THE VACCINE PHARMACOVIGILANCE SYSTEM OF KENYA

KUGO CHEPKEMBOI LINET (BPHARM)

U51/70416/2013

DEPARTMENT OF PHARMACOLOGY AND PHARMACOGNOSY

SCHOOL OF PHARMACY

UNIVERSITY OF NAIROBI

A THESIS SUBMITTED IN PARTIAL FULFILMENT FOR THE AWARD OF MASTER OF PHARMACY IN PHARMACOEPIDEMIOLOGY AND PHARMACOVIGILANCE BY THE UNIVERSITY OF NAIROBI

APPROVAL BY SUPERVISORS

This research thesis has been submitted with our approval as university supervisors.

DR. G.O. OSANJO, PhD

Department of Pharmacology & Pharmacognosy

School of Pharmacy

University of Nairobi

Signature…….. Date……..

DR. M. OLUKA, PhD

Department of Pharmacology & Pharmacognosy

School of Pharmacy

University of Nairobi

Signature…….. Date……..

DR. N. MUNGAI

Department of Pharmacology & Pharmacognosy

School of Pharmacy

University of Nairobi

Signature…….. Date……..

DECLARATION OF ORIGINALITY FORM

Name of student:	Kugo, Linet Chepkemboi
Registration number:	U51/70416/2013
College:	Health Sciences
Faculty/School/Institution:	Pharmacy
Department:	Pharmacology and Pharmacognosy
Course name:	Pharmacoepidemiology and Pharmacovigilance
Title of work:	The Vaccine Pharmacovigilance System of Kenya.

DECLARATION

1. I understand what plagiarism is and I am aware of the university's policy in this regard.
2. I declare that this thesis is my original work and has not been submitted elsewhere for examination, award of a degree or publication. Where other people's work or my work has been used, this has properly been acknowledged and referenced in accordance with the University of Nairobi requirements.
3. I have not sought or used the services of any professional agencies to produce this work.
4. I have not allowed, and shall not allow anyone to copy my work with the intention of passing it off as his or her own.
5. I understand that any false claim in respect of this work shall result in disciplinary action in accordance with the university's plagiarism policy.

Signature…… Date…….

KUGO LINET CHEPKEMBOI

ACKNOWLEDGEMENTS

I am grateful to the Almighty God for his providence.

I would like to acknowledge my supervisors Dr. G. Osanjo, Dr. M. Oluka and Dr. N. Mungai for their input and invaluable support.

I am greatly indebted to Dr. F. Okalebo for showing me the way when I was lost.

My sincere appreciation goes to The Moi Teaching and Referral Hospital for granting me the opportunity to pusue my studies.

Lastly I would like to thank the members of staff of the Unit of Vaccines and Immunization Services (UVIS) and the Pharmacy and Poisons Board who were instrumental during the data collection process.

DEDICATION

This work is fondly dedicated to my beloved son Kiplagat.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACRONYMS AND ABBREVIATIONS

ADR	Adverse drug reaction
AEFI	Adverse event following immunization
ARC	AEFI expert review committee
BC	The Brighton Collaboration
BCG	Bacillus Calmette-Guerin
CDC	Centre for Disease Control
CIOMS	Council for International Organizations of Medical Sciences
DSRU	Disease Surveillance and Response Unit
DT	Diphtheria-tetanus vaccine
DTP	Diphtheria-tetanus-pertussis vaccine
DTaP	Diphtheria-tetanus-pertussis (acellular) vaccine
DTwP	Diphtheria-tetanus-pertussis (whole-cell) vaccine
DVI	Division of Vaccines and Immunization
EPI	Expanded Programme on Immunization
FDA	Food and Drugs Authority
GAVI	Global Alliance for Vaccines and Immunizations
GMP	Good manufacturing practices
HHE	Hypotonic hyporesponsive episode
Hib	Haemophilus influenzae type b vaccine
ICH	International Conference on Harmonization
IPV	Inactivated poliovirus vaccine
KEMRI	Kenya Medical Research Institute
KEPI	Kenya Expanded Program on Immunization
KNH	Kenyatta National Hospital
KNPP	Kenya National Pharmaceutical Policy
LAV	Live attenuated vaccine
MAH	Market authorization holder
MMR	Measles-mumps-rubella vaccine

MoH	Ministry of Health
NIP	National immunization program
NITAG	National Immunization Technical Advisory Group
NRA	National regulatory authority
NCL	National control laboratory
OPV	Oral poliovirus vaccine
PCV	Pneumococcal conjugate vaccine
PIDM	Program for International Drug Monitoring
PPB	Pharmacy and Poisons Board
PSUR	Periodic safety updates report
SOP	Standard operating procedure
TSS	Toxic shock syndrome
UoN	University of Nairobi
UVIS	Unit of Vaccines and Immunization Services
VAPP	Vaccine-associated paralytic poliomyelitis
VPD	Vaccine-preventable disease
WHO	World Health Organization

DEFINITION OF TERMS

Adverse event following immunization (AEFI): Any untoward occurrence following immunization but which does not necessarily have a causal relationship with the vaccine.

Causality assessment: It is the determination of whether a causal relationship exists between a vaccine (and / or vaccination) and an adverse event.

Market authorization holder: a company which has been approved by the regulatory authority to market a medicinal product in the country.

National regulatory authority: this is a national agency responsible for ensuring that medicinal products released for public use are evaluated properly and meet international standards of quality and safety

Passive AEFI surveillance: This means that no active measures are taken to look for AEFI other than encouragement of health professionals and others to report safety concerns. Reporting entirely depends on the initiative and motivation of potential reporters.

Serious AEFI: An AEFI is considered serious if it results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or requires intervention to prevent permanent impairment or damage

Surveillance: The continuing, systematic collection of data that is analyzed and disseminated to enable decision-making and action to protect the health of populations.

Vaccine pharmacovigilance: Vaccine pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and communication of adverse

events following immunization and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization.

.

ABSTRACT

Background: Vaccines are biological products which are used to produce or enhance immunity against vaccine preventable diseases (VPDs). Public confidence in vaccines is critical to the success of any immunization programme. For a National Immunization Programme (NIP) to achieve high and sustained population coverage, the vaccines have to be perceived as being very safe by a majority of the population. The main aim of having a functional system for pharmacovigilance of vaccines is to facilitate early detection and analysis of adverse events following immunization (AEFI) and quick and appropriate response in order to minimize negative impact to the NIP and to the health of individuals.

Study objectives: The main objective of the study was to assess the Kenyan vaccine pharmacovigilance system. The specific objectives of the study were to analyse policy, law and regulations governing vaccine pharmacovigilance in Kenya; to assess the systems, structures and stakeholder coordination for vaccine pharmacovigilance; to determine signal generation and data management in vaccine pharmacovigilance; to assess risk assessment and evaluation in pharmacovigilance of vaccines; and to analyse risk management and communication in pharmacovigilance of vaccines.

Study design: A descriptive cross-sectional study was conducted. Ten key informants from the Pharmacy and Poisons Board (PPB) and the Unit of Vaccines and Immunization Services (UVIS) were selected based on purposive sampling. Data were collected using the Indicator-based Pharmacovigilance Assessment Tool (IPAT), a metric instrument designed and validated by Management Sciences for Health (MSH). The evaluation also involved review of relevant vaccine pharmacovigilance documents in the institutions assessed. A scoring system was used to quantify assessment results.

Study site: The study was carried out at the Pharmacy and Poisons Board (PPB) and the Unit of Vaccines and Immunization Services (UVIS).

Data analysis: Microsoft Excel was used to compute scores. For computation purposes, 2 points were awarded for each core indicator attained, 1 point for each supplementary indicator attained and 0 points when an indicator was not attained.

Results: The score in the area of policy, law and regulations was 50%. Lack of specific laws dedicated to pharmacovigilance and non-involvement of MAHs in post-marketing activities were the main weaknesses identified. Systems, structures and stakeholder coordination scored 24%. The basic structures of vaccine pharmacovigilance were not in place and there was insufficient coordination of stakeholders in the country. The score for signal generation and data management was 40%, risk assessment and evaluation scored 25%, while risk management and communication scored a paltry 12.5%.

Conclusion: Kenya had a system for pharmacovigilance of vaccines in place. The National Regulatory Authority (represented by PPB) and the National Immunization Program (represented by UVIS) were the institutions responsible for pharmacovigilance of vaccines at the national level. There were staffs assigned to carry out vaccine pharmacovigilance activities and a reporting tool for adverse events following immunization (AEFI). However, some gaps such as absence of specific legislation, lack of guidelines and absence of an organizational structure for vaccine safety were identified. These resulted in poor coordination of vaccine pharmacovigilance activities. These shortcomings hamper the ability of the country to effectively detect and manage vaccine safety issues.

There is need for the revision of the existing medicines legislation to incorporate elements of pharmacovigilance. It is also important to set up organizational structures with clear reporting lines for vaccine pharmacovigilance in order to improve vaccine safety monitoring in the country.

CHAPTER 1

INTRODUCTION

1.1 Background

The Kenya Expanded Program on Immunization (KEPI) was established in 1980 as part of the global Expanded Programs on Immunization (EPIs). Its mandate was to coordinate immunization against six common childhood diseases at that time namely: tuberculosis, poliomyelitis, whooping cough, diphtheria, tetanus and measles; and to provide tetanus toxoid immunization to all pregnant women (1). The Unit of Vaccines and Immunization services (UVIS) was established in 2007 and its mandate is to coordinate all vaccination services provided in Kenya. In 2001, three new vaccines were introduced to the KEPI schedule. They are yellow fever vaccine (introduced in two counties), Hepatitis B vaccine and Hemophilus Influenza type B vaccine (1). Pneumococcal Conjugate Vaccine (PCV) was introduced in 2011 (2) and Rota Virus vaccine in 2013 (1). Apart from EPI schedule vaccines, UVIS also coordinates tetanus vaccine for pregnant women, tetanus toxoid for trauma, vaccinations for special groups such as travelers and food handlers, routine emergency vaccinations for dog bites and snake bites, and vaccinations in response to outbreaks (1). It is estimated that 68 percent of children, of ages 12-23 months, in Kenya are fully vaccinated (3).

Development of vaccines has evolved over the years with evolving technologies (4). Vaccines can be grouped into seven classes based on the method of production (5). The first vaccines to be developed were based on live attenuated or inactivated pathogens and on inactivated toxoids (5). Examples of these are vaccines against tuberculosis (live attenuated), vaccines against pertussis (inactivated) and diptheria toxoid vaccine. Over the years polysaccharide vaccines against some strains of meningococcus and pneumococcus were developed (5). These vaccines were conjugated to carrier proteins to improve their immunogenicity. This gave rise to a class of vaccines known as glycoconjugate vaccines. An example is the vaccine against *Haemophilus influenzae.* Vaccines against pathogens such as hepatitis B virus, human papillomavirus, pertussis (acellular pertussis vaccine) and meningococcus B are made from purified recombinant protein antigens that form a non-infectious viral-like protein (VLP). Acellular pertussis vaccine has replaced whole cell pertussis vaccine in many countries since it has a better safety profile (4). Recent advances in

genomics contributed to the development of the first universal vaccine against type B meningococcus (5). In 2010, the American Food and Drug Administration (FDA) approved the first therapeutic vaccine known as Sipuleucel-T for treatment of prostate cancer (5).

Various institutions are involved in addressing vaccine-related safety issues globally. The Global Advisory Committee on Vaccine Safety (GACVS) was established in 1999 to advise the World Health Organization (WHO) on vaccine-related safety issues. WHO is, therefore, able to respond promptly, efficiently and with scientific rigor to safety issues of potential global importance (6). The Brighton collaboration (BC) was launched in 2000. It is an international, voluntary and independent collaboration of scientific experts. The collaboration develops standardized case definitions for AEFI and guidelines for data collection, analysis and presentation for global use (7). The Council for International Organization of Medical Sciences (CIOMS) and WHO established a joint working group on vaccine pharmacovigilance in 2005. The working group contributes in the development, review, evaluation and approval of AEFI case definitions as developed by the BC collaboration process. Additionally, the working group develops general definitions strictly focused on vaccine pharmacovigilance and they collaborate with other CIOMS working groups in particular that on Standardized medical dictionary for regulatory activities (MedDRA) Queries (SMQs) and CIOMS VIII on signal detection (8). The WHO Program for International Drug Monitoring (PIDM) offers a platform for the member states to collaborate in monitoring drug safety, notably in identification and analysis of new adverse drug reaction (ADR) signals from the data submitted to the WHO global individual case safety reports database by member countries (9). The Global Vaccine Safety Blueprint (GVSB) is a document developed by WHO. It sets out indicators to ensure that all countries have at least minimum capacity to ensure vaccine safety (10). The Global Vaccine Safety Initiative (GVSI) was set up to implement the blueprint strategy.

