Visceral Leishmaniasis Control in South Asia versus East Africa:
Is elimination feasible?

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VISCERAL LEISHMANIASIS CONTROL IN SOUTH-ASIA VERSUS EAST-AFRICA

Is elimination feasible?

A thesis submitted in partial fulfilment of the requirement for the degree of

Master in International Health

by

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Content

List of abbreviations

ACD	Active Case Detection
AVL	Anthroponotic Visceral Leishmaniasis
CDC	Centers for Disease Control and Prevention
CL	Cutaneous Leishmaniasis
DAT	Direct Agglutination Test
DDT	Dichlorodiphenyltrichloroethane
DNA	Desoxyribonucleic Acid
EA	East Africa
ELISA	Enzyme-Linked Immunosorbent Assay
EVM	Environmental Modification
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
FGT	Formol Gel Test
INGO	International Non-Governmental Organisation
IRS	Indoor Residual Spraying
ITN	Insecticide Treated Nets
LAB	Liposomal Amphotericin B
LEAP	Leishmaniasis East Africa Platform
LLIN	Long Lasting Insecticide treated Nets
MCL	Muco-Cutaneous Leishmaniasis
MSF	Médecins Sans Frontières
NDVI	Normalised Difference Vegetational Index
NTD	Neglected Tropical Diseases
PCD	Passive Case Detection
PCR	Polymerase Chain Reaction
PKDL	Post Kala Azar Dermatitis
PM	Paromomycin
RDT	Rapid Diagnostic Test
SA	South Asia
SSG	Sodium Stibogluconate
USD	United States Dollar
VL	Visceral Leishmaniasis
WHO	World Health Organisation

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Executive summary

Visceral Leishmaniasis is a lethal disease affecting mainly the poor in rural communities. Most affected persons live in South Asia, around the bordering areas of India, Bangladesh and Nepal, and in East Africa, around the bordering areas of Sudan, Ethiopia and South Sudan. It is a neglected tropical disease with a high burden in disease and economic impact which is still underestimated. The disease is transmitted by sand flies. Visceral leishmaniasis due to the parasite *L. donovani* is anthroponotic. Elimination of visceral leishmaniasis due to *L. donovani* is thought to be achievable especially in the South Asian region.

This thesis will explore the current available control measures in the two high endemic areas of South Asia and East Africa and assess the feasibility of eventual elimination. The methodology applied is a literature review of topics of possible control according to the disease transmission model. The differences in specific characteristics of the vector, VL disease expression, best diagnostic tools and effective treatment, geographic-environmental, cultural, political and regional aspects, have been considered. Extrapolations of results and conclusions is difficult. However overall lessons are to be learned.

Regarding vector control insecticide spraying demonstrated good results in South Asia and is one of the main pillars of control. This method is not explored in East Africa, probably due to differences in the vector characteristics. Where in East Africa insecticide treated bed nets have shown good results this was not matched in South Asia, partly due to lack and/or need of full coverage of nets in order to be effective as control measure. In both areas environmental measures are hardly explored and could provide more valuable in vector control. Unfortunately despite the abundance of vector characteristic studies some important facts like breeding sites and effective environmental measures are not known.

To effectively reduce the parasite burden in the human host early case diagnosis and treatment have become another important control measure in South Asia. Over the last decade diagnosis and treatment of visceral leishmaniasis have significantly improved. Regional differences in efficacy of diagnosis and treatment have resulted in different possibilities in South Asia versus East Africa. Whereas the costs and functioning of health systems also play a big role. Possible improvement of access to effective diagnosis and treatment depends on availability of health facilities with proper knowledge on visceral leishmaniasis symptoms and management. The often either expensive and/or toxic drugs and long treatment regimens create even more access problems. Research has proven shorter regimens with less side effects effective. But implementation depends on national programmes.

Actively searching for patients is planned by the South Asian collaboration of visceral leishmaniasis elimination. However post kala-azar dermal leishmaniasis, where parasites move to the skin after visceral leishmaniasis and can still be transmitted, remains difficult to treat. This can remain a cause of ongoing transmission and/or re-emergence of the disease, specifically in South Asia. While in East Africa the biggest challenge in treatment is reducing the parasite burden in HIV co-infected patients. This is why for now elimination seems not yet feasible. New control measures need integration and full implementation first before other conclusions can be drawn.

In the meanwhile it remains important to prevent outbreaks of the disease to prevent spreading of the disease and its endemic areas. Whereas outbreaks can cause high rate of mortality this is often not recognized internationally. Vaccination, while thought to be achievable, is still not feasible at this point in time. Overall better surveillance of the disease and its incidence is important to recognize the burden. International commitment to control visceral leishmaniasis and recognition is highly needed.

Introduction

Leishmaniasis is caused by a parasite named leishmania from the family of trypanosomatidae. There are at least 29 species known and of these there are about 20 types found in humans for which the taxonomy still remains challenging (WHO, 2010). These parasites are protozoal, vector born and use the sand fly as the vector. Roughly 800 species of sand flies exist of which 93 sand fly species are proven vectors of leishmaniasis. However the classification of these sand flies is still under discussion. In general it is assumed that the human biting species are divided in *Phlebotomus* for the Old World and *Lutzomyia* for the New World (WHO, 2010). The (reservoir) host can be human or other type of animal, depending the parasite species and/or sand fly species, the dog being one of the most well-known (WHO, 2010).

In the parasitic life-cycle, see figure 1, in general the sand fly becomes infectious by taking a blood meal with amastigotes of the leishmania parasite from the skin of a human or animal, depending parasite species. Anthroponotic leishmaniasis (instead of zoonotic leishmaniasis) does not involve an animal host and the parasite is transmitted from human to human via the sand fly. In the sand fly the amastigotes transform to promastigotes which then again are infectious for the new host in which the promastigotes transform to amastigotes (Gill, 2009).

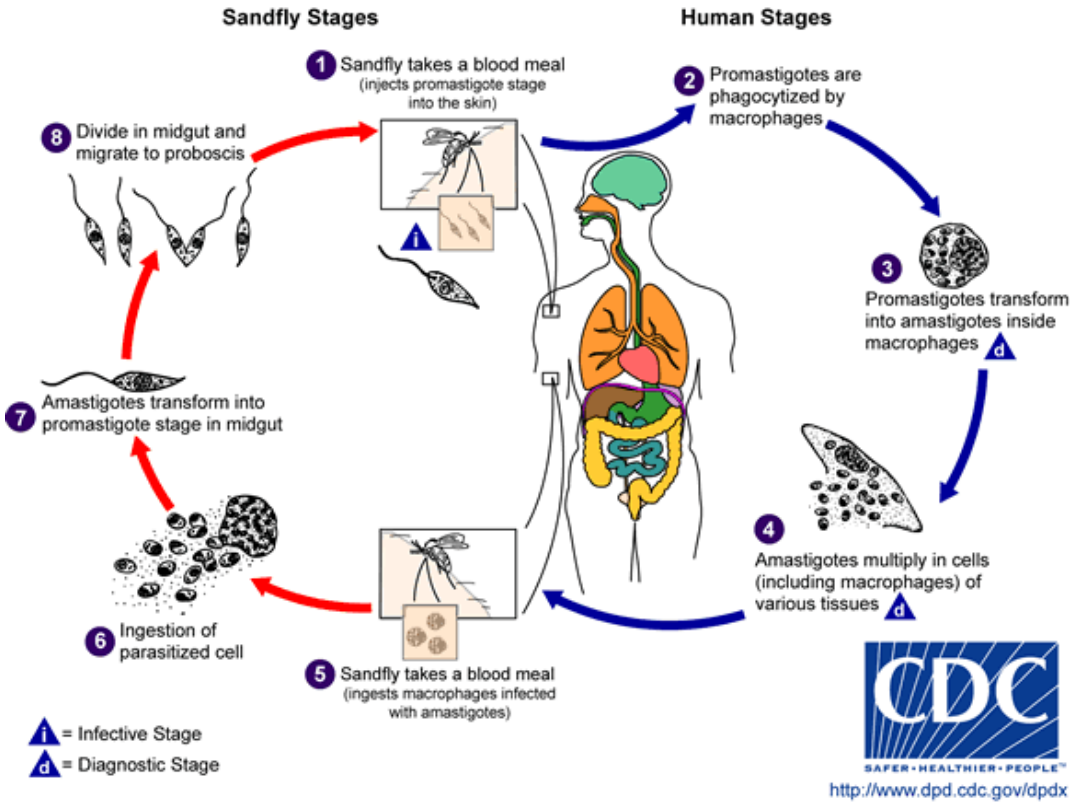

Figure 1: Lifecycle of Anthroponotic Visceral Leishmaniasis (CDC, 2013).

Depending parasite species and some factors within the host, including genetics and immunological condition, the disease leishmaniasis has a wide variation of clinical expression. From the single non-severe cutaneous lesion to the lethal visceral leishmaniasis. In literature leishmaniasis is often divided in 3 clinical forms being cutaneous (CL), muco-cutaneous (MCL), or visceral leishmaniasis (VL). Many

infected persons do not develop clinical disease. These persons have an asymptomatic infection (WHO 2010).

The most lethal variant is visceral leishmaniasis caused by the parasites of the Leishmania donovani complex (*L. donovani* and *L. infantum*). The incubation period is usually between 2 and 6 months but can vary between 10 days and 10 years (Gill, 2009). As mentioned development of the clinical disease depends on many factors and subclinical versus clinical rates in endemic situations vary between 9:1 in India and Nepal (Ostyn et al, 2011) and 0.3:1 to 11:1 in Sudan (Khalil et al, 2002). If clinical the visceral disease caused by *L. donovani* expresses itself by undulating fever, splenomegaly, malnutrition and in severe conditions pancytopenia. However this again depends on the geographical region (human factors and parasite type). For example in South Sudan the disease expresses also lymphadenopathy, while in India it does not and the supposed malnutrition is not so explicit either (observations from MSF field work, 2012). Compared to VL in South Asia, VL in East Africa is usually associated with more severe presentation and complications (MSF, 2012). The disease will be fatal if not treated and with treatment can still have case-fatality rates of 10-20% (Alvar et al, 2012). Diagnosis is based upon microscopic visualization of the parasite in splenic aspirate, bone marrow or lymph node aspirates. And can be diagnosed with a clinical case definition and a serological rapid test in low-resource settings. Treatment depends on local drug sensitivity but is often of long duration, with serious side effects and/or expensive, e.g. daily i.m. injections of pentavalent antimonials for 30 days (Gill, 2009; WHO, 2010). Even after successful treatment, complete elimination of the parasite from the body is rare, however effective cell-mediated immunity and recovery will in general develop (Murray et al, 2005). Sometimes the parasites move to the skin during the immune response causing temporary or permanent skin lesions with parasites called post kala-azar dermal leishmaniasis (PKDL) (WHO, 2010).

Problem Statement and Objectives

Epidemiology

Until recently the actual prevalence and incidence was not known and still most data are inadequate. In 2010 Alvar, et al. (2012) have tried to estimate the global burden of the disease. Considering still a high level of underreporting they have estimated about 1.6 million new leishmaniasis cases worldwide per year of which about 0.2-0.4 million visceral leishmaniasis cases. Over 90% of the VL cases occur in India, Bangladesh, Sudan, South Sudan, Ethiopia and Brazil (Alvar et al 2012).

According to the global health estimates of the WHO in 2011 regarding cause of death in the topic parasitic and vector borne diseases leishmaniasis comes 2nd to malaria, see table 1 (WHO, 2013a).

Global Health Estimate 2011	
Cause of Mortality	**Total Mortality Numbers (All ages, both sexes)**
Malaria	589,219
Leishmaniasis	53,675
Rabies	35,007
Dengue	24,376

Table 1: Annual mortality numbers due to parasitic and vector borne diseases; of 2011. Data from WHO international website (WHO, 2013a).

