

Cost-Effectiveness Analysis of DAT and rK39 as Rapid Diagnostic Tests for Visceral Leishmaniasis in Wajir County - Kenya.

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Declaration

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Dedication

I dedicate this work to the people of Wajir whose long suffering from the afflictions of Visceral Leishmaniasis have inspired me and I hope my work will make a difference in their lives.

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I acknowledge the support of my family during my study for this degree, the motivation from my classmates of the year 2006 and the guidance of my supervisors Dr Dismas Ongore, Dr Tom Olewe and Dr Paterson Muriithi.

List of Abbreviations

| | |
|------------------|--|
| AIDS | Acquired Immunodeficiency Syndrome. |
| AMREF | African Medical Research Foundation. |
| CBS | Central Bureau of Statistics. |
| CEA | Cost Effectiveness Analysis. |
| CER | Cost Effectiveness Ratio. |
| CL | Cutaneous Leishmaniasis. |
| DALYs | Disability Adjusted Life Years. |
| DAT | Direct Agglutination Test. |
| Diamed-IT LEISH™ | Common commercial brand of DAT used in Kenya. |
| DNA | Deoxy-ribonucleic acid. |
| ELISA | Enzyme Linked Immunosorbent Assay. |
| FD-DAT | Freeze Dried DAT. |
| GoK/GOK | Government of Kenya. |
| HIV | Human Immunodeficiency Virus. |
| IFAT | Indirect fluorescent antibody test. |
| IHA | Indirect heamagglutination test. |
| INGO | International Non-Governmental organization. |
| KA | Kala-azar. |
| KDHS | Kenya Demographic Health Survey. |
| KEMRI | Kenya Medical Research Institute. |
| KES / KShs | Kenya Shillings. |
| KNBS | Kenya national Bureau of Statistics. |
| L. chagasi | Leishmania chagasi, one of the species of the KA parasite. |
| LD bodies | Leishman Donovan Bodies. |
| Merlin | Medical Emergency Relief International, a medical charity. |
| MSF | Medecins Sans Frontieres, a medical charity. |
| NEP | North Eastern Province. |
| rK39 | repeat Kinesin 39 - is a rapid dipstick serological test for Kala-Azar made using cloned antigen of 39 amino acid repeats of a kinesin like gene found in <i>Leishmania chagasi</i> , instead of whole <i>Leishmania</i> parasites |
| EPI-INFO | Public domain epidemiology statistical software |
| SA | Splenic Aspirate |
| SPSS | Statistical Package for the Social Sciences |
| MOH/MoH | Ministry of Health |
| DCPP | Disease Control Priorities Project |
| WHO | World Health Organisation |
| VL | Visceral Leishmaniasis. |
| PCR | Polymerase Chain Reaction |

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Abstract

Visceral Leishmaniasis or Kala-Azar is a chronic systemic disease characterized by fever, weight loss and weakness and, if left untreated, death. Diagnosis of KA is by direct visualization of the parasites in a culture medium or in host tissue; or by serological demonstration of antigen nuclear material or antigen-antibody reaction by way of a variety of laboratory tests.

The research was a determination of technical efficiency of two most commonly used laboratory tests for screening and diagnosing Kala-Azar (KA) in Wajir County in North Eastern Province of Kenya in the year 2008 by way of a cost-effectiveness analysis. These tests were Direct Agglutination Test (DAT) and a rapid dipstick test called rK39™. The rK39, at the time of the study, was not recognized by Ministry of Health because there was inadequate information on its performance in the Kenyan context. However, in Wajir, rK39 was more available than DAT. Additionally, DAT was cumbersome to use in Wajir as it required that specimens be shipped to Nairobi where the actual testing was done. Hence, there was the need to recommend a diagnostic kit that was cost effectively suitable for use in Wajir.

The study therefore sought to conduct cost effectiveness analysis on the use of DAT and rK39 as diagnostic kits for KA in Wajir, Kenya. A hospital-based, cross-sectional descriptive study was done. Quantitative secondary data of newly suspected Kala-Azar cases seen in Wajir County Hospital and subjected to both DAT and rK39 and splenic aspiration in the year 2008 was collected using specific data collection forms. Collected data comprised the study subjects' Kala-Azar (KA) test results and monetary costs related to KA testing using DAT and rK39 tests. Data was analyzed using the computer based statistical software Statistical Package for Social Sciences (SPSS) version 14. A cost effectiveness ratio was calculated as the cost per morbidity averted relative to the obligatory morbidity associated with the absence of correct diagnosis and treatment of KA. Ease of test performance calculated as number of test steps and the requisite skills and equipment was used as adjunct measure of test suitability for Wajir.

The study found the average cost-effectiveness ratio of DAT was 812 while that of rK39 was 57. The rK39 test was therefore found not only effective but also more cost effective and easier to perform compared to DAT. These findings correlated well with findings of other DAT and rK39 cost and effectiveness studies done in East Africa, Asia and South America where KA is endemic. The study thus recommended rK39 test for adoption by Ministry of Health as first line screening test for Kala Azar in Wajir. It was also recommended that more studies of the prevalence of KA in Wajir and other regions of Kenya be done so that tests for KA can be segregated by regional predictive value.

Definition of operational terms

Cost – In business and accounting, cost is the monetary value of materials or inputs used up to acquire or produce something. In economics, a cost is the monetary value of the best next alternative that is given up as a result of a choice decision. The business definition is used through-out this thesis.

Cost-effectiveness analysis (CEA) - economic analysis that compares the relative expenditure (costs) and outcomes (effects) of two or more courses of action.

Diagnostic algorithm - Procedure or series of steps that can be used to solve a problem. A flow chart is a visual representation of an algorithm.

Leishmaniasis – Are parasitic diseases caused by protozoan flagellates of the genus *Leishmania*. Parasites infect numerous mammal species, including humans, and are transmitted through the infective bite of an insect vector, the phlebotomine sand fly.

Performance of a test - Test performance testing verifies that a test meets the speed and effectiveness specifications set by the regulatory body.

Predictive Value of a test – is the proportion of cases in a population with positive/negative test results that are correctly diagnosed by the test.

Sensitivity – refers to how best a test detects positive cases. Suppose 10 subjects are screened for a disease and in reality all 10 have the disease but test is positive only for 8 people, then this test is only 80% sensitive.

Serological test - test on a sample of blood serum done to detect serum antibodies or antibody-like substances that appear specifically in response to infection by certain diseases.

Specificity – refers to how best a test detects negative cases. Suppose 10 persons are tested for a disease and all 10 people are positive for that disease when in reality only 8 people have the disease, then the test used here is 80% specific.

Visceral Leishmaniasis or Kala-Azar (KA) – a form of Leishmaniasis that primarily affects internal body organs. It is differentiated from cutaneous Leishmaniasis that affects the skin primarily.

Chapter 1: Introduction

1.1 Background

Visceral Leishmaniasis (VL) or Kala-Azar (KA) is a chronic human and canine disease. In humans it presents with fever, abdominal organ enlargement, gland swelling, anaemia, loss of weight and weakness and, if left untreated, death. The disease is caused by a protozoan parasite, *Leishmania donovani* or *Leishmania infantum*, and is transmitted by sand flies. It was first described in the late 19th century and the causative intracellular parasite was identified. It was named Leishmaniasis and the causative intracellular parasite Leishman Donovan (LD) bodies, after the scientists who first described it. Two main forms exist, the visceral Leishmaniasis (commonly referred to as Kala-Azar) and the cutaneous Leishmaniasis. A muco-cutaneous and visceral-cutaneous form also exists (*Cook et al, 2003*).

Laboratory diagnosis of KA is done by demonstration by direct visualization of the parasitic form (amastigotes or LD bodies) in a culture medium or in human or host tissue specimen (the aspirate); or by serological demonstration of antigen nuclear material (DNA) or antigen-antibody reaction. Of these, the tissue aspirate is the gold standard test for diagnosis of KA in Kenya. Tissue aspirates are 100% specific. However, different tissue aspirates show different sensitivities namely splenic aspirate at 90 - 95%, bone marrow aspirate at 64 - 92% and lymph node aspirate at 52 - 65% (*Kager, 1983*). The most commonly used serological tests are the formal gel, Direct Agglutination Test (DAT) and the recently introduced dipstick test called rK39. In Kenya, DAT is more commonly used and is the recommended first line screening test of KA. Titres >1:3200 of DAT have been found to have a sensitivity of 94% and a specificity of 72% (*Zijlstra, 1992*). Lower titres are less specific because of the high prevalence of anti-leishmanial antibodies due to past infections. Although DAT was specifically developed for the field, it is still difficult to use in remote conditions. This is because antigen production needs specialized laboratories and is laborious and expensive. Secondly, DAT needs a cold chain of continuous refrigeration. It also needs correct titre setting, cross checking with controls, and meticulous implementation. Finally, the method is time consuming and requires considerable training of the staffs (*Meredith, 1995*). Improvements were made by the introduction of freeze dried DAT antigen, replacing the unstable aqueous antigen. There however still existed need for a simpler, faster, non-invasive but reliable test to screen for KA in the field and this led to the development of the dipstick test called rK39 test. The rK39 was developed as a serological test using the cloned antigen of 39 amino acid repeats of a kinesin-like gene found in *Leishmania chagasi*, instead of whole *Leishmania* parasites (*Zijlstra, 1998*).

Resource limitations compel decision makers worldwide to make choices on how best to invest in public health. Investments which promise to address the most pressing health problems while bringing the greatest health gains are often chosen above all others. (*World Bank, 1993*). Cost-effectiveness analysis (CEA) is an essential evaluation tool that allows policymakers and health planners to compare the health gains that various interventions can achieve with a given level of inputs. It is the primary tool for comparing the cost of a health intervention with the expected health gains (*Gold et al., 1996*). An intervention can be

understood as any activity using human, financial and other inputs, which aim to improve health. The health gain might be reducing the risk of a health problem, the severity or duration of an illness or disability, or preventing death. If the health outcome is the same, for example preventing death from measles either by immunizing a child or by treating the disease, then analysts need only compare the costs of different interventions that can achieve that outcome. The result is a cost-effectiveness ratio, expressed as cost per outcome. A common measured outcome of CEA is the disability adjusted life years (DALYS), (*Gold et al., 1996*). The measured outcome can then be compared across various types of services or various service locations that perform the same function. The ratio is always discussed in relative terms, as there is no “best” or absolute level of cost-effectiveness.

CEA is used to compare the costs and the values of different health care interventions in creating better health and longer life. Many new medical products and interventions are expensive and CEA can help to evaluate whether the benefits they offer justifies the expenditures put on them relative to other choices (*Gold et al., 1996*). This understanding of the costs and outcomes of comparative interventions is essential for public- and private-sector decision makers to make informed decisions about using health care resources efficiently. Cost effectiveness analysis requires health outcomes to be expressed in common units so that comparisons among interventions can be made.

The Disease Control Priorities Project (DCPP) - a project of the World Bank, the World Health Organization and the Bill & Melinda Gates Foundation - estimates that in terms of disability-adjusted life years (DALYs), Leishmaniasis ranks as the world’s third most important vector-borne disease and annually account for 2.4 million DALYs (*Cattand et al., 2006*). This makes it a disease of great significance. In Kenya the disease has been reported in the counties of Baringo, Kitui, Isiolo, Marsabit, Garissa, Wajir and Mandera. Wajir is one of the administrative Counties of North-Eastern Province (NEP) of Kenya. The NEP is one of the eight provinces in the country. Currently the County is subdivided into 4 districts– Wajir East, South, West and North. Wajir County has an area of 56,501 square kilometers (*Survey Department Wajir, 1996*). Geographically the County is vast, semi-arid and topologically flat with open plains and patches of grassland. There are many tall ant-hills spread over the County which together with the seasonal flooding after rains make it a conducive breeding environment for sand flies.

Wajir County has population of 661,941 from the 2009 national census (*KNBS, 2010*). Information available from the Kenya National Bureau of Statistics (KNBS) and the Kenya Demographic Health Survey (KDHS, 2008) of the Government of Kenya (GOK) shows that seventy percent of the population of Wajir County is mostly rural, poor and nomadic pastoralist. Nomadic pastoralism predisposes the population to bites by the sand flies because the population has to traverse vast areas of plains as they tend their livestock and often sleep out in the open and rest on the anthills (*Merlin Press Release, 2008*). The remaining thirty percent is scattered in few urban dwellings. The major economic activity in Wajir is livestock pastoralism but the semi-arid climate and regular droughts greatly affects livelihoods and food security. The result is a high level of poverty and perennial malnutrition, which are known risk

factors for contracting KA. Nutritional survey done in 2008 showed that thirty four percent of under-fives are chronically underweight (*KDHS, 2008*).

Documented KA cases have been reported from the North Eastern Province in sporadic epidemics since 1935 (*Marlet, 2003*). Seasonal flooding and nomadic lifestyle of the population increase the risk of exposure to the phlebotomine sand fly vector. Most recent outbreak of KA was in 2008 when the neighboring Isiolo County was also affected (*Merlin Press Release, 2008*).

1.2 Statement of Research Problem

In 2008, DAT and rK39 were the tests used for KA diagnosis and screening respectively in Wajir. There were however many operational challenges to testing for KA in Wajir (*Merlin Press Release, 2008*) namely:-

1. Screening tests were used to diagnose KA.
2. Only DAT was recognized by Kenya MoH as screening and diagnostic test for KA in remote/field settings like Wajir. Testing by DAT however has limitations when used in resource-deprived areas and field situations like Wajir for the reasons that its antigen production is expensive and requires specialized laboratories and is time consuming (*Zijlstra, 1998*). In Wajir DAT testing was done only when there was transport to Nairobi where the assays were done at the KEMRI laboratories.
3. The rK39 was the newer screening method that overcame the above mentioned limitations of DAT and was increasingly being used in Wajir to diagnose KA but was not yet recognized by MOH as diagnostic of KA because it was not adequately studied in the local context. Despite this it was often the only test done consistently during the 2008 Wajir KA outbreak because it was easy to perform and could be completed at the field level.
4. Splenic aspiration carries the risk of severe haemorrhage. It requires specialized operator skills and facilities to be safely undertaken (*Thakur, 1997*). In resource limited Wajir County, doing splenic aspirates was a big challenge. From the observation of the medical charity *Merlin*, the solitary medical doctor at the Wajir County Hospital only occasionally performed splenic aspirates. This was when he was present (and this was infrequent) and the laboratory had reserves of donated blood that would be useful in case of complications after the aspirate.
5. *Merlin* also observed that during the KA outbreak of 2008, the four county health centres plus the county hospital diagnosed KA using all the three tests randomly. The choice of tests depended on its availability, its cost and how comfortable the staffs were to perform the test. All the three KA tests were equally accepted as valid to diagnose KA (*Merlin Press Release, 2008*).

In summary testing of KA in Wajir was problematic because it was unstructured, fraught with operational challenges and employed a test unauthorized by the Ministry of Health.

1.3 Rationale for the study.

Kala-Azar (KA) has a significant impact in Wajir. The region is rural and poor. Kala-Azar exacerbates the poverty of the sufferers and their families. The incidence of KA in Wajir and Kenya in general is not known but successive epidemics of KA have been reported in Wajir and neighboring regions for a long time in cycles of ten years. Each time thousands of cases were screened yet it was not known whether all suspected sufferers accessed formal health services. In the year 2008 alone, one NGO (Merlin) working in collaboration with the MOH screened approximately 400 suspected cases of KA. Screening and diagnosis of KA remains difficult in rural endemic areas and practical and reliable tests are badly needed (*Chappuis, 2003*). This was true in Wajir where the choice of test method for KA testing was not structured and screening tests were used as diagnostic tests (*Merlin Press Release, 2008*).

Worldwide there is ongoing pressure to control health care spending which has created a surge of interest in "cost-effective" health care. The relationship between the cost of health care and benefits to the public has come under scrutiny from multiple sources. The use of some expensive new technologies may contribute to a rapid increase in health insurance premiums while providing little or no benefit to the patient (*New York Times, 2001*). Cost-effectiveness analysis of DAT and rK39 in Wajir County was important because:-

1. In Wajir both DAT and rK39 were used as both screening and diagnostic tests and they were used randomly. There was lack adequate local knowledge to aid in KA test selection. This caused confusion to health workers and put extra expenses to the patients and healthcare system. Resources could get wasted in that way.
2. There was paucity of documented CEA for these KA screening tests in Kenyan context.

This study was thus aimed at providing health workers and decision makers with the information to use to design appropriate KA diagnostic guidelines for regions like Wajir. The MOH had in the past after related studies, made appropriate changes to diagnostic and treatment guidelines for diseases like Tuberculosis and Malaria whose regional endemicity, disease manifestation and drug resistance patterns varied and it was hoped the same would be considered for Leishmaniasis.

Chapter 2: Objectives, Study Question and Conceptual Framework.

2.1 General Objective

To conduct cost effectiveness analysis of DAT and rK39 in Wajir County, Kenya.

2.2 Specific Objectives

1. To determine the cost of testing for KA with DAT and rK39;
2. To evaluate the processes involved in performing the DAT and rK39 tests;
3. To calculate and compare cost-effectiveness ratios of testing for KA with DAT and rK39.