In Kenya, the National Policy Guidelines on immunization, 2013 has set out both long-term and short-term steps to be followed when an adverse event following immunization (AEFI) occurs. It also stipulates that guidelines on management of AEFI must be made available or be suitably displayed to health workers offering immunization services. The UVIS, in its comprehensive multi-year plan 2013-2017, has committed itself to improving surveillance of AEFI through production of guidelines, provision of adequate tools and offering AEFI-specific training (2).

A landscape analysis carried out by WHO in low and middle income countries (LMICs) revealed a consistent mismatch between the perceived available infrastructure and experience in pharmacovigilance of vaccines(11). This could be due to sub-optimal utilization of existing systems (11). This mismatch was seen mainly in low income countries. By 2004, only 68% of all countries were reported as having a national system for reporting AEFI. Of those found in LMICs, only 25% were considered to be adequately functioning (12).

1.2 Problem Statement

Immunizations are powerful public health interventions with long-lasting positive impact on both the individual and the community (7). An increase in vaccine coverage has greatly reduced the incidence of the target vaccine preventable diseases (VPDs) (13). A number of VPDs have become so rare that most parents (and even health-workers) are no longer familiar with their risks and complications. In such instances, the actual or perceived risk of experiencing an AEFI may outweigh the actual or perceived benefit of immunization to an individual or the community (7) leading to a decline in uptake of immunization. Studies have shown that a decrease in immunization leads to increased incidences of VPDs in individuals and even outbreaks in the community (13). In 2003, polio vaccination was suspended for one year in Nigeria after religious leaders in Northern Nigeria alleged that the OPV had been contaminated with anti-fertility drugs. This resulted in a massive rebound of polio cases and a global outbreak of polio. The suspension caused 80 percent of the world's cases of polio during the stoppage (14).

1.3 Justification of the study

AEFI surveillance should be part of all immunization programmes since it helps to sustain public confidence in the immunization programme (15). Public trust in vaccines is important in the success of any vaccination programme (16). Public awareness of vaccine safety has increased as a result of increased access to information through various media; healthcare providers have also become more vigilant as a result of strengthened AEFI training (15). These have resulted in an increase in the number of concerns raised regarding the quality and safety of vaccines and, therefore, more information is demanded by both the public and the providers.

AEFI surveillance may help to distinguish coincidental reactions from vaccine-related reactions and other immunization reactions. This, in turn, avoids inappropriate responses to

AEFI reports that can create a sense of panic in the public (15). Through AEFI surveillance, it is possible to identify and correct immunization-related reactions.

Until recently, vaccines used in LMIC followed the WHO EPI that was based on administration of Bacillus Calmette-Guerin vaccine (BCG), Oral Polio Vaccine (OPV), diphtheria, tetanus and whole cell pertussis, and measles vaccines during the first year of life (16). Most of these products were manufactured in industrialized countries and had been used for many years which allowed their safety profiles to be well documented (16). The creation of the Global Alliance for Vaccines and Immunizations (GAVI) in 2000 resulted in increased vaccine coverage both in respect to EPI coverage and in supporting addition of new vaccines such as Haemophilus influenzae type b (Hib), yellow fever, rotavirus and pneumococcal conjugate vaccines to immunization schedules (16). The safety profiles of the newer vaccines have not been well documented hence surveillance of AEFI in LMICs need to be strengthened.

Vaccines such as BCG, yellow fever and epidemic meningitis are predominantly used in LMICs (16). Additionally, vaccines used in industrialized countries may vary substantially from those used in LMICs. For example, combination vaccines with acellular pertussis (DTaP) are used in industrialized countries while whole cell pertussis (DTwP) is used in LMICs; and most industrialized countries have switched from Oral poliovirus vaccine (OPV) to Inactivated poliovirus vaccine (IPV) (16) (10). Both acellular pertussis and IPV have better safety profiles than their counterparts (15).

Vaccinees in LMICs may also present with a different spectrum of adverse events compared to those in industrialized countries. This may arise from differences in nutritional status and morbidities (16). It is, therefore, necessary for LMICs to have adequate vaccine pharmacovigilance systems in place to ensure that the safety of vaccines used specifically in these countries is being monitored.

1.4 Research Question

Does Kenya have a functional system for vaccine pharmacovigilance?

1.5 Study Objectives

1.5.1 Main Objective

To investigate the pharmacovigilance of vaccines system in Kenya with the aim of identifying areas for improvement

1.5.2 Specific Objectives

1. To analyse policy, law and regulation governing vaccine pharmacovigilance.
2. To assess the systems, structures and stakeholder co-ordination for vaccine pharmacovigilance.
3. To determine signal generation and data management in vaccine pharmacovigilance.
4. To analyse risk assessment and evaluation in pharmacovigilance of vaccines.
5. To analyse risk management and communication in vaccine pharmacovigilance.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

Vaccines are one of the most cost effective public health tools (17). Vaccination has led to the complete elimination of small-pox while polio has been eliminated in some regions of the world. Currently approximately 2 to 3 million deaths from measles, whooping cough, diphtheria and tetanus are prevented annually through immunization (18). A vaccine is a biological product that produces or enhances immunity to a particular vaccine preventable disease (VPD). Vaccines used in National Immunization Programs (NIPs) usually have a favorable risk benefit profile, however, just as with drugs, the use of vaccines is sometimes associated with adverse events (16). An adverse event following immunization (AEFI) is any untoward occurrence following immunization but which does not necessarily have a causal relationship with the vaccine (15). AEFI can occur in any immunization program but their effects can be minimized using a well structured and managed AEFI reporting and investigation system (19). Pharmacovigilance is the science of detection, assessment, understanding, responding to and preventing adverse drug reactions, including reactions to vaccines. Post marketing monitoring of vaccines is essential in measuring the frequency of known adverse events and in identifying new adverse events (15). Through monitoring, it is also possible to identify sub-populations in whom use of a vaccine is contraindicated (16).

Immunization safety surveillance calls for close collaboration between the National Regulatory Authority (NRA) and the National Immunization Program (NIP) since they are both responsible for the safety of vaccines (20). The NRA in Kenya is the Pharmacy and Poisons Board (PPB). It regulates the practice of pharmacy and the manufacture and trade in drugs and poisons. The NRA has the overall responsibility of ensuring that all pharmaceuticals used in the country are of good quality, are efficacious and are safe for use. One of these institutions needs to be the focal point of immunization safety surveillance (20). Ideally, a country should have three levels of immunization safety surveillance namely: the national level, the intermediate level and the service provider level (15). Figure 1 shows the responsibilities and activities at each level of program implementation.

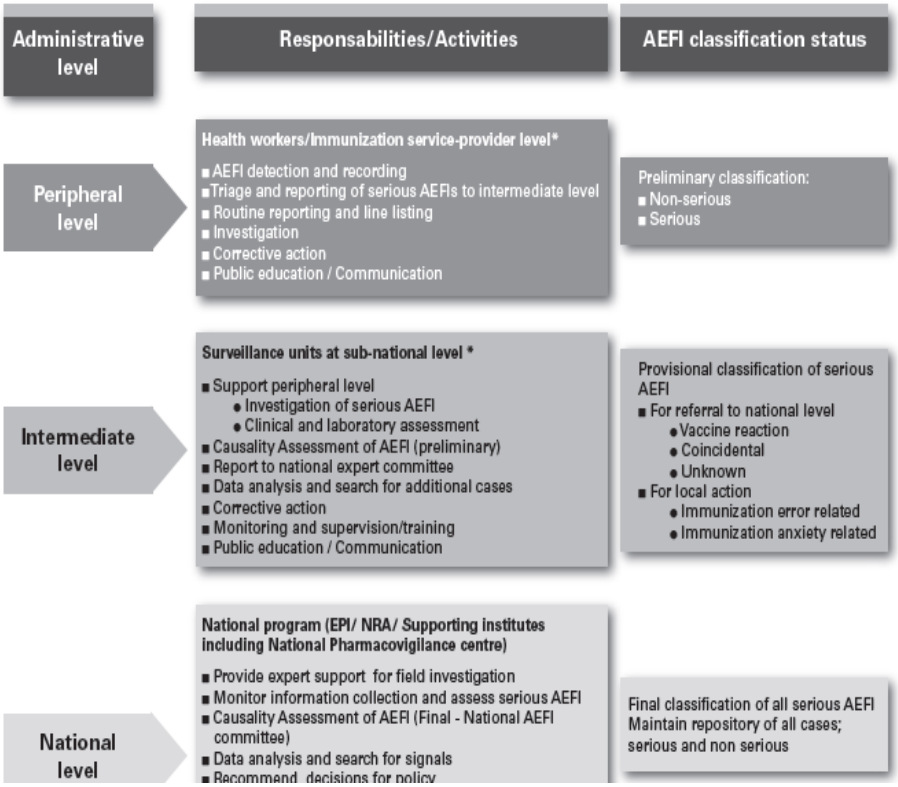


Figure 1: Program implementation level, responsibility and surveillance activities. Source: Global manual on surveillance of Adverse Events Following Immunization **(15)**.

2.2 Vaccine pharmacovigilance system

A pharmacovigilance system is "the coordinated and interdependent functioning of activities to improve benefits and reduce harm related to the use of vaccines by the public through the efficient mobilization of various stakeholders and resources at all levels and in all sectors"(21). The system should incorporate activities and resources at facility, county national and international levels and foster collaboration among a wide range of partners who contribute to ensuring vaccine safety (22). Figure 2 shows the framework of a functional system of pharmacovigilance of vaccines. Establishing and sustaining such a system requires building of institutional capacities. Capacity building is the creation of an enabling environment with appropriate policy and legal framework, institutional development that include community participation, human resource development, and strengthening of managerial systems (21). According to Potter and Brough, systemic capacity building can be achieved by applying a four-tier hierarchy of needs namely: structures, systems and roles; staff and infrastructure; skills; and tools (23). Figure 3 illustrates the capacities and resources required for a functional pharmacovigilance system.

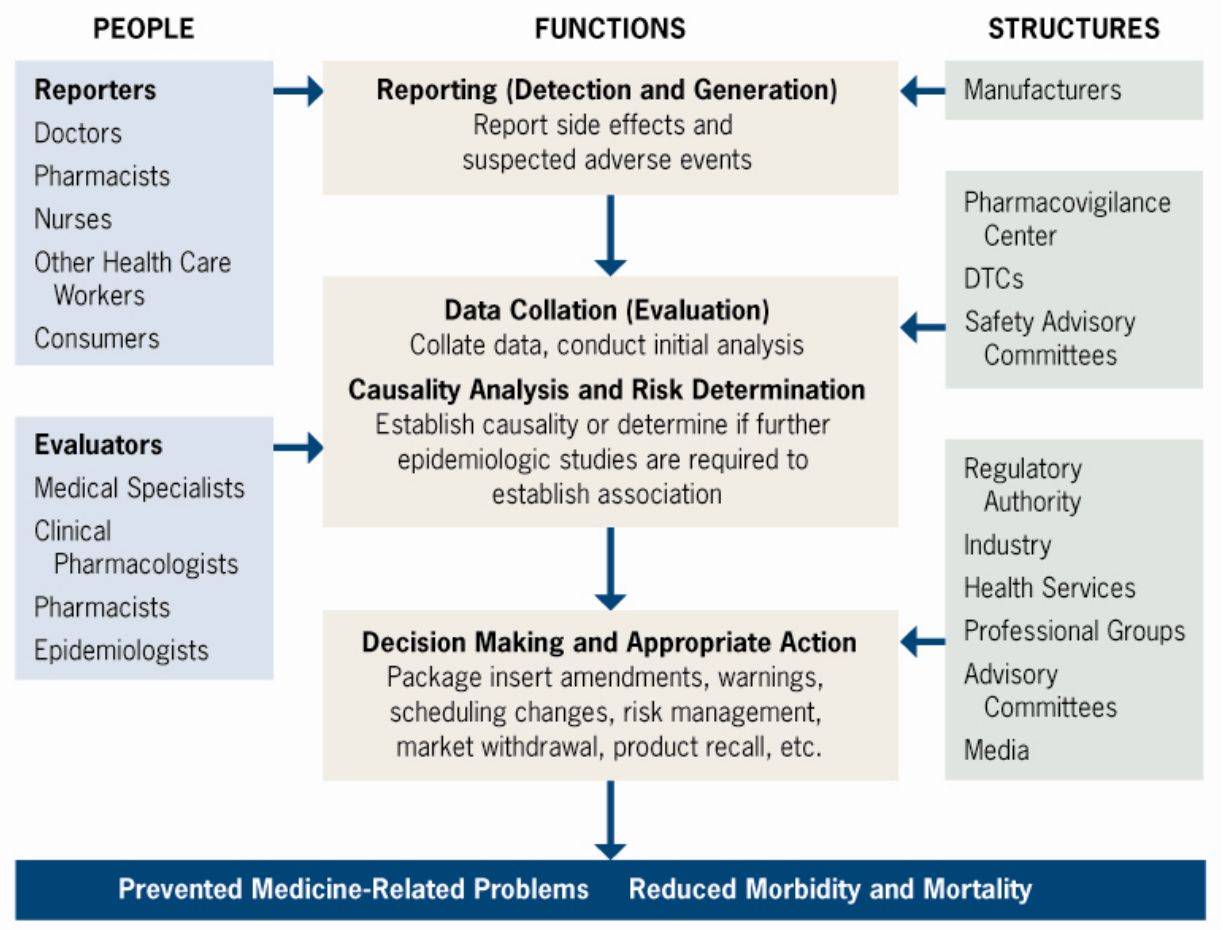


Figure 2: a comprehensive framework showing the people, structures and functions involved in pharmacovigilance of vaccines **(15)**

