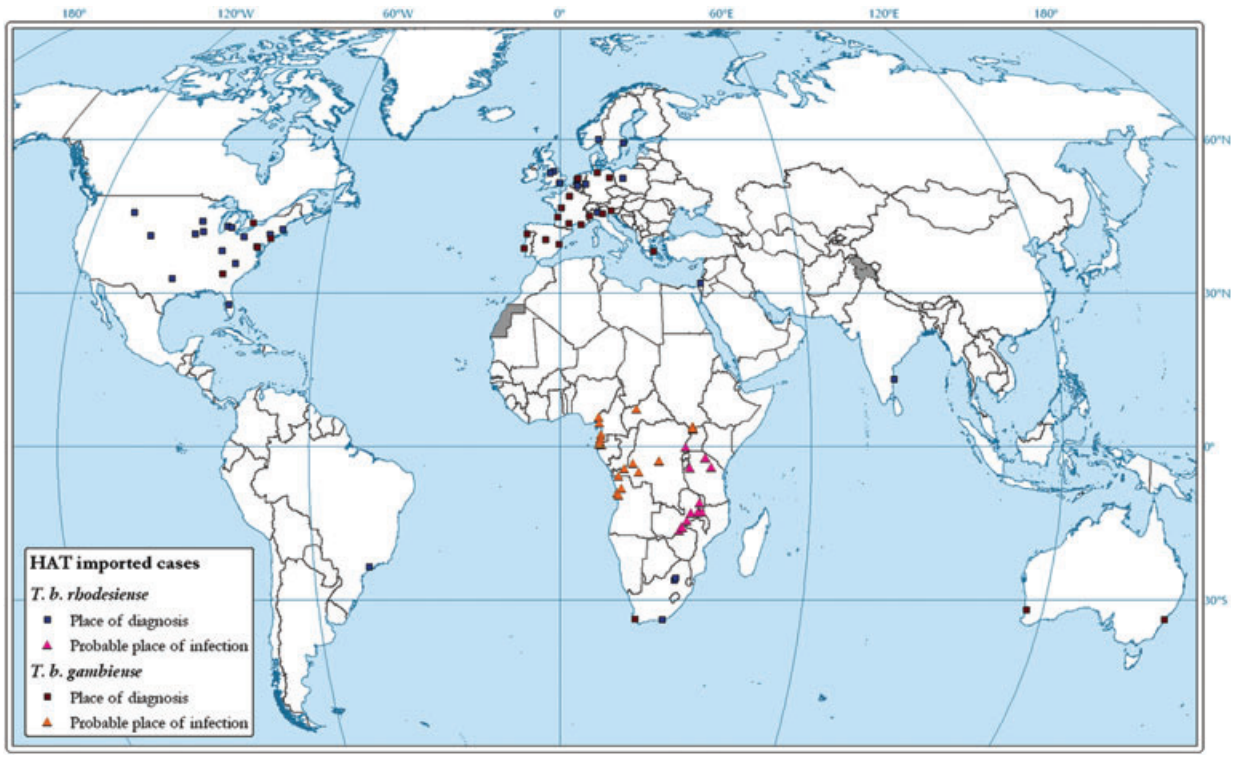

Figure 1 HAT cases diagnosed in non-endemic countries (2000–2010). Squares represent the place of diagnosis; triangles indicate the probable place of infection. For one *Trypanosoma brucei gambiense* case originating from Western Africa and diagnosed in Athens (Greece), the probable place of infection is not available. Similarly, for one *Trypanosoma brucei rhodesiense* case originating from the Serengeti NP (United Republic of Tanzania) and diagnosed in the United States, the place of diagnosis is not available.

lymphoma, mental disorders (reactive depression, psychosis, post-traumatic stress, and substance abuse), brain cancer (glioma, metastatic), tuberculosis, meningitis, neurosyphilis, collagen vascular diseases, typhoid fever, and human immunodeficiency virus opportunistic infections.

In 14 cases diagnosis of Gambiense HAT was achieved after the infected individual had been living outside DECs for several years (1–7 years), showing the very slow progression of this form of HAT.

Treatment and Outcome

Among the 56 cases of Rhodesiense HAT diagnosed in first stage, 89% were treated with suramin, 7% with pentamidine, and 4% with a combination of suramin and pentamidine. Among the 12 cases diagnosed in second stage, 58% were treated with suramin and melarsoprol, 25% with melarsoprol only, and 17% with pentamidine and melarsoprol.