Since CL and MCL only very rarely result in fatal complications we can safely assume almost all deaths are caused by VL which is commonly caused by either *L. donovani* or *L. infantum* (WHO, 2010). VL is distributed worldwide and occurs in focal distribution. The affected regions are the Mediterranean, the Americas, Africa and Asia, see figure 2 (Chappuis et al, 2007).

Figure 2: Visceral Leishmaniasis distribution worldwide (source: Chappuis et al, 2007).

Whereas VL in the New World, the Americas, is caused solely by the parasite *L. infantum* (*L. chagasi*). In the Old World it can be caused by both *L. donovani* as *L. infantum*. It seems the more East, the more *L. donovani* becomes predominant (WHO, 2010). Especially in the high endemic foci in East Africa around the south-eastern part of Sudan and in South Asia around the north-eastern part of India. In South Asia the countries India, Bangladesh and Nepal share the same geographical area and vector and account for 73% of the global annual reported VL cases. In East Africa the countries Sudan, Ethiopia and South Sudan share the same vector and account for 13% of the global annual reported VL cases, see table 2 and figure 3 (Alvar et al, 2012). While VL has also been reported in Kenya, Somalia and Uganda other vectors have been incriminated in these areas (WHO, 2010). The most common causing parasite of VL in East Africa is *L. donovani*. While in South Asia *L. donovani* is the only causing parasite of VL. It has been suggested in literature that VL has been born in Sudan and currently thrives in India.

To estimate the exact VL burden is difficult because of several factors. VL is characteristically confined geographically in endemic foci and within endemic areas foci of high and low transmission exist with for example incidence numbers of < 1 to 10 new VL cases annually per 1,000 persons in South Asia (Bern et al, 2008) and < 1 to 60 new VL cases annually per 1,000 persons in East Africa (Mueller et al, 2011). There is a problem of stigma due to the skin lesions of PKDL. And foremost an economic impact due to the high costs of seeking care on multiple occasions, diagnosis and treatment in a population that already suffers of poverty (Bern et al, 2008). There is a link between VL and poverty due to the economically driven migration of non-immune people, poor housing conditions and poor nutrition leading to a higher risk of contracting and developing clinical VL (Alvar et al, 2006). During outbreaks in non-endemic areas all ages and sexes are more or less equally affected, in endemic areas it depends

on exposure and previous immunity and often the children and/or adolescents are affected (WHO, 2010). Specifically in East Africa regular epidemics of 3-5 years duration every 6-10 years have been described (MSF, 2012). Often severe due to several factors, e.g. forced migration in war and unstable health systems (Bern et al 2008). While in South Asia epidemics also occur overall the incidence seems a bit more stable. However it has been noticed that endemic foci shift to neighbouring areas after several years when host saturation occurs (Bern et al, 2008).

Region	Country	VL annual case count reported	VL annual incidence estimated
The Americas (Mexico, Guatemala, Honduras, El Salvador, Nicaragua, Colombia, Venezuela, Brazil, Bolivia, Paraguay, Argentina)		3668	4,500 – 6,800
	Brazil	*3,481*	*4,200 – 6,300*
Mediterranean (Portugal, Spain, France, Monaco, Italy, Malta, Slovenia, Croatia, Bosnia and Herzegovina, Montenegro, Albania, Bulgaria, Macedonia, Greece, Cyprus, Turkey, Syria, Lebanon, Jordan, Israel, Palestine, Egypt, Libya, Tunisia, Algeria, Morocco)		875	1,200 – 2,000
Middle East – Central Asia (Iraq, Saudi Arabia, Yemen, Oman, Iran, Turkmenistan, Uzbekistan, Kazakhstan, Ukraine, Georgia, Armenia, Azerbaijan, Kyrgyzstan, Tajikistan, Afghanistan Pakistan, China)		2,496	5,000 – 10,000
	Iraq	*1,711*	*3,400 – 6,800*
South East Asia (Sri Lanka, India, Nepal, Bhutan, Bangladesh, Thailand)		42,623	162,100 – 313,600
	India	*34,918*	*146,700 – 282,800*
	Bangladesh	*6,224*	*12,400 – 24,900*
	Nepal	*1,477*	*3,000 – 5,900*
East Africa (Sudan, Eritrea, Djibouti, Ethiopia, South Sudan, Uganda, Kenya, Somalia)		8,569	29,400 – 56,700
	Sudan	*3,742*	*15,700 – 30,300*
	South Sudan	*1,756*	*7,400 – 14,200*
	Ethiopia	*1,860*	*3,700 – 7,400*
Global Total		58,227	202,200 – 389,100

Table 2: Reported VL cases vs. Estimated VL cases; per region, out of which high-endemic countries have been highlighted (reported numbers have been an average over a 5 year period before the year 2007 to 2010 depending region. Estimates are based on additional data and studies) (Alvar et al, 2012).

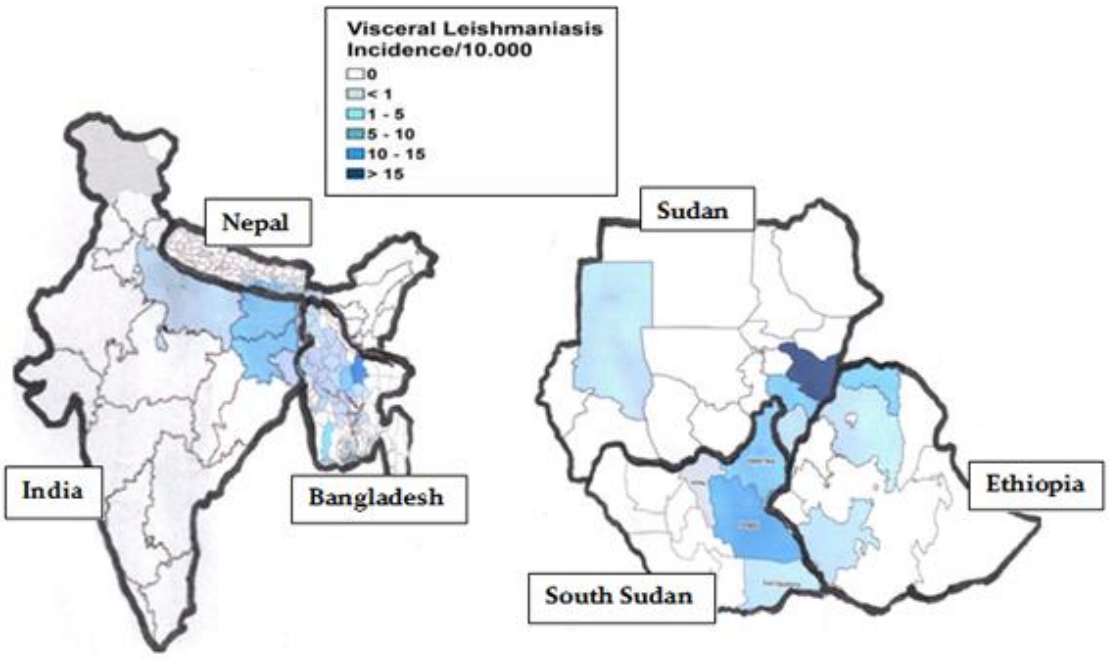

Figure 3: Visceral Leishmaniasis Incidence maps; in 2008/2009, South Asia on the left (India, Nepal and Bangladesh) and East Africa on the right (Sudan, Ethiopia and South Sudan) adapted from Alvar et al, 2012.

Problem

In conclusion there are many VL patients who will die without treatment. Instead of the roughly 53,000 patients reported annually its estimated that there are probably up to 400,000 patients per year. Which number comes close to the reported number of malaria patients per year (589,219), see table 1 and 2. Most patients are concentrated in 3 regions of which 2 share a similar parasite species, East Africa and South Asia, see figure 3. On top of the endemic incidence frequent epidemics occur which have high mortalities and can spread the disease to non-endemic areas. Unfortunately the disease occurs in the remote areas and is associated with poverty which probably is one of the causes the disease does not get the attention it deserves. For example in East Africa mapping of foci show endemic areas around the border areas, areas with many conflicts and other remote areas, see figure 4.

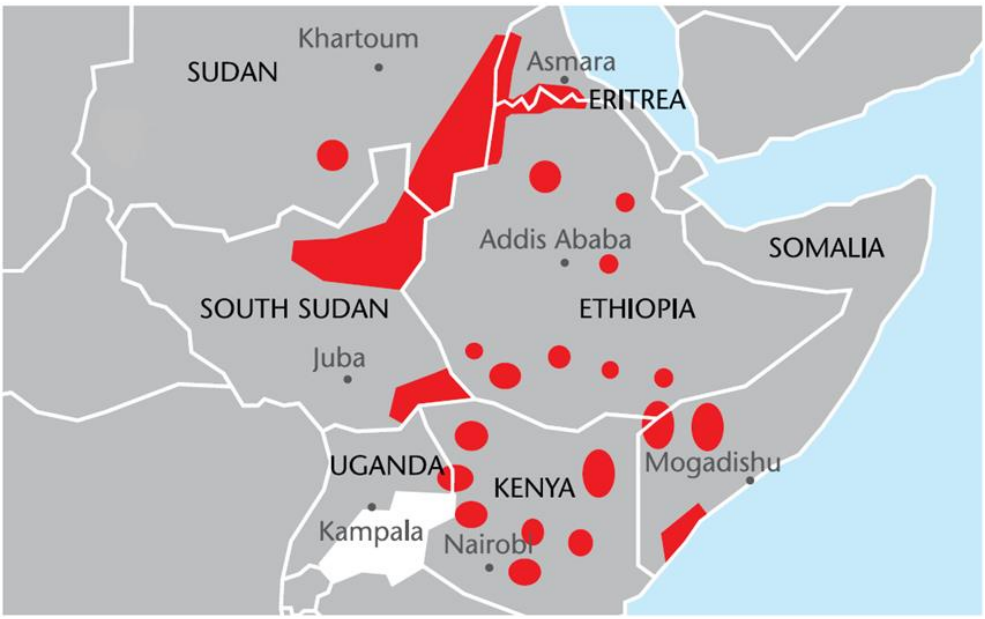

Figure 4: VL endemic foci in East Africa; Map adapted from malaria consortium/COMDIS with the courtesy of K. Ritmeijer (malaria consortium, 2010).

Leishmaniasis has been neglected as a significant burden for infectious disease since long. It was not until the World Health Assembly of 2007 that Leishmaniasis was recognised as an important Neglected Tropical Disease (NTD). In the report of this 60th assembly, it was recognised that many people were at risk, infected and an increasing amount of new patients occurred every year. The lack of accurate information regarding epidemiology, understanding of the disease and its control was also recognised (World Health Assembly, 2007). In the roadmap towards NTD impact reduction of 2012 the WHO does mention leishmaniasis, unfortunately it seems most efforts are directed towards preventive medication for other diseases like food-borne trematodes. For leishmaniasis an aim has been set to reduce CL in the Mediterranean and it is expected that VL in South Asia will be 100% detected by 2020. However no preventive measures are mentioned and VL in East Africa is not discussed (WHO, 2012). In this document leishmaniasis is referred to as a complex disease. On the other hand authors have suggested VL to be able to get eliminated due to several factors. VL due to *L. donovani* is anthroponotic, no need to control an animal reservoir. It is geographically confined and clustered. And recently there have been quite some developments in diagnosis and treatment. These factors are thought to make it feasible to eliminate VL at least in South Asia (Picado et al, 2011). The vector can be controlled with insecticides, people can get protected with bed nets, human reservoirs can get reduced with early case diagnosis and treatment including active case detection (ACD) and developing a vaccine was thought to be possible (WHO, 2010). In such the disease at least can be controlled and probably even eliminated from certain regions.

