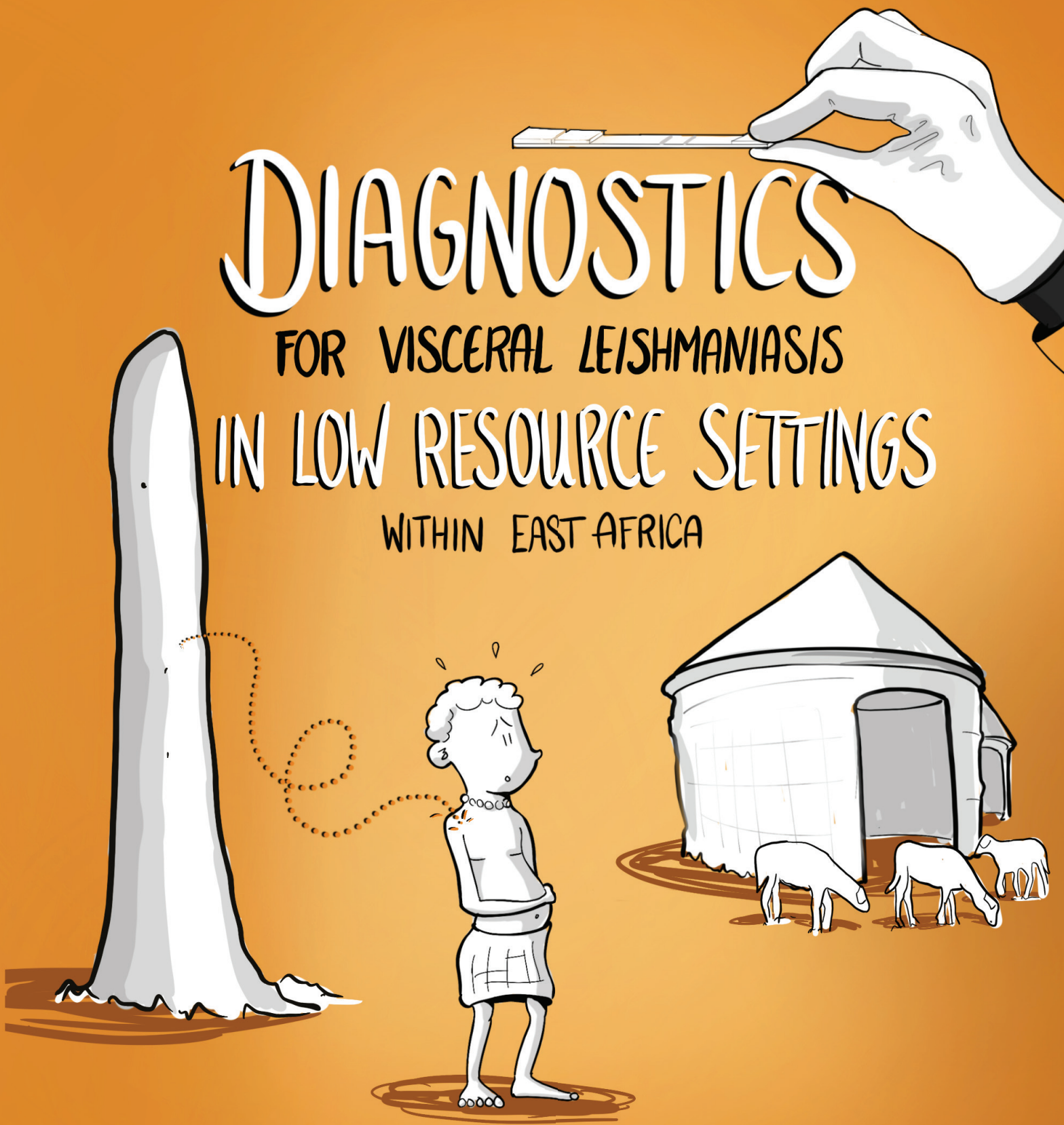
DIAGNOSTICS

FOR VISCERAL LEISHMANIASIS IN LOW RESOURCE SETTINGS

WITHIN EAST AFRICA



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Diagnostics for Visceral Leishmaniasis in low resource settings within East Africa

Master Thesis

Astrid ten Bosch

APRIL 2019

Preface

After six months of working on this project, I can say that this was one of the most interesting, exciting and challenging projects I have been doing so far.
Not only did I got the chance to emerge myself into a completely new context by going to the low resource settings in Kenya and Uganda, I had the pleasure of working together with many inspiring and knowledgeable people. Therefore, I would like to **thank all of you who helped me along the way.**

First of all, I would like to thank my supervisors **JC** and **Jo** for their time and willingness to think along with me throughout the project. Every meeting resulted in many insights, and the honest and clear feedback kept me going.

I want to thank **Michel** and **Mitasha** for being the best travel buddies I could have imagined. I am very happy to have met you during the field trip in Kenya and Uganda and throughout this project. And thanks for all your effort during our sessions and meetings. Also, I would like to thank **Cees** for all the energy during the field trip, the impressive driving skills in a 4-wheel drive and the beautiful photographs you made during the trip.

I want to say thank you to the **all people who have been contributing to the field trip** in Kenya and Uganda and whom I had the pleasure of speaking. Especially, to **Damaris, Hellen, Anyona and Johnstone** who have not only provided me with many valuable insights but were great accompany too!

A special thanks to **Charity Kamau** and **Koert Ritmeijer from MSF Netherlands** for your valuable insights and willingness to help!

Also, I would like to thank **Delft Global Initiative** for the warm welcome during their lunches and providing the network to meet many inspiring people working on global projects.

I would like to say thank you to my **dear friends and family** who have helped me going through this project, for the support and listening ears when I needed to ventilate.For always having faith in me, even when I did not.

Lastly, I want to say thanks to **Freek**, for all his effort to make the drawings come alive in a movie.

Thank you all, I could not have done it without you!

Enjoy reading

Astrid

Pokot boy in Baringo County, KENYA.

Glossary

DEFINITIONS AND ABBREVIATIONS

Definitions

Leishmania: the parasite which spends part of its life in a sand-fly and part in the blood and other tissues of a human or animal.

Leishmaniasis: The disease which is the result of an infection with the *Leishmania* parasite. Leishmaniasis can occur in several forms such as **mucocutaneous leishmaniasis (ML)**, **cutaneous leishmaniasis (CL)** or **visceral leishmaniasis (VL).** In this case, the project focusses on visceral leishmaniasis.

Kala-azar: This is another name for visceral leishmaniasis.

Patient: A person who has Leishmaniasis (in this project visceral leishmaniasis). This can be someone who has been diagnosed with VL or someone who has not been tested but has VL.

Asymptomatic case: A person who is infected with the *Leishmania* parasite, but does not have clinical symptoms (yet).

Symptomatic case: A person who is infected with the *Leishmania* parasite and has clinical symptoms.

Suspected case: A person that shows clinical symptoms of VL and therefore is suspected to have VL.

Relapse (case): A person who has been infected and treated, but is not 'cured' and develops symptoms again.

Reinfection (case): A person who has been infected and treated, but has been infected again by the *Leishmania* parasite.

Technical principle: The DNA detection principle which is currently being developed at the Faculty of Applied Sciences at the Delft University of Technology.

Specificity: The ability of the diagnostic test to identify those patients without the disease (Lalkhen & McCluskey, 2008).

Sensitivity: The ability of the diagnostic test to identify those patients with the disease (Lalkhen & McCluskey, 2008).

(VL) context: The context of Visceral Leishmaniasis in endemic areas.
Note: In this report, when talking about the VL context it is about the context of VL in the endemic areas in East Africa. In the case of South Asia or South America VL context, this will be explicitly mentioned.

Case management: The quality of the delivered VL care which is provided to VL patients.

VL care: This definition covers both VL diagnostic practices and VL treatment.

Context Variation: The variation between the context of VL in different endemic regions in the world (For Example the context of VL in East Africa compared to South Asia).

Diagnostic setting: The environment in which the diagnostic test is used.

Diagnostic test: The tool which can be used to test if a person has VL or not.

User: A person who is using the diagnostic test to test if a person has Visceral Leishmaniasis.

Abbreviations

AS	Applied Sciences, Department of Bionanoscience, Kalvi Institute of Nanoscience at the Faculty of Applied Sciences (Delft University of Technology)
CHO	Chief Health Officer
CHV	Community Health Volunteer
CHW	Community Health worker
CL	Cutaneous Leishmaniasis
DND*i*	Drugs for Neglected Diseases
IDE	Industrial Design Engineering faculty (Delft University of Technology)
KEMRI	Kenya Medical Research Institute
LRS	Low resource Settings
MSF	Medicines Sans Frontieres *(also known as Doctors without Borders or Artsen zonder grenzen)*
NGO	Non-governmental Organisation
RDT	Rapid Diagnostic Test
rK39	Rapid Diagnostic Test rK39
UoN	University of Nairobi
VHT	Village Health team
VL	Visceral Leishmaniasis *(is the same as Kala-azar)*
WHO	World Health Organisation

Executive Summary

This report is the result of a graduation project in the domain of the Neglected Tropical Disease (NTD): **Visceral Leishmaniasis (VL)** in low resource settings in **East Africa**. The project aims to find promising ways to **fit a technical principle,** which is being developed at the TUDelft, **in the context of VL**. VL endemic regions in Eastern Uganda and North-Western were visited during a two-week field trip to understand the context of VL.

The context of Visceral Leishmaniasis

VL is a parasitic disease which is endemic in several parts in the world including East Africa. The disease is **strongly related to poverty and mainly persists in remote and poor areas** where health care services are limited. **VL affects the internal organs and is fatal if untreated.**

There are many barriers complicate **access VL diagnostics** and treatment, such as the limited **number of facilities, large distances, lack of trained staff** and **low index of suspicion by health care workers.** VL is often **misdiagnosed** as the symptoms of VL are similar to many other diseases. In addition, current diagnostic practices have **limitations in their performance (unreliable),** especially in East Africa. More reliable diagnostic practices require more advanced tools and skills which are not available in most VL endemic areas.

Thus, there is a need for a more reliable diagnostic test for the African VL context.

The technical principle

The technical principle can be integrated on a diagnostic test strip **to test a patient for VL**. Based on a sample, it can separate and amplify the pathogens and detect their DNA with a CRISPR/Cas9 system. The result is a colourimetric read-out which indicates whether or not the patient has VL.

This technical principle is based on **DNA detection,** which enables **reliable test results independent of someone's immune system**. Additional advantages of this technical principle are that it is **quick** and **broadly applicable**.

Applying the technical principle in the context of VL

To understand where the technical principle could be implemented, a session was held with the team of IDE and Applied Sciences (TUDelft). This session resulted in the creation of **seven scenarios** which represent unique ways to **combine the features of the technical principle** into a diagnostic test **which fits a diagnostic setting** in the context of VL and **matches a local need.**

After evaluation with Médecins Sans Frontières, the **two most 'promising' scenarios** are selected based **on the feasibility of the technical principle,** the **contextual fit** and the **local need**. The two selected scenarios are:

- **'Screening & Confirming" scenario**
- **"Test-of-cure" scenario**

By detailing the selected scenarios, **five variables** where identified which **clarify that the diagnostic setting influences the features of a diagnostic test**.

These are:

1) **(geographic) location**
2) **resource availability**
3) **(medical) background of the user**
4) **diagnostic moment**
5) **patient status**

Requirements are composed to see how the diagnostic setting affects the diagnostic test.

The categorisation of the requirements and diagnostic setting variables have resulted in **four different diagnostic tests** - each with a **unique set of requirements.**

‘Pokot’ boys are responsible for the cattle. Baringo, KENYA.

Introduction

HOW TO READ THIS REPORT?

This report presents the results of a graduation project of 20-weeks done at the Faculty of Industrial Design Engineering in collaboration with the Faculty of Applied Sciences at the TU Delft. The report is structured in five Sections which serve as a guideline throughout this report, see Figure 1.

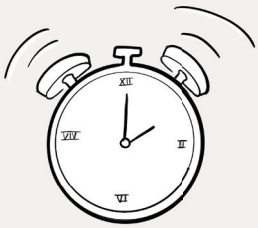
In the first **SECTION I: PROBLEM FRAMING**, the project scope and approach of this project are introduced. This entails a short introduction of the challenges within the context of Visceral Leishmaniasis and the technical principle which served as a starting point of this project (Chapter 1: Project Scope). In addition, this Chapter introduces the objective and research questions of this project. Next, the approach and methods to answer these research questions are explained (Chapter 2: Approach).

SECTION II: CONTEXT, aims to give a better understanding of the context of Visceral Leishmaniasis. In Chapter 3, the disease, current diagnostic practices and treatment procedure are described. Chapter 4 builds on this to explain the challenges within the of Visceral Leishmaniasis in East-Africa. Moreover, this Chapter explains the barriers that VL patients face to get tested for VL and receive treatment.

In **SECTION III: TECHNICAL PRINCIPLE,** the technical principle which serves as the starting point of this project is introduced. Chapter 5, explains what the technical principle is and the stage in the development of this technical principle. Furthermore, the benefits of the technical principle compared to current diagnostic practices are explained.

This project aims to find promising ways to implement the technical principle into a diagnostic test to improve the disease management of VL in the context. Therefore, **SECTION IV: FUTURE APPLICATION** will focus on combining knowledge from the Context and the Technical principle. This section aims to find promising ways to implement the technical principle benefits into the context. Therefore, scenarios are created which each present a unique way to combine the technical principle in the context of VL in Chapter 6. Additionally, the two most promising scenarios are selected based on feedback from experts. Chapter 7 focusses at the diagnostic setting in which a diagnostic test could be used. This involves identifying the diagnostic setting variables and how the diagnostic setting influences what a diagnostic test should be like. In Chapter 8, requirements are composed and categorised which results in several diagnostic tests which are suitable for a diagnostic setting in the context of VL.

SECTION V: EVALUATION, Chapter 9 aims to evaluate the project. First, the diagnostic tests as proposed in Chapter 8 are evaluated, which results in several recommendations. Next, the project is concluded to see if the research questions have been answered. Lastly, the limitations and implications of this research are discussed which results in recommendations for future research. In addition, this Section includes a personal reflection which summarises the learnings and experiences while working on this project with great pleasure!



Do you have limited time to read everything ?

& want to know more about the context?
Then go straight to the Section II: Context to find out more about the context and challenges of Visceral Leishmaniasis.

p. 35

& want to know more results of this project?
Then go straight to the Section IV: Future application to start reading about the ways promising ways to combine the technical principle with the context of VL.

p. 89

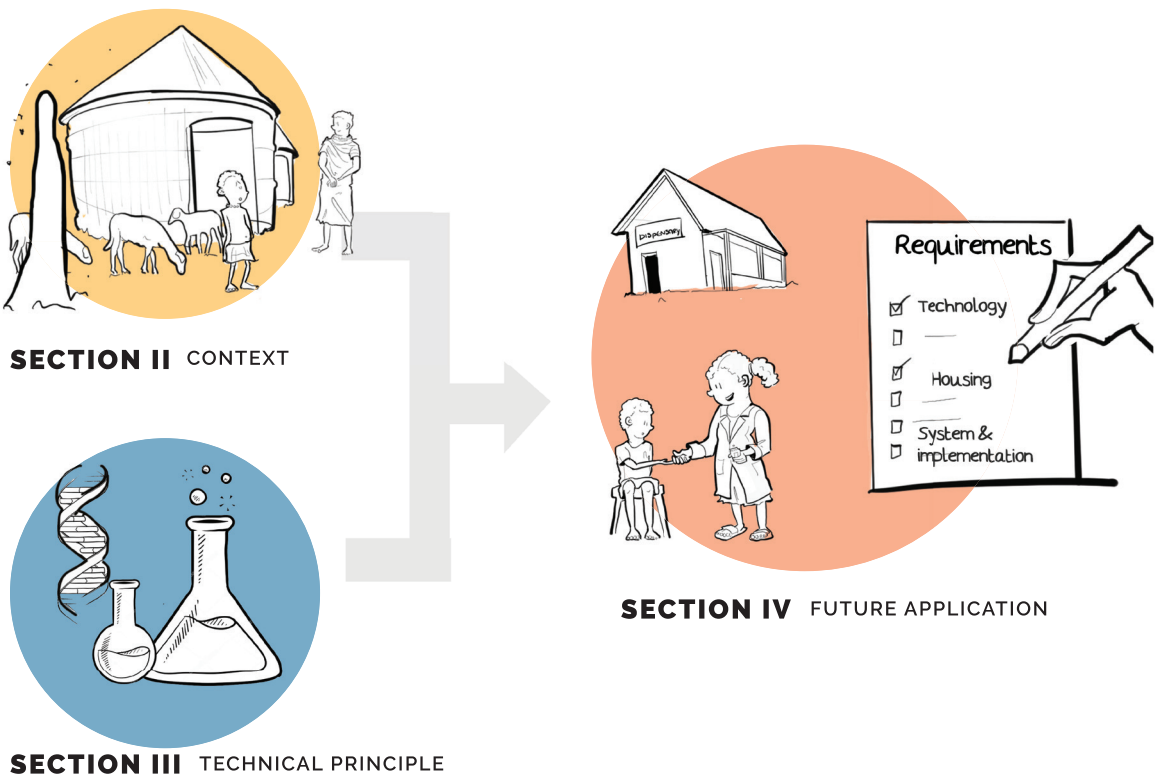


Figure 1: This thesis is divided into three main Sections.

Content

SECTION IV FUTURE APPLICATION

SECTION V EVALUATION

SECTION I

Problem framing

This Section: Problem framing, has the goal to introduce the context of the problem and the scope of this project. Moreover, this section introduces the project objective, the research questions and the approach which will help to get answers to these questions.

Pokot community, living close to Anthills which are breeding nests of sand-flies that carry *Leishmania*, Baringo County, KENYA.

SECTION I PROBLEM FRAMING

Chapter 01 PROJECT SCOPE

This Chapter introduces the context of VL and the technical principle which serve as a starting point of this project. In addition, the structure of this thesis and the objective are explained. Lastly, this Chapter describes the research questions which need to be answered to achieve the objective.

1.1 The context of this project

MATCHING A TECHNICAL PRINCIPLE WITH A CONTEXT

1.1.1 Visceral Leishmaniasis (VL)

This project takes place in the domain of the Neglected Tropical Disease (NTD): **Visceral Leishmaniasis** (ET Guerrero, 2017). Leishmaniases are a group of diseases which are caused by parasites from more than 20 different *Leishmania* species (Colmenares M, 2002). The disease is transmitted to humans by the bite of infected female sand-flies. Worldwide, there are 2 million new cases of Leishmaniasis each year, and 556 million people are at risk of acquiring the infection (Handman, 2001).

Leishmaniasis occurs in several forms of which Visceral Leishmaniasis (VL) and Cutaneous leishmaniasis (CL) occur most frequently (WHO, n.d.). CL is a skin infection which may cause a large number of lesions, which can cause severe disability. When the ulcers heal, they invariably leave permanent scars, which are often the cause of serious social prejudice (WHO, n.d.).

VL affected pokot community in East-Pokot, Kenya

The focus of this project is on VL, **which is the most severe form of the disease** and is endemic in the areas which are visited during a field trip. It is estimated that there are **50,000 to 90,000 new VL cases on a yearly base** of which 90% occurs in the rural areas of India, Sudan, South Sudan, Kenya, Somalia, Ethiopia and Brazil (DNDi, 2018).

The epidemic trends and dynamics of VL vary a lot between South Asia and East Africa.

This project focusses on the **VL endemic areas in East Africa** due to its stronger presentation, fragile state and **the higher need for improved diagnostics** (Medicins sans Frontieres, 2012). Within East Africa, the VL endemic regions of Kenya and Uganda are selected field trip as English is well spoken in this region, it is politically stable and has two VL treatment centres: in Amudat and Kimalel.

In East Africa, outbreaks of VL frequently occur (WHO, n.d.). Visceral Leishmaniasis is **strongly related to poverty** and mainly persists in remote, **impoverished areas** where there are **limited health care** services (DNDi, n.d.). VL is often associated with **malnutrition, population displacement, poor housing, a weak immune system and lack of financial resources** (WHO, n.d).

Treatment for VL is available at treatment centres. However, especially in low resource settings, it is **difficult to diagnose the disease** in an early stage due to the **limited number of facilities, the lack of trained staff** and the **low index of suspicion**

by health care providers. Furthermore, the initial symptoms of VL (e.g. fever, weight loss) are similar to other diseases, such as Malaria and therefore it is often misdiagnosed for other diseases (Bern, 2016).

The fatality rate for Visceral Leishmaniasis is as high as 100% in two years.
(WHO, 2018)

1.1.2 VL diagnostics

Figure 2: Rapid Diagnositc Test rK39.

Even though there are several ways to diagnose VL, current diagnostic tests and procedures have its limitations. Especially in East Africa this is the case. Serological diagnoses such as the rK39 rapid diagnostic test (RDT) (Figure 2) and the Direct Agglutination test (DAT) exist but are based on the detection of antigens in the body.

Definitions || What does it mean?

Sensitivity -the ability of the diagnostic test to idenfity those patients with the disease.

Specificity - the ability of the diagnostic test to idenfity those patients without the disease.

In South Asia, the rK39 antigen-based rapid diagnostic test (RDT) can be used alone to confirm and exclude primary VL in clinically suspected patients (Medicins Sans Frontieres, 2012). For example, the sensitivity and specificity have been proven to be respectively 100% and 98% in India (Sundar, 1998). However, multiple studies have shown that the performance of the same diagnostic test is not that good in East Africa (Ritmeijer et al., 2006). The sensitivity of the rK39 in East Africa are generally low (Boelaert et al., 2007). The sensitivity and specificity vary between 80% to 90% (Medicins Sans Frontieres, 2012).

Due to this low sensitivity of the rK39 RDT in East Africa, it is important to do another confirmation diagnosis among clinically suspected primary VL patients who got a negative RDT test result. Such a confirmation diagnosis can be done through microscopic examination of spleen or bone marrow aspirates or sophisticated serological techniques (such as DAT) (Mbui et al., 2013). However, a confirmation diagnosis requires more advanced tools, settings or skills which are often not available in these low resource settings (Sundar, 2002).

Thus, more sensitive and specific RDTs are needed for the African VL context.

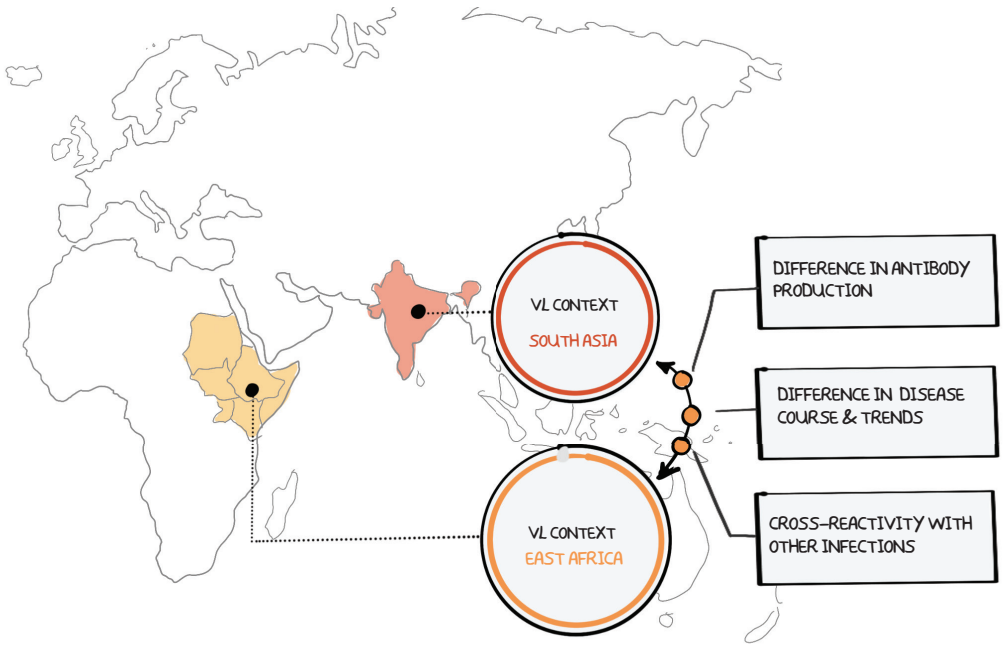


Figure 3: Variations in the performance of current serological tests between East Africa and South Asia.

1.1.3 Difference in performance of VL diagnostics

There are several reasons which can explain a difference in the performance of serological tests between South Asia and East Africa (Figure 3).

Difference in antibody production

The authors of a study into the sensitivity of rK39 antigen-based dipstick tests in Sudan argued that VL patients in Sudan develop a lower concentration of antibodies against the K39 antigen compared to VL patients in South Asia (Diro et al., 2015). Thus, the differences in antibody responses between East African and South Asian VL patients can cause a difference in the performance of the diagnostic tests.

Alteration in disease course and endemic trends

The presentation and epidemic trends of VL are very different between South Asia and East Africa (Médecins Sans Frontières, 2012). In South Asia, VL has a relative milder presentation. However, in East Africa, VL comes in epidemic waves and is strongly related to population displacement of non-immune populations, weak national health infrastructures and the prevalence of HIV co-infections (WHO, n.d.).

Interestingly, the response to liposomal amphotericin B treatment differs between HIV/VL co-infected patients from East Africa and India. In India, this treatment is safe and effective in treating HIV /VL co-infected patients. However, in East Africa, the same treatment is not effective in many cases, not even in higher doses. (Médecins Sans Frontières, 2012).

Cross-reactivity with other infections

The prevalence of other diseases can also have an impact on the accuracy of the diagnostic tests. Kiros & Regassa (2017) argued that cross-reactivity with other epidemiological infections such as malaria and tuberculosis could affect the performance of the rK39.

Thus, the different epidemiolocal diseases in East Africa and South Asia can explain the difference in performance of serological tests.

Besides, East Africa has the highest VL HIV co-infection rate. This coinfection causes an alteration in the disease course. (Diro et al., 2015) HIV can affect the antibody production of VL, which can cause lower sensitivities of the rK39 and DAT serological diagnostic tests (Kiros & Regassa, 2017). Furthermore, whether HIV or VL was acquired first may also affect the performance of such serological tests (Alvar et al., 2008).

1.1.4 Technical principle

The researchers at the faculty of Applied Sciences at the TU Delft are developing a new technical principle which involves a CRISPR/Cas9 system which can be used to detect the pathogens DNA from a sample. ("Testing of parasitic DNA", 2016).

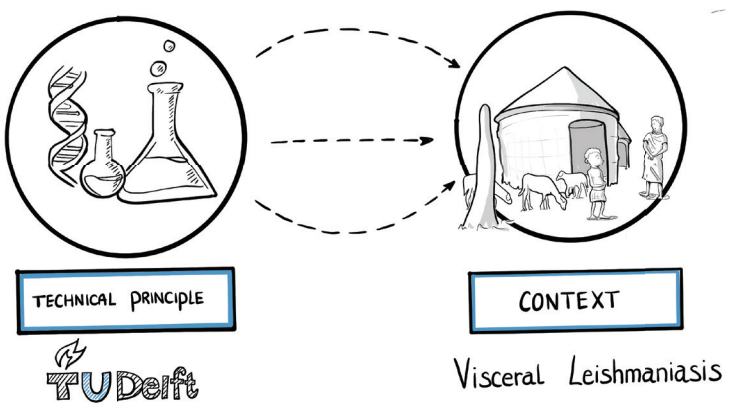
> This detection of DNA of the pathogen will be more consistent and will work independently of the person's immune response.

Therefore, it can distinguish between current and previous infections, unlike current rapid diagnostic tests. This technical principle is the start of developing a range of point-of-care diagnostic tests to diagnose infectious diseases such as Visceral Leishmaniasis in low resource settings.

1.1.5 Project focus

The technical principle has the potential to be used in a diagnostic test that probes to diagnose patients with (neglected) infectious diseases in low resource settings. Integrating this technical principle into a potentially low-cost diagnostic test which is suitable for the context is a highly promising alternative to current diagnostic procedures. However, there is a lack of understanding about the current diagnostic practice, the healthcare system and facilities in the context of VL.

Therefore, the focus of this project is on getting a more in-depth understanding of the context of VL in East Africa, which will help to find promising ways to integrate the technical principle into a diagnostic test which is suitable for the context and has a positive effect on the disease management.



1.1.6 Objective

To identify promising ways to implement the technical principle into a diagnostic test for (Visceral) Leishmaniasis which is suitable for low resource settings within East Africa.

1.2 Research questions

WHAT NEEDS TO BE ANSWERED IN THIS PROJECT?

Four main research questions are composed to be able to fulfil the objective. These research questions are structured based on the three main SECTIONS of this thesis (Figure 4).

SECTION II: CONTEXT

RQ1: What are the current diagnostic practices and challenges within the health care system of Visceral leishmaniasis in East Africa?

To answer this research question, it is essential to understand not only the disease but the entire health care system and challenges connected to VL care. In addition, the challenges related to inaccessibility and unreliability of current diagnostic procedures and the barriers that VL patients face need to be made explicit. Therefore, theory exploration is combined with a field trip. This research question is split up in sub-questions which can be found in Appendix A-1.

SECTION III: Technical principle

RQ2: What are the benefits of the technical principle compared to current diagnostic practices?

First, the essential characteristics of the technical principle under development at Applied Sciences need to be made explicit. An understanding of the current diagnostic practices will help to clarify the benefits of this technical principle.

SECTION IV: FUTURE APPLICATION

RQ3: What are promising ways* to implement the technical principle to a diagnostic setting in the context of VL?

To answer this question, it is essential to identify what the definition of a 'promising way' is.

** A promising way represents a unique way to combine the features of the technical principle into a diagnostic test which fits the diagnostic setting in the context of VL and matches a local need.*

To identify these 'promising ways', it is important to answer three questions:

- **What is feasible for the technical principle?**
  It is crucial to understand the technical principle and what is and is not feasible. This information can be retrieved from Section III: Technical principle.

- **Where would a diagnostic test fit in the context of VL?**
  To answer this question, it is essential to understand the differences between diagnostic settings within the context of VL where a diagnostic test could be implemented. This information can be retrieved from Section II: Context.

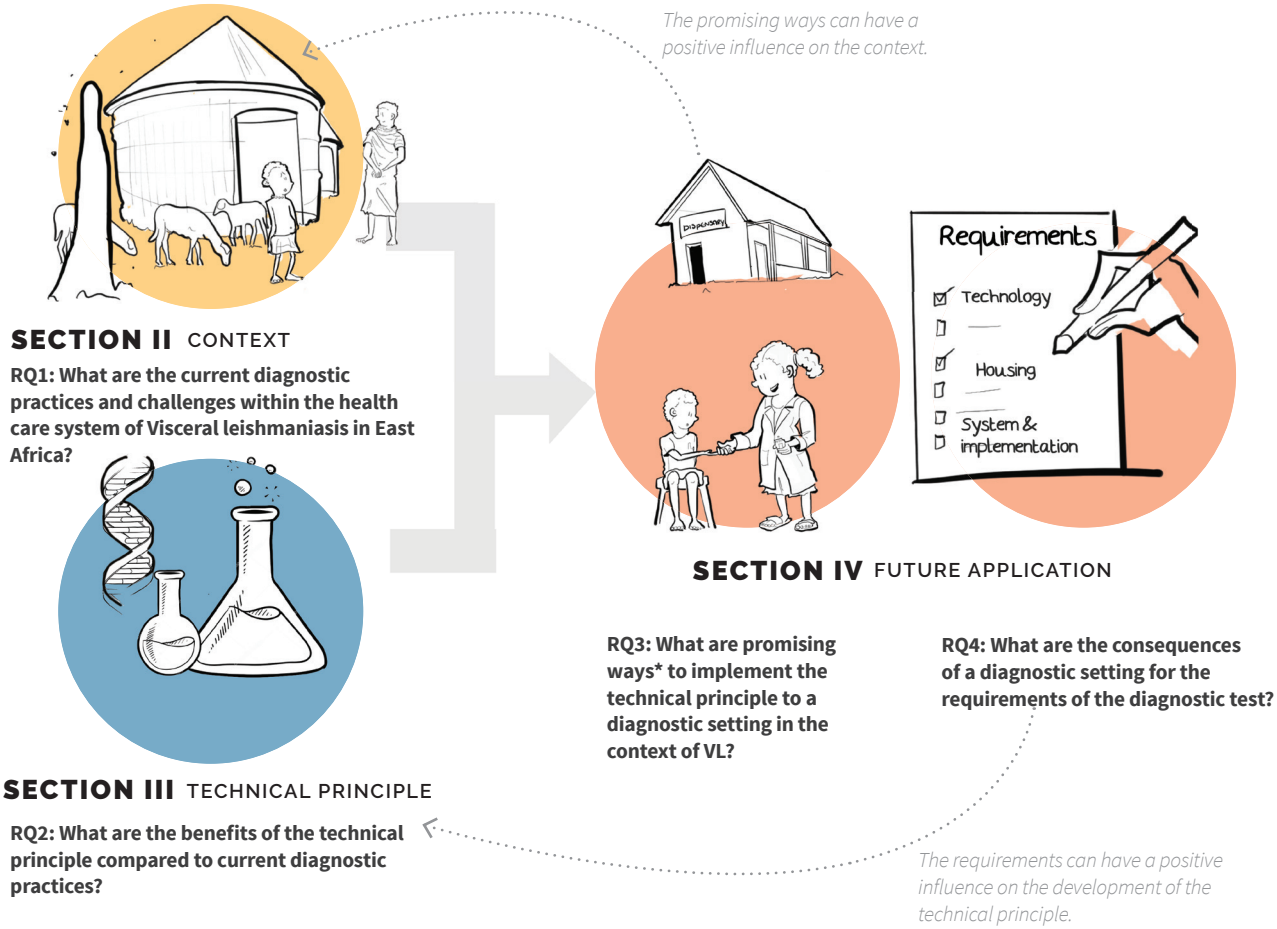


Figure 4: Structure of the thesis.

- **Is there a local need?**
  It is important to understand the challenges in current VL case management to understand the local needs in the case management of VL. This will help to identify where the technical principle could have a positive influence on case management of VL. This information can be retrieved from Section II: Context.

It is important to understand that there are multiple 'promising' ways to apply the technical principle to a contextual fit. Therefore, there are multiple 'diagnostic settings' in which the technical principle could be implemented.

For successful implementation of the technical principle into a diagnostic test which suitable for the context, it is necessary to see how the diagnostic setting affects the requirements of a diagnostic test. Thus, introducing the fourth Research Question.

RQ4: What are the consequences of a diagnostic setting for the requirements of the diagnostic test?

It is necessary to define the features of a diagnostic test that are recommended to facilitate successful usage in the diagnostic setting. Therefore, diagnostic settings and their effect on the required characteristics of a diagnostic test need to become clear. By understanding the diagnostic settings, requirements for diagnostic tests can be formulated which are important for a diagnostic test to succeed in the context. This results in solutions for diagnostic tests based on specific diagnostic settings.

Man who is helping out when the 4-wheel drive got suck in East-Pokot, Kenya.
The approach was to put rocks in the jeep to make it heavier (this was no success by the way).

SECTION I PROBLEM FRAMING

Chapter 02 APPROACH

The previous Chapter 01: Project scope, explains the structure of the project and the research questions which need to be answered. This Chapter builds on that by describing the approach and methods to answer the research questions. The methods and approach are discussed per Section.

2.1 Approach of Section II

CONTEXT

2.1.1 Theoretical exploration

The theoretical exploration has multiple purposes which are visible in Figure 5.

1) Understand

Help to get a better understanding of VL, the context of VL and the challenges that are part of the case management of VL.

2) Prepare

Theory helps to prepare research materials for the field trip, such as frameworks, templates and questionnaires.

3) Reflect

Theory helps to reflect on the findings throughout the project either by confirming or contradicting the finding. Moreover, theoretical exploration is used to compare outcomes from the field trip with information from other VL endemic areas to understand context variations.