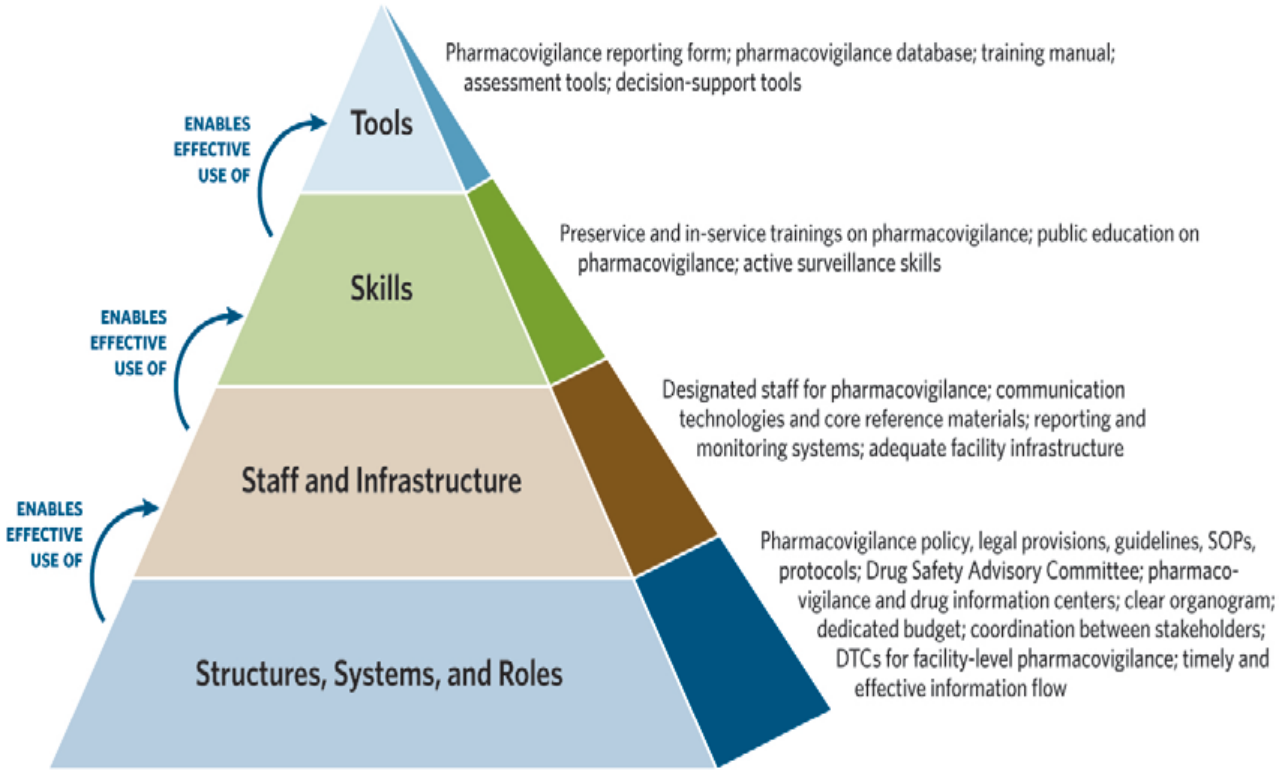


Figure 3: Capacity-Building Model for Pharmacovigilance. Adapted from Systemic capacity building: A hierarchy of needs

2.3 Classification of AEFI

AEFI can be classified based on the cause of the reaction or based on the seriousness and frequency of the reaction (15). The cause specific vaccine reactions are further classified into five categories namely: vaccine product-related reactions, vaccine quality defect-related reactions, immunization error-related reactions (programme errors), immunization anxiety-related reactions and coincidental events (15). Vaccine product-related reactions are attributable to the inherent properties of the vaccine product (16). They occur even when a vaccine has been prepared, handled and administered correctly (15). The reaction may be an idiosyncratic immune-mediated reaction or it may occur as a result of replication of vaccine-associated microbial agent. Vaccine quality defect-related reactions occur due to one or more quality defects of the vaccine (or its administration device) that occurred during the manufacturing process (20). Examples of such quality defects include insufficient inactivation of wild-type vaccine agent and product contamination during manufacturing. Such incidences were fairly common in the early years of immunization programs but have become rare since the introduction of Good Manufacturing Practices (GMP) (15). Immunization error-related reactions (also known as programme errors) arise from technical errors in vaccine storage, preparation, handling or administration. These reactions are,

therefore, preventable (15). Immunization anxiety-related reactions arise from anxiety of the vaccine recipient about the vaccination, for example a teenager fainting after immunization (15). Coincidental events are not caused by vaccination but are a chance occurrence or are caused by underlying illnesses.

Based on frequency of occurrence, AEFI can be classified as very common (>=10%), common (>=1% and <10%), uncommon (>=0.1% and < 1%), rare (>= 0.01% and < 0.1%) and very rare (< 0.01%) (15). Common minor vaccine reactions include local site reactions and fever (15) . These reactions are usually self-limiting and rarely require symptomatic treatment. However, reactions caused by live attenuated vaccines can be serious and even fatal in severely immunocompromised individuals (20). An AEFI is serious if it results in death, hospitalization or prolongation of hospitalization, or results in persistent or significant disability/incapacity, or is life-threatening (15). Most of the rare and serious vaccine reactions such as seizures, thrombocytopenia, hypotonic hyporesponsive episodes (HHEs) and persistent inconsolable screaming usually do not lead to long-term problems (20). Anaphylaxis is potentially fatal but treatable without leaving any long-term effects.

2.4 Steps in AEFI Surveillance

There are several steps involved in immunization safety surveillance namely: case detection (reporting), AEFI investigation, analysis of AEFI data, causality assessment and corrective actions and follow-up (20). The reporting of AEFI mainly relies on spontaneous reporting by health-workers (24). Awareness regarding monitoring and management of AEFI is crucial in the success of a passive surveillance system (17, 13). Regular training and awareness programmes should be conducted to update the knowledge and keep the interest of the primary reporters (20). In a study done in Australia, AEFI reporting was found to be infrequent among all cadres of health-workers with reporting being lowest in the cadres that had the least training on AEFI reporting (25). Health-workers in the private sector should also be encouraged to report AEFI to the public health authorities (15). Each country should come up with a list of events to be include in its reporting system as reportable events (15). An AEFI report should ideally be made as soon as possible so that an immediate decision can be made on the need for action and investigation.

An AEFI investigation may involve rigorous scientific evaluation of an AEFI or it may be a simple assessment. Not all AEFI reported need to be investigated. Criteria must be developed to guide on which AEFI require investigation (15). Serious AEFI and AEFI

clusters need to be investigated immediately with assistance from the central level (26). The main aim of an investigation is to determine the cause of an AEFI and implement follow-up action (15). An investigation should identify any immunization error related reactions and distinguish them from vaccine reactions and coincidental events. Investigators should focus on identifying system problems rather than blaming individuals (15). Figure 4 shows the steps involved in an AEFI investigation.

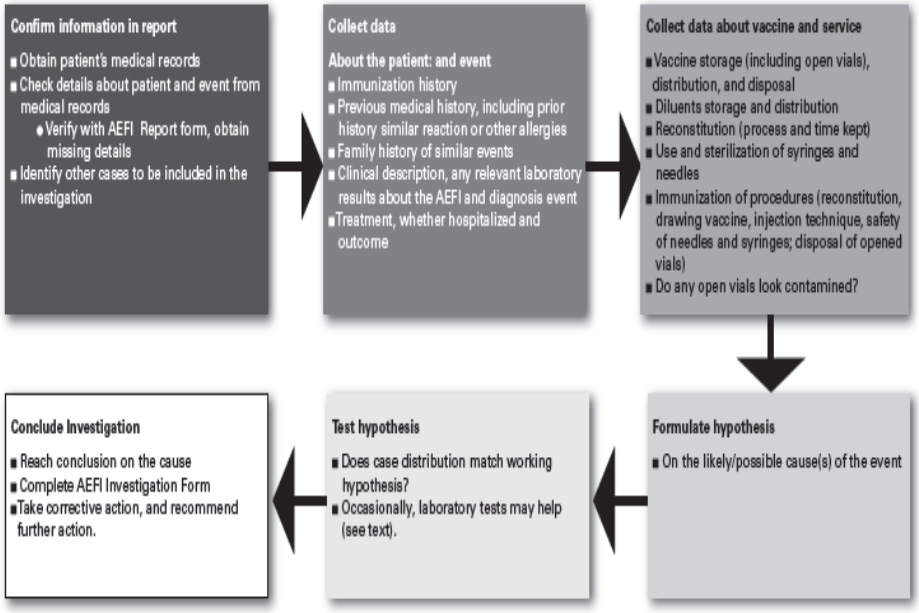


Figure 4: Steps involved in AEFI investigation **(15)**

Analysis of AEFI data may be carried out at both the national and sub-national level. Analysis at the national level is important in identifying rare vaccine adverse events and detecting signals. Analysis at the sub-national level helps in identifying program errors and ensuring corrective action is effected (15). Examples of AEFI data to be analyzed include: total AEFI reported, reported AEFI by place, cluster and time, cluster analysis and reported AEFI by antigen.

Causality assessment is the systematic review of data on an AEFI case with the goal of determining the likelihood of causal association between the event and the vaccine received (18). Causality assessment can be done at various levels namely the individual level, the population level and in the context of investigating signals. Causality assessment should ideally be carried out by a reviewing team of experts drawn from various relevant specialties.

All serious AEFI and AEFI occurring at a higher than normal frequency or at an unusual severity should be selected for causality assessment (15). Signals generated from individual and clustered reports and any AEFI recommended by the review team for assessment should also be selected for causality assessment (18).

The actions to be taken after an AEFI occurs depend on the nature and severity of the AEFI. Mild symptoms such as fever can be managed by assuring the parents and by administering anti-pyretic agents if necessary. Management of severe events such as anaphylaxis requires that emergency equipment be at hand in all immunization centres. Communication and training are follow-up actions that have long-term effects. Communication to key stakeholders, especially in times of crises must be handled carefully. In a survey carried among various experts in vaccine pharmacovigilance from LMICs, risk communication was perceived as the most underdeveloped area of vaccine safety overall (11).

2.5 Types of immunization safety surveillance

2.5.1 Passive surveillance

Passive surveillance relies on voluntary AEFI reporting from immunization service providers/hospitals/parents to the AEFI surveillance system. Passive surveillance theoretically allows anyone in the country to report (15). Due to the wide coverage, passive AEFI surveillance can detect early unknown serious AEFI. The main disadvantage of this type of surveillance is under-reporting (24) and therefore, it cannot be used to determine whether the rate of an adverse event has increased. Other disadvantages are reporting of unconfirmed diagnoses, lack of denominator data and unbiased control groups (27).

2.5.2 Active surveillance

Active surveillance is primarily used to characterize profile, rates and risk factors for AEFI (15). Newly introduced vaccines and special immunization campaigns need active surveillance and/or epidemiological studies to augment the passive surveillance. Active surveillance may be carried out for selected AEFI at selected institutions (sentinel sites) or in the community setting (cohort event monitoring).

2.5.3 Ad hoc studies

These are epidemiological studies done to further expand AEFI surveillance activities. They include case-control studies, cohort studies and case-series studies (15).

2.6 Examples of immunization safety surveillance systems

In the USA, the vaccine adverse events reporting system (VAERS) was established in 1990 and is dedicated to reporting vaccine adverse events. It is monitored by both the Centre for Disease Control (CDC) and the Food and Drugs Authority (FDA). Health workers, state immunization providers, vaccine manufacturers and vaccine recipients can report AEFI. The first rotavirus vaccine was introduced in 1999. The VAERS detected an increased risk of intussusception associated with it and it was withdrawn from the market (28). It has been used to monitor the adverse events associated with influenza vaccine containing thiomersal (29).