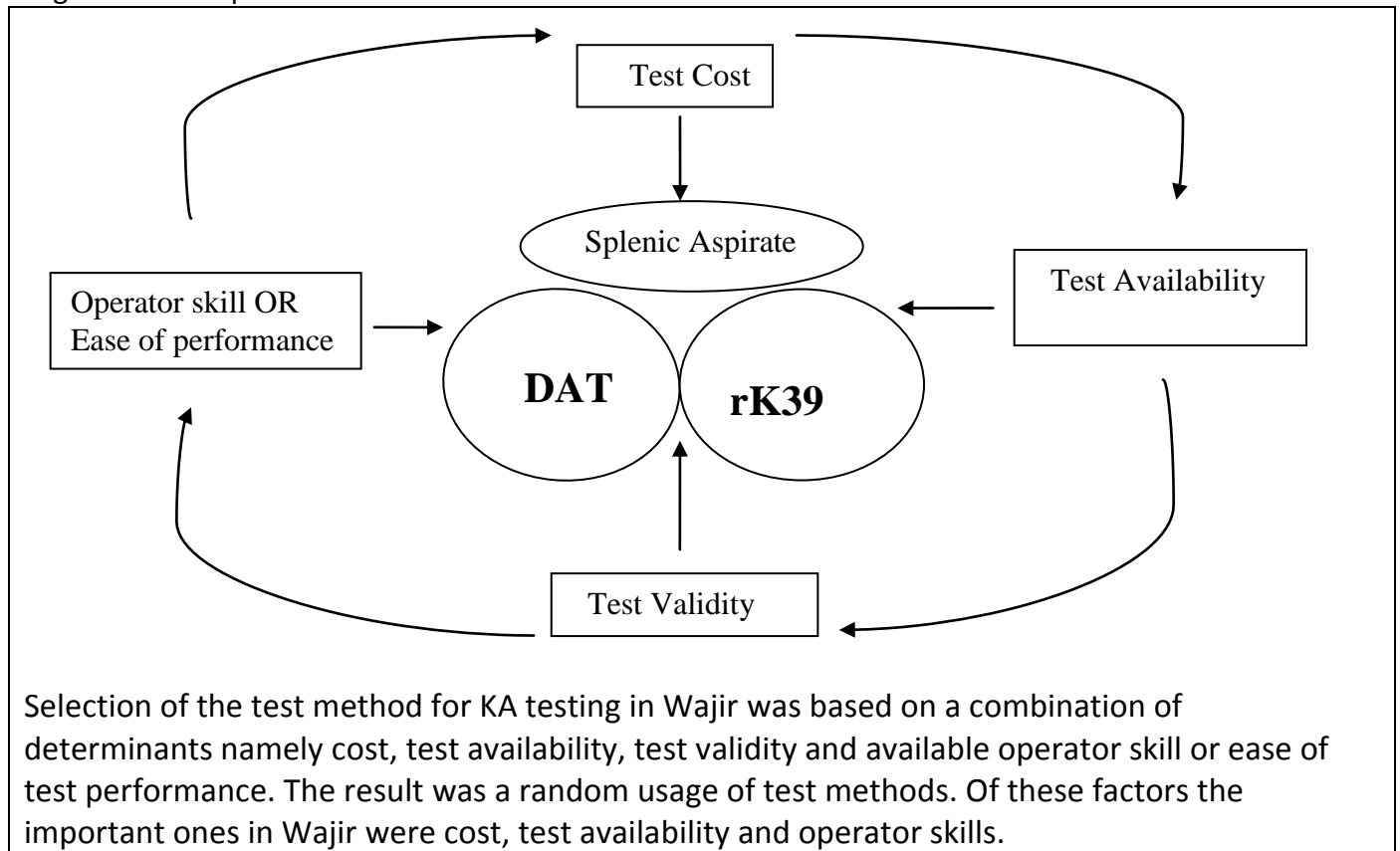
2.3 Research Question

Is the cost-effectiveness of testing for Kala-Azar in Wajir County with DAT or rK39 the same?

2.4 Conceptual framework.

The conceptual framework used for the research is illustrated below in the diagram (Figure 1) and further explained in the Table (Table 1).

Figure 1: Conceptual Framework



Selection of the test method for KA testing in Wajir was based on a combination of determinants namely cost, test availability, test validity and available operator skill or ease of test performance. The result was a random usage of test methods. Of these factors the important ones in Wajir were cost, test availability and operator skills.

Source: - Researcher.

Table 1: Theoretical Framework

| | |
|--------------------|---|
| Research Question | Is the cost-effectiveness of testing for Kala-Azar in Wajir County with DAT or rK39 the same? |
| Variables | <ol style="list-style-type: none"> 1. Independent variables – Study tests, DAT and rK39 and control test, Splenic Aspirate. 2. Dependent variables – validity of test, cost of test and ease of test performance. |
| Theory | The cost-effectiveness of testing KA in Wajir with DAT or rK39 was unknown resulting in random use of both tests depending on test and supporting infrastructure availability. |
| Theory assumptions | <p>There was in Wajir:-</p> <ol style="list-style-type: none"> 1. Unavailability of the WHO recommended diagnostic tests for KA resulting in usage of screening tests as rK39 to diagnose KA (<i>Merlin Press Release 2008</i>). 2. Inconsistent availability of DAT and rK39 tests. 3. Logistical difficulties in performing DAT test. 4. Lack of recognition of rK39 by MOH as a screening test for KA. (<i>Kala-Azar Diagnostic Guide. Ministry of Health, 2001 and Malaria Consortium (2010) Leishmaniasis control in eastern Africa</i>) |
| Study validation | Determination of cost effectiveness of DAT and rK39 for testing KA in Wajir would help MOH make a decision about the role of both tests as first line tests for KA in Wajir and other similar settings in the country. |

Source: - Researcher.

Chapter 3: Literature Review

3.1 Definition and Case definition of KA

3.1.1 Definition and cause

Leishmaniasis are a group of parasite transmitted diseases caused by protozoa of the genus *Leishmania*. The parasites infect humans and other mammalian species. Visceral Leishmaniasis which is locally called Kala-Azar (KA) in India is a variant of Leishmaniasis that primarily affects internal body organs (Cook et al, 2003).

3.1.2 Variants

Leishmaniasis present clinically as visceral, cutaneous and muco-cutaneous types depending on species of infecting parasite and the immune responses of the hosts (Cook et al, 2003). Visceral Leishmaniasis (VL), caused by species of the *L. donovani* complex, is usually fatal if untreated. Mucocutaneous Leishmaniasis, caused by the *L. braziliensis* complex, is highly disfiguring and mutilating, and it can be fatal because of secondary complications. Cutaneous Leishmaniasis (CL), caused by the *L. major*, *L. donovani*, and *L. braziliensis* complexes, may be a simple, self-limiting skin ulcer, but it can be disabling when numerous lesions occur. Diffuse cutaneous Leishmaniasis, caused by the *L. mexicana* and *L. aethiopica* complexes, is longer lasting because of deficient immune responses (Cattand et al., 2006). Leishmanial infection does not always lead to clinical disease in all cases as asymptomatic and subclinical forms are frequent (Gulati et al., 2009).

3.1.3 Transmission

Leishmaniasis are transmitted between hosts by the bite of an insect vector called the phlebotomine sand fly - *Phlebotomus martini*, (Cook et al., 2003). Worldwide, transmission of the disease is thought to be anthroponotic. A study in Kenya revealed that transmission occurs in and around houses, but whether this occurs in the rest of the region is unknown (Ngumbi et al., 1998). Termite hills are the favoured breeding and resting sites of *P. martini*. Generally however, information on local phlebotomine vector behaviour and risk factors for infection in Kenya is limited so disease prevention is still low (Ngumbi et al., 1998). Minor forms of transmission include sexual contact, congenital route and through blood transfusion (Cook et al., 2003)

3.1.4 Case definition

Suspected case: - A person with splenomegaly and fever of more than 15 days duration, not responding to anti-malarials and antibiotics (NVBDCP India, 2005).

Confirmed case: - A person fitting definition of suspected case whose tissue biopsy demonstrates presence of *Leishmania* parasites by way of direct visualization, growth in tissue culture or by parasitic DNA isolation (NVBDCP India, 2005).

3.1.5 Clinical presentation

The classical presentation of Kala-Azar is prolonged fever, asthenia, weight loss, anemia, splenomegaly, hepatomegaly and sometimes adenopathy. Splenomegaly appears early and increases gradually in relation to the duration of the disease. The subclinical forms of the disease have been described in the endemic areas (*Gulati et al., 2009*). Anaemia is responsible for an extreme paleness of the skin and mucosa which in Indian patients gives their skins a dark-greyish discolouration that in local language is called Kala-Azar (*Cook et al., 2003*)

3.2 Epidemiology of KA

Leishmaniasis has worldwide distribution ranging from intertropical zones of America and Africa, and extending into temperate regions of South America, Southern Europe and Asia. It affects as an estimated 350 million people throughout all these regions (*Cook et al., 2003*). World-wide there are an estimated 500,000 new cases of VL and more than 50,000 deaths from the disease each year (*Desjeux, P. 2004*). In the underdeveloped countries, Leishmaniasis remains a major public health problem. Over the last 15 years, endemic regions have been extending and there is a sharp increase in the number of recorded cases of the disease (*WHO, 1998*). Incidence in Kenya is not known, however it is estimated that Visceral Leishmaniasis in the eastern part of Africa causes at least 4 000 deaths annually (*Reithinger et al., 2007*). In east African countries epidemic outbreaks occurred in Sudan (1984–1994 and 1996-1997), Kenya and Ethiopia (2000–1) and Ethiopia and Eritrea (1997–1998) (*Schaefer et al., 1995; Chappuis et al., 2005*)

Much of KA in Africa is concentrated in East Africa (*Marlet et al., 2003*). Different profiles of cases with KA and outcomes have been described in East Africa. In Ethiopia, KA is commonly observed as an opportunistic infection in HIV infected adults with documented mortality rates up to 18.5% (*Diro et al., 1995*). In Upper Nile, Sudan, the majority of cases reported during a major outbreak from 1984 to 1994 were adults with death rates of 38–57% (*Schaefer, 1994*). In other regions of Sudan and in West Pokot of Kenya and Uganda it presents mainly as a pediatric problem. In the endemic area of Baringo County in Kenya changing lifestyle has led to a decreasing proportion of new KA cases among men (*Schaefer, 1994*).

In Kenya the disease is described in three provinces namely NEP, Eastern and Rift Valley. It is in Kenya caused by *L. donovani*. Previous reports of *L. infantum* are now considered misidentifications (*Jamjoom et al., 2004*). The main sandfly vector is *P. martini*, which breeds in termite hills, animal burrows, tree holes and house walls (*Mutinga et al., 1990*). It was first identified as the vector of *L. donovani* during an outbreak in Meru district in 1966, and has since then been incriminated as the VL vector in Rift Valley, Eastern and North Eastern Provinces, but the full extent of its geographical distribution remains unknown (*Heisch et al., 1962, Johnson et al., 1993*). Other possible vectors have been identified in North Eastern Province, including *P. celiae* and *P. vansomeranae*, both of which are associated with termite hills (*Heisch et al., 1962, Marlet et al., 2003., Heisch et al., 1956*). The only confirmed VL reservoir in Kenya is man. No animal reservoir is yet to be identified (*Mutinga et al., 1989*).

The actual incidence in Kenya is not known (*Schaefer et al., 1994; Ngumbi et al., 1998*). The incidence for KA in Wajir is also not known. The first recorded cases in Kenya were in 1935 (*Ashford et al., 1987*). Wajir County is however believed to have earlier had endemic pockets of KA before 1935. Seasonal flooding, open plain with tall anthills (see Figure 1) and the nomadic lifestyle of the population in Wajir increase the risk of exposure to the phlebotomine sand fly vector. Cutaneous Leishmaniasis has not been reported in Wajir (*Marlet, 2003*).

A recorded history of KA in Wajir County is summarized here below:-

1935: reported cases in Wajir and Mandera (*Ashford et al., 1987*)

1940: Second World War, outbreak of KA in battalion of servicemen in Wajir County (*Cole et al., 1942; Cole 1944*).

1950: major epidemic in the neighbouring Kitui and Isiolo Counties (*Fendall, 1952*)

1980: Outbreak of KA in Wajir and Mandera (*Sang, 1980*)

2001: 349 KA cases treated in Garissa, Wajir and Mandera (*Marlet, 2003*).

2008: Over 400 cases reported at the County Hospital (*Merlin Press Release, 2008*).

2010: A new outbreak reported (*Njau, 2010*).

Few studies have investigated KA risk factors in Kenya, and many reports are restricted to an examination of distribution by age, sex and occupation, or evaluations of immunity based on the Leishmanin skin test (*Manson-Bahr, 1961, Southgate, 1964, Southgate and Oriedo, 1967*). Several risk factors, including socio-economic status, proximity of compounds to termite hills, indoor transmission, cattle ownership, low use of mosquito nets and malnutrition, have been proposed, although a clear and consistent relationship between these factors and VL risk is difficult to demonstrate (*Schaefer et al., 1995*). For example, various studies have investigated the association between VL and living close to termite hills, which were thought is the resting and breeding place of *P.martini* (*Johnson et al., 1993*). Results were inconsistent and varied, with some studies in Kitui finding a positive association (*Heisch, 1954, Southgate, 1964, Southgate and Oriedo, 1962*), while no relationship is found in other areas such as Baringo and Machakos (*Schaefer et al., 1995a, Ho et al., 1982*). Visceral Leishmaniasis tends to be restricted to dry, hot lowland areas (*Kungu et al., 1972*). Increases in VL incidence have been associated with the rainy season. Sandfly density is greatest during and shortly after the rainy season, and thus it is likely that transmission during this period is greatest. Evidence from Kitui district supports this hypothesis, as peak VL incidence lagged six months behind the rainy season and peak sand fly density, correlating with the approximate six-month incubation period of the disease (*Southgate, 1977*).

Figure 2:- Wajir County plains with open grasslands, acacia trees and termite anthills



Source: - Researcher, 2008.

3.3 Impact of KA

Leishmaniasis has significant impact, both economic and social. In 2001, Leishmaniasis killed an estimated 51,000 people, including 40,000 in South Asia and 8,000 in Sub-Saharan Africa, representing 0.3 percent and less than 0.1 percent, respectively, of all deaths (Cattand *et al.*, 2006). Economically, Treatment for Leishmaniasis is expensive, especially for VL. For many countries, the cost of treating all Leishmaniasis patients would far exceed their total health budgets. In addition to drug costs, the additional costs of drug delivery can be high, especially

for patients in remote areas (*Cattand et al., 2006*). Social impact is seen in survivors of Leishmaniasis. Even self-limiting CL can leave disfiguring scars, which have associated stigma and may affect marriage prospects. Cutaneous Leishmaniasis can be disabling when lesions are numerous, and the most severe form, recidivans Leishmaniasis, is difficult to treat, long-lasting, and disfiguring (*Cattand et al., 2006*).

Victims of Leishmaniasis are generally “the poorest of the poor.” Research among the Pokot people of Kenya and Uganda identified low socioeconomic status and malnutrition as a major risk factor for VL (*Kolaczinsk et al., 2009*). A similar conclusion emerged from research in Bangladesh, India, and Nepal (*Mondal et al., 2009*). Leishmaniasis, however, “is not only the disease of the poor but a source of poverty itself”. It not only prevents the sufferer from working or studying, but VL also requires lengthy treatment far beyond poor families’ means (*Adhikari et al., 2009*)

To date in Kenya, no public health programmes by MoH or the private operators exist to prevent KA. It is evident from the figures of recent outbreaks above that KA has had a big negative impact in Wajir and is a public health problem. For example, the incidence of 349 reported cases treated by the medical charity Medecins Sans Frontiers (MSF) and MoH between May 2000 and February 2001 calculates to an incidence rate of 118/100,000 basing on population of Wajir County in 1999 as 294,290 (*KDHS 1999*). In 2008, 400 suspected cases were screened by a medical charity, Merlin and MoH in Wajir County Hospital, which calculates to an incidence rate of 60/100,000 using the 2009 KNBS census figures of Wajir County of 661, 941 (*KNBS, 2009*). Considering the nomadic culture and poor health seeking behaviour of the communities of Wajir it is safe to assume that the actual incidence during each of these outbreaks multiplied several fold. Thus in spite of the little published data what is on record shows that KA occurs frequently and affects many people in Wajir County.

3.4 Screening of KA

Screening and eventual diagnosis of KA is based on clinical presentation, epidemiological elements and non-specific biological parameters. Diagnosis is confirmed in the laboratory by direct detection of parasites (*Cook et al., 2003*). Detection of the parasitic form (amastigotes or LD bodies) in human or host tissue specimen, the tissue aspirate is the gold standard test for diagnosis of KA (*Kager, 1983*). Different tissue aspirates show different sensitivities for KA diagnosis namely splenic aspirate at 90 - 95%, bone marrow aspirate at 64 - 92% and lymph node aspirate at 52 - 65%. The most commonly used serological tests are the formal gel, Direct Agglutination Test (DAT) and the recently introduced rapid dipstick test called rK39.

The World Health Organization (WHO) diagnostic policy guidelines for health services in endemic areas states that a diagnostic policy should be drawn up that is specific for the health service, as the available laboratory techniques depend strongly on the level of the health system. This is summarized in Table 2 and guides that first-line centres and rural district hospitals in highly endemic areas, the rK39 antigen-based immuno-chromatographic test should be used (*World Health Organization TRS 949, 2010*)

Table 2:- *Minimal platform of techniques for diagnosis of visceral Leishmaniasis in highly endemic areas, by health system level (World Health Organization TRS 949).*

| Level of health system | Diagnostic tests |
|-----------------------------------|--|
| Primary health care centre | rK39 antigen-based immunochromatographic test |
| District hospital | rK39 antigen-based immunochromatographic test, direct agglutination test ¹ (DAT). Microscopy on bone marrow, spleen or lymph node aspiration ² |
| Tertiary care (referral hospital) | Serology: rK39 antigen-based immune chromatographic test, direct agglutination test, other serological test (e.g. IFAT, ELISA) Microscopy: on samples of buffy coat, spleen, bone marrow, lymph nodes. Culture or PCR |

¹ Direct agglutination tests should be used only if proper supervision and quality assurance are available at district

² Spleen and other aspirations should be performed only by experienced medical personnel and if facilities to treat bleeding complications are available.

Thirty studies evaluating DAT and thirteen studies evaluating the rK39 dipstick found the combined sensitivity estimates of DAT and the rK39 dipstick were 94.8% and 93.9% respectively. The rK39 dipstick showed a sensitivity of 97% and a specificity of 71%. In one study in Nepal, DAT was up to 99% sensitive with a low cut-off titre (1:400) but its specificity did not exceed 82% even with a high cut-off titre (1:51 200). The researchers concluded that diagnostic performance of the DAT and the rK39 dipstick for KA was good to excellent and seem comparable and that both tests could be used for screening suspect patients in endemic areas (*Chappuis, 2003 and 2006*). Both DAT and rK39 are therefore considered valid for screening for KA. Both DAT and rK39 as tests for KA also meet the scientific criteria for selecting a screening or diagnostic test (table 3).

Table 3: Criteria for a useful screening or diagnostic test (*Sullivan, 2004*).

| |
|--|
| Disease should be serious or potentially so. |
| Disease should be relatively prevalent in the target population |
| Disease should be treatable |
| Treatment should be available to those who test positive. |
| The test should not harm the individual. |
| The test should accurately classify diseased and non-diseased individuals. |

In Kenya, DAT is more commonly used and the recommended first line screening and diagnostic test of KA by the MOH. DAT titres >1:3200 have been found to have a sensitivity of 94% and a specificity of 72% (*Zijlstra, 1992*). DAT was specifically developed for the field but it is still difficult to use in remote conditions because it is laborious, requires high technical expertise and is expensive to manufacture (*Meredith, 1995*). A simpler, faster, non-invasive dipstick test called rK39 was developed to screen for KA in the field. The rK39 was developed using the cloned antigen of amino acids of a gene found in *Leishmania chagasi* (*Zijlstra, 1998*). Thirteen studies evaluating the rK39 dipstick found an average sensitivity of 97% and a specificity of 71% (*Chappuis, 2003 and 2006*).