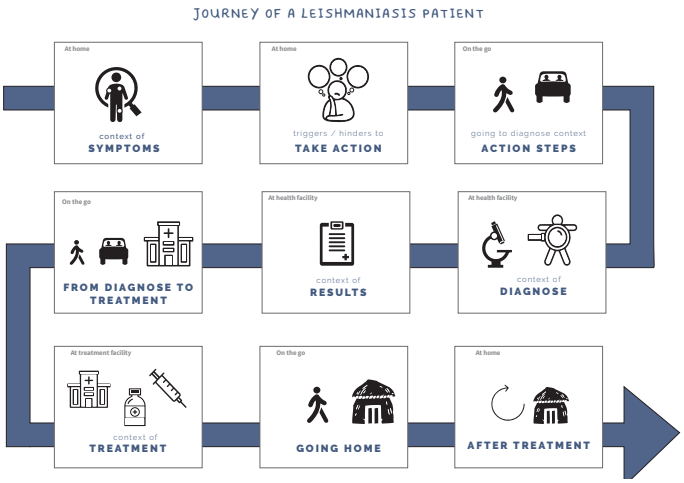


Figure 5: Patient journey as support during interview

Frameworks & templates

There are several aspects which have to be taken into account to give people in LRS access to diagnostics. According to Peters et al. (2008), the quality of healthcare in developing countries can be divided into four categories: geographic accessibility, availability, acceptability, financial affordability. Each of them having a supply-and-demand element (Peters et al., 2008). Based on those four A's, a framework is composed (See Appendix A-1) which helped in the preparation of semi-structured interviews and observations prior to the field trip. In addition, the templates will help to structure information about the accessibility to VL care during theoretical exploration and the field trip. The framework composed by Aranda, Jagtap & Moultrie (2016) is used during the field trip to get a holistic overview and understanding of the current context of VL. See Appendix A-1 for this framework.

In addition to the frameworks, a patient journey template is created to get information about the current barriers that VL patients face to access diagnostics and treatment (see Figure 5). Lastly, an observation template is created which will help to process and structure information during the observations. See Appendices A-1 and A-3 for these templates and their usage.

Questionnaires

Theoretical exploration helps to prepare a list of questions for the field trip which will facilitate a more in-depth understanding of the context. See Appendix A-1 for this list of questions.

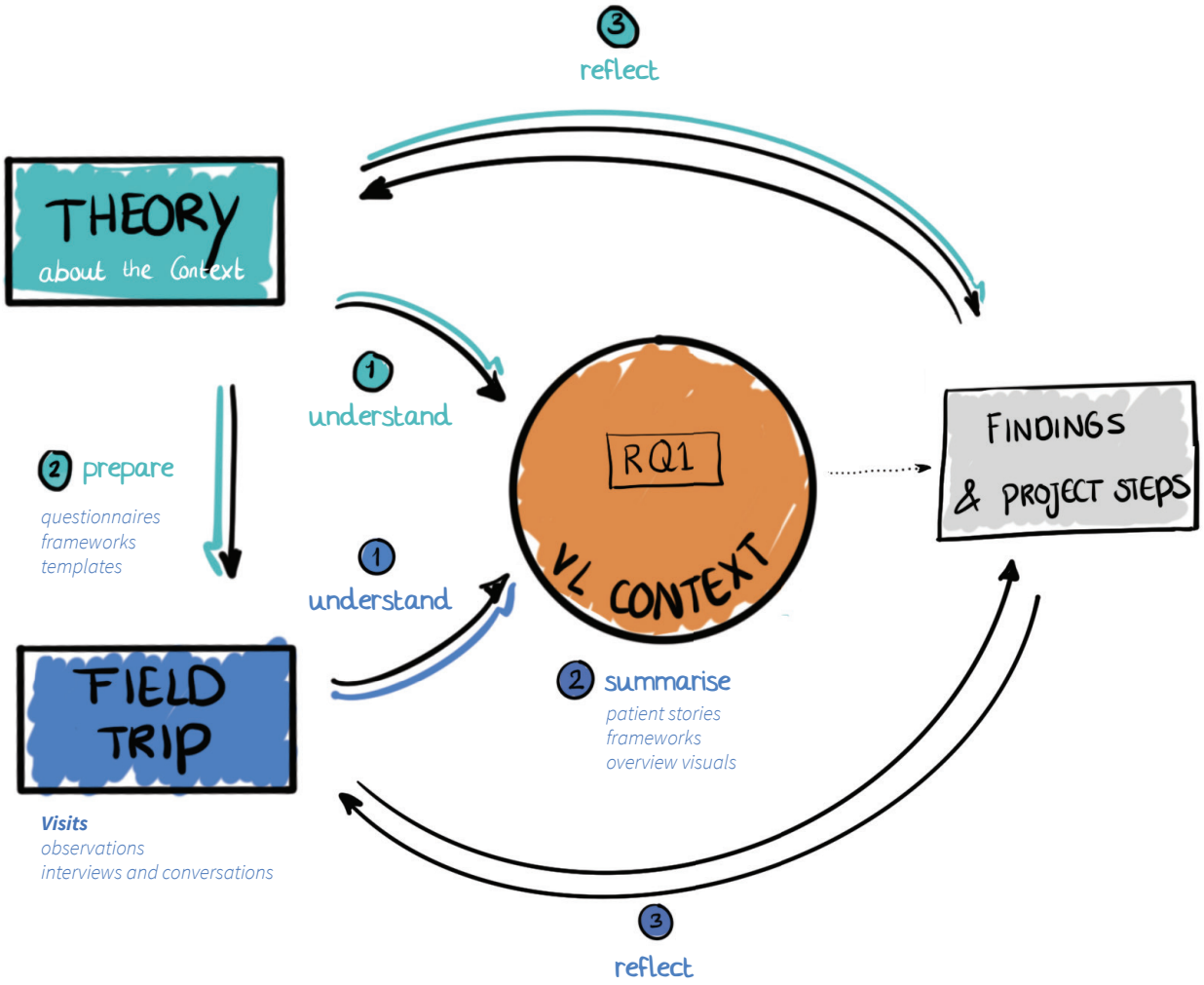


Figure 6: How the theory has supported the field trip.

Field trip

In addition to the theoretical exploration, a two-week field trip to VL endemic areas in Eastern Uganda and North-Western Kenya is done to get a more in-depth understanding of the context. This VL endemic region is selected as English is well spoken in this region, it is politically stable (compared to some other VL endemic areas) and has two VL treatment centres in Amudat and Kimalel.
During this trip, several health facilities, organisations and communities are visited (Figure 7). See Appendix A-2 for the itinerary of the field trip. At all the locations which have been visited, information is gathered by doing observations and informal interviews.

1) Understand

Observations

Observations are done to get an understanding of the living conditions of people and the health care system and facilities in VL endemic areas. Observation templates are used to summarise and write down the most important insights.

(Informal) interviews and conversations

'Informal' conversations are executed with doctors, lab technicians, nurses, midwives, CHV's, CHW's, county administrators and health care workers, to get an understanding of the context of VL. This involves, understanding the pros and cons of current diagnose and treatment procedures and the main limitations in current case management of VL. The list of questions which is prepared (Appendix A-1) is used to keep track of which questions have been answered and which ones still need to be asked. Depending on who is spoken to, different questions are picked out from this list.

During the field trip, the two frameworks which can be found in Appendix A-1, are used to keep an overview of the insights gathered but also to identify knowledge gaps during the field trip. Similarly, a patient journey template is used to get information about the current barriers VL patients face to access diagnostics and treatment. Thus, more in-depth insights into the barriers patients with VL face and the challenges in the health care system can be gathered by having a conversation with a public health officer.

2) Summarise

The information gathered during the field trip is structured into patient stories and visuals with the aim of summarising the insights. Processing the insights from the field will be the starting point to use this SECTION and SECTION III Technical principle to move towards SECTION IV: Future application.

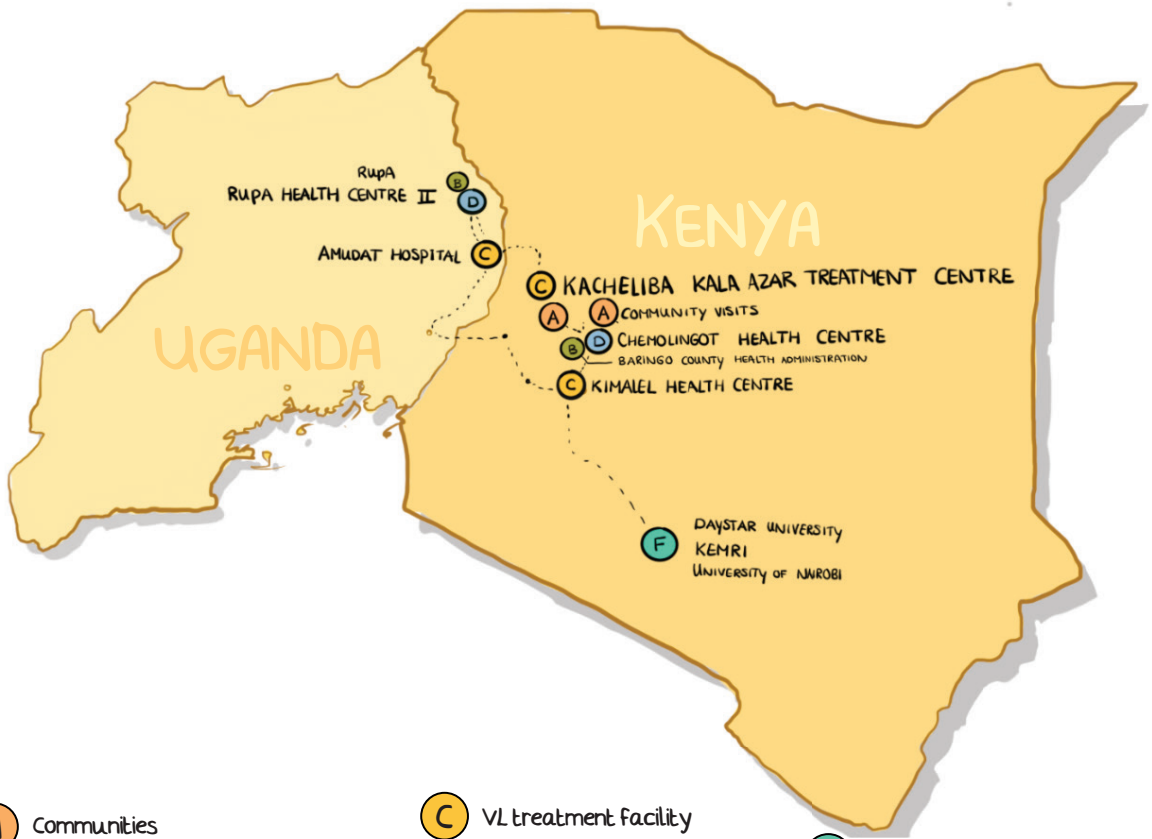
Patient stories

The information from the field trip serves as a backbone to create several 'patient stories'. Thus, these fictional stories are composed by combining all information collected from interviews and stories about actual patients from the field trip. The goal of creating patient stories is to get a better understanding of the journey that patients have to go through and the factors which influence why some patients have more challenging journeys than others.

Overview visualisation

A visual overview will help to structure all information gathered during the field trip in an accessible way.

Figure 7: Communities, health care facilities and organisations are visited during the field trip.



A Communities

B (sub)-county administration

C VL treatment facility

D Health care facility

F Organisations

Several communities are visited in Kenya to get an idea of the living conditions in VL endemic areas. Thus, in total four households have been visited which are part of the Pokot tribe.
When travelling through Kenya and Uganda, meetings with county and sub-county administrations are held to introduce the visit and get permission to enter the county or sub-county.

During this field trip, multiple health care facilities are visited including health centres, sub-county hospitals, VL treatment centres and a dispensary. When visiting these facilities, there was the chance to speak to doctors, community health volunteers, community health workers, lab-technicians, nurses and midwives, sub-county administrators and physicians. In Kenya these visits were accompanied by the Kenyan collaborators from KEMRI and the University of Nairobi. In Uganda the visits were accompanied by contacts at Amudat Hospital. Table 1 shows more details about the facilities which are visited and who was spoken to.

In Kenya, partners from KEMRI and the University of Nairobi joined the visits to communities and health facilities. Before the take-off to the rural areas in Kenya, the headquarters of KEMRI and the dean (and VL expert) from the Daystar University in Nairobi were visited.

	What ?	How many ?	Where ?	Key informants
A	Communities / houses	6	East-Pokot, Kenya	Pokot women, men and children
B	Sub-county ad-ministrators	2	Baringo county health admin-istration, Kabarnet, Kenya	Moses Mulamba (County-PHO) Leah Cherutich (County-Health promotion) Salinah Labatt (County-Reproductive HO) Samuel Ruto (County-Community Health services) Zachariah Kimwetich (County-In-charge special program)
			Rupa, Uganda	RupMr. Godfrey Lotuk, the sub-county chief
	Health Facilities			
C	Kala-azar treatment centers	4	Kacheliba, Kenya	Kacheliba Kala azar treatment cneter Dr. Jane Mbui, Centre For Clinical Research, KEMRI Dr. Mark Riongota, Clinician Kacheliba Sub-District Hospital
			Amudat, Uganda	Dr. Patrick Sagaki, in-charge of Amudat Hospital, Uganda Dr. Andrew (on-site physician) Dr. Lorenz (trials physician) Ms. Jane (lab Technician) Mr. Francisco Masaai, Trainee CHW.
			Kimalel, Kenya	Dr. Abass Ali, Med. Superintendent Ms. Mercy, Lab Technician.
D	Health care facility	3	Rupa, Uganda	Rupa health center II Mr. Korobe Fontiano, Lab technician Ms. Sara and Ms. Martha (mid wives)
			Chemolingot, Kenya.	Chemolingot Health center Dr. Kipasang Marichi (Med. Superintendent) Samali Joel, (sub-county clinical officer) Mr. Elijah Plilan (PHO sub-county community strategy) Ms. Jane, CHV
			Nyangung, Kenya	A nurse, name unknown
		1	Dispensaries at Baringo County, Kenya	Out of order
	Organisations (visited or joined)			
F	Organisations	2	Daystar University KEMRI University of Nairobi	Dr. Martha Kiarie-Makara (Dean of School of Engineering and Health) Dr. Damaris Muhia (Biomedical research scientist at KEMRI) Johnstone Ingonga (Biochemist at KEMRI) Anyona Joseph (junior researcher at KEMRI) Ms. Hellen Nyakundi (public health officer)

Table1: Overview of health facilties, communities and organisations visited and key informants.

2.2 Approach of Section III

TECHNICAL PRINICIPLE

2.2.1 The technical principle

It is essential to understand the basics of the technical principle. Therefore, multiple conversations and meeting are held with the researchers from Applied Sciences to understand how the technical principle works. By simplifying and visualising this information, the technical principle becomes more communicable to experts and laypeople.

2.2.2 The benefits

The knowledge about currently available diagnostic practices from the field is combined with the understanding of the technical principle. This will help to create an overview of the main benefits and distinguishing factors of the technical principle in comparison with current diagnostic practices. These benefits will serve as a starting point of Section IV.

2.3 Approach of Section IV

FUTURE APPLICATION

The knowledge of the context of VL and the technical principle are combined in Section IV (Figure 8).

2.3.1 Diagnostic setting variables

Both the field trip and theoretical exploration have resulted into getting a better understanding of the context. Insights about the context of VL have resulted in identifying variations between diagnostic settings. These variations between diagnostic settings are a result of 'diagnostic setting variables'. There are five critical diagnostic setting variables:

1) the knowledge of the **user**
2) the geographic **location**
3) the **resources** available at the location
4) the **diagnostic moment**
5) the **patient** status

These variables of a diagnostic setting will have consequences for the features of the diagnostic test.

2.3.2 Scenarios

From these variables, it becomes clear that there are different ways to implement the technical principle into a diagnostic setting. Therefore, scenarios are created by making promising combinations of the benefit of technical principle in a diagnostic setting (in the context of VL) which fulfil a local need.

Validate Scenarios

The scenarios are validated by discussing them with experts. The goal of this discussion is to select the two most promising ways of implementing a technical principle benefit to a diagnostic setting. Feedback is received from experts in two phases: first, a discussion is being held with Médecins Sans Frontières (MSF) to get verbal feedback on the scenarios. Secondly, a feedback form with the scenarios is used to receive input from stakeholders met during the field trip. Based on the feedback and discussion with MSF, a feedback form with scenarios is composed and send out to the stakeholders and collaborators met during the field trip. This feedback form has the purpose of seeking confirmation or contradictions about the scenarios in relation to the feedback received from MSF.

2.3.3 Influence of diagnostic setting on the diagnostic test

The two selected scenarios are detailed to understand how the diagnostic setting influences the features of the diagnostic test during another session with IDE and AS (see Appendix C-2). Detailing the scenarios will help to set requirements for diagnostic tests. Based on the insights from detailing the scenarios, the diagnostic settings are analysed in more detail. The diagnostic setting variables are important to consider as they influence the features of the diagnostic test. As became clear, the two most important diagnostic setting variables which influence the features of the diagnostic test are:

1) the resources available
2) the (medical) background of the user.

These two variables are further specified which helps to prepare the diagnostic test to be suitable for a broader variety of diagnostic settings.

2.3.4 Decomposition

To get a better understanding of how the diagnostic setting influences the features of the diagnostic test, several layers around the diagnostic test and diagnostic setting are identified. These layers will

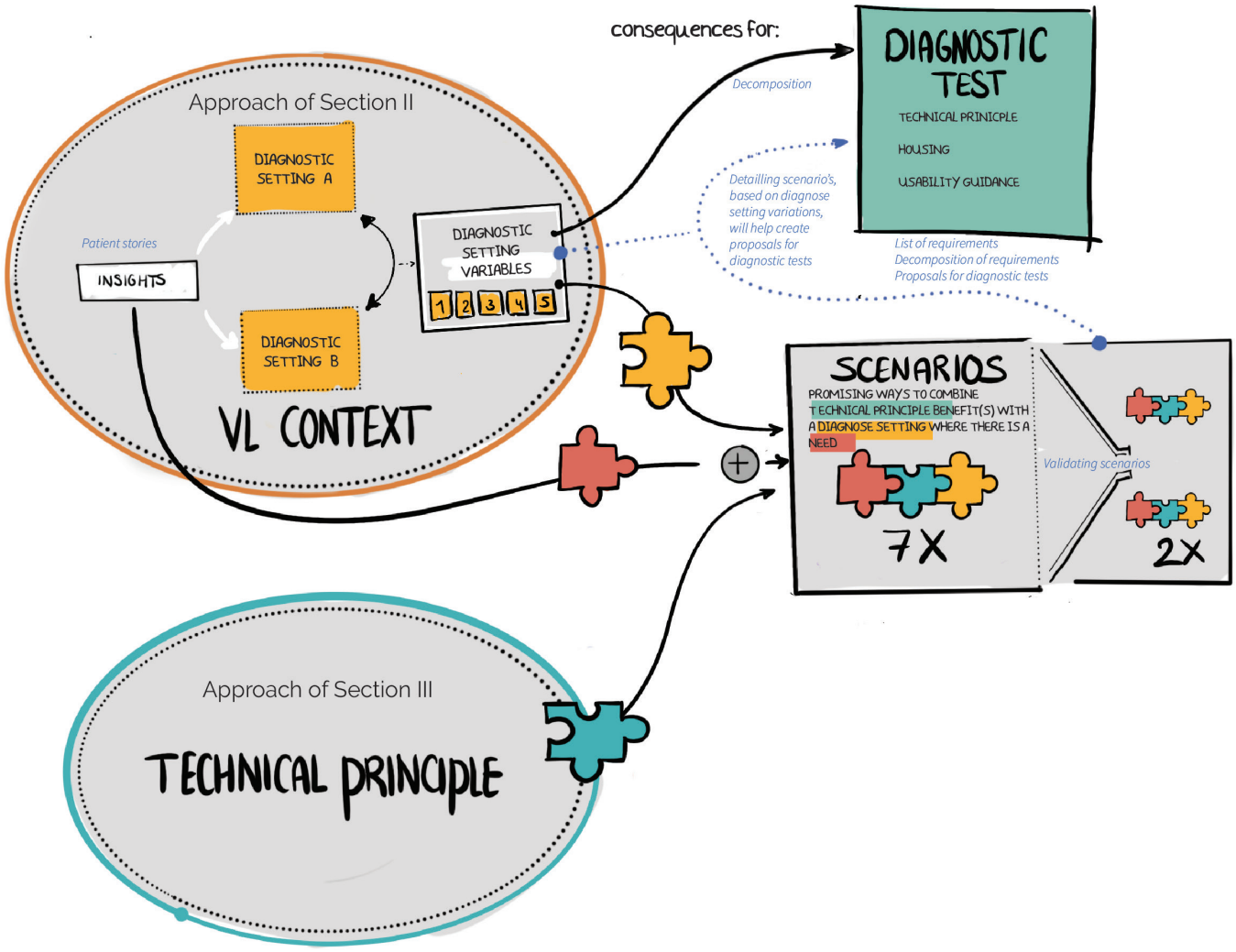


Figure 8: Approach of Section IV.

help to get a better understanding on how the diagnostic setting variables influence the diagnostic test. In addition, they will help in the translation towards diagnostic tests which are suitable in the diagnostic setting in which they are used.

2.3.5 Requirements

Based on detailing the selected scenarios, requirements for the diagnostic test are composed. See Appendix E-1 for the list of requirements. This list of requirements contains the important requirements that the diagnostic test needs to meet, based on a diagnostic setting.

Categorising requirements

The requirements can be sorted based on the diagnostic setting variables and decomposition as mentioned earlier. This will help to understand how the diagnostic setting influences the features of the diagnostic test. Categorising the requirements will help to translate them into diagnostic test proposals which vary from each other based on the diagnostic setting in which they are used.

2.3.6 Diagnostic test proposals

The categorised requirements are translated into proposals for diagnostic tests which are suitable for their diagnostic setting. Therefore, several diagnostic tests are created as a result of a combination of context-specific requirements and general requirements.

SECTION II

Context

Chapter 03: Visceral Leishmaniasis
Chapter 04: Challenges of Visceral Leishmaniasis

This Section of the Report has the function of getting an understanding of the visceral leishmaniasis and the context of this disease in endemic areas in East Africa. Hence, this section is split up into two chapters. In Chapter 3, visceral leishmaniasis and its symptoms are explained, followed by a description of the current diagnostic practices and treatment procedure. Chapter 4 builds upon this information by describing the challenges to access healthcare and the barriers that VL patients face. Information in this section is a combination of theory exploration and a field trip.

Ant hills, the breading nests of the sand-flies which carry *Leishmania* parasites. KENYA

SECTION II CONTEXT

Chapter

03

VISCERAL LEISHMANIASIS

In this Chapter, visceral leishmaniasis is introduced with the aim to understand the disease, diagnostic practices, treatment process and stakeholders involved in the case management.

3.1 Visceral leishmaniasis

WHAT IS THIS DISEASE AND CONTEXT LIKE?

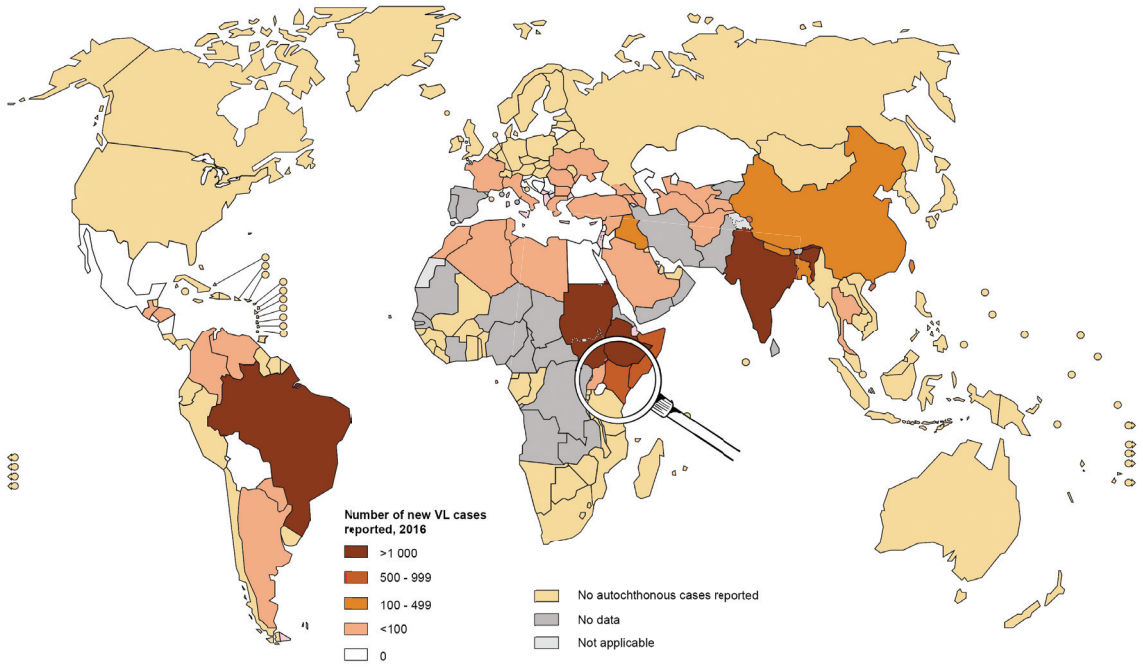


Figure 9: Status of endemicity of visceral leishmaniasis worldwide in 2015 (WHO, 2015)

3.1.1 The *Leishmania* parasite

Leishmaniasis is a parasitic disease that is classified as a neglected tropical disease (NTD).

Leishmaniasis occurs in several forms which the most common types are cutaneous leishmaniasis (CL) and visceral leishmaniasis (VL) ("CDC - Leishmaniasis", 2018).

The *Leishmania* parasite is transmitted to humans by the bite of an infected female sand fly. These sand-flies are most active during night-time hours, from dusk to dawn. ("CNC – Leishmaniasis", 2018).

This project focusses is on VL in East Africa due to its stronger presentation, fragile state and **the higher need for improved diagnostics** (Medicins sans Frontieres, 2012). Within East Africa, the VL endemic regions of Kenya and Uganda are selected field trip as English is well spoken in this region, it is politically stable and has two VL treatment centres: in Amudat and Kimalel.

3.2.1 Leishmaniasis

Visceral leishmaniasis is endemic in several parts of the world (see Figure 9), including East Africa.

Yearly, there are between **50 000** to **90 000** new cases of VL occur worldwide.
(WHO, 2018)

In 2017, 94% of the new cases were reported to WHO from seven countries: Brazil, Ethiopia, India, Kenya, Somalia, South Sudan and Sudan (WHO, 2018). Especially in the South-East Asia region, the number of VL cases is decreasing and has been effective towards the elimination of the disease. However, in East Africa elimination of VL is not yet in the picture (Ritmeijer, 2018).

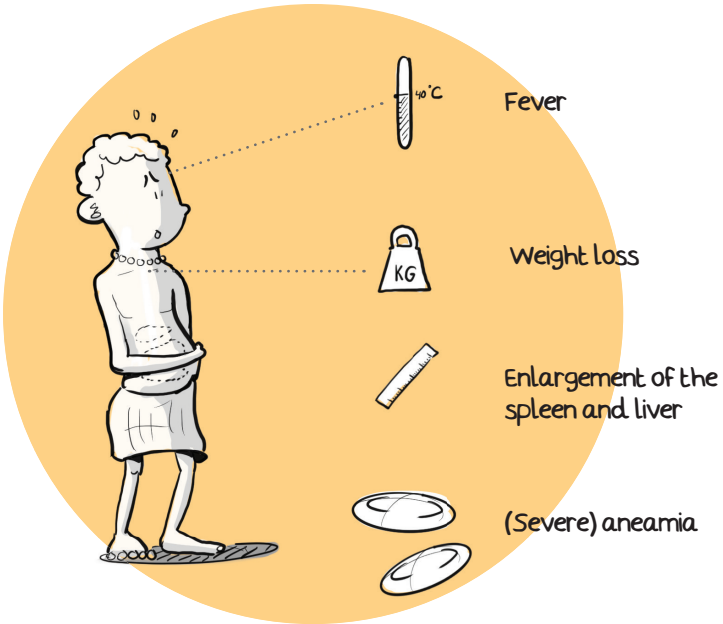


Figure 10: Most common symptoms of Visceral Leishmaniasis

What?

Visceral leishmaniasis is also called the disease of the poor, as it mainly affects the impoverished people who do not have a protective house and often have a weak immune system due to co-infections and malnutrition.

The incubation time of visceral leishmaniasis varies between people. Although it typically develops within 2 to 6 months, there are cases where it can take up to years before someone starts developing symptoms ("CDC - Leishmaniasis", 2018).

However, not everyone who is infected with the *Leishmania* parasite develops visceral leishmaniasis (the disease) as it will only present when someone's immune system is compromised. Therefore, people in higher risk are those with a weaker immune system due to young age, malnutrition, co-infections and immunosuppressive diseases such as HIV (WHO, 2018).

A person who is infected but does not present any symptoms (yet) is called an asymptomatic case. These asymptomatic cases are reservoirs of the disease. In addition to humans, oxen jackals and dogs can be reservoirs (WHO, 2018).

Symptoms

VL usually presents with fever, weight loss, general malaise, enlargement (swelling) of the spleen and liver, and severe anaemia in case of low blood counts ("CDC - Leishmaniasis", 2018) (Figure 10). In the case of VL, the parasite affects the internal organs such as the spleen, liver and bone marrow which makes it a life-threatening form of the disease.

> The case fatality rate of visceral leishmaniasis is around 100% if the disease is left untreated.
>
> (WHO, 2018)

VL weakens the patient's body, and therefore VL patients often die due to secondary bacterial infections such as diarrhoea, tuberculosis or pneumonia, massive bleeding or severe anaemia (WHO, 2018).

3.1.3 Who?

As mentioned previously, people with a compressed immune system have more risk to develop the disease. Kolaczinski et al., (2008) argues that nutritional and co-infected factors affect whether or not someone infected actually develops VL.

However, there are other factors which influence the chance of getting infected with Leishmania. Kolaczinski et al. (2008) came up with a framework for socio-economic, environmental, behavioural and nutritional/coinfection variables in the Pokot county.

> The most important factors which influence the risk of getting infected with *Leishmania* are the presence of vector breeding places such as termite mounds, ant hills or acacia trees near the house and the sleeping conditions.
>
> (WHO, 2018)

From conversations with Dr Andrew at Amudat hospital in Uganda and Dr Abass at Kimalel health centre, it became clear that the VL patients they receive at these treatment centres are mostly young boys.

> Patients at the visited treatment centres are mostly boys between 2-15 years old.

These boys are part of the Pokot tribe. In this tribe, boys are sleeping outside and thus are most exposed to sand-flies during the night (See Figure 13). Therefore, sleeping conditions and the presence of vector breeding places have an impact on the risk of getting infected with Leishmania.

VL patients at Amudat Hospital, Uganda.

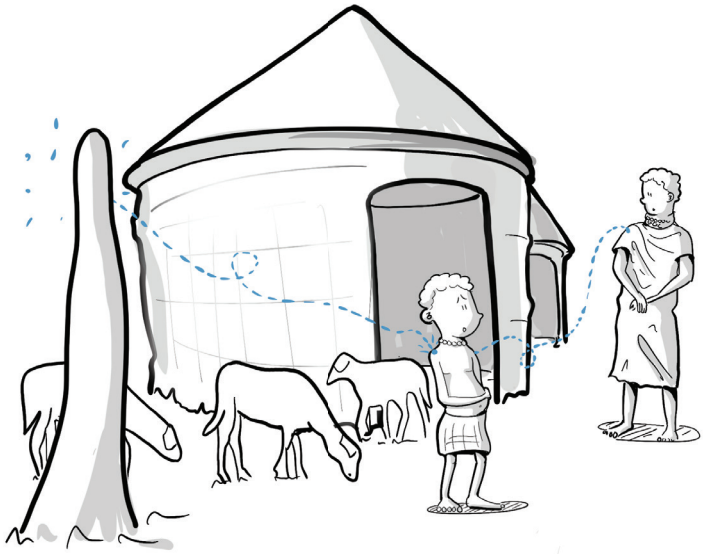


Figure 12: The affected communities often live close to ant hills which are breading nests for vectors.

3.1.4 Vector control

As the leishmaniasis parasites are transferred from human to human and human to animal through sand-flies, it is essential to be protected against these 'vectors'. However, in areas where this disease is endemic, these relatively simple measurements are complicated.
The houses are often surrounded by anthills and offer no protection and bed nets and insecticide are not available (CDC,2018) (Figure 12).

Several organisations are involved in vector surveillance, to reduce the exposure to these 'vectors'. Vector control programmes focus either on improving housing conditions to offer protection or investigating parasite reservoirs.
However, vector control remains challenging as the living conditions of the affected people are basic and changing these situations is extremely difficult. When aiming for elimination of VL, vector control programmes are crucial.

Figure 13:
Boys and men of the Pokot tribe sleep outside on these 'mattresses'.

3.2 Visceral Leishmaniasis Care

DIAGNOSTIC PRACTICES AND TREATMENT PROCEDURES

3.2.1 Current diagnostic practices

In order to receive treatment, VL patients have to be diagnosed first. Early diagnosis is crucial as this can improve the outcomes for the patient after treatment and reduce the damage to internal organs. VL can be diagnosed in several ways. These are: parasitological diagnosis, serological diagnosis and molecular diagnosis (see Figure 14). Each of them are discussed in more detail.

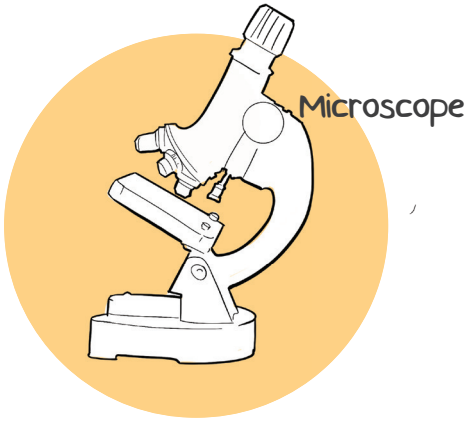
Figure 14: Three categories of diagnostics.

The serological diagnostic test: rK39. Most common diagnostic test to test someone for VL, Kimalel Health Centre, Kenya.

Figure 15: Parasitological diagnosis of VL through microscopic examiniation of bone marrow or splenic aspiration.

PARASITOLOGICAL DIAGNOSIS

This way of diagnosing is based on analysing the parasites though microscopy examination (Figure 15). Therefore, a tissue (bone marrow or splenic) aspiration is required.

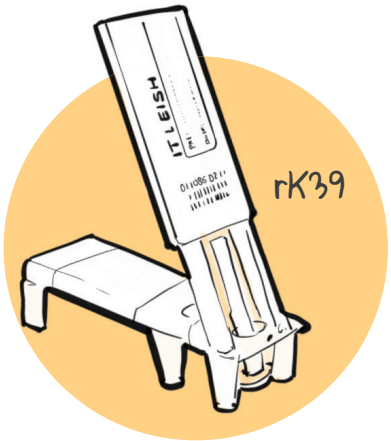


Officially, the gold standard for diagnosing VL is through parasitological examination (De Ruiter et al., 2014). However, from the field trip, it became clear that parasitological examination through splenic aspiration or bone marrow aspiration is **limited to the more 'advanced' health care facilities** and treatment centres. The reason for this is that **this procedure is risky and uncomfortable and requires a high level of skills** which are often unavailable in primary health care facilities. But even at some treatment centres, such as Kimalel health centre, the staff does not execute a parasitological diagnosis because of the risks involved. So, a patient is put on treatment after getting a positive test result on an serological test which is combined with the presence of clinical symptoms. The lack of skills to do a parasitological examination results in an issue for patients with a relapse or reinfection. **A parasitological diagnosis is the only way to test a VL patient with a relapse or reinfection.**

A parasitological diagnosis is required in case of clinical trials. So patients who are part of this clinical trial will get a parasitological confirmation. Consequently, donors make sure that there are sufficient resources (skills and money) at these facilities to do a parasitological diagnosis during clinical trials. Amudat and Kacheliba hospital are places which are visited during the field trip which are part of clinical trials.

SEROLOGICAL DIAGNOSIS

This way of diagnosing is based on analysing the immune system. Serological tests detect either *Leishmania* antigens or antileishmanial antibodies in blood samples (Singh & Sundar, 2015). Multiple serological tests have been developed for VL, such as the Rapid Diagnostic Test rK39 (the IT LEISH test from Diamed) and the Direct Agglutination test (DAT).



rK39 Rapid Diagnostic Test

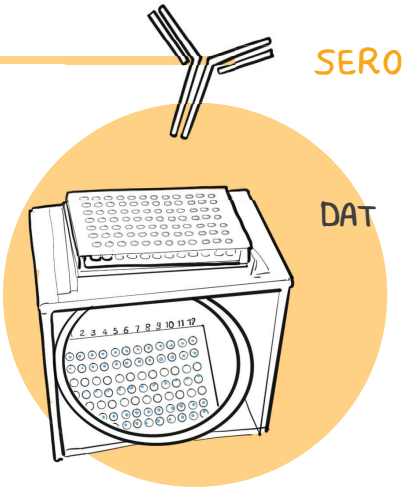
From the field trip, it became evident that **rK39 is often the only diagnostic test available before a patient is put on treatment**. Due to the lack of skilled staff at many of the health care facilities in rural areas, there is no option to do a parasitological examination. These serological tests have been developed to replace parasitological methods for the diagnosis of visceral leishmaniasis in the field (Chappuis et al., 2006). According to Dr Abas from Kimalel health centre, it is prevalent that patients start a treatment based on the combination of a positive rk39 with clinical symptoms. As the treatment is very intense and toxic and rK39 has several implications, starting treatment on a positive rk39 result combined with clinical symptoms is risky.