In this thesis we will describe the efficacy of different control measures for visceral leishmaniasis due to *L. donovani* in South Asia versus East Africa in order to give adapted recommendations and assess the feasibility of possible elimination. This will be discussed using the transmission model, see figure 4.

Specific objectives:

- Describe current control measures directed at the vector
- Describe current control measures directed at the host
- Describe preventive measures for VL in general
- Compare the results of efficacy and possibility in both regions (South Asia and East Africa)

Methodology

The searches have been conducted through the PubMed database with several combinations of key terms, see box 1. No limitations (language or year of publication) have been used. From these results articles have been hand-selected for relevance to the international health nature of the thesis and control measures in regard of the topic of "visceral leishmaniasis" due to "leishmania donovani" in "South Asia" or "East Africa", leaving out non-relevant detailed clinical and microbiological articles. Relevant references from the published articles have been added. For more background grey literature the WHO and national websites have been searched and the most common reference books on tropical medicine and infectious diseases read.

Key terms for database search:

"Visceral Leishmaniasis", "Leishmania Donovani", "kala-azar", "control", "vector", "host", "early case", "diagnosis", "treatment", "active case finding/detection", "epidemic/outbreak", "vaccines", "prevention" and "*country*" (being India, Bangladesh, Nepal, Sudan, South Sudan or Ethiopia)

Box 1: Key terms for database search regarding VL control in South Asia versus East Africa.

A model has been developed based on the transmission of anthroponotic VL considering possible points of control or prevention. Vector control has been divided in controlling transmission from vector to human by indoor residual spraying (IRS), insecticide treated nets (ITN) and environmental modification (EVM) and others. Host control has been divided in controlling/reducing the human reservoir of parasites by diagnosing and treating patients as early as possible, active finding of new cases and treating special infectious cases. Whereas overall prevention of VL is discussed by addressing outbreak management (preventing disease spread) and vaccination (preventing disease development), see figure 5.

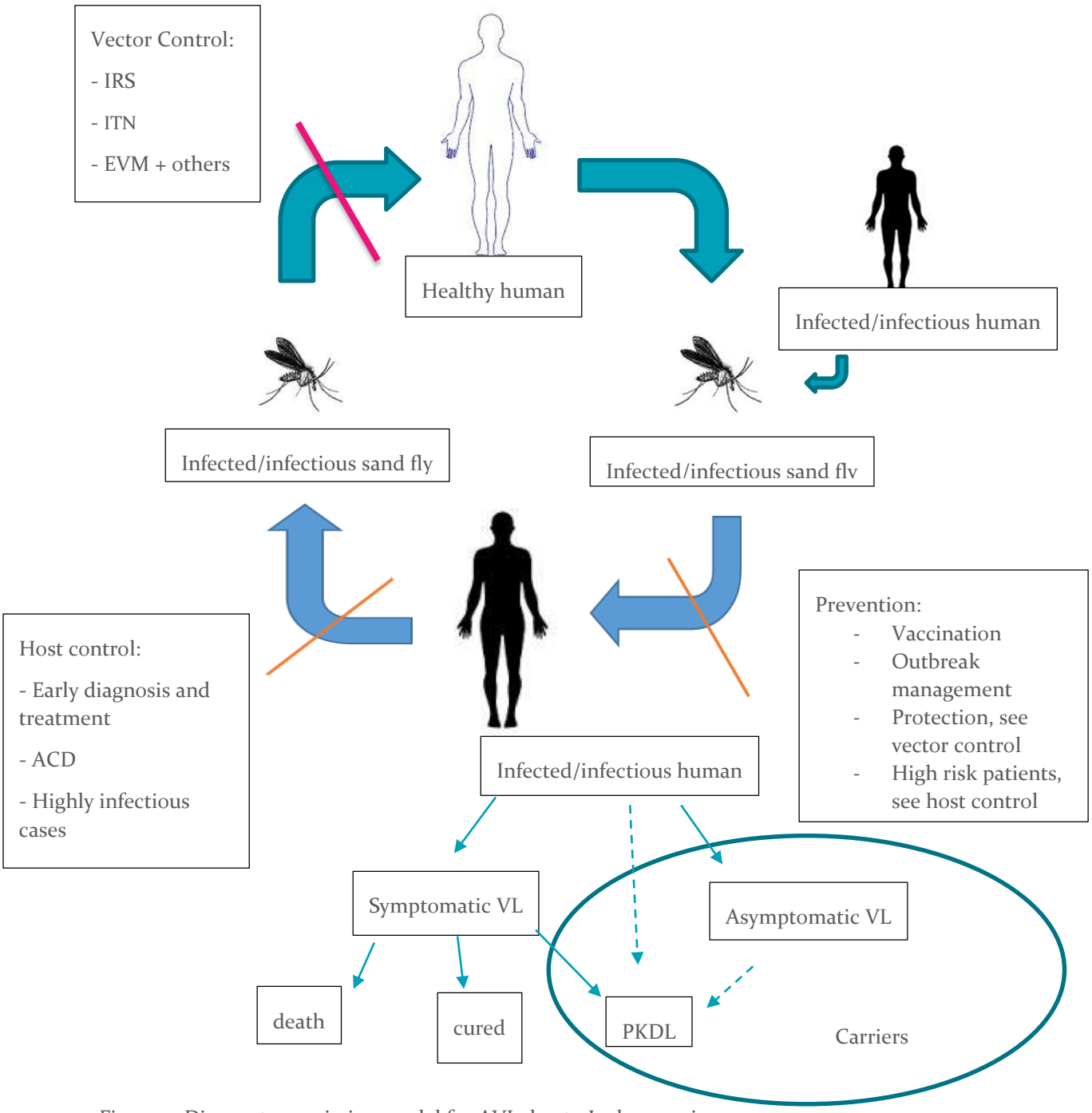

Figure 5: Disease transmission model for AVL due to L. donovani

Vector control

The vector for VL due to L. donovani is the sand fly, specifically from the genus phlebotomus. Out of which many types are known with very different characteristics. The specific incriminating vector in South-Asia is the *Phlebotomus Argentipes*. And the vector in East-Africa is the *Phlebotomus Orientalis*, where some others have been mentioned. Those vectors have been associated with a different leishmania parasite strain (Gelanew et al, 2010; Elnaiem et al, 2011; WHO, 2010).

Leishmaniasis vector control has been combined with control of other vector-borne diseases, e.g. malaria. For which most VL endemic areas in South Asia are free or have occasional low-transmission of malaria (0-1 case per 1,000 population). While in East Africa the endemic region has a high malaria transmission (> 1 case per 1,000 population), in both regions mostly due to p. falciparum (WHO, 2013b). The main method of vector control depends usually on the behaviour of the sand fly, e.g. endophilic (spraying insecticide indoors), peri-domestic (include outdoors and animal habitats spraying) or sylvatic (spraying resting sites in forests, e.g. trees or clearing bushes/trees) (WHO, 2010).

Beside the geographical difference there are some behavioural differences between the 2 types of sand flies relevant for understanding and using the best adapted control measures. In general sand flies develop from eggs in 7-10 days to larvae, in 21 days to pupae, in 10 days to adults. The females need blood meals for egg development, and both sexes feed with sugar meals, e.g. honey dew. The life expectancy of the sand fly is unknown in general and depends on species, so far estimated averages have been between 9 to over 30 days, flight dispersion is a maximum of 1-2 km, often less with a speed of 1 m/sec., most breeding sites are unknown but expected in a moist and rich of micro-organic matter environment, for resting sites most tend to prefer cool and humid niches (WHO, 2010). More specific characteristics of the sand fly in South Asia versus the sand fly in East Africa are provided in table 3.

Sand fly characteristics	P. argentipes	References	P. orientalis	References
Anthropohilic	Yes	WHO, 2010	Yes	Elnaiem, 2011 (review)
Zoophilic	Yes	WHO, 2010	Yes	Elnaiem , 2011
Endophagic vs exophagic (biting in- vs outdoors)	No specific data/studies found		Poor data, no consistent findings Suggestions: tree cavities and porcupine dwellings, not thought to be in human dwellings	Elnaiem, 2011
Biting behaviour	Ideally around 23:00-24:00 hrs. with some seasonal variation Multiple feeds during oviposition	Dinesh et al, 2001 WHO, 2010	Conflicting data: 18:30 -22:00 and 05:45-07:00 hrs. vs throughout the night Single feed during oviposition	Elnaiem, 2011 WHO, 2010
Blood meal preference	Prefers cattle over humans	Dinesh et al, 2001	Prefers cattle over humans	Gebre-Michael et al, 2010
Habitat	Peri-domestic	WHO, 2010	Mainly sylvatic : Association with acacia-balanites forests on black cotton soils Some found peri-domestic/domestic	Elnaiem, 2011 Widaa et al, 2012
Endophilic vs Exophilic (resting in- vs outdoors)	Endophilic	WHO, 2010; Bern et al, 2008	Conflicting evidence, most state exophilic	Elnaiem, 2011
Breeding sites	Alkaline soil, e.g. cattle sheds outdoor	Singh et al, 2008; Ghosh et al, 1991	Poor data. No specific data/studies found	
Dispersal	No specific data/studies found		300-700 meter	Elnaiem, 2011
Seasonal pattern	2 annual density peaks around May and October	Picado et al, 2010a	1 annual density peak around April (complete disappearance around September)	Elnaiem, 2011
Positive enhancers of sand fly density	Higher temperature	Picado et al, 2010a		
Negative enhancers of sand fly density	More rainfall	Picado et al, 2010a		
Infection rate of sand flies with leishmania donovani parasite	Annual average 1.50% (0.84-2.84%) As high as April-June 4.90-17.37% mentioned	Tiwary et al, 2013 Tiwary et al, 2012	Annual average 2.5% (range 1.9-5%) As high as 9.6% mentioned	Elnaiem, 2011 Elnaiem, 2011; Schorser et al, 1992
Insecticide susceptibility	For DDT 4% (43-100% after 24 hrs.) and deltamethrin 0.05% (99% after 1 hr.)	Dinesh et al, 2010	No specific data/studies found	

Table 3: *P. argentipes* and *P. orientalis* characteristics; summary of evidence based studies and results, including source.

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To develop control measures it is important to properly understand the vectors' behavioural pattern. Even though ecological studies regarding the vector for leishmaniasis have not been put in the recommendations for control in the WHO "control of the leishmaniasis" 2010. It has been mentioned that vector control measures in East-Africa have been difficult to develop due to lack of knowledge on the ecology of the vector (Elnaiem, 2011). Recently more effort has been put into understanding the vector and its characteristics, see results in table 3. Most in coherence with previous knowledge and some new results but also some seemingly conflicting results (Tiwary et al, 2012; Tiwary et al, 2013). Conflicting data results have been explained by the differences of the many factors involved for the vector, e.g. environmental influences of temperature, humidity and availability of specific micro-organic matter. Some researchers have tried to use remote sensing studies using geographical information systems (GIS) in order to identify endemic foci with the normalized difference vegetational index (NDVI) and other environmental features. In Gedaref state, Sudan, the VL incidence seemed to correlate with the distance from 2 rivers and a positive correlation with average-high rainfall and low-mean NDVI (Elnaiem et al, 2003). In India this method has also shown a positive correlation between VL incidence and low altitude, higher population density, average temperature around 23°C, relative humidity of 85%, low NDVI (Bhunia et al, 2010)

In respect to previous information some of the risk factors of getting bitten by an infected sand fly in South-Asia are in such associated to sleeping outside or on the ground, sleeping in houses with mud-plastered walls and cracks, close to small areas of water and vegetation next to other factors for contracting VL as closeness of VL patients, poverty, nutritional status, etcetera (Bern et al, 2010). Whereas in East-Africa most people have been thought to contract VL from travelling through forests, e.g. with their cattle (Elnaiem, 2011).