3.4.1 Screening/Diagnosis of KA in Kenya.

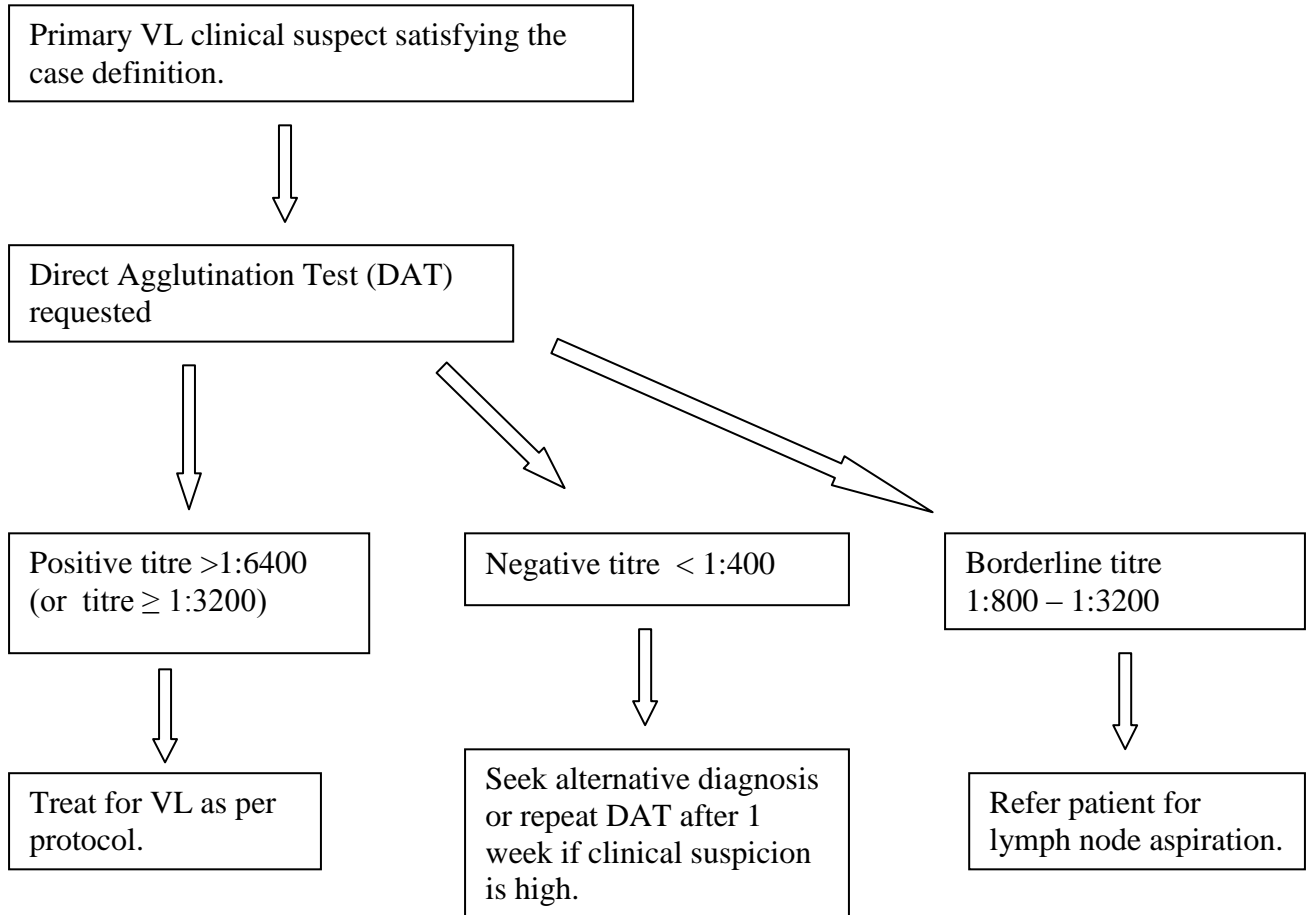
Algorithm of KA screening and diagnosis.

The MOH developed a diagnostic guideline for KA for primary health care system based on WHO diagnostic guidelines. The MOH diagnostic guideline is summarized in the algorithm in Figure 3.

3.4.2 Challenges of KA testing in Wajir.

The two screening tests for KA, DAT and rK39 were available in Wajir and were used variably by MOH as well as medical charities operating in Wajir. MOH officially recognized DAT only as baseline diagnostic test of KA (Figure 3). However, laboratory testing for KA in Wajir County Hospital was done using DAT and rK39 in keeping with the Medecins Sans Frontiers (MSF) algorithm (figure 5). Occasionally splenic aspirates were done when skilled clinicians and laboratory support services were available. Until now the District hospital has at most two junior doctors and this coupled with the poor infrastructure at the hospital and the high workload makes the doctor often unavailable for the splenic aspirate (*Merlin Press Release, 2008*). As a result, most of the diagnosis of KA in Wajir was done by a combination of clinical examination, formal gel test, rK39 and DAT.

Figure 3:- MOH Diagnostic Algorithm of KA.



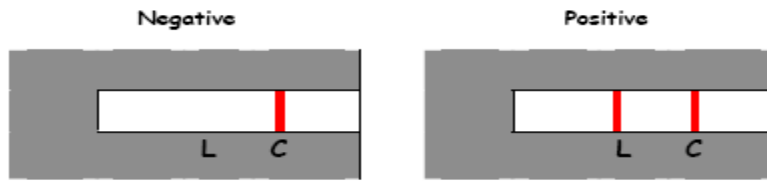
Source: - Kala-Azar Diagnostic Guide. Ministry of Health, 2001.

3.4.3 Performing rK39, DAT and splenic aspirate tests.

Repeat Kinesin 39 (rK39)

Repeat Kinesin 39 - is a rapid dipstick serological test for Kala-Azar made using cloned antigen (recombinant protein) of 39 amino acid repeats of a kinesin like gene found in *Leishmania chagasi*. Variants of rK39 protein are rK9, rK26, rKE16 etc. which have been used in test kit development but with less effectiveness compared to rK39 (Mohapatra et al., 2010). *Diamed-IT LEISH™* was the most common trademark of rK39 in Kenya and Wajir County. Other common trademarks worldwide include *Kalazar Detect™* from Inbios, *Leishmania Rapid Test Strip* from Intersep and *Recombinant K39 Strip Test* from Arista Biologicals (Maia et al., 2012). *Diamed-IT LEISH™* is a test strip for KA testing using whole blood or serum (figure 4). It is easy to use and read and gives results in 10 minutes as a visible colour change on the test strip (Koert et al., 2006). Urine is also used for testing using other types of test strips

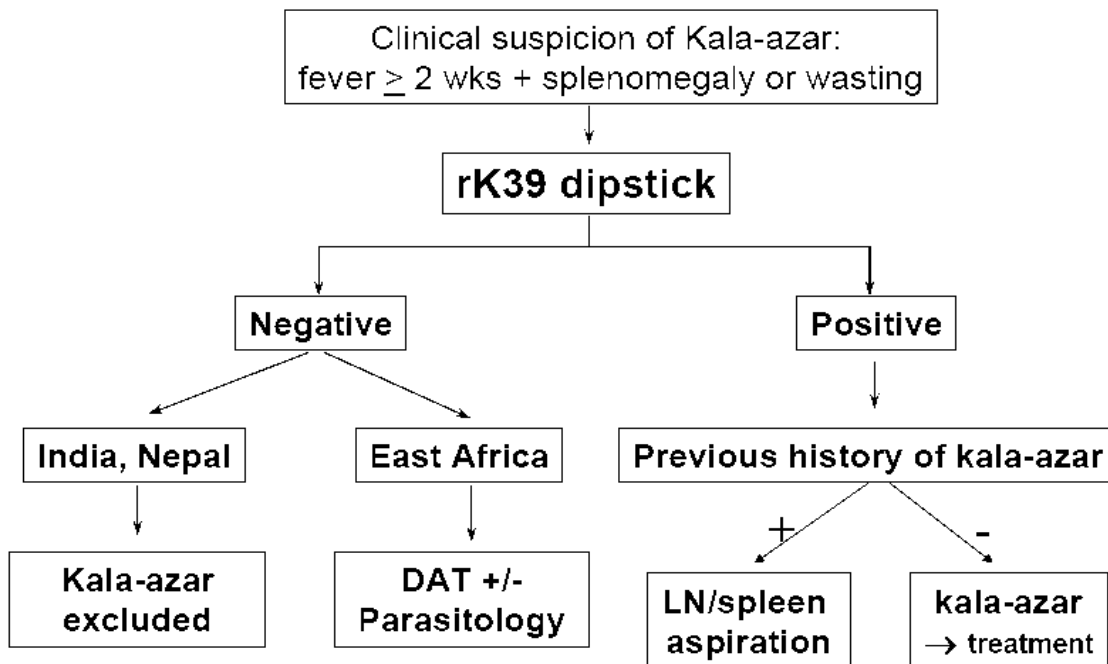
Figure 4:- rK39 dipstick testing for KA using whole blood or serum.



Source:- TCS Biosciences Ltd, 200.

Figure 5:- Medecins Sans Frontieres (MSF) Diagnostic Algorithm for KA.

Field diagnostic algorithm



Source:- Dr François Chappuis, Geneva University Hospital & Médecins sans Frontières (MSF). Geneva Forum: «Global Access to Health», 2006.

Direct Agglutination Test (DAT)

DAT test is done by applying a drop of whole blood on a special filter paper, which is then sent to the laboratory for titration and assay. Blood is collected from the finger or a vein and dropped onto the filter paper, which is then preserved in a foil paper before being sent to the laboratory. At the laboratory, serial dilutions of the patient's blood are titrated with the Leishmania antigen. Cut off dilution for a positive test on DAT varies from 1:800 to 1:6400 (Maia et al., 2012). The test is incubated at room temperature for 8 - 12 hours and then read (Boelaert et al., 2007). A reaction with the antigen at a preset minimum titration denoted a positive test. Only in Nairobi were found laboratories that do this test (Merlin Press Release, 2008). This need for specialized laboratory and the delay in reading results were some of the already cited drawbacks of DAT testing in Wajir.

Splenic aspirates

Aspiration of the spleen is done under local anaesthetic by the intercostal route or the abdominal route for those with large spleens (>3cm below costal margin). Wide bore needles are used. Aspirates are examined parasitologically for the presence of amastigotes. Pain may occur immediately after aspiration and requiring a few analgesic tablets. Gastro-intestinal haemorrhage is the greatest risk and is managed with blood transfusion (*Thakur, 1997*).

3.4.4 Ministry of Health Policy for Screening and Diagnosis of KA.

Ministry of Health policy and KA diagnostic algorithm as well as those used by medical charities like MSF recognized DAT only as the baseline test for KA, (*Njau J, 2010*). However in Wajir rK39 was then widely used to screen and diagnose KA. Specimens from Wajir were usually shipped to Nairobi Kenya Medical Research Institute (KEMRI) or African Medical Research Foundation (AMREF) laboratories for analysis and results communicated to the field one or two weeks later (*Merlin Press Release, 2008*).

Compared to universal standards, the diagnosis of KA in Wajir was below standards and was time consuming. Definitive diagnosis of KA should be based on the detection of the parasite or its DNA in patient specimens, the nature of which depends on the type of Leishmaniasis being tested (*Cook et al., 2003*). This means that the tests used commonly in Wajir were screening not diagnostic tests. Because of the low socio-economic status of the Wajir County, however the standard tests will take a while before they are universally available.

Studies on the diagnostic performance of DAT compared to rK39 have been done in many of the regions of the world where KA is endemic namely Asia, Mediterranean coast, South America and Sub-Saharan Africa. In a meta-analytic study of the diagnostic performance of the DAT and rK39 diagnosis of KA, the performance of DAT and rK39 dipstick were compared using different studies that had been done between the years 1986 and 2004 (*Chappuis et al., 2006*). The selection criteria was original studies evaluating DAT or rK39 dipstick with clinical visceral Leishmaniasis as target condition; adequate reference classification; and absolute numbers of true positive, true negative, false positive, and false negative observations available or derivable from the data presented. Thirty studies evaluating DAT and thirteen studies evaluating the rK39 dipstick met the inclusion criteria. The combined sensitivity estimates of DAT and the rK39 dipstick were 94.8% (95% confidence, interval 92.7% to 96.4%) and 93.9% (87.7% to 97.1%), respectively. The researchers concluded that diagnostic performance of the DAT and the rK39 dipstick for KA was good to excellent and seem comparable.

An East African study compared three diagnostic tests for KA; the freeze-dried direct agglutination test (FD-DAT), the rK39 dipstick and a urine latex antigen test (KAtex), were evaluated for use in primary care in East Africa and the Indian subcontinent (*Boelaert et al., 2000*). Clinical suspects were prospectively recruited and tissue, blood and urine samples were taken. Direct microscopic examination of tissue smear, and FD-DAT, rK39 and KAtex were

performed. Sensitivity and specificity with 95% confidence level were estimated using Bayesian latent class analysis. On the Indian subcontinent both the FD-DAT and the rK39 strip test exceeded the 95% sensitivity and 90% specificity target, but not so in East Africa. Sensitivity of the FD-DAT was high in Ethiopia and Kenya but lower in Sudan, while its specificity was below 90% in Kenya. Sensitivity of the rK39 was below 80% in the three countries, and its specificity was only 70% in Ethiopia. KAtex showed moderate to very low sensitivity in all countries. FD-DAT and rK39 can be recommended for clinical practice on the Indian subcontinent. The study concluded that in East Africa, their clinical use should be carefully monitored and that work was needed to improve existing formats, and to develop better KA diagnostics.

3.5 Cost Effectiveness Analysis

Cost-Effectiveness Analysis (CEA) is a principal analytic tool which compares the cost of an activity, called an *intervention*, with the known or expected health gain (*Gold et al., 1996*). The results of such an evaluation are typically summarized in a cost-effectiveness ratio (CER), where the denominator reflects the gain in health from the candidate intervention and the numerator reflects the cost of obtaining that health gain. This ratio corresponds to the concept of (health) value for money. Favoring activities that are more cost-effective over those that are less so is consistent with the ethical view that "limited resources for health should be allocated to maximize the health benefits for the population served" (*World Bank, 1993*). The central purpose of cost effectiveness analysis is to compare the relative value of different interventions in creating better health or longer life. A cost effectiveness analysis provides information that can help decision makers sort through alternatives and decide which one best serves their programmatic and financial needs (*Gold et al., 1996*)

Cost-effectiveness and disease burden are related because effectiveness is the reduction in burden caused by an intervention. This relationship holds true at the individual level. The magnitude of a health problem—the total burden in the population—is irrelevant for marginal changes in resource allocation. However, it matters for large changes from the status quo. Health interventions demand managerial capacity as well as financial and physical resources, and managerial ability may be stretched thin if it has to deal with a large number of interventions. In consequence, it may be efficient to concentrate on relatively few and somewhat less cost-effective interventions, provided they attack substantial burdens, rather than many other interventions that are more cost-effective but affect only small burdens. Moreover, even for a cost-effective intervention, high prevalence or incidence may make the cost of covering the whole potential beneficiary population prohibitive (*Levin et al., 2001*) .

Cost-effectiveness is only one of at least nine criteria relevant for priority setting in health if the object is to decide how to spend public funds (*Musgrove 1999*). Others are cost itself, equity, adequacy of demand and public attitudes and wants. Two criteria—whether an intervention is a public good and whether it yields substantial externalities—are classic justifications for public intervention, because private markets could not supply them efficiently, just as in other sectors. The emphasis is on value for money—that is, whether an

intervention is worth buying, not who pays for it and when one is choosing which public goods to buy, several criteria become irrelevant, and cost-effectiveness can be used as the chief or even the only consideration. Cost-effectiveness can similarly determine what to include in a mandatory universal public package of health care alongside competitive voluntary insurance (Smith, 2005).

It is noteworthy however that cost-effectiveness analysis measures technical efficiency, not allocative efficiency meaning that the most cost-effective alternative is not necessarily the most useful, qualitative or most worth doing - meaning that it may not be allocatively efficient (Boardman et al, 1996). When allocative efficiency is required a cost-utility analysis or cost-benefit analysis is done and these two measures are used most in the health care domain. There are two main approaches in measuring health related quality of life: disability adjusted life years (DALYs) and quality adjusted life years (QALYs). DALYs assign each health state on a scale and calculates the years of healthy life lost while QALYs oppositely assigns to the scale by calculating the years of healthy life gained by intervention (Mullahy et al., 2001). Usually QALYs is used in cost-utility analysis while DALYs is used in cost-effectiveness analysis.

The main shortcoming of cost-effectiveness analysis is that cost data can be extremely hard to find in developing countries (Garber, 2000). Ideally, cost-effectiveness analysis should include direct costs such as doctors' or nurses' time and supplies used as well as indirect costs such as a portion of administrative costs. Still, the cost of equipment also needs is spread across its many uses (Gold et al., 1996). Cost-effectiveness can conflict with both kinds of equity—that is, the more cost-effective of two interventions may also lead to a less equitable distribution of health benefits.

Equity and cost-effectiveness are compatible when a cost-effective intervention is provided to only part of the population that would benefit from it because everyone in the group suffers from the same problem (Levin et al., 2001). Then expanding coverage will generally also promote horizontal equity. When an intervention is reaching only part of a potential beneficiary population and those not benefiting tend to have more severe illness, then expanding coverage can improve both horizontal and vertical equity.