Usability of Rk39

By analysing the usage of the rk39 in the field (by a lab-technician and CHW in training), several insights were found considering the usability. During the field trip, several users performing an rk39 were filmed during usage and asked what they thought of the test. See Appendix F-2 for the detailed insights from the observations of the usage of the test.

Implications of rK39

- As rK39 is antigen-based, patients with a relapse or re-infection cannot be tested with as they still have antibodies in their body after treatment.
- The response of rK39 RDT is less effective in East Africa demonstrating sensitivities between 70% and 94%. (Singh & Sundar, 2015). This lower sensitivity means some people get a negative test result while they are infected with Leishmania.
- Even though the ASSURED criteria from WHO (WHO, 2017) claim that RDT's such as rK39 should be user-friendly, there are still many usability errors with rK39. According to Charity Kamau from Médecins Sans Frontières Amsterdam, human errors are often happening when using an rK39 test. See Appendix F-2 for more information about usability errors of the rK39.



SEROLOGICAL DIAGNOSIS

Direct Agglutination test (DAT)

This serological test (Figure 16) is semiquantitative and if antibodies are present in the sample, agglutination is visible by the naked eye (Chappuis et al., 2006).

- This test is dependent on electricity as the storage of the antigens have to be kept at 2-8 degrees and requires skilled staff. Both these factors make DAT unsuitable to in most health facilities. (Singh & Sundar, 2015). During the field trip it became evident that only in well-financed treatment centres such as Amudat Hospital resources were available to do DAT tests.
- Similarly to the rK39, the DAT is antigen-based. Therefore, patients with a relapse or re-infection cannot be tested with DAT as they still have antibodies in their body after treatment.

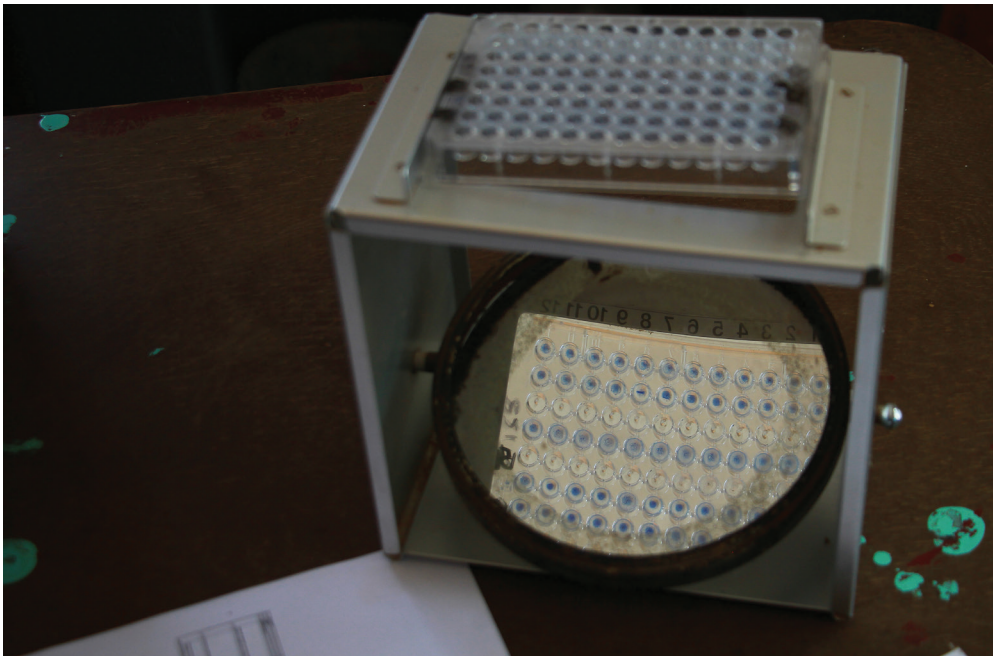
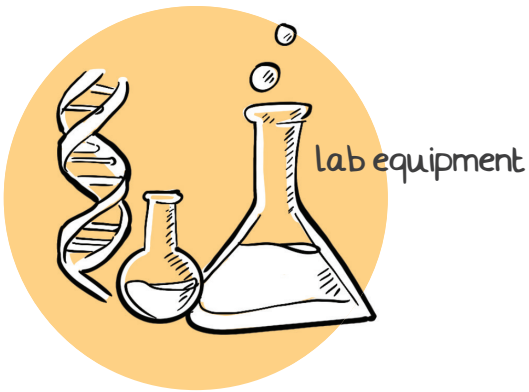


Figure 16: The semiquantitative Direct Agglutination Test (DAT), used at Amudat Hospital.

MOLECULAR DIAGNOSIS

This way of diagnosing focusses on analysing biological markers in the genome and proteome.



Molecular diagnoses are not suitable for the field (yet).

Currently, there are no suitable molecular tests for the field as they require a high level of skills and are expensive (Singh and Sundar, 2015).

During the field trip, it became clear that there are no molecular diagnoses been done in the context of VL in the visited regions.

Although the principle of molecular diagnostics is promising and very accurate, these techniques are not that yet applicable in the field. According to Singh and Sundar (2015), the costs are high and their clinical benefits, when applied in resource-constrained settings, are still in debate.

The technical principle in this project (Section III) can be categorised as a molecular diagnosis.

The technical principle would be part of this diagnostic category.

Which diagnostic practice?

From the field trip it became clear that visceral leishmaniasis in East Africa is diagnosed by using the rK39 test, the DAT (direct agglutination test) or through parasitological examination through tissue aspiration. It depends on the health care facility and resources available which diagnostic test or procedure is done.

In most cases, VL is diagnosed based on the combination of clinical symptoms and a positive rK39 test result.

Officially, a patient should get a confirmatory diagnosis through parasitological examination, but in reality, this is exceptional. Table 2 shows an overview of the places visited during the field trip and the way VL is diagnosed in these places. Besides, this Table also shows who is testing patients for VL at these facilities.

Who is using the diagnostic test?

In most of the facilities which are visited, lab-technicians are responsible for testing patients for VL. Usually, there are one or two trained lab-technicians trained to do an rK39 test. However, the definition of 'trained' is very broad, which means the level of actual skills can vary enormously. According to Charity Kamau from MSF, a lab-technician can be someone who has a three-year official training

Health care level	Where?	WHO?	HOW?
At community level		Community health worker (CHW)	rK39
At community level		Health organisation (by lab-technicians or doctors)	rK39
Dispensary / primary health centre	Rupa II Health care center in Uganda	Midwife / lab technician / nurse	rK39
Health care centre (soon becomes a treatment facility)	Chemolingot sub-county hospital	Lab-technician	rK39
Treatment facility	Amudat Hospital	Lab-technician	rK39, splenic or bone marrow aspiration and DAT
Treatment facility	Kimalel health centre	Lab-technician	rK39
Treatment facility	Kacheliba hospital	Lab-technician	rK39, splenic or bone marrow aspiration and DAT

In the field in Uganda by the CHW

In Amudat district in Uganda, there are two Community Health Workers who have been trained from Amudat Hospital (VL specific facility) to diagnose patients in the field. Thus, these two CHW's are screening communities on their motorbikes and can test patients with the current rK39 rapid diagnostic test. In this case, a vehicle will be arranged from Amudat to come to pick up the patient.

Screening days in Kenya

In Baringo county (Kenya), screening days are held once in a while to screen entire communities after gathering at a central spot. During this screening days, there is expert staff such as doctors, lab technicians, nurses who can query and test diseases among which VL. A vehicle will be arranged for them to come to pick up the patient.

Table2: Overview of the different diagnostic tests and procedure which are used at the vistited health facilities.

or someone who was picked from the street and trained to take this responsibility. Besides lab-technicians, other people who are testing patients for VL, such as midwives and nurses and Community Health Workers (CHWs).

3.2.2 Baseline measurements

When it is decided that the patient should be put on treatment, several baseline measurements are executed. These measurements include a haemogram and a kidney and liver functioning test (Abass, 2018). Besides, a patient is tested on HIV as HIV/VL co-infected patients receive a different treatment.

3.2.3 VL treatment

Although the treatment options in Africa have improved during the last 20 years, challenges remain (see Figure 17).

Until 2010, liposomal amphotericin B was used which required 30 days of injections. This lengthy process resulted in a costly treatment with frequently occurring side effects (DNDi, 2018). Luckily since 2010, there is a new treatment recommended by WHO, which is now **the first-line treatment for VL in East Africa** (DNDi , 2019). This treatment consists of a combination of **sodium stibogluconate and paromomycin (SSG&PM)** and is the result of a partnership for six years between several organisations such as MSF, WHO, LEAP and DNDi which resulted in a safe and effective new treatment. **This treatment reduced the treatment time from 30 days to 17 days and is less expensive.** Another advantage of the SSG&PM combination is that it helps **fight resistance to treatment** (DNDi, 2011).

However, even though the current treatment is a significant improvement compared to older treatments, it is **still suboptimal as there are still issues with toxicity, affordability and accessibility** (DNDi, 2019). The current SSG&PM treatment is **expensive** as it costs approximately $600 to treat one patient. Besides the treatment requires hospitalisation for 17-days due to the daily injections, the toxicity and the monitoring.

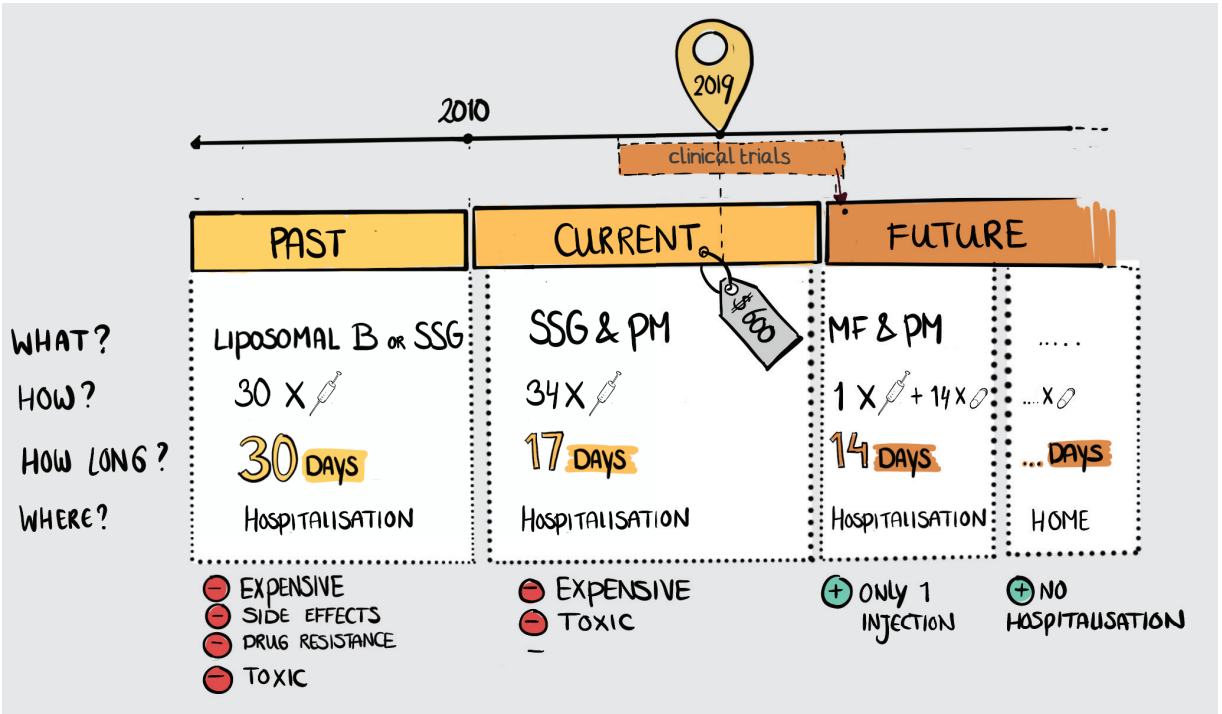


Figure 17: Development of VL treatment in East Africa.

In the long term, DNDi has the aim to develop a safe, effective, low-cost and short-course oral treatment for VL. (DNDI, 2018). However, if and when this could be realised is still questionable. Nonetheless, since 2016 clinical trials to test a new treatment combination of Paromomycin and Miltefosine are ongoing in a partnership with DNDI, LEAP and other partners. If the new combination is proven safe and efficacious, it would be able to replace the injectable drug SSG (sodium stibogluconate) for Miltefosine, an oral drug and thus adapt the treatment to 14 days with a single injectable and one oral daily drug (Mbui, 2018).
See Figure 17 for the timeline of the development of the treatment.

Treatment for high risk patients

Patients who are severely sick, pregnant or HIV co-infected are put on another treatment. For these patients, the first line treatment is Liposomal amphotericin B (Ambisome®). This treatment is the safest antileishmanial drug and requires a cold chain (WHO, 2012).

Ward for VL patients in Amudat Hospital, Uganda.

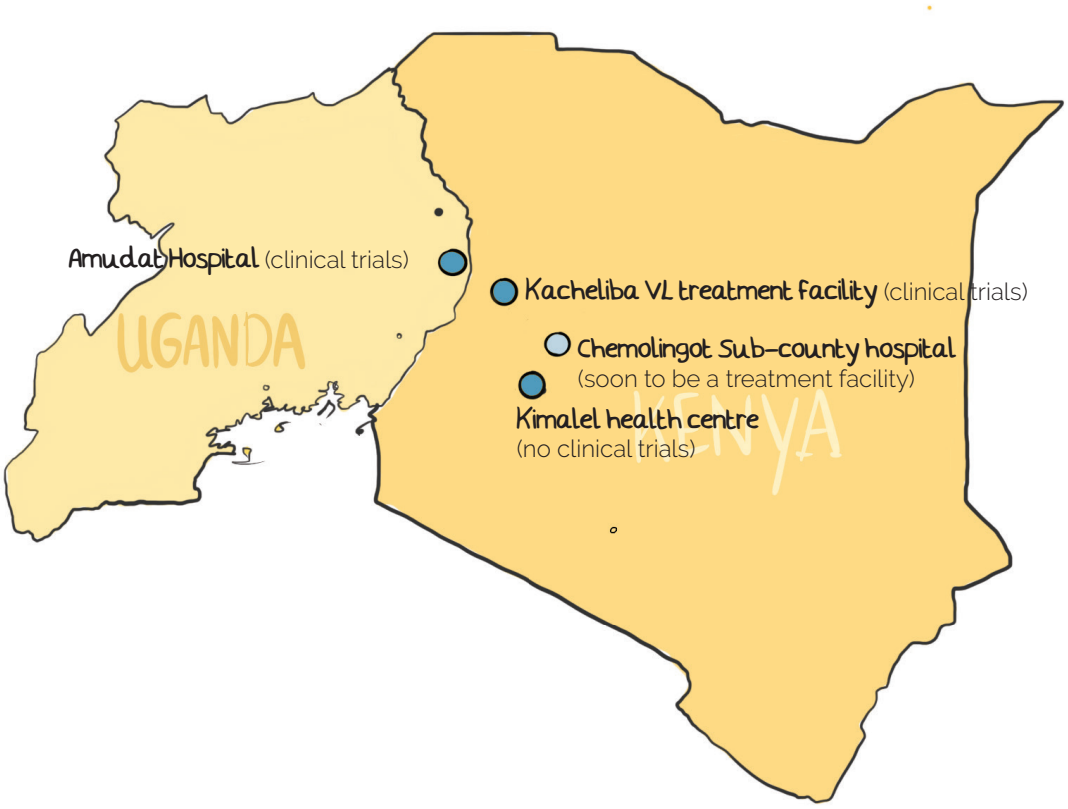


Figure 18: VL treatment centres in Kenya and Uganda.

Where to get treated?

There are limited treatment facilities in VL endemic areas in Kenya and Uganda. Figure 18 shows the **three treatment facilities that are located in the Rift Valley districts of Baringo and Turkana and the Pokot district.** These facilities have been visited during the field trip. As visible, **Amudat hospital is the only VL treatment facility in Uganda.**

In addition to the treatment centres in Baringo, Turkana and Pokot, there are **several other VL treatment centres in Kenya.** These are located in the other VL prevalent regions in the North Eastern districts of Isiolo, Wajir and Mandera which neighbour with Somalia and Ethiopia (Njau, n.d .).

The exact number and locations of these treatment centres is unknown.

Thus, Baringo county only has two places where they treat VL: **Kimalel health centre** and **Kacheliba**. A third treatment centre is being built in Chemolingot which would improve accessibility to treatment.

However, the affected communities come from **remote areas and have to cross large distances to get to a treatment facility**. For example, the Pokots have to travel around 80 km to go to Kimalel Health centre. Similarly, the Turkanas in Kenya prefer travelling to Amudat (Uganda) due to tribal conflicts, which is a distance of at least 100 km.

Treatment facilities are often established and/or funded by donors such as MSF and DNDi. Kacheliba Kala-azar Center, Kenya.

3.2.4 Stakeholders

VL case management programmes are donor dependent as governments of countries where VL is endemic are not funding VL diagnoses and treatment procedures. The most important donors for VL programmes are DNDi and WHO.

WHO

WHO is a health organisation who works worldwide to promote health with the aim to keep the world safe and serve the vulnerable (WHO, n.d.).

DNDi

Drugs for Neglected Diseases initiative (DNDi) is a non-profit drug research and development organisation that is developing new treatments for neglected diseases. They work on various diseases including Leishmaniasis (DNDI, n.d.). In the case of VL in East Africa, DNDi is performing clinical trials for the development of a new treatment at Kacheliba and Amudat Hospital.

MSF

This non-profit organisation is carrying out health interventions and medical care worldwide. In terms of VL, they lead various projects, but not in the areas which were visited in the field trip.

KEMRI

The Kenyan Medical Research Institute (KEMRI) is carrying out health research in Kenya for public health. KEMRI is focussing both on VL vector control research as well as clinical trials on treatment which they participate in together with DNDi.

The harsh living conditions of the Pokot communities in Kenya.

SECTION II CONTEXT

Chapter

04

CHALLENGES OF VISCERAL LEISHMANIASIS

The previous Chapter introduced the disease and the diagnostic practices and treatment process. This Chapter builds on this with the aim to understand the challenges of VL in East Africa. The information is gathered from theoretical exploration and the field trip. First, the challenges in VL case management are described, followed by the barriers that VL patients face.

4.1 Receiving VL care

WHAT ARE THE CHALLENGES TO RECEIVE VL CARE?

There are multiple challenges and barriers in the health care system of VL which complicate getting a diagnosis and treatment (in time). According to Peters et al. (2008), the quality of health care can be determined by four A's: geographic Accessibility, Availability, Acceptability and financial Affordability. A framework which is inspired on these four A's (See Figure 19) helps to understand the challenges to access VL diagnostics and treatment. Thus, the challenges within the context of VL are explained by the elements in this framework.

To receive VL someone needs to:

- **Have VL**
- **Be aware** of having VL or interact with someone who is aware of VL (awareness)
- **Decide** to seek care (Health care seeking behaviour)
- **Access** VL care
  - (geographic) Accessibility
  - Availability
  - Acceptability
  - Financial Affordability

Each of these determinants is discussed in this Chapter.

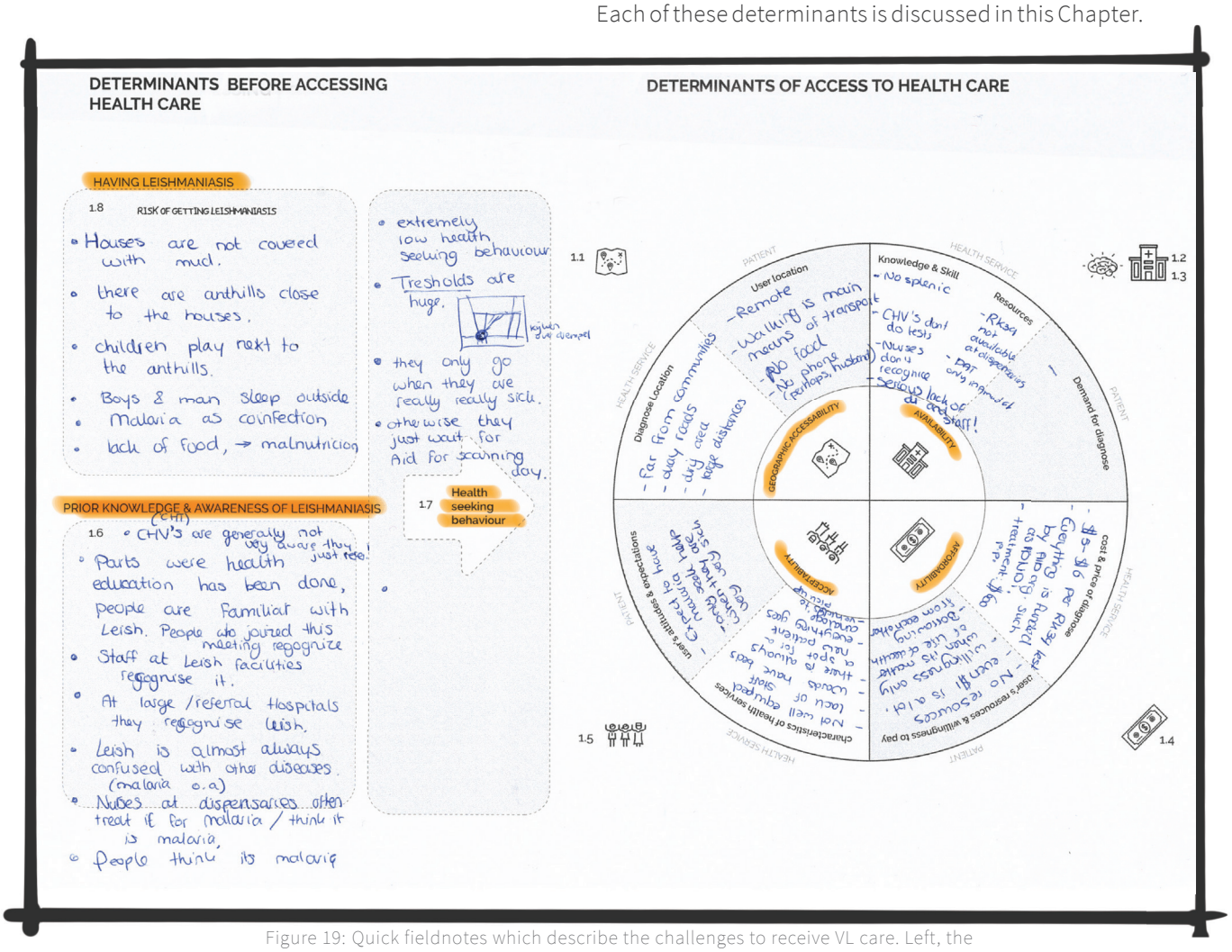


Figure 19: Quick fieldnotes which describe the challenges to receive VL care. Left, the determinants before accessing VL care. Right (circle), the determinants of accessing care.

4.1.1 Having leishmaniasis

As explained in Chapter 03, the risk of getting Visceral leishmaniasis depends on multiple factors.

Most important risk factors to get infected with the *Leishmania* parasite are unprotected houses, outside sleeping circumstances and the presence of anthills and termite moulds.

The most important factors that influence whether someone develops visceral leishmaniasis are the status of someone's **immune system** and whether someone is **malnourished or co-infected**.

4.1.2 Awareness of leishmaniasis

Whether someone is able to query VL, depends on the a**wareness of the disease** and the **medical background of that person**. From the field trip, it became clear, that there is often a low index of suspicion and awareness of VL by health care workers. This can be explained by the lack of health education about VL.

Health education has a significant impact on the awareness of both people in the community and health care workers. When no health education has been provided, the awareness of Visceral Leishmaniasis is generally low.
In general, it depends on the medical background of the staff if they can query VL. In most higher level health care facilities such as sub-county hospitals, the staff is able to query VL. On the contrary, at lower health care facilities such as dispensaries and primary health facilities, the staff is often unable to do this.

As became clear, the level of awareness of VL by staff strongly depends on how much health education is done in that region. For example, in the Baringo county in Kenya, extensive health education was done which results in a higher level of awareness among health care workers and people living in the affected communities.

Nonetheless, it is important to note that it can be **challenging to recognise VL**, even when someone has a medical background or has attended health education. There are three main reasons why this is the case.

- The initial symptoms of VL (fever, general malaise) are **similar to many other fever-related tropical diseases**.
- VL can **present differently** between patients as it is dependent on someone's immune system.
- The **presence of co-infections** complicates the recognition of VL as co-infections often mask the symptoms of VL.

These reasons, increase the changes of misdiagnosing VL for another disease such as Malaria, Tuberculosis, Typhoid. This can result in mistreatment where a VL patient receives oral malaria medication instead of being referred to a VL treatment.

Pokot communities live very remote. Kenya

4.1.3 Health care seeking behaviour

The health care seeking behaviour of VL patients is generally very late. The reasons can be explained by the barriers that patients face in terms of accessibility, availability, acceptability and affordability.

4.1.4 Access VL care

(Geographic) Accessibility

From the field trip, it became clear that geographic accessibility plays an important role in health-seeking behaviour and overall access to VL diagnostics and treatment in Kenya and Uganda. Several barriers were found which make it difficult for patients to get to a health facility and get a VL diagnosis and treatment.

Distance to diagnostics

The number of health facilities is low, so the facilities which offer diagnostics for VL and treatment are distributed over a large area.
On average someone has to walk around 10 – 20 km to get to the nearest health facility, which is in most cases a dispensary. Unfortunately, this does not mean this facility has the resources (skills and equipment) to test a patient for VL. Usually, at primary health care facilities, only basic health care services are provided and there are usually no diagnostic tests available nor the knowledge to diagnose a patient with VL. Therefore, a patient is either misdiagnosed (and potentially treated for the wrong disease) or referred to another health care facility.

These large distances to health facilities often result in late health seeking behaviour.

By the time someone decides to seek care, the person is already very sick.

Distance to treatment

Similarly, when a VL patient receives a positive (VL) test result, the patient still has to go to a treatment facility.

There are only three VL treatment centres in the visited area in Kenya and Uganda. One in **Kimalel** and one in **Amudat (Uganda)** and one in **Kacheliba.** Therefore, the distances to a health facility to get a diagnose and to a treatment facility to get treatment are large.
As a result, patients generally arrive at a treatment centre when they are very weak. In some cases, patients are diagnosed with VL do not even go or reach a treatment facility as it is too or the mother cannot leave the other children behind when taking one child.

Walking as the only means of transportation

Living in these communities means living very remote. In these areas, there is a lack of transportation and infrastructure, and almost no one owns a vehicle.

Hence, walking is the most common way to move around and get to a health facility.

In the case of referral to a treatment centre, a patient has to walk even further. Consequently, the lack of transportation and large distances make access to VL care challenging for patients.
In short, there are three options to get to a treatment centre: by foot, arranging a vehicle (and pay) or be picked up by a health aid organisation or health care facility. The latter option is dependent on the health care facilities and funding from aid organisations.
The road quality influences the ease to access to a particular area for both the patients as well as health organisations. In the areas which are visited during the field trip, only the 'larger cities' are connected through paved roads, leaving the communities with poor infrastructure. Therefore, four-wheel drives are not a luxury in the rural areas of Uganda and Kenya. Healthcare workers, aid organisations and doctors use them to get to the communities. However, patients do not have this luxury and are forced to either be picked up by a health facility or walk.

Climate conditions

Both the Baringo county in Kenya and the Karamoja region in Uganda have a dry climate. However, during the rainy season, heavy rain can result in temporary flooding's. These temporary flooding's results in impassable roads due to wild rivers and the lack of bridges to cross these rivers. Everyone who wants to cross the river will have to wait. It usually takes around 1 or 2 days, but can be longer if more rain falls. So, the climate does influence access to health facilities for both the patients and health organisations (and workers).

Actively seeking cases by health care

Some treatment facilities have an active role in finding new patients. This is mostly the case during clinical trials, where treatment facilities need patients that match a specific profile. Active case finding for clinical trial purpose happens in Amudat and Kacheliba Hospital during clinical trials.

In Uganda, the staff from Amudat hospital goes to the field approximately every two weeks to find new cases. A doctor and a CHW (who speaks the local languages) go to the field to either screen suspected cases at the communities or come and pick up patients from the communities who need care. This activity happens around the Moroto district in Uganda.
In other cases, healthcare workers or aid organisations travel to communities to set up screening days. These days are not VL specific but are set up to screen and treat people from communities on multiple diseases. These screening days are held around the Pokot tribes in Chemolingot (Nyakundi, 2018).

When these screening days are held depends on the urge. Aid organisations visit the communities in Baringo (Kenya) when there is an urgent need, such as a large number of children who need to get vaccinations. When KEMRI, UON and ICIPE join forces and go to the communities, they take multiple experts: lab technicians, doctors, translators and CHVs. They will ask the CHVs before the screening day to invite all people from the community to come to a central location for a screening day. The team will set up everything for a full day of screening.

Health care centres are often very basic equiped, Nginyand, Kenya.

Availability

Unfortunately, in these rural areas where VL is endemic there is often a lack of low resources which makes it challenging to test someone for VL. There is a lack of available resources in terms of knowledge and equipment.

Lack of knowledge

In most of the health facilities in rural areas in Kenya and Uganda, there is a severe lack of trained staff. One of the reasons for this is that most of the educated people go to urban areas and do not stay in the rural areas.

> ***"It is difficult to keep the doctors in the bushes"***
>
> Dr Patrick Sagaki, Amudat hospital

In addition, whether or not someone is able to query VL depends on the level of training of staff and if health education has been done in the region. Community Health Volunteers (CHVs) and Village Health Teams (VHTs) at the community level are generally not able to query VL. Even though CHVs and VHTs are the links between the health care system and the communities, they are typically trained for a limited number of scenarios and are not paid (which in some cases affects their commitment). Whether health care workers at the lowest health facilities such as nurses, midwives and Community health extension workers (CHEWs) can query VL depends on the fact if health education has been done.

As mentioned earlier in this Chapter, it can be complicated to recognise and diagnose a patient with VL due to differences in disease presentation between patients. Therefore, even when health education has been done, it is still questionable whether nurses, midwives and CHEWs are always able to recognise VL.

At larger health facilities or hospitals, lab technicians do an rK39 test. They are trained to test patients for VL.
A parasitological examination is only executed by well-trained staff such as doctors because of the risks involved in splenic and bone marrow aspirations. It depends on the skilled staff available at a treatment facility whether or not splenic or bone marrow aspiration is done.

Lack of resources: Medicines and equipment

Without the availability of equipment and diagnostic tests, it is not possible to test a patienf for VL. As became clear from the field trip, the supply chain of diagnostic tests is not constant. Therefore, diagnostic tests can get out of stock. Thus, getting rK39 tests to health care facilities is challenging, mainly because it takes a long time before tests are delivered at the facility. The Rk39 IT Leish tests have to come all the way from France which can take up to 6 months before they arrive at the designated facility.
Regularly, rK39 tests are out of stock at health care facilities. When this happens, facilities borrow them from each other or refer their patients to another health facility.
As donors fund all diagnostic test kits, health care facilities can lend and borrow diagnostic test kits from each other without it affecting their budget. Borrowing happens by making a phone call or just passing by a nearby facility.

At all facilities visited during the field trip, the data of the patients are collected in a paper logbook. This data generally includes the patient's name, age, gender and community. When a patient is diagnosed with VL, baseline measurements will be done. The result of these baseline measurements, such as the weight, presence of co-infections and HB value is written down in the logbook.

Affordability

As the governments of Kenya and Uganda do not pay for VL treatments or diagnostics, VL case management is entirely dependent on external donors. Therefore, donors have the power to decide how the money gets divided among different VL treatment centres. As became clear from the field trip, this division is often based on the experience of a treatment facility and if they are part of a clinical trial. This means that treatment facilities such as Amudat Hospital receive more money compared to Kimalel as they have more experience and are part of a clinical trial programme.

Donors fund all VL related costs at the facilities visited during the field trip. This results in 'free' VL diagnostics and treatment for patients. However, the affordability of VL care goes beyond direct health care related costs.

There are often additional costs for patients which are not directly related to the VL care itself

These costs include transportation costs, hospital fees et cetera. Even though treatment and diagnostics are free in most cases in Kenya and Uganda, patients are often forced to make additional costs. This can be somewhat difficult for patients. As VL treatment is long, the patients cannot do their daily tasks for almost three weeks, which might also affect their income.
These additional costs and the inability to work during the time someone is hospitalised are barriers that harm the health-seeking behaviour of VL patients.

Costs of diagnostics and treatment

The costs of one rK39 test are around $5-$6, which is too expensive for patients to purchase this themselves. Luckily for the patients, at the health facilities that are visited the diagnostic procedures are paid by donors. However, the costs of a diagnostic test are nothing compared to the costs of the current treatment. The current 17-day treatment for Visceral Leishmaniasis costs around 60000 Kenyan shillings (600 $) and requires hospitalisation for the full length of the treatment. These treatments are donor funded.

Acceptability

Acceptability is about the characteristics of the health services as well as the user's attitudes and expectations towards these health services. Often, patients in rural areas seek care when they are severely sick due to several barriers they will face.

Level of trust

Doctors and lab-technicians are well trusted in the area that is visited during the field trip. However, tribal languages can be an issue as most doctors do not speak the local language. The CHV's in Kenya and VHT's in Uganda are people from the community who are selected by the community to have a health responsibility and therefore trusted. Even though the community members trust them, CHV's and VHT's generally lack the training to query VL. Often they are only trained for a couple of scenarios such as malaria, diarrhoea and malnutrition.

In Uganda, there are so-called community health workers (CHW's), who get training from Amudat hospital intending to search for VL patients in the communities actively. After finishing the training, these CHW's have to visit all the communities in the area to get familiar with the people in the

VL patients at Amudat Hospital, Uganda.

communities and gain trust. These CHW's speak the local language which helps in communication but also makes them more trustworthy. Thus, when such a CHW diagnoses a patient with VL, it is likely that the people from the community will trust this diagnosis and referral.

Sample

In terms of the sample, patients generally do not like the prick that is required to take a blood sample. However, due to the high prevalence of malaria in these areas, people are used to getting pricked to give a blood sample to be tested for the disease. According to doctors from the field trip, splenic and bone marrow aspirations are painful and invasive procedures, which are disliked by the patients. In contrast, a blood sample through a finger prick is minimally invasive.

Perceptions of VL

VL patients generally experience a long and tough journey to access VL care. From the field trip, it became clear that this can affect the attitude and perception towards VL of other people living in VL endemic areas.

This has been supported by research which has been done in endemic areas in Sudan about perceptions on VL (also called Kala-azar)(Sunyoto et al., 2008). Sunyoto et al. (2008) found that people in VL endemic areas often believe that VL only appears after other diseases have been cured. Therefore, they think it is required to be tested and treated for many other diseases before it is possible to get diagnosed with VL.

"Kala-azar is a dishonest disease. If there is any other disease in your body, then kala azar will not appear in the test until you get rid of all the diseases you have."

[FGD, Male, Tabarak Allah]
(Sunyoto et al., 2018)

In addition, this research indicates that people in endemic VL areas in Sudan feel blessed when they finally get a VL diagnosis. People are congratulating each other with the result, which shows how 'hard' they think it is to get a VL diagnosis.

