Strengthening the public downstream SLD supply chain for MDR-TB: Lessons learnt from a Western Cape Case Study

by

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Declaration

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Abstract

Strengthening the public downstream SLD supply chain for MDR-TB: Lessons learnt from a Western Cape Case Study

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Systemic problems in the supply chain of second-line anti-TB drugs (SLDs) for multidrug-resistant tuberculosis (MDR-TB) are well documented and contribute significantly to the difficulties preventing successful control of the disease. Though literature contains a wealth of proposed changes to global SLD supply chain policies, there is a significant research gap related to quantitative modelling of the SLD supply chain to accurately predict the expected impact of these proposed changes on the availability and delivery of SLDs. The global SLD supply chain consists of two components: (i) the "upstream" component which includes all activities from the manufacturing of the active pharmaceutical ingredient through to the warehousing of drugs prior to shipment; and (ii) the "downstream" component which includes in-country warehousing and delivery of drugs to various healthcare facilities. In this research study, a downstream SLD supply chain is modelled using real-world data. The model is built for one SLD used in the MDR-TB treatment regimen, namely amikacin. This research forms part of a bigger study that will eventually incorporate both the upstream and the downstream components of the supply chain into a single model. A model of the current downstream segment of the supply chain for SLDs in the Western Cape was developed using a System Dynamics modelling approach. The model has been built and validated using real-world data provided by the Western Cape Department of Health (WCDoH). This model has been used as a platform for: (i) studying the behaviour and stability of the downstream component of the global SLD supply chain; and (ii) testing the

impact of various supply chain policy changes that have been proposed. In addition to the modelling results, an analysis of the WCDoH data has also produced a number of insights into the function of the downstream supply chain, examples of these include:

- 13% of SLDs ordered by the Cape Medical Depot (CMD) are only received more than three months after the order date by suppliers; and
- 267% more units of amikacin than what is required on average are available at the CMD every month, leading to ineffective inventory management.

The modelling results show that the factor that will most likely lead to the biggest improvement in the performance of the SLD supply chain is reduced lead time. Therefore, selecting suppliers that provide shorter lead times should be a priority. Furthermore, the results show that significant opportunities could be unleashed by adjusting the policy for determining the desired minimum and maximum levels of stock at the CMD. This research makes a contribution by: (i) increasing the understanding of the strengths and weaknesses of the SLD supply chain; (ii) quantitatively evaluating the expected impact of suggested changes to the global SLD supply chain; and (iii) proposing a methodology that can be used to model and evaluate other downstream medication supply chains.

Uittreksel

Versterking van die openbare 'stroomaf' SLD voorsieningsketting vir MDR-TB: Bevindinge van 'n gevallestudie wat op die Wes-Kaap gefokus is

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Sistemiese probleme in die voorsieningsketting van tweede lyn teenmiddels (SLDs) vir multi-weerstandbiedende tuberkulose (MDR-TB) is goed gedokumenteer en dra aansienlik by tot die voorkoming van die probleem en om die siekte suksesvol te beheer. Alhoewel literatuur menigte voorgestelde wysigings vir die globale SLD ketting beleide bevat, is daar 'n beduidende navorsingsgaping wat verband hou met kwantitatiewe modellering van die SLD ketting. Dit lei daartoe dat die verwagte impak van hierdie voorgestelde wysigings aan die beskikbaarheid en die lewering van SLDs nie akkuraat kan voorspel word nie. Die globale SLD voorsieningsketting bestaan uit twee komponente: (i) die "stroomop" komponent wat alle aktiwiteite van die vervaardiging van die aktiewe farmaseutiese bestanddeel insluit tot by pakhuise van die teenmiddels voor dit versprei word; en (ii) die "stroomaf" komponent wat binnelandse pakhuise en aflewering van die teenmiddels na verskeie gesondheidsfasiliteite. In hierdie navorsingstudie is 'n stroomaf SLD voorsieningsketting gemodelleer met behulp van werklike data. Die model is gebou vir een SLD wat gebruik word in die MDR-TB behandelingsstelsel, naamlik amikasien. Hierdie navorsing vorm deel van 'n groter studie wat beide die stroomop en stroomaf komponente van die voorsieningsketting in 'n enkele model inkorporeer. 'n Model van die huidige stroomaf afdeling van die voorsieningsketting vir SLDs in die Wes-Kaap is ontwikkel deur 'n Stelsel Dinamika Modellering benadering. Die model is gebou en bekragtig met behulp van werklike data wat deur die Wes-Kaapse Departement van Gesondheid (WKDvG) voorsien is. Hierdie

model is gebruik as ‘n platform vir: (i) die bestudering van die gedrag en stabiliteit van die stroomaf komponent van die globale SLD voorsieningsketting; en (ii) om te toets wat die impak van verskeie voorgestel voorsieningsketting beleidsveranderinge is. Bykomend tot die modellering resultate, het ‘n ontleding van die WKDvG data ook ‘n aantal insigte van die funksie van die stroomaf voorsieningsketting geidentifiseer. Voorbeelde van hierdie sluit in:

- 13% van SLDs wat bestel word deur die Kaapse Mediese Depot (CMD) word slegs meer as drie maande na die beveldatum deur verskaffers ontvang; en
- 267% meer eenhede van amikasien as wat benodig word, word gemiddeld beskikbaar gestel deur die CMD elke maand, wat lei tot oneffektiewe bestuur van voorraad.

Die modellering resultate toon dat die faktor wat waarskynlik sal lei tot die grootste verbetering in die doeltreffendheid van die SLD voorsieningsketting is, om lei tyd te verminder. Daarom moet die keuse van verskaffers wat korter lei tyd aanbied ‘n prioriteit wees. Verder toon die resultate dat beduidende verbeteringe geskep kan word deur die beleid vir die bepaling van die gekose minimum en maksimum vlakke van voorraad aan die CMD aan te pas. Hierdie navorsing lewer ‘n bydrae tot: (i) die verhoging van die begrip van die sterk- en swakpunte van die SLD voorsieningsketting; (ii) die kwantitatiewe evaluering van die verwagte impak van voorgestelde wysigings aan die globale SLD voorsieningsketting; en (iii) stel ‘n metode voor wat gebruik kan word om ander stroomaf medikasie voorsieningskettings te evalueer.

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The Author,
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Dedications

It is with my deepest gratitude that I dedicate this thesis to my loving parents, Adel̂ and Wilhelm, who have offered unwavering love, support and encouragement.

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Nomenclature

Acronyms

ABS Agent-based simulation

Am Amikacin

AMRH African Medicines Regulatory Harmonization

API Active pharmaceutical ingredient

ARV Anti-retrovirals

BC Base case

CAS Complex adaptive system

CDC Centers for Disease Control and Prevention

CLD Causal loop diagram

CMD Cape Medical Depot

CSC Centre for Statistical Consultation

DES Discrete-event simulation

DOTS Directly observed treatment, short-course

DR-TB Drug-resistant tuberculosis

DS-TB Drug susceptible tuberculosis

DST Drug susceptibility testing

EMA European Medicines Agency

EMR Electronic medical records

FDA Food and Drug Administration

FEFO First-expired, first-out

FIFO First-in, first-out

FLD First-line anti-TB drugs

FPP Finished pharmaceutical product

GDF Global Drug Facility

GDP Gross domestic product

GLC Green Light Committee

GLI Global Laboratory Initiative

GSCF Global Supply Chain Forum

HIV Human immunodeficiency virus

ICC Intraclass correlation coefficient

INH Isoniazid

IOM Institute of Medicine

LPA Line probe assay tests

MCC Medicines Control Council

MDR-TB Multidrug-resistant tuberculosis

NDoH National Department of Health

NRA National Regulatory Authority

POC Point-of-care

PQ Pre-qualification

PRP Patient ready pack

QALY Quality-adjusted life-years

QA Quality assured

R&D Research and Development

RIF Rifampin

SCC Supply Chain Council

SCM Supply chain management

SCOR Supply Chain Operations Reference Model

SD System Dynamics

SLD Second-line anti-TB drugs

SRS Strategic rotating stockpile

TB Tuberculosis

USAID United States Agency for International Development

WHO World Health Organisation

XDR-TB Extensively drug-resistant tuberculosis

Terminology

Air ticket levy mechanism A mechanism used to raise money for TB

DOTS A programme launched by the WHO to control adherence to TB drug regimens

DOTS-Plus A programme launched by the WHO to prevent the further spread of MDR-TB

Runge-kutta integration A numerical method used to solve differential equations (involves successive approximations)

Z-score Statistical measurement that indicates how many standard deviations an element is from the mean

Model Variables

$\bar{D_{HF}}$ Average monthly health facility demand

α Exponential smoothing constant

B_{CMD} Backlogged orders at the CMD

$\bar{C_A}$ Average monthly drug consumption

C_H Holding costs

C_O Ordering costs

C_{Ob} Obsolescence costs

C_S Shortage costs

D_{CMD} CMD demand

D_{HF} Health facility demand

EOQ	Economic order quantity
IP	Inventory position
$\bar{LT}$	Average monthly supplier lead time
LT	Supplier lead time
O_{Am}	Obsolete drugs
PC	Production cycle
PP	Procurement period
R	Supplier reliability
ROP	Reorder point
S_0	Drugs to CMD
S_1	Drugs to health facilities
S_{CMD}	Inventory on hand at the CMD
SD_C	Standard deviation of consumption
SD_{LT}	Standard deviation of lead time
SF	Safety factor
SL	Service level
SS	Safety stock levels
C_T	Total costs
T_E	Shelf-life of amikacin
T_{max}	Maximum desired level of stock in months
T_{min}	Minimum desired level of stock in months

Chapter 1

Introduction

This chapter introduces the global problem of multidrug-resistant tuberculosis (MDR-TB) and therefore the rational for this study. The primary focus of this research project is expressed in terms of the aim and objectives listed in section 1.3. The outline of the methodology that will be followed to achieve the aim of this research is shown in Figure 1.2, followed by a description of the structure of this report.

1.1 Background

Starting in 2008, the Institute of Medicine's (IOM) forum have held six workshops across the globe to address the global drug-resistant tuberculosis (DR-TB) crisis. The goals of these workshops, amongst others, were to: understand the magnitude of the drug resistance problem; identify the key barriers to effective control of the spread of the disease; and develop an execution plan for confronting the global crisis. These workshops have highlighted the fact that the under-performance of the supply chain that delivers second-line drugs (SLD) for the treatment of DR-TB specifically, is hindering the efforts to control DR-TB; thereby creating the need to investigate the performance of the SLD supply chain.

1.2 Problem Definition

With 1.4 million deaths per year globally, tuberculosis (TB) is the second largest infectious disease killer. TB is caused by the *Mycobacterium tuberculosis* bacterium that mainly affects the lungs, but can also attack any other part of the body, such as the kidney, spine, and brain. TB is contagious and is transmitted from person to person through air; however is completely curable with a standard six month treatment regime. Regrettably however new drug-resistant strains of TB have emerged due to interrupted or incomplete

TB treatment. One of the strains that have developed is MDR-TB, which is resistant to the two most powerful first-line anti-TB drugs (FLDs) used to treat drug susceptible TB (DS-TB): isoniazid (INH) and rifampin (RIF). Extensively drug-resistant TB (XDR-TB) is another more serious strain that has emerged, as this strain is resistant to INH, RIF, as well as other anti-TB drugs. DR-TB strains therefore require new drugs for treatment, known as SLDs. MDR-TB has become a public health emergency across the globe, with the BRICS (Brazil, Russia, India, China and South Africa) countries carrying the burden of almost 60% of all notified DR-TB cases (International Union Against Tuberculosis and Lung Disease, 2012). In 2011, only one in five patients estimated to be infected with MDR-TB were diagnosed and treated, showing the true magnitude of this health crisis (International Union Against Tuberculosis and Lung Disease, 2012). The incidences of MDR-TB and XDR-TB are increasing globally; cases of diagnosed MDR-TB increased from 62, 000 to 84, 000 between 2011 and 2012 (World Health Organization, 2013*b*). There are many causes for the spread of the disease, however research has shown that the under-performing supply chain for SLDs accounts for most of these causes (Nicholson *et al.*, 2013; Olson *et al.*, 2014). The MDR-TB SLD supply chain is under-performing in terms of the timely procurement and delivery of quality SLDs to the infected patients. This results in patients missing critical doses of medicine and further contributes to the resistance of the bacteria.

The global SLD supply chain faces many challenges and barriers, which directly increases the TB bacteria's resistance to drugs used to treat drug susceptible TB. Some of these challenges include demand uncertainty, a lack of suppliers and fragmentation in the SLD supply chain. These challenges are discussed in Chapter 2 in more detail. Many of these issues are interrelated, making it difficult to isolate which interventions will have the greatest positive impact on the supply chain. There have been many suggestions made by various speakers at each of the IOM workshops to improve the efficiency of the SLD supply chain, however few have actually been tested or put into practise. It is therefore suggested that the SLD supply chain be modelled in order to test the suggestions made and to assess the impact these proposed solutions will have on the supply chain. Developing this model will be a start to finding the key solutions to the problems faced within the SLD supply chain, in order to improve the existing supply chain. A successful supply chain has the potential to contribute significantly to ensuring an uninterrupted supply of SLDs to every patient suffering from DR-TB, at prices that are reasonable enough for the majority of patients, in hopes of treating DR-TB successfully on a global scale.

The global SLD supply chain is divided into an upstream segment operated internationally and a downstream segment operated domestically. However only the downstream segment of the supply chain will be modelled in order to test the changes and the impacts thereof on a smaller, more accurate scale.

Figure 1.1 shows that the highest number of MDR-TB cases estimated to have occurred amongst notified pulmonary TB cases occurs in Russia, China, and India; however relative to a population of 143 million, 1,386 million and 1,252 million respectively, the relative burden is higher in South Africa with a population of only 53 million (World Health Organisation, 2014). Furthermore Table 1.1 shows the actual number of notified MDR-TB cases in 2013 in each of these countries. Both Figure 1.1 and Table 1.1 illustrate that South Africa is a good representation of MDR-TB globally due to the high burden, and therefore will be the focus of this study. In order to scale down an area for investigation for this research project even further, Table 1.2 shows that the over the years 2005-2010, KwaZulu Natal and the Western Cape have had the highest prevalence of MDR-TB in South Africa specifically (Statistics, 2012). Therefore for the purpose of this study, only the downstream segment of the SLD supply chain in the Western Cape, South Africa, will be modelled, as it provides a good representation for the global burden.

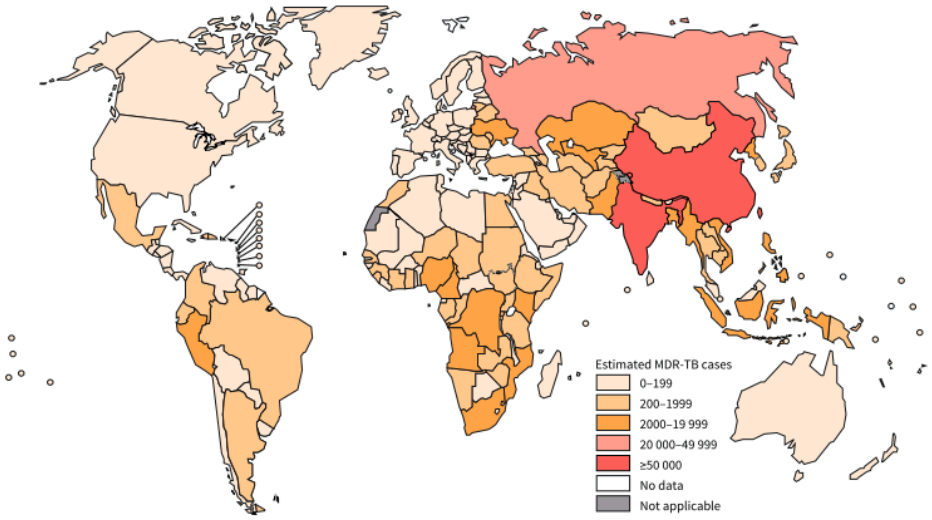


Figure 1.1: Number of MDR-TB cases estimated amongst notified pulmonary TB cases in 2013 (Source: *Global Tuberculosis Report*. WHO, 2014.)

Table 1.1: Number of notified cases of MDR-TB in 2013 (Source: World Health Organisation (2014))

Country	MDR-TB cases
China	4,183
India	35,385
Russian Federation	13,521
South Africa	26,023

Table 1.2: Number of diagnosed cases of MDR-TB in each province in South Africa, 2005-2010 (Source: Alrabea (2012))

Province	2005	2006	2007	2008	2009	2010
Eastern Cape	545	836	1,092	1,510	1,858	1,782
Free State	151	198	179	381	253	267
Gauteng	676	732	986	1,028	1,307	934
KwaZulu-Natal	1,024	2,200	2,208	1,573	1,773	2,032
Limpopo	40	77	91	185	204	126
Mpumalanga	134	139	506	657	446	312
North West	203	225	397	363	520	158
Northern Cape	155	188	199	290	631	353
Western Cape	1,192	1,179	1,771	2,220	2,078	1,422

1.3 Aims and Objectives

1.3.1 Aim

Develop a model of a downstream MDR-TB SLD supply chain in the Western Cape, and use this model to make recommendations on the most effective mechanisms for strengthening this supply chain.

1.3.2 Objectives

- Develop a model of the Western Cape public healthcare downstream MDR-TB SLD supply chain;

- Develop a thorough understanding of the strengths and weaknesses of the downstream MDR-TB SLD supply chain by assessing and comparing to the SCOR model;
- Test the impact of changes to the downstream supply chain as proposed by the IOM Forum by using the model;
- Test the impact of changes to the operational parameters on the supply chain based on the analysis of the strengths and weaknesses; and
- Make recommendations on the changes to the SLD supply chain that will be the most effective in strengthening this supply chain.

1.4 Research Design

This project will be undertaken as an empirical study into potential suggestions for improvement of the SLD supply chain. This research relies on both primary and secondary data, analysing quantitative and qualitative data for modelling and simulation. The primary data collection consists of semi-structured interviews, telephone calls and emails to obtain both qualitative and quantitative data. A range of secondary data is used for this study, namely: books; journals; articles; and websites. The main source of secondary data is provided by the Western Cape Department of Health (WCDoH), which consists of numerical data regarding the orders and dispatches of SLDs to and from the Cape Medical Depot (CMD). The data provided by the WCDoH is necessary to evaluate the performance of the current SLD supply chain and develop a model of the supply chain. This data is analysed and explored in order to find meaningful relationships and trends that will aid in evaluating the performance.

1.5 Research Methodology

Figure 1.2 illustrates the steps that will be followed to achieve the aim and objectives set out in Section 1.3 for this research project. The model developed will represent one SLD in the downstream segment of the SLD supply chain in the Western Cape, and will be verified and validated using real-world data provided by the WCDoH.

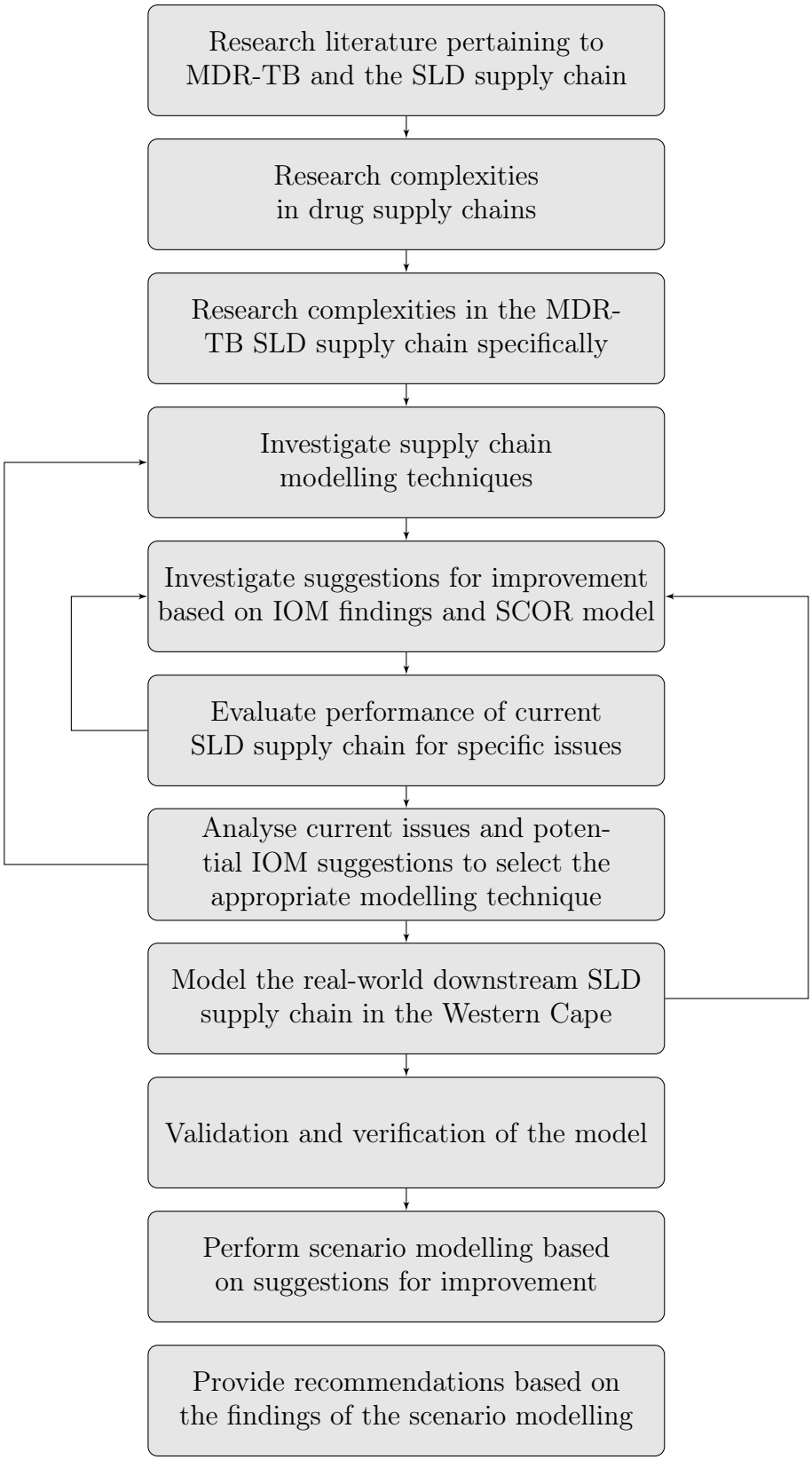


Figure 1.2: Research methodology

1.6 Structure of the Report

Chapter 2 describes, in detail, the global problem of MDR-TB and more specifically the barriers faced in confronting the crisis. This chapter also includes background on the MDR-TB SLD supply chain and the challenges currently being faced with regard to effectively procuring and delivering quality assured SLDs to patients. Chapter 2 also briefly describes the treatment of MDR-TB and more specifically paediatric MDR-TB.

Chapter 3 classifies a supply chain as a complex adaptive system (CAS), based on the defining criteria of a complex adaptive system. Chapter 3 then proceeds to describe the process of building a model and provides information on the modelling techniques that are currently used to model supply chains specifically. These techniques include: analytical modelling; process modelling; and simulation modelling. The paradigms within these modelling techniques are then discussed in detail, with the focus on simulation modelling specifically.

Chapter 4 lists the suggestions and solutions proposed by the participants in the IOM Forums on how to confront the global MDR-TB crisis. Furthermore, the performance attributes highlighted in the Supply Chain Operations Reference (SCOR) model that will be tested to evaluate the current downstream SLD supply chain is also listed. The best practises that are used to improve these performance attributes are added to the IOM suggestions made to improve the supply chain. Based on these suggestions that will be tested with the model, systems dynamics is chosen as the simulation paradigm that will be used to model the downtream SLD supply chain.

Chapter 5 describes the process of how the supply chain model is developed and validated using three of the five phases of systems dynamics: problem structuring; causal loop modelling; and dynamic modelling. The performance of the current supply chain is also evaluated in this chapter by testing the attributes: reliability; responsiveness; and robustness.

Chapter 6 describes the final two phases of the five phases of systems dynamics: scenario planning and modelling; and implementation. The various policies, variables and strategies that will be simulated to test the suggestions proposed at the IOM workshops, and the suggestions made based on the performance of the supply chain are listed and discussed. The variables and policies that will be tested include: supplier lead time; supplier reliability; desired stock levels; safety stock levels; and reorder policies. The results obtained after running these scenarios are recorded and discussed.

Chapter 7 analyses the results obtained from the simulations using a pareto

set. Recommendations are then provided on how to decide on the optimal pareto solution. These recommendations include using: gross domestic product (GDP); quality-adjusted life-year (QALY) calculations; and population simulations. Moreover, recommendations on the methodology used to complete this study will be presented, based on the limitations of systems dynamics as a simulation paradigm. Finally, recommendations for future research in this field will be provided and discussed.

1.7 Conclusion: Introduction

This chapter gives a concise description of the global MDR-TB crisis, the challenges that are currently being faced with confronting this problem and therefore the need for this research. The over-arching aims and objectives for this research project, as well as the methodology that will be followed in order to achieve these objectives are also discussed. Chapter 2 will discuss, in detail, the challenges that are being faced globally in addressing the the MDR-TB crisis, with focus on the under-performing MDR-TB SLD supply chain.

Chapter 2

Real-World Problem

This chapter provides background on both DS-TB and DR-TB, focusing on MDR-TB and how this specific strain developed. The IOM Forum held various workshops across the globe with the aim of understanding the magnitude of the drug-resistance problem and determining the key issues to effective treatment. These specific barriers and key issues that are hindering the control of efficient distribution of quality assured anti-TB drugs and the prevention of the transmission of MDR-TB are discussed in detail in this chapter. The IOM workshops recognised that one of the biggest issues is the under-performing MDR-TB SLD supply chain. Therefore each of the bottlenecks throughout the SLD supply chain that are preventing the efficient procurement and delivery of quality drugs to patients are highlighted and discussed; with the aim of finding solutions to strengthen this supply chain.

2.1 Management of Tuberculosis

(TB) is a contagious and airborne disease that mainly affects the lungs. TB has been around for millennia and is also known as the disease of poverty (The Global Fund to Fight AIDS, Tuberculosis and Malaria, 2014). It is caused by the bacterial micro-organism, tubercle bacillus or *Mycobacterium tuberculosis*, and is potentially fatal (National Institute of Allergy and Infectious Diseases, 2009). Globally, TB is one of the leading causes of deaths by infectious diseases, second only to AIDS (Giffin and Robinson, 2009). It is estimated that one-third of the global population carry the bacillus *Mycobacterium tuberculosis*; and although many will never become active, the bacillus is responsible for approximately $4,700$ deaths daily (Keshavjee and Seung, 2008; Olson *et al.*, 2011).

DS-TB can however be treated by a regimen of FLDs over a certain time period, depending on the infection. FLDs are the standard and preferred choice for treating TB and consist of: INH; RIF; ethambutol; pyrazinamide; and

streptomycin (World Health Organization, 2010). However new, potent strains of TB have emerged that are resistant to some of the available FLDs. DR-TB is becoming a major global health risk that is accelerating. The drug-resistant strains can be grouped into either MDR-TB or XDR-TB. MDR-TB is defined as the strain of TB bacteria that has become resistant to at least two of the best antibiotics in the first line drug regimen, namely INH and RIF. Globally it is estimated that $450,000$ people developed MDR-TB and $170,000$ people died from MDR-TB in 2012 (World Health Organization, 2013*a*). The worst case of DR-TB is XDR-TB, as it is resistant to at least: INH; RIF; any fluoroquinolone (an antibiotic); and at least one of the second-line injectable drugs: kanamycin; capreomycin; streptomycin; or amikacin (World Health Organization, 2013*d*). In general SLDs are necessary when certain FLDs fail to treat the disease, or when the disease becomes resistant to the FLDs. Therefore SLDs have become necessary to effectively treat patients with DR-TB. SLDs used to treat DR-TB are grouped as follows (World Health Organization, 2010):

- First Line Oral Agents (FLDs);
- Injectable Agents;
- Fluoroquinolones; and
- Oral Bacteriostatic Second Line Agents.

Although FLDs are used to treat drug susceptible TB, 'First Line Oral Agents,' namely: ethambutol and pyrazinamide can also be used in combination with the SLDs used to treat MDR-TB if the microorganism is not yet resistant to those drugs. The SLDs used to treat DR-TB are not only very expensive, less potent and more toxic in comparison to the FLDs used to treat susceptible TB, but they also require a drug regimen that can last up to two years or more (Nicholson *et al.*, 2013).

To control TB, the World Health Organisation (WHO) launched a global programme called 'directly observed treatment, short-course' (DOTS) in the early 1990s, where an appointed agent directly monitors patients swallowing their anti-TB drugs (Volmink and Garner, 2007). The Global Drug Facility (GDF) was established in 2001 to increase access to high quality TB drugs in order to expand the DOTS program. DOTS is based on a six month treatment regimen with FLDs: isoniazid, rifampin, pyrazinamide, and ethambutol for new patients and an eight month regimen with streptomycin added to the original regimen for re-treatment patients (Pooran *et al.*, 2013). The World Health Organization (2014) emphasises that the DOTS strategy combines five components, namely:

- Political commitment with increased and sustained financing;

- Case detection through quality-assured bacteriology;
- Standardised treatment regimen with supervision and patient support;
- An effective drug supply and management system (uninterrupted supply of anti-TB drugs); and
- Monitoring and evaluation system and impact measurement.

2.2 Management of MDR-TB

MDR-TB developed due to: (i) a lack of stringent quality control on the drugs used to treat TB, allowing substandard and counterfeit drugs to enter the market; and (ii) patients not taking their medicine on a daily basis in the correct doses. This resulted in a resistance to the TB drug regimen (Nicholson *et al.*, 2013).

DOTS was however designed for drug susceptible TB and therefore did not address MDR-TB; leading to the introduction of DOTS-Plus. DOTS-Plus is built upon the five DOTS components to include treatment of MDR-TB with SLDs. The goal of DOTS-Plus is to prevent the further spread of MDR-TB; however the barrier to implementation of the strategy was the limited access to, and the high costs of SLDs (World Health Organization, 2000). The Green Light Committee (GLC) initiative was therefore established between 1998 and 2000 by the WHO and the Stop TB Partnership in response to the high demand for low cost SLDs. The GLC serves as a technical advisory body to the WHO and the Stop TB Partnership, and performs tasks such as: reviewing applications from countries that request quality assured (QA) SLDs at reduced prices and promoting technical assistance. This initiatives aim is to control the emergence of resistance to SLDs by ensuring the use of only QA SLDs at affordable prices. Quality assurance programs help guarantee that patients receive drugs that are safe, effective and are of an acceptable quality thereby contributing to controlling the further spread of DR-TB.

2.3 Key Issues around MDR-TB

There have been six workshops across the globe, organised by the IOM: two in Washington DC; China; India; Russia; and South Africa. These workshops addressed DR-TB and the problems associated with controlling the disease. The names of these IOM workshops, where each particular one took place, and in which year are listed in Table 2.1.

Table 2.1: Institute of Medicine Forum workshops

Code	Workshop	Country	Year
W1	Addressing the threat of drug-resistant tuberculosis: A realistic assessment of the challenge	Washington DC	2008
W2	The emerging threat of drug-resistant tuberculosis in Southern Africa. Global and local challenges and solutions	South Africa	2010
W3	The new profile of drug-resistant tuberculosis in Russia. A global and local perspective	Russia	2010
W4	Facing the reality of drug- resistant tuberculosis in India. Challenges and potential solutions	India	2011
W5	Developing and strengthening the global supply chain for second-line drugs for multidrug-resistant tuberculosis	Washington DC	2012
W6	The global crisis of drug-resistant tuberculosis and leadership of China and the BRICS: Challenges and opportunities	China	2013

All of the six workshops have reached the same conclusion: DR-TB has become a major global issue and there are many aspects that need to be addressed before the disease can be: (i) treated at lower costs for the patients; and (ii) prevented on a global level. The reports written on each of the workshops summarised the key themes discussed at the respective workshops. The key topics of conversation at each IOM workshop are summarised in Table 2.2.

The issues listed in Table 2.2 are either: (i) due to an under-performing SLD supply chain; or (ii) negatively affect the SLD supply chain to some extent. To effectively treat patients with MDR-TB, an uninterrupted supply of QA SLDs is necessary. Therefore a well-performing global SLD supply chain is critical to ensure the timely procurement of high-quality SLDs in order to control the spread of the disease and treat the patients that are currently infected.

This study will focus on identifying the key factors that negatively affect the performance of this supply chain. The supply chain for QA SLDs has many barriers and inadequacies that make the supply chain as a whole ineffective in delivering an uninterrupted supply of SLDs. Addressing these weaknesses in

the supply chain is critical to preventing TB strains with more drug-resistance and to controlling the strains that already occur.

Table 2.2: Key issues discussed at each IOM workshop

Key Issues	W1	W2	W3	W4	W5	W6
Regulatory challenges	x	x			x	x
Information management	x	x	x	x	x	x
Drug shortages				x	x	x
Financing of MDR-TB SLDs					x	
Limited and erratic demand				x		
Limitations of global TB estimates	x		x			
The role of HIV in the spread of MDR-TB	x	x				x
The importance of infection/transmission control	x	x	x	x		x
Limited diagnostic capacity	x	x	x	x		x
Low rates of treatment	x	x	x			
The need for new TB drugs	x		x			
DR-TB in children		x	x	x		x
Surveillance and tracking of DR-TB		x				

2.4 The MDR-TB Supply Chain

There is general agreement around research pertaining to this field of study that the spread of DR-TB is mainly due to the under-performing SLD supply chain (Yadav, 2011; Mostaghim, 2012; Nicholson *et al.*, 2013). "The SLD supply chain remains in a state of disarray" (Yadav, 2012). One of the key messages identified by individual speakers at the IOM workshop in Washington DC, 2012 was that the failure to target and amend the SLD supply chain issues will lead to drug resistance, morbidity and ultimately increased mortality (Nicholson *et al.*, 2013). Furthermore Mostaghim (2012) states that addressing two crucial barriers in the SLD supply chain: (i) the high prices; and (ii) the

limited availability of QA drugs could potentially: reduce the incidence of infection; and increase the number of patients on treatment.

2.4.1 Complexities in Drug Supply Chains

A potential result of inefficient supply chains, that do not succeed in the timely procurement and delivery of the right drugs to the right patients, is the increased spread of disease and sickness. Shah (2004) is of the opinion that most drug supply chains, including the MDR-TB SLD supply chain, face the same difficulties and complexities:

- **Uncertainty in demand.**
  This uncertainty arises due to: competition; discontinuation of drugs due to new formulations; and price.
- **Uncertainty in the approval of new drugs.**
  There is uncertainty about which drugs will be successful in trials, aswel as which treatment regimen will be optimal and with what dosage.
- **Production development.**
  This complexity arises during the development of the actual process by which the drugs should be manufactured. Chemistry and yield optimisation will drive the development of this process.
- **Capacity planning.**
  The problem of allocating manufacturing capacity to sites during clinical trials. This complexity arises specifically in the design phase, where capacity needs to be balanced with future demand.
- **Production planning and scheduling.**

Section 2.4.2. gives a detailed overview of the complexities encountered in the SLD supply chain, specifically for MDR-TB.

2.4.2 Unique Characteristics of the MDR-TB SLD Supply Chain

The presentations given by Keshavjee and Seung (2008); Yadav (2012); Mostaghim (2012) and Atun (2012) at the IOM workshop that took place in Washington DC, 2012 give an overview of the barriers, challenges and needs that prevent the SLD supply chain from delivering an uninterrupted supply of SLDs to MDR-TB patients. The report written on the workshop summarises these presentations, revealing that although thoughts on the specific weaknesses in the SLD supply chain might differ in severity, fundamentally there is an agreement on the majority of the challenges that are being faced (Nicholson *et al.*,

2013). Figure 2.1 illustrates the basic MDR-TB SLD supply chain.

Figure 2.1 shows that the SLD supply chain is divided into upstream and downstream segments. The upstream supply chain is global, while the downstream is domestic. Due to the fact that the supply chain for MDR-TB SLD is predominantly donor funded, the upstream and downstream segments of the supply chain are decoupled from one another (Yadav, 2012). This has unique implications with regard to price, demand, scale-up and financing. Yadav (2012) stressed the fact that the relationship between price and volume is not the same as the relationship between cost and volume. The extent to which the change in producer cost is reflected in the buyer price is dependent on the market structure that is itself dependent on the competition in the market and the effectiveness of the procurement institutions (Nicholson *et al.*, 2013). Yadav (2012) performed a modelling exercise where he doubled the demand for one SLD treatment; however the cost of the drugs for the suppliers only decreased by a maximum of approximately 17% and the price for consumers by 8%.

Furthermore the two segments are financed differently: the upstream segment is financed by the GDF and the downstream is financed domestically by each respective country. Yadav (2012) states that a unique situation therefore exists with regards to demand elasticity due to this financial structure. He explains that demand is relatively inelastic to changes in the internationally financed segment, meaning that a small change in cost will barely affect the demand. On the other hand, the domestically financed segment is demand elastic, where a small change in price will have a large impact on the demand from consumers. The demand curve will therefore be uniquely shaped with the beginning of the curve being relatively flat with a change in cost, followed by a jump at a certain point, where the domestic segment is predominant. More research is however required to identify the point at which the demand will trigger a price decrease for consumers (Nicholson *et al.*, 2013).

2.4.3 General MDR-TB SLD Supply Chain Challenges

The remaining part of this chapter discusses in more detail the unique challenges faced by the SLD supply chain, as listed in Table 2.2. This section discusses the challenges faced throughout both the upstream and the downstream segments of the supply chain. Subsections 2.4.4 and 2.4.5 will discuss the specific challenges faced within each segment.

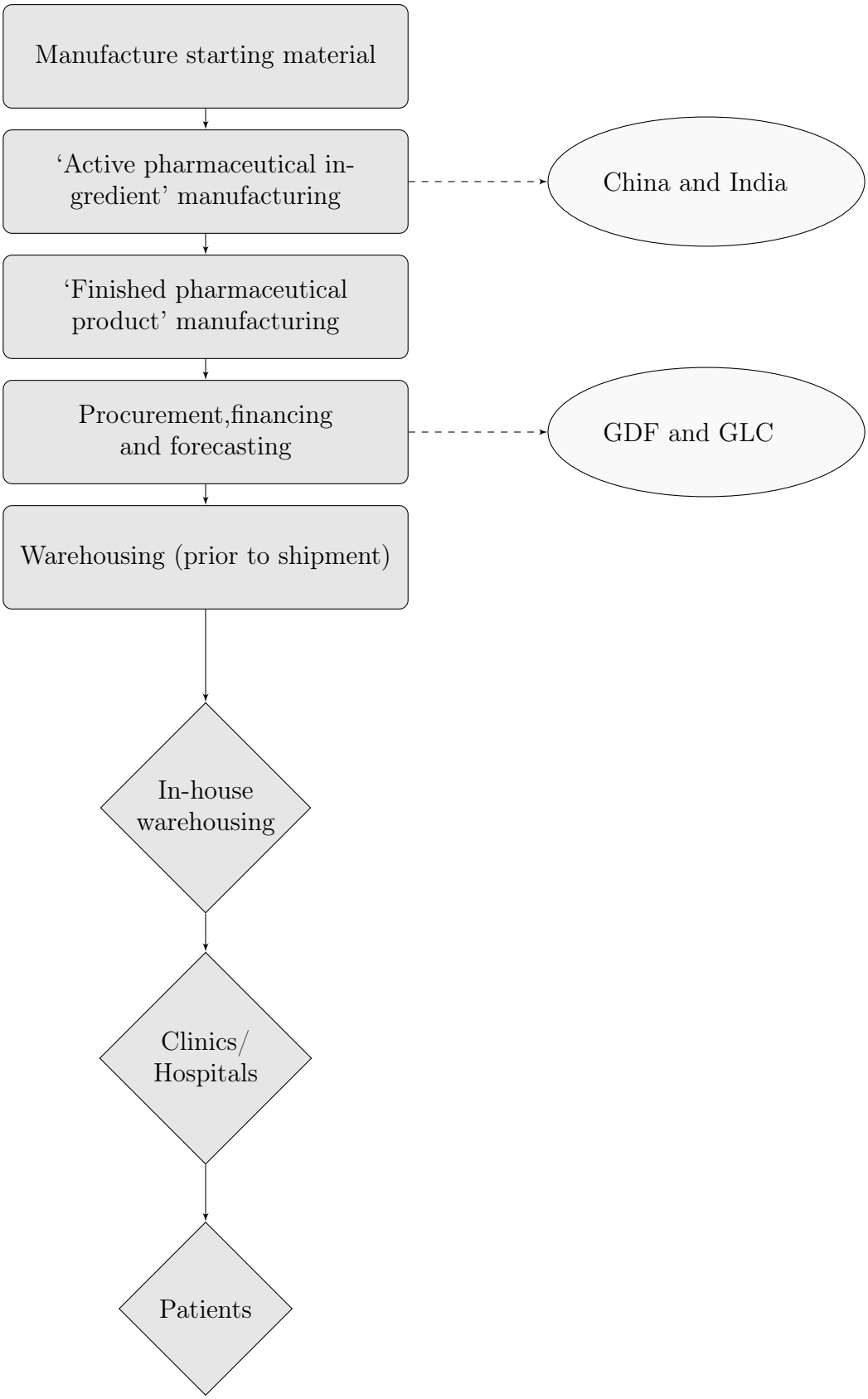


Figure 2.1: The basic MDR-TB SLD supply chain (adapted from Yadav (2012))

2.4.3.1 Regulatory Challenges

MDR-TB patients' access to SLDs is restricted due to the regulatory pathway shown in Figure 2.2. Figure 2.2 also shows that low-income countries have to wait much longer for QA SLDs than high-income countries, as they are highly dependent on donor procurement.

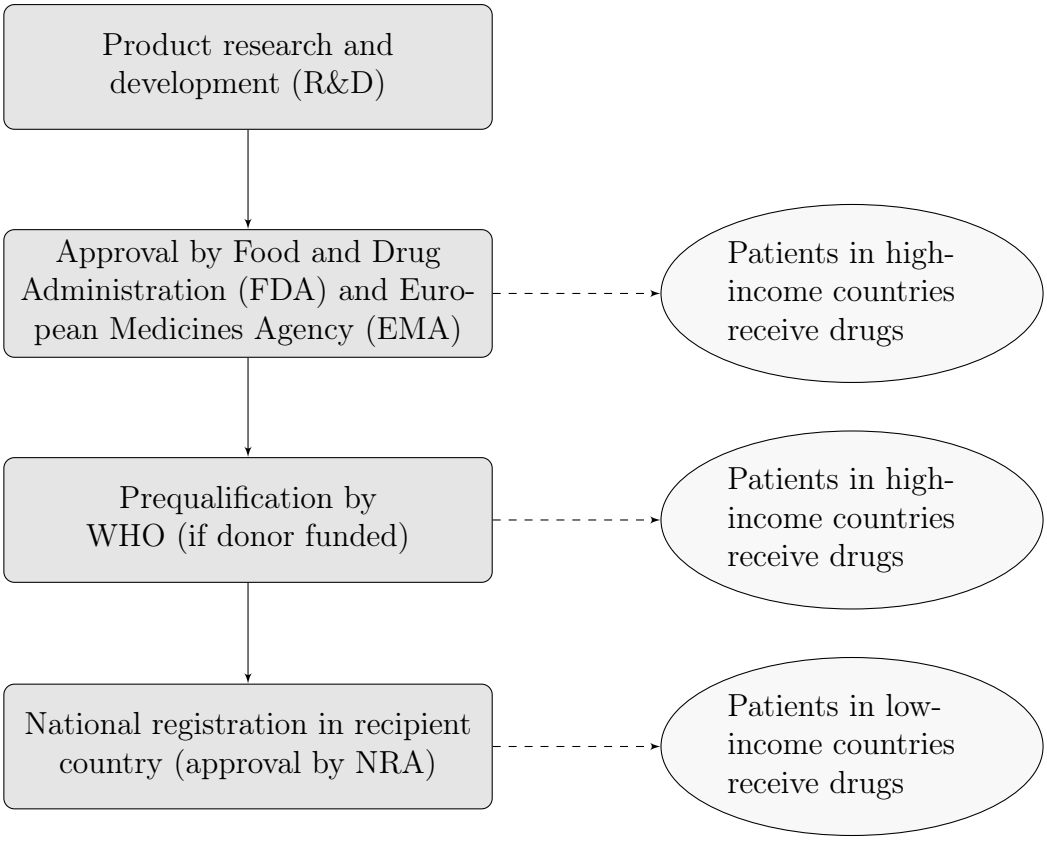


Figure 2.2: Drug regulatory pathway (adapted from Ahonkhai (2012))

In high-income countries the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) can approve products in one-step, creating a direct pathway to patients. These countries also procure the drugs themselves creating an efficient pathway. However the low-income countries are faced with a slow, three-step process for donor procurement, either from the Global Fund or from UNITAID. UNITAID is a global health organisation hosted by the WHO to increase funding for greater access to treatments for HIV, Malaria and TB in low-income countries (UNITAID, 2014). The three-step process faced by low-income countries includes:

- Approval by regulatory authorities (FDA and EMA) in the manufacturing country;

- WHO prequalification; and
- Approval from the National Regulatory Authority (NRA) in the country of delivery.

In order for low-income countries to be eligible for SLD procurement with donor funding, the desired SLDs must pass through the WHO pre-qualification (PQ) process to affirm its quality and safety. This PQ process is especially a problem as there are extra delays in registering new suppliers, as both the response and uptake to invitations for PQ is low (Hedman, 2012). The drug must then be registered by the NRA in the beneficiary country, otherwise it cannot be procured by the donor agency. This regulatory pathway is not only fragmented between low- and high-income countries; further fragmentation occurs in the low-income countries as the NRA approval time varies for each country of delivery (Ahonkhai, 2012).

Regulatory harmonization was found to improve this fragmented system. The African Medicines Regulatory Harmonization (AMRH) was therefore formalised and launched in 2012 in East Africa to streamline approval for regulators and manufacturers and to increase access to safe, effective products. This collaboration moved from a system with many countries in Africa, to six regions each with a group of countries in Africa. The countries are grouped into the six regions that are illustrated in Figure 2.3. In other words, the AMRH aims to improve the fragmented system of product registration in Africa, by focusing on regions within the African continent (Ahonkhai, 2012).