In India, the National Pharmacovigilance program was launched in 2004. The responsibility of AEFI surveillance lies with the public health departments of state governments which then report to the NRA. Data are collated and compiled at the department of preventative and social medicine in major hospitals (19).

2.7 Vaccine safety issues

All vaccines can potentially cause injection site reactions, fever and other systemic reactions, and rarely anaphylaxis (16). Live attenuated vaccines can induce a mild form of the disease and very rarely the severe disease; measles vaccine causes a mild rash in 5% of the recipients and the risk of paralytic disease after a dose of oral polio vaccine is 0.3 per million doses (16). The acceptable level of harmful effects of vaccines is extremely low since they are normally given to healthy individuals and also to a large segment of the population. This means that even rare effects may translate into a significant number of people affected. Additionally, as vaccine preventable diseases become less prevalent as a result of immunization programmes, the public becomes increasingly intolerant to AEFI. A single serious event or a cluster of events may reduce the public confidence in immunization programs leading to a decline in immunization rates. Passive surveillance is the cornerstone of monitoring post-licensure safety of vaccines. The main goal of post marketing surveillance of vaccines is early detection of adverse events.

Since the introduction of vaccines, there have been several cases of harmful effects of vaccines to the recipients. During the early stages of vaccine development, a number of these cases were attributed to quality defects during the manufacturing process. Other cases can be attributed to the inherent properties of the vaccine product and some cases are due to human error. In 1930 in Luebeck, Germany, 256 newborns were vaccinated with oral BCG. In the

subsequent months, 130 developed tuberculosis and 77 died. Investigations revealed that the batch had been contaminated by a virulent strain of *Mycobacterium tuberculosis* during the manufacturing process (9, 5). A mass influenza vaccination campaign against H1N1 virus strain was carried out in the USA in 1976. It was suspended after an unacceptably high occurrence of Guillain-Barre syndrome (GBS) was attributed to the vaccine. At least 500 cases of GBS were diagnosed, 25 of which were fatal (16). The first licensed rotavirus vaccine (Rotashield^{TM}) was withdrawn from the market after it was found to increase the risk of intussusception in children. The vaccine adverse events reporting system (VAERS) in the USA detected the signal and subsequent investigations confirmed the increased risk leading to the withdrawal. In April 2008, four children died in India after receiving measles vaccine. The deaths occurred within 15 to 20 minutes after vaccination. No resuscitative equipment was available at the site of vaccination. Investigations into the incident identified human error as the most likely cause of the AEFI and that these deaths were most likely preventable (19).

Serious adverse events attributed to vaccines are rare. Many claims are usually made associating vaccines with adverse events without any scientific evidence. Such vaccine scares based on rumors can profoundly disrupt immunization programs. They should be addressed promptly by vaccine safety experts by collecting evidence to either support or refute the claims. An example of a vaccine scare based on poor science was the hypothetical association of MMR vaccine to autism. This led to a massive drop in MMR coverage in the UK from 92% in 1995/96 to 80% in 2003/04 resulting in various measles outbreaks (16). Numerous studies have failed to find an association between MMR vaccine and autism (30). In 2003, polio vaccination was suspended for one year in Nigeria after religious leaders in Northern Nigeria alleged that the OPV had been contaminated with anti-fertility drugs. This resulted in a massive rebound of polio cases and a global outbreak of polio. The suspension caused 80% of the world's cases of polio during the stoppage (14). Recently in Kenya, it was alleged that the tetanus toxoid vaccine being administered to women of child-bearing age contained human chorionic gonadotropin (β-HCG) for population control. This rumor could have a negative impact in the fight against maternal and neonatal tetanus (MNT). Having a functional AEFI surveillance system with an effective communication strategy could minimize the negative impact that such rumors have on the NIP.

CHAPTER 3

METHODOLOGY

3.1 Study Design

A descriptive cross-sectional study method was employed. Ten key informants from the PPB and UVIS were interviewed. The evaluation also involved collection and review of relevant pharmacovigilance-related documentation in the institutions assessed. A scoring system was used to quantify assessment of results.

3.2 Study site

The study was carried out at the Pharmacy and Poisons Board (PPB) and at the Unit of Vaccines and immunization services (UVIS). The PPB is the National Drug Regulatory Authority in Kenya. It was established under the Pharmacy and Poisons Act, Chapter 244 of the laws of Kenya. The Board regulates the Practice of Pharmacy and the Manufacture and Trade in drugs and poisons. The PPB has the mandate of ensuring that all pharmaceuticals used in the country are safe, efficacious and of good quality. In 2004 the Department of Pharmacovigilance was set up at the Pharmacy and Poisons Board with a vision to develop, implement and continuously upgrade an appropriate system for detecting, reporting and monitoring adverse drug reactions (ADRs).

The immunization programme in Kenya is managed by the UVIS. The UVIS falls within the department of preventive and promotive health services under the Ministry of Health. The unit has been in existence since 1980 when it was established as Kenya Expanded Program on Immunization (KEPI). It was renamed the Division of Vaccines and Immunization (DVI) in 2008 and later the Unit of Vaccines and Immunization Services. The UVIS collaborates with the PPB in monitoring and addressing vaccine safety issues.

3.3 Study population

The study population was key informants at the PPB and the UVIS, specifically those involved in pharmacovigilance. Additionally, all relevant pharmacovigilance-related documents in the institutions assessed were reviewed.

3.4 Sample Size and Sampling Techniques.

Purposive sampling technique was used to recruit interviewees. The inclusion criterion employed was PPB and UVIS members of staff who are involved in addressing vaccine safety issues. The head of Pharmacovigilance at the PPB and the head of the UVIS were consulted to help identify these staff. A list of all those willing to be interviewed was made and a discussion held with each one of them individually to determine the most convenient times to carry out the interviews. The sample size was determined by the data saturation point, that is, the point where no new themes emerged from the interview data. A census approach was used to review the relevant pharmacovigilance related documentation in these institutions.

3.5 Research Instruments and Data Collection Techniques

The indicator-based pharmacovigilance assessment tool (IPAT) (appendix VI) was used to collect data. IPAT was designed and validated by management sciences for health (MSH) through its strengthening pharmaceutical systems (SPS) programme. Its specific purpose is to assess pharmacovigilance systems in developing countries. IPAT indicators are categorised into five components which represent a functional pharmacovigilance system. The components are policy, law and regulation (4 indicators); Systems, structures and stakeholder coordination (15 indicators); signal generation and data management (6 indicators); risk assessment and evaluation (8 indicators) and risk management and communication (10 indicators). The indicators are further classified into core (C) and supplementary (S). A country is considered to have a minimally functional pharmacovigilance system if it achieves all the core indicators. Achievement of the supplementary indicators reflects the level of sophistication of the pharmacovigilance system.

An interview guide was generated from IPAT and used to conduct structured interviews. The interviews were conducted only after the purpose of the interview had been explained to the interviewee and he/she had filled and signed the informed consent form. The proceedings of the interviews were captured in writing and transcription was done as soon as an interview was over. Additional information was collected from relevant pharmacovigilance-related documents to serve as evidence in support of interviews.

Various studies have been carried out using the IPAT. In 2011, a study was carried out in nine sub-sahara African countries (including Kenya) by MSH using IPAT to assess the pharmacovigilance systems (31). The tool has been used to assess pharmacovigilance systems in African countries such as Ghana, Rwanda and Burkina Faso. It has also been used in Europe to assess systems in Ukraine and in Asia to compare pharmacovigilance systems across five Asian countries.

3.6 Exclusions

For the purposes of this study, indicators number 2.12, 3.1, 5.1, 5.8 and 5.10 were not used. This is because they were more relevant in assessing the national pharmacovigilance system as opposed to assessing pharmacovigilance in the immunization programme.

3.6 Data Analysis

Data analysis was both qualitative and quantitative. Microsoft excel was used to compute scores. For scoring purposes, 2 points were allocated for a core indicator fulfilled, 1 point for a supplementary indicator fulfilled and 0 points when an indicator was not fulfilled. For quantitative indicators (2.13, 4.4, 5.3, 5.4, 5.5, 5.6, 5.7 and 5.10) critical thresholds have been set as described in IPAT (appendix 3).

3.7 Ethical considerations

Approval to conduct the study was sought and granted from Kenyatta National Hospital/University of Nairobi Ethics Review Committee (Appendix I, approval number P59/02/2015). All the study participants consented to being interviewed. The interviews were carried out at the PPB and UVIS from 7th September, 2015 to 29th September, 2015. The names of the key informants were not recorded during data collection and processing. Each informant was assigned a code to maintain anonymity. Administrative approval was also sought from the PPB (appendix 2) and UVIS.

3.8 Dissemination plan

The findings of this study will be disseminated to the PPB, the UVIS, the MoH department of preventative services and other stakeholders in the form of an executive summary. The study findings will also be published in a peer-reviewed journal.

CHAPTER 4

RESULTS

4.1 Key informants

The table below gives a brief description of the key informants interviewed. Five informants were from the PPB and five informants from the UVIS. The interviewees included five pharmacists, two pharmaceutical technologists and three public health officers.

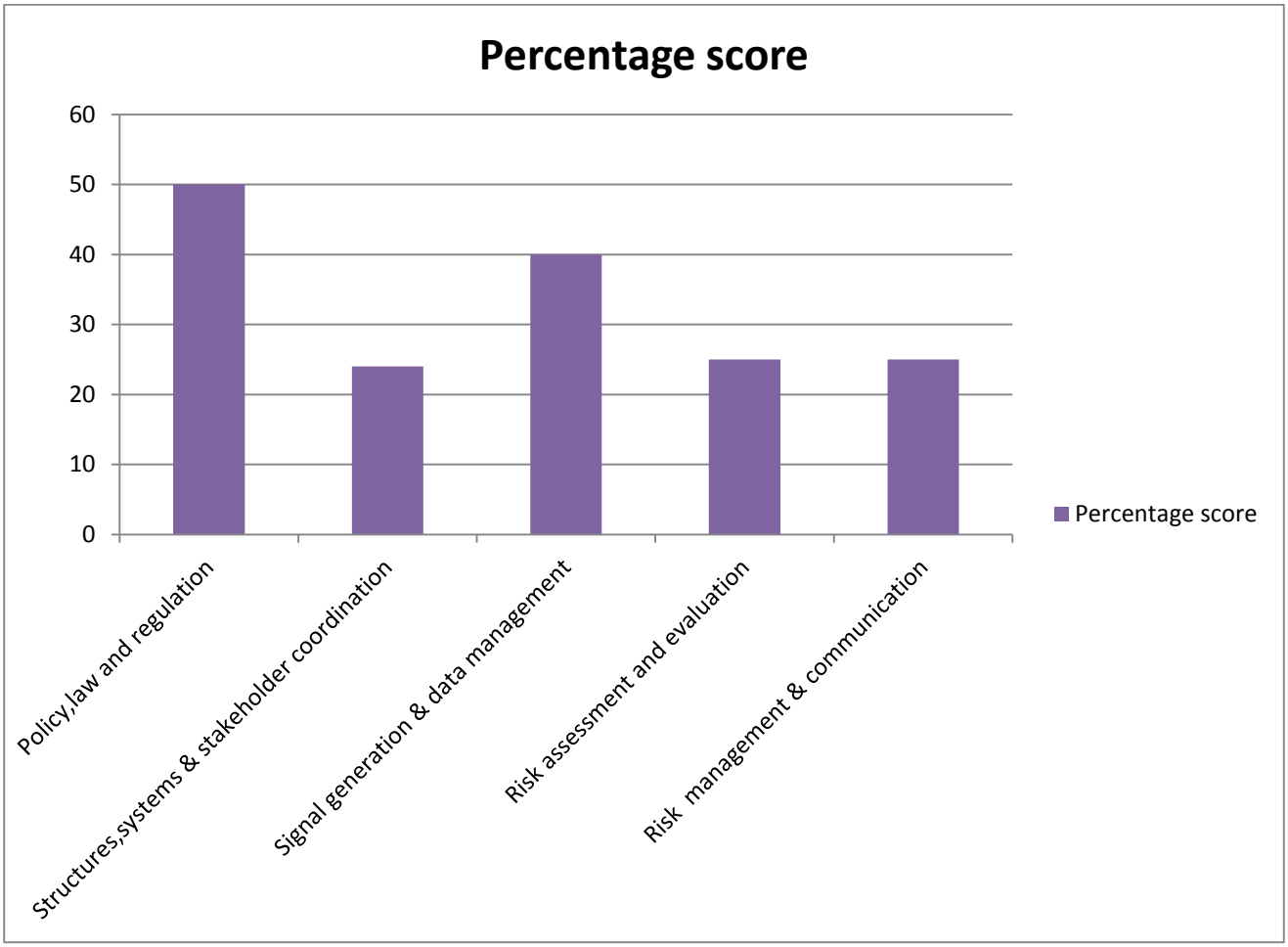
Table 1: Description of key informants

Unit	Cadre	Number of informants	Job designation
PPB	Pharmacist	1	Pharmacovigilance
	Pharmacist	1	Quality assurance and medicines information
	Pharmaceutical technologist	2	Pharmacovigilance
	pharmacist	1	Drug registration
UVIS	Pharmacist	2	Pharmacovigilance of vaccines
	Public health officer	1	Pharmacovigilance of vaccines
	Public health officer	2	Training

4.2 Key findings

The assessment revealed that none of the five pharmacovigilance areas assessed scored above 50%. Policy, law and regulation had the highest score of 50% and structures, systems and stakeholder coordination had the least score of 24%.

