Epidemiology of *Trypanosoma brucei rhodesiense* Sleeping Sickness in Eastern Uganda

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Declaration

I, Dr Martin Odiit (MD), do declare that I composed this thesis, that it is my own work and that it has not been submitted for any other degree or professional qualification except as specified.

Signed..... .....

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List of Abbreviations

AIDS	Acquired Immune Deficiency Syndrome (AIDS)
AVHRR	Advanced Very High Resolution Radiometer images
BOD	Burden of Disease
CATT	Card Agglutination Test for Trypanosomiasis
CDR	Crude Death Rate (CDR)
CI	Confidence Interval
CSF	Cerebrospinal Fluid
CNS	Central Nervous System
COCTU	Coordinating Office for the Control of Trypanosomiasis in Uganda
DALYs	Disability Adjusted Life Years
DFID-AHP	Department For International Development (British Government)-Animal Health Programme
DOT	Direct Observed Therapy
dT	Diurnal temperature difference images
EATRO	East African Trypanosomiasis Research Organization
ETM	Enhanced Thematic Mapper
FITCA	Farming in Tsetse Control Areas of Eastern Africa
GBDS	Global Burden of Disease Study
GIS	Geographical Information Systems
GPS	Global Positioning System
HAT	Human African Trypanosomiasis
HMIS	Health Management Information Systems
LIRI	Livestock Health Research Institute
MOF	Ministry of Finance and Economic Development
MOH	Ministry of Health
MONR	Ministry of Natural Resources
NOAA	National Oceanic and Atmospheric Administration
PAF	Population Attributable Fraction
NDVI	Normalised Difference Vegetation Index
RFLP	Restriction Fragment Length Polymorphism

RR	Relative Risk
RSS	Rhodesiense sleeping sickness
SD	Standard Deviation
SRA	Serum Resistance Antigen
SS	Sleeping Sickness
Tcap	Tasseled cap transformation
TM	Thematic Mapper
UN	United Nations
YLL	Years of Life Lost
YLD	Years of Life Lived with Disability
WHO	World Health Organization

Abstract

Sleeping sickness is now recognized as one of the recent re-emerging but neglected diseases. In Uganda and the rest of sub-Saharan Africa, old foci of sleeping sickness persist despite donor-funded projects and there is evidence of expansion of these foci. The World Health Organization acknowledges a high level of undiagnosed sleeping sickness cases and has identified surveillance and treatment as the major control strategy for sleeping sickness. However, to date there have been no clear epidemiological surveillance markers applied for monitoring the burden of the disease at control implementation levels. There is therefore a need to obtain markers for surveillance and to apply these to monitor and improve this important strategy of sleeping sickness control, hence, the objective of this study.

Data of sleeping sickness patients from 1987 to 2002 were collected from Tororo, Busia and Soroti districts. Using the ratio of early to late stage patients in an affected population, data from (Livestock Health Research Institute) LIRI hospital in Tororo district were applied to develop a model for estimation of sleeping sickness under-detection. The model was applied to data from a recent outbreak of sleeping sickness in Soroti district to determine the burden of the disease. Geographical information systems (GIS) were applied to quantify the effect of distance from the health units on early detection of sleeping sickness. A semi-structured questionnaire was administered to prospective sleeping sickness patients to determine their treatment seeking behavior. Spatial and temporal trends of sleeping sickness with and without control are described using the SatScan method for spatial temporal clustering. The potential role of remote sensing in surveillance of sleeping sickness was explored using a processed Landsat 7 series satellite image to determine association of land cover classes, vegetation indices, population density, distance to wetlands, distance to the sleeping sickness hospital to the outcome of village scale disease geographical distribution generated using GIS.

In the Tororo and Busia area, for every 3 reported patients, 2 went undetected. The Disability Adjusted Life Years (DALYs) for sleeping sickness in the Soroti outbreak are greatly increased when under-detection is taken into account. There is a strong effect of distance to health unit on the surveillance of sleeping sickness. Children and

adolescents are less likely to be detected in early stage. During times of low incidence, the proportion of late stage detected patients increases. Most of the delay to diagnosis is attributable to service provider delay and most patients are referred to the sleeping sickness referral hospital by the community and not the health system. Proximity to wetlands and to the sleeping sickness hospital, low population density, vegetation wetness and smaller area of short grassland and larger area of cropland were significantly associated with the distribution of sleeping sickness affected villages in Tororo and Busia districts.

Surveillance of sleeping sickness can be monitored by applying the early to late stage ratio of sleeping sickness as an epidemiological tool to determine the level of under-detection and subsequently the burden of disease. Optimal distribution of fixed post diagnostic units will greatly improve rhodesiense sleeping sickness surveillance. Surveillance programmes should regularly update health workers in the primary health care units in the vicinity of sleeping sickness affected populations. Similarly, the affected communities can be resourcefully used to refer sleeping sickness suspects to the appropriate health care facilities. Timely responsive disease surveillance and intervention can prevent spread of sleeping sickness. Remotely sensed maps can assist in accurately describing sleeping sickness foci and therefore, the area requiring application of control interventions

Chapter 1 Introduction

Diseases such as sleeping sickness are known to be re-emerging and yet have been recognized as among the neglected diseases (Jannin *et al.*, 2001). There have been commendable combined public- and private-sector initiatives to tackle this neglected disease especially in the free provision of drugs (Etchegorry *et al.*, 2001) but a considerable amount of effort is still required to improve the control of sleeping sickness (Cattand *et al.*, 2001). The economies of countries that are affected by sleeping sickness are ranked amongst the poorest of the poor (World Bank, 2000). Therefore, the need for cost-effective ways of control cannot be over emphasised. The epidemiology of the disease is characterised by a focal distribution, with foci persisting and expanding during epidemics (WHO, 1998). This focal nature has implications on the assessment of the burden of sleeping sickness and on the targeting of control operations to reduce costs but ensure effectiveness. Studies of risk factors of distribution of sleeping sickness at sub-national levels are lacking and the data obtained from such studies can be used for the planning and implementation of control programmes. Due to the focalisation of occurrence of this disease, it is important to describe the burden at sub-national and outbreak levels.

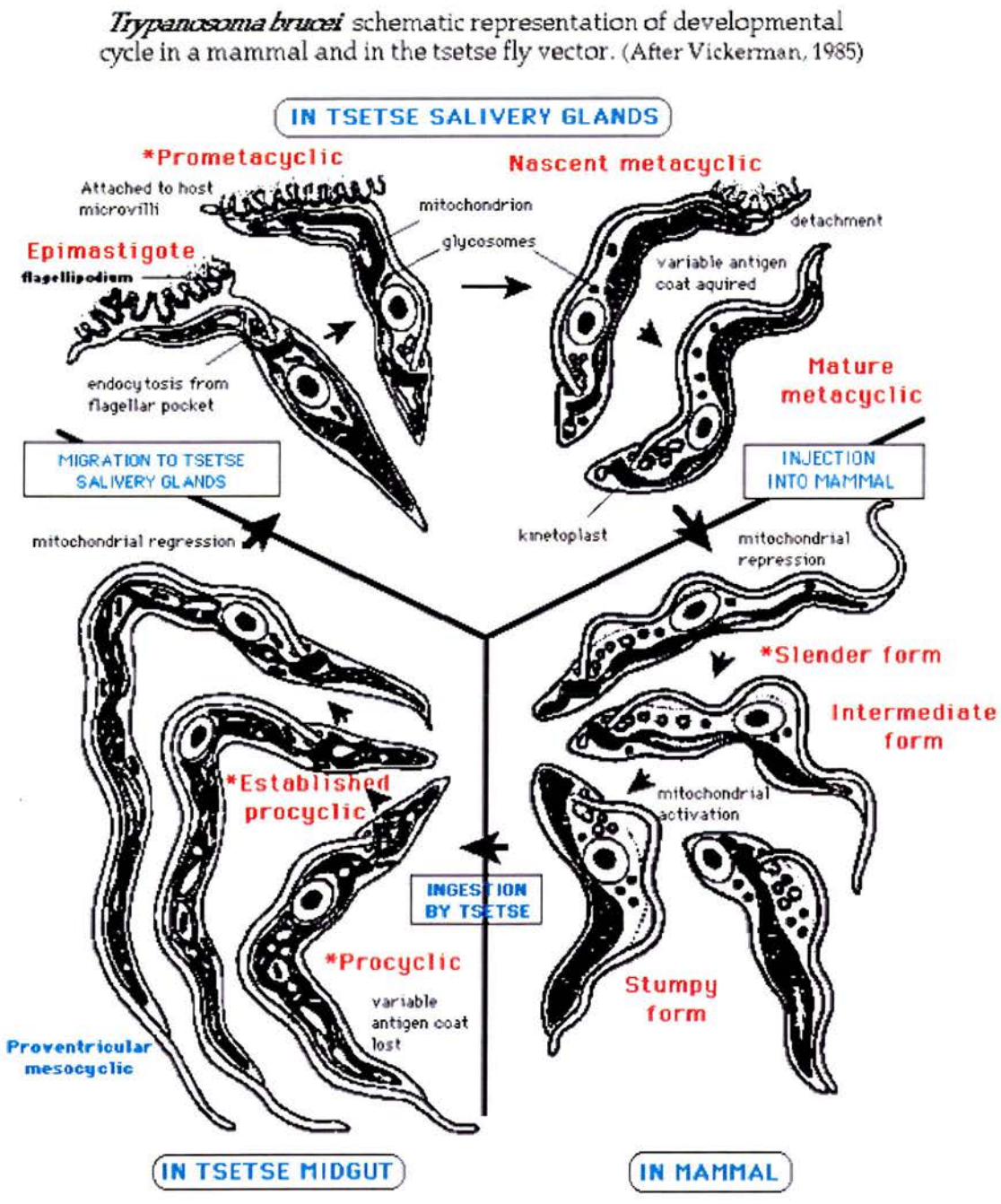
Good surveillance and treatment of sleeping sickness is important for planning, early patient detection and disease control and monitoring (WHO, 1998). Specifically, for sleeping sickness control to be rationally targeted and in order to prevent outbreaks, the surveillance of the disease has to be improved. However, markers for surveillance of sleeping sickness have not been well identified and applied at control implementation level and although it is accepted that there is gross under-detection of sleeping sickness (WHO, 2002), the exact magnitude of the problem has remained unknown. Allocation of resources is determined by the relative burden of diseases and therefore, good estimates of disease burden are necessary for planning. The tsetse fly has preferable tsetse habitats and climate, and the distribution of sleeping sickness is very much linked to the distribution of tsetse and available hosts. It is an arduous task to determine the distribution of tsetse at high resolution levels e.g. village or homestead levels. However, the distribution of human and livestock

populations and infections can more easily be estimated and the distribution of tsetse suggested by the distribution of vegetation types. Detailed analysis of the distributions of sleeping sickness patients, land cover and other potential spatial risk factors is now possible due to the increasing availability of powerful Geographic Information System (GIS) software. Geographical risk analyses can therefore be performed and strategies for targeting surveillance of sleeping sickness can thus be designed.

1.1 Biology of sleeping sickness

Human African trypanosomiasis, also known as sleeping sickness, is a result of an infection by blood-borne haemoflagellate protozoan parasites of two sub-species: *Trypanosoma brucei gambiense* or *Trypanosoma brucei rhodesiense*, causing two forms of the disease. *Trypanosoma* belong to the family trypanomastidae of the order kinetoplastida. The two human infective trypanosomes belong to the subgenus, *Trypanozoon.* A more chronic form of the disease is caused by *T. b. gambiense* and is found in west and central Africa and an acute form caused by *T. b. rhodesiense* is found in east and southern Africa (WHO, 1998). The life cycle of the parasite is complex, involving many stages in both the tsetse fly and the mammalian host (Figure 1.1).

Figure 1.1. Developmental cycle of human infective trypanosome



The female tsetse fly produces a single egg, which hatches to a first stage larva in the uterus where it develops and moults (Carpenter, 1912). A third stage larva is then deposited on the ground. One full-grown larva is produced every 9-10 days and pupates in light or sandy soil. A puparial period follows and an adult fly emerges in about 30 days. The lifespan of the tsetse is three to four months. Since at least 17 days are required for the development of *Trypanozoon* species in the tsetse, the daily survival rate of these flies is crucial to sleeping sickness transmission. The most important vector responsible for the transmission of sleeping sickness in eastern Uganda is *Glossina fuscipes fuscipes* (Okoth, 1986). *G. f. fuscipes* belongs to the subgenus palpalis that are described as riverine tsetse. Experiments have shown that *G. f. fuscipes* has poor water storage and is therefore restricted to hygrophytic habitats near water in lacustrine or riverine habitats (Jackson, 1945). Human population and distribution of animals are important factors associated with the distribution of the *palpalis* group of tsetse (Baldry, 1980). Age of fly at infective feed has been shown to be important with younger flies being more likely to get infected (Van Hoof *et al.*, 1937; Wijers, 1958). However, age is apparently less critical with *G. f. fuscipes* and *T. b. rhodesiense* with little difference in susceptibility being observed between 2 and 11 days (Harley, 1970). The close contact of man and the vector contact is particularly important for the transmission of sleeping sickness and the incidence of a disease may have little relationship to the density of the tsetse present (Page & McDonald, 1959).

For the sleeping sickness caused by *T. b. rhodesiense*, the time between the bite of an infected tsetse to the first sign of illness is usually within one to three weeks (Apted, 1970), sometimes following a trypanosomal chancre, a local inflammatory lesion at the site of the bite (WHO, 1998). Invasion of the blood is characterized by irregular headaches, fevers and body aches. As the disease progresses, it further invades the lymphatics causing lymphadenopathy, and there is weight loss, rash, itching, weakness and oedema. The sleeping patterns get distorted rather than hypersomia (Buguet *et al.,* (2001), giving the disease its name. *T. b. rhodesiense* disease progresses to central nervous system involvement with nervous impairment more

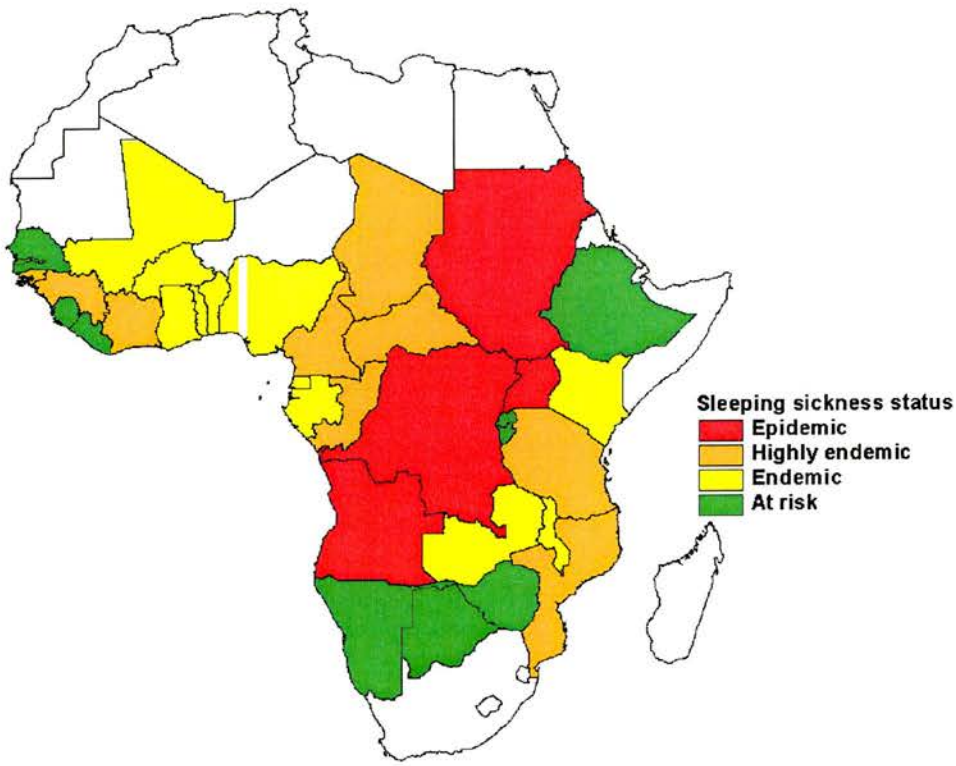
rapidly (3 weeks to 2 months) (Odiit *et al.*, 1997a) than *T. b. gambiense*. The patient may have convulsions and become comatose. Clinical signs are generally non-specific and thus provide only a guide to diagnosis.

Trypanosomes escape the initial host defence mechanisms by antigenic variation of parasite surface glycoproteins (Ritz, 1914). By evading the humoral immune system, the parasite expresses its virulence and during the resulting parasitaemia, pathological changes occur in the central nervous, cardiovascular, and haematolymphatic systems. These pathological effects are due to immune-mediated reactions against antigens on tissues in the affected systems, causing meningo-encephalitis, pancarditis, haemolysis and anaemia. Hypersensitivity reactions cause skin manifestations such as urticaria, pruritus and oedema.

1.2 Global burden of sleeping sickness

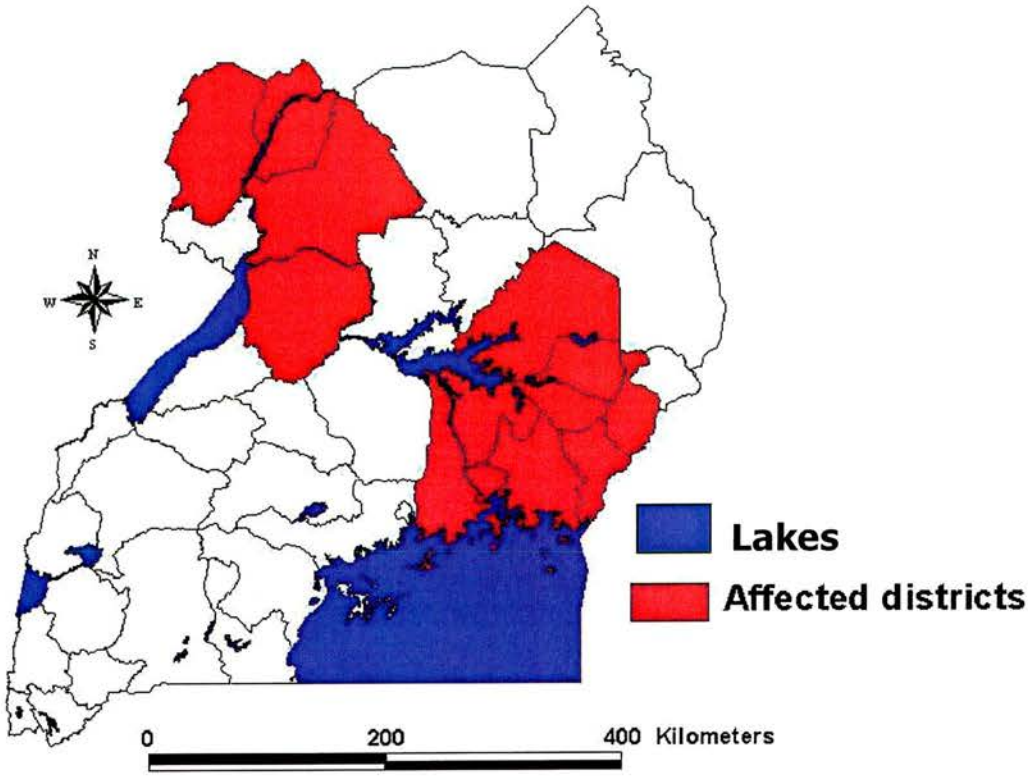
Sleeping sickness is restricted to tropical sub-Saharan Africa (WHO, 1998). The disease is a re-emerging problem and the World Health Organization estimates that there are 300,000-500,000 people infected with sleeping sickness. Sixty million people are at risk in 36 countries while only 3-4 million are under surveillance, resulting in the reporting of only 45,000 cases per year (WHO, 2002). Amongst infectious diseases, the burden of sleeping sickness (measured in DALYs) is ranked highly (World Health Report, 2000). There is variation in endemic status of sleeping sickness across countries in the tsetse belt with high incidence currently being reported in the Democratic Republic of Congo, Angola, Sudan and Uganda (WHO, 1999b) (Figure. 1.2). Sleeping sickness and poverty are closely linked. The countries affected by sleeping sickness rank amongst the poorest of the poor countries (World Bank, 2000). For instance, the Gross National Product per capita for Uganda is, for example, estimated at US $320 and the public expenditure on health at 1.8% of the Gross Domestic Product (World Bank, 2000).

Figure 1.2. Distribution of sleeping sickness by country



In Uganda, gambiense sleeping sickness is found in the northwest and rhodesiense sleeping sickness is found in the eastern parts of the country (Figure 1.3). In both parts of the country, *Glossina fuscipes fuscipes* is the vector identified as responsible for the transmission of the disease. Rhodesiense sleeping sickness (RSS) is a more acute illness. Often the disease occurs in outbreaks and sometimes in epidemics with loss of many of lives (Mbulamberi, 1989). However, it is acknowledged that the basic reproductive rate, $R_{0,}$ (Anderson, 1998) of trypanosomes is low (Rogers & Williams, 1993), resulting in a disease with long periods of apparent very low endemicity, occasionally interrupted by epidemics. R_0 determines the ability of the parasite to perpetuate itself. It is defined as the average number of new infections produced by it throughout its life time. R_0 must be greater than one for the parasite to maintain itself. Despite the low R_0 and several donor-funded projects to control sleeping sickness in southeastern Uganda, the disease remains uncontrolled and there is evidence of expansion of its foci (Enyaru *et al.*, 1999; Fèvre *et al.*, 2001). Control programmes using the current approaches are often too expensive to sustain after donor funding has ceased. This is compounded by the fact that many governments of the affected countries do not allocate adequate funding for sleeping sickness control activities

Figure 1.3. Map showing districts in Uganda that are endemic for sleeping sickness.



1.2.1 Burden of disease estimation: the DALY

For health policy to be effective, it requires reliable quantification of burden of disease. The Global Burden of Disease Study (GBDS) is designed towards the development of a rational evidence-based health policy (Murray & Lopez, 1996). The assessment of cost-effective health interventions and prioritisation in health policy and research can be facilitated by more accurate burden of the disease estimates. However, one major problem in developing countries and most especially in sub-Saharan Africa (SSA) is the lack of epidemiological and demographic data (Kaufman *et al.*, 1997). GBDS extrapolates epidemiological data that is available, using cause of death models and expert judgements (Murray & Lopez, 1996). There is therefore the need for more area and disease specific epidemiological data to enable more accurate estimations of burden of disease (BOD). There have been several conceptually different measures proposed for measuring BOD, such as mortality rates, different forms of years of life lost (YLL) and the disability-adjusted life years (DALY) that is inclusive of YLL (Gardner, 1990; Lee, 1998; Murray, 1994). The DALY is the current measure used in the GBDS. DALYs are the sum of the present value of years lost through premature mortality, and the present value of years of future life time adjusted for the average severity of any mental or physical disability caused by disease or injury. Therefore, DALYs measure something 'lost' and health programmes aim at their reduction. DALYs were first introduced in the World Development Report (World Bank, 1993) and the Diseases Control Priorities Review (Jamison *et al.,* 1993) as a method for estimating the global burden of disease as an outcome measure for use in cost-effectiveness analysis. In 1996, another version of the DALY was developed and is currently used (Murray & Lopez, 1996).

1.3 History of sleeping sickness

Trypanosomes were first detected in man in a steamboat captain on the River Gambia in 1901 by R. M. Forde. Forde described the clinical features in the patient (Forde, 1902a,b) but he thought these were due to filariasis. Dutton (1902) later identified the parasite as a trypanosome, which he described and named

Trypanosoma gambiense. However, it was Castellani (1903a,b) and Bruce (1908) who associated the parasite with the disease, which was already known at the time. Again it was Castellani (1903c) who first demonstrated the parasite in the cerebrospinal fluid. In 1908, *T. b. rhodesiense* was found in northern Rhodesia (Zambia) in two Europeans who became infected in the Luangwa valley and both died after approximately 6 months (Stephens & Fantham, 1910). The first recorded epidemic in Uganda occurred on the shores of Lake Victoria (Christy, 1903a,b) and is believed to have been caused by *T. b. gambiense*. It is suggested that the causative agent in this outbreak may have actually been *T. b. rhodesiense* as was the case for subsequent outbreaks in this area (Koerner *et al.*, 1995). However, Gibson (1996) disputes this suggestion. The vector identified as responsible for the epidemic was *Glossina palpalis*, later defined as *G. f. fuscipes* (Bruce & Nabarro, 1903). It is believed that sleeping sickness had been on the northern shores of Lake Victoria since 1896 (Christy, 1903a,b; Ford, 1971). It was estimated that more than 200,000 people died in Buganda and Busoga between 1898 and 1906. By 1905, the number of reported patients reached 100,000 and people were evacuated to a minimum distance of 3 km from the lakeshore and in some areas up to 24 km from the lake (Duke, 1919). Clearing of bush and treatment with atoxyl were recommended as the control measures for sleeping sickness at the time (Koch *et al.*, 1909).

In the early 1940s, another sleeping sickness epidemic occurred in the area (Mackichan, 1944). By 1943, 2,432 patients were recorded with 274 deaths. The first recorded patient was a schoolboy from Busoga detected in Kampala whilst he was visiting. In 1941, the epidemic was shown to be due to *T. b. rhodesiense*. This marked the first identification of *T. b. rhodesiense* in Uganda. It was concluded that *G. pallidipes* was the vector of the disease in this epidemic (Duke, 1944). It was not until 1960, that *T. b. rhodesiense* was detected in wild *G. palpalis* (*G. f. fuscipes*) that this fly was believed to play a role in the transmission of this parasite (Southon & Robertson, 1961). It appeared then that *T. b. gambiense* had been completely replaced by *T. b. rhodesiense* (Robertson & Baker, 1958). It is thought that the source of the epidemic in the 1940s was the west side of Lake Victoria in Tanzania. The disease persisted into the sixties perhaps because of the increased fishing activity

as evidenced by a high male incidence compared to females (Roberston, 1963). Of all patients between 1954 and 1960, 85% were males and there was a reduction of patients in July and October when there was a seasonal reduction in fishing.

Before 1976, the disease appeared to be under control with only sporadic cases presenting in the area north of Lake Victoria. However, in 1976, there was an epidemic. Between 1976 and 1983, 19,974 sleeping sickness patients were detected. The first reported case was detected in June 1971 north of Busesa, outside the known *G. f. fuscipes* infested area, the only vector known at the time (Matovu, 1982; Abaru, 1985). The breakdown of control services associated with political turmoil as well as the change in agricultural practices with resultant bush encroachment led to the larger epidemic in 1976. It is believed that the epidemic spread from the old focus in Busoga, on the shores of Lake Victoria (Gibson & Gashumba, 1983; Mbulamberi, 1989). In the early 1980s, aerial spraying of tsetse using insecticides was carried out and it temporarily reduced the incidence of sleeping sickness (Kangwagye *et al.*, 1987). However, by the late 1980s, the incidence had begun to rise and the disease spread further eastwards (Lancien, 1991; Enyaru *et al.*, 1992) into Tororo and Busia districts. A large tsetse trapping operation using 13,000 impregnated pyramidal tsetse traps over an area of 39,000km^2 was instituted and surveillance and treatment of both human and cattle populations carried out (Lancien, 1991). By 1992, the number of patients had reduced to less than 500 but has remained at an incidence of over 200 patients per year.

1.4 Diagnosis of sleeping sickness

Due to the non-specificity of the clinical features and the toxicity of the drugs, the demonstration of the trypanosome is mandatory globally before treatment can be administered to a sleeping sickness patient (WHO, 1998). Microscopic examination of the blood or gland or lymph node aspirate is therefore a necessity but these methods have low sensitivity (Cattand & de Raadt, 1991). The most common diagnostic technique applied in the field is the stained thick smear. However, the wet film and the haematocrit centrifugation test (Woo, 1970) are also commonly used.

Due to the costs of staffing and equipping sleeping sickness treatment facilities, there are few health units equipped for diagnosing and treating the disease. The problem of poor accessibility for diagnosis and subsequently treatment may be alleviated by the use of mobile teams. However, this is only more rewarding where a valid screening test is commercially available. The Card Agglutination Test for Trypanosomiasis (CATT) is such a test that has good sensitivity and specificity (Magnus *et al.*, 1978) but it is only useful for the *T. b. gambiense* sleeping sickness. A similar test for *T. b. rhodesiense* is required before mobile teams can used for routine diagnosis and treatment of this form of the disease. Since *T. b. rhodesiense* sleeping sickness is more acute often causing death within 6 months of infection, a screening test would be even more beneficial than it is in the *T .b. gambiense* form of the disease. In eastern Uganda, mobile teams are used during outbreaks to increase the awareness of the population and detect patients that may have not yet sought health care. The costs of maintaining mobile teams are not affordable by the economies of countries affected by sleeping sickness and therefore, they are often used in epidemic situations and with donor support. The optimisation of the distribution of fixed post diagnosis and treatment may be a more sustainable strategy especially in between epidemics of sleeping sickness. Community health workers referring clinical suspects to the fixed post diagnosis units may complement this strategy.

The detection of the trypanosome in gland or lymph node aspirate or blood is always followed by a lumbar puncture to determine whether there is involvement of the central nervous system (CNS) (also known as the late stage) because drugs used when the CNS is involved are different from those used when the parasite is still restricted to the haemato-lymphatic system (also known as the early stage) (WHO, 1998). The criteria used for determination of CNS involvement are as follows: white blood cell counts above 5 cells/mm^3 or the demonstration of trypanosomes or protein levels above normal (25mg percent) in the cerebrospinal fluid (CSF). In Uganda, the former two criteria are generally used because they are easier to perform and do not require reagents.

There have been attempts to determine if the criteria for treatment can be adjusted to reduce the number of patients receiving melarsoprol treatment, which is very toxic. It has been proposed that the number of cells to determine CNS involvement be raised to 20 cells/mm^3 (Doua *et al.*, 1996). There is still not enough evidence for the change in the cut-off point for the number of cells/ mm^3 in the CSF (Doua *et al.*, 1996, Miezan *et al.*, 1998) and therefore, the WHO recommended criteria for staging are still used.

1.5 Treatment of sleeping sickness

The costs of treatment for sleeping sickness are estimated to be more than US$ 100 per adult patient (WHO, 1998). In addition, sleeping sickness patients are almost always from poor, rural backgrounds (Okia *et al.*, 1994). For these reasons, it is the policy of the government of Uganda to exempt sleeping sickness patients from cost-sharing in health units. Currently, the broad guidelines for the treatment of sleeping sickness in Uganda are those recommended by the World Health Organization (WHO, 1998). Pentamidine is used for treating the early-stage of sleeping sickness caused by *T. b. gambiense* but has a low efficacy for the *T. b. rhodesiense* sleeping sickness. It is effective for treatment as long as there is no detectable involvement of the central nervous system. The dosage used is 4 mg of pentamidine base per kg of body weight. A total of 7 injections are given daily, intramuscularly. Drug resistance appears not to be an important problem in the use of pentamidine for the treatment of *T. b. gambiense*. The side effects seen include pain and induration or sterile abscess formation at the site of injection, vomiting, abdominal pain, hypotension, syncope, hypoglycaemia and peripheral neuritis.

Suramin is used for the treatment of the early stage of *T. b. rhodesiense* because although the duration of treatment is longer than that for pentamidine and administered intravenously, there is no primary resistance to suramin reported for *T. b. rhodesiense.* It was first introduced for the treatment of sleeping sickness in 1921 (Apted, 1970). The dosage used is 20 mg/kg body weight. Intravenous injections are given every 7 days and with a maximum of 7 injections. The side effects observed

include pyrexia, pain in the joints and soles of the foot, skin rash and desquamation and hypersensitivity reactions. Exfoliative dermatitis is a rare but severe adverse reaction that may cause death as a result of total loss of skin with resultant dehydration.

Melarsoprol (Freidheim, 1951) also known as Mel B is the drug used to treat late stage sleeping sickness due to both *T. b. rhodesiense* and *T. b. gambiense* sleeping sickness in Uganda. The maximum dosage for each injection is 3.6 mg/kg body weight. Currently, two regimes for the treatment comprising several series of injections, each separated by an interval of one week are used (WHO, 1998). One regime starts with 2.5ml and the other with 0.5ml but both totalling to 35 mls of a 36 g/litre solution of Melarsoprol.

The most serious side effect of melarsoprol is reactive encephalopathy often occurring between the third injection of the first course and the beginning of the second course. The onset may be sudden or the condition may develop slowly with fever, headache, tremor, slurring of speech, convulsions and finally, coma. It occurs in 5% of the patients and the incidence of fatality due to these reactions is approximately 1% (Odiit *et al.*, 1997a). However, the fatality of the untreated disease is believed to be 100%, making the decision to treat an ethical necessity. The treatment of these reactions includes the use of corticosteroids, hypertonic solutions to combat cerebral oedema, rapidly acting anticonvulsants, and subcutaneaous adrenaline. Other adverse reactions include diarrhoea, jaundice and dermatitis but these conditions are generally not life threatening.

There is no recent evidence of resistance of *T. b. rhodesiense* to melarsoprol, although in the early 1970s, melarsoprol treatment failure of 12 (3.4%) out of 358 treated patients was reported (Ogada, 1974). It is mandatory to follow-up systematically all treated patients to ascertain that they have been cured. It is recommended that patients be seen every 6 months over a two-year period (WHO, 1998). In addition to a full clinical and parasitological examination, a lumbar puncture should be carried out on the patients; the CSF can thus be examined for any

increase in leukocyte counts or presence of trypanosomes that would indicate that a relapse has occurred. However, due to the painful nature of the lumbar puncture procedure, most patients resent returning for follow-up once they have began to feel better. Active follow-up to ensure compliance is not affordable. Therefore, less invasive and painful methods of ascertaining cure need to be developed. It is possible that with low treatment failure rates and lack of systematic follow-up, patients with treatment failure may be missed. Periodic active follow-ups of cohorts of sleeping sickness patients should be done to monitor drug efficacy.

Treatment failure for *T. b. gambiense* to melarsoprol is emerging. Legros *et al.*, (1999a,b) report a melarsoprol treatment failure rate of 26.9% among 428 patients treated in north-western Uganda. Legros *et al.* (1999b) emphasise the need for second-line drugs to treat patients that have already received one or several full course(s) of melarsoprol.

Following studies carried out on vervet monkeys (Burri *et al.*, 1994), pharmacokinetic data from other similar studies carried out on *T. b. gambiense* patients indicated that the course of melarsoprol in an adult can be reduced from a period of between 25 to 36 days (WHO, 1998) to just ten days, greatly cutting down the costs of hospitalisation (Burri *et al.*, 1995). A randomized trial comparing the standard treatment schedule with this new concise regimen showed the same levels of parasitological cure (100%) and adverse effects (16-17 %) as well as better compliance with the new regime (Burri *et al.*, 2000). The adaptation of the new concise regime is being monitored. It would not be advisable to adapt this model to the treatment of the late stage of *T. b. rhodesiense* because the pharmacokinetics may be dissimilar given that this disease is much more severe than *T. b. gambiense*. Therefore, the blood brain barrier may be more affected allowing for higher levels of melarsoprol in the CNS and possible neurological side effects. A study of the pharmacokinetics of melarsoprol in late stage *T. b. rhodesiense* infections is therefore necessary.

Difluoromethyl ornithine (α-DFMO) is not effective against *T. b. rhodesiense* (Iten *et al.*, 1995; Matovu *et al.*, 1997) but is useful for the treatment of late stage *T. b. gambiense* (Doua *et al.*, 1987). It is presently available for use in Uganda for the treatment of relapses of melarsoprol treatment. Recently, the production of this drug has been suspended. The use of nifurtimox has been suggested where DFMO is not available for treating melarsoprol refractory patients. This drug is very toxic but has been reported to be effective for curing some *T. b. gambiense* patients including those with late stage melarsoprol-refractory disease (WHO, 1998).

1.6 Economic importance of tsetse-transmitted African trypanosomiasis

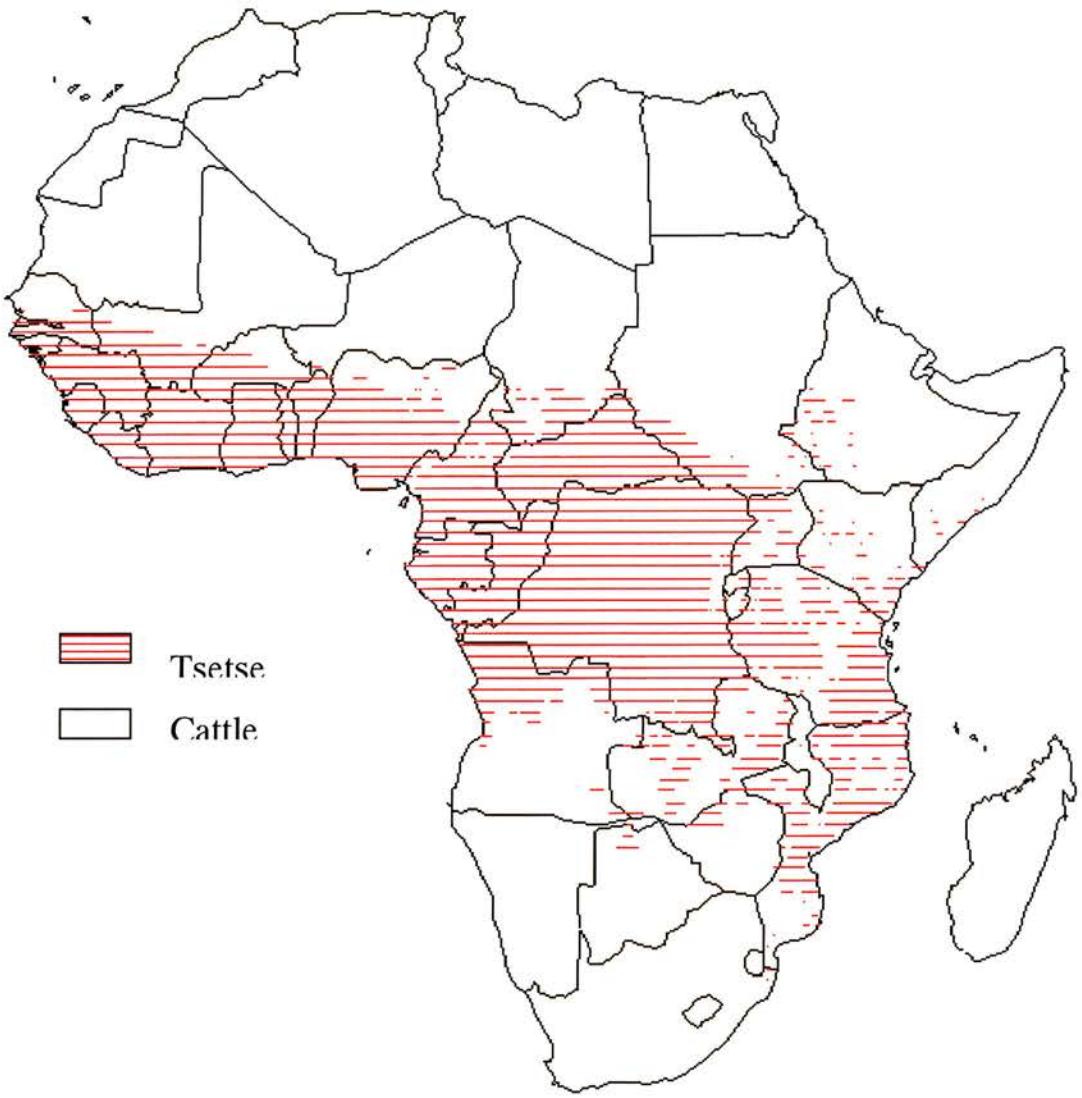
Tsetse-transmitted trypanosomes are important parasites for both animals and humans in Africa. Nagana (African animal trypanosomiasis (AAT)) is a major constraint to livestock production and affects economic development and settlement in tropical Africa (Swallow, 2000). The important species for livestock disease are *T. congolense*, *T. vivax* and *T. brucei brucei*; the latter is not easily distinguishable from *T. b. rhodesiense* that affects both cattle and man (Ford, 1971) except by restriction fragment length polymorphism (RFLP) and recently by the Serum Resistance Antigen (SRA) gene) (Hide *et al.*, 1994, Welburn *et al*, 2001) There is therefore, an economic burden in both livestock and human populations. Animal burden tends to be expressed in dollar terms while the relative burden of disease in humans is measured using the Disability Adjusted Life Year (DALY) (Murray, 1994; WHO, 1999a). The DALY burden is discussed at length in Chapter 3.

1.6.1 Losses due to animal trypanosomiasis

The distribution of tsetse flies covers an area of approximately 10 million square km, 300 million people and about 50 million cattle (Budd, 1999; Kristjanson *et al.*, 1999; Swallow, 2000; WHO, 1999a). Generally, where the tsetse challenge is very high such as in central Africa, the cattle density is low or cattle are not present at all (Figure 1.4). Therefore, there are economic losses in terms of cattle exclusion and

where there are cattle, in terms of production losses i.e. potential increases in income in those areas currently under-used by cattle due to the trypanosome disease constraint. It is estimated that there is US$1.3 billion lost per year in direct losses, e.g., milk and meat off-take (Swallow, 2000). Overall agricultural production losses are estimated to be US$5 billion (Budd, 1999). These are some of the few economic impact studies done on livestock trypanosomiasis, which are continental level estimates and neither adequately highlight human disease burden nor describe the local situation at or within country level.

Figure 1.4. Map showing the distribution of cattle and tsetse in Africa



1.6.2 Losses due to human trypanosomiasis (sleeping sickness)

WHO/World Bank burden of disease studies (WHO, 1999a) estimate the continental DALY to be 1.141 million for sleeping sickness, 34.506 million for malaria and 5442 for tuberculosis million. Malaria is considered a major vector-borne disease burden with emerging problems of antimalarial drug resistance. Tuberculosis is a chronic disease with increasing incidence, drug resistance and is associated with HIV infection. It must be acknowledged that there is gross under-detection of sleeping sickness because where outbreaks or epidemics occur, the disease is associated with areas with civil unrest and poor rural populations (Mbulamberi, 1989; Okia *et al.*, 1994). Unlike malaria, sleeping sickness is always fatal if not treated and the costs of treatment are high.

1.7 Focalisation of sleeping sickness

The geographic distribution of rhodesiense sleeping sickness (RSS) is limited by the distribution of vector and reservoir hosts with the exact geographical location of the foci occurring within these limits being currently unexplained. South-eastern Uganda where the species of tsetse *G. f. fuscipes* is found has long been considered the focus of rhodesiense sleeping sickness (RSS) (Mackichan, 1944; Robertson, 1957; Morris, 1959; Ormerod, 1961; Robertson & Baker, 1958; Abaru, 1985; Mbulamberi, 1989). Recent studies indicate that areas further north and west of the focus are now also endemic (Enyaru *et al.*, 1999; Fèvre *et al.*, 2001). The focality of sleeping sickness has long been reported but other than one study carried outside the previously known endemic focus (Fèvre *et al.*, 2001), there have been no cluster studies like those carried out on the distribution of types of cancers (Glick, 1979; Kulldorff & Nagarwalla, 1995; Hjalmars *et al.*, 1996) nor have these residual foci been accurately mapped (Scott, 1970). The possible aetiological factors explaining the occurrence of clustering are related to human-fly contact. Peridomestic breeding sites of *G. f. fuscipes* in a sleeping sickness focus in Busoga, Uganda were identified in coffee and banana plantations, and in *L. camara* thickets and around houses (Okoth, 1986).

1.8 Land cover and the risk for sleeping sickness

The last epidemic in south-eastern Uganda lasted from 1976 to the early 1990s (Abaru, 1985; Mbulamberi, 1989; Lancien, 1991; Enyaru *et al.*, 1992). The vector associated with the epidemic was *G. f. fuscipes*. The reason for the outbreak is believed to be a result of cessation of cotton growing, which used to occur between Lakes Victoria and Kyoga and which involved the control of the local vegetation that excluded flies (Koerner, *et al.*, 1995). Cotton growing was abandoned during the 1970s, and the shrubby weed *L. camara* and later *G. f. fuscipes* invaded the area. A similar growth of *L. camara* was associated with an outbreak of sleeping sickness, involving the same species, in the Alego district of Central Nyanza, Kenya in the 1960s (Willet, 1965). One theory for the occurrence of the Alego outbreak was previous heavy rains in 1961 with a rise of the Lake Victoria level by 7ft by 1961 (Ford, 1971). *G. f. fuscipes* is believed to have moved inland with the shoreline.