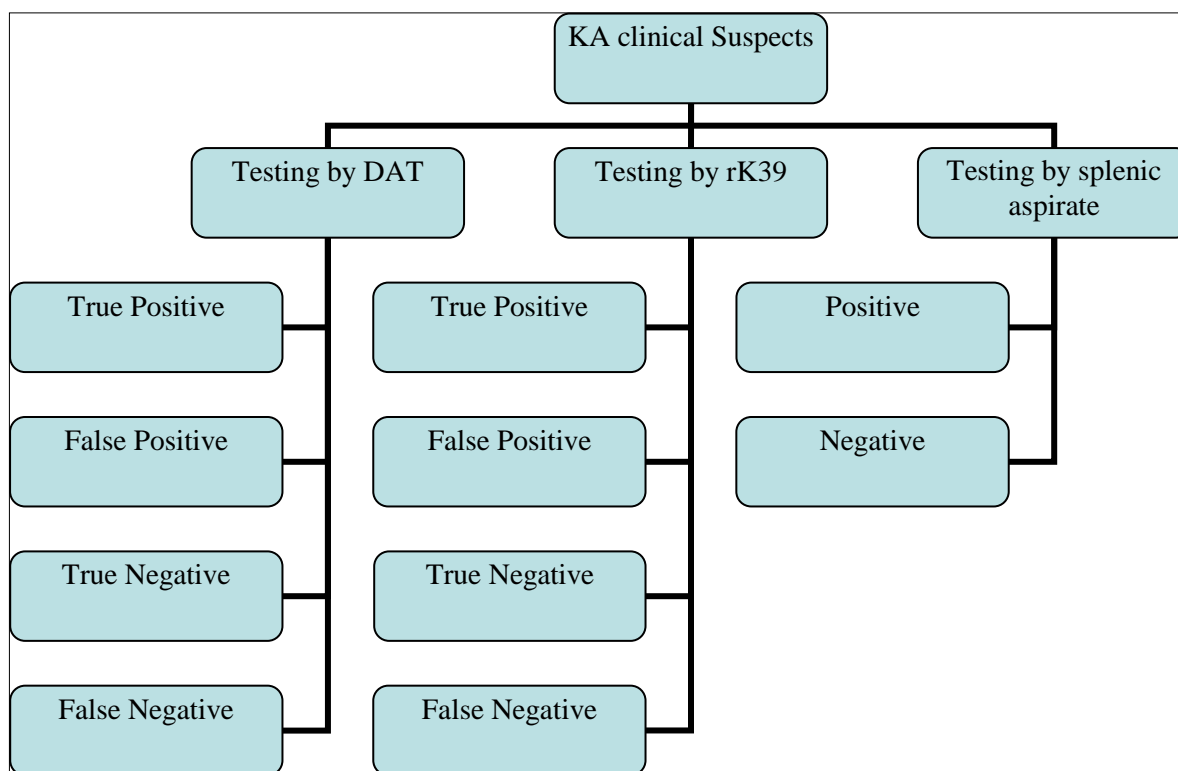
Local studies of cost-effectiveness of common disease diagnostic tests were not available. This was especially true of Kala-Azar tests. What local studies were available were those on comparison of Kala-Azar diagnostic tests' sensitivities and specificities which I have already cited in preceding pages.

Chapter 4: Materials and Methodology.

4.1 Study design

This was a hospital-based, cross-sectional, descriptive study of the technical efficiency, by way of cost-effectiveness analysis, of testing KA suspected patients in Wajir County with DAT and rK39. Clinical decision analysis approach and diagnostic odds ratio were for results analysis. A decision tree describing the possible alternative testing strategies (figure 6) together with their probabilities was used to make a judgment of clinical and economic consequences of each possible testing strategy. The probabilities were test validities attached to the various KA testing strategies in Wajir.

Figure 6:- Decision Tree for competing testing strategies for KA in Wajir



Source: - Researcher.

The branches of the decision tree lead to the following outcomes:-

1. KA – correctly diagnosed
2. KA – erroneously diagnosed
3. KA – correctly undiagnosed
4. KA – erroneously undiagnosed

Secondary medical records of newly suspected KA cases seen in Wajir County Hospital and subjected to splenic aspirate test and both DAT and rK39 from January to December 2008 was used. A cost effectiveness ratio was calculated as the cost per morbidity averted. The study period was chosen to coincide with the period of the recent reported outbreak of KA in Wajir

in the year 2008. A study of records of cases at Wajir County Hospital was done. Study subjects were the suspected patients' laboratory records indicating the results and costs of the three KA tests namely rK39, DAT and splenic aspirate.

The tests under study were rK39 and DAT but splenic aspirate had a special supportive role in the study. It was used a control test to determine the validity (sensitivity and specificity) of both rK39 and DAT because it is the gold standard test for diagnosis of KA in Kenya. As such if the results of rK39 or DAT agreed or disagreed with those of splenic aspirate the rK39 or DAT was deemed valid or invalid and thereafter its specificity and sensitivity could be calculated as illustrated in table 5 below. In the end the data collected from the records under study was quantitative and binary for each test subject for all tests i.e.:-

1. Test results – negative or positive for KA for each of the three tests. From these results, the rK39 and DAT validity was determined i.e. which test was true or false positive or negative.
2. Costs of test - a monetary value spend in doing each test. This determined which test was more or less costly.
3. Ease of performance – a chart for the number of steps and processes involved in performing each test at the laboratory. This was used to determine the ease of test performance.

4.2 Variables

Independent Variables.

Tests under study – DAT and rK39 and Splenic Aspirate as the control test.

Dependent Variables.

Validity, Cost of and Ease of Performance of test.

4.3 Study Area

Wajir County

The study was carried out in Wajir County Hospital which is the only referral/secondary healthcare level hospital in Wajir County. Wajir County is one of the three counties that make up the North Eastern Province (NEP). Wajir has a total area of 56, 501 square kilometres. The population was 661, 941 (KNBS, 2010) and was mostly nomadic pastoralists (seventy percent). The remaining thirty percent were scattered in few urban dwellings. Poverty levels were high and livelihoods depended on livestock which were adversely affected by the weather. The drought of 2008 for example killed about 75% of the stocks.

Table 4: Wajir County - Population and Size.

| Division | Area (km ²) | Population (2009) |
|----------|-------------------------|-------------------|
| Total | 56,501 | 661, 941 |

Source: Survey Department (Wajir)-1996, KNBS 2009 census.

4.4 Target population

Target population was all secondary laboratory records for year 2008 relating to all the patients who were suspected of KA as per the case definition. This population was a sub-set of the medical records of the general population of inhabitants of Wajir County who presented at the county hospital with medical suspicion of Kala-Azar.

4.5 Study population

Study population was all secondary laboratory records for year 2008 relating to all the patients suspected of KA as per the case definition and were tested with splenic aspirate, DAT and rK39 tests.

Inclusion criteria was records of first time patients suspected of KA as per the case definition, who presented at the Wajir County Hospital in 2008 and who had rK39, DAT and splenic aspirate tests done on them. First time patients refers to those who had contracted disease for the first time (and excluded re-lapsed or re-treatment cases)

In the **exclusion criteria** all records that were illegible, indeterminate or incomplete as far as test results and/or cost of tests done were excluded.

4.6 Sampling procedure

Convenience sampling was done whereby all laboratory records on KA suspected patients who were tested with splenic aspirate, DAT and rK39 in the year 2008 and met the inclusion criteria, were studied. Convenience sampling was chosen because a sampling frame constructed as per the inclusion-exclusion criteria yielded a small frame of 65 records thereby making the need of classical sampling unnecessary.

4.7 Sample Size

Because convenience sampling was done, all laboratory records on KA suspected patients who met inclusion-exclusion criteria were included in the study. From the sampling frame constructed 65 records met the criteria and thus all the 65 records were included in the study making the sample size 65. This sample was a sub-set of the records of the general population of inhabitants of Wajir County who attended hospital suspected of Kala-azar and thus statistical inferences could be derived from them and applied to the general Wajir population.

4.8 Data type, data collection and tools

Dichotomous, nominal quantitative data relating to DAT and rK39 was collected in this study. The data was collected thus:-

1. Test results for splenic aspirate, DAT and rK39 tests done on suspected KA patients. From these results, the tests validity was determined.

2. Costs related to testing suspected patients for KA using DAT and rK39. From these costs average costs related to testing for DAT and rK39 was calculated.
3. Procedural steps involved in performing the DAT and rK39 tests. From these steps the ease of performance of the tests was determined.

Data was collected by:-

1. Review of secondary data of all tested suspected KA cases.
2. Review of financial records of all suspected KA cases.
3. Review of the testing procedures used for rK39 and DAT.

Data was collected using a specific data entry sheets and comprised the following:-

1. Itemised test results for rK39, DAT and splenic aspirate.
2. Itemised monetary costing of rK39 and DAT test elements for each patient.
3. Listing of procedural steps undertaken for rK39 and DAT for each patient tested.

A sample of each of the data entry sheets used is provided in Appendix 2 and 3.

4.9 Data processing and analysis

Clinical decision analysis and Diagnostic Odds Ratio (DOR) were the principle approaches to analysis. Data was analyzed by standard statistical quantitative methods. Data was organized using EPI-INFO version 3.3.2 for Windows to enhance quality and minimize entry errors. Statistical Package for Social Sciences (SPSS) version 14 for Windows was used for analysis. Cost-effectiveness ratio was calculated as the cost per morbidity averted. Ease of test performance was an additional measure to the cost-effectiveness. The resultant conclusions were a statement on which test was more cost-effective in the Wajir setting. The discussion below illustrates model approaches that was used to achieve the three basic study objectives namely determination of test validity, ease of test performance and cost of testing.

4.9.1 Standard approaches used to test validity, cost and ease of test performance.

a) Determination of test validity.

The Table 5 summarizes how the tests validity was determined.

Table 5:- Test validity.

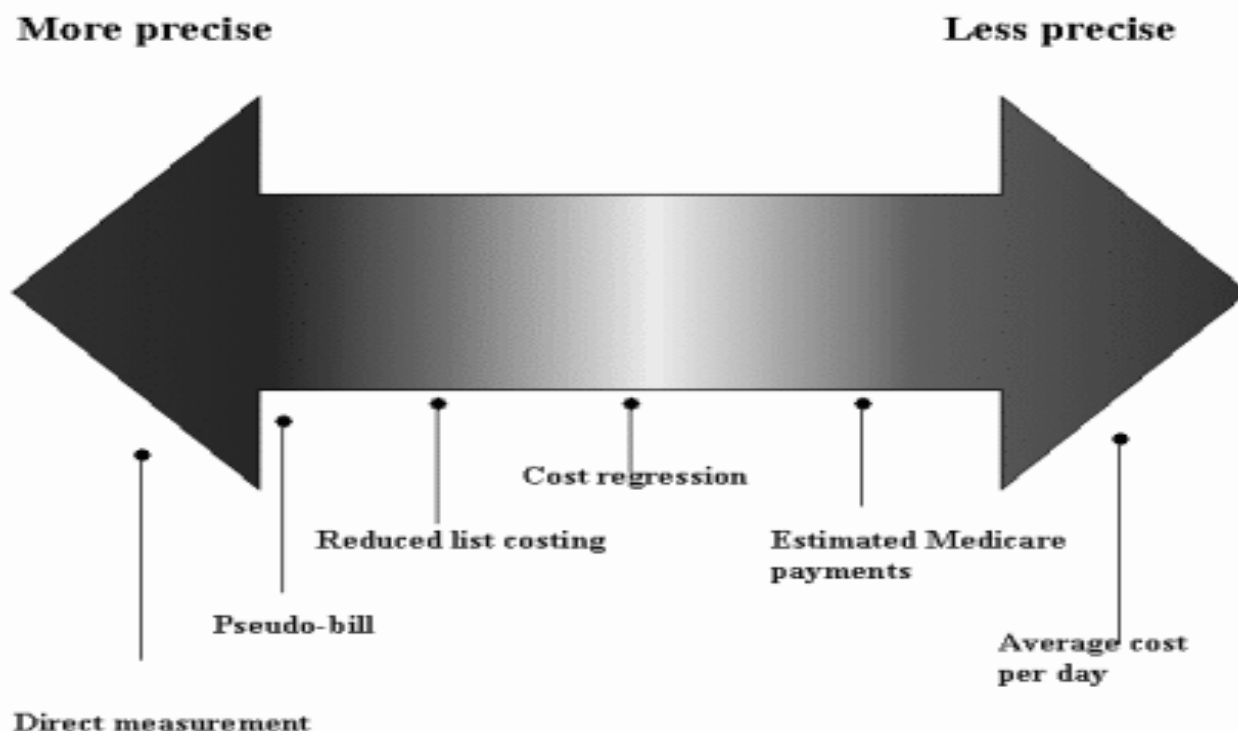
| | | | |
|----------------------|---|--|------------------------------------|
| Positive test | True Positive (A) Splenic Aspirate(SA) +ve but rK39 or DAT +ve | False Positive (B) SA -ve but rK39 or DAT +ve | All Positives (A+B) |
| Negative test | False Negative (C) Splenic Aspirate (SA) +ve but rK39 or DAT –ve | True Negative (D) SA –ve but rK39 or DAT –ve | All Negatives (C+D) |
| Population | All infected (A+C) | All uninfected (B+D) | All population (A+B+C+D) |

Source:- WHO Somalia Office, 2008

b) Determination of test cost.

Cost determination for health interventions was difficult to undertake. A spectrum of cost determination methods (see Figure 7) was considered as a guide principle. Accounting and billing systems use direct measurement methods, whereby very detailed estimates of time and products (inputs) are combined with unit costs to estimate total costs. The highly precise methods, such as direct measurement, are extremely challenging because a single inpatient stay or outpatient procedure might have hundreds or thousands of inputs. Even when there was just a single input, such as a pill of medication, the cost can vary by location or day. Researchers can use less precise methods, such as an average cost per day. These methods are easier than the more precise methods to use, but their ease of use comes at a cost of decreased precision. Researchers need to identify the level of precision necessary for their study (Garber, 2000).

Figure 7:- Methods of cost estimation.



Source:- Garber, 2000.

Blending two or more methods in a study is frequently needed because a researcher might need to estimate the cost of an intervention and the cost of subsequent health care (Garber, 2000). This study used direct laboratory cost measurement to determine the costs incurred to test for KA using DAT and rK39. As will be discussed in detail later, costing in this study was however problematic and hence a limitation of the study because of the existing inadequate cost records the study area.

c) Determination of ease of performance of rK39 and DAT.

For the ease of doing the test the study compared a listing of the steps, processes and material inputs involved in each test namely the steps, time taken and the skills involved. The

test with least steps/processes/inputs was considered the one with most ease of performance. Table 6 summarizes how this was to be captured.

Table 6:- Ease of test performance.

| | DAT test | | | rK39 test | | |
|-------|------------|--------------|----------------------------|------------|--------------|----------------------------|
| | Test steps | Process time | Special skills & equipment | Test Steps | Process time | Special skills & equipment |
| 1 | | | | | | |
| 2 | | | | | | |
| TOTAL | | | | | | |

Source:- Researcher

4.10 Minimization of error

Minimization of error and bias was done at three contiguous levels:-

1. Selection bias – All study population was studied without sampling.
2. Recall bias - Data was collected from existing records only.
3. Matching – The study subjects selected had undergone all the three tests.
4. Data analysis - To reduce operator error computer based statistical software (SPSS version 14) was used.
5. Confounders – The exclusion of relapse and re-treatment cases from the study population eliminated confounding due to latency and reverse sero-conversion.

4.11 Limitations of study at the data collection stage

- 1 Inadequate local data on KA – Data on the KA situation in Kenya and Wajir was inadequate especially disease occurrence rates and epidemiologic patterns.
- 2 Inadequate technical expertise – Qualified medical staffs in Wajir were inadequate and so only a few splenic aspirates were done limiting the sample size.
- 3 Test cost determination –most of the test kits were donated to the Wajir County Hospital and so ascribing a cost of procurement to them was difficult.

4.12 Ethical considerations

Ethical issues were taken into consideration in two main areas.

Ethical issues related to the study. Authority for the study was sought from the Ethics Committee of the University of Nairobi and the Kenyatta National Hospital, which is mandated by the MOH to give such authority. At the Wajir County Hospital the authority of the hospital management committee was sought.

1. Ethical issues concerning the subjects of the study. The study was done on patient's records only. Standard stipulations of clinical ethics like clinical information confidentiality and appropriate accountability and feedback were observed.

Chapter 5: Results and Analysis

Data collection was done between 1st and 18th April 2012 at Wajir County Hospital, KEMRI Nairobi Laboratories and Merlin Kenya Country Offices. A total of 364 patients were seen during the year 2008 out of which 65 newly suspected patients had all the three tests done on them. Data collected was exclusively secondary and was in three categories:-

1. Test results of Kala-Azar suspected patients who underwent all the three KA tests rK39, DAT and splenic aspirate.
2. Monetary cost of rK39, DAT and splenic aspirate test for each patient paid directly by the patient and incurred by the testing facility.
3. Listing and discussion of the procedural steps undertaken by the testing facility to do the rK39, DAT and splenic aspirate test and special equipment required.

The data was collected using the data forms shown in the Appendix 2 and 3 and the next section summarizes the data obtained and calculations derived from it.

5.1 Summary Results I – Test Validity

65 study cases whose KA test results were studied are summarized in Table 7.

Table 7:- Wajir study results summary

| | Result Description | DAT (titre >1:3200) | rK39 |
|---|---------------------------|-------------------------------|-------------|
| 1 | True +ve | 50 | 48 |
| 2 | False +ve | 2 | 5 |
| 3 | All +ve | 52 | 53 |
| 4 | True –ve | 12 | 9 |
| 5 | False –ve | 1 | 3 |
| 6 | All -ve | 13 | 12 |
| 7 | Total | 65 | 65 |

Source:- Researcher

5.2 Summary Results II – Cost and Ease of Test Performance

**Note1:- Only cost of test equipment and materials was considered. Cost of depreciation of equipment, labour, utilities and time was not considered*

**Note 2:- All DAT testing was done by AMREF in Nairobi while all rK39 were done at the Wajir County Hospital. All splenic aspirates were done and examined by the hospital.*

Table 8 summarizes the data obtained concerning the cost of the KA tests and the ease of performance of the tests.

Table 8: - Cost and Ease of Performance of DAT and rK39 in Wajir.

| Test Detail | DAT | rK39 | SA |
|--|--------------|------------|--------|
| *Note:- All cost in Kenya shillings (KES) | | | |
| Average cost per patient health service (laboratory) costs. | 747 | 45 | 900 |
| Average cost per patient screening costs | - | - | - |
| Ease of test performance (steps involved) | 4 | 2 | 5 |
| Ease of test performance (time spent at testing) in minutes/days. | 1445 minutes | 10 minutes | 3 days |
| Ease of test performance (number of specialised skills required) | 2 | 1 | 6 |
| Ease of test performance (number of specialised equipment required) | 7 | 0 | 7 |

Source:- Researcher

Operational definitions:-

1. *Health service costs or laboratory costs – costs incurred by the laboratory to procure and avail test material and specialised equipment*
2. *Screening costs – costs paid by the patient at the laboratory to have the test done.*
3. *Specialised skills – skills that the human resource at the laboratory require in order to undertake the test.*
4. *Specialised equipment – equipment at the laboratory that was exclusively used for testing KA using either of the testing methods under study.*

5.3 Results Analysis

Clinical decision analysis and diagnostic odds ratio (DOR) were used to analyze the results in order to calculate the cost-effectiveness. The tests DAT and rK39 were used independently as non-competing choices during this time and therefore average cost-effectiveness ratio for both was calculated and compared.