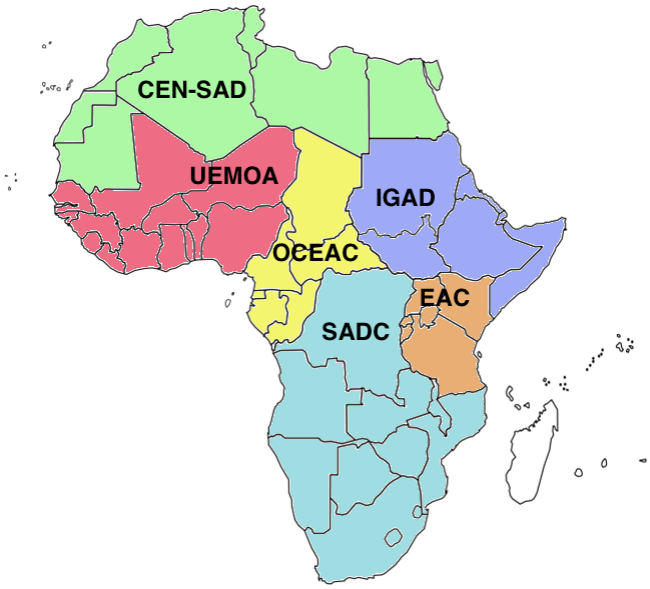


Figure 2.3: Regulatory harmonisation for the six regions in Africa (adapted from Ahonkhai (2012))

2.4.3.2 Information System Challenges

Table 2.2 illustrates that information management was one of the issues discussed at each of the six workshops, showing the importance of this factor. Information systems are critical to the success of the SLD supply chain, as information management can be applied in multiple ways to address issues associated with the SLD supply chain (Nicholson *et al.*, 2013; Olson *et al.*, 2014). Nordenberg (2013) states that the data and information that is used to support a global supply chain is a supply chain on its own. Public health programs require the following three supply chains to be successful: human resources, products, and information supply chains. However Nordenberg (2013) states that many challenges still exist with information distribution in the rural healthcare system, as there is poor integration with hospitals at national and regional levels. The WHO Global Laboratory Initiative (GLI) stated that "the critical lack of TB laboratory capacity constitutes a global crisis, requiring a paradigm shift in providing laboratory policy guidance, quality assurance and knowledge creation within a global and integrated laboratory network". Not only is laboratory capacity insufficient, but laboratories have programs that are focused on specimens, therefore their information system requirements are not aligned with clinics or public health programs. Nordenberg (2013) states that "Information is a public health intervention," and a proper TB/DR-TB information supply chain will be able to:

- Prevent emergence of drug resistant strains;
- Treat patients more effectively;
- Track infection control risks; and
- Improve contact tracing and follow up.

If MDR-TB cases are identified earlier, less resistance will develop and fewer people will spread the disease; therefore diagnosis should be used to drive treatment. However the data produced by diagnostics need to be collected, managed and shared properly for the disease to be controlled (Olson *et al.*, 2012).

Information systems have many advantages, and can strengthen the SLD supply chain in many ways. Improving the efficiency of information management systems could make demand forecasting more accurate and prevent stock-outs, thereby strengthening the supply chain (Olson *et al.*, 2014). An information system with the correct type and amount of data can aid in evaluating the impacts of treatment regimen time-lines and appropriateness of the treatment regimen for each patient. Electronic medical records (EMR) systems is an example of this type of information system. EMR's can be used to store information about patients, which will provide more accurate and reliable data

for forecasting. Although collecting the information for EMR is relatively straightforward, the challenge lies in finding the appropriate resources (tools and training) for the information to be accurate. EMR's integrate information management into the broader health system. Some of the core variables that should be collected and stored in an EMR are (Fraser, 2012):

- Demographics;
- Program enrolment date;
- Start date for drugs;
- Drug regimen (drugs and doses);
- Smear and culture results;
- Previous medications;
- Adverse events;
- Treatment status;
- Treatment outcome; and
- Outcome date.

Evidence of reduced medication errors and better follow-up of diseases has driven the implementation of EMR in hospitals; however developing countries still offer challenges such as lack of infrastructure and lack of local technical support and knowledge.

2.4.3.3 Second-line Drug Shortages

The risk of stock-outs occurring is high due to the high price and the short shelf-life of SLDs, therefore DOTS programs have been specifically focused on reducing stock-outs (Yadav, 2011). These stock-outs result in delayed treatment initiation and treatment interruptions, triggering a temporary suboptimal treatment regimen until the appropriate drugs are available again. This increases the challenge of efficiently procuring and delivering the SLDs. Drug shortages can occur at both global and national levels:

- **Global-Level SLD Shortages.**
  Pre-made SLDs are often stored in warehouses for several months before the required paperwork and procurement processes are completed for shipment, after which the drugs are then kept in additional warehouses (Nicholson *et al.*, 2013). Thereby the shelf-life is already low before it is received by the patient. SLDs are too expensive to manufacture if the completed drug is kept in storage for the majority of its shelf-life,

which is only 24 months, thereby creating hesitancy to produce SLDs without proper forecasts. Global shortages are also a result of reliance on a single source for QA active pharmaceutical ingredients (API) and a limited supplier pool. Furthermore many SLDs have only one producer, therefore a shortage is likely to occur if a problem occurs with even one batch of drugs.

- **National-Level SLD Shortages.**
  The leading cause of stock-outs at a national-level is the uncertainty in the timing of the availability of funds. The funds for the purchase of the drugs have to be available before the procurement process can begin (Olson *et al.*, 2012). Due to the fact that strict regulations must be followed before the GDF can distribute funds, delays occur frequently and it becomes difficult to predict when funds will become available (Yadav, 2011).

2.4.3.4 Financing Challenges

Every process in the supply chain requires financial support from multiple organisations in both the private and public sector. Since the SLD supply chain is predominantly donor funded, the dynamics and financial drivers differ significantly from a commercial supply chain. This is due to the fact that the donors are non-profit organisations. The GDF collaborates with the Green Light Committee (GLC) and is predominantly funded by the Global Fund, UNITAID, and USAID.

One of the organisations that fund the SLD supply chain is the United States Agency for International Development (USAID). Cheri Vincent, TB team leader of USAID described the following SLD supply chain challenges from the USAID's perspective.

- **Funding mismatch and inflexibility.**
  An analysis of 21 countries that compared the number of MDR-TB patients enrolled in a treatment regime to the number of available treatment regimes revealed that only 39% of the funds available were used for MDR-TB treatment (Vincent, 2012). Moreover, the countries that don't meet their MDR-TB treatment objectives lose these unused funds and SLDs. However, countries that are scaling up MDR-TB treatment faster than SLDs are available to them cannot benefit from these SLDs that aren't being used in other countries. It is therefore suggested that more flexibility in funding would allow resources to be matched to countries more appropriately (Nicholson *et al.*, 2013).

- **Inefficient country supply chain system.**
  Vincent (2012) lists the following as causes for the inefficiencies:

  - Slow government procurement and financial processes;
  - Limited capacity to forecast due to unpredictable MDR-TB program scale-up rates;
  - Complicated Global Fund procedural and grant requirements; and
  - Decentralised and parallel supply chain systems.

- **Limited number of suppliers and high prices for SLDs.** These two issues are interrelated, as an increase in suppliers will promote competition and therefore reduce prices. Vincent (2012), states that having two suppliers for each SLD is an important milestone; however few suppliers are willing to produce QA SLDs due to the limited incentives (Vincent, 2012).

UNITAID is essentially a central pharmaceutical drugs purchasing facility, that negotiates reductions in prices from pharmaceutical firms. UNITAID is unique in the fact that a large amount of the funding they receive come from the air ticket levy mechanism (UNITAID, 2015). The organisation (UNITAID) explains that this mechanism includes charging passengers an air ticket levy above the cost of the ticket. This levy is simply added to an existing airport tax and can range from $1 for economy-class tickets to $40 for first class passengers. Thus far nine countries have implemented this mechanism. UNITAID funding not only allowed the GeneXpert to be rolled out in 21 recipient low- and middle-income countries, but also achieved a 40% price reduction for this rapid TB test. Furthermore, UNITAID's response to the frequent stock-outs was the strategic rotating stockpile (SRS). The SRS includes enough medicine for 5,800 MDR-TB treatments which can be accessed at short notice for emergency situations (UNITAID). The lead times for urgent orders decreased from 101 days in 2007 to 30 days in 2011. In order to ensure that the medicines are kept within their shelf-life limits, the medicines are routinely checked and rotated by the CDC.

Although there are many initiatives and funding options available from these organisations, the SLD supply chain still faces many problems. Atun (2012) highlights the major funding shortfall, which has a direct impact on MDR-TB diagnosis and treatment. It was estimated that funding requirements for MDR-TB would be $7.1 billion, of which only $ 3.6 billion was approved by the GDF in 116 countries between 2002 and 2010. However as specified by Atun (2012), domestic funding needs to be mobilised to address the emerging MDR-TB, as the GDF target is to fund 50 % of the MDR-TB treatment needs. He also states that the funding shortfall is preventing the implementation of push and pull mechanisms. Push mechanisms are required to create incentives for suppliers and manufacturers to enter the market, while pull mechanisms are required for demand creation. This is as a result of supplier and manufacturer hesitancy

to enter this kind of market. Without these mechanisms, the supply chain will continue to under-perform without the opportunity to scale-up (Atun, 2012).

2.4.4 Upstream Supply Chain Challenges

These issues are specific to the upstream segment of the supply chain. Mostaghim (2012) explained that the two biggest challenges in the upstream segment are the high prices and the limited availability of QA SLDs. These challenges are as a result of: limited and unpredictable demand; restricted market structure; and low volumes of API and finished pharmaceutical products (FPP) production.

Mostaghim (2012) lists the four elements that factor into pricing of SLDs by manufacturers as:

- True cost of manufacturing;
- Monopoly premium;
- Risk premium; and
- Economies of scale.

The 'true cost of manufacturing' relates to the actual costs of raw materials and labour for all the manufacturing processes that are involved in producing SLDs. The 'monopoly premium' refers to the fact that there is a lack of competition amongst manufacturers in the SLD market. The 'risk premium' refers to the premium that manufacturers charge due to the risk they feel they are taking when investing in the SLD market, as there is poor visibility into the market (Mostaghim, 2012). Lastly the 'economies of scale' or the 'cost of sub-scale manufacturing' refers to the high costs that are associated with sub-scale batch size manufacturing. The batch sizes are driven by demand, emphasising the need for volume of demand to be high and consistent (Mostaghim, 2012). The combination of these four elements factor into why SLDs are so expensive to manufacture. The three elements: 'monopoly premium'; 'risk premium; and 'cost of sub-scale manufacturing' are effectively non-essential elements of price and can be eliminated by increasing volumes and creating competition between manufacturers (Kimerling, 2012).

Olson *et al.* (2012) highlight that these high prices not only strain national TB programs but also exacerbate drug shortages.

2.4.4.1 Limited and Erratic Demand

The most prominent problem with the upstream supply chain is the limited and unpredictable demand. This is as a result of:

- **Limitations of global TB estimates.**
  Globally approximately 94,000 patients with MDR-TB were notified to the World Health Organisation (WHO) in 2012, however the WHO estimates this to be number to 450,000 (World Health Organization, 2013*a*). Of the 94,000 people eligible for MDR-TB treatment, 77,000 started on treatment in 2012. The most recent available treatment success rate is from the statistics available from patients that started MDR-TB treatment in 2011, which was 48% globally. Giffin and Robinson (2009) is of the opinion that the incidences of DR-TB are underestimated due to the fact that: drug resistant surveys have not been conducted in many of the countries in Africa; the current diagnostic methods are inadequate for HIV infected people; and the availability of diagnostic laboratories are limited in many countries. However, the World Health Organization (2013*a*) highlights that one of the main reasons for the low detection rates in many parts of the world is the existence of the private sector, in which national authorities are not notified of TB cases.

- **Lack of pooled procurement.**
  The WHO have restrictions about conducting pooled procurement and the ability to negotiate prices with suppliers, which according to Keshavjee and Seung (2008), are the key barriers to improving SLD prices. All procurement using Global Fund dollars are required to go through the GLC which is an agency of the WHO, restricting pooled procurement. Keshavjee and Seung (2008) is of the opinion that manufacturers have no real forecast of the potential demand to work with due to the lack of pooled procurement. According to Comstock (2012), there are many benefits of enforcing pooled procurement:

  - The promotion of a fair strengthened market;
  - The management of gaps and duplication in supply;
  - The increased product availability (avoid stock-outs);
  - The compliance with national and donor rules;
  - The enhancement of purchasing power;
  - The ability to focus on product harmonisation;
  - The implementation of stringent quality requirements; and
  - The access to broad expertise and best practices.

  However the challenges with implementing pooled procurement include: customer specific product requirements, country registration demands, constraints of donor or national procurement regulations and weak collaboration between donors and national authorities (Comstock, 2012).

- **Poor demand forecasting.**
  Demand forecast models play very significant roles in the supply chain of SLDs. Amongst other roles, the models: match the supply with the demand in order to eliminate the lag time; allow funders to plan purchases and allocate resources efficiently; and encourages the development of new drugs as manufacturers have a realistic picture of the future market potential (Giffin and Robinson, 2009). Insufficient forecasting contributes to opaque markets for drug manufacturing and therefore results in a limited number of manufacturers and the lack of new drug developments. An 80% accurate forecasting model, two months into the future and projecting at least 24 months is necessary to improve the drug supply (Bloom, 2013). After all six IOM workshops were completed, it was suggested that aggregated requests from various countries for SLD procurement would provide better demand forecasts and therefore a more stable total demand. Reliable forecasting requires information such as (Bloom, 2013):
  - Number of patients enrolled for each TB program;
  - Number of patients taking drugs;
  - Types of drugs being used by each patient;
  - Lead times for shipping each drug; and
  - Lead times for manufacturing each drug.

- **Fragmentation.**
  Fragmentation occurs at each point in the supply chain in a number of different ways. Fragmentation results in too many alternatives and therefore prevents the formation of an efficient and streamlined supply chain. Firstly, there is no standard regimen for the treatment of MDR-TB with SLDs, which results in fragmentation in the demand for specific SLDs. It is proposed that the introduction of new drugs and regimens into the market will only fragment the market more by giving clinics more options for drug administration to their patients (Nicholson *et al.*, 2013). However, new drugs are vital to treat new strains of DR-TB, therefore the supply chain needs to be efficient, stable and robust enough to handle the changes without failing (Giffin and Robinson, 2009). The definition of the quality of these SLDs also varies between countries resulting in fragmentation in the market amongst the drug manufacturers. The next stage of fragmentation occurs at the packaging level. The same drugs are packaged differently and therefore require different procurement agents. Therefore, although different manufacturers are available for a single drug, different specifications for inner and outer packaging result in only one eligible manufacturer for each specific mode of packaging and tendering. In effect this results in a monopoly of each manufacturer and

procurement agent, thereby increasing the prices of the drugs (Nicholson *et al.*, 2013). The time taken for approval of the drugs also varies between countries and therefore further increases fragmentation in the TB drug market. Finally, the manner in which patients are managed and the methods used for record-keeping vary amongst locations and patients, further fragmenting the supply chain (Giffin and Robinson, 2009).

The GLC procurement process, and any other approved programs should therefore be aligned, clear and consistent to reduce the fragmentation.

2.4.4.2 Restricted Market Structure

According to Olson *et al.* (2012), the markets for SLDs are small and uncertain. This is due to the fact that the suppliers and manufacturers are at risk of producing and supplying drugs that will not be purchased, and the health facilities are at risk of purchasing drugs that will not be used. SLD manufacturing is often order-driven, rather than forecast-driven due to the limited and erratic demand. Due to the high costs of suboptimal batch manufacturing, many manufacturers have minimum volume thresholds for production; however waiting for the volume of orders to reach this minimum threshold results in longer lead times (Yadav, 2011). Furthermore, some manufacturers only procure the API's after receiving the purchase order even though very few sources of API's are available, lengthening the time taken to receive orders. This erratic demand prevents manufacturers and suppliers from having stock of SLDs on hand and makes new suppliers and manufacturers hesitant to enter the SLD market. The lack of suppliers is not only increasing the price, but is hindering the drug procurement process (Olson *et al.*, 2012). In 2012 there were 12 formulations on the WHO list for pre-qualified SLDs, produced by only three manufactures. This small group of suppliers also exposes the global supply chain to the risk of stock-outs if the demand outweighs the supply capacity (Nicholson *et al.*, 2013).

Moving toward a functional SLD market requires three principles (Olson *et al.*, 2012):

- Quantifying the risk;
- Aggregating the risk on a global level; and
- Sharing the risk amongst the individuals involved in the supply processes.

Risk can be quantified by having accurate demand forecasting, as this would aid in allowing manufacturers and suppliers to plan ahead based on future demand. This would result in less hesitancy from suppliers and manufacturers to enter the SLD market. Risk can be aggregated by global, rather than

country-by-country ordering for the purpose of smoothing the erratic demand. One way of sharing the risk between countries would be to implement a rotating stockpile where countries can shift supplies to one another if drug consumption projections are not met (Olson *et al.*, 2012). This virtual stockpile could also prevent stock-outs on a national-level.

2.4.4.3 Low Volumes of API and FPP

The batches of APIs that are currently manufactured are relatively small due to the limited demand. Suboptimal batch manufacturing is more expensive and results in inflated prices for the FPP. Eighty five percent of the world's TB APIs, which includes the API's used for SLDs, are supplied by China as they are the world leaders in fermentation chemistry (which the production of API relies on). This causes a problem because the availability of these API's have been limited due to the fact that the producers in China have not been pre-qualified by WHO to sell the drugs internationally (Nicholson *et al.*, 2013; Olson *et al.*, 2014). The API's are the most important component in the production of SLDs, therefore this has a major impact on the overall availability of SLDs.

2.4.5 Downstream Supply Chain Issues

The downstream segment of the SLD supply chain includes: the in-house warehousing storage; the delivery of drugs to the clinics and hospitals; and the treatment of patients. The challenges faced by the downstream segment include;

- Public tendering;
- Ineffective inventory management;
- Limited diagnostic capacity;
- Suboptimal adherence to treatment regimens;
- Lack of transmission control;
- Low rates of treatment; and
- Need for new drugs and regimens.

2.4.5.1 Public Tendering

South Africa is one of the countries with the highest prevalence of TB, however most TB drugs in South Africa are procured on a competitive basis through the public sector.

Public tendering can be a problem when the submitted tender is too small for the demand. If this is the case, the National Department of Health (NDoH) would have to do a buy-out to replace stock-outs, which is significantly more expensive than a tender. Countries that procure SLDs through donor-funding (predominantly high MDR-TB burden countries) are financially constrained and are therefore highly dependent on these public tenders to ensure stock-outs don't occur.

2.4.5.2 Ineffective Inventory Management

As discussed in Subsection 2.4.3.3, one of the biggest issues within the supply chain is the occurrence of stock-outs. Ineffective inventory management increases the risk of experiencing shortages. Running a well-functioning inventory system is one of the biggest challenges within the downstream segment of the SLD supply chain. This is due to the fluctuating demand. Schaaf (2014) highlights the fact that, with the exception of the Cape Medical Depot (CMD), the medical depots in South Africa frequently experience shortages. In addition to the restrictions experienced due to the regulatory pathway, Schaaf (2014) lists the following factors that contribute to shortages occurring at health facilities:

- Health facilities forget to order on time;
- Health facilities forget to order; and/or
- Health facilities don't order enough.

Yadav (2012) emphasises the need for determining the optimal stocking pattern in order to reduce the occurrence of shortages and keep the holding costs to a minimum. However, determining the optimal stocking pattern requires accurate demand forecasts and well-functioning reorder policies. Reorder policies within medical depots are often unable to accurately ensure the right amount of stock, due to poor forecasting. Furthermore, shortages occur because of delays in procurement due to an inadequate number of suppliers.

2.4.5.3 Limited Diagnostic Capacity

The WHO set the targets of having at least one culture laboratory per five million people and at least one laboratory that has the capability for drug susceptibility testing (DST) per five million people. South Africa has reached both of these targets; however 14 of the 27 high MDR-TB burden countries had not reached the targets by 2012 (World Health Organization, 2013*a*). The 27 'high burden' countries are: Armenia; Azerbaijan; Bangladesh; Belarus; Bulgaria; China; Democratic Republic of the Congo; Estonia; Ethiopia; Georgia; India; Indonesia; Kazakhstan; Kyrgyzstan; Latvia; Lithuania; Myanmar; Nigeria; Pakistan; Philippines; Republic of Moldova; Russian Federation;

South Africa; Tajikistan; Ukraine; Uzbekistan; and Viet Nam.

In order to have accurate global MDR-TB estimates, effective methods of diagnosis along with diagnostic capacity need to be used. Sputum smear microscopy was developed over 125 years ago, and is usually the first TB diagnostic test done, especially in countries with a high rate of TB infection (Lawn and Nicol, 2012). Sputum is a fluid produced in the lungs and is tested for the presence of TB bacteria. If TB bacteria are present in the sputum then the results are recorded as smear positive (World Health Organization, 2010). However, the results of patients co-infected with HIV will be recorded as smear negative. The problem lies in the fact that patients are only diagnosed with TB if the results are smear positive, therefore the data on the incidence of TB is highly underestimated. In order to properly control TB, more accurate data on the incidence of TB is of paramount importance. Unfortunately 90% of people infected with TB come from low- and middle-income countries, where sputum smear microscopy and chest radiology are still heavily relied upon for diagnosis, due to the fact that it is inexpensive (Lawn and Nicol, 2012). However, although this method is inexpensive and easy to perform it cannot differentiate between drug-resistant and drug susceptible TB (Van Rie *et al.*, 2010). Only after the patient has been diagnosed with TB are additional culturing tests done to diagnose MDR-TB.

Culture tests are highly sensitive and can therefore: differentiate between drug susceptible and drug-resistant TB; and diagnose TB in HIV-infected individuals (Van Rie *et al.*, 2010). However the drawbacks of this method, as stated by Van Rie *et al.* (2010), include: a turnaround time between two and six weeks due to the slow growth of TB bacilli; the need for biosafety infrastructure; the high costs associated with these tests; and the complexity when compared to sputum microscopy. Therefore this method cannot be implemented in resource-limited settings.

Sputum smear microscopy and culturing tests require that the samples taken from the patients be transported to a laboratory for testing. The laboratories then need to test the samples for TB, after which the results then need to be transported or transmitted (i.e. electronically) back to the health facility from where it came. Although the procedure for smear examination is quite fast (1 day), culturing takes considerable longer, delaying treatment initiation (CDC, 2011). Due to the drawbacks experienced with both of these methods, cost-effective and accurate point-of-care (POC) TB testing is critical to ensure treatment can begin immediately after diagnosis. POC implies that a diagnosis can be made at the point where consultation occurs and provides a result that allows treatment to start on the same day as the consultation. Due to increased investments in TB research in the past decade, there have been many breakthroughs with regard to POC testing (World Health Organization,

2013*a*). In 2008, line probe assay tests (LPA) were recommended by WHO to detect MDR-TB. These rapid molecular tests use positive sputum specimens or cultures to detect resistance to RIF. In 2010, a new device called the GeneXpert MTB/RIF had been created to simultaneously detect TB and the resistance of the bacteria to RIF. This device detects MDR-TB in only two hours as opposed to the four weeks taken for culturing. The GeneXpert cartridge system has the following features:

- Macro- and microfluidics can be processed;
- Large volumes can be concentrated and purified;
- Contamination is unlikely as it is a closed system; and
- Analysis can be performed immediately.

This has increased the number of patients diagnosed with MDR-TB and the time in which they have been diagnosed. By the end of June 2013, 3.2 million test cartridges had been procured globally, with South Africa procuring 60% of the total. South Africa is aiming to position the GeneXpert MTB/RIF as a replacement for microscopy in detecting TB (World Health Organization, 2013*a*).

2.4.5.4 Suboptimal Adherence to Treatment Regimens

The critical advantage of this rapid diagnosis with POC is the reduction of patient dropout.

Throughout the process of diagnosis to initiation onto the appropriate treatment, many patients are 'lost' in the system. These patients dropout due to:

- The diagnosis process taking too long, i.e. laboratory testing;
- The patient not being able to return to the clinic to receive his/her results; and
- Not obtaining the results from the laboratory or the clinic.

It is therefore assumed that POC will help with initiation of treatment, as the result is available while the patient is still in the health-care facility - whether it be a house, clinic or a hospital (Olson *et al.*, 2011a). The challenge however still lies in the fact that treatment regimens cannot be adhered to and completed unless there is a constant supply of QA SLDs.

2.4.5.5 Lack of Transmission Control

Infection with drug-resistant TB is not only due to inadequate TB treatment, but also due to transmittance. MDR-TB can be transmitted directly from one person to another further spreading the drug-resistant strains. Therefore the importance of undiagnosed cases in the spread of the disease is underappreciated (Giffin and Robinson, 2009). Furthermore, effective global transmission control is critical in order to prevent the proliferation of the disease. However implementing effective transmission control in resource-limited settings involve a number of challenges including (Nardell, 2008):

- Ventilation systems that are too expensive to install and maintain;
- Lack of technical expertise to implement building design for triage and separation;
- Health workers and patients not wearing respirators as they feel stigmatised;
- Infected health workers in high burden settings (therefore they don't practice transmission control);
- Lack of technical expertise for the use of germicidal UV lamps;
- The belief that DOTS will solve the MDR-TB problem; and
- The mistaken belief that drug-resistant strains are less virulent than drug susceptible strains.

A lack of transmission control exacerbates the spread of the MDR-TB, putting more pressure on the SLD supply chain, further accelerating the need for a scale-up of the supply chain.

2.4.5.6 Low Rates of Treatment

Currently treatment levels for MDR-TB cases are low, as MDR-TB treatment projects have only two options for procurement of SLDs (Keshavjee and Seung, 2008):

- Procuring QA SLDs from the GDF, through the GLC; and
- Procuring drugs of unknown quality through state procurement mechanisms or the open market.

Only 0.2-0.5 % of the estimated five million cases of MDR-TB were treated with QA SLDs through GLC-approved programmes between the years 2000 and 2009, while approximately 70% received either drugs of unknown quality or no treatment at all. Keshavjee and Seung (2008) estimate that less

than 10% of the 70% will receive drugs of unknown quality and under varying programmatic conditions. The rest of the patients affected with MDR-TB (approximately 29.5 %) passed away (Nicholson *et al.*, 2013). Therefore the majority of MDR-TB cases are left untreated. The World Health Organization (2013*c*) emphasised that the majority of new MDR-TB cases occurred in the 'BRICS' countries (60%). The 'BRICS' countries being: Brazil; the Russian Federation; India; China; and South Africa.

2.4.5.7 Need for New Drugs and Regimens

The lack of new drugs to fight both drug susceptible and drug-resistant TB is a gap in the global fight against TB. Chou *et al.* (2008) observed that the last major breakthrough in TB treatment was the discovery of rifampin in the 1970s. He also noted that TB drug development experienced its 'golden age' between the 1940s and the 1960s when all the most common FLDs were discovered and developed. TB drug research has since then been stagnant, which threatens the gains made by antiretrovirals (ARV), as people infected with HIV risk dying from the curable disease, TB. According to Chou *et al.* (2008), there are seven new drug candidates in the TB pipeline, however this number is not sufficient to address the millions that are infected. As not all of these drugs will be approved, the pool of novel drug candidates needs to be kept full. It is also not sufficient that candidate drugs are merely entering the TB pipeline; these drugs need to be better than the existing ones by ensuring (Chou *et al.*, 2008):

- Decreased duration of treatment;
- Decreased pill burden;
- Trouble-free dosing with ARVs;
- Increased efficacy against drug-resistant TB; and
- The ability to treat paediatric TB.

Not only are the current candidate drugs in the TB pipeline associated with side effects, but some have not been tested in people taking ARVs, even though TB is the leading killer of people infected with AIDS. Children are also typically excluded from TB drug research and none of the candidate drugs have been tested in children (Chou *et al.*, 2008).

2.5 MDR-TB Treatment

MDR-TB is not only difficult to treat, as the bacteria is resistant to the two most powerful anti-TB drugs, but it is also very costly. The cost of just the

drugs for MDR-TB patients can be 50 to 200 times higher than the drugs for TB patients (Falzon *et al.*, 2010). This is due to the fact that SLDs cost more than FLDs and the treatment regime for MDR-TB lasts longer.

2.5.1 Adult MDR-TB Treatment

Table 2.3 shows the grouping of the SLDs used to treat MDR-TB. The SLDs are grouped according to efficacy and drug class, with Group One containing the most potent drugs. The FLDs used to treat TB (except INH and RIF) are in Group 1 of MDR-TB treatment, as they are the most potent and the best tolerated if the bacillus is not yet resistant to these drugs (World Health Organization, 2010).

The guidelines for the treatment of TB (2010) states that the MDR-TB treatment regimen should consist of at least four drugs with almost certain effectiveness against the infecting organism; one from each Group in hierarchical order. If there is resistance to all drugs in a one Group, the number of remaining drugs needed to complete a regimen of at least four drugs should come from Group Four. Only if a regimen has fewer than four effective drugs should drugs from Group Five be added to the regimen.

The intensive phase is the duration of treatment that includes an injectable agent from Group Two, which should continue for six to eight months. The continuation phase starts right after culture conversion and should continue for a minimum of 18 months (this includes the intensive phase) using the same drugs as in the intensive phase, without the injectable agent. According to the 'Standard Treatment Guidelines and Essential Medicines List for South Africa', 18 months of treatment is usually required for a person suffering from MDR-TB. The patient should be hospitalised for the initial four months of the intensive treatment, after which a clinic will do the follow-ups until the end of treatment. The dosages of drugs are administered depending on the mass of the patient according to the 'Standard Treatment Guidelines and Essential Medicines List for South Africa'. Table 2.4 shows which drugs are used from each Group, along with the doses for MDR-TB treatment in South Africa specifically. If a patient is specifically following the regimen shown in Table 2.4, that patient will use: kanamycin; moxifloxacin; ethionamide; terizidone; and pyrazinamide during the intensive phase, followed by using all drugs except kanamycin for the duration of the treatment (continuation phase).

Table 2.3: Groups of drugs to treat MDR-TB (Source: World Health Organization (2010))

Group	Name	Drugs
1	First-line oral agents	Pyrazinamide (Z)
		Rifabutin (Rfb)
		Ethambutol (E)
2	Injectable agents	Kanamycin (Km)
		Amikacin (Am)
		Capreomycin (Cm)
		Streptomycin (S)
3	Fluoroquinolones	Ofloxacin (Ofx)
		Levofloxacin (Lfx)
		Moxifloxacin (Mfx)
4	Oral bacteriostatic second-line agents	Ethionamide (Eto)
		Protionamide (Pto)
		Cycloserine (Cs)
		Terizidone (Trd)
		Para-aminosalicylic acid (PAS)
5	Agents with unclear efficacy	Clofazimine (Cfz)
		Linezolid (Lzd)
		Amoxicillin/Clavulanate (Amx/Clv)
		Imipenem (Ipm)
		Thiacetazone (Thz)
		High-dose Isoniazid (High-dose H)
		Clarithromycin (Clr)

Table 2.4: Standardised regimen for MDR-TB treatment in South Africa (Source: National Department of Health (2012))

Drug	**<50 kg**	**50-65 kg**	**>65 kg**
Kanamycin	$500 - 700$ mg	1000 mg	1000 mg
Moxifloxacin	400 mg	400 mg	400 mg
Ethionamide	500 mg	750 mg	$750 - 1,000$ mg
Terizidone	750 mg	750 mg	$750 - 1,000$ mg
Pyrazinamide	$1,000 - 1,750$ mg	$1,750 - 2,000$ mg	$2,000 - 2,500$ mg

2.5.2 Paediatric MDR-TB Treatment

The efforts to control MDR-TB in children face additional challenges, as TB drug research does not typically include children. DR-TB in children is under-diagnosed and under-reported, therefore efforts are underfunded (Perez-velez *et al.*, 2010). It is estimated that globally, one million cases of paediatric TB occur annually (Olson *et al.*, 2011). According to an epidemiological surveillance undertaken at the Tygerberg Children's Hospital in the Western Cape between 1994 and 2009, there is a high prevalence of drug-resistant TB specifically in the Western Cape, with an increasing number of children contracting DR-TB (Olson *et al.*, 2011a).

It has been found that MDR-TB in children results mainly from transmitted drug-resistance (90%) (Olson *et al.*, 2011a). Schaaf (2014), Department of Paediatrics and Child Health, University of Stellenbosch strongly suggests that once adults in a household present with TB, the entire household should be screened. Schaaf (2014) states that the biggest problem with treating children that have DR-TB is that the drugs are not designed for children. SLDs are rarely produced in paediatric formulations or appropriate tablet sizes. The dosages in each pill are too high for children and the pills either need to be cut, crushed or diluted to get the right dosage. The basic principles of the MDR-TB treatment regimen are the same as for children as for adults, however the dosages are subject to age-related change and mass. The pharmacokinetics, which include: absorption; distribution; metabolism; and excretion as well as the toxicity of drugs in children differ from those in adults (Poorana Ganga Devi and Swaminathan, 2013). The current dosing recommendations for children are based on adult mg/kg doses that are scaled down. Therefore dosing is likely to be inaccurate, leading to blood concentrations that are either toxic or sub-therapeutic which results in vomiting after children have ingested the

drugs. (Poorana Ganga Devi and Swaminathan, 2013; Lessem *et al.*, 2013).

In South Africa it is expensive to register a new drug with the Medicines Control Council (MCC), therefore even if companies do have the right drugs for children, they are reluctant to register these drugs. Schaaf (2014), stated that the FDA and EMA need to create rules to ensure that new drugs are child friendly. Extensive research must still be done on child-friendly formulations and paediatric pharmacokinetics to make the treatment of MDR-TB in children effective.

2.6 Conclusion: Real-World Problem

This chapter discussed the global epidemic of MDR-TB, highlighting the underperforming SLD supply chain as one of the main causes for the spread. Six IOM workshops have been held around the world to discuss the growing problem of DR-TB. This chapter highlights the main themes and findings presented at these workshops. The specific issues in both the upstream and downstream segments of the supply chain that are acting as barriers to the success of the supply chain are also summarised in detail.

Chapter 3 will discuss the techniques available for modelling supply chains, in order to model the real-world downstream supply chain.

Chapter 3

Modelling Supply Chains

This chapter describes the concept of modelling supply chains and why models are so useful for decision-making. Furthermore a supply chain is characterised as a complex adaptive system (CAS) to be modelled appropriately for decision-making. Finally, the paradigms of modelling techniques available for modelling supply chains are described; along with their suitability to specific problems.

In an attempt to increase supply chain performance and achieve the supply chain management objective of meeting customer demand with minimal lead-times for high quality products at low costs; companies need to have a better understanding and better visibility of the entire supply chain (Keramati, 2011). Supply chains are integrated systems involving upstream and downstream flows that are rarely ever linked in a linear way, therefore supply chain decision-making is a complex process. Modelling and analysis is therefore critical in the decision stage to gain a better understanding and to predict system performance (Biswas and Narahari, 2003). Appropriate models and studies are needed to aid in making decisions in such complex networks (Behdani, 2012).

3.1 Modelling

Very simply, a model can be described as a miniature representation of something and more specifically a graphical, mathematical or physical representation of a concept, system or an aspect of the real-world. Models are developed because they are on a smaller scale and thus easier to work with than the real system. Models use equations to represent the interconnectedness of a real-world system and only contain the relevant features to achieve a specific objective (Ford, 2009).

Modelling can therefore be described as the action of building a simplified representation of a system, with the goals of: facilitating understanding; providing predictions of the system's performance measures; and/or solving problems

(Altiok and Melamed, 2010).

3.2 Complex Adaptive Systems

3.2.1 Overview of Complex Adaptive Systems

Organisations that exhibit adaptivity and exist in complex environments with numerous interactions should be identified as a complex adaptive system (CAS) (Pathak *et al.*, 2007). Throughout literature there is general agreement with regard to the specific characteristics that define a CAS. The definitions and properties of a CAS as described by Choi *et al.* (2001); Surana *et al.* (2005) and Behdani (2012) are summarised below.

Choi *et al.* (2001) list the principles of a CAS, stating that the underlying dynamics of CASs fall under three main sections: internal mechanisms, environment and the co-evolution of both the internal mechanisms and the environment. These principles are listed in Table 3.1.

Table 3.1: Underlying dynamics of a CAS

Internal Mechanisms	**Co-evolution**	**Environment**
Self-organisation & Emergence	Quasi-equlibrium	Dynamism
Connectivity	Non-linear	Rugged landscape
Dimensionality	Non-random future	

Surana *et al.* (2005) have a very similar viewpoint and list the typical characteristics of a CAS as:

- Non-linear dynamics involving spatial and temporal effects;
- Coexistence of competition and cooperation;
- Strongly coupled degrees of freedom;
- Quasi-equilibrium state;
- Adaption and evolution;
- Structures spanning several scales; and
- Emergent behaviour and self-organisation.

Finally, Behdani (2012) classifies the properties that characterise a CAS into micro- and macro-level properties. The micro-level properties refer to the building blocks of the system and the macro-level properties describe the outer structure of the system. Table 3.2 divides the list of characteristics used to describe a CAS under either micro- and macro-level properties.

Table 3.2: Micro- and macro-level properties of a CAS

Micro-Level Properties	**Macro-Level Properties**
Numerousness & Heterogeneity	Emergence
Local interactions	Self-organisation
Nestedness	Co-evolution
Adaptiveness	Path dependency

The characteristics that define a CAS, as described by Choi *et al.* (2001); Surana *et al.* (2005) and Behdani (2012) are all very similar and can be summarised under the main headings: emergence and self-organisation, co-evolution and adaption, coexistence of competition and cooperation, non-linear dynamics, quasi-equilibrium, nestedness and path dependency.

3.2.1.1 Emergence and Self-organisation

Surana *et al.* (2005) state that emergent systems emerge through a natural process of order and spontaneity. Furthermore, as emphasised by Choi *et al.* (2001) and Behdani (2012), the behaviour of the CAS as a whole also emerges from the interactions between the individual sub-systems, thereby making it self-organising. Therefore emergent behaviour is the process whereby new properties and patterns arise without external influence on the system (self-organisation) (Choi *et al.*, 2001; Behdani, 2012).

3.2.1.2 Co-evolution and Adaption

The components in a CAS changes over time (Behdani, 2012). According to Choi *et al.* (2001), this constant evolution creates a dynamic system. Kaisler and Madey (2009) reiterate that a CAS has the ability to change its behaviour in response to changes in the environment to maintain some invariant state.

3.2.1.3 Coexistence of Competition and Cooperation

A CAS consists of an aggregate of agents and connections between these agents (Choi *et al.*, 2001). These numerous elements interact with each other at both

social and physical levels. As stated by Surana *et al.* (2005), the different individuals in a complex system regularly have conflicting objectives, therefore competition results in the sharing of resources or the contention of them.

3.2.1.4 Non-linear Dynamics

Complex systems behave in a non-linear manner, in other words the magnitude of an input is not necessarily matched to the output (Choi *et al.*, 2001). Therefore there is usually no direct correlation when events take place within the system. Surana *et al.* (2005) specifies that the characteristics of a CAS change as the workload and configurations change, thereby creating non-linear behaviour.

3.2.1.5 Quasi-equilibrium

A complex system tends to maintain a quasi-equilibrium state even in response to disturbances; however when the equilibrium state is disrupted, a structural change results (Choi *et al.*, 2001; Surana *et al.*, 2005). This structural change results in small events causing a cascade of changes which lead to a system reconfiguration. Therefore control and stabilisation become very challenging in such a system (Choi *et al.*, 2001).

3.2.1.6 Nestedness/Dynamism

The environment of a CAS is made up of many smaller CASs, therefore changes to one system cause changes to others, triggering collective environmental changes (Choi *et al.*, 2001; Behdani, 2012). CASs can be changed through altering the boundaries of the system with connections amongst agents. Moreover these environment changes can impose new rules and norms within the system (Choi *et al.*, 2001).

3.2.1.7 Path Dependency/Non-random future

Current, and future states and decisions in a CAS depend on past states and decisions (Choi *et al.*, 2001). Therefore past decisions made by an individual entity will constrain the current and future options for the entire system. Choi *et al.* (2001) emphasise the fact that although determining the exact behaviour of a system in the future is impossible, there are patterns of behaviour that can be used for an approximate prediction due to the path dependency factor.

3.2.2 Supply Chains as Complex Adaptive Systems

CASs consists of many mutually interacting subsystems that adapt over time without any centralised control over the system (Surana *et al.*, 2005). According to Surana *et al.* (2005), recognising that a supply chain is a CAS can lead to

effective ways of understanding and modelling their dynamics. Supply chains can therefore be solved and optimised by making use of approaches that are similar to those used for CASs. A number of literature sources are available framing supply chains as CASs. Table 3.3 summarises the properties supply chains possess that frame them as CASs.

Table 3.3: Framing a supply chain as a CAS

CAS property	Supply chain property
Emergence and Self-organisation	A supply chain emerges with no one external factor deliberately controlling it (Choi *et al.*, 2001). Decisions made downstream lead to amplifying effects upstream eg. bull-whip effect and robustness (Surana *et al.*, 2005).
Co-evolution and Adaption	The supply chain is constantly evolving to: keep up with competition; and satisfy customers. A supply chain reacts to the environment and actions of other actors in the supply chain, thereby making changes to both organisational goals and supporting infrastructure (Surana *et al.*, 2005). The actors in the supply chain change their perceptions and policies based on previous interactions and the changing economy.
Coexistence of Competition and Cooperation	In a supply chain, the various entities either have conflicting or mutual objectives and therefore either share resources or don't (Surana *et al.*, 2005).
Non-linear Dynamics	Customers can make transactions at any time with no regard for the existing workload at any point in the supply chain. The characteristics of the network change as the workload differs, resulting in non-linear dynamic behaviour (Surana *et al.*, 2005). Furthermore, supply chains have a wide geographical span, contributing to the non-linear character of the network.
Quasi-equilibrium	The supply chain tends to remain stable in response to external factors.
Nestedness/Dynamism	Each entity in the supply chain has a plant and each of these plants too have internal departments (Behdani, 2012). The membership of a supplier base is constantly reshuffled (Choi *et al.*, 2001).
Path Dependency/Non-random future	Each decision downstream in the supply chain influences future states and causes oscillating changes upstream (Choi *et al.*, 2001). Past decisions made by an individual entity in the supply chain will constrain the current options for the entire system.

3.3 Supply Chain Modelling Techniques

A supply chain performs the following functions: procurement of materials; transformation of these materials into finished products; and the distribution

of these finished products (Ivancevich and Duening, 2005). Supply chains have been shown to be complex and therefore require appropriate models and simulation studies to manage this complexity and broadness. Although vast amounts of literature are available on supply chain modelling techniques; very few agree on the taxonomy. Furthermore there is limited literature available regarding modelling methodologies that would aid in evaluating which techniques are appropriate for specific supply chains.

Starting in 1998, supply chain modelling techniques have been grouped in different ways, creating various taxonomies. Beamon (1998) classified supply chain modelling into four groups namely: deterministic analytical models; stochastic analytical models; economic models; and simulation models. Four years later, Min and Zhou (2002) classified supply chain modelling into: deterministic models; stochastic models; hybrid models; and IT-driven models. Hung *et al.* (2006) classified supply chain models into only two groups: analytical models; and simulation models. Penlope (2007) then classified the models into the groups: process models; statistical models; neural networks; discrete-event models; mathematical models; and systems dynamics models. Cope (2008) subdivided analytical models into: mathematical models; simulation models; spreadsheet process maps; and hybrid models, whereas Acar *et al.* (2010) subdivided analytical models into: deterministic models; stochastic models; and hybrid models. Keramati (2011) divided the models into: process models; statistical models; and mathematical models, where mathematical models were further subdivided into hybrid models, optimisation models, IT-driven models, analytical models and simulation models. Finally, Mohammadi and Mukhtar (2013) classified modelling into: analytical models; process models; and simulation models, where analytical models were further subdivided into mathematical models, statistical models and economic models.

Making use of all the different taxonomies provided in literature, many researchers support the idea that supply chain models should be classified as deterministic, stochastic and hybrid at the broadest level (Beamon, 1998; Min and Zhou, 2002; Keramati, 2011). Deterministic models contain only model parameters that are fixed and certain, whereas stochastic models take random parameters into accounts (Keramati, 2011). Hybrid models are a combination between deterministic and stochastic models. The taxonomy for supply chain modelling techniques that will be used for this research project is shown in Figure 3.1, and is adapted from Mohammadi and Mukhtar (2013):

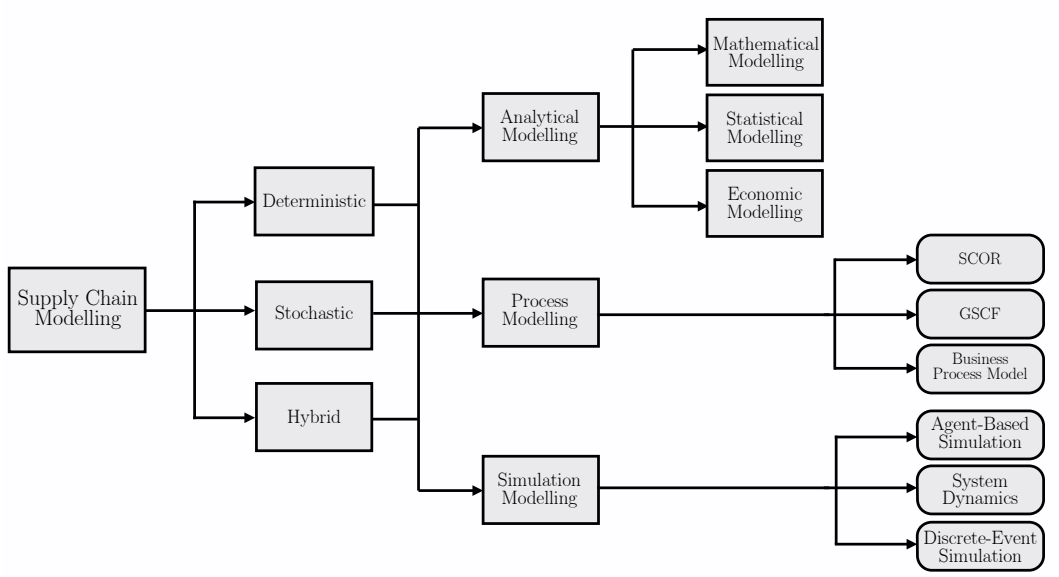


Figure 3.1: Classification of supply chain modelling techniques (adapted from Mohammadi and Mukhtar (2013))

The three most prominent modelling techniques for supply chains, as classified by Mohammadi and Mukhtar (2013) and shown in Figure 3.1; namely analytical, process and simulation models will be discussed in more detail.

3.3.1 Analytical Modelling

An analytical model is created by a set of equations or algorithmic procedures, which are then solved. The solutions to the equations are used to obtain performance measures (Altiok and Melamed, 2010). In other words it is a set of equations describing performance (Caliri, 2010). An analytical model describes the collection of measured and calculated behaviours over a finite period of time. Analytical models concisely describe a problem, provide a closed series of solutions, allow the easy assessment of impacts caused by changes in inputs and outputs and has the ability to reach an optimal solution (Campuzano and Mula, 2011). However the limitations of analytical modelling may include: the mathematics behind the problem being too complicated; or that the required assumptions may not be realistic enough.