Prediction of the occurrence of sleeping sickness in time and space may be used to assist in averting morbidity and mortality due to the disease. Analysis of sleeping sickness patient data from south-east Uganda and mean Normalised Difference Indices (NDVIs) suggests that satellite imagery may be used to monitor spatial variation in disease risk and may contribute towards the production of risk maps of vector-borne diseases so that scarce health service resources can be targeted at areas of greatest need (Rogers & Williams, 1993). NDVI is used as a measure of plant growth, vegetation cover and biomass production from multispectral satellite data. In Togo, maps of high-risk areas of disease transmission have been produced (Hendrickx *et al.*, 1997). The incidence of sleeping sickness in Tanganyika was found to be related to seasonal variation in temperature with a significant correlation between the monthly mean maximum temperature and the number of patients diagnosed during the next one or two months, high temperatures being related to high incidence (Fairbairn, 1948). In Kenya, a rhodesian sleeping sickness outbreak in 1980 followed the highest rainfall in the months of April and May in the previous 10 years (Wellde *et al.,* 1989).

It has been shown that on the lake shore of Lake Victoria the density of *G. f. fuscipes* was correlated with the width of the lacustrine forest (Glasgow, 1954). However, since then, there has been severe destruction of the vegetation. The implications of this destruction to the distribution and abundance of *G. f. fuscipes* and therefore, to the current risk for sleeping sickness have not been evaluated. Development of the land may initially cause an increase in infection due to the intrusion of the tsetse habitat by people (Apted *et al.,* 1963; Robertson, 1963). It is clear that the size of the fly-belt (Ford & Katondo, 1977) is diminishing under the pressure of population. However, the rate at which this is happening and its association to changes in sleeping sickness incidence is not clear. Changes in the distribution of *Glossina morsitans* and *Glossina fusca* in Africa over the next 50 years have been predicted (Reid *et al.*, 1997a,b). Morris (1951) showed that a reduction of tsetse habitat especially by the removal of riverine forest could bring about a sustained reduction in the risk of human infection.

It is now generally accepted that environmental factors are important as risk factors for the acquisition of sleeping sickness (WHO, 1998). Some environmental factors, such as proximity to and activities near bush thickets, especially along rivers, are considered to be of significance. However, their significance has not been quantified and used for the development of risk maps and priority areas of control. Other factors such as the significance of peridomestic transmission (Okoth, 1986) are still controversial and need to be assessed relative to the distribution of sleeping sickness. Tsetse can be present in abundance but with the absence of infected hosts, transmission of disease may be limited. Cattle have been demonstrated to be an important reservoir of the rhodesiense sleeping sickness and therefore may play a major role in its spread (Onyango *et al.*, 1965; Maudlin *et al.*, 1990; Hide & Tait, 1991; Hide *et al.*, 1994, Fèvre *et al.*, 2001). In 1956 and 1966 in Uganda, *G. f. fuscipes* were reported in abundance along the Malaba river in the vicinity of the East African Trypanosomiasis Research Organisation (EATRO), but there was no evidence of infection in human beings, cattle and in the *G. f. fuscipes* (Roberstson, 1957; Mwambu & Odhiambo, 1967). However, at the lake shore tsetse were in abundance, with infections in man, cattle and the tsetse. In 1980, a tsetse survey

revealed plenty of *G. f. fuscipes* in the River Osia also neighbouring EATRO but there were no sleeping sickness patient reports from this area at the time (Okiria, 1981). It is apparent that *G. f. fuscipes* feeding habits in south-east Uganda are due to the availability of hosts and domestic livestock especially cattle and pigs are becoming increasingly important in this respect (Burridge *et al.*, 1970; Moloo, 1980; Okuna *et al.*, 1986; Maudlin *et al.*, 1990; Waiswa *et al.*, 2003) and therefore parasite hosts targeted control is apparently very important.

1.9 Surveillance of sleeping sickness

The available methods of sleeping sickness patient detection in south-eastern Uganda are as follows: fixed-post patient finding accounts for over 90% of the patients detected, while less than 10% of the patients are detected through either mobile teams or by sleeping sickness assistants (SSAs). Proximity to health units may affect the distribution of reported patients of sleeping sickness (see Chapter 4). This effect is also important in understanding the public health impact of the distribution of health units for sleeping sickness for surveillance and control. In 1995, following the observation that despite the reinforcement of several national control programmes, sleeping sickness could not be curbed, WHO requested stronger international coordination (WHO, 1999b). A new programme against sleeping sickness was established with additional human and financial resources. In addition to strengthening these tools and programmes, WHO has decided to focus efforts on the development of an epidemiological surveillance system and an information system. In central and west Africa, WHO has used GIS to promote the understanding of the distribution of gambiense sleeping sickness (GSS) to enhance targeting of screening, treatment and vector control (Cattand, 2001; Cattand *et al.*, 2001). There have been attempts to design frameworks for evaluation of surveillance of GSS e.g Shaw & Cattand, 2001. It is therefore important to use empirical data to identify epidemiological markers for sleeping sickness surveillance that can be applied to these frameworks.

Since rhodesiense sleeping sickness (RSS) causes obvious symptoms, under-detection is likely to be less than in the milder form gambiense sleeping sickness (GSS). But the symptoms of RSS are fever commonly associated with severe headache, joint and muscle pains, complicating its differential diagnosis. Due to the lack of pathognomic signs and the toxicity of the drugs used for treating sleeping sickness, diagnosis of sleeping sickness is strictly based on the demonstration of the parasite in blood, gland aspirate or cerebrospinal fluid (WHO 1998).

The countries where sleeping sickness occurs are generally very poor (Kuzoe, 1993; World Bank, 2000) and may not be able to sustain current control strategies. Delimitation of the optimal location of control programmes is therefore a priority if it can reduce costs. A geographical targeted approach to control is now being encouraged (Brooker *et al.*, 2000a) and there have been attempts to apply similar ideas to malaria, onchocerciasis and sleeping sickness (Rogers & Williams, 1993; Ngoumou *et al.*, 1994; Omumbo *et al.*, 1998; Snow *et al.*, 1999). The criticism of using a cartographic approach has been that maps were difficult to update easily and comparisons between areas shown on different maps was difficult (Yoon, 1995). However, this has all been made easier by the application of geographical information systems (GIS).

1.10 Utility of Geographical Information Systems (GIS) for public health and epidemiology

A Geographical Information System (GIS) is defined as an organized collection of computer hardware, software, geographic data and personnel designed to efficiently capture, store, update, manipulate, analyze and display all forms of geographically referenced information (Maguire, 1991). Every mapped feature is linked to a record in a tabular database and may be related to records in other databases making analysis of geographical data possible. GIS have been identified as useful tools for operational and applied field research in epidemiological and public health aspects of sleeping sickness (Mayer, 1983; Gesler, 1986; Twigg, 1990; Marshal, 1991; Scholten & de Lepper, 1991; Walter, 1993; Briggs & Elliot, 1995; Loslier, 1994; Clarke *et al.*,

1996; Smans & Esteve, 1996; Vine, 1998; Robinson, 1998; Rushton, 1998; Moore & Carpenter, 1999). GIS are novel research tools that have not yet been applied to understand the epidemiology of human African trypanosomiasis on a scale that can be useful for sub-national control programmes. The increasing availability of GIS presents an opportunity to introduce into epidemiological studies in Uganda, temporal and spatial elements that are often neglected (Scholten & de Lepper, 1991; Rogers & Williams, 1993) to understand further the epidemiology and to improve the control of sleeping sickness. Advances in the analysis of spatial data or vector borne diseases using GIS and global and local spatial statistics allow for a quantitative analysis of the aggregation and degree of clustering of disease, patients, vector distribution and their determinants (Upton & Fingleton, 1985; Gesler, 1986; Getis & Ord, 1992; Kitron *et al*, 1992; Beck *et al.*, 1994; Kitron *et al.*, 1994; Brown *et al.*, 1995; Glass *et al*, 1995; Clarke *et al.*, 1996; Ord & Getis, 1995; Getis & Ord, 1996; Kitron *et al.*, 1996).

The main objective of applying GIS and spatial data analysis in public health and epidemiology is to enable informed decision analyses for disease intervention, but its application in this regard is still limited (Openshaw, 1996; Burrough & McDonnell, 1998). It needs to be evaluated for use at sub-national levels because of its focality.

Examples of GIS applied to improved disease control are few but results show the potential of the technology. GIS has been applied for decision analysis in the interventions of animal trypanosomiasis. In eastern Zambia, GIS was used to combine data for six environmental variables: cattle density, human population density, land designation, relative arable potential, crop use intensity and proximity to existing control operations (Robinson *et al.*, 1999). The distribution of tsetse in the area was predicted using multivariate methods (Robinson *et al.*, 1997). Veterinarians and biologists working in the region established criteria weights for the input variables and the data were integrated using weighted linear combination to prioritize areas for animal trypanosomiasis control. The results of this analysis were used to delimit the optimal location of community-based tsetse control program in the Eastern Province of Zambia.

GIS was used in the implementation of the DOTS (directly observed therapy, short course) control strategy for tuberculosis in northern KwaZulu/Natal, South Africa. GIS distance and buffering functions were used to show and quantify how much a community-based programme increases access to tuberculosis treatment, and promote its further use for decision support and programme management in developing countries (Porter, 1999; Tanser & Wilkinson, 1999).

Diurnal temperature difference images (dT) from the Advanced Very High Resolution Radiometer (AVHRR) were created and tested for association with the relative risk distribution of schistosomiasis (Malone *et al.*, 1994, Abdel-Rahman *et al.*, 1997). AVHRR is a radiation detection imager that can be used for remotely determining the surface of the earth temperature. An inverse relationship was found between dT values and prevalence of *Schistosoma mansoni.* It was proposed that AVHRR thermal difference maps (Hastings & Emery, 1992; Cracknell, 1997) could be used to predict environmental risk of schistosomiasis.

Many health studies have used remotely sensed data for monitoring, surveillance, or risk mapping, especially of vector borne diseases (Linthicum, 1987; Hugh-Jones, 1989; Beck *et al.*, 1997; Robinson *et al.*, 1997; Brooker *et al.*, 2002). Most of these studies have used data from USA Landsat, the French Systeme Pour L'Observation de la Terre (SPOT) and the National Oceanic and Atmospheric Administration Advanced Very High Resolution Radiometer (NOAA AVHRR) (Beck, 2000). The World Health Organization Global Malaria Control Strategy has advocated the use of satellite imagery by control services to provide environmental information for malaria stratification, monitoring and early warning (Thomson *et al.*1997, 1999). Remote sensing has been use as a landscape epidemiological tool to identify villages at high risk for malaria transmission (Beck *et al.*, 1994, 1997, Hacker & Legters, 1994).

1.11 Control of sleeping sickness in eastern Uganda

Since the epidemic in the 1980s, the control of sleeping sickness eastern Uganda has been attempted using three approaches. Firstly, there has been patient detection and treatment at 17 fixed post sleeping sickness treatment centres. This approach was strengthened by the use of sleeping sickness assistants who were trained to make thick blood smears from sleeping sickness suspects and to take the smears for examination at the nearest sleeping sickness treatment centres. Mobile teams comprising of a clinician and microscopists were used whenever an increase in the number of cases of the disease was noted in a particular area. The second approach was vector control by the use of tsetse pyramidal Lancien traps impregnated with deltamethrin at a density of 10 traps per square km (Lancien *et al.*, 1990; Lancien, 1991). Trials of the use of insecticide treated cattle as a tsetse control method (Thomson, 1987; Warnes *et al.*, 1999) were carried out in small areas in Buteba, Mukuju, Masaba and Masafu subcounties (Lancien, 1991; Okiria *et al.*, 2002). Aerial spraying was carried out in Busoga in the 1980s (Kangwagye, 1987). The third approach was control of the animal reservoir by treatment of all cattle found to have trypanosomiasis by microscopic examination using trypanocides. Most of these activities were funded by assistance from the European Union (EU). However, when the funding from the EU ceased, maintenance of the control campaign, particularly the tsetse trapping, was not possible because of the costs of the operations. There is therefore a need to identify a more cost-effective and sustainable strategy for the control of sleeping sickness in eastern Uganda that can be afforded by governments in endemic countries.

1.12 Objectives

1.12.1 Broad objective

The broad objective of this study was to identify and develop epidemiological surveillance tools for *T. b. rhodesiense* sleeping sickness and apply them in the determination of the burden of the disease and evaluation of case finding strategies.

1.12.2 Specific objectives

The specific objectives of the study were to:

1. determine to the level of under-detection of *T. b. rhodesiense* sleeping sickness in eastern Uganda;
2. determine the burden of *T. b. rhodesiense* sleeping sickness outbreaks
3. determine the spatial and temporal risk factors for early detection and thus under-detection of *T. b. rhodesiense* sleeping sickness;
4. assess the health seeking behaviour among *T. b. rhodesiense* sleeping sickness patients;
5. describe the spatial and temporal trends of *T. b. rhodesiense* sleeping sickness at village scale;
6. explore the utility of remote sensing for identification of village scale risk factors for *T. b. rhodesiense* sleeping sickness.

1.13. Ethical considerations

The anonymity of subjects was maintained throughout. All invasive procedures for the collection and testing of specimen were carried out as part of the sleeping sickness control programme. All persons who tested positive for sleeping sickness during surveys were transported to the nearest sleeping sickness treatment centre and treated. In general, no additional procedures on patients, beyond what was already done, were required for this study.

Chapter 2 Quantifying the level of under-detection of *Trypanosoma brucei rhodesiense* sleeping sickness cases

2.1 Summary

To quantify formally the level of under-detection of *Trypanosoma brucei rhodesiense* sleeping sickness during an epidemic in Uganda, a decision tree model was developed. The values of the model parameters are estimated from previously published records of the duration of symptoms prior to presentation and the ratio of early to late stage cases in 760 sleeping sickness patients presenting at LIRI hospital, Tororo, Uganda during the 1988 to 1990 epidemic of sleeping sickness. For the observed early to late stage ratio of 0.47, it is estimated that the level of under-detection in the catchment area of LIRI hospital was 0.39 (95% CIs 0.37–0.41). Based on this value, it is calculated that for every one reported death of sleeping sickness, 12.0 (95% CIs 11.0-13.0) deaths went undetected. The measure of early to late stage presentation provides a tractable measure that may be used across sub-Saharan Africa to determine the level of sleeping sickness under-detection and to gauge the effects of interventions aimed at increasing treatment coverage.

2.2 Introduction

Sleeping sickness is likely to be highly under-reported as outbreaks tend to occur mainly among the rural poor and during civil strife when control measures are difficult to apply (Mbulamberi, 1989; Okia *et al.*, 1994). In addition, the main tool used for diagnosing sleeping sickness at the field level is microscopy, and the sensitivity of diagnosis by this method is low (Cattand & de Raadt, 1991).

Estimating the true occurrence of sleeping sickness under such circumstances is, therefore, difficult. To date, crude estimates based on historical records of sleeping sickness surveillance and case finding rates have been used. WHO has reported a steep increase in reported sleeping sickness cases despite a ten-fold reduction in the population under surveillance from the mid 1970s to present (WHO, 2000a). Using this information, WHO estimates that there are approximately 300,000-500,000 new cases of sleeping sickness but only 45,000 are reported, that is, approximately 10 infected to one reported case, indicating a high level of under-detection (WHO, 1998).

Sleeping sickness progresses from hemato-lymphatic (early stage) to meningo-encephalitic (late stage) involvement and if untreated kills the patient (WHO, 1998). In the case management of sleeping sickness, the detection of trypanosomes in gland or lymph node aspirates or blood is always followed by a lumbar puncture to determine whether there is involvement of the central nervous system (CNS) (WHO, 1998). Drug treatment when the CNS is involved is different from that used when the parasite is still restricted to the hemato-lymphatic system (WHO, 1998). No melarsoprol treatment failures for late stage treatment have been reported for *T. b. rhodesiense* sleeping sickness although approximately 26% treatment failure has been reported in late stage *T. b. gambiense* sleeping sickness patients in parts of Uganda (Legros *et al.*, 1999a,b). Rhodesiense sleeping sickness is mainly detected mainly by passive case finding, with patients presenting at a health facility and diagnosis based on microscopic detection of trypanosomes (WHO, 1998). The level of under-detection associated with such passive case finding systems is believed to be high, but is as yet, not quantified.

A decision tree model of sleeping sickness presentation is described to estimate the proportion of cases that went undetected in the catchment area of LIRI hospital, a specialist sleeping sickness hospital located in an endemic focus of the disease in Tororo District, south east Uganda. The parameter values of the model are estimated from empirical data on the duration of illness in sleeping sickness cases prior to hospital presentation and the ratios of early to late stage cases. The implications of the findings for the true burden of sleeping sickness and policy decisions aimed at alleviating this burden are discussed.

2.3 Materials and methods

2.3.1 Hospital records and case definitions

Data previously published by Odiit and colleagues (Odiit *et al.*, 1997a) on admission patterns to the LIRI sleeping sickness hospital between 1988 and 1990 were utilized to estimate rates of progression of the disease necessary for the calculation of under-detection using the model described in this paper. LIRI sleeping sickness hospital is situated in Tororo district, an area endemic for sleeping sickness (Enyaru *et al.*, 1992). The data set used in this study is the most up-to-date, extensive and comprehensive dataset of its kind. A total of 760 patients were diagnosed with sleeping sickness based on the WHO criteria of detection of trypanosomes in blood, cerebral spinal fluid, gland or chancre aspirate (WHO, 1998). A sleeping sickness case is defined as late stage if examination of cerebrospinal fluid (CSF) revealed white blood cell counts above 5 cells/mm^3 or the presence of trypanosomes, and as early stage if the CSF was normal. The clinical features for sleeping sickness are not useful for distinguishing between the early and late stage, which necessitates the invasive procedure of a lumbar puncture.

Of the 760 patients, 240 were classified as early stage, 515 as late stage and for 5, the stage of disease was not recorded. Therefore, 755 were used in the analysis. Out of

40 patient deaths that were not due to adverse reactions, duration of symptoms was available for 30 of them. The duration of symptoms between onset and presentation at hospital was recorded for 472 late stage patients including the 30 deaths with records.

2.3.2 Model structure

A decision-tree model structure is shown in Figure 2.1, and the parameters defined in Table 2.1. It is assumed that there is no increased mortality due to sleeping sickness in the early stage of the disease; this is a conservative assumption, in terms of estimating the proportion of sleeping sickness cases that die undetected. A proportion of sleeping sickness cases will present at a health facility as early stage patients, E, with a probability f_{early}. The proportion of cases that do not present at early stage, $\bar{E}$, either present as late stage cases, L, with a probability f_{late}, or die undetected, U, with a probability $1\text{-}f_{late}$.

Therefore, the model has only three possible outcomes for each sleeping sickness case: (1) presentation with early stage disease, E, with probability f_{early}, (2) presentation with late stage disease, L, with probability $(1\text{-}f_{early})f_{late}$ or (3) dying undetected, U, with probability $(1\text{-}f_{early})(1\text{-}f_{late})$, where E, L and U are all proportions and sum to 1.

Figure 2.1. Structure of the decision tree model for rhodesiense sleeping sickness. The boxes are the different outcomes of sleeping sickness cases. The arrows show the directions of clinical progression. Probabilities are shown in italics.

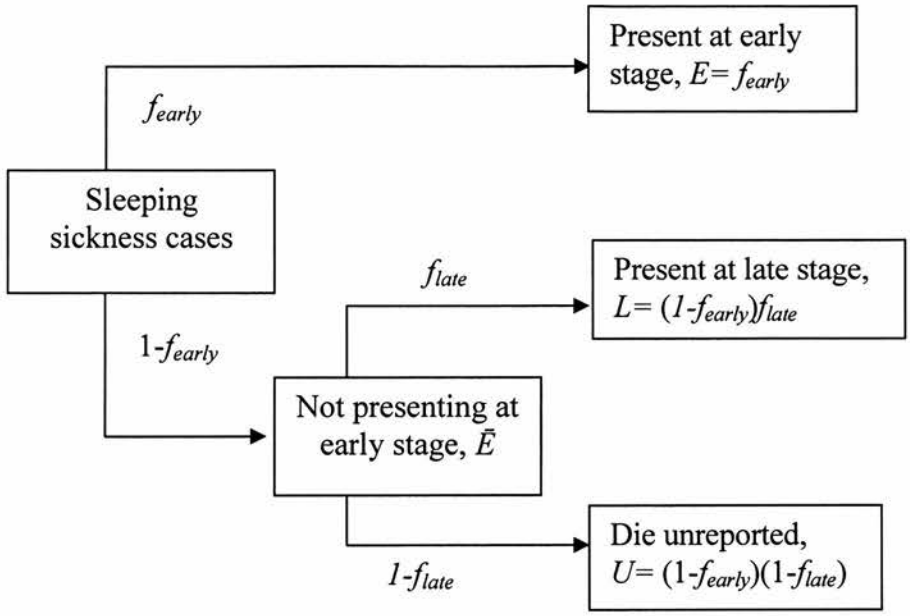


Table 2.1. Definition of decision tree model parameters

Model state	
E	Proportion of sleeping sickness cases presenting as early
$\bar{E}$	Proportion of sleeping sickness cases not presenting as early
L	Proportion of sleeping sickness cases presenting as late, not early
E/L	Ratio of early to late cases – estimated from empirical data
Rates	
l_t	Hazard function for onset of symptoms at which late stage cases present at health facilities – estimated by survival analysis, using a Weibull distribution with parameters α_l and λ_l
u_t	Hazard function for onset of symptoms at which late stage cases die – estimated by survival analysis, using an exponential distribution with parameter λ_u
Probabilities	
f_{early}	Probability of presenting at early stage, calculated using E/L and f_{late}
f_{late}	Probability of presenting at late stage, calculated by numerical simulation of integrals of the rates at which late stage cases present at health facilities, l, and die of sleeping sickness, u
Outputs	
U	Proportion of sleeping sickness cases that die undetected
D	Number of undetected deaths (cases)

2.3.3 Parameter estimation

Neither f_{early} nor f_{late} can be calculated analytically from the available data. However, f_{late} may be determined numerically by estimating the competing hazard functions at which a patient not presenting at early stage will either present as late stage, l_t, or dies, u_t at time t. The dynamics of moving from $\bar{E}$ to either L or U, through time t, may be described by the following integrals:

By setting $\bar{E}_{t=0}$ to1, then

$$f_{late} = \int_{t=0}^{t=\infty} l_t \bar{E}_t \, dt \qquad \text{(Equation 2.1)}$$

and

$$1 - f_{late} = \int_{t=0}^{t=\infty} u_t \bar{E}_t \, dt. \qquad \text{(Equation 2.2)}$$

The hazard functions l_t and u_t were estimated from survival analyses of time from onset of symptoms to late stage presentation for 472 late stage patients and the subset of 30 patients dying due to sleeping sickness, respectively (Figure 2.2). It is assumed that the survival curves derived for the 30 patients that died were the same as for all sleeping sickness cases that die. Weibull distributions of the form

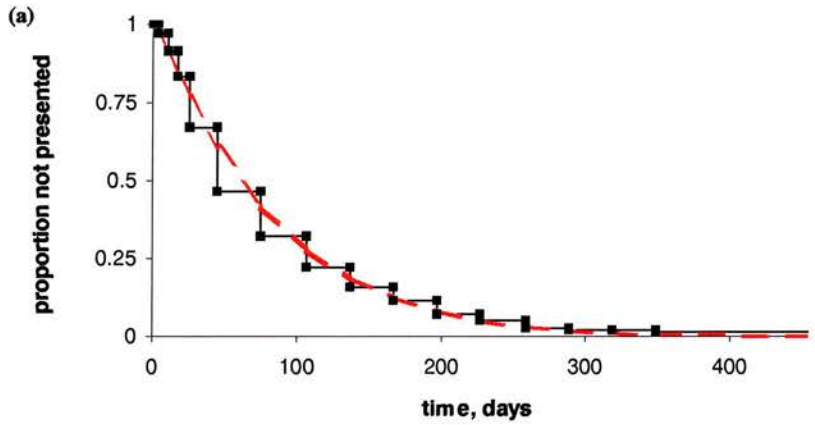
Table 2.2. Survival analysis parameter estimates of rates of occurrence of late stage patients and undetected deaths

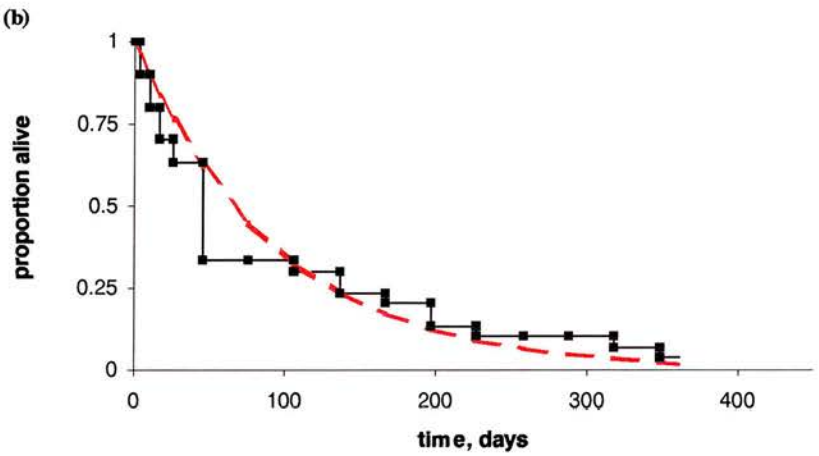
Rates	Scale parameter (λ)	Confidence Intervals (CIs)	Shape parameter (α)
Late stage presentation, l_t	7.3×10^{-3}	$(6.7\text{-}8.0) \times 10^{-3}$	1.11
Undetected death, u_t	1.1×10^{-2}	$(0.7\text{-}1.5) \times 10^{-2}$	1

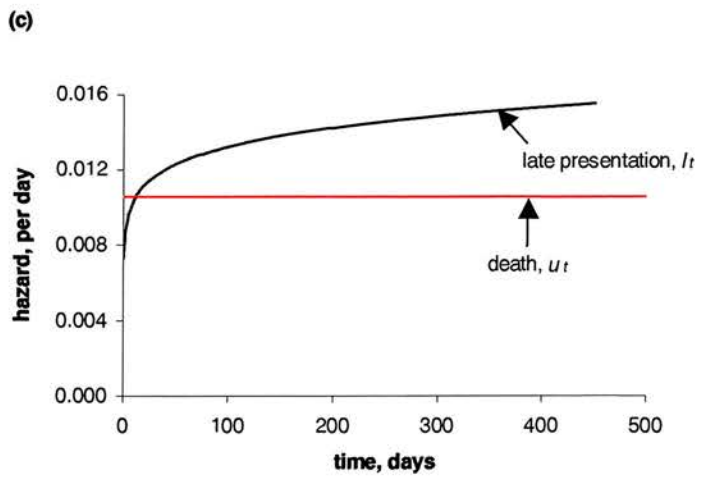
$$h_t = \alpha\lambda t^{\alpha-1}, \qquad \text{(Equation 2.3)}$$

in which h refers to either l or u, λ is the scale parameter, and α is the shape parameter, were fitted to the survival data using MINITAB (State College, PA, USA) statistical software (Burrows, 1999). The value of α was only relevant if it was significantly different ($p<0.05$) to 1, otherwise it was set to 1 and Equation 2.3 reduced to $h_t = \lambda$, an exponential distribution. This was then applied to the survival curve for the deaths. Using the hazard functions l_t and u_t estimated from the survival analyses, the parameter f_{late} was then derived by numerical iteration of the integral equations 2.1 and 2.2, assuming a starting condition of $\bar{E}_{t=0} = 1$. The numerical iteration was conducted in Microsoft Excel using a one-day time step.

Figure 2.2. The observed (black lines and filled squares) and fitted survival curves (broken lines) for time of presentation of sleeping sickness cases:
(a) 472 patients presenting as late stage cases and (b) 30 late stage cases dying of sleeping sickness within one week of admission. The fitted hazard functions for late stage presentation, l_t, and death, u_t, using parameter values given in Table 2.2, are shown in (c).







The parameter f_{early} was derived by expressing the probability in terms of the ratio E/L and f_{late}. By definition

$$\frac{E}{L} = \frac{f_{early}}{(1 - f_{early}) f_{late}}, \qquad \text{(Equation 2.4)}$$

which are rearranged to give

$$f_{early} = \frac{\frac{E}{L} f_{late}}{1 + \frac{E}{L} f_{late}}. \qquad \text{(Equation 2.5)}$$

where f_{late} is estimated using the procedure described above and the ratio E/L is equivalent to the observed ratio of early to late stage cases recorded at LIRI hospital (Odiit *et al.*, 1997a).

The level of under-detection, that is the proportion of infections resulting in undetected deaths U, was then simply calculated as

$$U = (1 - f_{early})(1 - f_{late}). \qquad \text{(Equation 2.6)}$$

After calculating f_{early}, the number of deaths not reported, D, can be calculated from the equation

$f_{early} = 240/ (755+D)$ (Equation 2.7)

where f_{early} is the ratio of early cases (240) to total cases (detected (755) and undetected, D).

2.3.4 Monte Carlo simulation

The survival analysis gives a joint maximum likelihood estimation of α and λ. The analysis assumes that the estimate of λ is normally distributed with a mean and standard deviation as estimated from the survival analysis. To obtain the 95% confidence intervals of the model outputs, a Monte Carlo simulation was used to calculate the distribution of l_t and u_t respectively (Snedecor & Cochran, 1989). These estimates were used to determine f_{late}. The decision tree model (Figure 2.1) was simulated for 1000 iterations. At each iteration, values of λ describing l_t and u_t were chosen at random from their respective normal distributions, while α was held constant. The model simulation was conducted in Microsoft Excel. To test for sensitivity and robustness, the rates, l_t and u_t were adjusted by plus or minus 10% variation of λ to determine the effect on the estimates of the model.

2.4 Results

2.4.1 Survival analyses

The results of the survival analyses are shown in Table 2.2, and the observed and fitted survival functions displayed in Figure 2.2. For l_t, the Weibull distribution gave a value of α significantly different from 1 (χ^2= 8.7, 1df, P=0.003). For u_t, α was not significantly different to 1 (χ^2= 1.7, 1df, P=0.187) so the Weibull collapsed to an exponential distribution.

2.4.2 Model outputs

Using the observed early to late stage ratio of 0.47 (240/515), the results of the Monte Carlo simulation suggest that on average, only 0.20 (95% CIs 0.19–0.20) of all sickness cases present with early stage disease (Table 2.3) The average probability of a sleeping sickness case dying undetected was 0.39 (95% CIs 0.37–0.41), giving an estimated total of 478 (95% CIs 440–521) additional deaths over and above the 40 reported non drug related deaths at LIRI hospital. If it is assumed that all the undetected cases that failed to receive treatment died of sleeping sickness, then for each one of the deaths recorded at LIRI hospital, there were an estimated 12.0 (95% CIs 11.0–13.0) undetected deaths in the catchement area of LIRI hospital.

Adjusting the estimate λ for l_t by plus 10% resulted in a decrease of 8% to a ratio of 1:11.0 (95% CIs 10.0-11.9) of detected to undetected deaths or 437 (95% CIs 401-477) undetected deaths, while adjusting by minus 10% resulted in an increase of 11% to a ratio of 1:13.3 (95% CIs 12.1-14.4) or 530 (95% CIs 485-575) undetected deaths. Adjusting the estimate λ for u_t by plus 10% resulted in an increase of 11% to a ratio of 1:13.3 (95% CIs 12.2-14.4) of reported to undetected deaths or 530 (95% CIs 486-575) undetected deaths, while adjusting by minus 10% resulted in a decrease of 10% to a ratio of 1:10.7 (95% CIs 9.8-11.6) or in 430 (95% CIs 393-465) undetected deaths. Adjustments of these inputs have an approximately proportional effect on the model estimates indicating that the model is quite robust.

Table 2.3. Summary of model outputs

	Output		
	Mean	**Lower 95% CI**	**Upper 95% CI**
Proportion presenting at early stage, $E=f_{early} = 240/(755+D)$	0.20	0.19	0.20
Probability of a case that does not present at early stage, $\bar{E}$, presenting at late stage, f_{late}	0.52	0.50	0.54
Proportion presenting at late stage, $L=(1-f_{early})f_{late} = 485/(755+D)$	0.42	0.41	0.43
Proportion cases dying undetected, $U=(1-f_{early})\ (1-f_{late}) = (D)/(755+D)$	0.39	0.37	0.41
Total number of undetected deaths, D	478	440	521
Number of undetected deaths per reported death	12.0	11.0	13.0

CI= Confidence Interval

2.5 Discussion

This is the first attempt to estimate under-detection for sleeping sickness based on a framework taking into account the progression of the disease and utilizing sleeping sickness case records. Public health professionals and decision makers can use this model to define which regions in the country need to get priority for sleeping sickness funds. In Chapter 3, the model is applied to sleeping sickness outbreak area to improve the calculation of the Disability Adjusted Life Years (DALYs) due to rhodesiense sleeping sickness.

The data used in the model were obtained from an area (Odiit *et al.*, 1997a) with a relatively low expected probability of under-detection, having better health service and other infrastructure compared to other sleeping sickness areas in Africa. Although the model estimates are conservative in the sense that they assume no increased death rate due to early stage disease, they still reveal significant under-detection; for every three reported cases in the LIRI hospital catchment area, approximately two additional cases went undetected and the persons died of the disease.

The case fatality rate on admission of rhodesiense sleeping sickness to LIRI hospital was approximately 6% with 40 reported deaths (Odiit *et al.* 1997a) compared to an estimated 500 undetected deaths during 1988-90 epidemic peak, as estimated by the model. Therefore, for every one patient dying on admission approximately 12 are dying unseen. There are no local vital statistics to verify this. National estimates put the crude death rate (CDR) at approximately 20 per 1000 (UN, 1997) indicating 18,000 deaths per year in the LIRI hospital catchment area of approximately 900,000 people (1991 national census projections). Therefore, the model estimates for the area indicate that sleeping sickness contributed to just under 1% of the total deaths but the fraction would have been higher in some age groups because adults are more at risk for acquiring sleeping sickness than children. Statistics are not available for comparison to other infectious diseases (e.g. malaria, tuberculosis, AIDS). However, the opportunities of preventing the deaths of the sleeping sickness cases are greater

than for many other diseases (e.g. AIDS) and the sleeping sickness cases may die without being recognized by the health system. These estimates of deaths due to sleeping sickness emphasize the magnitude of the burden of sleeping sickness especially where it occurs in epidemics in areas with poor surveillance (WHO, 2000a). Currently, the major burden of sleeping sickness is due to mortality but if a greater proportion of cases could be detected, almost all of the deaths would be preventable.

In south-eastern Uganda, between 1976 and 1983, there was an epidemic of sleeping sickness due to the breakdown of control services associated with political turmoil as well changes in agricultural practices with resultant bush encroachment (Abaru, 1985; Matovu, 1982; Mbulamberi, 1989). A total of 19,974 sleeping sickness cases were detected and the early to late ratio was approximately 0.5. This suggests that approximately 13,000 people could have died undetected in south-eastern Uganda during this time out of a population at risk estimated to be 3 million people (1991 population census) during the epidemic. Going by the national crude death rate (CDR), there were an estimated 60,000 deaths per year in the entire south-eastern Uganda. Therefore, the model estimated that deaths due to sleeping sickness accounted for approximately 1% of the total deaths. This low percentage contribution cannot be easily detected given the poor quality of vital statistics available in the area at that time.

The conservative assumption that most sleeping sickness cases progress to the late stage before they die from the disease is supported by empirical evidence (Odiit *et al.*, 1997a). It is assumed that the duration of symptoms to death for undetected cases is the same as the reported deaths of patients who succumb to the disease while in hospital. This is a safe assumption since patients who died as a result of drug reactions were excluded from this group and this is the best obtainable estimate given that it is not possible to analyze death rates of undetected cases. Sensitivity analyses by adjusting λ estimates for l_t and u_t by plus or minus 10% indicated that the under-detection estimates are fairly robust to changes in these hazard rates. Although data from 1988 to 1990 is used for designing the model, the data are still applicable to the

present day because the sleeping sickness detection and treatment policies have not changed since the data were collected.

There is a lack of reliable statistics and under-detection of disease in sub-Saharan Africa because of, amongst other reasons, infra-structural and costs constraints (Snow *et al.*, 1999). As a result, disease estimates are often guesses based on a clinical and not a diagnostic basis. To solve this problem, other epidemiological methods have been used in other infectious diseases in Africa to determine the true burden of disease. The prevalence of helminthic infections in the Republic of Cameroon was estimated from data on infection prevalence in school children (Brooker *et al.*, 2000b) following an earlier study showing that infection prevalence in school children is higher than in the entire community (Guyatt *et al.*, 1999). In Mali, the prevalence rate of schistosomiasis in school children was used as an index of endemicity in the community (Traore *et al.*, 1998). In the Republic of Cameroon, estimates of the number of cases of schistosomiasis in the country have been made using models (Ratard *et al.*, 1992). A decision tree approach for estimation of rabies under-detection in Tanzania has also been reported recently (Cleaveland *et al.*, 2002). However, there have been no equivalent studies for sleeping sickness. The results of such studies improve the accuracy of estimates of disease burden that are measured using disability-adjusted life years (DALYs) (Murray, 1994) which need estimates of true mortality in their calculation (See chapter 3).

This study emphasizes the need to improve surveillance of sleeping sickness. Strategies that improve both passive and active case findings should be addressed. These will include increased awareness among the affected communities and their health workers as well as commitment of more resources for health services at the local level. Given the high mortality of this zoonotic disease, preventive measures such as chemotherapy of the livestock reservoir for trypanosomiasis can greatly reduce the risk of outbreaks occurring in rhodesiense sleeping sickness endemic areas like eastern Uganda with predominantly agro-pastoral agricultural systems (Fèvre *et al.*, 2001; Welburn *et al.*, 2001; Wendo, 2002). The model designed in this

study provides a means of assessing the cost-effectiveness of these interventions by quantifying the potential deaths that can be averted.

The use of the early to late ratio is a simple disease measure that is readily available in all sleeping sickness areas because of the necessity to stage sleeping sickness patients by lumbar puncture and CSF examination to determine how they will be treated. Thus, the method presented could be applied more widely to better estimate the actual burden of sleeping sickness in rural Africa. This has important implications for health policy in as far as allocation of resources is concerned. The burden of sleeping sickness is currently grossly under-estimated and may contribute to relative under-funding for surveillance and awareness campaigns that are crucial in reducing deaths for this treatable disease.

The model was designed specifically for a *T. b. rhodesiense* endemic area where the disease is more rapidly progressive to death than in *T. b. gambiense*. However, the early to late ratio of sleeping sickness cases may also be used to give an indication of the level of under-detection and death in a *T. b. gambiense* area. Although accurate data on the clinical progression of sleeping sickness is available for rhodesiense (Odiit *et al.*, 1997a), it is difficult to obtain similar data for gambiense perhaps because of the variability in the length of clinical stages and the generally very long period of illness (Apted, 1970). However, specific studies of clinical progression could be carried out to obtain estimates of the average durations of the stages to allow application of a similar model to gambiense sleeping sickness.

In conclusion, this measure of early to late stage presentation provides a practical method that may be used across sub-Saharan Africa to estimate the level of under-detection of sleeping sickness and the consequent burden of disease as well as to gauge the effects of interventions aimed at increasing sleeping sickness diagnosis and treatment coverage. Improved case finding strategies will most certainly greatly reduce death due to sleeping sickness. Estimates of burden of disease of specific outbreaks can be estimated applying this methodology.

Chapter 3 Estimating the burden of rhodesiense sleeping sickness during an outbreak in Serere, Uganda

3.1 Summary

The burden of sleeping sickness was estimated for an outbreak of sleeping sickness in Serere, Uganda. This study identified the unique characteristics affecting the burden of rhodesiense sleeping sickness such as age, severity of illness, level of under-detection and duration of hospitalisation and uses estimates of these to calculate the burden of the disease on the population and the health services. In addition, the study compares the relative contribution of mortality and morbidity to the DALY estimate given the high level of under-detection of this disease. Taking into account under-detection of rhodesiense sleeping sickness increases the Disability Adjusted Life Years (DALY) estimate by 14 times and age weighting increases the DALY estimate by 5%. The age productive function curve from Murray (1994) had a close fit to the sleeping sickness case distribution. Sleeping sickness cases occupied more patient admission time during 1999 than all other infectious diseases diagnosed other than malaria in Serere health centre. The DALY estimate for sleeping sickness in Serere shows that the burden is much greater than might be expected from its relative reported incidence. The estimated burden of disease provides a better indication of the importance of sleeping sickness and should influence local decision makers in the provision of both human and veterinary services to reduce its burden.

3.2 Introduction

The health burden ranking for Africa for sleeping sickness is high at 2.05 million DALYs (disability adjusted life years) compared to malaria (36.8 million), tuberculosis (8.7 million), meningitis (3.6 million), schistosomiasis, (1.6 million) and polio (0.8 million) (WHO, 2000b).

The DALY is a commonly used index for expressing the burden of disease, and is a generic health measure incorporating both mortality and morbidity. It is used to gauge the public health importance of different diseases (Murray, 1994; Murray & Lopez, 1996). The DALY was developed to enable health policy and research to prioritise disease and for assessment of cost-effectiveness. Currently, it is mainly applied by the World Bank and the WHO for global burden of disease estimations (World Bank, 2000; WHO, 2000b).

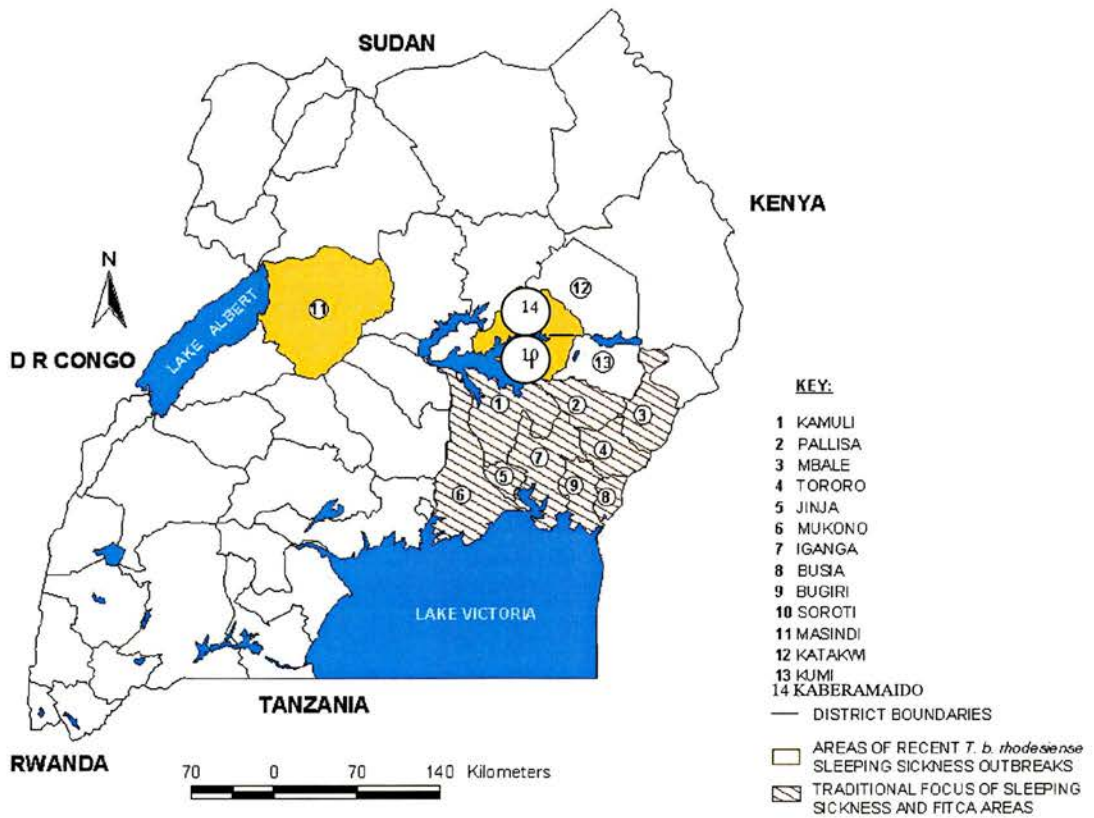
In Uganda, there have been a series of epidemics of sleeping sickness reported from the beginning of the 20th century (Christy 1903a,b; Mackichan, 1944; Abaru, 1985; Mbulamberi, 1989). Given that sleeping sickness tends to occur where there is a breakdown in control and affects mainly poor people, it is likely to be under detected compared to other diseases (Mbulamberi, 1989; Okia *et al.*, 1994). Sleeping sickness is always fatal if not treated and the costs of treatment, usually requiring hospitalisation, are high. Because of this, it is particularly important to assess the cost burden to the health services in addition to the aggregate burden to individual patients. If uncontrolled, the tendency of sleeping sickness to become epidemic means that the DALYs averted per infection prevented or cured are high. Estimates of the cost-effectiveness of alternative treatments of gambiense sleeping sickness have been made and melarsoprol treatment was associated with an incremental cost per life and DALY saved of US $ 209 and US $ 8, respectively (Politi *et al.*, 1995)

Rhodesiense sleeping sickness is a more acute disease than the gambiense form and available evidence supports the hypothesis that cattle are an important reservoir of *T. b rhodesiense* (Onyango *et al.*, 1965; Hide *et al.*, 1996; Fèvre *et al.*, 2001). It appears that current estimates of sleeping sickness burden are based on parameters of the more

common gambiense type (WHO, 2000b) because rhodesiense sleeping sickness is not as common or widely distributed. However, in its major focus of eastern Uganda, it has been responsible for many deaths throughout the 20th century. Because of its local importance, focal pattern of occurrence, rapid progression and zoonotic nature compared to gambiense sleeping sickness, it is important to specifically estimate the burden of rhodesiense sleeping sickness on communities in eastern Africa. For example, trypanosomiasis control in this area will have public health as well as veterinary benefits.