Quantitative indicators of test performance namely test specificity, sensitivity and predictive values were calculated. Test performance was further analysed by the odds ratio. The odds ratio is a familiar statistic in epidemiology, expressing the strength of association between exposure and disease. As such it also can be applied to express the strength of the association between test result and disease. This was done in this study. While test specificity, sensitivity and predictive values are good indicators of test performance their interpretation is dependent on disease prevalence which in this study was not known. The odds ratio as an alternative indicator of test performance is an option that is not prevalence dependent, and may be easier to understand, as it is a familiar epidemiologic measure (*Afina S et al., 2003*)

Data collected was entered on computer statistical software SPSS 14 from where it was analyzed. Cost and effectiveness were separately calculated then a final calculation of the cost-effectiveness ratio was done. Ease of test performance was used as a parameter

supplementing cost-effectiveness in making a judgment about the suitability of each test in Wajir.

5.4 Validity of DAT and rK39 in Wajir.

Test validity for DAT and rK39 in Wajir was the sensitivity, specificity, predictive values and odd's ratios calculated from the results data as defined below:-

1. *Test Sensitivity* – the probability that a test was positive for a true patient.
2. *Test Specificity* - the probability that a test was negative for a non-patient.
3. *Test Positive Predictive value (PPV)* – the probability that a patient will have the condition given a positive test result.
4. *Test Negative Predictive Value (NPV)* - the probability that a patient will not have the condition given a negative test result
5. *Diagnostic Odds Ratio* – strength of association between test result and disease.

The results obtained in Wajir based on the generic test validity Table were summarized in Tables 9 and 10:-

Table 9:- Wajir study 2x2 Table for DAT

| | | | |
|---------------|-----------------------------|-----------------------------|-----------------------------|
| Positive test | (TP) True Positive (A) = 50 | (FP) False Positive (B) = 2 | All Positives (A+B) =52 |
| Negative test | (FN) False Negative (C) =1 | (TN) True Negative (D) = 12 | All Negatives (C+D) =13 |
| Population | All infected (A+C) = 51 | All uninfected (B+D) = 14 | All population (A+B+C+D)=65 |

Source:- Researcher

Table 10:- Wajir study 2x2 Table for rK39

| | | | |
|---------------|-------------------------|---------------------------|-----------------------------|
| Positive test | True Positive (A) = 48 | False Positive (B) = 5 | All Positives (A+B) =53 |
| Negative test | False Negative (C) =3 | True Negative (D) = 9 | All Negatives (C+D) =13 |
| Population | All infected (A+C) = 51 | All uninfected (B+D) = 14 | All population (A+B+C+D)=65 |

Source:- Researcher

From the tables above the calculations of test validity in Wajir are shown below:-

5.3.1.1 Sensitivity = (True +ve / True +ve + False -ve) x 100%

Sensitivity of DAT in Wajir = $(50 / (50+1)) \times 100\% = 98\%$

Sensitivity of rK39 in Wajir = $(48 / (48+3)) \times 100\% = 94.7\%$

5.3.1.2 Specificity = (True -ve / True -ve + False +ve) x 100%

Specificity of DAT in Wajir = $(12 / (12+2)) \times 100\% = 86\%$

Specificity of rK39 in Wajir = $(9 / (9+5)) \times 100\% = 64\%$

5.3.1.3 Positive Predictive Value (PPV) = TP/(TP+FP)

The positive predictive value of DAT in Wajir = $50 / (50+2) = 96\%$

The positive predictive value of rK39 in Wajir = $48 / (48+5) = 91\%$

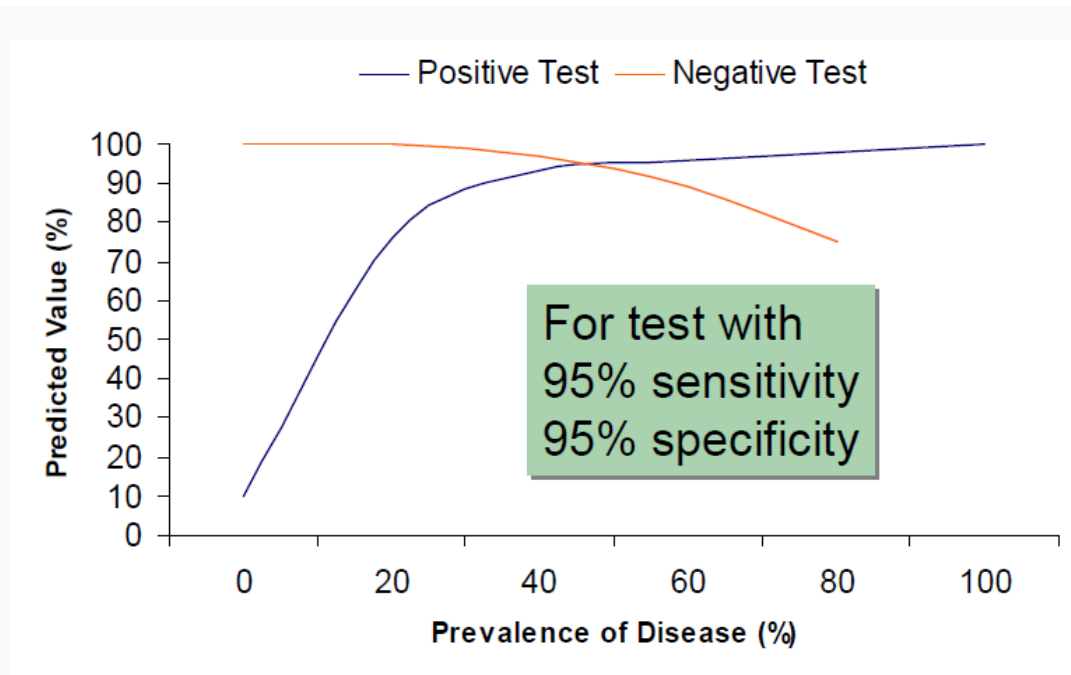
5.3.1.4 Negative Predictive Value (NPV) = TN/(TN+FN)

The negative predictive value of DAT in Wajir = $12 / (12+1) = 92\%$

The negative predictive value of rK39 in Wajir = $9 / (9+3) = 75\%$

The predictive value of a test depends on the prevalence of a disease in the population tested, and the sensitivity and specificity of the test itself, (*Johns Hopkins University and Sukon Kanchanaraksa, Creative Commons Attribution, 2008*). Generally as the prevalence of a disease in a population rises the positive predictive value (PPV) of the disease's test also rises while the negative predictive value (NPV) falls. This relationship is summarized in the Figure 8.

Figure 8:- Relationship between disease prevalence and test predictive value.



Adapted from Mausner JS, Kramer S. *Epidemiology: an Introductory Text*. Philadelphia, WB Saunders 1985, p221.

The prevalence of KA in Wajir/Kenya was not known therefore the actual predictive values for DAT and rK39 in Wajir could not be calculated. It is however estimated that Visceral

Leishmaniasis in the eastern part of Africa causes at least 4 000 deaths annually (*Reithinger R et al., 2007*). World-wide there are an estimated 500,000 new cases of VL and more than 50,000 deaths from the disease each year (*Desjeux, P. 2004*).

5.4.1 Diagnostic Odds Ratio (DOR)

DOR is defined as the ratio of the odds of disease in test positives relative to the odds of disease in test negatives.

$$\text{DOR} = (\text{TP}/\text{FP}) / (\text{FN}/\text{TN}) \text{ or } \text{PPV}/(1-\text{PPV}) / (1-\text{NPV})/\text{NPV}$$

Confidence intervals for range estimates and significance testing was calculated as:-

$$\text{SE}(\log \text{DOR}) = \sqrt{(1/\text{TP} + 1/\text{TN} + 1/\text{FP} + 1/\text{FN})}$$

A 95% confidence interval of the log DOR was chosen and calculated thus:-

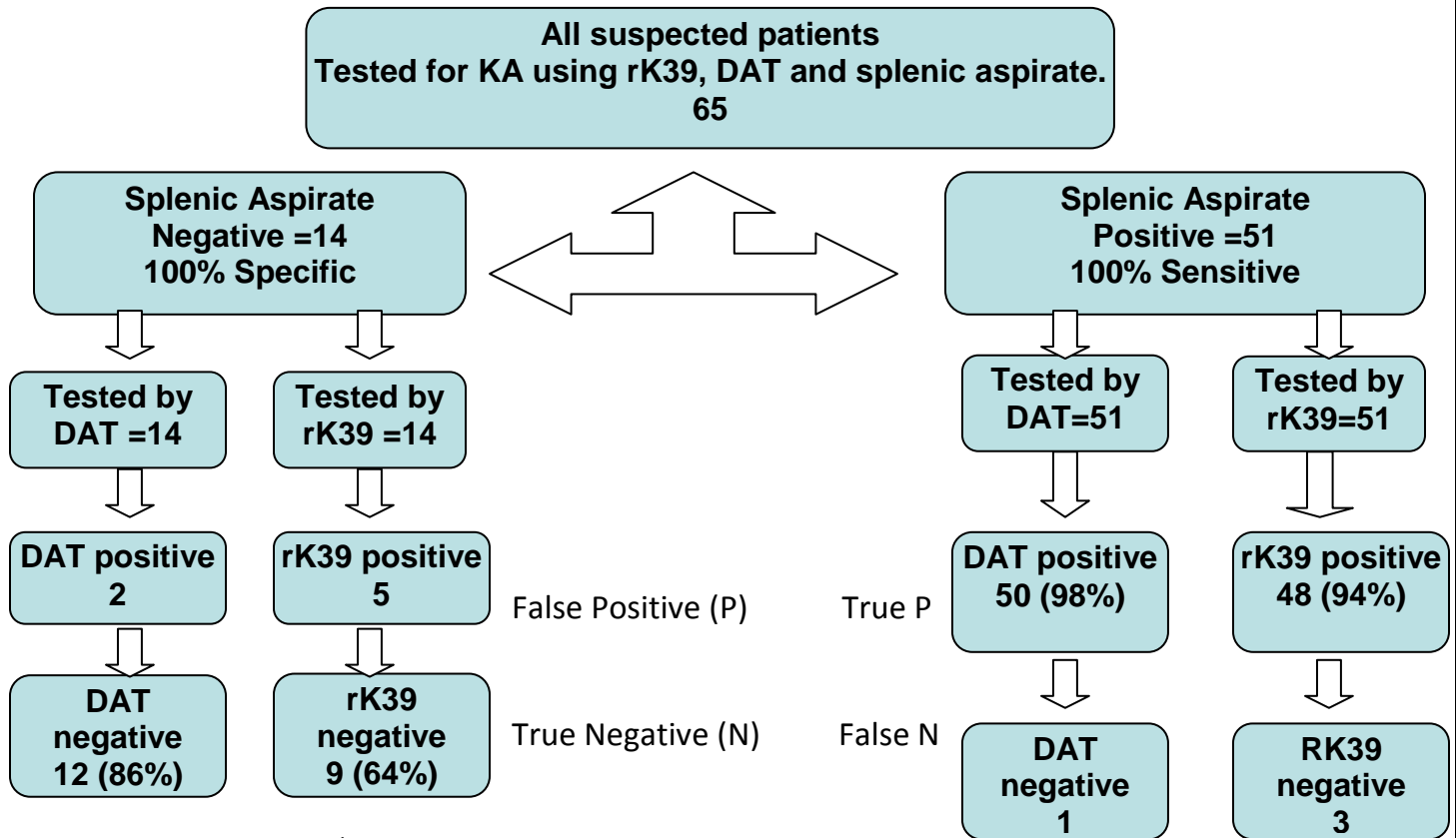
$$\log \text{DOR} + \text{ or } - 1.96\text{SE}(\log \text{DOR})$$

Calculations

1. DOR of DAT = $(50/2) / (1/12) = 300$
2. DOR of rK39 = $(48/5) / (3/5) = 16$
3. SE(logDOR) of DAT = $\sqrt{(1/50)+(1/12)+(1/1)+(1/2)} = 1.725$
4. SE(logDOR) of rK39 = $\sqrt{(1/48)+(1/9)+(1/3)+(1/5)} = 0.789$
5. 95% confidence interval
 - a) DAT = range from $1.725-(1.96 \times 1.725)$ to $1.725+(1.96 \times 1.725) = -1.656$ to 5.106
 - b) rK39 = range from $0.789-(1.96 \times 0.789)$ to $0.789+(1.96 \times 0.789) = -0.757$ to 2.335
6. DOR of DAT at 95% confidence interval = 298.344 to 305.106
7. DOR of rK39 at 95% confidence interval = 15.243 to 18.335

In summary the decision tree for KA testing in Wajir containing test validity results (specificity, sensitivity and predictive values) is shown in Figure 8

Figure 9: - Decision tree result for test validity in Wajir.



Source:- Researcher

5.5 Cost and Ease of performance of DAT and rK39 in Wajir

5.5.1 DAT Cost/Patient

Laboratory cost

DAT antigen = 4,000 KES for 8 tests = 500 KES/test or patient

DAT equipment (re-usable) = 16,050 KES for 65 patients = 247 KES per patient

Screening cost

DAT was done free of charge = 0 KES

5.5.2 rK39 Cost/Patient

Laboratory cost

RK39 kit = 1,125 KES for 25 tests = 45 KES/test or patient

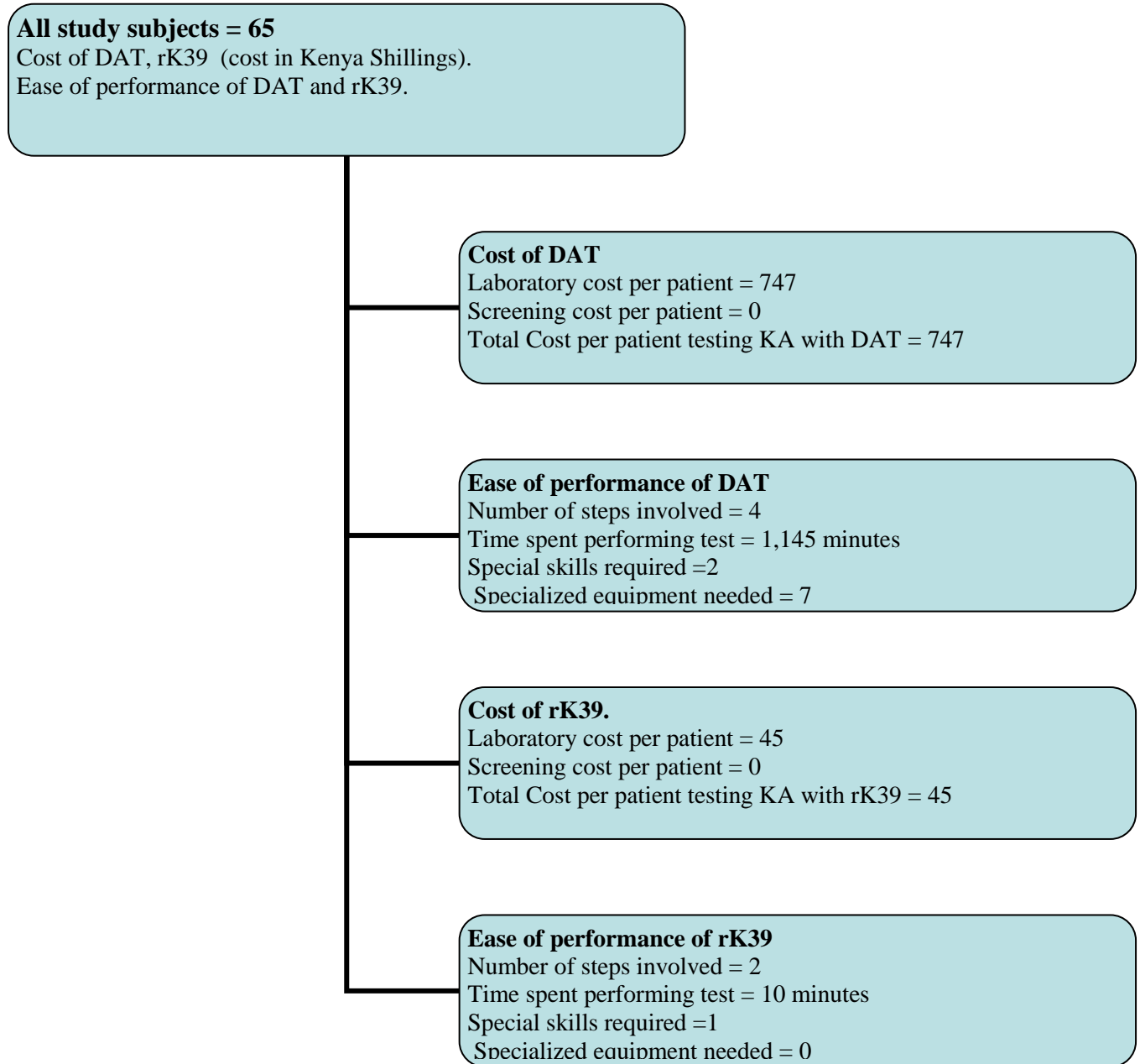
rK39 equipment = no specialised equipment required for rK39 = 0 KES

Screening cost

rK39 was done free of charge = 0 KES

The summary decision tree for cost and ease of performance of DAT and rK39 in Wajir is shown in Figure 10.

Figure 10: - Decision tree result for cost and ease of performance of DAT and rK39 in Wajir.



Source:- Researcher

5.6 Cost Effectiveness Analysis (CEA)

CEA took into account three key components on the KA testing decision tree in Wajir:-

1. Test probability estimates
2. Test effectiveness
3. Test cost
4. Sensitivity Analysis

5.6.1 Test Probability Estimates

These were derived from the results of DAT and rK39 validity in Wajir. These probabilities as shown in the Table 11 were used in the decision analysis.

