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Evaluation of vaccines cold chain monitoring during distribution from litha vaccines to the medical depots in Gauteng

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EVALUATION OF VACCINES COLD CHAIN MONITORING DURING DISTRIBUTION FROM LITHA VACCINES® TO THE MEDICAL DEPOTS IN GAUTENG

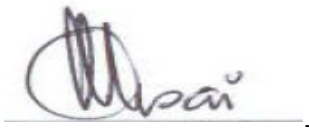
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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science in Medicine, Pharmaceutical Affairs

Johannesburg, 2016

DECLARATION

I Princess Mmaphuti Mosai, declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Master of Science in Medicine, Pharmaceutical Affairs at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



02nd day of November 2016 in Johannesburg

DEDICATION

This work is dedicated to:

My loving husband Themba,
for his understanding and support throughout the period of this study;

My two boys, Thando and Phila for their inspiration

Love you guys

ABSTRACT

An uninterrupted cold chain is very important in maintaining the quality and the potency of vaccines. The aim of this study was to assess if the cold chain is maintained at 2°C-8°C during vaccine distribution from Litha Vaccines® to the different depots in the Gauteng Province in RSA. To establish if Litha Vaccines® has a secure cold chain and was not exposing the vaccines to the risk of compromised quality and efficacy. The vaccines were dispatched from Litha with 2 CCM cards, 2 FW's and 1 data logger per shipper. These were dispatched to the 4 different depots in Gauteng. Two sites declined to participate in the study.

The receiving manager at the depot completed the questionnaire which was designed for the purposes of this study to collate important information on the shipment. The temperature data was downloaded from the data logger at Litha after the delivery of the vaccines to assess the temperature recordings for the particular shipment.

Of the 186 CCM cards analysed, none had a colour change. All the 186 Freeze watches were intact. This confirmed that the vaccines were not exposed to undesirable storage conditions during transportation to the depots.

The total number of data loggers evaluated was 86. The maximum temperatures of all the loggers were constant between 5°C-9°C whereas the minimum temperatures were between 2°C-8°C. Eighty seven percent of all the readings were within the recommended temperature range of 2°C-8°C. The integrity and the quality of the vaccines were not compromised.

The study found that although the results were satisfactory there is still a lot of room for improvement. Cold chain monitoring studies such as this one need to be conducted frequently and in different points of the vaccine distribution channel including the storage facilities and the immunization points. Failure to monitor the cold chain all the way means that efforts to maintain the cold chain might be futile since the end user might still receive a vaccine that has lost its potency along the distribution channel.

It is crucial to emphasize the importance of continuous staff training on proper vaccine handling and the need for evaluation of vaccine monitoring processes. The managers need to ensure that there are clear guidelines and vaccine handling standard operating procedures (SOP's) on cold chain maintenance and staff training informed by the Good Distribution Practices.

Due to the effects of climate change and global warming, the study might need to be validated for the hotter summer months.

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- My parents Malakia (May your soul rest in peace Papa) and Letia Tsipa; and my siblings, Ali, Babikie, Selina and Lebo for their support, love and just being part of my life;
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GLOSSARY OF TERMS

Cold Chain	A temperature controlled supply chain, where a product should maintain a given temperature range throughout the supply chain
Data Logger/Gemini Data Logger	Temperature recording device
Freeze Watch/Cold Mark Freeze	Temperature monitoring device used to monitor the temperature of vaccines that should not be exposed to temperatures below 0°C
Gauteng	One of the 9 provinces in South Africa and a major economic hub in the country
Immunisation	Vaccination or injection of a killed or weakened infectious organism in order to protect the body against infectious diseases
Litha Vaccines	The leading supplier of paediatric vaccines to the public sector in the country, based in Gauteng
Medical Depot	Government storage facility for vaccines and other medical suppliers before they are distributed to the hospitals and the clinics
n.d.	No date of publication was provided on the webpage referenced
Shake Test	A test done using two vaccine vials to assess if the one vial was froze
Shipper	A box used to pack vaccines for transportation
The Biovac Institute	A Public Private Partnership with the department of Science and Technology within the Litha Biotech Division. Based in Cape Town, it distributes vaccines mainly in the Western Cape Province
Tiny Tag Talk 2	See Gemini data logger
Vaccines	A medicinal product that produces immunity, therefore protecting the body from disease.
Vaccine potency	The vaccines stability or its specific ability or capacity to effect a given result

LIST OF ABBREVIATIONS

BCG	-	Bacillus Calmette Guerin
CCM's	-	Cold Chain Monitor Cards, used to estimate the length of time that vaccines have been exposed to high temperatures.
CDC	-	Centre for Disease Control and Prevention
°C	-	Degrees Celsius
DPT/ DTaP	-	Diphtheria, Tetanus and Pertussis
DT	-	Diphtheria and Tetanus
EPI	-	Extended Programme on Immunization, South African government's programme to ensure delivery of immunisation services to the children.
FW	-	Freeze Watch
GAVI	-	Global Alliance for Vaccines and Immunization
GCP	-	Good Clinical Practice
GDP	-	Good Distribution Practice
GISS	-	Goddard Institute for Space Studies
GLP	-	Good Laboratory Practice
GMP	-	Good Manufacturing Practice
GPP	-	Good Pharmacy Practice
GSP	-	Good Storage Practice
GWP	-	Good Warehouse Practice
GxP	-	GMP, GLP, GCP, GDP, GWP, GSP or GPP
HBV	-	Hepatitis B Virus
Hep B	-	Hepatitis B Vaccine
HIB/ Hib	-	Haemophilus Influenza type B
IPV	-	Inactivated Polio Vaccine
MCC	-	Medicines Control Council, a statutory body that was established in terms of the Medicines and Related Substances Control Act (Act 101 of 1965), to oversee the regulation of medicines in South Africa.
MMR	-	Measles, Mumps and Rubella combined vaccine
MOH	-	Ministry Of Health
OOC	-	Out of Cold Chain. A strategy that was implemented by Indonesia, Vietnam and China for delivery of HepB vaccine when labelled VVM's are monitored
OPV	-	Oral Polio Vaccine
PCV	-	Pneumococcal Conjugated Vaccine
RV	-	Rotavirus Vaccine
SAWS	-	South African Weather Services

SS	-	Minimum Sample Size
SOP	-	Standard Operating Procedure
Td	-	Tetanus and reduced amounts of diphtheria vaccine
TT	-	Tetanus Toxoid
UNICEF	-	United Nations Children's Fund
VVM	-	Vaccine Vial Monitor, a small patch or a round disc of heat sensitive material placed on a vaccine vial to register cumulative heat exposure.
WHO	-	World Health Organization

CHAPTER 1

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1 THE COLD CHAIN

A supply chain is a system of organisations (companies or departments), people, technology, equipment, vehicles, policies, procedures, information and resources involved in moving a product from a supplier or manufacturer to a customer. Cold chain refers to a temperature controlled supply chain. An unbroken cold chain is an uninterrupted series of storage and distribution activities of a product which maintain a given temperature range throughout the supply chain ("The Complete Book on Cold Storage, Cold Chain and Warehouse with Controlled ... - NPCS Board of Consultants and Engineers - Google Books," 2015.)

The cold chain extends from the point of manufacturing to the point of administration and is governed by guidelines for temperature and equipment requirements at each level of storage and distribution. Cold chain is used to help extend and ensure the shelf life of products such as fresh agricultural produce, frozen foods, photographic films, some chemicals, blood, organs and pharmaceutical drugs and vaccines (Gyesley, 1991). The ambit of this study was cold chain monitoring of vaccines. Vaccines are powerful public health tools that save millions of lives each year. The efficiency and potency of vaccines are however; extremely dependant on the effectiveness of the cold chain maintenance processes (Matthias et al., 2007).

Vaccines and other biological products are different from regular pharmaceuticals and need to be managed differently. Proteins are commonly used in the production and manufacture of vaccines. The protein structure and function is affected by extreme temperatures. The stability of proteins is limited at high and low temperatures ("Protein structure and function at low temperatures - PubMed - NCBI," 1990.). This contributes to the sensitive nature of vaccines to temperature changes with some being more sensitive to heat and others more sensitive to cold temperatures. It is for this reason that vaccine storage and transportation conditions are specific and need to be maintained with consistency.

The cold chain in this context is a series of storage and transport links designed to preserve vaccine potency by maintaining the appropriate temperature until the vaccine is administered to its recipient, the end user. The cold chain is the key element to potent vaccines.
Maintaining the cold chain means maintaining vaccines at the required temperature throughout manufacturing, distribution, storage and use. Further, vaccines exposure to heat

or freezing conditions especially during transportation from one centre to another; and also at points of immunisations; needs to be prevented.

Vaccines that have expired or have been exposed to adverse temperatures should never be used. Vaccines that are affected in this manner are at a risk of losing their potency and their effectiveness. This leads to wasted vaccines or patients receiving vaccines that do not protect them from diseases as intended or that can make them sick. Thus maintaining the vaccine cold chain is an essential part of a successful immunisation programme (Cheriyan, 1993).

Vaccines are manufactured and packaged by pharmaceutical companies in different countries overseas. They are then transported by different routes to their destination countries all over the world i.e. by ship, air or road transport under cold chain conditions. From the port of entry; vaccines are subsequently transported to the main distributor in the country.

The vaccines are stored at this Central distribution point where they await purchase orders from the central depots. The depots are supplied by the main distributor and they are responsible for distribution to the clinics and hospitals according to the demand.

In the South African context, Litha Vaccines® (the main vaccines distributor in the country), receives the vaccines from overseas countries via air or ship. From the port of entry in Durban (Durban harbour or King Shaka International airport), Cape Town (Cape Town harbour or Cape Town International airport) and Johannesburg (OR Tambo International Airport) the vaccines are then transported by road to Litha Vaccines® in Meadowview Johannesburg. The company has since relocated to Midrand, Gauteng. Here the vaccines remain in storage awaiting the purchase orders from the depots and some of the hospitals and clinics.

To ensure the quality of the medicines entering South Africa, the MCC (Medicines Control Council) requires that the applicant confirms the imported product's integrity prior to release for sale in the country. This should be done by:

- Identification, assay and other relevant tests performed locally on the final product or
- Return of samples to overseas testing laboratories or the manufacturers that supplies the product for identification, assay and other relevant testing.

It is important to note that the MCC prefers local testing of the final product and may recommend a local laboratory.

The cold chain distribution process in vaccines is an extension of Good Manufacturing Practice (GMP) environment. All drugs and biological products are required to adhere to GxP (GMP, GLP, GCP, GDP, GWP, GSP and GPP) covering all steps from drug development to distribution.

- GMP - Good Manufacturing Practice
- GLP - Good Laboratory Practise
- GCP - Good Clinical Practice
- GDP - Good Distribution Practice
- GWP - Good Wholesale Practice
- GSP - Good Storage Practice
- GPP - Good Pharmacy Practice

The GxP is enforced by various health regulatory bodies around the globe. In South Africa, it is the Medicines Control Council (MCC). As such the distribution and storage processes must be validated to ensure that there is no negative impact on the efficacy, safety or quality of the product (Bishara, 2006).

Due to the presence of multiple uncontrolled variables in the distribution process, for e.g. different weather conditions from one area to another, different levels of personnel skills and competence in vaccine handling, availability of appropriate validated vehicles, equipment failure and storage space concerns amongst others, and the sensitive nature of vaccines, developing an appropriate temperature monitoring programme is essential to protect the quality of the product and to ensure patient safety (Bishara, 2006).

Safe storage of vaccines cannot be ensured without adhering to the recommended guidelines. Provisions of adequate equipment and training for staff in maintaining the cold chain and the use and care of equipment are important components of a successful immunisation programme (Thakker and Woods, 1992).

Guidelines exist at both national and local levels to minimise exposure of vaccines to adverse temperatures during transportation and storage. The national guidelines in the UK recommend that firstly, vaccines received are immediately placed under the required storage conditions (Oral polio vaccine at -20°C and other vaccines at 2°C-8°C) and that a nominated, trained person should be responsible for vaccine storage. This person should be able to work to a written procedure developed to meet local needs (Thakker and Woods, 1992).

Secondly, the temperature of the refrigerator should be monitored with a minimum and maximum thermometer irrespective of whether the refrigerator incorporates a thermometer dial or not. The maximum and minimum temperatures should be recorded regularly. Written procedures should indicate the action to be taken if the temperature goes outside the specified range.

Thirdly, if the refrigerator has no automatic defrosting facility, the stock should be stored in an alternative refrigerator or cool box during manual defrosting.

Fourthly, reconstituted vaccine must be used within the manufacturers recommended period. Vaccines vary in their sensitivity to adverse storage conditions and manufacturers offer guidelines for storage temperatures to ensure potency.

The effect of adverse temperatures on vaccines is cumulative. This study by Thakker et al, 1992, showed poor adherence to the national guidelines for vaccine storage and exposure of vaccines to a wide range of temperatures. A questionnaire survey distributed among practice nurses in Hampshire and Dorset also showed lack of awareness of the recommended storage conditions for vaccines (Thakker and Woods, 1992).

The South African guidelines (MCC SA guide to GWP) state that, for facilities to achieve and maintain the standard requirements for adequate cold chain management the following should be adhered to:

- All vaccines should be kept in the refrigerator between 2°C and 8°C except OPV which should be kept at -20°C.

- The refrigerator or cold room must be connected to an alarm system in the event of a power failure or if the refrigerator temperatures limits are exceeded.

- The refrigerator or cold room must be connected to a standby generator or other emergency power system to ensure uninterrupted power supply in the event of a power failure.

- There must be a written procedures in place for:
  - Handling vaccines in the event of a power failure.
  - Handling of temperature deviations.
  - Cold chain management.
  - Warehouse and refrigerator temperature monitoring, recording and control.
  - Calibration of measuring devices.
  - Transportation and goods in transit.
  - Products that require special storage/ handling.

- Refrigerators, cold rooms and freezers used to store thermolabile pharmaceutical products should:
  - Be well maintained.
  - Be equipped.
  - Be free from frost build-up.
  - Allow for adequate air distribution and orderly storage within the chamber. Good storage practices and loading configurations should not lead to the obstruction of air distribution.
  - Have sensors for continuous temperature monitoring and alarms located at the points representing the temperature extremes.

- The refrigerator or cold room must be mapped in terms of temperature.

- Products should not be stored in areas shown by temperature mapping to present a risk (e.g. in the airflow from the refrigeration unit).

- Sufficient space should be maintained to permit adequate air circulation especially between shelving. If the refrigerator is filled to capacity, the effect on temperature distribution should be investigated.

- Ensure that no condensation from chillers collects or drips onto product or collects inside the facility.

- On receipt of a shipment of thermolabile stock, all cold chain items should be moved to the refrigerator within the shortest possible time from offloading the truck.

- When a lagged container used for transportation of the product is opened, all cold chain products must immediately be removed and exposed to the refrigerator's temperatures,

in order to maintain the cold chain. Checks should be done to ensure that the cold chain has been maintained during transportation.

- Each facility must assign a person and a deputy who are responsible for the vaccine fridge. This person may be the Vaccinator and will properly pack vaccines in the fridge, monitor fridge temperatures, defrost and clean the fridge as required, report malfunctioning and take action when there is power failure and when the fridge is not functioning.

- Only vaccines should be stored in the vaccine fridge. Do not keep food in the same fridge as the vaccines.

- Every vaccine fridge should have a fridge tag or a thermometer in the fridge.

- Cooler boxes used during vaccination should have a thermometer.

- Fridge temperature should be recorded twice daily.

1.2 THE VALUE OF VACCINES

A vaccine is a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and keep a record of it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters ("WHO | Vaccines," n.d.).

Vaccines are given to healthy individuals and mostly the results are unseen, with people and children protected from most of the dreaded diseases of the past. Vaccination protects adults and children from dangerous but preventable diseases. The World Health Organisation (WHO) says immunisation saves 3 million lives a year (Matthias et al., 2007).
With the exception of safe water, no other modality, not even antibiotics, has had such a major effect on mortality reduction as vaccines had (Ngcobo and Cameron, 2010). In pre-vaccine era, epidemics were highly feared, as millions of people died from diseases about which there was little understanding. It is estimated that smallpox caused as many as 60 million deaths during the 17th century.