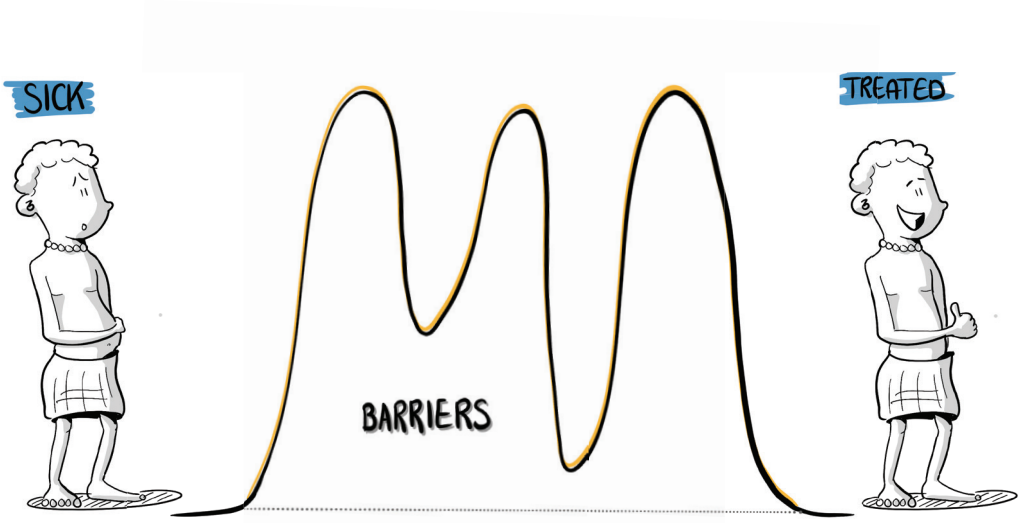
Interestingly, people in these VL endemic areas blame the disease for being difficult to diagnose, rather than the inaccessibility unreliability of VL diagnostics in the health care system.

"The demon accompanying kala-azar is the fact that the disease does not appear easily. So when you meet the doctor for diagnosis, you may feel tired and exhausted. You have nothing at home. Before you do the test, they say 'your medicines are this and that', and 'we test, you give the money' You have no money to pay them. Here you feel worried and anxious... Afterwards when kala-azar appears, you say thanks and praise to Allah. This is a blessing."

[FGD, Male, Bazoora]
(Sunyoto et al., 2018)

4.2 Challenges for VL patients

WHAT ARE THE CHALLENGES THAT VL PATIENTS FACE?



VL patients face many barriers to receive VL care.

4.2.1 Patient stories

Based on the insights gathered and stories heard during the field trip, seven fictional 'patient stories' are set up. The goal of these 'patient stories' is to understand the barriers patients face who suffer from VL (See Figure 20). One of the stories (Story II) can be read on the next page. See Appendix B-1 for the other stories.

From these patients stories, it becomes clear that there is a lot of variation possible between the journeys that different patients face. Thus, it depends on a patient whether their journey is relatively easy or tough. Even though every story is different, all patients who suffer from Visceral Leishmaniasis face a tough and long journey which involves a lot of barriers to getting access to VL care. By composing the stories, it became clear that every patient journey can roughly be divided into sevn phases which are described and visualised in more detail at 4.2.2.

These phases are:

1) **Getting infected**
2) **Being sick** (passive)
3) **Seeking care** (active)
4) **Getting diagnosed with VL**
5) **Getting to a treatment facility**
6) **Getting treatment**
7) **Being treated and going home**

How easy or tough the journey of a VL patient through these seven phases is, depends on several factors which are discussed here.

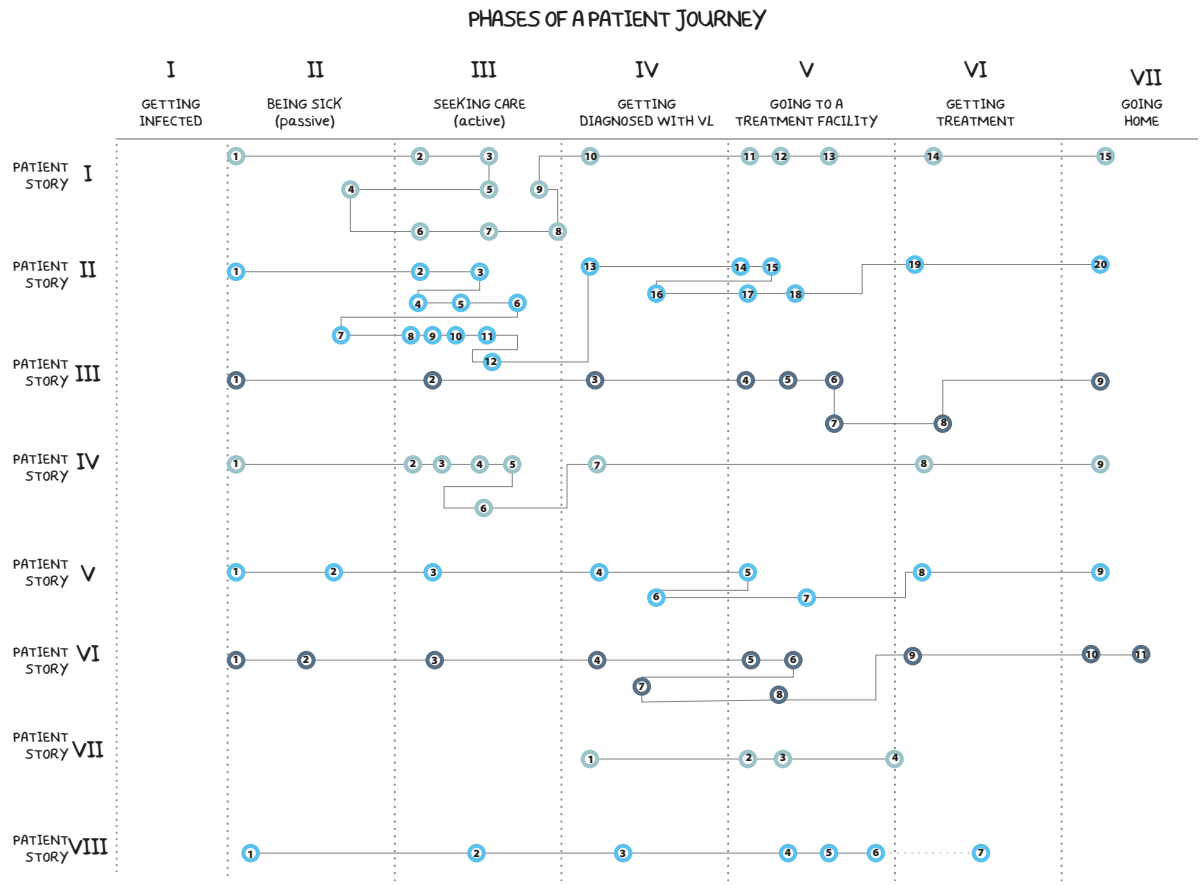


Figure 20: Seven fictional stories of VL patients.

Story II: A 5-year-old referred multiple times.

1. Someone is not feeling well for a while. This young girl is 5 years old and has a fever and general malaise for quite some time now.
2. Her mother assumes it is malaria and goes to the counter to get malaria drugs
3. She takes the medication for a couple of weeks but doesn't get better
4. Mom asks the neighbour what she thinks it is. But she doesn't know. So weeks pass by
5. Now she gets really sick. Her spleen starts to swell. So mother decides to take her to the dispensary
6. At the dispensary, they check her on malaria. They test and the results are negative. However, they are sure it is malaria, "I mean, all the symptoms are those of malaria". So they prescribe another dose and send the girl home.
7. She is not feeling better at all. She gets sicker and sicker
8. Mom takes her again to the dispensary and tells them: "this cannot be malaria, I need help"
9. The nurse agrees that it cannot be malaria and tests the girl on all kind of things (TB, ….) All of them give a negative result
10. So she is referred to the health facility. Mom takes the girl to the health Centre on foot.
11. At the Health Center, the girl is again tested for several things including malaria. But the nurse queries that it might be VL. So the patient is referred to Chemolingot to test.
12. Mom carries the child to Chemolingot which is 20 km further, so hours of walking.
13. When they arrive at Chemolingot, the girl gets tested and indeed she has VL. She is referred to Kimalel to start treatment
14. The staff calls to Kimalel and they send a car to come to pick up this sick 5-year-old. The mom goes back home as the kid can be taken by car.
15. The car comes and brings the girl to Kimalel.
16. When she arrives at Kimalel, she is again tested on VL with Rk39. The result is positive so she gets all other tests such as liver function et cetera before starting treatment.
17. However, her HB value is so low (less than 4.0) that she is sent to Kabarnet to get a blood transfusion before starting treatment.
18. She is brought to Kabarnet by car to get a blood transfusion. This takes about a week before she is back at Kimalel to start the treatment.
19. After a week, she is brought back at the Kimalel facility and starts treatment.
20. 17 days later she is brought back to her family, treated.

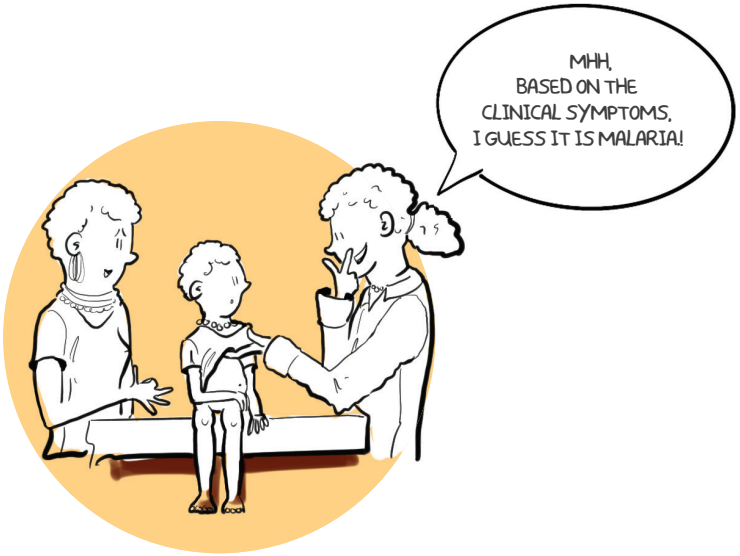


Figure 21: VL patients are often misdiagnosed with Malaria, Typhoid, or tuberculosis.

Misdiagnosing

Even when someone reaches a health care facility, the staff will most likely not be able to query VL. Instead, it is likely that they will diagnose a patient with another disease due to similarities in symptoms and lack of VL awareness (See Figure 21).

Often, VL is misdiagnosed due to the low degree of suspicion of health workers and the confusion between VL and other diseases.

Due to the high prevalence of other tropical diseases such as malaria, the chances that someone who presents with fever, general malaise et cetera has malaria are larger than VL. These misdiagnosed patients often receive medication for the disease they are diagnosed with. For example, many VL patients get diagnosed with malaria first which results in getting oral antimalarial without getting tested for it. Staff usually assumes it is malaria due to the high prevalence of this disease in the areas. In this case, a VL patient is likely to come back to a health facility when not feeling better after taking antimalarials for two weeks. Now, it is more likely that the staff at the health facility will query another disease and test. Due to many these misdiagnoses, it takes a long time before a patient finally gets diagnosed with VL.

Lack of health education

Health education influences the ability of patients, surroundings and health care workers to recognise VL. Therefore, health education can have a positive influence on the journey of VL patients. When health education is done in a region, it is more likely that health care workers and patients are aware of VL and can recognise VL in an earlier stage.
On the contrary, when no health education has been done in the region, it is less likely that staff at primary health facilities can recognise VL and test a patient for VL.

"Lucky patients are the ones that present where we have done health education"

Hellen Nyakundi

Late health seeking behaviour

According to Ms Hellen Nyakundi (Public health officer), there are many people in these rural areas that have VL and know they are sick but do not seek care because of the inaccessibility to a treatment or diagnostic facility. There are many reasons why people do not seek care such as the lack of money, not having anyone to leave their children to or the fear of other tribes which need to be crossed along the way. (Hellen, 2018).

This large number of barriers result in patients not going at all (and die) or going in a late stage when they are very sick. According to Dr Patrick Sagaki, VL patients are usually very ill when they arrive at Amudat Hospital (treatment facility). They are anaemic and usually have been screened for malaria and tuberculosis prior to getting referred to Amudat for VL treatment.

Distance

As already mentioned, the distance to a facility is one of the most challenging barriers that patients face when seeking care. As patients are usually very sick when finally seeking care, there is a severe risk that VL patient will not even reach the facility and die along the way.

Unequal man and woman decision-making power

As became clear from the field, women from the Pokot tribe have less decision making power compared to men. In most cases, the woman has to get approval from her husband before taking her child or herself to a facility. This lack of decision-making power affects the time it takes before a woman decides to either go herself or take her child to a facility.

Tribal conflicts

Another barrier which influences the access to health facilities are the tribal conflicts in the visited VL regions. The Pokots and the Turkanas in Kenya and Uganda are often in a conflict which makes it unsafe for both tribes to cross the area of the other tribe. Tribal conflicts result in people from communities not seeking health at all or going to another facility to make sure they do not have to cross an unsafe area. Dr Patrick Sagaki mentioned that tribal conflicts result in the fact that Pokot patients from Kenya often feel more save going all the way to Amudat (Uganda) instead of going to Kimalel (which is closer and in Kenya).

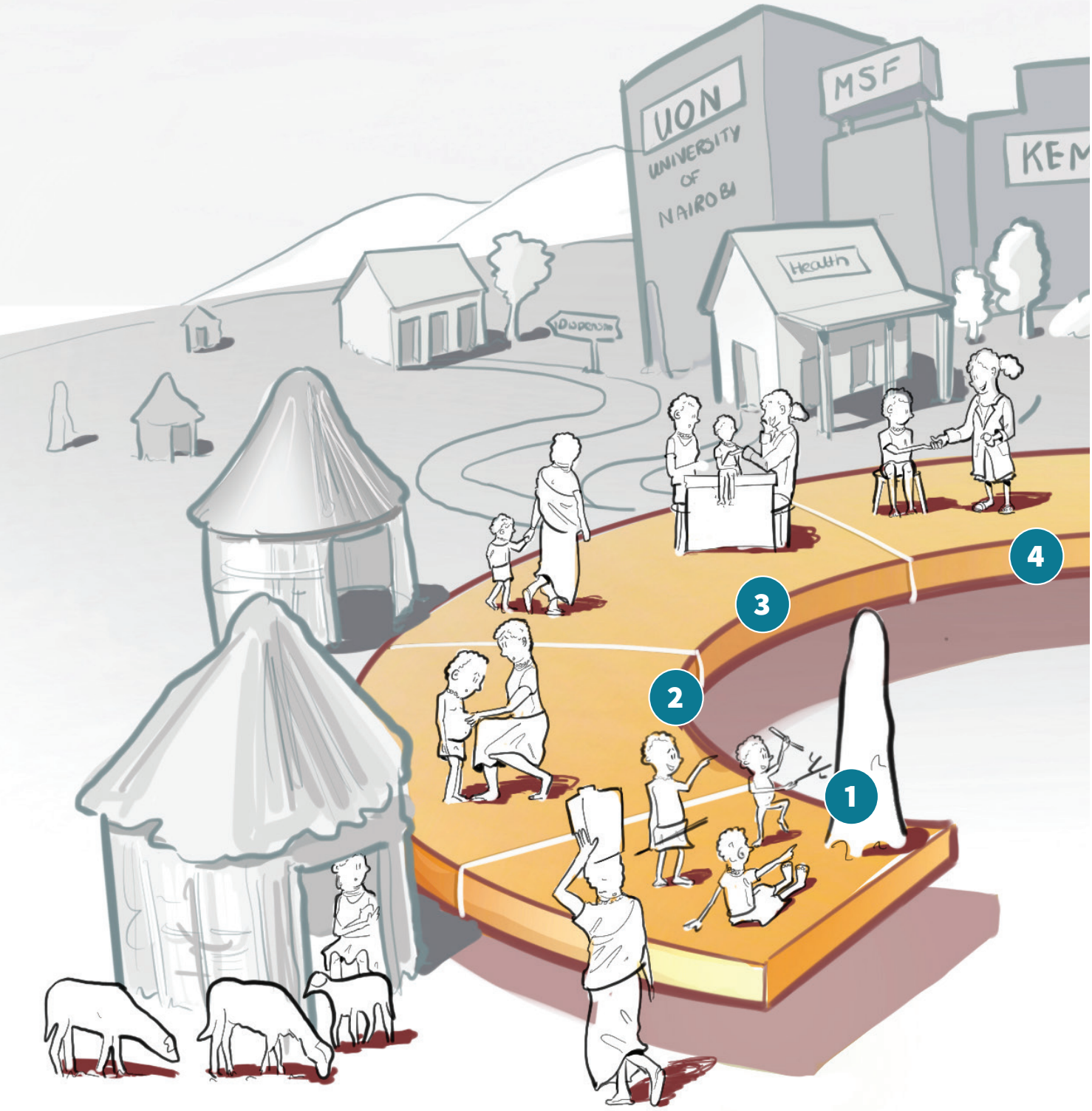
Seeking care through traditional healing

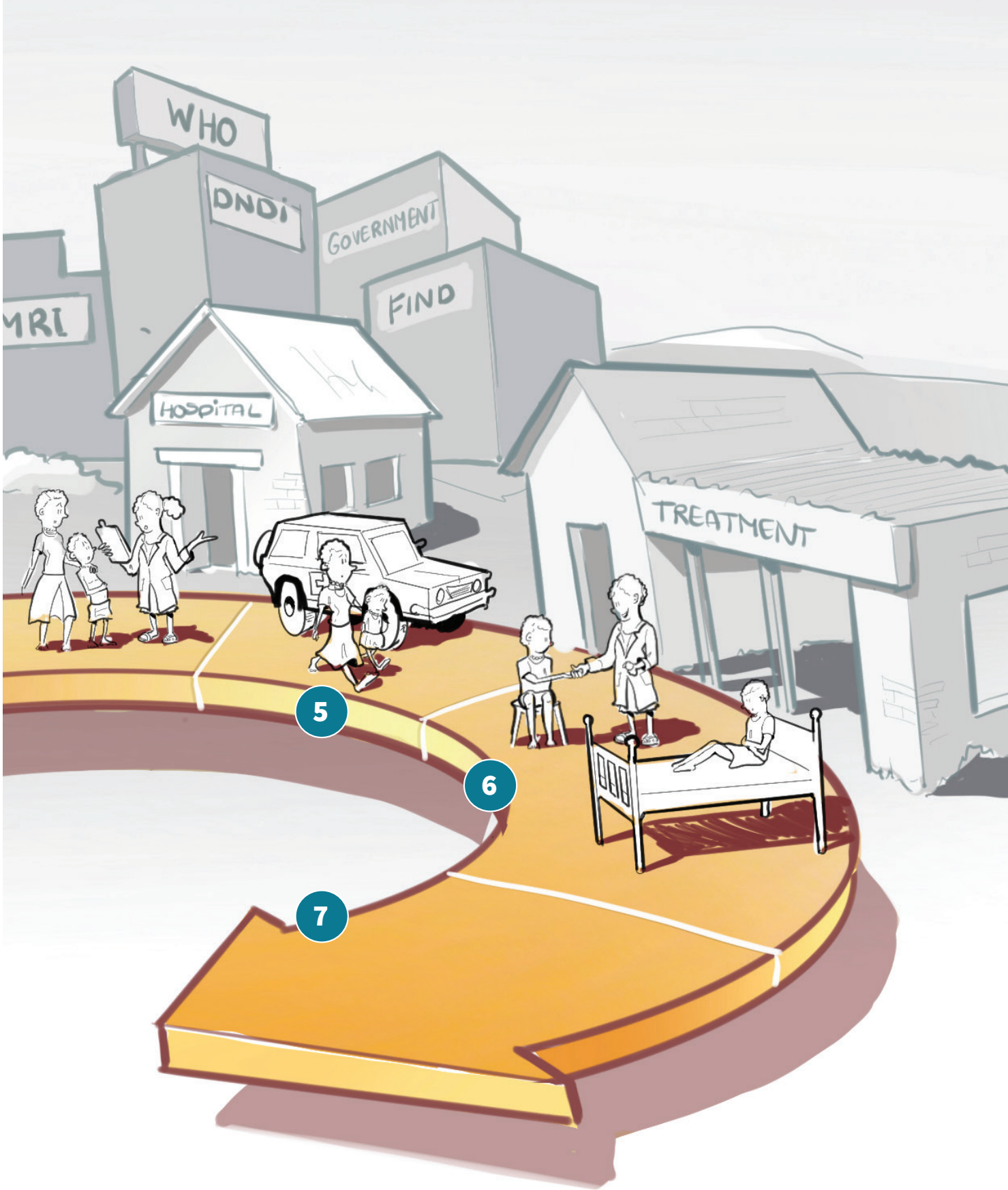
From the field trip, it became clear that VL patients often go to a traditional healer before seeking care at a health facility as traditional healers are often closer located to home. Traditional healing frequently releases some of the symptoms for a while, but will not cure VL. Ultimately patients still have to go to a health facility. Hence, traditional healing delays the process of getting treatment.

Unavailability of staff

From the field trip, it became clear that lab-technicians regularly leave the health facility to go to the field for 1 or 2 days. Due to the shortage of staff, there are often no other staff members who can take over their tasks. Thus, during these days there is no-one who will be able to do a diagnose (rk39) at that facility, so patients have to wait and suffer until the lab-technicians are back.

THE STEPS THAT VL PATIENTS HAVE TO TAKE TO RECEIVE VL CARE.

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4.2.2 Barriers for a patient

An overview is created (see Figure 22) which combines the insights from the patient stories with those of the access to VL care framework. The goal of this visual and explanation is to understand the challenges that patients face from being sick to being treated (and hopefully cured).

1 At Home: exposure to vectors

The affected people have a pastoralist nature, which means they are mobile and mainly live off their cattle. Living in communities means living very remote. Depending on the tribe there are different traditions. In general, a Pokot man has 3 to 5 wives whom all have their hut in a compound with around 5-10 children. Life is very basic out here; the climate is harsh, and there is hardly food or water. The wives are responsible for taking care of the children, doing the household and fetching water. The children usually play or help their mom. The boys are in charge of the cattle.

Their houses is often surrounded by ant hills, which function as a breeding nest for sand-flies. The houses are often poorly built and do not give any protection which increases the risk of being exposed to Leishmania infected sand-flies. The boys and men sleep outside in the Pokot tribe, whereas in the Tucana tribe, the girls sleep outside. Sleeping outside increases the risk of getting infected because of exposure to sand-flies.

2 Being sick (passive)

When infected with *Leishmania*, it depends on someone's immune system whether or not that person develops VL. In case someone falls sick, it is common to try to fix it in the community by traditional healing. The first symptoms are often fever, general malaise and weight loss. In a later stage, other symptoms appear such as spleen and liver enlargement and anaemia.

3 Seeking care (active)

When someone starts to become very sick, it is time to seek care. Usually, it takes a long time before someone decides to go to a facility. In most cases, someone is very sick (it's a matter of life or death) before they finally go. Unfortunately, seeking care does not result in immediately being diagnosed with VL. The unawareness of VL and inaccessibility and unreliability of VL diagnostics make it difficult for a VL patient to get diagnosed with VL.

4 Getting diagnosed with VL

Depending on the facility, there are several ways to test someone for VL (Chapter 3.2). In most cases, a VL diagnosis is a combination of clinical signs and symptoms and the rapid diagnostic test rK39. Lab-technicians mostly use this diagnostic test. However, due to the short shelf life of the rK39 (one year) and the lack of a constant flow of VL patients, rK39 tests are often expired before they are used. In addition, rK39 tests are antigen-based which makes them unsuitable for testing relapsed or re-infected VL patients. Also, rK39 does not perform very well in East Africa due to low specificity and sensitivity. At some treatment centres, such as Kacheliba and Amudat Hospital, parasitological examinations are done as a confirmation before treatment. However, not all treatment facilities have the resources and skills to do a parasitological examination.

5 Getting to a treatment facility

After a patient is diagnosed with VL, the patient is referred to a treatment facility. The distance to a treatment facility depends on where the patient is diagnosed. Moreover, it depends on the VL treatment facility whether transportation is arranged to come to pick up the patient. For example, at Amudat hospital patients are picked up from the communities as they need specific patients for clinical trials.

According to Hellen Nyakundi, patients often get diagnosed with VL in Chemolingot (Kenya) but then do not go to Kimalel health centre for treatment. The reason for not going is the distance of 70 km between Chemolingot and Kimalel.

6 Getting treatment

In most cases, VL patients arrive at the facility when they are very sick and suffer from severe anaemia and a low HB-value. According to Koert Ritmeijer from MSF, in routine, clinical signs and symptoms are combined with a serological test such as rk39, and with no history of VL, this is enough confirmation to put a patient on treatment. Also, a series of baseline measurements are executed to adjust the treatment to a specific patient. In Kenya, in case patients have an HB value lower than four, they have to go to Kabarnet hospital to get a blood transfusion before starting treatment in Kimalel. When a patient needs to get blood transfusion at another

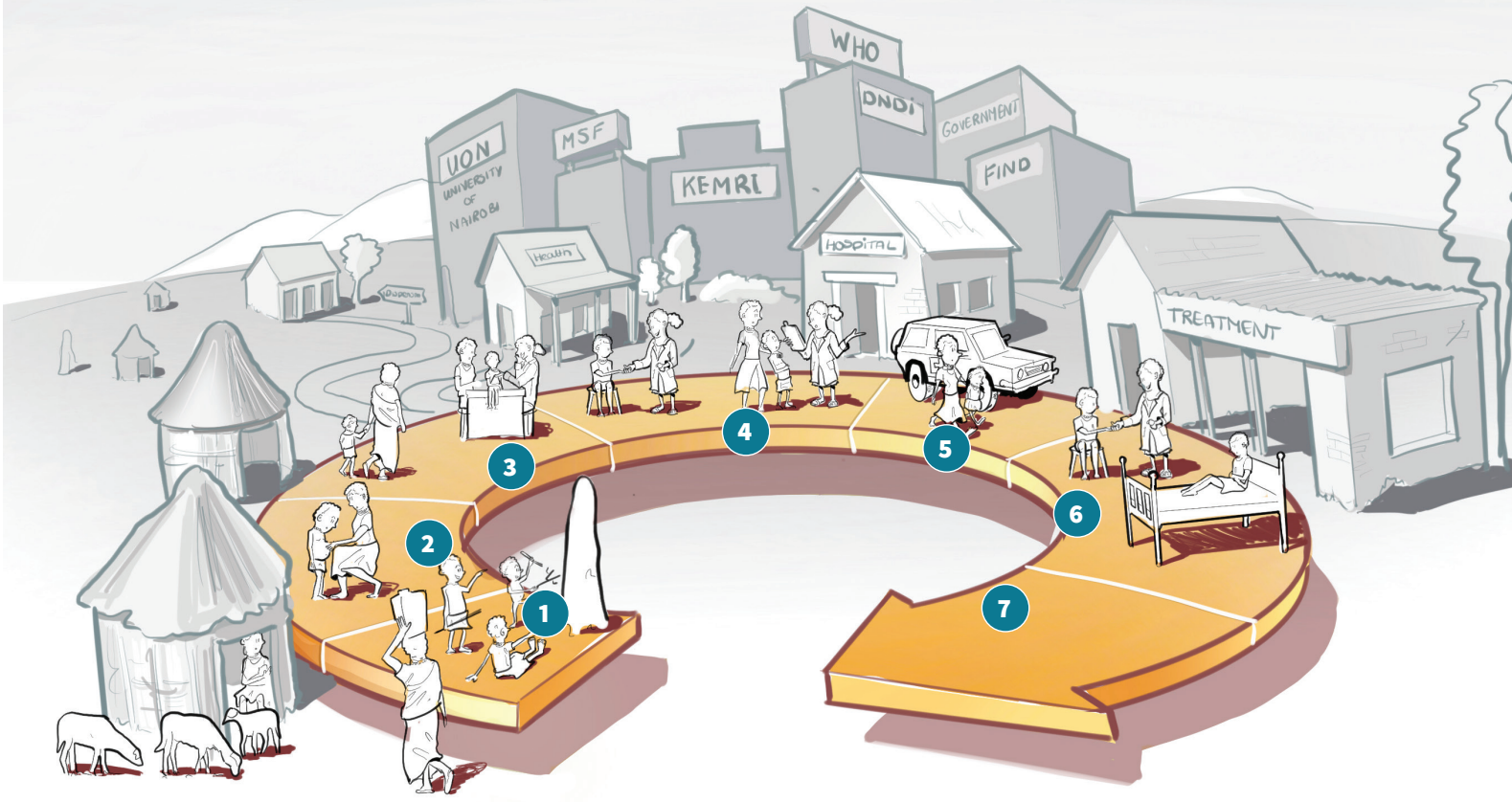


Figure 22: Overview of the steps which a patient needs to take to receive VL care.

hospital, the treatment centre arranges transportation. In the case of clinical trials, patients get a confirmation diagnosis through tissue aspiration prior to the treatment. Treatment consists of dual injections for 17 days (see Chapter 3.2 for more information about the treatment). Patients do not have contact with their families while they are being treated. Unfortunately, this family often does not come to pick up the child when he or she died during the treatment.

7 Being treated and going home

When patients do not present any clinical signs anymore and have completed the 17-day treatment, they are declared as cured and sent home. Unfortunately, being treated does not always mean that the patient is cured. According to Koert Ritmeijer (2018), approximately 5 to 10% of the cases in East Africa results in relapses. Yet, there is no diagnostic test which can indicate if someone is really cured.

Patients go home either by foot or car. The latter is possible when a hospital receives money to arrange transportation to pick up and drop off patients.

SECTION III

Technical principle

Chapter 05: Technical principle

This section of the report focusses on getting an understanding of the technical principle which is being developed as a starting point of the project. Chapter 5 gives a more in-depth understanding of the features of the technical principle. In addition, the benefits of the technical principle compared to current diagnostic practices are made explicit based on the insights and knowledge gathered in Section II: Current context.

The technical principle is being developed in the lab at the Faculty of Applied Sciences at the TU Delft.

SECTION III Technical principle

Chapter 05

Technical principle

This Chapter explains the technical principle currently being developed at the Faculty of Applied Sciences at the Delft University of Technology which serves as the starting point of this project. Besides explaining what the technical principle is and in which phase of development it is, this chapter the benefits of the technical principle compared to current diagnostic practices.

5.1 Technical principle

HOW DOES THE TECHNICAL PRINCIPLE WORK AND HOW FAR IS THE DEVELOPMENT?

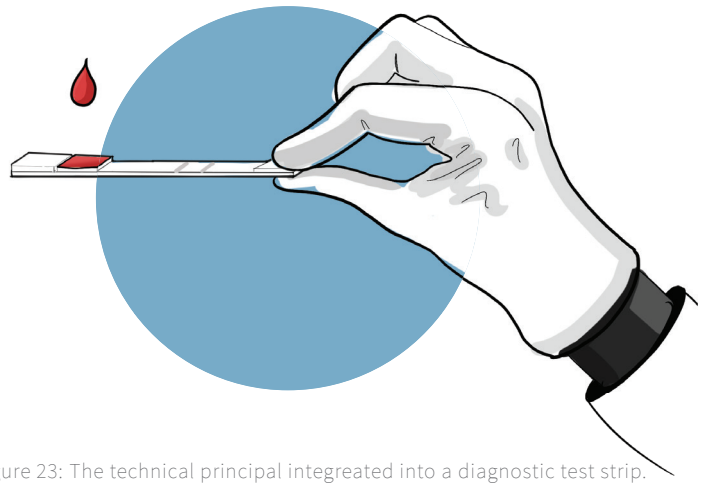


Figure 23: The technical principal integreated into a diagnostic test strip.

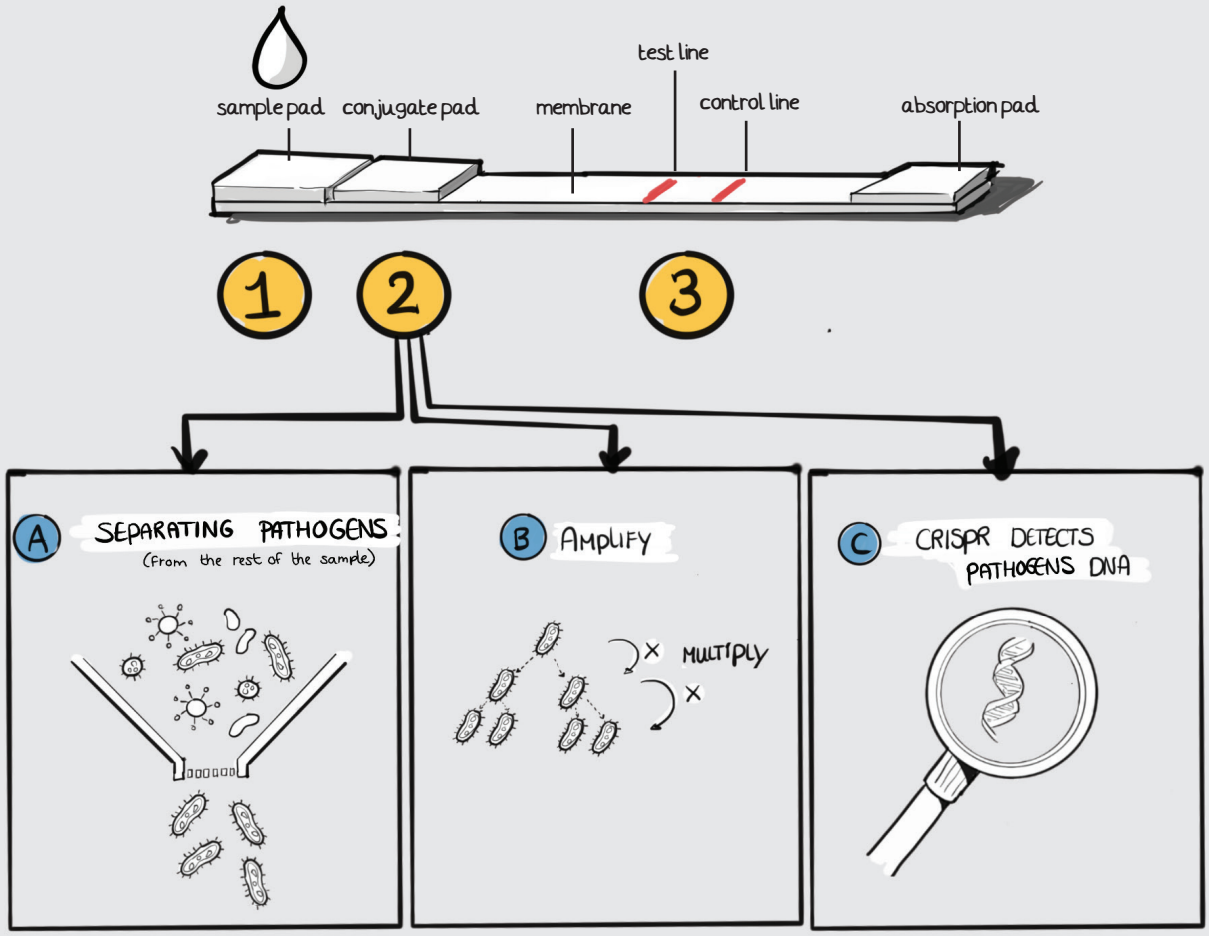
5.1.1 What?

When infected with the *Leishmania* parasite, pathogens are generated. As there are multiple species of *Leishmania* parasites, it depends on the species whether the person gets visceral or cutaneous Leishmaniasis. In Kenya and Uganda only visceral leishmaniasis was seen, the applications of the technical principle are focussed on VL. The technical principle which is being developed at Applied sciences involves a CRISPR/Cas9 system which will enable detection of the DNA of these pathogens from a sample. ("Testing of parasitic DNA", 2016). The aim is to use this technical principle for a point-of-care diagnostic test such as a Rapid Diagnostic Test (RDT).

5.1.2 How does it work?

This DNA detection technical principle will be integrated into a diagnostic test strip (Figure 23) which is similar to those of lateral flow assays. The working of this technical principle on a diagnostic test strip is explained in four steps which can be seen in Figure 24.

Figure 24: Overview of the steps which a patient needs to take to receive VL care.



1 First, a sample is added to a sample pad. This sample pad absorbs the sample. Currently, the technical principle is simultaneously being developed for two sample types: blood and urine.

2 Next, the sample migrates to the conjugate pad.
In case of an antigen-based RDT (such as the current rk39), the conjugated pad stores the antigens and labels. If the pathogen of Leishmaniasis is present, the immobilised conjugated antigens and labels with bind to the target and continue to migrate along the test (Abingdon Health, n.d.).

However, as this technical principle is based on DNA instead of antigens, there will be no antigens stored on the conjugate pad. Instead, the pathogens causing the disease are extracted and recognised.

A) This is done by separating the pathogens from the rest of the sample.
B) Amplify (multiply) until there is sufficient DNA which can be detected. In case there is insufficient DNA (few circulating pathogens) there is a need for amplification. This can be due to a small sample size in case of droplet of blood (10 to 20uL blood) or an infection in a very early phase.
C) After DNA has been extracted, it will be recognised through the CRISPR/Cas9 system.