Table 11: - Decision Analysis Probabilities

| | Test | Baseline DAT Titre >1:3200 (Wajir) | Plausible range DAT Titre 1:400 – 1:6400 (from literature review) | References for literature Review (for plausible range) |
|---|---------------------|--|--|---|
| 1 | Specificity DAT | 0.86 | 0.6 - 1 | El Safi SH et al, 1989 El Masum MA et al, 1995 Boelaert M et al 1999 |
| 2 | Sensitivity DAT | 0.98 | 0.8 - 1 | El Harith et al, 1986 and 1988 Okong'o Odera EA et al, 1993 Boelaert M et al 1999 |
| 3 | Specificity rK39 | 0.64 | 0.6 – 0.85 | Zijlstra EE, 1991 and 1998 Chappuis et al 2003 and 2006 |
| 4 | Sensitivity rK39 | 0.94 | 0.7 – 0.95 | Boelaert M et al 1999 and 2000 Zijlstra EE, 1991 and 1998 |

Source:- Researcher

5.6.2 Test Effectiveness

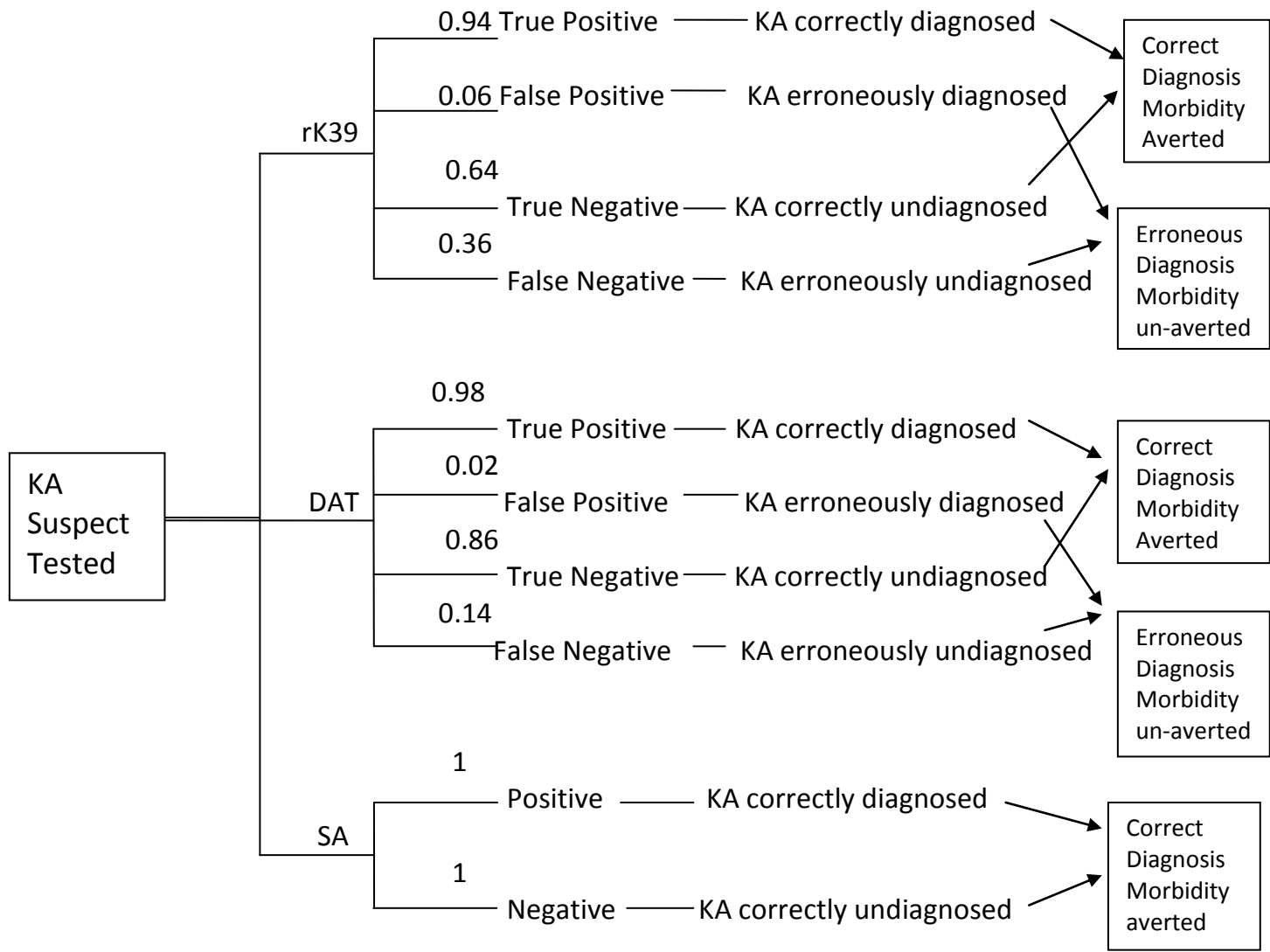
Effectiveness of KA test in this study was considered as morbidity or suffering averted relative to the obligatory progressive morbidity associated with the absence of correct diagnosis and treatment of KA. The test which averted morbidity the most was the most effective. It is worth noting that this study was focused on technical efficiency of the KA diagnosis and this informed the choice of CEA as the economic analysis method of choice. Treatment of KA was not under study and likewise allocative efficiency of KA testing or treatment was not under study

Figure 6 (on page 30) shows the possible outcomes arising from KA testing using these tests. Since morbidity or suffering could not be quantitatively measured, an outcome's effectiveness was determined by stating either: -

- i. Yes = that KA morbidity was averted as result of a correct diagnosis, or
- ii. No = that KA morbidity was not been averted as a result of incorrect diagnosis.

This therefore allowed the actual decision tree for the results of Wajir to be constructed with their respective probabilities and is presented in Figure 11:-

Figure 11: - Decision Tree for KA testing in Wajir using rK39, DAT and Splenic Aspirate.



Source:- Researcher

Table 12:- Effectiveness of KA test outcomes.

| | Test Result | Test Outcome | Effectiveness (pay-off) | Probability | Weighted Effectiveness (expected value) |
|-------------|--------------------|---|--------------------------------|--------------------|--|
| DAT | | | | | |
| 1 | True Positive | KA correctly diagnosed | Yes (1) | 0.98 | 0.98 |
| 2 | True Negative | KA correctly undiagnosed | Yes (1) | 0.86 | 0.86 |
| 3 | 1+2 | Correct diagnosis. Morbidity Averted | Yes (1) | 0.92 | 0.92 |
| 4 | False Positive | KA erroneously diagnosed | No (-1) | 0.02 | -0.02 |
| 5 | False Negative | KA erroneously undiagnosed | No (-1) | 0.14 | -0.14 |
| 6 | 4+5 | Erroneous Diagnosis. Morbidity Un-averted | No (-1) | 0.08 | -0.08 |
| rK39 | | | | | |
| 1 | True Positive | KA correctly diagnosed | Yes (1) | 0.94 | 0.94 |
| 2 | True Negative | KA correctly undiagnosed | Yes (1) | 0.64 | 0.64 |
| 3 | 1+2 | Correct diagnosis. Morbidity Averted | Yes (1) | 0.79 | 0.79 |
| 4 | False Positive | KA erroneously diagnosed | No (-1) | 0.06 | -0.06 |
| 5 | False Negative | KA erroneously undiagnosed | No (-1) | 0.36 | -0.36 |
| 6 | 4+5 | Erroneous Diagnosis. Morbidity Un-averted | No (1) | 0.21 | -0.21 |
| SA | | | | | |
| 1 | Positive | KA correctly diagnosed | Yes(1) | 1 | 1 |
| 2 | Negative | KA correctly undiagnosed | Yes(1) | 1 | 1 |

Source:- Researcher

5.6.3 Test cost

Table 13: - Cost of screening KA suspects in Wajir by DAT and rK39.

| Cost per patient | Test type – DAT | Test type – rK39 |
|---|-----------------|------------------|
| Total Costs | 747 | 45 |
| Total health service (laboratory) costs | 747 | 45 |
| Total screening costs | - | - |
| Total costs per patient | 747 | 45 |

Source:- Researcher

5.6.4 Average Cost Effectiveness Analysis of rK39 and DAT in Wajir.

The average effectiveness of each outcome was calculated by its pay-off value weighted by its probability of occurring which came from the test validity results in Table 11. Because the effectiveness in this case was a qualitative result (yes or no), a unit (1) was assigned, positive for yes and negative for no to each, as the pay-off value in order make easier the weighting by probabilities. The final effectiveness for each outcome was shown in the Table 12.

The average cost effectiveness ratio for each competing testing approaches for KA in Wajir was calculated and is shown in the Table 14.

Table 14:- Average Cost Effectiveness Ratios of Screening KA in Wajir by rK39 and DAT.

| | Description | Test type DAT | Test type rK39 |
|---|--|---------------|----------------|
| 1 | Average cost per test | 747 | 45 |
| 2 | Average Effectiveness per test | 0.92 | 0.79 |
| 3 | Average Cost-Effectiveness Ratio (ACER) (Cost per KA Morbidity Averted) = (1/2) | 812 | 57 |

Source:- Researcher

5.7 Sensitivity Analysis

5.7.1 Critical Components

One-way (univariate) sensitivity analysis was performed on the parameters of DAT and rK39 test probability and cost that were subject to uncertainty. The results were later aggregated in a Tornado diagram. Four critical components of DAT and rK39 testing in Wajir were considered in this analysis, namely:-

- a) Prices/cost of tests
- b) Sensitivity and specificity of tests
- c) Effectiveness
- d) Patient heterogeneity e.g. multiple exposures to KA (relapses of disease)

a) *Prices/cost of tests*

Sensitivity analysis of price of DAT and rK39 was done by assuming price changes in either direction at fixed measures of 15% and 30%, the results which are presented in Table 15.

Table 15: - Sensitivity Analysis range of Cost.

| Cost per patient | Less by 30% | | Less by 15% | | 0 | | More by 15% | | More by 30% | |
|---|-------------|------|-------------|------|-----|------|-------------|------|-------------|------|
| | DAT | rK39 | DAT | rK39 | DAT | rK39 | DAT | rK39 | DAT | rK39 |
| Total Cost | 523 | 32 | 635 | 38 | 747 | 45 | 859 | 52 | 971 | 59 |
| Total health service (laboratory) cost. | 523 | 32 | 635 | 38 | 747 | 45 | 859 | 52 | 971 | 59 |
| Total screening costs | - | - | - | - | - | - | - | - | - | - |
| Total costs per patient | 523 | 32 | 635 | 38 | 747 | 45 | 859 | 52 | 971 | 59 |

Source:- Researcher

b) *Sensitivity and specificity of tests*

The earlier published plausible ranges for sensitivity and specificity were used for analysis. Both extremes of the plausible ranges were used to calculate test effectiveness and are summarized in the Table 16.

Table 16: - Sensitivity analysis range of Test Validity.

| | Test | Extreme left of plausible range | Baseline | Extreme right of plausible range | Plausible range |
|---|------------------|---------------------------------|----------|----------------------------------|-----------------|
| 1 | Specificity DAT | 0.6 | 0.86 | 1 | 0.6 – 1 |
| 2 | Sensitivity DAT | 0.8 | 0.98 | 1 | 0.8 – 1 |
| 3 | Specificity rK39 | 0.6 | 0.64 | 0.85 | 0.6 – 0.85 |
| 4 | Sensitivity rK39 | 0.7 | 0.94 | 0.95 | 0.7 – 0.95 |

Source:- Researcher

c) *Effectiveness*

The analysis range for effectiveness of the test outcomes was summarized in the Table 17.

Table 17:- Sensitivity Analysis range of Effectiveness of KA test outcomes.

| Test description | | | | Extreme left of plausible range | | Baseline (Wajir) | | Extreme right of plausible range | |
|------------------|---------------|--------------------------------------|-------------------------|---------------------------------|------------------------|------------------|------------------------|----------------------------------|------------------------|
| | Test Result | Test Outcome | Effectiveness (pay-off) | Probability | Weighted Effectiveness | Probability | Weighted Effectiveness | Probability | Weighted Effectiveness |
| DAT | | | | | | | | | |
| 1 | True Positive | KA correctly diagnosed | Yes (1) | 0.8 | 0.8 | 0.98 | 0.98 | 1 | 1 |
| 2 | True Negative | KA correctly undiagnosed | Yes (1) | 0.6 | 0.6 | 0.86 | 0.86 | 1 | 1 |
| 3 | 1+2 | Correct diagnosis. Morbidity Averted | Yes (1) | 0.7 | 0.7 | 0.92 | 0.92 | 1 | 1 |
| rK39 | | | | | | | | | |
| 1 | True Positive | KA correctly diagnosed | Yes (1) | 0.7 | 0.7 | 0.94 | 0.94 | 0.95 | 0.95 |
| 2 | True Negative | KA correctly undiagnosed | Yes (1) | 0.6 | 0.6 | 0.64 | 0.64 | 0.85 | 0.85 |
| 3 | 1+2 | Correct diagnosis. Morbidity Averted | Yes (1) | 0.65 | 0.65 | 0.79 | 0.79 | 0.9 | 0.9 |

Source:- Researcher

d) Multiple exposures to KA (relapses of disease)

Multiple exposures and relapses of KA affect testing because they increase the chances of false positives even after cure is achieved (Sundar et al., 2000). In this study however this uncertainty was controlled or eliminated by the inclusion-exclusion criteria followed in the study methodology where only new suspected cases of KA were studied.

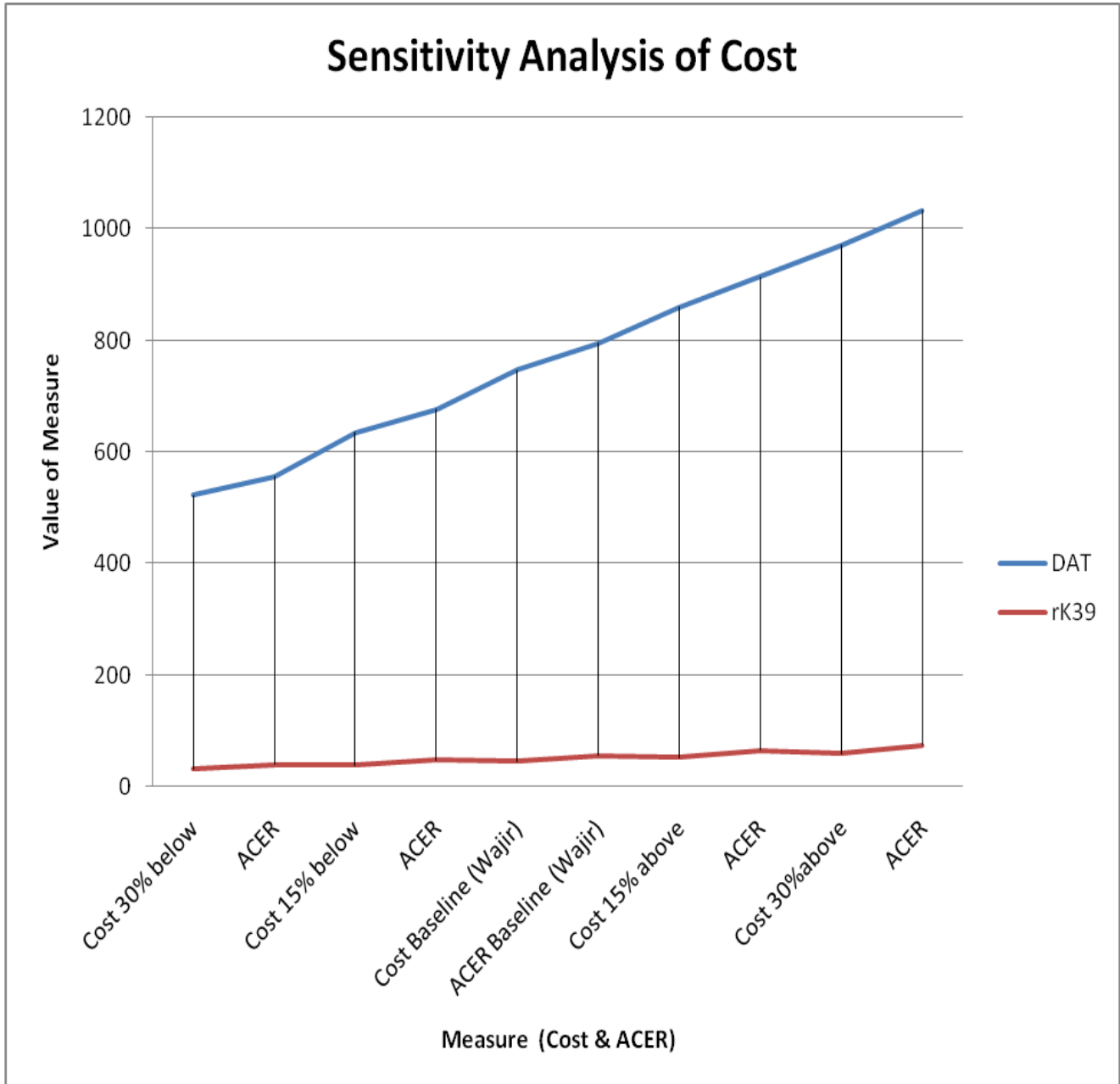
5.7.2 Actual Sensitivity Analysis

Finally the sensitivity analysis considering each of these critical components was calculated in the Table 18. Analytical charts of each component are also presented in the charts in Figure 12-14 and they consistently showed that the CER of DAT was higher than of rK39 in the sensitivity analysis of all the critical components