3.3.2 Process Models

According to Cope (2008), process models are static, deterministic tools that do not take changes or variability in the system into consideration. These models logically capture the systems components and behaviours with respect to the modelling objectives. According to Keramati (2011), process models

can be descriptive, prescriptive, iconic or symbolic. The following types of process models are used to model supply chains:

3.3.2.1 Supply Chain Operations Reference Model

The Supply Chain Operations Reference (SCOR) model is an example of a process model as it provides a framework for metrics, best practises and processes. SCOR is based on six distinct management processes (Supply Chain Council, 2012): plan; source; make; deliver; return; and enable. These key management processes focus on the efficiency of internal processes, which therefore makes it more suitable for internally focused environments and not for organisations looking for extended supply chain efficiency. SCOR also identifies five core supply chain performance attributes: reliability; responsiveness; agility; costs; and asset management (Supply Chain Council, 2012). This model is therefore ideal for defining supply chains and for providing a basis for supply chain improvements (Keramati, 2011). Moberg and Vitasek (2008) state that the SCOR model was developed to provide a standard for measuring supply chain performance and allowing users to address, improve and communicate supply chain practices. This model is therefore focused on processes that use the concept of continuous improvement in the organisation. The SCOR model is therefore most appropriate for decision making and resource allocation.

3.3.2.2 Global Supply Chain Forum Model

According to Moberg and Vitasek (2008), the Global Supply Chain Forum (GSCF) model focuses on the integration of services. The GSCF model shows that supply chain management (SCM) represents a single company's orientation for total effectiveness and efficiency by integrating eight key processes throughout the supply chain (Campuzano and Mula, 2011):

- Customer relationship management;
- Customer service management;
- Demand management;
- Order fulfillment;
- Manufacturing flow management;
- Supplier relationship management;
- Product development and commercialisation; and
- Returns management.

This model however does not provide benchmarking information like the SCOR model. Therefore this model is most appropriate as an enhancement for advanced supply chains with established measurements and frameworks. The model also works better for supply chains that have a more constant demand (Moberg and Vitasek, 2008).

3.3.2.3 Business Process Model

A business process is the combination of activities in an organisation being structured in logical order. A business process model provides an understanding of the business process itself. The process is defined as a specific ordering and steps of work activities with clearly defined inputs and outputs. The model therefore illustrates the steps and activities involved in a specific process in a business (Sparx Systems, 2004).

3.3.3 Simulation Modelling

Altiok and Melamed (2010) define simulation modelling as the process of creating a computer representation that is executed to produce a number of sample histories. Campuzano and Mula (2011) characterise a simulation model as being quantitative, mathematical, computer-based and dynamic. According to Campuzano and Mula (2011), simulation models can describe highly complex systems and can either be used to experiment with non-existing systems or with existing systems. Furthermore simulation modelling is not solved through mathematical analysis and therefore does not require advanced mathematics. Simulation can also be an important tool in uncovering the causes and effects of supply chain performance. However the drawback with simulation modelling is that the models cannot generate a closed set of solutions i.e. each change in an input variable requires a separate solution, however it allows the observation of output in terms of input values. Another drawback mentioned by Campuzano and Mula (2011), is the challenge of validating a simulated model.

The objectives of supply chain simulation are as follows (Campuzano and Mula, 2011):

- Understanding all parts of the supply chain and its processes to generate knowledge;
- Proposing different scenarios and performing what-if analyses to improve the supply chain;
- Determining the robustness of a strategy without disturbing the real supply chain; and
- Quantifying the benefits resulting from the decision making.

According to Borshchev and Filippov (2004); Owen *et al.* (2010); Heath *et al.* (2011) and Behdani (2012), three main paradigms have been researched for the simulation of specifically complex systems. These paradigms are: system dynamics; discrete-event simulation; and agent-based simulation.

3.3.3.1 System Dynamics

System dynamics (SD) can be described as a computer-aided approach for solving complex problems in terms of policy design (Angerhofer and Angelides, 2000). SD is a deterministic modelling methodology that was created in the 1950s by Jay Forrester (Lane and Sterman, 2011). Forrester defined SD as "the study of information feedback characteristics of industrial activity to show how organisational structure, amplification (in policies), and time delays (in decisions and actions) interact to influence the success of the enterprise" (Angerhofer and Angelides, 2000). To capture the complexity of the system, the 'feedback loop' concept was suggested by Forrester in 1969. Therefore the feedback loop is the basic building block of a complex system and SD is a feedback-based simulation paradigm (Behdani, 2012). Control is exercised in SD by varying the ratio of input variables, in order to change flows and therefore levels (outputs). Sterman (2000) states that the main objective of modelling with SD is to understand the structural causes that result in specific behaviour of a system.

According to Angerhofer and Angelides (2000), SD has been used in various domains:

- Corporate planning and policy design;
- Energy and the environment;
- Economic behaviour;
- Software engineering;
- Biological and medical modelling;
- Dynamic decision making;
- Complex non-linear dynamics;
- Theory development in natural and social sciences; and
- Supply chain management.

The reason SD is applied to so many domains is because it can combine both qualitative and quantitative information (Brailsford and Hilton, 2001; Heath *et al.*, 2011). The qualitative model identifies elements that are crucial to the

system and then presents them in influence diagrams or causal loop diagrams where they are connected by arrows and 'S' and 'O' signs to show the direction of influence. The 'S' stands for same i.e. the variables move in the same direction, and the 'O' shows that they move in opposite directions. Feedback loops can either be classified as 'balancing loops' (negative) or 'reinforcing loops' (positive). Balanced loops retain a steady state, whereas reinforcing loops result in uncontrolled growth (Brailsford and Hilton, 2001; Heath *et al.*, 2011). However the overall effect of all the feedback loops in a complex system, such as a supply chain, cannot be determined with only the causal loop diagram as it may not be obvious which feedback loop dominates the system. This is where it becomes necessary to quantify the system (Heath *et al.*, 2011; Behdani, 2012). In a quantitative model, the causal loop diagram gets replaced by a flow diagram, called a 'stock-flow model'. A series of stocks (levels) and flows (rates) are used to model the system. Stocks are accumulations of rates of flow and flows are outputs of decision rules (Behdani, 2012). The state changes are continuous and the model is solved with differential equations (mostly numerical integration) (Brailsford and Hilton, 2001; Behdani, 2012).

Making use of SD modelling for supply chain management specifically, dates back to 1958. Forrester (1958) simulated a basic supply chain consisting of: a factory; a factory warehouse; distributors; and retailers with information flows throughout the supply chain. The feedback principle of SD facilitates modelling and qualitative simulation analysis to design and control the supply chain structure (Campuzano and Mula, 2011). Furthermore Campuzano and Mula (2011) state that SD facilitates experiments with supply chains. SD modelling can therefore promote high-level understanding of large systems and capture aspects of supply chain behaviour; specifically the 'bullwhip effect' (Dale Compton *et al.*, 2005).

System dynamics is usually used at higher, strategic levels to gain insight into the interactions between parts in a complex system and how they influence an overall system (Brailsford and Hilton, 2001). The aim of SD modelling is to gain an understanding of the feedback dynamics and system behaviour. The main strength of SD lies in modelling the adaptiveness in a complex system, as feedback loops are the key drivers of dynamic behaviour in a SD model (Sterman, 2000). The use of feedback loops and delays makes it possible to model a highly complex and dynamic system at a high level over time. However the drawback of high level modelling of complex systems is that it is done with uncertainty, and therefore parameters must be estimated carefully (Dale Compton *et al.*, 2005). This uncertainty can be found in the data used in the model, the assumptions made during modelling and the difficulty in modelling human behaviour.

3.3.3.2 Discrete Event Simulation

Discrete-event simulation (DES) models systems as networks of queues and activities (Brailsford and Hilton, 2001). The conceptual model in DES is an activity diagram (analogous to a causal loop diagram in SD), which shows the logic of the flow of entities through queues and activities. According to Altiok and Melamed (2010), in this paradigm of simulation, the model possesses a state at a point in time. This state is a set of data that captures the variables of the system and can thus be defined in many ways. The state's path over time is a step function whose jumps are triggered by discrete events (Altiok and Melamed, 2010). Kleijnen (2004) and Campuzano and Mula (2011) describe the two main characteristics of DES as: (i) representing individual events; and (ii) incorporating uncertainty. The evolution of the model is run by a chronologically ordered event list over time. In other words, the events are listed in their scheduled order of occurrence with the event at the top of the list being the most impending event. The occurrence of an event results in taking an event off the list and executing it.

The general algorithm for the DES simulator is an infinite loop of the following steps (Altiok and Melamed, 2010):

- **Step one**:
  Set the simulation clock to an initial time and generate and schedule events;
- **Step two**:
  If the event list is empty, terminate the simulation. If the list is not empty unlink the imminent event from the event list;
- **Step three**:
  Advance the clock to the time of the imminent event and execute it; and
- **Step four**:
  Loop back to step two.

Altiok and Melamed (2010) state that the DES paradigm has a distinct feature wherein nothing changes the state except the occurrence of an event. In other words the state stays constant in-between events. Large and complex systems can be represented by DES, as the processing of events can be as detailed as desired, and increasingly complex systems can be built from subsystem components (Altiok and Melamed, 2010). However the drawback is that DES models often require large amounts of data (Brailsford and Hilton, 2001).

3.3.3.3 Agent-Based Simulation

Agent-based simulation (ABS) is based on local interaction between agents (Macal and North, 2006). Therefore no central authority exists controlling

the operation of the system or the movement between states. Macal and North (2006) describe agents as discrete entities with unique characteristics and behaviours. The essential characteristics of an agent are (Macal and North, 2010):

- An agent is uniquely identifiable;
- An agent has behaviours;
- An agent has a state that changes with time;
- An agent is social as it has dynamic interactions with other agents; and
- An agent is autonomous and self-directed.

An agent's capability to act autonomously is the most important characteristic of an agent. Agents can therefore act on their own and make independent decisions without external control (Macal and North, 2010). In addition to their essential characteristics, agents may also be: adaptive; goal-directed; and heterogeneous (in terms of their resources, memory and sophistication) Examples of agents range from robots to people to organisations (Macal and North, 2006). According to Macal and North (2010), an ABS model has three elements:

- A set of agents and their behaviours;
- A set of agent relationships and methods of interaction (a topology of connectedness defines how and with whom they interact); and
- The agent's environment (agents interact with both other agents and the environment).

Agents are required to repeatedly execute their interactions for the model to run. Agent-based modelling is unique in the fact that the modelling begins and ends with the agent's perspective (Macal and North, 2006). ABS models have been applied to supply chains due to the fact that the models have proven to be appropriate for studying complex systems. ABS models are specifically used in the context of supply chains in two ways: (i) calibration of the agent parameters with real-world data; and (ii) exploration of operating policies and modes of operations (Zhang and Bhattacharyya, 2004). More specifically Owen *et al.* (2010) state that ABS is most appropriate for the following supply chain themes: information sharing; human behaviour; supply chain optimisation; distributed supply chain; collective customer collaboration; market dynamics; e-manufacturing optimisation; supply chain dynamics; and modelling control elements.

Summary of Paradigms:
The main properties of the three simulation paradigms are summarised in Table 3.4. Furthermore, the three paradigms can also be classified according to their approach. The ABS modelling approach models a system by modelling the individual entities and interactions that make up a system; which is described as the 'bottom-up approach.' Whereas SD modelling is done by breaking a system into its main parts and modelling the component interactions; known as the 'top-down approach' (Heath *et al.*, 2011). According to Behdani (2012), DES also has a 'bottom-up approach' in terms of modelling.

Table 3.4: Main characteristics of SD, DES and ABS (adapted from Behdani (2012))

Property	**System Dynamics**	**Discrete-Event Simulation**	**Agent-Based Simulation**
Oriented toward	System	Process	Individual
Entities	Homogeneous	Heterogeneous	Heterogeneous
Dynamic behaviour driver	Feedback loops	Event occurrence	Agents, decisions, interactions
Mathematical formulation	Stock and flow	Event, activity, process	Agent, environment
Time	Continuous, discrete	Discrete	Discrete
Experiment method	Changing system structure	Changing process structure	Changing agent rules (interaction rules) & system structure
Structure	Fixed system	Fixed process	Not fixed system

3.4 Data Availability

The data available for the process of modelling will also be a factor when deciding which modelling technique to make use of. Because this is a public healthcare study, there are limitations in collecting data due to confidentiality

and ownership of data (Nicholson *et al.*, 2013). According to Wallengren *et al.* (2011), more recent data has shown that the burden of DR-TB has been underestimated. Data about product-use, patient enrolment rates and plans from in-country DR-TB programs is also lacking (Nicholson *et al.*, 2013). As for data transparency, there is some disagreement about whether the data should be fully disclosed due to security concerns.

Throughout the whole MRD-TB SLD supply chain there is inadequate data collection, which will limit the data collection process for this study. Limited data availability will affect the detail to which the model can be created, and therefore some processes may need to be lumped together which will lead to model simplification. The danger of model simplification is the fact that critical system components may be missed, which may cause difficulties with model validation (Chung, 2004). According to Heath *et al.* (2011), the data requirements for a SD model is generally less than that for a DES model.

3.5 Conclusion: Modelling Supply Chains

This chapter introduced the concept of modelling supply chains and discussed the modelling techniques that are available to model supply chains, namely: analytical models; process models; and simulation models. Furthermore, the supply chain is classified as a CAS in order to select the most appropriate modelling technique. However as specified by Surana *et al.* (2005) and Behdani (2012) simulation has been the primary tool for modelling CASs. This is due to the fact that it is a challenge to determine which individual strategies leads to the collective behaviour of such a complex system i.e. reverse engineering. Simulation however makes these investigations possible (Surana *et al.*, 2005). There are also various other reviews which have investigated simulation modelling in supply chains: Beamon (1998); Angerhofer and Angelides (2000); Min and Zhou (2002); Terzi and Cavalieri (2004); Akkermans and Dellaert (2005); Campuzano and Mula (2011). Therefore the primary focus of this chapter is on simulation modelling, as it will be the method used to model the SLD supply chain, discussing in detail the three main paradigms thereof: SD; DES; and ABS.

Chapter 4 will discuss the selection methodology used to identify the paradigm chosen to model the downstream MDR-TB SLD supply chain. Furthermore, the suggestions made at the IOM Forum workshops for strengthening the global MDR-TB SLD supply chain, and the best practises for supply chain performance improvement as highlighted in the SCOR model will also be discussed. The type of issues that are tested using a model is one of the most prominent factors when deciding which modelling technique to use. These

suggestions and best practises will therefore also be evaluated to aid in the process of selecting the appropriate modelling technique.

Chapter 4

Confronting the Real-World Problem

This chapter highlights the suggestions that have been proposed at the six IOM Forum workshops to control the global spread of MDR-TB. The suggestions that are both relevant to strengthening the supply chain specifically and within the scope of this study will be analysed and then tested using a model, to investigate their impact on the overall supply chain. Additionally this chapter highlights the specific performance attributes that are used to evaluate a supply chain, as well as the best practises that should be used to improve upon the performance of the supply chain. The performance attributes that will be tested include: reliability; responsiveness; and agility, as listed in the SCOR model. Finally, based on these suggestions and best practises, the process by which the appropriate simulation paradigm was chosen to model the downstream SLD supply chain is described.

4.1 IOM Suggestions for Confronting the Global MDR TB Crisis

This section lists and describes the IOM's potential strategies for combating the various problems with MDR-TB, as discussed in Chapter 2. The suggestions will be divided into two main categories: (i) 'general strategies'; and (ii) 'supply chain strategies,' as only the proposed solutions regarding the physical supply chain will be investigated in this study. These strategies have however not yet been tested or implemented, thereby requiring a model to simulate the effects and impacts that these suggestions will have on the supply chain.

4.1.1 General Suggestions

These suggestions combat the general MDR-TB crisis; and although they affect the supply chain they are not directly related to the physical supply chain. Therefore these proposed solutions will not be able to be tested in the SLD supply chain model.

4.1.1.1 Diagnostics and Laboratory Capacity

Due to the limitations of smear microscopy (the most common TB detection test), there is an urgent need for point-of-care (POC) testing and an increase in in-country laboratory capacity. Specific suggestions to address the diagnosis problems, listed from Keshavjee and Seung (2008) in the white paper for the Institute of Medicine of the National Acadamies include:

- Giving priority to research and funding for immediate development and deployment of POC testing for both TB and MDR-TB, globally;
- Utilising excess laboratory capacity in wealthy regions for the TB culture testing of low income countries;
- Improving in-country laboratory networks and coordination of private laboratories, i.e. a central body should be in charge of the entire laboratory network (Olson *et al.*, 2014);
- Giving priority to paediatric treatment (diagnostic techniques cannot identify many cases of paediatric TB);
- Creating long-term on-site technical assistance for TB culturing and testing; and
- Increasing sustainable funding from donors for the construction of laboratories.

Olson *et al.* (2011) state that although candidates for POC testing exist (as discussed in Chapter 2), strategies need to be put in place to make them mainstream. However, Olson *et al.* (2011a) note that developing POC testing for the mainstream will require safe laboratory and health care infrastructure to protect against drug-resistant TB. There is also an urgent need to develop more laboratory tests that are capable of not only detecting drug-resistant strains of TB but also drug susceptibility to new anti-TB drugs. According to Hoffner (2013), more resources should be made available for implementing more rapid tests, as wide as possible.

4.1.1.2 Quality Drug Supply

One of the major causes of the rapid spread of MDR-TB is the manufacture of counterfeit SLDs. There are a number of approaches that have been suggested by the various participants in the workshops to address this problem; which include:

- Increasing the number of manufacturers of QA SLDs, to both lower prices and ensure availability (Keshavjee and Seung, 2008);
- Developing a mechanism to make these QA drugs available at pre-negotiated prices to programs purchasing via the GDF (Keshavjee and Seung, 2008);
- Developing an operational strategy to improve demand forecasting (Nicholson *et al.*, 2013; Olson *et al.*, 2014);
- Developing a mechanism for pooled procurement to increase the predictability of the demand (Nicholson *et al.*, 2013);
- Reducing the GDF procurement barriers to allow countries to directly purchase drugs from their own quality assured suppliers (single suppliers and manufacturers are not enough)(Giffin and Robinson, 2009; Olson *et al.*, 2011);
- Increasing the buffer stock of SLDs with optimal size, scope and design to facilitate rapid delivery of drugs (Keshavjee and Seung, 2008; Nicholson *et al.*, 2013);
- Increasing options available for treating MDR-TB, by optimising current treatment regimens (Keshavjee and Seung, 2008);
- Developing new anti-TB drugs by increasing TB clinical trial capacity (Keshavjee and Seung, 2008);
- Providing incentives to countries to procure QA drugs (Bloom, 2013);
- Creating public-private partnerships to do what neither can do alone (Bloom, 2013); and
- Strengthening the regulatory authorities in high burden MDR-TB countries, and in countries that export the drugs (Olson *et al.*, 2011).

4.1.1.3 Infection Control and Treatment Delivery

The global crisis of MDR-TB can only be controlled if the further spread of the disease can be prevented. Due to the fact that drug-resistant TB can be transmitted from person to person and that it can be transmitted so easily through the air, transmission control is critical. Suggestions pertaining to preventing

specifically transmission of MDR-TB include: patient management; starting treatment as early as possible to reduce transmission; and exploring whether making use of surgery to reduce transmission is possible (Olson *et al.*, 2012). Nardell (2013), advocates a paradigm with the acronym FAST to refocus TB transmission control, as it should be as important a focus of attention as new methods for diagnosis:

- **Find** TB cases.
  The focus should be on rapid molecular diagnosis in order to start treatment as soon as possible to slow the rate of transmission.

- **Active** case finding.
  The focus here is on cough surveillance at all entrance points of hospitals. The cough detection should lead to diagnosis and ultimately effective therapy within a matter of days. The incidence of TB amongst the health care workers should also be monitored.

- **Separate** safely and reduce exposure.
  Environmental control, and respiratory protection are critical until the effective treatment is carried out. The building design and engineering capacity need to support and implement these controls. Health care workers should be given comprehensive preventative therapy for TB.

- **Treat** effectively based on drug susceptibility testing (DST).
  Rapid molecular DST should be done with technologies such as the GeneXpert MTB/RIF in order to treat for the correct strain of TB.

Treatment delivery is just as critical as transmission control, as successful treatment will not only prevent further transmission, but also save lives. Suggestions made by Keshavjee and Seung (2008) in the white paper for the Institute of Medicine of the National Acadamies for improving treatment delivery include:

- Promoting universal treatment for both drug susceptible and drug-resistant TB with national TB control strategies in order to build capacity for MDR-TB treatment;

- Integrating universal treatment for TB into HIV treatment initiatives;

- Improving the international technical assistance provision system for successful regional MDR-TB treatment programs;

- Implementing ambulatory-based treatment, as it has the potential to be a safe means of treating the largest amount of patients in the shortest amount of time;

- Training villagers to become community health workers in resource-poor environments to establish community-based care (partnerships between the health care system and communities);
- Scale-up of successful treatment programs;
- Collaborating with private-sector laboratories and treatment providers; and
- Integrating infection control into national TB control strategies.

4.1.1.4 Financing

The procurement of SLDs is an expensive task, therefore the issue of how to best finance this procurement resonated through the report written on the fifth IOM workshop held in Washington DC in 2012. There have been many suggestions with regard to innovative financing strategies. Nicholson *et al.* (2013) states that participants discussed two important factors to consider with regards to financing: (i) the expansion; and (ii) the increased predictability and flexibility of the funding pool. It is suggested that the improved predictability could potentially improve the market health and facilitate program implementation. On the other hand, the improved flexibility could possibly reduce the finances lost to 'use' and match resources more appropriately with number of patients (Nicholson *et al.*, 2013).

Pooled financing is one of the flexible financing strategies suggested by the participants in the workshops. This mechanism would allow the withdrawal of funds from a larger pool, sidestepping the process of having to access funds in advance when the requirements are uncertain, due to inaccurate demand forecasting (Nicholson *et al.*, 2013). Bloom (2013) suggests increased funding from the Global Fund and an up-front pooled capital fund to reduce the need for separate negotiations with producers. Additional financing strategies that were proposed include 'push' and 'pull' mechanisms. 'Pull' mechanisms create demand, while 'push' mechanisms create incentives to enter the market. Table 4.1 lists the push and pull strategies suggested by Atun (2012), to address the funding shortfalls and unpredictable financing.

Vincent (2012), suggests four opportunities that the Global Fund and other donors should support through the GDF, that she assumes will half current procurement time delays:

- Promotion of flexible and pooled funding;
- Expansion of the strategic rotating stockpile (SRS) to expedite delivery to countries and provide flexibility to match supply with demand;

- Supporting local production of QA SLDs in BRICS countries (high MDR-TB burden countries) to provide incentives for them to use QA SLDs and QA API/FPP; and
- Shifting the focus of donors from FLDs to SLDs by freeing up more funds for SLDs.

Table 4.1: Innovative push and pull mechanisms

Push Strategies	**Pull Strategies**
Public private partnerships	Long term instruments (TB bond)
R&D credits	Expanded health insurance (domestic level)
Accelerated approval	Catastrophic risk insurance to cover MDR-TB (domestic level)
	Venture capital - impact funds
	Outcome-based financing (reward successful approaches)

Furthermore USAID have a three-pronged approach for making affordable, quality SLDs available around the world:

- **Improve and expand global SLD supply chain.**
  To achieve this USAID suggest: coordinating with and providing global support for the GDF; harmonising treatment regimes; and shifting support and data from FLDs to SLDs.
- **Engage manufacturers in production of QA SLDs.**
  Promoting QA SLDs involves: assisting API and FPP manufacturers to become prequalified; increasing the number of API sources; supporting development of guidelines to expedite registration of prequalified SLDs; supporting the development of public pharmacopeial standards; and improving diagnostic tests.
- **Assist countries in securing QA SLDs.**
  In order to do this USAID will need to provide technical assistance at a country level. This technical assistance involves: early warning systems for stockouts; in-country and regional assistance in pharmaceutical management; developing new training platforms; improving information management systems; and promoting surveillance of SLD utilisation and TB/HIV co-medication safety.

4.1.2 Supply Chain Strategies

These proposed suggestions directly affect the physical supply chain and are assumed to strengthen the MDR-TB SLD supply chain if they are put into practise. Many of these suggestions have already been discussed along with the general suggestions, however are emphasised here as solutions that relate to the physical supply chain operations. These suggestions are only mentioned briefly here, with all the necessary detail set out in Chapter 6, where the different suggestions are analysed.

4.1.2.1 Providing Incentives to Suppliers and Manufacturers

As previously mentioned, one of the biggest challenges in the SLD supply chain is the lack of suppliers and manufacturers of QA drugs. An increase in quality assured manufacturers will not only decrease the prices of SLDs but also increase their availability (Keshavjee and Seung, 2008). The high risks facing suppliers along with the low incentives are direct causes of suppliers being hesitant to enter the SLD market. Many participants in the workshops discussed implementing incentives to get more manufacturers and suppliers to enter the SLD market and to get manufacturers to produce QA drugs (Nicholson *et al.*, 2013). One of the ways to create incentive includes aggregating and sharing risk between all the players throughout the drug supply chain (Giffin and Robinson, 2009; Olson *et al.*, 2012).

4.1.2.2 Operational Strategy for Improved Forecasting

The suggestion provided by Bloom (2013) to improve demand forecasting includes linking TB forecasting with the forecasting of other diseases and drugs - such as HIV and malaria - whilst also having input from experts from both the public and private sector. It has also been suggested that the development of an operational strategy to improve demand forecasting be prioritised (Nicholson *et al.*, 2013). Furthermore regular interaction should be facilitated with manufacturers around demand forecasting. Developing a mechanism for pooled procurement, as well as bundling SLDs with other well-established drug supply chains, could possibly increase the predictability and volume of demand thereby improving demand forecasting (Nicholson *et al.*, 2013).

4.1.2.3 Inventory Management

Nicholson *et al.* (2013) suggest maintaining a buffer inventory of SLDs with optimal size and scope to ensure a constant supply of SLDs. This should not only reduce lead times, but also prevent stock-outs when forecasting is incorrect and demand surpasses the forecast. This buffer inventory could be translated into either safety stock or desired drug inventory in a warehouse or health facility. Proper inventory control policies and procedures should be put

into practise to: (i) avoid stock-outs; and (ii) provide reliable data for estimating order quantities (Phanouvong *et al.*, 2011). Good stock management procedures, as suggested by Phanouvong *et al.* (2011) include:

- Record receipt and distribution of all drugs to TB depots and health facilities;
- Record receipt and dispensing of all drugs in inpatients and outpatients on a regular basis;
- Store drugs appropriately i.e. no direct sunlight, access security;
- Rotate stocks to ensure shortest expiry date is in the front and most easy to access-FEFO (first-expired first-out) and FIFO (first-in first-out) principles should be applied;
- Review stock levels everytime an issue is made to ensure the stock is above the set minimum level; and
- Maintain buffer stocks at all levels of TB care facilities.

4.1.2.4 Harmonisation and Standardisation

Fragmentation is another bottleneck in the SLD supply chain. Increased harmonisation and standardisation in the supply chain is necessary to reduce the barriers to entry of SLDs into the market (Olson *et al.*, 2012). The processes that should be standardised include:

- The WHO pre-qualification procedures;
- The quality-assured qualification process; and
- The product registration system.

The facilitation of regulatory harmonisation will reduce the delays experienced with drug approval and distribution. Furthermore, drugs that are pre-qualified by the WHO or stringent regional regulatory authorities should not have to go through additional regulatory reviews within individual countries, therefore Bloom (2013) suggests that regional regulatory agreements should be implemented to avoid repeated validations by agencies in each country.

4.1.2.5 Information Systems

Bloom (2013) is of the opinion that the most limiting factor in the supply of drugs is a lack of information. Therefore the information systems throughout the supply chain need to be improved upon. Nicholson *et al.* (2013) suggests the development of universal, standardised bar coding for products, coupled with mobile information technology to track drug supply and stock-outs. The implementation of EMR systems for MDR-TB programs is also crucial for data collection. Fraser (2012) makes the following information technology suggestions to improve the MDR-TB SLD supply chain specifically:

- Standardised national and international coding of medical products to track shipments;
- Standardised bar coding of medications and products containing: name, batch number, expiry date and authentication ID; and
- Standardised reporting formats for medication stocks and status.

Giffin and Robinson (2009) emphasise that the most vital role that information technology will play in the TB crisis is the sharing of diagnostic data between countries and projects.

4.2 SCOR Best Practices

In addition to investigating the suggestions made at the IOM workshops, this section will discuss the best practices that have been chosen by SCOR practitioners due to the positive impacts these practices have on the performance of a supply chain. SCOR defines best practices as practices that are current, structured and repeatable (Supply Chain Council, 2012). The SCOR process reference model was established for the evaluation and comparison of all supply chain activities, therefore the SCOR model is used to evaluate the performance of the current SLD supply chain and eventually provide recommendations for improvement where necessary, based on the best practices.

4.2.1 Performance Attributes

These best practices refer to improving the following performance attributes highlighted in the SCOR model: reliability; responsiveness; agility; cost; and asset management efficiency. Due to the lack of data and the fact that it is out of the scope of this study (based on the aim and objectives), this study will not investigate cost and asset management. These attributes refer to how efficiently finances and assets, respectively, are currently being used within the supply chain, on which data is not available for this study. Therefore only the

best practices applicable to reliability, responsiveness and agility will be considered and further investigated in this study. However, the additional costs that are incurred for each scenario tested using the model will be investigated later in the evaluation phase.

The Supply Chain Council (2012) describes a performance attribute as: "a grouping of metrics used to describe a strategy." As discussed in section 3.3.2.1; the attributes used to measure a supply chain's performance, along with their definitions as defined by the Supply Chain Council (SCC) are discussed in Table 4.2.

Table 4.2: SCOR performance attributes

Performance Attribute	Definition
Reliability	Reliability refers to the supply chain's ability to perform tasks: on-time, with the right quantity, and with the right quality.
Responsiveness	Responsiveness refers to the speed at which these tasks are performed.
Agility	Agility refers to the ability for the supply chain to respond to external factors that cannot be controlled, such as demand. Supply chains should be robust enough to not only adapt to these changes, but to adapt fast.
Cost	The costs referred to here are the operating costs, such as labour, material and transportation costs.
Asset Management Efficiency	As the name implies, this attribute refers to efficiently and effectively utilising assets within the supply chain, namely cash.

The SCOR model highlights the best management practices that produce better process performance in terms of reliability, responsiveness and agility in a supply chain. Table 4.3 lists the best practises that have been identified by SCOR to improve the overall performance of the supply chain.

Only the best practices available for improvement on the weakest performance points that are also in the scope of this research project will be further investigated using the model. The evaluation of the performance of the current SLD supply chain will be completed in Section 5.4, after which the weakest performance attributes will be identified.

Table 4.3: SCOR best practices

Reliability	**Responsiveness**	**Agility**
Demand Management	Transportation Optimisation	Long Term Supplier Agreement/ Partnership
Demand Planning	Sales and Operations Planning	Optimised Supplier Count
Inventory Optimisation	Inventory Management using Supply Chain Network Optimisation	Vendor Collaboration
Vendor Collaboration	Purchase Order Management	Business Rule Review
Sales and Operations Planning	Long Term Supplier Agreement	Strategic Sourcing
Convergence of SCOR with Lean and Six Sigma	Convergence of SCOR with Lean and Six Sigma	Convergence of SCOR with Lean and Six Sigma

4.3 Selection of Modelling Methodology

The different modelling techniques available for supply chains have been discussed in Chapter 3, along with the suitability of each for different situations. As the aim of this research is to test improvements for strengthening the downstream MDR-TB SLD supply chain, and simulation modelling has the ability to propose different scenarios and perform 'what-if' analyses; it is the most appropriate modelling technique for this study.

Of the three most prominent paradigms of simulation modelling (DES, SD and ABS) that have been discussed in Chapter 3; DES and SD are the two that are the most widely used tools for: (i) decision support systems in supply chain management (Tako and Robinson, 2012); and (ii) problem-solving in the healthcare domain (Brailsford and Hilton, 2001). Tako and Robinson (2012) have explored the application of both DES and SD in the context of supply chain management. Furthermore, the characteristics of ABS (shown in Table 3.4) are: oriented towards the individual; based on discrete time events; and not a fixed structure with individual decisions driving the dynamic behaviour. These are not the characteristics of a supply chain, therefore this paradigm is not considered for this specific study.

4.3.1 Comparison of Simulation Paradigms

In order to decide which simulation paradigm is most appropriate - assuming the choice is between DES and SD - Lane (2000) and Brailsford and Hilton (2001) list criteria on which the selection should be based. This list is shown in Table 4.4. However these rules are not fixed and still require the judgement of the modeller. Furthermore Brailsford and Hilton (2001) believe that the decision may depend more on the purpose of the model than the actual system being modelled.

Table 4.4: Criteria used to choose between SD and DES (adapted from Brailsford and Hilton (2001))

Criteria	**System Dynamics**	**Discrete-Event Simulation**
Scope	Strategic	Operational
Variability	Low priority	High priority
Tracking individuals	Low priority	High priority
Number of entities	Large	Small
Timescale	Long	Short
Perspective	Holistic (dynamic complexity)	Analytic (detail complexity)
Resolution	Homogenised entities (continuous)	Individual entities, decisions and events
Data Sources	Broadly drawn	Numerical
Outputs	Understanding of structural sources of behaviour modes	Point predictions and performance measures
Purpose	Policy making	Decisions (optimisation, prediction)

4.3.1.1 Supply Chain Management Issues

As mentioned before, Brailsford and Hilton (2001) believe that the purpose of the model is one of the most important criteria to evaluate when selecting a simulation paradigm. Table 4.4 shows that the purpose of a simulation model

is either strategic (policy making) or operational (decision making). Decisions made within supply chain management are either: strategic; tactical; or operational, therefore Tako and Robinson (2012) have identified, and grouped into either strategic or operational categories, the most common logistics and supply chain management issues. The list is ordered from the most strategic issues down to the most operational issues in Figure 4.1.

The suggestions provided by the IOM workshops that will be tested in the model fall under the following supply chain management issues: supply chain optimisation; inventory planning/management; and planning and forecasting demand. Figure 4.1 shows that these issues fall under operational issues. Literature available on matching the simulation paradigm to the type of issue shows that SD and DES have both been used for strategic and operational issues. There have been many claims that SD is more suitable for strategic and policy level issues rather than operational issues (Borshchev and Filippov, 2004; Tako and Robinson, 2012). However, there are other views that have expressed the suitability of using SD to model issues at operational levels. Owen *et al.* (2010) has contradicted the general belief that SD modelling is more suitable for strategic level modelling and has shown that SD can be used effectively for any issue, ranging from strategic to operational. Owen *et al.* (2010) has proven this by tabulating the type of simulation paradigm that has been used for various types of issues in many different research areas. These tabulated results show that although SD has been used more frequently for strategic problems, there are many instances where SD is used to model at an operational level. Moreover, Morecroft and Robinson (2005) states that no straightforward distinction exists when comparing the two approaches for suitability. As this research project will be developed further relating to more upstream supply chain strategic issues, where SD has been used more frequently, and the research done by Owen *et al.* (2010) shows that SD is effective for both operational and strategic issues, SD is chosen to be the most appropriate paradigm for this study.

Figure 4.1: Supply chain management issues listed in order from the most strategic to the most operational (adapted from Tako and Robinson (2012))

4.3.2 Selecting Simulation Software

There are various system dynamics simulation software packages available for modelling supply chains. These models are built using the elements: stocks; flows; and converters, with focus on the feedback structure of the model. System dynamics software is designed for simulating business systems, organisational systems, simple engineering systems and scientific systems (GoldSim Technology Group, 2007). Cavana and Maani (2000) list the general purpose system dynamics software: Stella; Vensim; Powersim; *iThink*; DYNAMO;

DYSMAP; and COSMIC. Furthermore, in order to address the real-world problems in supply chains, simulation software should have the following capabilities (GoldSim Technology Group, 2007):

- **Integrate uncertainty and variability.**
  The software must represent uncertainty regarding the input data and the system dynamics and reveal the results in terms of the range of possible outputs.
- **Explicitly represent discrete events.**
  The dynamics of a supply chain are affected by random discrete events. These events will influence the overall performance and agility of the supply chain and therefore need to be represented along with the full range of consequences.
- **Promote a top-down hierarchical structure.**
  The software should allow for multi-layer models to allow greater detail at each level, as supply chains are very complex.

It would also be beneficial if the simulation software has the capability to link with external data repositories, in order to receive the most recent information when updating the model.

Vensim is the software chosen to model the MDR-TB SLD supply chain due to the fact that it is used: (i) to improve the performance of real systems (Ventana systems Inc); and (ii) is being used by other masters students at the Industrial Engineering Department, therefore support and expertise is readily available. According to Ventana systems Inc, Vensim emphasises: high quality; reality checks; connections to data and sophisticated calibration methods; instant output; and model analysis and optimisation.

4.4 Conclusion: Confronting the Real-World Problem

This chapter summarises the suggestions for combating the MDR-TB crisis that have been proposed by various individuals at the six IOM workshops. The suggestions have been categorised into two main groups: (i) general suggestions; and (ii) supply chain suggestions. Furthermore, the best practices identified by SCOR for improving the performance of a supply chain are also identified. The proposed suggestions and best practices that are in the scope of this research study will be tested using the supply chain model, therefore the most popular simulation paradigms are evaluated and compared in order

to select an appropriate method for building this model. Two of the most important criteria used to compare the paradigms are the 'scope' and 'purpose' of the model. The purpose of a model is to aid in making decisions, in this case supply chain management decisions. The proposed supply chain suggestions are grouped into supply chain management themes in order to determine what kind of decisions need to be modelled (strategic or operational). These themes include: supply chain optimisation; inventory planning/management; and planning and forecasting demand, which are categorised under operational decisions. Both SD and DES modelling have been shown to be suitable for modelling operational level decisions, however SD is selected to model the downstream SLD supply chain as this model will be developed further for future research encompassing strategic decisions, which SD is shown to be most commonly suited for.

Chapter 5 will discuss the process that will be followed to develop and build the systems dynamics supply chain model.

Chapter 5

Modelling the Real-World Problem with System Dynamics

The downstream MDR-TB SLD supply chain is modelled using the systems dynamics software Vensim. This chapter outlines the five phase model-building process, proposed by Cavana and Maani (2000), that is followed in this study to develop and build the simulation model of the supply chain. Only the first three phases, namely: problem structuring; causal loop modelling; and dynamic modelling will be discussed in detail in this chapter. The final two phases will be discussed in Chapter 6. The first three phases include the following steps: defining the problem; collecting the necessary data; building the stock and flow model; performing validation on this model; and analysing the performance of the current supply chain.

According to Altiok and Melamed (2010), building a model contains the following major steps:

- Problem analysis and information collection;
- Data collection;
- Model construction;
- Model verification;
- Model validation;
- Designing and conducting experiments;
- Output analysis; and
- Final recommendations.

More related to systems dynamics, the 'original' phases in system dynamics model development, as proposed by Randers (1980) included: conceptualisation; model formulation; model testing; and implementation. According to

Keating (1999), more recent system dynamics practices fall into five general phases, namely: model analysis; model design; model formulation; model testing; and model intervention and implementation.

Cavana and Maani (2000) have recently proposed a more refined five phase process of systems thinking and modelling:

- **Phase one**:
  Problem structuring;
- **Phase two**:
  Causal loop modelling;
- **Phase three**:
  Dynamic modelling;
- **Phase four**:
  Scenario planning and modelling; and
- **Phase five**:
  Implementation and organisational learning.

This five phase process of systems thinking and modelling will be applied to the real-world problem in order to develop the simulated model of the SLD supply chain. The activities involved in each of the first three phases, will be described in the following subsections.

5.1 Problem Structuring

Cavana and Maani (2000) specify that this phase involves identifying the issues to model, along with defining the scope and boundaries of the study. The scope of this study is only focused on the downstream segment of the supply chain, which is limited to the in-house warehousing (Cape Medical Depot) and the health facilities. All drugs received from suppliers for the Western Cape are stored at the CMD, from where they are dispatched to the various health facilities, therefore the CMD and the health facilities will be the focus of this study. The gathering of all the preliminary information and data is also completed in this phase. The data for this study was received directly from the CMD.

5.1.1 Themes to Model

Many suggestions have been made on how to confront the global MDR-TB crisis at the various IOM workshops; however only the suggestions that refer specifically to the strengthening of the downstream MDR-TB SLD supply

chain and that can be tested using the model will be evaluated. Furthermore, the performance of the current downstream SLD supply chain in the Western Cape will be evaluated based on the attributes as highlighted in the SCOR model: reliability; responsiveness; and agility. The best practices that are available for improving upon the weakest attributes in the supply chain, based on the performance analysis and that can also be tested with the model will be evaluated along with the relevant IOM suggestions.

The performance of the current supply chain is evaluated and analysed in Section 5.4. The final themes that will be tested using the supply chain model are based on: (i) the IOM suggestions; and (ii) the results of the performance analysis. These themes are listed and discussed in Section 6.1.

5.1.2 Input Data Collection

The following list of data required to build the supply chain model was requested from the WCDoH, dating back to 2004:

- A list of all of the CMD's suppliers of second-line anti-TB drugs and the list of medication supplied by each of them to the CMD.
- A list of all of the facilities that are supplied by the CMD.
- The complete list of orders for second-line TB drugs received by the CMD, containing the following data fields:
  - From which facility;
  - For what quantity of each drug ordered;
  - On which dates; and
  - An order identifier ID (if available).
- The complete list of second-line TB drugs orders dispatched by the CMD, containing the following data fields:
  - From which facility;
  - For what quantity of each drug ordered;
  - On which dates; and
  - An order identifier ID (if available).
- The complete list of second-line TB drugs orders placed by the CMD, containing the following data fields:
  - From which facility;
  - For what quantity of each drug ordered;

  - On which dates; and
  - An order identifier ID (if available).

- The complete list of second-line TB drugs received by the CMD, containing the following data fields:
  - From which facility;
  - For what quantity of each drug ordered;
  - On which dates; and
  - An order identifier ID (if available).

- A complete list of stock-outs and obsolete stock;
- A complete list of the running balances for each drug in inventory; and
- The reorder quantity calculation method.

5.2 Causal Loop Modelling

This phase involves identifying the main variables in the supply chain, as well as their relationships to each to other in order to develop a causal loop diagram (CLD).

CLDs depict the causal relationships between various variables in a system. Variables and arrows are the basic elements in a CLD. Cavana and Maani (2000) define a variable as a condition, action or decision that can be influenced by other variables, while arrows indicate association between two variables. The relationships between variables can either move in the same (S) direction if they are directly correlated, or in opposite (O) directions if they are inversely correlated. Once variables are linked together in a connected path, a causal loop is formed (Cavana and Maani, 2000). This path need not be circular, but it needs to be closed, starting and ending on the same variable. The two general types of causal loops - balancing and reinforcing loops - represent feedback processes for all causal loops:

- **Balancing Loops:**
  Cavana and Maani (2000) define balancing loops as self-regulating loops that seek stability and return to control i.e. negative feedback loops. A balancing loop could also aim for a specific goal, which would result in the cycle repeating itself until the target is reached.

- **Reinforcing Loops:**
  Cavana and Maani (2000) define reinforcing loops as positive feedback loops that can represent either ‘growing’ or ‘declining’ systems. In a

growing system the variables continue to increase for each cycle in the loop, whereas in a declining system the opposite takes place. Any action in a reinforcing loop influences more of the same action in the loop.

Figure 5.1 illustrates the relationships between each variable in the downstream MDR-TB SLD supply chain, with 'S' depicting the same behaviour and 'O' depicting opposite behaviour. This CLD is inclusive of variables that influence or affect the downstream SLD supply chain and variables that are influenced and affected by the supply chain, however not all of these variables are tested and will therefore not be integrated into the dynamic model. The core loops in the CLD are named with either 'Bs' or 'Rs' to indicate balancing or reinforcing processes. Furthermore, the CLD illustrates that the total cost of the supply chain within the scope of the study includes: cost of backlogs (shortage costs); obsolescence costs; and inventory holding costs.

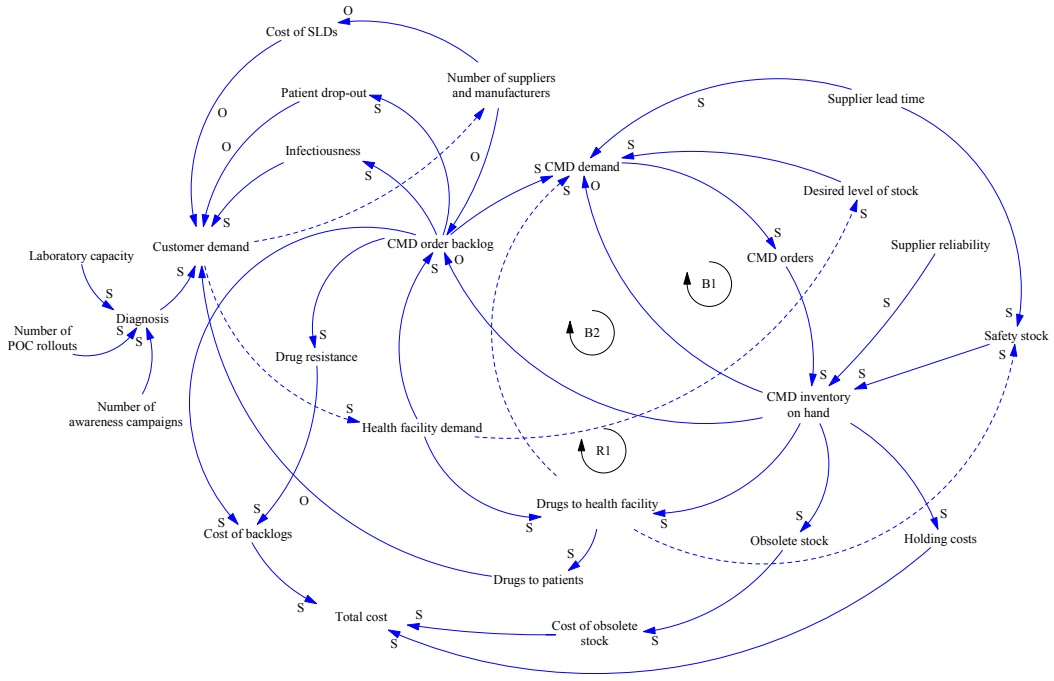
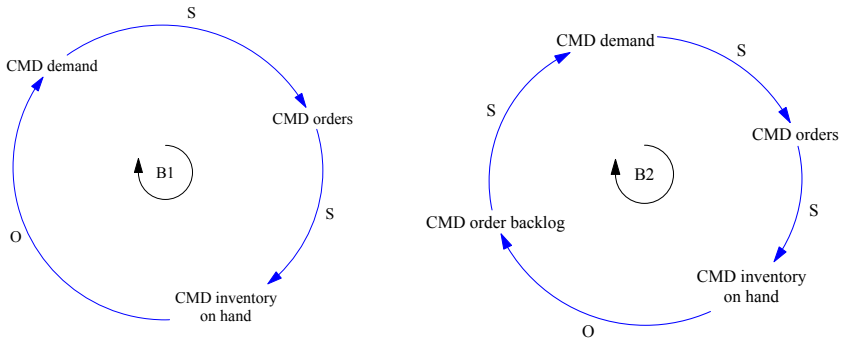


Figure 5.1: Causal loop diagram for the MDR-TB SLD supply chain

Figure 5.1 will be broken up into the core balancing and reinforcing loops that are present in the CLD in order to describe the relationships between the most important variables. The balancing loops (B1 and B2) are illustrated in Figure 5.2 and the reinforcing loop (R1) in Figure 5.3.