The two most studied vector control measures have been insecticide residual spraying (IRS) in order to reduce vector density and insecticide treated nets (ITN) in order to protect humans from getting bitten by the vector. Furthermore studies regarding environmental control measures, like environmental modification (EVM), have been performed to reduce vector density as some newer but rarely described strategies involving for example treating cattle with insecticides.

Indoor Residual Spraying

Insecticide spraying for VL has been commonly used in India since the 90s with DDT. After the introduction of the regional VL elimination strategy in 2005 also more often in Nepal with lambdacyhlotrin, but sporadically in Bangladesh (Picado et al, 2012). Few studies assessing the effectiveness of IRS in vector control for the sand fly P. argentipes in South-Asia have been found and analysed. No studies regarding IRS have been found for East-Africa.

It is difficult to compare these data due to many factors to be considered. Like the seasonal differences in sand fly densities as described in table 4. But also a high variation in sand fly densities in different geographical areas. And the seasonal variation of VL incidence and its varied incubation period. Testing sand fly densities pre versus post IRS might reduce confounding geographical environmental factors of two different areas but is depended on seasonal variation in sand fly densities, see table 3. While a sprayed versus non-sprayed area reduces confounding in seasonal variety it does depend on geographical including host factors like genetics and socio-economic status. Other simultaneously occurring interventions, like incentives for reporting cases or bed net use, can interfere with the data outcomes as well.

IRS Region, Timeframe and Insecticide	Sand fly density Pre vs Post	IRS vs no IRS	Pre vs Post controlled	House Holds positive for sand flies	Sand fly bites	VL incidence	Source
India, From 1950-1970 (malaria eradication campaign)						0 cases reported during few years	Ostyn et al, 2008; Picado et al, 2012
India (Uttar Pradesh) 1991: 1st round in June and 2nd round in August DDT		100% reduction (335 in unsprayed vs 0 in sprayed village)					Kaul et al, 1994
India (Bihar state) 2007: February- April DDT	30% reduction (141 pre- vs 99 post spraying, 3 months interval)			63% reduction (115 pre- vs 42 post spraying)		53% reduction (2,958 cases Dec 2006 vs. 1,407 in Dec 2007)	Kumar et al, 2009
South Asia (overall) Nov 2006 – April 2007			72.4% reduction[1]				Joshi et al, 2009
India (Bihar state) Nov 2006 – April 2007 DDT 5%			124% reduction[1]				Joshi et al, 2009
Bangladesh (Mymensingh district) Nov 2006 – April 2007 Deltamethrin	78% reduction (595 pre- vs 129 post spraying, 6 months interval)	77% reduction (1140 in unsprayed vs 261 in sprayed village)	94% reduction[1]				Joshi et al, 2009 Chowdhury et al, 2011a
Nepal (sarlahi, sunsari and morang districts) Nov 2006 – April 2007 Alpha-cypermethrine			52.5% reduction[1]				Joshi et al, 2009

Table 4: IRS efficacy in VL; summary of evidence based articles, including source.

[1] No specific data available: unreproducible, based on a mathematical model: pre vs post and controlled

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In respect to the data in table 4 IRS seems an effective vector control method. Due to the peri-domestic nature of the sand fly in SA insecticide spraying would be expected to be effective, preferably when sprayed around February-March and August-September (Picado et al, 2010). For East-Africa it seems more difficult since the vector has pre-dominantly found to be sylvatic (Elnaiem et al, 2011). Referring to an old study in 1965 by Turner et al., the results mentioned a temporary reduction in vector density after insecticide house spraying and fogging of Acacias in Southern Sudan (Elnaiem et al, 1999).

Especially due to experiences from the past IRS has become popular as a control method for VL in South Asia. During the eradication campaign for malaria in the 1950s to 1970s with extensive IRS VL had been eliminated from the region. However after ending IRS strategy VL re-emerged in epidemic forms (Picado et al, 2012). A study in 1991 in India suggests high efficacy with DDT spraying that has not been repeated since (Kaul et al, 1994). This could be due to differences in study design, e.g. interval of 6 months versus 3 months, or due to other factors. Upcoming DDT resistance has been suggested in Bihar state, India, where a reduction in mortality of sand flies after exposure to DDT has been observed (Dinesh et al, 2010). At the same time the numbers could be enhanced with other interventions, like health education (Kumar et al, 2009). A cluster randomized trial has been set up and tried to avoid confounding factors as much as possible when comparing the three interventions of IRS, ITN and EVM. IRS seemed more effective than the others but has been performed under controlled conditions (Joshi et al, 2009).

Regarding programmatic issues the performance of IRS through national programmes have been assessed by Chowdhury et al in India and Nepal (Chowdhury et al 2011b). In general staff at (sub)district seemed quite familiar with the technical guidelines and procedures for IRS. However the performance of IRS was of substandard quality, observed by bio-assays and chemical analyses of walls sprayed, specifically in one of the Nepalese sites (Chowdhury et al 2011b). Consequently in India a toolkit for monitoring and evaluation of IRS for VL control has been field tested (Huda et al, 2011). It can be understood that IRS is a challenging intervention as it is expensive. So proper management is important to have an impact and a monitoring and evaluation system would be useful to detect any issues to deal with (Huda et al, 2011). Many divers shortcomings during the process have been identified and the writers suggested the M&E toolkit to be implemented by the 3 countries in South Asia.

Currently the WHO recommends for South Asia to do large scale spraying during epidemics both indoor as outdoor including animal shelters. In endemic areas only infected villages can be sprayed according to seasonal patterns (WHO, 2010).

Insecticide Treated Nets

Since the sand fly P. argentipes in South-Asia has been known to be peri-domestic and active at night, suggesting as well feeding at night (Picado et al, 2012) ITN would seem to be a good vector control measure to prevent VL infections in South Asia. For East-Africa again this seems less likely to be effective except if nets are used when sleeping outside and during travelling.

Most studies in South-Asia have been part of a large set up operational research project called KALANET community trial exploring the use of long lasting insecticide treated nets (LLIN), for which some of the results have been reported separately, see table 5. Part of the KALANET project was a baseline survey on bed net ownership in India and Nepal. In India 59% and in Nepal 86% identified a vector causative of VL and in India 82% of the houses had at least 1 bed net vs. 70% in Nepal. Most nets were not impregnated with insecticides. Often the poor people did not have the nets (Vanlerberghe et al, 2010).

ITN Region, Timeframe and net used	Sand fly density Pre vs post	ITN vs no ITN	Pre vs Post controlled	Sand fly bites/blood feeding	VL incidence	Source
India (Bihar state) 2006: April-June PermaNet 2.0 and OLYSET vs. untreated nets (156 Mesh)		0% reduction (no significant reduction of female P. argentipes density in House Holds with ITN vs untreated net)				Dinesh et al, 2008
India and Nepal Sept 2006 – Dec 2007 Untreated nets				85,5% reduction (in pre- vs post intervention % of female P. argentipes blood fed)		Picado et al, 2009[1]
India and Nepal Sept 2006 – Dec 2007 PermaNet 2.0 (156 Mesh)		63% reduction (851 in ITN vs 2290 sand flies in control clusters collected during 12 months)		9% reduction (in sand fly exposure in ITN vs control clusters)	0% reduction (No significant reduction in sero-conversion measured with DAT[2] in ITN vs control clusters)	Picado et al, 2010b[1]; Picado et al, 2010c[1]; Gidwani et al, 2011[1]
South Asia (overall) Nov 2006 – April 2007 PermaNet 2.0			43.7% reduction[3]			Joshi et al, 2009
India Nov 2006 – April 2007 PermaNet 2.0			298% reduction[3]			Joshi et al, 2009
Bangladesh Nov 2006 – April 2007 PermaNet 2.0	81% reduction (682 pre- vs 132 post intervention)	76% reduction (1140 in control vs 273 in intervention village)	68% reduction[3]			Joshi et al, 2009; Chowdhury et al, 2011a
Nepal Nov 2006 – April 2007 PermaNet 2.0			19% reduction[3]			Joshi et al, 2009
Bangladesh March 2008 – august 2009 Impregnating nets			60% reduction[3]			Mondal et al, 2010
Sudan (acacia forest) 1995: June Nets (156 Mesh)				100% ITN vs 78% untreated nets reduction in sand fly bites (32.0 no net vs 6.92 untreated net vs 0 ITN bites/man/night)		Elnaiem et al, 1999
Sudan (Gedaref state) Oct 1998 – March 2001 ITN (156 Mesh)					27.4% reduction in VL cases/village/month after ITN introduction (adjusted for pre-intervention incidence)	Ritmeijer et al, 2007

Table 5: ITN efficacy in VL; summary of evidence based articles, including source. [1]part of KALANET trial [2]lower DAT cut-off titre used then for diagnosing VL in clinical suspected cases [3] No specific data available: unreproducible, based on a mathematical model: pre vs post and controlled

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The results of efficacies of bed nets in these studies are difficult to compare due to similar reasons previously mentioned in IRS. In addition there might be a difference in insecticide impregnation and Mesh sizes of the nets. Sand flies are smaller than mosquitoes and a smaller Mesh size of bed nets (>200 holes per inch^2) is advised (Ostyn et al, 2008). However when treated with insecticides small Mesh does not have to be used and nets of 156 holes per inch^2 have proven effective (WHO, 2010). Furthermore people from control villages often used (untreated) nets which cannot be removed for ethical reasons.

Untreated nets can demonstrate a significant reduction in sand fly bites of people, e.g. from 21.5% to 2.7% of blood fed female *P. argentipes* in Nepal and India combined. Where blood initially had been 62% from humans, after intervention this was reduced in human blood index to 42%. Suggesting possible diversion of blood feeding to other animals (Picado et al, 2009). When insecticide treated nets had been used instead of untreated nets the sand fly density was reduced with an estimation of 25% per house corrected for the interference of sporadic spraying. While at the same time the sand fly density in the nearby cattle sheds did not increase (Picado et al, 2010b). Suggesting a significant impact of the insecticide in the nets. However data on the topic of sand fly dispersion amongst households versus cattle sheds varies. In the same trial no reduction in sero-conversion to *L. donovani* infection between the ITN versus control cluster after 2 years was found. However in this trial some people from the control clusters had been using untreated nets and sporadic IRS occurred (Picado et al, 2010c). The sand fly exposure did reduce by 12% after 1 year and 9% after 2 years, when *P. argentipes* saliva antibodies had been measured in people from the ITN versus control cluster (Gidwani et al, 2011). The sand fly density also reduced in the community trial but not as much as IRS did (Joshi et al, 2009). However when ITNs are used only in few houses the study on household level observed no reduction in sand fly density (Dinesh et al, 2008).

In such ITN can be quite effective for personal protection, can demonstrate some reduction in sand fly density at community-level when they are used by all households. Whether this level of sand fly density has been reduced enough to have an impact on actual VL incidence is not demonstrated in South Asia. Whereas in East Africa there is impact shown on VL incidence, see table 5.

In East Africa a small trial of 3 volunteers demonstrated a reduction in sand fly bites using bed nets in the Acacia forest. This same study also estimated the exposure for sand fly bites to be less than 2 hrs./day for over 89% of the people. Assuming exposure starts at sunset and end at bedtime, when using a net (Elnaiem et al, 1999). An evaluation of a mass distribution of bed nets in Sudan with health education actually showed a reduction in VL incidence. In this retrospective study a coverage of 95% of the area was created, bed net usage showed strong seasonal variation depending on night temperature and the presence of nuisance insects and was < 10% during the hot season, dry season, coinciding with the peak of the VL transmission. After 2 years < 50% of the bed nets were still in use. An overall reduction of 27% in VL incidence (increasing to 59% 17-20 months post distribution) for a total cost of 6.40 USD per net distributed made this a successful strategy (Ritmeijer et al, 2007).