3 Lastly, the detection of this DNA and specific reaction will initiate a chain reaction which produces a visible colour readout. This readout consists of a control line to confirm if the test is working as intended followed by a test line which indicates the presence or absence of the specific pathogen.

Housing

The technical principle has the potential to be used as a Rapid Diagnostic test, which are famous for their simplicity to use and have the primary function to confirm the presence or absence of pathogens. In the case of this technical principle, the readout will be based on qualitative results, which means that the test readout will indicate either the presence or absence of the specific pathogen. These dipstick tests occur in all kinds of formats. The tests can be integrated into a housing (cassette) with the aim to support functionality and user-centric design goals ("Lateral Flow Rapid Diagnostics: How Does a Lateral Flow Device Work?", n.d.).

Sample

As the technical principle is broadly applicable it can be used for different sample sources. As mentioned earlier, blood and urine are both being explored at the lab. If both these samples are proven to be working, the suitability and acceptability of the samples in the context will determine which of the samples is preferred. For example, urine is a non-invasive sampling alternative compared to a droplet of blood which is a bit more invasive. However, a droplet of blood is still minimally invasive compared to vein puncture, bone marrow and splenic aspiration. However, it depends on the setting in which the diagnose is done whether or not a non-invasive alternative such as urine is more suitable than a blood sample.

Which sample is most suitable for diagnosing VL depends on several context variables:

Resources available to get the sample

Based on the field trip, it became clear that in most diagnostic settings there are no toilet facilities to give patients privacy to urinate. This lack of toilets can have a negative influence on the willingness of the patients to give this sample. In addition, taking a urine sample requires additional resources such as cups to collect the urine and cleaning tools. Similarly, taking a blood sample requires some resources such as an alcohol pads, gloves and tissues. However, as most RDT's are blood-based, resources to do a blood-based diagnose are often available even at low resource settings.

Environment impact of the sample (and disposal facilities)

The environmental impact of the sample should be considered as there is (clinical) waste involved. In case of a urine sample, this can be a cup which either needs to be cleaned or disposed. In case of a blood sample there is clinical waste which should be carefully disposed to avoid contamination.

Expertise and training required to work with the sample

Based on the field trip it became clear that taking a blood sample does not require a lot of expertise. However, training is important as blood samples should be carefully handed to avoid contamination.

Ability of the patient to give the sample
It is important to consider whether the patient is able to give a certain sample. For example, infants or elderly are often unable to give a spit sample. Similarly, for a urine sample it should be considered whether a patient has enough liquid in the body to urinate (dehydration).

Acceptance to give and use the sample
It is important to take into account what kind of samples are accepted by the patients. For example, from the field trip it became clear that people are used to getting a finger prick as most RDT's used for other diseases are blood based.

Technical feasibility of this sample: is there (enough) DNA in it?
It is important to consider whether a sample contains sufficient DNA so the technical principle can detect the pathogens from this sample.

5.1.3 Phase of development

Based on the technology readiness levels (TRL) which describes the maturity level of a particular technology or technical principle, this technical principle can be labelled as a phase two development (of a nine-point scale). Phase two means that the technical principle is in its proof of principle phase.

The technical principle development can be divided into several steps, which are currently being developed simultaneously.

Step 1: Extraction of the pathogens DNA from a human sample. Amplifications might be necessary when finding out that there is less DNA in the sample than priory expected.

Step 2: Specific detection/reaction (second step in detection) - CRISPR/cas9 based.

Step 3: Visual Readout with a control and a test line. In case there is insufficient DNA: few circulating pathogens, there is a need for amplification in this step as well. This can be due to a small sample size in case of droplet of blood (10 to 20uL blood) or an infection in a very early phase.

At the moment, these steps work individually, and it is possible to get test results in three hours with advanced lab equipment. However, further optimisation is required to combine these steps into a single diagnostic test strip which works independently on this lab-equipment. Also, optimisations might be needed when finding out that the samples contain less DNA than priory expected.

VL specific as first disease

As the diagnostic test is based on direct DNA detection it should be able to recognise the pathogens causing the disease, which in this case will be the *Leishmania* parasite. Therefore, the technical principle will first be optimised and made specific for different forms of Leishmaniasis. As mentioned earlier, the technical principle is broadly applicable and so can be used for all kinds of diseases. Hence, when the technical principle is proven to be working for detecting *Leishmania* parasites, it can be adapted to diagnose other diseases too.

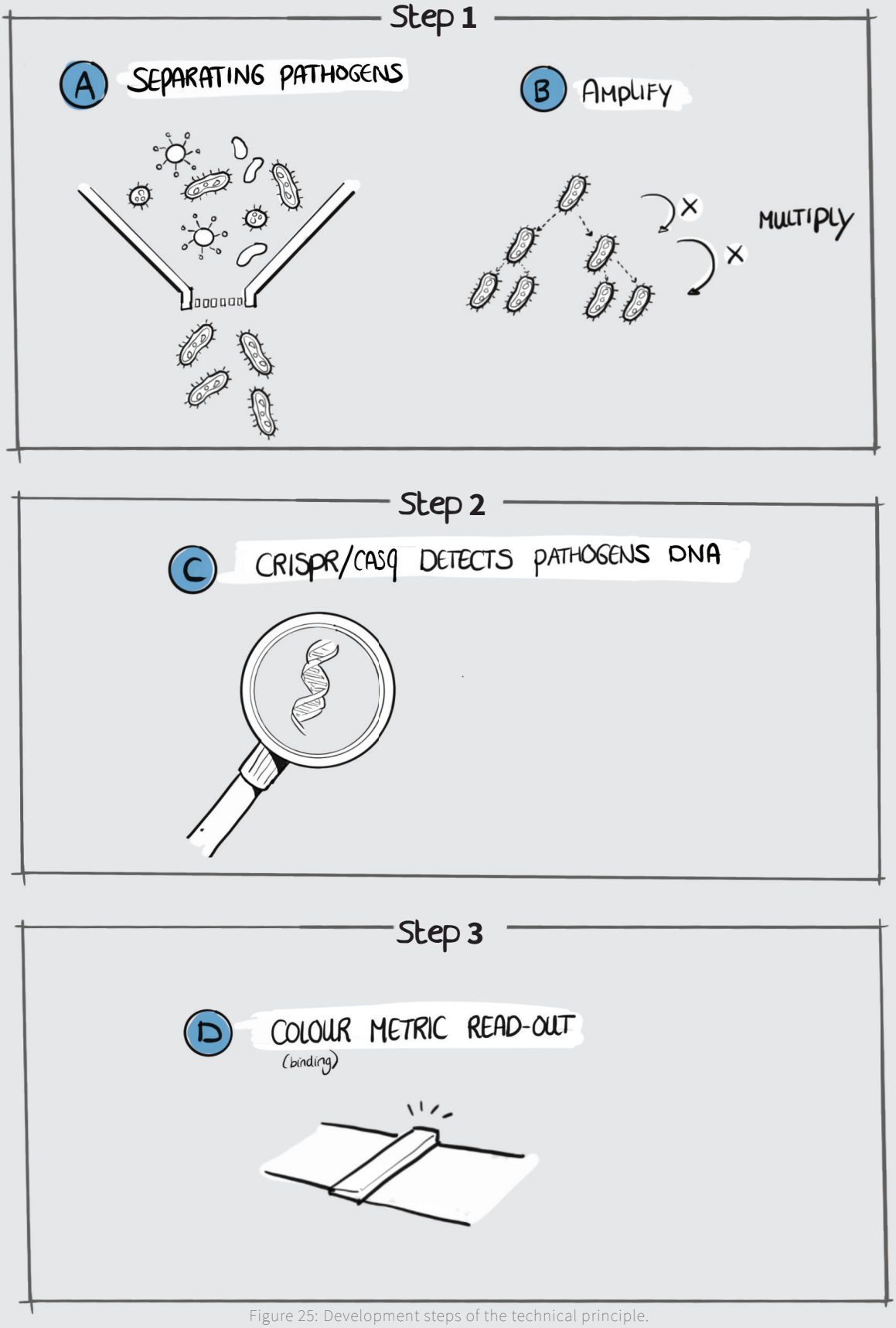
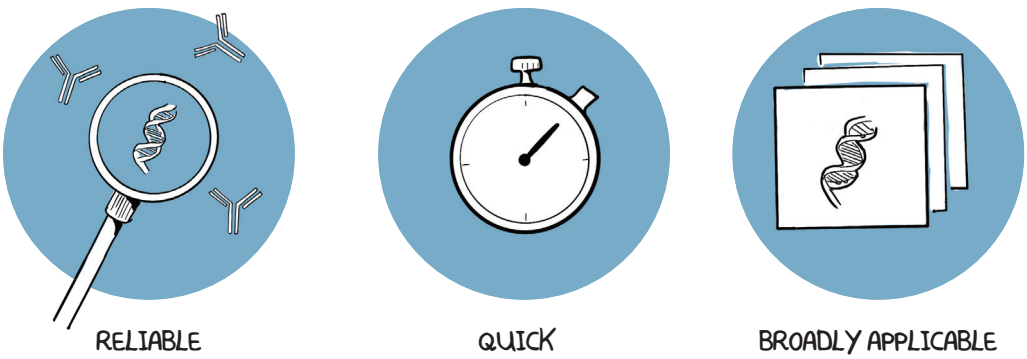


Figure 25: Development steps of the technical principle.

5.2 Benefits of the technical principle

WHAT ARE THE BENEFITS?

It is important to understand the added value of this technical principle compared to current diagnose practices. Compared to current diagnose practices (See Chapter 3.1), this technical principle has two distinguishing characteristics.



Reliable

Instead of detecting antigens as most rapid diagnostic tests do, this technical principle is based on **DNA detection.**
This enables **reliable** test results **independent of someone's immune system**. Thus, it does not matter if someone has just been infected, is relapsed or re-infected.

Thus, DNA detection results in:

- Reliable test results in **early phase** after a person gets infected with *Leishmania*.
- Reliable test results when testing people with **relapses** and **re-infections** of VL.

Quick & broadly applicable

Other advantages of this technical principle are that it is **quick** and **broadly applicable**.

As the technical principle is broadly applicable, it has great promises to detect not only VL but other infectious diseases in low resource settings worldwide.

Due to the broad applicability, it is possible to:

- **Multiplex** to test somone for multiple diseases simultaneously.
- create **seperate diagnostic tests** which are suitable for other diseases.

SECTION VI

Future application

Chapter 06: Implementing the technical principle in a diagnostic setting
Chapter 07: The diagnostic setting
Chapter 08: Proposals for future diagnostic tests

This Section of the report aims to integrate the knowledge from SECTION II: Context and SECTION III: Technical principle to come up with future applications of the technical principle in the context of VL.
This Section is divided into three Chapters. In Chapter 6, scenarios are created which each represent promising ways to implement the technical principle in the context of VL. Based on the feedback from MSF and other stakeholders the two most promising scenarios are chosen. Chapter 6 describes the reasoning behind this choice. These selected scenarios are detailed in Chapter 7, which the aim to see how the diagnostic setting influences the features of the diagnostic test. In Chapter 8, requirements are created. The requirements are categorised which helps to translate them into several diagnostic tests designs which are suitable for its diagnostic setting.

CURRENT Situation

IS THE CURRENT SITUATION OF VL LIKE IN KENYA & UGANDA?"

PRO'S & CONS OF RK39

(+) (−)

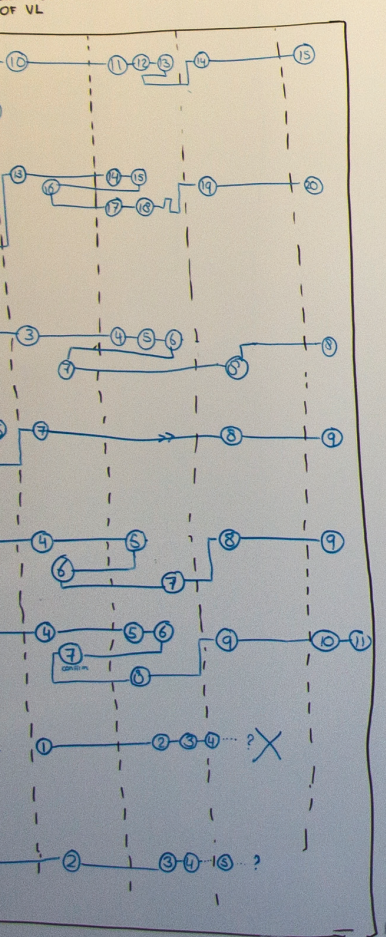
STORIES

3 GETTING CONFIRMATION OF VL

4 TAKING ACTION

5 GETTING TREATMENT

6 GETTING HOME



WE CAN MAKE A BETTER DIAGNOSTIC KIT.

BUT WHO WOULD (and who wouldn't) BENEFIT FROM IT?

? What are we actually trying to solve?

VECTOR CONTROL & PREVENTION

DIAGNOSE

TREATMENT

FUTURE OF CRISPR

WHAT COULD THE FUTURE LOOK LIKE WITH THIS NEW KIT?

SCENARIO'S

HOW COULD WE MAKE AN IMPACT WITH THIS DIAGNOSTIC KIT?

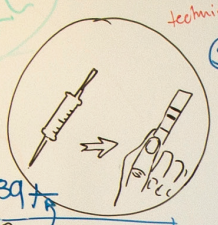
& what would the consequences of this be?

ALL

technician looses job

boost preparedness

1



Cheaper diagnostics

No expensive BM or splenic

only 1x test at POC results will be forwarded

> Helps with lack of staff issues!

RK39

KIT AS REPLACEMENT OF BONE MARROW OR SPLENIC ASPIRATION

@ Health Facilities (Amudat & Kimaleli)

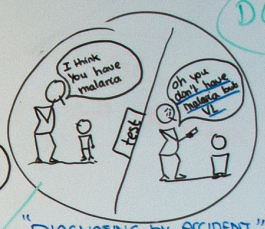
> DONOR & FACILITY WOULD BENEFIT

all P.O.N closer

DOCTORS

HC / HF

4



"DIAGNOSING BY ACCIDENT"

INTEGRATING KIT WITH MALARIA JOURNEY

OR OTHER DISEASES!

@ Health Facilities & dispensaries

PATIENTS PERSPECTIVE

DONOR: Less $ wrong medications & tests.

malaria foundation

GOVERN ELI PROG

multiple

EVERYONE GETS TESTED

Awareness

multiple diseases

direct treatment

2

increasing nr of cases

$ more expensive

• SHOULD GO HAND IN HAND WITH VECTOR CONTROL!

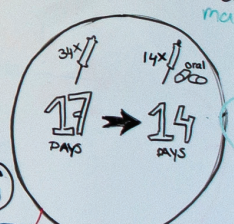
• potentially could decrease spreading of disease

ELIMINATION

KIT AT THE SCREENING DAYS

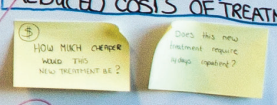
(incl asymptomatic cases)

5



NEW

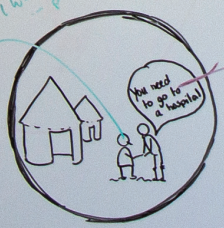
REDUCED COSTS OF TREATMENT



SELECT +/- ② FOR GRADUATION

Asymptomatic Low early stage

I want to play games



3

From treatment Perspective, would it be possible to treat all these cases?

$ would it be cheaper to treat if people in better condition $ early treatment?

→ better recovery

→ more productive

PATIENT PERSPECTIVE:

TESTING AT THE LOWEST LEVEL

@ COMMUNITY LEVEL

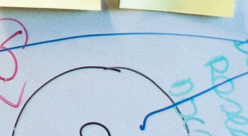
"Giving them a reason to go to a facility"

VHT'S OR CHV'S

Patient → Recovery

Relapse

ALL

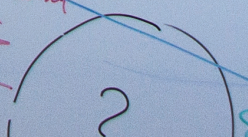


Follow up ~~TEST~~

Cure

DONORS Reconditions DISEASES

Read Out — Reliable — Data



NO AIRPORT NRW

RICH PEOPLE

Session to identify ways to implement the technical principle in the context of VL.

SECTION IV FUTURE APPLICATION

Chapter

06

IMPLEMENTING THE TECHNICAL PRINICPLE IN A DIAGNOSTIC SETTING

The goal of this Chapter is to identify promising ways to implement the technical principle in the context of VL by creating scenarios. Each scenario represents a way of combing the benefits of technical principle (SECTION III) in the context of VL (SECTION II).

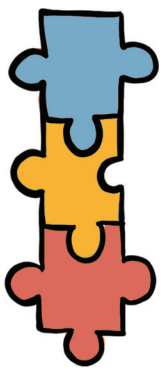
During a 3-hour session with the team from Applied Science and IDE, seven promising scenarios are created (See Appendix C-1 for more information about this session). Each of these scenarios is explained and visualised in this Chapter. Based on the feedback from experts from Médecins Sans Frontières (MSF) as well as stakeholders met during the field trip, the two most promising scenarios are selected. This selection is based on three aspects: the feasibility for the technical principle, the suitability in a diagnostic setting in the context of VL and how well it matches a local need.

6.1 Scenarios

HOW TO COMBINE TECHNICAL PRINCIPLE BENEFITS IN THE CONTEXT OF VL?

There are multiple ways to implement the technical principle in the context of VL. Therefore, several scenarios are created during a 3-hour session with the team of IDE and AS. More about this session can be found in Appendix C-1.

Each scenario represents a unique way of combing **the features of the technical principle** into a diagnostic test which **fits the diagnostic setting** in the context of VL and **matches a local need**. Therefore, the scenarios vary based on these three elements:



WHAT ?
The **benefit of the technical principle** in the scenario.

WHERE ?
The **diagnostic setting** in the context of VL in which the scenario takes place.

WHY ?
The **local need** in VL case management will be fulfilled with this scenario.

When looking at the diagnostic setting, there are five critical diagnostic setting variables which distinguish one diagnostic setting from the other (Figure 26). These diagnostic setting variables are further explained in Chapter 7 and are taken into account when creating the scenarios.

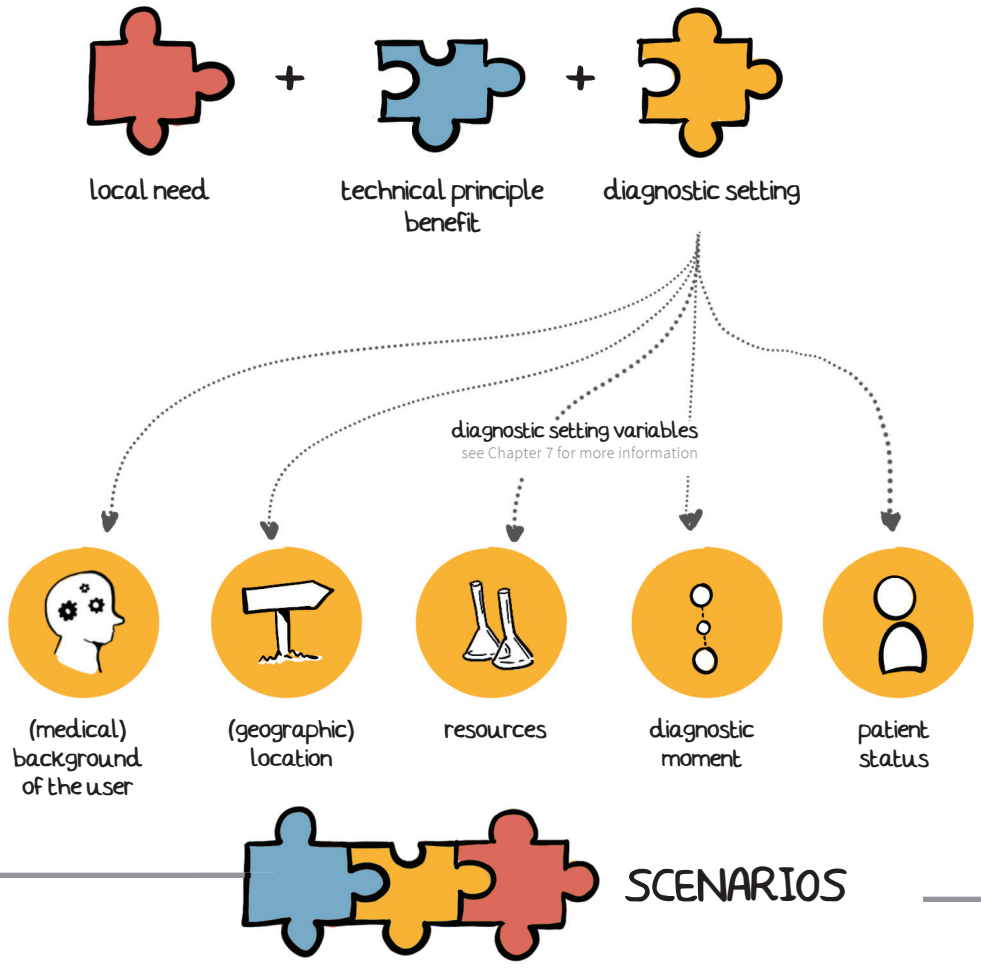
1) the (medical) background of the user *
2) the geographic location
3) the resources available at the location
4) the diagnostic moment
5) the patient status

**the person who is testing a suspected case for VL.*

Overview of Scenarios

An overview is created (See Figure 27) which shows the composition of each scenario based on the three elements: the benefits of the technical principle , the fit in a diagnostic setting and the local need it fulfils.
The first row describes the 'local' needs which are addressed with each scenario.
Secondly, each scenario implements the technical principle to a diagnostic setting. Therefore, the second column of Figure 27 shows which benefits of the technical principle are applied to each scenario. A description of the application of these benefits can be found on page 94.
Lastly, the diagnostic settings vary between scenarios. Thus, the third column of Figure 27 shows how the scenarios differ from each other based on the diagnostic settings. More information about diagnostic settings and variables can be found in Chapter 7.

Figure 26: Every scenario is a combination of a benefit of the technical principle in a diagnostic setting which fits a local need.



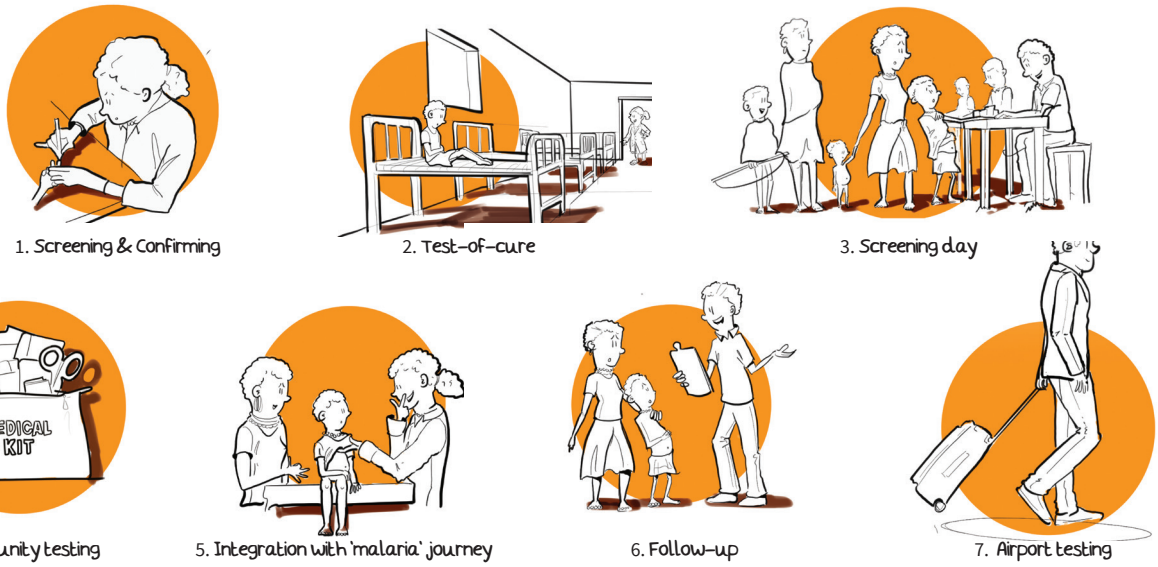
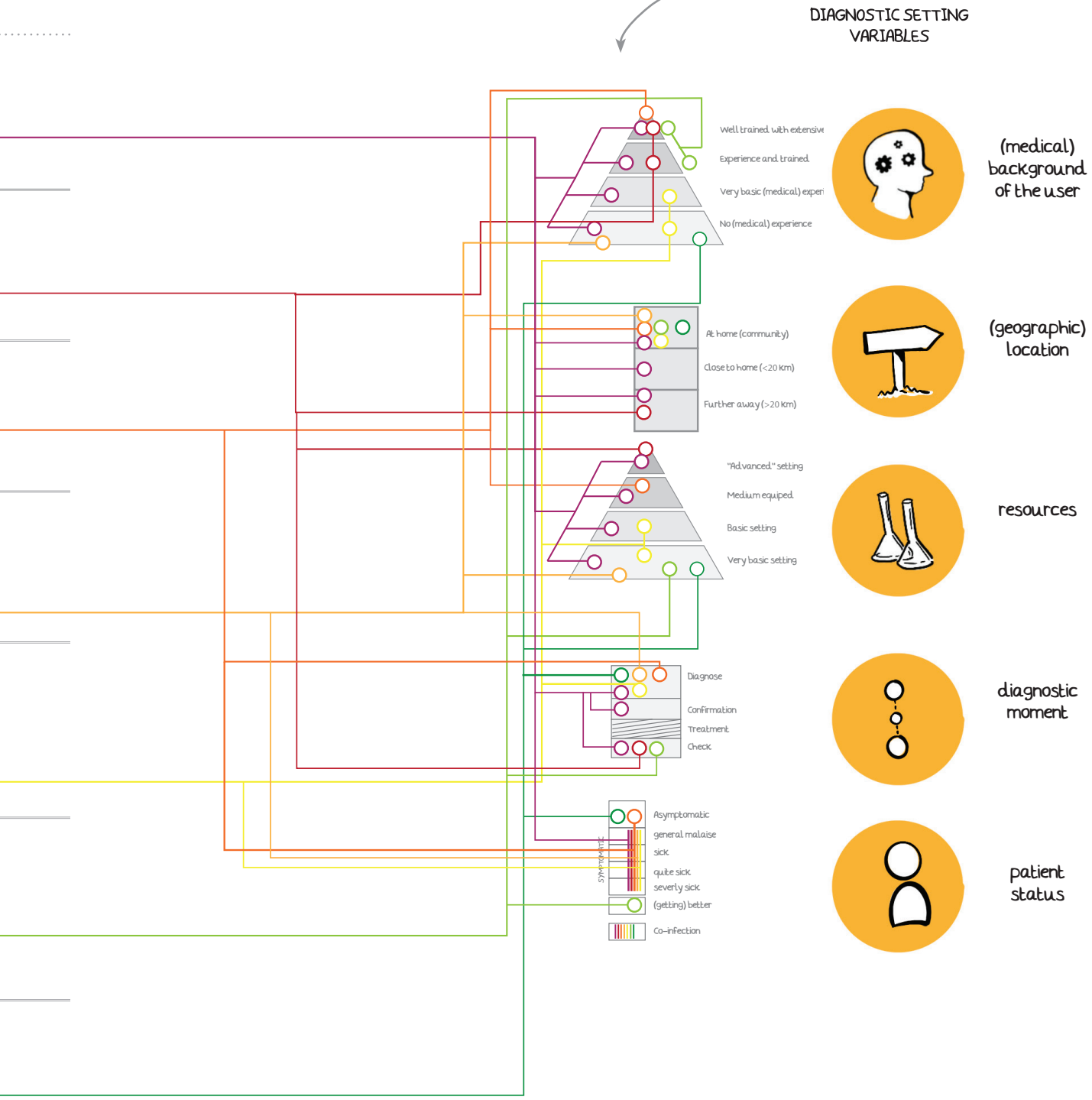


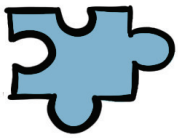
Figure 27: Overview of the three 'pieces' of every scenario.

SCENARIOS	LOCAL NEED	TECHNICAL PRINCIPLE BENEFIT * SEE THE NEXT PAGE FOR THE DESCRIPTION	DIAGNOSTIC SETTING
 1. Screening & confirming	There is a need for **more reliable VL diagnostics** which can be implemented at every diagnostic setting to be **accessible** to the people.	1 Early diagnosis 5 Confirmatory test	
 2. Test-of-cure	There is a need for a diagnostic test which can be used as a test-of-cure which is not so **invasive** and does not require advanced resources and skills. *Reason: Currently, the only way to test a patient of being cured is through invasive tissue aspirations.*	3 Test-of-cure 4 Relapse & re-infection	
 3. Screening day	There is a need for a diagnostic test which can be used to screen people in communities on various fever-related diseases simultaneously. *Reason: VL affected communities are generally affected by many diseases.*	1 Early diagnosis 2 Diagnosis of asymptomatic cases 4 Relapse & re-infection 6 Multiplexing enables detection of co-infections	
 4. Community testing	There is a need for a diagnostic test which can be used by CHV's or VHT's to test someone with fever-related symptoms on multiple diseases simultaneously. *Reason: VL diagnostics are not easily accessible and it is difficult to distinguish the VL from other diseases.*	1 Early diagnosis 4 Relapse & re-infection 6 Multiplexing enables detection of co-infections	
 5. Integration with 'malaria' journey	There is a need for a multiplex diagnostic test which enables health care workers to test someone with symptoms that are common for infectious-diseases on multiple diseases simultaneously. *Reason: VL is often confused with other symptom-related diseases.*	1 Early diagnosis 4 Relapse & re-infection 6 Multiplexing enables detection of co-infections	
 6. Follow-up	There is a need for a diagnostic test which can be used to follow-up a patient after treatment to see if treatment was successful or not (relapse). *Reason: Current rapid diagnostic tests are antigen-based and so cannot be used for a follow-up.*	3 Test-of-cure 4 Relapse & re-infection	
 7. Airport testing	There is a need for a diagnostic test which can test whether a people who have been to VL endemic areas are infected with the *Leishmania* parasite. *Reason: People who are reservoirs of the Leishmania parasite might help to spread the disease (outside of endemic areas).*	1 Early diagnosis 2 Diagnosis of asymptomatic cases	

Do you want to know about these Diagnostic setting variables?

Keep on reading or go straight to Chapter 8.





Application of the benefits of the technical principle

As discussed in Chapter 5, the technical principle promises to be quick, reliable and broadly applicable. These benefits can be applied in the scenario in different ways (Figure 27). Therefore, the application of these benefits is discussed here.

1 Early diagnosis

The technical principle allows direct DNA detection, so people can be tested as soon as they have been infected with the *Leishmania* parasite. In contrast with the current rapid diagnostic test (rK39) which is antigen-based, this technical principle enables detection of the parasite in an early phase after infection (even before someone develops symptoms) and is independent of someone's immune system.

2 Diagnosis of asymptomatic cases

Some people might get infected, but do not develop the disease. These asymptomatic cases can still be detected due to the direct DNA detection which this technical principle offers.

3 Test-of-cure

After treatment, antibodies will persist in the body for quite some time. Therefore, it is impossible to use current serological tests (rK39 and DAT) as a test-of-cure. In contrast, this technical principle is DNA based and can be used to test if someone is cured (test-of-cure).

4 Relapse & re-infection

In addition to a test-of-cure, this technical principle can be used to test patients with a relapse or re-infection which is not possible with the current serological tests.

5 Confirmatory test

The technical principle has the potential to be more accurate which can result in a high sensitivity and specificity. Therefore, this technical principle has the potential to be used as a confirmatory test which can contribute to the elimination of bone marrow or splenic aspiration procedures.

6 Multiplexing enables detection of co-infections

Due to multiplexing, it is possible to test for numerous diseases simultaneously. Multiplexing can be used to check if a patient has a co-infection such as HIV/VL or Malaria/VL. Besides that, testing for multiple diseases simultaneously can be of great benefit when screening entire communities. This will reduce the risk of misdiagnoses through confusion between diseases. How many diseases could be multiplexed and whether this affects the sensitivity and specificity is still unknown.

7 Alternative diagnostic tests

This technical principle is applicable to all kinds of infectious diseases. Therefore, the technical principle can be integrated separate diagnostic tests which are suitable for different diseases.

① SCREENING & CONFIRMING

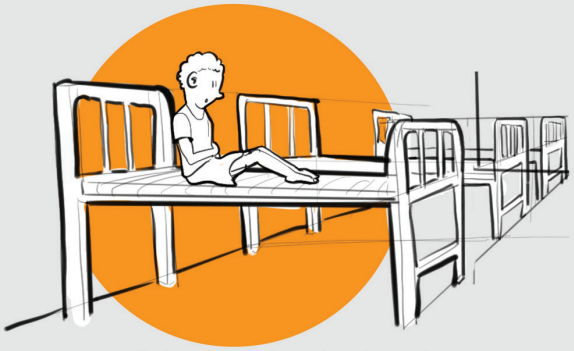
This DNA based test is accurate and independent of the person's immune system, which makes it suitable for both a screening and confirmatory test. (Thus replacing bone marrow aspiration, splenic aspiration and repetition of using rK39).

A sick person can get a VL confirmation test at any level: community, dispensary, health centre, hospital or treatment centre.

Someone can be tested based on a pinprick of blood.

A positive test result will be taken to a treatment facility.

When patient presents at the freatment centre there is no need to do another diagnostic test. The results from the test done at another health facility are enough to start treatment.



Patient is put on treatment.

2 TEST OF CURE

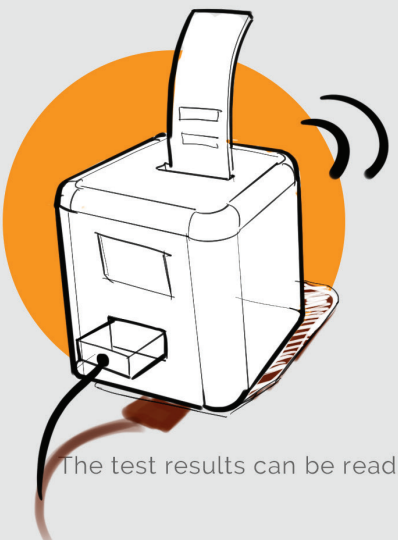
This DNA based test can detect the patient's response to treatment after a primary infection. This test can also be used to collect data during clinical trials.

A patient at a VL treatment centre is called for a check up after finishing the treatment.

A minimally invasive diagnostic test is used.

Based on a pinprick of blood,

The patient can be tested for response to treatment.



The test results can be read out.

3 SCREENING DAY

This DNA based multiplex test is independent of the person's immune system and screens for multiple diseases simultaneously and detects both symptomatic and asymptomatic VL cases.

The CHV announces screening day.

People from the communities gather at the screening day.

Everyone lines up to get tested.

Everyone gets tested for multiple diseases with one test

The test results are written down.

Positive symptomatic cases are brought to a treatment facility

Asymptomatic cases can either be treated as symptomatic cases or should get a follow up.

People who are tested negative for VL are given suplements or other medication if needed.

4 COMMUNITY TESTING

This simple multiplex test can test someone on multiple diseases simultaneously and thus identify VL and a co-infection close to home.

Someone in the community is sick

and decides to speak to the CHV / VHT.

CHV or VHT has a basic kit with a diagnostic test which can test a person for multiple diseases simultaneously.

This very simple diagnostic test can be done by the CHV or VHT.

The CHV or VHT is using the diagnostic test.

Someone is diagnosed with VL and has a reason to go to a treatment facility.

5 INTEGRATION WITH 'MALARIA' JOURNEY

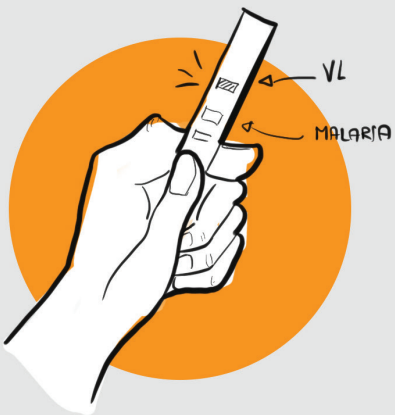
This multiplex test can test someone for multiple diseases simultaneously and thus reduces the delay caused by confusion between VL and other diseases.

Someone is feeling sick

and goes to the nearest health facility.

At this facility the nurse suspects malaria.

She uses a multiplex test for malaria and VL.



The results indicate that it is VL and not malaria.

So she refers the patient to a VL treatment centre.

6 FOLLOW UP active from health care side

This DNA based test can detect the parasite level after primary infection and thus can be used as a follow-up test after treatment.