Figure 5: Key findings



4.3 Policy, law and regulation

An assessment of the aspects of policy, law and regulations governing vaccine pharmacovigilance was done using four indicators. The results are shown in table 2 below. Only two indicators were attained giving a score of three (3) out of six (6).

Table 2: Indicators on law, policy and regulation

	Policy, law and regulation		
Indicator no	**Pharmacovigilance area**	**Type of indicator**	**Score**
1.1	Existence of a national policy document taking pharmacovigilance into account	C	2
1.2	Specific reference to pharmacovigilance in the national medicines legislation /similar legislation	C	0
1.3	Legal provision for MAH to report adverse events	S	0
1.4	Legal provision for MAH to conduct post-marketing surveillance activities	S	1
	Total score		**3**
	Percentage score (%)		**50**

Key; MAH refers to market authorization holder, C is core indicator and S refers to supplementary indicator. For scoring purposes, 2 points were allocated for a core indicator fulfilled, 1 point for a supplementary indicator fulfilled and 0 points when an indicator was not fulfilled

A review of the Kenya National Policy Guidelines on Immunization found that it covered various topics on vaccine safety including management and reporting of AEFI, storage and transportation of vaccines, safe injection practices, safe disposal of vaccination waste and immunization of special groups. The Pharmacy and Poisons (Registration of drugs) Rules has set out conditions for registration of new drugs. Rule (9), sub-rule (2) states that certain drugs may be given conditional registration and require the MAH to conduct clinical trials after registration to establish quality, safety and efficacy. A review of safety reports submitted to the PPB revealed that 32 PSURs had been submitted by the time of the study but none of them was for vaccines.

4.4 Systems, structures and stakeholder co-ordination

Fourteen (14) indicators were used to assess the structures, systems and stakeholder coordination of vaccine pharmacovigilance in Kenya. The results are shown in table 3 below. Only four (4) indicators were attained; two of which were core indicators and two were supplementary. The total score was six (6) out of twenty four (24)

Table 3: Indicators on structures, systems and stakeholder coordination

	Structures, systems and stakeholder coordination		
Indicator no.	**pharmacovigilance area**	**Type of indicator**	**Score**
2.1	Existence of a vaccine pharmacovigilance unit	C	0
2.2	Clear mandate, roles and responsibilities of the pharmacovigilance unit	C	0
2.3	Availability of question and answer service on vaccine safety	C	0
2.4	Designated staff for vaccine pharmacovigilance	C	2
2.5	Existence of a budget for vaccine pharmacovigilance activities	C	0
2.6	Existence of ARC/vaccine safety advisory committee	C	0
2.7	Existence of national vaccine pharmacovigilance guidelines	C	0
2.8	Existence of patients' safety SOPs	C	0
2.9	Existence of basic communication material for reporting/providing information	C	2
2.10	Existence of a bulletin on safety of vaccines	C	0
2.11	Existence of basic material in the PV unit	S	1
2.13	Healthcare professionals trained on vaccine PV last year	S	0
2.14	Existence of a platform of coordination across all PV stakeholders	C	0
2.15	Membership with the WHO UMC	S	1
	Total score		**6**
	percentage score		**24**

Key:PV refers to pharmacovigilance

From the assessment, it was identified that the UVIS had 3 staff members designated responsibilities for pharmacovigilance of vaccines but their roles were not limited to pharmacovigilance activities. The three included two pharmacists and one public health

officer. The unit had basic communication technologies for reporting and provision of information. The communication technologies included several desktop and laptop computers, internet, telephones and e-mail. The staff also had access to various core reference materials. The reference materials found at UVIS included the Kenya National Pharmaceutical Policy (KNPP), the Pharmacy and Poisons Act CAP 244, list of registered vaccines, WHO pharmaceutical newsletter, National Policy Guidelines on Immunization, Immunization Manual for Healthworkers and Global Manual on Surveillance of AEFI.

The UVIS had no bulletin featuring vaccine safety nor did it contribute vaccine safety articles to any newsletter in the past year. It was reported that no platform existed for coordination of stakeholders in vaccine pharmacovigilance. A map of the stakeholders was also not availed. Respondents from PPB reported that plans were underway to link pharmacovigilance of vaccines activities to the activities of the national pharmacovigilance centre.

The assessment revealed that the NIP had no pharmacovigilance unit and no clear mandate for vaccine pharmacovigilance. There was no documentation on the organizational structure, roles, responsibilities and reporting lines. The roles played by the national pharmacovigilance centre and the UVIS in vaccine pharmacovigilance were not clearly defined. The UVIS did not have a question and answer service for vaccine safety-related issues. However, the respondents from UVIS reported that they occasionally received calls from health workers regarding vaccine safety issues. Despite the fact that AEFI surveillance was included as an activity in UVIS comprehensive multi-year plan (CMYP) 2013-2017, no budget was dedicated for pharmacovigilance. There were no national AEFI guidelines but it was reported that its development was in progress. A draft of the guidelines was presented and reported to be a joint effort between the PPB and the UVIS. Respondents from the UVIS reported that the draft guidelines were ready for printing and distribution but there were no funds for carrying out the exercise. At the time of the study, the national ARC had not been constituted but it was reported that an ad hoc ARC was constituted as need arose.

It was reported that no formal training had been offered to HCWs on pharmacovigilance of vaccines. Respondents from UVIS, however, reported that immunization service providers had been given some training on AEFI surveillance as part of introduction of rotavirus vaccine to the immunisation schedule in the country.

4.5 Signal generation and data management

Aspects of signal generation and data management were assessed using five (5) indicators, all of which were core indicators. Two indicators were attained to give a score of four (4) out of ten (10). The results are shown in table 4 below

Table 4: Indicators on signal generation and data management

	Signal generation and data management		
indicator no.	**Pharmacovigilance area**	**Type of Indicator**	**Score**
3.2	Existence of a database for tracking vaccine pharmacovigilance activities	C	0
3.3	Existence of a form for reporting AEFI	C	2
3.4	Existence of a form for reporting suspected defective product quality	C	2
3.5	Existence of a form for reporting suspected vaccination errors	C	0
3.6	Existence of a form for reporting suspected vaccination failure	C	0
	Total score		**4**
	Percentage score (%)		**40**

The UVIS had an AEFI reporting form (Appendix VII) but the interviewees reported that the form had not been widely distributed due to lack of funds to print and distribute them. The reporting form contained all the core variables as advised by WHO (15). A form for reporting poor quality medicinal products is printed and distributed by the PPB. No reports on poor quality vaccines had been submitted at the time of the study. There was no form for reporting treatment and/or vaccination failure and medication errors. There was no database for collating AEFI reports in Kenya. The respondents at the PPB reported that they enter the AEFI reports they receive into their database while those at UVIS report that they file the reports they receive.

4.6 Risk assessment and evaluation

Analysis of aspects of risk assessment and evaluation in vaccine pharmacovigilance was carried out using eight (8) indicators. Only two of the indicators assessed were attained to give a score of three (3) out of twelve (12) points. The results are shown in table 5 below.

Table 5: Indicators on risk assessment and evaluation

	Risk assessment and evaluation		
Indicator no	**Pharmacovigilance area**	**Type of indicator**	**Score**
4.1	Number of medicine utilization reviews in the last year	S	1
4.2	Vaccine product quality survey in the last five years	S	0
4.3	Incidence of vaccination errors quantified in the last year	S	0
4.4	Number of AEFI reports received in the last year	C	0
4.5	Number of active surveillance activities in the last five years	C	2
4.6	Percentage of vaccinees in whom AEFI were reported last year	C	0
4.7	Percentage of vaccinees who experienced vaccination failure	C	0
4.8	Percentage of patients for whom serious unexpected AEFI were reported in the last year	S	0
	Total score		3
	Percentage score (%)		25

Only one AEFI report was received in the national pharmacovigilance centre in the year 2014. There was no system at UVIS for reporting incidences of immunization errors and unexpected adverse events. No product quality survey for vaccines had been carried out in the last five years. The UVIS reported to have carried out vaccine utilization reviews in 2014 and 2015. In 2015, a review of post-introduction uptake of rotavirus vaccine was undertaken. In 2014 a review of the uptake of vaccines in the country was carried out. One active surveillance study (the Vaccine Adverse Events in Kenya) was retrieved from the PPB database on clinical trials. It was carried out from 2011 to 2013 by the Kenya Medical Research Institute (KEMRI) to evaluate the risk of AEFI following administration of pneumococcal conjugate vaccine (PCV 10).

4.7 Risk management and communication

Seven (7) indicators were used to assess various components of risk management and communication. Only two (2) indicators were attained to give a score of one (2) out of eight (8). The results are shown in table 6 below

Table 6: indicators on risk management and communication

	Risk management and communication		
Indicator no	**Pharmacovigilance area**	**Type of Indicator**	**Score**
5.2	Pre-qualification scheme of vaccine manufacturers	S	1
5.3	Number of vaccine safety information received and addressed last year	S	0
5.4	Percentage of publications of any vaccine information bulletins	S	0
5.5	Number of vaccine safety issues of local relevance identified from outside sources	S	0
5.6	Number of letters sent to health care professionals on vaccine safety	S	0
5.7	Average time lag between identification of serious AEFI and communication to health care professionals	C	0
5.9	Community education activities on vaccine safety	S	1
	Total score		2
	Percentage score (%)		25

All vaccines used in Kenya are prequalified by WHO and registered by the PPB. The UVIS does not keep a register of the safety information requests it receives though the respondents said that they sometimes receive calls regarding vaccine safety. There were also no registers of safety alert letters developed and distributed. The time lag between identification of serious AEFI and communication to health care workers could not be determined as there were no records. Several television and radio interviews were given in 2014 and 2015 on vaccine safety. The key informants reported that the UVIS relies on communication from WHO on vaccine safety. The respondents could not tell whether any such information had been used locally.

CHAPTER 5

DISCUSSION

5.1 Policy, law and regulation

Existence of pharmacovigilance policy indicates that a country is highly committed to improving medicine safety. A policy statement of pharmacovigilance is the guiding document and authority that mandates the need, scope, direction and activities a country should carry out. The Kenya National Pharmaceutical Policy (KNPP) 2008 only mentions pharmacovigilance in passing. The WHO recommends that essential statements on Pharmacovigilance should be included in the National medicine policy (NMP) (21). Examples of essential statements on pharmacovigilance are: commitment to monitor the safety and effectiveness of medicine, vaccines and medical devices, and government commitment to fund pharmacovigilance activities (21). Though the Kenya national policy guidelines on immunization 2013 have not mentioned vaccine pharmacovigilance, it has- notably- covered various topics on vaccine safety and effectiveness. The topics covered include management and reporting of AEFI, storage and transportation of vaccines and vaccine diluents, safe injection practices, vaccinating special groups (for example, pregnant women and the immunocompromised) and disposal of vaccination waste. The policy, however, lacks essential statements on pharmacovigilance of vaccines and this may be construed as lack of commitment from the government on vaccine pharmacovigilance. In the current multi-year plan for 2013-2017, the ministry of health (through UVIS) has emphasized its commitment in ensuring vaccine safety by improving AEFI surveillance (2).

The Pharmacy and poisons Act CAP 244 is the principal law governing the profession of pharmacy and the trade in drugs and poisons in Kenya. Laws and regulations provide legal backing for pharmacovigilance and medicine safety activities. The Kenya pharmacy and poisons Act does not address pharmacovigilance and has no section that requires MAHs to report serious ADRs to the PPB. The assessment determined that the PPB has been encouraging MAHs of all registered medicinal products in Kenya to submit PSURs through sensitization sessions. At the time of the study, no PSURs had been submitted for vaccines. This may mean that vaccine safety is not considered as important as safety of other medicinal products.