In India actual bed net usage was also found to be low, < 50%. Even though most thought fumes, bed nets and keeping environment clean were an effective protective measure. Most reasons stated for not using a net were economical hurdles, too big of a family, no space, discomfort in heat and alcohol addiction.

Environmental Modification and Others

Another vector control method would be environmental modification. For example since the association between the habitat of acacia-balanites forests with the vector *P. orientalis* seems so strong that villages more than 1 km away from these forests do not seem to be endemic for VL (Elnaiem, 2011). One might consider to take away the trees, or move the villages. No specific studies regarding Environmental Modification have been done in East Africa. Only indirect assumptions and suggestions have been made, e.g. an area in Sudan where VL re-emerged after ending deforestation due to charcoal

production (Khalil et al, 2008). In South-Asia so far only wall plastering with mud/lime has been studied. Since the cracks are suspected habitats for sand flies and the lime might adjust the alkaline in the mud making the area less attractive for sand flies as an habitat.

EVM **Region, Timeframe and Method**	**Sand fly density**	**Source**
South Asia (overall) Nov 2006 – April 2007	42.0% reduction[1]	Joshi et al, 2009
India (Bihar state) Nov 2006 – April 2007 Lime/mud wall plastering	108% reduction[1]	Joshi et al, 2009
Bangladesh (Mymensingh district) Nov 2006 – April 2007 Mud wall plastering + incentive	9% reduction[1] Not significant	Joshi et al, 2009
Nepal (sarlahi, sunsari and morang districts) Nov 2006 – April 2007 Lime/mud wall plastering	4 - 51% reduction[1]	Joshi et al, 2009

Table 6: EVM efficacy in VL; summary of evidence based articles, including source. [1] No specific data available: unreproducible, based on a mathematical model: pre vs post and controlled

The lime/mud wall plastering had not significantly reduced sand fly densities in one site in Nepal and in Bangladesh. Similar contradicting evidence for mud only plastering has been mentioned in the past. However the lime actually was expected to reduce indoor sand fly breeding. Unfortunately the effect that had been measured was of short duration (6 months) despite follow-up. And the costs had been higher than for the IRS and ITN intervention (Joshi et al, 2009). Despite this lack of evidence the WHO recommends environmental measures, e.g. sanitation in peri-domestic areas and housing improvement (WHO, 2010).

Others

As shown previously in table 3 it seems the sand flies in both regions prefer to feed on cattle and therefore it has been suggested that cattle can prove to be zoo-prophylactic (Gebre-Michael et al, 2010). However studies regarding the association between the risk of getting VL and proximity of cattle has been conflicting (Bern et al, 2010). The proximity of cattle can both increase the abundance of sand flies as can it be protective as preferred blood meal (Bern et al, 2010). A study has been done in India regarding administration of a broad-spectrum insecticide, fipronil, to cows. A significant effect was seen in the mortality of sand flies after feeding on these cows and mortality of larvae of the p. argentipes in the faeces of these cows without any side-effects due to the medicine in the cows (Poché et al, 2013).

Conclusive

In general IRS seems quite effective in South Asia in reducing sand fly densities. However currently the risk of insecticide tolerance or even resistance is creating possible future limitations and reductions in effectiveness. For East Africa there is some evidence that IRS might be effective but no studies or other type of results back up this assumption. While ITN do protect humans from getting bitten by the sand flies it seems difficult to provide an overall reduction in sand fly density or VL incidence unless a high coverage of ITN use is achieved. EVM has seemed a practical approach in this vector borne disease with such a geographic-environmental confined endemicity no good and efficacious control measures have been described. For this more evidence on actual breeding sites is needed in both regions.

Host control

As previously discussed the vectors both in South-Asia as in East-Africa are zoophilic. And some leishmania parasites have an animal reservoir (zoonotic), e.g. *L. infantum* causing VL (WHO, 2010). Despite the fact that *L. donovani* in both settings has been described anthroponotic solely recent studies have disputed the fact.

In both regions *L. donovani* has been found with PCR in dogs, whereas in East Africa as well in rodents (Elnaiem et al, 2001; Alam et al, 2013). A study in Ethiopia did not find visualisation of parasites in sero-prevalent dogs (Bashaye et al, 2009). In South Asia cattle have been found sero-prevalent but no DNA or visualisation of parasites and therefore no infection was found ((Bhattarai et al, 2010; Alam et al, 2011). While in Sudan *L. donovani* has been cultured from the lymph nodes in dogs (Dereure et al, 2003).

In East Africa despite evidence for *L. donovani* parasite in animals especially dogs may play a role in the transmission dynamics but we cannot conclude them to be a reservoir host (Hassan et al, 2009). They seem to be neglectable compared to the human reservoir. In South Asia the possibility is even less likely and in such we cannot incriminate these animals as a reservoir host but have to bear in mind the possibility.

Identifying the human so far as the only reservoir host for *L. donovani* causing VL. Humans can be infected in several ways the one more infectious (to the sand fly) then the other. Most importantly the asymptomatic versus symptomatic persons, PKDL and HIV/VL co-infection patients.

Asymptomatic vs. Symptomatic

Patients can be infected with *L. donovani* without getting clinical VL. For example in a village in Sudan during an outbreak about 90% of the population was sero-converted and about 21% actually developed clinical VL between 1996 and 1999 and a long asymptomatic (1- 2 years) but infected period has been found for some adults (Bucheton et al, 2002). Factors for developing clinical VL during this outbreak were amongst others, the presence of dogs, cows and balanites trees, age, gender and ethnic origin, not correlated with socio-economic factors or daily activities. After the outbreak developing clinical VL was strongly associated with a single tribe and in such it was postulated that the most important factor was the host genetics and the possible role of these within the immune system/response (Bucheton et al, 2002; Bucheton et al, 2003). In East Africa rates of developing clinical VL has also exceeded asymptomatic sero-conversion rates (1.6-2.4 clinical cases for 1 subclinical case) (Zijlstra et al, 1994). While in endemic areas in South Asia about 10% of sero-converted individuals develop clinical VL (Ostyn et al, 2011).

How infectious these asymptomatic individuals are to others depends partly on the parasite burden which is inversely related to the effective cell mediated immunity and delayed type hypersensitivity (Murray et al 2005). In India, Bihar state, blood smears for parasitology of *L. donovani* even though not so sensitive, did yield a 1.3% of asymptomatic patients with proven parasites in peripheral blood (Sharma et al, 2000). A mathematical model of data in the Indian subcontinent estimated a rough 2.5% probability of a sand fly to get infectious feeding on an asymptomatic host concluding that transmission of *L. donovani* is predominantly driven by these asymptomatic hosts, whom are not eligible for treatment now. However this model was performed under many assumptions one of them being that the parasite was homogenously spread amongst humans and sand flies (Stauch et al, 2012).

Having a patient with VL nearby is a strong risk factor for developing both subclinical as clinical VL (Bern et al, 2010; Perry et al, 2013; Bimal et al, 2005). The question remains if it is reasonable and feasible to mass treat asymptomatic patients in order to reduce the parasite burden in the human host. So far it has not been proven in experimental studies that sand flies can become infectious after biting an asymptomatic individual (xenodiagnostic studies). Even though if this would be proven to be important

in disease transmission actual treatment of asymptomatic individuals would be hampered with current available diagnostics and treatments. So far there are no possible safe prophylactic options.

Early Case Diagnosis and Treatment

Diagnosis based on clinical symptoms can be standardised by using a case definition, e.g. used by MSF is "history of prolonged fever (2 weeks or more) with splenomegaly and/or lymphadenopathy and/or wasting" (MSF, 2014). However the signs and symptoms are not specific enough to differentiate VL from other conditions and additional testing is needed (WHO, 2010). This test should be highly sensitive to avoid missing a lethal disease and highly specific since treatment is expensive and can have a lot of toxic effects. The test should be able to make a distinction between asymptomatic infection and clinical disease, easy to use in field conditions and cheap (Chappuis et al, 2007). Several diagnostic tools are available of which the actual visualisation of the parasites still is the golden standard (WHO, 2010). Most of these tests however show different sensitivity and specificity results in East Africa versus South Asia.

Current diagnostic tools

Parasite detection

Leishmania amastigote visualisation through microscopy has a high specificity. Though sensitivity varies, bone marrow (53-86%), lymph node aspirates (53-65%) and spleen (93-99%) with the latter comprising of a (though limited) risk of life-threatening haemorrhage (~ 0.1%) (WHO, 2010). However the accuracy of microscopy depends on the technical level of the laboratory and its reagents (Chappuis et al, 2007). Recently PCR screening of blood samples of suspected VL cases have shown sensitivity rates between 70-100% and specificity has increased remarkably. In such PCR can help quantify the parasite burden, but so far no field adapted test has been developed (Srivastava et al, 2011). The same for culture, even though sensitive and reproducible, very costly, time-consuming, high technology laboratories are needed. And thus seldom used for clinical diagnosis but more often for research purposes (Srivastava et al, 2011). These techniques are not feasible in the field or rural areas where the VL is highly endemic (Chappuis et al, 2007).

Antibody and Antigen detection

Antibody detection in VL is challenging due to the fact that it does not distinguish an asymptomatic infection or past disease from a symptomatic acute disease. And in such it should be combined with a case definition and cannot be used for diagnosis of a possible VL relapse (Chappuis et al, 2007). Serological tests in high quality laboratories like ELISA (enzyme-linked immunosorbent assay) and a western blot are difficult to use in the field but have a very good diagnostic accuracy in VL (WHO, 2010). For field use there are special serological tests developed, rapid diagnostic tests (RDT). For which the most commonly known, used and studied are the direct agglutination test (DAT) and the rK39 antigen-based immunochromatographic test (rK39) (WHO, 2010).

The DAT has a sensitivity of 92.7-96.4% and a specificity of 93.9-98.7% and it is a relative simple test, but needs equipment, trained staff, overnight incubation and cold-chain (Chappuis et al, 2006; Chappuis et al, 2007). For which the latter has improved by the use of freeze dried antigen, there still is need for overnight incubation in the fridge (Srivastava et al 2011). The rK39 is a rapid test easy to use in the field and cheap. High sensitivity and specificity of the rK39 RDT (rapid diagnostic test) made it popular in India and several commercial tests became available on the market. In India instead of East Africa there is also a RDT on the market based on rKE16 antigen. Unfortunately the sensitivity and specificity of the same RDT format varies according to region, see table 7 (Cunningham et al, 2012). This is suspected to be due to the difference in the parasite genomics between South Asia and East Africa. The parasite strain genetics in East Africa seems more heterogeneous in comparison to the more homogeneous genetics of the L. donovani strain in South Asia (Bhattacharyya et al, 2013). And East Africans produce less antibodies (directed to rK39) then South Asian persons (Chappuis et al, 2007).

Test	*East Africa* Sensitivity	Specificity	*South Asia* Sensitivity	Specificity	Source
RDT rK39	67.6 – 87.2%	90.8 – 96.4%	98.8 – 99.6%	96.0 – 97.6%	Cunningham et al, 2012
RDT rKE16	36.8 – 73.2%	96.4 – 98.0%	92.8 – 100%	99.2 – 100%	Cunningham et al, 2012
DAT	93.2%	96.1%	97.1%	95.7%	Chappuis et al, 2006

Table 7: rK39 + rKE16 antigen based RDTs, and DAT sensitivity and specificity in South Asia vs. East Africa

Combining the DAT with the rK39 can optimise diagnostic accuracy and has been recommended for East Africa with sensitivity of 96% and specificity of 98.7-99.3% (Mansour et al, 2009; Srivastava et al, 2011). This advice for diagnosing clinical suspect VL patients is even more so validated for patients with HIV (ter Horst et al, 2009).