The vaccination era started in 1796, with Edward Jenner developing a vaccine against smallpox, the ultimate success of Jenner's efforts, was finally realised in 1979, when the

WHO certified that smallpox has been eradicated, the first infectious disease to be globally eradicated through immunisation (Baker, 2010).

Since then, new targets have been set by the WHO, to eradicate poliomyelitis and measles, and to significantly reduce the burden of many other infectious diseases by means of successful immunisation programmes and other public health measures.

Prior to 1974, vaccination programmes in developing countries were restricted to the urban elite, and children of school going age were the main target, in spite of the fact that the younger children are often more vulnerable to the diseases. Less than 5% of children under the age of one year were being vaccinated against six killer diseases: polio, diphtheria, tuberculosis, pertussis (whooping cough), measles and tetanus (Baker, 2010).

In 1974, the WHO initiated the Expanded Program on Immunisation (EPI) with the aim of making immunisation available to every child by 1990. Almost 80% of children below the age of one year were being vaccinated by 1990 (Baker, 2010).

Immunisation has been called one of the best buys in health. This success has led to substantial efforts to develop new vaccines against a range of infectious agents responsible for significant childhood morbidity and mortality (Ngcobo and Cameron, 2010).

As research and development, clinical trials, registration and marketing have become lengthy, complex and expensive process, so too health authorities and donor organisations have weighed up the cost of a new vaccine in light of efficacy and effectiveness, perceptions and priorities, and the capacity of a country to deliver and sustain expanded immunisation programmes. It is therefore not surprising that in many developing countries, often the very places where the vaccines are most needed; it can take decades before a new childhood vaccine is introduced (Ngcobo and Cameron, 2010).

The benefits of immunization have increased with the addition of new vaccines, but so have the costs. A decade ago, the vaccines used in most developing countries cost only about US$1 per child. Today, with the addition of combination vaccines, the vaccines alone cost as much as US$14 per fully immunized child (“IMMUNIZATIONbasics - SnapShots Volume 8,” 2008.).
Immunisation currently remains one of the most cost effective health interventions. According to the WHO every dollar spent on vaccine saves seven dollars in medical costs and 25 dollars in overall costs related to vaccine preventable diseases.

The vaccine market segment in developing countries is estimated to be about $3 billion USD of which 5% is wasted annually (Chaudhri et al., 2012). The market for vaccines in developing countries is small. The global market for vaccines is about $6 billion a year. Developing country markets account for about half of total vaccine sales by volume, but only account for about 5 percent or less of total revenue from the sales of vaccines.

Spending on vaccines used in developing countries has increased a little in recent years with the establishment of GAVI and the Vaccine Fund; but the developing country market value is clearly very small relative to the market in rich countries and relative to other pharmaceuticals. Refer to Figure 1.1 below to compare the market sizes for different pharmaceutical categories.

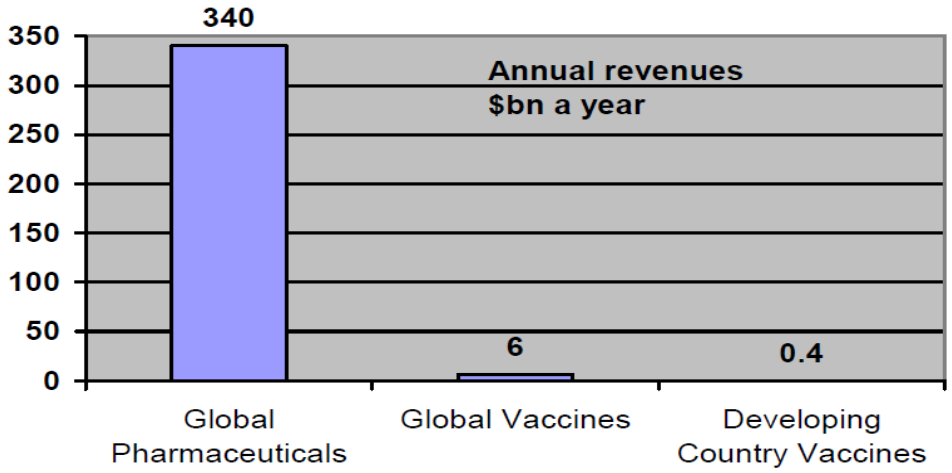


Figure 1.1: Market Sizes for Pharmaceutical Categories

Immunisation is safe and getting safer and more effective all the time as a result of medical research and on-going review by medical scientists. Although side effects following immunisations do occur, they are usually mild and clear up quickly ("Immunisation | Western Cape Government," 2013.).

After the successful eradication of small pox, WHO launched the global Polio Eradication Initiative in 1988 to eradicate poliomyelitis. Mass immunisation campaigns with Oral Polio Vaccine (OPV) in children less than five years of age is one of the key strategies to achieve this goal. Reported cases of polio decreased from over 350 000 in 125 countries in 1988 to 905 cases. Exposure to high temperatures is detrimental to OPV and the vaccine loses its potency at a rate of 4-13% per day at 25°C, 11 -21% per day at 31°C, and 26-34% per day at 37°C (Samant et al., 2007). All vaccines except oral polio should be stored and transported at temperatures of between 2°C - 8°C while polio is to be kept at -20°C. Deviations from these recommended temperatures will cause the vaccines to lose their potency. (Matthias et al., 2007).

Freeze-dried vaccines (e.g. BCG, measles, measlesmumps-rubella) may be kept frozen, or at 2–8 ◦ C. Other adsorbed liquid vaccines (e.g. diphtheria-tetanus-purtussis, diptheria-tetanus, diphtheria-tetanus-purtussis-hepatitis B combined, and hepatitis B) should be stored and transported at 2–8 ◦C. Exposure to heat will shorten vaccine shelf life, while freezing vaccines that should not be frozen will cause irreversible loss of potency (Techathawat et al., 2006).

1.2.1 **Different Types of Vaccines**

The first human vaccines against viruses were based using weaker or attenuated viruses to generate immunity. Vaccines are made using several different processes:

- They may contain live viruses that have been attenuated (weakened or altered so as not to cause illness). Protection from this type of vaccine typically outlasts that provided by a killed or inactivated vaccine.

- Inactivated or killed organisms or viruses. They tend to provide a shorter length of protection than live vaccines, and are more likely to require boosters to create long term immunity.

- Inactivated toxins (for bacterial diseases where toxins generated by the bacteria and not the bacteria themselves cause illness). Immunisations created using inactivated toxins are called toxoids.

- Segments of the pathogen (this includes both subunit and conjugate vaccines). Both subunit and conjugate vaccines contain only pieces of the pathogens they protect against (“Different Types of Vaccines — History of Vaccines,” n.d.)

Refer to table 1.1 for the different types of vaccines.

Table 1.1: Types of Vaccines

Vaccine Type	Vaccine of this Type
Live, attenuated	Measles, mumps, rubella (MMR combined vaccine) Varicella (chickenpox) Influenza (nasal spray) Rotavirus
Inactivated/ killed	Polio (IPV) Hepatitis A
Toxoid (inactivated toxin)	Diphtheria, tetanus (part of DTaP combined immunisation)
Subunit/ conjugate	Hepatitis B Influenza (Injection) Haemophilus influenza type b (Hib) Pertussis (part of DTaP combined immunisation) Pneumococcal Meningicoccal

1.2.2 Vaccine Side Effects and Adverse Events

A vaccine is a medical product, which is designed to protect from disease, but like any other medication it can also cause side effects.

Most side effects from vaccination are mild, such as:

- Soreness, swelling or redness at the site of injection.
- Fever
- Rash
- Achiness

Serious side effects are rare, but may include life-threatening allergic reaction or seizure ("Vaccine Side Effects and Adverse Events - History of Vaccines," n.d.)

1.2.3 Common Myths and Misconceptions about Vaccination

Vaccines safety concerns can diminish parents' willingness to vaccinate their children. Although parents overwhelmingly share the belief that vaccines are a good way to protect their children from disease, these same parents express concerns regarding the potential adverse effects and especially seem to question the safety of newer vaccines. Although information is available to address many vaccine safety concerns, such information is not reaching many parents in an effective or convincing manner (Freed et al., 2010).

A lot of paediatricians and family physicians have experienced at least one vaccine refusal in a year but far fewer physicians observed an increase in their occurrence (Freed et al., 2010).

Efforts to maintain and improve immunisation coverage need to also target those with attitudes/ beliefs/ behaviours indicative of vaccine safety concerns, as well as those with socioeconomic and health care access problem (Freed et al., 2010).

1.2.4 Extended Programme on Immunisation in South Africa (EPI (SA))

In South Africa, immunisation is routinely given against such diseases of childhood as Measles, Neonatal Tetanus, Poliomyelitis, Haemophilus Influenza type B, Hepatitis B, Tuberculosis, Diphtheria, Pertussis, Pneumococcal disease and Rotavirus. All these vaccines are in the government's EPI ("Microsoft Word - EPI vaccines revised Oct 2010.doc - South-Africa-EPI-vaccines-revised-Oct-2010.pdf," 2010).

Current National EPI Schedule: (New EPI guidelines revised October 2010, Department of Health). This schedule will be effective from April 2009.

Table 1.2: Current National EPI Schedule without Pentavalant* vaccines

Age of Child	Vaccine Needed	How and Where is it Given?
At birth	▪ OPV (0) Oral Polio Vaccine ▪ BCG Bacillus Calmette Guerin	Drops by mouth Intradermally/ right arm
6 weeks	▪ OPV (1) ▪ RV (1) Rotavirus Vaccine ▪ DTP/HIB(1) Diphtheria, Tetanus, Pertussis, and Haemophilus influenza type B combined ▪ Hep B(1) Hepatitis B Vaccine ▪ PCV(1) Pneumococcal Conjugated Vaccine	Drops by mouth Liquid by mouth Intramuscularly/ left thigh Intramuscularly/ right thigh Intramuscularly/ right thigh
10 weeks	▪ OPV (2) ▪ DTP/HIB(2) ▪ Hep B(2) Hepatitis B Vaccine	Drops by mouth Intramuscularly/ left thigh Intramuscularly/ right thigh
14 weeks	▪ OPV (3) ▪ RV (2) Rotavirus Vaccine ▪ DTP/HIB(3) ▪ Hep B(3) Hepatitis B Vaccine ▪ PCV(2)	Drops by mouth Liquid by mouth Intramuscularly/ left thigh Intramuscularly/ right thigh Intramuscularly/ right thigh
9 months	▪ Measles Vaccine(1) ▪ PCV(3)	Intramuscularly/ left thigh Intramuscularly/ right thigh
18 months	▪ OPV(4) ▪ DTP(4) Diphtheria, Tetanus, Pertussis ▪ Measles Vaccine(2)	Drops by mouth Intramuscularly/ left arm Intramuscularly/ right arm
6 years	▪ OPV(5) ▪ Td vaccine Tetanus and reduced amount of diphtheria vaccine	Drops by mouth Intramuscularly/ left arm
12 years	▪ Td vaccine Tetanus and reduced amount of diphtheria vaccine	Intramuscularly/ left arm thigh

Table 1.3: Current National EPI Schedule with Pentavalant* vaccines

Age of child	**Vaccine needed**	**How and Where is it given?**
At birth	OPV(0) Oral Polio Vaccine	Drops by mouth
	BCG Bacillus Calmette Guerin	Intradermally / Right arm
6 weeks	OPV(1) Oral Polio Vaccine	Drops by mouth
	RV (1) Rotavirus Vaccine	Liquid by mouth
	DTaP-IPV//HIB(1) Diphtheria, Tetanus, acellular Pertussis, Inactivated Polio Vaccine & Haemophilus influenzae type b combined	Intramuscularly / Left thigh
	Hep B(1) Hepatitis B Vaccine	Intramuscularly / Right thigh
	PCV(1) Pneumococcal Conjugated Vaccine	Intramuscularly / Right thigh
10 weeks	DTaP-IPV//HIB(2) Diphtheria, Tetanus, acellular Pertussis, Inactivated Polio Vaccine & Haemophilus influenzae type b combined	Intramuscularly / Left thigh
	Hep B(2) Hepatitis B Vaccine	Intramuscularly / Right thigh
14 weeks	RV (2) Rotavirus Vaccine	Liquid by mouth
	DTaP-IPV//HIB(3) Diphtheria, Tetanus, acellular Pertussis, Inactivated Polio Vaccine & Haemophilus influenzae type b combined	Intramuscularly / Left thigh
	Hep B(3) Hepatitis B Vaccine	Intramuscularly / Right thigh
	PCV(2) Pneumococcal Conjugated Vaccine	Intramuscularly / Right thigh
9 months	Measles Vaccine(1)	Intramuscularly / Left thigh
	PCV(3) Pneumococcal Conjugated Vaccine	Intramuscularly / Right thigh
18 months	DTaP-IPV//HIB(4) Diphtheria, Tetanus, acellular Pertussis, Inactivated Polio Vaccine & Haemophilus influenzae type b combined	Intramuscularly / Left arm
	Measles Vaccine (2)	Intramuscularly / Right arm
6 years	Td vaccine Tetanus & reduced amount of diphtheria vaccine	Intramuscularly / Left arm

12 years	Td vaccine Tetanus & reduced amount of diphtheria vaccine	Intramuscularly / Left arm

** Pentavalant vaccine is a vaccine that protects against five major infections in one shot: diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae type b (Hib).*

The EPI in South Africa was introduced in 1974. The programme however remained fragmented because of the apartheid system until 1995, when the national EPI was formed through the unification of all immunisation services in the country. Since then, there have been significant advances in immunisation services delivery in South Africa.

1.3 VACCINE COLD CHAIN MONITORING

World Health Organisation's (WHO) guidelines for establishing or improving primary and intermediate vaccine stores as well as the vaccine manufacturer product inserts recommend that all vaccines except oral polio should be stored and transported at temperatures of between 2°C - 8°C while polio is to be kept at -20°C (Matthias et al., 2007). Also every refrigerator, freezer and cold store used for vaccine storage must be fitted with an independent temperature monitoring device. It is a GPP requirement that an automatic alarm system should be available to alert staff whenever the temperature of the vaccine is outside the safe limits. There should be reliable protection against failure at all times of day and night.

Proper temperature monitoring is key to proper cold chain management. Temperature must be checked and recorded by a responsible member of staff twice daily, once when the office or clinic opens and once at the end of the day. There should also be a back-up staff member who will review the temperature logs at least weekly. All staff members working with vaccines should be familiar with proper temperature monitoring.

The equipment and the people that handle the vaccines (from manufacturing to administering) are very important elements in maintaining the cold chain. Therefore the cold chain is as strong as its weakest link (Wirkas et al., 2007). An estimated 17% - 37% of providers expose vaccines to improper storage temperatures, and refrigerator temperatures are more commonly kept too cold than too warm (Centers for Disease Control and Prevention (CDC, 2003)).

Freezing temperatures can irreversibly reduce the potency of vaccines required to be stored at 2°C -8°C. Certain freeze-sensitive vaccines contain an aluminium adjuvant that precipitates when exposed to freezing temperatures. This results in loss of the adjuvant effect and vaccine potency. Physical changes are not always apparent after exposure to freezing

temperatures and visible signs of freezing are not necessary to result in a decrease in vaccine potency.

Although the potency of the majority of vaccines can be affected by storage temperatures that are too warm, these effects are usually more gradual, predictable and smaller in magnitude than losses from temperatures that are too cold. In contrast, OPV requires being stored in continuously frozen states and will lose potency when stored above the recommended temperature range (Centers for Disease Control and Prevention (CDC, 2003)). Adequate cold chain infrastructure and compliance are paramount for preserving the quality of the vaccines as they are distributed.

There are simple strategies that can be used to reduce freezing, e.g. selective transport and storage of vaccines at ambient temperatures, the use of Vaccine Vial Monitors (VVM's) to reduce the risk associated with heat damaged vaccines and policy changes that allow limited storage of freeze sensitive vaccines at temperatures greater than 2°C-8°C, that would enable flexible vaccine distribution strategies that could reduce vaccine freezing, reduce costs and increase capacity (Nelson et al., 2004).