Balancing loop 'B1' includes the CMD demand, CMD orders and CMD inventory on hand. An increase in the demand placed by the CMD, increases the number of orders placed, which in turn increases the CMD inventory on hand. However an increase in the CMD inventory on hand will decrease the CMD demand. Balancing loop 'B2' consists of the same variables as in 'B1', but also includes the CMD order backlog. An increase in CMD inventory on hand will decrease the CMD order backlog and therefore also decrease the CMD demand.



(a) B1 (b) B2

Figure 5.2: Balancing loops in the CLD

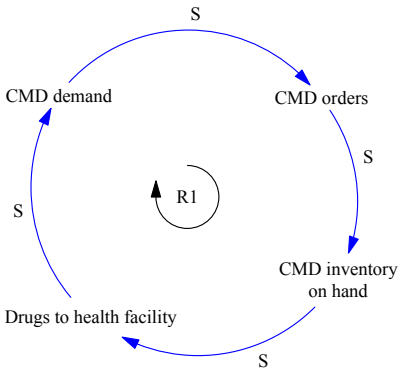


Figure 5.3: Reinforcing loop in the CLD

Finally each variable in the reinforcing loop 'R1' which includes: CMD demand; CMD orders; CMD inventory on hand; and drugs dispatched to health facilities will influence more of the same action for each cycle in the loop i.e. an increase in the CMD demand increases the CMD orders sent which increases the CMD inventory on hand, thereby enabling the CMD to dispatch more drugs to the health facilities.

5.3 Dynamic Modelling

Causal loop modelling is a powerful tool for qualitative data, however CLDs are no longer effective when quantitative data need to be analysed. Deeper dynamic issues can be investigated in a computer simulation model. The advantages of a computer simulation model include (Cavana and Maani, 2000):

- Storing vast amounts of information;
- Clearly formulating assumptions and causal relationships;
- Modifying assumptions for other experiments with ease;
- Multiple use for alternative model experiments;
- Performing experiments with different policies and structures with the same model;
- Explicitly integrating uncertainties into the model;
- Identifying sensitive parameters easily by repeating simulations;
- Graphically representing results; and
- Understanding the behaviour of the real-world system.

Cavana and Maani (2000) also lists the advantages of using the systems dynamics approach specifically to model real-world systems. These advantages include:

- Clear understanding of nature and direction of relationships in the system being modelled;
- Altering policies throughout the simulation as they are dependent on the state of the system at a point in time (the state is changed by feedback effects of past actions);
- Including both linear and non-linear relationships in the model;
- Integrating delays (physical and information) into the model; and
- Modelling information lacking statistical data, such as 'soft' behavioural relationships.

The first steps of the dynamic modelling phase, as described by Cavana and Maani (2000) involve developing a conceptual model, followed by defining all the relevant variables to develop a stock-flow diagram of the system. In this study the stock-flow diagram will be developed in Vensim. Detailed data

and information is then collected and integrated into the stock-flow diagram in order to develop a simulation model. Once the simulation model is ready, steady state i.e. business as usual conditions are simulated in order to carry out validation of the model. The final step in this phase requires that a sensitivity analysis be performed; which includes varying all of the model parameters by approximately 10%, as suggested by Cavana and Maani (2000), to test whether the overall effect on the system is what one would reasonably expect with such a small change.

5.3.1 Conceptual Model

This conceptual model is merely developed to give an overall map of the system. In this case, the conceptual model only illustrates the downstream segment of the supply chain in the Western Cape. Therefore this model will centre around the warehouse (specifically the CMD), showing the supply of the drugs from the suppliers to the CMD and the dispatch of these drugs to the relevant health facilities. The conceptual model for this supply chain is shown in Figure 5.4.

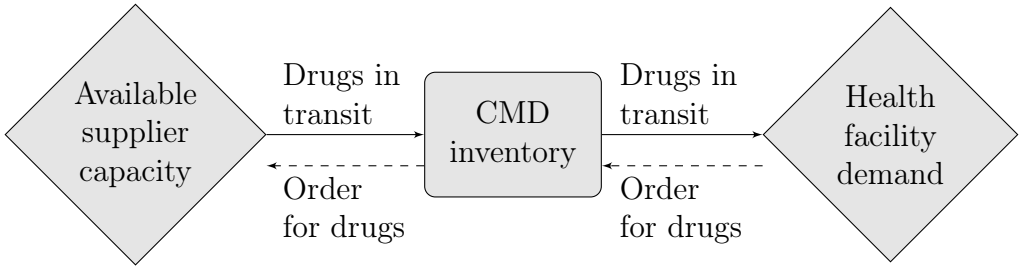


Figure 5.4: Conceptual model for the downstream MDR-TB SLD supply chain

5.3.2 Stock-Flow Diagram of MDR-TB SLD Supply Chain

A system that is modelled with system dynamics is described in terms of stocks (levels), flows (rates), converters and feedback loops. The stocks are depicted as blocks and represent accumulated quantities, while flows are depicted as double lined arrows that represent the changes to the stock over time ('physical' flows). Converters are merely variables that represent intermediates, such as constants and behavioural relationships in the system. Converters make the model easier to understand by splitting complicated equations into simpler components (Cavana and Maani, 2000). The stock-flow diagram of the SLD supply chain, built in Vensim is illustrated in Figure 5.5. As described in

Subsection 3.3.3.1 the arrows in the stock-flow diagram illustrate the relationship between variables and the letter 'S' describes the same direction of flow while 'O' communicates the opposite direction of flow.

The following subsection describes the process followed to develop the stock-flow diagram, as shown in Figure 5.5.

5.3.2.1 Model Boundaries

The time boundary for this model is between 0 and 120 months representing all the months between December 2004 and December 2010. The results are calculated in time steps of 0.03125 months, but saved every month in the simulation. Euler and Runge-Kutta (up to fourth-order) are the techniques available for numerical integration of the differential equations in Vensim. Euler integration is the default in Vensim as it is the most basic integration technique, however it is not always appropriate. Euler is appropriate for higher levels of uncertainty in the model, higher speed requirements and a lack of specificity requirements (Musango *et al.*, 2015). Higher-order Runge-Kutta methods are more accurate than Euler methods and therefore require more computation time, however these methods cannot be used when large uncertainties are present (Simonović, 2009). This supply chain model is small enough so that execution speed is not a factor, the majority of the parameters are certain, and accuracy is required for the purpose of this model; therefore fourth-order Runge-Kutta integration is used in this model.

Referring to the CLD in Figure 5.1 and the stock and flow diagram in Figure 5.5, the exogenous, endogenous and excluded variables are listed to communicate the model boundaries. An exogenous variable refers to a factor whose values is independent of the other variables in the system, whereas an endogenous variable's value is determined by other variables in the system.

- Endogenous variables:
  - Safety stock;
  - Reorder point;
  - CMD demand;
  - CMD orders;
  - CMD order backlog;
  - Drugs to CMD inventory;
  - CMD inventory on hand;
  - Inventory position;
  - Obsolete stock;

  - Drugs to health facilities;
  - Drug resistance.

- Exogenous variables:
  - Health facility demand;
  - Supplier lead time;
  - Supplier reliability;
  - Desired levels of stock (min and max);
  - Service level (Z-score);
  - Cost of SLDs;
  - Production cycle; and
  - Amikacin expiration time.

- Excluded variables:
  - Number of POC rollouts;
  - Number of awareness campaigns;
  - Laboratory capacity;
  - Diagnosis;
  - Customer demand;
  - Number of manufacturers and suppliers;
  - Patient drop-out;
  - Infectiousness; and
  - Drugs to patients.

5.3.2.2 Modelling Methodology

The treatment regimen for MDR-TB includes at least four drugs that should be taken for the duration of treatment (18 to 24 months), however the injectable agent should only be taken for the first six to eight months of treatment. As discussed previously in Section 2.5, the injectable agents include: amikacin; kanamycin; capreomycin; and streptomycin. Crofton *et al.* (1997) state that amikacin and kanamycin should be considered as the same drug as resistance to any one of them induces complete cross-resistance. Cross-resistance in this case is defined as the resistance to a drug due to exposure from a similar acting drug. Crofton *et al.* (1997) further state that resistance to amikacin-kanamycin also induces resistance to streptomycin, however retains susceptibility to capreomycin. Therefore resistance to amikacin will most likely lead to resistance of kanamycin and streptomycin, leaving capreomycin as the only susceptible

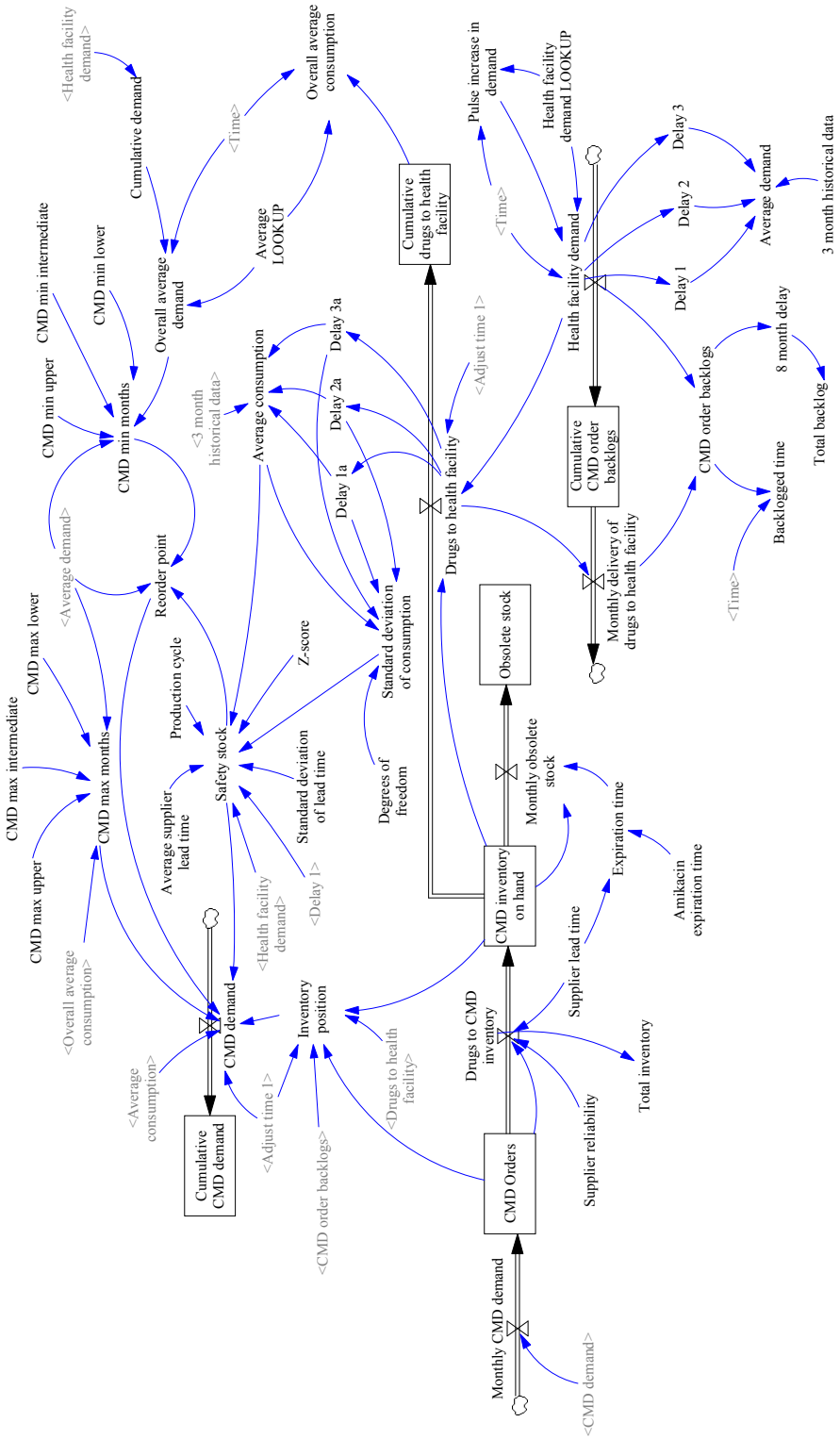


Figure 5.5: MDR-TB SLD supply chain model

drug to MDR-TB in Group 2. Therefore only amikacin (Am) will be modelled in the supply chain as it also represents both kanamycin and streptomycin.

In order for the model to represent the real-world supply chain, the real total demand for only amikacin from each health facility to the CMD for the past 10 years was integrated into the model as a lookup function, called health facility demand (D_{HF}). The lookup function returns the value of the real total demand for amikacin from each of the health facilities that the CMD supplies to for each month starting in December 2004 and ending in December 2014.

The health facility demand is then used to calculate the reorder point (ROP) for the CMD, shown in (5.3.1). Currently, as defined by the CMD, the reorder point is a function of the average health facility demand per month ($\bar{D_{HF}}$) over the previous 12 weeks (three months) and the minimum desired level of inventory on hand, expressed in months (T_{min}).

$$ROP = \bar{D_{HF}} \times T_{min}. \tag{5.3.1}$$

The minimum and maximum desired level of inventory on hand can be changed as often as desired by the pharmacist responsible for that section of the warehouse, based on demand, and therefore cannot be modelled accurately. However based on historical data, the minimum level is set at three levels: lower; intermediate; and upper. These values were determined based on data and trends over the past 10 years. At times when the average demand over the previous three months ($\bar{D_{HF}}$) exceeds the overall average demand over the 10 years, the intermediate variable is used, when $\bar{D_{HF}}$ is double the overall average demand the maximum variable is used and finally when $\bar{D_{HF}}$ is lower, T_{min} is replaced by the lower variable.

If the inventory on hand at the CMD (S_{CMD}) reaches this reorder point and if the level of inventory at this reorder point is greater than the inventory position (IP), then an order should be placed by the CMD. The CMD inventory on hand is increased by the drugs that are in transit to the CMD from the suppliers (S_0), shown in (5.3.6) and decreased by: (i) the drugs that are dispatched to the health facilities (S_1); and (ii) the drugs that have become obsolete (O_{Am}). The obsolete stock is calculated as any inventory that stays in the CMD for longer than 30 months (shelf-life). The inventory position is dependent on: the inventory on hand at the CMD; the stock that has been ordered by the CMD but not received yet i.e. drugs in transit to the CMD (S_0); the backlogged orders at the CMD (B_{CMD}) i.e. shortages; and the drugs that are dispatched to the health facilities (S_1). The drugs that are dispatched to the health facilities is equal to the health facility demand (D_{HF}), unless there is insufficient inventory on hand (S_{CMD}), in which case the inventory on hand is dispatched and the outstanding quantity is backlogged. The CMD

order backlog (B_{CMD}) is defined as the health facility demand that cannot be filled due to shortages in stock at the CMD. These variables are calculated as follows:

$$S_{CMD}(t) = S_{CMD}(0) + \int [S_0 - S_1 - O_{Am}]dt, \tag{5.3.2}$$

$$IP = S_{CMD} + S_0 - B_{CMD} - S_1, \tag{5.3.3}$$

$$B_{CMD} = D_{HF} - S_1. \tag{5.3.4}$$

The quantity of the order that needs to be placed by the CMD (reorder quantity) is represented by the variable CMD demand (D_{CMD}) and is a function of: the average consumption of drugs per month ($\bar{C_A}$) over the previous three months; the maximum desired level of inventory on hand, expressed in months (T_{max}); the level of safety stock (SS); and the inventory position (IP). T_{max} is calculated in the same way as T_{min} discussed earlier, with lower, intermediate and upper values. The level of safety stock (SS) for the base case model is zero as the CMD does not have safety stock policies, however this variable will be altered during scenario planning. The formula for reorder quantity is as follows:

$$D_{CMD} = T_{max} \times \bar{C_A} + SS - IP. \tag{5.3.5}$$

The CMD demand can only be fulfilled by suppliers if the suppliers have the capacity. Therefore the number of drugs in transit to the CMD (S_0) is dependent on: the reliability (R) of the suppliers for each type of drug; the supplier lead time for each drug (LT); and the CMD demand (D_{CMD}), as shown in (5.3.6). The reliability of the suppliers and their lead times are calculated from real data. The supplier reliability value used in the model is the calculated average over the 10 year period, whereas the lead time is integrated into the model as a normal distribution random function with the lead times varying between the minimum and maximum based on the average and standard deviation of the data.

$$S_0 = \frac{D_{CMD} \times R}{LT}. \tag{5.3.6}$$

5.3.2.3 Initial Stock Values

The stocks in the model require initial values before the simulation can be executed. An initial value of zero is assumed for all the stocks in the model, except for CMD inventory on hand and the CMD orders. The initial value for these variables were taken from real data as the at the end of December 2004.

5.3.3 Validation and Verification

Sargent (1998) emphasises that model verification and validation are critical when developing a simulation model. The verification process refers to ensuring that the computer program and implementation are correct, whereas validation refers to the process of substantiating that a model possesses a satisfactory range of accuracy consistent with the purpose of the model (Sargent, 1998). Both Sargent (1998) and Cavana and Maani (2000) stress that there is no set of specific tests that can be applied to validate a dynamic model. Coyle (1983) highlights the main tests that a system dynamics model should be subjected to: validation tests for the overall behaviour of the model; verification tests to confirm that the operating mechanisms in the real system have been correctly recorded in the model; and legitimisation tests to ensure the model obeys the 'laws' of system structure. Furthermore, Coyle (1983) lists the following criteria to carry out the validation, verification and legitimisation tests:

- The causal loop diagram should correspond to the statement of the problem and the 'laws' of system structure;
- The equations should correspond to the causal loop diagram i.e. the individual 'relationships' in the model should be defendable in their own right;
- The model's equations should be dimensionally valid;
- The model should not produce any unrealistic outputs;
- The model should behave 'like' the real system;
- The behaviour of the model should be plausible;
- The model should maintain 'conservation of flow' (i.e. the total quantity entering the system should be accounted for with the quantities within, and leaving the system); and
- The equations should make sense when inputs take on extreme values (i.e. test the model when it is shocked).

Additionally, a System Dynamics Model Documentation Tool (SDM-Doc) is used to create a HTML - based document of the supply chain model built in Vensim. This SDM-Doc lists and describes all of the equations and variables that are used to develop the model. This document helps with model assessment and development, highlighting structural issues, and is therefore a further validation of the physical structure of the model. Moreover, this document can be referred to in order to understand the model and to expand upon for further research. This SDM-Doc is included in Appendix C.

5.3.3.1 Validation and Verification Results

The tests listed above were carried out with the simulated base case model of the supply chain that is illustrated in Figure 5.5. The processes followed to perform these tests, and the results thereof are discussed below:

- **CLD validity:**
  The problem statement of the study is: to evaluate the performance of the downstream SLD supply chain; to test proposed suggestions for improvement to the supply chain; and to provide further suggestions for improvement. The causal loop diagram includes all the relevant variables in the supply chain, and the relationships between them in order to carry out the aim of the study.

- **Equation validity:**
  An inspection of the model equations showed that the directions of the relationships in the CLD match the direction of the equations in the simulated model. In other words the equations result in the correct action of each variable based on their relationships with other variables.

- **Dimensional consistency of equations:**
  All equations are dimensionally valid as all the units on the right-hand side of each equation match the units on the left-hand side. In Vensim every equation in the simulated model is subjected to dimensional analysis in order to ensure dimensional consistency. Vensim showed no unit errors on the completed model.

- **Unrealistic results:**
  Analysing the outputs of each variable that cannot show negative results showed that no unrealistic outcomes are present in the results i.e. negative inventory or negative demand. The analysis of the results of the base case model also show that no variable produces runaway results.

- **Similarity to real system:**
  In order to determine whether the model behaves like the real system, a statistical analysis was done on the two sets of data (modelled and real) for the following variables:

  - CMD demand;
  - CMD inventory on hand; and
  - Drugs to health facility.

  However, due to the fact that the data is a time series, the data has to be classified as 'stationary' before any correlation analysis can be done. A stationary time series is defined as a dataset with constant statistical

properties over time (Nason, 2006). If non-stationary time series data is used in a regression model, there is a possibility that the results could show significant relationships even if the variables are unrelated. This is known as spurious regression. A qualified statistician confirmed that the data is indeed stationary data. Once the data is classified as stationary, the data can be seen as independent points and therefore correlation analysis can be done to test the similarity of the data. The similarity of the data was evaluated by calculating the intraclass correlation coefficient (ICC). The appropriateness of using this coefficient was confirmed at the Centre for Statistical Consultation (CSC) at Stellenbosch University. The ICC is a measure of the reliability of measurements, in this case the reliability of the model data compared to the real data. These data sets represent a two-way model as the data is measured at the same points for both datasets, and the differences at these points are relevant, therefore the ICC of absolute agreement will be tested. The results of the ICC of agreement for the amikacin model is shown in Table 5.1. The closer the ICC is to one, the greater the similarity.

Table 5.1: Intraclass correlation coefficients

Variable	**ICC**
Drugs to health facility	0.85
CMD inventory	0.69
CMD demand	0.60

Due to the dynamism of the SLD supply chain, and the fact that reorder policies can be overridden in times of crisis, the model will not be able to represent the real-world with 100% accuracy. For example in 2008 there was a significant spike in the demand for amikacin, which the current reorder policies would not have been able to cover, therefore the CMD ordered a larger quantity of amikacin than what the reorder equation recommended. This reorder policy flexibility has a direct effect on the CMD demand, which is the variable with the lowest ICC value, and an indirect effect on the CMD inventory, which explains why the model does not accurately represent the real data in these emergency instances. This is shown in Figures 5.6 and 5.7. However the model follows the overall trend of the real data and shows ICC values above 0.5, therefore representing the real supply chain adequately enough to perform scenario analyses.

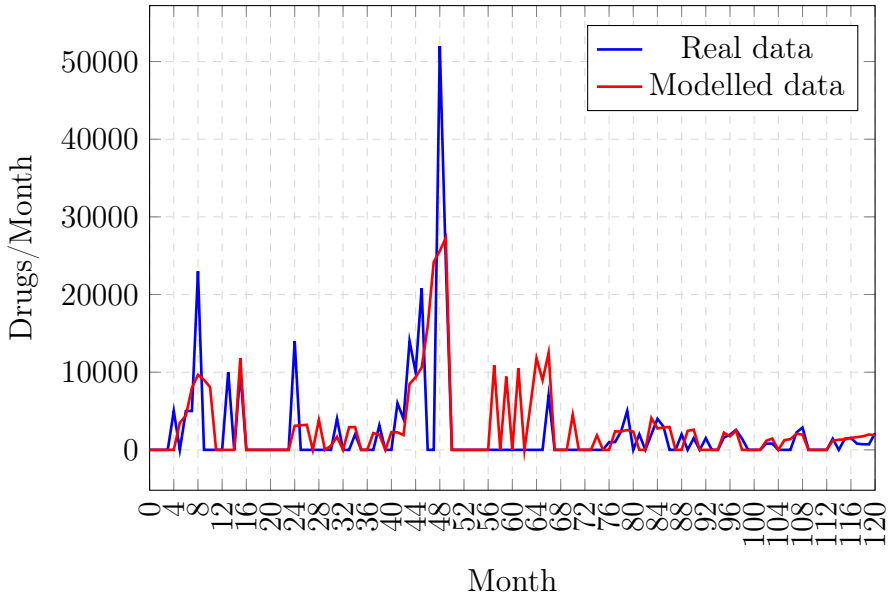


Figure 5.6: Similarity of CMD demand real-world and modelled data

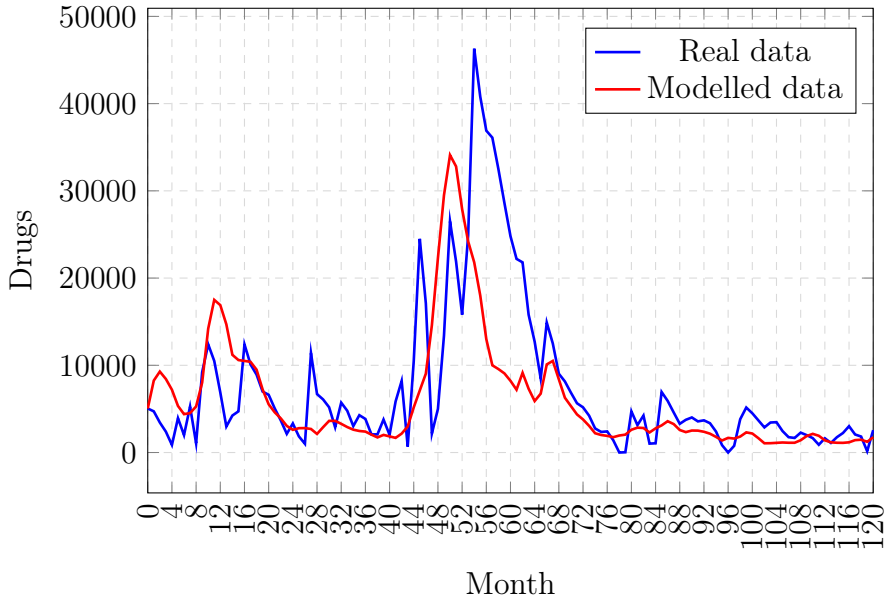


Figure 5.7: Similarity of CMD inventory real-world and modelled data

- **Plausibility:**
  The model behaves in the way that it is expected to behave. The aim of the model is for the CMD to deliver the drugs to the health facilities based on the demand received from the health facilities, whilst minimising shortages as far as possible. The results of the base case model show

that the drugs that are dispatched to the health facilities are always following the same pattern as the health facility demand.

- **Conservation of flow:**
  This involved a thorough check of all stocks and flows. All inputs into the model are balanced with the outputs i.e. all the health facility demand integrated into the model is accounted for by either being fulfilled by the CMD or backlogged.

- **Extreme conditions:**
  The model was subjected to a pulse train function in the health facility demand to shock the system. This involved a 150% increase at months 30, 60, 90 and 120. The behaviour of this pulse function is illustrated in Figure 5.8. This situation could occur if more people are diagnosed with MDR-TB due to either awareness and diagnosis campaigns or the rollout of POC testing in certain areas. Although the demand increases by 150% in a month, this is moderated by the fact that the reorder point is based on the average demand from the previous 3 months and the fact that the minimum levels of stock are also increased when demand increases, thereby increasing the CMD demand. Since the extra demand puts pressure on both the CMD and the suppliers there are extra backlogged orders i.e. shortages, however the results of the extreme test shows that this model is robust enough to be able to satisfy the spikes in demand. This is due to the fact that the demand is dynamic and unstable under normal circumstances.

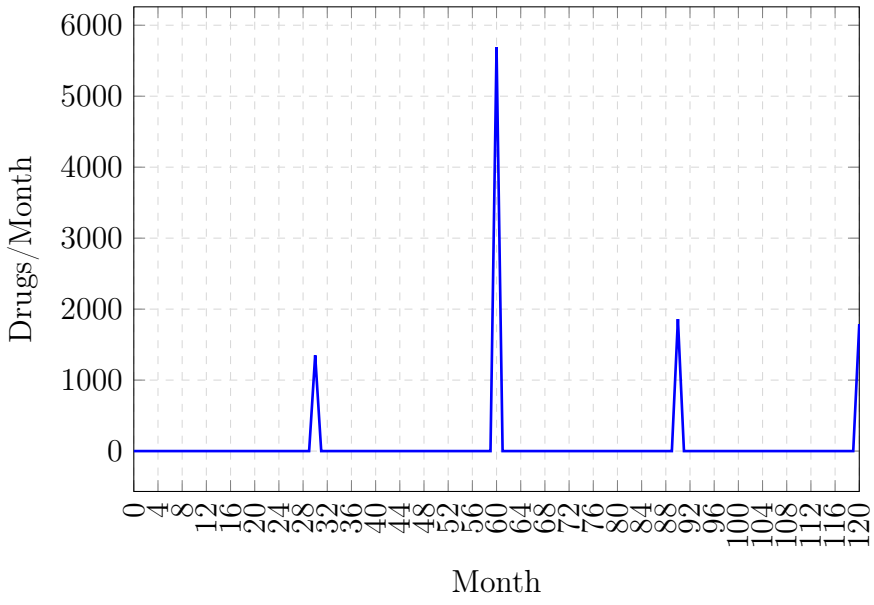


Figure 5.8: Pulse increase in demand to test model behaviour

This test demonstrates the ability of the model to return to base case conditions after the shock, which demonstrates that the balancing and reinforcing loops are working well.

5.3.4 Sensitivity Analysis

During the development of a model, initial parameters are often estimated or unknown. Therefore in order to use a model with confidence, the behaviour of the model when these uncertain parameter values are varied considerably must be studied (Cavana and Maani, 2000). Pruyt (2007) states that sensitivity analysis is a common way to reduce uncertainties in the field of systems dynamics. Furthermore, Cavana and Maani (2000) state that the purpose of a sensitivity analysis is to identify the most sensitive parameters in order to put more effort into improving the estimates of these parameters. The magnitude of the change in the model behaviour with the model parameter changes will determine the degree of sensitivity of each model parameter. The most important variables (key variables) in the model and therefore the ones that will be monitored for the purpose of the sensitivity analysis include:

- Cumulative drugs to health facility;
- Cumulative order backlog; and
- Cumulative CMD inventory on hand.

The exogenous variables that are altered in the base case model to perform the sensitivity analysis are summarised in Table 5.2. Each variable will be increased and decreased by 10% to test the sensitivity of the model. The health facility demand is not a constant variable, as it varies every month and therefore increases and decreases by 10% every month with a step function in Vensim.

The results of the sensitivity analysis are depicted in Table 5.3. The base case values for each key variable are shown in the top row of Table 5.3. The values shown in columns to the left are the new cumulative values for each key variable with either a 10% increase or decrease in the exogenous variables. The key variables are tested at the end of the 10 year period and are therefore cumulative values over the 10 year period. The values in the columns to the right show the percentage change in the key variables after altering the exogenous variables. These values show that the cumulative changes observed aren't significant, as a small change in the exogenous variables only produces small, realistic changes in the key variables.

Table 5.2: Sensitivity experiments

Variables	Base Case	10% decrease	10% increase
CMD min level (months)	2	1.8	2.2
CMD max level (months)	4	3.6	4.4
Supplier lead time (months)	1.2	1.08	1.32
Supplier reliability (%)	0.98	0.88	1.08
Health facility demand (drugs/month)		STEP(-10%)	STEP(+10%)

Table 5.3 shows that the most sensitive exogenous variable, which results in the biggest effect on the key variables, is the health facility demand. Therefore the health facility demand will affect the model the most and should be the most accurate. The health facility demand is based on real data and is built into the model as a lookup function, ensuring its accuracy. The second most sensitive exogenous variable is the supplier lead time, which varies from 0.25 months to 5.6 months, however the lead time that is used in the model varies around the mean value using a random normal function.

Furthermore, Table 5.3 indicates that the key variable that is most affected by altering the exogenous variables is the cumulative order backlog. To test how sensitive this variable is, a Monte Carlo simulation is done. Monte Carlo simulation explores the sensitivity of a complex system by varying certain parameters within constraints. To test the sensitivity of cumulative order backlogs, a Monte Carlo simulation is done in Vensim with the supplier lead time changing between the minimum and maximum, as it is the most sensitive exogenous variable that is not 100% accurate. The results of the Monte Carlo simulation, with a minimum and maximum lead time of 0.25 and 5.6 respectively, are shown in Figure 5.9. The model is shown to be well reasoned in Figure 5.9 as the variability of shortages increases significantly with a change in supplier lead time. A 100% confidence interval shows that the shortages can range from anywhere between $35,000$ and $200,000$ units of amikacin as the lead time changes, which is exactly what is expected of the model.

Table 5.3: Change in key variables when the model is increased and decreased by 10%

	Drugs to health facility (, 000 drugs)				**Order backlog (, 000 drugs)**				**CMD inventory on hand (, 000 drugs)**			
Base Case	249				22.5				270			
	-10%		+10%		-10%		+10%		-10%		+10%	
CMD min level	248	(0.4%)	250	0.4%	23.8	6.7%	21.5	(4.4%)	268	(0.74%)	272	0.74%
CMD max level	251	0.8%	250	0.4%	24.1	7.1%	21.4	(4.9%)	268	(0.74%)	272	0.74%
Supplier lead time	252	1.2%	245	(1.6%)	19.3	(14.2%)	26.1	16%	275	1.8%	265	(1.8%)
Supplier reliability	245	(1.6%)	252	1.2%	26.7	18.7%	19.6	(12.9%)	264	(2.2%)	274	1.5%
Health facility demand	224	(10%)	274	10%	20.1	(10.7%)	24.9	10.7%	243	(10%)	297	10%

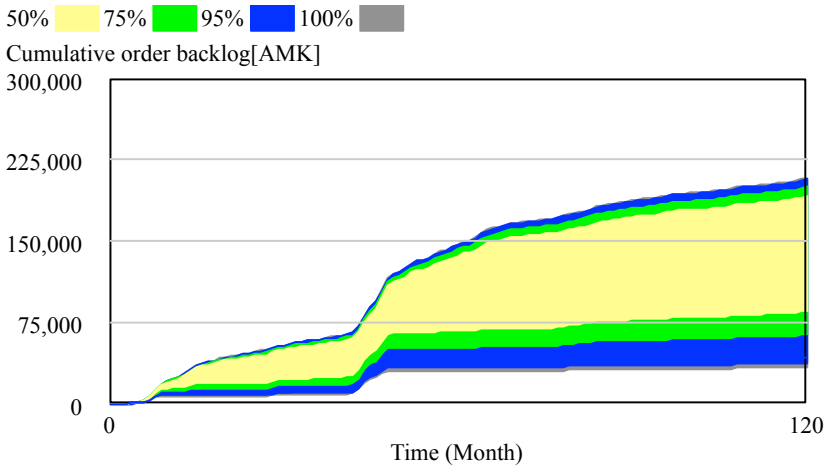


Figure 5.9: Sensitivity of supplier lead time on cumulative CMD order backlog

5.4 Performance Analysis of the Current SLD Supply Chain

The completion of the dynamic modelling phase is followed by the scenario modelling and planning phase. However prior to any scenario modelling, the current performance of the supply chain will be evaluated. The performance will be tested by evaluating the performance attributes set out in the SCOR model, as discussed in Subsection 4.2.1. The performance of the current SLD supply chain is analysed with the data provided for all of the drugs listed in Table A.1. The equations used to evaluate each performance attribute (reliability, responsiveness and agility), and the subsequent results thereof are discussed in the following subsections. SCOR metrics will be used as a standard for measurement of the performance of the supply chain. There are three levels of metrics used to evaluate the performance attributes. SCOR defines level one metrics as the diagnostics for the overall health of the supply chain. Level two metrics in turn help to identify the root causes of performance gaps for a level one metric, while level three metrics serve as diagnostics for level two metrics. The three performance attributes will be tested as follows:

5.4.1 Reliability

'Perfect order fulfilment' is the level one metric used to measure supply chain reliability. Perfect order fulfilment is based on four level two components, namely: quantity delivered; delivery time compared to customer commit date; documentation accuracy; and product condition upon delivery. However the data provided by the CMD allows only the evaluation of the quantity delivered. The quantity delivered is calculated with the level two metric '% of

orders delivered in full' defined in (5.4.1). As defined in SCOR, an order is only delivered in full if the quantities received match the ordered quantities i.e. are not less or more than the quantities ordered by the customer. Therefore perfect order fulfilment will be based on only the '% of orders delivered in full' component. Perfect order fulfilment will be evaluated for both the suppliers that supply to the CMD and the CMD that supplies to the health facilities in the Western Cape. In terms of this model the variables 'Health facility demand,' will be compared to 'Drugs to health facility' and 'CMD orders,' will be compared to 'Drugs to CMD inventory'. It is important to note that this attribute is evaluated independently of the time taken to fulfil the orders.

The SCOR model calculates the '% of orders delivered in full' as follows:

$$\frac{(Total\ number\ of\ orders\ delivered\ in\ full)}{(Total\ number\ of\ orders\ delivered)} \times 100\%. \tag{5.4.1}$$

5.4.1.1 Supplier: '% of orders delivered in full'

Each MDR-TB SLD is supplied to the CMD by a supplier that has been contracted for up to two years. On average the suppliers have delivered 95% of the orders they have received in full over the past 10 years. The reliability for each year is illustrated in Figure 5.10.

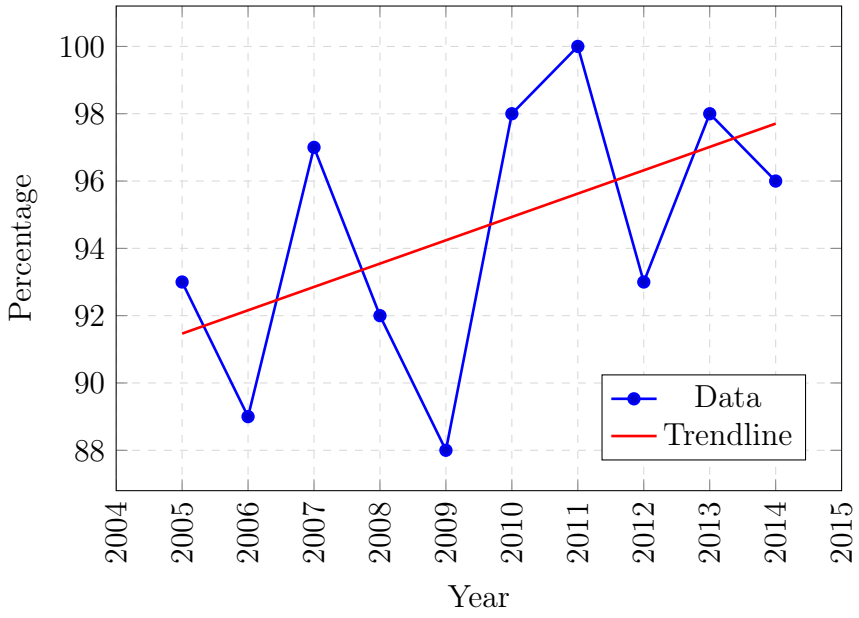


Figure 5.10: Supplier reliability between the years 2005 and 2014

The trendline in Figure 5.10 shows a steady increase in the reliability of the supply of amikacin over the past 10 years. The decrease in reliability in the

years 2008 and 2009 can be attributed to the sudden increase in demand for amikacin during those years. Figure 5.10 illustrates that the reliability of the current suppliers is acceptable. However is should be noted that this performance attribute was calculated with a disregard to time and partial deliveries of drugs i.e. only the final quantity delivered was evaluated. There were many instances where the delivery was only partially delivered at first with the remaining drugs being delivered at a later stage.

The time taken to deliver the drugs to the CMD will be evaluated in the following subsection, when the responsiveness of the supply chain is evaluated.

5.4.1.2 CMD: '% of orders delivered in full'

The CMD distributes second line anti-TB drugs to 345 health facilities across the Western Cape. The results show that, on average, approximately 91.5% of the orders have been filled perfectly over the past 10 years, regardless of the lead time. The reliability for each year is illustrated in Figure 5.11.

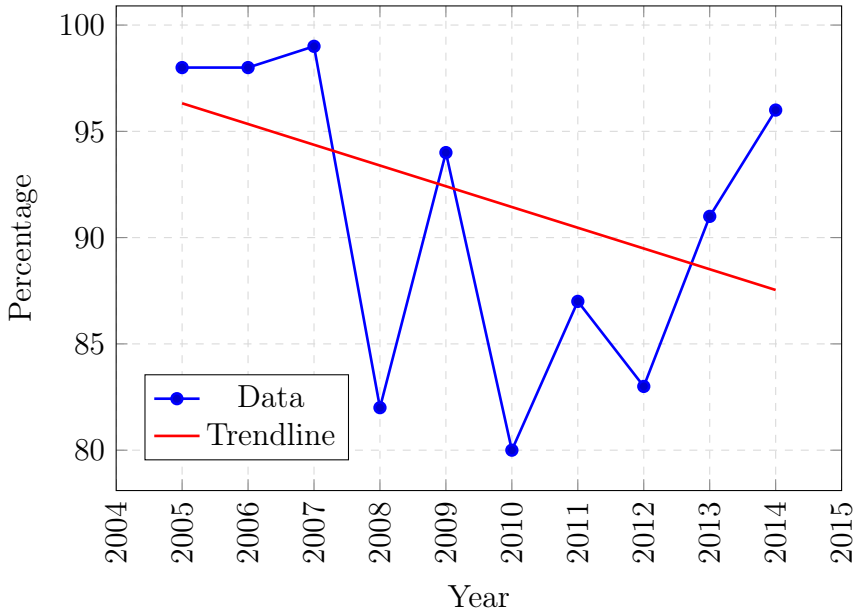


Figure 5.11: CMD reliability between the years 2005 and 2014

Figure 5.11 shows a decreasing trend for the reliability of the CMD, despite the increase in the supplier reliability. Again the significant decrease from almost 100% to 82% in 2008 can be attributed to the significant spike in demand in 2008. However, despite the decreasing trend, the past three years have shown a steady increase with 2014 showing 96% reliability.

5.4.2 Responsiveness

'Order fulfilment cycle time' is the level one metric used to evaluate responsiveness in a supply chain. This cycle time starts from the time an order is received and ends with the customer acceptance of each individual order. The level two metrics that contribute to the total cycle time are: source cycle time; make cycle time; deliver cycle time; and delivery retail cycle time. However the data available does not show the time taken to perform each of these activities, but rather the total time taken between the day an order is placed and the day the order is either delivered to the CMD or dispatched by the CMD. The order fulfilment cycle time is calculated using (5.4.2). Therefore this fulfilment cycle time is the cumulative cycle time for all the activities that are required to fill and deliver an order (Supply Chain Council, 2012).

$$\frac{Sum\ cycle\ times\ for\ all\ orders\ delivered}{Total\ number\ of\ orders\ delivered}. \tag{5.4.2}$$

5.4.2.1 Supplier responsiveness

The order fulfilment cycle times for the suppliers for each year are illustrated in Figure 5.12. The majority of the orders take longer than 40 days to be delivered to the CMD, with the average cycle time in 2008 being approximately 70 days. The figure does however show a decreasing trend, illustrating that the suppliers are improving on their responsiveness with an order taking an average of only 30 days to be delivered in 2014.

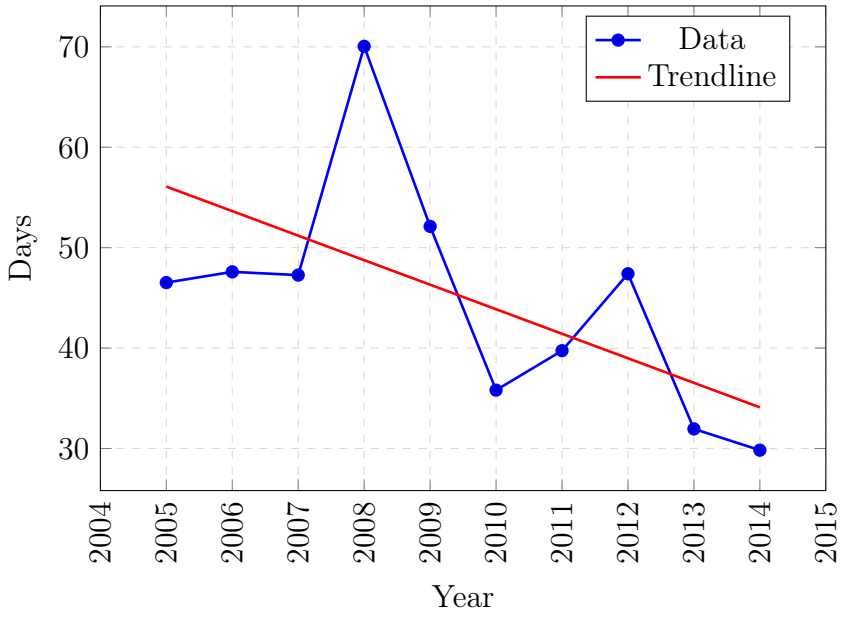


Figure 5.12: Supplier responsiveness between the years 2005 and 2014

Additional calculations were done to determine the responsiveness of the suppliers if the orders are required to be filled within two weeks, and then one month, which is necessary for perpetual purchasing. Finally the supplier responsiveness is evaluated by determining the percentage of orders that take longer than 3 months to be filled. These results are illustrated in Figure 5.13.

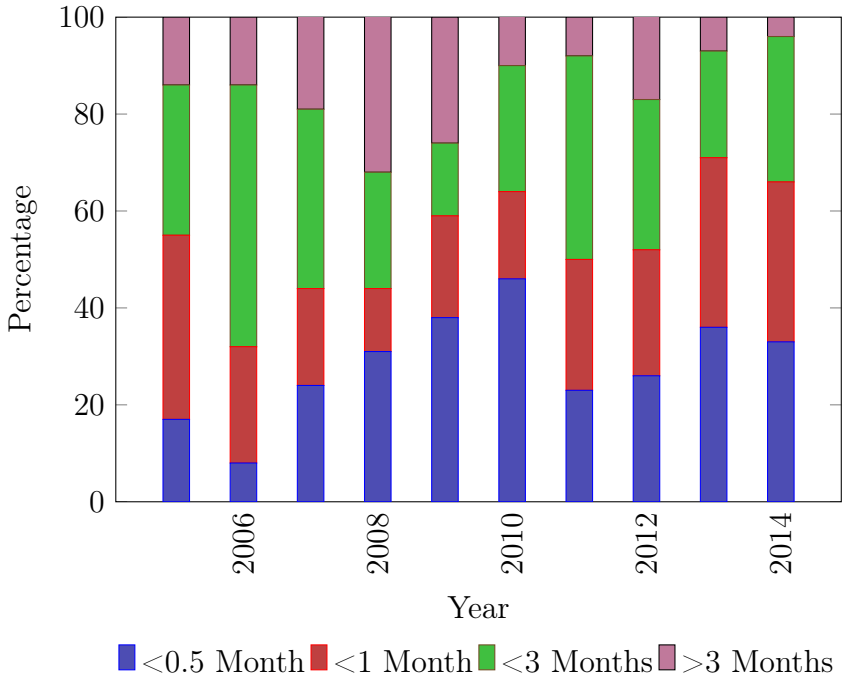


Figure 5.13: Supplier responsiveness for specific time intervals

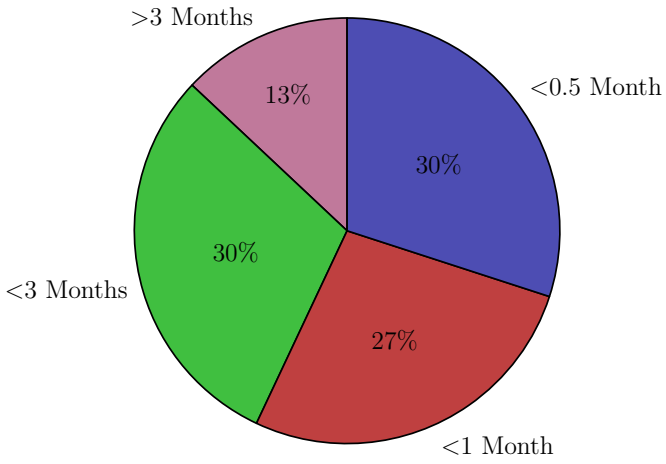


Figure 5.14: Supplier responsiveness by percentage

The pie chart in Figure 5.14 shows that only 57% of all orders are filled within one month from the time an order is placed. Furthermore, 13% of the orders are only fulfilled after 3 months. Supplier responsiveness is therefore one of the most prominent problems within the SLD supply chain.