This Chapter examines how the unique features of rhodesiense sleeping sickness influence its burden on the local population and health services in Serere health sub-district (health services implementation level) in Soroti district (Figure 3.1) in eastern Uganda. Decision makers at sub-national or district levels, responsible for planning local disease control programmes, can apply these methods for priority setting.

Figure 3.1. Map of Uganda showing the endemic districts for rhodesiense sleeping sickness and the position of the new outbreak districts.



3.3 Materials and Methods

3.3.1 Health burden indices

Two health burden indices are estimated for a rhodesiense sleeping sickness outbreak in Serere health sub-district, Uganda. The first index is the DALY (Murray, 1994). The second is to estimate the costs to the Serere health sub-district based on the total costs of hospitalization and treatment. Both measures of burden were estimated for the calendar year 1999 from patient records of the Serere health centre.

3.3.2 Disability Adjusted Life Years

DALY calculations followed the methods used in the first Global Burden of Disease study (Murray & Lopez, 1996), and subsequent World Health Report estimates (WHO, 2000b). The calculations employed a discount rate of 3% and were conducted with and without age-weighting.

The features of rhodesiense sleeping sickness that need to be considered in DALY estimation are its severity of illness, case fatality rate, duration of disability, and age-specific production losses. The information required to calculate the DALY for rhodesiense sleeping sickness are summarized in Table 3.1.

Table 3.1. Information required for the estimation of disability-adjusted life years (DALYs) for rhodesiense sleeping sickness (SS).

Information type	**Specific data required**	**Data sources**
Years-of-life-lost (YLL)	1) Number of deaths	- health unit records of case fatality - case under-detection estimates
	2) Life expectancy	- life tables
	3) Distribution of age at death	- health unit records of case age (with or without age-weighted case fatality rate and under-detection rate)
Years-of-life-lived with disability (YLD)	1) Number of cases	- health unit records of cases - case under-detection estimates
	2) Disability weighting	- estimated from examining rhodesiense SS patients (Murray, 1994)
	3) Duration of illness	- health unit records of cases
	4) Age-weighting of productivity	- health unit records of ages of cases

3.3.3 Years of life lost

The number of sleeping sickness deaths in Serere health sub-district, Uganda was estimated as a function of the number of detected deaths and the estimates of case under-detection (see Chapter 2). Two under-detection values, 0% and 48% were applied. Forty eight percent (95% CI, 46%-48%) under-detection was obtained for estimates made using a model for under-detection described in Chapter Two with 4 early and 56 late-stage detected cases entered into the model. This means that for every three cases presenting at the health facility, approximately four went undetected and died. All undetected cases are assumed to remain undetected, receiving no treatment and resulting in death.

The life expectancy at the age of death was based on a hypothetical population derived from an African standard life table with a life expectancy at birth of 50 years (UN, 1982), which was representative of the population in the Serere health sub-district. The distribution of age of death was estimated from the distribution of ages of all cases of sleeping sickness admitted to Serere health centre. The assumption was that the case fatality rate is constant across age.

3.3.4 Years of life lived with disability

T. b. rhodesiense is a more severe disease (WHO, 1998). A disability weighting of 0.81 was used as estimated from the disability weighting definitions given by Murray (1994) (Table 3.2). This disability weighting was assumed to be constant across ages and stages of illness. Patients with rhodesiense sleeping sickness are unable to go to work or school. Duration of illness was the mean duration of hospital stay obtained from the sleeping sickness case records at Serere health centre for 1999. The estimate for duration of illness did not account for post-treatment disability; although, physical and mental retardation in children caused by sleeping sickness has been reported (WHO, 1997). The estimates presented are thus conservative with respect to long-term disability.

Table 3.2. Definitions of disability weighting (Murray, 1994)

Class	Description	Weight
1	Limited ability to perform at least one activity in one of the following areas recreation, education, procreation or occupation	0.096
2.	Limited ability to perform most activities in one of the following areas: recreation, education, procreation or occupation	0.220
3	Limited ability to perform activities in two or more of the following recreation, education, procreation or occupation	0.400
4	Limited ability to perform most activities in all the following areas: meal preparation, shopping or housework.	0.600
5.	Needs assistance with instrumental activities of daily living such as meal preparation, shopping or housework.	0.810
6.	Needs assistance with activities of daily living such as eating, personal hygiene or toilet use	0.920

3.3.4.1 Age distribution of sleeping sickness cases and other common infections at Serere Hospital

In view of the age weighting factor in DALY estimates, the relative impact of sleeping sickness, malaria and tuberculosis in different age groups were compared. This was done by calculating the age distribution of sleeping sickness, malaria and tuberculosis cases recorded at the Serere health centre and comparing it to the age-productivity function curve of Murray (1994). The age-productivity function curve distributes the contributions of different ages to society with the children and the elderly regarded as being less productive.

3.3.5 Costs to the local health system

The costs to the health system per sleeping sickness patient were estimated as the product of mean hospital stay in days times a standard daily cost. Mean hospital stay was calculated as the total hospital stay due to sleeping sickness divided by the number of

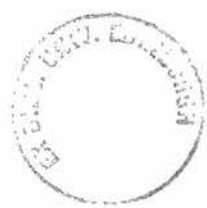
sleeping sickness cases, diagnosed parasitologically, at the Serere health centre during 1999. A standard cost per hospital day in 1999 was estimated in consultation with staff at the Serere health centre. The staff considered that the daily hospital costs similar for all diseases for which patients were admitted to their health centre is estimated it at US$ 2 per patient based on expenses on staff and maintenance of buildings and utilities. The drug costs for sleeping sickness are estimated to be US$ 35 and US$ 63 for early and late stage patients respectively (WHO, 1998). However, the costs of sleeping sickness drugs are currently met by the World Health Organization.

The relative hospital costs of sleeping sickness to all other diseases for which patients were admitted at the Serere health centre were compared. For each disease, total hospital stay in 1999 was calculated and multiplied by the standard cost per hospital day as described above. Tuberculosis was excluded from this analysis because of the current strategy of direct observed therapy (DOT) in lieu of hospital admission. HIV/AIDS was also excluded because of its association with concurrent opportunistic infections and no HIV testing was carried out to objectively diagnose the condition.

3.4 Results

3.4.1 Disability Adjusted Life Year (DALY) estimates for rhodesiense sleeping sickness

The age-specific number of detected cases, detected deaths, estimated undetected cases/deaths (assuming 0 or 48% under-detection), and non-age-weighted discounted YLL (DYLL) are listed in Table 3.3. If all cases were detected (0% under-detection) then the non-age weighted total YLL would be only 54. Of greater importance was under-detection. Only three deaths were recorded at the health centre while it is estimated that 80 deaths due to sleeping sickness went undetected (see Chapter 2). The age-specific, non-age-weighted, total YLLs for 48% under-detection are also listed, summing to a total of 1336. If age-weighting is applied, the total YLL estimate increases to 1550.



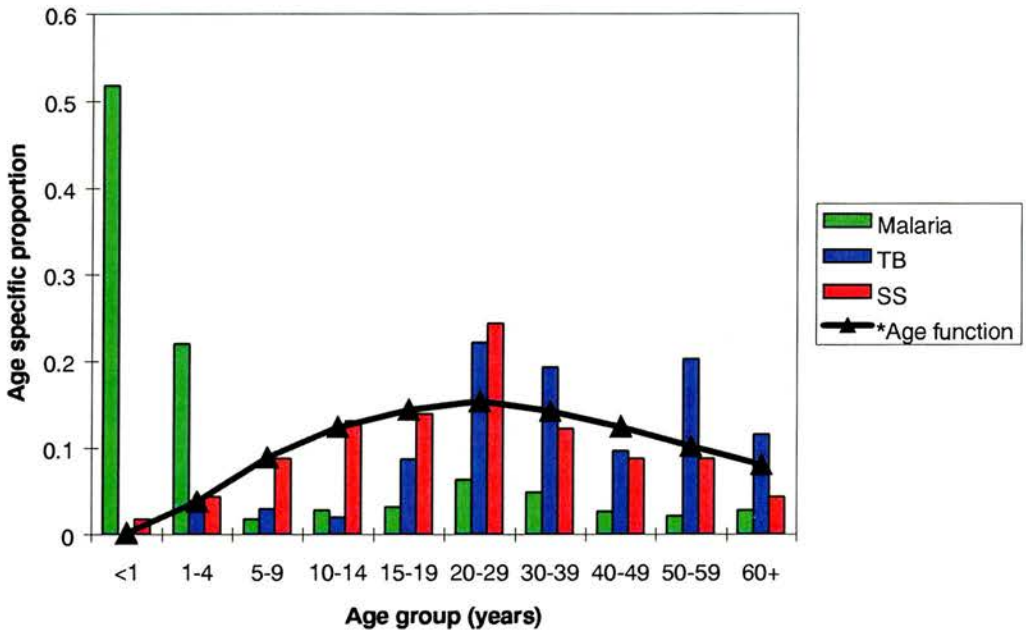
The years of life lived with disability (YLD), for cases that recovered due to treatment are listed in Table 3.4. The non-weighted total YLD is 64. If age-weighting is applied the total YLD estimate increases to 72.

The total estimated DALY for rhodesiense sleeping sickness, based on 48% under-detection and non-age-weighting, for 1999 in Serere was 1459 compared to 118 based on 0% under-detection (Table 3.5). The majority (92%) of this DALY burden was due to mortality in undetected cases.

3.4.1.1 Comparison to age distribution of other diseases

The age distribution of sleeping sickness, malaria and tuberculosis cases at the Serere health centre differed. Figure 3.2 shows the age distribution for 763 malaria cases admitted to the Serere health centre in 1999, 104 tuberculosis cases treated in 1999 and 115 sleeping sickness cases admitted to the Serere health centre between January 1999 and August 2000. The age distribution of sleeping sickness cases has a peak in the 20-29 age category. Rhodesiense sleeping sickness thus affects the most productive age groups as illustrated by the close association between its age distribution and the age-productivity function curve of Murray (1994) (see Figure 3.1). For malaria, the age distribution is skewed with the majority of cases being less than 5 years of age. Tuberculosis age distribution is also skewed with the majority of cases occurring among adults.

Figure 3.2. Age distribution of malaria, sleeping sickness and tuberculosis patients admitted to Serere health centre compared to the age- productivity function curve



Age-productivity function curve (Murray, 1994).

Table 3.3. Years of Life Lost (YLL) due to rhodesiense sleeping sickness in Serere, Uganda, 1999

Age of onset (years)	Detected cases	Detected deaths	Undetected cases/deaths (at 48%)	Total deaths	DYLL per death[a]	Total YLLs[a,c]	Total YLLs[a,d]	DYLL per death[b]	Total YLLs[b,c]	Total YLLs[b,d]
0-9	14	0	12.9	12.9	28	0	366	36	0	458
10-19	13	0	11.9	12.0	27	0	323	36	0	428
20-29	13	1	11.9	13.0	25	25	327	31	31	408
30-39	1	0	0.9	0.9	23	0	21	25	0	23
40-49	5	0	4.6	4.6	20	0	94	19	0	89
50-59	6	1	5.5	6.5	17	17	111	14	14	88
60+	8	1	7.4	8.4	11	11	95	7	7	57
Total	60	3	55	58		54	1336		52	1550

[a] – non-age-weighted estimate

[b] – age-weighted estimate

[c] _ no under-detection weighted

[d] _ under-detection weighted

Table 3.4. Years of Life Lived with Disability (YLD) due to rhodesiense sleeping sickness in Serere, Uganda, 1999.

Age of onset (years)	Reported Cases	Total cases*	YLD per recovered case		Total YLDs[a,c]	Total YLDs[a,c]	Total YLDs[b,c]	Total YLDs[b,d]
			Non-weighted	Age-weighted				
0-9	14	27	1.071	0.801	15.0	28.8	11.2	21.5
10-19	13	25	1.071	1.486	13.9	26.7	19.3	37.1
20-29	13	25	1.071	1.632	13.9	26.7	21.2	40.7
30-39	1	2	1.071	1.520	1.1	2.1	1.5	2.9
40-49	5	10	1.071	1.305	5.4	10.3	6.5	12.5
50-59	6	12	1.071	1.066	6.4	12.3	6.4	12.3
60+	8	15	1.071	0.743	8.6	16.4	5.9	11.4
Total	60	115			64.2	123.3	72.1	138.5

[a] – non-age-weighted estimate

[b] – age-weighted estimate

c – no under-detection

[d] – under-detection

* – reported and unreported cases

Table 3.5. The DALY burden due to sleeping sickness at Serere health facility, Soroti District, Uganda, in 1999.

	Sleeping Sickness	
	Observed	48% under-detection
Cases	60	115
In-patients	60	60
Deaths	3	58
YLLs	54 (52)	1336 (1550)
YLDs	64 (72)	123 (139)
DALYs	118 (124)	1459 (1689)

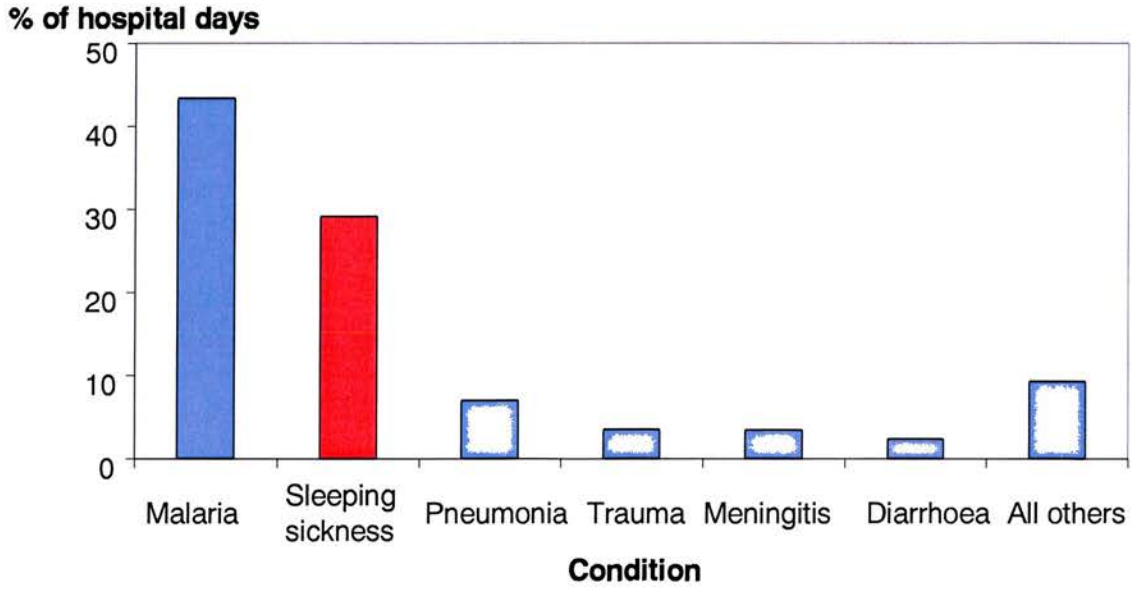
The YLLs, YLDs and DALYs figures in parenthesises where calculated with age weighting, while those outside the parentheses were calculated without age-weighting. Taking into account under-detection of rhodesiense sleeping sickness increases the Disability Adjusted Life Years (DALY) estimate by 14 times and age weighting increases the DALY estimate by 5 %.

3.4.2 Costs to the local health system of rhodesiense sleeping sickness

The 60 sleeping sickness patients at Serere health centre in 1999 stayed in hospital for a total of 2156 days. Thus, the mean hospital stay per patient was 36 days. The standard daily health cost estimated by health staff at the Serere health centre was Uganda shillings 3,500 (approximately US$ 2) per day. Therefore, the total cost to the Serere health system in 1999 was 7,546,000 Uganda shillings (approximately US$ 4,300). However, if the drug costs (not met by the district and national health services but donated by WHO) are included then for the total cost for 56 late stage cases was approximately, US$ 3528 and that of the 4 early stage cases, US$ 140, giving a total of US$ 3668 (6,235,600 Uganda shillings). Therefore, the costs of treating the 60 patients was 13,781,600 Uganda shillings or US$ 7,700 equivalent to US$ 128 per patient.

The proportion of hospital days by disease provides a reasonable estimate of the relative costs to the Serere health system of different diseases, as the daily hospital costs are relatively constant across diseases. The proportions of hospital days for the 6 most common causes of admission are shown in Figure 3.3. Malaria accounted for approximately 40% of hospital days and sleeping sickness, 30%.

Figure 3.3. Percent of hospital days by condition at Serere health centre in 1999.



3.5 Discussion

Many countries in sub-Saharan Africa (SSA) are devolving implementation of health service delivery to the local level (Jeppsson, 2001). Local burden of disease estimates can play an important role in health sub-districts allowing a rational allocation of resources to the highest priority diseases. The DALY is currently the most widely accepted measure for estimating the burden of human disease (World Bank, 2000). In this Chapter, it has been shown that with relatively small amounts of available data from a local in-patient health centre, useful estimates for the components of the DALY can be made. For example, the estimates for case-fatality rate and age-specific case distribution based on the 60 sleeping sickness patients at the Serere health Centre in 1999 are virtually identical to estimates made in previous larger studies at the LIRI sleeping sickness hospital in eastern Uganda (Odiit *et al.*, 1997a,b). Thus, DALY estimates for local planning purposes can be readily estimated from local health centre data using the data outlined in Table 3.2.

WHO estimates the treatment costs (hospitalisation and drugs) per patient of sleeping sickness to be in the order of greater than US$ 120 (WHO, 1998). The WHO estimate is similar to the present estimate of US$ 128. In addition to DALY estimates, hospital costs are also an important planning tool for local health decision makers. These data can be simply derived from in-patient records. As a starting point, it is assumed that hospitalisation costs are relatively standard across diseases. However, this is not completely true. Drugs for the treatment of sleeping sickness are administered parentally and are costly. Due to toxicity of the drugs used, complications are frequent and increase the costs of treatment. Clearly, costs to individual patients beyond those to the local health system are also important. Future investigations will include these costs.

This is the first study to estimate the DALY for *rhodesiense* as opposed to *gambiense* sleeping sickness. Given that sleeping sickness of both types is invariably fatal if not treated and that sleeping sickness surveillance is relatively weak (WHO, 1998), it is not surprising that mortality, particularly mortality due to undetected cases, dominates the DALY estimate. Given that 95% of treatments for rhodesiense sleeping sickness were successful at Serere health centre, there appear to be great potential benefits in enhancing strategies for identifying undetected sleeping sickness cases. Such strategies are investigated in Chapters 4, 5 and 7.

Although this study does in general represent the true situation, it has a few limitations. The study did not take into account any post-treatment disability due to sleeping sickness. This is difficult to quantify because there are no systematic follow-ups of sleeping sickness cases post-treatment. A study in Cameroon (WHO, 1997) showed that children with a past history of sleeping sickness had significantly lower weight, height and mid-arm circumference and spent more years in school. Comparison with HIV/AIDS for causes of bed occupancy could not be objectively assessed because HIV testing was not carried out. A study conducted in an urban hospital medical ward in Uganda identified HIV/AIDS as a major contributor to bed occupancy (Tembo *et al.*, 1994).

Despite its accepted use (World Bank, 2000; WHO 2000b), there are some criticisms of the DALY methodology. Paalman (1998) are concerned about the variations in the strengths and weakness of databases and value judgements of disability weightings. Musgrove (2000) highlights age weighting as a controversial parameter of the DALY given the argument of preference for saving young adult lives over those of young children or elderly people. Nonetheless, in the absence of better alternatives, the DALY still remains the most objective way for allocation of resources.

Recent economic impact assessments of animal and human trypanosomiasis have not given adequate coverage to the public health burden of the disease (Budd, 1999; Kristjanson *et al.*, 1999; Swallow, 2000). The *T. b. rhodesiense* sleeping sickness DALY estimates in eastern Uganda indicate that where *T. b. rhodesiense* sleeping sickness outbreaks occur, it has an important impact on human health. This public health impact needs to be considered in overall tsetse and trypanosomiasis control planning. Trypanosomiasis in cattle is an important veterinary problem in much of Uganda and East Africa. Both tsetse control and treatment of cattle fall under the mandate of the Ministries of Agriculture of most governments in Africa. The treatment of livestock for trypanosomiasis is one of the important control strategies where *T. b. rhodesiense* sleeping sickness occurs because cattle are the main reservoir of human-infective trypanosomes (Onyango *et al.* 1965; Hide *et al.*, 1996; Fèvre *et al.*, 2001). The results of burden of rhodesiense sleeping sickness should be transmitted to the agricultural sector departments responsible for control of tsetse and animal trypanosomiasis. This should increase the priority ranking of tyrpanosomiasis control in the agricultural sector. Therefore, the economic benefits of coordinated control of animal and human trypanosomiases in rhodesiense sleeping sickness areas can be immense because of the double benefits to both agriculture and public health.

In conclusion, the burden of rhodesiense sleeping sickness on the population and the health services in Serere, Uganda during an outbreak, has highlighted that mortality due to undetected cases was the major contributor to its burden on the local population and although sleeping sickness cases may be fewer than of other conditions, they consume an important proportion of in-patient time in the health unit. Therefore, an outbreak of rhodesiense sleeping sickness is very costly to the health services. Because sleeping sickness has a focal distribution in time and space, local estimates can be important in helping local health providers allocate their scarce health care and public health surveillance resources, to cater for the increased requirements by the health units within a sleeping sickness outbreak area. The data required to make these estimates can be obtained relatively easily from local hospital records. This burden of sleeping sickness can be reduced greatly by improving the

surveillance and control of the disease and therefore, reducing the level of under-detection.

Chapter 4 Spatial and temporal risk factors for the early detection of *T. b. rhodesiense* sleeping sickness patients in Tororo and Busia districts

4.1 Summary

To apply Geographical Information Systems (GIS) to study the effects of distance to health facility on early detection of *T .b. rhodesiense* sleeping sickness, records of sleeping sickness patients from 1987 to 2001 from Tororo and Busia district were reviewed for their village of origin and clinical stage (early or late). All villages that reported sleeping sickness and fixed post-diagnostic sleeping sickness health units in Tororo and Busia districts, Uganda were geo-referenced. Early and late stage patient detection patterns by health units were spatially analysed using a geographical information system. Contour maps of distance of sleeping sickness patients to health units were generated and the relationship between early sleeping sickness patient detection and distance from the sleeping sickness hospital was quantified using odds ratios (OR). Out of 1316 sleeping sickness patients admitted at LIRI and Busolwe hospitals and Lumino health centre from Tororo and Busia districts, 471 (35.8%) were early, 825 (62.7%) were late while 20 (1.5%) were not staged. 585 (44.5%) came from within a 10km radius of the reporting health units. Using univariate analysis, the proportion of early stage patients detected was found to be significantly associated with patients originating from within 10km radius of the health unit ($P<0.0001$), to adults (>19 years) ($P<0.0001$), active sleeping sickness patient detection ($P<0.05$) and with annual parish incidence ($P<0.0001$). The significant association of early sleeping sickness patient detection to proximity to health unit was maintained after adjustment for confounding variables ($P<0.001$). Applications of GIS and the early to late stage sleeping sickness cases ratio are an informative and powerful means of determining efficiency of surveillance of sleeping sickness. The results of this study have implications for health care provision in *T. b. rhodesiense* sleeping sickness areas.

4.2 Introduction

Sleeping sickness is an important public health problem in eastern Uganda causing epidemics (Abaru, 1985; Mbulamberi, 1989) and has spread further in the northern direction (Fèvre *et al.*, 2001). There have been several control programmes in the area but still the disease persists. These programmes have been based on case findings and treatment; tsetse control using impregnated traps and sometimes live-bait technology (Lancien, 1991). Cattle have been shown to be a reservoir of sleeping sickness (Onyango *et al.*, 1965; Hide *et al.*, 1994) and restocking of cattle sourced from the endemic area into the northern part of this *rhodesiense* focus has been reported as a major cause of the further spread of the disease (Fèvre *et al.*, 2001). Mass treatment of cattle has thus begun as another control option.

Sleeping sickness surveillance has been identified as an essential step towards the elimination of sleeping sickness (Cattand *et al.*, 2002; WHO, 2002). Epidemiological surveillance (Thacker *et al.*, 1988) of disease can only be regarded as complete with the timely delivery of information collected to implementers of control activities (Orenstein & Bernier, 1990). Early patient detection of most diseases is important for both control of the disease and prognosis of the individual patient. In Uganda, as with many sleeping sickness endemic countries, surveillance of sleeping sickness is unacceptably poor. Approximately more than half the sleeping sickness patients are detected when they are in the late stage. Many sleeping sickness patients go undetected and die of this fatal illness if untreated (see chapter 2). The prognosis of sleeping sickness in the late stage is significantly poorer than in the early stage of the disease (Odiit *et al.*, 1997a), and the drugs used in the treatment of late stage sleeping sickness are very toxic when compared to those used in the treatment of the early stage (WHO, 1998).

The causes of weak surveillance and thus a greater proportion of late stage sleeping sickness patients may be either patient factors or the health system, and include poverty of the sleeping sickness endemic countries, poverty of the sleeping sickness patients and the low sensitivity of the sleeping sickness diagnostic techniques (World

Bank, 2000; Okia *et al.*, 1994, Cattand & De Raadt, 1991). In Eastern Uganda, there are only 17 functional designated sleeping sickness treatment centres in a sleeping sickness endemic area of approximately 45,000 sq.km. Therefore, there is approximately only one such centre per 2500 square km. These centres also serve as the diagnostic centres for sleeping sickness. The distribution of health units is a major factor in the efficient provision of health services (Perry & Gessler, 2000). In the case of sleeping sickness, that requires diagnosis by microscope, the distribution of such health units is very important in the surveillance of the disease. However, the selection of health units is often static and spatial data on surveillance efficiency has not been used to assess the pattern of surveillance structure distribution. Studies on the effects of distance on accessibility to health care and the optimization of distances for different levels of health care have been carried out (Morrill & Earickson, 1968; Morrill *et al.*, 1970; Shannon *et al.*, 1969). Patients are more likely to seek health care at the nearest health care unit (Shannon *et al.*, 1969; Rahaman *et al.*, 1982; Stock, 1983; Kloos, 1990; Muller *et al.*, 1998). In developing countries, where health infrastructure is limited, it is assumed that patients will generally use the nearest facility since most of them travel on foot (Stock, 1983). This may have important implications for sleeping sickness where designated diagnosis and treatment facilities are sparsely distributed.

Socio-economic factors may also have an effect on the use of health services. Various studies have identified factors such as religion, income, availability of transport, quality of health care, perceived level of sickness and occupation (Engunjobi, 1983; Habib & Vaughan, 1986; Van der Stuyft *et al.*, 1996). Although these factors are important, they will vary widely from patient to patient and are not measured on routine visits. Therefore, planners may not easily access them. However, equitable geographical distribution of health facilities is often the criterion for planning most health services.

While some studies have been carried out to determine the risk factors for the acquisition of sleeping sickness (Okia *et al.*, 1994; Laveissiere *et al.*, 1994), equivalent studies spatially analysing the distribution of early stage patients as a

measure of the efficiency of surveillance are lacking. The ever increasing availability, power and "user friendliness" of Geographical Information Systems (GIS) software makes its application more simple in public health for such spatial analyses. The application of GIS to strengthen epidemiological surveillance for sleeping sickness has been advocated by the World Health Organization (WHO, 1999b; Cattand *et al.*, 2001). This study applies GIS to study the effects of spatial and temporal factors on early detection of sleeping sickness.

4.3 Methods

4.3.1 Definitions

A "case" was defined as a sleeping sickness patient that presented in the early stage while a "control" was defined as a sleeping sickness patient that presented in the late stage. All sleeping sickness patients are staged on admission by examining the CSF after a lumbar puncture for the purposes of determining which drugs are to be used for treatment of the disease (WHO 1998). The late stage is defined as when alterations in CSF are observed with increases in white blood cell counts to more than 5 per cumm or with the finding of trypanosomes in the CSF, otherwise, the patient is considered to be in the early stage.

4.3.2 Study area

Tororo and Busia districts are located in eastern Uganda at the border with Kenya and cover an area of approximately 3500 square km (Figure 4.1, Figure 1.3). The population was 628,000 people according to the 1991 census population (MOF, 1992) projections for 1998 with 95% of the population in the rural area. The population is composed mainly of subsistence farmers some of whom keep livestock.

The river Malaba separates the two districts and there are several streams running from Mount Elgon in the east into Lakes Kyoga and Lake Victoria. The sleeping sickness patients were diagnosed from LIRI and Busolwe hospitals and Lumino Health Centre.

4.3.3 Patient records

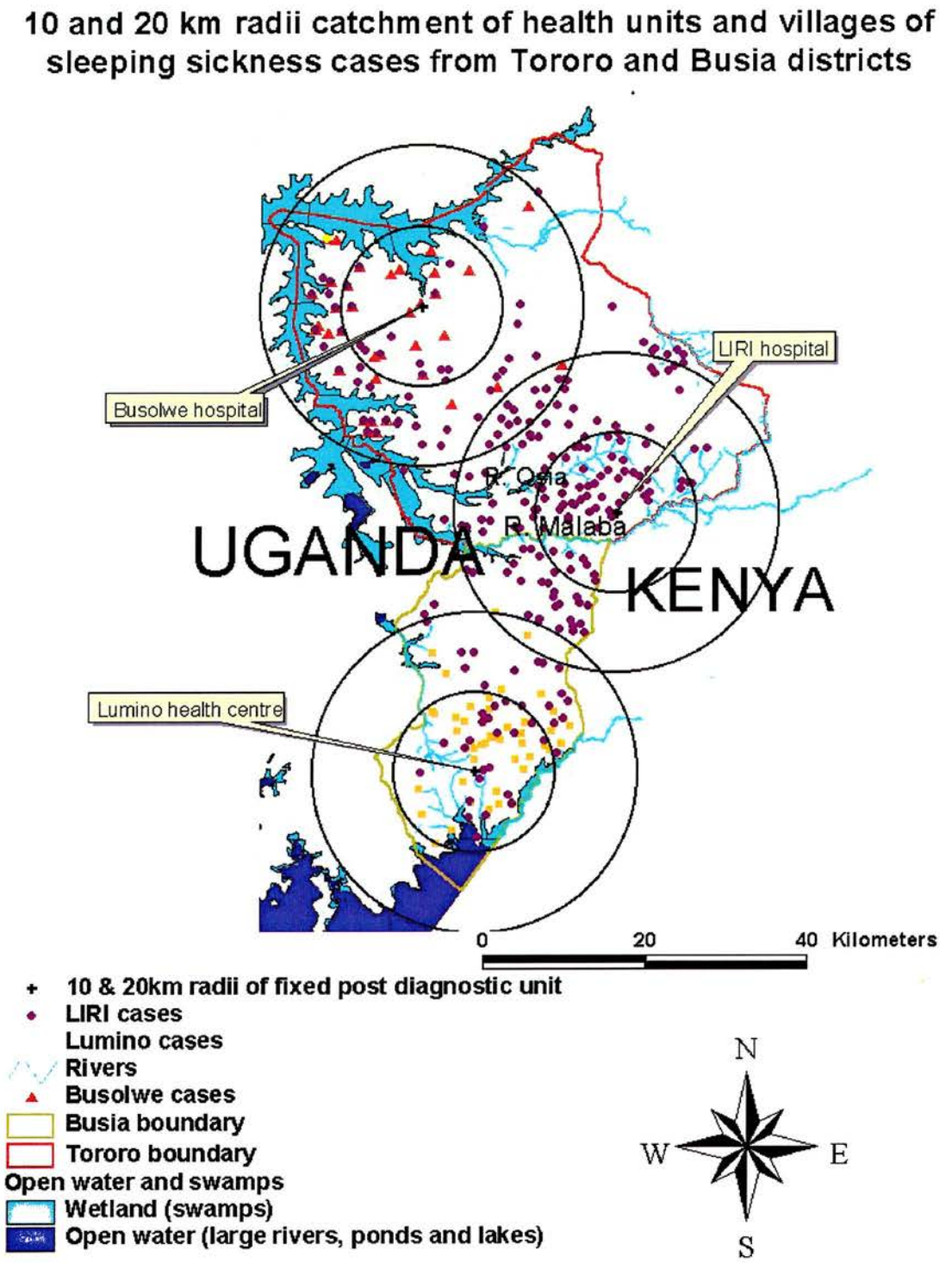
Records of all sleeping sickness patents attending LIRI hospital from 1987 to 2001 from Tororo and Busia districts were reviewed. Spatial, demographic and temporal factors of sleeping sickness patients who had presented in the late stage were compared with those that had presented in the early stage. Patient records included the name of the patient, date of admission, age, sex, health unit, geographical origin

to the village level, ethnic group, stage and mode of patient detection (active/passive).

4.3.4 Geographical information systems

The positions of all villages that had reported sleeping sickness and LIRI and Busolwe hospitals as well as Lumino Health Centre were geo-referenced using a Geographical Positioning System (GPS) manufactured by Garmin model No 12. The datum was set at WGS 84. The GIS software ArcView version 3.1 (ESRI, 1998) was used to display the position of the villages and health units and to generate 10 km radius contours around the health units (Figure 4.1).

Figure 4.1. SS Health unit catchments



4.3.5 Data processing and statistical methods

The coordinates obtained were entered into a Dbase file format and imported into ArcView GIS version 3.1. Using distance function applications of ArcView GIS, the distances of villages from where the patients came were stratified at 10 km strata from health units (Figure 4.1). Queries on village positions were resolved by repeat visits to the villages. Age was categorised into 0-19 (children and adolescents) and 20 plus (adults) years. Date of admission was categorised into wet (March to May and September to October) and dry season (December to February and June to August) since activity patterns related to subsistence farming may affect time of presentation to health units. Other than using the annual incidence for the entire study area as a variable, annual parish incidences were calculated because it was argued that awareness might be a result of high disease incidence within the closest vicinity. A parish is the next administrative level to the village. Initial data analysis was done through tabulating each risk or protective factor by case or control status. Estimates of the effect of each risk or protective factor were made using logistic regression models with case/control status (early/late stage) as the outcome. For each factor, which had a statistically significant association with late stage presentation of sleeping sickness (likelihood ratio χ^2 test statistic P-value <0.05), confounding by other factors was assessed. Potential confounders were defined as variables that had a 'significant' association with risk of late stage presentation, where 'significant' was defined as an effect with likelihood ratio χ^2 test statistic P-value <0.20 (Maldonado & Greenland, 1993a,b). Interaction was assessed between each risk or protective factor in the final model.

4.4 Results

4.4.1 Descriptive statistics

Between 1987 and December 2001, there were 1316 sleeping sickness patients from Tororo and Busia districts admitted and treated at LIRI and Busolwe hospitals and Lumino Health Centre from Tororo and Busia districts. Out of the 1316 sleeping sickness patients, 471 (35.8%) were early, 825 (62.7%) were late, while 20 (1.5%) were not staged. 585 (44.5%) came from within a 10 km radius of the health unit. The annual parish incidence was less or equal to 8 for 543 sleeping sickness cases and greater than 8 for 753 sleeping sickness cases. 1296 cases were used in the analysis because 20 did not have records of staging of illness. The descriptive statistics of these 1296 patients is summarised in Table 4.1. 354 (27.4%) of the patients were children or adolescents of less than 20 years. 1207 (93%) of the patients were detected passively i.e. came to the hospital on their own. 578 patients (44.6%) were from the Adhola tribe while the rest were mainly from the Teso (278 (21.5%)), Samia (252 (19.4%)) and Nyole (173 (13.3%)) tribes. The male to female ratio was 3:2 (775:521). The patients were predominantly (>98%) Christians. 667 (51.5%) of the patients reported during the wet season while the other 48.5% (629) reported in the dry season. During the years 1987 to 1988 and 1994 to 2001 only LIRI hospital was functioning as a diagnostic centre in the Tororo and Busia districts.

4.4.2 Univariate analysis

There was a significant linear correlation ($P< 0.001$) between increasing distance from the reporting health unit and being detected as a late stage patient (Figure 4.2). Similarly, reported sleeping sickness incidence rates were higher nearer LIRI hospital (where >80% of the cases were reported) than further away (Figure 4.3). The trend of association between increasing distance from the reporting health unit and being detected as a late stage patient remains when the data was disaggregated into years when LIRI only was the functional sleeping sickness treatment centre, and other years when other health units were diagnosing and treating sleeping sickness.

Children and adolescents were significantly ($P<0.001$) more likely to be detected in the late stage. In addition, early stage patient detection was more significantly ($P<0.001$) likely during years of high incidence in a given parish (Table 4.1 and Figure 4.3). Gender, season and ethnic groups were not significantly ($p>0.05$) associated with early stage presentation.

Table 4.1. Results of univariate analysis, showing the crude odds ratios (OR) and their 95% confidence intervals (CI) for 1296 patients

Variable	Number of: Early cases	Late cases	cOR	CI for cOR	*P*
Age in years*					
≤19	96	258	0.56	(0.43-0.73)	<0.001
> 20	375	565			
Season					
Dry	221	408	0.90	(0.72-1.13)	0.41
Wet	250	417			
Distance from reporting SS health unit in km					
0-10	248	335	1.63	(1.29-2.04)	<0.001
>10-20	149	257			
>20-30	46	116			
>30-40	22	70			
>40-50	6	47			
Annual parish incidence (cases per 10000/year)					
≤8	159	384	0.59	(0.46-0.74)	<0.001
>8	312	441			
Mode of patient detection					
Active	23	66	0.59	(0.36-0.96)	0.04
Passive	448	759			
Gender					
Female	187	334	0.96	(0.77-1.22)	0.83
Male	284	491			
Ethnic group					
Adhola	218	360	1.11	(0.89-1.40)	0.39
Teso	115	163			
Samia	76	176			
Nyole	56	117			
Other	253	465			
Health unit					
LIRI	379	724	0.57	(0.42-0.78)	<0.001
Other	92	101			
Religion					
Christian	464	812	1.06	(0.42-2.68)	0.09
Moslem	7	13			

*Two patients had no age records

Figure 4.2. Proportion of early stage cases out of all SS cases by distance from reporting health unit

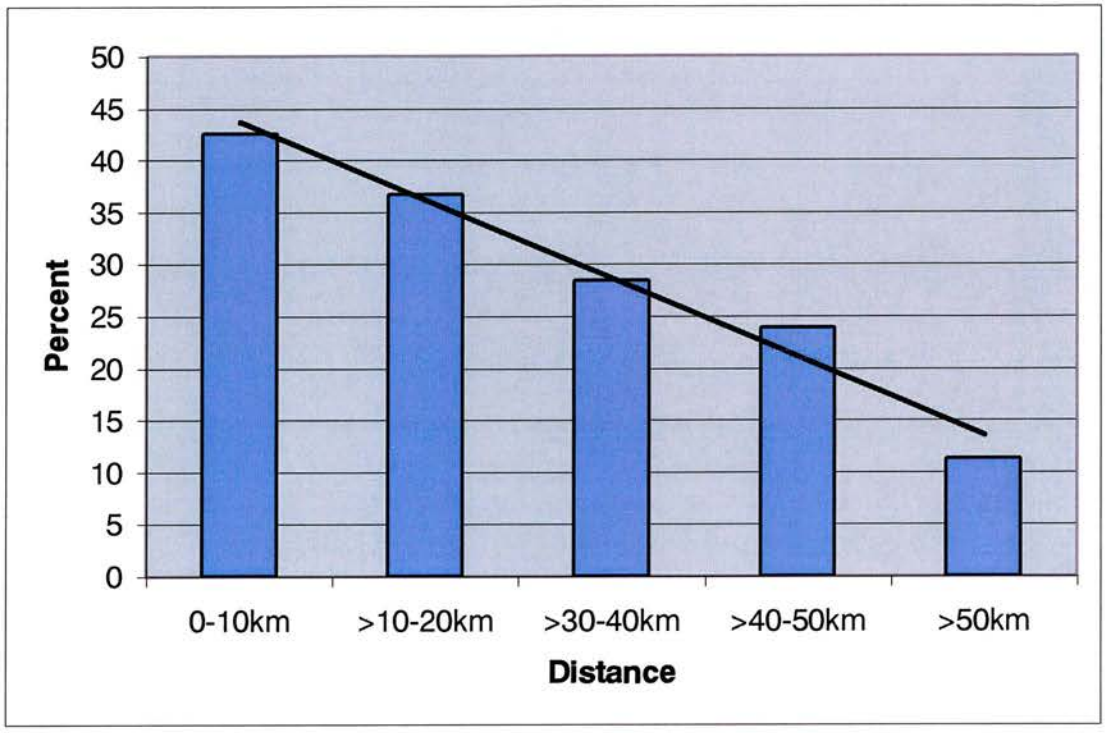


Figure 4.3. Sleeping sickness incidence rate per 10,000 people by distance from LIRI hospital

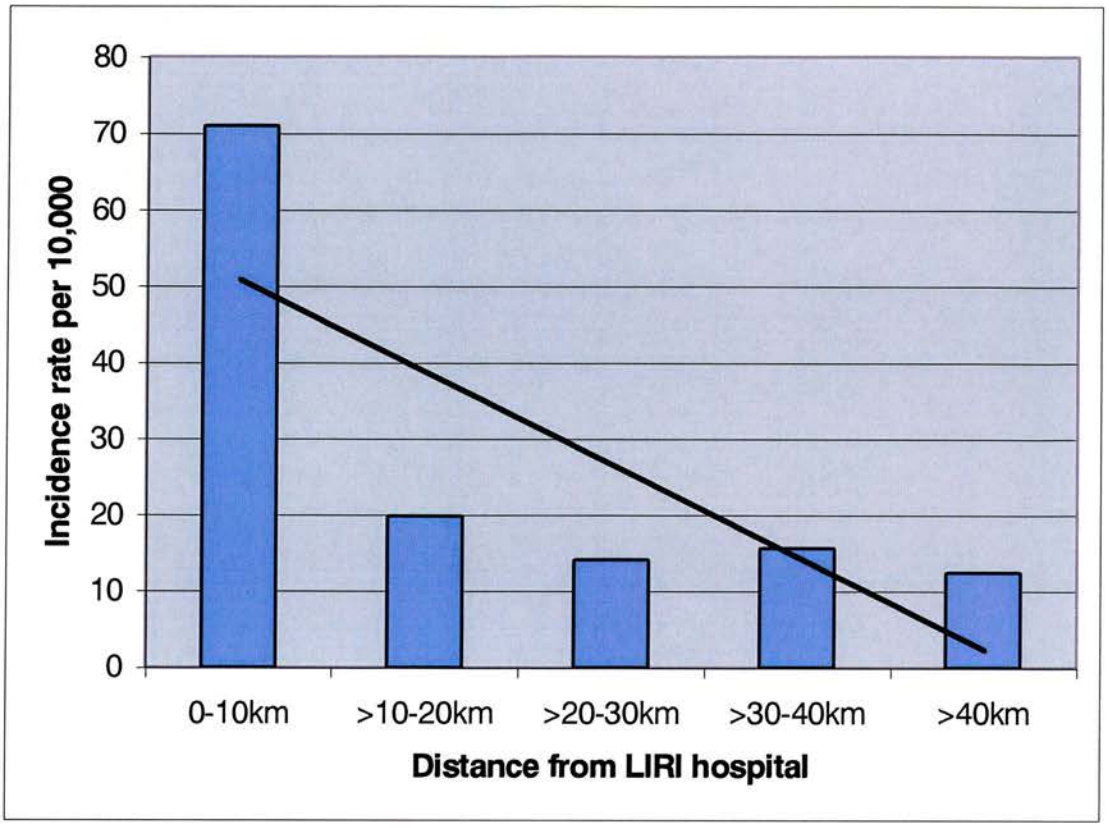


Figure 4.4. Distribution of 1296 sleeping sickness cases by stage and by distance to reporting health unit during years when all 3 health units were sleeping sickness treatment centres

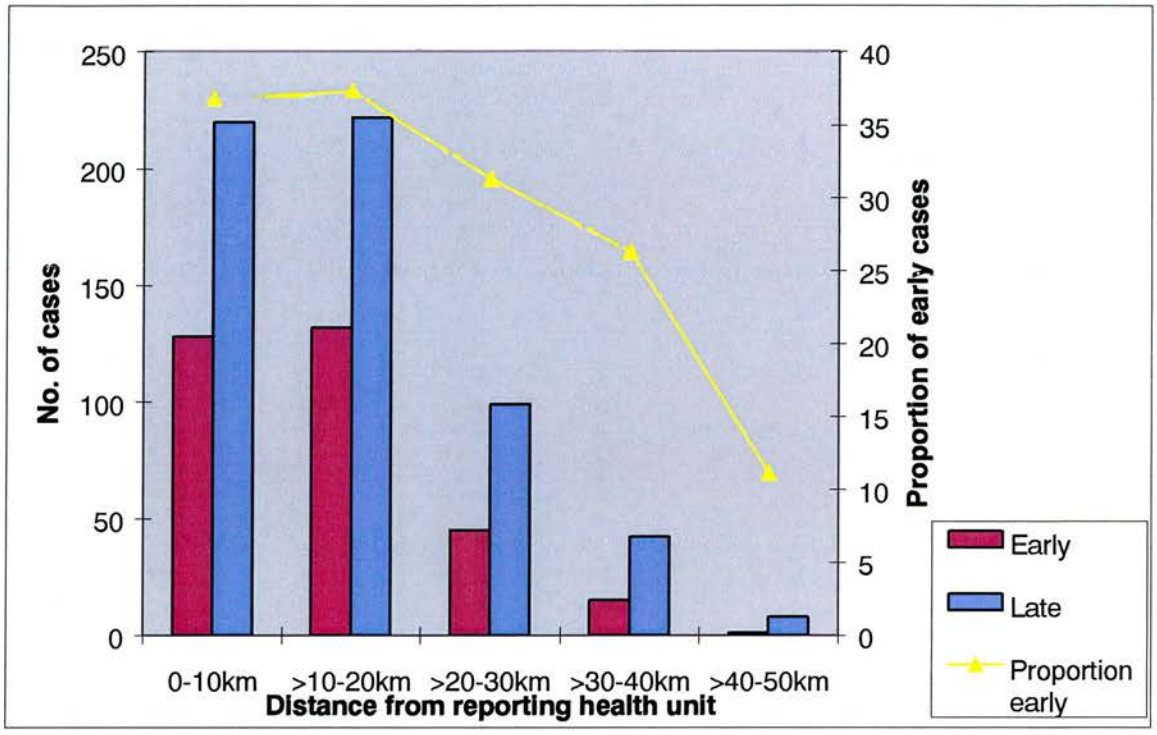
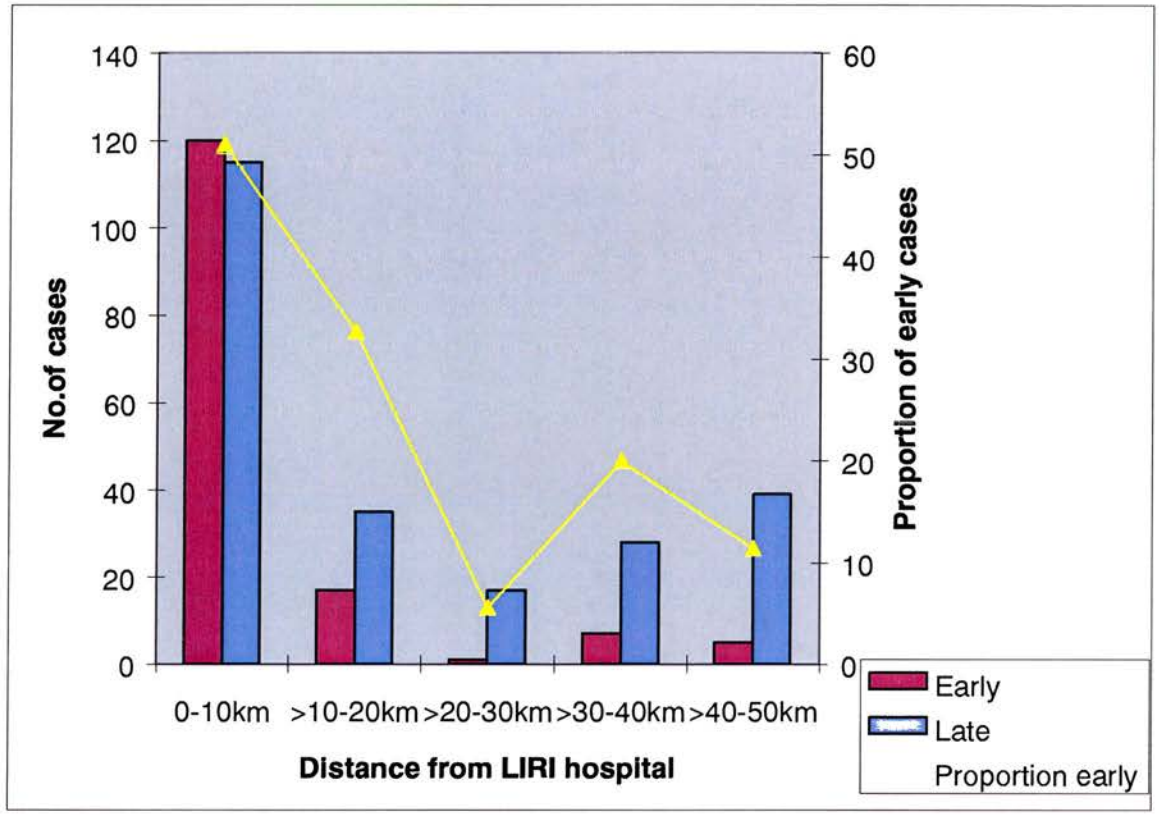


Figure 4.5. Distribution of 1296 sleeping sickness cases by stage and by distance to reporting health unit during years when only LIRI hospital was the sleeping sickness treatment centre



4.4.3 Multivariate analysis

Table 4.2 summarises the results of the logistic regression. Four factors remained significantly associated with late stage presentation after controlling for other factors: distance from the reporting diagnostic centre, age of patients, annual parish sleeping sickness incidence and health unit. There were no significant interactions.