Studies conducted in Australia, Canada, Hungary, Malaysia, Mongolia, Pakistan, the United Kingdom and the United States have found widespread freezing at many stages of the vaccine distribution system. Improperly adjusted refrigeration equipment, poor compliance with cold chain procedures, inadequate monitoring and poor understanding of the dangers of freezing result in frequent cold chain freezing (Nelson et al., 2004).

Further, it was demonstrated that the high level of freezing recorded in this study, is not limited to the Indonesian provinces. The finding that 75% of hepatitis B vaccines were exposed to sub-zero temperatures supports evidence of serious freezing problems in other parts of the world, including several developed countries (Nelson et al., 2004).

Evaluation of cold chain processes is particularly important in regions where there is evident immunisation failure or the emergence of vaccine preventable illnesses in warmer climates. In developing countries, faulty procedures may occur more commonly than is generally believed. This remains crucial and may occur in any part of the world. The cold chain still remains a highly vulnerable element of any immunisation programme, both in developing and developed countries (Grasso et al., 1999).

Vaccine manufacturers recommend storage conditions for their vaccines and clearly state that they do not guarantee the potency of the vaccines if they have not been stored at the

correct temperature. Improving vaccine preparation technology in order to develop vaccines that retain their potency and efficacy despite exposure to elevated temperatures is much more difficult than establishing an effective cold chain. Paying careful attention to transportation and storage is very important to avoid loss of vaccine potency.

In tropical countries, the importance of maintaining the cold chain is recognised, but in temperate countries it has been given little attention until recently (Briggs and Ilett, 1993). Briggs et al, 2003 found that the only successful means of transporting vaccines without excessive warming was by car, and this depended on the speed of transit. The use of cool boxes was so rare that he couldn't comment on their potential effectiveness.

Using validated cool boxes, calibrated loggers, improved staff training and random monitoring exercises like this one would improve a potentially hazardous situation. In many developing countries, a cold chain infrastructure is not available, especially in remote and rural areas. In attempts to achieve better coverage of vaccination, Indonesia, Vietnam and the Hunan area of China have successfully implemented an Out of Cold Chain (OCC) strategy for delivery of the HepB vaccine when labelled VVMs are monitored (Ren et al., 2009).
Generally there are three common reasons for taking vaccines OCC: 1) to provide ready access for health care workers to vaccines for time-sensitive administration (such as birth dose); 2) to ease cost and efforts of outreach trips; 3) to prevent exposure to freezing temperatures that can occur in vaccine carries (Robertson et al., 2010.).

However, the OCC transport strategy does not appear to be appropriate for some areas and some reasons. The above mentioned study by (Ren et al., 2009) found that vaccines have been transported OCC for a long time during winter as part of the immunisation program in China but there had never been an in-depth evaluation of the strategy prior to this study. The results of the study showed that there were failings in the current vaccine delivery strategy in remote areas of China, which could prevent the immunisation program's success.

The OCC vaccine delivery strategy is not suitable for China's western plateau in winter and cannot replace the vaccine cold chain system. As soon as the results of this study were available, several areas began to establish their own cold chain system (Ren et al., 2009). To prevent perinatal transmission of Hepatitis B virus (HBV), the WHO recommends that the first dose of HepB vaccine be given within 24 hours after birth. This presents a challenge in remote areas with limited cold chain infrastructure and where many children are born at home (Wang et al., 2007).

As a strategy to improve coverage of the HepB vaccine after birth dose; the WHO recommends the use of VVMs in combination with proper training of vaccine providers. HepB vaccines can be stored without refrigeration when labelled with VVMs. HepB vaccine maintains its potency for 1-3 months at temperatures up to 37°C and can be safely stored outside the cold chain in tropical climates. Indonesia has successfully introduced an out of cold chain strategy for delivery of the HepB vaccine birth dose nationwide, storing vaccines in the homes of village midwives to make the vaccine more readily available for home births (Wang et al., 2007).

Although the strategy is highly promising, its departure from standard cold chain practices and concerns about the logistics of home based immunisation have limited its introduction in other countries (Wang et al., 2007).

This study explored the feasibility and effectiveness of a village based out of cold chain strategy for improving timely administration of HepB vaccine birth dose in rural areas of Hunan Province, China. It further explored the use of a prefilled injection device (Uniject) to administer HepB vaccine in villages outside the cold chain.
The study also showed that timely administration of the first dose of HepB vaccine to new-borns can be substantially improved through public awareness efforts and provider training and especially for infants born at home, through storage of vaccines in the villages outside the cold chain and administration of vaccines by village health workers.

This study confirmed the findings of the studies in Vietnam, Indonesia and China that have shown that HepB vaccine is stable when used outside the cold chain. The most common concerns about taking vaccines out of cold chain and hospital infrastructure are temperature exposure and injection safety which were not found to be problems in this study.

In fact, the results of temperature monitoring show that storing vaccine within the cold chain may be problematic if as observed here, the vaccine is subjected to freezing in cold chain refrigerators. Taking vaccine out of cold chain could potentially decrease the risk of vaccine damage caused by inadvertent freezing. This strategy could be beneficial not only in geographically isolated areas, but also in urban areas where cultural differences impede access to clinic based immunisation (Wang et al., 2007).

1.3.1 Cold Chain Equipment and Vaccine Storage Areas

High cost of vaccines, coupled with the fact that even short durations of exposure to temperatures outside the normal range can cause irreversible damage, necessitates the need for having robust storage equipment as well as continuous temperature monitoring and reporting systems (Chaudhri et al., 2012).

Preventing loss of vaccine potency during storage and handling is increasingly important as new, more expensive vaccines are introduced. Problems with vaccine storage are common and mainly relate to inadequate monitoring of cold storage units (Bell et al., 2001).

A study done in India to evaluate the relationship between VVMs and cold chain infrastructure also revealed weaknesses in the cold chain mechanism. The study attributed the weakness in the cold chain to the loss of vaccine potency. The conclusion from this study was that the cold chain for the OPV was not adequately maintained at primary and sub health centres in this rural district of India (Samant et al., 2007).

However this study used VVM to evaluate cold chain and did not include evaluation of the cold chain equipment or temperature maintenance requirements. The literature provides little evidence of studies systematically evaluating the relationship between the VVM, the cold chain equipment and the healthcare infrastructure in rural area in India.
There is little evidence in the literature on the evaluation of a cold chain for OPV in rural areas of India. Current data indicate that 24% of vaccine carriers across all levels of the cold chain were not compliant. The study found that overall; the cold chain compliance across all levels in this rural district was 60,4%.

As distance from the district hospital increases, there is concomitant difficulty in maintaining the cold chain. Another issue of concern is power supply at primary community health centres in this rural district. Electrical power or an alternative source of energy is crucial to the maintenance of the cold chain. Frequent power failures during the summer months are crucial to this (Samant et al., 2007).

In general, the VVM's were found to have more colour change as the distance travelled increased. There is a need to strengthen the cold chain at its farthest point and improve the effectiveness of low cost measures such as the provision of adequate ice packs and vaccine carriers.

Every immunization program must assess cold chain equipment needs periodically and replace broken equipment not worth repairing ("IMMUNIZATIONbasics - SnapShots Volume

8," 2008). There is often a lack of field based procurement and repair plans, which means that cold chain and logistics inventories are not sufficiently linked with new equipment projections. The risk is that broken and malfunctioning equipment will not be timely and properly maintained thus negatively affecting the potency and effectiveness of the affected vaccines.

Poor and unreliable energy sources, a common problem in developing countries, weaken the effectiveness of equipment and shorten its lifespan. Also, equipment in remote areas is difficult to reach with timely and routine maintenance, which are necessary to avoid more costly repairs or replacement. Proper maintenance will reduce the risk of exposing vaccines to adverse temperatures. Countries need to develop or update policies for the purchase, repair and replacement of cold chain and transport equipment.

Tanzania is a role model for good cold chain and logistics management. ("IMMUNIZATIONbasics - SnapShots Volume 8," 2008). At the central level, Tanzanian EPI has a cold chain and logistics section that forecasts equipment needs, procures the equipment and allocates it across the country. It also develops guidelines and standards for cold chain equipment, conducts supportive supervision, repairs defective cold chain equipment and coordinates cold chain trainings for technicians ("IMMUNIZATIONbasics - SnapShots Volume 8," 2008).
Literature review also yields reports on a number of shortcomings concerning the cold chain such as power failures and improper and inadequate maintenance of cold chain equipment.

The study by (Grasso et al., 1999) found that in some offices in Italy (Private Sector), no refrigeration was available. Physicians obtained vaccines from neighbouring facilities and used them immediately. None had a maximum and minimum thermometer and none monitored the internal temperature of the refrigerator. Where there is no evidence of the conditions of storage or the duration of vaccine exposure to those conditions, vaccine potency cannot be guaranteed.

Some fridges were used to store food and drinks and others some drugs and laboratory specimens. The findings of this study were consistent with those from other studies that found problems with vaccine storage and handling. The study highlighted serious problems with vaccine transportation and storage that could jeopardise the success of an immunization programme.

In particular, most of the staff responsible for vaccine storage had poor knowledge about maintaining the cold chain and were unaware of recommendations on vaccine storage.

Storage of food and laboratory specimens in vaccine refrigerators meant that the fridges were opened frequently and that both the code of practise for storing vaccines and the food hygiene regulations were broken. There is a need for daily temperature monitoring in all the fridges.

Simple measures that can be taken to guarantee vaccine potency and success of an immunisation programme:

- Refrigeration should contain maximum and minimum thermometer.
- Storage temperatures should be recorded twice daily.
- Storage of items other than vaccines should be avoided to avoid repeated opening of the refrigerator.
- Vaccines should never be stored on the fridge door shelves.
- Vaccines to be maintained under appropriate conditions during transportation.
- Provision of adequate equipment and personnel.
- Staff training in maintaining the cold chain and taking care of equipment.
- Implementation of a properly designed monitoring and control system.
- Awareness of the loss of potency of incorrectly stored vaccines is increased.
- Adherence to the national guidelines on vaccine storage and transportation.
- Local guidelines should address the safe storage of vaccines during transportation as well (Grasso et al, 1999).

1.3.1.1 **Refrigerator/freezer**

Vaccine storage units must be selected carefully and used properly. A combination refrigerator/freezer unit sold for home use is acceptable for vaccine storage if the refrigerator and freezer compartments each have a separate door. However, vaccines should not be stored near the cold air outlet from the freezer to the refrigerator. Many combination units cool the refrigerator compartment using air from the freezer compartment.

Refrigerators without freezers and stand-alone freezers usually perform better at maintaining the precise temperatures required for vaccine storage, and such single-purpose units sold for home use are less expensive alternatives to medical specialty equipment. Any refrigerator or freezer used for vaccine storage must maintain the required temperature range year-round, be large enough to hold the years largest inventory and be dedicated to storage of biologics (i.e., food or beverages should not be stored in vaccine storage units).

In addition, vaccines should be stored centrally in the refrigerator or freezer, not in the door or on the bottom of the storage unit, and sufficiently away from walls to allow air to circulate.

Thus the thermometer should be placed in a central location in the storage unit, adjacent to the vaccine (Centers for Disease Control and Prevention (CDC, 2003)).

The fridge door should be opened only when absolutely necessary, and for the shortest time possible. A fridge with a glass door is recommended to allow staff to check items in the refrigerator without the need to open the door. Light sensitive vaccines will have to be stored in the original boxes to be protected from light. Food and beverages should not be kept in the refrigerator used for vaccine storage.

1.3.1.2 **Thermometers**

Thermometers provide the simplest and cheapest way to monitor temperature although they lack some important features for cold chain monitoring e.g., they only show current temperature but will not show information such as daily max/min temperatures or deviations from the normal temperature range (Chaudhri et al., 2012).

Different types of thermometers can be used, including standard fluid filled, min-max, and continuous chart recorder thermometers. Standard fluid filled thermometers are the simplest and least expensive products, but some models may perform poorly. Product temperature thermometers (i.e. those encased in bio safe liquids) might reflect vaccine temperature more accurately. All thermometers used for monitoring vaccines storage temperatures should be calibrated and certified appropriately (Centers for Disease Control and Prevention (CDC, 2003).

1.3.1.3 **Cold chain monitoring devices**

In addition, there are a number of other devices in the market used to monitor the temperature throughout the distribution chain. These can be used as back up monitoring system as well. Some are electronic and others are not. The choice of which device to use is determined among other factors by:

- What you need the device to monitor (to monitor heat or cold conditions),
- The price of the device, the equipment and the software required to download the information from the device,
- Accuracy of the device,
- What information you can get from the device (if you only want to know if the stock was exposed to heat or you want to know the actual temperature and how long the stock was exposed to these temperatures),
- Type of vaccine transported (is it heat or cold sensitive vaccine).

To list but a few of these devices, there are cold chain monitor (CCM) cards, Freeze Watches, Vaccine Vial Monitors (VVM), attached to the actual vaccine or its packaging, Q-tags, Freeze tags, Tiny-tag Temperature loggers, Temptales, etc.

1.3.1.4 **Vaccine vial monitors**

VVM is a small patch or a round disc of heat sensitive material placed on a vaccine vial to register cumulative heat exposure. A direct relationship exists between the rate at which the VVM changes colour and ambient temperature. The lower the temperature, the slower the colour change and the higher the temperature, the more quickly the colour changes. The VVM is a crucial tool to monitor potential problems with potency of OPV in the field, especially in developing countries where poor infrastructure and insufficient resources present a number of challenges maintaining the cold chain.

In order to maintain the potency of Oral Polio Vaccine (OPV) over extended periods, the World Health Organisation (WHO) has recommended a protocol for temperature maintenance and equipment requirements at each level in the cold chain system. The WHO uses the VVM to assess the maintenance of the cold chain at each level in the storage and distribution of the OPV. The VVM is designed to progressively and permanently change its colour if exposed to high temperatures over an extended period of time (Samant et al., 2007).

It is necessary to monitor the VVM which predicts the vaccine potency at the time of vaccine administration. The WHO introduced the VVM technology for heat labile vaccines with a twofold intent: to reduce vaccine wastage and to identify heat damaged stock, thus preventing less efficacious vaccines from being administered to children (Samant et al., 2007).

UNICEF and WHO have estimated that the use of VVMs, even if only on basic vaccines, saves the global health community US$ 14 million per year by preventing the discard of undamaged vaccines (Samant et al., 2007).

Because it was not possible to precisely monitor the potency of an individual vial, health care workers would often have to destroy vaccines when the integrity of the cold chain had been compromised.

This recent development of introducing the VVMs now enables health workers to verify whether an individual vial of vaccine has been exposed to excessive heat. The VVM consists of a heat sensitive label which is placed on the vaccine vial to register and reflect the combined effects of time and temperature (Aylward et al., 1998).

A study was conducted in Nepal to evaluate the impact of VVMs on vaccine wastage and to monitor the cold chain at the point of use during National Immunization Days (NIDs). This study indicated the capacity of VVMs both to substantially reduce the wastage of OPV vials which have been returned from outreach immunisation sites and to facilitate the monitoring of the cold chain in the field.

Of the approximately 6000 vials that had been outside of the permanent cold chain for more than 3 days, only 14 had a VVM reading which suggested that the vaccine should not be used due to excessive heat exposure. Thus in the absence of the VVMs it may have been appropriate to destroy 33% of the returned vials despite fact that the OPV was still potent.

Further investigation on the study suggested a systematic error in reading of the VVM by 1 supervisor. However, even omitting the results of that supervisor, 50 of 8000 vials that were found in the vaccine carriers at the time of supervision were shown to be heat damaged. This clearly indicated that in those situations where one had to question the integrity of the cold chain, VVMs provided the capacity to selectively discard from the cold box or vaccine carrier only those vials which were potentially heat-damaged vials (Aylward et al., 1998).

Other studies have reported a knowledge deficit concerning VVMs among healthcare workers. (Thakker and Woods, 1992) reported only 67% of healthcare workers being aware of the VVM. Another study conducted in New Delhi, India, reported 82% of the healthcare workers being familiar with the VVM during a polio immunization drive (Samant et al., 2007).