5.4.2.2 Cape Medical Depot Responsiveness.

The Annual Report, written by the Western Cape Department of Health (WCDoH (2011) evaluates the service level of the CMD for orders that are dispatched within 48 hours of receipt. Figure 5.15 illustrates the percentage of all orders placed by health facilities that were dispatched within two days from the CMD. These results show an average responsiveness of 76% over the 10 year period. The CMD could increase this value with sales and operations planning, which will be discussed in more detail in Section 6.1.

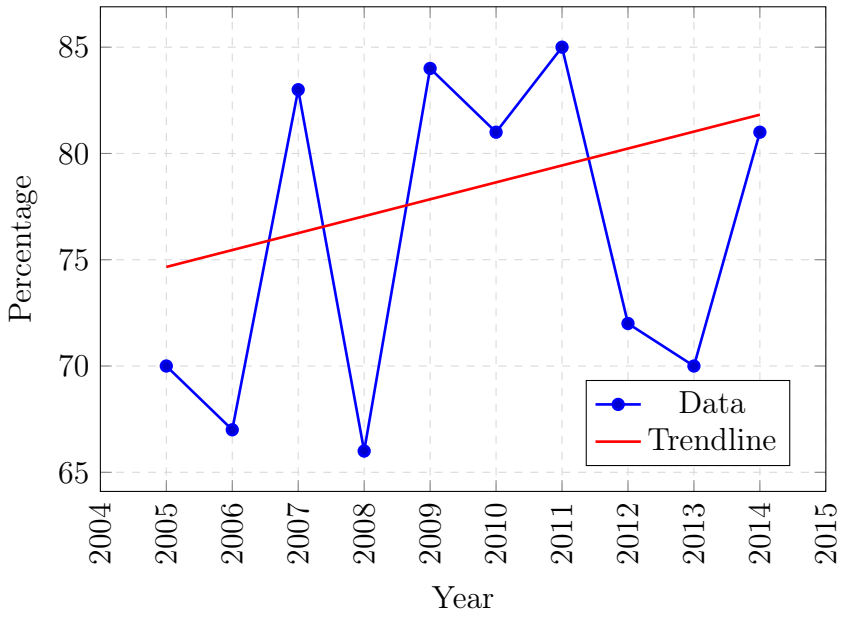


Figure 5.15: CMD responsiveness between the years 2005 and 2014

5.4.3 Agility

Agility refers to the ability of supply chain management policies to withstand unplanned changes in external variables. Supply chain flexibility is the level one metric used to test this attribute. The Supply Chain Council (2012) calculates this flexibility by calculating the number of days required to achieve an unplanned sustainable 20% increase in quantities delivered. This includes the time required to achieve a 20% increase in: raw materials; production;

and quantity delivered. To test the number of days required to achieve a sustainable 20% increase in quantities delivered, a step function is incorporated into the health facility demand to evaluate how long it will take to achieve a sustainable 20% increase in drugs delivered to the health facilities. The results show that the 20% increase in demand is satisfied immediately, owing to the fact that the CMD's order quantities are based on having stock for a maximum time of either 4, 5 or 6 months, depending on the previous 3 months' consumption and the purchasing is based on perpetual purchasing.

A series of spikes in demand of 20% were also included in the model to test for agility against a more aggressive change. These results also show that the supply chain is very robust and can handle relatively small increases in demand (such as 20%).

Evaluation of the current supply chain has shown that a combination of long lead times and unpredictable demand exists. Rushton (2010) explains that this combination tends to lead to high levels of safety stock to ensure an agile supply chain. The fact that the supply chain is so agile implies that high levels of inventory are available at the CMD. The model is simulated at the base case conditions to test how high these inventory levels are. Figure 5.16 shows the percentage of inventory on hand that is over- or understocked every month. There is on average 267% more units of amikacin than is required each month. Therefore, it is crucial for the CMD to implement effective inventory management policies.

5.4.4 Performance Analysis Findings

Although the reliability and agility of the supply chain is acceptable, the responsiveness (especially from the supply side) should be reviewed for improvement. One of the best practices available for responsiveness improvement is effective inventory management. Furthermore, although the SLD supply chain is shown to be agile, the inventory management is shown to be inadequate with an average of 267% more units of amikacin on hand than what is necessary every month.

5.4.4.1 Unacceptable Lead Times

The analysis of the performance of the supply chain shows that the biggest gap for improvement lies in reducing supplier lead times. Although it is necessary to maintain a buffer inventory, shorter lead times between receipt of order and delivery would ensure a smaller stockpile. It is presumed that the lead time is determined by a number of factors in this supply chain: supplier; order quantity; and type of drug. These factors are investigated with the data available and used to determine which extra policies should be tested using

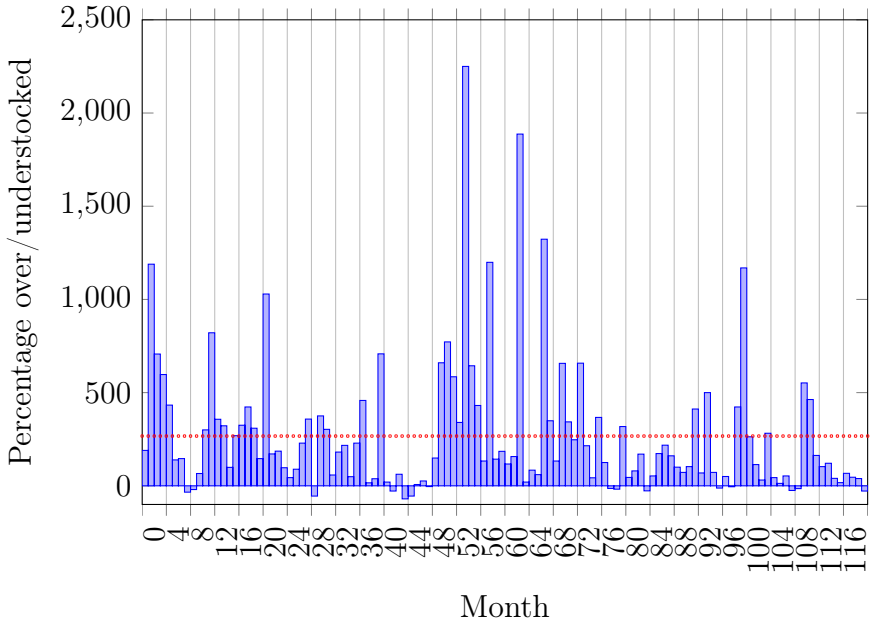


Figure 5.16: Percentage of surplus (or deficit) inventory on hand at the CMD

the supply chain model.

Before the lead time is altered through scenario modelling, the effect of both: (i) the quantity of the order from the CMD; and (ii) the supplier on the lead time, will be tested. Note that these tests are done on all second-line anti-TB drugs that are stocked at the CMD. Table A.1 lists these drugs.

- **Order Quantity:**
  If there is indeed a correlation between the CMD order quantity and the supplier lead time, then regression can be used to predict the lead time based on the order quantity. Regression is a statistical method used to make predictions. Performing a regression analysis assumes that there is a linear relationship between the independent and dependent variables; the order quantity and lead time in this case. Figure 5.17 illustrates the relationship of the order quantity and the lead times on a scatterplot. The lead time is the dependent variable, as it is the variable that is being predicted. The straight line in Figure 5.17 represents the *regression line*, and is defined as the 'best fitting' line through the data where the sum of the squared distances between each individual point and the regression line is a minimum.

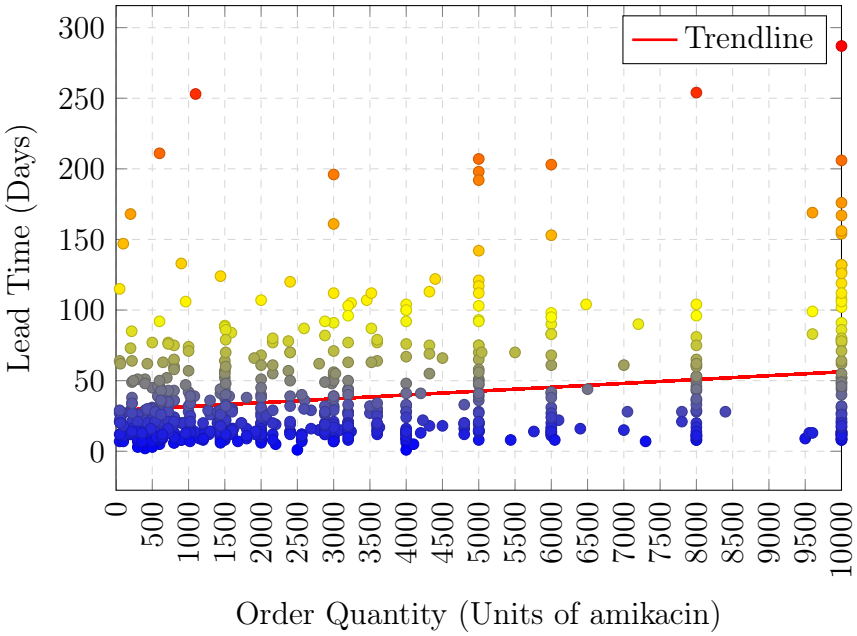


Figure 5.17: Correlation between order quantity and supplier lead time

Regression analysis done in Excel gives the equation of the regression line as:

$$y' = 28.9 + 0.0027x. \tag{5.4.3}$$

However to determine if the relationship between the order quantity and lead time is a strong one, further regression analysis is done. The results are summarised in Table 5.4. The coefficient of determination, or R squared signifies how strong the relationship between the two variables are. The coefficient of determination for this case is 0.13, signifying a weak relationship between order quantity and lead time.

Table 5.4: Regression statistics for correlation between order quantity and supplier lead time

Regression Statistics	
R Square	0.12
Residual Variance	1661.1
Standard Error	40.75

The regression analysis shows that attempting to improve supplier lead time by controlling order quantities is likely to be unsuccessful and should therefore not be implemented at the CMD. Therefore modelling scenarios that include altering the order quantities to test the impact on lead time will not be tested.

- **Supplier:**
  The effect of the supplier on the lead time is tested in this subsection. Each supplier is given a pseudonym in the form of letters (A-M). The results in Figure 5.18 show that the supplier has a significant impact on the time it takes for drugs to reach the CMD. The lower position of the box in Figure 5.19 shows that the majority of the suppliers deliver within approximately 50 days. Furthermore, Figure 5.18 shows that only two suppliers (A and B) show poor lead times, while Figure 5.19 shows that these suppliers are outliers. However, supplier B has been contracted by the CMD since 2007. Although this is an external variable that the CMD has no control over, it is important to take note of the significance of selecting a supplier that performs well in terms of lead time.

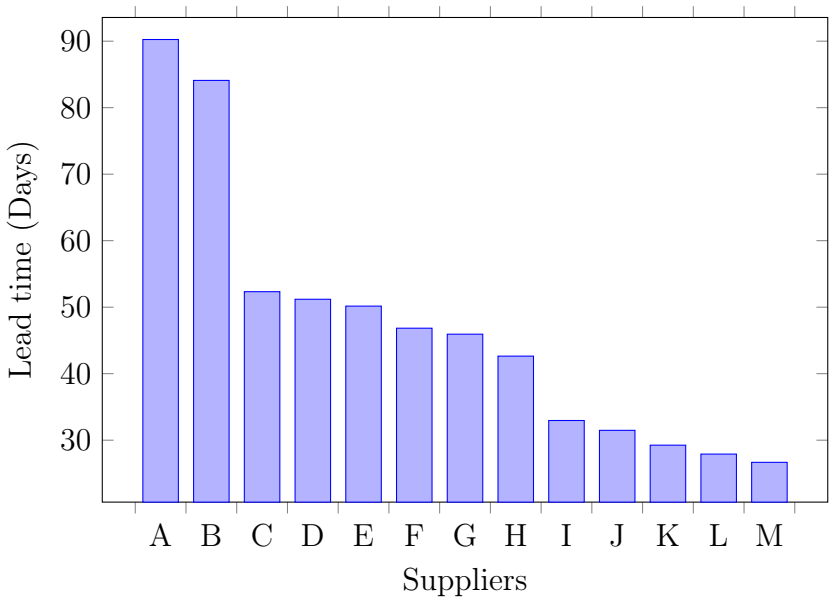


Figure 5.18: Correlation between supplier and supplier lead time

The results of the scenario modelling phase in Chapter 6 will show that the supplier lead time has a significant impact on the performance of the supply chain, showing the importance of selecting a supplier that achieves shorter lead times.

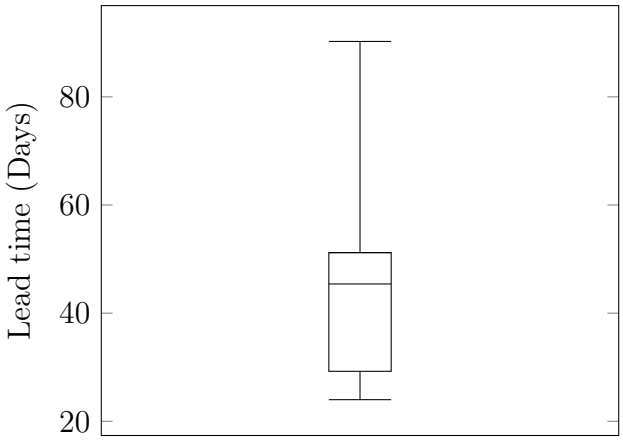


Figure 5.19: Distribution of supplier lead time for different suppliers

5.5 Conclusion: Modelling the Real-World Problem

This chapter is primarily focused on building a model of the downstream SLD supply chain using systems dynamics. The model is developed by following three of the five phases used for systems thinking and modelling, as proposed by Cavana and Maani (2000): problem structuring; causal loop modelling; and dynamic modelling. The themes of concern are first identified after which the relevant data is collected in order to simulate and model the issues. After the problem is structured, the causal loop model is developed in order to build a stock-flow diagram, which is validated against real-life data. Finally, the performance of the current downstream supply chain is evaluated.

The results of the performance analysis shows that the most troubling problem is the long supplier lead times. The reliability and robustness within the supply chain are acceptable, however the responsiveness (especially from the supplier side) is inconsistent and under-performing, thereby requiring improvement. Further investigation shows that the lead times are affected by the supplier, however not the quantity ordered by the CMD. Furthermore, although the current supply chain is shown to be robust, the CMD have very high levels of stock that are not being used effectively thereby requiring inventory management interventions. Effective inventory management has become the most crucial theme for strengthening the downstream SLD supply chain, as it has been: proposed as one of the solutions for strengthening the supply chain at the various IOM workshops; listed as a best practise for improving responsiveness; and shown to be ineffective in the current supply chain.

The remaining two phases of the five phase process, namely: scenario planning and modelling; and implementation will be discussed in Chapter 6. The outcomes and results of the scenario planning and modelling will also be displayed, analysed and discussed in Chapter 6.

Chapter 6

Data Analysis and Findings

This chapter discusses the final two phases of the five phase model-building process: scenario planning and modelling; and implementation. The themes that will be tested (through scenarios) using the simulated model are also listed and discussed. The scenarios involve altering variables, policies and strategies in order to provide suggestions for improvement. Thereafter, the quantification process that will be used to measure the overall performance of the supply chain for each scenario, for the purpose of comparing the different policies is explained. Finally the various scenarios will be tested by altering variables and policies in the simulation model. These results will be represented both in graphical and tabular forms to allow for easy communication.

6.1 Scenario Planning and Modelling

This section lists the various scenarios that will be tested in the supply chain model as discussed in the problem structuring phase, in order to evaluate the overall performance of the supply chain.

According to Cavana and Maani (2000), a scenario is intended to provide possible future conditions, not a future state. Becker (1983) explains that scenarios can be used for three distinct purposes:

- To provide common ground for people involved in planning within an organisation;
- To asses the performance of alternate strategies and policies and to estimate their risk; and
- To estimate whether policies can either prevent or assist the conditions of a scenario from coming out.

In scenario planning, both policies and strategies are altered and tested to evaluate performance attributes under varying conditions. According to Ca-

vana and Maani (2000), policy experiments refer to how a manager uses the information in the system in the design of policies. Policy experiments can be done by either changing the parameters of the policies or the structure of the policies. Policy structures can be changed by either the addition of new variables or by linking different variables in the model, or both. The policies and strategies that will be tested in this study are a combination of: (i) the suggestions proposed at the IOM workshops in Subsection 4.1.2; and (ii) the best practices for responsiveness as highlighted in Table 4.3 and discussed in Subsection 5.4.4.

Subsection 4.1.2 lists five main themes of improvement as suggested by the IOM, which include: providing incentives to suppliers and manufacturers; improved forecasting; inventory management; harmonisation and standardisation; and information systems. Providing incentives to suppliers and manufacturers, as well as harmonisation in the supply chain are upstream supply chain issues and therefore cannot be tested with the downstream model. Information systems form part of both the upstream and downstream segment of the supply chain. Although the available data is limited and does not include the type of data needed for EMR system, one aspect of information systems that is tested in the model is the tracking of stock shortages. Inventory management will be tested in a variety of different ways, which includes altering: desired levels of stock; safety stock policies; and reorder policies. Finally, a form of demand forecasting will be tested through using exponential smoothing to calculate the reorder quantity for the CMD.

As discussed in Subsection 5.4.4, the weakest performance attribute in the current supply chain is responsiveness. The best practises that are available for improving responsiveness are shown in Table 4.3, however not all of them can be tested in this study. Convergence of SCOR with lean and sigma six cannot be tested due to the limited availability of data. The data available in this study consists of aggregate data and therefore is not suitable to test for lean and sigma six. Purchase order management can also not be tested as this involves the documentation process followed when ordering stock, on which no data is available. The long term supplier agreement is contracted out by the NDoH and is therefore out of the CMD control. Finally, the best practices that can be tested using the model include: inventory management; and sales and operations planning. Sales and operations planning will be tested with: supplier lead time; supplier reliability; and customer service level. One of the goals of sales and operations planning is to determine the balance between supply and demand (inventory management). Operations planning is necessary to manage, amongst others: unacceptable lead times; ineffective bottlenecks; excessive obsolescence; and product shortages (Smith and Offodile, 2007). Although the SLD supply chain is shown to be robust, the reason is due to unnecessarily high inventory levels, therefore inventory management is

also investigated to improve the attribute within the current supply chain.

Table 6.1: Summary of themes that will be tested

Themes to Model
Inventory management
Demand forecasting
Sales and operations planning

In order to test the themes summarised in Table 6.1, the following variables, policies and strategies will be applied using the supply chain model:

- Supplier lead time;
- Supplier reliability;
- Inventory management:
  - Desired levels of stock;
  - Safety stock policies; and
  - Reorder policies.

6.1.1 Supplier Lead Time and Reliability

The supplier lead time and reliability vary considerably in the data as new suppliers are contracted every two years. These two variables will be altered using the data available from the CMD. These variables will be tested using constant values throughout the model and by making use of random functions between the minimum and maximum values. The worst and best values extracted from the data for both variables will also be tested to evaluate the difference in performance when the supply chain is operating at its best and at its worst.

6.1.2 Inventory Management

Embrey (2012) states that inventory management is the heart of the pharmaceutical supply chain. Inventory is kept on hand in order to (Embrey, 2012):

- Ensure availability;
- Maintain confidence in the supply chain;

- Reduce unit costs by buying in bulk;
- Avoid stock-out costs;
- Reduce ordering and transport costs; and
- Make provisions for fluctuations in demand.

6.1.2.1 Desired Levels of Stock

Currently these variables are changed by pharmacists on a regular basis based on a variety of factors, of which the most prominent one is demand. During the scenario analysis these parameters will be tested by comparing the outcomes when these levels are kept constant throughout the year.

6.1.2.2 Safety Stock Policies

The CMD defines drug shortages, or as they name it 'dues-out', as orders that cannot be filled i.e. backlogged orders. If the inventory on hand cannot satisfy the demand from the health facilities, the outstanding orders are backlogged. In order to avoid backlogged orders, the inventory on hand should always be sufficient to satisfy the demand, without being excessive so that obsolete stock becomes a problem. Embrey (2012) explains that a common way to measure the performance of a public warehouse is to measure the service level provided to the clients, in this case the health facilities. Safety stock is an important factor in preventing shortages and ensuring the promised service level to clients. The service level (SL) is calculated after the initial shipment using (6.1.1). However there are cases where public warehouses make partial shipments, i.e. the items are delivered in stages, which lowers the service level.

$$SL = \frac{No.\ of\ items\ issued}{No.\ of\ items\ ordered} \times 100. \tag{6.1.1}$$

Currently the CMD does not have a safety stock policy, but rather a defined minimum stock level that determines when orders should be placed, i.e. the reorder point. This reorder point is calculated using the minimum and maximum number of months that stock is desired to be on hand, however these levels are not predetermined with a set policy. These levels are set regularly by the pharmacist responsible for the section housing a specific drug at his/her own discretion. This is a key characteristic of the perpetual inventory model.

However, the safety stock and minimum stock levels are not analogous. Figure 6.1 shows the ideal inventory model, to prevent stock-outs and reduce costs. The ideal inventory model shows that the reorder point takes the lead time into account in order to receive stock before safety stock needs to be used. If there is however no safety stock and the supplier takes longer to deliver than expected, the inventory on hand will become zero, resulting in a stock-out.

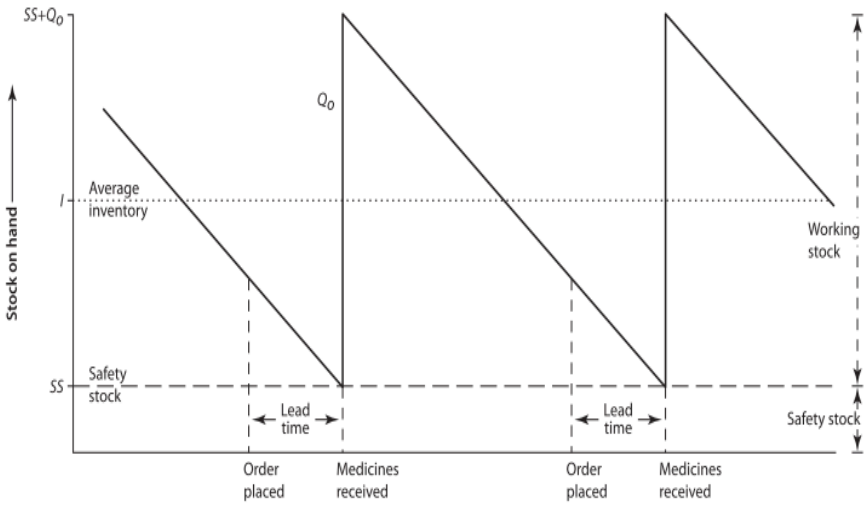


Figure 6.1: Ideal inventory control model (Source: Embrey (2012))

Therefore, various safety stock policies will be tested using the model to determine whether a safety stock policy would be beneficial, and if so which policy shows the most potential for balancing the fluctuations in demand and lead time. Embrey (2012) explains that there are many ways to estimate the level of safety stock required to achieve specific levels of performance, however they all consider two factors: average consumption; and average lead time, $\bar{LT}$. Due to the fact that both the lead time and the demand fluctuates considerably in the SLD supply chain, the standard deviation of consumption and lead time as well as the corresponding z-score for service level based on a normal distribution ($\mathrm{N}(\mu;\sigma)$) are factors that will be used to forecast safety stock.

6.1.2.3 Reorder Policies

The policies that will be tested include: reorder frequency; reorder quantity; and reorder point.

- **Reorder frequency:**
  Two groups of inventory control models are available for different situations; based on reorder frequency (Embrey, 2012):

  - Periodic review models; and
  - Perpetual review models.

  Orders are placed at regular planned intervals in periodic models, whereas orders are placed at any time, as the situation demands, in perpetual

models. Pharmaceutical supply chains most commonly use: annual purchasing; scheduled purchasing; perpetual purchasing; and draw-downs control models (Embrey, 2012). The supply chain for SLDs uses the perpetual review model; where the user or the minimum stock level determines when orders should be placed and the quantities thereof. In this model, the inventory on hand should be assessed on a regular basis in order to make sure orders are placed at specified reorder levels. Due to the dynamic behaviour of the purchasing in this model, the average inventory and safety stocks are lower than with other models. Due to the fact that many shortages still occur in the CMD with this model, despite the high levels of stock, the periodic review model will also be tested using the supply chain model to test for any improvements.

- **Reorder point:**
  Due to lead times being relatively long, inventory levels decrease to zero even after an order has been placed at the reorder point (ROP). This reorder point will be altered by adding safety stock to the level of inventory and by altering the point at which orders are placed to make sure they are placed earlier to account for the long lead times. One of the most popular formulas for calculating the reorder point is:

$$ROP = \bar{D_{HF}} \times \bar{LT} + SS. \tag{6.1.2}$$

  Currently the CMD calculate the reorder point based on the following formula:

$$ROP = \bar{D_{HF}} \times T_{min}, \tag{6.1.3}$$

  where the average demand is based on the previous three months' demand history. The reorder point will be altered according to the reorder policy being tested. Wherever the minimum and maximum stock level formula is used the reorder point will be calculated using the current reorder point policy, shown in (6.1.3). Alternatively, the reorder point will be calculated using (6.1.2) for any policies that do not make use of the minimum and maximum level stock level formula.

- **Reorder quantity:**
  The CMD demand (D_{CMD}) is analogous to the reorder quantity in this model and therefore each method for determining the reorder quantity will be represented by D_{CMD}. This research project will focus on the following methods available for calculating reorder quantity:

  - Economic order quantity
  - Exponential smoothing; and

– Minimum and maximum stock level formula.

The most common method for calculating reorder quantity is to calculate the economic order quantity (EOQ):

$$EOQ = \sqrt{\frac{2 \times D_{HF} \times C_O}{C_H}}, \tag{6.1.4}$$

where C_O and C_H represent the ordering costs and the holding costs respectively. The economic order quantity is calculated to minimise the total inventory holding costs and ordering costs when placing an order quantity. This calculation is based on the following assumptions:

– The ordering cost is constant;
– The demand rate is known and spread evenly; and
– The lead time is known and fixed.

These assumptions do not hold for the real-world problem, therefore the economic order quantity method is not appropriate for this supply chain and will not be tested using the stimulated model.

Another method available for calculating the reorder quantity is to forecast the demand and then order based on the forecast. The demand for the next period is predicted using exponential smoothing. Exponential smoothing calculates the projected demand for the period based on previous months' demand and a smoothing constant (α), which should be tested with each individual case. Exponential smoothing is calculated as follows:

$$D_{CMD(t)} = \alpha \times D_{HF} + D_{CMD(t-1)} \times [1 - \alpha]. \tag{6.1.5}$$

Finally Embrey (2012) describes the minimum and maximum stock level formula, which the CMD is currently using to calculate reorder quantity once the reorder point is reached. As described in the name, the minimum and maximum stock-level formula requires that a theoretical minimum and maximum level of stock be predetermined to ensure a sufficient quantity of stock, without creating obsolete stock. The demand is then calculated using:

$$D_{CMD} = T_{max} \times \bar{C_A} + SS - IP. \tag{6.1.6}$$

The exponential smoothing formula and the minimum-maximum stock level formula will be compared using the simulated model, to test the impact on performance.

6.2 Implementation and Evaluation Criteria

In order to make the decision of whether a policy or strategy should be implemented or changed, a method of quantification of the overall performance of the system for the purpose of comparing various policies is necessary (Cavana and Maani, 2000).

In order to quantify how these policies will affect the supply chain, 'stock performance' and 'cost performance' will be evaluated. Although the 'cost' attribute could not be evaluated during the performance analysis of the current supply chain due to lack of data, the cost performance that is evaluated here is based on the additional costs that the CMD would incur based on the results of the different scenarios. These evaluation criteria will be further divided into the sub-criteria as shown in Table 6.2.

Table 6.2: Evaluation criteria for scenario modelling

Stock Performance
Shortages
Obsolete stock
Total inventory
Cost Performance
Inventory holding costs
Obsolescence costs
Replacement therapy costs (shortage costs)
Total costs

To evaluate the policy and strategy changes and their effect on cost and stock performance, the simulated model must be further expanded in Vensim to include the following variables:

- Holding costs;
- Obsolescence costs;
- Base therapy costs;
- Replacement therapy costs; and

- Total costs.

The expanded model is illustrated in Figure 6.2.

6.2.1 Stock Performance

The following criteria will be measured to test the impact of changes on the stock performance of the supply chain.

6.2.1.1 Shortages (B_{CMD})

It is important to note that this variable is not necessarily a stock-out, where the inventory decreases to zero, but rather a shortage that prevents satisfying an order. This variable is represented as order backlogs and is evaluated to make sure a policy is implemented that results in the least number of shortages. When testing the effect of parameter changes on shortages, the cumulative order backlogs variable will be evaluated at month 120 i.e. the total number of shortages over the 10 year period, calculated as follows:

$$B_{CMD}(t) = B_{CMD}(0) + \int [D_{HF} - S_1]dt. \tag{6.2.1}$$

6.2.1.2 Obsolete Stock (O_{Am})

In order to reduce shortages, additional inventory should be available in the CMD at all times. However, this could possibly result in an increase of expired stock. Therefore this variable will be evaluated to make sure that the number of obsolete drugs do not become an additional problem in the supply chain. The data does show that it is a rare occurrence for drugs to expire, or to be declared obsolete at the CMD, therefore it is assumed that the CMD follows the correct rotation policy to ensure the oldest drugs are dispatched first. Amikacin has a total shelf-life of 36 months, however by the time the drugs have reached the CMD the shelf-life is already considerable lower. For the purpose of this model it is assumed that the maximum shelf life of amikacin (T_E) is 30 months by the time it reaches the CMD.

Systems dynamics is unable to measure discrete events and therefore will not be able to measure the shelf-life and activity of each individual drug in the CMD. Therefore there is no accurate way to model this variable with the current systems dynamics model. The only way to measure this variable with systems dynamics is to assume that inventory stored in the CMD longer than a certain period of time each month will expire. This period of time is calculated as the 30 months minus the time taken to deliver the drugs to the CMD (LT), i.e. the remaining shelf-life once the drugs are delivered to the CMD. It is important to note that this method of calculating obsolete stock will result in

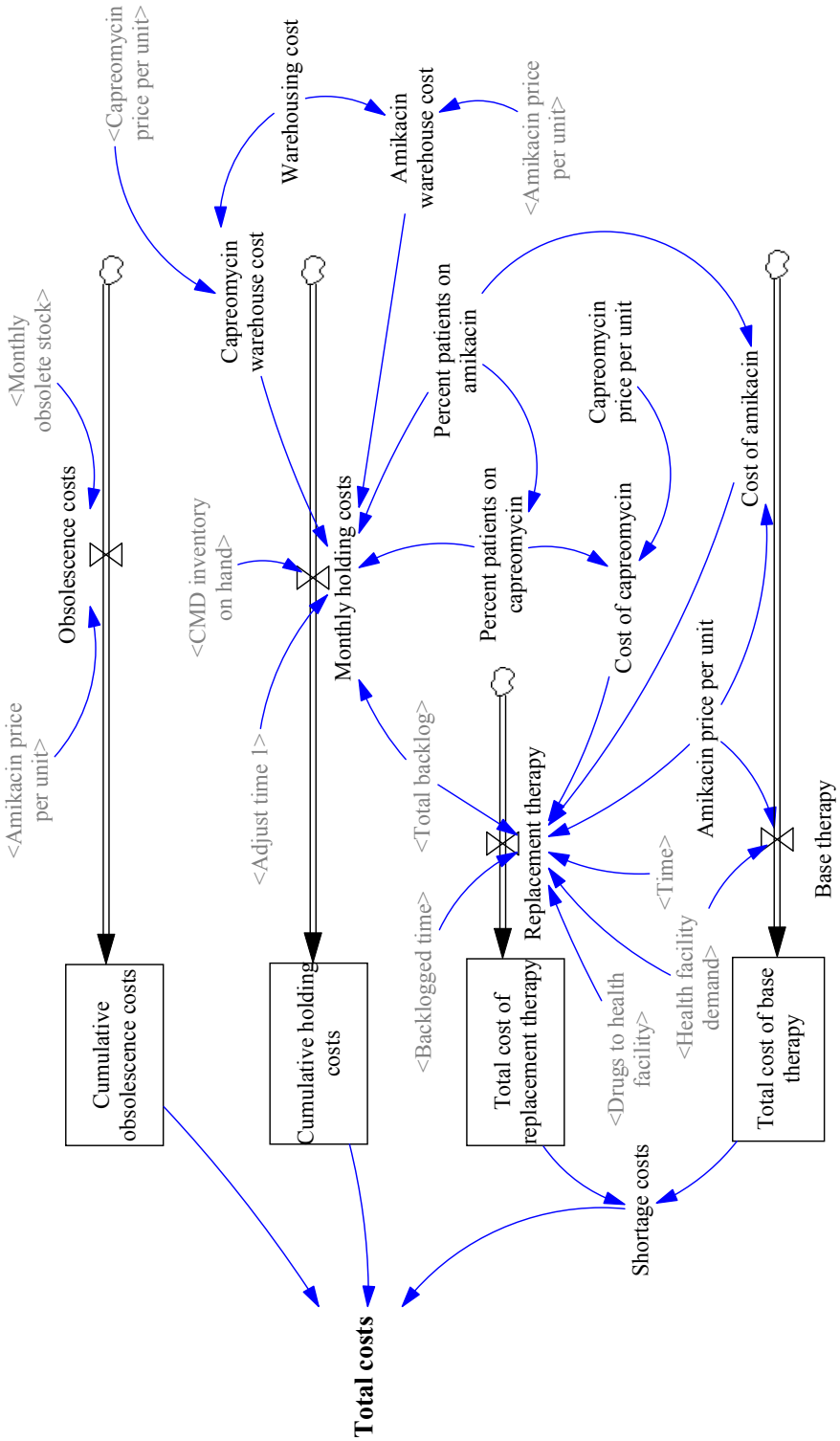


Figure 6.2: Expanded MDR-TB SLD supply chain model

considerably higher quantities of obsolete stock than what is currently being realised at the CMD. However, this method is the only one available to take obsolete stock into account when comparing the different policies, and the obsolescence costs are significantly lower than the holding costs and shortage costs, therefore the impact of this variable will not be significant. To make provision for obsolete stock the following formula will be used:

$$O_{Am}(t) = O_{Am}(0) + \int [\frac{S_{CMD}}{T_E - LT}]dt. \tag{6.2.2}$$

6.2.1.3 Total Inventory

A surplus of inventory is needed in order to ensure the prevention of stock-outs, however holding extra inventory incurs additional costs. This variable is evaluated to compare the total inventory ordered by the CMD, to the total number of shortages. This variable can evaluate and compare scenarios that accumulate high quantities of inventory but produce different amounts of shortages, to evaluate which scenarios are wasteful in terms of the amount of inventory required to achieve the performance.

6.2.2 Cost Performance

The following criteria will be measured to test the impact of changes on the cost performance of the supply chain. According to Embrey (2012), one of the goals of inventory management is to balance holding costs on one hand and shortage costs on the other. Therefore these costs need to be identified and analysed to achieve this balance.

6.2.2.1 Inventory Holding Costs (C_H)

The cost of storing inventory at the CMD is assumed to be 25% of the value of the inventory on hand every month (Vermorel, 2013; Hou, 2013; REM Associates). This is another factor that will be taken into consideration when testing safety stock policies, as the holding costs contribute to a large portion of the total costs. Inventory holding costs are a function of:

- Capital costs;
- Storage space costs;
- Inventory services costs; and
- Inventory risk costs.

6.2.2.2 Obsolescence Costs (C_{Ob})

The total financial loss of amikacin that is disposed of will be added to the expenses of the supply chain. Obsolescence costs are a function of: the quantity of drugs expired (O_{Am}); and the cost per unit of amikacin. As discussed earlier, this cost is considerably lower than both the holding costs and shortage costs and will therefore not a have a significant impact on the total costs.

6.2.2.3 Replacement Therapy (Shortage) Costs (C_S)

Shortages of drugs cause interruptions in treatment and can therefore possibly result in the following:

- Increased infectiousness;
- Allocation of substitute drugs;
- Resistance to the drug that is out of stock;
- Development of XDR-TB;
- Patient drop-outs; and, in extreme cases
- Death.

In order to quantify the total cost of a shortage, the effects of stock-outs as listed above need to be quantified: however the infectiousness; development of XDR-TB; drop-out rate; and number of deaths will be not be quantified in this study. Therefore the cost of a shortage will be a function of the cost of allocating substitute drugs and the cost of resistance to amikacin, and therefore kanamycin and streptomycin. Furthermore it should be noted that the conservative approach will be taken to do this evaluation and therefore the most extreme cases will be evaluated, i.e. resistance to amikacin ensues as soon as a dosage is skipped and treatment is interrupted.

As discussed in Section 2.5.1, the regimen that should be followed for an adult that suffers from MDR-TB includes amikacin for the first eight months. Amikacin is interchangeable with kanamycin and capreomycin, however Crofton *et al.* (1997) suggest that amikacin and kanamycin should be seen as the same drug, as they are equally active and therefore resistance to amikacin results in resistance to kanamycin. Firstly the assumption is that if amikacin is out of stock, then the CMD will have to replace it with capreomycin, as there will still be susceptibility. Secondly if amikacin is out of stock, a patient's regimen will be interrupted which will create resistance to amikacin and therefore kanamycin. Therefore, for the remainder of the treatment the patient needs to complete the eight month course with capreomycin instead (replacement

regimen), incurring additional costs for the CMD.

The cost of the replacement will be evaluated over the eight months following a shortage, as amikacin is only taken during the first eight months of a MDR-TB treatment regimen. For example, a shortage of 10 units of amikacin will result in 10 units of amikacin being replaced by 10 units of capreomycin for the next eight months, as 10 treatments would have been interrupted. Therefore there are patients that may only have one month left of the eight month phase after the shortage and will therefore only need to take capreomycin for one more month and there are patients that will start their regimen on capreomycin at the point of a shortage and end eight months later on capreomycin. On the other hand there are also patients who will only start treatment once the shortage is over and the amikacin stock has already been replenished. These patients can start on amikacin one month into the eight month evaluation period or in the last month of the evaluation period. This eight month phase is shown graphically in Figure 6.3, illustrating the patients and the length of their respective treatment regimens. Figure 6.3 shows that approximately 53% of the patients will need to be on the replacement regimen for the eight months following a shortage, while 47% can remain on amikacin. Therefore more than 50% of the costs will be for the procurement of capreomycin and the rest for the procurement of amikacin during the eight month period following a shortage. These shortages will also affect the holding costs, as the CMD would have to have capreomycin on hand in times of replacement therapy.

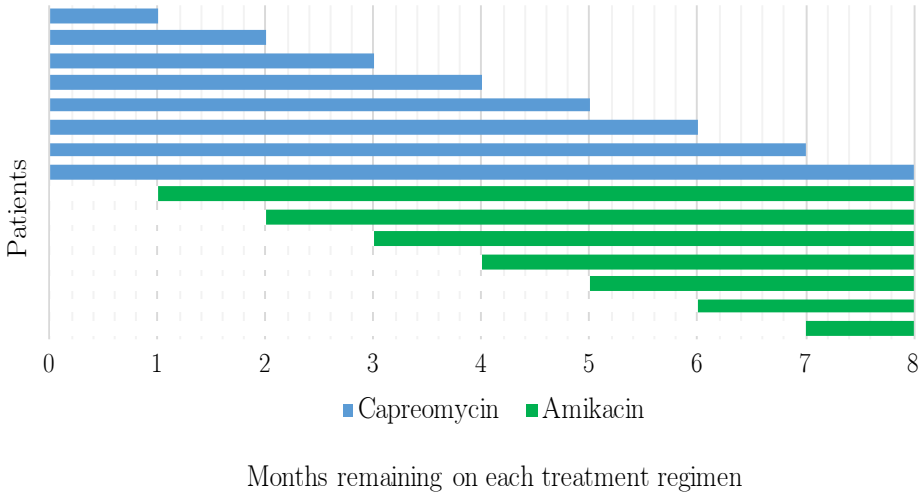


Figure 6.3: Impact of a stock shortage

The cost of shortages will be the difference between the therapy costs when no shortages are experienced, and when shortages are experienced over the 10

year period.

The unit costs of both amikacin and capreomycin are required to calculate the overall cost performance of the supply chain. These unit costs are shown in Table 6.3.

Table 6.3: Unit cost of amikacin and capreomycin

Cost per drug	Amikacin	Capreomycin
Unit price	\$ 2.06	\$ 6.25
Holding costs	\$ 0.02	\$ 0.05

It should be noted that a stock-out at the CMD does not equate to a stock-out in a health facility, however without data from health facilities and the fact that a conservative approach is being followed, the assumption is that a shortage in the CMD directly translates to a shortage in a health facility and therefore an interruption in a patients' treatment regimen.

6.2.2.4 Total Costs

The total costs are made up of: the holding costs; the obsolescence costs; and the shortage costs as shown in (6.2.3). The cumulative cost of therapy i.e. when there are no shortages and all orders are satisfied by the CMD, is approximately \$560,000, therefore when the replacement therapy is equal to this cost then there are no shortages and all orders are filled. The shortage costs show the difference between replacement and base therapy costs.

$$C_T = C_H + C_{Ob} + C_S. \tag{6.2.3}$$

6.2.3 Evaluation Criteria Analysis

The results, insights and recommendations of the scenario modelling phase will be communicated through the use of these evaluation criteria. In effect this is a multi-objective minimisation function, as the aim is to ensure the lowest total cost and the lowest number of shortages. The results of the evaluation criteria from each scenario, namely the total shortages and the total costs will be plotted against each other on a scatter plot in order to determine the optimal solutions. A pareto set will be created and used in the following chapter to identify the most optimal solutions obtained from the scenario modelling.

6.3 Scenario Results

This section will test the impact that certain variables in the supply chain will have on the overall performance of the supply chain. As previously discussed in Section 6.1, the following policies will be altered and tested:

- Supplier lead time;
- Supplier reliability;
- Desired levels of stock;
- Safety stock policies; and
- Reorder policies.

Before changing any parameters in the model, the base case (BC), i.e. the current operation is first evaluated. The performance of the current supply chain with the exogenous variables set as shown in Table 6.4 results in a total cost of $\$880,000$ over the 10 years, as shown in Table 6.5. The stocks and costs shown in Table 6.5 are all cumulative quantities over the 10 year period, 2005-2014. The holding and shortage costs make up the majority of the total costs to the CMD, therefore any scenarios that reduce these costs will result in the lowest total cost. However, a balance needs to be found between inventory levels and shortages as these are competing objectives. The cumulative demand over the 10 year period from health facilities for amikacin is $272,000$ units, therefore inventory levels higher than this are surplus. The results of the base case (BC) model will be shown in each table for the different scenario sets for easy reference.

Table 6.4: Base case values

Parameter	Value
Lead Time	$0.25 > < 5.6$ months
Reliability	98%
Minimum level	2, 3, 4 months
Maximum level	4, 5, 6 months
Safety Stock	0

The base case shows that enough inventory is available over the 10 year period to cover the demand, however there are still many shortages. This indicates poor planning and operations management. The shortages occur due to the fact that CMD reorder quantities are based on demand for the previous three

months. Figure 6.4 shows that the health facility demand spikes at month 43, however the spike is only translated to the CMD inventory in month 47. The required stock only arrives a few months later, resulting in an inability to satisfy the spike in demand and creating too much inventory in the months following the spike in demand. Furthermore the minimum and maximum levels of stock are also changed based on the demand history. Therefore, the minimum and maximum levels will be adjusted in the months showing demand spikes, producing more inventory in the months following a spike in demand.

Table 6.5: Base case stock and cost performance

Criteria	Cumulative values
Shortages	19,200 units
Obsolete stock	25,700 units
Total inventory	275,000 units
Holding costs	\$603,000
Obsolescence costs	\$53,000
Shortage costs	\$224,000
Total costs	\$880,000

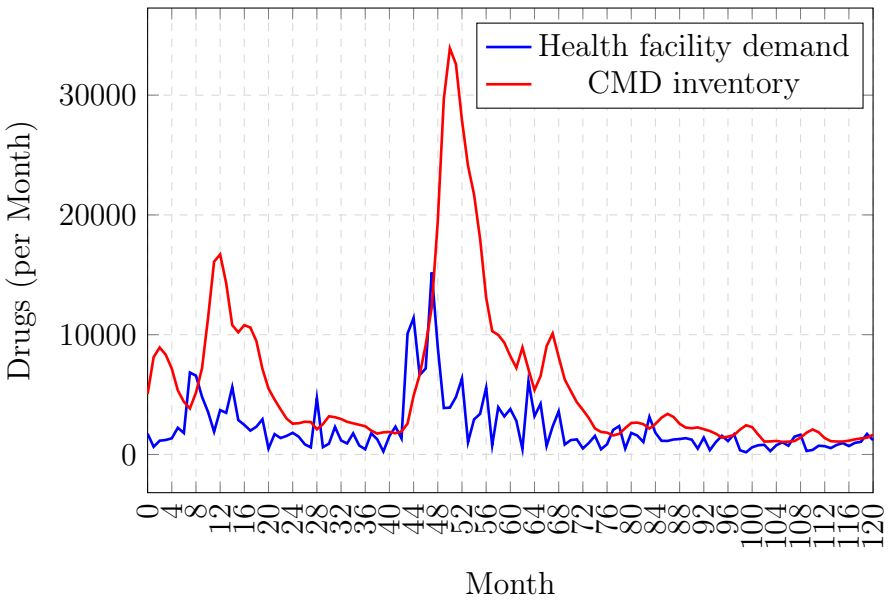


Figure 6.4: Relationship between health facility demand and CMD inventory

The following subsections show the results of the scenario modelling.

6.3.1 Supplier Lead Time(LT)

As shown in Figure 5.14 approximately 13% of the SLDs that are ordered by the CMD take more than three months to be delivered by the suppliers, therefore lead time is one of the biggest bottlenecks in this supply chain. The lead time will be tested by altering the time in the model to evaluate the impact on the supply chain.

To test the effect that the supplier lead time has on the performance of the downstream segment of the supply chain, three different scenarios are run. The supplier lead times that are tested are statistics that are obtained from the real data for amikacin over the past 10 years, namely: minimum lead time; average lead time; and maximum lead time to fulfil an order. The minimum time taken to fulfil an order is approximately a week, whilst the maximum lead time is calculated to be more than 5 months. Tables 6.6 and 6.7 show the stock and cost performance results respectively, after running the different simulations on the model.