5.1.1 Implications of lack of policy, law and regulations

The pharmacy and poisons Act does not require MAHs in Kenya to report serious ADRs to the PPB. This limits the capacity of PPB to mandate post-marketing safety commitments of vaccine licence holders and other medicinal products licence holders(32). This also means that manufacturers and MAHs of vaccines and other medicinal products used in Kenya will be minimally engaged in vaccinovigilance. Requirements can be placed on registration to ensure effectiveness and safe use of medicinal products and vaccines in the country. These requirements may include: requirement for mandatory reporting of all adverse events related to the product, including those that occurred outside the country; requirement for post-authorization safety studies; requirement for routine and timely provision of all new information obtained that is related to safety and effectiveness of the product; and requirement for submission of periodic safety update reports (PSURs) (32).

5.2 Systems, structures and stakeholder coordination

A comprehensive pharmacovigilance system requires the development of sustainable systems and structures with clearly defined roles to allow effective use of available staff and infrastructure (22) as illustrated in figure 2. Effective stakeholder coordination is important since it ensures that there is effective communication between the national immunization programme, the national pharmacovigilance centre and various other stakeholders involved in vaccine safety. This minimizes any safety gaps that may exist and avoids duplication of roles. It also allows opportunities for leveraging resources to be exploited (22). Examples of vaccine safety stakeholders that could be mapped include the hospitals, PPB, the national pharmacovigilance centre, Disease Surveillance and Response Unit (DSRU), National Immunization Technical Advisory Group (NITAG), MAH, manufacturers, WHO PIDM and GACVS.

SOPs are necessary to standardize provision of pharmacovigilance services. Written SOPs for vaccine pharmacovigilance activities were not available. Training as an indicator is measured using the target set by IPAT. A minimum of 5 percent of professional health care workers (HCWs) -including physicians, pharmacists and nurses- need to have been trained on pharmacovigilance in the previous year for this indicator to be attained. Kenya has approximately 48,791 doctors, pharmacists and nurses (33) and would be expected to have trained at least 2,439 in vaccine pharmacovigilance

5.2.1 Implications of weak systems, structures and stakeholder coordination

National pharmacovigilance guidelines serve as a blueprint of how pharmacovigilance is coordinated in a country. The current guidelines in Kenya focus heavily on drugs without any mention of vaccine or medical devices. The country does not have guidelines on immunization safety surveillance. According to WHO, national AEFI guidelines are a critical component in carrying out post market surveillance activities for vaccines (34). AEFI guidelines can be contained in comprehensive national guidelines for health products safety surveillance or they can be stand-alone. Implications of lack of AEFI guidelines can be clearly seen in the inability to map out stakeholders of vaccine pharmacovigilance. Development and implementation of guidelines will serve as a basis for coordination of activities among various stakeholders. The lack of dedicated budget, SOPs, newsletters, question and answer service, ARC and a pharmacovigilance unit indicate inability and lack of capacity to detect and effectively address vaccine safety issues.

No pharmacovigilance training was organised by the immunization programme for central-level or service provision level staff. HCWs are the primary reporters of AEFI (15). To improve case detection they need to have good knowledge on AEFI and on the aim of AEFI surveillance. This can be achieved through regular training programmes. A study carried out in the country in 2014 reported that only 29.2% of nurses working in Nairobi city council hospitals had good knowledge on AEFI surveillance (35). Training is also necessary to maintain the enthusiasm among the reporters (15). The implication of lack of training is witnessed from the negligible number of AEFI reports received at the UVIS and at the pharmacovigilance centre. In the year 2014 only one AEFI report was received at the national pharmacovigilance centre. The total number of reports retrieved from UVIS and PPB was five. This makes it very difficult to detect vaccine safety issues.

5.3 Signal generation and data management

Pharmacovigilance of vaccines involves signal detection, signal evaluation and risk management (4, 20). A signal is a reported association between the use of a vaccine and a subsequent untoward event that could be a possible indication of a previously unknown or poorly documented causal relationship, that is deemed to be of sufficient likelihood to justify verification (36). Signal detection is achieved through reporting of suspected adverse events (20). It is important that AEFI reporting forms be widely distributed in the health facilities offering vaccination services in order to facilitate reporting (15). Reporting can be improved further by making the forms available online and accessible to the public. The UVIS has an

AEFI reporting form but the interviewees reported that the form had not been widely distributed due to lack of funds to print and distribute them. The reporting form contained all the core variables as advised by WHO (15).

Pharmacovigilance covers monitoring of ineffectiveness, medication errors and product quality. A form for reporting poor quality medicinal products is printed and distributed by the PPB though no reports on suspected poor quality vaccines had been submitted at the time of the study. The National Quality Control Laboratory (NQCL) in the country has no capacity to test the quality of vaccines used in the country. In case a report is submitted and there is need to test the quality of the vaccine, samples are sent to laboratories out of the country.

A national database for collating, managing and retrieving AEFI reports is one of the requirements for minimal capacity for vaccine safety activities (10). There was no database for collating AEFI reports in Kenya.

5.3.1 Implications of lack of adequate systems for signal generation and data management

Signal generation in many countries relies on sensitized health workers who report suspected adverse events (32). Poor availability of AEFI reporting forms in health facilities implies that AEFI surveillance activities in Kenya are impaired. This results in low reporting rates (32).

5.4 Risk assessment and evaluation

Risk assessment is triggered by the generation of signals. It is important to assess and evaluate signals, especially those that are of public health importance (32). Any comprehensive pharmacovigilance system needs to periodically review adverse events through passive surveillance and evaluate significant safety issues through active surveillance (22). Signals can be generated only when adverse events are reported. An analysis of AEFI reporting rates over a period of 10 years showed an average of 11.4 reports per 100,000 distributed doses of vaccines (37). Using this rate, Kenya would be expected to have generated 22.8 assuming 200,000 doses were distributed in 2014 but only one AEFI report was received in the national pharmacovigilance centre in the year 2014. No product quality survey for vaccines had been carried out in the last five years. This may be due to the cost implications of sending vaccine samples out of the country for testing or due to the fact that all vaccines procured in the country are WHO pre-qualified. Characterizing incidence of preventable AEFI helps to develop strategies on how to reduce their occurrence (38).

5.4.1 Implications of limitations in risk assessment and evaluation

When little effort is made to generate and evaluate signals, opportunities to learn about safety of vaccines in real-life is lost. From the assessment, it is clear that opportunities to collect AEFI data have not been exploited. This means that this information cannot be used to inform immunization protocols in the country.

5.5 Risk management and communication

The indicators used to assess risk management and communications recognise the role of prevention in pharmacovigilance. If implemented, they can significantly reduce the incidence of harm of vaccines.

All vaccines used in Kenya are prequalified by WHO and registered by the PPB. Prequalification provides assurance that the vaccines meet consistent quality standards every time. The UVIS does not keep a register of the safety information requests it receives though the respondents said that they sometimes receive calls regarding vaccine safety. There were also no registers of safety alert letters developed and distributed. The time lag between identification of serious AEFI and communication to health care workers could not be determined as there were no records. Several television and radio interviews were given in 2014 and 2015 on vaccine safety. This only occurred after allegations of HCG-contaminated tetanus toxoid vaccine and death of two children after measles jab.

Safety issues of local relevance from outside sources can be used to prevent harm in the local population. It is very beneficial for countries without full capacity to generate signals. The key informants reported that the UVIS relies on communication from WHO on vaccine safety. The respondents could not tell whether any such information had been used locally.

5.5.1 Implications of limitations in risk management and communication

Risk management and communication has high impact in preventing harm (32). The assessment showed that these opportunities are under-utilised. This means that significant vaccine safety issues which would have otherwise been prevented may occur.

CHAPTER 6

CONCLUSION AND RECOMMENDATIONS

6.1: Conclusion

Kenya had a system for pharmacovigilance of vaccines in place. The National Regulatory Authority (represented by PPB) and the National Immunization Program (represented by UVIS) were the institutions responsible for pharmacovigilance of vaccines at the national level. There were staffs assigned to carry out vaccine pharmacovigilance activities and a reporting tool for adverse events following immunization (AEFI). However, some gaps such as absence of specific legislation, lack of guidelines and absence of an organizational structure for vaccine safety were identified. These resulted in poor coordination of vaccine pharmacovigilance activities. These shortcomings hamper the ability of the country to effectively detect and manage vaccine safety issues.

6.2: Recommendations

Revise relevant legislation to adequately address safety monitoring

The pharmacy and poisons Act CAP 244 lacks provision for pharmacovigilance. It needs to be revised to incorporate modern articles of pharmacovigilance such as mandatory reporting by MAHs, post-marketing surveillance commitments and conditional registration of new medicinal products. Additionally, regulations need to be developed to enhance compliance by the MAHs.

Define minimum requirements for pharmacovigilance in the immunization programme

The MoH should define minimum requirements for pharmacovigilance activities in all public health programmes, including the national immunization programme. Such requirements can include: development of pharmacovigilance plans before introduction of a new vaccine, a focal person for pharmacovigilance who is a liaison with the pharmacovigilance at the PPB and include pharmacovigilance indicators (such as data on outbreaks which may suggest inefficiency of vaccines and AEFI rates).

Develop and disseminate AEFI guidelines and SOPs

AEFI guidelines need to be developed and distributed widely. The guidelines should include most of the following components:

- Objectives of the system
- A list of reportable AEFI
- Case definition
- Information on how to report AEFI for both EPI and non-EPI vaccines
- Process of data analysis and feedback
- Investigation process, especially for serious AEFI and AEFI clusters
- Process of communicating to patient, parents, community and country when necessary.

Coordinate stakeholders

Pharmacovigilance of vaccines is the responsibility of various stakeholders including, UVIS, PPB, academic researchers, pharmaceutical industry, donors, immunization service providers and the public. The coordinated functioning of all the stakeholders is important for strengthening the system.

The first step in this process is mapping of all the stakeholders of vaccine pharmacovigilance. The roles and responsibilities of these stakeholders should be identified. These will enable identification of gaps and opportunities for synergy, help in planning and improve coordination.

Develop a database for collating and retrieving AEFI data

UVIS in collaboration with PPB needs to develop a database for AEFI data. The vaccine adverse events information management system (VAEIMS) is software developed by the international vaccine institute in collaboration with WHO. It allows transfer of AEFI data from the periphery to a central database. It also allows transfer from the national database to vigibase (global database). This software can be adapted for use locally and it is available free of charge to all countries. It is recommended that this software be used in Kenya.

Training of health workers

Routine training on AEFI monitoring and management should be provided to all health workers especially immunization service providers. Health workers are the primary reporters of AEFI and effort should be made to ensure that they are adequately trained to identify and report AEFI cases.

Improve communication to health workers and the public.

Efforts should be made to convey vaccine safety information to health workers in a timely and effective manner. There should be regular publications on vaccine pharmacovigilance in a newsletter or a bulletin. Safety alerts should also be sent out to health workers as need occurs. The public should also be sensitized on AEFI reporting.

Dedicate a budget to vaccine pharmacovigilance

Most of the pharmacovigilance activities can only be carried out if there is a dedicated budget for them. The funding needs to be stable and adequate for the activities. Mapping of stakeholders can identify opportunities of leveraging for funds from the various stakeholders.

Pharmacoepidemiological studies

The UVIS and PPB should develop memoranda of understanding with universities and research institutions to carry out pharmacoepidemiological studies on vaccines

Recommendation for further studies

It is recommended that a baseline assessment of the national pharmacovigilance system be undertaken using IPAT. This will help to identify gaps in the system and also identify opportunities and resources that can be utilized for vaccine pharmacovigilance. This allows the systems to work in tandem with each other and not parallel to each other.

REFERENCES

1. Ministry of Health Kenya. National Policy Guidelines on Immunization. Ministry of Health Kenya; 2013.

2. Division of Vaccines and Immunization Comprehensive Multi-Year Plan 2013-2017 [Internet]. Available from: http://www.nationalplanningcycles.org/sites/default/files/country_docs/Kenya/cmyp_kenya_2013-2017_1.pdf

3. Kenya National Bureau of Statistics. Kenya Demographic and Health Survey 2014 . Key Indicators [Internet]. 2014 [cited 2015 Sep 9]. Available from: http://www.knbs.or.ke/index.php?option=com_phocadownload&view=category&download=718:kenya-demographic-health-survey-2014-key-indicators-report&id=125:kenya-demographic-health-survey-2014&Itemid=599

4. Plotkin S. History of vaccination. Proc Natl Acad Sci. 2014 Aug 26;111(34):12283–7.

5. Delany I, Rappuoli R, De Gregorio E. Vaccines for the 21st century. EMBO Mol Med. 2014 Jun;6(6):708–20.

6. Folb PI, Bernatowska E, Chen R, Clemens J, Dodoo ANO, Ellenberg SS, et al. A Global Perspective on Vaccine Safety and Public Health: The Global Advisory Committee on Vaccine Safety. Am J Public Health. 2004 Nov 1;94(11):1926–31.