1.3.1.5 **Cold chain monitor cards**

Each Cold Chain Monitor (CCM) card has a heat sensitive indicator which is in the form of a strip with four windows (A, B, C and D in this case, in some cases it is marked 1, 2, 3 and 4) and is effective in indicating whether the vaccines were exposed to higher than recommended temperatures or not. The higher the temperature is above the CCM card threshold, the more rapidly the colour changes to pink, which is irreversible even when exposed to lower temperatures again.

An exploratory study was done in the Northern territory of Australia to determine the links in the cold chain, what vaccine monitoring had been done and whether the vaccines had been exposed to temperatures that could put them at risk of losing potency (Miller and Harris, 1994).

This study found that cold chain monitors were regularly separated from vaccines on arrival at the health facilities and simply stored randomly in the fridge. Since monitors cannot be representative of vaccine exposures when handled in this manner, the monitors and vaccines were then placed in sealable plastic bags to prevent separation.

A study done by Hanjeet et al. (1996) in Kelantan, Malaysia was to evaluate cold chain monitoring during the vaccine's transport and storage from central Kuala Lumpur to Kelantan. An analysis was carried out on a total of 883 cold chain monitor (CCM) cards. The results showed that 65% of all cards had a colour change in window A, 16.6% had a colour change in window B and 4.4% in window C. Only 13.4% of all cards remained white, showing that those vaccines were within the correct temperature range. And out of 234 freeze watches analysed, 2 had turned purple.
This was therefore an indication that there were weaknesses in the cold chain management system in Malaysia and that the system needed strengthening. According to the study, similar findings were reported in Europe, India and Egypt.

This same study also brought to light issues such as lack of contingency plans during power cuts, inadequate training of staff, pharmacists, storekeepers and all attendants in the cold chain maintenance procedure, inadequate equipment for storage of large quantities of stock and the malfunctioning of equipment.

1.3.1.6 **Freeze watch**

On the other hand, the freeze watch is used to monitor temperatures of vaccines which should not be exposed to temperatures below 0°C. The liquid in the freeze watch remains colourless at temperatures above 0°C, it only changes colour if the vaccine was exposed to temperatures below 0°C.

1.3.1.7 **Cold box**

A cold box is an insulated container with a tight fitting insulated lid. The temperature inside the box is maintained by ice packs and/or gel packs. The cold box is designed for:

- Collection and transportation of vaccines at temperatures between 2°C and 8°C.
- Storage of vaccines during maintenance periods e.g. during cleaning of refrigerator.
- Storing vaccines during immunisation sessions/clinics.
- Emergency storage of vaccines, e.g. during breakdowns of cold chain equipment or power failures.

1.4 **VULNERABILITIES OF THE COLD CHAIN**

1.4.1 Healthcare Personnel

Studies suggest that knowledge of appropriate management of the cold chain is poor in the healthcare personnel meant to handle the vaccines. Breaks in the cold chain are more frequent and the vaccine potency is compromised more when vaccines have been stored for too long (Haworth et al., 1993).

For some health care workers, the term “cold chain” implies, incorrectly, that avoiding heat is the sole objective, and that unduly low temperatures would not be an issue for vaccine storage and delivery (Ren et al., 2009).

1.4.2 Accidental Freezing of Vaccines

Freezing of vaccines is also a problem because there has been a lot more focus in the industry on protecting vaccines from the heat and less focus on protecting them from the freezing conditions (Wirkas et al., 2007). As a result, accidental freezing of vaccines is largely an overlooked problem (Matthias et al., 2007). Vaccines are easily frozen when they are pushed up against the evaporator plate of a domestic refrigerator or when they are placed in cooler boxes for transportation and come into contact with the ice packs or frozen gel packs, with insufficient ventilation in the compartment.

A vaccine cold chain freezing study in Port Moresby, Papua New Guinea (PNG) highlights technology needs for hot climate countries (Wirkas et al., 2007). In this study 14 data loggers were packed with vaccine vials at the national vaccine store and sent to peripheral locations in the health system.

The temperatures that the data loggers recorded during their passage along the cold chain indicated that heat damage was unlikely, but that all vials were exposed to freezing temperatures at some time. The commonest place where freezing conditions existed was during transport. The freezing conditions were likely induced by packing the vials too close to the ice packs that were themselves too cold, and with insufficient insulation between them.

This situation was rectified and a repeat dispatch of data loggers demonstrated that the system had indeed been rectified. Avoiding freeze damages becomes even more important as the price of freeze-sensitive vaccines increases with the introduction of more multiple-antigen vaccines.

This low-cost high tech method of evaluating the cold chain function is highly recommended for developing and industrialised nations and should be used on a regular basis to check the

integrity of the vaccine cold chain. The study highlights the need for technological solutions to avoid vaccine freezing, particularly in hot climate countries.

The study also revealed the human behavioural element of the cold chain which is the incorrect packing of vaccines in vaccine carriers for transport between stores and the field. Retraining in the way vaccines are packed should improve the situation in the short term. A wider lesson to be learned from this study is that the entire cold chain, however well it is installed, is vulnerable to human error.

Published reports and field evidence now demonstrate that freezing of vaccines in the cold chain is common place, potentially resulting in the widespread delivery of vaccines whose potency has been compromised by the disassociation of antigen from the adjuvant. These studies have been in hot climate countries such as Ethiopia, India, Indonesia and Malaysia; and in mixed climate countries such as Australia, Taiwan and Turkey and cooler countries (Wirkas et al., 2007).

Increased awareness of the danger of accidental freezing has prompted studies of the cold chain, designed to characterize the risks of vaccine exposure to freezing temperatures. However there had never been a systematic review or cross-comparison of these studies. This paper by (Matthias et al., 2007) attempted to review and analyse the current global data on freezing temperatures within the vaccine cold chain.

This analysis highlighted that accidental freezing is pervasive, occurring in both developing and developed countries as well as within both the storage and transport segments of the cold chain.

In the six studies that analysed the exposure of vaccine shipments to freezing temperatures as they travelled through both shipment and storage segments of the cold chain from either national or regional stores all the way to health clinics, the findings were even more striking; between 75% to 100% of the vaccine shipments were exposed to freezing temperatures at least once during the distribution process. These comprehensive studies suggest that the risk of damaging freeze-sensitive vaccines is present in virtually every stage of the cold chain.

Across the four scenarios analysed (developed versus developing country, transport versus storage) the average proportions of exposure ranges from 14% to 35%.

Epidemiological studies have pointed to vaccine freezing as a possible contributor to low immune response in vaccinated individuals and the existing literature relating freeze

exposure to potency loss is compelling enough to suggest some degree of impact on immune response (Matthias et al., 2007).

The recommendations from this study to minimize accidental freezing are these simple and proven tools available today:

- To investigate vaccine freezing in cold chains; immunisation programmes are to use temperature monitoring studies such as the one the researcher is conducting to identify where the problems are.

- To apply innovative cold chain practices, e.g. using cool water packs instead of frozen ice packs during cold box transport to avoid the freezing commonly associated with improper ice-pack conditioning, storing the more heat stable vaccines in air conditioned rooms and conducting limited transport at ambient temperatures.

- To improve training; educating vaccine managers and handlers about freeze sensitive vaccines, providing clear guidelines and vaccine handling procedures.

- Update cold chain infrastructure; improved cold chain equipment is an important aspect of freeze prevention.

- To take advantage of vaccines' heat stability; freezing temperatures damage freeze sensitive vaccines more quickly than ambient temperatures. Vaccine vial monitors, required on all vaccines distributed by UNICEF, allow vaccine programs to utilise the natural heat stability of some vaccines to expose them to temperatures warmer than 8°C for limited time without the risk of heat-damage.

- To create a system-wide policy to avoid freeze damage; policy changes (at the global and country level) are needed to prioritise the prevention of freezing in the cold chain and apply resources to raising awareness, training and equipment infrastructure.

1.4.3 **Lack of Adequate Cold Chain Infrastructure**

Lack of cold chain infrastructure i.e. cold chain equipment (vehicles and refrigerators), adequate vaccine storage areas and insufficient resources is a major problem especially in remote and rural areas. There must be a contingency plan to safeguard the vaccine if there is a long power cut or if the refrigeration equipment fails, for e.g. having a power generator on site and a written emergency retrieval and storage procedure.

The cumulative effect of inadequate transport, poor storage and exposure in consulting rooms during clinics may be considerable.

The study done in Northern territory of Australia, showed that despite availability of reliable sources of power, modern refrigeration equipment with ready access to parts/repairs, and reliable transportation, vaccines can easily be exposed to temperatures outside the recommended range during transportation and storage at health facilities, whether rural or urban (Miller and Harris, 1994).

A lot more vaccines were at risk of deterioration owing to extended storage (i.e. from overstocking). Considering that the vaccines usually reached the health facility in one day or less, storage of vaccines for more than one month is unnecessary (Miller and Harris, 1994).

Multi-dose vials that were kept for more than one session after opening and giving clients vaccines to store at home by GP's also added to the risk of deterioration of the vaccines. The greatest exposures occurred during storage (Miller and Harris, 1994).

The first cold chain study that was done in Europe, Hungary: Transport and storage of vaccines in Hungary, proved that even in a temperate climate and with a reasonably well organised public health service there can be significant weaknesses in the transportation and storage of vaccines. The vaccines were exposed to sufficiently high temperatures, there were significant delays and exposures during transportation of vaccines, the quality of the two models of refrigerators and the methods of storage cannot ensure safe storage at all times and the vaccines were stored for too long at the child health centres (Lugosi and Battersby, 1990).

1.4.4 **Traditional Customs and Beliefs**

According to local custom in some minority areas, new-born infants cannot be taken out of the home during the first month after birth. This poses a challenge where home births are a norm. At home immunisation is the only way to deliver the first HepB vaccine dose on time among these populations.

1.5 **RISKS ASSOCIATED WITH POOR COLD CHAIN MAINTANANCE**

The loss of vaccine effectiveness due to cold chain exposures to adverse conditions is cumulative, permanent and irreversible.

Vaccines are one of the most important tools we have to protect the health of our nation's most vulnerable citizens, the children. Although routine immunisation has greatly reduced

the incidence of these diseases, outbreaks do occur from time to time. This raises questions on the effectiveness of the immunisation programme, for the proper functioning of which the cold chain is vital. High coverage would have little meaning if the vaccines administered had lost their potency (Hanjeet et al., 1996).

An improperly functioning cold chain can lead to wasted vaccines, missed opportunities to immunize due to lack of vaccines, and children receiving vaccines that do not protect them as intended or that actually make them sick ("IMMUNIZATIONbasics - SnapShots Volume 8," 2008).

Vaccination not only protects the individual but curb the spread of disease within the community. There only needs to be a certain percentage of individuals within the community who are immunised (herd immunity), then the spread of that disease will be prevented. There are no effective alternatives to immunisation for protection against some serious and sometimes deadly infectious diseases.

If immunisation coverage drops for conditions like measles, outbreaks may occur. It is important to maintain a high level of immunisation coverage even when the condition is becoming rare. Failure to maintain high measles immunisation coverage can lead to re-emergence and outbreaks, as it happened in the United States in 1989-1991. The measles epidemic was responsible for 55 000 cases and more than 120 deaths ("Immunisation | Western Cape Government," 2013).

In a country like India where there is a weak health infrastructure, unsanitary conditions and overcrowding, communicable diseases like poliomyelitis find a conducive environment. A combination of the above factors is believed to be responsible for the increased incidence of polio in India from April through to June each year (Samant et al., 2007).

1.5.1 A Successful Immunisation Programme Relies on a Number of Factors

- Maintaining the vaccine cold chain from the time of manufacture until the vaccine is administered to the recipient to ensure that vaccine potency is maintained.

- Staff involvement. Vaccine management is the responsibility of all staff. Staff should be trained or educated on how to appropriately store vaccines, read and record daily refrigerator temperatures and reset data loggers and vaccine refrigerator monitors or any other temperature monitoring device used in the practice.

- Adequate equipment, like refrigerators, appropriate validated vehicles, data loggers, thermometers etc.

- Accessibility to replacement equipment or service areas to avoid or minimise equipment breakdowns
- Availability of back-up minimum/maximum thermometer or data logger in the refrigerator in case of battery or technical failure on the primary thermometer.

- Availability of back-up power supply in the event of extended power outage e.g. Power generators.

- Adequate storage facilities or space to allow enough stock handling and minimise stock outs.

- Decentralisation of the vaccine distribution and delivery system where possible. This will reduce transit time and exposure to unfavourable temperatures during transportation.

- Adequate staff complement to ensure staff members are not overworked to minimise chances of medical errors.

- Full support from the community. Parents should be willing to vaccinate their children and any vaccine safety concerns they might have should be discussed with the health care professional.

1.5.2 How to Handle a Break in the Cold Chain

Any out of range temperatures should prompt immediate action to fix the problem, with the results of these actions documented. The disruption in the cold chain should be investigated to correct the problem and prevent reoccurrence.

If the adsorbed vaccines (DPT, DT or TT) have been frozen, particles will form in the vaccine. These particles will sink quickly to the bottom of the vial. An easy way to check whether such a vaccine has been frozen is to do a “shake test” with a vial from the suspected stock, and if possible, together with a vial which has never been frozen.

A shake test is done by taking the two vials and shaking them vigorously and the rates at which the cloudy material separates from the clear fluid in the two vials should be compared. If the suspected vial rapidly clears and the material sinks to the bottom of the vial much more quickly than the material in the unfrozen vial, do not use, it has probably been frozen.

One should seek the advice of the manufacturer if there are any concerns of cold chain breach. While waiting for the manufacture’s recommendations, the affected vaccines should be immediately marked “do not use” with date and time, isolated and kept at recommended storage temperature (“MOH Guidelines on how to maintain the vaccine cold chain”, 2005).

1.6 BACKGROUND OF TEST PRINCIPLES USED IN THE STUDY

1.6.1 Cold Chain Monitor Cards (CCMs)

Each CCM card has a heat sensitive indicator which is in the form of a strip with four windows (1, 2, 3 and 4) and is effective in indicating whether the vaccines were exposed to higher than recommended temperatures or not. The CCM cards are used to estimate the length of time that vaccines have been exposed to high temperatures. The indicator operates by recording the cumulative effect of exposure to temperatures above 10°C (“123”) and 34°C (“4”) (Lugosi and Battersby, 1990), i.e. the first 3 windows of the indicator (1,2 and 3) will change gradually and irreversibly from white to pink when the temperatures are above 10°C. First 1 will change then 2 and then 3. The 1, 2 and 3 indicators change relatively slowly, for instance, at a temperature of 21°C, window 1 changes its colour entirely in 2 days; window 2 in 6 days and window 3 in 11 days, as shown in Figure 1.2. Window 4 will change colour if exposed to temperatures of above 34 ºC for at least 2 hours.

To interpret the CCM card:

- If windows 1, 2, 3 and 4 are all white, use vaccines normally.

- If windows 1 only, 1 and 2, or 1, 2 and 3 are completely pink, but window 4 is still white it means that the vaccine has been exposed to a temperature above 10ºC but below 34ºC for the number of days as shown behind the CCM card (see Figure 1.2*).*

- If window 4 is pink it means that there has been a break in the cold chain of a temperature higher than 34ºC for a period of at least two hours. This would indicate that a serious cold chain failure has occurred, the vaccines cannot be used and an immediate investigation is needed.