Table 18:- Sensitivity Analysis by Cost, Test Validity and Effectiveness. Source:- Researcher

| | Description | DAT | rK39 |
|---|--|------|------|
| | Baseline | | |
| 1 | Average cost per test | 747 | 45 |
| 2 | Average Effectiveness per test | 0.92 | 0.79 |
| 3 | Average Cost-Effectiveness Ratio (ACER) or morbidity averted | 812 | 57 |
| | Analysis 1 (price 30% less) | | |
| 1 | Average cost per test | 523 | 32 |
| 2 | Average Effectiveness per test | 0.92 | 0.79 |
| 3 | Average Cost-Effectiveness Ratio (ACER) | 568 | 41 |
| | Analysis 2 (price 15% less) | | |
| 1 | Average cost per test | 635 | 38 |
| 2 | Average Effectiveness per test | 0.92 | 0.79 |
| 3 | Average Cost-Effectiveness Ratio (ACER) | 690 | 48 |
| | Analysis 3 (price 15% more) | | |
| 1 | Average cost per test | 859 | 52 |
| 2 | Average Effectiveness per test | 0.92 | 0.79 |
| 3 | Average Cost-Effectiveness Ratio (ACER) | 934 | 66 |
| | Analysis 4 (price 30% more) | | |
| 1 | Average cost per test | 971 | 59 |
| 2 | Average Effectiveness per test | 0.92 | 0.79 |
| 3 | Average Cost-Effectiveness Ratio (ACER) | 1055 | 75 |
| | Analysis 5 (sensitivity low extreme plausible range) | | |
| 1 | Average cost per test | 747 | 45 |
| 2 | Effectiveness per test | 0.8 | 0.7 |
| 3 | Average Cost-Effectiveness Ratio (ACER) | 934 | 64 |
| | Analysis 6 (sensitivity high extreme plausible range) | | |
| 1 | Average cost per test | 747 | 45 |
| 2 | Effectiveness per test | 1 | 0.95 |
| 3 | Average Cost-Effectiveness Ratio (ACER) | 747 | 47 |
| | Analysis 7 (specificity low extreme plausible range) | | |
| 1 | Average cost per test | 747 | 45 |
| 2 | Effectiveness per test | 0.6 | 0.6 |
| 3 | Average Cost-Effectiveness Ratio (ACER) | 1245 | 75 |
| | Analysis 8 (specificity high extreme plausible range) | | |
| 1 | Average cost per test | 747 | 45 |
| 2 | Effectiveness per test | 1 | 0.85 |
| 3 | Average Cost-Effectiveness Ratio (ACER) | 747 | 53 |
| | Analysis 9 (effectiveness low extreme plausible range) | | |
| 1 | Average cost per test | 747 | 45 |
| 2 | Average Effectiveness per test | 0.7 | 0.65 |
| 3 | Average Cost-Effectiveness Ratio (ACER) | 1067 | 69 |
| | Analysis 10 (effectiveness high extreme plausible range) | | |
| 1 | Average cost per test | 747 | 45 |
| 2 | Average Effectiveness per test | 1 | 0.9 |
| 3 | Average Cost-Effectiveness Ratio (ACER) | 747 | 50 |

Figure 12:- Sensitivity Analysis by cost

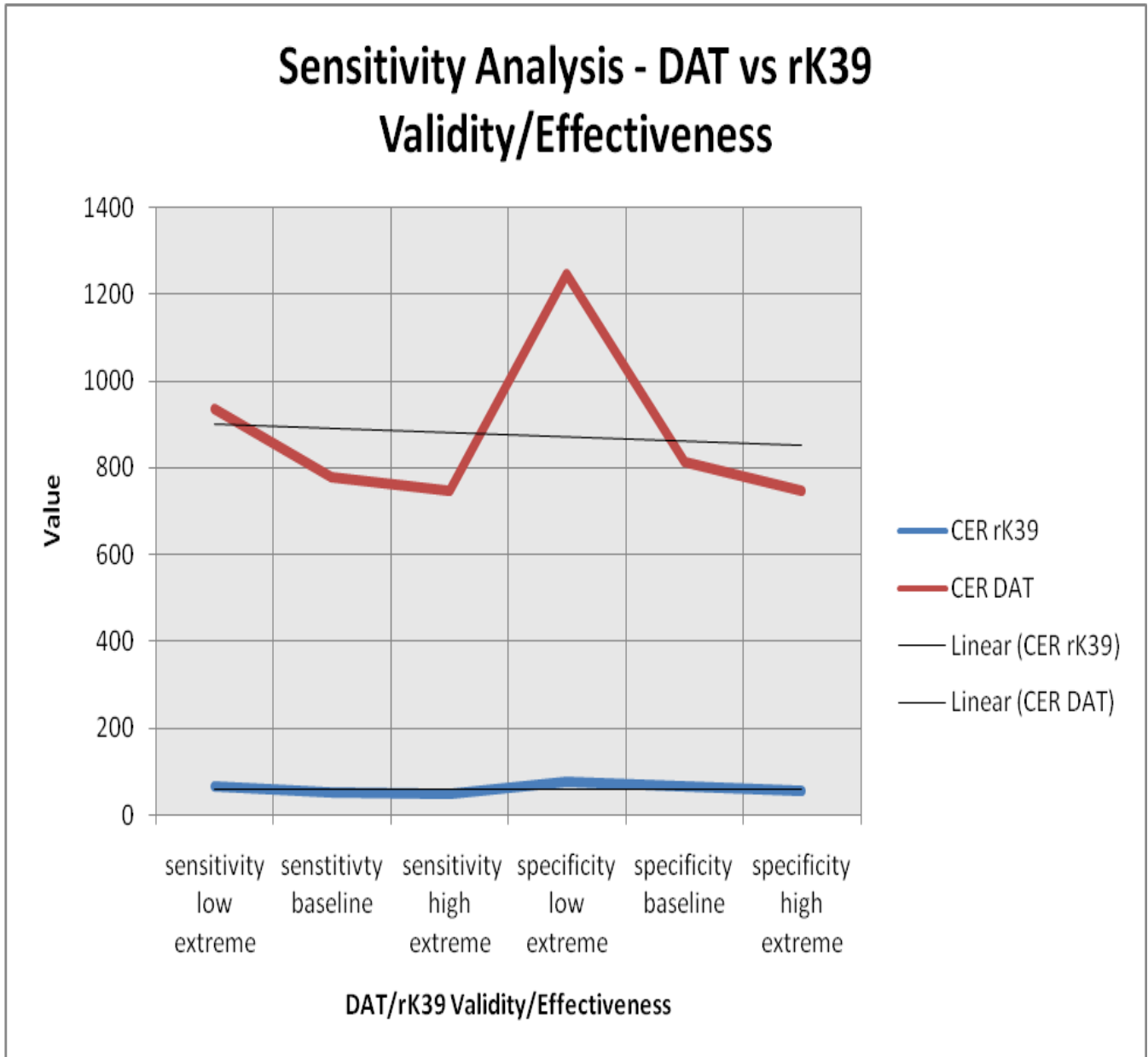


Source:- Researcher

Increasing the cost in both tests increased the CER which was an expected finding. Varying the cost of DAT and rK39 by up to more than half (60%) did not cause significant approximation of the CER of the two tests. The DAT CER remained higher than that of rK39 even when cost of DAT was reduced by 60% while rK39 cost remained constant.

The opposite adjustment of costs caused an even wider difference in CER with DAT CER remaining consistently higher than rK39 CER. Therefore the sensitivity analysis of cost, despite the acknowledged cost information deficiencies, proved that the CER findings of this study were reliable and representative of the real situation in Wajir.

Figure 13:- Sensitivity Analysis by test validity/effectiveness (trend-lines included)



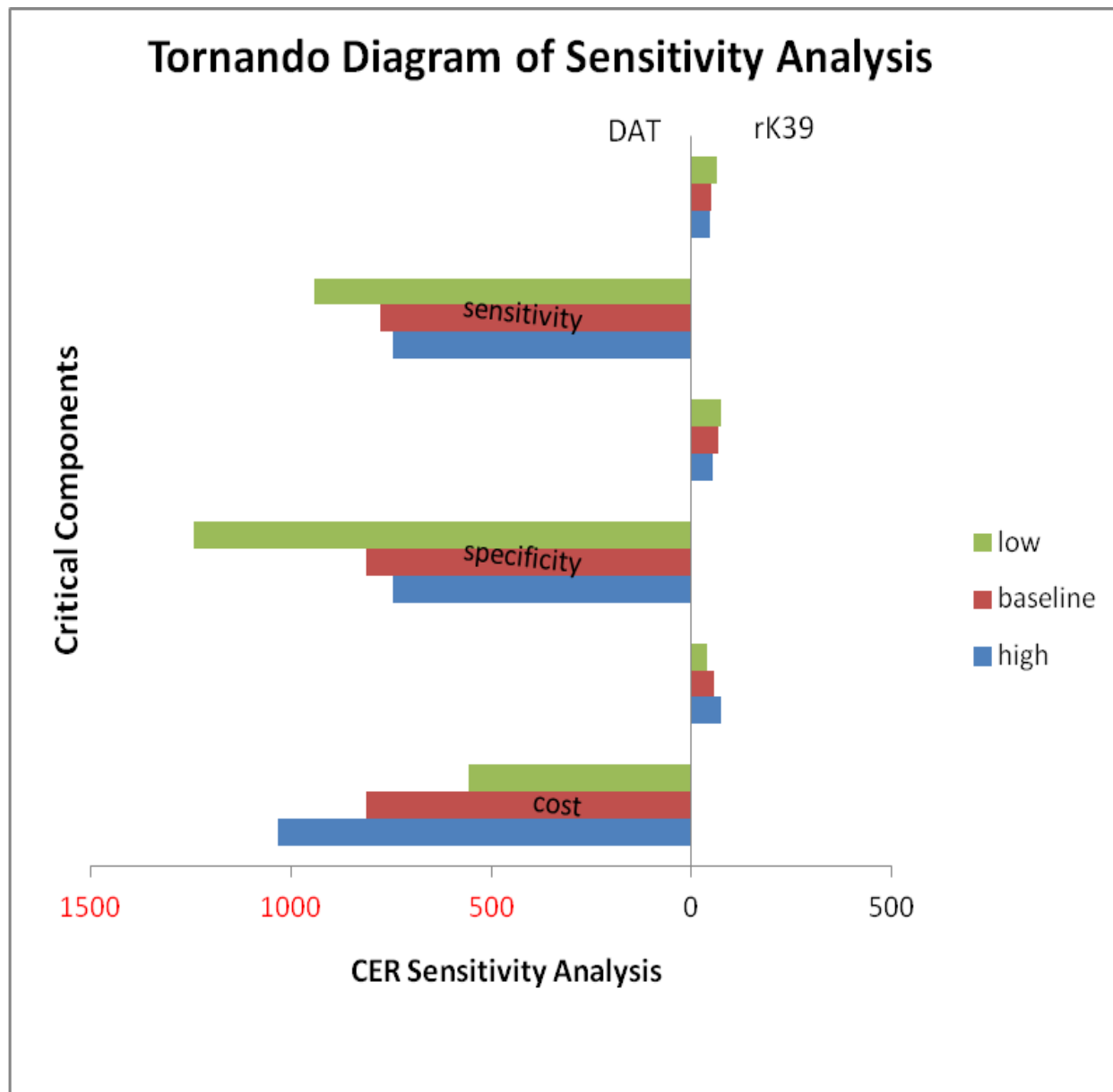
Source:- Researcher

Varying the possible test validities along the plausible range from the low extreme to the high extreme replicated the results of the cost sensitivity analysis and the CER findings of this study because the CER of DAT here also remained higher than that of rK39 within a similar scale. The trend line showed that the CER of both DAT and rK39 reduced as the validity moved towards the high extreme which was the expected finding.

5.7.3 Tornado Diagram

A tornado diagram combining all the trends of sensitivity analysis by cost and validity was drawn and is shown in Figure 15.

Figure 14:- Tornado diagram

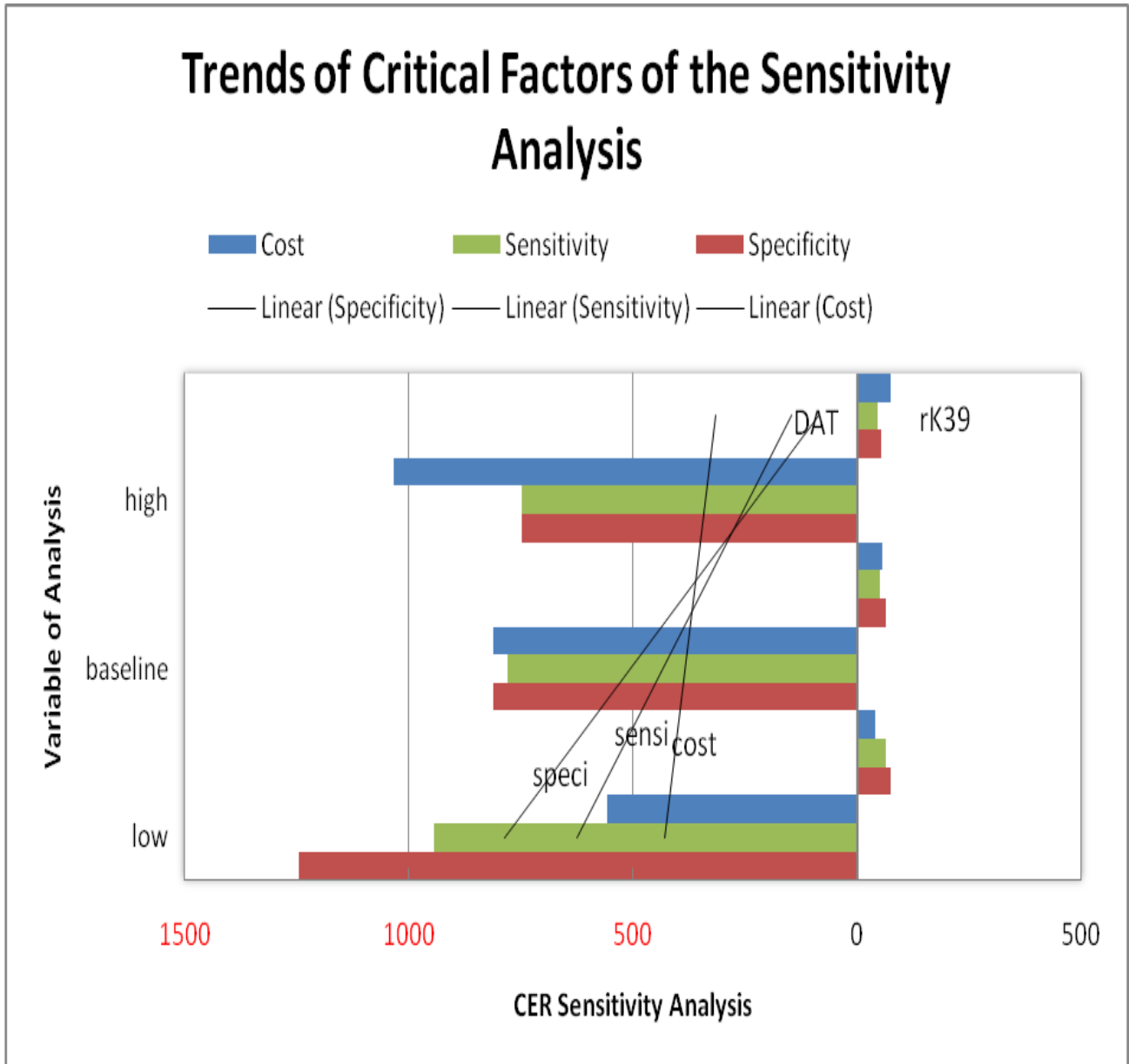


Source:- Researcher

The tornado diagram above summarised the earlier findings of sensitivity analysis and re-confirmed the finding that the CER of DAT was significantly higher than that of rK39 even when all the important components of the cost-effectiveness analysis were considered.

From the tornado diagram it was observed that specificity was the one component that had the greatest effect on the average cost effectiveness of KA (Figure 15 and Table 19). This finding is in keeping with the fact that KA being invariably fatal if not treated, highly specific tests are more important than highly sensitive ones during disease screening (Loong TW, 2003).

Figure 15:- Trends of Sensitivity Analysis



Source:- Researcher

Key

Speci = specificity

Sensi = sensitivity

The trend lines for each critical component are shown in the Tornado diagram above. The trend line for specificity had the highest gradient change meaning specificity caused the most change of cost-effectiveness ration during the study.

Table 19:- Trends of Components

| | DAT | DAT | DAT | rK39 | rK39 | rK39 | Analysis | | |
|------------------------|--------|-----------|---------|--------|-----------|---------|-------------------|--------------------|--------------------------|
| | lowest | Base line | highest | lowest | Base line | highest | difference lowest | difference highest | difference of difference |
| CER Cost varied | 556 | 812 | 1033 | 40 | 57 | 74 | 516 | 959 | 443 |
| CER Specificity varied | 1245 | 812 | 747 | 75 | 65 | 53 | 1170 | 694 | 476 |
| CER Sensitivity varied | 943 | 778 | 747 | 64 | 50 | 47 | 879 | 700 | 179 |

Source:- Researcher

5.8 Limitations of the study at analysis stage

1. Prevalence of KA in Wajir was not known and this prevented calculation of predictive values of the tests in the Wajir situation. This calculation would inform whether or not these tests capture a significant proportion of the affected Wajir population so as to be considered as tests of public health significance.
2. Cost estimation – Costing for this study was very limited. The study did not include costs of labour, utilities used during testing like water and electricity, depreciation of test equipment and the time spent on the tests. This would have made the cost estimates more accurate. It was generally difficult to calculate costs because of paucity of information. It will be useful in future, as more cost information becomes available, more detailed costing be made and more refined cost-effectiveness ratio be calculated.

Chapter 6:- Discussion

6.1 Effectiveness

Specificity, Sensitivity and Predictive Value

The currently available serodiagnostic tests for VL are based on four major formats: Direct agglutination (DAT), indirect immunofluorescence (IFAT), ELISA and immunochromatography. The DAT and IFAT classically utilize whole promastigotes to screen for antibodies, while the p-ELISA uses a crude lysate of promastigotes. Immunochromatographic tests, and a newer ELISA have been developed using the recombinant protein rK39, which is a kinesin-like gene found in *Leishmania chagasi*. This Wajir study compared the cost and effectiveness of rK39 and DAT and among its findings were a specificity of rK39 of 64% and sensitivity of 94.7% while DAT had specificity of 86% and sensitivity of 98%.

Comparing the effectiveness of rK39 strip test and the DAT, several issues arise. The DAT has the ability to detect low levels of antibodies due to the mosaic of antigens present in the extract. This sensitivity can come at a cost in specificity, as some of these antigens are cross reactive (Veeken *et al.*, 2003). Both tests also being serological tests may give false positive results because patients can have antibody present for months after cure of disease, and while still asymptomatic. The differences in sensitivity and specificity by region can also be due to ethnic background, environment, severity of infection, or differences in *L. donovani* genotype (Iqbal, 2002). Further, co-infection with different infectious diseases can affect diagnosis with both DAT and rK39 showing cross reactivity in patients infected with diseases such as tuberculosis, HIV, and malaria (Sundar, 2006; Sinha, 2008). Statistics range from 5% rK39 false positives for patients with only malaria or TB (Sundar, 2006) to 27% rK39 false positives for HIV patients (Sinha, 2008). In this Wajir study no co-diagnosis of other cross reacting infections was done.