Table 4.2. Multivariate analysis: results of the final model, showing the crude odds ratios (cOR) and adjusted odds ratios (aOR) and their 95% confidence intervals

Variable	Number of: Cases	Controls	cOR	CI for cOR	aOR	CI for aOR	*P*
Distance from reporting SS health unit in km:							
≤10	248	335	0.61	(0.49-0.77)	0.70	(0.55-0.89)	0.004
>10	223	490					
Age in years*:							
≤19	96	258	0.56	(0.43-0.73)	0.56	(0.43-0.74)	0.0000
>20	375	565					
Annual parish incidence (cases per 10000/year):							
≤8	159	384	1.71	(1.35-2.16)	1.66	(1.31-2.12)	0.0000
>8	312	441					
Health unit:							
LIRI	379	724	1.74	(1.28-2.37)	1.56	(1.13-2.15)	0.006
Other	92	101					
Mode of patient detection:							
Active	23	66	1.69	(1.04-2.76)	1.55	(0.94-2.57)	0.09
Passive	448	759					

*Two cases had no age records.

4.5 Discussion

Geographical Information Systems (GIS) have been used as a tool for evaluating sleeping sickness surveillance efficiency, that is, to map and analyze the sleeping sickness early to late stage patient ratio patterns of villages around three sleeping sickness fixed-post health units in Tororo and Busia districts. This is a novel approach to assessing sleeping sickness surveillance. In Chapter 2, it has been shown that that the level of under-detection can be quantified using the early to late ratio of sleeping sickness patients. The study has shown that there is a significant relationship between the distance to the reporting health units and being detected in the early stage. Similarly, the reported incidence rate for sleeping sickness was highest nearer LIRI hospital from where over 80% of the patients were reported, suggesting lower case detection rates further away. Distance to fixed-post health facilities therefore appears to be a very important spatial risk factor of late stage patient detection in *T. b. rhodesiense* sleeping sickness areas and thus under-detection. Regular optimization of the distribution of fixed-post sleeping sickness diagnostic facilities may greatly reduce late stage presentation and deaths associated with this disease. Health workers and the affected communities need to be updated on the distribution of the disease especially during years of low incidence and to be alerted of the delayed detection of sleeping sickness in children. Improvement of the capacity of diagnosis of health units in the district may ensure detection of sleeping sickness patients in the early stage and reduce mortality associated with this disease. Setting up new health units would be costly; however, there are already established government and private laboratories with microscopes in the affected areas. Currently, only a few of these health units diagnose and refer sleeping sickness cases, perhaps because they are not designated as sleeping sickness treatment centres. There is therefore a need to regularly update the microscopists and the clinical workers in these other health units about the diagnosis of sleeping sickness and to actively involve them in the surveillance of sleeping sickness. Public–private partnerships in the Uganda health services are being advocated (Birungi *et al.*, 2001) and in this regard, private health institutions may play an important role.

The contribution of health care services has been highlighted as a necessity for a sound and sustainable disease control policy. Moerman *et al.* (2003) observed that assuming all interventions are cost-effective, their impact on mortality and morbidity will only be marginal if access to proper care is not guaranteed and therefore, it is the responsibility of scientists and health managers to highlight to policy makers and donor agencies the importance of an accessible and well functioning health-care system at all levels for the control of specific diseases. The present study emphasises this by demonstrating the effects of distance to health unit on early case detection.

Some authors argue that Euclidean (straight line) distance is not an optimal measure of accessibility (Shannon *et al.*, 1973; Diechmann, 1997) because it does not take into account physical barriers such as hills, rivers and the road network. Since a large number of people either walk or use bicycles as their main form of transport, Euclidean distances are a good proxy for accessibility in a rural population. Although there is an overlap in the catchment areas of the three sleeping sickness diagnostic centres beyond a 20 km radius, it is important to note that sleeping sickness reports from the Lumino Health Centre 20 km catchment radius stopped after 1993 most probably due to increased surveillance and treatment as well as tsetse control. In addition, before 1989 and 1990 for Lumino and Busolwe hospitals respectively, LIRI hospital was the sole sleeping sickness diagnostic centre. This may explain why most cases were detected in time and place around LIRI hospital over the entire time period. In the analysis, the problem of overlap is taken care of by including time and centre in the model and by plotting separately the spatial effects on the proportion of early stage cases for years when LIRI hospital was the only functional sleeping sickness treatment centre, and other years; the trend was maintained in both analyses.

An independent association between young age and late stage presentation has also been demonstrated perhaps because children and adolescents rely on the adults for decisions to take the patients for treatment. Although sleeping sickness appears to be more prevalent among the adults, it is important that health workers test children for sleeping sickness in endemic areas. The apparent reduction in early case detection during years of decreased incidence in a specific parish is indicative of annual parish

incidence being an important temporal risk factor. This may be associated with decreased awareness among the health workers and communities during periods of low incidence. During such times, surveillance teams should have awareness campaigns for all health workers and communities in areas where few patients are being reported.

Since all sleeping sickness patients were included in the study, there is in principle, no selection bias. Only patients with parasitological confirmation of trypanosomiasis are treated as patients and therefore, all patients recruited into the study certainly had sleeping sickness. Bias of misclassification is also unlikely because qualified and long serving laboratory technicians were involved in the examination of CSF for the staging of the disease. Although not found to be statistically significant, efforts must be made to carry out active surveillance where there are many late cases, particularly in areas not easily accessible to passive surveillance.

Emphasis on passive case finding is an approach suitable for *T. b. rhodesiense* and not *T. b. gambiense* because the former is symptomatic while the latter is often asymptomatic in the early stage (WHO, 1998) and therefore requires frequent active screening using serological tests (Magnus *et al.*, 1978). However, the GIS approach in general, for mapping trends in sleeping sickness disease and sero-prevalence distribution has been applied in *T. b. gambiense* areas (Cattand *et al.*, 2002). The data collected is then analysed to evaluate control operations such as case search, diagnosis, treatment and vector control.

National and district health planners should aim towards high early sleeping sickness patient detection at all health facilities. District health managers should regularly geo-locate where sleeping sickness patients come from and position fixed-post diagnosis at the nearest location to the current origin of the sleeping sickness patients. Clinics reporting low percentage of early stage patients should be further investigated to determine whether their quality of service differs from other clinics or whether the differences are due to the distance sleeping sickness patients have to

travel to the clinic. In Chapter 5, the health seeking behaviour among sleeping sickness patients is examined.

In conclusion, since fixed post (passive) sleeping sickness patient finding is cheaper than using active means, and that there are several fixed health units in the area, this study demonstrates that great potential exists for improving health care provision for sleeping sickness and thus, control of the disease in eastern Uganda. It also shows the utility of GIS and the early to late stage case ratio in evaluating surveillance of sleeping sickness. These surveillance tools and methodology are therefore advocated for control programmes for targeting *T. b. rhodesiense* sleeping sickness.

Chapter 5 Assessing health seeking behaviour among sleeping sickness patients in eastern Uganda

5.1 Summary

To study the patterns of health seeking behaviour among sleeping sickness patients in Eastern Uganda, data on socio-demographic and clinical characteristics, health seeking behaviour and delays to presentation and diagnosis were collected from diagnosed sleeping sickness patients. Analysis of odds ratios (OR) was used to examine factors associated with delay. Among 119 patients, median total delay to diagnosis was 2 months with service provider delay contributing a greater proportion than patient delay. Patient and service provider delays were both independently associated with sleeping sickness patients presenting in the late stage. The absence of a blood examination test at the first visit is associated with service provider delay. Most patients were referred to the sleeping sickness hospital by either the community or on their own initiative and not by the health system. There is considerable delay between symptom onset and diagnosis among sleeping sickness patients with a median of 60 days. Substantial delay was attributable to the service provider failure to diagnose sleeping sickness among symptomatic individuals. A deterministic model structured on the possible routes of a sleeping sickness infection to either diagnosis or death through the health system or out of it, showed that out of a total of 73 deaths, 62 (85%) entered the health care system but were not diagnosed, 11 died without seeking health care from a recognised health unit while 62 (33 %) of the remaining 186 died despite seeking appropriate health care. The sleeping sickness health information system needs to be improved and cheap and simple diagnostics are needed.

5.2 Introduction

Late stage presentation is associated with increased risk of death and transmission of sleeping sickness. Therefore, understanding health seeking behaviour of rhodesiense sleeping sickness patients is very important for sleeping sickness surveillance programmes. Although studies of health seeking behaviour have been carried out in other chronic diseases such as tuberculosis (Beyers *et* al., 1994; Liam *et al.*, 1997; Lawn *et al.*, 1998; Steen & Mazonde, 1998; Lonnroth *et al.*, 1999; Sherman *et al.*, 1999; Wandwalo & Morkve, 1999; Salaniponi *et al.*, 2000), similar studies on sleeping sickness are lacking. A study of *Trypanosoma brucei gambiense* sleeping sickness cases in the Democratic Republic of Congo observed that women tended to present with less advanced disease than men probably due to differences in health seeking behaviour (Pepin *et al.*, 2002). Consequently, this study investigated the health seeking behaviour among diagnosed sleeping sickness patients in eastern Uganda where rhodesiense sleeping sickness is endemic. Its specific objectives were to:

1. characterise a cross section of sleeping sickness patients;
2. determine the time between onset of symptoms and diagnosis of sleeping sickness;
3. examine the relative contributions of patient and provider attributable delay;
4. describe patterns of health seeking behaviour to first presentation and to diagnosis;
5. examine the association of socio-demographic, clinical and knowledge factors to the time to first presentation and to diagnosis;
6. estimate the number and proportion of sleeping sickness cases who enter into the health care system but are not diagnosed.

5.3 Materials and methods

5.3.1 Setting and population

This study was conducted in LIRI hospital, a sleeping sickness hospital in Tororo district in the eastern region of Uganda, which is mainly a rural area with agro-

pastoral subsistence farming. In Tororo district, there are four hospitals, seven health centres and several private clinics. Two of these hospitals treat sleeping sickness, however, all of the hospitals and three health centres are equipped to diagnose the disease. All sleeping sickness patients are admitted and registered at the time of diagnosis. Clinical staging based on cerebrospinal fluid (CSF) findings was carried out in all patients to decide on the treatment to be administered.

5.3.2 Patient identification and interview

A semi-structured questionnaire was administered to all patients (or attendants if the patient was not capable of answering) who came for treatment between December 2000 and September 2002. A sleeping sickness patient was diagnosed by the finding of trypanosomes either in his or her blood or CSF. The questionnaire covered the following information: clinical symptoms such as fever, headache, body aches, swelling of feet, dizziness, chancre and socio-demographic characteristics such as age, sex, education level, occupation, ownership of radio or bicycle or cows, type of house and tribe; perceptions of kind of illness, knowledge of trypanosomiais control methods and facilities and trypanosomiasis control practices such as cattle treatment and insecticide application; and health seeking behaviour characteristics such as type of health unit first visited, source of money for costs accrued while ill, number of visits to health centre before diagnosis, whether blood was examined at first visit, who influenced going to sleeping sickness hospital, what the diagnosis was on the first presentation, distance to sleeping sickness hospital and mode of travel to the sleeping sickness hospital.

5.3.3 Definition of diagnosis delay

Patients were asked to estimate the time since they fell ill with the current diagnosis of sleeping sickness. Total delay was defined as duration from onset of symptoms to diagnosis. During the interview, the reasons for the total delay were explored. Patient delay was defined as the time between the onset of symptoms to the first presentation to a recognised health service provider. Health service provider delay was defined as

the time between first presentation to diagnosis. Cut off times for categorising patient delay was set at 14 days due to the severity of rhodesiense sleeping sickness with patients expected to seek attention immediately and at 30 days for service provider in case of a missed diagnosis at the first presentation. Home visits were made to ascertain the information obtained from patients while in the hospital by interviewing the heads of the homesteads and to geo-reference the homesteads so as to determine accurately the distance travelled to LIRI hospital. Geo-referencing was carried out using a Garmin 12 GPS receiver in WGS datum. Medical forms of the patients obtained while attending other health units were read to objectively determine dates and diagnoses made.

5.3.4 Data management and statistical analysis

Data, including both coded answers and text responses, were entered into Microsoft Excel and analysis conducted in Epi Info 2002. Delay data in days are presented as medians. Odds ratios (OR) and 95% confidence intervals (CI) were calculated in risk analyses to investigate factors that may be predictive of patient delay and service provider delay or late stage disease. Population attributable fractions (PAFs) of factors significantly associated with service provider delay and PAFs of patient and service provider delays for late stage occurrence were calculated to show how important each of the significantly associated factors were in public health terms in the population. PAF is the proportion by which the outcome (delay or late stage) may be reduced if the factor were eliminated.

5.3.5 Quantification of undiagnosed deaths in the health-care system for rhodesiense sleeping sickness

5.3.5.1 Model structure

A deterministic model structured on the possible routes of a sleeping sickness infection to either diagnosis or death through the health system or out of it was developed to quantify the number and proportion of undiagnosed deaths in the health

care system for rhodesiense sleeping sickness during the diagnosis of the 119 sleeping sickness cases in this study (Figure 5.1).

The health-care system for rhodesiense sleeping sickness (SS) is modelled by using a set of differential equations. In this section, a stage refers to the modelling stage, not the clinical stage. Each patient starts as an early case in the community (E_C) and follows one of the six possible routes as described below. In Route 1, an early case in the community (E_C) reports to the health-care system and becomes an early-reported case (E_S), who eventually is diagnosed and treated as an early case (E_T). In Route 2 and 3, an early case in the community (E_C) enters the health-care system as an early case (E_S), who subsequently becomes a late case of sleeping sickness while still in the heath-care system (L_{S1}). In Route 2, a late case can be diagnosed and treated (L_{T1}) whereas in Route 3, a late case might die from SS while still in the health-care system (D_{S1}). In Route 4, an early case in the community (E_C) develops SS further and becomes a late case (L_C), who subsequently dies from the disease while still in the community (D_C). In Routes 5 and 6, an early case in the community (E_C) becomes a late case (L_C), who then subsequently enters the health-care system as a reported late case (L_{S2}). In Route 5, a patient enters the health-care system as a late case (L_{S2}) and gets to be diagnosed and treated (L_{T2}) whereas in Route 6, such a late case dies from SS while still in the health-care system (D_{S2}). Figure 5.2 summaries the structure of the model. Times between the model stages have a notation T_{ij} denoting time from stage i to stage j.

$$\boldsymbol{T}_{E_C E_T} = \boldsymbol{T}_{E_C E_S} + \boldsymbol{T}_{E_S E_T} \qquad \text{(Route 1)} \qquad \text{(Equation 5.1)}$$

$$\boldsymbol{T}_{E_C L_{T1}} = \boldsymbol{T}_{E_C E_S} + \boldsymbol{T}_{E_S L_{S1}} + \boldsymbol{T}_{L_{S1} L_{T1}} \qquad \text{(Route 2)} \qquad \text{(Equation 5.2)}$$

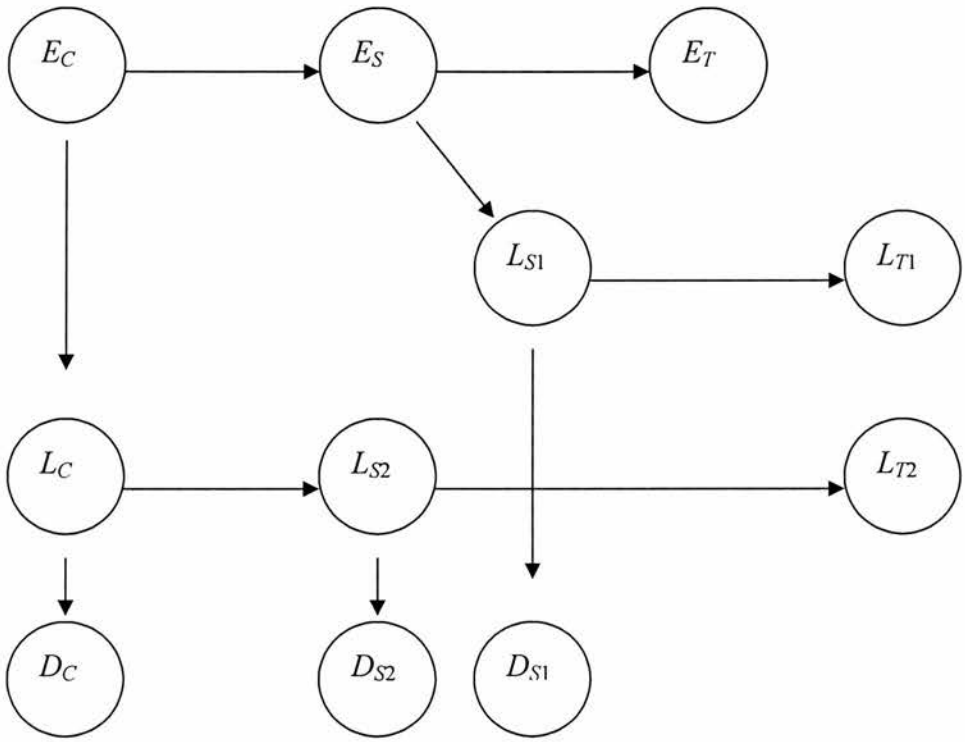
$$\boldsymbol{T}_{E_C D_{S1}} = \boldsymbol{T}_{E_C E_S} + \boldsymbol{T}_{E_S L_{S1}} + \boldsymbol{T}_{L_{S1} D_{S1}} \qquad \text{(Route 3)} \qquad \text{(Equation 5.3)}$$

$$\boldsymbol{T}_{E_C D_C} = \boldsymbol{T}_{E_C L_C} + \boldsymbol{T}_{L_C D_C} \qquad \text{(Route 4)} \qquad \text{(Equation 5.4)}$$

$$T_{E_C L_{T2}} = T_{E_C L_C} + T_{L_C L_{S2}} + T_{L_{S2} L_{T2}} \quad \text{(Route 5)} \quad \text{(Equation 5.5)}$$

$$T_{E_C D_{S2}} = T_{E_C L_C} + T_{L_C L_{S2}} + T_{L_{S2} D_{S2}} \quad \text{(Route 6)} \quad \text{(Equation 5.6)}$$

Figure 5.1. Model structure for the sleeping sickness health-care system
E = early case, L = late case, C= community, S = health system, T = diagnosed and treated, *1* = patients enter system as early, *2* = patients enter system as late, *Tij* = time from model stage *i* to model stage *j*.



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5.3.5.2 Model parameters

The known parameters in the model are $T_{E_C D_C} = T_{E_C D_{S1}} = T_{E_C D_{S2}} = 108$ days, the time from stage E_C to D_C or D_{S1} or D_{S2} i.e. mean duration to death from rhodesiense sleeping sickness estimated from the mean duration of symptoms to death in patients dying on admission due to sleeping sickness and not drug reactions (Odiit *et al.*,

1997). The parameter $\boldsymbol{T}_{E_C E_S}$ = 16 days is obtained from the mean duration to the first visit to the health unit as reported by sleeping sickness cases diagnosed as early cases among the 119 sleeping sickness cases recruited into the present study. Similarly, the time $\boldsymbol{T}_{E_S E_T}$ = 29 days is obtained from the same subset of the sleeping sickness cases diagnosed as early cases and is the time from their first visit to the health care system to diagnosis. The time $\boldsymbol{T}_{E_C L_{T1}} = \boldsymbol{T}_{E_C L_{T2}}$ = 94 is estimated from the mean duration of symptoms to diagnosis as a late case (Odiit *et al.*, 1997). The final densities (end outcomes) of the model structure E_T = 45 and $(L_{T1} + L_{T2})$ = 74 are obtained from the 119 rhodesiense sleeping sickness cases recruited into this study. $D_C + D_{S1} + D_{S2}$ = 78 (95% CI 72-85) is the estimate of unreported (undetected) deaths using the model for estimating case under-detection in Chapter 2. The only unknown time interval is $\boldsymbol{T}_{E_S L_{S1}}$. It can be deduced that at the beginning of the model, there were approximately 197 infections in the community, which is the total sum of all end outcomes. Therefore, the initial conditions were E_C = 197, while all other outcomes in the model had a population density of zero. The known parameters were then entered into the model described.

5.3.5.3 Model dynamics

A model stage i has a population density of N_i (where i can either be E_C, E_S, E_T, L_C, L_{S1}, L_{S2}, L_{T1}, L_{T1}, L_{T2}, D_C, D_{S1} or D_{S2}). The rate of change in the population density for stage i is modelled as:

$$\frac{dN_i}{dt} = In_i - Out_i, \qquad \text{(Equation 5.7)}$$

where In_i and Out_i are the rates of immigration into and emigration out of stage i respectively. Assuming a stage j occurs before stage i, then In_i is:

$$In_i = r_{ji} N_j, \qquad \text{(Equation 5.8)}$$

where r_{ji} is a parameter that measures the rate of transition from stages j to i, and N_j is the population density of stage j. If a stage i is the origin of a route, then In_i is equal to zero. Assuming a stage k occurs after stage i, then Out_i is:

$$Out_i = r_{ik} N_i, \qquad \text{(Equation 5.9)}$$

where r_{ik} is a parameter that measures the rate of transition from stages i to k. If a stage i is the end of a route, then Out_i is equal to zero. If individuals in stage i can either enter stages k or m, then Out_i must include those entering stage k from stage i:

$$Out_i = r_{ik} N_i + r_{im} N_i, \qquad \text{Equation 5.10)}$$

where r_{im} is a parameter that measures the rate of transition from stages i to m. The parameter measuring the transition rate between two stages, say from j to i, is defined as:

$$r_{ji} = 1/T_{ji}, \qquad \text{(Equation 5.11)}$$

where T_{ji} is the time taken for an individual to move from stage j to stage i.

5.3.5.4 Model simulation

With estimated initial conditions and parameters, the model is simulated by solving numerically the system of differential equations using the 4th order Runge-Kutta method (Press, 1992). The simulation is terminated once all the stages except those in the end of each route (i.e. E_T, L_{T1}, L_{T2}, D_C, D_{S1}, D_{S2}) have zero population densities. The population densities of those stages in the end of each route are then noted. From a range of values, the best estimate of the unknown time interval $\boldsymbol{T}_{E_S L_{S1}}$ is selected to ensure that all the model end outcomes are consistent with the data used. This value is then used to estimate the number of deaths while in the health care system (D_{S1}+ D_{S2}).

5.4 Results

127 sleeping sickness patients were interviewed during the study period. Eight patients were later excluded from the analysis of patient or service provider delay because of incomplete information on duration of illness.

5.4.1 Socio- demographic and clinical characteristics

The socio-demographic and clinical characteristics of the 119 sleeping sickness cases included in the analysis are shown in Tables 5.1 and 5.2. The patients were mainly (88.2%) greater than 14 years and 63.9% were males. Most patients were poor with 90.8% living in non-permanent housing structures (mud walls) and 92.4% without salaried employment and dependant on subsistence farming. About half (54.6%) of the patients owned a bicycle, a radio (56.3%), and/or cows (50.4%). About 85% had not attained education beyond primary level. Most patients had symptoms with over 80% presenting with fevers, headaches, body aches or dizziness. However, history of chancre lesions (41.2%) and/or swelling of the feet (37.0%) was reported by less than half of the patients.

Table 5.1. Clinical characteristics of 119 patients

Variable	**number (percent)**
Chancre	
Yes	49 (41.2)
No	70 (58.8)
Dizziness	
Yes	98 (82.4)
No	21 (17.6)
Headache	
Yes	113 (95.0)
No	6 (5.0)
Fever	
Yes	114 (95.8)
No	5 (4.2)
Generalised body aches	
Yes	111 (93.3)
No	8 (6.7)
Swelling of feet	
Yes	44 (37.0)
No	75 (63.0)
Clinical stage	
Early	45 (37.8)
Late	74 (62.2)

Table 5.2. Socio-demographic characteristics of 119 patients

Variable	number (percent)
Age (years)	
0-14	14 (11.8)
15-34	43 (36.1)
35-54	37 (31.1)
55-74	19 (16.0)
≥ 75	6 (5.0)
Sex	
Male	76 (63.9)
Female	43 (36.1)
*Occupational status	
Part time farmer	9 (7.6)
Full time farmer	110 (92.4)
*Education	
None	37 (31.1)
Primary	64 (53.8)
Secondary and above	18 (15.1)
Bicycle in home	
Yes	65 (54.6)
No	54 (45.4)
Radio in home	
Yes	67 (56.3)
No	52 (43.7)
Cows in home	
Yes	60 (50.4)
No	59 (49.6)
Type of house	
Hut	81 (68.1)
Semi-permanent	27 (22.7)
Permanent	11 (9.2)
Tribe	
Adhola	59 (49.6)
Teso	41 (34.5)
Samia	4 (3.4)
Nyole	5 (4.2)
Other	10 (8.4)

*Head of household in case of children and adolescents

5.4.2 Perceptions, knowledge and practices

Perceptions, knowledge and practices among 119 sleeping sickness patients are shown in Table 5.3. At the time of diagnosis, most (67.2%) patients thought they had malaria, while the majority of the rest (16.8%) suspected AIDS. About 88.4% knew that a tsetse bite is the cause of sleeping sickness. Two thirds of the respondents had seen a sleeping sickness case before diagnosis. The patients were aware of the existence of the sleeping sickness hospital (84.9%), the use of traps (95.0%), cattle as a sleeping sickness reservoir (81.5%) but less than half (36.1%) were aware that pour-on insecticides could be used for control of tsetse. Of the 59 patients' homesteads that kept cattle, half (51.6%) reported having ever treated their livestock for trypanosomiasis while only 10.2% had ever applied pour-ons (insecticides) on their cattle.

5.4.3 Health Seeking Behaviour

Health seeking characteristics among sleeping sickness patients are presented in Table 5.4. Most patients first reported to either a private clinic (43.7%) or public health unit (health centre or hospital) (52.9%) with only one (0.8%) admitting that he had first seen a traditional healer. However, 6 others reported visiting a traditional healer at one time during their illness. Only 14 (11.8%) visited the health unit once before diagnosis and treatment. The rest had to pay between 2 and 7 visits to health units before they were diagnosed and treated. Blood examination was carried out in 45% of the patients during their first presentation to a recognized health unit. At first presentation, most were diagnosed as having malaria (72.3%) while 19.3% were diagnosed as having sleeping sickness. Only 22.6% were referred to the sleeping sickness hospital by either the public (11.7%) or private health system (10.9%) while the rest (77.4%) either decided on their own or were influenced by family members, neighbours, local leaders and organizations to think they had sleeping sickness. Only one fifth of these patients came from within 5 km of the sleeping sickness hospital but 73.2% were carried to the hospital on their own or hired bicycles (69.8%) or by

foot (3.4%). Funds to cover the SS related health care were mainly (54.7%) obtained through sale of agricultural produce.

Table 5.3. Perceptions, knowledge and practices among rhodesiense sleeping sickness cases

Variable	number (percent)
Perception of kind of illness at time of diagnosis	
Malaria	80 (67.2)
AIDS	20 (16.8)
Witchcraft	6 (5.0)
Other	13 (11)
Cause of sleeping sickness	
Tsetse bite	104 (87.4)
Other	15 (12.6)
Seen a sleeping sickness case before	
Yes	78 (65.5)
No	41 (34.4)
Aware of sleeping sickness hospital	
Yes	101 (84.9)
No	18 (15.1)
Aware of potential reservoir status of cattle	
Yes	97 (81.5)
No	22 (18.5)
Aware of tsetse traps	
Yes	113 (95.0)
No	6 (5.0)
Aware of pour-ons for tsetse control	
Yes	43 (36.1)
No	76 (63.9)
Treats cows for trypanosomiasis*	
Yes	30 (50.8)
No	29 (49.2)
Applies pour-on insecticides*	
Yes	6 (10.2)
No	53 (89.8)

*Only homes with cattle

Table 5.4. Health seeking behaviour characteristics

Variable	number (percent)
Type of health service first visited	
Private clinic	52(43.7)
Health centre	11(9.2)
Hospital	52(43.7)
Traditional healer	1(0.8)
Other	3(2.5)
Source of money for health expenses	
Sold agricultural produce (chicken, goats crop produce etc)	64 (54.7)
Other (children, salary, NGOs etc)	55 (45.3)
No. of visits tohealth units	
1	14 (11.8)
2	21 (17.6)
3	40 (33.6)
4	25 (21.0)
>5	19 (16.0)
Blood examined at first presentation	
Yes	53 (44.5)
No	66 (55.5)
Who influenced going to sleeping sickness hospital?	
Self	11 (9.2)
Family	44 (37.0)
Neighbours	35 (29.4)
Public health system	14 (11.7)
Private health system	13 (10.9)
Other	2 (1.6)
Diagnosis at first presentation	
Malaria	86 (72.3)
Sleeping sickness	23 (19.3)
Other	10 (8.4)
Distance of patients home from SS hospital	
0-5km	24 (20.2)
>5 to 10 km	70 (58.8)
>10 to 20km	11 (9.2)
>20km	14 (11.8)
Mode of travel to sleeping sickness hospital	
Walking	4 (3.4)
Bicycle	83 (69.8)
Vehicle	32 (26.8)

Estimates of patient delay and service provider delay are shown in Table 5.5. Applying the definitions given above for patient delay and service provider delay, 52.1% and 50.4% of the patients had patient and service provider delays respectively. The median patient, service provider and total delays were two and half weeks, one month, and two months respectively.

Table 5.5. Estimation of delay

Variable	**number (percent)**
Patient delay	
Yes	62 (52.1)
No	57 (47.9)
Service provider delay	
Yes	60 (50.4)
No	59 (49.6)
Median patient delay	17 days (Two and a half weeks)
Median service provider delay	30 days (One month)
Median total delay	60 days (Two months)

Odds ratios (OR) for analyses of patient and service provider delays for associated factors are presented in Table 5.6. Of all factors tested, blood not being examined at the first presentation, was significantly ($P<0.05$) associated with service provider delay (OR 0.45, 95% CI 0.22-0.95) and not staying in a permanent house was significantly ($p<0.05$) associated with patient delay (OR 0.18, 95% CI 0.02-0.93). In Table 5.6 factors associated with patient delay are shown. Both patient and service provider delays were each significantly ($P<0.05$) associated with a patient being diagnosed in the late stage. The OR for patient delay was 2.98 (95% CI 1.38-6.43) while that for service provider delay was greater at 7.29 (95% CI 3.1-17.14). The results show that having a blood examination on the first visit will reduce service provider delay by as much as 38% (PAF), while living in a non-permanent house is associated with 70% (PAF) of the patient delay. Elimination of service provider

delay would result in an 80% (PAF) reduction in late stage presentation while elimination of patient delay will result in a 55% (PAF) reduction in late stage occurrence.

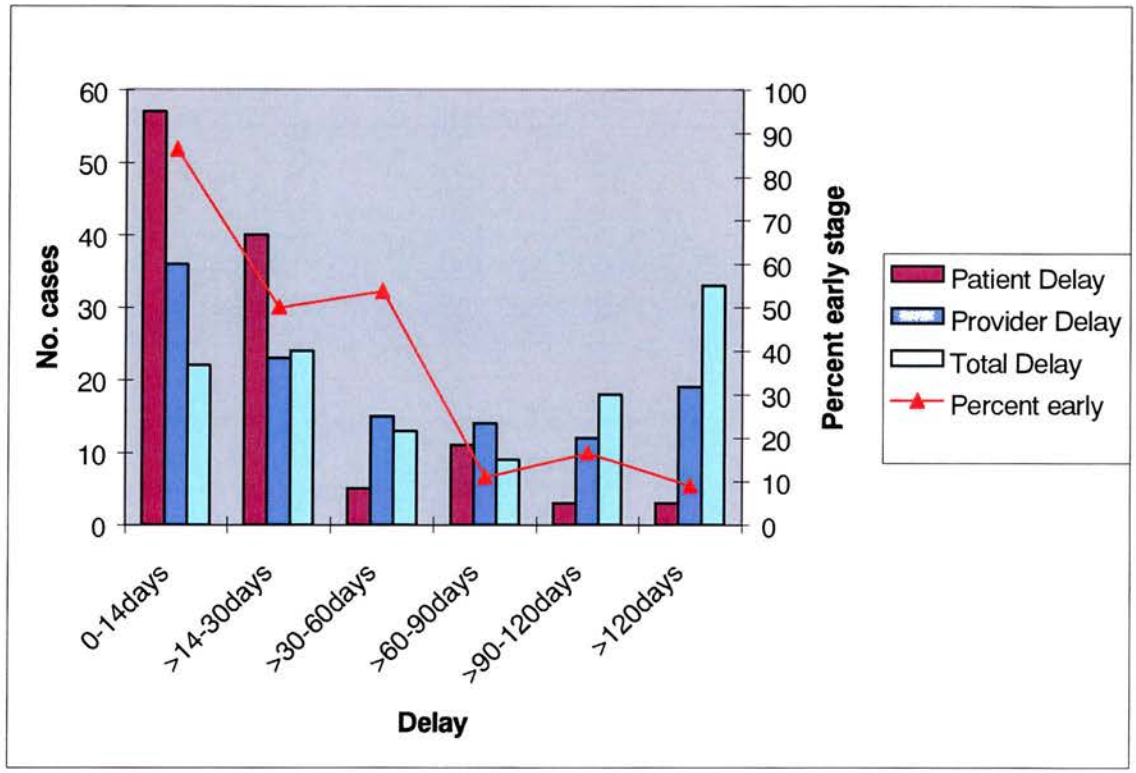
Table 5.6. Factors associated with "patient delay" and "service provider delay"

	Patient delay	**Service provider delay**
FACTOR	**OR (95% CI) (PAF)**	**OR (95% CI) (PAF)**
Blood examined on first presentation	NA	0.45 (0.22-0.95) (38%)
Permanent house	0.18 (0.02-0.93) (70%)	NA
Late stage	2.98 (1.38-6.43) (55%)	7.29 (3.1-17.14) (80%)

OR = Odds Ratio, CI = Confidence Interval, PAF = Population Attributable Fraction, NA =Not applicable

In Figure 5.2 the trends in total, patient and service provider delays are compared to the proportion of early and late stage cases. At one to two months of total delay, the proportion of early stage cases is 53.8%.

Figure 5.2. Trends in total, patient and provider delays and proportions of early stage cases



There is no significant association between patient and service provider delays indicating that they were independent of each other (Table 5.7).

Table 5.7. Relationship between patient and service provider delays

Patient Delay	**Provider delay**	
	No	Yes
No	34 (59.6%)	23 (40.4%)
Yes	25 (40.3%)	37 (59.7%)

$P>0.05$

Socio-demographic, clinical and knowledge factors were not found to be significantly associated with visiting health units for a maximum of two times before being diagnosed (Tables 5.8, 5.9 and 5.10). However, blood examined on the first visit to a health unit or paying a first visit to a public health unit were significantly ($P<0.05$) associated with diagnosis within two visits to a health unit (Table 5.11). Nonetheless, using multivariate analysis, it was found that of these two significant variables, blood examined on the first visit to a health unit remained as the only significant ($p<0.05$) variable.

Table 5.8 Socio-demographic risk factors for visiting a health unit for a maximum of two times before diagnosis of sleeping sickness

Variable		No of visits ≤ 2	No of visits >2	OR	CI	*P*
Age						
	0-19 years	7	26	0.6	0.2-1.4	>0.05
	> 20 years	28	58			
Sex						
	Female	13	30	1.1	0.5-2.4	>0.05
	Male	22	54			
Education status*						
	Primary or less	22	60	0.7	0.3-1.6	>0.05
	Secondary	13	24			
Tribe						
	Adhola	13	46	0.5	0.2-1.1	>0.05
	Other	22	38			
Religion						
	Catholic	18	45	0.9	0.4-2.0	>0.05
	Other	17	39			
House type						
	Non-permanent	31	77	0.7	0.2-2.6	>0.05
	Permanent	4	7			
Bicycle in home						
	Yes	18	47	0.8	0.3-1.8	>0.05
	No	17	37			
Cows in home						
	Yes	23	37	2.4	1.0-5.5	>0.05
	No	12	47			
Radio in home						
	Yes	22	45	1.5	0.7-3.3	>0.05
	No	13	39			
Employment*						
	Part time farmer	1	4	0.4	0.0-3.5	>0.05
	Full time farmer	22	32			

*Head of household in case of children and adolescents
OR = Odds Ratio, CI = Confidence Interval, *P*= significance

Table 5.9. Clinical risk factors for visiting a health unit for a maximum of two times before diagnosis of sleeping sickness

Variable	No of visits		OR	CI	*P*
	≤ 2	>2			
Chancre					
Yes	19	30	2.1	1.0-4.8	>0.05
No	16	54			
Fever					
Yes	35	79	-	-	>0.05
No	0	5			
Headache					
Yes	32	81	0.4	0.1-2.1	>0.05
No	3	3			
Generalised body aches					
Yes	33	78	1.3	0.2-6.6	>0.05
No	2	6			
Dizziness					
Yes	27	71	0.6	0.2-1.9	>0.05
No	6	10			
Swelling of feet					
Yes	10	34	0.6	0.2-1.7	>0.05
No	25	50			
Weakness					
Yes	22	33	2.0	0.9-20.0	>0.05
No	1	3			
Weight loss					
Yes	19	28	1.4	0.4-5.2	>0.05
No	4	8			
Aware of live bait					
Yes	13	30	1.1	0.5-2.6	>0.05
No	22	54			
Seen SS case before					
Yes	22	56	0.9	0.4-1.9	>0.05
No	13	28			

OR = Odds Ratio, CI = Confidence Interval, *P*= significance

Table 5.10. Knowledge risk factors for visiting a health unit for a maximum of two times before diagnosis of sleeping sickness

Variable	No of visits ≤2	>2	OR	CI	*P*
Aware of traps					
Yes	32	81	0.4	0.1-2.1	>0.05
No	3	3			
Aware of SS reservoir potential of cattle					
Yes	29	68	1.1	0.4-3.2	>0.05
No	6	16			
Aware of SS hospital					
Yes	28	73	0.6	0.2-1.7	>0.05
No	7	11			
Aware of tsetse traps					
Yes	32	81	0.4	0.1-2.1	>0.05
No	3	3			
Treated cows for nagana					
Yes	11	19	0.8	0.3-2.3	>0.05
No	12	17			
Used live bait					
Yes	3	3	1.7	0.3-9.0	>0.05
No	20	33			

OR = Odds Ratio, CI = Confidence Interval, *P*= significance

Table 5.11. Treatment seeking risk factors for visiting a health unit for a maximum of two times before diagnosis of sleeping sickness

Variable	No of visits ≤ 2	No of visits >2	OR	CI	*P*
*Blood examined on first visit					
No	7	59	0.1	0.0-0.3	0.01
Yes	.28	25			
Mode of travel to SS hospital					
Walk or bicycle	24	61	0.7	0.3-1.7	>0.05
Vehicle	11	20			
**Type of health unit first visited					
Private	10	42	0.4	0.2-0.9	0.05
Public	25	41			
Distance from SS hospital					
0-10km	30	64	1.9	0.6-5.4	>0.05
10 km					

*Remained significant on multivariate analysis
** Not significant on multivariate analysis
OR = Odds Ratio, CI = Confidence Interval, *P* = significance

5.4.4 Undiagnosed deaths in the health system

Running the model with known parameters enables the estimation of the following unknown parameters: $T_{E_C L_C}$ = 32 days; $T_{L_C L_{S2}}$ = 16 days; $T_{E_S L_{S21}}$ = 16 days, D_{S1} = 38 deaths; D_{S2} = 24 deaths; and D_C = 11 deaths. Therefore the model estimates a total of 73 deaths which is within the 95% Confidence Interval for the estimates of undiagnosed deaths estimate by the model for estimation of under-detection outlined in Chapter 2. Out of a total of an estimated undetected 73 deaths, 62 (85%) entered the health care system but were not diagnosed. Out of 197 initial infections, 11 died without seeking health care from a recognised health unit. Therefore 62 (33 %) of the remaining 186 died despite seeking appropriate health care.