Others

As mentioned in severe VL pancytopenia has been often described. In a study in Nepal the test of counts of white blood cells, red blood cells and platelet was found to be highly specific (98%) but not so sensitive (16%) compared to the spleen aspiration in suspected VL patients (Boelaert et al, 2004). The formerly used Formol Gel Test (FGT) which measures high titres of non-specific antibodies, often found in VL, is not recommended for use anymore by the WHO (WHO, 2010).

Making a diagnosis in a control effort is a balance between finding the patient in time to prevent death and finding as much possible infectious patients to control transmission. The diagnostic tools provide VL to be diagnosed early enough to be asymptomatic, e.g. in India where a seroprevalence study with DAT and rK39 showed 21% seropositive individuals of whom 22% developed clinical VL within 3 months (Sinha et al, 2008). Despite this possibility still quite some delayed presentations result in multi-organ failure and death due to VL in the tertiary clinics in India (Malatesha et al, 2007).

Current available treatment

Several drugs are available for VL treatment, all of them with either severe toxic side effects and/or high costs, or long treatment duration, see Box 2. Several combination therapies have been tried and studied in order to achieve a short treatment course with as less side effects as possible and efficacious for VL treatment. Which again varies according to region.

Pentavalent Antimonials

Since the 1940s the antimonials, e.g. sodium stibogluconate (SSG), have been the mainstay treatment for VL with an overall good cure rate (>90%). However they have many toxic side effects and in India and Nepal drug resistance has been reported (unresponsiveness up to 60%) (WHO, 2010). It is usually given intramuscular (or slowly intravenously with risk of thrombosis) at a dose of 20 mg/kg/day for 30 days (WHO, 2010). Side effects of gastrointestinal symptoms like nausea and vomiting are associated with pancreatitis and a higher risk of death. Other possible severe side effects include arthralgia, hepatitis, renal failure and cardiotoxicity (Moore et al, 2010). The injections are painful and the relative high occurrence of cumulative toxic effects makes the use of the drug dangerous especially in elderly (>45 years of age) and unacceptable in HIV positive patients (den Boer et al, 2009; Chappuis et al, 2011). SSG has shown an increased risk of spontaneous abortion in pregnant patients (Mueller et al, 2006). The costs had been high and since the production of a more affordable generic product in the 1990s SSG has become more available especially in East Africa (from almost 200 to 50 USD per patient of 35 kg) (den Boer et al 2009).

Paromomycin

This drug, an aminoglycoside, initially developed as a broad spectrum antibiotic and for intestinal protozoal infections, has first proven effective in VL in 1980 (den Boer et al, 2009). It is to be used intramuscular with side effects of pain at injection site and dose limiting toxicity: ototoxicity, seldom renal toxicity or hepatotoxicity (WHO, 2010). It is cheaper and has less side effects then SSG, however due to its long half-life it has a potential for drug resistance. Combination therapy has been promoted (Moore et al, 2010). The drug is not widely available and not yet officially registered in all endemic countries (den Boer et al, 2009). Its moderate/poor efficacy in East Africa is limiting its use to combination therapies only (Musa et al, 2012).

Amphotericin B

Amphotericin B, initially developed for fungal infections, has been reintroduced as treatment for visceral leishmaniasis in 1990s in India after the discovery of SSG tolerance (Sundar et al, 2004). The drug is highly efficacious but has dose-limiting severe side effects, e.g. hypokalaemia, nephrotoxicity and thrombocytopenia, next to less severe infusion reactions as chills, rigor and fever (WHO, 2010). Consequently the liposomal formulations of amphotericin B has proven similar efficacy but with less side effects and shorter treatments with higher doses have been possible. Unfortunately the costs are very high (WHO, 2010).

Miltefosine

Originally developed for cancer treatment this oral drug also showed anti-leishmanial properties in the 1990s. Used daily for 28 days it showed a similar efficacy to conventional amphotericin B in India. The efficacy of this regimen in East Africa has not yet been confirmed. Even though the gastrointestinal side effects, like nausea, vomiting and diarrhoea, were higher with miltefosine side effects were usually only mild/moderate. Unfortunately the drug is possible toxic for male reproductivity and teratogenic. The long half-life makes the drug very prone to drug resistance development (den Boer et al, 2009; Moore et al, 2010).

Others

In the past pentamidine has been used as 2nd line for SSG. However it is less effective than amphotericin B and has severe side effects (e.g. anaphylactic shock, diabetes mellitus) and now has limited use (WHO, 2010; Moore et al, 2010). Sitamaquine derives from primaquine and has been used with variable results and severe side effects (Moore et al, 2010).

Box 2: Drugs for VL treatment and their side effects and limitations.

Currently the first line treatment for VL recommended by the WHO in East Africa is a combination of pentavalent antimonials, e.g. sodium stibogluconate (SSG) with paromomycin (PM) daily injections during 17 days. And in South Asia the first line has been recommended to be liposomal amphotericin B (LAB) as a single dose or daily for 3-5 days (WHO, 2010).

While SSG is quite effective in East Africa it has potential severe toxic side effects and a relative long treatment duration of 30 days of painful intramuscular injections. The treatment has become more acceptable by combining SSG with paromomycin as treatment. While paromomycin in itself does not have high cure rates in East Africa and is prone to develop drug resistance the combination works well. Next to better cure rates the SSG/PM combination showed serious reduction of mortality rates in retrospect and equal to better efficacy and safety in a randomized controlled trial, a reduction of costs, treatment duration and potentially a lower risk of drug resistance development (Melaku et al, 2007; Musa et al, 2012; Seaman et al, 1993).

Due to the reduced efficacy of SSG in South Asia this treatment is no longer promoted in this region. Several possible reasons for reduced efficacy have been put forward, e.g. incomplete treatment courses due to costs of full treatment and cheaper, poor quality products (Moore et al, 2010) or interruption of outpatient treatment (Rijal et al, 2009). Since the drug has a short half-life and seems less prone to drug resistance development it has also been suggested that other factors like arsenic contamination of groundwater in India can reduce the efficacy of SSG (Perry et al, 2011). In this region liposomal amphotericin B is promoted. Even though very efficacious in treating VL, unfortunately this treatment is very expensive, see table 8 (den Boer et al, 2009). Recently research has shown a single dose of LAB to be as efficacious as conventional amphotericin B with reduced costs, partly since hospitalisation is not needed (Sundar et al, 2010), see table 8.

	SSG 30 days	**SSG/PM 17 days**	**Conventional Amphotericin B 30 days**	**LAB 2-4 days**	**LAB single dose**	**Source**
Drug efficacy	35-95%		> 97%		SA only 91%	Den Boer et al, 2009
Drug costs per VL treatment of 35 kg patient in USD	55.8	44	20	252	126	Den Boer et al, 2009
Costs including hospitalisation in USD in SA			436		148	Sundar et al, 2010

Table 8: short overview of costs for VL treatment regimens; adapted from den Boer et al, 2009.

Even though LAB is also effective in East Africa, a shortened course is not that feasible as in South Asia because of the much higher total dose needed (Moore et al, 2010). The costs and need of cold chain does not make this drug easy to use in low-resource settings despite its quick reduction in parasites. So far WHO has only recommended LAB for settings when unresponsiveness to antimonials exceed a certain threshold. So it can be used as first line in the South Asian context but the combination of SSG and PM stays as recommendation for first line treatment in East Africa for now (WHO, 2010; Moore et al, 2010).

For now the WHO is assisting the low-income countries in East Africa with donations of VL drugs like antimonials, LAB and PM. However the access to these drugs still depend on local health systems and/or INGOs (den Boer et al, 2011). While in South Asia, middle-income countries like India, free donations are not available. Discussions are ongoing to provide these countries with the drugs for non-profit prices (den Boer et al, 2011).

Even with the above mentioned drugs specific to treat VL, true clinical management of VL comprises of a lot more. VL can present itself with dangerous complications and intercurrent infections, like pneumonia, chronic diarrhoea, severe malnutrition in need of dietary support, anaemia or infections due to poor bone marrow performance and immune system, higher risk of developing severe malaria and bleeding problems due to thrombocytopenia. All in need of skilled staff and essential drugs (Moore et al, 2010).

Accessibility to diagnosis and treatment

Recently it has been estimated that more than 50% of the patients in need do not have access to VL diagnosis and treatment (den Boer et al, 2011). Mostly due to the high costs of diagnosis and treatment and the long duration of treatment creating secondary costs due to the loss of income. For example in South Asia, in 2003 a study in Bangladesh, in two VL endemic villages revealed high costs related to VL disease. Even though officially VL diagnosis and treatment was to be free of charge in the local government district hospital (roughly 3-8 km from the villages). In this study 113 VL patients were interviewed and besides high costs other access problems were mentioned. For initial diagnosis patients had visited on average 6 health care providers (village doctor, traditional healer, private provider and government hospital), all at least once visited the government hospital. They had paid around 81% of their annual per capita income. Including indirect costs the totals varied but exceeded the annual per capita income. The costs varied from informal payments (79% of the patients) in the free of charge government hospital to high costs for treatment at private providers due to drug scarcity or poor diagnostic tools at the government hospital (Sharma et al 2006). Similar results and causes have been obtained by a study in Nepal in 2004. This study showed that 67% of these households were already poor and an additional 20-26% fell below poverty line due to the costs and the loans covering the costs which continued to provide a vicious circle of poverty (Adhikari et al, 2009). In 2006 in India, despite free of charge diagnosis and treatment in the public sector and NGO's, the costs still consisted of 28% of the average annual household income. For these patients about 4 months occurred between onset of symptoms and start of treatment, including a 1 month diagnostic time-frame. Most visited unqualified traditional healers and spend their money on private practitioners, which is significantly more costly than the NGO's. Travel costs were highest for reaching the hospital (Sundar et al, 2010b).

While in East Africa access to diagnosis and treatment is hampered more due to access problems to health care systems in general. Especially in the (post-)conflict areas in South-Sudan and Sudan. Most VL cases are treated by the INGO's and efforts of international research projects (Reithinger et al, 2007). In Sudan recently a study regarding costs and access of VL diagnosis and treatment has been done. VL diagnosis and treatment is provided free of charge by public health facilities which also receive funds from international organisations. Costs were also studied from a provider's perspective. This seemed to vary between 117 and 366 US$ per patient, about 13-38% of the total costs of the hospital. Out of the 75 patients visiting these public hospitals, most had already visited 3 other health care providers based upon proximity, and again the total costs of the VL patients consisted of about 23% of the annual average household income or 122% of the average annual per capita income (Meheus et al, 2013). However not only costs have a high impact on access problems. Specifically in South Sudan access to treatment centres have been correlated with other factors like problems accessing facilities due to rainy seasons and 'impassable rivers' or dangers of passing due to violent conflicts. MSF treatment centres in South Sudan have witnessed many deaths due to these access problems for treatment of VL in their facilities and actually estimated based on their data in 1999-2002 that about 45% of the VL patients in their catchment area probably have not been able to access their facilities and died (Collin et al, 2006).

Active Case Detection

Most patients are found passively when they seek healthcare despite mentioned access problems. In order to reduce the human host reservoir of parasites one could actively seek and treat patients with the available diagnostics and treatments, active case detection (ACD). The theoretical idea would be that the available time/presence of the human reservoir host would be reduced ultimately reducing and controlling VL. There are different approaches assessed in the literature. The most resource intensive and exhaustive method would be the blanket approach. Which is thought to be the golden standard.

In the Blanket approach health workers do a house to house search for suspected VL and PKDL cases. In the Camp approach some villages are visited with mobile teams and after community sensitization people are invited to visit the camp when having fever. In the Index Case approach possible contacts, usually in a 50-200 mt radius of a known VL or PKDL case, are assessed for suspected VL. And in an Incentive Based approach the village health workers receive an incentive for any newly detected VL case in his area.