Among the six Gambiense HAT cases in first stage, 83% were treated with pentamidine and 17% with suramin. However, 100% of the cases diagnosed in second stage were treated with eflornithine.

One case of HAT Gambiense and three cases of Rhodesiense died during treatment, showing an important case-fatality rate: 4.3% (4.4% for Rhodesiense and 3.8% for Gambiense). Deaths were related to late diagnosis or to toxicity of melarsoprol (encephalitic reaction).

Discussion

In non-DECs, it is usually non-mandatory to report HAT cases. Therefore, information on cases diagnosed in the past was related to voluntary publication in scientific journals or collection of data gathered by some authors.[35–38] Today, distribution of HAT drugs is the sole responsibility of WHO and they cannot be obtained on the market with the exception of pentamidine. To treat HAT cases diagnosed in non-DECs, pharmacy services have to request drugs from WHO and provide epidemiological, parasitological, biological, and clinical data. This information enables WHO to maintain an HAT surveillance system and a comprehensive database for non-DECs. For instance in a recent review[39] on HAT in non-DECs for 20 years (1990–2010), 68 cases were reported, whereas in this article, we report 94 cases for 11 years only (2000–2010). Therefore, due to current accurate information it is difficult to compare current and past trends of HAT occurrence in non-DECs.

While the majority of HAT cases reported by DECs correspond to the Gambiense form (97%),[2] the opposite is true for imported cases in non-DECs, where 72% of

cases are caused by *Trypanosoma brucei rhodesiense* and 28% by *Trypanosoma brucei gambiense*. It is difficult to establish the number of migrants and refugees traveling to non-DECs from HAT transmission areas, and even more difficult to ascertain how many of them are affected by HAT. However, the proportion of Gambiense to Rhodesiense HAT cases diagnosed in non-DECs is lower than one would probably expect.

Several factors could explain the observed pattern. First, the acuteness and high parasitemia of Rhodesiense HAT lead to a relatively easy and quick diagnosis. Most of the cases of *T b rhodesiense* infection were diagnosed 1 to 3 weeks after exposure, 97% of them by blood smear. By contrast, Gambiense HAT can often be misdiagnosed with a number of different illnesses leading to a delay in diagnosis of 3 to 12 months. Second, but not less important, exported cases of Rhodesiense are usually associated to tourists belonging to the middle or upper class, who enjoy access to health care in a way not comparable with that of refugees and migrants more affected by Gambiense HAT. The latter categories comprise illegal immigrants who may suffer from limited access to the health care system in the country where they migrated to. Importantly, tourists are much more likely to travel to Rhodesiense areas than to Gambiense areas.

In the rural African milieu where health systems are weak, HAT is frequently misdiagnosed with other pathologies. Unfortunately, this also occurs in non-DECs, in this case not for weaknesses of the health systems but because of weaknesses of knowledge and awareness among health care staff. This may lead to sophisticated tentative diagnosis with invasive diagnostic methods and unnecessary treatments. This is more evident in Gambiense HAT where only 8% of reported cases were diagnosed by examination of lymph obtained from enlarged gland puncture, despite the fact that this simple and relatively non-invasive method provides approximately 50% of cases diagnosed in the field.[40] By contrast, during the study period, most cases of Gambiense HAT were fortuitously diagnosed through CSF examinations, including brain biopsy, blood marrow puncture, or gland biopsy.

However, pentamidine, the first line drug to treat first stage of the Gambiense form, can be purchased in the market without need to request it from WHO. This fact could lead in our study to a certain underestimation of first-stage cases of *T b gambiense*.

When an HAT case is detected in a group of refugees originating from Gambiense areas, special attention should be given to the whole group as there is likely to be a common history of engagement in at-risk activities. The same applies to *T b rhodesiense*, as it is not infrequent to observe more than one case in the same group of tourists. On two occasions in the study period a relative presented with the disease only a few days after the first case had been diagnosed.[13,19]

Difficulties in getting treatment referred in the first years of the study period[4,6,8] were dramatically improved by setting up anti-trypanosome drug repositories in the main reporting hospitals or in national pharmacy services. Improvement is also linked to better dissemination of information on anti-trypanosome drugs availability and on the procedures to obtain these drugs.