5.5 Discussion

Delayed diagnosis of sleeping sickness is likely to be associated with a worse prognosis, and of particular public health importance, delay of treatment of sleeping sickness is likely to be associated with an increased number of newly infected persons caused by the initial infected person. This study shows that there is considerable delay between onset of symptoms and diagnosis among sleeping sickness patients in eastern Uganda. While patient delay contributes substantially to late patient presentation, an important preventable period of morbidity in the community was caused by failure of recognized health services to diagnose sleeping sickness among symptomatic patients. In addition, approximately 85% of the patients that die undiagnosed do enter the health system but are not detected and one third of those that do enter the health system die undiagnosed. This emphasises the need to improve case detection.

There are some limitations to the information collected. Patient recall of the duration of illness may not be that accurate, especially in longer illnesses, despite the repeated probing to validate responses. However, the findings of a strong correlation between clinical late staging and duration of illness indicates that the accuracy of duration of illness reported by patients was adequate for purposes of defining delay. It is also assumed that all delays after the initial presentation at a health unit is due to service provider, whereas some could have been due to patient factors. However, diagnosis of sleeping sickness or referral of patients to the appropriate hospital, if done by the provider at the first presentation, will most certainly have reduced service provider delay. In addition, there was no significant association between service provider and patient delay.

This study indicates that the use of private clinics as the first contact of a recognized health service is important. Referrals by these clinics, however, were only made by a few. On the other hand, the community (neighbours, family and self) were instrumental in referral of the patients to the sleeping sickness hospital. Therefore, timely sensitization of the affected communities during outbreaks may improve

sleeping sickness surveillance. Radio has been identified as a most reaching out media in Soroti district (Susanna Thorpe, Wren Media, *personal communication*) and can be used for this purpose. Another potential way of involving sleeping sickness patients in control of the disease, is through control of the sleeping sickness reservoir in cattle and in tsetse flies by treating cattle with trypanocides and applying pour-on insecticides to cattle to control tsetse, since half of the patients kept cattle in their homesteads. The need for community consultations before designing health programmes has also been observed in the context of malaria transmission and has been highlighted in another study conducted in a rural population in Uganda (Kengeya-Kayondo *et al.*, 1994). The findings of that study suggested that without prior research, malaria programmes which aim at vector control and early diagnosis and treatment of cases may prove ineffective and that information, education and communication programmes should be designed, implemented and evaluated with the full participation of the target population at every stage.

In Chapter 4, it has been shown that there is an association between clinical stage (early/late) and increased distance to diagnostic health facility, especially beyond 20 km. However, in this study, most patients came from within 20 km of the sleeping sickness hospital. Although 80% of the patients came from Euclidean distances of greater than 5 km, the recommended health care coverage distance, more than 70% travelled on bicycles or walked to the sleeping sickness hospital.

Studies of health seeking behaviour among sleeping sickness patients are difficult to obtain in the literature. However, health seeking behaviour studies in other chronic diseases such as tuberculosis have been reported widely (Sherman *et al.*, 1999; Wandwalo & Morkve, 1999; Salaniponi *et al.*, 2000). In these studies, patient delay is frequently more than service provider delay, perhaps because chronic cough is quite easily associated with tuberculosis compared to the non-specific symptomatology of sleeping sickness. In a study conducted on sleeping sickness data from the Democratic Republic of Congo, women were found to be more likely to have less advanced disease than men (Pepin *et al.*, 2002). The plausible explanation was that women might have better health seeking behaviour than men. This

explanation is supported by another study in Cameroon that showed that in general, women tend to participate more keenly in case-finding sessions aimed at detecting sleeping sickness cases among the asymptomatic population (Asonganyi & Ade, 1994). However, in this study, sex was not associated with diagnosis delay, most probably because *T. b. rhodesiense* sleeping sickness case-finding is mainly at fixed-post (passive) health units rather than through active case-finding as is carried out for *T. b. gambiense* sleeping sickness (WHO, 1998).

The findings of this study suggest that one important way of reducing delays in diagnosis among rhodesiense sleeping sickness patients is improvement of investigation and referral of patients presenting with symptoms at the primary care level. This study revealed that nearly all patients use recognised health units as their first contact. Only 42% were appropriately managed, that is, sleeping sickness diagnosis was made (19.3%) or referral to a sleeping sickness hospital (22.7%) took place. Approximately two-thirds of the patients presented to the sleeping sickness hospital after self-referral or insistence of the patient's family members and neighbours. Often it is the government health units that are better equipped with microscopes, and this explains the significant association between government health units and sleeping sickness diagnosis. Patients from homes that had permanent house structures represent a more wealthy and informed population and therefore are more likely to seek health care earlier than the poorer population.

In conclusion, this treatment seeking behaviour study has revealed that, in addition to increasing awareness of the communities, the health system outside the traditional sleeping sickness treatment centres should become more involved in sleeping sickness control and made aware of the existence of sleeping sickness when an outbreak is occurring. They can then refer the patients and suspected sleeping sickness patients to the established sleeping sickness treatment centres for appropriate management. Sleeping sickness control programmes can set up geographically sensitive health information systems that are efficient and responsive to the local endemic condition by carrying out operational research on the treatment seeking behaviour of the target population. In this way, delays in sleeping sickness

diagnosis will be reduced. In the longterm, cheap and simple diagnositics should be developed.

Chapter 6 Spatial and spatio-temporal trends of *T. b. rhodesiense* sleeping sickness in Tororo and Busia districts, Uganda, from 1987 to 2001

6.1 Summary

Trypanosoma brucei rhodesiense sleeping sickness is a fatal epidemic-prone protozoal zoonotic disease transmitted by an arthropod vector, *Glossina*, occuring in foci in sub-Saharan Africa. However, the analytical description of spatial and temporal occurrence of the outbreaks at control implementation levels is lacking. The presence of spatial and temporal clusters may indicate a common time and place transmission of the same parasites within the mammalian-fly cycle, thus presenting an opportunity for targeted control. This study looked for evidence of significant spatial temporal clustering of sleeping sickness cases at village level. A total of 1316 sleeping sickness reported patients from Tororo and Busia districts between 1987 and 2001 were analysed. The spatial distribution was analysed by applying the SaTScan method to determine if there was spatial and spatial-temporal clustering of sleeping sickness. Significant village scale spatial and spatial-temporal clustering of sleeping sickness was observed after initial occurrence of a few cases and persisted in and around villages where there was none or delayed control intervention. Implementation of control of tsetse and that of the cattle reservoir of sleeping sickness was not timely responsive to prevent spread of the disease but reduced the length of endemicity of villages when compared to areas where no control was applied.

6.2 Introduction

Sleeping sickness is reported to be endemic in several countries in Africa (WHO, 1999b). However, the distribution of sleeping sickness in these countries is very focalised. Most studies of the distribution of sleeping sickness and tsetse have been at continental level (Rogers & Randolph, 1989). The geographic distribution of rhodeisense sleeping sickness (RSS) is limited by the distribution of vector and reservoir hosts with foci occurring within these limits. The south-east of Uganda where the species of tsetse *G. f. fuscipes* is found has long been considered the focus of RSS (Mackichan, 1944; Robertson, 1958; Ormerod, 1961; Abaru, 1985; Mbulamberi, 1989). Although, the focalisation of sleeping sickness is acknowledged (WHO, 1998), there have been no cluster analysis studies like those carried out on the distribution of cancers (Kulldorff & Nagarwalla, 1995; Hjalmars *et al.*, 1996) with the exception of an out break in Soroti (Fèvre *et al.*, 2001). Neither have these residual foci been accurately mapped (Scott, 1970). The possible aetiological factors explaining the occurrence of clustering are related to human-fly contact. Peridomestic breeding sites of *G. f. fuscipes* in a sleeping sickness focus in Busoga, Uganda were identified in coffee and banana plantations, and in *L. camara* thickets and around houses (Okoth, 1986).

The eco-epidemiological pattern of sleeping sickness is complex and interactions between several potential spatial and temporal factors are responsible for their complexity. These factors include movement of infected livestock into the tsetse-infested districts (Fèvre *et al.*, 2001), political and economic upheavals with no control operations (Mbulamberi, 1989) and increasing contact of the population with the vector through encroachment of the tsetse habitat as a result of the ever-growing population. As a result of these interactions, various sizes of epidemics of sleeping sickness, a disease classified as epidemic-prone, may occur (WHO, 2002). Due to these complex interactions and varying magnitudes of the sleeping sickness public health problem, continuous monitoring of temporal and spatial trends is important so as to tailor control measures to the current local situation and to evaluate the impact of control.

In eastern Uganda, the sleeping sickness epidemic that occurred from 1976 eventually spread to Tororo and Busia districts in the late 1980s to the early 1990s (Lancien *et al*, 1990; Enyaru *et al*., 1992). Various control methods were put in place in Tororo and Busia districts (Lancien, 1991; Okoth *et al.*, 1991; Magona *et al*., 1998) to contain the epidemic. The broad objective of this study was to describe the spatial and temporal trends of sleeping sickness over a period of 15 years using sleeping sickness case records of patients from Tororo and Busia districts. Specifically, the objectives were as follows:

1) To map the spatial and temporal trends of sleeping sickness;
2) To determine if there was significant village scale spatial and temporal clustering of sleeping sickness;
3) To compare the lengths of occurrence of disease in areas with or without control

By quantifying the annual space clustering of all reported cases in the health units in the study area, occurrence and risk of local transmission can be evaluated. This information and methods are of use to the district sleeping sickness control programmes in evaluating the impact of surveillance and control efforts.

6.3 Materials and methods

6.3.1 Study design

A cross sectional study of villages that have reported sleeping sickness in Tororo and Busia districts from 1987 to 2001 was carried out by examining sleeping sickness records, mapping and analysing disease distribution.

6.3.2 Study area

The study area consisted of Tororo and Busia districts. South-eastern Uganda is drained by the source of the river Nile and its tributaries between the lakes Victoria and Kyoga. Tororo and Busia districts are found along the eastern border of Uganda (Figure 3.1). The total population of Tororo and Busia districts in the 1991 census was 555,674 and was estimated to be growing at a rate of 2.5 percent per annum (MOF, 1992). The population is a mixture of the Nilotic, Nilo-hamitic and Bantu tribes. The main occupation is small-scale mixed farming with subsistence growing of food crops and livestock rearing. Farmers rear cattle, goats, pigs and sheep and poultry. The types of crops grown are maize, millet, groundnuts, cassava, sweet potatoes and rice in these two districts. Drugs for the treatment of sleeping sickness are provided free of charge by the ministry of health. Suramin is used to treat the early stage of the disease and Melarsoprol is used to treat the late stage. The Ministry of Health is the sole supplier of these drugs and they can only be administered in prescribed health units. Tsetse are controlled by use of impregnated pyramidal traps (Lancien, 1991). A sleeping sickness control programme, co-funded by the Uganda government, European Economic Community (EEC) (Lancien *et al.*, 1990, Lancien, 1991) and the Organization of African Unity Inter-African Bureau of Animal Resources (OAU/IBAR) (Magona *et al.*, 1998) was implemented from 1987 to 1997 and led to the reduction of sleeping sickness in S.E Uganda.

6.3.3 Data sources

6.3.3.1 Patient data

Data on confirmed sleeping sickness cases from LIRI and Busolwe hospitals as well as Lumino Health Centre during the period 1987-2001 were obtained from the Ministry of Health. The patient records included information on the village of origin and date of admission.

6.3.3.2 Demographic and geographic data

All available data on location and year of diagnosis of sleeping sickness was entered into a geographic database, with a degree of spatial precision at village level. Population data for village levels was obtained from the 1991 population census (MOF, 1992). Latitude and longitude coordinates for all villages listed in the census data were geo-referenced using a Global Positioning System (GPS) to the centre of settlement in the village. The ArcView GIS software package (ESRI corporation, NY) (ESRI, 1998) is used to produce maps of village sleeping sickness case numbers, sleeping sickness village clusters and area of tsetse control measures.

6.3.4. Chronology of sleeping sickness control intervention

The years of application of sleeping sickness control measures, in particular areas in Tororo and Busia districts were obtained from minutes of the monthly sleeping sickness control project meetings and from publications (Lancien *et al.*, 1990; Lancien, 1991; Okoth *et al.*, 1991; Magona *et al*, 1998). The major intervention was tsetse control by insecticide impregnated pyramidal traps with a few instances of ground spraying of insecticides and application of pour-ons on cattle. Selective treatment of cattle on the basis of demonstration of parasites by microscopy was also carried out. The annual trends in number of sleeping sickness cases that reported more than 10 cases between 1987-1999 were plotted on graphs.

6.3.5 Data analysis

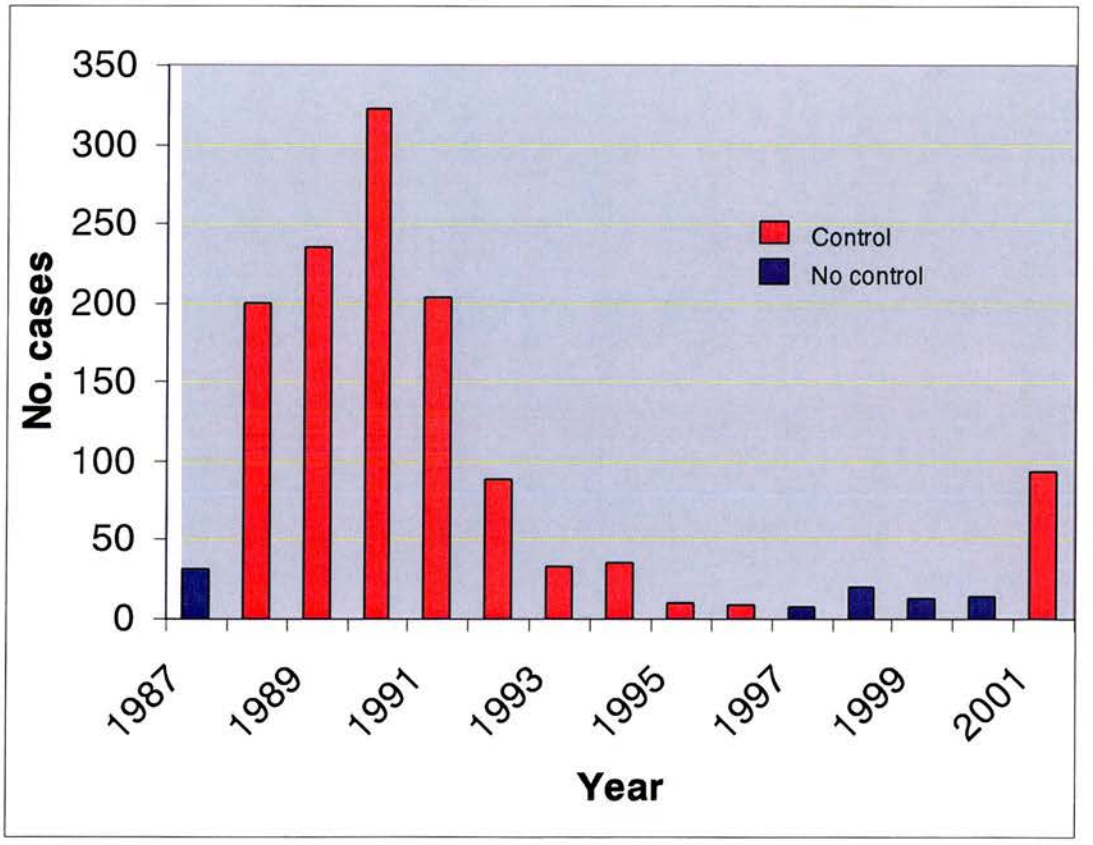
The location and time of significant space-time clusters in the villages of Tororo and Busia districts were analysed using the spatial-scan statistic of the software SaTScan (Kulldorff & Nagarwalla, 1995). This was done for the period from 1987 to 2001. This spatial-scan statistic locates the centre and radius as well as the period of significant clustering. The probability model used in SaTScan was based on a Poisson distribution. A Poisson model was used in the spatial scan because the background population represented a certain risk mass. This statistic adjusts for the heterogeneity of the underlying population and detects clusters of any size located anywhere in the study region regardless of their shape. SaTScan searches iteratively for case clusters using a continuously variable, circular window size to detect spatial clusters in large areas, while controlling for the underlying population structure (Kulldorff & Nagarwalla, 1995; Hjalmars *et al.*, 1996). To test for spatial clustering by year, the spatial scanning window was set at a maximum spatial cluster size of 50 percent of the total population in the study area. While to test for spatial-temporal clustering throughout the study period, the spatial scanning window was set at a maximum spatial cluster size of 20km radius to give a diameter of approximately half the length of the study area. The temporal scanning window was set at 72 months because this was the maximum number of consecutive years that a village reported sleeping sickness (Figure. 6.2). The cluster was centred at any of the village locations in the initial analysis for clustering. A likelihood ratio is calculated for each circle for the alternative hypothesis that there is an increased risk of disease within the circle against the null hypothesis that the risk inside the circle is the same as the risk outside it. The most likely cluster is that with the largest likelihood ratio. The statistical significance of this largest likelihood ratio is assessed by determining its distribution under the null hypothesis through Monte Carlo simulation (1000 simulations performed). This takes care of the problem of multiple testing associated with the method due to searching for the most suitable village position as a cluster centre. Secondary clusters were only determined if their radii were not overlapping. Using ArcView GIS, spatial and spatial-temporal clusters were drawn on disease distribution maps.

6.4 Results

6.4.1. Description of sleeping sickness reported incidence

In Tororo and Busia districts, 1316 *T. b. rhodesiense* sleeping sickness cases were reported between 1987 and 2001, from LIRI and Busolwe hospitals and Lumino Health Centre. The annual incidence of sleeping sickness from 1987 to 2001 showed two peaks at the beginning and end of the period (Figure 6.1). The reduction in the first peak corresponded to the period of the donor –funded sleeping sickness control project and occurred after the cessation of donor-funded control.

Figure 6.1. Annual number of sleeping sickness cases and years of donor funded control, 1987 to 2001



6.4.2. Spatial and spatio-temporal clustering of sleeping sickness cases

Generally, there was significant ($P<0.05$) spatial clustering of sleeping sickness in all years from 1987 to 2001 in Tororo and Busia districts and the clusters and their relative risks (RR) for sleeping sickness are shown in Figures 6.2 to 6.16. The spatial clusters in the early years (1987 to 1988) (Figures 6.2 and 6.3) were of small radii (< 5 km). However, the cluster sizes increased in 1989 to 1990 to 34 km and 44 km (Figures 6.4 and 6.5) showing the quick expansion of high rates of transmission within 3 years. In 1991, the large size cluster split into two small clusters, probably due to the application of control measures (Figure 6.6) meanwhile two other clusters occurred. From 1992 to 1996, significant sleeping sickness clustering mainly occurred at the northern edge of the control area but the disease was apparently under control south of the clustering where control measures had been in place for longer (Figures 6.7 to 6.11). From 1997 to 1999, clustering occurred outside the area control had been implemented but had since stopped (Figures 6.12 to 6.14). During these years, the disease appeared to be under control in the controlled area. From the year 2000 (Figures 6.15 to 6.16), sleeping sickness occurrence and clustering was again observed where it first occurred in 1987 and 1988 and the cluster size had increased by year 2001 when control interventions resumed. During the same period (2000 to 2001), the disease persisted in areas where no control intervention had been applied at all. Spatio-temporal clustering occurred from 1998 to 2001 in the north west of the study area and in 2001 in the eastern part of the area Figure 6.17 suggesting new resurgences that may result in larger outbreaks if not controlled effectively.

Figure 6.2. Spatial distribution of sleeping sickness cases by village and of significant clusters in 1987
The relative risk (RR) of infection within the cluster is shown.

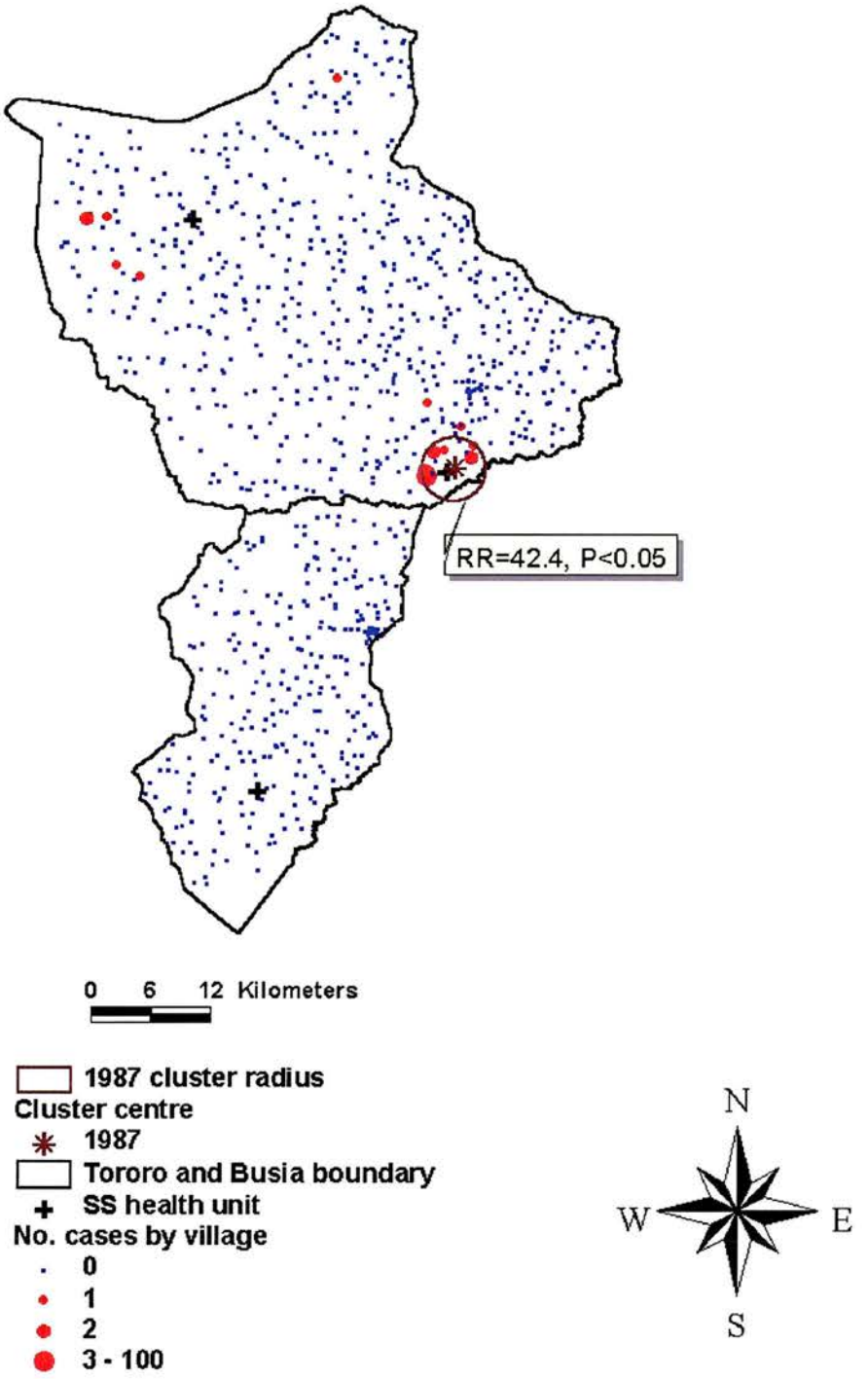


Figure 6.3. Spatial distribution of sleeping sickness cases by village and of significant clusters in 1988
The relative risk (RR) of infection within the cluster and the area under control is shown.

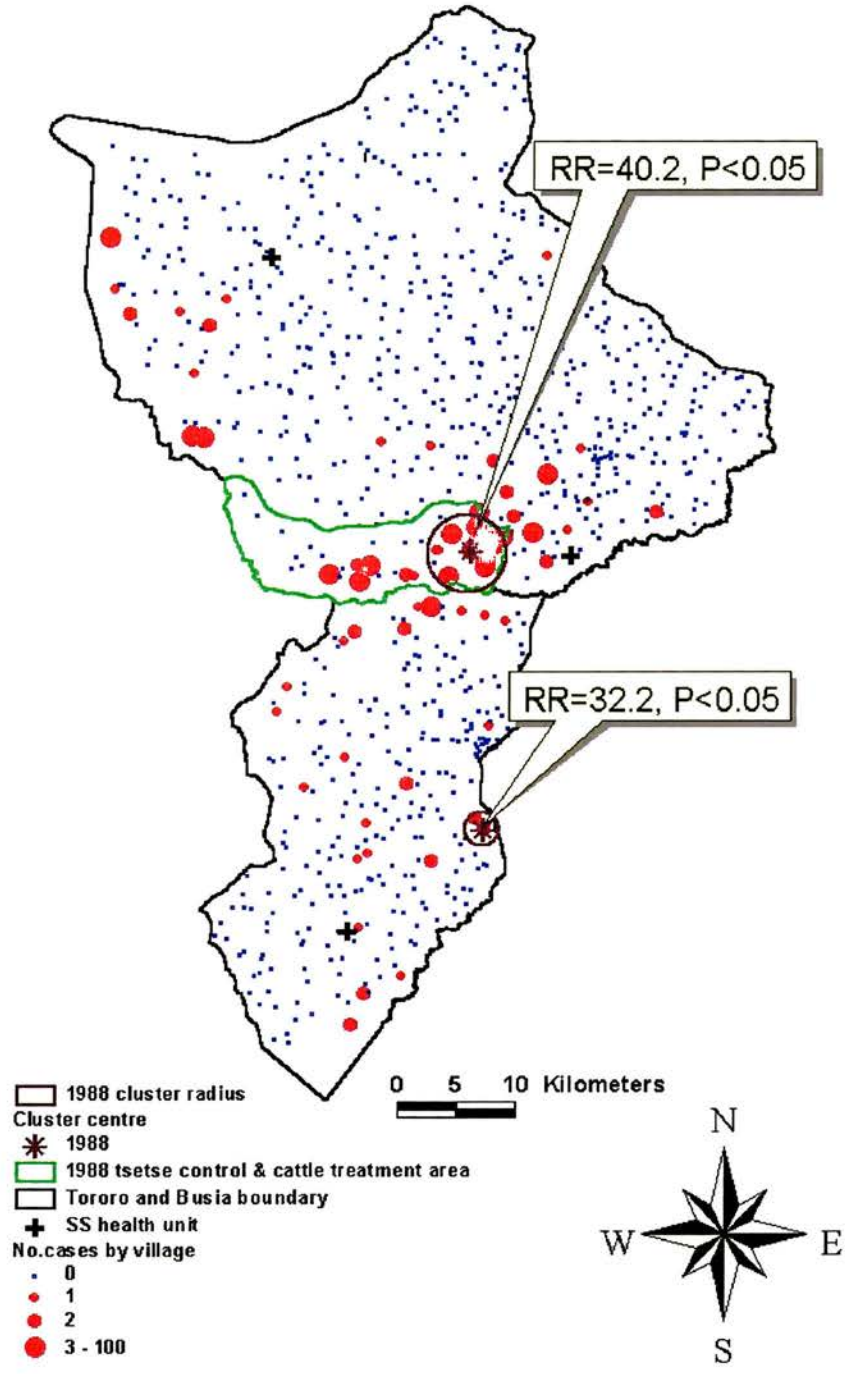


Figure 6.4. Spatial distribution of sleeping sickness cases by village and of significant clusters in 1989
The relative risk (RR) of infection within the cluster and the area under control are shown.

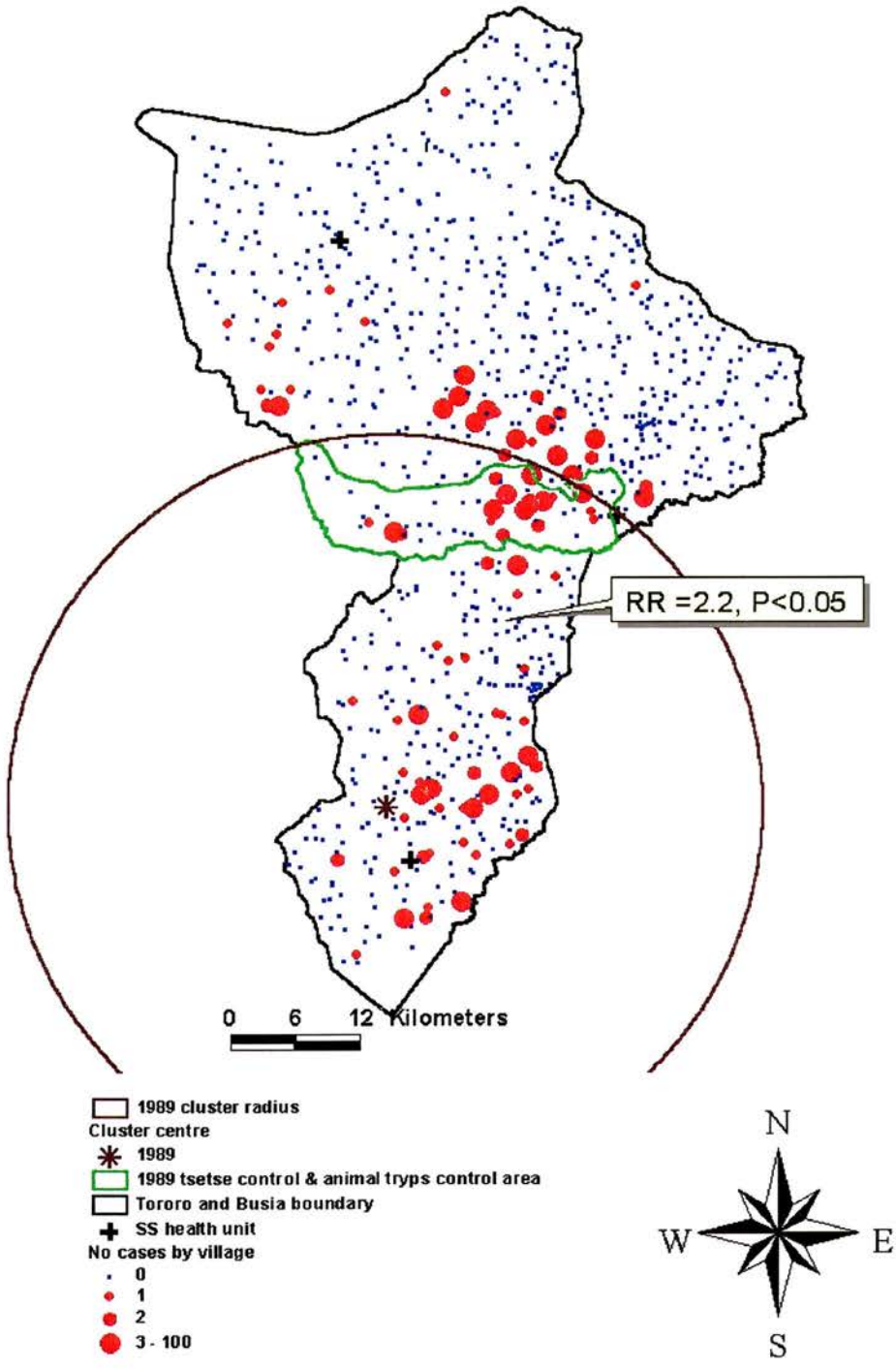


Figure 6.5. Spatial distribution of sleeping sickness cases by village and of significant clusters in 1990
The relative risk (RR) of infection within the cluster and the area under control are shown.

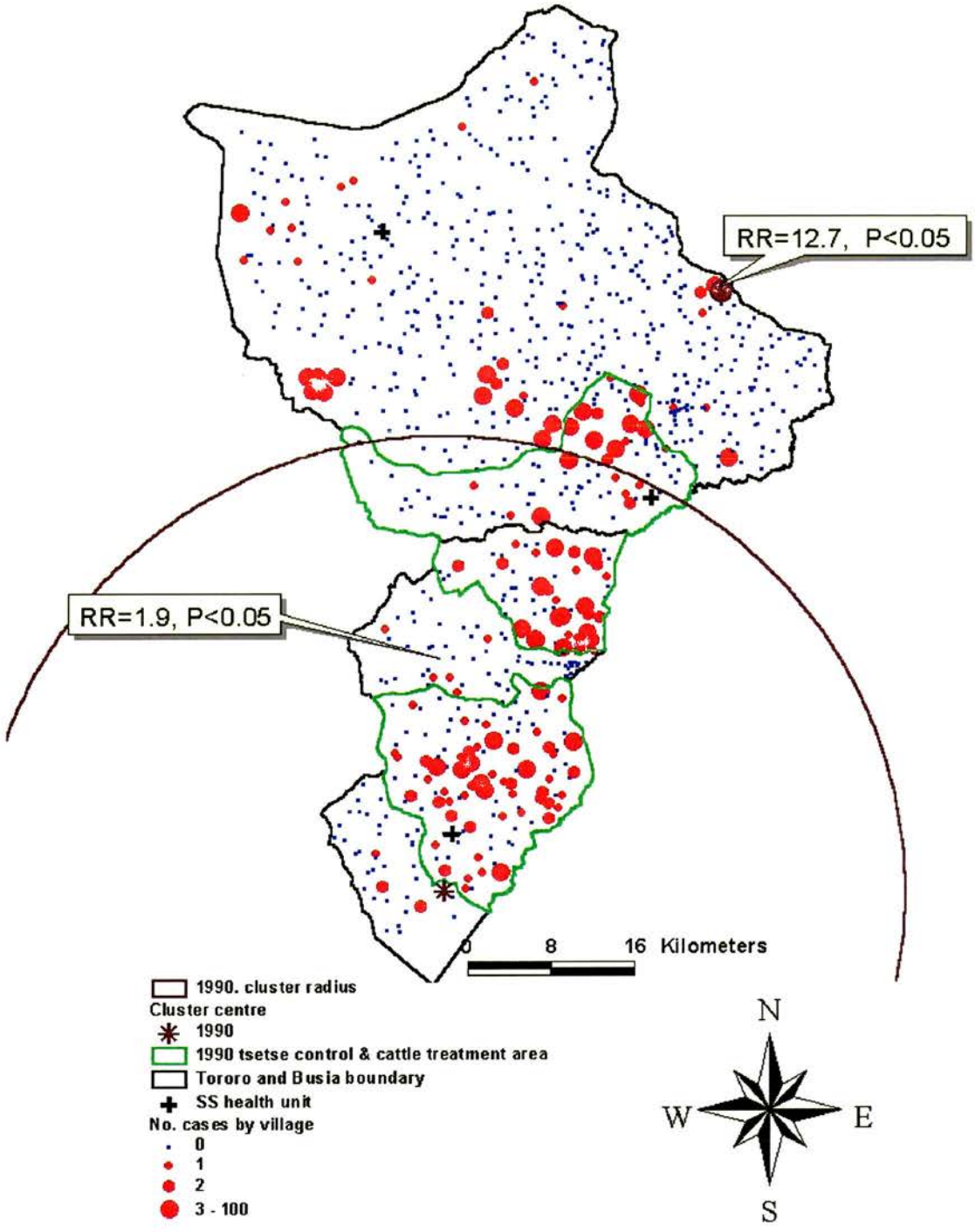


Figure 6.6. Spatial distribution of sleeping sickness cases by village and of significant clusters in 1991
The relative risk (RR) of infection within the cluster and the area under control are shown.

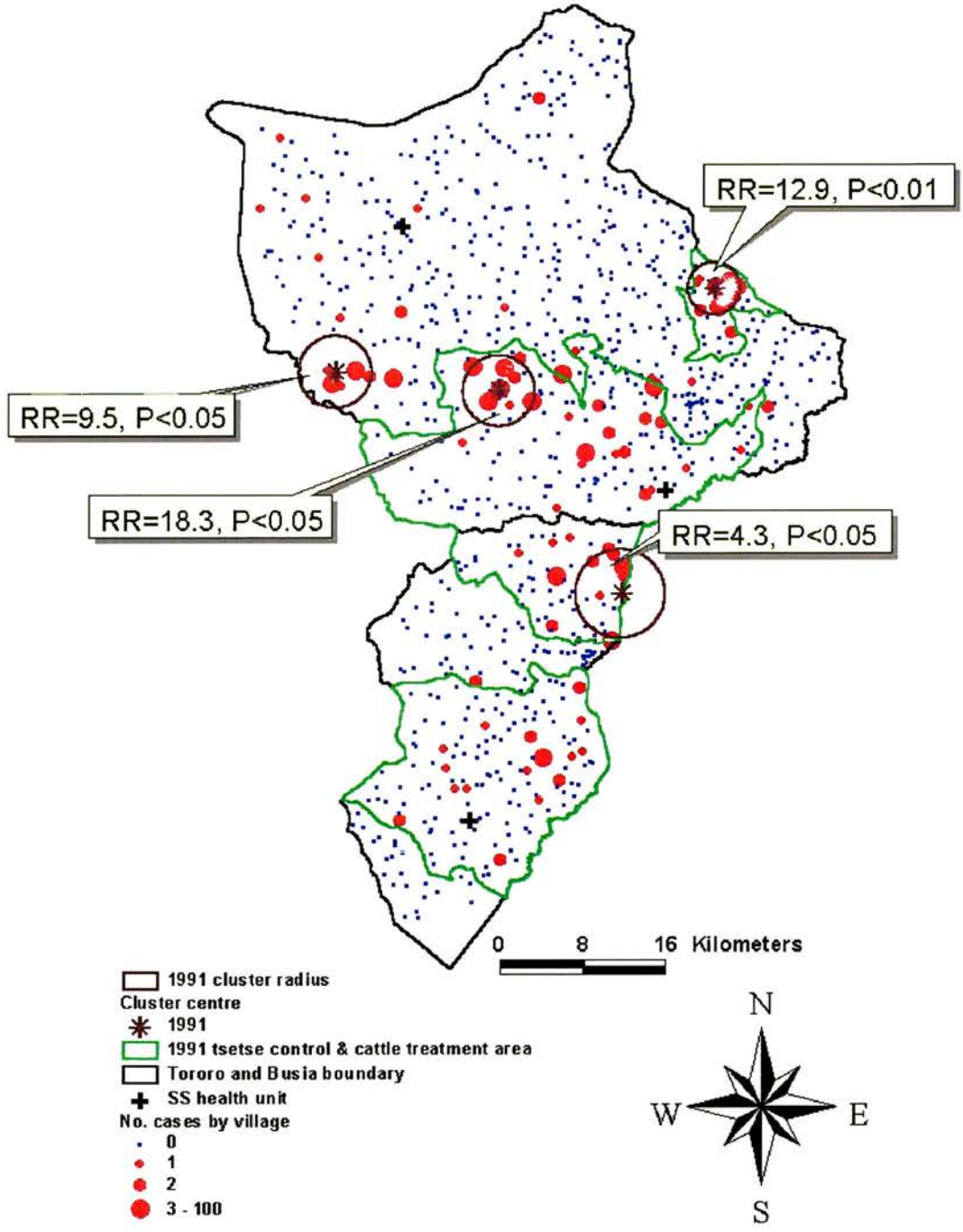


Figure 6.7. Spatial distribution of sleeping sickness cases by village and of significant clusters in 1992
The relative risk (RR) of infection within the cluster and the area under control are shown.

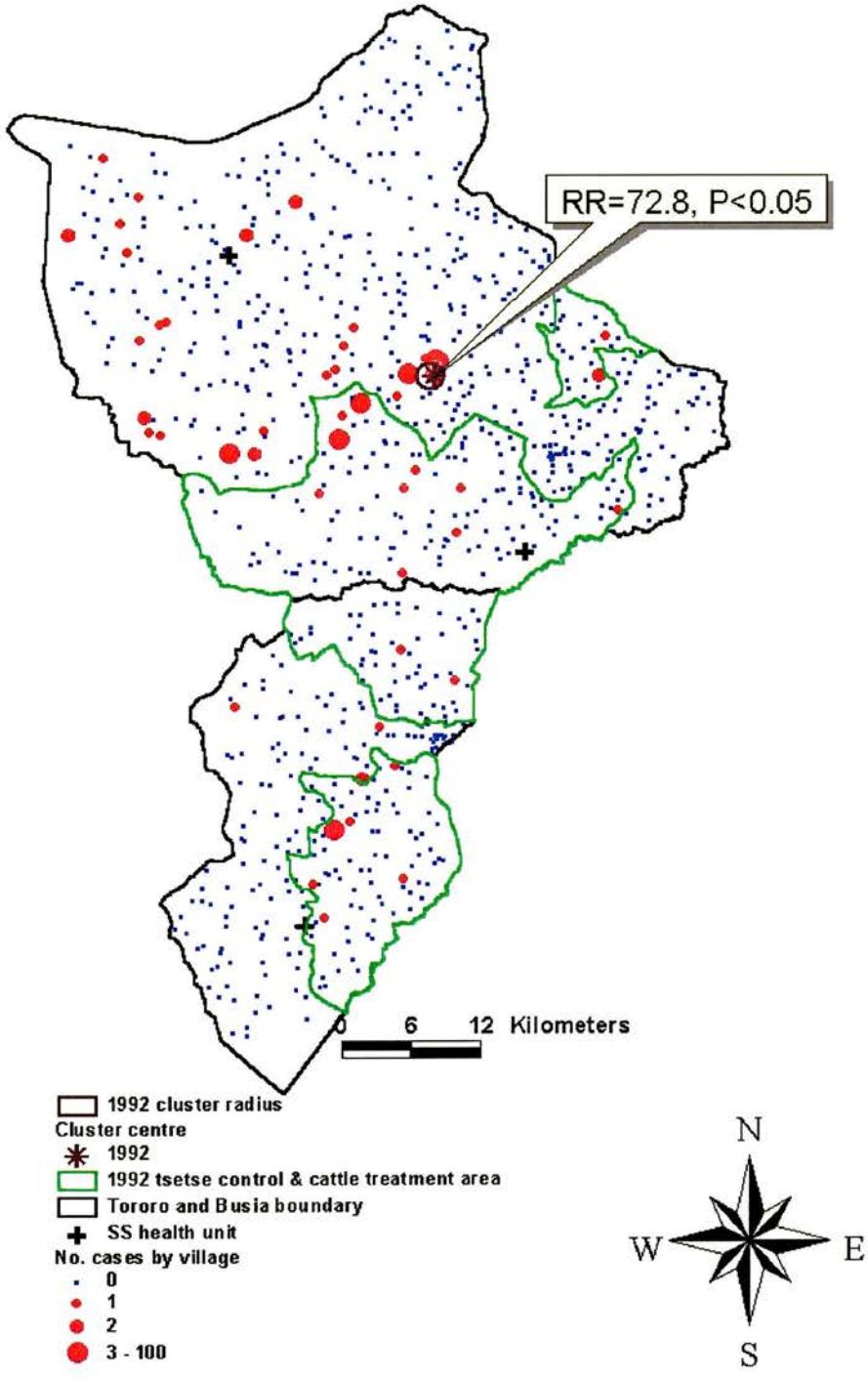


Figure 6.8. Spatial distribution of sleeping sickness cases by village and of significant clusters in 1993
The relative risk (RR) of infection within the cluster and the area under control are shown.