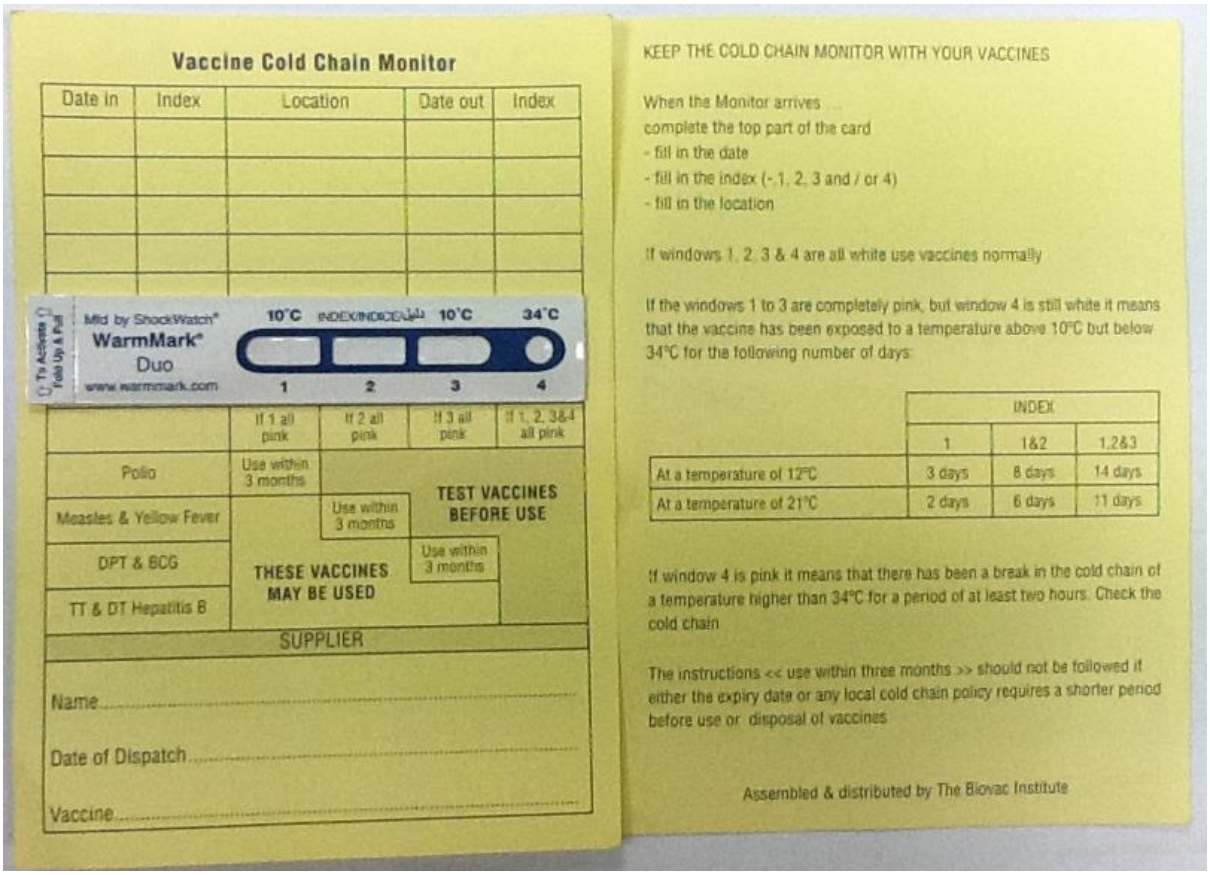


Figure 1.2: Vaccine Cold Chain Monitor

The CCM cards are not potency indicators but show whether the vaccines had been exposed to or above the stated temperatures for longer than the stated time limits (Lugosi and Battersby, 1990). The potency of the vaccine cannot be determined by the status of the cold chain monitor card. Vaccines delivered through UNICEF are shipped with one CCM card per 3000 doses of vaccines.

The higher the temperature is above the CCM card threshold, the more rapidly the colour changes to pink, which is irreversible even when exposed to lower temperatures again. The manufacturer recommends that the CCM cards be refrigerated for at least 30 minutes before activation. Activation is carried out by pulling out the tab on the left hand side of the strip (Hanjeet et al., 1996). On each CCM card, are written the instructions to interpret the readings.

1.6.2 Cold Mark Freeze

The cold mark freeze watch is used to monitor temperature of vaccines which should not be exposed to temperatures below 0°C. The freeze watch consists of a small bulb of red liquid at the end of a glass tube, which remains colourless at temperatures above 0°C (see Figure 1.3). If the vaccine is exposed to temperatures below 0°C for more than an hour, the bulb in the glass tube is broken and the liquid is exposed, then the glass tube will look purple and no longer clear (Hanjeet et al., 1996).



Figure 1.3: Cold Mark Freeze Watch

1.6.3 Gemini Data Loggers

Data loggers are continuous temperature recording devices, which offer a historical record of refrigerator/ vaccine temperature. The data logger has a limited life for recording data, they do not continue indefinitely but stop automatically when the memory is full (Wirkas et al., 2007).

Gemini data loggers (Tiny tag talk 2) are the size of a 35mm film canister (see Figure 1.4). They are reliable, cylindrical battery operated electronic devices used for monitoring temperature ("Tinytag News | Temperature data loggers: Tinytag Talk 2," n.d.).This device records the actual temperature in the shipper carrying the vaccines and the surrounding area where it's placed at different pre-set intervals. A computer is then required to download the data via a USB cable to be able to view the temperatures which the vaccines were exposed to and for how long they were exposed to all those different temperatures during transportation or at the storage area.

Tiny tag Explorer Software is used for this. It is a data logging software package that makes it possible to configure, view and analyse data. It's called SWCD-0040 as per manufacturer. It's an intuitive windows program for all tiny tag data loggers. The offloaded data can be presented either as a summary or in detailed, configurable graphical or tabular views.



Figure 1.4: Tiny Tag Talk 2

1.7 VACCINES COLD CHAIN MONITORING IN SOUTH AFRICA

All vaccines used in the EPI in SA, are manufactured according to strict safety requirements and are evaluated by the MCC to ensure efficacy, quality and safety before registration and approval for marketing. In addition, these vaccines meet WHO standards of quality, safety and efficacy.

The first week of August has been declared National Immunisation Awareness Week in South Africa.

Despite the advances in the national EPI in the country, there is some evidence that RSA faces a number of challenges. The vaccination coverage is low, with only two-thirds of children estimated to receive the full series of three doses of the DTP vaccine by one year of age, measles outbreaks are often and the community knowledge of immunization is low (Wiysonge et al., 2012).

This study by (Wiysonge et al., 2012) found that the main challenges were linked to health care workers having insufficient knowledge of vaccines, immunisation and cold chain; the public with anti-immunisation rumours and reluctance from parents to immunise their children and the health system with insufficient financial and human resources.

Other challenges included high staff turnover, poor communication among stake holders and sub-optimal collaboration between the public and private health sectors.

Currently, Litha Vaccines®, a biopharmaceutical company based in Gauteng, Meadowdale is the main distributor of these vaccines to the public sector, and they deliver to different depots in all the 9 provinces in RSA.

In light of what has been discussed above, the question is whether the vaccines transported by Litha Vaccines® to our local provincial depots are maintained at 2°C - 8 °C throughout distribution as per WHO and manufacturer's recommendations.

The cooler boxes and the packing configurations that were used at the time this study was conducted at Litha Vaccines® Meadowdale had never been validated before. There has also been no studies published on the South African cold chain or its monitoring, so there was no documented data that proved that these shipments are really transported at these temperatures, except the use of cold chain monitors with which we never get formal reports from the depots if these monitors are satisfactory or not.
The healthcare workers in the country rely on the national policies and guidelines governing immunisations, vaccines storage and distribution and the cold chain thereof. Are the vaccines being exposed to unsafe temperatures or not with the current distribution system?
We also do not have any formal cold chain monitoring/ validation systems or studies going on. This then means that we are not able to pick up on problems that may arise timeously and efficiently address them before we suffer the maximum impact.

Thus the need for this study: Evaluation of vaccines cold chain monitoring during distribution from Litha Vaccines to the Medical Depots in Gauteng.

1.8 AIMS AND OBJECTIVES OF THE STUDY

The aim of the study was to assess if the cold chain is maintained at 2°C - 8°C during vaccine distribution from Litha Vaccines® to the different depots in the Gauteng Province in RSA, to establish if Litha Vaccines® has a secure cold chain. The objectives of the study were:

1. To monitor or assess the actual temperatures at which the vaccines were transported from Litha Vaccines to the medical depots in Gauteng.

2. To assess the number of Cold Chain Monitor (CCM) cards that was negatively affected by the adverse temperatures on these routes.

3. To assess the number of freeze watches that was negatively affected by the adverse temperatures on these routes.

1.9 LIMITATIONS OF THE STUDY

- This study made no attempt to evaluate monitoring of the cold chain at the depots or at immunisation points (clinics and hospitals). The depots, clinics and hospitals have their own standard operating procedures that are aimed at monitoring the cold chain and evaluating the cold chain monitoring in their daily operations.

- The study did not look at the conditions of the vaccine storage equipment at Litha or at the depots.

- This study also did not attempt to measure possible loss of potency associated with the out of the recommended range temperatures. The link has already been well established on the loss of potency associated with vaccine freezing (Wirkas et al., 2007).
- The study was carried out in the cooler autumn and winter months, a possible revaluation might be necessary to validate the study during the hotter summer months.

Failure to monitor the cold chain all the way means that efforts to maintain the cold chain might be futile since the end user might still receive a vaccine that has lost its potency along the distribution channel.

CHAPTER 2

2. RESEARCH METHODOLOGY

2.1 STUDY DESIGN

This was a quantitative retrospective study in which the information was extracted from the temperature monitoring devices after each delivery to the sites over a discreet period of time.

3M type Cold Chain Monitor cards (CCM cards), cold mark type Freeze Watches (FW) and the Gemini data loggers were used to monitor the vaccines cold chain.

The temperature readings were recorded by the data loggers at 5 minute intervals during the trips from Litha Vaccines to the medical depots. The temperature was downloaded from the data loggers at Litha Vaccines after each trip using the tinytag explorer software.

The temperature readings were observed in relation to factors such as the weather season in that period, the outside temperature on that particular day, the time of day when the vaccines were transported and the vaccine handler's level of competence in vaccine handling.

A questionnaire (see Appendix 1) was designed for the purposes of this study. This was to gather the information regarding the CCM cards and the FW's from the receiving managers at the depots. The qualifications or the job title of the vaccine handler was recorded on the questionnaire.

This questionnaire was then sent back to Litha immediately after delivery with the Litha driver to be analysed. It included information about the time of delivery, the outside temperature on the particular day and which side of the shipper the affected monitoring device was found. The packing configuration of the shipper is in Figure 2.1 below, section 2.5.

The study was only looking at the vaccine storage conditions during transit from Litha Vaccines to the medical depots in relation to GDP. It was not looking at the conditions of the storage equipment at Litha or at the depots (GWP).

2.2 SAMPLE SIZE

The sample size estimation was done using the formulae:

$$SS = \frac{Z^2 * (P) * (1-P)}{C^2}$$

SS - minimum sample size.

P - Prevalence of CCM cards and FWs temperature deviations from the required.

Z - Z-value 1.96 for 95% confidence level.

C - Confidence interval, degree of precision.

$$SS = (1.96)^2 \times 50\% \times (1-50\%) / (0.05)^2$$
$$= 3.8416 \times 0.5 \times 0.5 / 0.0025$$
$$= 384$$

P was given as 50% as we did not get any returns at Litha Vaccines, from cold chain maintenance problems from the public sector as explained further in section 2.6 below. Therefore the minimum sample size for this study was 384 CCM cards, 384 FWs and 192 tiny tag loggers. Thus 64 CCM cards, 64 FWs and 32 tiny tag loggers were to be evaluated per site.

The Prevalence (P) for sample size calculation was taken as 50% as that would give us the maximum sample size that can be used as per statistical principles, in consultation with the statistician, Gitau T at Wits University.

To cover the required sample size, we had 3-4 trips per site using on average 10 data loggers per trip.

Only 10 data loggers were available for the study. The loggers are an expensive resource hence they are not routinely used at Litha Vaccines for day to day deliveries to the depots. The loggers have to be calibrated once a year and the batteries also need to be replaced as often as required.

There needs to be proper staff training on how the logger is utilised and written procedures on how to use/handle the data loggers, how to retrieve them after the daily trips and ensure they are not lost or missing and what to do in case of malfunctioning of the loggers. The company will also need to have the appropriate equipment (computer and the software) to be able to download the data.

Additional human resources might be required to be able to download and assess the loggers daily.

2.3 PARTICIPANTS

The study was conducted in South Africa, in the Gauteng Province. Litha Vaccines® is the main distributor of vaccines in the public sector in the country. They also distribute to the private sector, but for the purposes of this study, we were only evaluating the distribution in the public sector.

The company also distributes adult vaccines but again the focus was only on the children's vaccines so as to put perspective for the EPI managers in the province. Among various vaccine end users, the paediatrics segment has the largest share of the market and is expected to grow at the highest Compound Annual Growth Rate (CAGR) of 11,8% from 2014 to 2019 ("Vaccines Market worth $57.8 Billion by 2019," 2015).

Litha Vaccines® distributes vaccines in all the nine provinces but the study focused only in 1 province, Gauteng province where Litha Vaccines® is also based. Gauteng is 1 of the main economic hubs in the country.

We only looked at the first leg of the distribution chain i.e. from Litha Vaccines® to the main 6 depots in Gauteng which are:

- Auckland Park/ Husthill Depot
- Pretoria Regional Pharmacy
- West Rand Regional Pharmacy
- Vaal Regional Pharmacy
- Langlaagte Depot
- Hillbrow Pharmacy

The 4 sites (Hillbrow Pharmacy, Auckland Park Depot, Langlaagte Depot and West Rand Regional Pharmacy) are all at a distance of around 18, 2 km away from Litha Vaccines. Pretoria regional pharmacy is 56, 9 km away from Litha whereas Vaal Regional Pharmacy is 91,7 km away. All the sites are located in the urban areas with similar patient demographics. The sites largely service the no income to low income groups of the patient population. The majority of the patients are from previously disadvantaged communities.

On a daily basis, the shipments are subjected to effects of traffic congestion versus taking longer routes with better traffic flow. These sites all experience similar weather and climate conditions.

If any of the sites could not participate in the study for one reason or another, we could extrapolate the results to those sites due to the similarities in the sites.

As per routine, after the vaccines have been received at Litha, they are distributed to the different depots in all the nine provinces from whence they are then distributed to the clinics, hospitals and immunisation centres.

2.4 MATERIALS

A temperature monitoring device is an essential and critical requirement for temperature monitoring of vaccines. All equipment used for recording, monitoring and maintaining temperature and humidity conditions should initially be validated and thereafter calibrated on a regular basis (Bishara, 2006).

The temperature monitoring devices should be calibrated to within 1 degree of accuracy. This should be done annually, as these devices tend to lose their accuracy over time. As they get less accurate, it may result in wastage of potent vaccines. To ensure optimum function of the device, the batteries should be changed every 6 months (Vaccine Storage and Handling Guidelines, Ontario, 2013).

The devices used in this study were:

- Cold Chain Monitor Cards
- Cold Mark Freezes
- Gemini data loggers

CCM cards and the FW's are routinely used at Litha Vaccines®. Chapter 1, section 1.6 provides full details with respect to the devices.

2.5 PROCEDURE AND METHOD

Vaccine damage depends on the ambient temperature and the duration of exposure to adverse temperatures, therefore any assessment of the vaccine cold chain should document both variables (Wawryk et al., 1997).

Unlike heat sensitive monitoring cards, cold sensitive freeze watches cannot provide an accurate indication of the cumulative time of exposure of a vaccine to cold. Therefore we used electronic data loggers to measure temperature and time. Thus, the study also provided

data on the time and duration of exposure at temperatures below 0°C, in the assessment of the cold chain.

Procedure:

- Vaccines are routinely dispatched with one CCM card and one FW from Litha Vaccines®.

- For the purposes of this study, one additional CCM card and one additional FW were added together with one tiny tag logger per shipper for the vaccines destined to the depots.

- The CCM cards and the data loggers were stored in the fridge (2°C -8°C) until required for use.

- The CCM cards were activated on leaving Litha Vaccines® and the calibrated data loggers were pre-set to record the temperature every 5 minutes on their journey to the depots. The data loggers are calibrated once a year.

- The FWs were stored at room temperature (25°C) to prevent accidental exposure to freezing conditions as they are always active.

- One CCM card and one freeze watch were placed at the bottom of the shipper and also on the top side of the shipper while the tiny tag logger was placed only on the top side of the shipper, as shown in Figure 2.1.