Some studies in this regard have been done, most in South Asia. All of these studies have used a similar clinical case definition followed by an rK39 rapid test for confirmation of VL. The studies have been performed in known endemic areas for VL with estimated incidences of VL around 0-600 new cases per 10,000 persons in East Africa and 5-31 new cases per 10,000 persons in South Asia, through passive case detection (PCD). See results in table 9.

Study Region and Time frame	Country	Blanket approach % new VL cases in all patients screened	Blanket approach PKDL detected	Blanket approach % new VL cases found with ACD additional to PCD	Camp approach % new VL cases of all patients visited	Camp approach % new PKDL cases of all patients visited	Index case approach % new VL amongst contacts screened	Index case approach % new PKDL amongst contacts screened	Incentive based approach	Source
East Africa 2011 May-June	Sudan	0.02% (16 out of 95,609 persons screened)	0.3% (of which 82% mild PKDL)	2%						Mueller et al, 2012
South Asia, 2003 September	India				5.4% (20 patients out of 368 visits)					Thakur, 2007
South Asia 2008 January-May	overall	0.03% (46 out of 161,184)	0.02% (32 cases)	17%						Hirve et al, 2010
	India, 2 sites	0.02% and 0.06% (8 and 19 vs 40,317 and 33,9128)	0% and 0.03% (14 cases)	6.7% and 17%						Hirve et al, 2010
	Nepal[1]	0.01% (7 out of 57,713)	0%	38.8%						Hirve et al, 2010
	Bangladesh	0.04% (12 out of 29,226)	0.07% (21 cases)	60%						Hirve et al, 2010
South Asia 2009 May-Sept	overall	0.02% (28 out of 165,850)	0.04% (65 cases)	60%	3.4% (22 out of 649)	6.4% PKDL (42 cases)	5.1% (12 from 236)	6.4% PKDL (15 cases)	23 (out of 29 cases detected with blanket)	Singh et al, 2011
	India	0.01% (9 out of 90,669)	0.01% (5 cases)		2.1% (8 out of 388)	No PKDL	5% (7 from 138 index cases)	No PKDL	19 (out of 25 cases detected with blanket)	Singh et al, 2011
	Nepal	0.01% (5 out of 35,081)	0%		3.6% (3 out of 83)	No PKDL	0% (0 from 19 index cases)	No PKDL	4 (out of 4 detected with blanket)	Singh et al, 2011
	Bangladesh	0.03% (14 out of 40,100)	0.15% (60 cases)		5.1% (9 out of 178)	24% PKDL (42 cases)	6.3% (5 from 79 index cases)	19% PKDL (15 cases)	No data	Singh et al, 2011
South Asia 2010 March/July-April	India				2.2% (5 out of 225 visits)	0.4% PKDL (1 case)	8.3% (3 from 36 index cases)	2.8% PKDL (1 case)		Huda et al, 2012
	Nepal				5.1% (3 out of 59)	0% PKDL	0% (0 from 45 index cases)	0% PKDL		Huda et al, 2012
	Bangladesh				11.5% (40 out of 349)	4% PKDL (14 cases)	No data			Huda et al, 2012

Table 9: ACD efficacy in VL; 1: NB in Nepal instead of house to house survey: Index case approach + house to house survey around index case used.

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In general the results from the blanket approach does not yield many new patients for all persons screened. In the study in East Africa, Sudan, which was actually a baseline survey for another study, the results had been disappointing considering the high VL incidence. The authors believed this was due to the fact the survey had been carried out in a low VL incidence period and good access to VL diagnosis and treatment was available in the nearby area, provided by an INGO (Mueller et al, 2012).

In South Asia more studies have been done. In 2003 a study in India demonstrated disappearance of VL for 3 years in a specific village after a camp approach identifying 21 new VL cases followed by IRS and regular surveillance (Thakur, 2007). Other studies focussed at comparing different ACD strategies. While percentage of new VL cases found amongst patients screened in blanket approach remains low, the actual amount of new cases versus VL cases detected passively have been moderate-high varying between 6.7 and 60%, see table 9. This seems to indicate that poor surveillance and/or poor access might be the problem in these areas. And it might not be a promising result to promote ACD as a control measure. Especially considering the costs involved. These varied amongst region and approach, e.g. Blanket approach 112-629 USD, Camp approach 22-661, Index approach 149-200 and Incentive approach 50-543 USD per newly detected VL/PKDL case (Singh et al, 2011). The sensitivity for detecting new VL cases of the ACD approaches have been variable. For the Camp approach 79%, for the Index approach 43% and for the Incentive based approach 79% of the VL cases detected by blanket approach were found (Singh et al, 2011). The results have initiated the authors to recommend to use a camp approach in high VL endemic areas, Index Case approach in high-moderate VL endemic areas and Incentive Based approach in low VL endemic areas (Singh et al, 2011). ACD reduces treatment delay (27 vs 47 days) even after having sought care. And considering the substantial amount of newly detected PKDL patients found it could be an effective part in control of VL (Hirve et al, 2010).

Introducing ACD as control measure in national programmes has shown many constraints and the outcome in cost-effectiveness is reduced (higher costs, lower yields) towards an operational research setting. Problems found during the assessment of an ACD approach in South Asia have been lack of preparatory information to the community (promotional activities), lack of funds and supply, inadequate patient record keeping, poor skills of medical personal and a high rate of defaulters from treatment in Bangladesh (Huda et al, 2012). Having a lack of personnel was not considered a limiting factor. A follow-up study revealed that the additional workload of a camp should not cause a problem to involve this in national programmes in India, Nepal and Bangladesh (Naznin et al, 2013).

Special Cases

PKDL

After treatment and following immune response it has been mentioned to be rare to eliminate all parasites from the human body (Murray et al, 2005). For some the parasites tend to surface to the skin due to the immune response causing a typical rash varying from macular, maculopapular to nodular, called Post Kala-azar Dermal Leishmaniasis (PKDL). This complication has mainly been associated with *L. donovani* and is prevalent in both South Asia as East Africa (Zijlstra et al, 2003).

In East Africa PKDL can start during VL and/or its treatment or within 6 months after treatment (interval 0-13 months), mostly in children and occurs in about 50-60% of the VL cases. About 8% of the PKDL cases in Sudan did not have a previous history of clinical VL. In East Africa most patients heal spontaneously within a year (about 84%) the ones remaining with lesions after a year and/or have severe PKDL including mucosal lesions need treatment. The treatment being SSG daily for 2-3 months (Zijlstra et al, 2003). While in South Asia, the PKDL starts usually about 2-3 years after treatment (interval 6 months-23 years), mostly in young adults, and occurs in 5-10% of the cases, 15-20% had no previous history of VL. Here the lesions do not spontaneously heal and a treatment of SSG daily for 4 months is necessary (Zijlstra et al, 2003).

Diagnosis is often clinical, not to be confused with other dermatological diseases like leprosy. The serological tests are not useful (a history of possible treated VL is usually present), and skin smears have a low yield of 20-30%, increasing to 40% or even higher (up to 100%) from nodular instead of papular lesions in South Asia versus East Africa. The lesions are difficult to treat, often needing long duration of daily, toxic SSG injections while the patients do not feel ill (no fever, only skin lesions). Usually after cure the patients stay immune however during immune suppression e.g. by another disease VL can reoccur. However PKDL patients are a known reservoir in the community. It is suggested in several studies to be the causative reservoirs inter-epidemically. Since sand flies have been proven to become infected after feeding on PKDL cases in India (Zijlstra et al, 2003). The latter theory has recently been disputed in India by Singh et al, where significant variations amongst parasite strains in VL versus PKDL patients have been found (Singh et al, 2011). Even though this does not seem a strong argument it does remain clear that PKDL is still not properly understood and its diagnosis and management is even more challenging than clinical VL.

Recent studies show high incidences of PKDL up to 18% within 2 years after VL in Bangladesh, while PKDL incidence seems to reduce in India in patients treated with LAB and miltefosine. An improvement in diagnosis has only been achieved by PCR methods (up to 40-75% diagnostic accuracy) (Mondal et al, 2011). While the WHO recommended therapy for PKDL in East-Africa remains daily SSG injections for 1-2 months or secondly LAB for 20 days. In South Asia the recommendations have become conventional amphotericin B over 4 months or secondly miltefosine for 12 weeks (WHO, 2010). LAB for 20 days has shown high cure rates in India it is unfortunately very costly. And miltefosine daily for 60 days also showed high cure rates, but is prone to drug resistance development (Mondal et al, 2011). Despite these ongoing developments in treatment they remain more toxic and of longer duration then the already difficult to accept treatment for VL. And the disease itself is not lethal for the patients. But PKDL is important to treat from a public health perspective especially when elimination is the aim. High defaulter rates in Bangladesh from PKDL patients found with ACD have been mentioned making it difficult to control this type of human reservoir (Huda et al, 2012).

HIV co-infected

Another special case is the VL patient with HIV co-infection due to the high parasite load in the peripheral blood and in such a probable more contagious reservoir host than others. Both *L. donovani* as the HIV virus like the macrophage and it seems that the leishmania parasite induces the activation of the HIV virus, while the HIV infection induces uncontrolled parasite growth. Thus resulting in the very high parasitaemias in peripheral blood (Alvar et al 2008). So HIV patients do not only seem to be highly susceptible of contracting VL but they also provide a high parasite burdened host for others.

Although VL may show atypical clinical presentation in HIV co-infected patients (especially in case of disseminated VL). The clinical presentation of VL is usually similar in HIV infected and non HIV infected individuals. It might be more difficult to recognise due to other opportunistic infections. The rK39 rapid test is less sensitive in HIV co-infected cases, due to lower antibody production. However the DAT and parasite visualisation is still reliable. The biggest problem in VL and HIV co-infected cases is the difficulty in treatment. They are known to have lower cure rates, higher drug toxicities, more frequent relapses and higher mortality rates compared to VL in non-HIV infected individuals (Alvar et al 2008). For a VL patient to recover with treatment it is essential to build up a cell-mediated immune response and in such a HIV co-infected patient needs HIV treatment to restore some of this. Unfortunately access to HAART is not universally available. It is difficult to obtain reliable data on epidemiology since for a long time, and still, VL is not on the list of AIDS defining conditions in some countries. Overall the greatest challenge has been in Ethiopia where seasonal migrant workers, resettlements and additionally the transport, military personnel and sex workers have aided to the increase of VL and HIV co-infection (Alvar et al, 2008). Some data are listed in table 10.

	National adult or antenatal HIV prevalence in 2006 Alvar et al, 2008	HIV prevalence amongst VL/PKDL patients in 2006 Alvar et al, 2008	Adult HIV prevalence in 2011 WHO, 2014	MSF unpublished data on HIV prevalence in VL patients; in 2012 MSF-OCA
India	0.36%	1.5% - 6.3%	No data	< 1%
Bangladesh	< 0.1%	No data	< 0.1% (< 0.1 - < 0.1%)	< 1%
Nepal	0.5%	5.7%	< 0.3% (< 0.2 - < 0.7%)	No data
Sudan	1.6%	3.6 – 8.1%	< 0.4% (< 0.3 - < 0.5%)	2.3%
South Sudan	No data	No data	No data	2.5%
Ethiopia	3.5%	15-40%	< 1.4% (< 1.3 - < 1.6%)	15.7%

Table 10: HIV and HIV-VL co-infection rates; data found in literature by Alvar et al, 2008, WHO website, WHO, 2014, and MSF unpublished data of local projects.

Regarding control of the human reservoir an HIV positive individual can become a highly infectious and persistent infectious source. While at the same time these HIV-VL co-infected patients can put a burden on the already scarce and expensive resources needed for VL diagnosis and treatment. To prevent disease spreading HIV positive patients could be assessed for VL in VL endemic areas. And HAART should be available in HIV and VL combined endemic areas.