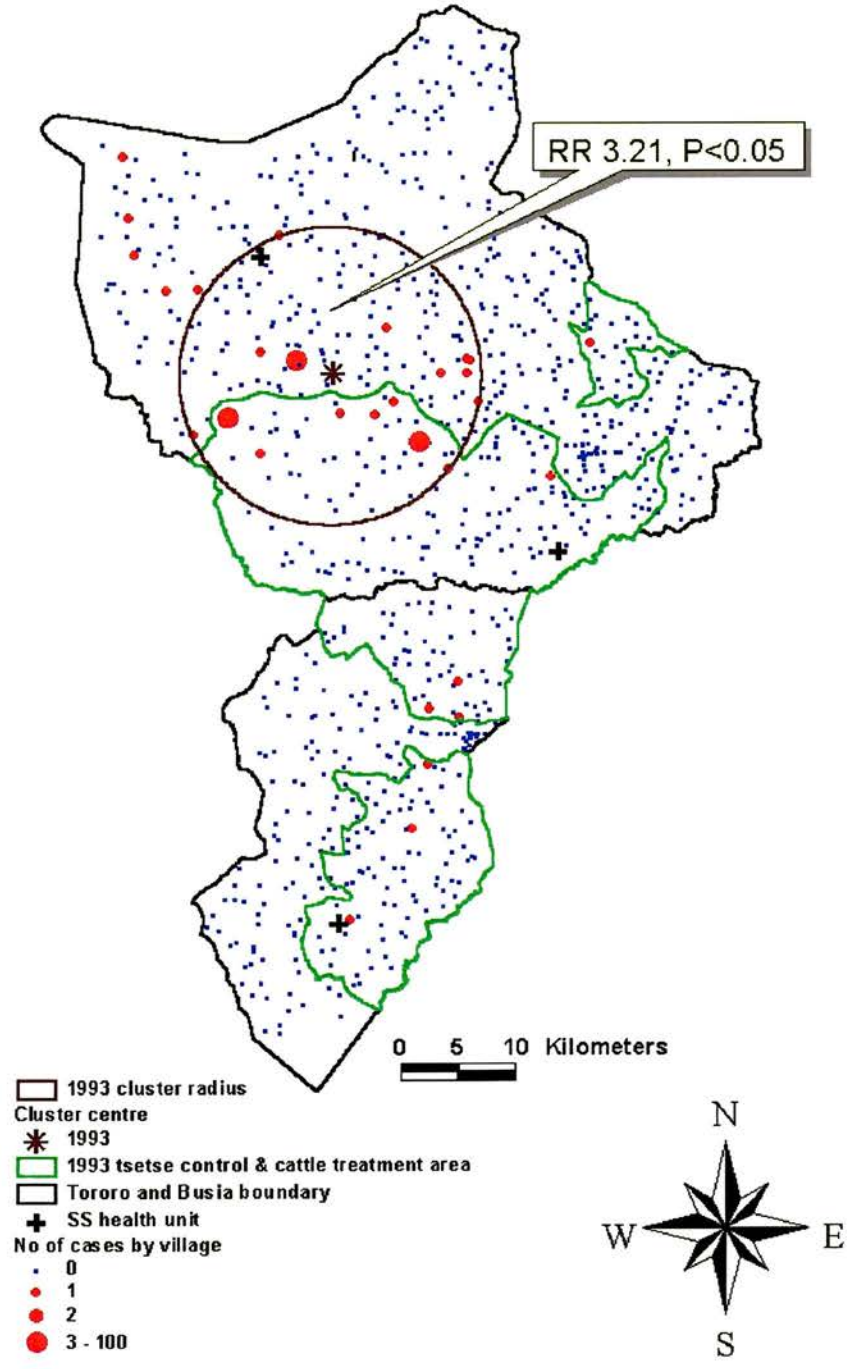


Figure 6.9. Spatial distribution of sleeping sickness cases by village and of significant clusters in 1994
The relative risk (RR) of infection within the cluster and the area under control are shown.

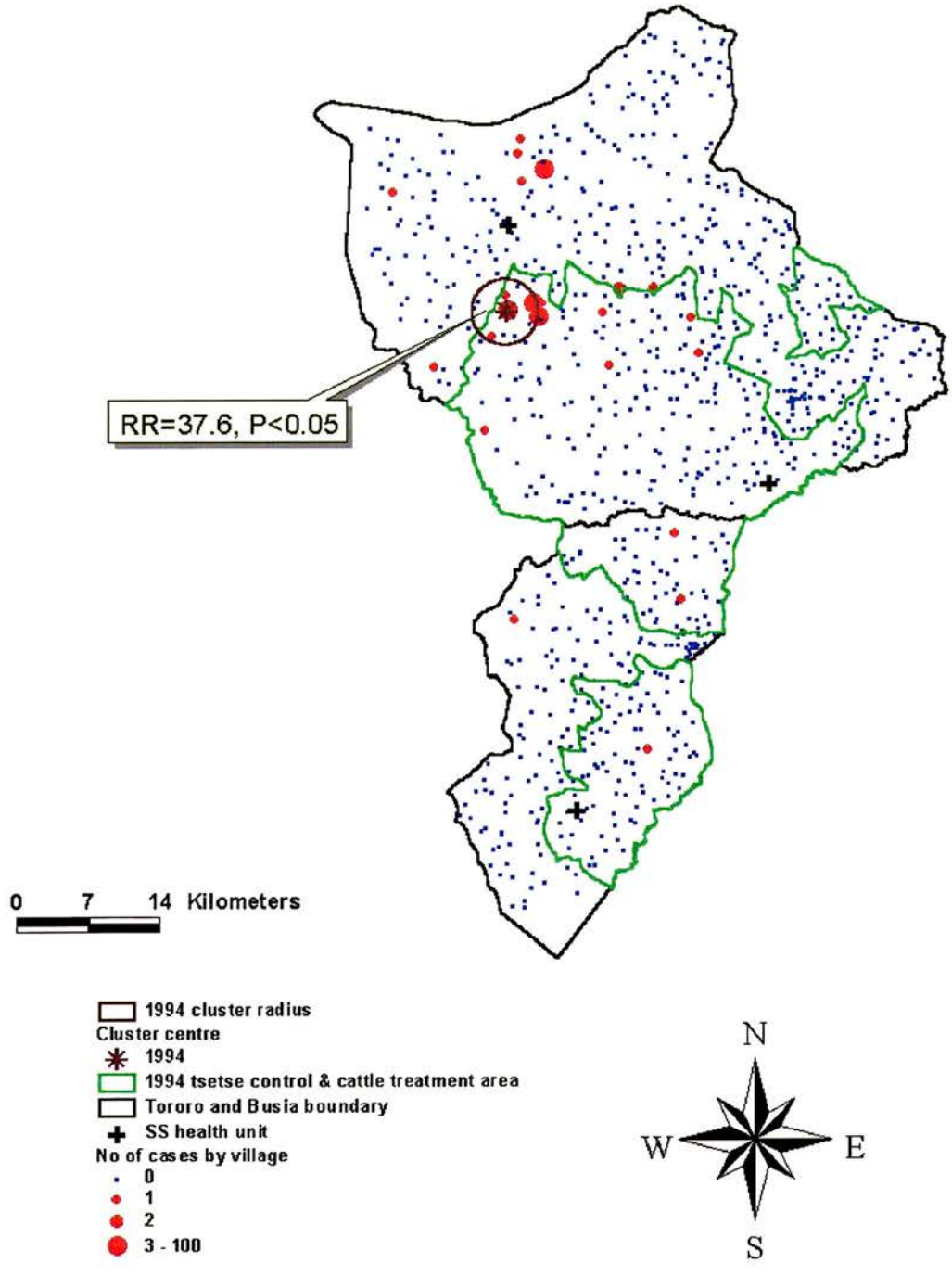


Figure 6.10. Spatial distribution of sleeping sickness cases by village and of significant clusters in 1995
The relative risk (RR) of infection within the cluster and the area under control are shown.

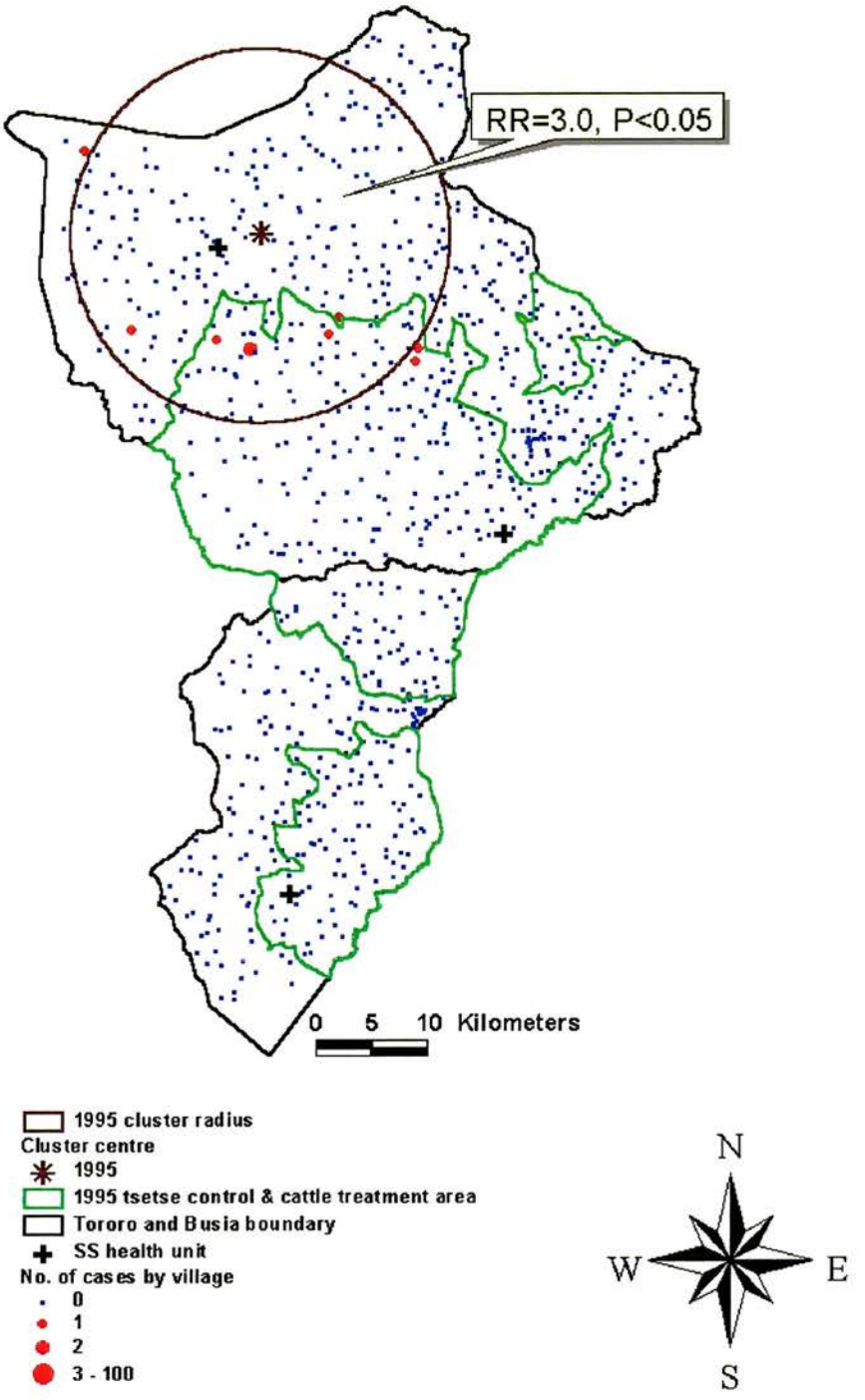


Figure 6.11. Spatial distribution of sleeping sickness cases by village and of significant clusters in 1996
The relative risk (RR) of infection within the cluster and the area under control are shown.

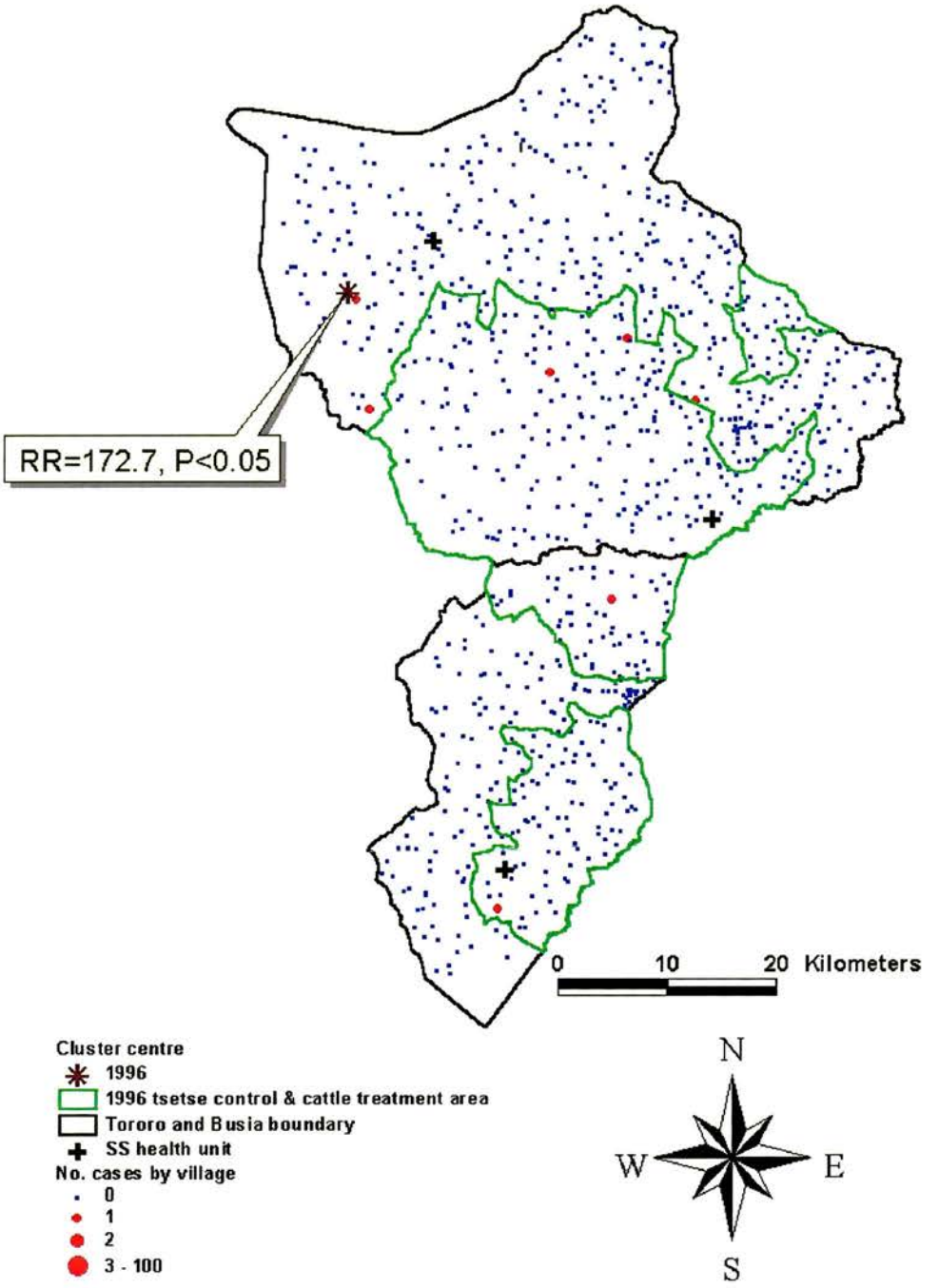


Figure 6.12. Spatial distribution of sleeping sickness cases by village and of significant clusters in 1997
The relative risk (RR) of infection within the cluster is shown.

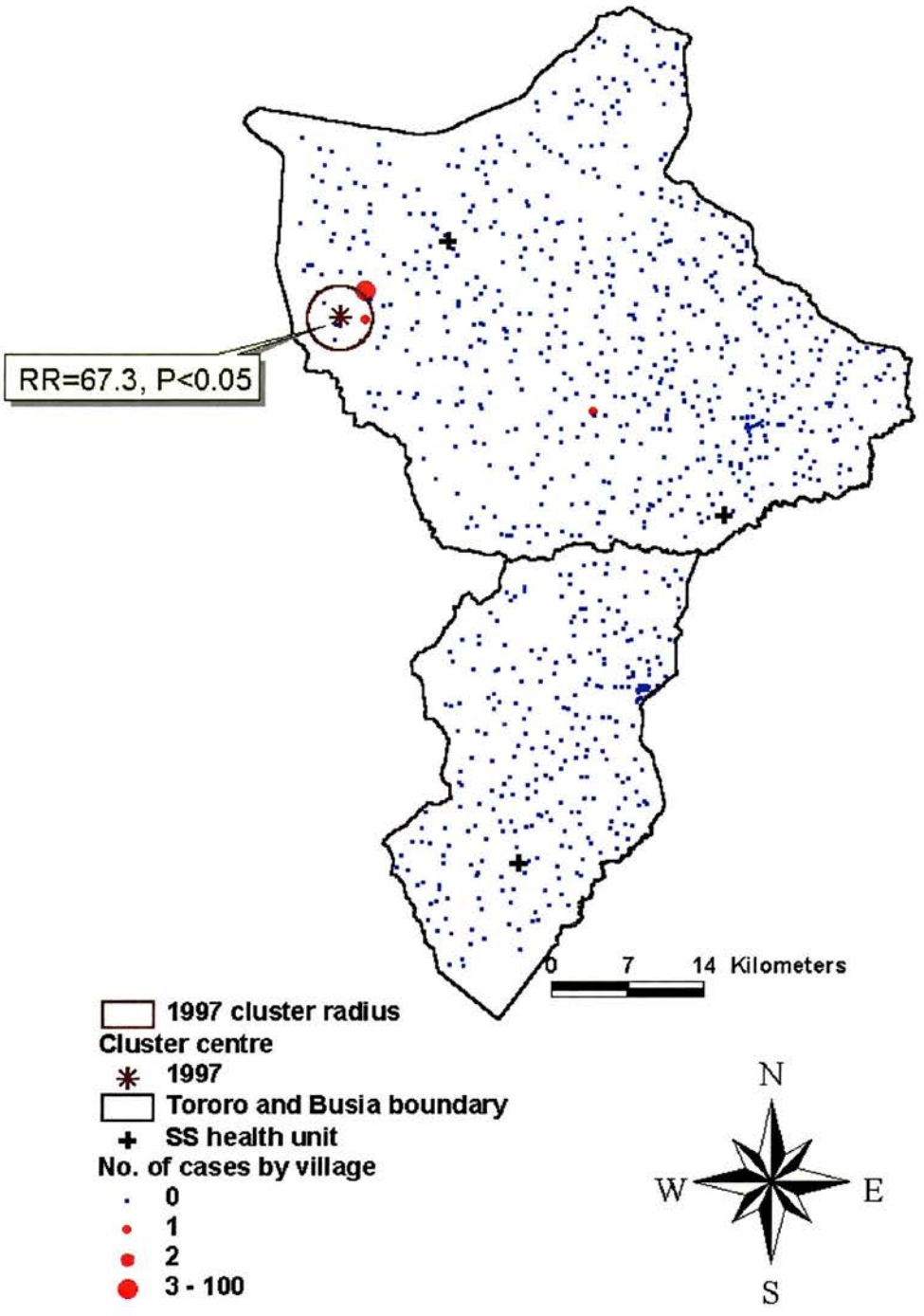


Figure 6.13. Spatial distribution of sleeping sickness cases by village and of significant clusters in 1998
The relative risk (RR) of infection within the cluster is shown.

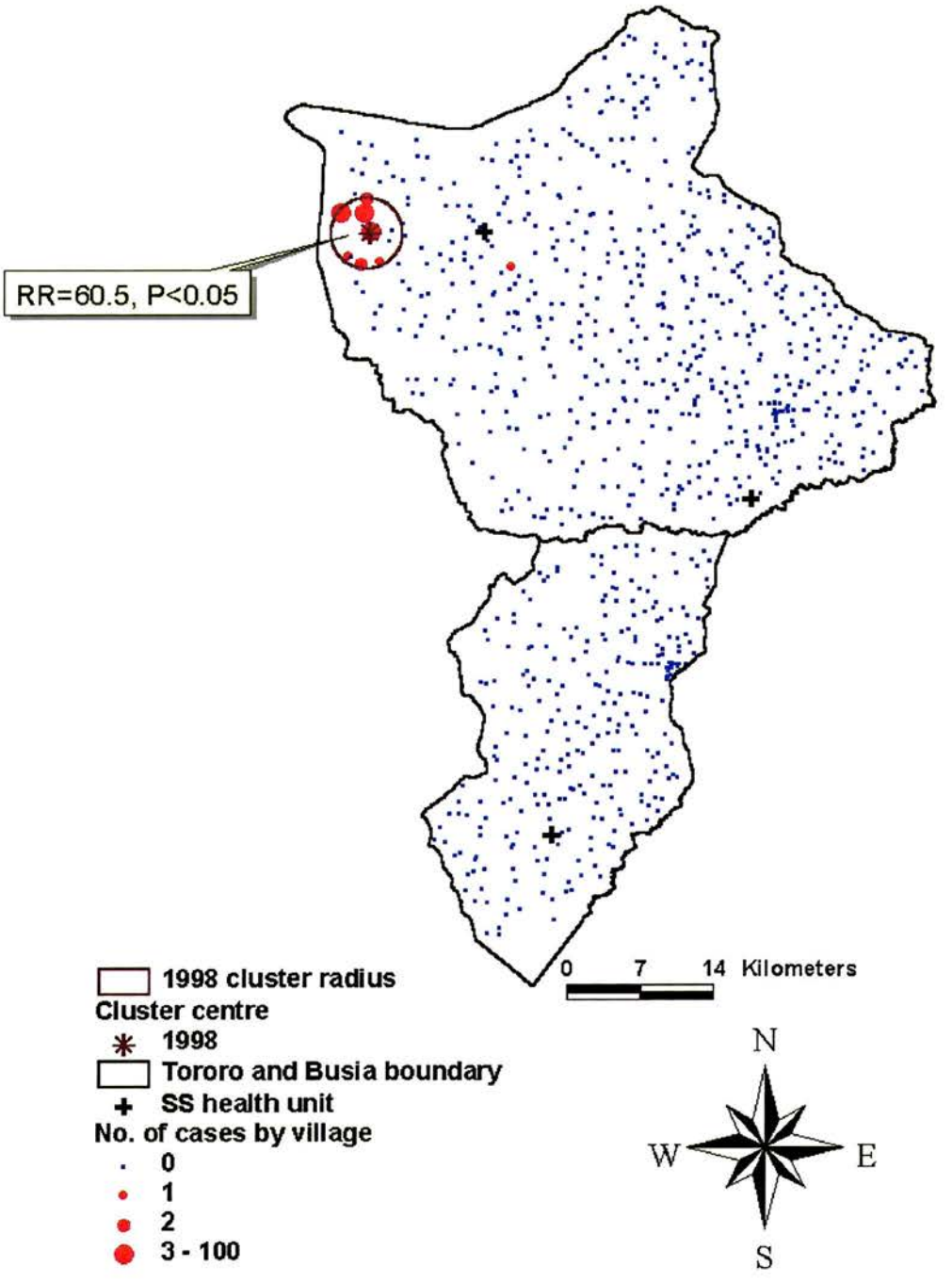


Figure 6.14. Spatial distribution of sleeping sickness cases by village and of significant clusters in 1999
The relative risk (RR) of infection within the cluster is shown.

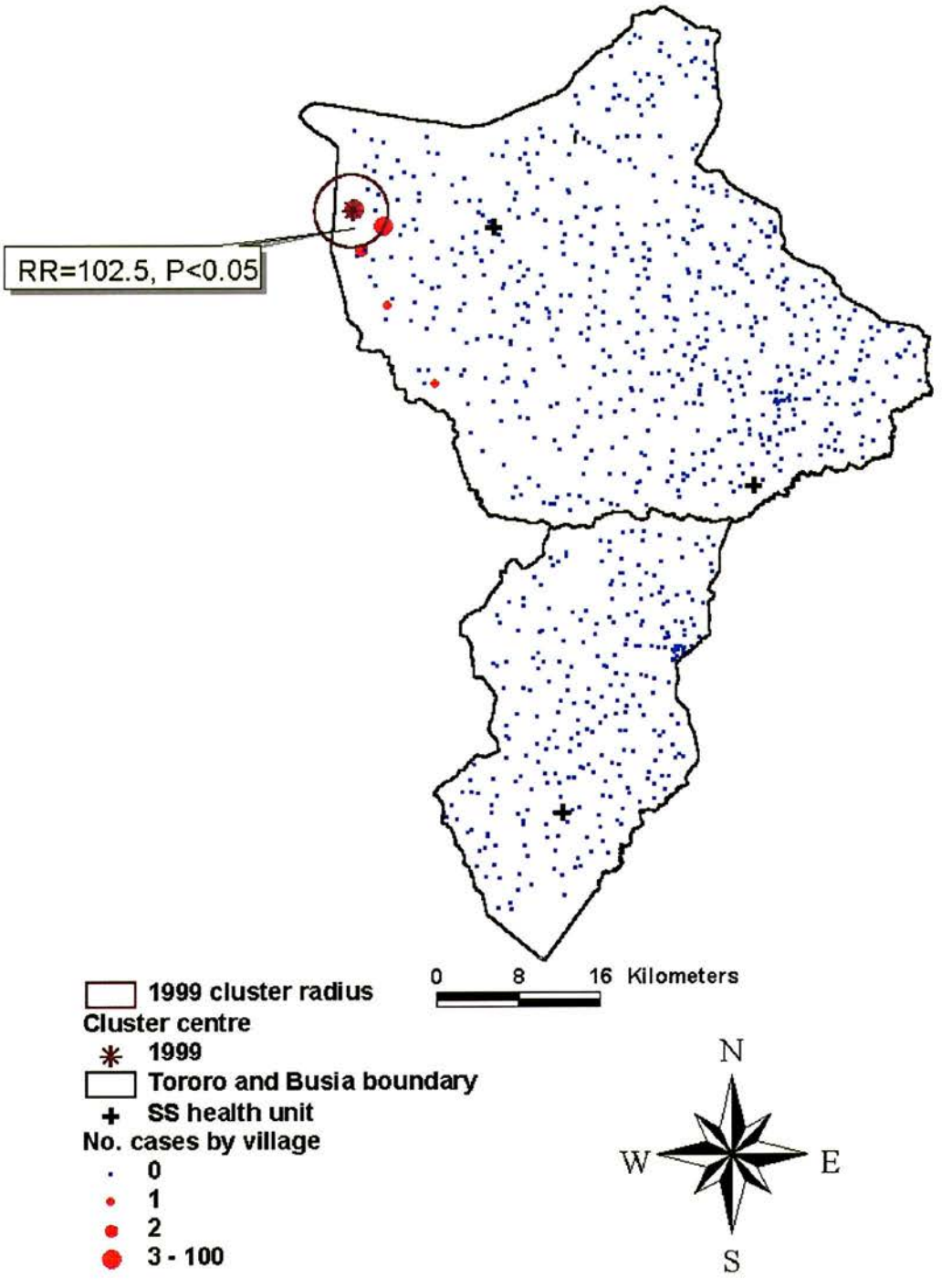


Figure 6.15. Spatial distribution of sleeping sickness cases by village and of significant clusters in 2000
The relative risk (RR) of infection within the cluster is shown.

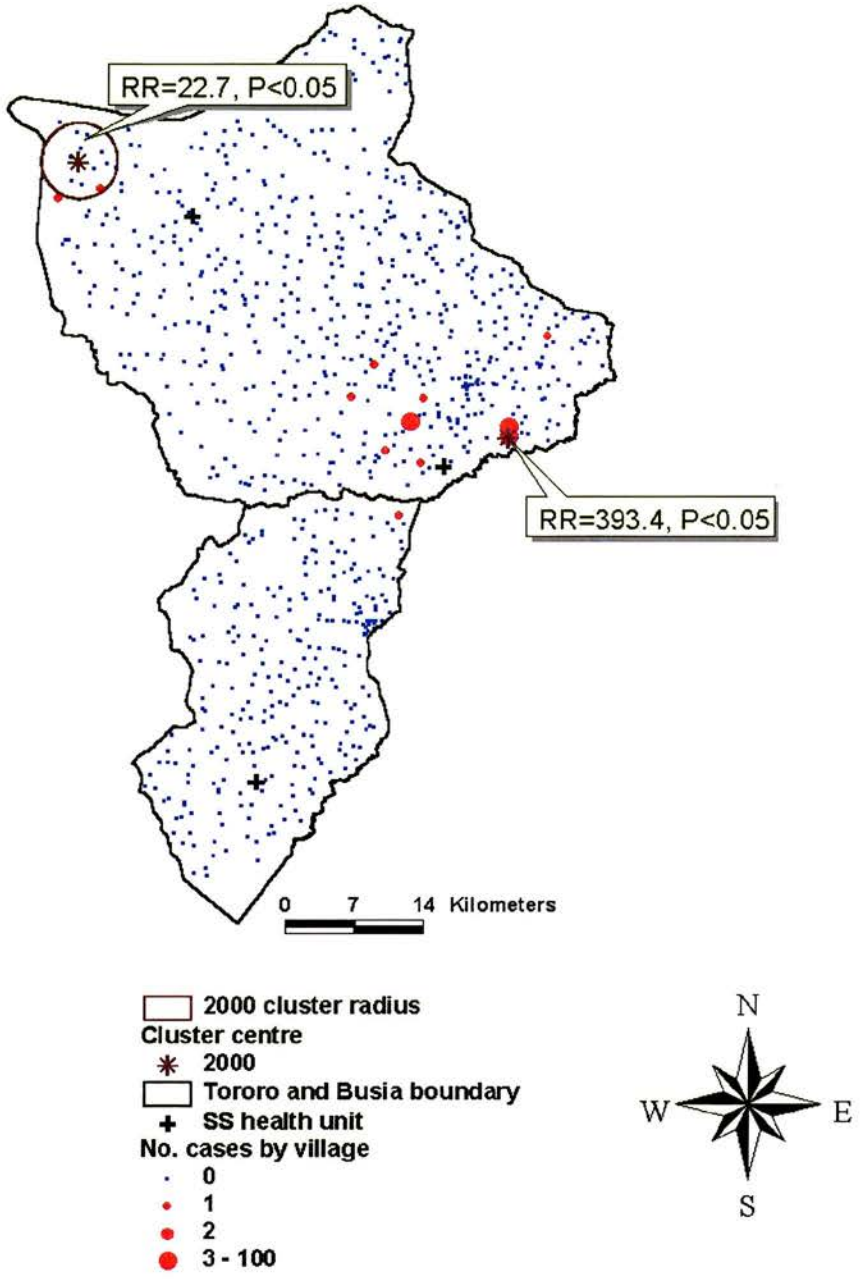


Figure 6.16. Spatial distribution of sleeping sickness cases by village and of significant clusters in 2001
The relative risk (RR) of infection within the cluster and the area under control are shown.

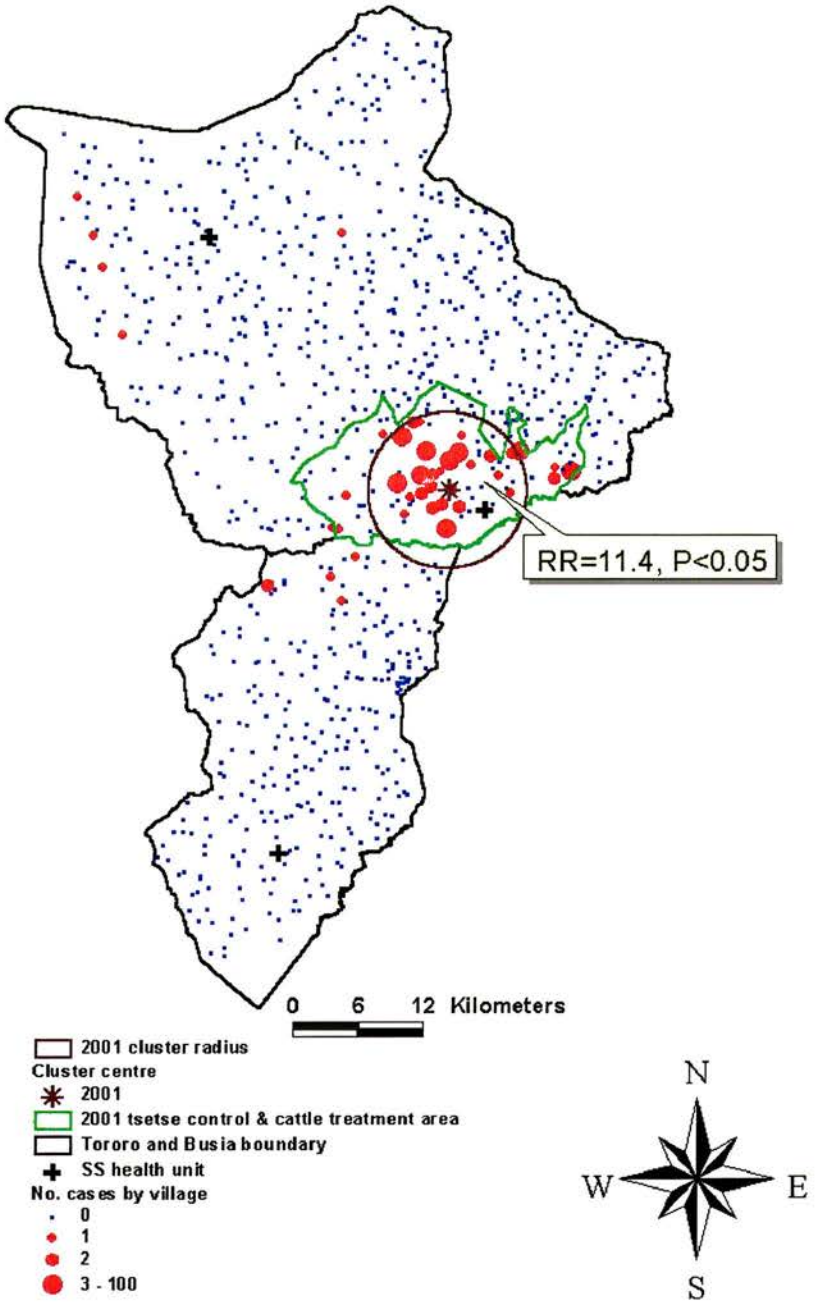
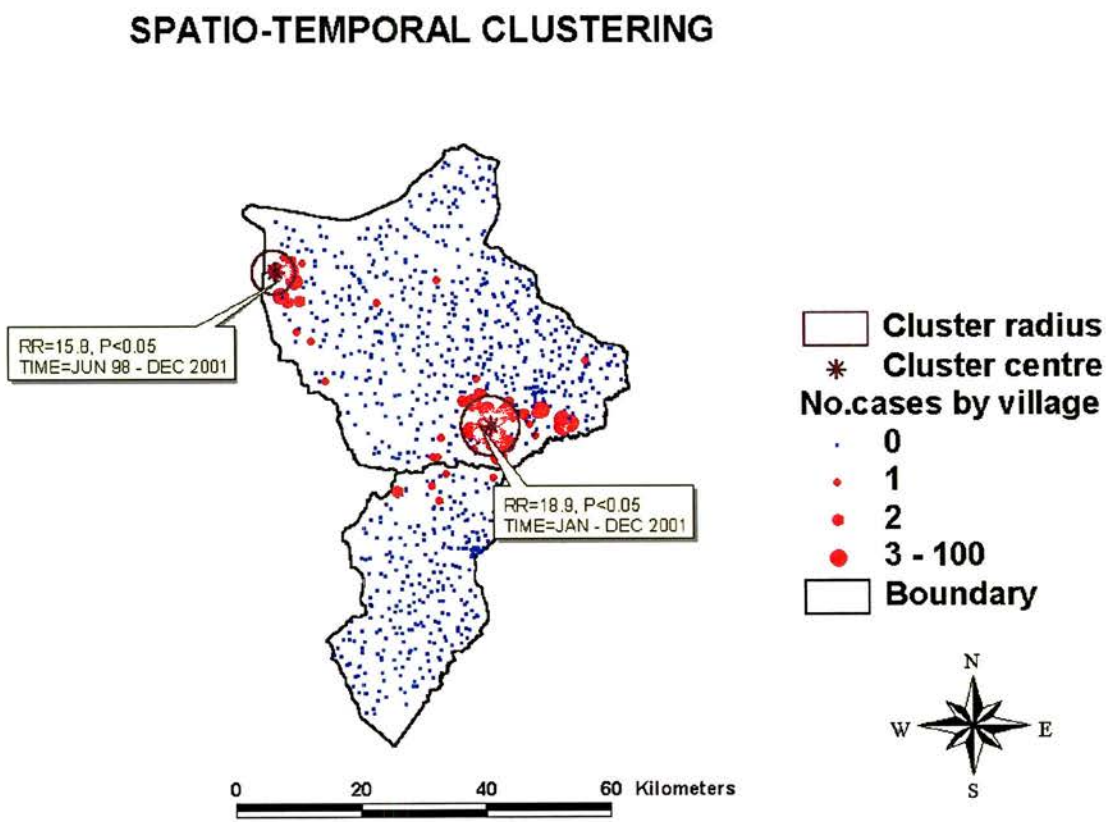


Figure 6.17. Spatio-temporal clustering of sleeping sickness from 1987 to 2001.
Significant spatio-temporal clustering occurred only between June 1998 and the year 2001 although there was annual spatial clustering each year.



6.4.3. Lengths of occurrence of sleeping sickness in villages with or without control

176 (61%) of the villages that reported sleeping sickness did so for one year, 216 (75%) for within a maximum of two consecutive years between 1987 and 1999 (Figure 6.18). One village reported sleeping sickness for 6 consecutive years and was in an area where there was no tsetse control intervention. During the same period, 288 villages reported sleeping sickness cases. Out of the 288 villages, 91 (32%) reported only one case of sleeping sickness during the period under review (Figure 6.19). Three villages reported over 35 cases while 27 villages reported more than 10 cases. Figures 6.20-6.24 are graphs of trends of numbers of sleeping sickness cases in villages that reported more than 10 sleeping sickness cases. The reduction in number of cases was greater and quicker in villages where tsetse control was applied when compared to where there was no tsetse control and the disease resurged earlier in areas where there was no control at all (Figures 6.20 to 6.26). Figures 6.2 to 6.16 are maps showing the spatial distribution of sleeping sickness cases by village, of significant clusters and areas of application of control. These figures show that villages where no tsetse control intervention was applied continued to report sleeping sickness until 1999 while all villages where tsetse control was applied ceased to report sleeping sickness after 1994. In addition, villages where tsetse control was applied did not report sleeping sickness for more than 4 years post-application of the control (Figure 6.26).

Figure 6.18. Frequency of villages by number of consecutive years of reported cases by village in Tororo and Busia districts, 1987-1999

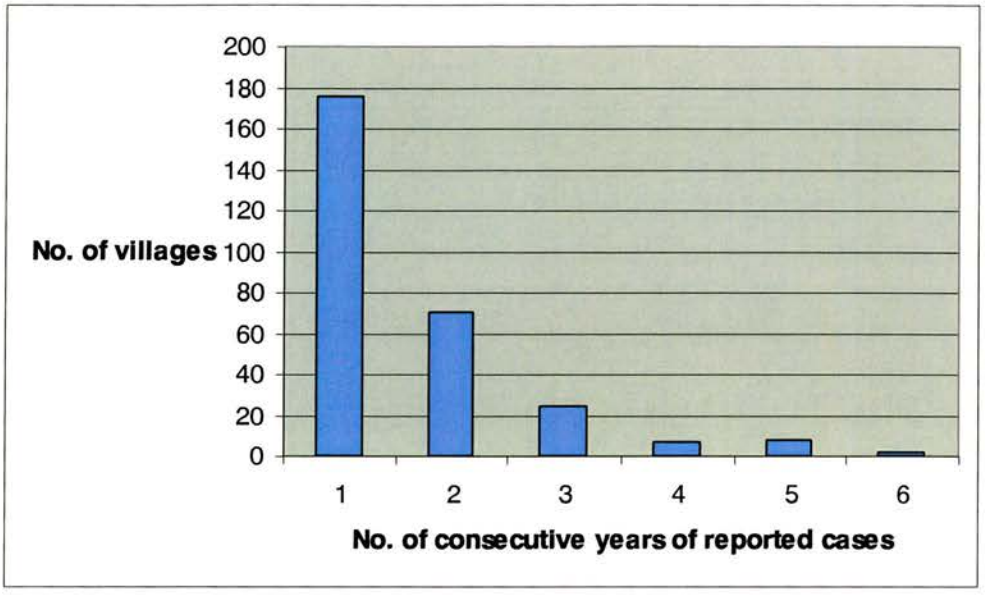


Figure 6.19. Frequency of villages by number of cases reported from 1987 to 1999.