It is important to note that these scenarios are simulated using the current policies at the CMD, i.e. high minimum and maximum desired stock levels shown in Table 6.4.

Table 6.6: Effect of supplier lead time on stock performance

Code	Lead Time (months)	Shortages	Obsolete stock	Total inventory
BC	**Variable**	19,200	25,700	275,000
LT1	**0.25**	6,220	33,600	297,000
LT2	**1.2**	22,500	24,500	270,000
LT3	**5.6**	158,000	5,430	114,000

The results indicate that the supplier lead time has a large impact on both the stock and cost performance. If the CMD experiences the minimum lead time for every order using their current operations and policies, they will limit the amount of shortages to approximately 622 ($\frac{value\ in\ table}{10\ years}$) units of amikacin per year. There are 25,000 more units of amikacin than what is necessary in this case (the cumulative demand for amikacin was 272,000 units). This is due to the minimum and maximum levels of stock being so high to accommodate for the variable lead time, with the minimum stock level being three months on

average.

Table 6.7: Effect of supplier lead time on cost performance

Code	Lead Time (months)	Holding costs	Obsolescence costs	Shortage costs	Total costs
BC	**Variable**	$603,000	$53,000	$224,000	$880,000
LT1	**0.25**	$702,000	$69,200	$92,200	$863,000
LT2	**1.2**	$598,000	$50,400	$249,000	$897,000
LT3	**5.6**	$129,000	$11,200	$562,000	$701,000

The CMD calculates reorder quantities based on high minimum and maximum levels as the current lead times fluctuate significantly. Therefore when constant shorter lead times are tested the inventory levels will increase significantly, creating high levels of obsolete stock and high holding costs. Under normal circumstances shorter lead times will result in: more frequent ordering; a decrease in inventory on hand; lower obsolete stock; and lower obsolescence and holding costs. Tables 6.6 and 6.7 show that this is not the case. Therefore, if the CMD were to improve the supplier lead time, the method of calculating the desired levels of stock would need to be adjusted to lower desired levels, or a different policy for calculating reorder quantity would need to be implemented.

The following scenario shows the impact of shorter lead times with the current minimum and maximum desired stock levels lowered from the base case scenario to correspond to the shorter lead times. The minimum desired stock levels are decreased to between 1 and 2 months, while the maximum levels are decreased to between 2 and 4 months. Shorter lead times will also be tested along with different reorder policies in Subsection 6.3.6. Table 6.9 shows that decreasing the supplier lead time and adjusting the desired stock levels accordingly will decrease the total costs by $206,000.

Table 6.8: Effect of supplier lead time on stock performance-adjusted policy

Code	Lead Time (months)	Shortages	Obsolete stock	Total inventory
BC	**Variable**	19,200	25,700	275,000
LT4	**0.25**	13,800	18,400	273,000

Table 6.9: Effect of supplier lead time on cost performance-adjusted policy

Code	Lead Time (months)	Holding costs	Obsolescence costs	Shortage costs	Total costs
BC	**Variable**	$603,000	$53,000	$224,000	$880,000
LT4	**0.25**	$448,000	$37,900	$188,000	$674,000

6.3.2 Supplier Reliability(R)

The supplier reliability for amikacin is generally very acceptable with an average reliability of 98%. To test the effect of supplier reliability on the performance of the supply chain, the reliability is set to 50%, 80% and 100%, even though historical data shows that the reliability is never below 80%. This parameter refers to receiving the correct quantity of amikacin, based on the orders received from the CMD, regardless of the lead time. The results are displayed in Tables 6.10 and 6.11.

Table 6.10: Effect of supplier reliability on stock performance

Code	Reliability	Shortages	Obsolete stock	Total inventory
BC	**98%**	19,200	25,700	275,000
R1	**50%**	53,200	16,400	231,000
R2	**80%**	26,800	23,400	265,000
R3	**100%**	18,700	26,000	276,000

Table 6.11: Effect of supplier reliability on cost performance

Code	Reliability	Holding costs	Obsolescence costs	Shortage costs	Total costs
BC	**98%**	$603,000	$53,000	$224,000	$880,000
R1	**50%**	$425,000	$33,800	$368,000	$827,000
R2	**80%**	$566,000	$48,200	$268,000	$883,000
R3	**100%**	$606,000	$53,500	$220,000	$879,000

Once again the results show that having less inventory has a positive impact on the cost performance, even with an increase in the frequency of shortages.

This is again due to the high levels of desired stock (minimum and maximum levels). However, if the reliability were to decrease to 50%, the shortages would increase to almost three times that of the base case. Although the scenario set at 50% shows the lowest total cost, the scenario running at 100% reliability shows a decrease in shortages and total cost when compared to the scenario run at 80% reliability.

6.3.3 Desired Stock Levels

This variable is changed on a regular basis by a pharmacist, depending on the nature of the demand over the past three months. Some of the factors considered by the pharmacists include (Deacon, 2015):

- Average supplier lead times;
- Seasonal variations in demand and supply;
- Anticipated external factors; and
- Capacity available in the warehouse.

These pharmacists are responsible for different sections of the warehouse and can alter these desired stock levels in their respective sections at their own discretion, as often as desired. Therefore, not only are the changes inconsistent in each section, but the changes across the various sections are not aligned. This is due to the fact that a policy is not available to aid the pharmacists in determining the optimum stock levels as the situation demands. This unregulated process has resulted in ineffective inventory management.

To test the impact of minimum and maximum number of weeks, scenarios are modelled where the desired stock levels are kept constant. The maximum level of stock can be calculated based on the minimum level of stock and the procurement period (PP), as shown in the following formula:

$$T_{max} = T_{min} + PP. \tag{6.3.1}$$

The procurement period (PP) is defined as the time between an order to a supplier and the next scheduled order (Embrey, 2012). The current supply chain is based on perpetual and not periodic purchasing, therefore the procurement period is not constant but rather fluctuating. However, the data shows that on average six orders are placed every year. Therefore for this calculation the procurement period is set at two months. Two scenarios are run where T_{min} is set at both two and three months (based on real-data), and the T_{max} variable is set at four and five months respectively.

Table 6.12: Effect of static desired stock levels on stock performance

Code	Stock levels (months)	Shortages	Obsolete stock	Total inventory
BC	**Variable**	19,200	25,700	275,000
DS1	**Static (2 & 4)**	30,500	17,500	255,000
DS2	**Static (3 & 5)**	17,600	25,900	277,000

Table 6.13: Effect of static desired stock levels on cost performance

Code	Stock levels (months)	Holding costs	Obsolescence costs	Shortage costs	Total costs
BC	**Variable**	\$603,000	\$53,000	\$224,000	\$880,000
DS1	**Static (2 & 4)**	\$416,000	\$36,000	\$266,000	\$718,000
DS2	**Static (3 & 5)**	\$547,000	\$53,300	\$201,000	\$801,000

The results show that setting the minimum and maximum levels of stock at constant values reduces the total cost when compared to the base case. This is due to the fact that minimum and maximum levels are currently set using historical demand; which fluctuates significantly. Setting the desired minimum and maximum levels of stock to three and five months respectively not only decreases the total costs, but also the number of shortages, when compared to the base case. However, the CMD would have to have sufficient space to store a five month supply of amikacin every time an order is placed if the static level policies are implemented. However, keeping the desired stock levels constant will require safety stock to address unexpected increases in demand. Scenarios will be modelled in Subsection 6.3.6 that integrate safety stock into constant desired stock level scenarios.

6.3.4 Safety Stock Policies

The first scenario that will be tested is the very basic safety stock formula as shown in (6.3.2). A safety factor (SF) is added to the current method of calculating CMD demand, to cope with the variations in both lead time and demand from the health facilities. The scenario was tested with a safety factor of 1.5, where an extra 50% is added to the original reorder quantity.

$$SS = D_{CMD} \times SF. \tag{6.3.2}$$

The second scenario will provide a constant safety stock level over the 10 years and will be calculated based on the fact that the CMD shows an average backlog of 4,000 units of amikacin per month in the base case scenario.

In the third scenario the safety stock will be calculated based on a desired service level and the fact that the consumption and lead time pattern both have large fluctuations. Embrey (2012) explains that when both the consumption and lead times are highly variable, the standard deviation of both variables should be calculated to set safety stock levels using (6.3.3).

$$SS = Z \times \sqrt{(\frac{LT}{PC} \times SD_C^2) + (C_A^2 \times SD_{LT}^2)}. \tag{6.3.3}$$

The Z value represents the desired service level, i.e. confidence level according to statistical analysis to achieve the service level. The CMD aims to never have stock-outs and therefore a service level of 100% is tested. The corresponding Z-score for a confidence level of 99.9% is 3.09. The safety stock is evaluated every month and therefore the production cycle (PC) is one month. The standard deviations and averages are calculated over one production cycle.

The left hand side of (6.3.3), namely:

$$SS = \sqrt{(\frac{LT}{PC} \times SD_C^2)}, \tag{6.3.4}$$

focuses on demand variability, while the right:

$$SS = \sqrt{(C_A^2 \times SD_{LT}^2)}, \tag{6.3.5}$$

focuses on lead time variability. Finding the dominant influence on safety stock requirements, i.e. the part of the equation that results in higher safety stock requirements, helps decide which improvements to focus on. In this case the model shows that the variability in lead time is the dominant influence on safety stock levels and should therefore be the focus of improvements.

In the final scenario the quantity of safety stock will be determined based on the previous months demand and the current demand. The percentage increase in health facility demand from the previous month will be used to calculate the safety stock for the current month based on the following formula:

$$SS = \frac{D_{HF}(t) - D_{HF}(t-1)}{D_{HF}(t-1)} \times D_{HF}(t). \tag{6.3.6}$$

Table 6.14: Effect of safety stock on stock performance

Code	Safety stock	Shortages	Obsolete stock	Total inventory
BC	**No SS**	19,200	25,700	275,000
SS1	**SF**	11,200	40,600	299,000
SS2	**Constant**	7,280	41,800	306,000
SS3	**SD**	5,700	66,200	332,000
SS4	**% increase**	4,610	31,900	296,000

Table 6.15: Effect of safety stock on cost performance

Code	Safety stock	Holding costs	Obsolescence costs	Shortage costs	Total costs
BC)	**No SS**	\$603,000	\$53,000	\$224,000	\$880,000
SS1	**SF**	\$850,000	\$83,600	\$140,000	\$1.07M
SS2	**Constant**	\$741,000	\$85,900	\$100,000	\$927,000
SS3	**SD**	\$1.19M	\$136,000	\$84,600	\$1.41M
SS4	**% increase**	\$659,000	\$65,700	\$67,000	\$792,000

Overall these safety stock policies merely add inventory to the high levels of inventory currently on hand at the CMD. Therefore the inventory pattern found in the base case stays the same, i.e. the same unnecessary spikes in the level of inventory are still present. Although extra stock is ordered to cover for variations in demand, the extra stock also arrives too late.

The standard deviation formula (6.3.3) calculates the safety stock requirements based on the fact that a shortage should never occur, even with the large fluctuations in both demand and lead time, therefore the formula overcompensates and results in surplus inventory on hand every month. The holding costs and the costs of obsolete stock are too high to implement this safety stock policy. The basic safety stock policy too incurs high costs and also produces large amounts of shortages. The final safety stock policy shows the most potential, as it incurs the lowest total cost and lowest number of shortages when compared to the base case and the other safety stock scenarios.

6.3.5 Reorder Policies

This section will focus on policies that relate to reordering, namely: reorder frequency; reorder points; and reorder quantities. The CMD is currently using perpetual purchasing and calculating the reorder quantity with regularly changing minimum and maximum desired levels of stock.

6.3.5.1 Reorder Frequency

The base case model is developed to represent the current situation at the CMD, where reorder frequency is based on perpetual purchasing. However, according to Embrey (2012) this method is not ideal for supplier lead times longer than a month, which the CMD often experiences.

As previously discussed in Subsection 5.4.1.3, periodic purchasing refers to placing demands at regular scheduled intervals. Therefore the calculation for CMD demand (D_{CDM}) will be adjusted to ensure orders are placed at regular intervals. These regular intervals are called procurement periods (PP) i.e. the time between placing orders. The scenarios include placing orders every one, two and three months respectively. The reorder quantity is based on the calculation currently used by the CMD, however adjusted for the procurement period. The stock ordered at every interval would need to cover the demand for that procurement period as well as the supplier lead time, until the next order can be placed. Historical data shows that most of the lead times fall below 2.4 months, therefore the lead time that will be used to evaluate these scenarios is 2.4 months, which is the average plus one standard deviation. The following formula is used to calculate the reorder quantity:

$$D_{CMD} = \bar{D_{HF}} \times (\bar{LT} + PP) + SS - IP. \tag{6.3.7}$$

Table 6.16: Effect of periodic purchasing on stock performance

Code	Periodic purchasing	Shortages	Obsolete stock	Total inventory
BC	**Perpetual**	19,200	25,700	275,000
PP1	$\bar{D_{HF}} \times 3.4$	22,100	23,100	269,000
PP2	$\bar{D_{HF}} \times 4.4$	30,900	23,500	261,000
PP3	$\bar{D_{HF}} \times 5.4$	34,000	24,200	258,000

The results in Tables 6.16 and 6.17 show that the best outcome is to order on a monthly basis to compensate for the variable health facility demand. A procurement period of longer than a month increases the number of shortages

Table 6.17: Effect of periodic purchasing on cost performance

Code	Periodic purchasing	Holding costs	Obsolescence costs	Shortage costs	Total costs
BC	**Perpetual**	$603,000	$53,000	$224,000	$880,000
PP1	$\bar{D_{HF}} \times 3.4$	$525,000	$47,600	$242,000	$814,000
PP2	$\bar{D_{HF}} \times 4.4$	$545,000	$48,400	$267,000	$861,000
PP3	$\bar{D_{HF}} \times 5.4$	$552,000	$49,900	$262,000	$864,000

due to the variability in demand. Neither the demand nor the lead time is stable enough to calculate the reorder quantity based on data older than a month, therefore orders should rather be placed more frequently based on more current data. Moreover, it should be noted that procurement periods longer than a month increases the total holding costs even though the total inventory is lower, showing the ineffective use of inventory. Finally, ordering on a monthly basis results in the lowest total cost when compared to the base case and the other scenarios, and the least number of shortages when compared to the other scenarios.

6.3.5.2 Reorder Quantity

The CMD is currently using the minimum and maximum stock level formula to determine reorder quantity. This method has however shown that the inventory levels are unnecessarily high at times when demand is low and inadequate when demand is high, as shown in Figure 6.4. As discussed in Subsection 5.4.2.3, EOQ and exponential smoothing are additional methods that are available to calculate reorder quantity. The assumptions on which EOQ is based do not hold in this supply chain and therefore will not be tested using the model. However, exponential smoothing is tested in this section, with each scenario being tested with a different smoothing constant (α), as shown in Tables 6.18 and 6.19. As the minimum and maximum stock level formula is not used to calculate the reorder quantity in this scenario, the reorder point is calculated using the average supplier lead time plus one standard deviation (2.4 months), as defined in (6.1.2), instead of the minimum desired level of stock.

Overall this set of scenarios results in the lowest total costs, but also the highest number of shortages. The exponential smoothing method is a forecasting method and therefore uses the demand from the previous month to calculate the current demand. The reason this method produces lower reorder quantities is because this calculation is based on previous months' demands, which fluctuates significantly. The demand from health facilities is too unstable for this method of reordering, unless enough safety stock is on hand to cover for

the months that experience considerable increases in demand.

Table 6.18: Effect of exponential smoothing on stock performance

Code	Exponential smoothing	Shortages	Obsolete stock	Total inventory
BC	**Min-max**	19,200	25,700	275,000
ES1	$\boldsymbol{\alpha = 0.1}$	122,000	8,510	154,000
ES2	$\boldsymbol{\alpha = 0.5}$	70,200	13,900	211,000
ES3	$\boldsymbol{\alpha = 0.9}$	59,400	15,300	223,000

Table 6.19: Effect of exponential smoothing on cost performance

Code	Exponential smoothing	Holding costs	Obsolescence costs	Shortage costs	Total costs
BC	**Min-max**	\$603,000	\$53,000	\$224,000	\$880,000
ES1	$\boldsymbol{\alpha = 0.1}$	\$232,000	\$17,500	\$496,000	\$746,000
ES2	$\boldsymbol{\alpha = 0.5}$	\$350,000	\$28,500	\$376,000	\$755,000
ES3	$\boldsymbol{\alpha = 0.9}$	\$384,000	\$31,600	\$352,000	\$768,000

6.3.6 Combination of Best Scenarios

The next set of scenarios include altering and combining the various policies and variables tested earlier to test for any improvement on the original scenarios. The safety stock and lead time scenarios show the most potential for decreasing the number of shortages experienced. Shorter lead times will ensure that sudden spikes in health facility demand be translated to the CMD inventory in time for the increased demand, thereby reducing the excess stock following a demand spike. Safety stock ensures that additional stock is available when demand increases unexpectedly.

The first set of scenarios that are tested include combining the best run from the safety stock scenario set with the best runs from the other scenario sets, with regards to number of shortages. The results from the safety stock scenario set show that the final scenario results in the greatest decrease in number of shortages. This safety stock policy will be therefore integrated into the best runs in: the supplier lead time scenario set (0.25 months); the periodic purchasing scenario set (monthly ordering); the exponential smoothing scenario

set ($\alpha = 0.9$); and the desired stock levels scenario set, where the minimum and maximum levels of stock are set at three and five months respectively. Tables 6.20 and 6.21 show the results after running the following four scenarios:

1. Minimum lead time (0.25 months) with safety stock;
2. Periodic purchasing with safety stock;
3. Exponential smoothing reorder quantity with safety stock; and
4. Static desired minimum and maximum stock levels with safety stock.

Table 6.20: Effect of safety stock combination scenarios on stock performance

Code	Shortages	Obsolete stock	Total inventory
CS1	2,910	22,800	288,000
CS2	5,560	27,500	290,000
CS3	9,590	24,300	283,000
CS4	3,130	31,700	298,000

Table 6.21: Effect of safety stock combination scenarios on cost performance

Code	Holding costs	Obsolescence costs	Shortage costs	Total costs
CS1	\$498,000	\$47,000	\$44,500	\$590,000
CS2	\$550,000	\$56,700	\$83,200	\$690,000
CS3	\$516,000	\$87,300	\$117,000	\$948,000
CS4	\$595,000	\$50,000	\$129,000	\$695,000

Tables 6.20 and 6.21 show that improving the lead time results in the biggest improvement with regards to total cost and number of shortages. Therefore, to further test the impact of lead time, additional combination scenarios will be run. As discussed earlier, decreasing the lead time with the current desired levels of stock does not accurately show the effect of reduced lead times due to the high levels of desired stock. Instead of adjusting the minimum and maximum levels using the current perpetual purchasing, shorter lead times will be tested using periodic purchasing along with safety stock.

Furthermore, keeping the minimum and maximum levels of stock constant (combination scenario 4) shows the second best result with regards to shortages, and will therefore also be tested with reduced supplier lead times. Due to the lead times being shorter, the lower minimum and maximum desired levels of stock tested in Subsection 6.3.3 will also be tested, i.e. 2 and 4 months.

In summary, Tables 6.22 and 6.23 show the results after running the following combined scenarios:

5. Periodic purchasing with minimum lead time and safety stock;
6. Static levels of stock (3 & 5 months) with minimum lead time and safety stock; and
7. Static levels of stock (2 & 4 months) with minimum lead time and safety stock.

Table 6.22: Effect of lead time combination scenarios on stock performance

Code	Shortages	Obsolete stock	Total inventory
CS5	9,740	16,100	274,000
CS6	211	38,600	309,000
CS7	811	29,900	299,000

Table 6.23: Effect of lead time combination scenarios on cost performance

Code	Holding costs	Obsolescence costs	Shortage costs	Total costs
CS5	\$437,000	\$33,200	\$147,000	\$618,000
CS6	\$647,000	\$79,800	\$3,240	\$730,000
CS7	\$538,000	\$61,600	\$12,700	\$613,000

6.3.7 Scenario Findings

Due to the competing objectives: (i) shortages; and (ii) total cost, there is no simple way to evaluate which scenario shows the most potential. However the results show that the combined scenarios show the biggest improvement with regards to both number of interrupted treatments (shortages) and total cost.

The results of these two objectives from each of the scenarios tested will be plotted on a scatter plot in Chapter 7 in order to compare and evaluate.

6.4 Conclusion: Data Analysis and Findings

This chapter focuses on the last two phases of systems thinking and modelling. The systems dynamics model of the SLD supply chain developed in Chapter 5 is used to test various scenarios, based on: suggestions made at the IOM workshops; and the performance analysis of the current supply chain. A summary of the themes that are tested are shown in Table 6.1. The effect of these scenarios on both: (i) stock levels; and (ii) cost performance are evaluated to aid in the decision-making process of whether policies should be changed or implemented. The groups of policies that are tested include:

- Supplier lead time;
- Supplier reliability;
- Desired levels of stock;
- Safety stock levels; and
- Reorder policies.

Shortages and stock-outs of SLDs are unacceptable due to the consequences thereof, which include: patient drop-out; resistance and development of XDR-TB; increased infectiousness; and possibly death. Therefore the supply chain should be stable and robust enough to ensure adequate inventory. However, safety stock is required to prevent shortages, which increases inventory holding costs. These costs are approximately 25% of the value of the stock on hand and therefore contribute to a large portion to the total costs. As described in Subsection 2.4.3.2, financing of MDR-TB is a challenge, thereby requiring that policies that reduce costs be implemented. Therefore there are two competing objectives for the CMD: (i) to reduce costs; and (ii) prevent shortages. Each of the scenarios tested are evaluated for these two variables in order to decide which policies show the most potential for improvement. Overall, reducing lead times and implementing a safety stock policy results in the biggest improvements. The detailed comparison and analysis of each scenario will be done in Chapter 7. Chapter 7 will also discuss the conclusions of this research project and provide recommendations for further research.

Chapter 7

Conclusion and Recommendations

This chapter analyses the stock and cost impact of the interventions tested in Chapter 6 on the SLD supply chain, by plotting holding costs against number of interrupted treatments. A pareto set of the best interventions, and combinations thereof is obtained. Moreover, the decision-making tools that are available for comparing the different pareto solutions are discussed. Recommendations will be provided for both; improving the performance of the downstream SLD supply chain based on the scenario modelling results; and the suitability of the methodology followed in this study. The limitations of the system dynamics model will also be discussed as opportunities for improvement. Finally, suggestions for the improvement of this study in future research will be presented.

7.1 Analysis of Scenario Modelling Results

The interventions tested in Chapter 6 are evaluated in terms of their impact on stock and cost in the supply chain. A summary of each scenario tested, the changes in variables for each scenario and the impact of each scenario on total cost and number of shortages is provided in Table 7.1. The number of interrupted treatments and total costs, which include: obsolescence costs; holding costs; and shortage costs, are the focus of the evaluation for each intervention. The total cost and total shortages (number of interrupted treatments) are plotted against one another for each scenario tested in Chapter 6. These points are plotted on Figure 7.1 and grouped according to the scenario sets in Chapter 6. The x axis represents the total cost and the y axis represents the total number of shortages, and therefore the total number of interrupted treatments over the 10 year period.

Table 7.1: Summary of tested scenarios and their results

		Variables							
		Lead time (Months)	Reliability	Stock levels (Months)	Safety stock	Periodic purchasing (Monthly frequency)	Exponential smoothing	Shortages	Total costs
Scenarios	LT4	0.25						13,800	\$674,000
	LT2	1.2						22,500	\$897,000
	LT3	5.6						158,000	\$701,000
	R1		50%					53,200	\$827,000
	R2		80%					26,800	\$883,000
	R3		100%					18,700	\$879,000
	DS1			2 & 4				30,500	\$718,000
	DS2			3 & 5				17,600	\$801,000
	SS1				SF[1]			11,200	\$1.07M
	SS2				4,000[2]			7,280	\$927,000
	SS3				SD [3]			5,700	\$1.41M
	SS4				% increase [4]			4,610	\$792,000
	PP1					1		22,100	\$814,000
	PP2					2		30,900	\$861,000
	PP3					3		34,000	\$864,000
	ES1						$\alpha = 0.1$	122,000	\$746,000
	ES2						$\alpha = 0.5$	70,200	\$755,000
	ES3						$\alpha = 0.9$	59,400	\$768,000
	CS1	0.25			%increase			2,910	\$590,000
	CS2				%increase	1		5,560	\$690,000
	CS3				%increase		$\alpha = 0.9$	9,590	\$948,000
	CS4			3 & 5	%increase			3,130	\$695,000
	CS5	0.25			%increase	1		9,740	\$618,000
	CS6	0.25		3 & 5	%increase			211	\$730,000
	CS7	0.25		2 & 4	%increase			811	\$613,000

[1] Safety stock calculated with a safety factor (SF)

[2] Safety stock set at a constant of 4,000 units

[3] Safety stock calculated with standard deviation formula

[4] Safety stock calculated based on % increase in demand

7.1.1 Pareto Optimal Solutions

This is a multi-objective minimisation decision as both total cost and number of interrupted treatments should be as low as possible. Multi-objective optimisation involves simultaneously optimising several objectives, that are often competing. This is the case in this research study as decreasing the number of shortages is likely to result in an increase in holding costs, and therefore total costs. In order to compare the points in Figure 7.1 and determine the optimal points, a pareto optimal set is generated.

A pareto solution can be described as a solution wherein an improvement in one objective function will result in deterioration of any other objective value. A pareto optimal set involves a complete set of these solutions. Therefore each pareto optimal solution in effect achieves a trade off between the objective functions.

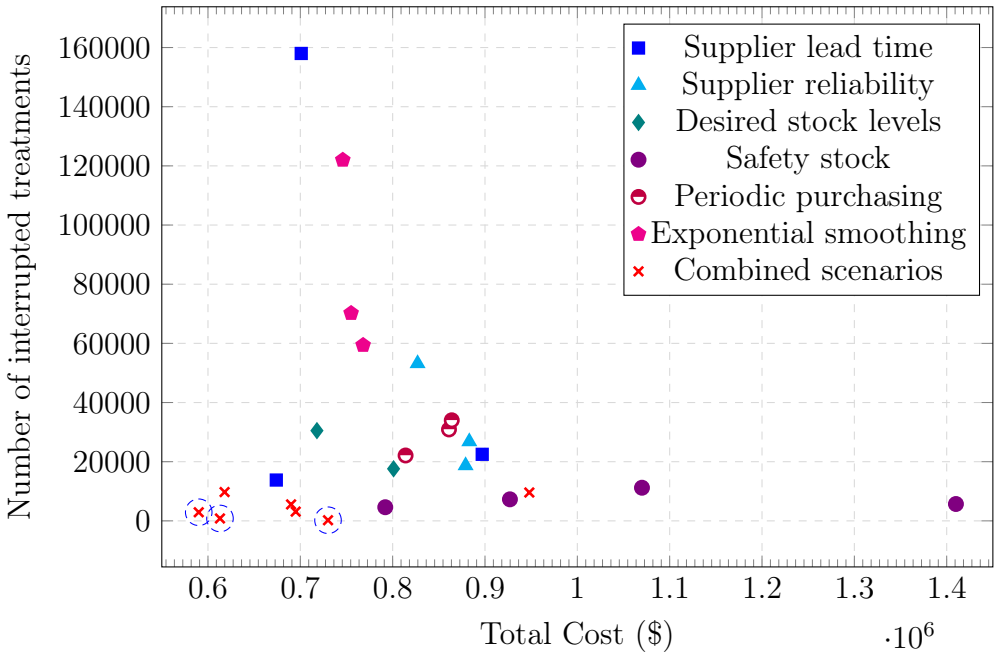


Figure 7.1: Scenario modelling results

The pareto set is highlighted in Figure 7.1 using the dotted circular markers. The coordinates of each pareto solution is recorded in Table 7.2.The long lead times and fluctuating supplier lead times are the most prominent problems experienced within the downstream SLD supply chain. The long lead times result in stock arriving too late to satisfy sudden spikes in demand, and further creates an unnecessary surplus in stock following a demand spike. The effect

of the fluctuating supplier lead times can be seen when analysing the left hand side of the standard deviation safety stock equation (6.3.3) compared to the right hand side. The dominant influence on safety stock requirements in this equation is the variable supplier lead time, indicating the need for improvement. The significant impact supplier lead time has on the performance of the supply chain is illustrated by the fact that each pareto solution depicts a scenario wherein the lead time is set to the minimum (0.25 months).

Table 7.2: Pareto solutions

Code	Shortages	Total cost
CS6	211	$730,000
CS7	811	$613,000
CS1	2,910	$590,000

The results of the scenario modelling phase has shown that improving lead times can improve the performance of the supply chain significantly, therefore emphasis should be placed on improving this variable. The findings in Subsection 6.2.1 show that, if the supply chain operates as it is currently, controlling order quantities in an effort to decrease lead times is likely to be unsuccessful. However the findings also show that the supplier has a notable effect on the duration of the lead times. Unfortunately the data has shown that one of the suppliers with the worst average lead time has been contracted since 2007 and is still supplying SLDs to the CMD. Many suggestions have been proposed regarding improving the performance of the SLD supply chain, however due to the long and variable lead times and the impact of the supplier on lead time, supplier selection has become the biggest factor. Therefore selecting suppliers that perform well in terms of lead time should be a priority. Unfortunately, the supplier lead time cannot readily be improved upon by the CMD as it is a variable that is out of their control. The supplier contracts are awarded by the NDoH in Pretoria, normally for a contract period of two years, according to responses received on tenders. Although the process whereby suppliers are chosen is driven by the NDoH, it is important to note the impact that supplier lead time has on the performance of the supply chain. The lead time should therefore be one of the highest weighted factors when selecting suppliers.

Furthermore the results in Chapter 6 show that the CMD have excess levels of inventory following a spike in health facility demand due to the fact that the desired levels of stock change according to historical demand. The demand is however too dynamic to change the levels of stock based on historical data.

Two of the pareto solutions show that keeping desired levels of stock constant reduces both the costs and the number of shortages experienced at the CMD. The scenario modelling results have shown that ordering safety stock when demand fluctuates, instead of altering the minimum and maximum desired levels of stock produces better results.

7.1.2 Effect of Lead Time on Total Costs

The total costs and number of interrupted treatments are competing objectives in this study because of the long supplier lead times. In cases where lead times are long, safety stock is required to ensure availability and make provisions for fluctuations in demand. Storing extra stock increases inventory holding costs and obsolescence costs, however the obsolescence costs do not have as high an impact on total costs as inventory holding costs. Inventory holding costs make up a very large portion of the total costs and therefore policies that minimise holding costs should be implemented. This includes reducing supplier lead times in order to avoid the need for safety stock. Reduced lead times will increase the frequency of orders, reduce the required inventory on hand and therefore reduce the holding costs. The impact that supplier lead time has on the holding costs are tested and shown in Figure 7.2. The cumulative holding costs are calculated using the minimum, maximum and average lead time from real data (0.25, 1.2 and 5.6 months) when the same customer service level is provided to the health facilities, i.e. the same number of drugs are dispatched to the health facilities in each scenario. To provide the same service level, the CMD would have to pay more than double over the 10 year period if the supplier lead time is 5.6 months as opposed to 0.25 months.

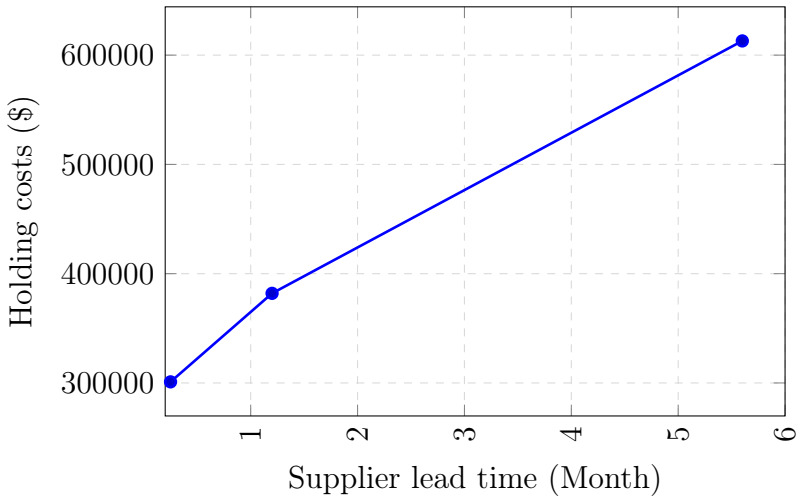


Figure 7.2: Effect of supplier lead time on cumulative holding costs

7.2 Recommendations to Stakeholders

As mentioned earlier, the greatest contribution to performance improvement in the supply chain is the reduction of supplier lead time. Supplier selection has a significant impact on lead time and is therefore the biggest factor in lead time reduction. Although the suppliers are contracted through the NDoH every two years, the CMD could possibly provide incentives to the current suppliers to deliver within a certain period of time. In addition to reducing lead times within the supply chain, the CMD could consider policy changes using the results obtained from the scenario modelling phase to aid in the decision-making process. The results show the generation of a pareto set with three optimal solutions, thereby requiring decision support tools to select the best intervention for all stakeholders involved. Furthermore, the results show that the current reorder policies are dominated by the minimum and maximum desired levels of stock that are changed as often as desired by different pharmacists responsible for different sections of the CMD at their own discretion. This has created ineffective inventory management, with 267% more units of amikacin in stock on average than what is required every month. The scenario modelling has shown that interventions are available that could be implemented to improve inventory management.

7.2.1 Decision-Making Tools

Each point in Figure 7.1 represents the impact of a different intervention/policy, or a combination thereof. The pareto set offers three optimal solutions for improving the downstream supply chain, however the supply chain cannot operate at each pareto solution simultaneously. A decision-making tool is therefore necessary in order to decide which pareto solution, and therefore intervention, is best for: the CMD; the health facilities; and the patients alike. It is therefore suggested to take the following three factors into account in order to determine the optimal pareto solution. These concepts are discussed in more detail in Section 7.6.

7.2.1.1 GDP

The gross domestic product (GDP) per capita is one of the determinants used to establish health expenditure. The GDP is a measure of a country's economic health and can therefore be used as an indicator to determine how much money is available for TB R&D and TB treatment. Between the years 2010 and 2014, South Africa has spent approximately 8.9% of the total GDP on health expenditure (World Bank Group, 2015). Increasing inventory levels to prevent shortages when lead times are poor has a significant impact on the cost of operating the supply chain and therefore requires further funding. Therefore the GDP should be used to determine how much extra funding can

be allocated to MDR-TB specifically. However, the consequences of increased TB incidence may actually negatively impact the GDP more significantly than allocating extra funds.

The burden of TB has significant social and economic implications for a country. According to the Global Alliance for TB Drug Development (2013) TB is a debilitating disease that mostly affects the working class, with 75% of TB cases affecting people between the ages of of 15 and 54. This results in diminished labour capacity as people infected with TB are significantly less productive than healthy people, stunting economic prosperity (Hart). Lonnroth (2011) explains that research has shown that there is a strong correlation between high TB incidence in a country and low gross national per capita income.

7.2.1.2 Population Simulations

In order to test the impact of increased infectiousness and the possible development of XDR-TB when treatment regimens are interrupted, population simulations should be developed. Population simulations can be used to simulate future trends based on current data. The future trend of newly diagnosed XDR-TB and MDR-TB cases due to treatment interruptions and stock-outs can be developed using current data on shortages and rates of infection. Comparing the cost of having more patients on longer treatments regimens using more expensive drugs to the cost of storing extra inventory will aid in the decision-making process of whether more money should be spent to prevent shortages and improve lead times.

7.2.1.3 Quality-Adjusted Life Years

In order to determine what additional costs will be necessary to improve the lives of patients, and how many lives these additional costs will actually improve, a quality-adjusted life-year (QALY) calculation should be done. The total additional costs incurred to reduce shortages to gain one extra QALY can be calculated to determine which interventions from Figure 7.1 are the most economically viable. QALY's are explained in more detail in Section 7.6.

7.2.2 Reorder Policy Analysis

As discussed earlier the minimum and maximum desired levels of stock are changed without policies and can be changed as often as desired. The lack of a policy with regards to reorder quantity has led to ineffective inventory management. It is suggested that a decision-making policy with regards to reorder policies during demand fluctuations be implemented. A decision support system will aid in ensuring that consistent decisions are made even when a specific pharmacist is unavailable, to allow any other individual to make the

correct decision.

A decision tree is a decision support tool that uses a schematic tree shaped diagram to determine a course of action. The branching method is used to show alternative decisions and every possible outcome of a decision. Xu *et al.* (2013) state that decision trees are commonly used in decision analysis to identify the strategy with the most potential to reach a specific goal. The goal in this case would be to identify the strategy which results in the most effective inventory management when demand and lead time fluctuate significantly.

Overall, for both increases and decreases in demand, the scenario modelling results show that keeping the desired levels of stock constant provide better results. However, to control shortages more aggressively the results show that ordering safety stock to make provision for demand increases, rather than altering the desired levels of stock is more effective. Figure 7.3 shows an example of a decision tree that could possibly be used by the CMD.

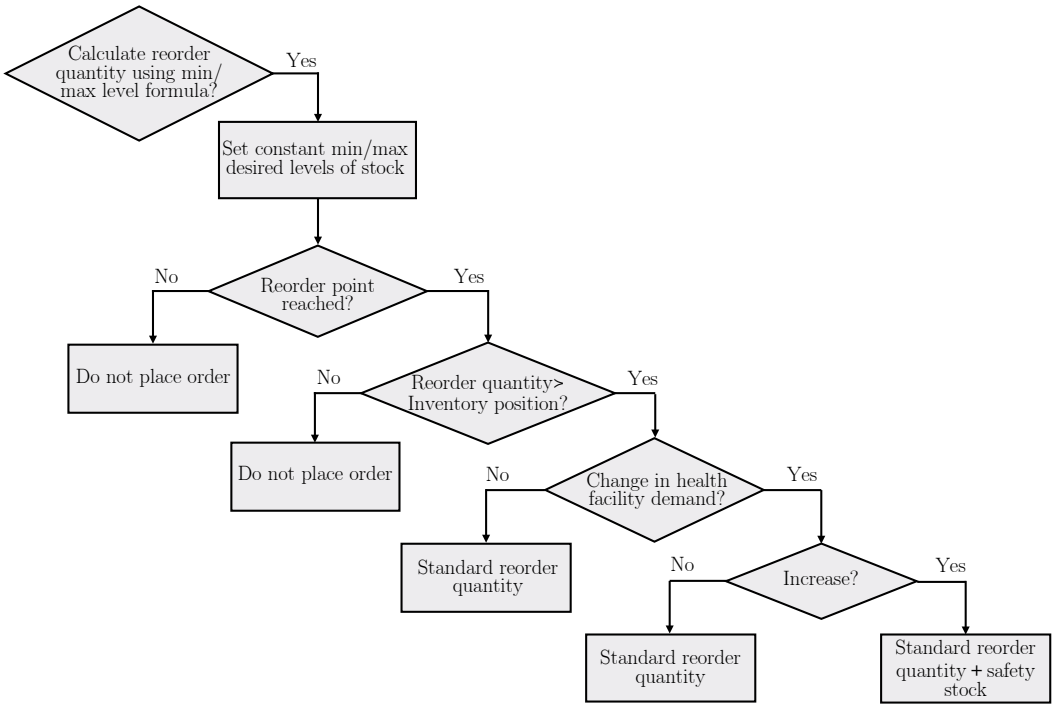


Figure 7.3: Inventory management decision flow chart

The diamond shapes show events and the blocks show actions. The standard reorder quantity policy and best safety stock policy (as shown in Subsection 6.3.4) used to calculate the CMD demand, as shown in the decision tree are calculated as follows:

$$D_{CMD} = T_{max} \times \bar{C}_A + SS - IP, \tag{7.2.1}$$

$$SS = \frac{D_{HF}(t) - D_{HF}(t-1)}{D_{HF}(t-1)} \times D_{HF}(t). \tag{7.2.2}$$

7.2.3 Impact of IOM Suggestions and Best Practices

The impact of the themes tested using the system dynamics model on the performance of the SLD supply chain are evaluated. The themes that were tested include: inventory management; demand forecasting; and sales and operations planning. The demand forecasting was tested through the use of exponential smoothing as a reorder quantity policy however, this showed no improvement. This is due to the fact that the SLD supply chain is predominantly donor funded, meaning that demand is unstable and irregular due to the fact that the demand is not voluntary (Haghani and Afshar, 2009). There will be periods of irregular demand at irregular intervals due to increased awareness campaigns or the improvement of diagnostic capabilities. However, inventory management and sales and operations planning had significant positive impacts on the performance of the supply chain which can be seen by: the various reorder policy interventions; the reduced lead time interventions; and the safety stock interventions.

7.3 Recommendations on the Methodology

Developing a model of a supply chain in order to test the impact of various interventions on the performance of the supply chain is the recommended methodology to follow. Running various scenarios on a model that represents a real-world system will give the best estimate on how the changes will impact the current system.

As discussed in Chapter 3, there are many different techniques available for modelling supply chains. The technique chosen should depend on the purpose of the study. System dynamics is the chosen methodology for this study, and is highly recommended for the purpose of this study and any similar projects. System dynamics aids in decision making processes about policies and strategies, and provides understanding of the non-linear behaviour of complex systems over time. It is not highly accurate for each individual entity i.e. each drug, but gives an accurate representation of the overall system. Furthermore, the software used to develop this systems dynamics model (Vensim) is also highly recommended as it is user friendly.

7.4 Model Assumptions and Limitations

This section discusses the limitations in the simulated model. These limitations are due to either the properties of system dynamics or the limited availability of data.

There are instances in the model where the limitations of system dynamics impact the accuracy of the model. Firstly, the state changes in systems dynamics are continuous, therefore individual units cannot be modelled. For example the obsolete stock is calculated as a percentage of the units of amikacin on hand for each month. Therefore the model overcompensates and produces more obsolete stock than what is actually produced. However, with system dynamics there is no way to track each individual drug through the stages of the supply chain to test if it does indeed expire. In order to track individual activities at discrete points of time, discrete event simulation should be used.

All of the necessary CMD data required to develop the downstream SLD supply chain was provided by the WCDoH, however there are some activities that cannot be modelled accurately. The minimum and maximum desired levels of stock can be changed regularly by a pharmacist, depending on: demand; external factors; warehouse capacity; and supplier lead time. These minimum and maximum levels only date back five years and are recorded as snapshots in the form of text files, therefore extracting this data is a laborious task. Since there is no set policy for determining these levels, the model cannot accurately represent the real-life situation. Therefore to represent the current supply chain, the levels are adjusted to fit the real-life trends. Furthermore, although there is a policy for determining reorder quantity, the CMD can override this in times of emergencies. The data shows instances where the quantity ordered is higher than what is calculated with the policy, therefore the model cannot represent these instances accurately. This is apparent during the validation process in Chapter 5, Subsection 5.3.3.

Finally, the data collected for this study was provided by the CMD and therefore the simulated model is developed around the CMD. The shortages that are calculated in this model are the shortages experienced at the CMD, and not necessarily at the health facilities. Due to the limited data, there is no accurate method of determining how and when these shortages affect each of the 345 health facilities that the CMD supplies to. Therefore the assumption was made that any shortages experienced at the CMD are immediately translated to shortages at the health facilities and therefore interruptions in treatment. This is one of the biggest limitations with the current model.

7.5 Suggestions for Future Research

This section discusses the possibilities of further research based on the findings of this research project.

7.5.1 Expanding the Model

This model is only developed for one second-line anti-TB drug, therefore the first suggestion is to develop similar models for the other second-line anti-TB drugs, to test if they behave in the same way and achieve the same results as this model. This model could also be used to test other pharmaceutical supply chains, adjusting the necessary parameters as necessary. Moreover, in order to represent the downstream supply chain more accurately, data should also be collected from both the health facilities and the suppliers in order to increase accuracy. The model developed for this study is focused only on the CMD, limiting what can be tested. As discussed earlier, data from both the CMD and the health facilities will aid in determining how long it takes for shortages in the CMD to be translated into shortages in the health facilities.

Furthermore, this model should be expanded to include the upstream segment of the supply chain. The upstream and downstream segments of the SLD supply chain are decoupled from one another in terms of financing, therefore creating unique implications with regard to the operations in each segment. Developing a model that integrates both segments of the SLD supply chain will not only allow better understanding of the global supply chain, but will also illustrate how the segments influence one another, and to what extent.

7.5.2 In-Depth Impact of Shortages

The overall effect of drug shortages and ultimately treatment interruptions can never be fully quantified, as shortages can create life threatening situations. This research project only takes the cost of substitute drugs due to resistance into account when treatments are interrupted. However the other factors that need to be considered when treatments are interrupted include: increased infectiousness; development of XDR-TB; patient drop-out; and possible death. This section provides suggestions on how to further quantify the impact of shortages on infectiousness, increased resistance and mortality.

7.5.2.1 Quality-Adjusted Life-Year Analysis

In order to determine the true cost of shortages and stock-outs it is suggested that more research should be done on quality-adjusted life-years (QALY). According to Prieto and Sacristán (2003), the QALY is the measure of the value of health outcomes. The QALY was developed to combine both the values of

length (quantity) of life and quality of life into a single measure. The QALY is calculated as follows:

$$QALYs\ gained = utility\ score \times additional\ years. \tag{7.5.1}$$

Utility scores are given to specific predetermined health states. These health state values vary from one (perfect health) down to negative values, depending on the problem. A utility of zero is equivalent to being dead, therefore health states with negative utilities are regarded as being worse than death. The additional years refer to the number of extra years generated in a health state due to some or other health intervention. Although the measure has ethical shortfalls, QALYs can be used as a common currency to asses the extent of health related benefits gained from interventions. Therefore comparisons between interventions can be made to establish priorities and cost benefits. Combining the cost of interventions with the QALY measure creates a cost-utility ratio. A cost-utility ratio indicates the additional cost associated with producing one extra year of perfect health (one QALY). Interventions can therefore be compared by assessing the additional costs for each QALY gained in order to decide which intervention shows the most potential.

7.5.2.2 Population Simulations

Poor adherence to and interruption of treatments can lead to prolonged infectiousness (Volmink and Garner, 2007). Furthermore, if treatment has gone on for long enough for the infectiousness to disappear, the patient can become infectious again if treatment is interrupted (World Health Organization, 2013*d*). In order to test the impact of increased infectiousness and the development of XDR-TB when treatment regimens are interrupted, population simulations should be developed. Population simulations can be used to simulate future trends based on current data. The future trend of new diagnosed XDR-TB and MDR-TB cases due to treatment interruptions and stock-outs can be developed using current data on shortages and rates of infection. These trends can be used to quantify the impact that treatment interruptions have on treatment costs in order to perform a cost-benefit analysis to estimate the amount of savings better inventory management may produce.