7. Kohl KS, Bonhoeffer J, Braun MM, Chen RT, Duclos P, Heijbel H, et al. The Brighton Collaboration: Creating a Global Standard for Case Definitions (and Guidelines) for Adverse Events Following Immunization. In: Henriksen K, Battles JB, Marks ES, Lewin DI, editors. Advances in Patient Safety: From Research to Implementation (Volume 2: Concepts and Methodology) [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2005 [cited 2014 Sep 8]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK20507/

8. MODULE 5 – CIOMS/WHO working group - WHO Vaccine Safety Basics [Internet]. [cited 2015 Sep 11]. Available from: http://vaccine-safety-training.org/cioms-who-working-group.html

9. MODULE 5 – WHO Programme for International Drug Monitoring - WHO Vaccine Safety Basics [Internet]. [cited 2015 Sep 11]. Available from: http://vaccine-safety-training.org/who-programme-for-international-drug-monitoring.html

10. Bramley D, Black S, Bonhoeffer J, Dodoo A, Eskola J, Larson H, et al. Global vaccine safety blueprint [Internet]. WHO; 2012. Available from: http://whqlibdoc.who.int/hq/2012/WHO_IVB_12.04_eng.pdf?ua=1

11. Global vaccine safety blueprint: The landscape analysis [Internet]. WHO; Available from: http://whqlibdoc.who.int/hq/2012/WHO_IVB_12.04_eng.pdf

12. Evidence and guidance on vaccine safety and effectiveness in subpopulations. Available from: http://edoc.unibas.ch/1437/1/20111208_ELECTRONIC_VERSION_MAK.pdf

13. Strom BL, Kimmel SE, Hennessy S. Pharmacoepidemiology. John Wiley & Sons; 2012. 977 p.

14. Kaufmann JR, Feldbaum H. Diplomacy And The Polio Immunization Boycott In Northern Nigeria. Health Aff (Millwood). 2009 Jul 1;28(4):1091–101.

15. WHO. Global Manual on Surveillance of Adverse Events Following Immunization [Internet]. WHO; 2014. Available from: http://www.who.int/vaccine_safety/publications/aefi_surveillance/en/

16. Global Advisory Committee on Vaccine Safety (GACVS), WHO secretariat. Global safety of vaccines: strengthening systems for monitoring, management and the role of GACVS. Expert Rev Vaccines. 2009 Jun;8(6):705–16.

17. Rosenthal S, Chen R. The reporting sensitivities of two passive surveillance systems for vaccine adverse events. Am J Public Health. 1995 Dec 1;85(12):1706–9.

18. GACVS, WHO secretariat. Causality assessment of an adverse event following immunization (AEFI) :User manual for the revised WHO classification [Internet]. World Health Organization; 2013. Available from: http://www.who.int/vaccine_safety/publications/aevi_manual.pdf

19. Gogtay NJ, Dhingra MS, Yadav A, Chandwani H. Vaccine policy, regulations and safety in India. Int J Risk Saf Med 21 2009 23–30 [Internet]. Available from: http://iospress.metapress.com/content/1564p14k2p761772/?issue=1&genre=article&spage=23&issn=0924-6479&volume=21

20. World Health Organization Regional Office for the Western Pacific. Immunization Safety Surveillance :Guidelines for immunization programme managers on surveillance of adverse events following immunization (second edition) [Internet]. World Health Organization; 2013. Available from: http://www.wpro.who.int/topics/immunization_safety/ImmunizationSafetySurveillance.pdf

21. Strengthening pharmaceutical systems. Indicator-Based Pharmacovigilance Assessment Tool: Manual for Conducting Assessments in Developing Countries [Internet]. World Health Organization; 2009. Available from: http://apps.who.int/medicinedocs/documents/s21303en/s21303en.pdf

22. Lebega O, Nwokike J, Walkowiak H. Safety of Medicinal Products in Ukraine: Assessment of the Pharmacovigilance system and its Performance [Internet]. 2012 [cited 2015 Sep 18]. Available from: zotero://attachment/132/

23. Potter C, Brough R. Systemic capacity building: a hierarchy of needs. Health Policy Plan. 2004 Sep 1;19(5):336–45.

24. Duclos P, Hockin J, Pless R, Lawlor B. Reporting vaccine-associated adverse events. Can Fam Physician. 1997 Sep;43:1551–60.

25. Parrella A, Braunack-Mayer A, Gold M, Marshall H, Baghurst P. Healthcare providers' knowledge, experience and challenges of reporting adverse events following immunisation: a qualitative study. BMC Health Serv Res. 2013 Aug 15;13:313.

26. World Health Organization. AEFI Investigation Aide Memoire [Internet]. World Health Organization; Available from: http://www.who.int/immunization/documents/792.pdf

27. Weigong Zhou et al. Surveillance for Safety After Immunization: Vaccine Adverse Event Reporting System (VAERS) --- United States, 1991--2001 [Internet]. CDC; 2003. Available from: http://www.cdc.gov/MMWr/preview/mmwrhtml/ss5201a1.htm

28. K Ehresman et al. Intussusception Among Recipients of Rotavirus Vaccine -- United States, 1998-1999. CDC;

29. McMahon AW, Iskander JK, Haber P, Braun MM, Ball R. Inactivated influenza vaccine (IIV) in children <2 years of age: Examination of selected adverse events reported to the Vaccine Adverse Event Reporting System (VAERS) after thimerosal-free or thimerosal-containing vaccine. Vaccine. 2008 Jan 17;26(3):427–9.

30. Committee to Review Adverse Effects of Vaccines, Board on Population Health and Public Health Practice, Medicine I of. Adverse Effects of Vaccines:: Evidence and Causality. National Academies Press; 2012. 894 p.

31. Choi Lynn Hye, David L, Nwokike Jude. Safety of Medicines in Sub-Saharan Africa: Assessment of Pharmacovigilance Systems and their Performance. [Internet]. 2011 [cited 2015 Dec 2]. Available from: http://apps.who.int/medicinedocs/documents/s19152en/s19152en.pdf

32. Nwokike J, Eghan K. Pharmacovigilance in Ghana: A Systems Analysis [Internet]. [cited 2015 Oct 10]. Available from: http://apps.who.int/medicinedocs/documents/s18075en/s18075en.pdf

33. Kenya National Bureau of Statistics. Kenya Facts and Figures 2014 [Internet]. [cited 2015 Nov 30]. Available from: http://www.knbs.or.ke/index.php?option=com_phocadownload&view=category&download=587:kenya-facts-and-figures-2014&id=20:kenya-facts-figures&Itemid=595

34. World Health Organization. WORLD HEALTH ORGANIZATION (WHO) - IMMUNIZATION, VACCINES & BIOLOGICALS (IVB)- JOINT MEDICAL PRODUCTS ASSESSMENT TOOLS OF NATIONAL REGULATORY SYSTEM [Internet]. [cited 2015 Nov 30]. Available from: http://www.who.int/immunization/sage/NRA_joint_assessment_tools.pdf

35. Knowledge, perceptions and practice of nurses on surveillance of adverse events following childhood immunization in Nairobi county, Kenya.pdf [Internet]. [cited 2015 Dec 10]. Available from: http://ir-library.ku.ac.ke/bitstream/handle/

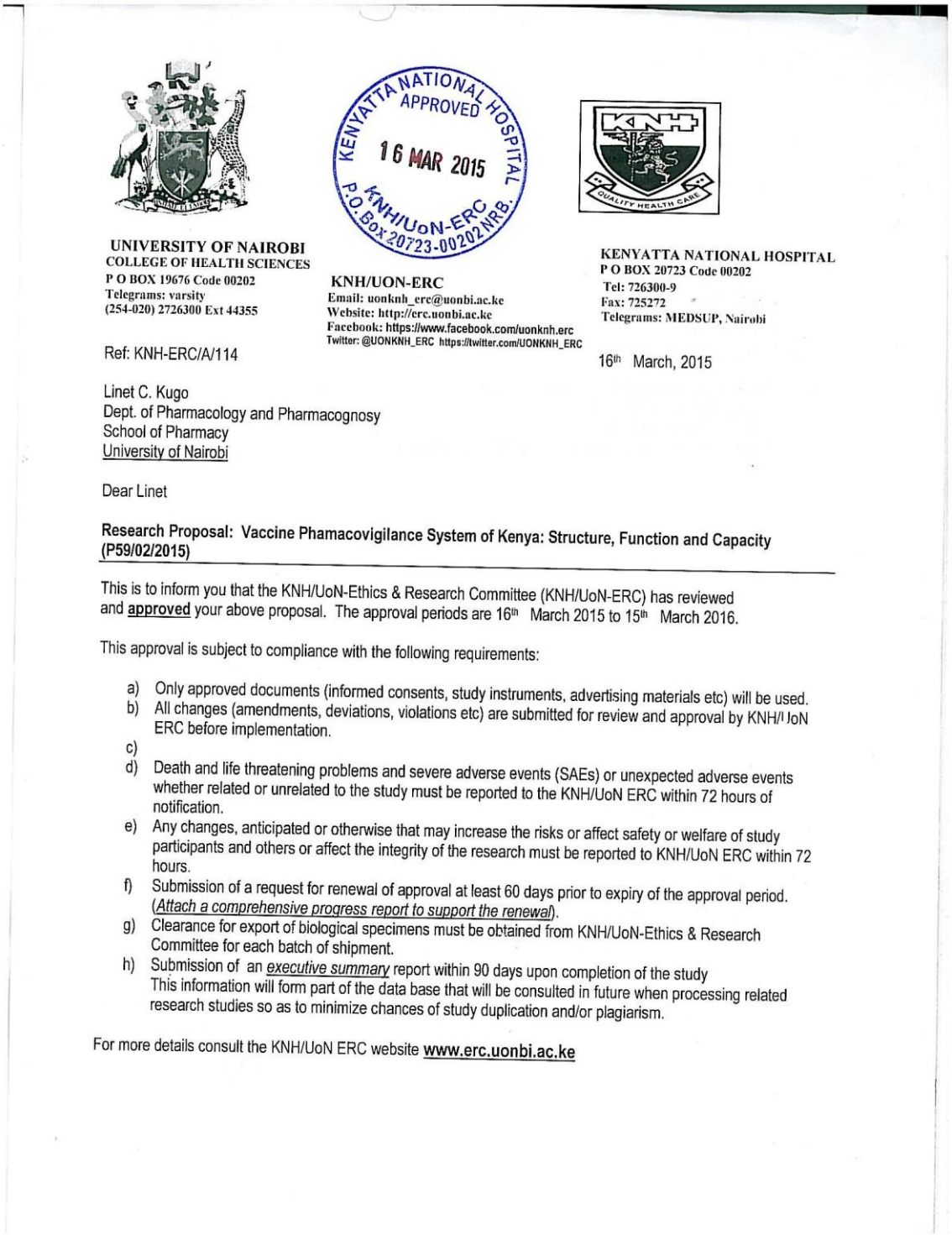
36. CIOMS_report_WG_vaccine.pdf [Internet]. [cited 2015 Oct 7]. Available from: http://www.who.int/vaccine_safety/initiative/tools/CIOMS_report_WG_vaccine.pdf

37. Weigong Zhou. Surveillance for Safety After Immunization: Vaccine Adverse Event Reporting System (VAERS) — United States, 1991–2001 [Internet]. 2003 [cited 2015 Oct 12]. Available from: http://www.cdc.gov/mmWR/PDF/ss/ss5201.pdf

38. Verma R, Khanna P, Bairwa M, Chawla S, Prinja S, Rajput M. Adverse events following immunization: Easily preventable in developing countries. Hum Vaccin. 2011 Sep 1;7(9):989–91.

APPENDICES

Appendix I: ERC approval



KENYATTA NATIONAL HOSPITAL APPROVED 16 MAR 2015 KNH/UoN-ERC P.O. Box 20723-00202 NRB.

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
(254-020) 2726300 Ext 44355

KNH/UON-ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/114

16th March, 2015

Linet C. Kugo
Dept. of Pharmacology and Pharmacognosy
School of Pharmacy
University of Nairobi

Dear Linet

Research Proposal: Vaccine Phamacovigilance System of Kenya: Structure, Function and Capacity (P59/02/2015)

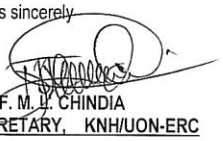
This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 16th March 2015 to 15th March 2016.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
c)
d) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.
e) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
f) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
h) Submission of an *executive summary* report within 90 days upon completion of the study This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH/UoN ERC website **www.erc.uonbi.ac.ke**

Yours sincerely



PROF. M. L. CHINDIA
SECRETARY, KNH/UON-ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director CS, KNH
The Chair, KNH/UoN-ERC
Supervisors: Dr. G.O. Osanjo, Dr. M. Oluka, Dr. N. Mungau

Appendix II: Student confidentiality agreement PPB

REPUBLIC OF KENYA

MINISTRY OF HEALTH

PHARMACY AND POISONS BOARD

STUDENT CONFIDENTIALITY AGREEMENT

In the course of evaluation of your study, you will gain access to certain information, which is proprietary to Pharmacy and Poisons Board and other interested parties.