A meta-analysis of different sero-diagnostic tests currently used for serodiagnosis of VL from all regions of the world was published in January 2012 by Maia *et al.* This was a systematic review and meta-analysis of studies evaluating serologic assays rK39 strip-test, rK39 ELISA, DAT, IFAT and ELISA with a promastigote antigen preparation (p-ELISA). The analysis was done to determine the accuracy of rK39 antigen in comparison to other antigen preparations. Fourteen papers fulfilled the inclusion and exclusion selection criteria. The summarized sensitivity for the rK39-ELISA was 92% followed by IFAT 88% and p-ELISA 87%. The summarized specificity for the three diagnostic tests was 81%, 90%, and 77%. Studies comparing the rK39 strip test with DAT found a similar sensitivity (94%) and specificity (89%). It was concluded that the rK39 protein used either in a strip test or in an ELISA is a good choice for the serodiagnosis of VL (Maia *et al.*, 2010). Another meta-analysis comparing the DAT and rK39 strip found that tests are comparable with DAT being 1% more sensitive and 2% more specific than rK39 (Chappuis *et al.*, 2006). The World Health Organization's Special Program for Research and Training in Tropical Disease (TDR) evaluated five different immunochromatographic tests utilizing either rK39 or rKE16. Testing was performed in East Africa, Brazil and on the Indian subcontinent, and sensitivities ranged from 36.8–100% and

specificities from 90.8–100%. No test was the clear winner across all regions and conditions (*TDR, WHO, 2010*). This Wajir study found a specificity of rK39 of 64% and sensitivity of 94.7% while DAT had specificity of 86% and sensitivity of 98%. This showed that DAT was both more sensitive (3%) and more specific (22%) compared to rK39 a finding which compares well with other published studies.

On the Indian Sub-Continent, few indicative studies were chosen to examine the sensitivity and specificity of FD-DAT and rK39. Overall, DAT appears to be more sensitive than rK39 in this region, with results varying between 92.6 and 100% sensitive for DAT and 87 and 100% for rK39 (*Sundar, 2006; Sinha, 2008; Ritmeijer, 2006; Boelaert, 2008*). Specificity varied widely between studies, but is always lower than sensitivity results. In East Africa, while fewer comprehensive studies have been done examining DAT and rK39, two recent studies have had similar results regarding sensitivity and specificity (*Ritmeijer, 2006; Boelaert, 2008*). By analyzing results from Sudan, Kenya, and Ethiopia, the average East African sensitivity for DAT was found to be 92.8% and for rK39 was found to be 79.1%, but with some results as high as 90.0% sensitive. As with Indian results, specificity varied widely for DAT and rK39. DAT had an average of 91.2% specificity while rK39 average 84.8%. However, in Sudanese studies, specificity was usually much greater than sensitivity (See Table 20). These findings were again generally replicated in this Wajir study but it was noted from all the studies that DAT and rK39 specificity and sensitivity can vary widely depending on location, implying more diagnostic research is still required to reduce this wide regional variation.

Table 20: Multi-centre study findings of sensitivity and specificity of DAT and rK39 in East Africa and the Indian subcontinent compared with Wajir Study findings

| Parameters | East Africa | | | Indian subcontinent | | Wajir Study |
|----------------------|-------------------|------------------|------------------|---------------------|------------------|-------------|
| | Ethiopia estimate | Kenya estimate | Sudan estimate | India estimate | Nepal estimate | Wajir Study |
| DAT | | | | | | |
| Sensitivity | 94.0 (80.0-99.8) | 98.8 (96.6-99.9) | 85.7 (77.0-92.7) | 98.3 (96.2-99.6) | 98.5 (94.8-100) | 98.0 |
| Specificity | 93.6 (77.4-99.8) | 81.9 (73.2-89.8) | 98.2 (94.8-99.9) | 91.0 (83.0-96.6) | 95.4 (87.1-99.6) | 86.0 |
| rK39 dipstick | | | | | | |
| Sensitivity | 75.4 (55.9-90.5) | 84.7 (78.6-89.8) | 77.9 (69.2-85.6) | 99.6 (98.4-100) | 96.5 (92.1-99.2) | 94.7 |
| Specificity | 70.0 (46.3-88.9) | 89.9 (83.2-95.1) | 91.8 (86.7-96.2) | 90.0 (81.2-96.4) | 90.9 (80.8-97.5) | 64.0 |

Adapted from Boelaert, 2008, column of Wajir results added by thesis author.

Table 21a: Comparison of multi-centre study of effectiveness, cost and additional requirements (ease of performance) in the Indian subcontinent and East Africa

| Parameters | Test (Multi-Centre Study in East Africa & Indian Sub-Continent) ^{a,b,c,d.} | | Wajir Study | |
|--|---|----------------------|------------------------------------|---------------------|
| | DAT | rK39 | DAT | rK39 |
| Sensitivity (%) ^a | | | | |
| Indian subcontinent | 98.2 (92.6-100) | 97.7 (87-100) | | |
| East Africa | 92.8 (77-99.9) | 79.1 (67-90) | 98.0 | 94.7 |
| Specificity (%) ^a | | | | |
| Indian subcontinent | 94.6 (83-100) | 89.4 (73-100) | | |
| East Africa | 91.2 (73.2-99.9) | 84.8 (46.3-99) | 86.0 | 64 |
| (Ease of Performance) Additional requirements ^b | Available antigen, several hours incubation | Test buffer solution | Additional time, skills, equipment | Only basic test kit |
| Cost per test ^c | \$2.50 | \$1-\$1.30 | KES 747 (\$8.3) | KES 45 (\$0.5) |
| Major cross-reactions ^d | malaria, TB | malaria, TB, HIV | - | - |

^a Sundar S et al, (June 2006); Sinha PK et al. (Mar 2008); Ritmeijer K et al. (2006); Boelaert M et al. (Jan 2008).

^b Sundar S et al, (June 2006).

^c Chappuis F et al. (Dec 2005); Boelaert M et al. (1999).

^d Sundar S et al, (June 2006); Sinha PK et al. (Mar 2008).

Table 21b:- Comparison of effectiveness, cost and additional requirements (ease of performance) of DAT and rK39 in Wajir. *This information is incorporated in Table 21a.

| | Description | Test type DAT | Test type rK39 |
|---|---|---------------|----------------|
| 1 | Average Sensitivity (%) | 98.0 | 94.7 |
| 2 | Average Specificity (%) | 86.0 | 64.0 |
| 3 | <i>Ease of performance</i> | | |
| | 1. Number of steps required to perform test | 4 | 2 |
| | 2. Number of specialised equipment required | 7 | 0 |
| | 3. Number of special skills required | 2 | 1 |
| 4 | Average cost in Kenya Shillings (and \$) | 747 (8.3) | 45 (0.5) |
| 5 | Average Cost-Effectiveness Ratio (ACER) | 812 | 57 |

Source:- Researcher

Meta-analysis is an important tool that drives direction for best evidences in medicine by comparing studies done in different places, environments and populations as long as the same question was used by different investigators. However meta-analysis on sensitivities and specificities of serological tests usually overlooks the heterogeneity introduced by variations in diagnostic thresholds between regions (Deeks JJ, 2001).

Diagnostic Odds Ratio

The value of a DOR ranges from 0 to infinity, with higher values indicating better discriminatory test performance. A value of 1 means that a test does not discriminate between patients with the disorder and those without it. Values lower than 1 point to improper test interpretation (more negative tests among the diseased). The DOR rises steeply when sensitivity or specificity becomes near perfect. Like specificity, sensitivity and predictive values DOR depend on disease severity. DOR is a global measure and cannot be used to judge a test's error rates at a particular prevalence meaning that two tests with an identical DOR can have different sensitivity and specificity and clinical consequences. (*Afina S et al., 2003*).

Estimated DOR for DAT for detecting KA at 95% confidence interval is 298.344 to 305.106 while that of rK39 ranges from 15.243 to 18.335. This means that for the DAT the odds for positivity among patients with KA is 300 times higher than the odds for positivity among subjects without KA while for the rK39 the odds for positivity is 15 times higher than odds for positivity among patients without KA. The finding of the DOR agrees with that of specificity, sensitivity and predictive values which show DAT as performing better than rK39. In this study however the prevalence of KA in Wajir was not known and this made the DOR not only useful but also mandatory in validating of the results of DAT and rK39 specificity and sensitivity and by consequence the whole study.

6.2 Cost and Cost- Effectiveness.

Both FD-DAT and rK39 can be offered at low costs, making feasible their usage in developing countries with endemic visceral leishmaniasis. In one 1999 study, DAT was calculated to cost \$2.50/test, including peripheral costs for materials and labor not included in packaged tests (*Boelaert, 1999*). In a 2005 study in Uganda, rK39 tests were found to cost between \$1 and \$1.30, depending on the manufacturer (*Chappuis, 2005*). Therefore, rK39 given its lower cost and the fewer additional requirements (Table 21a and 21b) is currently more feasible and cost-effective and easy to use in the field (*Stephanie Oberfoell, 2008*). The Wajir study found similar results in that the average cost-effectiveness ratio of DAT compared to rK39 was 812 and 57 respectively meaning rK39 was more cost-effective than DAT. Performing rK39 was also easier and required less time and equipment than DAT.

As mentioned earlier among the study limitations, the costing for this study was very limited. The study excluded costs of time, labour and utilities which would have made the cost estimates and the CER more precise. This situation arose because not all the cost information was available in the study records at the time of the study. Despite this, the cost information obtained was sufficient to validate the main finding the study made that DAT is less cost-effective compared to rK39. This is because the study found that DAT consistently scored higher than rK39 in terms of purchase price, length of time needed to do it, amount of equipment and complexity of labour/skills required. Since it is known that higher scores in each of these parameters directly increases the costs incurred for each parameter, then it can be assumed that DAT would still have scored a higher total cost compared to rK39 even if more cost information had been available at the time of the study. It will however be useful

in future, as more cost information becomes available, that more detailed costing be made and more refined cost-effectiveness ratio be calculated.

6.3 Summary

The Wajir study like other studies done elsewhere found higher scores of DAT than rK39 for sensitivity, specificity and cost. DAT also had more additional requirements making it less easy to perform compared to rK39. The lower costs of rK39 and its fewer additional requirements therefore made rK39 more cost-effective and easier to use in the field compared to DAT. There are however limits on how much both DAT and rK39 results can be accepted, especially in non-endemic areas because of the possibility for false negatives or positives and their usage should not be de-linked from the clinical presentation of test subjects or secondary (confirmatory) diagnostics tests such as liver biopsy should be used in addition.

Chapter 7:- Conclusions and Recommendations

The conclusions and recommendations presented in this chapter are statements on which test was more cost-effective and easier to perform in the Wajir setting and the recommended extra studies suggested to support this study.

7.1 Conclusions

1. The medical staffs in Wajir District Hospital often treated patients suspected of KA on clinical evidence only or this combined with one or more of these three tests rK39, DAT and splenic aspirate. This was not cost effective even when the test material, equipment and technical services was donated free of cost by donor organizations because as shown above, the different tests had contrasting cost-effectiveness.
2. Lack of public health programmes - It was also observed that health promotive and disease preventive measures to control KA like early and community level screening of susceptible people, vector control as well as health education were existing gaps in the intervention of the MOH and humanitarian agencies during the 2008 KA outbreak in Wajir. While the screening tests existed they were kept and used only at hospital level when in fact outreach, community level mass screening and health education would have gone a long way in alleviating the magnitude and severity of the outbreak.
3. Splenic aspiration which is the ideal test was only occasionally done because of the inadequate technical resources needed to perform it (*Merlin Press Release, 2008*). In total of 364 suspected patients of KA who presented at the Wajir County Hospital was 2008, only 65 (18%) new cases were tested by splenic aspirate. Alternative simple but reliable tests should be developed and provided for testing KA in Wajir by the Ministry of health. Serological tests like DAT and rK39 attempt to meet this need in Wajir. Serological tests are however limited because they do not accurately distinguish acute disease from sub-clinical or past disease because the tests remain positive for several months after treatment (*Zijlstra EE et al, 1991*).
4. Uncertainty remains about the KA situation in Kenya because exhaustive studies have not been done. Disease prevalence and test performance of DAT and rK39 in different populations of the country are ill-studied (*Schaefer et al., 1994; Ngumbi et al., 1998*). Sensitivity analysis was thus done on this study results to address the important uncertainties that still exist. Three areas namely cost and validity (sensitivity and specificity) were adjusted. The differences in the cost-effectiveness ratios of DAT and rK39 were unaffected when the cost and validity was adjusted by up to 60% which was an implausibly high adjustment given the evidence from different settings where these tests have also been used. In all cases the findings of the sensitivity analysis supported the primary finding that rK39 was more cost-effective than DAT. The lack of information about prevalence of KA in Wajir/Kenya was however a limitation because this study could not use it to make a declaration of the predictive values of DAT and rK39 in Wajir as further evidence to support their adoption by Ministry of Health. Effectiveness of a test is largely determined by its validity. In the case of KA because it is invariably fatal if not treated the

specificity of the screening test is more important than sensitivity (*Loong TW, 2003*). In this study it was observed from the Tornado Diagram that specificity had the greatest effect on cost-effectiveness for both DAT and rK39. A multicentre study has shown that DAT loses validity in the field as a consequence of handling and storage problems (*Boelaert M et al., 2000*). This finding can be extrapolated to other tests including rK39. In this study DAT was not done in Wajir but in Nairobi however both Wajir and Nairobi qualify as field locations because the tests were imported into Kenya. DAT and rK39 had an average effectiveness (average of specificity and sensitivity) of 92% and 79% respectively. This means DAT was effective in 9 out of 10 people while rK39 was effective in 8 out of 10 people. Both levels of effectiveness were high and for an area like Wajir where there are recorded high incidences of KA over the years (*Fendall, 1952; Ashford et al., 1987; Marlet, 2003; Njau, 2010*), even though KA prevalence was not presently known, it can be concluded that DAT and rK39 were both useful tests for screening of KA in Wajir. Although DAT and rK39 were not recommended by the WHO for diagnosis of KA and although MOH did not recommend rK39 as baseline test for KA in Kenya, the results of effectiveness of DAT and rK39 in this study coupled with the limitation of resources in Wajir should enable MOH allow for rational use of rK39 as first line screening test to control KA in Wajir.

5. The average cost-effectiveness ratio of DAT compared to rK39 was 812 and 57 respectively. Performing DAT required more equipment than rK39 and the cost of equipment pushed higher the CER ratio for DAT. The average cost of DAT compared to rK39 was 747 KES and 45 KES per unit test of which the cost of equipment for DAT and rK39 contributed 33% and 0% respectively to the total cost of the tests. The average effectiveness was measured as morbidity or suffering averted relative to the obligatory progressive morbidity associated with the absence of correct diagnosis and treatment of KA. The average effectiveness of DAT compared to rK39 was 0.92 and 0.79 respectively. The rapid test rK39 was thus found was more cost-effective than DAT.
6. Ease of test performance – This study aimed to supplement information from DAT and rK39 cost-effectiveness with the ease of test performance. An ideal test should be both cost-effective and easy to perform. Ease of test performance was determined by assessing what and how many special skills were required, what and how many specialized equipment were required and how long it took to complete each test. Overall DAT required more skills and equipment and took more time to perform compared to rK39. This coupled ideally with the findings of cost-effectiveness and reinforced the conclusion that compared to DAT, rK39 was the choice test for screening KA in Wajir which MOH should adopt.

7.2 Recommendations

1. The rK39 having been found in this study to be not only effective but also more cost effective and easier to perform compared to DAT should be adopted by MOH and should replace DAT as the first line screening test for Kala Azar in Wajir.
****Note:-** In June 2012, two months after the conclusion of this study, the Ministry of Health published revised national guidelines for KA diagnosis and for the first time allowed rK39 to be used as first line screening and diagnostic test for KA. (*MOH Kenya. June 2012*).
2. MOH should develop a public health programme to control KA in Wajir with important components as early, community level mass screening for KA during epidemic prone seasons as well as health education and vector control components. Because rK39 has shown in this study to be cost-effective and easy to perform at community level it should be recommended for incorporation into community level KA control programme where it can easily be used for early screening as well as diagnosis of active KA cases before they are referred to the hospitals for more tests and treatment.
3. The prevalence of KA in Wajir and other regions of Kenya should be studied so that the screening tests for KA can be segregated by regional predictive value
4. More detailed cost determination studies should be done for KA testing in Wajir so that a more refined and accurate cost effectiveness ratio for the common tests of KA in Wajir is obtained.

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Annexes/Appendices

Appendix 1:- Wajir County



Source: - Survey Department (Wajir), 1996.

Appendix 2:- Data Entry Sheet 1- Test result and cost of test.

| SUSPECTED KA PATIENT RESULTS AND COST OF INDIVIDUAL TEST. | | | | | | | | | | | | | | | | |
|---|------|-------------|-----|-----|-----------|----------------|-----------------|------|------|----------|-----|------|----------|---------|------|----------|
| | DATE | DATA NUMBER | SEX | AGE | RESIDENCE | ADMISSION DATE | CASE DEFINITION | RK39 | DATE | FEE PAID | DAT | DATE | FEE PAID | SPLENIC | DATE | FEE PAID |
| 1 | | | | | | | | | | | | | | | | |
| 2 | | | | | | | | | | | | | | | | |
| 3 | | | | | | | | | | | | | | | | |
| 4 | | | | | | | | | | | | | | | | |
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| 23 | | | | | | | | | | | | | | | | |
| 24 | | | | | | | | | | | | | | | | |

Source:- Researcher

Appendix 3:- Data Entry Sheet 2 - Cost and ease of test performance.

| Data number (Corresponding to data sheet 1) | DAT test | | | | rK39 test | | | | SA |
|--|----------------------------------|------------|--------------|--|----------------------------------|------------|--------------|--|----------------------------------|
| | Cost of test To the hospital. | Test steps | Process time | Special skills & equipment required. | Cost of test To the hospital. | Test Steps | Process time | Special skills & equipment required. | Cost of test To the hospital. |
| 1 | | | | | | | | | |
| 2 | | | | | | | | | |
| 3 | | | | | | | | | |
| 4 | | | | | | | | | |
| 5 | | | | | | | | | |
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| 14 | | | | | | | | | |
| 15 | | | | | | | | | |
| 16 | | | | | | | | | |
| 17 | | | | | | | | | |
| TOTAL | | | | | | | | | |
| AVERAGE | | | | | | | | | |

Source:- Researcher

END.