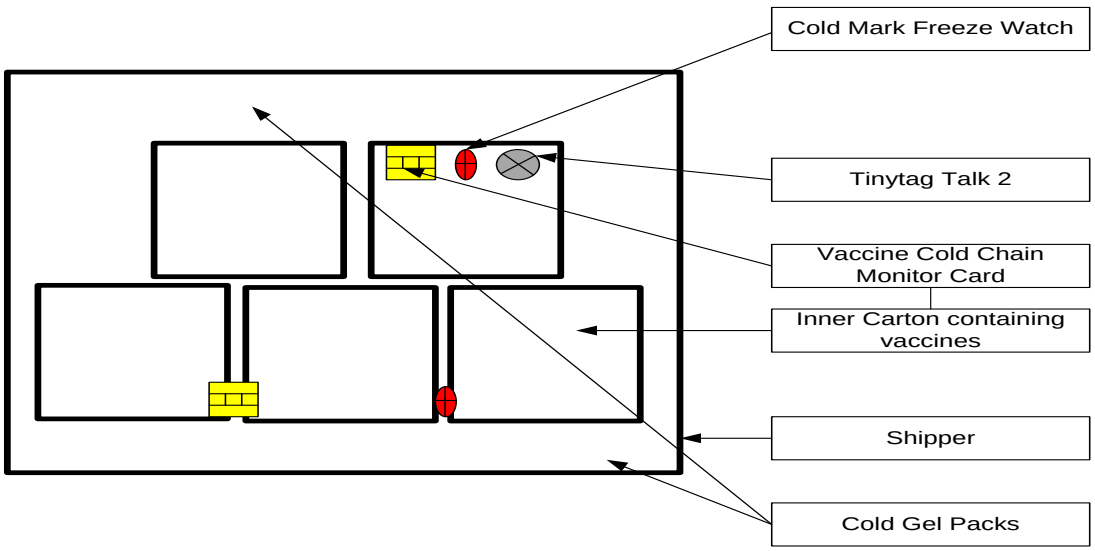


Figure 2.1: Vaccine Shipper Configuration (Front View)

- After each delivery, the receiving manager at the depot assessed the cold chain monitoring devices i.e. the CCM cards and the FWs.

- The receiving manager then provided information on the status of the vaccine cold chain when the vaccines were received at that particular depot based on the information retrieved from the CCM cards and the FWs.

- The information provided by the receiving managers was captured by filling in a questionnaire (Appendix 1) that was specifically designed for the purposes of this study immediately on receipt of the delivery.

- The information in the Appendix 1 included the number of CCM cards that were found in the shipper, the number of the CCM cards that were affected by inadvertent temperatures and the extent to which the CCM cards were affected.

- This would give an indication as to whether the vaccines were exposed to the temperatures above 10°C at any point in this journey or not.

- The same information was also captured for the FWs found in the shipper on receipt. The FW's are used to monitor the temperature of vaccines which should not be exposed to temperatures below 0°C.

- The FW will only capture the fact that the vaccine was exposed to freezing temperature at some point on the journey for more than an hour or not. It is not possible to assess the extent to which the FW or the vaccine was affected by the undesirable temperatures.

- The questionnaire also seeks to find out, where in the shipper, the affected device was found i.e. either at the bottom part of the shipper or at the top part of the shipper. Please see Figure 2.1 above for the packing configuration.

- The driver then took the questionnaire and the Tiny tag logger with, to Litha Vaccines® where the information on the data logger was downloaded on a computer and analysed.

- The information on the questionnaire was also analysed as received.

The trips to the depots were taken as follows:

1. **Hillbrow Pharmacy:**
   - There were 4 shipments that we sent to Hillbrow Pharmacy.
   - The first shipment was sent on the 20th March 2012 sending Prevenar and Rotarix with 9 data loggers.
   - The second shipment was sent on the 25th April 2012 sending Prevenar with 4 data loggers.
   - The third shipment was sent on the 19th June 2012 also sending Prevenar with 10 data loggers.
   - The last shipment was sent on the 20th August 2012 sending Pentaxim with 8 data loggers.
   - Each shipper had 2 CCM cards and 2 freeze watches as per protocol. One on top and one at the bottom of the shipper.

2. **Auckland Park Depot**
   - We sent 3 shipments to Auckland Park Depot.
   - The first shipment was sent on the 8th June 2012 sending Prevenar with 9 data loggers.
   - The second and third shipments were sent on the 30th July and 13th August 2012 respectively and they were both transporting Penatxim with 10 data loggers each.
   - Each shipper had 2 CCM cards and 2 freeze watches.

3. **Langlaagte Depot**
   - At Langlaagte depot, we sent 4 shipments.
   - The first was on the 16th May 2012, transporting Prevenar with 10 data loggers.
   - The second shipment was on the 29th May 2012, transporting Pentaxim with 10 data loggers.
   - The third shipment transported Prevenar on the 06th June 2012 with 10 data loggers also.
   - The last shipment was on the 12th July 2012 and was transporting Prevenar with 2 data loggers.
   - Each shipper had 2 CCM cards and 2 freeze watches.

4. **West Rand Regional Pharmacy**
   - We sent 2 shipments to the West Rand Regional Pharmacy.
   - The first transporting Pentaxim was on the 24th August 2012 with 8 data loggers.
   - The second shipment was transporting Measles and Td on the 18th December 2012 and had only 2 data loggers.
   - Each shipper had 2 CCM cards and 2 freeze watches.

No shipments were evaluated for Pretoria Regional Pharmacy and Vaal Regional Pharmacy due to the unwillingness of the sites to participate in the study.

2.6 CURRENT COLD CHAIN MONITORING

Currently at Litha, we do not get any returns due to cold chain maintenance deviations from the public sector. Reasons for this differ from one depot to another but it would also be largely to the fact that:

- In some depots, stock is not assessed on arrival for cold chain maintenance and therefore, we are not able to confirm if that stock was transported within required temperatures or not. The people in charge at the depots have to check the conditions of the CCMs and FWs before storing or dispatching the vaccines. Should there be any deviation on the CCM cards and FW's, they are to follow up with Litha Vaccines for further investigation and they should adhere to their internal processes and procedures.

- Some depots will store the stock in the fridge on arrival and only attend to it when attending to their orders to the clinics and hospitals. At this point, should there be a deviation in the CCM cards and FW's they will alert Litha Vaccines for further investigation.

- Not having enough staff complement to assess stock on receipt for cold chain compliance or deviations thereof.

- Lack of training on proper procedures for the staff members, such that if there was a bridge in the cold chain, it can be immediately investigated to establish the cause and prevent recurrence.

Basically, the cold chain principles are adhered to in some instances (certainly from Litha's perspective) but there is no cold chain monitoring happening at all, anywhere in the distribution chain. This is why this study is of such significance. Is the cold chain maintained in this distribution leg?

The returns we get from the private sector are largely due to courier failures which often results in cold chain failure and not necessarily because of cold chain failure. For e.g. the courier company delivering the stock at a wrong address and the recipient not knowing about the storage conditions of the contents and thus storing it outside the fridge. Sometimes the courier

company would take too long, for example, the whole weekend or if there is a holiday in between, with the parcel in their hands before taking it to the customer (doctor’s room or nurse), etc.

CHAPTER 3

3. RESULTS AND DATA ANALYSIS

3.1 SUMMARY

There was a response rate of 50%. Six sites were to be evaluated for cold chain monitoring. Only 3 were fully evaluated as per protocol with data available for analysis i.e. Hillbrow Pharmacy, Langlaagte Depot and Auckland Park/Hursthill Depot.

Vaal Regional Pharmacy declined to be part of the study while Pretoria Regional Pharmacy only gave verbal consent and declined to give written and signed consent and therefore the sites could not be evaluated.

The West Rand Pharmacy was unable to gather enough data to allow for analysis for purposes of this study due to the low number of orders received from this site. Thus this site was also excluded in the final report.

Table 3.1 below shows a summary of the trips taken in the study and the data that was analysed.

Table 3.1: A summary of the Trips Taken in the Study and the Devices Analysed for All Sites

Site	No of Trips	No of CCM's Analysed	No of FW's Analysed	No of Data Loggers
Hillbrow Pharmacy	4	62	62	31 launched and 24 analysed
Auckland Park Depot	3	60	60	30 launched and analysed
Langlaagte Depot	4	64	64	32 launched and analysed

Details of the trips and the data analysed are shown in tables 3.2 – 3.5 below for each site that participated in the study.

3.1.1 Hillbrow Pharmacy

Table 3.2: Trips and Devices Analysed for Hillbrow Pharmacy

Trip No.	Date	Temperature Reading in Johannesburg (Min-Max, °C)*	Name of Vaccine	No of Loggers	No of Loggers Analysed	No of CCM's Analysed	No of FW's Analysed	Duration of the Trip
1	20/03/2012	12.3 - 28.1	Prevenar and Rotarix	9	6	18	18	09:16-11:31
2	25/04/2012	9.1 - 15.2	Prevenar	4	0	8	8	09:00-11:08
3	19/06/2012	6.0 - 19.7	Prevenar	10	10	20	20	08:15-12:30
4	20/08/2012	7.0 - 26.5	Pentaxim	8	8	16	16	09:45-11:05
Total				**31**	**24**	**62**	**62**	

*Weather data provided by the South African Weather Services

- Thirty one data loggers were launched but 24 were available for analysis. Seven data loggers were incorrectly launched.
- The first shipment transported Prevenar and Rotarix with 9 loggers on the 20/03/2012. Three of the loggers had inconsistent data.
- The 2nd shipment transported Prevenar with 4 loggers on the 25/04/2012. All the 4 loggers were incorrectly launched and had inconsistent data.
- The 3rd shipment transported Prevenar with 10 loggers on the 19/06/2012.
- The 4th shipment transported Pentaxim with 8 loggers on the 20/08/2012.
- Of the 31 loggers that were launched, 24 were correctly launched and were analysed.
- A total of 7 loggers had inconsistent data. The reason for this is unclear, the loggers may have been incorrectly programmed, there may have been an error in the data retrieval process or the loggers may have malfunctioned. Thus data from these loggers was not included in the report.
- A total of 62 CCM cards and 62 FWs were analysed.

3.1.2 Auckland Park Depot

Table 3.3: Trips and Devices Analysed for Auckland Park Depot

Trip No	Date	Temperature Reading in Johannesburg (Min-Max, °C)*	Name of Vaccine	No of Loggers	No of Loggers Analysed	No of CCM's Analysed	No of FW's Analysed	Duration of the trip
1	08/06/2012	2.5 - 21.0	Prevenar	10	10	20	20	08:00-10:30
2	30/07/2012	2.0 - 20.4	Pentaxim	10	10	20	20	08:45-13:15
3	13/08/2012	-0.1 - 18.4	Pentaxim	10	10	20	20	10:30-15:00
Total				**30**	**30**	**60**	**60**	

*Weather data provided by the South African Weather Services

- Thirty data loggers were analysed.
- The first shipment transported Prevenar with 10 loggers on the 08/06/2012.
- The 2nd shipment transported Pentaxim with 10 loggers on the 30/07/2012.
- The 3rd shipment transported Pentaxim with 10 loggers on the 13/08/2012.
- All the 30 loggers were correctly launched and data was analysed.
- A total of 60 CCM cards and 60 FW's were analysed.

3.1.3 Langlaagte Depot

Table 3.4: Trips and Devices Analysed for Langlaagte Depot

Trip No	Date	Temperature reading in Johannesburg (Min-Max, °C)*	Name of Vaccine	No of Loggers	No of Loggers Analysed	No of CCM's Analysed	No of FW's Analysed	Duration of the trip
1	16/05/2012	4.6 - 20.7	Prevenar	10	10	20	20	07:40-13:15
2	29/05/2012	4.4 - 19.9	Pentaxim	10	10	20	20	08:30-11:30
3	06/06/2012	3.5 - 20.6	Prevenar	10	10	20	20	08:00-11:50
4	12/07/2012	3.7 - 19.8	Prevenar	2	2	4	4	07:50-11:00
Total				**32**	**32**	**64**	**64**	

*Weather data provided by the South African Weather Services

- Thirty two loggers were analysed.
- The first shipments transported Prevenar with 10 loggers on the 16/05/2012.
- The 2nd shipment transported Pentaxim with 10 loggers on the 29/05/2012.
- The third shipment transported Prevenar with 10 loggers on the 06/06/2012.
- The 4th shipment transported Prevenar with 2 loggers on the 12/07/2012.
- A total of 64 CCM cards and 64 FWs were available for analysis.

3.1.4 West Rand Regional Pharmacy

Table 3.5: Trips and devices analysed for West Rand Regional Pharmacy

Trip No	Date	Temperature reading in Johannesburg (Min-Max, °C)*	Name of Vaccine	No of Loggers	No of loggers Analysed	No of CCM's Analysed	No of FW's Analysed	Duration of the Trip
1	24/08/2012	11.4 - 29.0	Pentaxim	8	0	16	8	08:00-11:45
2	18/12/2012	15.7 - 27.1	Measles and Td	2	2	4	4	08:00-13:55
Total				**10**	**2**	**20**	**12**	

*Weather data provided by the South African Weather Services

- The first shipment transported Pentaxim with 8 loggers on the 24/08/2012.
- The 2nd shipment transported Measles and Td on the 18/12/2012 and had 2 loggers.

- Only 2 loggers were correctly launched and thus this data was not analysed for the report because the data is statistically insignificant.
- A total of 20 CCM cards and 12 FW's were analysed but was not included in the final report since all data from this site was not included.

3.1.5 Pretoria Regional Pharmacy

This site declined to participate in the study. The site gave only verbal consent and declined to give written, signed consent and therefore the site could not be evaluated.

3.1.6 Vaal Regional Pharmacy

This site declined to participate in the study citing lack of willingness from the pharmacy manager to be part of the study.

3.2 RESULTS AND DATA ANALYSIS

3.2.1 Sites

The 3 sites that were evaluated (Hillbrow Pharmacy, Auckland Park Depot and Langlaagte Depot) are all at a distance of around 18,2 km away from Litha Vaccines. West rand regional pharmacy is also at the same distance. Pretoria regional pharmacy is 56, 9 km away from Litha whereas Vaal Regional Pharmacy is 91,7 km away.

Loosing Pretoria regional pharmacy and Vaal regional pharmacy in the study meant we were not able to evaluate the effectiveness of the cold chain monitoring at longer distances than 18, 2 km.

50% response rate was adequate as it is representative of 66% of the sites. These 4 sites are all within the same radius from Litha Vaccines, they are all based in Johannesburg and they are the busiest sites with the most orders from Litha Vaccines compared to Vaal and Pretoria regional pharmacies.

This is due to the fact that these sites service a larger population base. The sites had similar patient demographics. They largely service the no income to low income groups of the patient population and the majority of the patients are the previously disadvantaged communities. The majority of the higher income population utilises the private health sector in South Africa.

3.2.2 Cold Chain Monitor Cards

All the 186 CCM cards analysed, none had a colour change. This indicates that the vaccines transported throughout the study were not exposed to temperatures higher than 10°C at any

point in the journey to the depots as also confirmed by the data from the data loggers. Refer to the details below in 4.2.3.

3.2.3 **Freeze Watches**

All the 186 FW's were intact confirming that no vaccine was exposed to temperatures below 0°C for more than an hour at any point in their journey to the depots. This is also confirmed by the data from the data loggers.

3.2.4 **Tiny Tag Loggers**

The total number of loggers evaluated was 86. The maximum temperatures of all the loggers were constant between 5°C-9°C whereas the minimum temperatures were between 2°C-8°C.

Below is Figure 3.1 an example of the graph showing data downloaded from the logger data.