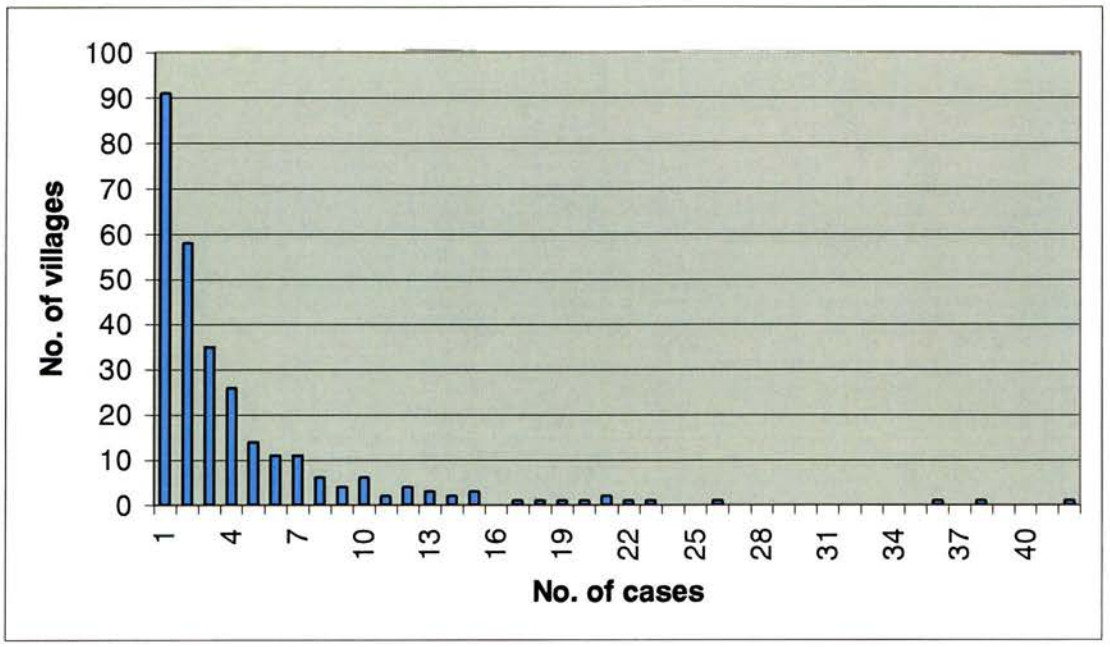


Figure 6.20. Number of SS cases by year and types of tsetse control in villages that reported more than 10 cases (Mulanga, Bugerere, Malangha, Bugwera, Amonikakine and Atapara)

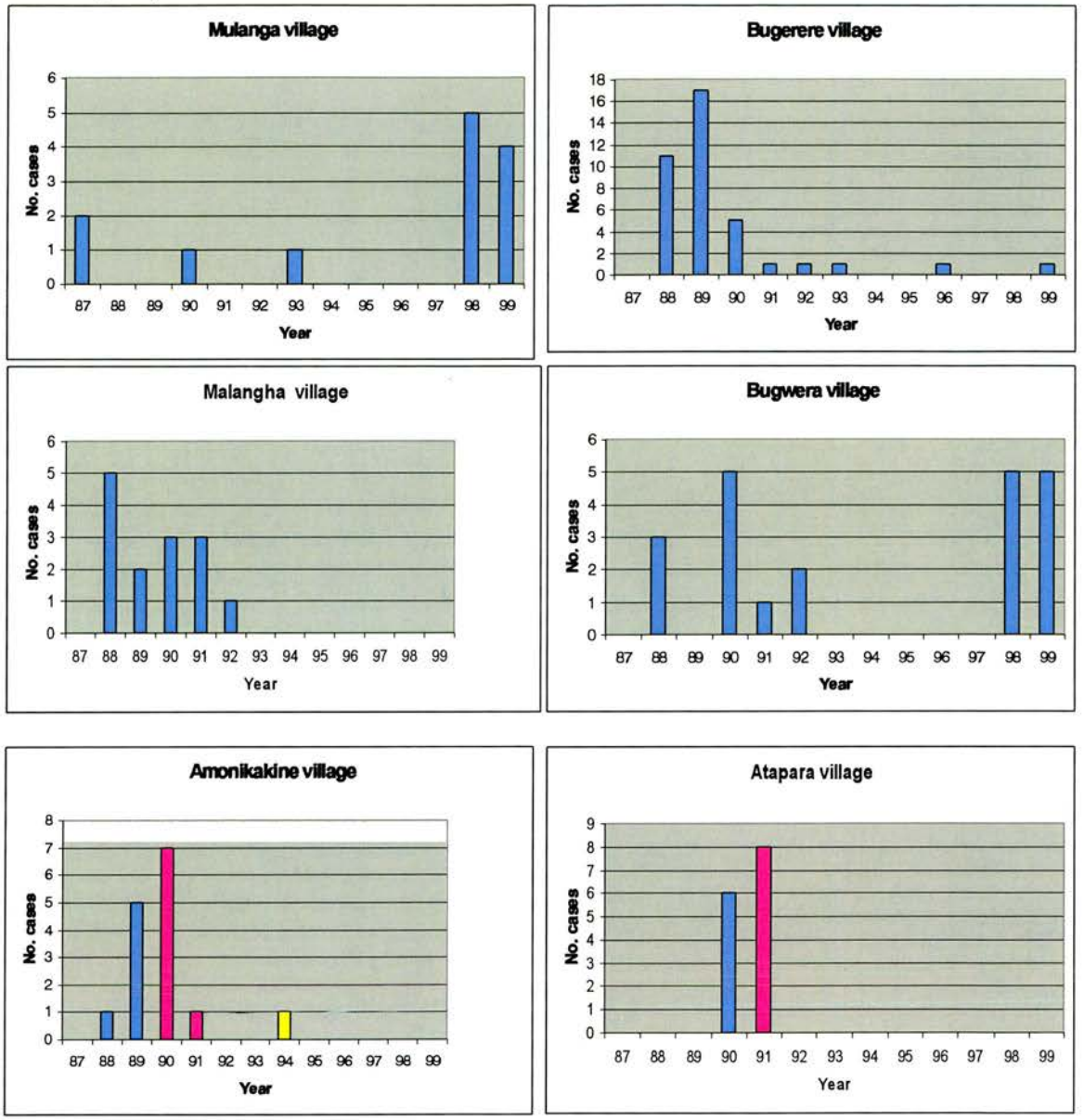
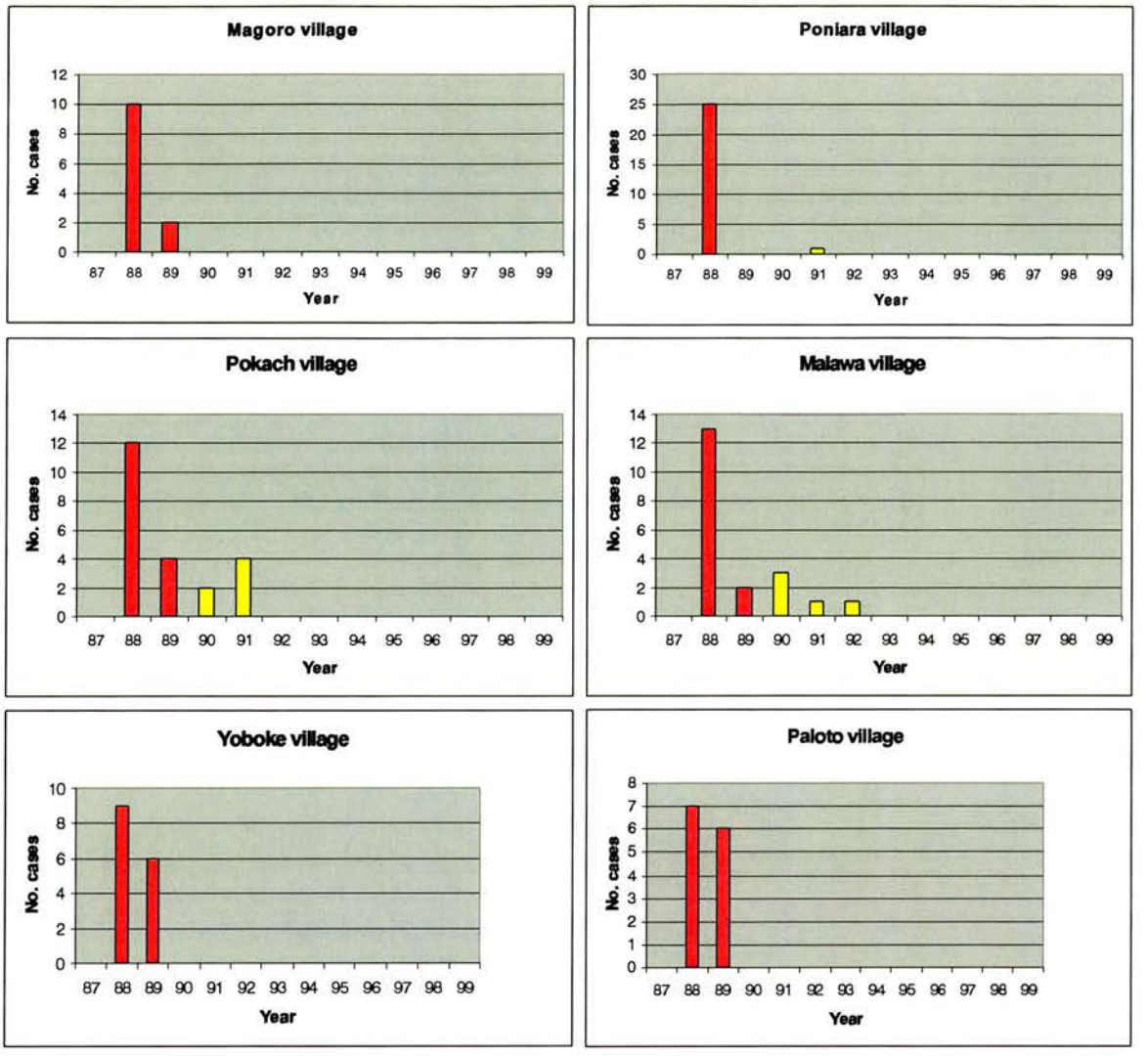


Figure 6.21. Number of SS cases by year and types of tsetse control in villages that reported more than 10 cases (Magoro, Poniara, Pokach, Malawa, Yoboke and Paloto)



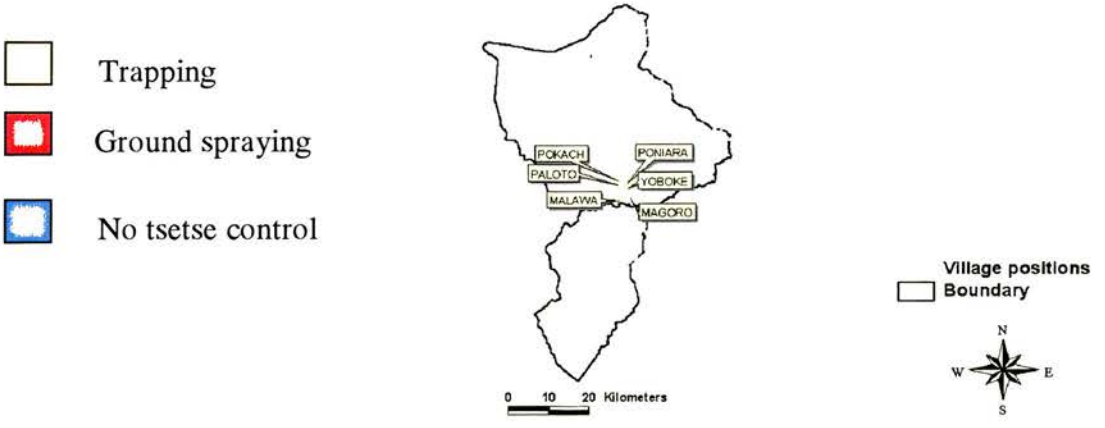
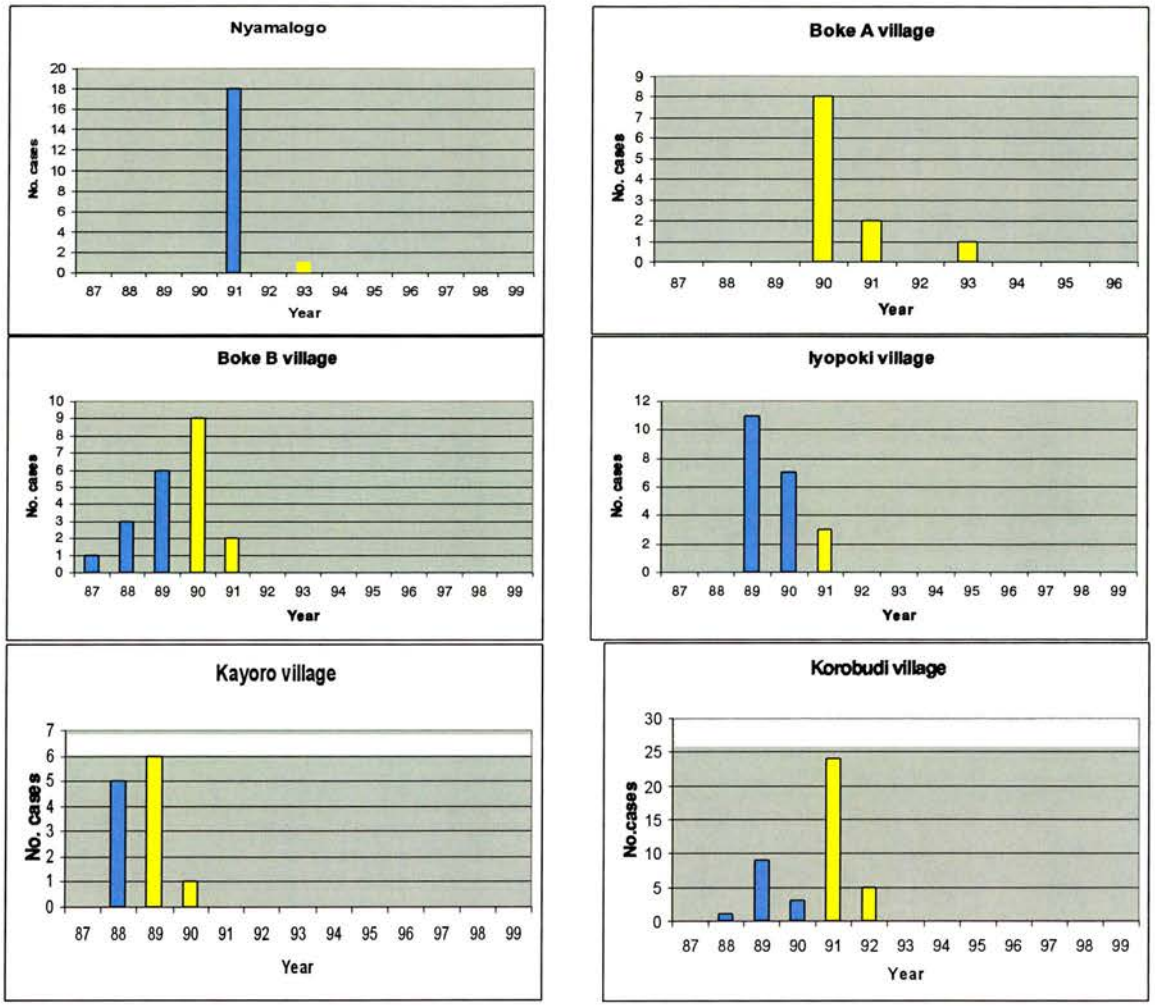


Figure 6.22. Number of SS cases by year and types of tsetse control in villages that reported more than 10 cases (Nyamalogo, Boke A, Boke B, Iyopoki, Kayoro and Korobudi



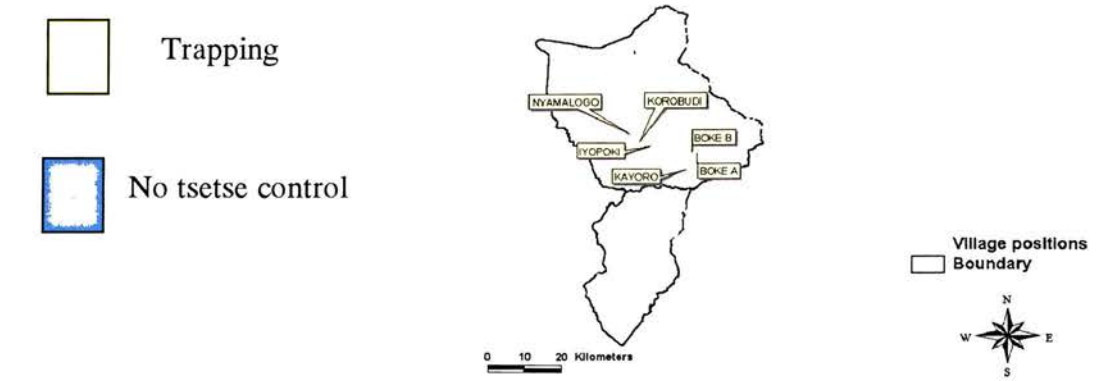


Figure 6.23. Number of SS cases by year and types of tsetse control in villages that reported more than 10 cases (Pajwenda, Kisote, Busabi, Liyonga-Wagunga, Kasipodo and Ayago B)

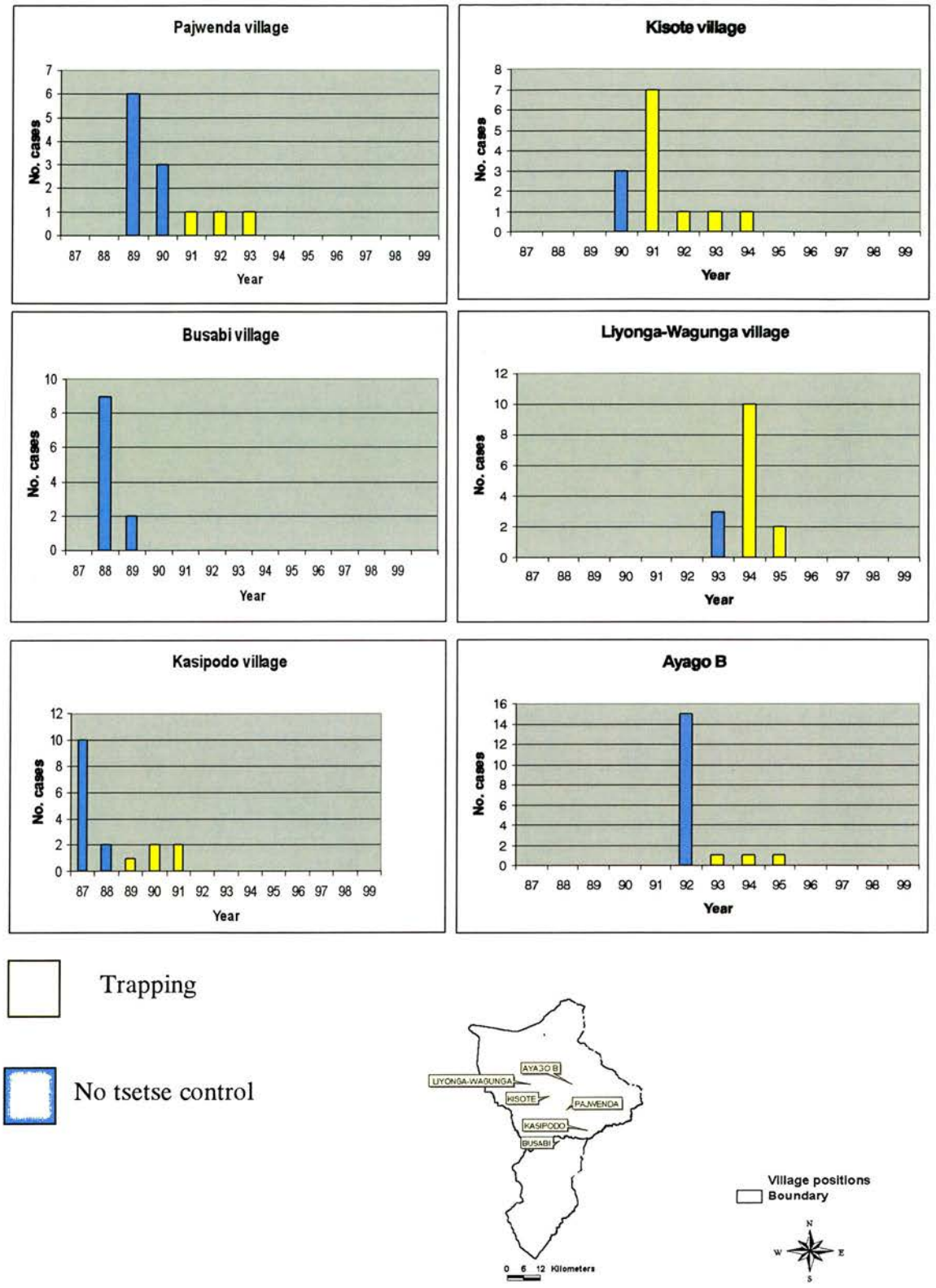
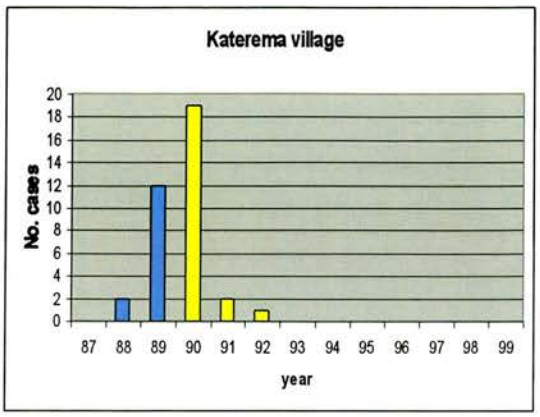
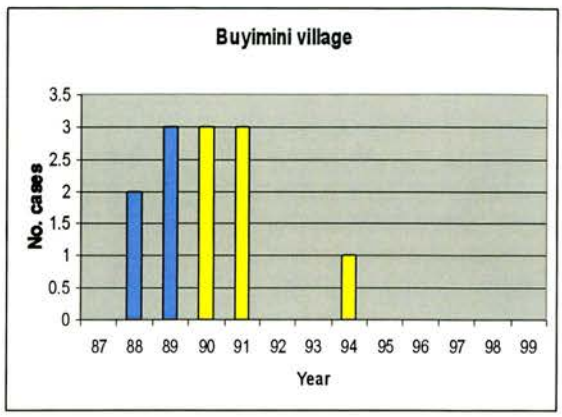


Figure 6.24. Number of SS cases by year and types of tsetse control in villages that reported more than 10 cases (Katerema B and Buyimini)





Trapping

No tsetse control

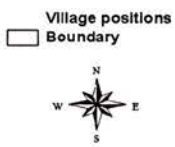


Figure 6.25. Total number of sleeping sickness cases by year and type of tsetse control in villages that reported more than 10 cases

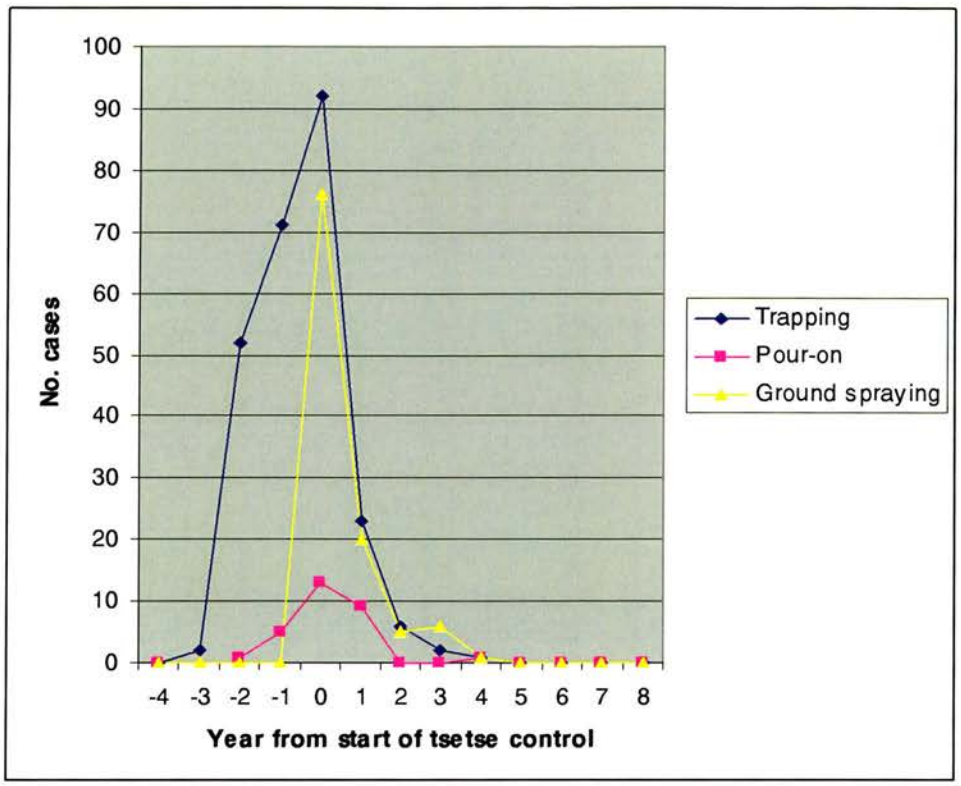
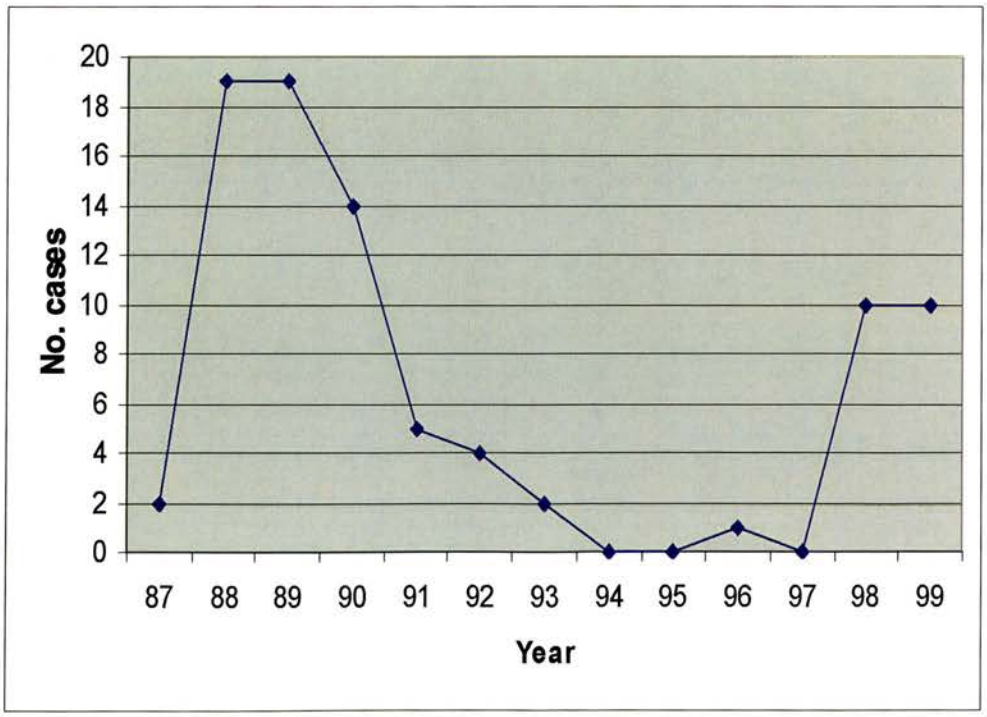


Figure 6.26. Total number of sleeping sickness cases by year in villages that reported more than 10 cases but had no tsetse control



6.5 Discussion

This study aimed at contributing to a better comprehension of the trends of *T. b. rhodesiense* sleeping sickness by analysing the spatial and temporal distribution in Tororo and Busia districts of 1316 cases of the disease in the period 1987 to 2001. The datasets used in this study are based mainly on passive detection of the cases. Although, they may not estimate the true incidence of the disease in Tororo and Busia districts, they are useful in giving an indication of infection trends and an estimate of the efforts necessary to control sleeping sickness and can reveal changing geographical patterns of the disease.

The annual number of sleeping sickness cases in Tororo and Busia districts varied from year to year over the 15 years but generally, there were peaks at the beginning (1988 to 1992) and end of the period (2001) separated by a period with relatively low numbers. Although intervention did appear to reduce the incidence of sleeping sickness, similar but less dramatic reductions were observed in areas where there was no tsetse control intervention at all. However, areas where there were not tsetse control operations had a resurgence of the disease earlier than where there was no control at all suggesting a longer-term benefit of tsetse control. Similarly, areas where there had been under tsetse control began reporting sleeping sickness once the control operations ceased but not for several years. There is an association between the resurgence of sleeping sickness and the cessation of donor-funded control of the disease (Lancien *et al.*, 1990, Lancien, 1991; Magona *et al.*, 1998). A sleeping sickness control project funded by the European Economic Community (now known as European Union) and the Organization of African Unity Inter African Bureau for Animal Resources (OAU/IBAR) was in place from 1988 to 1997. This emphasises the need for commitment of resources to by endemic governments and development sleeping sickness strategies that are less donor dependent, i.e., affordable, acceptable and effective. Currently, the major control strategies for sleeping sickness in Uganda are case finding and treatment, tsetse control using insecticide impregnated traps and live-baits and treatment of cattle with trypanocidal drugs because livestock have been

proven to be an important reservoir of the disease (Onyango *et al.*, 1965; Hide *et al.*, 1994; Fèvre *et al.*, 2001). These activities are once again being supported by a European Union funded project called "Farming in Tsetse Control Areas of Eastern Africa (FITCA). Studies examining ways of encouraging communities to participate in these control strategies are necessary to ensure continuity in the absence of donor supported control activities. In Chapter 6, opportunities for involving communities in case finding, control of the cattle sleeping sickness reservoir and vector control through use of live baits (insecticides applied to cattle) are determined. During this epidemic, selective treatment of cattle based on microscopy for trypanosomes was carried out. There is now evidence that traditional parasitological methods by microscopy have very low sensitivity when compared to polymerase chain reaction (PCR) testing (Picozzi *et al.*, 2002). This indicates that block treatment of all cattle may be justifiable after parasitological detection of trypanosomes in a small cross section of the cattle population. Block treatment may result in quicker control of sleeping sickness clusters.

The distribution of sleeping sickness shows significant clustering in all years from 1987 to 2001. It is apparent that sleeping sickness outbreaks rarely lasted longer than one year in any single village perhaps because sleeping sickness has a low basic reproductive rate (Rogers & Williams, 1993). However, in areas where sleeping sickness control intervention were not applied, the disease persisted in villages for much longer and significant clusters of sleeping sickness did develop, and tended to spread locally. Clustering would occur after an initial occurrence of a few isolated cases and before the initiation of a definite control programme for the affected areas emphasising the necessity of having a control programme that is timely responsive to the occurrence of even a single case. This also means that it is necessary to have sensitive disease surveillance structures to detect the disease occurrence at the earliest possible stage but complemented by timely responsive sleeping sickness control interventions. Tsetse control operations using impregnated traps are generally complex requiring a lot of planning and resources and this may explain the delays in action resulting in the clustering of sleeping sickness occurrence before any action

was taken. More rapid methods of intervention need to be applied to prevent consolidation and spread of the disease.

Most of the cases occurred around the basins of the rivers Osia and Malaba basins (Figure 4.1). However, the reporting effect of the proximity of a sleeping sickness hospital to these rivers must be considered. In Chapter 7, the distribution of villages that reported sleeping sickness during the period under review and those that did not is examined in relation to the distance to the main sleeping sickness hospital. It is possible that the clustering seen around the hospital may have been due to increased chance of diagnosis for patients in nearer villages. However, there were clusters observed elsewhere further away from the sleeping sickness diagnostic facilities. The place of residence at onset of illness of a patient was used to determine the affected villages because it was most reasonably the likely origin of infection since movement of people in this area is quite limited.

The predominance of villages reporting a few patients for only a short time suggests that cow-to-man transmission may be more important in eastern Uganda than man-to-man transmission. Cattle have been demonstrated to be an important reservoir of rhodesiense sleeping sickness and therefore, may play a major role in its spread (Onyango *et al.*, 1965; Maudlin *et al.*, 1990; Hide & Tait, 1991; Hide *et al.*, 1994). Using biochemical evidence of the magnitude of the sleeping sickness animal reservoir in cattle and from blood meal analyses, Maudlin *et al.* (1990) estimated that tsetse are 500 times more likely to feed on cattle than man (Hide *et al.*, 1996). Therefore, control by mass treatment of the animal reservoir may be a cost-effective measure in stopping the transmission of sleeping sickness. Selective treatment of livestock using trypanocides based on parasitological results was used but now there is evidence for the poor sensitivity of parasitological methods (Picozzi *et al.*, 2002) indicating that block treatment of cattle in instances of low parasitological prevalence by microscopy may be more beneficial. It is quite probable that block treatment would lead to longer disease free periods since the presence of the vector without the parasite would not result in transmission.

In conclusion, spatial clustering was characteristic of sleeping sickness occurrence in Tororo and Busia districts between 1987 and 2001, presenting an opportunity for targeted application of sleeping sickness control measures. Tsetse control interventions reduced the duration of persistence of sleeping sickness clusters where it was applied, but was often put in place after the development of significant clustering indicating the need for more timely responsive action. Sleeping sickness recurred in the same areas after the cessation of donor supported control and therefore there appears to be donor dependency of sleeping sickness control, probably because the current traditional approaches are expensive. A timely responsive, parasite targeted, sustainable strategy is therefore recommended. Ways of improving case detection and treatment and involving communities were examined in Chapters 4 and 5. The risk factors for the spatial distribution of sleeping sickness villages and clusters are examined in Chapter 7.

Chapter 7 Remote sensing as a surveillance tool to identify villages at high risk for sleeping sickness

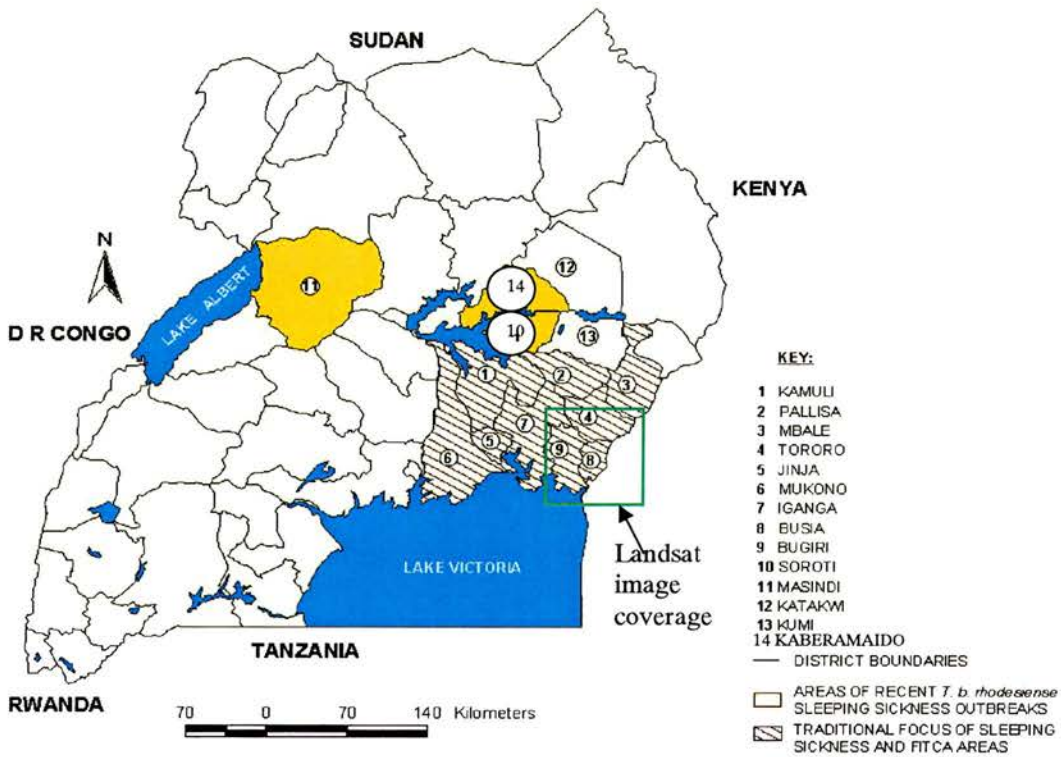
7.1 Summary

Sleeping sickness is a vector-borne disease whose distribution is highly influenced by tsetse habitat and availability of mammalian hosts. Geographic information systems (GIS) and remote sensing were used to identify villages at high risk for sleeping sickness as defined by reported incidence. Landsat Thematic Mapper ™ satellite data were digitally processed to obtain a map of land cover, and a tasseled cap transformation (Tcap) carried out to determine indices of wetness and greenness. GIS functions were used to determine the areas of land cover types and average wetness and greenness within 2 km radii of 747 villages where sleeping sickness incidence had been calculated. The relationships between sleeping sickness presence and absence and land cover types or Tcap indices for greenness and wetness were examined using backward binary logistic regression. The analysis found proximity to wetlands, low population density, more wetness more cropland and less grassland to be predictive of sleeping sickness presence with distance to the sleeping sickness hospital as an important confounder These findings demonstrate the potential of remote sensing and GIS to characterise village-scale risk of sleeping sickness in endemic regions. This approach may be particularly useful where sleeping sickness occurs in the presence of poor surveillance capabilities resulting in no intervention at all.

7.2 Introduction

Sleeping sickness tends to occur focally. Although these foci tend to recur, there is now evidence of expansion of existing ones (Fèvre *et al.*, 2001). For instance, in eastern Uganda, sleeping sickness is now reported north of the known rhodesiense focus (Figure 7.1). The movement of infected cattle from areas endemic for sleeping sickness has been implicated in the cause of this new outbreak in an area where sleeping sickness was not known to be endemic (Fèvre *et al.*, 2001) but where tsetse were prevalent. These movements of cattle brought the sleeping sickness disease agent, *Trypanosoma brucei rhodesiense*, into contact with the vector, *Glossina fuscipes fuscipes*. The traditional interventions to control sleeping sickness are case finding and treatment, tsetse control and treatment of the livestock reservoir of the disease. In Uganda, these interventions currently being are carried out at sub-national levels by the national sleeping sickness control programmes supported by the European Union funded projected "Farming in Tsetse Control Areas of Eastern Africa (FITCA)". Therefore, to prevent further spread of the disease, it is important to determine accurately areas of potential risk for effective targeting of disease prevention efforts.

Figure 7.1. Map of sleeping sickness endemic districts of Uganda showing the location of Tororo and Busia districts and the coverage of the Landsat satellite image



Tsetse densities and infection rates are major entomological determinants of sleeping sickness transmission risk (WHO, 1986). Tsetse maps have not been updated in recent years. The last tsetse maps of Uganda were produced by Ford and Katondo in 1970 (Gouteux, 1990). Tsetse distribution maps, though very necessary to delineate areas of potential risk, are expensive to produce through ground-based approaches of vector surveys. *G. f. fuscipes* is a riverine tsetse species whose distribution and density varies with vegetation composition, as it relates to habitat suitability (Baldry, 1980). For example, riverine areas that have been depleted of trees and shrubs do not provide favourable environments for survival of tsetse and their larvae. Similarly, the absence of ungulate hosts may not favour the presence of tsetse. These relationships mean that where sleeping sickness is endemic, land cover typology may be a useful indicator of sleeping sickness risk in villages.

Land cover and vegetation indices can be mapped over large areas using remotely sensed data to provide an integrated picture of the distribution that is often difficult to appreciate from the ground. Land cover corresponds to a bio-physical description of the earth's surface. It is that which overlays or currently covers the ground. This description allows bio-physical categories to be distinguished e.g. areas of vegetation, bare soil, hard surfaces and wet areas. Previous studies have used satellite-based remote sensing data and geographic information systems (GIS) to identify and map vector-borne and other diseases' habitats for rift valley fever, tick borne encephalitis, schistosomiasis and helminth infections (Linthicum, 1987; Daniel & Kolar, 1990; Hugh-Jones, 1989; Hugh-Jones *et al.*, 1992; Pope *et al.*, 1992; Abdel-Rahman *et al.*, 1997; Brooker *et al.*, 2000a; Brooker *et al.*, 2002). There have been some studies exploring remotely sensed environmental factors that may be associated with tsetse and trypanosomiasis distribution (Rogers, 1991; Rogers & Randolph, 1991; Rogers & Williams, 1993; Kitron *et al.*, 1996; Robinson *et al.*, 1997). Rogers & Randolph (1991) have shown that the distribution and abundance of tsetse flies can be related to Normalised Difference Vegetation Indices (NDVIs) (Tucker *et al.*, 1985). The NDVI is one of the most common vegetation indices derived from remotely sensed data and is computed by the product of two electromagnetic

wavelengths (near infrared)/near infrared + red. Maps showing the vegetation of Africa (Tucker *et al.*, 1985) have been produced using NDVIs. Certain land cover types may be of greater public health importance due to activities of man and abundance of tsetse per se may not necessary mean potential human-vector contact. Therefore, the use of disease distribution as an outcome in the studies of remote sensed data may provide additional information to what is obtainable from tsetse distribution.

Remote sensed data is obtained from satellite images. The Landsat satellite uses a thematic mapping tool to collect electromagnetic radiation reflected off the surface of the earth, hence its name, Landsat Thematic Mapper ™ (http://landsat.gsfc.nasa.gov). The most recent satellite, Landsat 7, was launched on the 15th April 1999 and uses an enhanced thematic mapper (ETM). The thematic mapper collects the data separately but simultaneously in 9 wavelength bands for discrimination of landscape features allowing for categorisation of land into its use. There are two techniques that can be used to achieve this function. They are called the unsupervised and the supervised land classifications (ERDAS Field Guide, 1995). In unsupervised land classification, the software e.g. ERDAS Imagine (ERDAS Field Guide, 1995) selects the classes on its own while in supervised classification, the user guides image processing software in selecting classes. Supervised classification is carried out on an unsupervised classified image.

Tasseled cap transformation is another method of enhancing spectral information content of Landsat ™ data (Lillesand & Kiefer, 1987). The tasseled cap index relates TM bands (1-5 and 7) to measures of vegetation (greenness), soil (brightness) and the relationship of soil and canopy moisture wetness.

Landsat Thematic Mapper data have a spatial resolution of 28.5m x 28.5m in most bands and therefore these data may be useful in characterising differences in key land cover and spectral indices differences among and within villages that are associated with highly local patterns in vector distribution and disease risk. If such differences could be observed, they might also be used to distinguish high from low risk villages

then this remote sensing/GIS approach could provide a means for detailed mapping of sleeping sickness areas within the districts.

7.3 Materials and methods

7.3.1 Study area

The study area was Tororo and Busia districts in eastern Uganda (Figure 7.1) that was within the area covered by the Landsat image used in the analysis (Section 7.3.3.1). They were 747 census villages that met this criterion each with an area of approximately 0.5 to 5 sq.km. Within the study area, many wetlands drain into Lakes Kyoga and Victoria. The climate has two distinct wet (September to November and March to May) and dry (June to August and December to February) seasons. There is growing land pressure with people encroaching on the swamps. The riverine species *G. f. fuscipes* is considered to be the main vector for sleeping sickness (Okoth, 1986). The human population belongs to four main ethnic groups; the Adhola, Teso, Samia and Nyole. There are mainly rural mixed farmers, growing subsistence crops and rearing small holdings of cattle.

7.3.2 Data collection

Central positions in settlements in villages were selected and geo-referenced using a geographical positioning system (GPS) by Garmin No. 12. Sleeping sickness data for all these villages for the years 1987 to 2001 were obtained from the Ministry of Health. The case data analysed in this study were obtained from the records of three treatment centres: LIRI Hospital, Lumino Health Centre and Busolwe Hospital. Populations of the villages were obtained from the 1991 national population census and projected by a population growth rate of 2.5% to the 1998 population. Wetland maps were obtained from the Ministry of Natural resources, Wetlands division.

7.3.3 Processing of satellite image

7.3.3.1 Satellite data preparation

The satellite image was processed using ERDAS Imagine version 8.4 and Arc View GIS version 3.2. The scene used was from the Landsat Enhanced Thematic Mapper (ETM), series 7 taken on the 13th February 2001, at day time, cloud cover 9%,

datum option WGS 84, map projection UTM zone 36S and geotiff format. The image comprised 9 spectral bands: 6 infra-red (resolution 28.5 m x 28.5 m); 2 thermal (resolution 57 m x 57 m); 1 panchromatic (resolution 14.25 m x 14.25 m). The image was exported from ERDAS to ArcView GIS in Tiff format. Individual bands were converted to grids using a nearest neighbour re-sampling technique with a pixel size of 14.25 m x 14.25 m used for all bands and images maintained in the Tiff format. The image was re-imported into ERDAS and reconstructed as a multi-band image before re-exporting it back to Arc View GIS for warping.

The ArcView GIS Image Warp function was used to compare ground control points (GCPs) of 1999 topographic maps at a 1:50,000 scale. Topographic maps obtained from the Uganda department of Lands and Surveys were digitally scanned and saved in JPEG files and re-projected to satellite image projection. Scanning distortions were corrected using 8 ground control points (GCPs) (grid line intersections) read off the map and typed into Image Warp programme. Second order polynomial fit was used to correct scanning errors. Scanned and geo-registered maps were used to geo-rectify the Landsat image using clearly defined points on the image e.g., road intersections that could be located on the topographic maps. Of 45 candidate GCPs, 15 were retained in the model used to rectify the image using a third order polynomial. The Error Root Mean Squares (RMS) were: X error of 4.49 and Y error of 4.71 which were good because they were less than the pixel size of 14.25 m. The satellite image was then suitable for classification

7.3.3.2 Land cover determination

Unsupervised classification was performed using ERDAS Imagine. This process creates thematic raster layers by letting the software identify statistical patterns in the multi-spectral data without using ground truth data. The ISODATA algorithm was used to create 20 classes. This is a clustering method that uses a minimal spectral distance formula to form clusters using arbitrary cluster means. The programme iterates until a maximum number of iterations or maximum number of unchanged pixels has been reached between iterations. Six iterations and a 95% convergence threshold were used.

185 ground truth points that were within continuous (more than 16 pixels) and therefore homogenous areas of the class were selected for ground truthing to explain the meaning of the classes in the unsupervised classification. Classes 1 and 2 (water) were excluded because they were very clearly identifiable. Each point was visited and described according to a land cover classification of water, shallow swamp, deep swamp, natural forest, riverine forest, shrub, cropland, short grassland and long and dense grassland. Variations within a land cover class type were also noted where they were clear intra-class differences. Positions of points within swamps were viewed from a distance. All these data were entered into a database. These ground truthed points were then used to carry out a supervised classification that was used in the analysis by providing signatures to guide ERDAS Imagine in classifying the land cover.

7.3.3.3 Tasseled cap transformation

Tasseled Cap transformation (Tcap) offers an alternative way to optimise data visualisation for vegetation studies (Lillesand & Kiefer, 1987). Tcap values were derived by transforming the unsupervised classified Landsat TM satellite image. Tcap is based on three data axes, which define the three components of vegetation characteristics (Crist *et al.*, 1986, Crist & Kauth, 1986): Brightness is a weighted sum of all bands, defined in the direction of the principal variation in soil reflectance; Greenness is orthogonal to brightness, a contrast between the near-infrared and visible bands that is strongly correlated to the amount of green vegetation in the scene; and Wetness relates to canopy and soil moisture (Lillesand & Kiefer, 1987). A simple calculation (linear combination) then rotates the data space to present the axes to the user.

To determine whether Tcap values are statistically related to incidence rates at the 747 villages during the 15 year period, Tcap values were calculated using data from all Landsat channels to produce wetness, greenness and brightness (dryness) indices; each pixel being assigned a vector value based on variable proportions of signals for each of these three indices (ERDAS Field Guide, 1995).

7.3.4 Spatial data extraction

The database file of villages was converted in ArcView into a shapefile and then converted into a raster file using ArcView Spatial Analyst. Shapefiles are the GIS data in a vector format i.e. points lines or polygons. For purposes of data extraction, the shapefiles were converted into grid formats (i.e. pixel data) for compatibility with ArcView GIS analysis functions. ArcView GIS was used to quantify the areas of each land cover class surrounding each village. It generated polygons (i.e. buffers) extending 2 km from a village central point for each of the 747 villages; these buffers were then overlaid on the Landsat TM-derived supervised classification image to calculate the area of each landuse cover class surrounding each village. Two km was chosen because it has been reported that *G. f. fuscipes* makes a linear advance on average of only 20 m a day (Williams *et al.*, 1992) while it is estimated that a rural farmer would travel typically less than one km away from his home to his farmland, grazing land, or to collect firewood or water because homes were in villages of less than 5 sq. km. The buffers were also overlaid on the Tcap images for wetness and greenness to calculate the mean, median and standard deviation of each spectral index for each buffer area. Brightness was excluded because this measure includes reflectance from roofs and roads, which were not of interest in this study. The outputs of the ArcView GIS functions were exported into Microsoft Excel. The number of sleeping sickness cases by village and the distance of villages from the sleeping sickness hospital determined by Arc View GIS were added to the set (Figure 7.2). Parish population densities (MOF, 1992) were included as well as distances from wetlands as determined by ArcView GIS.