Active follow-up is done after a patient has finished treatment.

A health care worker ask the patient to test him/her.

The 'ex-patient' is being tested at the community.

Luckily there is no case of a relapse.

The health care worker tells the patient the results of the test.

7 AIRPORT TESTING

This DNA based test is independent on the person's immune system which makes it suitable to detect asymptomatic cases in a very early stage. Identifying Leishmania carriers can result in the prevention of further spreading the disease.

Someone returns from a VL endemic area.

He purchases a VL self-test.

At home he tests whether he has this disease

6.2 Selecting scenarios

WHAT ARE THE MOST PROMISING SCENARIOS?

6.2.1 Selection criteria

From these seven scenarios, the two most 'promising' scenarios can be selected for further detailing. The selection of the scenarios are based on the following criteria:

- How **feasible it is to implement this technical principle** in a diagnostic test in this scenario.
- How well this scenario would it **fit in a diagnostic setting** in the context of VL.
- How well this scenario **meets a local need** in case management.

The two selected scenarios are

The "screening & confirming" Scenario

&

The "test-of-cure" Scenario

These two scenarios are chosen based on the feedback from Charity Kamau*and Koert Ritmeijer* from Médecins Sans Frontières (MSF) and various stakeholders met during the field trip.
As the meeting with MSF was more elaborated and controlled than the feedback received from stakeholders, the selection of scenarios is mainly based on feedback which is provided by MSF.

**In this Chapter, Charity Kamau and Koert Ritmeijer ard reffered to as MSF.*

6.2.2 Médecins Sans Frontières

According to MSF, the 'test-of-cure' scenario and the 'screening & confirming' scenario were most promising. The feedback on all the scenarios discussed during the meeting can be found in Appendix D-1.
The reason for the choice of the two scenarios is described on the next pages.

MEDECINS SANS FRONTIERES

REASON FOR SELECTING

SCENARIO I:

"Screening & Confirming"

One of the most important reasons for MSF to select the "screening & confirming" scenario is the increased sensitivity which is lacking in the current serological diagnostic test rk39. Thus, this scenario is chosen because of the benefit of the technical principle. However, to get a better understanding of the full reasoning of MSF, additional clarification is asked by a follow-up email and phone call.

MSF responded that the ideal diagnostic test in this scenario would be a more sensitive diagnostic test (technical principle benefit) for the lowest level where you have staff trained to recognise the symptoms of VL (diagnostic setting). Thus, this scenario was preferred by MSF as it offers a more reliable diagnostic test which is accessible to the people (as it can be implemented at the lowest health care level possible.

Diagnose setting is important

According to MSF, it is essential to carefully consider where this diagnostic test will be used and who will use it. MSF clarified that where the diagnostic test can be used is not defined by a specific health care level (as this may vary enormously between regions), but instead is determined by the level of staff and the level of resources available at a facility. Besides that, MSF proposes to design a diagnostic test for lay people, whom they defined as: "people with basic math and writing skills without medical training".

During the meeting became clear that that querying VL can become rather complicated in case of co-infections and thus potentially (too) complicated for a minimally trained CHVs. Hence, it is necessary to consider whom to give the responsibility to test people for VL.

Change in focus of this scenario

Initially, the focus of this scenario was on having one diagnostic test which could be used at every health care level for screening and confirming purposes. This would be possible due to the high sensitivity and specificity which the technical principle has to offer. With this, the aim of this was to get rid of the repetition of diagnosing the same patient over and over . In addition, it would replace parasitological diagnoses.

However, based on the meeting with MSF it became clear that repetitive testing is not such a bad thing and will inevitably happen in the case of VL. Repetition is done to rule out procedural errors and be sure that it is required to put a patient on a toxic, lengthy and expensive treatment.

Of course, a patient should not be tested six times, but a couple of times would not be a problem according to MSF. So, instead of making a diagnostic test which is used once during the journey, the diagnostic test needs to be affordable enough to enable repetition.

REASON FOR SELECTING

SCENARIO II:

"Test-of-cure"

The “test-of-cure” scenario is selected as it can fill a crucial gap in current VL case management with the technical principle. MSF experts confirmed that a test-of-cure is essential for better case management of VL, not only during clinical trials but after treatments in general.

According to Koert Ritmeijer, there are a lot of questionable responses to the treatment. Current diagnostic practices that can be used to test a patient for being cured, are invasive and require advanced resources and skills.

Thus, a test-of-cure would be crucial. Particularly immune-compromised patients, who have a high risk of getting a relapse, will benefit from this “test-of-cure” scenario. With this scenario, patients can either get a confirmation of being cured or an indication of relapse in an early phase. As approximately 5-10% of the treated patients get a relapse, it essential to identify these in an early stage after treatment. Current serological tests (DAT and rk39) cannot be used to confirm relapses, which is why this scenario is crucial according to MSF experts.

Therefore, the “test-of-cure” scenario fills a critical gap in current case management by implementing the benefits that technical principle has to offer.

6.2.3 Feedback from stakeholders

Feedback forms were sent out to stakeholders from the field trip. This resulted in five responses among which people from KEMRI, UON and a health care officer.

As became clear from the feedback, **the stakeholders do not contradict the choices of MSF**. However, they selected two additional scenarios as promising. These are: Scenario 4: "Community testing" and Scenario 3: "Screening day".

The feedback from stakeholders resulted in several interesting findings, which are briefly described here. See Appendix D-1 for a more detailed description of the feedback.

The **"screening & confirming"** scenario is seen as promising by all of the respondents. Interestingly, the reasoning for choosing this scenario differs between MSF and the stakeholders.

- MSF chose this scenario based on the potential of increased sensitivity at the point of care: more reliable diagnostics which are accessible for testing people.

- The stakeholders chose this scenario as it could replace tissue aspiration procedures. Thus, it has the potential to be used as a reliable and not-so-invasive confirmation test prior to treatment.

"this is the best-case scenario. Aspirates are invasive and need highly skilled personnel"

Ms. Hellen Nyakundi
about the 'screening & confirming' scenario

"First, this is the way to go, most patients have expressed invasiveness of some management procedures such as bone marrow and splenic aspiration"

Mr. Korobe Fontiano, Lab technician
about the 'screening & confirming' scenario

MSF selected the **test-of-cure** scenario as it is crucial in VL case management. Interestingly, several stakeholders chose other scenarios as more promising than the test-of-cure scenario. One of the reasons for selecting different scenarios is the fact that the test-of-cure scenario would be less urgent. It will only help the patients that reach a treatment facility and **will not improve access to diagnostics for everyone.**

From the feedback from stakeholders it became clear that a test-of-cure will have a positive effect on VL case management. However, some of the stakeholders selected "the community testing" and "Screening day" scnearios as more promising. as it contributes to the goal of bringing diagnostics closer to the homes of people.

"this is a positive outcome as antigens stay in the body long after the patient is healed and current tests cannot test for cure, so this fills a critical gap"

Ms. Hellen Nyakundi
about the test-of-cure scenario

A Community Health Worker is testing a person for VL at Rupa Health Centre II, UGANDA.

SECTION IV FUTURE APPLICATION

Chapter

07

THE DIAGNOSTIC SETTING

This Chapter focusses on the diagnostic setting in which a diagnostic test could be used. Therefore, the aim is to show that the diagnostic setting influences the features of the diagnostic test. First, a decomposition will help to make the distinction between the diagnostic test, the diagnostic setting and VL context. Next, the most promising scenarios which are selected in Chapter 6 are detailed based on the diagnostic setting. Diving into the diagnostic setting of the two scenarios will help to understand which diagnostic test features are required.

Next, the diagnostic settings of the two selected scenarios are detailed. Lastly, the relation between the diagnostic setting and the diagnostic test will be further explored.

All steps made in this Chapter will help to set up requirements for a diagnostic test. These requirements can be translated into proposals for diagnostic tests in Chapter 08: Proposals for future diagnostic tests.

7.1 diagnostic test & diagnostic setting

THE ROLE OF THE DIAGNOSTIC TEST, DIAGNOSTIC SETTING AND CONTEXT OF VL

Lab technician in the diagnostic setting in Kimalel Health Centre, Kenya.

To further detail the scenarios, it is essential to clarify the role of the diagnostic test, the diagnostic setting and the VL context. Therefore, a decomposition helps to understand that there are multiple diagnostic settings in the context of VL (see Figure 28).

The diagnostic test:

The tool which can be used to test a person for VL.

The diagnostic test includes the technical principle, the housing and the instructions on how to use it (usability guidance).

The diagnostic setting:

The environment in which the diagnostic test is used.

This includes the diagnostic setting variables such as the background of the user, the (geographic location), the available resources, the diagnostic moment and the status of the patient.

The (VL) context:

The entire context of VL, which includes the health care system and case management.

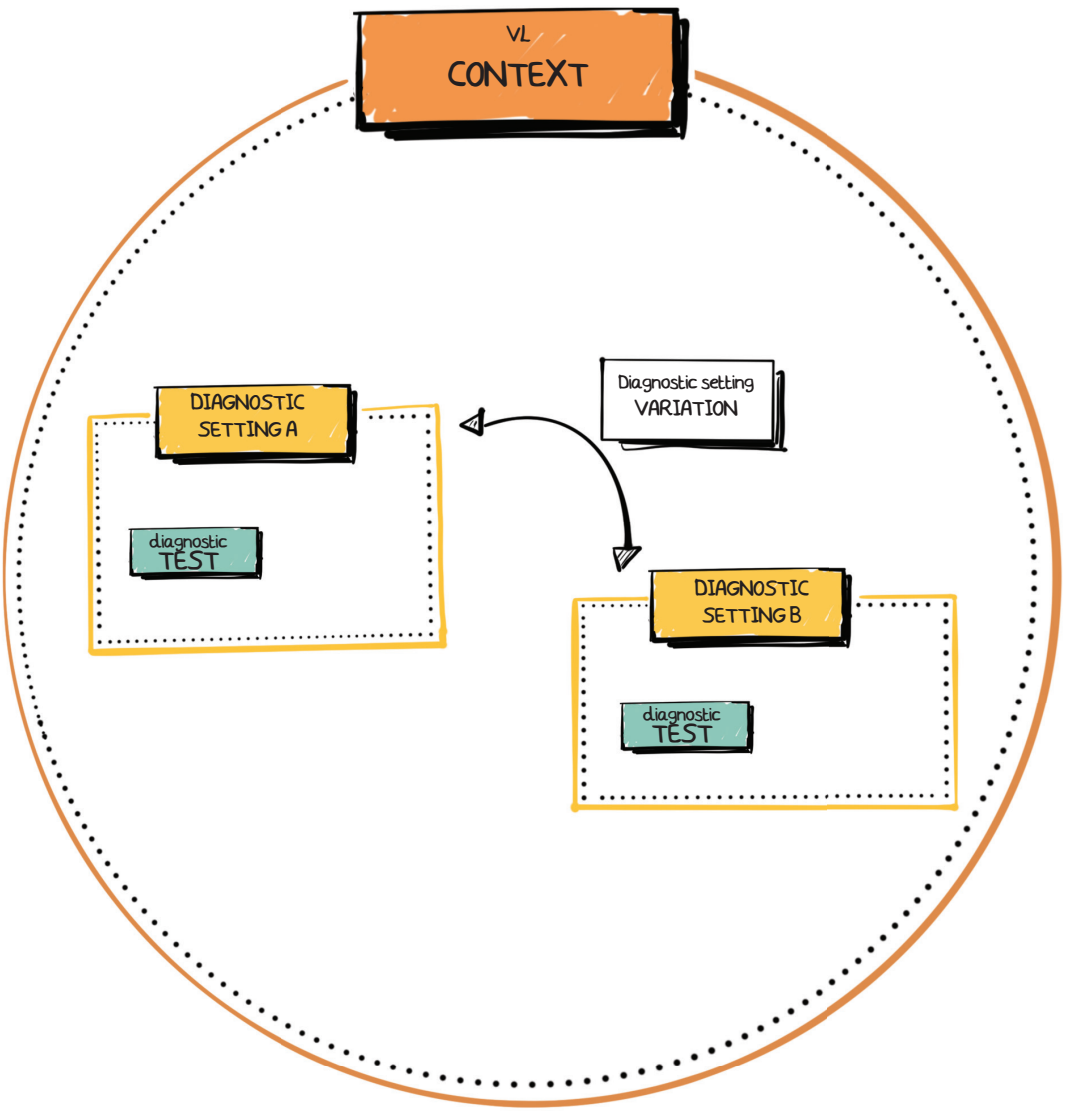


Figure 28: Diagnostic settings in the VL context vary from each other based on 'diagnostic setting variables'.

7.2 Detailing diagnostic setting(s)

WHAT'S THE DIAGNOSTIC SETTING OF THE TWO SCENARIOS LIKE?

Based on this decomposition, the scenarios are detailed during a two-hour session with the team of Applied Sciences and IDE. More detailed information about the setup and results of this session can be found in Appendix C-2 .
The aim detailing the diagnostic settings of the two selected scenarios is to identify requirements which are specific for each scenario and can be integrated into a list of requirements.
During this session, the diagnostic settings of the two scenarios are detailed based on the:

- **occupation of a user** of the diagnostic test in the scenario.
- **health care level** where the scenario takes place.

Figure 30 and 31 show one detailed diagnostic setting of each scenario. The other detailed diagnostic settings for the two scenarios can be found in Appendix C-2.

Insights:
By detailing the two selected scenarios based on the user and health care level, it becomes these elements influence the features of a diagnostic test. However, it becomes clear that there are still multiple diagnostic settings possible for each scenario. During the session, the two selected scenarios are detailed based on combinations of the occupation of the user and the health care facility which have been seen during the field trip.

7.2.1 Diagnostic settings for the "screening & confirming" scenario

In the case of the "Screening & confirming" scenario, the diagnostic test could be used at multiple health care levels. See Table 3 for the combinations of the occupation of the users and health care facility which are applicable for this scenario as seen in the field.
Figure 30 shows the detailed screening & confirming scenario for combination 2: a nurse or midwife testing people for VL at a primary health facility. The other explicit combinations of the diagnostic settings for this scenario can be found in Appendix C-2.

	The diagnostic settings of the 'screening & confirming' Scenario	
NR	WHO? The occupation of the user	WHERE? The health care level/facility
1	Community Health care worker (CHV) or Village Health Team (VHT)	In the communities
2	Nurse or Midwife	In primary health facility
3	Lab-technician	In health care centres or sub-county hospitals
4	Lab-technician	In VL treatment centres

Table3: Combinations of who and where as seen in the field.

7.2.2 Diagnostic setting variation for the test-of-cure

During the session, it became clear that the diagnostic setting of the test-of-cure is still questionable as this depends on when it is possible to test a patient for being cured. This depends on the specificity of the technical principle and the number of pathogens that are still present in a patient's body after treatment. This crucial gap in knowledge needs to be filled to know whether or not a test-of-cure would be feasible. Therefore, it is important to answer these questions:

How long does the pathogens DNA persist in the patient's body after treatment?

When is this pathogens DNA level low enough to do a test-of-cure?

Based on these questions, there are two logical diagnostic settings for a test-of-cure. These two combinations can be found in Table 4.
Figure 31 shows the detailed test-of-cure scenario for diagnostic setting 1: A lab-technician at a VL treatment centre. The other explicit combination for the diagnostic setting of this scenario can be found in Appendix C-2.

Note
The diagnostic settings of the scenarios are detailed based on the combinations of the occupation of the user (of the diagnostic test) and a specific heath care level as seen in the field. However, according to Charity Kamau from MSF, the occupation of a user does not always say something about their skill level (MSF, 2019).
For example, a lab-technician (occupation) can be very skilled at one facility and limited trained at another facility. Similarly, the health care level of a diagnostic test does not necessarily say something about the resources available. For example, Kimalel health centre is a level II health care centre. However, in terms of resources, this facility is way more advanced than an 'actual' level II health centre such as in Nginyand.
Therefore, it becomes clear that **the diagnostic setting** should be described **in variables that are more accurate than the specific occupation of a user and health care level.**

	The diagnostic settings of the 'screening & confirming' Scenario		
NR	WHO? The occupation of the user	WHERE? The health care level/facility	Application When is this combination applicable?
1	Lab-technician	In VL treatment centres	In case it is possible to test a patient soon after treatment (within several days), so the patient is still at the treatment centre.
2	Nurse or Midwife	In primary health facility	When a patient cannot be tested immediately after treatment, primary health facilities are the closest to the homes of people, which makes a follow up (weeks or months) after treatment more accessible for them.

Table4: Combinations of who and where as seen in the field.

Figure 29: Detailed “Screening & Confirming” scenario based on the health care facility and the user.

Diagnose setting

What is the environment in which the diagnostic test is used like?

Health care facility (level)

This scenario takes place at the lowest health care levels, such as primary health facilities and dispensaries. These facilities are generally around 20 km away from the communities.
At this level, only basic primary health services are provided, such as basic immunisation. There are no doctors at this level, only nurses or midwives. In case of a more complicated case, the patient is referred to another health care level, such as a sub-county health centre. The facilities opening hours are varying depending on the facility. This health care level is very remote and thus often has to deal with supplies being out of stock. Also, there this health care facility is resource constrained.

(occupation of the) user

The user of the diagnostic test in this scenario is a health care worker working at a primary health facility. This user is either a nurse or a midwife with basic medical training (this can vary enormously). This person (depending on if health education has been done), can query VL or not.
This user is literate and attended school and gets paid for this job.

(How) does the diagnostic setting influence the specifications of the technical prinicple?

(How) does the user influence the specifications of the technical principle?

How does the diagnostic setting influence the housing?

How does the user influence the housing?

Is there a need for additional interventions to support the diagnostic test based on the diagnostic setting?

Is there a need for additional interventions to support the diagnostic test based on the user?

(How) do the specifications influence the housing?

Specifications of the technical principle

What specifications are required for a diagnostic test in this scenario?

The test should be sensitive and specific, and give reliable test results irrespective of the person's immune system and if the person has a relapse, primary infection or re-infection.

The test should give results within 15/20 minutes after sample collection. This is because the patient should not wait for hours at a facility for the results as this will demotivate them going in the first place.

Housing

What housing features are required for a diagnostic test in this scenario?

The test should be simple to interact with, because of the limited training of these health care workers.
Also, they work at a very basic health care level with no lab-equipment and thus the test should function without equipment.
At this facility, gloves, needles and alcohol pads are most likely available because of the procedures they have to do here, so the test does not necessarily have to be independent of these essential tools.

As health care workers would get additional responsibility of diagnosing VL, the housing of the diagnostic test should facilitate correct read-out and usage.

Supporting interventions

What supporting interventions are required for a diagnostic test in this scenario?

As treatment cannot be given at this health care level, the user needs to refer a patient to a treatment facility.
It is crucial to refer correctly: to the right hospital where VL treatment is provided, instead of to a referral hospital where they do not offer VL treatment.
Thus instructions (for example in the form of a poster) should be designed to help these primary health care workers to guide their patients in the best possible way.

Figure 30: Detailed “Test-of-cure” scenario based on the health care facility and the user.

Diagnose setting

What is the environment in which the diagnostic test is used like?

Health care facility (level)

At the treatment centre, experts are available. Still, there might be a lack of trained staff, but in general, there are nurses, doctors and lab-technicians available at such a facility. However, issues with lack of staff remain.
Approximately 12 patients are treated here per month.
Testing takes place inside in the lab where there are tables and a chair for the patient to sit on. Appropriate bins are present for clinical waste.
Data of patients is written down in logbooks. It depends on the setting, but often there are no refrigerators, centrifuges or other heavy lab-equipment available.

(occupation of the) user

At such a treatment centre, the lab-technicians will be using the diagnostic test.
Lab-technicians are educated and trained and experienced with using diagnostic tests. In this case, they are working at a VL treatment centre and thus are very familiar with the disease.
As seen in the field, there are often around two lab-technicians working in a treatment centre, which means they have to do much work with the two of them. Qualified lab technicians are trained and experienced with using RDT's. Potentially this ab-technician does not speak the local language.

(How) does the diagnostic setting influence the specifications of the technical principle?

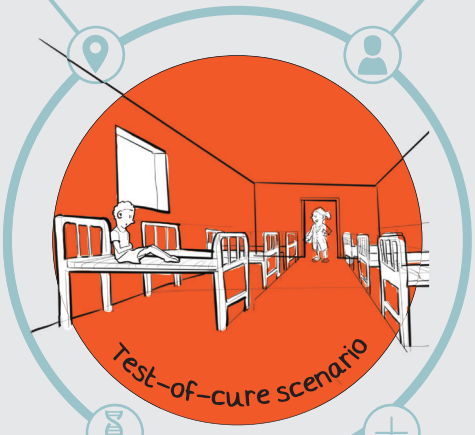
(How) does the user influence the specifications of the technical principle?

How does the diagnostic setting influence the housing?

How does the user influence the housing?

Is there a need for additional interventions to support the diagnostic test based on the diagnostic setting?

Is there a need for additional interventions to support the diagnostic test based on the user?



(How) do the specifications influence the housing?

Specifications of the technical principle

What specifications are required for a diagnostic test in this scenario?

The diagnostic test has to be sensitive and specific to test if a patient is cured after treatment.

Ideally, test results are quantitative, so the diagnostic test can already be used during the treatment to detect response to treatment.

Assuming that the patient is still hospitalised and needs to wait, the test does not have to give test results as quick as in other scenarios. The test results should maximum present itself in a day after sample collection.

Housing

What housing features are required for a diagnostic test in this scenario?

Lab-technicians are experienced in doing diagnosis. Thus, they can perform several steps to test someone for VL. However, it is desired to have an easy test as this will speed up the time spend to do a diagnose.

Thus, if the diagnostic test requires some steps, this would not be an issue. Also, at level 3 health care they have basic medical equipment such as needles, alcohol pads and things available, so they do not need to be part of the kit.

Supporting interventions

What supporting interventions are required for a diagnostic test in this scenario?

It is desired to facilitate an easy way to store the data of patients.
Ideally, this would combine the patient's data 1) upon arrival 2) during treatment 3) after treatment (Test -of-cure).

7.3 How the diagnostic setting influences the diagnostic test

LAYERS WHICH CONNECT THE DIAGNOSTIC TEST TO THE CONTEXT OF VL

The diagnostic setting influences what the diagnostic test should be like and how it would be used. However, the specific occupation of a user and health care level are not the most accurate way to describe a diagnostic setting. The reason for this is that the occupation of a user and health care level do not necessarily say something about the skills, location and resources at that diagnostic setting.
Thus, the diagnostic setting is further decomposed.
Therefore, several layers within and around the diagnostic test are identified, which help to comprehend how the 'diagnostic setting' influences the features of the diagnostic test (See Figure 31 and 33). These layers connect the technical principle at the core to the context of VL. Based on these layers, it is possible to understand how the context and diagnostic setting influence the technical principle and the other way around.

Diagnostic test

1) Technical principle layer

At the core of the diagnostic test, the technical principle can be found which includes all technical principle features on a test strip. More information about the technical principle can be found in SECTION II Chapter 5.

2) Housing layer

The technical principle is surrounded by a housing which facilitates usage and protects the test strip from its surrounding.

3) Usability guidance layer

Usability guidance is needed to facilitate that the diagnostic test is used correctly by the user (layer 4). This includes elements such as use cues on the housing, instruction sheets, readout instructions and training.

Diagnostic setting

As mentioned priorly, the diagnostic setting is the environment in which the diagnostic test is used. Therefore, this layer involves several variables which define a diagnostic setting and distinguish diagnostic settings from each other. Therefore, the diagnostic setting layer involves **five diagnostic setting variables,** which affect the diagnostic test. These are:

- The (medical) background of the **user**
- The (geographic) **location**
- The availability of **resources**
- The **diagnostic moment**
- The **patient status**

VL context

These diagnostic settings are part of a health care system and VL context. Therefore, this layer includes the context of the disease and the health care system around multiple diagnostic settings which vary from each other based on diagnostic setting variables.

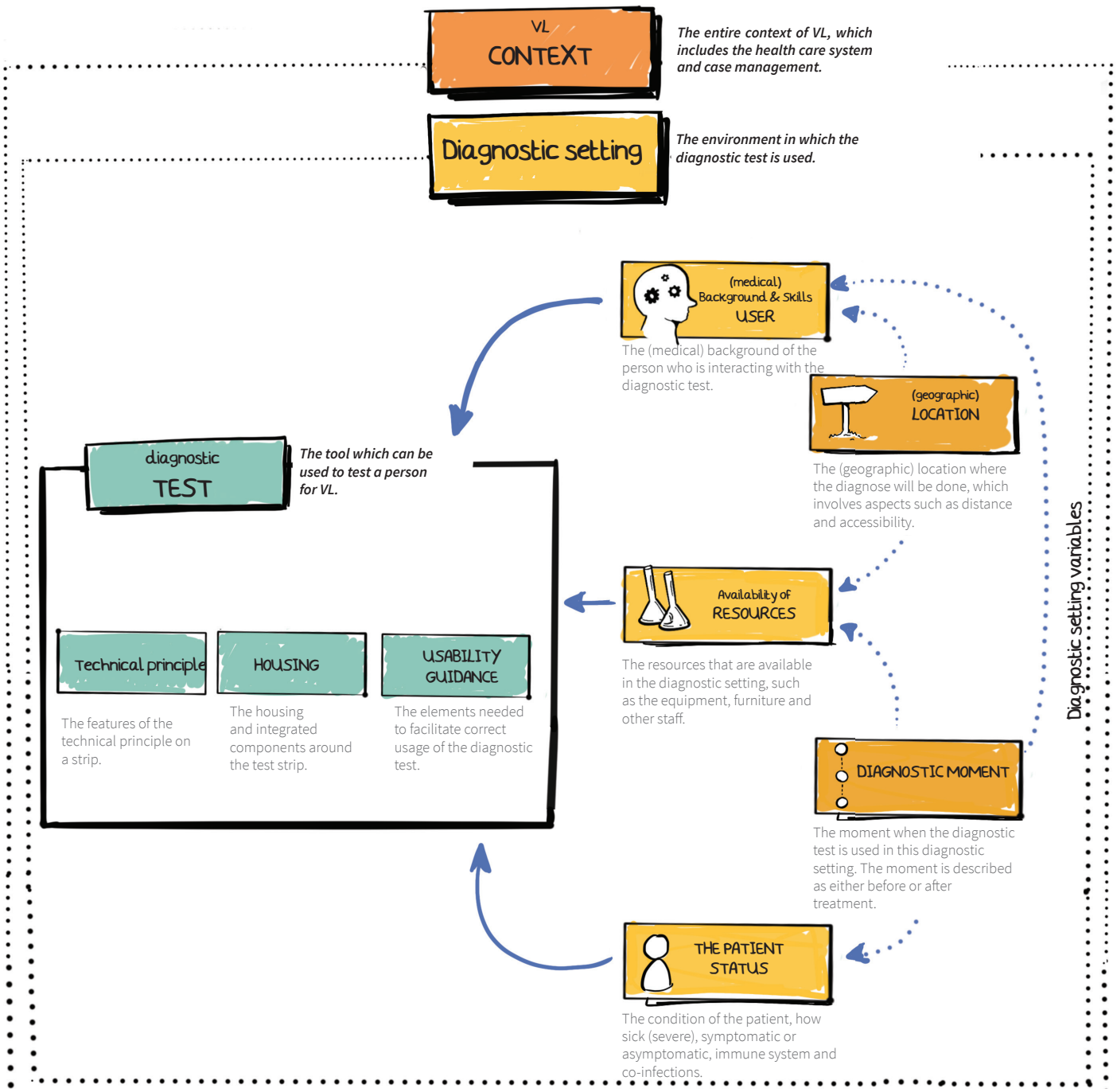


Figure 31: An overview of the diagnostic test in a diagnostic setting in the context of VL.

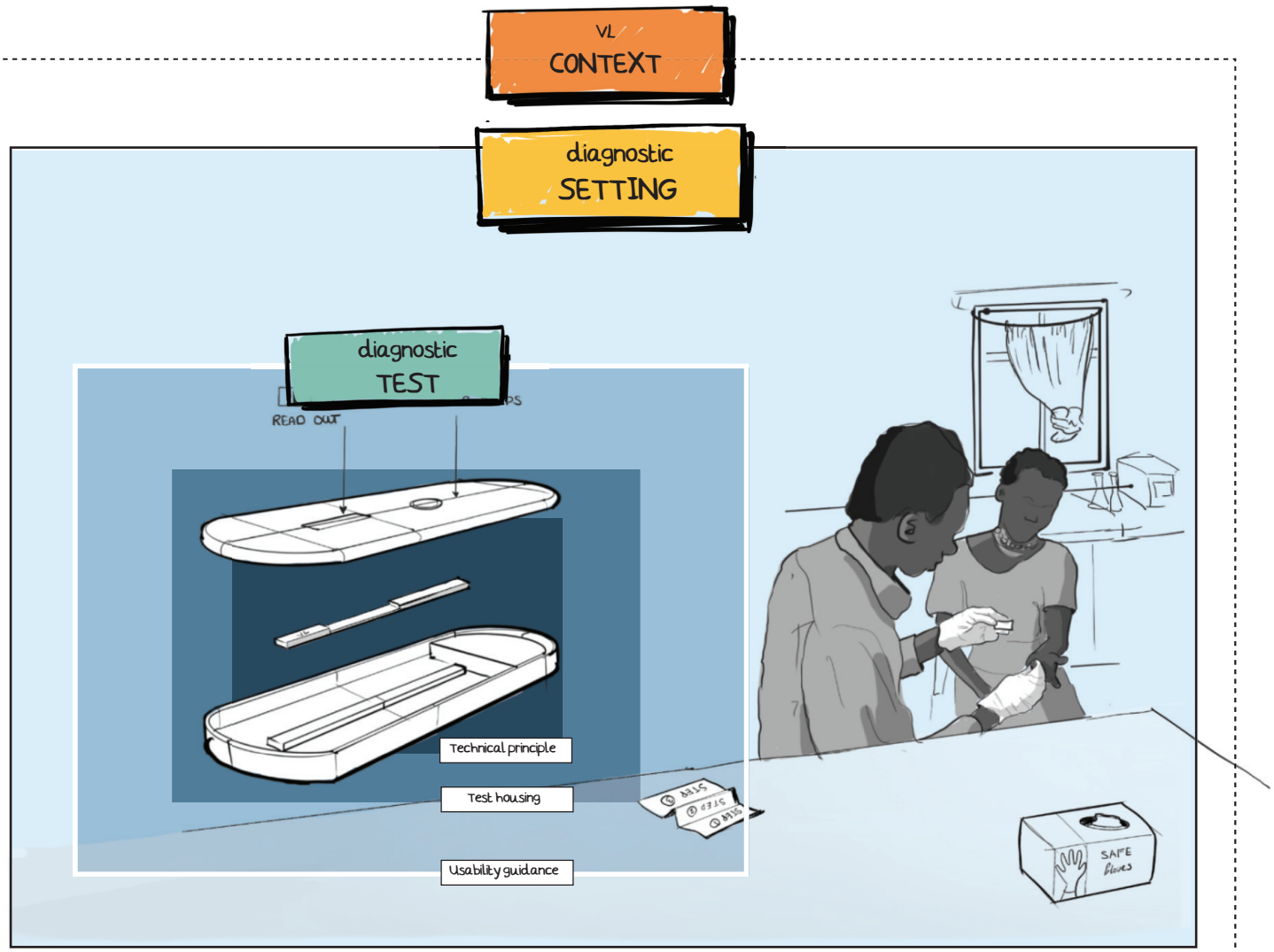


Figure 32: Diagnostic test in a diagnostic setting.

7.4 Diagnostic setting variables

HOW DO DIAGNOSTIC SETTINGS VARY FROM EACH OTHER?

7.4.1 Influential variables

The diagnostic settings of the two scenarios are detailed and result in a decomposition into five diagnostic setting variables (Chapter 7.3).
Hence, from the five diagnostic setting variables (Figure 33), there are two variables which directly influence the specifications of the diagnostic test. These are:

- **The resources** which are available in the diagnostic setting, such as the equipment, furniture and other staff.
- **The (medical) background of the user** who is using the diagnostic test in the diagnostic setting.

These two diagnostic setting variables consist of several 'levels' (See Figure 34 and 35). These levels influence the recommended diagnostic tests and therefore are further detailed.

** The patient status (the condition of the patient who is diagnosed with VL) also influences the diagnostic test. However, the technical principle aims to give reliable test results independent of the immune system of a patient. Therefore, potential variation between the status of patients will be covered in the general requirements (See Chapter 8).*

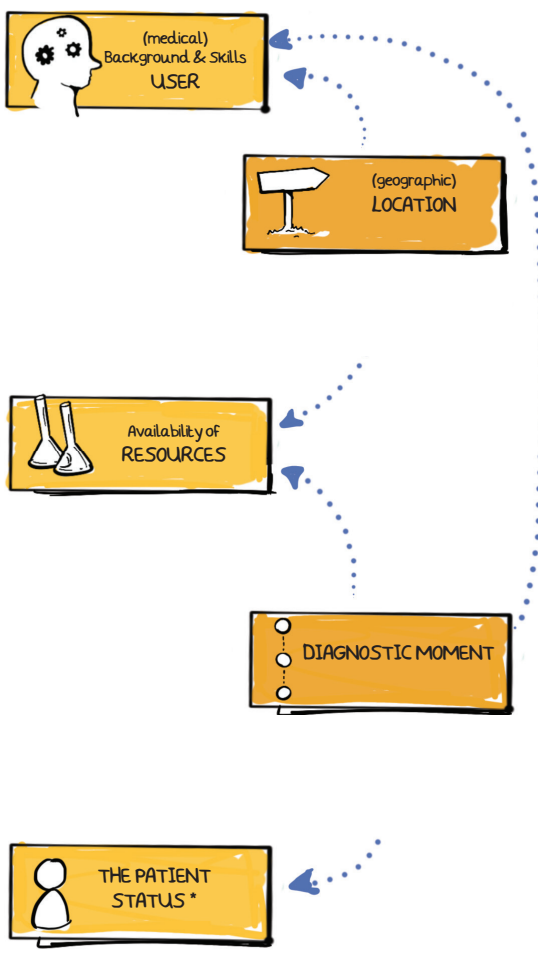


Figure 33: Diagnostic setting variables.

Diagnostic setting at Chemolingot Sub-county Hospital, Kenya.

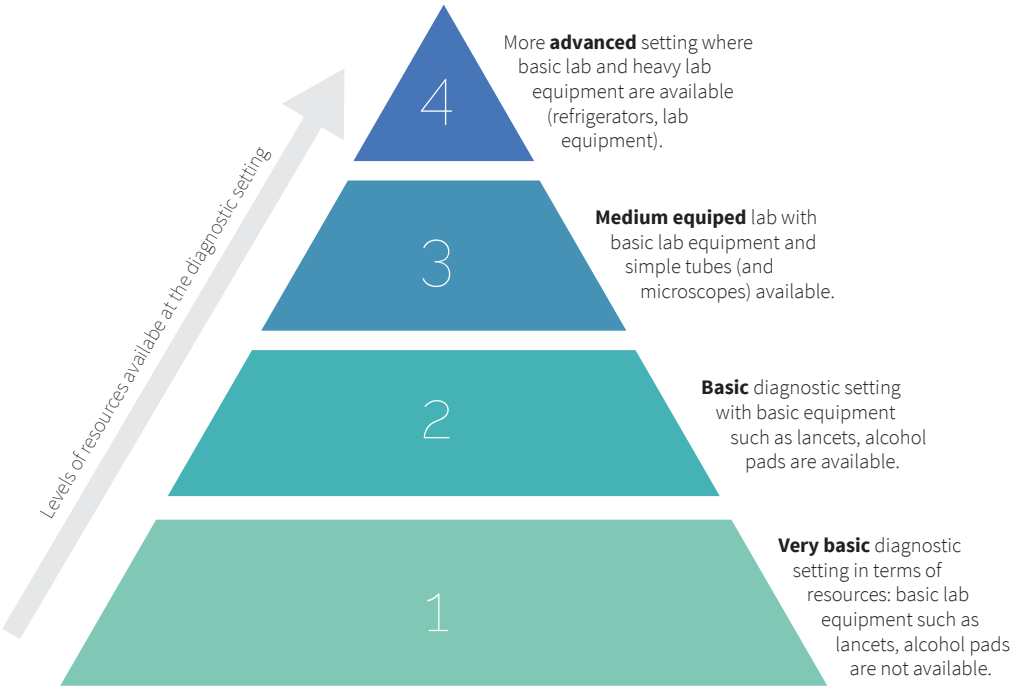


Figure 34: Variations between available resources at diagnostic settings.