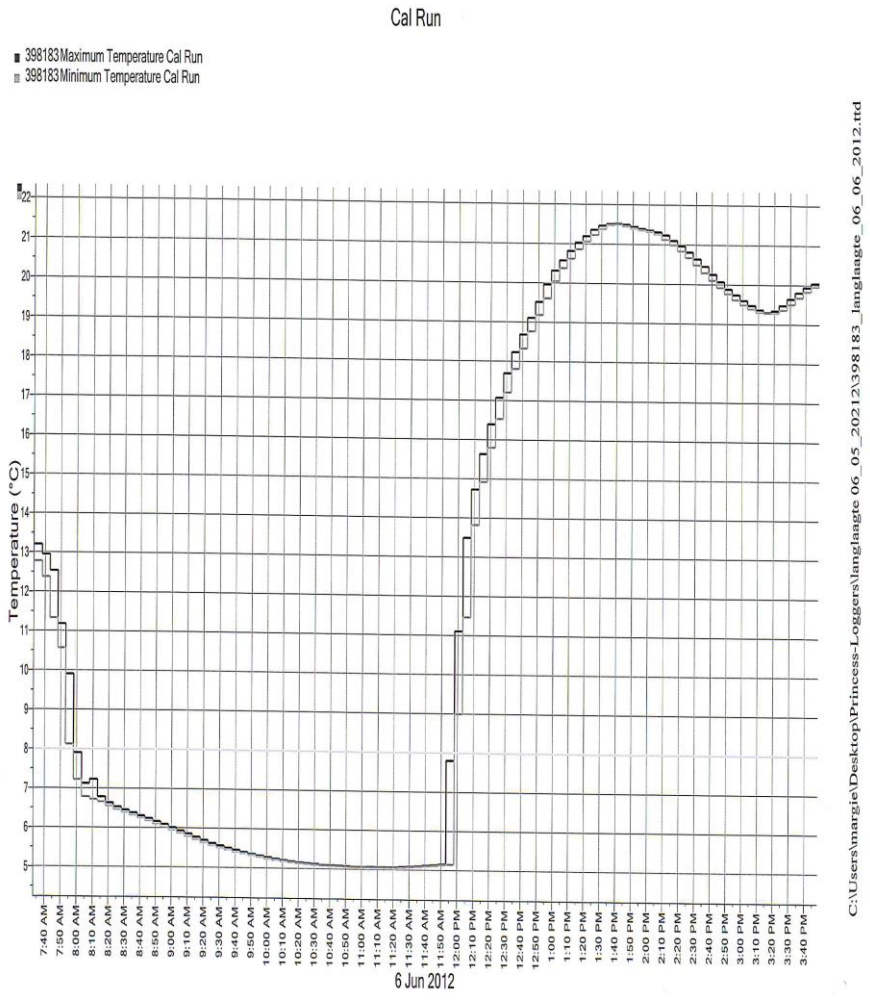


Figure 3.1

Table 3.6: Maximum and Minimum Temperatures for all the Trips in all the 3 Sites from the Data Loggers

Trips	Logger 1	Logger 2	Logger 3	Logger 4	Logger 5	Logger 6	Logger 7	Logger 8	Logger 9	Logger 10
Hillbrow Pharmacy										
Trip 1: 20/03/2012; 09:16-11:31; 28.1°C										
Min(°C)	Invalid	7.297	7.068	7.112	Invalid	6.778	5.743	Invalid	8.301	N/A
Max(°C)	Invalid	9.866	8.029	9.749	Invalid	8.855	6.464	Invalid	8.485	N/A
Trip 2: 25/04/2012; 09:00- 11:08; 15.2°C										
Min(°C)	Invalid	Invalid	Invalid	Invalid	N/A	N/A	N/A	N/A	N/A	N/A
Max(°C)	Invalid	Invalid	Invalid	Invalid	N/A	N/A	N/A	N/A	N/A	N/A
Trip 3: 19/06/2012; 08:15- 12:30; 19.7°C										
Min(°C)	5.695	6.022	5.948	5.635	5.702	4.790	4.421	5.602	4.961	4.856
Max(°C)	7.765	7.672	7.288	7.288	6.857	7.486	6.703	7.582	6.915	7.036
Trip 4: 20/08/2012; 09:45- 11:05; 26.5°C										
Min(°C)	6.433	7.701	5.549	7.008	6.320	6.341	5.513	6.297	N/A	N/A
Max(°C)	7.045	8.602	6.560	8.357	6.651	7.603	6.386	7.784	N/A	N/A
Auckland Park Depot										
Trip 1: 08/06/2012; 08:00- 10:30; 21**°C**										
Min(°C)	4.868	5.175	6.143	5.843	6.024	5.841	6.197	6.219	6.000	6.490
Max(°C)	7.518	7.663	7.884	7.977	7.122	7.465	7.672	7.644	6.936	8.104
Trip 2: 30/07/2012; 08:45-13:15; 18.4°C										
Min(°C)	4.092	2.234	2.708	3.681	4.788	3.277	3.302	2.087	3.444	3.366
Max(°C)	8.494	7.888	7.759	7.679	7.357	7.541	6.759	7.149	5.822	8.658
Trip 3: 13/08/2012; 10:30- 15:00; 20.4°C										
Min(°C)	4.119	6.651	7.106	7.756	4.421	4.429	6.789	3.366	3.814	5.606
Max(°C)	7.080	8.881	8.884	9.103	7.736	7.939	9.375	5.109	7.986	8.332
Langlaagte Depot										
Trip 1: 16/05/2012; 07:40-13:15; 20.7°C										
Min(°C)	6.936	5.455	5.119	5.967	6.332	6.647	6.551	6.822	7.334	7.057
Max(°C)	8.736	7.390	6.576	8.402	8.201	8.319	9.995	7,761	7.975	9.700
Trip 2: 29/05/2012; 08:30-11:30; 19.9°C										
Min(°C)	9.718	6.017	6.567	6.677	6.337	5.901	5.750	6.330	6.065	6.000
Max(°C)	9.938	7.617	7.979	7.993	7.502	7.984	7.841	7.514	7.256	7.847
Trip 3: 06/06/2012; 08:00-11:50; 20.6°C										
Min(°C)	5.544	5.146	4.768	5.053	5.342	6.313	4.446	5.808	6.483	5.676
Max(°C)	7.119	7.145	6.346	6.454	7.254	7.143	6.226	7.560	7.219	6.817
Trip 4: 12/07/2012; 07:50-11:00; 19.8°C										
Min(°C)	5.441	4.756	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Max(°C)	7.676	7.112	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

The maximum and minimum temperatures recorded on the data loggers during the trips are shown in table 3.6 above for each of the 3 sites and for all the trips. The table also shows the duration of the trip and the maximum temperature of Johannesburg on the particular day. The weather information was provided by the South African Weather Services.

Hillbrow Pharmacy had 8 (17%) readings that were above 8°C. Auckland Park Depot had 8 (13%) readings that were above 8°C. Langlaagte Depot had 7 (11%) readings that were above 8°C. There were no temperature readings that went below 2°C for all the sites.

In total there were 23 incidents of temperature readings that were above 8°C, which was 13% of all the temperature readings. Eighty seven percent of the readings were within the recommended temperature range of 2°C - 8°C.

Table 3.7: Data Analysis Showing Average Temperatures and How Many Logger Readings are Above 8(°C) and Below 2(°C)

Hillbrow Pharmacy	**Min (°C)**	**Max (°C)**	**Average Temp (°C)**	**Recommended range 2°C <n<8°C**	**n<2°C**	**n>8°C**
Trip 1: 20/03/2012; 09:16-11:31; 28.1 °C	5.743	9.866	7.812	6(50%)	0(0%)	6(50%)
Trip 2: 25/04/2012; 09:00- 11:08; 15.2°C	N/A	N/A	N/A	N/A	N/A	N/A
Trip 3: 19/06/2012; 08:15- 12:30; 19.7°C	4.421	7.765	6.311	20(100%)	0(0%)	0(0%)
Trip 4: 20/08/2012; 09:45- 11:05; 26.5°C	5.513	8.602	6.884	14(88%)	0(0%)	2(12%)
Total				40(83%)	0(0%)	8(17)%
Auckland Park Depot						
Trip 1: 08/06/2012; 08:00- 10:30; 21.0 °C	4.868	8.104	6.739	19(95%)	0(0%)	1(5%)
Trip 2: 30/07/2012; 08:45-13:15; 20.4°C	2.087	8.658	5.404	18(90%)	0(0%)	2(10%)
Trip 3: 13/08/2012; 10:30- 15:00; 18.4°C	3.366	9.375	6.724	15(75%)	0(0%)	5(25%)
Total				52(86%)	0(0%)	8(13%)
Langlaagte Depot						
Trip 1: 16/05/2012; 07:40-13:15; 20.7°C	5.119	9.995	7.364	14(70%)	0(0%)	6(30%)
Trip 2: 29/05/2012; 08:30-11:30; 19.9°C	5.750	9.938	7.242	18(90%)	0(0%)	2(10%)
Trip 3: 06/06/2012; 08:00-11:50; 20.6°C	4.768	7.560	6,193	20(100%)	0(0%)	0(0%)
Trip 4: 12/07/2012; 07:50-11:00; 19.8°C	4.756	7.676	6.246	4(100%)	0(0%)	0(0%)
Total				57(89%)	0(0%)	7(11%)

As shown in Table 3.7 above, all the trips recorded an average reading that is within the recommended range of 2°C -8°C. The actual average temperature readings ranged from 5.404°C to 7.812°C. None of the readings were above 10°C, which is the temperature at which the change in window 1 of the CCM becomes visible.

The graphs below compare the average temperatures of the trips per site (Figures 3.2-3.4), whereas Figure 3.5 compares the average temperatures for all trips across all sites.

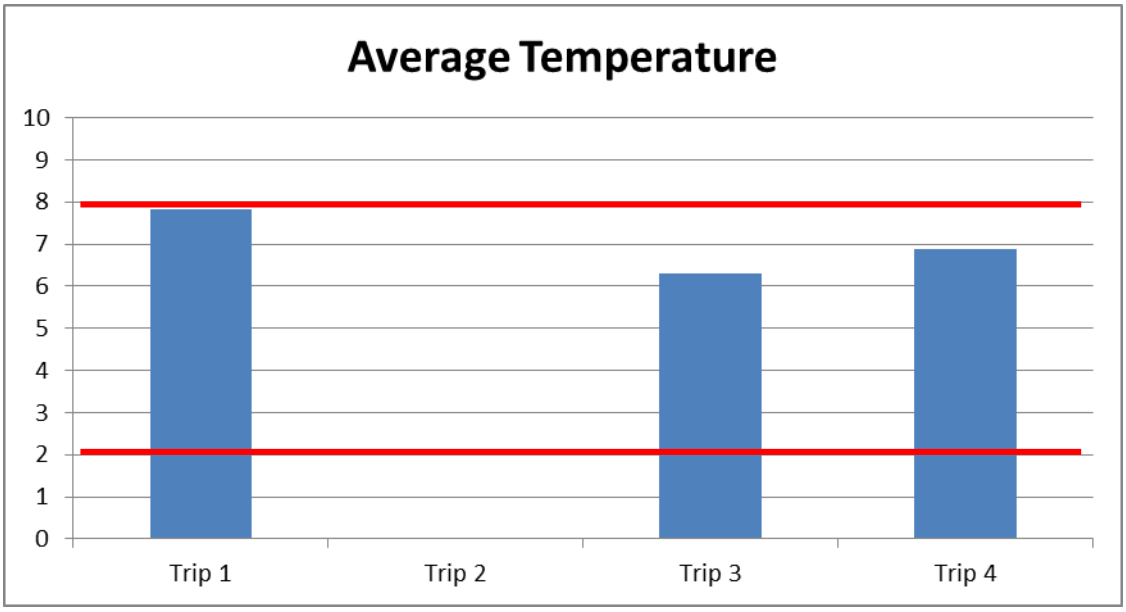


Figure 3.2: Average Temperatures (°C) for all the Trips at Hillbrow Pharmacy

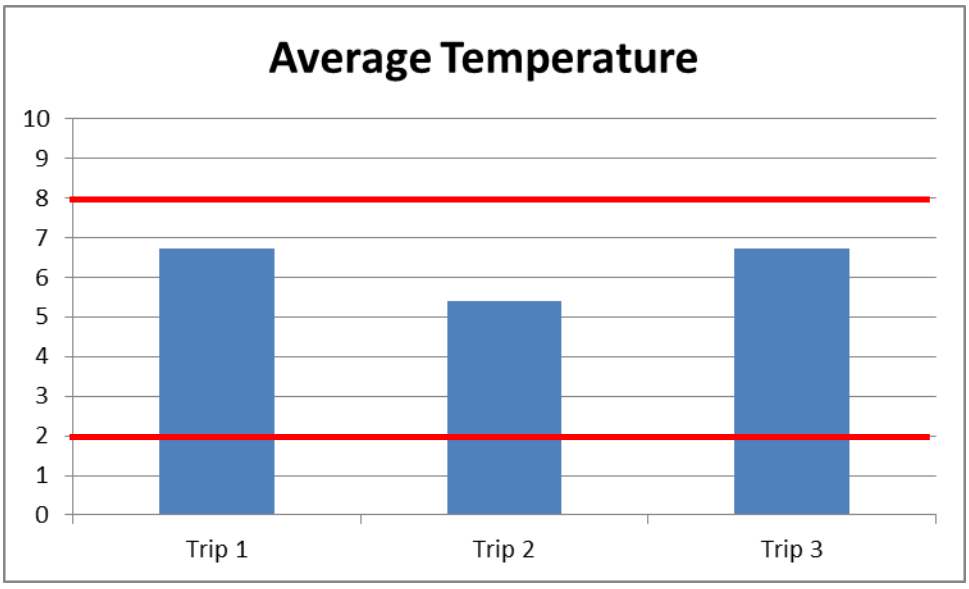


Figure 3.3: Average Temperatures (°C) for all the Trips at Auckland Park Depot

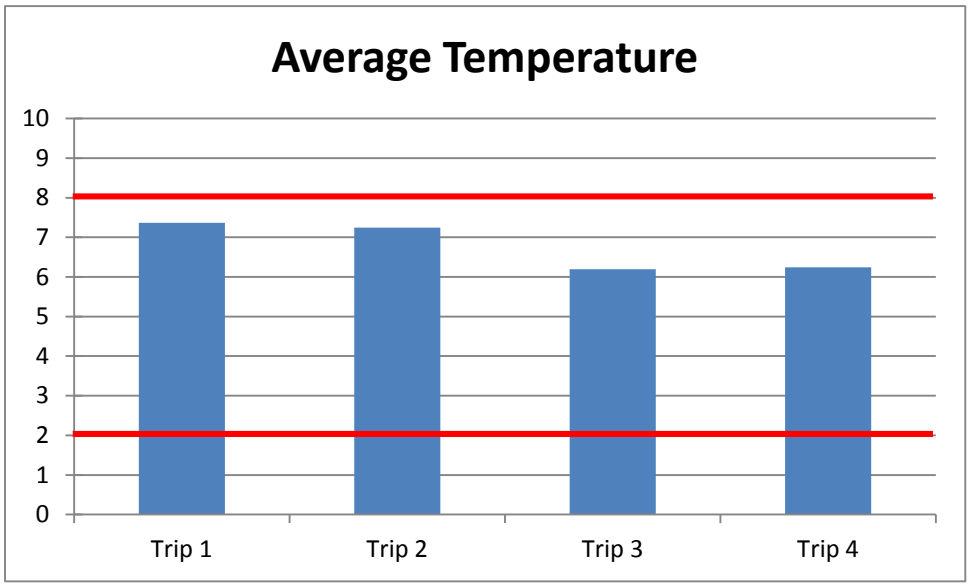


Figure 3.4: Average Temperatures (°C) for all the Trips at Langlaagte Depot

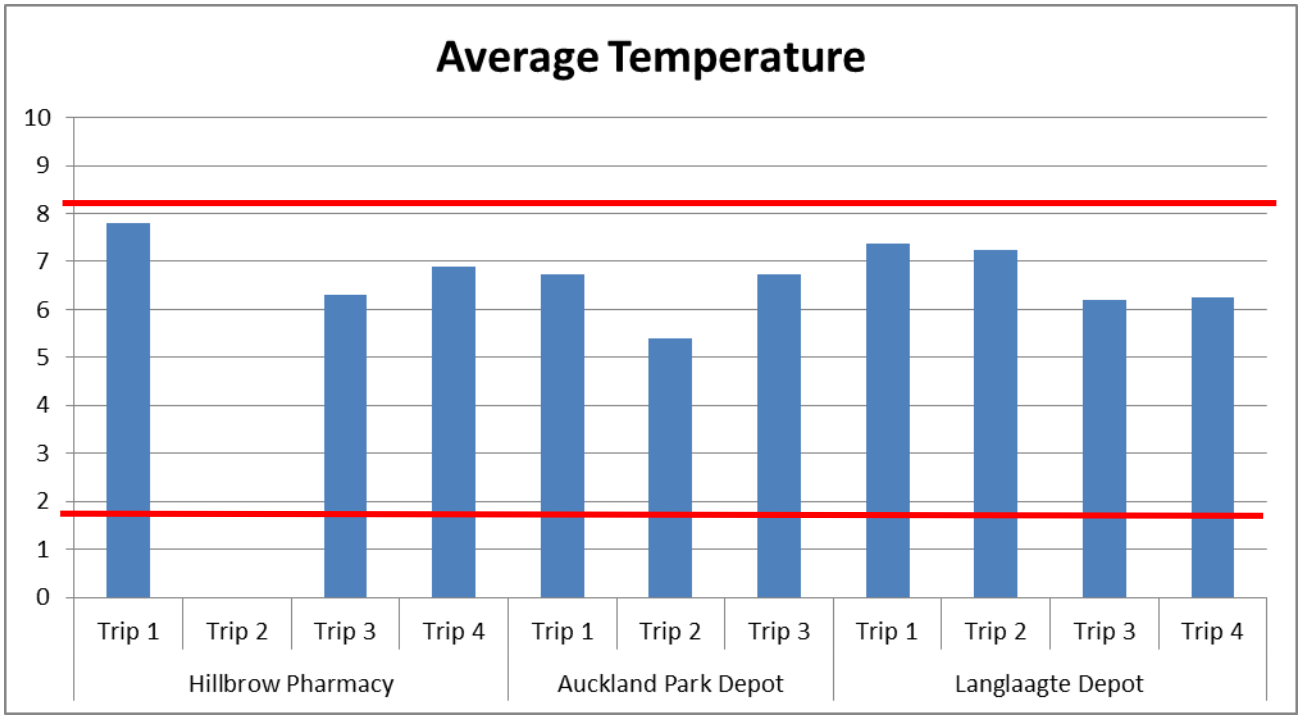


Figure 3.5: Average Temperature (°C) across all Sites for all Trips

All the bars in graph 10 are below 8°C. As previously mentioned there were no temperature recordings that were below 2°C. This shows that the vaccines at Litha Vaccines are transported at the recommended temperature range of between 2°C -8°C.