During the study period, all second-stage cases of Gambiense HAT were treated with eflornithine, while in the field the percentage of eflornithine usage hardly reached 30%. Interestingly, with regard to treatment, four first-stage cases of Rhodesiense HAT were successfully treated with pentamidine only (A. Moore, P. Malgorzata, and N.E. Reiner, personal communication).

As the probable places of infection and contact with tsetse flies are obtained from patients' interviews, we have to accept a degree of uncertainty given that, in some instances, several places of infection were possible. In this light, interviews can be considered to be providing an orientation rather than hard evidence. However, in the case of Rhodesiense HAT, patients usually remember quite clearly where they were attacked and bitten by tsetse flies.

Limitations notwithstanding, available data from HAT surveillance in non-DECs provides valuable information on hot-spots of transmission that complements data collected in DECs, thereby helping to plan control and surveillance in countries with weak surveillance systems.

For example, a cluster of cases diagnosed in 2001 in travelers to Tanzanian NPs, especially the Serengeti, was suggestive of a change in the local epidemiology.[6] In Uganda, autochthonous Rhodesiense cases are reported from south-eastern districts only, while surveillance in non-DECs also provided information on infections contracted in the south-western part of the country, in two travelers visiting the Queen Elizabeth NP. Similarly, in Zimbabwe, only one case was detected by national health facilities during the study period, but five exported cases of travelers having visited Mana Pools NP were recorded. In addition, two Zimbabwean nationals were detected out of the country. Therefore, we have not included in our series two cases reported by Rocha et al.[25] concerning a hypothetical sexually and congenitally transmitted HAT that occurred in the United States.

Conclusions

Awareness of the fact that HAT is still a risk for travelers and migrants is an essential prerequisite to ensure correct and early diagnosis, to avoid unnecessary distress to patients, and to reduce the risk of lethality. An accurate geographical anamnesis is crucial, as so is the search for key signs such as enlarged para-cervical and supra-clavicle glands for *T b gambiense* and chancre for *T b rhodesiense* infections. Indeed more than three quarters of Rhodesiense HAT cases presented chancre at diagnosis.

HAT surveillance in non-DECs may also raise questions related to difficulties in detecting exported HAT in recipient countries. For example, countries like France, Portugal, Spain, and Germany are predictably diagnosing cases in expatriates or migrants coming from former colonial territories in Gambiense areas.

The fact that drugs to treat HAT are not available on the market, except pentamidine, largely improved reporting of HAT cases diagnosed in non-DECs. Only 40% of the cases diagnosed in the period 2000 to 2010 were published in scientific papers, while 35% were only reported to WHO at the moment of drug request and 25% were reported to WHO and to epidemiological networks such as the Communicable Diseases Communiqué of the National Health Laboratory Services, South Africa (http://www.nicd.ac.za), ProMed (http://www.promedmail.org), GeoSentinel (http://www.geosentinel.org), and TropNetEurop (http://www.tropnet.net). Interestingly, all cases reported through these epidemiological networks are HAT Rhodesiense cases.

The current decline in HAT transmission in DECs[41] is accompanied by the increase in visitors from non-DECs to protected areas in transmission zones and by the increase in migrants from DECs to non-DECs.[42] Subsequently, albeit low, a risk exists of travelers acquiring HAT and of detecting the disease in migrants. The rarity of the disease in non-DECs, combined with nonspecific symptoms, makes diagnosis difficult.[43] Difficulties are often ascribable to lack of awareness, rather than to complexities in diagnostic techniques. This article draws attention to this disease in medical services in charge of travelers and migrants and reinforces information about the free availability of HAT drugs.[44] HAT drugs can be requested from WHO through Dr Pere P. Simarro (simarrop@who.int) or Dr José R. Franco (francoj@who.int).

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Disclaimers

The boundaries and names shown and the designations used on the maps presented in this article do not imply the expression of any opinion whatsoever on the part of WHO and FAO concerning the legal status of any country, territory, city, or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Shaded areas on maps represent regions for which there may not yet be full agreement.

The views expressed in this article are those of the authors and do not necessarily reflect the views of WHO and FAO.

Declaration of Interests

The authors state that they have no conflict of interests.

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