7.4.2 Resource levels

A distinction can be made between different 'levels' of available resources (Figure 34). At the 'lowest resource level', basic lab equipment such as lancets, alcohol pads and capillary tubes are not available. Besides, there is no basic furniture such as chairs or tables. At level 2, only basic lab equipment such as lancets, alcohol pads are available together with basic furniture. In the third level, basic lab equipment and some more advanced lab equipment are available, such as pipettes and a thermometer, Erlenmeyer's, beakers and a microscope. Lastly, in the highest resource level, both basic and heavy lab equipment is available, which includes a refrigerator, centrifuge and microscopy. From the field trip, it became clear that this level can most likely only be found in treatment centres where clinical trials are performed.

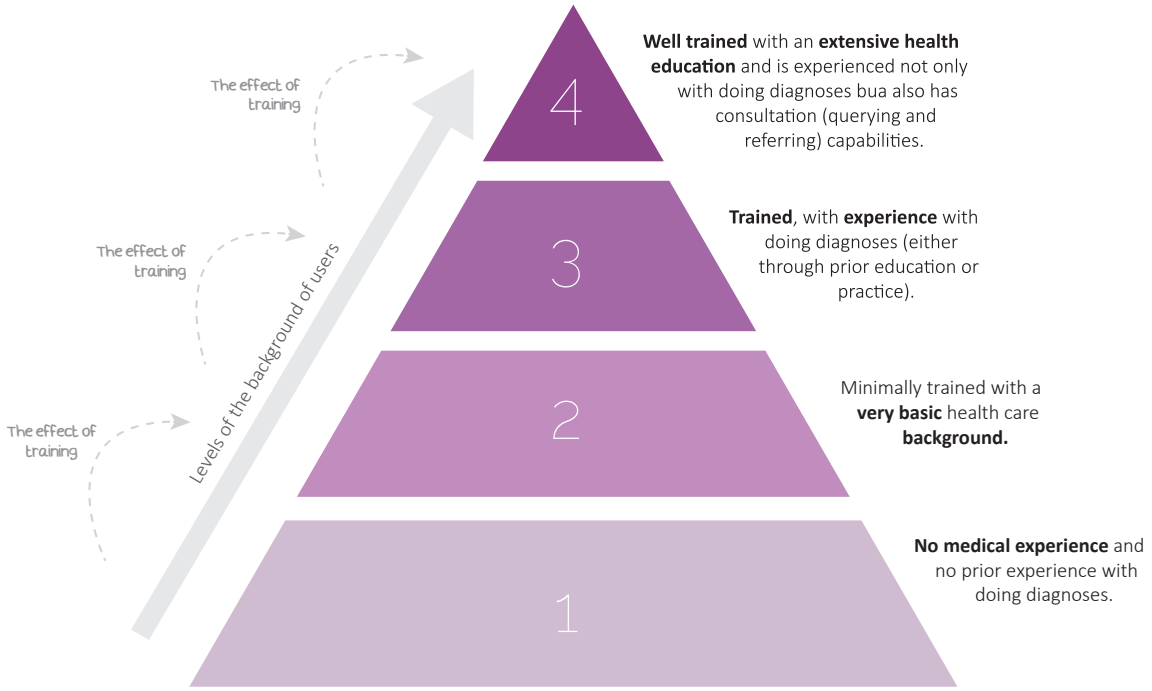


Figure 35: Variations between the (medical) backgound of users at diagnostic settings.

7.4.3 Background of the user-levels

The background and knowledge of the user can be split up in four different levels (Figure 35). First, there is the 'lowest level of background, which means the user has no medical experience and no prior experience with doing diagnoses. Next, there is the minimally trained user, who has primary health care experience. Examples of such users are nurses, midwives or lab technicians who are very poorly educated and trained.

Thirdly, there is the trained user, who has experience (either through prior education or practice) and knows about the disease. Lastly, there is the user with an extensive health education who has been trained for years. Examples of users at this level are doctors or well-trained lab-technicians.

It is important to point out that this level is focussed on the background of the user prior to receiving training on how to perform a diagnostic test. Thus, training can improve the skills of a user irrespective of the (medical) background of the user.

Training

The training before using the diagnostic test is excluded from the level background of the user. However, it is necessary to keep in mind that training is, in fact, crucial in the performance of a diagnostic test. From the field trip, it became clear that every user is expected to receive training before starting to use a diagnostic test. Of course, the intensity of training which is required before a user can do a diagnostic test depends on the (medical) background. Thus, a level four user hardly needs the training to perform a diagnostic test, whereas a user from level one needs to get more extensive training.

Training will not change the users (medical) background but will improve their (medical) skills and knowledge.

View on the Rift Valley in the Baringo County, Kenya.

SECTION IV FUTURE APPLICATION

Chapter

08

PROPOSALS FOR FUTURE DIAGNOSTIC TESTS

Detailing the two selected scenarios in Chapter 07 and decomposing the diagnostic test, diagnostic setting and context into layers will help to make the bridge towards proposals for a diagnostic test for VL in this Chapter.
First, requirements for the diagnostic test are created. These requirements are categorised into general requirements and context-specific requirements. Next, requirements are prioritised and categorised. This categorisation of the requirements results in proposals of diagnostic tests which are suitable for a diagnostic setting.
This Chapter aims to clarify how the diagnostic setting influences the features of the diagnostic test. Thus several diagnostic tests are proposed on specific diagnostic settings.

8.1 Requirements of the diagnostic test

WHAT ARE THE REQUIREMENTS OF THE DIAGNOSTIC TEST?

8.1.1 List of Requirements

Based on detailing of the two selected scenarios as described in Chapter 07, a list of requirements is created. This list includes requirements for diagnostic test (See Appendix E-1).
The requirements related to one of these 'groups:

- The technical principle
- Equipment
- Usability
- Read-out
- Robustness
- Affordability
- Environment

8.1.2 Decomposition of requirements

It depends on the diagnostic setting whether or not a requirement is applicable for a diagnostic test. Therefore, the requirements can be split up into

- **General requirements**
- **Context-specific requirements.** In addition, the context-specific requirements can be decomposed into:
  - **Resource-specific requirements**
  - **User-specific requirements**
  - **Scenario-specific**

See Figure 36 for the decomposition of these requirements.

8.1.3 Prioritise requirements

Besides sorting the requirements into categories as discussed earlier, the requirements can wbe prioritized. Ideally, all of the requirements are fulfilled by a diagnostic test, but this might not be feasible. Thus, pro's and con's for are found per requirement. Based on these pros and cons, the requirements can be prioritised on a scale from 1 to 6. See Appendix E-2 for the priority (1 to 6) of the requirements and the reasoning behind this priority.

Requirements

General requirements

Requirements that are applicable in both scenarios and all diagnostic settings. The general requirements can be found in Appendix E-1.

Example: A sports shoe should have laces to make sure it can be tight to the foot.
It does not matter who is wearing the shoe or where it is used, a sports shoe should always have laces.

Context-specific requirements

Requirements that are applicable because of a specific level of knowledge of a user, level of resources or a scenario. This means the context-specific requirements of the diagnostic test change when the diagnostic setting changes. These context-specific requirements can be decomposed into three parts:

Resource-specific

Requirements that are only applicable in a specific diagnostic setting. These requirements are dependent on the resources available at this diagnostic setting.

Example: A sports shoe should have a tracker which can be connected to a smartwatch to measure the speed of the runner.

This requirement is not applicable when the runner does not have a smartwatch. Therefore, it depends on the resources available whether this requirement is applicable.

User-specific

Requirements that are only applicable for a specific user (background of a user).

Example: A sports shoe should have extra damping to enable long-distance running.

This requirement is only applicable in case of professional runners who run long distances. Therefore, it depends on the user whether this requirement is applicable.

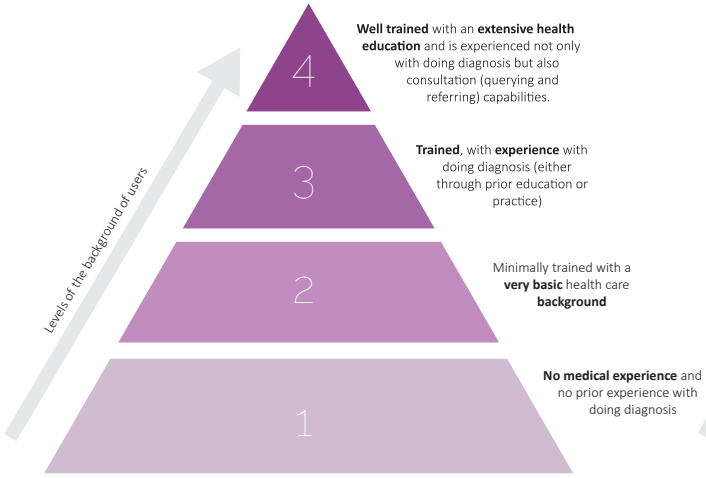
Scenario-specific

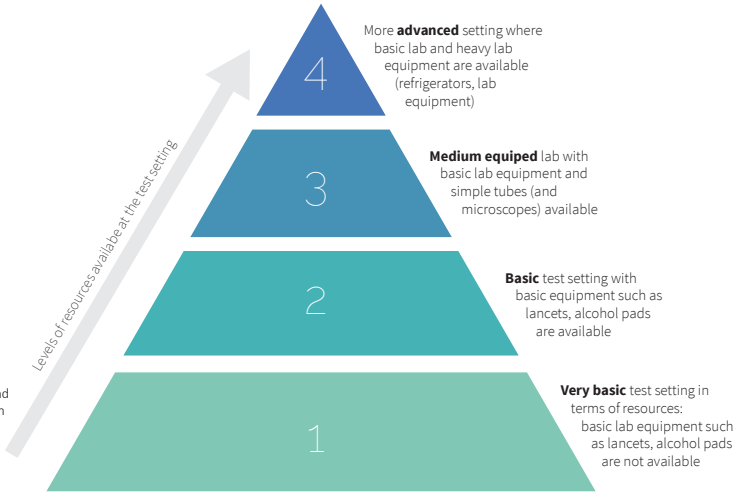
Requirements that are specific for a certain scenario.

Example: The sports shoe should have good shock damping during running.

This requirement is not applicable when the shoes are worn during grocery shopping and thus used for another purpose (scenario).

Figure 36: Decomposition of Requirements based on general and context-specific requirements.





User-specific requirements

Figure 37 shows the list of user-specific requirements, which are sorted on the levels of the background of the user. As visible, there are more requirements applicable when the diagnostic test is used by a user from the lowest 'level of medical background'. **Therefore, users who are part of the lowest 'level of medical background' are more demanding in terms of requirements.** As these users have a lower level of education and experience, they need a more straightforward diagnostic test and more guidance to be able using the diagnostic test as intended.

As visible, the higher the level of medical background of the user, the fewer requirements need to be fulfilled by the diagnostic test to help this user to use the diagnostic test correctly.

How this translates towards proposals for diagnostic tests can be seen in the next part of this Chapter: Proposal housing.

Resource-specific requirements

The requirements are also sorted on the level of resources available in the diagnostic setting (Figure 37). As becomes clear, the requirements which a diagnostic test needs to fulfil are different between a very basic and higher equipped diagnostic setting. As becomes clear from sorting these requirements, at a very basic equipped diagnostic setting more components should ideally be integrated into a diagnostic test. In contrast to a more equipped diagnostic setting where it is less essential to incorporate all components into one diagnostic test. How this translates towards proposals for diagnostic tests can be seen in the next part of this Chapter: Proposal housing.

Figure 37: Categorisation of the context-specific requirements based on the level or resources and background of the user.

What are the requirements of the diagnostic test based on diagnostic setting?

The requirements can be categorised based on the decomposition of the diagnostic test, diagnostic setting and VL context as earlier introduced in Chapter 7. Thus, all requirements are categorised into the three layers of a diagnostic test (Figure 38):

- **The technical principle**
- **The housing**
- **The usability guidance**

Together, these three layers shape the diagnostic test. The general requirements of the diagnostic test (see Figure 38) are applicable in every diagnostic setting (See Appendix E-1 for the list of general and context-specific requirements). However, the applicability of the context-specific requirements is influenced by the diagnostic setting in which the diagnostic test is used.
For example, the background of the user affects the applicability of the pink requirements. Thus, in case the user has no prior knowledge of doing diagnosis, the 'lightest' pink requirements become applicable. Similarly, when the diagnostic test is used in a diagnostic setting where they are hardly any resources available, the 'light' green requirements become applicable. Lastly, whether the diagnostic test is used as a test-of-cure or screening & confirming test (scenarios) affects which 'orange' scenario specific requirements are applicable.

Therefore, changes in the variables in the diagnostic setting, influences which 'package of requirements' is applicable for the diagnostic test.

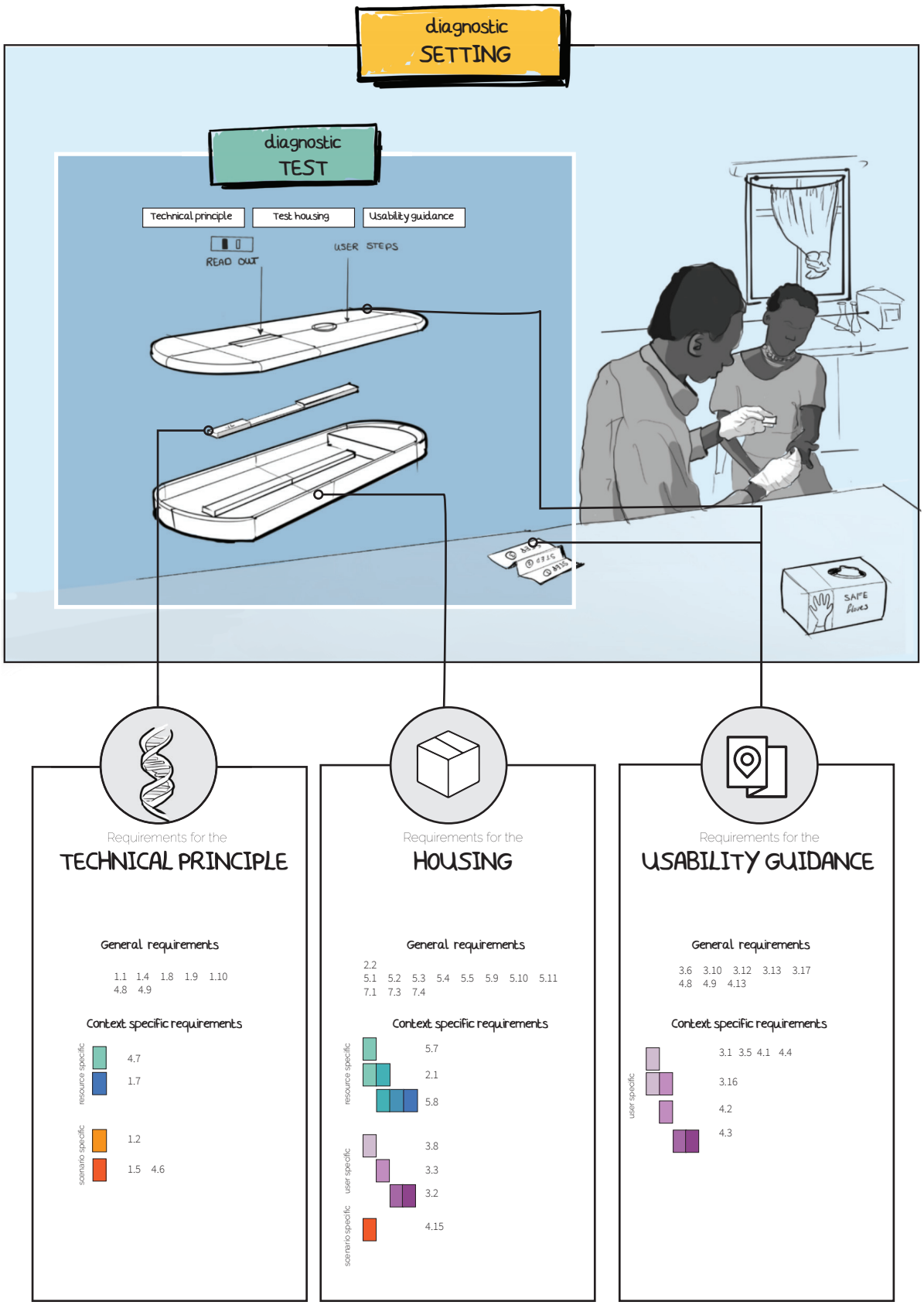


Figure 38: Categorisation of general and context-specific requirements into the three layers of the diagnostict test: 1) the technical principle 2) the housing and 3) the usability guidance.

8.2 Diagnostic test proposals

WHAT DOES A DIAGNOSTIC TEST LOOK LIKE BASED ON THE [redacted]?

8.2.1 Proposals

Based on these requirements, several diagnostic tests are composed with the aim to translate requirements to proposals for diagnostic tests. As mentioned earlier, the diagnostic setting plays an important role in what the diagnostic test should be like and the requirements which the diagnostic test needs to fulfil.
In more detail, the features of the diagnostic test depend on the resources available and the background of the user in a diagnostic setting. Thus, the different levels of resources and backgrounds of the user result in four different diagnostic tests (see Figure 39). Each of these diagnostic tests facilitate reliable test results, correct usage and prevent errors for that specific diagnostic setting.

Figure 40-43 shows the diagnostic tests in more detail which include the unique requirements. See Appendices F-1 and F-3 for the iterations and inspiration from existing RDTs, which resulted in these diagnostic tests.

8.2.2 Well-handled diagnostic test procedure

A well-handled diagnostic test procedure includes more than being able to use a diagnostic test. Therefore, each diagnostic test should facilitate the user through three steps:

1) **Query VL**
2) **Use** the diagnostic test
3) **Conclude** the test result (and either refer to a treatment facility or test for another disease)

Thus, the diagnostic tests are designed in such a way that they will guide each user through these three steps. More information about this can be found in Appendix F-4.

What do you see here?

There are two diagnostic setting variables: the resources available and background of the user which have the most influence the specifications of the diagnostic test. These two variables are split up into four levels.
Based on combinations of the levels of these two diagnostic setting variables, different diagnostic test are recommended. Each of these diagnostic tests have a unique set of requirements.

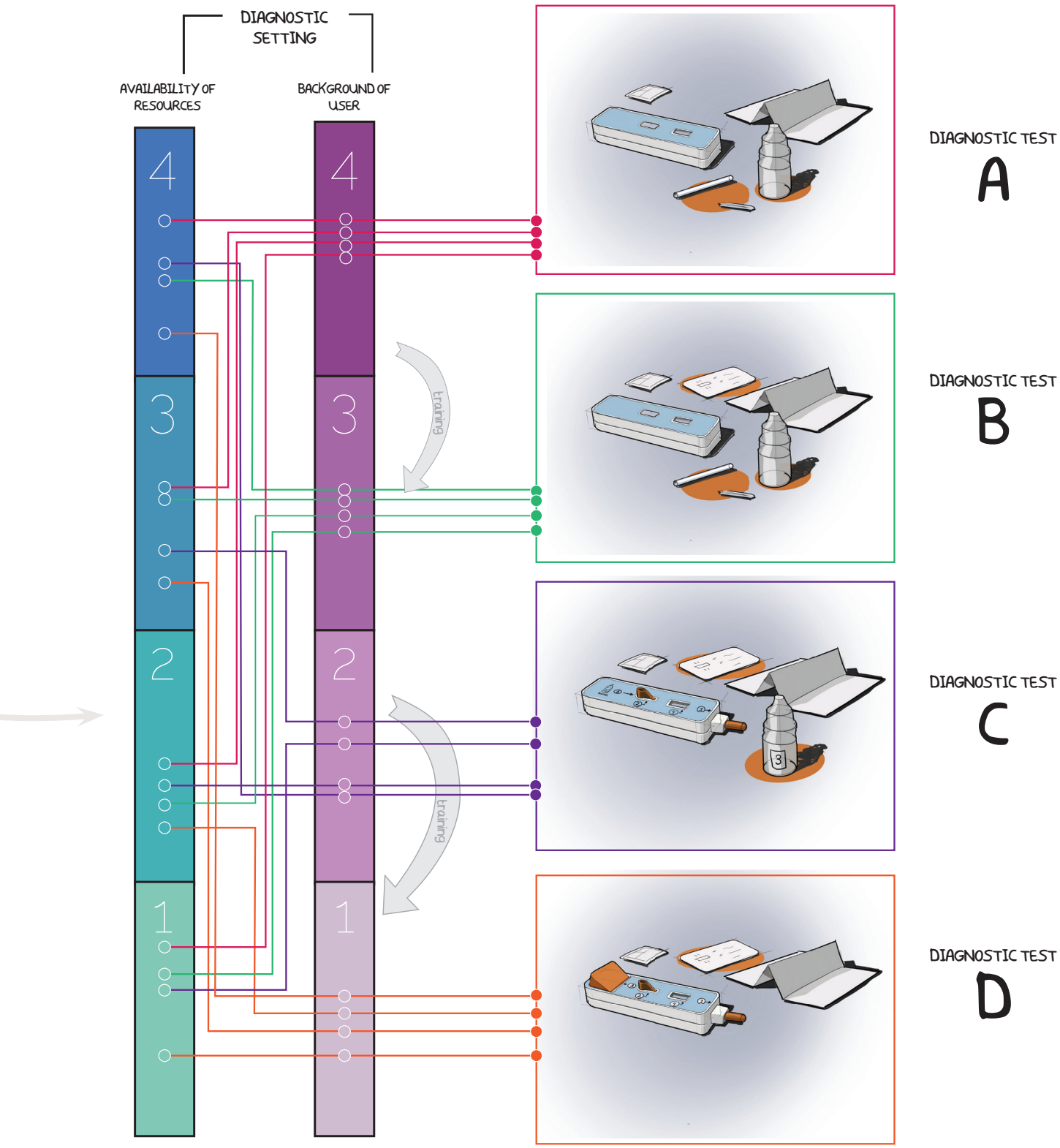


Figure 39: The level of resources and background of user at a diagnostic setting influence the features of a diagnostic test.

Diagnostic test A

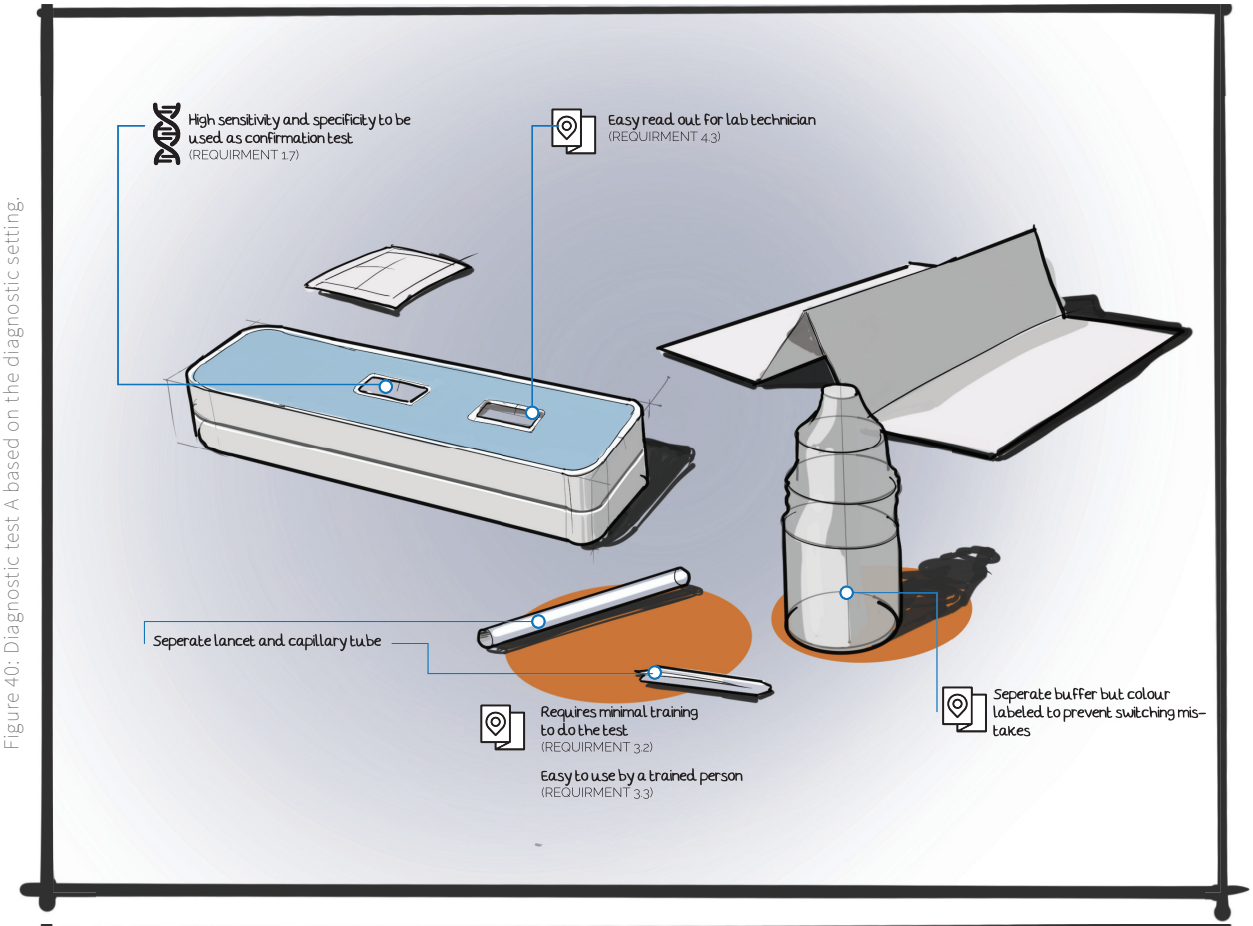


Figure 40: Diagnostic test A based on the diagnostic setting.

Diagnostic test B

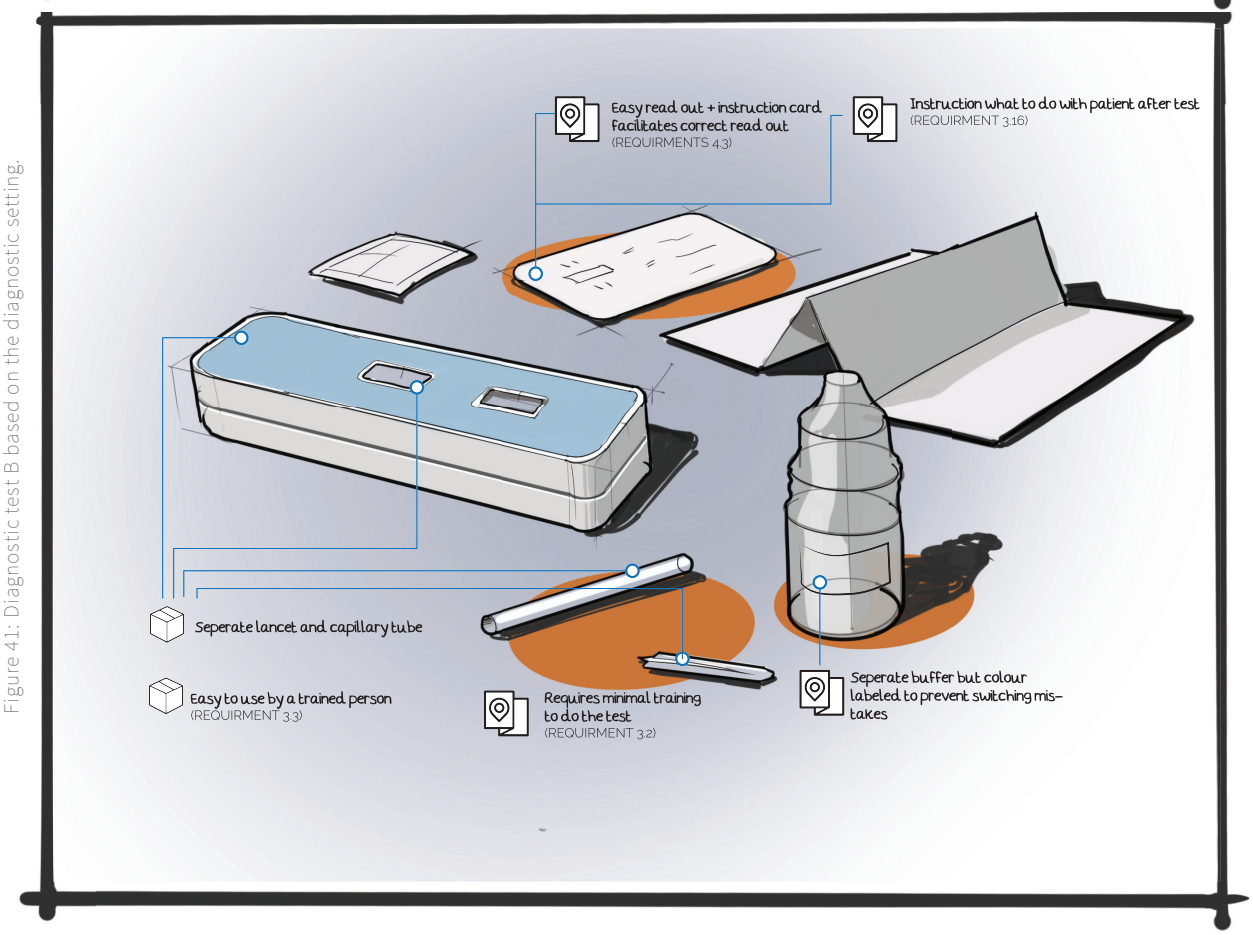
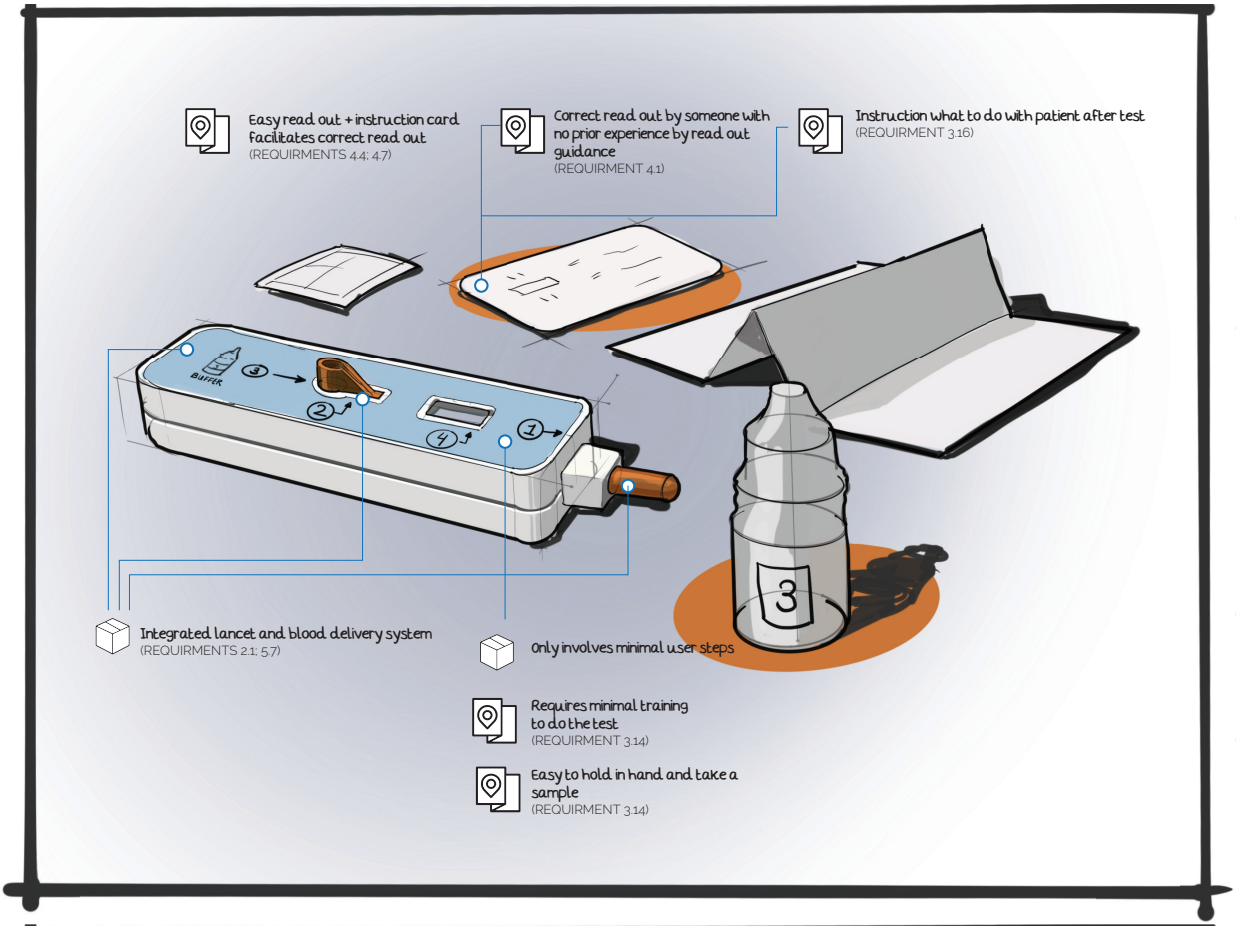
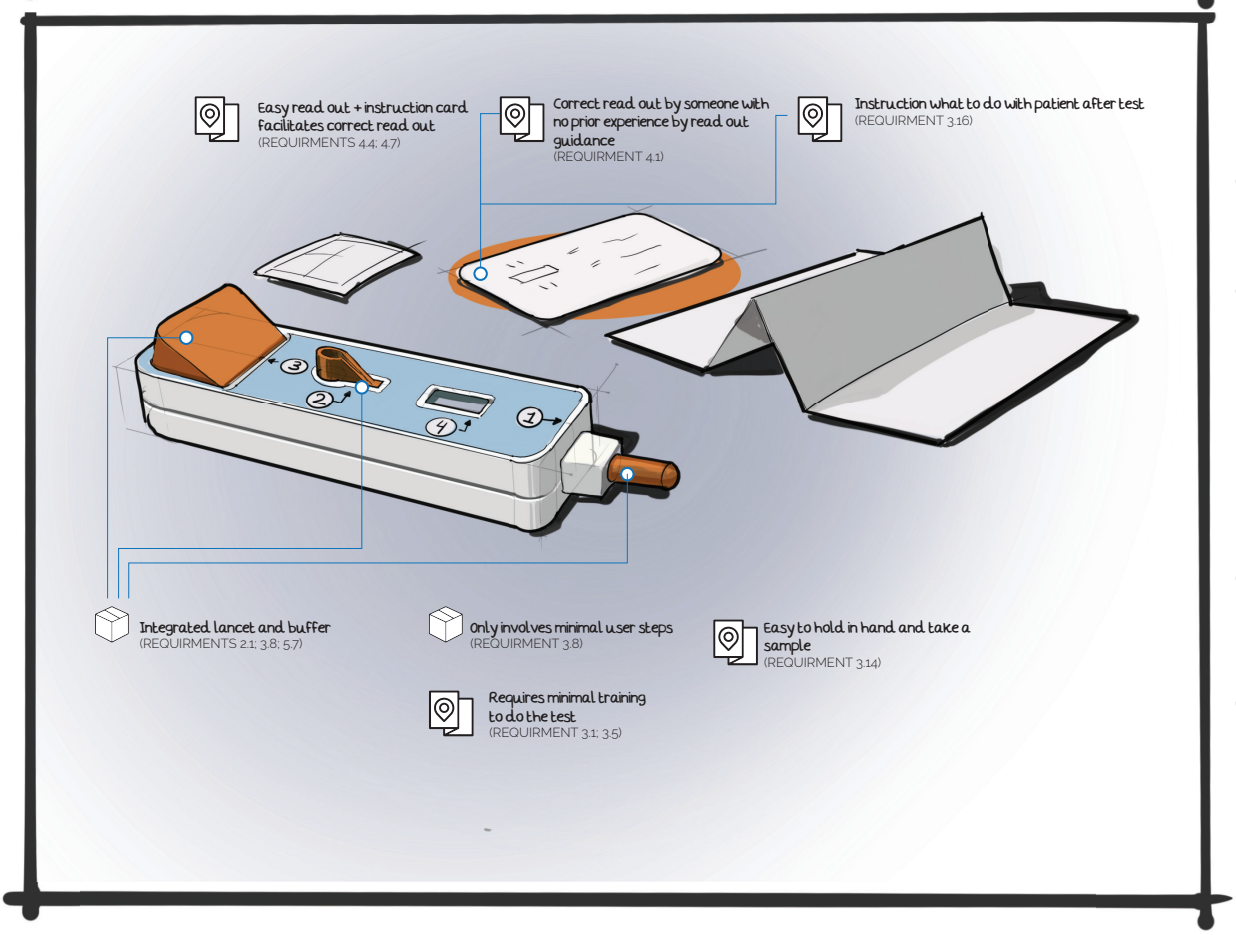


Figure 41: Diagnostic test B based on the diagnostic setting.