3.2.5 **Objectives versus the Results**

1. To assess the actual temperature at which the vaccines are transported from Litha Vaccines to the medical depots in Gauteng.

   - **Hillbrow Pharmacy:**
     - Seventeen percent of the temperature recordings from the loggers were above 8°C.
     - None of the loggers recorded temperatures of below 2°C.
     - Eighty three percent of the temperature recordings from the loggers were within the recommended temperature range of 2°C - 8°C.
     - The average temperatures ranged from 6.311°C - 7.812°C for the different trips. Details of all the temperatures recorded are above in table 4.

   - **Auckland Park Depot:**
     - Thirteen percent of the temperature recordings from the loggers were above 8°C.
     - None of the loggers recorded temperatures of below 2°C.
     - Eighty six percent of the temperature recordings from the loggers were within the recommended temperature range of 2°C - 8°C.
     - The average temperatures ranged from 5.404°C - 6.739°C for the different trips.

   - **Langlaagte Depot:**
     - Eleven percent of the temperature recordings from the loggers were above 8°C.
     - None of the loggers recorded temperatures of below 2°C.
     - Eighty nine percent of the temperature recordings from the loggers were within the recommended temperature range of 2°C - 8°C**.**
     - The average temperatures ranged from 6.246°C - 7.364°C for the different trips.

2. To assess the number of CCM cards that was negatively affected by adverse temperatures in these trips.
   - There was no colour change in all the CCM cards that were analysed which means none of the CCM cards were exposed to temperatures higher than 10°C at any point in their journey.

3. To assess the number of FW's that was negatively affected by adverse temperatures in these trips.
   - There were no broken FW's because none of them were exposed to temperatures below 0°C at any point in their journey.

Although the study was conducted during the cooler autumn and winter months, Litha Vaccines' system has shown to be robust enough as there were no temperatures recorded below 2°C in these cool conditions.

Studies suggest that in many vaccine cold chain systems, freezing is a more significant problem than unduly high temperatures (Techathawat et al., 2006). This proved not to be the case in this study.

The study might need to be validated in the hotter summer months where the temperatures in Johannesburg range from 25°C -28°C.

In reference to the MCC's guidelines to GWP on transportation of thermolabile products:

- The transportation process should not compromise the integrity and quality of pharmaceutical products.

- Delivery of pharmaceutical products requiring controlled temperatures should be in accordance with the applicable storage and transport conditions as mentioned in section 1.1 above.

These conditions were met in this study and the conclusion can be drawn that the product's quality and integrity were not compromised.

CHAPTER 4

4. CONCLUSIONS AND RECOMMENDATIONS

4.1 DISCUSSION AND CONCLUSIONS

Because vaccine damage depends on the ambient temperature and the duration of exposure to adverse temperatures, any assessment of the vaccine cold chain should document both variables (Wawryk et al., 1997).

The objectives of the study were met:

- To assess the actual temperature at which the vaccines are transported from Litha Vaccines to the medical depots in Gauteng.

- To assess the number of CCM cards that was negatively affected by adverse temperatures in these trips.

- To assess the number of FW's that was negatively affected by adverse temperatures in these trips.

Of all the 186 CCM cards analysed, none of them had a colour change. This indicates that the vaccines transported throughout the study were not exposed to temperatures higher than 10°C at any point in the journey to the depots. Although the CCM cards cannot show the exact temperatures that the vaccines were exposed to, it suggests that the cold chain was not broken in this case.

All the 186 FWs were also intact confirming that no vaccine was exposed to temperatures below 0°C for more than an hour at any point in their journey. This confirms that the cold chain monitoring process that is used at Litha Vaccines is adequate to protect the vaccines from exposure to undesirable temperatures.

The integrity and the quality of the product were not compromised.

This study was conducted over a period of 6 months. This was over the cooler autumn and winter months. The temperatures in these months in Johannesburg generally range from 18°C -23°C in autumn and from 16°C -19°C in winter. This could have contributed to the temperature of the loggers remaining below 8°C degrees. Even then, the system at Litha has proven to be robust to withstand the cooler temperatures in maintaining the cold chain.

According to NASA scientists, in the January 2014 analysis from NASA's Goddard Institute for Space Studies (GISS), the average global temperature has risen about 0.8°C since 1880 due to global warming. This study would possibly need to be revalidated under the high temperature conditions to provide a comprehensive report for the whole year evaluation of vaccine cold chain monitoring.

The data loggers provided accurate data that measured temperature related to time. The loggers responded virtually instantaneously to temperature change. While the data loggers revealed with great precision and clarity what was happening at any one time, there were a few loggers that had inconsistent data. The data on these loggers was not accurate. The reason for this is unclear, the loggers may have been incorrectly programmed, there may have been an error in the data retrieval process or the loggers may have malfunctioned. Thus the data from these loggers was not analysed.

The trips before and subsequent to these, to the same sites did not show the same abnormality on the loggers. The data logger results further confirmed the findings that the loggers were not exposed to undesirable temperatures during the trips to the different depots.

It is important to note that the data collected in this study only reflect the temperature that the loggers were exposed to; the Researcher cannot therefore conclude absolutely that the vaccines were exposed to the same temperatures. Variations in temperature in different areas of the shipper and variations in user/ operator compliance with the study protocol could lead to differences between temperatures of the logger and of the vaccine.

The discrepancies found in the data collected highlights the importance of continuous staff training on how to handle vaccines and the cold chain. At Litha, training is offered to the staff continuously and so was the case in this study to ensure that all parties understand what needed to be done and why. But even then we had data that was not satisfactorily completed, proving that the cold chain is as strong as its weakest link. Unfortunately the current cold chain processes will always be vulnerable to human error.

Studies suggest that knowledge of appropriate management of the cold chain is poor in the healthcare personnel meant to handle the vaccines (Haworth et al., 1993).

To ensure the quality of the medicines entering South Africa, the MCC requires that the applicant confirms the imported product's integrity prior to release for sale in the country. This is to be done by testing the imported product locally or by returning the samples overseas for testing. When the product's integrity has been confirmed, the product is then stored at Litha

Vaccines and awaits purchase orders from the depots and some of the hospitals and clinics. Litha Vaccines has internal SOP's on vaccine handling, storage and distribution to ensure that the quality and the integrity of the product are not compromised.

The study made no attempt to evaluate monitoring of the cold chain at the storage facilities or at immunisation points (clinics and hospitals). It is very critical to do so because failure to monitor the cold chain all the way means that efforts to maintain the cold chain might be futile since the end user might still receive a vaccine that has lost its potency along the distribution channel.

We did not look at the conditions of the vaccine storage equipment and vehicles at Litha or at the depots.

The cold chain compliance scores serve strictly as an objective measure based on the WHO-SA protocols and are not necessarily a measure of vaccine efficacy.

This study made no attempt to measure possible loss of potency associated with the out of the recommended range of temperatures. The objective was to establish if we a have a secure cold chain system. From our results, a conclusion can be drawn that there was no risk posed to the quality and efficacy of the products at Litha Vaccines during their distribution to the depots.

This was a local study, in one Province thus the transit times for the vaccines were quite short compared to all the other distances (i.e. to all the other 8 provinces not covered in the study) that the distributor services over and above the Gauteng Province under routine distribution. It also highlights the fact that the shorter the distance, the less likely it is for the vaccines to be exposed to undesirable temperatures since the gel packs also haven't lost their coldness in keeping the cold chain, bearing in mind that the gel packs were preconditioned as per the standard procedure.

All the trips were taken just after peak hour traffic and this contributed to the short transit times for deliveries.

Limited heat exposure may not cause vaccine damage. This was confirmed by the potency test results on measles vaccine in the study by Techathawat et al., 2006. This study aimed to identify the likelihood and extent of exposure to inappropriate temperatures in the vaccine cold chain system in Thailand, and to assess the effects of such exposure on vaccine potency.

It was reassuring to note that there was no heat or freeze damage observed as the vaccines passed down the cold chain, although not all parts of the distribution network was evaluated.

It is my hope that this study will raise further awareness of the need for such studies to be conducted continuously in the country as well as encourage immunisation program managers to design studies to investigate the state of their own cold chains and institute programmatic actions to prevent potential heat and freeze exposure.

4.2 RECOMMENDATIONS

The recommendations from this study are:

- Policy makers and regulators to make use of these studies and also conduct their own in order to adequately inform policy making and regulatory decision making in the country. There also needs to be strengthening of policymaker-implementer-researcher partnerships to create a health system that is effective, equitable and sustainable.
- Cold chain monitoring studies such as this one should be done frequently and in different points of the vaccine journey including at the storage facilities and immunization points. This will help to identify, solve problems and to strengthen staff capacity. Future research may focus on cold chain monitoring in the depots, clinics and hospitals, storage equipment and vehicles.
- Identification of cold chain trainers and supervisors and clear definition of their responsibilities for routine cold chain supervision particularly in the local distribution chain
- Advocating the use of cool water packs or gel packs instead of frozen ice-pack during cold box transport to minimize the risk of vaccine freezing. Validation of different packaging configurations will assist in decision making for the best configuration to be used.

- Temperature mapping of the storage facilities and transportation vehicles will help make informed decisions on vaccine handling.

- Qualification and validation of the cold chain equipment.

- Emphasize and improve staff training. Studies suggest that knowledge of appropriate management of the cold chain is poor in the healthcare personnel meant to handle the vaccines.

- Providing clear guidelines and vaccines handling procedures (SOP's). The managers need to ensure that there are clear guidelines and documented processes on cold chain maintenance and continuous training on the same for their staff.

- Packaging materials and transportation containers should be suitable to prevent damage of pharmaceutical products during transport. There should be written procedures on how to handle damage to containers, spillage or any other event or problem that may occur during transit of the vaccines.

- Adequate maintenance of transportation vehicles, storage equipment and monitoring devices.

- Freight forwarders and couriers that transport pharmaceutical products need to be licensed by the MCC. Alternatively pharmaceutical products should not be stored with these companies for extended periods of time.

- Drivers of vehicles should identify themselves and present appropriate documentation to demonstrate that they are authorised to transport the pharmaceutical products.

- Sufficient security should be provided to prevent theft and other misappropriation of products. Steps should be taken to prevent unauthorized access to pharmaceutical products being transported

- Delivery schedules should be established and routes planned taking local needs and conditions into account. For e.g. at certain times of the day, the outside temperatures might be more favourable to transport vaccines or certain routes might be less affected by slow traffic flow. This in an effort to ensure that the vaccines are delivered in the shortest time possible.

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APPENDIX 1

- **QUESTIONNAIRE**

APPENDIX 1

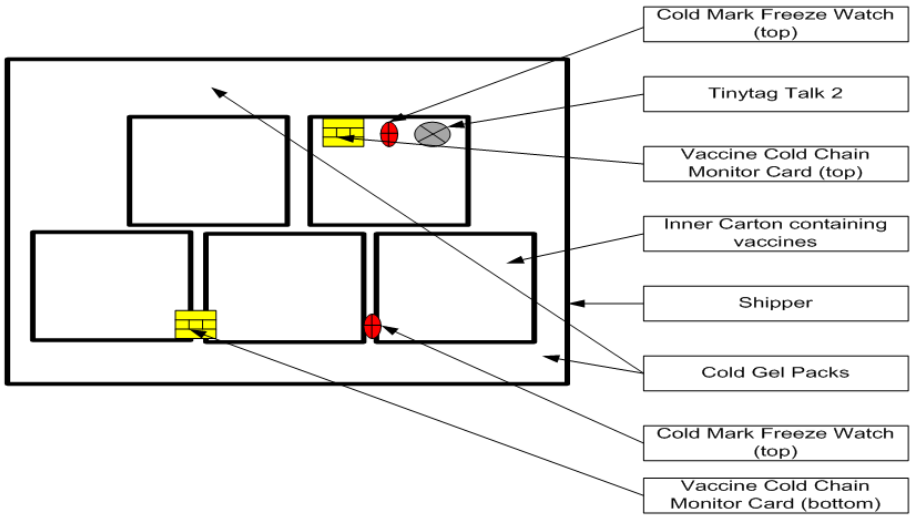
EVALUATION OF VACCINES COLD CHAIN MONITORING DURING DISTRIBUTION FROM LITHA VACCINES TO THE MEDICAL DEPOTS IN GAUTENG

Date:	Evaluator's code:
Time received:	Job Title:
Time logger was taken out: Name of Site:	Signature of evaluator and date:
Name of Vaccine/ Product:	Batch number:
	Expiry Date:
Number of shippers in the consignment:	
Number of Cold Chain Monitor cards in the consignment:	
Number of Cold Chain Monitor cards with a colour change: (see diagram for reference)	

Top	Window 1		Window 2		Window 3		Window 4	
Bottom	Window 1		Window 2		Window 3		Window 4	

Number of Cold Chain Monitor cards with a colour change on the top part of the shipper and the shipper number	
Number of Cold Chain Monitor cards with a colour change on the bottom part of the shipper and the shipper number	
Number of Freeze Watches in the consignment:	

Freeze Watch with colour change in the bulb (please circle)	Top	Bottom



For official use:

Number of Gemini tinytags:	
Gemini tinytag serial numbers:	
Time logger was placed in the shipper:	
Maximum outside temperature (At Litha) :	

Please fax to: **011 453 1304**
Attention **Princess Mosai**
Mobile **084 697 2232**

APPENDIX 2

ETHICS CLEARANCE LETTER

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Mrs Princess Mmaphuti Mosai

CLEARANCE CERTIFICATE	M110813
PROJECT	Evaluation of Vaccines Cold Chain Monitroing During Distribution from Litha Vaccines to the
Medical	Depots in Gauteng
INVESTIGATORS	Mrs Princess Mmaphuti Mosai.
DEPARTMENT	Department of Pharmacy & Pharmacology
DATE CONSIDERED	26/08/2011
M1108130DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 25/11/2011 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Ms S Naidoo

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

APPENDIX 3

TURN IT IN REPORT