List of References

Acar, Y., Kadipasaoglu, S. and Schipperijn, P. (2010). A Decision Support Framework for Global Supply Chain Modelling: An Assessment of the Impact of Demand, Supply and Lead-Time Uncertainties on Performance. *International Journal of Production Research*, vol. 48, no. 11, pp. 3245–3268.

Ahonkhai, V. (2012). Regulatory issues affecting MDR-TB SLDs: Defining the Problem. In: *Institute of Medicine Workshop: Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis*, Washington DC.

Akkermans, H. and Dellaert, N. (2005). The Rediscovery of Industrial Dynamics: The Contribution of System Dynamics to Supply Chain Management in a Dynamic and Fragmented World. *System Dynamics Review*, vol. 21, no. 3, pp. 173–186.

Alrabea, a. (2012). Annual Health Statistics.
Available at: http://www.moh.gov.sa/en/Ministry/Statistics/book/Documents/1433.pdf

Altiok, T. and Melamed, B. (2010). *Simulation Modeling and Analysis with Arena*. Elsevier.

Angerhofer, B.J. and Angelides, M.C. (2000). System Dynamics Modelling in Supply Chain Management: Research review. In: *Proceedings of the 2000 Winter Simulation Conference*, vol. 1, pp. 342–351.

Atun, R. (2012). Challenges and Barriers to Efficient Operation of Existing Supply Chain. In: *Institute of Medicine Workshop: Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant TB*, Washington DC.

Beamon, B.M. (1998). Supply Chain Design and Analysis: Models and Methods. *International Journal of Production Economics*, vol. 55, no. 1, pp. 1–22.

Becker, H.S. (1983). Scenarios. *Technological Forecasting and Social Change*, vol. 23, no. 2, pp. 95–120.

Behdani, B. (2012). Evaluation of Paradigms for Modeling Supply Chains as Complex Socio-Technical Systems. In: *Proceedings - Winter Simulation Conference*, Meadows 1989.

Biswas, S. and Narahari, Y. (2003). Object Oriented Modeling and Decision Support for Supply Chains. *European Journal of Operational Research*, vol. 153, no. 3, pp. 704–726.

Bloom, B.R. (2013). The Global Crisis of MDR-TB. Barriers, Needs and Potential Solutions For the Second Line Drug Supply Chain. In: *Institute of Medicine Workshop: The Global Crisis of Drug-Resistant Tuberculosis and Leadership of China and the BRICS. Challenges and Opportunities.*, Beijing.

Borshchev, A. and Filippov, A. (2004). From System Dynamics and Discrete Event to Practical Agent Based Modeling: Reasons, Techniques, Tools. *The 22nd International Conference of the System Dynamics Society.*

Brailsford, S. and Hilton, N. (2001). A Comparison of Discrete Event Simulation and System Dynamics for Modelling Health Care Systems. In: *Proceedings from ORAHS 2000*, pp. 18–39. University of Southampton.

Campuzano, F. and Mula, J. (2011). *Supply Chain Simulation: A System Dynamics Approach for Improving Performance.* Springer.

Cavana, R. and Maani, K. (2000). *A Methodological Framework for Integrating Systems Thinking and System Dynamics.* 2nd edn. Pearson, Auckland.

CDC (2011). TB Elimination - Diagnosis of Tuberculosis disease. Available at: http://www.cdc.gov/tb/publications/factsheets/testing/diagnosis.pdf

Choi, T.Y., Dooley, K.J. and Rungtusanatham, M. (2001). Supply Networks and Complex Adaptive Systems: Control Versus Emergence. *Journal of Operations Management*, vol. 19, no. 3, pp. 351–366.

Chou, L., Harrington, M., Huff, B., Jefferys, R., Swan, T., Syed, J. and Wingfield, C. (2008). 2008 Pipeline Report : HIV, Tuberculosis, Hepatitis B, and Hepatitis C: Drugs, Diagnostics, Vaccines, and Microbicides in Development. Tech. Rep.

Chung, C.A. (2004). *Simulation Modeling Handbook: A Practical Approach.* CRC Press

Comstock, G. (2012). Learning from Other Models: PEPFAR 's Supply Chain Management System Partnership for Supply Chain Management - Commercial and Non-Profit Organizations. In: *Institute of Medicine Workshop: Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis*, Washington DC.

Cope, D. (2008). *Automatic Generation of Supply Chain Simulation Models From SCOR Based Ontologies.* Ph.D. thesis, University of Central Florida.

Coyle, R. (1983). The Technical Elements of the System Dynamics Approach. *European Journal of Operational Research*, vol. 14, no. 4, pp. 359–370.

Crofton, J., Chaulet, P., Maher, D., Grosset, J., Harris, W., Horne, N., Iseman, M. and Watt, B. (1997). Guidelines for the Management of Drug-Resistant Tuberculosis. Tech. Rep.

Dale Compton, W., Ganjiang, G., Reid, P.P. and Grossman, J.H. (2005). *Building a Better Delivery System: A New Engineering/Health Care Partnership*. National Academies Press.

Deacon, E. (2015). MDR-TB Data Request, E-mail to E. Deacon [Online]. Available at: Eric.Deacon@sita.co.za

Embrey, M. (2012). *Managing Access to Medicines and Health Technologies*. Management Sciences for Health. Tech. Rep.

Falzon, D., Glaziou, P., Jaramillo, E., Mirzayev, F., Nathanson, E., Sismanidis, C., van Gemert, W., Weil, D. and Zignol, M. (2010). Multidrug and Extensively Drug-Resistant TB (M/XDR-TB). Global report on Surveillance and Response. Tech. Rep., World Health Organisation.

Ford, A. (2009). *Modeling the Environment*. 2nd edn. Island Press, Washington DC.

Forrester, J. (1958). Industrial Dynamics: A Major Breakthrough for Decision Makers. *Harvard Business Review*, vol. 36, no. 4, pp. 37–66.

Fraser, H.F. (2012). Information Management Issues. In: *Institute of Medicine Workshop: Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis*, Washington DC.

Giffin, R. and Robinson, S. (2009). Addressing the Threat of Drug-Resistant Tuberculosis: A Realistic Assessment of the Challenge: Summary of a Joint Workshop. Tech. Rep., Washington DC: The National Academies Press.

Global Alliance for TB Drug Development (2013). Economic Impact of TB. Available at: http://www.tballiance.org/why/economic-impact.php

GoldSim Technology Group (2007). Dynamic Simulation and Supply Chain Management. Tech. Rep.

Haghani, A. and Afshar, A. (2009). Supply Chain Management in Disaster Response. Tech. Rep. Department of Civil & Environmental Engineering University of Maryland College: Maryland.

Caliri, G.V. (2010). Introduction to Analytical Separations. Tech. Rep.

Hart, A. (). Tuberculosis in South Africa. Tech. Rep.

Heath, S.K., Brailsford, S.C., Buss, A. and Macal, C.M. (2011). Cross-Paradigm Simulation Modeling: Challenges and Successes. In: *Proceedings - Winter Simulation Conference*, pp. 2783–2797.

Hedman, L. (2012). Quality of 2nd Line Medicines for Tuberculosis. In: *Institute of Medicine Workshop: Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant TB*, Washington DC.

Hoffner, S.E. (2013). MDR, XDR and Untreatable TB from a Laboratory Perspective. In: *Institute of Medicine Workshop: The Global Crisis of Drug-Resistant Tuberculosis and Leadership of China and the BRICS. Challenges and Opportunities*, Beijing.

Hou, B. (2013). Do You Know Your Inventory Carrying Costs? Available at: http://www.opsrules.com/supply-chain-optimization-blog/bid/314279/Do-You-Know-Your-Inventory-Carrying-Costs

Hung, W.Y., Samsatli, N.J. and Shah, N. (2006 March). Object-Oriented Dynamic Supply-Chain Modelling Incorporated with Production Scheduling. *European Journal of Operational Research*, vol. 169, no. 3, pp. 1064–1076.

International Union Against Tuberculosis and Lung Disease (2012). DR-TB Drugs Under the Microscope. Sources and Prices for Drug-Resistant Tuberculosis Medicines. 2nd edition. Tech. Rep.

Ivancevich, J. and Duening, T.N. (2005). Digital Skills. In: *Management: Skills, Application, Practice and Development*, chap. Chapter 5, pp. 119–142. Atomic Dog Publishing.

Kaisler, S. and Madey, G. (2009). Complex Adaptive Systems: Emergence and Self-Organization, University of Notre Dame.

Keating, E.K. (1999). Issues to Consider While Developing a System Dynamics Model. Tech. Rep., Northwestern University.

Keramati, A.A. (2011). Supply Chain Integration: Modelling Approach. In: *European, Mediterranean & Middle Eastern Conference on Information Systems*, vol. 2011, pp. 75–85.

Keshavjee, S. and Seung, K. (2008). Stemming the Tide of Multidrug-Resistant Tuberculosis: Major Barriers to Addressing the Growing Epidemic. A White Paper for the Institute of Medicine of the National Academies. Tech. Rep.

Kimerling, M.E. (2012). SLD Financing Issues. In: *Institute of Medicine Workshop: Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant TB*, Washington DC.

Kleijnen, J.P.C. (2004). Supply Chain Simulation Tools and Techniques: A Survey. *International Journal of Simulation and Process Modelling*.

Lane, D.C. (2000). You Just Don't Understand Me: Modes of Failure and Success in the Discourse between System Dynamics and Discrete Event Simulation. Available at: http://www.lse.ac.uk/collections/operationalResearch/Default.htm

Lane, D.C. and Sterman, J.D. (2011). *Profiles in Operations Research: Jay Wright Forrester*. Springer: New York.

Lawn, S.D. and Nicol, M.P. (2012). Europe PMC Funders Group Xpert MTB / RIF assay: Development , Evaluation and Implementation of a New Rapid Molecular Diagnostic for Tuberculosis and Rifampicin Resistance. In: *Future Microbiol*, vol. 6, no. 9, pp. 1067–1082.

Lessem, E., Becerra, M.C., Ruffinen, C.Z., Mckenna, L., Brigden, G. and Furin, J. (2013). Administering Second-Line Antituberculous Medications to Children with Multidrug-Resistant Tuberculosis: A Qualitative Study. In: *International Workshop on Clinical Pharmacology of Tuberculosis Drugs*.

Lonnroth, K. (2011). Risk Factors and Social Determinants of TB. Tech. Rep., Stop TB Department, World Health Organisation.

Macal, C.M. and North, M.J. (2006). Introduction to Agent-Based Modeling and Simulation. In: *MCS LANS Informal Seminar*.

Macal, C.M. and North, M.J. (2010). Tutorial on Agent-Based Modelling and Simulation. *Journal of Simulation*, vol. 4, no. 3, pp. 151–162.

Min, H. and Zhou, G. (2002 July). Supply Chain Modeling: Past, Present and Future. *Computers and Industrial Engineering*, vol. 43, no. 1-2, pp. 231–249.

Moberg, C.R. and Vitasek, K. (2008). Time to Remodel. In: *Supply Chain Quarterly*.

Mohammadi, M. and Mukhtar, M.B. (2013). A Review of Object-Oriented Approach in Supply Chain Processes. In: *Advance in Information Sciences and Service Sciences*, vol. 5, pp. 9–17.

Morecroft, J.D.W. and Robinson, S. (2005). Explaining Puzzling Dynamics: Comparing the Use of System Dynamics and Discrete-Event Simulation. *Proceedings of the 23rd International Conference of the System Dynamics Society*, p. 115.

Mostaghim, S. (2012). MDR-TB Drugs: Challenges and Barriers to Efficient Operation of Existing Supply Chain. In: *Institute of Medicine Workshop: Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant TB*, Washington DC.

Musango, J.K., Brent, A.C., Jonker, W.D., York, T.A., Oosthuizen, J., Duminy, L. and Kock, I.H.D. (2015). A System Dynamics Approach to Understand the Implications of a Green Economy Transition in the Western Cape Province of South Africa. pp. 1–21.

Nardell, E. (2008). Lack of Institutional Tuberculosis Transmission Control. In: *Institute of Medicine: Addressing the Threat of Drug-Resistant Tuberculosis: A Realistic Assessment of the Challenge*, Washington DC.

Nardell, E. (2013). TB Infection Control Reconsidered (Redesign of Health Care Facilities, Administrative Controls and the Rapid Impact of Effective Treatment on Transmission). In: *Institute of Medicine: The Global Crisis of Drug-Resistant Tuberculosis and Leadership of China and the BRICS. Challenges and Opportunities*, Beijing.

Nason, G. (2006). Stationary and Non-Stationary Time Series. In: *Statistics in Volcanology*, 1994, pp. 129–143.

National Department of Health (2012). *Standard Treatment Guidelines And Essential Medicines List for South Africa*.

National Institute of Allergy and Infectious Diseases (2009). Tuberculosis (TB) Detailed Explanation.
Available at: http://www.niaid.nih.gov/topics/tuberculosis/Understanding/WhatIsTB/pages/detailed.aspx

Nicholson, A., English, R.a., Guenther, R.S. and Anne, B. (2013). Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis: Workshop Summary. Tech. Rep., Washington DC: The National Academies Press.

Nordenberg, D. (2013). Information Systems: Solutions to Enhance Laboratory Capacity in evaluation of New Diagnostics and Therapies. In: *Institute of Medicine Workshop: The Global Crisis of Drug-Resistant Tuberculosis and Leadership of China and the BRICS Challenges and Opportunities*, Beijing.

Olson, S., English, R. and Claiborne, A. (2011). The New Profile of Drug-Resistant Tuberculosis in Russia: a Global and Local Perspective: Summary of a Joint Workshop. Tech. Rep., Washington DC: The National Academies Press.

Olson, S., Lebovitz, Y. and Claiborne, A. (2011a). *The Emerging Threat of Drug-Resistant Tuberculosis in Southern Africa: Global and Local Challenges and Solutions: Summary of a Joint Workshop*. Tech. Rep., Washington DC: The National Academies Press.

Olson, S., English, R., Guenther, R.S. and Claiborne, A.B. (2012). Facing the Reality of Drug- Resistant Tuberculosis in India: Challenges and Potential Solutions: Summary of a Joint Workshop. Tech. Rep., Washington DC: The National Academies Press.

Olson, S., English, R. and Claiborne, A. (2014). The Global Crisis of Drug-Resistant Tuberculosis and Leadership of China and the BRICS Challenges and Opportunities: Summary of a Joint Workshop. Tech. Rep., Washington DC: The National Academies Press.

Owen, M., Albores, P., Greasley, A. and Love, D. (2010). Simulation in the Supply Chain Context: Matching the Simulation Tool to the Problem. In: *Proceedings of the Operational Research Society Simulation Workshop*, vol. 2010, pp. 229–242.

Pathak, S.D., Day, J.M., Nair, A., Sawaya, W.J. and Kristal, M.M. (2007). Complexity and Adaptivity in Supply Networks: Building Supply Network Theory using a Complex Adaptive Systems Perspective. In: *Decision Sciences*, vol. 38, no. 4, pp. 547–580.

Perez-velez, C.M. (2010). Drug-Resistant Tuberculosis in Children: South America Perspective. In: *Forum on Drug Discovery, Development and Translation Institute of Medicine*.

Phanouvong, S., Vrakking, H., Blanc, L., Wondemagegnehu, E., Moore, T., Rago, L., Mboussa, J., Norval, P., and Matji, R. (2002). Operational Guide for Tuberculosis Control Programmes on the Introduction and Use of Fixed-Dose Combination Drugs. Tech. Rep.

Pooran, A., Pieterson, E., Davids, M., Theron, G. and Dheda, K. (2013). What is the Cost of Diagnosis and Management of Drug Resistant Tuberculosis in South Africa? *PLOS ONE*, vol. 8, no. 1.

Poorana Ganga Devi, N.P. and Swaminathan, S. (2013). Drug-Resistant Tuberculosis: Pediatric Guidelines. In: *Current Infectious Disease Reports*, vol. 15, no. 5, pp. 356–363.

Prieto, L. and Sacristán, J. (2003). Problems and Solutions in Calculating Quality-Adjusted Life Years (QALYs). In: *Health and Quality of Life Outcomes*, vol. 1, p. 80.

Pruyt, E. (2007). Dealing with Uncertainties? Combining System Dynamics with Multiple Criteria Decision Analysis or with Exploratory Modelling. Tech. Rep., Delft University of Technology, pp. 1–22.

Randers, J. (1980). *Elements of the System Dynamics Method*. Productivity Press: Portland.

REM Associates (). Methodology of Calculating Inventory Carrying Costs. Tech. Rep., New Jersey.

Rushton, A., Croucher, P., Baker, P.(2010). *The Handbook of Logistics and Distribution Management*. 5th edn. Kogan Page Publishers.

Sargent, R. (1998). Verification and Validation of Simulation Models. In: *1998 Winter Simulation Conference. Proceedings*, vol. 1, no. 1, pp. 12–24.

Schaaf, H.S. (2014). Personal Interview: 7th March 2014. Tygerberg, Stellenbosch.

Shah, N. (2004). Pharmaceutical Supply Chains: Key Issues and Strategies for Optimisation. In: *Computers and Chemical Engineering*, vol. 28, no. 6-7, pp. 929–941.

Simonović, S.P. (2009). *Managing Water Resources. Methods and Tools for a Systems Approach*. UNESCO, London.

Smith, A.D. and Offodile, O.F. (2007). Exploring Forecasting and Project Management Characteristics of Supply Chain Management. In: *International Journal of Logistics Systems and Management*, vol. 3, no. 2, p. 174.

Sparx Systems (2004). The Business Process Model.
Available at: http://www.sparxsystems.com/downloads/whitepapers/The_Business_Process_Model.pdf

Statistics, A.H. (2012). Annual Health Statistics 2012. Tech. Rep.

Sterman, J.D. (2000). *Business Dynamics: Systems Thinking and Modeling for a Complex World*. Irwin McGraw Hill: New York.

Supply Chain Council (2012). *Supply Chain Operations Reference Model*. Tech. Rep.

Surana, A., Kumara, S., Greaves, M. and Raghavan, U.N. (2005). Supply-Chain Networks: A Complex Adaptive Systems Perspective. In: *International Journal of Production Research*, vol. 43, no. 20, pp. 4235–4265.

Tako, A. and Robinson, S. (2012). The Application of Discrete Event Simulation and System Dynamics in the Logistics and Supply Chain Context. In: *Decision Support Systems*, vol. 52, no. 4, pp. 802–815.

Terzi, S. and Cavalieri, S. (2004). Simulation in the Supply Chain Context: A Survey. In: *Computers in Industry*, vol. 53, no. 1, pp. 3–16.

The Global Fund to Fight AIDS Tuberculosis and Malaria (2014). Tuberculosis.
Available at: http://www.theglobalfund.org/en/about/diseases/tuberculosis/

UNITAID (). MDR TB Strategic Rotating Stockpile.
Available at: http://www.unitaid.eu/en/mdr-tb-strategic-rotating-stockpile

UNITAID (2014). About UNITAID.
Available at: http://www.unitaid.eu/en/who/about-unitaid

UNITAID (2015). Innovative Financing Mechanisms.
Available at: http://www.unitaid.eu/en/how/innovative-financing

Van Rie, A., Page-Shipp, L., Scott, L., Sanne, I. and Stevens, W. (2010). Xpert MTB/RIF for Point-of-Care Diagnosis of TB in High-HIV Burden, Resource-Limited Countries: Hype or Hope? In: *Expert Review of Molecular Diagnostics*, vol. 10, no. 7, pp. 937–946.

Ventana Systems Inc (). Vensim.
Available at: http://www.vensim.com

Vermorel, E. (2013). Inventory Costs (ordering costs, carrying costs).
Available at: http://www.lokad.com/definition-inventory-costs

Vincent, C. (2012). USAID ' s Approach to Improve SLD Access. In: *Institute of Medicine Workshop: Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant TB*, Washington DC.

Volmink, J. and Garner, P. (2007). Directly Observed Therapy for Treating Tuberculosis. Tech. Rep.

Wallengren, K., Scano, F., Nunn, P., Margot, B., Buthelezi, S.S.S., Williams, B., Pym, A., Samuel, E.Y., Mirzayev, F., Nkhoma, W., Mvusi, L. and Pillay, Y. (2011). Drug-Resistant Tuberculosis, Kwazulu-Natal, South Africa, 2001-2007. In: *Emerging Infectious Diseases*, vol. 17, no. 10, pp. 1913–1916.

Western Cape Department of Health (WCDoH) (2011). Part 3: Annual Financial Statements. Tech. Rep..

World Bank Group (2015). WorldBank Database. [Health Expenditure, Total (% of GDP)].
Available at: http://data.worldbank.org/indicator/SH.XPD.TOTL.ZS

World Health Organization (2000). DOTS-Plus & Green Light Committee: Improving Access to Second-Line Anti-TB Drugs, Geneva.
Available at: http://www.stoptb.org/assets/documents/resources/publications/technical/DOTS_test4.pdf

World Health Organization (2010). Treatment of Tuberculosis: Guidelines. Tech. Rep.

World Health Organization (2013*a*). Global Tuberculosis Report 2013. Tech. Rep.

World Health Organization (2013*b*). Multidrug-Resistant Tuberculosis (MDR-TB): October 2013 Update.
Available at: http://www.who.int/tb/challenges/mdr/MDR_TB_FactSheet.pdf

World Health Organization (2013*c*). Multidrug-Resistant Tuberculosis (MDR TB): March 2013 Update.
Available at: http://www.who.int/tb/challenges/mdr/MDR_TB_FactSheet.pdf

World Health Organization (2013*d*). TB Elimination: Extensively Drug-Resistant Tuberculosis (XDR-TB).
Available at: http://www.cdc.gov/tb/publications/factsheets/drtb/xdrtb.pdf

World Health Organization (2014). Pursue High-Quality DOTS Expansion and Enhancement.
Available at: http://www.who.int/tb/dots/en/

World Health Organisation (2014). Global Tuberculosis Report 2014. Tech. Rep.

Xu, G., Zong, Y. and Yang, Z. (2013). *Applied Data Mining*. CRC Press.

Yadav, P. (2011). MDR-TB: Challenges in Drug Supply Chain Logistics. In: *Institute of Medicine Workshop: Facing the Reality of Drug- Resistant Tuberculosis in India. Challenges and Potential Solutions*, New Delhi.

Yadav, P. (2012). Supply Chain for MDR-TB. Challenges and Ideas for Improvement. In: *Institute of Medicine Workshop: Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant TB*, Washington DC.

Zhang, Y. and Bhattacharyya, S. (2004). Learning to Order in Supply Networks: An Agent Modelling Study. In: Macal, C., Sallach, D. and North, M. (eds.), *Conference on Social Dynamics: Interaction, Reflexivity and Emergence*, pp. 703–715. Chigago.

Appendices

Appendix A

List of MDR-TB SLDs

Table A.1: MDR-TB SLDs stocked at the CMD

Drug Name
Amikacin sulphate injection 500mg;2ml;1's
Capreomycin 1g injection;10ml
Clofazimine capsules 100mg;100's
Ethambutol hydrochloride tablets 400mg;100's
Ethambutol hydrochloride tablets PRP 400mg;84's
Ethambutol hydrochloride, RIF, INH & pyrazinamide tablets 275, 150, 75, 400mg;500's
Ethambutol hydrochloride, RIF, INH & pyrazinamide tablets PRP 275, 150, 75, 400mg;100's
Ethambutol hydrochloride, RIF, INH & pyrazinamide tablets PRP 275, 150, 75, 400mg;112's
Ethambutol hydrochloride, RIF, INH & pyrazinamide tablets PRP 275, 150, 75, 400mg;28's
Ethambutol hydrochloride, RIF, INH & pyrazinamide tablets PRP 275, 150, 75, 400mg;40's
Ethambutol hydrochloride, RIF, INH & pyrazinamide tablets PRP 275, 150, 75, 400mg;56's
Ethambutol hydrochloride, RIF, INH & pyrazinamide tablets PRP 275, 150, 75, 400mg;60's
Ethambutol hydrochloride, RIF, INH & pyrazinamide tablets PRP 275, 150, 75, 400mg;80's
Ethambutol hydrochloride, RIF, INH & pyrazinamide tablets PRP 275, 150, 75, 400mg;84's
Kanamycin injection 1g;3ml;1's
Kanamycin injection 1g/3ml
Levofloxacin hemihydrate tablets 250mg;28's
Levofloxacin hemihydrate tablets 250mg;30's
Levofloxacin hemihydrate tablets 250mg;5's
Moxifloxacin hydrochloride tablets 400mg;30's
Moxifloxacin hydrochloride tablets 400mg;5's
Ofloxacin tablets 200mg;10's
Ofloxacin tablets PRP 200mg;28's
Ofloxacin tablets PRP 400mg;28's
Ofloxacin tablets PRP 400mg;56's
Para-amino salicylic acid 4g;30's
Terizidone capsules 250mg;100's

Appendix B

SDM Document

Documentation of SLD Supply Chain Model

View the 86 variables sorted by type, module, group, variable name, module/group/name, Level Structure, or in a view summary.

Model Assessment Results

Model Information	Number
Total Number of Variables	86
Total Number of State Variables (Level+Smooth+Delay Variables)	26
Total Number of Stocks (Stocks in Level+Smooth+Delay Variables) †	78
Total Number of Macros	0
Function Sensitivity Parameters	0
Variables with Source Information	0
Data Lookup Tables	0
Time Unit	Month
Initial Time	0
Final Time	120
Reported Time Interval	1
Time Step	0.03125
Model Is Fully Formulated	Yes
Modeler-Defined Groups	- No -
VPM File Available	- No -

Warnings	Number
Undocumented Equations	0
Equations with Embedded Data	39
Equations With Unit Errors or Warnings	Unavailable
Variables Not in Any View	0
Incompletely Defined Subscripted Variables	0
Nonmonotonic Lookup Functions	1
Cascading (Chained) Lookup Functions	0
Equations with IF...THEN...ELSE	10
Equations with MIN or MAX	0

Potential Omissions	Number
Unused Variables	0
Supplementary Variables	5
Supplementary Variables Being Used	0
Complex Variable Formulations (Richardson's Rule = 3)	11
Complex Stock Formulations	0

Types:				
L : Level (12 / 36) *	SM : Smooth (0 / 0) *	DE : Delay (14 / 42) * †	LI : Level Initial (0)	I : Initial (0)
C : Constant (25)	F : Flow (11)	A : Auxiliary (33)	Sub: Subscripts (1)	D : Data (0)
G : Game (0)	T : Lookup (2 / 4) ††			

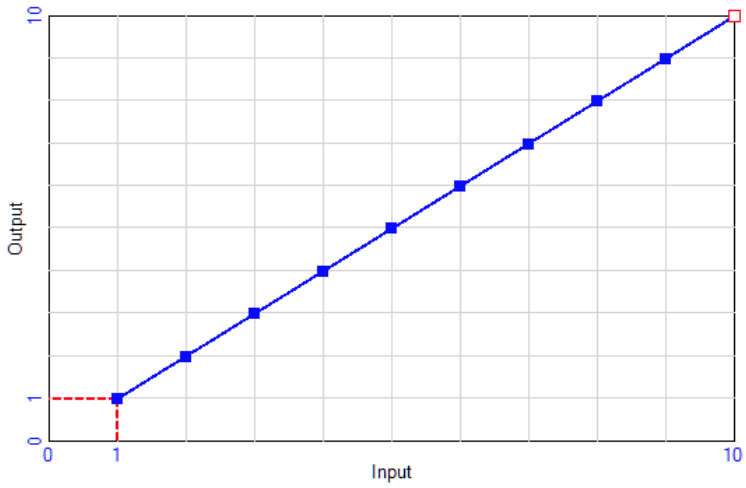
* (state variables / total stocks)
† Total stocks do not include fixed delay variables.
†† (lookup variables / lookup tables).

Groups:	Control (4) Simulation Control Parameters	SLD Supply Chain Model (82) (Default)			
Modules:	Default (86)				
Views:	View 1 (77)	COST (31)	View 3 (0)		

TOP View 1 (77 variables)

Module	Group	Type	Variable Name and Description
Default	SLD Supply	C	3 month historical data (Dmnl) = 3

	Chain Model (Default)		Description: Months historical data Present in 1 view: • View 1 Used by: • Average consumption - Average comsumption based on previous 3 months • Average demand - Average demand based on previous 3 months
Default	SLD Supply Chain Model (Default)	DE	8 month delay (drugs/Month) 8 month delay [Drugs] = DELAY FIXED (CMD order backlogs[Drugs] , 8 , 0) Description: 8 months following a shortage Present in 1 view: • View 1 Used by: • Total backlog - Total backlogs per month
Default	SLD Supply Chain Model (Default)	C	Adjust time 1 (Month) = 1 Description: Time for unit adjustment Present in 2 views: • View 1 • COST Used by: • CMD demand - The demand from the CMD • Drugs to health facility - Drugs that are dispatched to health facilities • Inventory position - Inventory position • Monthly holding costs - Monthly holding costs
Default	SLD Supply Chain Model (Default)	C	Amikacin expiration time (Month) = 30 Description: Amikacin shelf life Present in 1 view: • View 1 Used by: • Expiration time - Time left for amikacin in the CMD
Default	SLD Supply Chain Model (Default)	A	Average consumption (drugs/Month) Average consumption[Drugs] = (Delay 1a[Drugs]+Delay 2a[Drugs]+Delay 3a[Drugs])/3 month historical data Description: Average comsumption based on previous 3 months Present in 1 view: • View 1 Used by: • CMD demand - The demand from the CMD • Safety stock - Safety stock calculations • Standard deviation of consumption - Standard deviation of consumption
Default	SLD Supply Chain Model (Default)	A	Average demand (drugs/Month) Average demand[Drugs] = (Delay 1[Drugs]+Delay 2[Drugs]+Delay 3[Drugs])/3 month historical data Description: Average demand based on previous 3 months Present in 1 view: • View 1 Used by: • CMD max months - Upper desired stock level used • CMD min months - Lower desired stock level used • Reorder point - Point where inventory should be ordered
Default	SLD Supply Chain Model (Default)	L	Average LOOKUP = [(0,0)-(10,10)],(1,1),(2,2),(3,3),(4,4),(5,5),(6,6),(7,7),(8,8),(9,9),(10,10),(11,11),(12,12),(13,13),(14,14),(15,15),(16,16),(17,17),(18,18),(19,19),(20,20),(21,21),(22,22),(23,23),(24,24),(25,25),(26,26),(27,27),(28,28),(29,29),(30,30),(31,31),(32,32),(33,33),(34,34),(35,35),(36,36),(37,37),(38,38),(39,39),(40,40),(41,41),(42,42),(43,43),(44,44),(45,45),(46,46),(47,47),(48,48),(49,49),(50,50),(51,51),(52,52),(53,53),(54,54),(55,55),(56,56),(57,57),(58,58),(59,59),(60,60),(61,61),(62,62),(63,63),(64,64),(65,65),(66,66),(67,67),(68,68),(69,69),(70,70),(71,71),(72,72),(73,73),(74,74),(75,75),(76,76),(77,77),(78,78),(79,79),(80,80),(81,81),(82,82),(83,83),(84,84),(85,85),(86,86),(87,87),(88,88),(89,89),(90,90),(91,91),(92,92),(93,93),(94,94),(95,95),(96,96),(97,97),(98,98),(99,99),(100,100),(101,101),(102,102),(103,103),(104,104),(105,105),(106,106),

			(107,107),(108,108),(109,109),(110,110),(111,111),(112,112),(113,113),(114,114),(115,115),(116,116),(117,117),(118,118),(119,119),(120,120) Description: Y=x graph to calculate average demand Present in 1 view: • View 1 Used by: • Overall average consumption - Average consumption over the 10 years • Overall average demand - Average demand over the 10 years 
Default	SLD Supply Chain Model (Default)	C	Average supplier lead time (Month) Average supplier lead time[Drugs] = 1.2 Description: Average supplier lead time for amikacin Present in 1 view: • View 1 Used by: • Safety stock - Safety stock calculations
Default	SLD Supply Chain Model (Default)	A	Backlogged time (Month) Backlogged time[Drugs] = IF THEN ELSE(CMD order backlogs[Drugs]>0, Time, 0) Description: Time of backlogs Present in 2 views: • View 1 • COST Used by: • Replacement therapy - Replacement therapy regime
Default	SLD Supply Chain Model (Default)	F,A	CMD demand (drugs/Month) CMD demand[Drugs] = IF THEN ELSE(Inventory position[Drugs]>Reorder point[Drugs] , 0, IF THEN ELSE((((Average consumption[Drugs]*CMD max months[Drugs])-Inventory position[Drugs]+Safety stock[Drugs])/Adjust time 1)>=0,(((Average consumption[Drugs]*CMD max months[Drugs])+Safety stock[Drugs]-Inventory position[Drugs])/Adjust time 1),0)) Description: The demand from the CMD Present in 1 view: • View 1 Used by: • Cumulative CMD demand - Total CMD demand • Monthly CMD demand - CMD monthly demand
Default	SLD Supply Chain Model	L	CMD inventory on hand (drugs) CMD inventory on hand[Drugs] = ∫(Drugs to CMD inventory[Drugs]-Drugs to health facility[Drugs]-Monthly obsolete stock[Drugs]) dt + [5050] Description: CMD inventory on hand

	(Default)		Present in 2 views: • View 1 • COST Used by: • Drugs to health facility - Drugs that are dispatched to health facilities • Inventory position - Inventory position • Monthly holding costs - Monthly holding costs • Monthly obsolete stock - Monthly expired stock
Default	SLD Supply Chain Model (Default)	C	CMD max intermediate (Month) = 4 Description: Intermediate upper desired stock level Present in 1 view: • View 1 Used by: • CMD max months - Upper desired stock level used
Default	SLD Supply Chain Model (Default)	C	CMD max lower (Month) = 4 Description: Min upper desired stock level Present in 1 view: • View 1 Used by: • CMD max months - Upper desired stock level used
Default	SLD Supply Chain Model (Default)	C,A	CMD max months (Month) CMD max months[AMK] = IF THEN ELSE(Average demand[AMK]>(3*Overall average consumption[AMK]), CMD max upper, IF THEN ELSE(Average demand[AMK]>Overall average consumption[AMK],CMD max intermediate , CMD max lower)) CMD max months[EMB HCL] = 4 CMD max months[KM] = 4 Description: Upper desired stock level used Present in 1 view: • View 1 Used by: • CMD demand - The demand from the CMD
Default	SLD Supply Chain Model (Default)	C	CMD max upper (Month) = 4 Description: Max upper desired stock level Present in 1 view: • View 1 Used by: • CMD max months - Upper desired stock level used
Default	SLD Supply Chain Model (Default)	C	CMD min intermediate (Month) = 2 Description: Intermediate lower desired stock level Present in 1 view: • View 1 Used by: • CMD min months - Lower desired stock level used
Default	SLD Supply Chain Model (Default)	C	CMD min lower (Month) = 2 Description: Min lower desired stock level Present in 1 view: • View 1 Used by: • CMD min months - Lower desired stock level used
Default	SLD Supply Chain Model (Default)	A	CMD min months (Month) CMD min months[Drugs] = IF THEN ELSE(Average demand[AMK]>(2*Overall average demand[AMK]),CMD min upper , IF THEN ELSE(Average demand[AMK]>Overall average demand[AMK],CMD min intermediate , CMD min lower)) Description: Lower desired stock level used

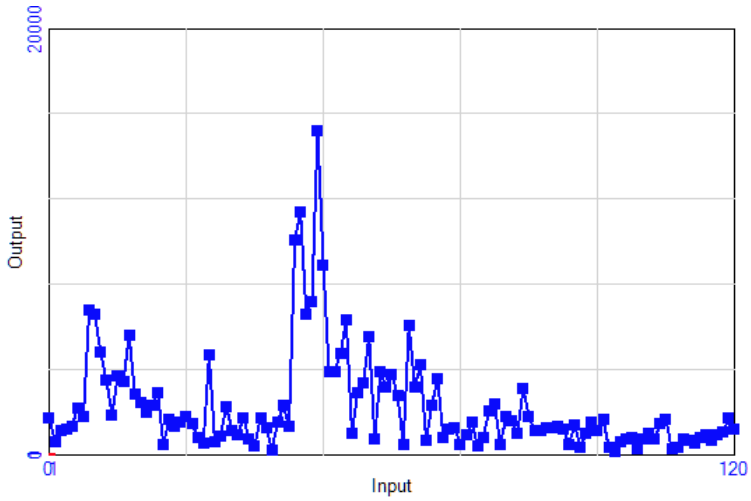
			Present in 1 view: • View 1 Used by: • Reorder point - Point where inventory should be ordered
Default	SLD Supply Chain Model (Default)	C	CMD min upper (Month) = 2 Description: Max lower desired stock level Present in 1 view: • View 1 Used by: • CMD min months - Lower desired stock level used
Default	SLD Supply Chain Model (Default)	A	CMD order backlogs (drugs/Month) CMD order backlogs[Drugs] = Health facility demand[Drugs]-Monthly delivery of drugs to health facility[Drugs] Description: Number of shortages per month Present in 1 view: • View 1 Used by: • 8 month delay - 8 months following a shortage • Backlogged time - Time of backlogs • delay A - 1 month delay • delay B - 2 month delay • delay C - 3 month delay • delay D - 4 month delay • delay E - 5 month delay • delay F - 6 month delay • delay G - 7 month delay • Inventory position - Inventory position
Default	SLD Supply Chain Model (Default)	L	CMD Orders (drugs) CMD Orders[Drugs] = ∫(Monthly CMD demand[Drugs]-Drugs to CMD inventory[Drugs]) dt + [8080] Description: Orders created by the CMD Present in 1 view: • View 1 Used by: • Drugs to CMD inventory - Drugs sent to the CMD • Inventory position - Inventory position
Default	SLD Supply Chain Model (Default)	L	Cumulative CMD demand (drugs) Cumulative CMD demand[Drugs] = ∫CMD demand[Drugs] dt + [0] Description: Total CMD demand Present in 1 view: • View 1 Used by: This is a supplementary variable.
Default	SLD Supply Chain Model (Default)	L	Cumulative CMD order backlogs (drugs) Cumulative CMD order backlogs[Drugs] = ∫Health facility demand[Drugs]-Monthly delivery of drugs to health facility[Drugs] dt + [0] Description: Total number of shortages over 10 years Present in 1 view: • View 1 Used by: This is a supplementary variable.
Default	SLD Supply Chain Model (Default)	L	Cumulative demand (drugs) Cumulative demand[Drugs] = ∫Health facility demand[Drugs] dt + [0] Description: Total demand over the 10 years Present in 1 view: • View 1

			Used by: • Overall average demand - Average demand over the 10 years
Default	SLD Supply Chain Model (Default)	L	Cumulative drugs to health facility (drugs) Cumulative drugs to health facility[Drugs] = ∫Drugs to health facility[Drugs] dt + [0] Description: Total drugs dispatched to health facilities over the 10 years Present in 1 view: • View 1 Used by: • Overall average consumption - Average consumption over the 10 years
Default	SLD Supply Chain Model (Default)	C	Degrees of freedom (Dmnl) = 120 Description: Degrees of freedom for standard deviation Present in 1 view: • View 1 Used by: • Standard deviation of consumption - Standard deviation of consumption
Default	SLD Supply Chain Model (Default)	DE	Delay 1 (drugs/Month) Delay 1[Drugs] = DELAY FIXED (Health facility demand[Drugs], 1, 0) Description: 1 month delay Present in 1 view: • View 1 Used by: • Average demand - Average demand based on previous 3 months • Safety stock - Safety stock calculations
Default	SLD Supply Chain Model (Default)	DE	Delay 1a (drugs/Month) Delay 1a[Drugs] = DELAY FIXED (Drugs to health facility[Drugs] , 1 , 0) Description: 1 month delay Present in 1 view: • View 1 Used by: • Average consumption - Average comsumption based on previous 3 months • Standard deviation of consumption - Standard deviation of consumption
Default	SLD Supply Chain Model (Default)	DE	Delay 2 (drugs/Month) Delay 2[Drugs] = DELAY FIXED (Health facility demand[Drugs] ,2 , 0) Description: 2 month delay Present in 1 view: • View 1 Used by: • Average demand - Average demand based on previous 3 months
Default	SLD Supply Chain Model (Default)	DE	Delay 2a (drugs/Month) Delay 2a[Drugs] = DELAY FIXED (Drugs to health facility[Drugs], 2 , 0) Description: 2 month delay Present in 1 view: • View 1 Used by: • Average consumption - Average comsumption based on previous 3 months • Standard deviation of consumption - Standard deviation of consumption
Default	SLD Supply Chain Model (Default)	DE	Delay 3 (drugs/Month) Delay 3[Drugs] = DELAY FIXED (Health facility demand[Drugs] , 3 , 0) Description: 3 month delay Present in 1 view: • View 1 Used by: • Average demand - Average demand based on previous 3 months
Default	SLD Supply Chain Model	DE	Delay 3a (drugs/Month) Delay 3a[Drugs] = DELAY FIXED (Drugs to health facility[Drugs] , 3 , 0) Description: 3 month delay Present in 1 view:

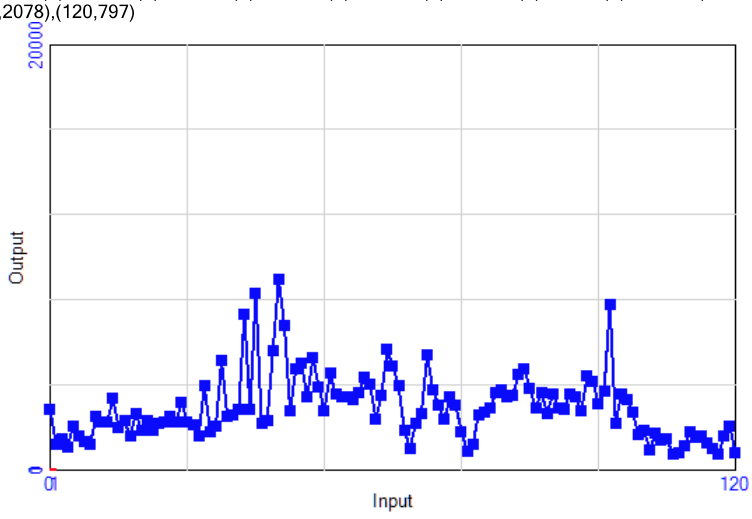
	(Default)		• View 1 Used by: • Average consumption - Average comsumption based on previous 3 months • Standard deviation of consumption - Standard deviation of consumption
Default	SLD Supply Chain Model (Default)	DE	delay A (drugs/Month) delay A[Drugs] = DELAY FIXED (CMD order backlogs[Drugs] , 1 , 0) Description: 1 month delay Present in 1 view: • View 1 Used by: • Total backlog - Total backlogs per month
Default	SLD Supply Chain Model (Default)	DE	delay B (drugs/Month) delay B[Drugs] = DELAY FIXED (CMD order backlogs[Drugs] , 2 , 0) Description: 2 month delay Present in 1 view: • View 1 Used by: • Total backlog - Total backlogs per month
Default	SLD Supply Chain Model (Default)	DE	delay C (drugs/Month) delay C[Drugs] = DELAY FIXED (CMD order backlogs[Drugs] , 3 , 0) Description: 3 month delay Present in 1 view: • View 1 Used by: • Total backlog - Total backlogs per month
Default	SLD Supply Chain Model (Default)	DE	delay D (drugs/Month) delay D[Drugs] = DELAY FIXED (CMD order backlogs[Drugs] , 4 , 0) Description: 4 month delay Present in 1 view: • View 1 Used by: • Total backlog - Total backlogs per month
Default	SLD Supply Chain Model (Default)	DE	delay E (drugs/Month) delay E[Drugs] = DELAY FIXED (CMD order backlogs[Drugs] , 5 , 0) Description: 5 month delay Present in 1 view: • View 1 Used by: • Total backlog - Total backlogs per month
Default	SLD Supply Chain Model (Default)	DE	delay F (drugs/Month) delay F[Drugs] = DELAY FIXED (CMD order backlogs[Drugs] , 6 , 0) Description: 6 month delay Present in 1 view: • View 1 Used by: • Total backlog - Total backlogs per month
Default	SLD Supply Chain Model (Default)	DE	delay G (drugs/Month) delay G[Drugs] = DELAY FIXED (CMD order backlogs[Drugs] , 7 , 0) Description: 7 month delay Present in 1 view: • View 1 Used by: • Total backlog - Total backlogs per month
Default	SLD Supply Chain Model	Sub [sub]	Drugs : AMK, EMB HCL, KM Description: Different types of drugs Present in 2 views:

	(Default)		• View 1 • COST Used by: • 8 month delay - 8 months following a shortage • Average consumption - Average comsumption based on previous 3 months • Average demand - Average demand based on previous 3 months • Backlogged time - Time of backlogs • Base therapy - Cost of base therapy per month • CMD demand - The demand from the CMD • CMD inventory on hand - CMD inventory on hand • CMD max months - Upper desired stock level used • CMD min months - Lower desired stock level used • CMD order backlogs - Number of shortages per month • CMD Orders - Orders created by the CMD • Cumulative CMD demand - Total CMD demand • Cumulative CMD order backlogs - Total number of shortages over 10 years • Cumulative demand - Total demand over the 10 years • Cumulative drugs to health facility - Total drugs dispatched to health facilities over the 10 years • Cumulative holding costs - Total holding costs • Cumulative obsolescence costs - Total obsolescence costs • Delay 1 - 1 month delay • Delay 1a - 1 month delay • Delay 2 - 2 month delay • Delay 2a - 2 month delay • Delay 3 - 3 month delay • Delay 3a - 3 month delay • delay A - 1 month delay • delay B - 2 month delay • delay C - 3 month delay • delay D - 4 month delay • delay E - 5 month delay • delay F - 6 month delay • delay G - 7 month delay • Drugs to CMD inventory - Drugs sent to the CMD • Drugs to health facility - Drugs that are dispatched to health facilities • Expiration time - Time left for amikacin in the CMD • Health facility demand - Demand from health facilities • Inventory position - Inventory position • Monthly CMD demand - CMD monthly demand • Monthly delivery of drugs to health facility - Drugs delivered monthly to health facilities • Monthly holding costs - Monthly holding costs • Monthly obsolete stock - Monthly expired stock • Obsolescence costs - Monthly obsolescence costs • Obsolete stock - Expired stock • Overall average consumption - Average consumption over the 10 years • Overall average demand - Average demand over the 10 years • Pulse increase in demand - Increases in demand to test for agility • Reorder point - Point where inventory should be ordered • Replacement therapy - Replacement therapy regime • Safety stock - Safety stock calculations • Shortage costs - Shortage costs • Standard deviation of consumption - Standard deviation of consumption • Total backlog - Total backlogs per month • Total cost of base therapy - Total cost of base therapy • Total cost of replacement therapy - Total cost of replacement therapy • Total costs - Total costs over 10 year period • Total inventory - Total inventory
Default	SLD Supply Chain Model (Default)	F,A 	Drugs to CMD inventory (drugs/Month) Drugs to CMD inventory[Drugs] = IF THEN ELSE(CMD Orders[Drugs]>0 , (CMD Orders[Drugs]*Supplier reliability[Drugs])/Supplier lead time[Drugs],0) Description: Drugs sent to the CMD Present in 1 view: • View 1 Used by: • CMD inventory on hand - CMD inventory on hand • CMD Orders - Orders created by the CMD • Total inventory - Total inventory
Default	SLD	F,A	Drugs to health facility (drugs/Month)