Conclusive

We can safely assume the human is the main/only reservoir host for *L. donovani* parasite in both settings. But especially in East Africa, we should not forget the possible potential of some animals becoming a reservoir host or possible inter-epidemic source of parasites. Asymptomatic infections do occur often but so far, in the absence of evidence of their role in transmission, no efforts or research has been put into the possible reduction of parasite burden in the reservoir host by treating asymptomatic individuals. Recently research and development in diagnostics and drugs have resulted in useful rapid tests for low-resource settings. As long as they are properly used with a case definition they can be helpful in diagnosing primary VL. But field adapted diagnostics for relapse, test of cure or inactive disease are lacking. While treatment regimens of shorter duration and with less toxic side effects have been under development the costs still remain challenging. Add to these the known access problems to the health facilities in general and to VL diagnosis and treatment specifically and we are far from having an ideal approach to reduce parasite reservoir in humans. Active Case Detection while studied has not yield promising results. It seems it is more important to improve the current reporting system and focus on active surveillance instead. While PKDL patients are successfully encountered through this strategy, whom are thought to be an important reservoir in between epidemics or can at least harbour parasites for a long period (years) in South Asia. It remains the question if the approach to track and treat PKDL patents with the current toxic, painful and long treatment regimens is ethical. A secondary to challenge to control the human reservoir is mounting in East Africa where HIV co-infected patients with VL have been shown to be highly infectious to other patients. The HIV co-infected patients are in need of special treatment to reduce the parasite successfully in their system for overall transmission reduction.

Prevention

Whereas control efforts discussed so far have focussed on reducing parasites in vector and host in order to achieve control. Prevention would be focussed on communities in general to prevent them of being confronted with the parasite and contracting the disease. Some measures of prevention do overlap with the discussed control efforts and in such will not be repeated here. For example personal protective measures as bed nets from getting bitten have already been discussed in the Vector Control chapter. Here shortly the importance of outbreak management in order to prevent spreading of the disease will be mentioned and the possible future opportunities of vaccination to break the transmission cycle.

Outbreak Management

Within the leishmaniasis VL due to *L. donovani* is known to cause large epidemics (WHO, 2010). For example in South Sudan, Western Upper Nile state, an area previously non-endemic of VL, an epidemic of VL started in 1984, shortly after the resurgence of the violent civil war in Southern Sudan. It was suggested that due to the war and following people movements of military personnel and refugees areas in Sudan and Ethiopia have become endemic. Involving factors like increased exposure due to hiding in the acacia forests, health systems falling apart and decreasing of nutrition status. VL has massively spread amongst the people in this area. A report based on multiple surveys and other data in the period 1984 to 1994 estimated around 100,000 people to have died of VL in the area (Seaman et al, 1996).

To understand and explain an epidemic is challenging, some other possible related factors have been environmental changes like reforestation with an influence on vector habitat (WHO, 2010). For example an area in central Sudan where an epidemic of VL has been described in the 80s had not been endemic for almost 25 years when the disease re-occurred. The cause was suspected to be due to the re-appearance of the acacia/balanites trees after the demand for charcoal had been reduced. Creating a favourable atmosphere for the sand flies (Khalil et al, 2008).

Epidemics have also been described in South Asia, e.g. in 1994 in Uttar Pradesh state, close to the highly endemic Bihar state. It was stipulated that this might be caused by migration of people from Bihar, this correlation was not found however in the door-to-door survey (Kumar et al, 1999). A high level of disease transmission was concluded, but other possible causes like environmental change or reduction in overall human immunity were not discussed (Kumar et al, 1999). The main referral hospital for VL in Nepal tried to identify possible VL endemicity expansion. While in general the amount of VL cases was reducing. The number of patients in non-endemic areas seemed to increase compared to the number of patients in endemic areas. It was not clear if this was due to migration of people or expansion of the endemic area. It was suggested by the authors that it might be due to the 'rapid urbanisation' and in such an increasing and more mobile population in Nepal and other areas of South Asia (Pun et al, 2011).

The ideal prevention and control measure would be to understand the factors involved and respond to (possible) outbreaks as soon as possible. This could prevent many deaths and an increase of endemic areas in the regions.

Vaccination

Last but not least we can consider vaccination as prevention for VL in order to control VL. Many have believed it to be possible to develop a vaccine for leishmaniasis because only a small percentage of persons getting infected with a VL parasite develops the disease and after that they develop life-long immunity (Evans 2011). However despite many efforts so far it has not been easy. Partly due to the broad variety of leishmania parasites and partly due to the not fully understood immunopathology in humans. It is difficult to mimic the immunological response of humans in an animal model since this immune response is not the same (Evans, 2011; Garg 2006). So far most advantages have been made for vaccination of the leishmania parasites causing cutaneous leishmaniasis, e.g. inoculation with virulent L. major parasites in Uzbekistan and the vaccination of dogs for *L. infantum* with different kinds of

second generation vaccines. The dog is an important end host for *L. infantum* just as the human is and in such important in the life cycle of *L. infantum* (Evans, 2011). Unfortunately for *L. donovani* there has not been made much progress. Only a very few attempts for vaccines made it to clinical trials, e.g. ALM + BCG has shown positive effect in Sudan (Satti, 2001) and LEISH-F1+MPL-SE vaccine was safe and well tolerated with an immunogenic response in India (Chakravart 2011). But so far no licensed anti-leishmanial vaccine for VL due to L. donovani has been made. And it is not expected that a vaccine will be developed any time in the coming 5-10 years (citation from Koert Ritmeijer, December 2013).

Discussion

While in South Asia national commitment towards controlling VL has resulted in multiple initiatives the countries in East Africa have not joined efforts until recently. In South Asia India started its VL elimination programme in the year 2003 with the objective of eliminating the disease by 2015 (Kumar et al 2009). In 2005 a VL elimination initiative in the Indian subcontinent was set up joining the efforts of the governments of Nepal, Bangladesh, India and the WHO (Picado et al, 2012). A memorandum of understanding to eliminate VL was signed by these governments (WHO, 2012b). The aim of the VL elimination programme for 2011-2015 is to reduce annual VL to < 1 VL and PKDL case per 10,000 population in the South Asian region by 2015 (WHO, 2012b). This strong political commitment and their initiative to cooperate with other partners and the community seems promising for VL control. The foundation of VL control remains IRS and Early Case Diagnosis & Treatment, like it has been in the past in India without much positive effect. Many guidelines regarding elimination, programme implementation and monitoring, preparation, case management and environmental management, etc., have been developed. Concrete national control plans still depend on governmental regulations. And due to several variations in disease presentation and management the programmes should be locally adapted. Indicators for monitoring and evaluation have been developed and are available on the WHO/TDR website (WHO, 2012b). This has all been part of the preparatory phase. Whereas the attack phase of 5 years will constitute of actual implementation of control activities directed at vector control and access to early case diagnosis and treatment. Followed by a consolidation phase of 3 years with active surveillance and an undetermined period of maintenance phase for surveillance of possible re-emergence of VL (WHO, 2012b). So far these efforts have resulted in promising results regarding treatment, like the feasibility of treating VL with single-dose LAB in primary health care centres in Bangladesh (Mondal et al, 2014). Since the problem of poor VL incidence figures have been recognised, the importance of proper surveillance is encouraged. The actual results in VL incidence reductions still awaits. Newer initiatives like addressing PKDL patients with appropriate and acceptable treatment or the use of GIS and remote sensing systems in assessing burden and control have been recognised. However especially regarding the latter South Asia might be able to learn from East Africa.

While in East Africa there does not seem to be such a strong regional political commitment due to other priorities as discussed in the introduction. There is a computer program linking health data and information from different sources like remote sensing programmes and ground-based measurements that has been successful in the past with predicting Rift valley fever outbreaks that has recently added sand fly characteristics to its program (Witt et al, 2011). However this effort and most others regarding VL management have been initiated by non-governmental actors. For example a document on leishmaniasis control in Eastern Africa determining the situation and analysing any gaps which has been created by the malaria consortium (malaria consortium, 2010). The conclusion had been a possible increase in leishmaniasis in East Africa due to several factors amongst others increasing migration, climate change and the co-incidence of HIV infection. While actual control activities are hardly existing apart from outbreak responses (malaria consortium, 2010). In the assessment in 2010 Sudan VL control has been part of governmental activities since 1996 with recently more efforts into national policies regarding control and governmental funding. Whereas the government in South Sudan has made NTD control as one of the priorities. They do not have governmental funding for VL. This country highly depends on non-governmental actors who have been switching the responsibilities for VL amongst themselves several times. In Ethiopia national guidelines on VL case management have been developed in 2006 with a national task force for VL elimination in 2007. However there is no government budget set aside for VL control or a standardised national reporting system (malaria consortium, 2010). The Leishmaniasis East Africa Platform (LEAP) has been encouraging research and development since 2003. Their mission in seeking simplified VL treatment has helped introducing SSG/PM combination strategy for 17 days as first line treatment in all East African countries (LEAP, 2013).

Conclusion and Recommendations

An integrated VL control approach has not been developed. The disease is hardly recognised for its high burden as a global disease. And the effects in mortalities, affected persons and economic impact is not known with the bigger part of international society and even experts. The WHO should have a much stronger lead since national governments even though involved do not spend enough attention to these disease often occurring at their border areas. National governments need to work together to direct efforts at these border areas and an international agency can help in enforcing these efforts.

India, the country with the highest numbers, is a strong player. It does focus a lot on its previous positive experience with IRS. Personally I see a need for other, more integrated approaches. And newer initiatives to be explored. Vector control could be optimised. While ideally more information on vector characteristics regarding breeding sites is needed. A proper review of literature in order to conclude these to be either highly variable or confined to moist environments can lead to more specific environmental measures. It might not be feasible to eliminate this type of breeding sites but communities can be educated on exposure sites. And so far hardly any information seems to be available on measures to attract and capture sand flies near households in order to reduce transmission. Due to their preference of feeding on cattle treating them and reducing the possible breeding site of their faeces seems a promising approach. While postulated that sand flies get attracted towards CO_2 output it is unlikely to introduce a CO_2 trap, other methods could be explored.

Measures of vector control like IRS can be optimised with the latest developments. And consistency should need to take place in both regions. The best approach seems to spray 2 times a year in South Asia and 1 time a year in East Africa. Since IRS has not been implemented yet in East Africa this effort could be combined with other control needs like the malaria intervention. ITN distribution has also proven effective. However considering the costs it would be advisable to properly prepare for possible elimination of VL by identifying target areas and mass distribute the nets to all households including health education. This health education should need to enforce the message of the difference of sand flies towards other insects, signs and symptoms of VL, importance of early diagnosis and treatment and facilities for best and free treatment available in the area. Many developments in reducing treatment regimens and making them safer are promising but need to be communicated to the people to increase access.

For actual elimination however focussing on the host seems the best approach. While active case detection is being implemented in South Asia to achieve elimination. This will not have the effect achieved when safe and acceptable treatment for PKDL patients do not exist. As long as these patients are present VL is likely to re-emerge despite all efforts done. The same for HIV-VL co-infected patients in East Africa. As long as these two types of patients do not have effective treatment regimens elimination will not be feasible in either region. Therefor I would like to suggest to wait with expensive large scale international elimination campaigns including ACD until these two problems have been solved. And only then an attempt to eliminate the disease could be made with a combination of IRS, mass distribution of ITN, newly adopted EVM, decentralised VL treatment centres followed by ACD through different approaches and strong surveillance.

If then elimination will be achievable will depend on the role of asymptomatic carriers for which not enough knowledge is available. In an ideal situation prophylaxes and a vaccine would be developed but this seems not feasible for at least another decade. Until then it is important to implement integrated control measures in all endemic areas for which close collaboration amongst endemic countries and international agencies is needed. But foremost to be able to eliminate VL in the future it is very important to generate more awareness of the enormous impact and burden of this killing disease worldwide.

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