Diagnostic test C

Figure 42: Diagnostic test C based on the diagnostic setting.



Diagnostic test D

Figure 43: Diagnostic test D based on the diagnostic setting.

8.2.2 Using a diagnostic test in a non-intended diagnostic setting

The diagnostic tests are recommended for specific diagnostic settings. However, this does not mean that a diagnostic test is automatically used incorrectly when used in another diagnostic setting than proposed.

For example, if diagnostic test D is used in a diagnostic setting with level 3 or 4 resources and background of the user, this does not automatically result in incorrect usage of the diagnostic test — however, the chances of incorrect usage increase. Therefore, 'lower level' diagnostic tests can be used in 'higher level' diagnostic setting, but simply increase the chance of incorrect usage.

On the contrary, when putting diagnostic test A at a diagnostic setting with level 1 or 2 resources and background of the user, this will simplify the usage of the diagnostic test.

Ideally, there will be one diagnostic test which can be used at all test settings to reduce the number of different diagnostic tests. A diagnostic test which would be suitable for every diagnostic setting would ideally meet all requirements. However, as this is probably not feasible, diagnostic test D would be ideal as this one aims to facilitate correct usage in a diagnostic setting with no resources and a user with no medical background. Therefore, this diagnostic test will automatically be usable by a more trained user in a more resource-rich diagnostic setting.

Still, the other diagnostic tests are useful as it might take more time to develop diagnostic test D due to the number of internal components. In addition, if VL diagnostics will move towards community-based testing, it might not be necessary to integrate all components into diagnostic proposal D. Therefore, the other diagnostic tests are still useful.

8.2.3 Training

As mentioned in Chapter 7, training has not been incorporated in the levels of background of the user. However, training does influence the ability to correctly use a diagnostic test. When users get more extensive training, they might be able to perform a 'higher' level diagnostic test without having a higher medical background.

However, it is essential to keep in mind that in these low resource settings there is often a lack of training opportunities due to lack of knowledge and finances. Therefore, in most cases, only basic training will be done. In that case, the user is not able to use a 'higher' level diagnostic test.

SECTION V

Evaluation

Chapter 09: Evaluation

This section of the project consists of one Chapter, which has the purpose of drawing conclusions and evaluating the process and results. First, Chapter 9 provides an evaluation of the diagnostic tests. This includes an evaluation of the project results and to what extend context variation has been taken into account. Based on this, recommendations are made to further develop the diagnostic test. Next, the research questions are answered in an overall conclusion of the project.
In addition, limitations and implications of the research are discussed followed by recommendations for future research. The aim of this is to reflect and indicate avenues for change in future studies. This Section ends with a personal reflection, which includes learnings abased on my journey during this graduation project.

Results of the rK39 can be evaluated after approximately 15 minutes.
Rupa Health Centre, UGANDA.

SECTION V: EVALUATION

Chapter 09

EVALUATION

This chapter aims to evaluate and conclude the project results and come up with recommendations for further development of the diagnostic tests and research. In addition, the implications and limitations of this research are discussed.

9.1 Evaluation

EVALUATION OF THE DIAGNOSIC TESTS WHICH ARE PROPOSED

This project presents the first attempt to more concretely come up with ways to implement this technical principle into the context of VL. Therefore, the diagnostic tests which are proposed in Chapter 8 should be seen as the first recommendations for diagnostic tests and the focus has not been on detailing them.

9.1.1 CONTEXT VARIATIONS

Are the diagnostic tests resistant to change?

For this project, VL has been studied with an emphasis on Kenya and Uganda. However, Leishmaniasis is endemic in other regions in East Africa and the world, such as South Asia (India and Bangladesh). It is essential to understand the possible context variations between different VL endemic areas in East Africa and worldwide, to facilitate a broader application of these diagnostic tests.

9.1.2 East African Context Variation

As the field trip took place in the VL endemic areas in Kenya and Uganda, the steps and decisions made during this project are based on the insights and information collected explicitly from these countries. Therefore, insights gathered from the findings are valid for these particular regions in Kenya and Uganda and cannot automatically be generalised for all VL endemic areas (in East Africa and worldwide). The disease context and the health care system can vary between endemic regions and countries in East Africa and especially worldwide.

Diagnostic setting variables

The diagnostic tests which are proposed in this project (Chapter 8) bear in mind some diagnostic setting variations in terms of available resources and (medical) background of the user. By taking into account potential variations in the level of medical background, the diagnostic tests become suitable for a variety of users irrespective of the VL endemic region.

For example, a lab-technician in Kenya might be well trained and be part of (medical) background level 3, whereas a lab-technician in Sudan might be part of (medical) background level 2. Therefore, the level of the background of the user is taken into account when creating diagnostic tests instead of a specific title of this user (lab-technician, midwife). Therefore, the proposed diagnostic tests in Chapter 8 are most likely suitable for other VL endemic areas in East Africa besides Kenya and Uganda. Even though variables in a diagnostic setting have been identified (Chapter 7) and are taken into account in developing the diagnostic tests (Chapter 8), it remains essential to carefully consider the characteristics of other diagnostic settings in other countries.

Example

As became clear from the meeting with MSF, HIV / VL co-infections are more prevalent in Ethiopia than in Kenya and Uganda. HIV/VL co-infections have an impact on the course of the disease, the treatment and outcomes of the treatment. Thus, it is possible that there are different requirements which apply to a diagnostic test for Ethiopia compared to Kenya and Uganda.

RECOMMENDATIONS

Consequently, it is essential to keep in mind that the proposals are based on insights from Kenya and Uganda. Even though diagnostic setting variables have been taken into account, some adjustments might be required to make the diagnostic tests suitable for other regions or countries.

Therefore, it is essential to further look into the possible variations between the VL endemic areas in Kenya & Uganda and other VL endemic areas in East Africa. This will help see whether enough diagnostic setting variation has been taken into account into the diagnostic test proposals to be suitable for a broader VL context.

9.1.3 Worldwide VL Context Variation

To enable worldwide application of the diagnostic tests in VL endemic areas, it is important to understand the possible context variations between East Africa and South Asia. Consequently, it is essential to ask the following question:

Would the proposed diagnostic tests also fit in the context of VL in South Asia?

Current serological tests perform differently in East Africa than in South Asia (See Figure 45). It is important to understand the reasons for this difference in performance, to withhold the proposed diagnostic tests in this report from a difference in performance in another continent. The three main reasons why current serological tests (rK39 and DAT) perform differently between East Africa and South Asia are:

- The difference in antibody production.
- The alteration in disease presentation, disease course and endemic trends.
- The cross-reactivity with other infections.

It is crucial to make sure that the proposed diagnostic tests which are based on field insights from East Africa, will not result in performance issues when used in South Asia. Therefore, it is important to evaluate the context variations between the continents to see whether the variations between East Africa and South Asia are covered in the diagnostic tests.

Incorporated diagnostic settings and context variables:

Diagnostic moment & patient status

All the reasons why current diagnostics tests perform differently in South Asia than in East Africa are related to two diagnostic setting variables:

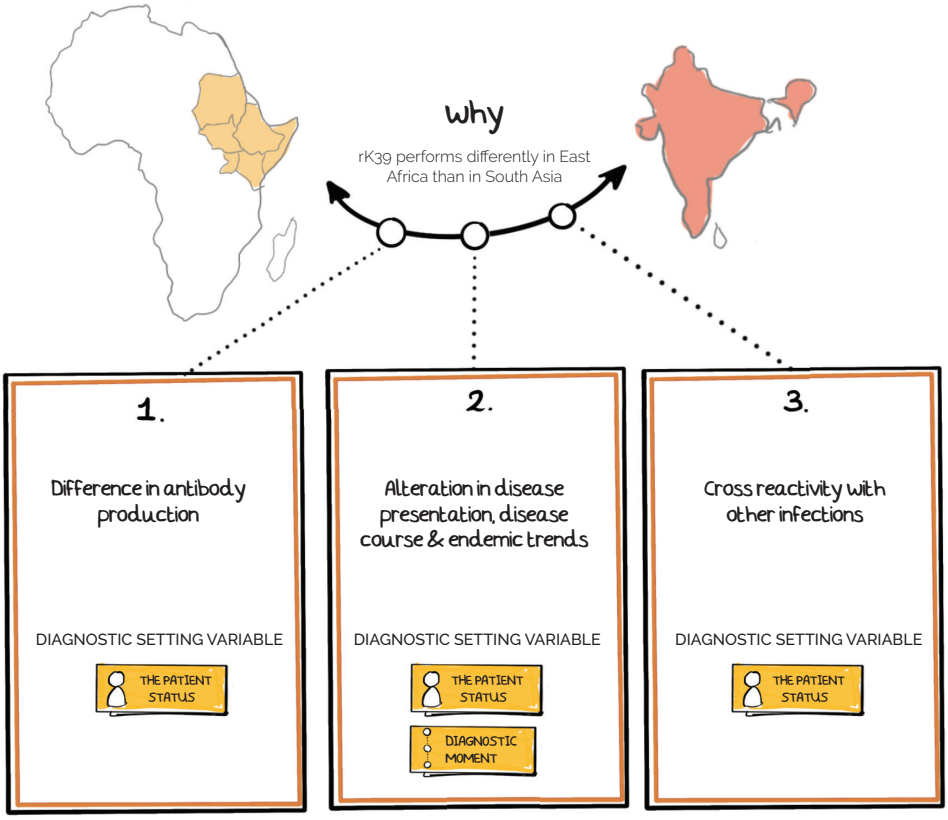


Figure 44: Variation in performance of rK39 between East Africa and South Asia.

1) The patient status

The condition of the patient who is diagnosed with VL. This variable includes aspects such as how sick the patient is, the symptoms and disease presentation and presence or absence of co-infections.

2) The diagnostic moment

The moment when the diagnostic test is used in this diagnostic setting. This can be either before, during or after the treatment.

Patient status

From the field, it became clear that there is a considerable variation between the status of patients within East Africa. However, it is likely that the contrast between patient statuses are even larger between East Africa and South Asia due to other epidemiological diseases, cross-reactivity with other infections (co-infections) and a difference in disease presentation.

The technical principle aims to give reliable test results independent of the immune system of a patient. Thus, potential 'patient status variation' are covered in the general requirements of the diagnostic test and should not affect the performance of the diagnostic test between these continents .

Diagnostic moment

The diagnostic practices and treatment procedures vary between South Asia and East Africa due to a difference in disease presentation and epidemiological dynamics.

For example, treatment in East Africa requires 17 days of hospitalisations whereas, in South Asia, treatment consists of a single-dose intravascular injection which eliminates lengthy hospital stays (DNDI, 2019).

These differences can affect the role of diagnostics in VL case management between East Africa and South Asia (diagnostic moment).

As visible in Figure 46, the diagnostic moment does

not directly affect the features of the diagnostic test. Therefore, the variations between diagnostic moments in East Africa and South Asia will most likely not affect the features of the diagnostic test but will influence the resources, location, patient status and background of the user.

As long as variations of the resources, patient status and background of the user in South Asia are incorporated in the diagnostic tests, they should be suitable for the South Asian context.

User & resources

The variables, background of the user and resources directly influence the features of a diagnostic test (Figure 46). These variables have been split up into four levels in Chapter 7, which take into account variations between available resources and users. Therefore, as long as the resources available and background of the user in South Asia can be categorised in of these levels, it can be assumed that the proposed diagnostic tests will also be applicable for South Asian context.

RECOMMENDATIONS

Variation East Africa – South Asia

It is necessary to understand the diagnostic settings (and variations) in South Asia to make sure the diagnostic tests which are proposed in this project are suitable for these settings.

In addition, more research is needed to see whether the proposed five variables are the only ones, or if there are additional variables in the South Asian context which have an impact on the diagnostic tests.

As it is crucial to understand the VL context and diagnostic settings in South Asia it is recommended to do a field trip and theoretical exploration of South Asia VL context.

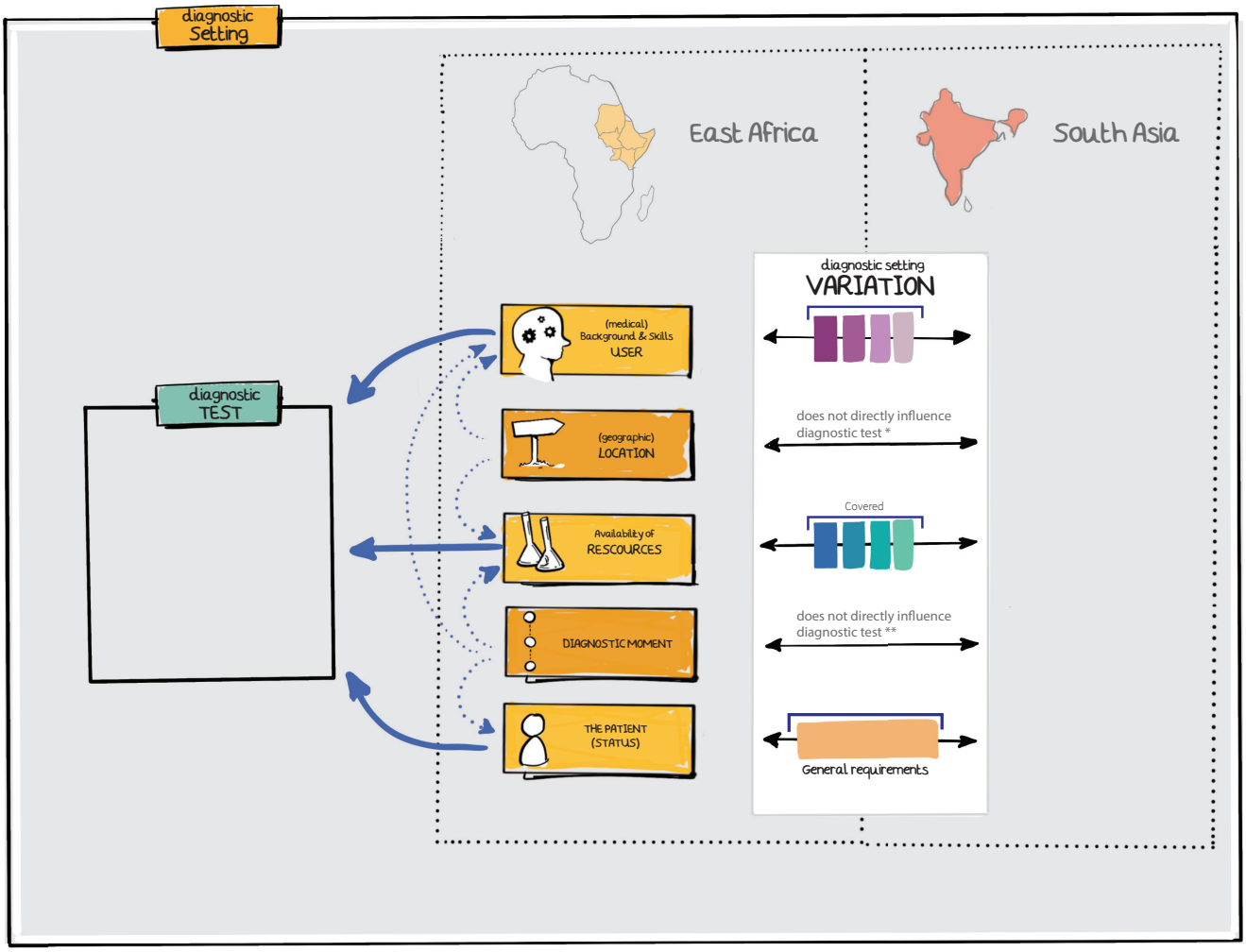


Figure 45: Based on the diagnostic setting variables: Would the diagnostic tests fit in East Africa and South Asia?

9.1.4Dynamic context

Will the diagnostic tests still work when the context of VL or technical principle change?

As the context of VL is dynamic, it will most likely keep changing in the future. Hence, it is important to keep an eye on these changes. At the moment, the technical principle in an early phase of development which means it will keep on developing. These developments of the technical principle might result in alterations and variations

RECOMMENDATION
It is important to keep track of the developments of the technical principle as well as the changes in the context of VL, to ensure diagnostic tests which are suitable for a future (nearly) VL context..

Contextual changes

Change of VL treatment
The focus of this project was on envisioning the technical principle integrated into a diagnostic test in a context where the treatment still requires hospitalisation for 17 days. However, it is crucial to take into account that the current treatment for VL is most likely not a permanent one. As DNDi is performing clinical trials on VL treatment and aims to develop an oral VL drug, treatment will most likely change in the future. A changing VL treatment will affect the case management of VL and thus automatically influence the role of VL diagnostics. If oral treatment will be introduced, diagnostics will play a different role and can potentially even help in the elimination of the disease in East Africa.

It is important to note that the proposed diagnostic tests are based on the current VL context where treatment requires 17 days of hospitalisation. It is important to consider a change in the VL treatment will affect the case management of VL and thus automatically influence the role of VL diagnostics. This could have an impact on the features of a diagnostic test.

RECOMMENDATION
Besides treatment, there are many other possible changes in the context of VL. Thus, it is recommended to keep up to date on the developments and changes in the context of VL and keep reflecting whether this will impact the role of diagnostics and thus the diagnostic tests.

Technical principle changes
Besides changes in the context of VL, it is important to take into account the potential changes in the course of development of the technical principle. As the technical principle is broadly applicable, this might result in a shift in the targeted disease. In this case, the context of this ‘new’ disease should be carefully studied.
In addition, it is important to keep track of the developments of the principle. For example, what seems feasible now, might turn out not to be feasible in a year. This works the other way around as well: what does not seem feasible for this technical principle now, might turn out to be feasible.

RECOMMENDATION
As the technical principle is still in an early phase of the development, it is important to keep track of the progress and changes. This will facilitate a better fit of the technical principle in a diagnostic test and diagnostic settings.

9.1.5 Further development

The technical principle is still in an early phase of development and the context of VL was unfamiliar at the start of this project. Therefore, the proposed diagnostic tests are the first recommendations to apply the technical principle to a diagnostic setting. Thus, there are still many steps which can be taken to develop the diagnostic tests further. Therefore, several recommendations are made.

- **Atmo diagnostics**

As the HIV tests from Atmo have inspired the creation of the diagnostic tests, it is recommended to understand more about the HIV tests from Atmo diagnostics. Therefore, it would be beneficial to take a look at the embodiments of Atmo diagnostics and see whether a partnership could be useful.
See Appendix F-3 for the overview of current diagnostic tests which have served as inspiration.

- **Evaporation**

One of the major challenges when integrating a buffer into a Rapid Diagnostic Test such as in diagnostic test D (Chapter 8), is that the buffer can evaporate when exposed to high temperatures. Solving these issues is out of the scope of this project.

RECOMMENDATION
For further development, it is recommended to understand how the HIV test from Atmo Diagnostics solves this issue.
How do they integrate a buffer? And how do they close off the buffer until being activated by pushing a button?

Waste

Amount of waste
Integrating several components (such as a needle and capillary tube) into a diagnostic test can have an impact on the size of the housing and number of internal components. Thus, this integration might affect the weight and materials which are needed for a diagnostic test. This might increase waste per diagnostic test.
Therefore, to further develop the diagnostic test, it is important to understand how other diagnostic test producers deal with waste.

Disposal of clinical waste
Correctly disposing of clinical waste is essential. Sharp items (such as needles) should be disposed of in a separate box. However, in case a needle is integrated into a diagnostic test, it should be safely stored.

Therefore, disposal or storage of clinical waste should be carefully considered, especially in the case of integrating parts which will be in contact with a blood sample such as needles and capillary tubes into a diagnostic test.

Test the diagnostic tests (in the field)

The diagnostic tests are created based on insights from theoretical exploration and field research and iterated upon based on feedback from stakeholders and experts. However, the proposed diagnostic tests have not been validated and tested in the original field setting.

To validate the usability of the proposed diagnostic tests, it is recommended to do usability tests with the intended users to see whether they work in the intended diagnostic settings.

However, it is recommended to test the diagnostic tests already closer to home and make some design iterations. Lay people (everyone who has no medical background) can be asked to do a fake VL diagnosis. This will help to understand the usability of the diagnostic test better and make some iterations. Based on these improvements, the diagnostic tests should be taken to the field to give them in the hands of actual users (see recommendation at the top of this box).

Qualitative test-of-cure

As the technical principle aims to be more specific (exact specificity is still unknown), it can detect the presence of pathogens in a very early stage. This means, that it is possible to test someone on VL even when that person has only very limited pathogens in the body. As became clear later in a later stage in the project, unfortunately, this might result in a positive test result when a patient only has few pathogens in the body after treatment. Thus, a patient can potentially still have remaining pathogens in the body will cause a positive test result even though the patient might be cured. Therefore, a test-of-cure might require quantitative readout to be able to detect the pathogens DNA.

It is important to understand whether or not pathogens are still present in the patient's body after treatment. Also, it is recommended to look into the feasibility of using the technical principle for quantitative read-out.

Chemolingot Sub-County Hospital, soon going to be another VL treatment centre, KENYA.

9.2 Conclusion

HAVE THE RESEARCH QUESTIONS BEEN ANSWERED?

SECTION II CONTEXT

Theoretical exploration was combined with a two-week field trip to the VL endemic regions in Kenya and Uganda. Information was gathered by conducting semi-structured interviews, doing observations and having informal conversations with health care workers, doctors, public health officers, midwives and nurses, lab technicians, community health volunteers and people living in communities.
This resulted in a more in-depth understanding of the context of Visceral Leishmaniasis in Kenya and Uganda which helped to answer **RQ1: What are the current diagnostic practices and challenges for Visceral leishmaniasis within the health care system in East Africa?** (See Section III).

It can be concluded that the **most critical challenges in the context of VL are the inaccessibility to VL care** (diagnostics and treatment) and the **unreliability of current diagnostic practices.**
There are many obstacles which cause issues with accessibility to VL care. The most important barriers that were identified during the field trip are the large distances, limited number of health care facilities, lack of resources & staff, low index of suspicion & awareness of VL by health care workers and people living in affected areas. In addition, VL is often misdiagnosed as the symptoms of VL are similar to other (epidemic) diseases.
All these barriers make it challenging for patients to get access to VL diagnostics and treatment.

In addition to the issues to access VL care, current diagnostic tests and procedures have their limitations in performance (unreliability). Diagnosing VL relies on the performance of the serological diagnostic test rK39 in combination with the presence of clinical symptoms. However, especially in East Africa, this rK39 diagnostic test does not perform well. In addition, serological tests (rK39 and DAT) are antigen-based, so unsuitable for testing patients with a relapse, re-infection or after treatment. More reliable confirmation diagnoses through microscopic examination of tissue aspirates or sophisticated serological techniques (such as DAT) require more **advanced tools and skills which are often unavailable.**
Therefore, there is a need for a more reliable diagnostic test which is suitable for low resource settings of VL in East Africa. Moreover, treatment for VL is lengthy, expensive and requires hospitalisation for 17 days in a row. Treatment is only provided at a limited number of places in East Africa which causes additional accessibility issues for patients.

Besides understanding the context, the benefits of the technical principle are made explicit.
To test a person for VL, the technical principle can be integrated on a diagnostic test strip. When

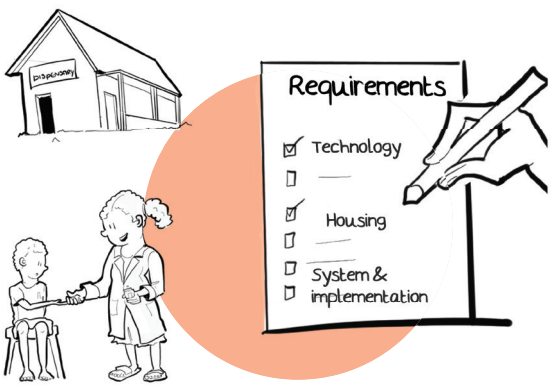
SECTION III TECHNICAL PRINCIPLE

someone is infected with the *Leishmania* parasite, pathogens will be generated in the body. By adding a blood or urine sample, the technical principle can detect the pathogens in roughly four steps:

1) **Separating** the pathogens from the rest of the sample.
2) **Amplify** the pathogens.
3) **Detecting** the pathogens DNA based on a CRISPR/cas9 system.
4) **Indicating** if the patient has VL or not based on a colour metric readout.

After understanding the technical principle and the current diagnostic practices from the field (part of RQ1), the benefits of the technical principle could be made explicit.

This resulted in answering **RQ2: What are the benefits of the technical principle compared to current diagnostic practices?**
The technical principle enables DNA detection. This results in **reliable test results independent on someone's immune system,** whether someone has an early stage infection, a relapse or reinfection. Current serological diagnostic tests (rk39 and DAT) are not able to do this.
In addition, this technical principle facilitates **quick** test results and is **broadly applicable**. Therefore, the technical principle has great promises to detect other infectious diseases worldwide. The technical principle can be multiplexed so multiple diseases can be tested simultaneously.



SECTION IV FUTURE APPLICATION

To understand where the technical principle could be implemented in the context of VL, a session with the team of IDE and Applied sciences was held. This session resulted in the creation of seven scenarios which all represent a unique way to **combine the features of the technical principle into a diagnostic test which fits the diagnostic setting in the context of VL and matches a local need**.

Thus, the scenarios answer **RQ3: What are promising ways* to implement the technical principle to a diagnostic setting in the context of VL?**

The following seven scenarios are created:

1) **Screening & confirming**
2) **Test-of-cure**
3) **Community testing**
4) **Screening day**
5) **Integration with 'malaria' journey**
6) **Follow-up**
7) **Airport testing**

All scenarios were evaluated with experts from Médecins Sans Frontières and several stakeholders from the field. Based on this feedback, the two most promising scenarios were selected. The selection of the most 'promising' scenarios was based on **feasibility of the technical principle**, **the contextual fit** and if there **a local need** (can it improve VL case management). The two selected scenarios are:

- **The test-of-cure scenario**

The test-of-cure scenario is chosen as it fills a critical gap in current case management *(current serological tests (DAT and rk39) cannot be used to confirm relapses)* by implementing the benefits that technical principle has to offer.

- **The screening & confirming scenario**

This scenario is chosen as it offers a more reliable diagnostic test *(technical principle benefit)* which is accessible to the people. Therefore, it matches the local need for more accessible and reliable diagnostics with the capabilities of the technical priniciple.

An additional session was held with the team of IDE and AS in which the diagnostic settings of the two selected scenarios were further detailed to facilitate a better fit in the context. This resulted in the understanding that **the diagnostic setting influences the features of the diagnostic test.** By zooming in at the diagnostic settings, five critical variables are identified which explain the variation between diagnostic settings. These are:

1. **the geographic location**
2. **the resources available**
3. **the background of the user**
4. **the diagnostic moment**
5. **the patient status**

These variables clarify **that** the diagnostic setting influences the features of a diagnostic test. However, to answer *RQ4: What are the consequences of a diagnostic setting for the requirements of the diagnostic test?* requirements need to be created to

see how the diagnostic setting actually affects the requirements for a diagnostic test.
Thus, requirements are composed and categorised which resulted in the division between general and context-specific requirements.

1) General requirements: *Requirements that are applicable for a diagnostic test irrespective of the diagnostic setting.*

2) Context-specific requirements: *Requirements where the applicability depends on the diagnostic setting.*

From the five diagnostic setting variables, two variables: **the resources available** and **the medical background of the user** have the most influence on the features and requirements of the diagnostic test.
Therefore, the context-specific requirements are further categorised based on these two variables and can be split into three groups:

- **Resource-specific requirements**
- **User-specific requirements**
- **Scenario specific requirements**

The categorisation of the requirements and diagnostic setting variables have resulted in **four different diagnostic tests. Each diagnostic test has a unique set of requirements**. With this, **RQ4: What are the consequences of a diagnostic setting for the requirements of the diagnostic test?** can be answered.

The diagnostic setting does influence the applicability of the context-specific requirements. The background of the user and the resources available at a diagnostic setting have the most influence on the features of a diagnostic test.

- The background of the user in a diagnostic setting is incorporated in the user-specific requirements. These user-specific requirements influence the housing and usability guidance of a diagnostic test.
  - The lower the (medical) background of the user, the more the user needs to be guided in the usage of the diagnostic test. Therefore, it is recommended to integrate more components (such as the needle, buffer and capillary tube) into the diagnostic test. Similarly, the higher the (medical) background of the user, the more intervention steps the user can handle. When a user has an extensive medical background, it is less crucial to integrate all elements into a diagnostic test.

- The level of resources available at a diagnostic setting affects the requirements for the technical principle and housing of the diagnostic test.
  - The lower the 'level' of resources available at a diagnostic setting, the more basic lab equipment (capillary tube, needle, alcohol swab) needs to be part of the diagnostic test kit. Also, the higher the 'level' of resources available at a diagnostic setting, the less important it is to integrate basic lab equipment into the diagnostic test.

The variation in patient status in a diagnostic setting are incorporated in the general requirements for the diagnostic test. This means, that when a patient is, co-infected, relapsed or re-infected, the technical principle needs to be able to detect all of these people irrespective of their immune system. Thus, the possible variations between patients (patient status) in a diagnostic setting have been incorporated into the general requirements for the technical principle.

9.3 Discussion

LIMITATIONS AND RECOMMENDATIONS

Lastly, the limitations of this research and the usability of the methods are discussed. Reflecting on the approach will help to indicate avenues for change in future studies.

Field trip

First, the representation of the field trip is reflected upon based on the visited facilities, communities and people encountered.

9.3.1 Representation of the visited locations and areas

Relatively 'calm' VL areas were visited

VL is endemic in several countries in East Africa and is related to civil and unrest conflict areas and population. Collin et al. (2014) noted that VL has a significantly higher incidence among populations during and following periods of unrest and conflict in Sudan and South Sudan. Jacobson (2011) and Hotez et al. (2014) suggested that these conflicts and the corresponding mass population displacements can complicate the disease course and vector surveillance.

However, the areas which were visited during the field trip of this project are not in civil conflict. Thus, the visited regions might alternate from other VL endemic areas in East Africa. Therefore, insights from Kenya and Uganda cannot automatically be generalised for East Africa.

Such VL endemic conflict areas in South Sudan and Sudan might have different characteristics in terms of diagnostic settings. For example, refugee camps in conflict areas 'attract' NGO's such as MSF who set up base camps to provide care to the people. Therefore, the diagnostic settings might differ in these conflict areas as seen in the field in Kenya and Uganda.

Before generalising the insights of this research for entire East Africa, it is recommended to understand more about the case management and context of VL in other countries (including those in conflict).

More communities and health facility visits in different VL endemic areas

During the trip, six communities and multiple diagnostic and treatment facilities have been visited. This helped to understand more about the context of VL in Western Kenya and North-East Uganda. However, as discussed in the 9.1 Evaluation, it is recommended to study the VL context of different endemic areas before generalising the obtained insights for a broader VL context.

9.3.2 Representation of the people

During the field trip, the team had the pleasure to speak to many people with different occupations and expertise. This resulted in a rich collection of insights which are based on the knowledge from a wide variety of people.

Language barriers

The communication with doctors, health care workers and employees was relatively easy as they spoke English. However, the patients and people in the communities only spoke the local language: Pokot.

Due to these language barriers, it was not possible to speak directly to patients at the treatment facilities in both Uganda and Kenya. Therefore, the patient stories in Chapter 4.2 are fictional and based on information and insights gathered during the field trip. However, for future research, it could be interesting to have conversations with VL patients to create more accurate patient stories. In that case, it is important to consider language barriers and arrange a translator.

During community visits, a CHV was involved who helped with the translation (from Pokot to Swahili to English and back). However, the number of

translations which were required to communicate with people from the tribes might have resulted in some misinterpretations (from both sides).

9.3.3 Research permit

Due to the lack of an official research permit, it was not possible to conduct 'formal' interviews in Kenya. Therefore, the interviews were covered into an 'informal' conversation style. In this way, the questions could be answered, without the need for a formal questionnaire.
This way of 'informal' interviews was suitable for the purpose of this study: understanding the context and the barriers related to VL. However, for future research, it is recommended to consider whether or not a research permit would be useful.

9.3. 4 Structured and flexible field approach

Even though there was a quite detailed travel schedule of the field trip, there were a lot of uncertainties which made it challenging to know what to prepare in terms of research material. Thus, by developing multiple questionnaires, tools and templates, it was possible to effectively and flexibly use the tools and questionnaires prepared dependent on the situation in the field. Although some of the prepared materials have not been used, this flexible approach of conducting information helped to get the most out of this field trip.
In addition, templates supported a structured way to collect information and insights. These templates helped to keep an overview of the collected information and helped to summarise information and find relationships between insights during the field trip. This has resulted in a more effortless way to translate all insights. Prepared frameworks and templates have been of great added value, not only during, but also after the field trip.

Post Field trip

9.3.5 Unclear distinguishing factors between the scenarios

The diagnostic setting variables were not (yet) clear during the creation of the scenarios. Throughout this project, this has resulted in some confusion both among myself and the team of Applied Sciences about the actual differences between the scenarios.

During the project, it became clear in what way the scenarios vary from the other (Chapter 6.1).
However, this unawareness of the exact distinguishing factors of the scenarios might have influenced the feedback received from stakeholders. For future research it is recommended to ask for feedback on each scenario specifically for the three elements: 1) Which scenario do you think is most feasible for the technical principle? 2) Which scenario fits best in the context of VL? 3) Which scenario has greatest impact on VL case managment.

9.3.6 The representation of the respondents of the feedback form

The feedback form (with the scenarios) was filled out by five respondents. Even though the respondents have a different expertise, they were all part of either KEMRI or the University of Nairobi.
It is recommended to evaluate the scenarios with people working in the (public) health sector in Kenya and Uganda to get feedback from more diverse group of respondents. Ideally this would be CHV's, doctors, public health officers and lab-technicians. Therefore, more respondents and a more diverse group of respondents would improve the quality of the feedback.

9.3.7 Requirements

It is important to note that when the requirements are not real requirements yet as they are not specific enough. Thus, this project refers to 'requirements' when in fact they are wishes. This is done from a convenience point of view as it is easier to talk about requirements than wishes.
When further developing the diagnostic tests as proposed in this project, it is recommended to make the requirements more specific.

9.4 Personal reflection

WHAT DID I LEARN FROM THIS PROJECT?

It has been a great pleasure to work on this project. Not only did I learn a lot from a new context, but this project also enabled me to learn about myself, personally and professionally.

Compared to the projects I have been doing throughout my study, this project was completely different in every single way. During my master IPD, I figured out that I am quite an all-around designer, but that my heart does not lie in 'product' design. Prior to this project, I figured that I did not want to do a typical 'design-project'. When this project came across, I had no idea what to expect. There was a technical principle which I did not understand (yet) and a context of a tropical disease in Africa which was entirely new to me. Even though this was slightly scary, I decided that it would be a great opportunity, not only to explore an entirely new context but to see if my capabilities could be applicable in such a project.

Throughout this project, I found joy in researching which came as a surprise as I had never envisioned myself as a researcher. I have always seen 'researching' as something which involves too much reading and too little hands-on tasks. However, during this project, I discovered that I am more analytic in my way of thinking than I thought. This project made me release that I am generally interested in trying to comprehend complex problems by structuring lots of information. Visual communication helped me to keep an overview of the complexity and keep everything communicable to my supervisors and stakeholders. One of my personal goals was to use visual communication to enhance conversations and enable project structure. Even more, than priory expected, this project was the perfect canvas to use my visualisation skills.

Lastly, I am proud of the fact that I went through this project without pushing myself too hard as was often the case in the previous (individual) project. I managed to carefully spend my energy and (most of the time) tame my perfectionism. By forcing myself to keep a quite strict 8h-a-day-policy, I was able to use my time efficiently while maintaining a good graduation-life-balance.

Being very critical and perfectionistic about my work often resulted in a sort of inner-disappointment of my accomplishments. However, during this project, I learned to recognise my sabotaging thoughts which helped me to be less harsh on myself and my results.

Of course there is still a lot to learn, but for now, I can say that it has been a great pleasure to work on this project. I am looking forward to applying my skills and learnings into a new project.

Pretending that I know what I'm looking at...
Kimalel Health Centre, Kenya.

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DIAGNOSTICS FOR VISCERAL LEISHMANIASIS IN LOW RESOURCE SETTINGS WITHIN EAST AFRICA

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