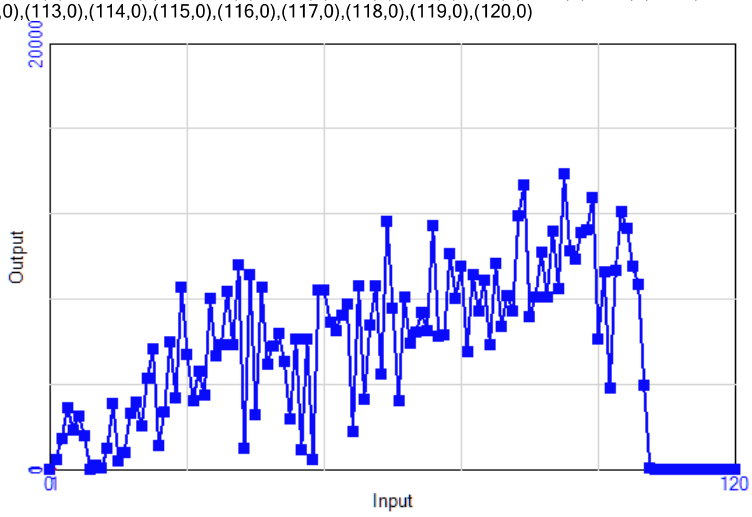
	Supply Chain Model (Default)		Drugs to health facility[Drugs] = IF THEN ELSE(CMD inventory on hand[Drugs]/Adjust time 1-Health facility demand[Drugs]>=0, Health facility demand[Drugs], IF THEN ELSE((CMD inventory on hand[Drugs]>0), (CMD inventory on hand[Drugs]/Adjust time 1), 0)) Description: Drugs that are dispatched to health facilities Present in 2 views: • View 1 • COST Used by: • CMD inventory on hand - CMD inventory on hand • Cumulative drugs to health facility - Total drugs dispatched to health facilities over the 10 years • Delay 1a - 1 month delay • Delay 2a - 2 month delay • Delay 3a - 3 month delay • Inventory position - Inventory position • Monthly delivery of drugs to health facility - Drugs delivered monthly to health facilities • Replacement therapy - Replacement therapy regime
Default	SLD Supply Chain Model (Default)	A 	Expiration time (Month) Expiration time[Drugs] = Amikacin expiration time-Supplier lead time[Drugs] Description: Time left for amikacin in the CMD Present in 1 view: • View 1 Used by: • Monthly obsolete stock - Monthly expired stock
Default	SLD Supply Chain Model (Default)	F,A	Health facility demand (drugs/Month) Health facility demand[Drugs] = Health facility demand LOOKUP[Drugs](Time)+Pulse increase in demand[Drugs] Description: Demand from health facilities Present in 2 views: • View 1 • COST Used by: • Base therapy - Cost of base therapy per month • CMD order backlogs - Number of shortages per month • Cumulative CMD order backlogs - Total number of shortages over 10 years • Cumulative demand - Total demand over the 10 years • Delay 1 - 1 month delay • Delay 2 - 2 month delay • Delay 3 - 3 month delay • Drugs to health facility - Drugs that are dispatched to health facilities • Replacement therapy - Replacement therapy regime • Safety stock - Safety stock calculations
Default	SLD Supply Chain Model (Default)	L 	Health facility demand LOOKUP (drugs/Month) Health facility demand LOOKUP[AMK] = [(0,0)-(120,20000)],(0,1740),(1,640),(2,1150),(3,1210),(4,1350),(5,2230),(6,1790),(7,6840),(8,6580),(9,4820),(10,3550),(11,1900),(12,3700),(13,3480),(14,5620),(15,2870),(16,2470),(17,1990),(18,2320),(19,2940),(20,490),(21,1700),(22,1370),(23,1550),(24,1810),(25,1480),(26,850),(27,590),(28,4690),(29,610),(30,900),(31,2300),(32,1170),(33,920),(34,1760),(35,750),(36,430),(37,1770),(38,1250),(39,250),(40,1540),(41,2320),(42,1340),(43,10090),(44,11400),(45,6630),(46,7180),(47,15240),(48,8940),(49,3880),(50,3910),(51,4790),(52,6340),(53,1030),(54,2930),(55,3390),(56,5570),(57,770),(58,3940),(59,3180),(60,3790),(61,2800),(62,460),(63,6110),(64,3200),(65,4230),(66,710),(67,2340),(68,3600),(69,830),(70,1200),(71,1260),(72,500),(73,970),(74,1551),(75,430),(76,850),(77,2050),(78,2370),(79,490),(80,1800),(81,1580),(82,1040),(83,3140),(84,1810),(85,1140),(86,1130),(87,1250),(88,1290),(89,1360),(90,1240),(91,490),(92,1410),(93,360),(94,1040),(95,1560),(96,1120),(97,1680),(98,350),(99,182),(100,600),(101,770),(102,810),(103,280),(104,770),(105,1020),(106,730),(107,1490),(108,1650),(109,290),(110,380),(111,730),(112,690),(113,530),(114,800),(115,950),(116,700),(117,970),(118,1060),(119,1718),(120,1190)



Health facility demand LOOKUP[EMB HCL] = [(0,0)-(120,20000)],(0,2883),(1,1204),(2,1465),
(3,1070),(4,2069),(5,1596),(6,1360),(7,1202),(8,2500),(9,2287),(10,2280),(11,3374),(12,1996),
(13,2327),(14,1582),(15,2660),(16,1866),(17,2342),(18,1872),(19,2220),(20,2257),(21,2523),
(22,2258),(23,3184),(24,2236),(25,2110),(26,1610),(27,4006),(28,1784),(29,2054),(30,5167),
(31,2534),(32,2586),(33,2833),(34,7346),(35,2837),(36,8344),(37,2187),(38,2315),(39,5609),
(40,8998),(41,6827),(42,2783),(43,4737),(44,5042),(45,3419),(46,5310),(47,3926),(48,2807),
(49,4551),(50,3556),(51,3452),(52,3457),(53,3301),(54,3645),(55,4372),(56,4046),(57,2384),
(58,3491),(59,5664),(60,4867),(61,3977),(62,1898),(63,1032),(64,2189),(65,2649),(66,5441),
(67,3779),(68,3045),(69,2385),(70,3424),(71,3026),(72,1837),(73,881),(74,1217),(75,2628),
(76,2701),(77,2935),(78,3618),(79,3780),(80,3434),(81,3514),(82,4522),(83,4764),(84,3831),
(85,2944),(86,3659),(87,2681),(88,3556),(89,2944),(90,2891),(91,3608),(92,3443),(93,2769),
(94,4423),(95,4166),(96,3109),(97,3735),(98,7765),(99,2202),(100,3560),(101,3351),(102,2696),
(103,1683),(104,1847),(105,958),(106,1742),(107,1382),(108,1470),(109,762),(110,822),
(111,1123),(112,1782),(113,1531),(114,1642),(115,1313),(116,1035),(117,765),(118,1629),
(119,2078),(120,797)



Health facility demand LOOKUP[KM] = [(0,0)-(120,20000)],(0,0),(1,520),(2,1450),(3,2930),
(4,1900),(5,2560),(6,1600),(7,30),(8,240),(9,110),(10,1010),(11,3100),(12,400),(13,800),
(14,2660),(15,3180),(16,2064),(17,4280),(18,5675),(19,1140),(20,2750),(21,6000),(22,3400),
(23,8610),(24,5440),(25,3260),(26,4611),(27,3510),(28,8042),(29,5359),(30,5915),(31,8397),
(32,5877),(33,9648),(34,1027),(35,9151),(36,2586),(37,8556),(38,4980),(39,5805),(40,6428),
(41,5110),(42,2370),(43,6180),(44,982),(45,6160),(46,480),(47,8450),(48,8440),(49,6920),

			(50,6540),(51,7260),(52,7770),(53,1810),(54,8660),(55,3350),(56,6780),(57,8660),(58,4490), (59,11700),(60,7590),(61,3230),(62,8110),(63,5920),(64,6450),(65,7370),(66,6560),(67,11470), (68,6310),(69,6350),(70,10160),(71,8090),(72,9580),(73,5560),(74,9155),(75,7470),(76,8900), (77,5890),(78,9700),(79,6740),(80,8200),(81,7480),(82,11930),(83,13400),(84,7230),(85,8130), (86,10230),(87,8150),(88,11240),(89,8550),(90,13880),(91,10300),(92,9900),(93,11150), (94,11250),(95,12820),(96,6150),(97,9310),(98,3870),(99,9380),(100,12120),(101,11340), (102,9590),(103,8720),(104,3950),(105,70),(106,0),(107,0),(108,0),(109,0),(110,0),(111,0), (112,0),(113,0),(114,0),(115,0),(116,0),(117,0),(118,0),(119,0),(120,0)  Description: Real values for health facility demand Present in 1 view: • View 1 Used by: • Health facility demand - Demand from health facilities • Pulse increase in demand - Increases in demand to test for agility
Default	SLD Supply Chain Model (Default)	A	Inventory position (drugs) Inventory position[Drugs] = (CMD inventory on hand[Drugs]+CMD Orders[Drugs]-(CMD order backlogs[Drugs]*Adjust time 1)-Drugs to health facility[Drugs]*Adjust time 1) Description: Inventory position Present in 1 view: • View 1 Used by: • CMD demand - The demand from the CMD
Default	SLD Supply Chain Model (Default)	F,A	Monthly CMD demand (drugs/Month) Monthly CMD demand[Drugs] = CMD demand[Drugs] Description: CMD monthly demand Present in 1 view: • View 1 Used by: • CMD Orders - Orders created by the CMD
Default	SLD Supply Chain Model (Default)	F,A	Monthly delivery of drugs to health facility (drugs/Month) Monthly delivery of drugs to health facility[Drugs] = Drugs to health facility[Drugs] Description: Drugs delivered monthly to health facilities Present in 1 view: • View 1 Used by: • CMD order backlogs - Number of shortages per month • Cumulative CMD order backlogs - Total number of shortages over 10 years
Default	SLD	F,A	Monthly obsolete stock (drugs/Month)

	Supply Chain Model (Default)		Monthly obsolete stock[Drugs] = IF THEN ELSE(CMD inventory on hand[Drugs]>0 ,CMD inventory on hand[Drugs]/Expiration time[Drugs],0) Description: Monthly expired stock Present in 2 views: • View 1 • COST Used by: • CMD inventory on hand - CMD inventory on hand • Obsolescence costs - Monthly obsolescence costs • Obsolete stock - Expired stock
Default	SLD Supply Chain Model (Default)		Obsolete stock (drugs) Obsolete stock[Drugs] = ∫Monthly obsolete stock[Drugs] dt + [0] Description: Expired stock Present in 1 view: • View 1 Used by: This is a supplementary variable.
Default	SLD Supply Chain Model (Default)	A 	Overall average consumption (drugs/Month) Overall average consumption[Drugs] = Cumulative drugs to health facility[Drugs]/Average LOOKUP(Time) Description: Average consumption over the 10 years Present in 1 view: • View 1 Used by: • CMD max months - Upper desired stock level used
Default	SLD Supply Chain Model (Default)	A 	Overall average demand (drugs/Month) Overall average demand[Drugs] = Cumulative demand[Drugs]/Average LOOKUP(Time) Description: Average demand over the 10 years Present in 1 view: • View 1 Used by: • CMD min months - Lower desired stock level used
Default	SLD Supply Chain Model (Default)	C 	Production cycle (1/Month) = 3 Description: Production cycle Present in 1 view: • View 1 Used by: • Safety stock - Safety stock calculations
Default	SLD Supply Chain Model (Default)	A 	Pulse increase in demand (drugs/Month) Pulse increase in demand[Drugs] = (STEP(Health facility demand LOOKUP[Drugs](Time)*1, 60))*0 Description: Increases in demand to test for agility Present in 1 view: • View 1 Used by: • Health facility demand - Demand from health facilities
Default	SLD Supply Chain Model (Default)	A 	Reorder point (drugs) Reorder point[Drugs] = (Average demand[Drugs]*CMD min months[Drugs])+Safety stock[Drugs] Description: Point where inventory should be ordered Present in 1 view: • View 1 Used by: • CMD demand - The demand from the CMD
Default	SLD Supply Chain Model	A 	Safety stock (drugs) Safety stock[Drugs] = (Z-score*SQRT((Average supplier lead time[Drugs]/Production cycle*Standard deviation of consumption[Drugs]^2)+(Average consumption[Drugs]^2*Standard deviation of lead time^2)))*0+4000*0+IF THEN ELSE(Health facility demand[Drugs]>Delay

	(Default)		1[Drugs]:AND:Delay 1[Drugs]>0, ((Health facility demand[Drugs]-Delay 1[Drugs])/Delay 1[Drugs])*Health facility demand[Drugs] , 0) Description: Safety stock calculations Present in 1 view: • View 1 Used by: • CMD demand - The demand from the CMD • Reorder point - Point where inventory should be ordered
Default	SLD Supply Chain Model (Default)	A	Standard deviation of consumption (drugs/Month) Standard deviation of consumption[Drugs] = SQRT(((Delay 1a[Drugs]-Average consumption[Drugs])^2+(Delay 2a[Drugs]-Average consumption[Drugs])^2+(Delay 3a[Drugs]-Average consumption[Drugs])^2)/Degrees of freedom) Description: Standard deviation of consumption Present in 1 view: • View 1 Used by: • Safety stock - Safety stock calculations
Default	SLD Supply Chain Model (Default)	C	Standard deviation of lead time (Month) = 1.18 Description: Standard deviation of lead time Present in 1 view: • View 1 Used by: • Safety stock - Safety stock calculations
Default	SLD Supply Chain Model (Default)	C	Supplier lead time (Month) Supplier lead time[AMK] = 0.25 Supplier lead time[EMB HCL] = 3 Supplier lead time[KM] = 2 Description: Supplier lead time Present in 1 view: • View 1 Used by: • Drugs to CMD inventory - Drugs sent to the CMD • Expiration time - Time left for amikacin in the CMD
Default	SLD Supply Chain Model (Default)	C	Supplier reliability (Dmnl) Supplier reliability[AMK] = 0.98 Supplier reliability[EMB HCL] = 0.9 Supplier reliability[KM] = 0.9 Description: Supplier reliability Present in 1 view: • View 1 Used by: • Drugs to CMD inventory - Drugs sent to the CMD
Default	SLD Supply Chain Model (Default)	A	Total backlog (drugs/Month) Total backlog[Drugs] = (delay A[Drugs]+delay B[Drugs]+delay C[Drugs]+delay D[Drugs]+delay E[Drugs]+delay F[Drugs]+delay G[Drugs]+"8 month delay"[Drugs]) Description: Total backlogs per month Present in 2 views: • View 1 • COST Used by: • Monthly holding costs - Monthly holding costs • Replacement therapy - Replacement therapy regime
Default	SLD Supply Chain Model (Default)	L	Total inventory (drugs) Total inventory[Drugs] = ∫Drugs to CMD inventory[Drugs] dt + [0] Description: Total inventory Present in 1 view: • View 1 Used by: This is a supplementary variable.

Default	SLD Supply Chain Model (Default)	C	Z-score (Dmnl) = 1.65 Description: Z-Score Present in 1 view: • View 1 Used by: • Safety stock - Safety stock calculations
TOP	COST (31 variables)		
Module	Group	Type	Variable Name and Description
Default	SLD Supply Chain Model (Default)	C	Adjust time 1 (Month) = 1 Description: Time for unit adjustment Present in 2 views: • View 1 • COST Used by: • CMD demand - The demand from the CMD • Drugs to health facility - Drugs that are dispatched to health facilities • Inventory position - Inventory position • Monthly holding costs - Monthly holding costs
Default	SLD Supply Chain Model (Default)	C	Amikacin price per unit (Dollar/drugs) = 2.06 Description: Cost per amikacin unit Present in 1 view: • COST Used by: • Amikacin warehouse cost - Cost to hold amikacin in warehouse • Base therapy - Cost of base therapy per month • Cost of amikacin - Total cost of amikacin • Obsolescence costs - Monthly obsolescence costs • Replacement therapy - Replacement therapy regime
Default	SLD Supply Chain Model (Default)	A	Amikacin warehouse cost (Dollar/drugs) = Amikacin price per unit*Warehousing cost Description: Cost to hold amikacin in warehouse Present in 1 view: • COST Used by: • Monthly holding costs - Monthly holding costs
Default	SLD Supply Chain Model (Default)	A	Backlogged time (Month) Backlogged time[Drugs] = IF THEN ELSE(CMD order backlogs[Drugs]>0, Time, 0) Description: Time of backlogs Present in 2 views: • View 1 • COST Used by: • Replacement therapy - Replacement therapy regime
Default	SLD Supply Chain Model (Default)	F,A	Base therapy (Dollar/Month) Base therapy[Drugs] = Amikacin price per unit*Health facility demand[Drugs] Description: Cost of base therapy per month Present in 1 view: • COST Used by: • Total cost of base therapy - Total cost of base therapy
Default	SLD Supply Chain Model (Default)	C	Capreomycin price per unit (Dollar/drugs) = 6.25 Description: Cost of capreomycin per unit Present in 1 view: • COST

			Used by: • Capreomycin warehouse cost - Cost to hold capreomycin in warehouse • Cost of capreomycin - Total cost of capreomycin
Default	SLD Supply Chain Model (Default)	A	Capreomycin warehouse cost (Dollar/drugs) = Capreomycin price per unit*Warehousing cost Description: Cost to hold capreomycin in warehouse Present in 1 view: • COST Used by: • Monthly holding costs - Monthly holding costs
Default	SLD Supply Chain Model (Default)	L	CMD inventory on hand (drugs) CMD inventory on hand[Drugs] = ∫(Drugs to CMD inventory[Drugs]-Drugs to health facility[Drugs]-Monthly obsolete stock[Drugs]) dt + [5050] Description: CMD inventory on hand Present in 2 views: • View 1 • COST Used by: • Drugs to health facility - Drugs that are dispatched to health facilities • Inventory position - Inventory position • Monthly holding costs - Monthly holding costs • Monthly obsolete stock - Monthly expired stock
Default	SLD Supply Chain Model (Default)	A	Cost of amikacin (Dollar/drugs) = Amikacin price per unit*Percent patients on amikacin Description: Total cost of amikacin Present in 1 view: • COST Used by: • Replacement therapy - Replacement therapy regime
Default	SLD Supply Chain Model (Default)	A	Cost of capreomycin (Dollar/drugs) = Capreomycin price per unit*Percent patients on capreomycin Description: Total cost of capreomycin Present in 1 view: • COST Used by: • Replacement therapy - Replacement therapy regime
Default	SLD Supply Chain Model (Default)	L	Cumulative holding costs (Dollar) Cumulative holding costs[Drugs] = ∫Monthly holding costs[Drugs] dt + [0] Description: Total holding costs Present in 1 view: • COST Used by: • Total costs - Total costs over 10 year period
Default	SLD Supply Chain Model (Default)	L	Cumulative obsolescence costs (Dollar) Cumulative obsolescence costs[Drugs] = ∫Obsolescence costs[Drugs] dt + [0] Description: Total obsolescence costs Present in 1 view: • COST Used by: • Total costs - Total costs over 10 year period
Default	SLD Supply Chain Model (Default)	Sub [sub]	Drugs : AMK, EMB HCL, KM Description: Different types of drugs Present in 2 views: • View 1 • COST Used by:

			• 8 month delay - 8 months following a shortage • Average consumption - Average comsumption based on previous 3 months • Average demand - Average demand based on previous 3 months • Backlogged time - Time of backlogs • Base therapy - Cost of base therapy per month • CMD demand - The demand from the CMD • CMD inventory on hand - CMD inventory on hand • CMD max months - Upper desired stock level used • CMD min months - Lower desired stock level used • CMD order backlogs - Number of shortages per month • CMD Orders - Orders created by the CMD • Cumulative CMD demand - Total CMD demand • Cumulative CMD order backlogs - Total number of shortages over 10 years • Cumulative demand - Total demand over the 10 years • Cumulative drugs to health facility - Total drugs dispatched to health facilities over the 10 years • Cumulative holding costs - Total holding costs • Cumulative obsolescence costs - Total obsolescence costs • Delay 1 - 1 month delay • Delay 1a - 1 month delay • Delay 2 - 2 month delay • Delay 2a - 2 month delay • Delay 3 - 3 month delay • Delay 3a - 3 month delay • delay A - 1 month delay • delay B - 2 month delay • delay C - 3 month delay • delay D - 4 month delay • delay E - 5 month delay • delay F - 6 month delay • delay G - 7 month delay • Drugs to CMD inventory - Drugs sent to the CMD • Drugs to health facility - Drugs that are dispatched to health facilities • Expiration time - Time left for amikacin in the CMD • Health facility demand - Demand from health facilities • Inventory position - Inventory position • Monthly CMD demand - CMD monthly demand • Monthly delivery of drugs to health facility - Drugs delivered monthly to health facilities • Monthly holding costs - Monthly holding costs • Monthly obsolete stock - Monthly expired stock • Obsolescence costs - Monthly obsolescence costs • Obsolete stock - Expired stock • Overall average consumption - Average consumption over the 10 years • Overall average demand - Average demand over the 10 years • Pulse increase in demand - Increases in demand to test for agility • Reorder point - Point where inventory should be ordered • Replacement therapy - Replacement therapy regime • Safety stock - Safety stock calculations • Shortage costs - Shortage costs • Standard deviation of consumption - Standard deviation of consumption • Total backlog - Total backlogs per month • Total cost of base therapy - Total cost of base therapy • Total cost of replacement therapy - Total cost of replacement therapy • Total costs - Total costs over 10 year period • Total inventory - Total inventory
Default	SLD Supply Chain Model (Default)	F,A 	Drugs to health facility (drugs/Month) Drugs to health facility[Drugs] = IF THEN ELSE(CMD inventory on hand[Drugs]/Adjust time 1- Health facility demand[Drugs]>=0, Health facility demand[Drugs], IF THEN ELSE((CMD inventory on hand[Drugs]>0), (CMD inventory on hand[Drugs]/Adjust time 1), 0)) Description: Drugs that are dispatched to health facilities Present in 2 views: • View 1 • COST Used by: • CMD inventory on hand - CMD inventory on hand • Cumulative drugs to health facility - Total drugs dispatched to health facilities over the 10 years • Delay 1a - 1 month delay • Delay 2a - 2 month delay • Delay 3a - 3 month delay

			• Inventory position - Inventory position • Monthly delivery of drugs to health facility - Drugs delivered monthly to health facilities • Replacement therapy - Replacement therapy regime
Default	SLD Supply Chain Model (Default)	F,A	Health facility demand (drugs/Month) Health facility demand[Drugs] = Health facility demand LOOKUP[Drugs](Time)+Pulse increase in demand[Drugs] Description: Demand from health facilities Present in 2 views: • View 1 • COST Used by: • Base therapy - Cost of base therapy per month • CMD order backlogs - Number of shortages per month • Cumulative CMD order backlogs - Total number of shortages over 10 years • Cumulative demand - Total demand over the 10 years • Delay 1 - 1 month delay • Delay 2 - 2 month delay • Delay 3 - 3 month delay • Drugs to health facility - Drugs that are dispatched to health facilities • Replacement therapy - Replacement therapy regime • Safety stock - Safety stock calculations
Default	SLD Supply Chain Model (Default)	F,A	Monthly holding costs (Dollar/Month) Monthly holding costs[Drugs] = (IF THEN ELSE(Total backlog[Drugs]>0 , CMD inventory on hand[Drugs]*(Capreomycin warehouse cost*Percent patients on capreomycin +Amikacin warehouse cost*Percent patients on amikacin) , (CMD inventory on hand[Drugs]*Amikacin warehouse cost)))/Adjust time 1 Description: Monthly holding costs Present in 1 view: • COST Used by: • Cumulative holding costs - Total holding costs
Default	SLD Supply Chain Model (Default)	F,A	Monthly obsolete stock (drugs/Month) Monthly obsolete stock[Drugs] = IF THEN ELSE(CMD inventory on hand[Drugs]>0 ,CMD inventory on hand[Drugs]/Expiration time[Drugs],0) Description: Monthly expired stock Present in 2 views: • View 1 • COST Used by: • CMD inventory on hand - CMD inventory on hand • Obsolescence costs - Monthly obsolescence costs • Obsolete stock - Expired stock
Default	SLD Supply Chain Model (Default)	F,A	Obsolescence costs (Dollar/Month) Obsolescence costs[Drugs] = Monthly obsolete stock[Drugs]*Amikacin price per unit Description: Monthly obsolescence costs Present in 1 view: • COST Used by: • Cumulative obsolescence costs - Total obsolescence costs
Default	SLD Supply Chain Model (Default)	C	Percent patients on amikacin (Dmnl) = 0.47 Description: Percent of patients on amikacin for 8 months Present in 1 view: • COST Used by: • Cost of amikacin - Total cost of amikacin • Monthly holding costs - Monthly holding costs • Percent patients on capreomycin - Percent of patients on capreomycin for 8 months
Default	SLD Supply Chain	A	Percent patients on capreomycin (Dmnl) = 1-Percent patients on amikacin Description: Percent of patients on capreomycin for 8 months

	Model (Default)		Present in 1 view: • COST Used by: • Cost of capreomycin - Total cost of capreomycin • Monthly holding costs - Monthly holding costs
Default	SLD Supply Chain Model (Default)	F,A	Replacement therapy (Dollar/Month) Replacement therapy[Drugs] = IF THEN ELSE(Total backlog[Drugs]>0,IF THEN ELSE(Health facility demand[Drugs]>Total backlog[Drugs] ,((Health facility demand[Drugs]-Total backlog[Drugs])*Amikacin price per unit)+Total backlog[Drugs]*(Cost of amikacin+Cost of capreomycin) ,Health facility demand[Drugs]*(Cost of amikacin+Cost of capreomycin)),IF THEN ELSE(Backlogged time[Drugs]=Time:AND:Backlogged time[Drugs]>0 , Drugs to health facility[Drugs]*Amikacin price per unit ,Health facility demand[Drugs]*Amikacin price per unit)) Description: Replacement therapy regime Present in 1 view: • COST Used by: • Total cost of replacement therapy - Total cost of replacement therapy
Default	SLD Supply Chain Model (Default)	A	Shortage costs (Dollar) Shortage costs[Drugs] = (Total cost of replacement therapy[Drugs]-Total cost of base therapy[Drugs]) Description: Shortage costs Present in 1 view: • COST Used by: • Total costs - Total costs over 10 year period
Default	SLD Supply Chain Model (Default)	A	Total backlog (drugs/Month) Total backlog[Drugs] = (delay A[Drugs]+delay B[Drugs]+delay C[Drugs]+delay D[Drugs]+delay E[Drugs]+delay F[Drugs]+delay G[Drugs]+"8 month delay"[Drugs]) Description: Total backlogs per month Present in 2 views: • View 1 • COST Used by: • Monthly holding costs - Monthly holding costs • Replacement therapy - Replacement therapy regime
Default	SLD Supply Chain Model (Default)	L	Total cost of base therapy (Dollar) Total cost of base therapy[Drugs] = ∫Base therapy[Drugs] dt + [0] Description: Total cost of base therapy Present in 1 view: • COST Used by: • Shortage costs - Shortage costs
Default	SLD Supply Chain Model (Default)	L	Total cost of replacement therapy (Dollar) Total cost of replacement therapy[Drugs] = ∫Replacement therapy[Drugs] dt + [0] Description: Total cost of replacement therapy Present in 1 view: • COST Used by: • Shortage costs - Shortage costs
Default	SLD Supply Chain Model (Default)	A	Total costs (Dollar) Total costs[Drugs] = Cumulative holding costs[Drugs]+Cumulative obsolescence costs[Drugs]+Shortage costs[Drugs] Description: Total costs over 10 year period Present in 1 view: • COST Used by: This is a supplementary variable.

Default	SLD Supply Chain Model (Default)	C VAB	Warehousing cost (Dmnl) = 0.25 Description: Holding costs Present in 1 view: • COST Used by: • Amikacin warehouse cost - Cost to hold amikacin in warehouse • Capreomycin warehouse cost - Cost to hold capreomycin in warehouse

TOP View 3 (0 variables)

Module	Group	Type	Variable Name and Description

List of 5 Supplementary Variables

Module	Group	Type	Variable (5)
Default	SLD Supply Chain Model	L	Cumulative CMD demand (drugs)
Default	SLD Supply Chain Model	L	Cumulative CMD order backlogs (drugs)
Default	SLD Supply Chain Model	L	Obsolete stock (drugs)
Default	SLD Supply Chain Model	A	Total costs (Dollar)
Default	SLD Supply Chain Model	L	Total inventory (drugs)

List of 1 Non-Monotonic Lookup Function

Module	Group	Type	Variable (1)
Default	SLD Supply Chain Model	L	Health facility demand LOOKUP (drugs/Month)

List of 10 Variables Using IF...THEN...ELSE Functions

Module	Group	Type	Variable (0)
Default	SLD Supply Chain Model	A	Backlogged time (Month)
Default	SLD Supply Chain Model	F,A	CMD demand (drugs/Month)
Default	SLD Supply Chain Model	C,A	CMD max months (Month)
Default	SLD Supply Chain Model	A	CMD min months (Month)
Default	SLD Supply Chain Model	F,A	Drugs to CMD inventory (drugs/Month)
Default	SLD Supply Chain Model	F,A	Drugs to health facility (drugs/Month)
Default	SLD Supply Chain Model	F,A	Monthly holding costs (Dollar/Month)
Default	SLD Supply Chain Model	F,A	Monthly obsolete stock (drugs/Month)
Default	SLD Supply Chain Model	F,A	Replacement therapy (Dollar/Month)
Default	SLD Supply Chain Model	A	Safety stock (drugs)

Formulation Complexity Summary (Violations of Richardson's Rule)

Module	Group	Type	Variable	Complexity Score
Default	SLD Supply Chain Model	A	Average demand (drugs/Month)	4
Default	SLD Supply Chain Model	A	Average consumption (drugs/Month)	4
Default	SLD Supply Chain Model	A	CMD min months (Month)	5
Default	SLD Supply Chain Model	C,A	CMD max months (Month)	5
Default	SLD Supply Chain Model	A	Standard deviation of consumption (drugs/Month)	5
Default	SLD Supply Chain Model	A	Inventory position (drugs)	5
Default	SLD Supply Chain Model	F,A	CMD demand (drugs/Month)	6
Default	SLD Supply Chain Model	F,A	Monthly holding costs (Dollar/Month)	7
Default	SLD Supply Chain Model	F,A	Replacement therapy (Dollar/Month)	7
Default	SLD Supply Chain Model	A	Total backlog (drugs/Month)	8
Default	SLD Supply Chain Model	A	Safety stock (drugs)	8

List of 39 Equations with Embedded Data

Module	Group	Type	Variable (39)
Default	SLD Supply Chain Model	DE	8 month delay (drugs/Month)
Default	SLD Supply Chain Model	A	Backlogged time (Month)
Default	SLD Supply Chain Model	F,A	CMD demand (drugs/Month)
Default	SLD Supply Chain Model	L	CMD inventory on hand (drugs)
Default	SLD Supply Chain Model	C,A	CMD max months (Month)
Default	SLD Supply Chain Model	A	CMD min months (Month)
Default	SLD Supply Chain Model	L	CMD Orders (drugs)
Default	SLD Supply Chain Model	L	Cumulative CMD demand (drugs)
Default	SLD Supply Chain Model	L	Cumulative CMD order backlogs (drugs)
Default	SLD Supply Chain Model	L	Cumulative demand (drugs)

Default	SLD Supply Chain Model	L	Cumulative drugs to health facility (drugs)
Default	SLD Supply Chain Model	L	Cumulative holding costs (Dollar)
Default	SLD Supply Chain Model	L	Cumulative obsolescence costs (Dollar)
Default	SLD Supply Chain Model	DE	Delay 1 (drugs/Month)
Default	SLD Supply Chain Model	DE	Delay 1a (drugs/Month)
Default	SLD Supply Chain Model	DE	Delay 2 (drugs/Month)
Default	SLD Supply Chain Model	DE	Delay 2a (drugs/Month)
Default	SLD Supply Chain Model	DE	Delay 3 (drugs/Month)
Default	SLD Supply Chain Model	DE	Delay 3a (drugs/Month)
Default	SLD Supply Chain Model	DE	delay A (drugs/Month)
Default	SLD Supply Chain Model	DE	delay B (drugs/Month)
Default	SLD Supply Chain Model	DE	delay C (drugs/Month)
Default	SLD Supply Chain Model	DE	delay D (drugs/Month)
Default	SLD Supply Chain Model	DE	delay E (drugs/Month)
Default	SLD Supply Chain Model	DE	delay F (drugs/Month)
Default	SLD Supply Chain Model	DE	delay G (drugs/Month)
Default	SLD Supply Chain Model	F,A	Drugs to CMD inventory (drugs/Month)
Default	SLD Supply Chain Model	F,A	Drugs to health facility (drugs/Month)
Default	SLD Supply Chain Model	F,A	Monthly holding costs (Dollar/Month)
Default	SLD Supply Chain Model	F,A	Monthly obsolete stock (drugs/Month)
Default	SLD Supply Chain Model	L	Obsolete stock (drugs)
Default	SLD Supply Chain Model	A	Percent patients on capreomycin (Dmnl)
Default	SLD Supply Chain Model	A	Pulse increase in demand (drugs/Month)
Default	SLD Supply Chain Model	F,A	Replacement therapy (Dollar/Month)
Default	SLD Supply Chain Model	A	Safety stock (drugs)
Default	SLD Supply Chain Model	A	Standard deviation of consumption (drugs/Month)
Default	SLD Supply Chain Model	L	Total cost of base therapy (Dollar)
Default	SLD Supply Chain Model	L	Total cost of replacement therapy (Dollar)
Default	SLD Supply Chain Model	L	Total inventory (drugs)

List of 26 State Variables

Module	Group	Type	Variable
Default	SLD Supply Chain Model	DE	8 month delay (drugs/Month)
Default	SLD Supply Chain Model	L	CMD inventory on hand (drugs)
Default	SLD Supply Chain Model	L	CMD Orders (drugs)
Default	SLD Supply Chain Model	L	Cumulative CMD demand (drugs)
Default	SLD Supply Chain Model	L	Cumulative CMD order backlogs (drugs)
Default	SLD Supply Chain Model	L	Cumulative demand (drugs)
Default	SLD Supply Chain Model	L	Cumulative drugs to health facility (drugs)
Default	SLD Supply Chain Model	L	Cumulative holding costs (Dollar)
Default	SLD Supply Chain Model	L	Cumulative obsolescence costs (Dollar)
Default	SLD Supply Chain Model	DE	Delay 1 (drugs/Month)
Default	SLD Supply Chain Model	DE	Delay 1a (drugs/Month)
Default	SLD Supply Chain Model	DE	Delay 2 (drugs/Month)
Default	SLD Supply Chain Model	DE	Delay 2a (drugs/Month)
Default	SLD Supply Chain Model	DE	Delay 3 (drugs/Month)
Default	SLD Supply Chain Model	DE	Delay 3a (drugs/Month)
Default	SLD Supply Chain Model	DE	delay A (drugs/Month)
Default	SLD Supply Chain Model	DE	delay B (drugs/Month)
Default	SLD Supply Chain Model	DE	delay C (drugs/Month)
Default	SLD Supply Chain Model	DE	delay D (drugs/Month)
Default	SLD Supply Chain Model	DE	delay E (drugs/Month)
Default	SLD Supply Chain Model	DE	delay F (drugs/Month)
Default	SLD Supply Chain Model	DE	delay G (drugs/Month)
Default	SLD Supply Chain Model	L	Obsolete stock (drugs)
Default	SLD Supply Chain Model	L	Total cost of base therapy (Dollar)
Default	SLD Supply Chain Model	L	Total cost of replacement therapy (Dollar)
Default	SLD Supply Chain Model	L	Total inventory (drugs)

List of 2 Views and Their 87 Variables*

	View 1	COST	
Total:	77	31	:Total
3 month historical data (in 1 view)	X		3 month historical data (in 1 view)
8 month delay (in 1 view)	X		8 month delay (in 1 view)
Adjust time 1 (in 2 views)	X	X	Adjust time 1 (in 2 views)

Amikacin expiration time (in 1 view)	X		Amikacin expiration time (in 1 view)
Amikacin price per unit (in 1 view)		X	Amikacin price per unit (in 1 view)
Amikacin warehouse cost (in 1 view)		X	Amikacin warehouse cost (in 1 view)
Average consumption (in 1 view)	X		Average consumption (in 1 view)
Average demand (in 1 view)	X		Average demand (in 1 view)
Average LOOKUP (in 1 view)	X		Average LOOKUP (in 1 view)
Average supplier lead time (in 1 view)	X		Average supplier lead time (in 1 view)
Backlogged time (in 2 views)	X	X	Backlogged time (in 2 views)
Base therapy (in 1 view)		X	Base therapy (in 1 view)
Capreomycin price per unit (in 1 view)		X	Capreomycin price per unit (in 1 view)
Capreomycin warehouse cost (in 1 view)		X	Capreomycin warehouse cost (in 1 view)
CMD demand (in 1 view)	X		CMD demand (in 1 view)
CMD inventory on hand (in 2 views)	X	X	CMD inventory on hand (in 2 views)
CMD max intermediate (in 1 view)	X		CMD max intermediate (in 1 view)
CMD max lower (in 1 view)	X		CMD max lower (in 1 view)
CMD max months (in 1 view)	X		CMD max months (in 1 view)
CMD max upper (in 1 view)	X		CMD max upper (in 1 view)
CMD min intermediate (in 1 view)	X		CMD min intermediate (in 1 view)
CMD min lower (in 1 view)	X		CMD min lower (in 1 view)
CMD min months (in 1 view)	X		CMD min months (in 1 view)
CMD min upper (in 1 view)	X		CMD min upper (in 1 view)
CMD order backlogs (in 1 view)	X		CMD order backlogs (in 1 view)
CMD Orders (in 1 view)	X		CMD Orders (in 1 view)
Cost of amikacin (in 1 view)		X	Cost of amikacin (in 1 view)
Cost of capreomycin (in 1 view)		X	Cost of capreomycin (in 1 view)
Cumulative CMD demand (in 1 view)	X		Cumulative CMD demand (in 1 view)
Cumulative CMD order backlogs (in 1 view)	X		Cumulative CMD order backlogs (in 1 view)
Cumulative demand (in 1 view)	X		Cumulative demand (in 1 view)
Cumulative drugs to health facility (in 1 view)	X		Cumulative drugs to health facility (in 1 view)
Cumulative holding costs (in 1 view)		X	Cumulative holding costs (in 1 view)
Cumulative obsolescence costs (in 1 view)		X	Cumulative obsolescence costs (in 1 view)
Degrees of freedom (in 1 view)	X		Degrees of freedom (in 1 view)
Delay 1 (in 1 view)	X		Delay 1 (in 1 view)
Delay 1a (in 1 view)	X		Delay 1a (in 1 view)
Delay 2 (in 1 view)	X		Delay 2 (in 1 view)
Delay 2a (in 1 view)	X		Delay 2a (in 1 view)
Delay 3 (in 1 view)	X		Delay 3 (in 1 view)
Delay 3a (in 1 view)	X		Delay 3a (in 1 view)
delay A (in 1 view)	X		delay A (in 1 view)
delay B (in 1 view)	X		delay B (in 1 view)
delay C (in 1 view)	X		delay C (in 1 view)
delay D (in 1 view)	X		delay D (in 1 view)
delay E (in 1 view)	X		delay E (in 1 view)
delay F (in 1 view)	X		delay F (in 1 view)
delay G (in 1 view)	X		delay G (in 1 view)
Drugs (in 2 views)	X	X	Drugs (in 2 views)
Drugs to CMD inventory (in 1 view)	X		Drugs to CMD inventory (in 1 view)
Drugs to health facility (in 2 views)	X	X	Drugs to health facility (in 2 views)
Expiration time (in 1 view)	X		Expiration time (in 1 view)
FINAL TIME (in 0 views)			FINAL TIME (in 0 views)
Health facility demand (in 2 views)	X	X	Health facility demand (in 2 views)
Health facility demand LOOKUP (in 1 view)	X		Health facility demand LOOKUP (in 1 view)
INITIAL TIME (in 0 views)			INITIAL TIME (in 0 views)
Inventory position (in 1 view)	X		Inventory position (in 1 view)
Monthly CMD demand (in 1 view)	X		Monthly CMD demand (in 1 view)
Monthly delivery of drugs to health facility (in 1 view)	X		Monthly delivery of drugs to health facility (in 1 view)
Monthly holding costs (in 1 view)		X	Monthly holding costs (in 1 view)
Monthly obsolete stock (in 2 views)	X	X	Monthly obsolete stock (in 2 views)
Obsolescence costs (in 1 view)		X	Obsolescence costs (in 1 view)
Obsolete stock (in 1 view)	X		Obsolete stock (in 1 view)
Overall average consumption (in 1 view)	X		Overall average consumption (in 1 view)
Overall average demand (in 1 view)	X		Overall average demand (in 1 view)
Percent patients on amikacin (in 1 view)		X	Percent patients on amikacin (in 1 view)
Percent patients on capreomycin (in 1 view)		X	Percent patients on capreomycin (in 1 view)
Production cycle (in 1 view)	X		Production cycle (in 1 view)
Pulse increase in demand (in 1 view)	X		Pulse increase in demand (in 1 view)
Reorder point (in 1 view)	X		Reorder point (in 1 view)

Replacement therapy (in 1 view)		X	Replacement therapy (in 1 view)
Safety stock (in 1 view)	X		Safety stock (in 1 view)
SAVEPER (in 0 views)			SAVEPER (in 0 views)
Shortage costs (in 1 view)		X	Shortage costs (in 1 view)
Standard deviation of consumption (in 1 view)	X		Standard deviation of consumption (in 1 view)
Standard deviation of lead time (in 1 view)	X		Standard deviation of lead time (in 1 view)
Supplier lead time (in 1 view)	X		Supplier lead time (in 1 view)
Supplier reliability (in 1 view)	X		Supplier reliability (in 1 view)
Time (in 2 views)	X	X	Time (in 2 views)
TIME STEP (in 0 views)			TIME STEP (in 0 views)
Total backlog (in 2 views)	X	X	Total backlog (in 2 views)
Total cost of base therapy (in 1 view)		X	Total cost of base therapy (in 1 view)
Total cost of replacement therapy (in 1 view)		X	Total cost of replacement therapy (in 1 view)
Total costs (in 1 view)		X	Total costs (in 1 view)
Total inventory (in 1 view)	X		Total inventory (in 1 view)
Warehousing cost (in 1 view)		X	Warehousing cost (in 1 view)
Z-score (in 1 view)	X		Z-score (in 1 view)
Total:	77	31	:Total
	View 1	COST	

* Includes Time, if used in a view. Excludes variables not present in any view.

Level Structure †

CMD inventory on hand[Drugs] = ∫(Drugs to CMD inventory[Drugs]-Drugs to health facility[Drugs]-Monthly obsolete stock[Drugs]) dt + [5050]
Drugs : AMK, EMB HCL, KM
Drugs to CMD inventory[Drugs] = IF THEN ELSE(CMD Orders[Drugs]>0 , (CMD Orders[Drugs]*Supplier reliability[Drugs])/Supplier lead time[Drugs],0)
Drugs to health facility[Drugs] = IF THEN ELSE(CMD inventory on hand[Drugs]/Adjust time 1-Health facility demand[Drugs]>=0, Health facility demand[Drugs], IF THEN ELSE((CMD inventory on hand[Drugs]>0), (CMD inventory on hand[Drugs]/Adjust time 1), 0))
Monthly obsolete stock[Drugs] = IF THEN ELSE(CMD inventory on hand[Drugs]>0 ,CMD inventory on hand[Drugs]/Expiration time[Drugs],0)

CMD Orders[Drugs] = ∫(Monthly CMD demand[Drugs]-Drugs to CMD inventory[Drugs]) dt + [8080]
Monthly CMD demand[Drugs] = CMD demand[Drugs]

Cumulative CMD demand[Drugs] = ∫CMD demand[Drugs] dt + [0]
CMD demand[Drugs] = IF THEN ELSE(Inventory position[Drugs]>Reorder point[Drugs] , 0, IF THEN ELSE((((Average consumption[Drugs]*CMD max months[Drugs])-Inventory position[Drugs]+Safety stock[Drugs])/Adjust time 1)>=0,(((Average consumption[Drugs]*CMD max months[Drugs])+Safety stock[Drugs]-Inventory position[Drugs])/Adjust time 1),0))

Cumulative CMD order backlogs[Drugs] = ∫Health facility demand[Drugs]-Monthly delivery of drugs to health facility[Drugs] dt + [0]
Health facility demand[Drugs] = Health facility demand LOOKUP[Drugs](Time)+Pulse increase in demand[Drugs]
Monthly delivery of drugs to health facility[Drugs] = Drugs to health facility[Drugs]

Cumulative demand[Drugs] = ∫Health facility demand[Drugs] dt + [0]

Cumulative drugs to health facility[Drugs] = ∫Drugs to health facility[Drugs] dt + [0]

Cumulative holding costs[Drugs] = ∫Monthly holding costs[Drugs] dt + [0]
Monthly holding costs[Drugs] = (IF THEN ELSE(Total backlog[Drugs]>0 , CMD inventory on hand[Drugs]*(Capreomycin warehouse cost*Percent patients on capreomycin +Amikacin warehouse cost*Percent patients on amikacin) , (CMD inventory on hand[Drugs]*Amikacin warehouse cost)))/Adjust time 1

Cumulative obsolescence costs[Drugs] = ∫Obsolescence costs[Drugs] dt + [0]
Obsolescence costs[Drugs] = Monthly obsolete stock[Drugs]*Amikacin price per unit

Obsolete stock[Drugs] = ∫Monthly obsolete stock[Drugs] dt + [0]

Total cost of base therapy[Drugs] = ∫Base therapy[Drugs] dt + [0]
Base therapy[Drugs] = Amikacin price per unit*Health facility demand[Drugs]

Total cost of replacement therapy[Drugs] = ∫Replacement therapy[Drugs] dt + [0]

Replacement therapy[Drugs] = IF THEN ELSE(Total backlog[Drugs]>0,IF THEN ELSE(Health facility demand[Drugs]>Total backlog[Drugs] ,((Health facility demand[Drugs]-Total backlog[Drugs])*Amikacin price per unit)+Total backlog[Drugs]*(Cost of amikacin+Cost of capreomycin) ,Health facility demand[Drugs]*(Cost of amikacin+Cost of capreomycin)),IF THEN ELSE(Backlogged time[Drugs]=Time:AND:Backlogged time[Drugs]>0 , Drugs to health facility[Drugs]*Amikacin price per unit ,Health facility demand[Drugs]*Amikacin price per unit))

Total inventory[Drugs] = ∫Drugs to CMD inventory[Drugs] dt + [0]

† Level Structure Report still under development.

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Argonne National Laboratory