Figure 7.2. Map of the unsupervised classified image with the parish boundary map of Tororo and Busia districts superimposed.
The image shown has been georectified.

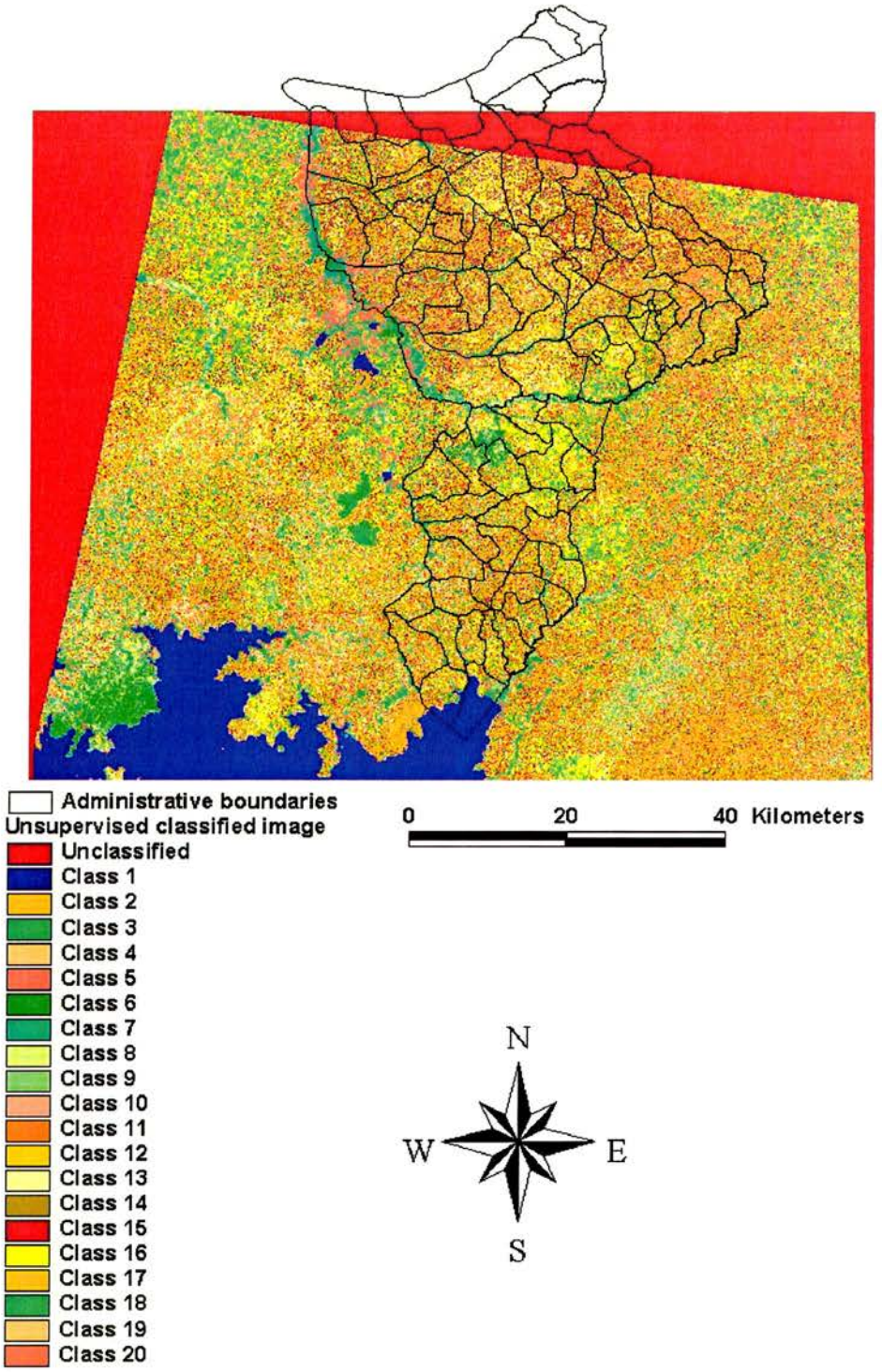


Figure 7.3. Map of a subset of village points used to construct 2 km buffers from which proportions of each land cover class type and means of greenness and wetness were extracted.
The position of the sleeping sickness hospital and the 10 km radius around it are also shown. This is a supervised land cover classified image.

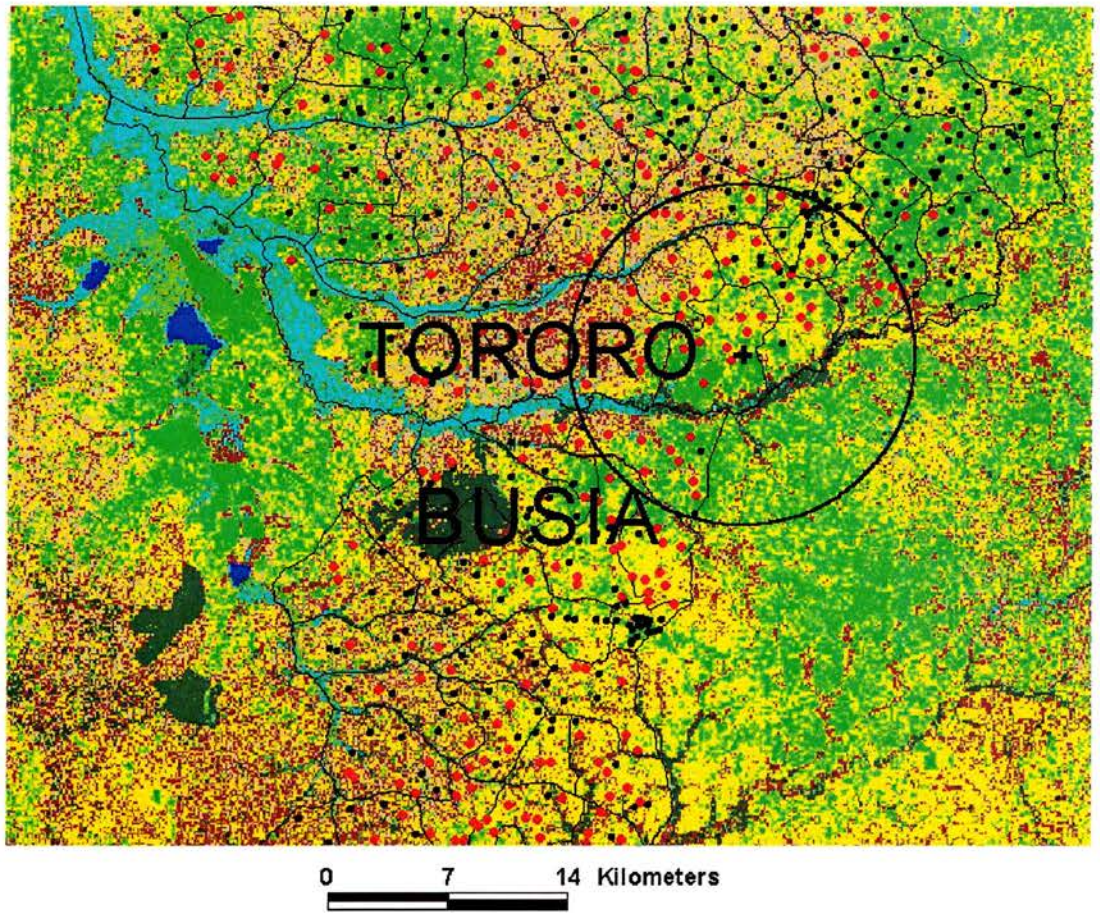


Figure 7.4. Map showing parish population densities and distribution of reported sleeping sickness presence and absence in villages in Tororo and Busia district, eastern Uganda, 1987-2001.

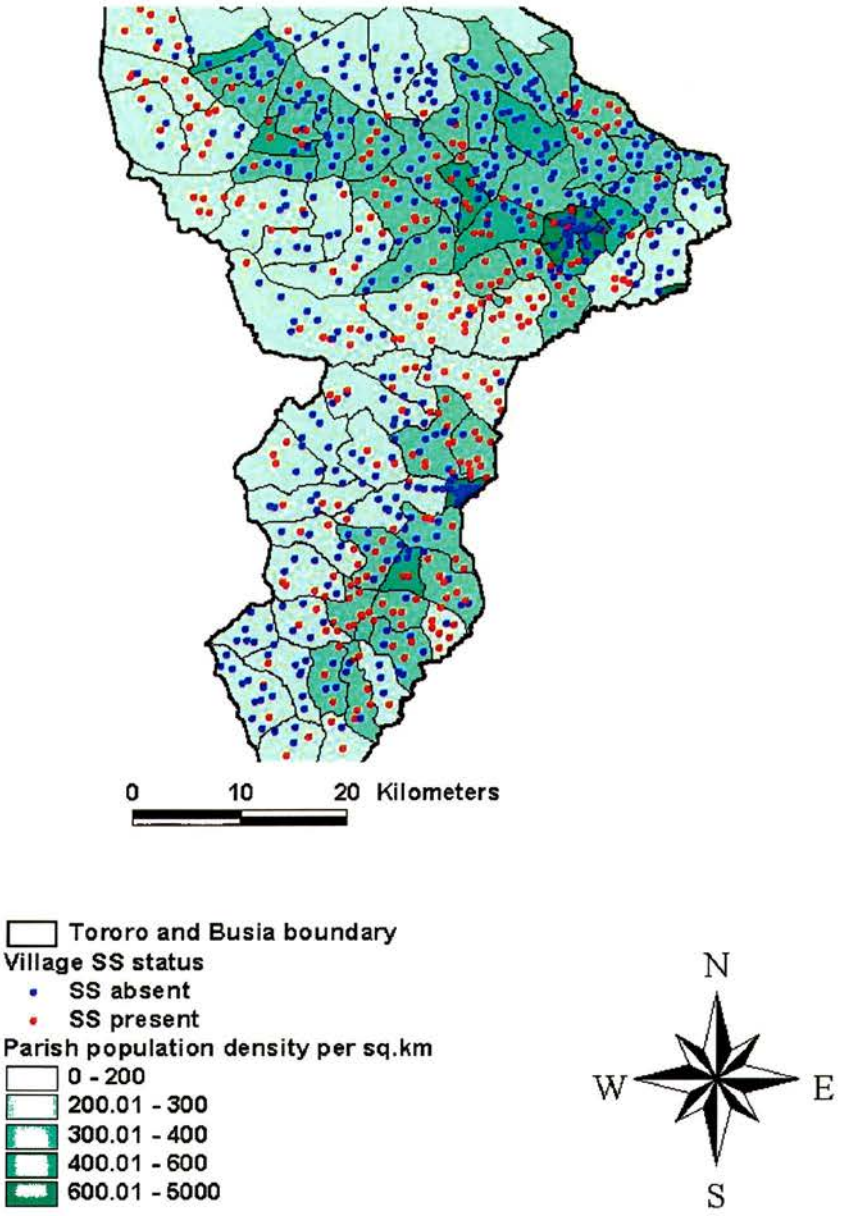
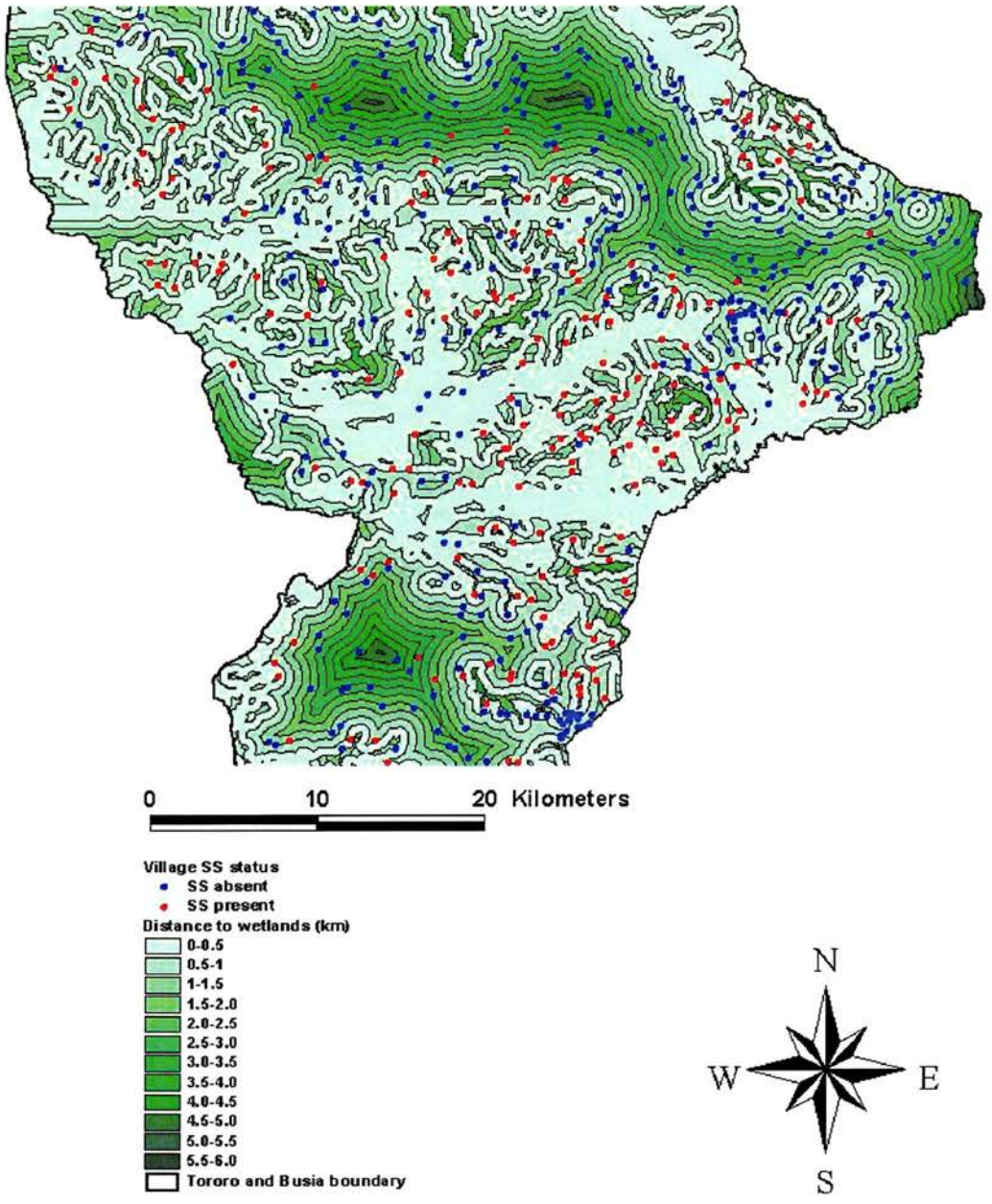


Figure 7.5. Map showing distance to wetlands and distribution of reported sleeping sickness presence and absence in villages in Tororo and Busia district, eastern Uganda, 1987-2001



7.3.5 Data analysis

Data was initially handled in Microsoft Excel and SPSS software to calculate numbers of infected villages using the sleeping sickness case reports for the years 1987 to 2001. Areas of the different land cover class types within 2 km of the GPS position were used in the analysis. For Tcap variables, mean wetness and mean greenness values were used. Although the values for mode and median wetness and greenness were available, means were chosen because there were little differences between them indicating that the values were normally distributed. Land cover class cover types and Tcap variables were analysed in separate models because they were derived from the same unsupervised classified image. Other variables included in the analyses were parish population density of the village, altitude, and distance from the sleeping sickness hospital and from the major wetlands. Using the outcome of presence and absence of sleeping sickness, univariate analyses followed by binary logistic backward regression analysis of variables with associations of significance of P <0.20 (Maldonado & Greenland, 1993a,b) was carried out. Variables were removed from the logistic equations until removal of none of the remaining variables significantly improved the prediction of presence or absence of sleeping sickness (i.e. the fit of the model).

7.4 Results

7.4.1 Sleeping sickness data

A total of 1,316 sleeping sickness cases were reported during the study period January 1987 to December 2001. Out of 747 villages, 285 of the villages reported at least one case while 462 did not report any cases. The annual incidence of sleeping sickness from 1987 to 2001 in the villages ranged from 0 to 35 per 10,000 people.

7.4.2. Unsupervised classification

The resultant image after a 20 classes unsupervised classification of the Landsat image is shown in Figure 7.1. Classes 1 and 2 were clearly open water and it was difficult to distinguish between forest and swamp in the unsupervised classified image because they had the same reflectance.

7.4.3. Tasseled cap transformation

The results of the means and standard deviations of mean wetness and mean greenness indices obtained after tasseled cap transformation of the Landsat image are shown in Table 7.1. The mean wetness index was 177.7 within the positive villages and 176.4 within the negative villages while the mean greenness index was 149.4 within the positive villages and 148.7 within the negative villages indicating that positive villages had more thick green vegetation than negative villages.

7.4.4. Supervised classification

Ten land cover types were distinguished: Open water, shallow swamp, deep swamp, natural forest, riverine forest, open shrub, dense shrub, cropland, long and dense grassland and short grassland (Figure 7.2). The general distribution of villages that reported and those that did not in relation to the supervised land cover classes is shown in Figure 7.2 The results of the means and standard deviations of the areas of supervised land cover types are shown in Table 7.1.

Table 7.1. Univariate analysis of prediction of presence/absence sleeping sickness (1987-2001) by land cover and tasseled cap (Tcap) variables of 747 villages in Tororo and Busia districts, eastern Uganda.

Variable	Present n= 285 mean ± SD	Absent n= 462 mean ± SD	*P* value
Crop (sq.m)	504.6 ± 14.5	489.5 ± 9.8	<0.001
Long & dense grass (sq.m)	72.2 ± 4.8	83.1 ± 3.6	0.06
Dense shrub (sq.m)	190.0 ± 6.6	182.5 ± 6.0	0.42
Deep swamp (sq.m)	14.4 ± 2.0	9.5 ± 1.2	0.02
Natural forest (sq.m)	31.9 ± 3.1	27.0 ± 2.8	0.26
Short grass (sq.m)	142.2 ± 9.1	164.4 ± 7.4	0.06
Open shrub (sq.m)	257.6 ± 12.9	267.7 ± 10.0	0.53
Riverine forest (sq.m)	15.7 ± 1.0	13.1 ± 0.7	0.03
Shallow swamp (sq.m)	17.8 ± 2.8	11.1 ± 1.3	0.02
Open water (sq.m)	3.5 ± 2.2	1.4 ± 0.8	0.29
Distance from hospital	-	-	<0.001
Distance from wetlands (km)	0.5 ± 0.5	1.1 ± 1.0	<0.001
Parish population density	302.8 ± 22.1	516.7 ± 36.7	<0.01
Wetness index	177.7 ± 0.3	176.4 ± 0.3	<0.001
Greenness index	149.9 ± 0.4	148.7 ± 0.3	<0.001
Altitude	1178.0 ± 4.0	1186.0 ± 3.0	0.08
Distance from cattle markets (km)	7.4 ± 4.0	7.5 ± 4.6	0.93

SD = Standard Deviation, n = number of villages

7.4.5. Regression analysis results

The results of the univariate analysis of the relationship of presence and absence of sleeping sickness to different land cover types and Tcap variables are shown in Table 7.1. Univariate analysis of each factor revealed that deep and shallow swamp, riverine forest, long and short grasslands population density, distance from wetlands, altitude and wetness were correlated with sleeping sickness presence or absence at a significance level of $P<0.20$. None of the other investigated variables showed an independent correlation with sleeping sickness presence or absence. After binary logistic regression of the land cover types, short grassland, distance to the wetlands and hospital remained significant ($P<0.05$) in the model while in the Tcap values model, wetness, distance to wetlands and to hospital and population density remained significant ($P<0.05$) in the equation. The estimated coefficients and standard errors of the landuse cover type model is shown in Table 7.2 while that of the Tcap model is shown in Table 7.5. The goodness of fit of the landuse cover type model is shown in Table 7.3 and that for the Tcap model in Table 7.6. Therefore, the relationships may be modelled as follows:

Probability of sleeping sickness in a village = $1/(1+e^{-z})$,
where for the land cover model,
Z= 2.315-(Distance to hospital x 1.034)-(Population density x 0.001)-(Distance to wetlands x 0.001)-(short grassland x 0.0001)+(cropland x 0.0001).
and for the Tcap model,
Z= -3.006-(Distance to hospital x 1.006)-(Population density x 0.001)-(Distance to wetlands x 0.001)+(wetness x 0.031)

The land cover model correctly predicted 81.2% of sleeping sickness negative villages and 46.3% of the sleeping sickness positive villages (Table 7.4). There was 67.9% overall prediction of sleeping sickness presence and absence in villages in Tororo and Busia between 1987 and 2001. The Tcap model correctly predicted 79.2% of sleeping sickness negative villages and 44.9% of the sleeping sickness

positive villages (Table 7.7). There was 66.1% overall prediction of sleeping sickness presence and absence in villages.

The relationship between population density and reported sleeping sickness reported presence or absence in the 747 villages is shown in Figure 7.3. There is a negative relationship between population density and sleeping sickness presence with sleeping sickness being more prevalent in low population density villages. The relationship between distance from wetlands and reported sleeping sickness distribution is shown in Figure 7.4. There is a negative relationship between distance to wetlands and sleeping sickness presence with a lesser proportion of positive villages further away from the wetlands.

Table 7.2. Coefficients of a logistic binary model predicting the presence and absence of sleeping sickness (SS) in different villages of Tororo and Busia districts, using observed disease data and land cover variables

Variable	B	SE	Wald	df	*P*	Exp(B)
Population density	-0.001	0.000	21.233	1	<0.0001	0.999
Distance from wetlands	-0.001	0.000	47.377	1	<0.0001	0.999
Distance from hospital	- 1.034	0.257	16.191	1	<0.0001	0.356
Cropland	<0.0001	0.000	4.572	1	0.033	1.000
Short grass	<0.0001	0.000	5.627	1	0.018	1.000
Constant	2.315	0.561	17.012	1	<0.0001	10.121

df = degree of freedom; SE = standard error; *P* = significance, B = coefficient

Table 7.3. Goodness of fit of a logistic binary model predicting presence and absence of sleeping sickness (SS) in different villages of Tororo and Busia districts using observed disease data and land cover variables

Variable	Model Log Likelihood	Change in -2 log likelihood	df	Significance of change
Population density	-441.101	31.512	1	<0.0001
Distance from wetlands	-461.914	73.139	1	<0.0001
Distance from hospital	-433.884	17.078	1	<0.0001
Short grassland	-428.270	5.851	1	0.016
Cropland	-427.637	4.584	1	0.032

df = degree of freedom

Table 7.4. Percentages of correct predictions of presence and absence of sleeping sickness (SS) in different villages in Tororo and Busia districts using disease data and land cover variables

	Predicted SS		
Observed SS (%)	Absent	Present	Correct prediction
Absent	375	87	81.2
Present	153	132	46.3
Overall			67.9

Table 7.5. Coefficients of a logistic binary model predicting the presence and absence of sleeping sickness (SS) in different villages of Tororo and Busia districts, using observed disease data and Tcap variables

Variable	B	SE	Wald	df	*P*	Exp(B)
Distance to hospital	-1.006	0.245	16.862	1	<0.0001	0.366
Population density	-0.001	0.000	19.334	1	<0.0001	0.999
Distance from Wetlands	-0.001	0.000	45.462	1	<0.0001	0.999
Wetness	0.031	0.016	3.724	1	0.054	1.031
Constant	-3.006	2.816	1.140	1	0.286	0.049

df = degree of freedom; SE = standard error; *P* = significance

Table 7.6. Goodness of fit of a logistic binary model predicting presence and absence of sleeping sickness (SS) in different villages of Tororo and Busia districts using observed disease data and Tcap variables

Variable	Model Log likelihood	Change in -2 log likelihood	df	Significance of change
Distance to hospital	-436.883	17.712	1	<0.0001
Population density	-442.604	29.155	1	<0.0001
Distance from wetlands	-462.513	68.972	1	<0.0001
Wetness	-429.918	3.783	1	<0.052

df = degree of freedom

Table 7.7. Percentages of correct predictions of presence and absence of sleeping sickness (SS) in different villages in Tororo and Busia districts using disease data and Tcap variables

	Predicted SS		
Observed SS prediction (%)	Absent	Present	Correct
Absent	366	96	79.2
Present	157	128	44.9
Overall			66.1

7.5 Discussion

Sleeping sickness can be described as an ecological disease because certain habitat factors affect its distribution. Athough the eco-epidemiology of sleeping sickness has long been known, there have been few attempts to map sleeping sickness in relation to land cover and vegetation indices. The identification of eco-epidemiological risk factors for sleeping sickness would allow sleeping sickness control programmes to prioritise areas for intervention.

This is the first study of its kind presenting a detailed analysis of village distribution in relationship to eco-epidemiological factors in Tororo and Busia districts. The study showed that in *G. f. fuscipes* infested rhodesiense sleeping sickness endemic areas, sleeping sickness presence or absence is associated with distance to wetlands, population density, short grass, cropland, wetness of vegetation and distance to the sleeping sickness hospital.

The association of sleeping sickness presence to the Tcap wetness index and distance from wetlands is in agreement with field-based studies of the landscape ecology of the palpalis group of tsetse (Jackson, 1945). The risk association observed with cropland is because cultivation involves the intrusion into tsetse habitats when clearing overgrown bush in either land left unattended since the last growing season, fallow land or new gardens. The population of Uganda is increasing at an average rate of 2.5% per annum (MOF, 1992). An inverse relationship between the incidence rate for sleeping sickness and population density by parish was observed and suggests that this increment in population may result in the destruction of the tsetse habitat and eventual reduction of sleeping sickness. The study provides further evidence of the association between population pressure and sleeping sickness with populated areas being less at risk most probably due to destruction of the tsetse habitat. Reid *et al.* (1997a,b) predicted changes in the distribution of *G. morsitans* and *G. fusca* over the next 50 years while Morris (1951) observed that a reduction of tsetse habitat especially by the removal of riverine forest, could bring about a sustained reduction in the risk of human infection. Related to reduction of bush and other dense vegetation, is the finding of a significant relationship between a larger area in a village of short grassland and absence of sleeping sickness.

It is possible that these variables influence the populations of tsetse and the reservoir hosts of *T. b. rhodesiense*. The analysis used patient data from the sleeping sickness treatment centres. There may be limitations with using sleeping sickness reported incidence to determine risk maps compared to using tsetse surveys. Under-detection of sleeping sickness is acknowledged and may result in misclassification of some villages. In Chapter 4, significant association was shown between both sleeping sickness incidence and the proportion of early cases to distance from the sleeping sickness hospital in this area. This demonstrated the decrease in sensitivity of surveillance beyond 10 km from the hospital. It is for this reason that the distance from the sleeping sickness hospital was included in the analysis, that is, to adjust for spatial effects of under-detection.

The satellite derived map of land cover shows heterogeneity in the distribution of land cover classes in the study area ranging from forests and shrub land, through farmed land, and grassland, to swamps and open water. These land cover classes surrounding villages change considerably within a few kilometres (Figure 7.3). Although land cover types may be appreciable by the eye in very small areas, variations over wider areas cannot and therefore, remote sensing and GIS functions present powerful means of revealing areas of sleeping sickness risk and thus of priority for surveillance and control. These results can be used to estimate risk in areas where reporting is likely to be low or where surveys cannot be easily carried out. The remote sensed risk factors could be combined with other variables to aid decision support for intervention. Such variables can include population, poverty, access to health services and of distribution of cattle. It can also be used to monitor changing risks resulting from changing land cover distributions.

This study focused on identifying variation in landuse cover and Tcap indices that may be associated with village-level disease risk. However, within the villages, homesteads most affected with sleeping sickness may be more closely associated with particular risk factors than in other areas of the village indicating the possible need for further accuracy in application of control options at a scale greater than the village. The vegetation indices used are easy to generate since the necessary

computer software is now increasingly available. Land cover and vegetation indices maps can be combined with sleeping sickness disease distribution maps to target high risk villages and assist the direction of public health resources to where they are most needed.

In conclusion, these results demonstrate that villages with high sleeping sickness risk can be identified by using remote sensing and GIS technologies. Distance to wetlands and population density are certainly the most important predictors and are readily available from maps and national human population censuses. The specific finding that sleeping sickness risk at village scale is related to the wetness index may be applicable to other areas where riverine tsetse species are vectors for sleeping sickness. In areas were the disease vector is present but the disease is not, this approach could provide a map of potential risk; that is, where vector–human contact is high and transmission would be significant given the introduction of infection. This approach will provide an important tool for disease surveillance programmes in that it enables localised assessment of risk based on geographic elements associated with high sleeping sickness risk. Remote sensing and GIS can therefore be used to more efficiently direct case finding as well as to focus control strategies, thus reducing costs.

Chapter 8 General Discussion

In this chapter the salient findings with respect to the six original objectives are discussed and the study design reviewed. Subsequently, the next section of the general discussion outlines the implications of the research for sleeping sickness control. Finally, implications for future research both on surveillance of disease and in particular, on the application of Geographical Information Systems are discussed

8.1 Development and application of epidemiological surveillance tools for *rhodesiense* sleeping sickness

In Chapter 2, an objective method for the estimation of under-detection of rhodesiense sleeping sickness has been developed. The method takes into account the clinical progression of the disease in that a sleeping sickness patient progresses from the early to late stage and subsequently succumbs to the disease. It assumes that death during the early stage is minimal when compared to that during the late stage and it uses estimates of duration of symptoms to death and to late stage from empirical data to determine competing rates of progression to these two outcomes. The finding of a magnitude of twelve times more undetected deaths than those reported calls for more efforts in improving case finding.

The burden of sleeping sickness in an outbreak situation was determined in Chapter 3 and provides a mechanism for ranking the importance of the disease when compared to other diseases in the same affected communities. It uses DALYs that are standard measures for burden of disease used by WHO and the World Bank but not often applied at levels where decisions are taken. Taking into account the level of under-detection as estimated in Chapter 2, demonstrates the importance of under-detection quantification in determination of disease burden. The burden estimation also describes the direct effect on the health services, an element often neglected in the ranking of disease. The estimation of burden in our study applies a model that was derived in this study. Sensitivity analysis revealed that the model is robust and therefore estimates of under-detection for use in the estimation of burden of sleeping sickness can be relied upon.

A significant association between the proportion of late stage patients and increasing distance from the health unit as well as the annual parish incidence was demonstrated in Chapter 4. GIS functions were used to estimate the distance in 10 km ranges of travelling to the reporting sleeping sickness treatment centre. Euclidean distance estimates are adequate for this purpose since most patients travel by bicycle or on foot. Annual parish incidences were used in the analysis as opposed to annual incidences for the whole area, with the expectation that high sleeping sickness incidence would increase awareness among the immediately affected population and thus early case detection.

In Chapter 5, delays in diagnosis were shown to be mainly due to missed diagnosis or inability to diagnose sleeping sickness as well as a result of poor socio-economic status. Importantly, service provider delay was quite significant in explaining late stage presentation. Definitions of service provider delay were based on the first contact with a recognised health worker to final diagnosis because the challenge to make a substantive diagnosis is the onus of the health worker who may cause further delay if he/she does not refer the patient. Many of the extra deaths quantified in Chapter 2 take place despite patients having already reported to the health care system.

In Chapter 6, there was significant spatial temporal clustering observed over the entire period, indicating that spread of infection can be contained by timely and effective control. Part of the spatial temporal trends of sleeping sickness observed could have been due to control measures that were in place. Despite application of control, there were villages that continued to report sleeping sickness annually for greater than one year and there is now evidence of resurgence of the disease in the study area. This further emphasises the need for timely application of control measures that should be targeted where the disease is reported. These methods should be sustainable after cessation of donor funding.

Land cover classification and tasseled cap transformation of a Landsat satellite image in Chapter 7 revealed associations with distance to wetlands, population density, cropland, short grassland and vegetation indices, providing an important way for discriminating sleeping sickness risk villages. Village shapes are not necessarily circular and equal and therefore our methodology does introduce some degree of error. However, the village points were checked for inclusion in the right parishes as per available polygonal parish boundary maps obtained from the National Biomass Study Project (MONR, Uganda, 1996). Therefore, the accuracy of the areas described was adequate for the purposes of the study.

The application of GIS to improve disease surveillance has its limitations. Control efforts may confound the association of the distribution of trypanosomiasis to the existence of tsetse habitat (Robinson *et al.*, 1999). In this study the distance to sleeping sickness hospital was a confounding factor for the endemic status of a village. There is lack of reliable statistics and under-detection of disease in Africa because of infra-structural and cost constraints (Snow *et al.*, 1999). As a result, disease estimates on the continent are often based on clinical and not on a diagnostic basis. The other problem that exists is the lack of trained technical staff in GIS in developing countries (Nijkamp & De Jong, 1987; Taylor, 1991). Local scientists who understand both the socio-economic context and technological aspects in which the systems will operate will make GIS very useful and effective. The costs of spatial data are most certainly an impediment of using GIS in some tropical countries (Briggs & Elliot, 1995).

Although there are quite a number of studies that use GIS in order to understand the spatial variation of disease to environmental factors, there are only a few that explore the association between disease distribution and the health care system (Zwarenstein *et al.*, 1991; Perry & Gessler, 2000; Tanser *et al*, 2001; Tanser, 2002). In this thesis, both applications were used.

8.2 Implications for control of sleeping sickness

Under-detection of sleeping sickness is acknowledged but has never been objectively estimated. However, in this study, a formula for the estimation of under-detection and the associated mortality of sleeping sickness is developed. The early to late ratio is suggested as an epidemiological indicator for under-detection for use by sleeping sickness surveillance programmes because staging of sleeping sickness patients is a routine procedure in all sleeping sickness control programmes. It can also be used to estimate the actual mortality due to sleeping sickness in a community and therefore the burden of the disease in that community. This was the first attempt at objectively quantifying the level of under-detection of rhodesiense sleeping sickness. Although, it is a conservative estimate that assumes no fatality due to early stage disease, it can be supported by the argument that a significant proportion of the few fatalities in the early stage are treatment related, e.g. due to exfoliative dermatitis or renal failure.

The estimation of burden of disease using indices such as the DALY should take into account under-detection. The DALY is a measure that is recommended by the World Bank and the WHO for use as a criterion in the allocation of resources to health services. In Uganda, the national programme for the control of sleeping sickness has been decentralised to the district level and therefore, the planning of allocation of resources for health services is carried out at the district. The DALY has not been routinely used for health planning in Uganda. During the last 10 years, only one national survey of burden of disease in Uganda was conducted in 1994 that was health unit based and only used mortality statistics. In this study the relative burden of disease of the top ten diseases in the study districts was determined. Rhodesiense sleeping sickness featured as the eighth in Iganga district but did not feature in the other four study districts in the sleeping sickness endemic area (MOH, 1996). However, this study indicates that sleeping sickness outbreaks often occur in areas smaller than a district. Such areas and their health units require special attention to resource allocation for case management and disease control in general. This study is the first one of its kind that has sought to determine the burden of sleeping sickness in an outbreak.

Mapping of the distribution of sleeping sickness cases from the diagnostic centres indicates that late case detection and thus under-detection is associated to distance from diagnosis especially beyond 20 km radius emphasising the need for optimising the distribution of fixed-post diagnosis. There are other health units in the two districts with the capacity to diagnose sleeping sickness but have not been involved in the sleeping sickness control programme activities because the health system has not taken the initiative to involve them. There is also increased early case detection when there is high disease incidence in a locality most probably associated with increased awareness. Adults are more likely to be diagnosed in the early stage than children and adolescents. Sleeping sickness surveillance programmes should bare in mind these variations in early case detection.

Health service provider delay appears to be an important factor in the causation of late stage presentation and thus fatality of sleeping sickness. In endemic areas, health service providers should regularly be reminded of the possibility of sleeping sickness even when their health units do not treat the disease. The results of this study suggest that the involvement of the community in referral of sleeping sickness suspects and generally in the treatment of their livestock and the application of pour-on insecticide may be an effective entry point for sleeping sickness control. Regular reminding and updating of health workers in sleeping sickness endemic areas most especially when there is evidence of sleeping sickness occurrence in the vicinity will most certainly increase their index of suspicion and improve the early detection of sleeping sickness cases.

The results of analysis of spatial and temporal trends of rhodesiense sleeping sickness indicate the need for the creation of a geographically sensitive, timely responsive health information and intervention system. This would avert the emergence of outbreaks. Passive case finding and treatment remains the major control strategy for rhodesiense sleeping sickness. The costs of improving the information system for passive case finding are minimal when you consider the costs of active case finding or vector control.

A cartographic approach to sleeping sickness control allows for delimitation of area of application of control. In this study it has been shown that GIS can provide an accurate and powerful means of determining which villages need to be given priority for application of tsetse traps, pour-on insecticides, block treatment of cattle and community sensitisation and therefore ensures optimal use of scarce resources. Whenever an outbreak occurs, its limits and relationship to the existing tsetse habitat should be described using GIS. Such an approach would not only reduce operation costs but also prevent expansion of outbreaks.

WHO has put emphasis on improving the performance of health systems and dedicated the world health report for the year 2000 to this cause. This thesis further demonstrates the spatial aspect of health systems research. With GIS, health systems coverage can be analysed spatially and effectively. Therefore, GIS has the potential to contribute to rational and more cost effective planning and resource allocation in sub-Saharan Africa.

8.3 Implications for future research on surveillance of sleeping sickness

There is now little doubt about the need to plan sleeping sickness control in a focal context. However, further operational research issues still remain. Development of a model for the estimation of under-detection of *T. b. gambiense* sleeping sickness can be carried out using the same procedure outlined in Chapter 2. Estimation of duration of illness to late stage and death can be carried out in a clinical setting with an adequate sample size of sleeping sickness patients to account for recall bias. In Chapter 3, the direct burden of sleeping sickness on the family and community at large was not determined by examining the impact of absence of family members either due to being affected by sleeping sickness or due to taking care of the sick when they are admitted. To quantify the potential contribution of other health units that are not currently involved in sleeping sickness surveillance, these units should be mapped out and their distribution compared with the current distribution of sleeping sickness. In this way, planning of the distribution of new sleeping sickness centres

can be rationally carried out. A patient-based health information system for sleeping sickness is recommended in Chapter 5. Such a system should be evaluated for its effect on early case presentation. There are questions on how to involve the immediately affected communities in control of the disease. Can a systematic referral system of sleeping sickness suspects be initiated at the sleeping sickness health units whereby the affected families are used to alert and bring other sick people for testing? Are there ways of involving all health units into sleeping sickness diagnosis and sometimes treatment? Within the most recent significant sleeping sickness clusters identified in Chapter 6, information should be sought on the source and movements of cattle to investigate the possible sources of infection. When data for cattle census is available, cattle population densities should be included in the model in Chapter 7 since they are known to be important mammalian hosts in this environment. Village scale resolution was used in the studies of Chapter 6 and 7, but more information may be obtained through homestead geo-referencing, as it appears that even within a village, sleeping sickness cases may be focalised. The investigation of associations with land cover and disease distribution would then require maps at a resolution of aerial photography to decipher differences in vegetation cover in small areas. Mechanisms for sharing the information with and ensuring action by actors responsible for vector control and treatment of the domestic animal reservoir need to be researched. Currently, vector control and mass treatment of livestock are a mandate of the Ministry of Agriculture while case finding and treatment of patients is for the Ministry of Health. This means that even funding of activities has taken a sectoral approach. Mechanisms of funding of activities of the Ministry of Agriculture by budgets from the Ministry of Health should be researched and advocated. In addition, a framework should be designed for integration of geographic information at the focal level into the routine surveillance of sleeping sickness.

Chapter 9 Conclusion

The key lessons learnt from this study are as follows:

- The early to late stage ratio is a useful tool for surveillance of sleeping sickness;
- Sleeping sickness burden to the community and health services can be overwhelming during outbreaks even with relatively few reported sleeping sickness cases;
- The optimal distribution of fixed-post diagnosis surveillance structures will greatly improve surveillance of rhodesiense sleeping sickness;
- Patient and service provider delays are both important in the causation of late stage presentation of sleeping sickness cases with the latter contributing to most of the delay;
- Involvement of communities in sleeping sickness surveillance and control appears to be an effective entry point for control programmes;
- Remote sensing can be used to chararacterise sleeping sickness village scale risk;
- Sleeping sickness can be controlled by timely responsive surveillance and control targeted using GIS.

The overall goal of this work was to develop and apply epidemiological surveillance tools for surveillance and control of sleeping sickness. This goal has been achieved through use of the early to late ratio to develop a decision tree model and through the application of this model to data from Serere and Tororo and Busia to determine the burden and the spatial and temporal distribution of under-detection of rhodesiense sleeping sickness. In addition, using GIS as a tool, evidence for the optimization of the distribution of sleeping sickness health facilities has been demonstrated as a potential risk factor for improving early case detection, and village-scale timely implementation of surveillance and control has been shown to be an important strategy for control. These findings suggest that the surveillance can be improved by timely sensitization of the affected communities and the primary health care service providers. Costs of control can also be reduced by reducing the geographical area of

application of control through targeting the distribution of the disease and the related ecosystem.

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Appendix

Questionnaire on health-seeking behaviour of sleeping sickness cases

(Administered to patient and next of kin)

Name……

N.O. K……

Age…….. Sex…….

Homestead GPS: E……N……

Village……..

Parish……

Subcounty……

County……..

District……

Date of Admission:……

Stage:……

Socio-demographic variables of patients

Educational status: Secondary and above (1), Primary (2), None (3)

Unable to read English: Yes (1), No (2)

Living house: Hut (1), Semi-permanent (2), Permanent (3)

Ethnicity: Adhola (1), Teso (2), Samia (3), Nyole (4), Other (5)

Marital status: Married (1), Not married (2)

Religion: Catholic (1), Protestant (2), Muslim (3), Other (4)

Work: Employed (1), Not employed (2)

Radio: Yes (1), No (2)

Bicycle: Yes (1), No (2)

Cows: Yes (1), No (2)

Symptoms among patients

Headache: Yes (1), No (2)

Fever: Yes (1), No (2)

General body aches: Yes (1), No (2)

Weakness: Yes (1), No (2)

Loss of weight: Yes (1), No (2)

Chancre: Yes (1), No (2)

Swelling of feet: Yes (1), No (2)

Dizziness: Yes (1), No (2)

Knowledge and perceptions of patients

Kind of disease patient thought: Malaria (1), AIDS (2), TB (3), Bewitched (4), Other (5)

Origin of disease: Tsetse fly bite (1), Other (2)

Aware of livestock reservoir for sleeping sickness: Yes (1), No (2)

Aware of use of live bait technology for tsetse control: Yes (1), No (2)

Aware of the use of traps for tsetse control: Yes (1), No (2)

Aware of nearest sleeping sickness treatment centre: Yes (1), No (2)

Seen a sleeping sickness case before: Yes (1), No (2)

Utilisation of health and veterinary services

Type of health facility first approached for help:
Private clinic (1), Health centre (2), Hospital (3) Traditional Healer (4), Outreach (5)

Attended sleeping sickness outreach activities: Yes (1), No (2), Not applicable (3)

No of visits to health units during current illness: One (1), More than one (2)

Health Unit	GPS	Date	Mode of Travel	Cost of travel	Cost of treat	Source of money	Blood exam	Diagnosis

Referred to sleeping sickness hospital: Yes (1), No (2)

Time from the onset of symptoms to first visit to health unit ……..
Upto 2 weeks (1)
>2 weeks to one month (2)
>One month to two months (3)
>Two months to three months (4)
>Three months to four months (5)
More than 4 months (6)

Time between first visit to a health unit and diagnosis for sleeping sickness……
Upto 2 weeks (1)
>2 weeks to one month (2)
>One month to two months (3)
>Two months to three months (4)
>Three months to four months (5)
More than 4 months (6)

Duration of symptoms before sleeping sickness diagnosis (…….):
Upto 2 weeks (1)
>2 weeks to one month (2)
>One month to two months (3)
>Two months to three months (4)
>Three months to four months (5)
More than 4 months (6)

Reasons reported for delayed diagnosis for sleeping sickness:

Lack of money (1)
Lack of correct diagnosis (2)
Illness considered mild (3)
Other reasons (4)

Treats cows for nagana: Yes (1), No (2), Not applicable (3)

Uses live bait technology: Yes (1), No (2)

Traps are deployed in village: Yes (1), No (2)