You shall treat such information (hereinafter referred to as "**the Information**") as confidential and proprietary to PPB or the aforesaid parties. In this connection, you agree:

(a) Not to use the Information for any purpose other than discharging your obligations under this agreement;
(b) Not to disclose or provide the Information to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

I shall not communicate your observations and/or findings as well as any resulting recommendations and/or decisions of your work to any third party, except as explicitly agreed by PPB.

I understand that any information (written, verbal or other form) obtained during the performance of my duties must remain confidential. This includes all information about members, clients, families, employees and other associate organizations, as well as any other information otherwise marked or known to be confidential.

I understand that any unauthorized release or carelessness in the handling of this confidential information is considered a breach of the duty to maintain confidentiality.

I further understand that any breach of the duty to maintain confidentiality could be grounds for immediate dismissal and/or possible liability in any legal action arising from such breach.

You confirm that you have no situation of real, potential or apparent conflict of interest including financial or other interests in, and/or other relationship with, a party, which:

(i) May have a vested commercial interest in obtaining access to any part of the Information referred to above; and/or

(ii) May have a vested interest in the outcome of evaluation of the application.

You shall promptly notify the Registrar, PPB of any change in the above circumstances, including if an issue arises during the course of your work.

All documents supplied to you in connection with this application shall be accepted in strict confidence and shall be held in safe and secure custody at all times.

I hereby accept and agree with the conditions and

Declaration:

I, the undersigned, do hereby agree to adhere to the provisions contained in this agreement.

I hereby declare that I ~~have~~/do not have (*delete what is NOT applicable*) a Conflict of Interest with the following application(s)/any of the applications that I have been requested to review (*delete what is NOT applicable*)

Reference number (s) of application (s) with which I have a conflict of interest

LINET CHEPKEMBOI KUGO
(Student Name)

(Signature)

14/05/15
(Date)

Appendix III: Information sheet

Appendix 2.1: Information sheet

Informed consent form for Participation in the Interview 'The vaccine pharmacovigilance system of Kenya: Structure, function and capacity.

Principal Investigator:

Dr. Linet Kugo

Masters Student, School of Pharmacy, University of Nairobi

Supervisors:

Dr. George Osanjo, School of Pharmacy, University of Nairobi

DR.M. Oluka, School of Pharmacy, University of Nairobi

Dr. N. Mungai, School of Pharmacy, University of Nairobi

Information Sheet

Introduction

My name is..... I am a student at the University of Nairobi pursuing a Master's degree in Pharmacoepidemiology and pharmacovigilance. This study is on 'The vaccine pharmacovigilance system of Kenya: structure, functions and capacity.' As we all know vaccine pharmacovigilance is critical in increasing the confidence of the population to vaccines leading to high vaccination coverage by the national immunization program.

You have been selected to participate in this study due to your expertise in pharmacovigilance of vaccines. Your participation is voluntary and refusal to participate will not result in any penalty. The interview will take approximately 40 minutes. It will involve an open discussion on your knowledge and experience regarding the study. With your approval, the interview will be tape-recorded and whatever information you provide will be held in strict confidence. The voices recorded will be masked to prevent identity of the interviewees. No names will be mentioned in the research reports and publications. Ethical approval for this study was sought from the

KNH/UoN ethics committee. This committee reviews research studies in order to protect the participants.

There are no expected risks due to your participation in this study. There might be no direct benefit from your participation but your contribution will lead to improvement in the field of pharmacovigilance of vaccines.

If you have any questions or concerns, feel free to contact me on cell phone number 0727235915 or the KNH/UoN ethics committee on telephone number 2726300 extension 44102.

Your co-operation and support is highly appreciated.

Appendix IV: Informed consent form

I have read and understood the information provided regarding the study and my questions regarding the study have been addressed. I willingly consent to participate in this study.

NAME OF PARTICIPANT:.....

SIGNATURE:.....

DATE:.....

Statement by the researcher:

I have provided all relevant information to the participant and answered all questions asked regarding the study. I have explained to the participant that his/her responses will be recorded in a note book and will be taped. I confirm that information requested has been provided voluntarily.

A copy of this informed consent has been provided to the participant.

NAME OF RESEARCHER:.....

SIGNATURE:.....

DATE:.....

In case of any questions or concerns, feel free to contact any of the following:

- The principal investigator Dr. L. Kugo on 0727235915,
- The lead supervisor Dr. G. Osanjo on 0721794666, or
- KNH/UoN ethics committee on 2726300 extension 44102

Appendix V: Interview guide

APPENDICES

APPENDIX 1: SEMI-STRUCTURED INTERVIEW GUIDE

1. Funding, structure, roles and responsibilities.
    - Is there a policy in place establishing a vaccine pharmacovigilance system in Kenya?
    - Which institution between PPB and UVIS has the overall responsibility in AEFI surveillance?
    - Are there staff assigned to carry out vaccine pharmacovigilance activities?
    - What are their roles? Are their roles clearly specified?
    - How many are they?
    - What is their educational background?
    - Which AEFI reports should be submitted?
    - Where are the reports submitted to?
    - Who receives a report first?
    - What happens after a report has been submitted?
    - Which institution/person has the overall responsibility for ensuring that appropriate corrective action and feedback regarding AEFI is carried out?
    - Which institution/person has the overall responsibility of communicating to the public and the media when the need arises?
    - Is there a budget for vaccine pharmacovigilance activities?
    - How are vaccine pharmacovigilance activities in the country funded? Is the funding adequate?
2. Training
    - Are there national training modules on AEFI surveillance?
    - Has training on AEFI surveillance been provided to health workers? How many health workers have been trained?
    - Has training been provided to select staff (immunization programme managers, pharmacovigilance staff etc)? How many have been trained?

3. Guidelines and procedures.
    - Are there national guidelines for AEFI surveillance?
    - Are the guidelines accessible to all health workers and immunization service providers?
    - Is there a standardized national AEFI reporting form?
    - Is the form accessible to health workers? Is it available online?
4. Review of safety information and sharing data among key personnel.
    - Is there a national database for management of AEFI information?
    - Is AEFI data analyzed regularly? Who does the analysis?
    - Is there a national ARC? What is the membership of the ARC? What are their terms of reference?
    - How are reports on serious AEFI handled?
    - How is information on serious AEFI cases, AEFI clusters and investigation reports disseminated among the various stake-holders?
    - Is there a process of assessing AEFI at county level to initiate necessary action when needed?

Appendix VI: Indicator-based pharmacovigilance tool (IPAT)

Indicator		Core/	Computation
Component 1. Policy, Law, and Regulation			
1.1	Existence of a policy document that contains essential statements on pharmacovigilance or medicine safety (stand alone or as a part of some other policy document)	Core	Check "**Yes**" if there are essential pharmacovigilance policy statements within the national pharmaceutical policy or other policy documents and that policy statement was developed or reviewed within the last
1.2	Existence of specific legal provisions for pharmacovigilance in the national medicines legislation or similar legislation	Core	Check "**Yes**" if specific requirements for pharmacovigilance or medicine safety are mentioned in the laws or the regulation.
1.3	Legal provisions require that the marketing authorization holder mandatorily report all serious ADRs to the national drug	Supplementary	Check "**Yes**" if there are specific legal requirements for the MAH to report all serious ADRs.
1.4	Legal provisions require the marketing authorization holder to conduct the same or similar postmarketing surveillance activities for products as required	Supplementary	Check "**Yes**" if there is a mention in laws/regulations that some products may be registered with restricted conditions due to safety concerns
Component 2. Systems, Structures, and Stakeholder Coordination			
2.1	Existence of a pharmacovigilance center or unit	Core	Check "**Yes**" if Official documents establish the existence of a pharmacovigilance center/unit or if the documented mandate of the program includes pharmacovigilance activities
2.2	Pharmacovigilance center or unit has a clear mandate, structure, roles, and responsibilities	Core	Check "**Yes**" if there is an official document with clear mandate, organizational structure, roles, responsibilities, and reporting lines for the pharmacovigilance center and

2.3	Existence of a medicine/vaccine information or pharmacovigilance service that provides AEFI and vaccine safety– related question-and-answer services	Core	Check "**Yes**" if key informant confirms that there is a vaccine safety– related question-answer service provided by the DIC or the pharmacovigilance center. And there are reports or a database to
2.4	A designated staff responsible for pharmacovigilance activities	Core	Check "**Yes**" if key informant confirmed that someone is responsible for AEFI monitoring and the job description verified this
2.5	Dedicated budget available for pharmacovigilance-related activities	Core	Check "**Yes**" if key informants confirm availability of budgets for pharmacovigilance activities or pharmacovigilance was funded by MoH or donors in the previous year
2.6	Existence of a national ARC	Core	Check "**Yes**" there is an official document constituting a national ARC and there are records to confirm that the committee met within the last year.
2.7	Existence of national AEFI guidelines updated within the last five years	Core	Check "**Yes**" if an official guideline document exists and if it has been updated in the last five years.
2.8	Existence of protocols or SOPs for improving patient safety relating	Core	Check "**Yes**" if any formal protocols or SOPs exist for improving patient safety
2.9	Existence of a minimum core list of communication technologies to improve access to safety reporting and provision of medicine information	Core	Check "**Yes**" if key informant confirms communication technologies are available. Examples of basic communication technologies are phones, fax, email address, computers, overhead
2.10	Existence of an AEFI or vaccine safety bulletin (or any other health-related newsletter that routinely features AEFI or vaccine	Core	Check "**Yes**" if key informant confirms the existence of a bulletin and the last edition/issue of the bulletin/newsletter was published within the last six months and
2.11	Percentage of predefined core reference materials available in the medicine information or pharmacovigilance center	Supplementary	Check "**Yes**"if pharmacovigilance-related core reference materials are available and in use at the center that provides AEFI and vaccine safety information.

2.13	Number of health care providers trained on vaccine pharmacovigilance in the last year	Supplementary	Enter number of staff trained if key informant confirms that health care providers were trained and that the trainings attended were formal pharmacovigilance trainings. Check "**Yes**" if more than 5% of professional health care workers (Physicians,
2.14	Platform or strategy exists for the coordination of pharmacovigilance activities at the national level	Core	Check "**Yes**" if key informant confirms that a formal platform exists for the coordination of vaccine pharmacovigilance activities and a Vaccine safety stakeholders' map is in place.
2.15	National pharmacovigilance center is a full or associate member of the WHO Collaborating Centre for	Supplementary	Check "**Yes**" if key informant confirms that the national pharmacovigilance center is a member of WHO/UMC and documentation exists to confirm it.

Component 3. Signal Generation and Data Management

3.2	Existence of a database for tracking pharmacovigilance activities	Core	Check "Yes" if key informant confirms existence of a central AEFI database and it was found to contain AEFI data from various
3.3	Existence of a form for reporting suspected AEFI	Core	Check "Yes" if key informant confirms availability of AEFI reporting forms
3.4	Existence of a form for reporting suspected product quality issues (as a subset in the AEFI form or as	Core	Check "Yes" if key informant confirms that a form for product quality is available
3.5	Existence of a form for reporting suspected medication errors (as a subset in the AEFI form or as a	Core	Check "Yes" if key informant confirms that a form for reporting vaccination errors is available
3.6	Existence of a form for reporting suspected vaccination failure (as a subset in the AEFI form or as a	Core	Check "Yes" if key informant confirms that a form for reporting suspected vaccination failure

Component 4. Risk Assessment and Evaluation

4.1	Number of medicine utilization reviews carried out in the last year	Supplementary	Check "**Yes**" if a vaccine utilizationreview/study has been carried out in the last year. Report of the study was circulated or published
4.2	Vaccine product quality survey conducted within the last five years	Supplementary	Check "**Yes**" if key informants reports that a vaccine quality survey has been carried out in the last 5 years and a report is available
4.3	Incidence of vaccination errors quantified in the last year	Supplementary	Check "**Yes**" if key informants reports that survey on the incidence of vaccination errors has been carried out in the last year and a
4.4	Number of ADR reports received in the last year	Core	Check "Yes" if key informant shows a register for documenting AEFI reports and that there is a minimum of 11.4 reports per
4.5	Number of active surveillance activities currently ongoing or	Core	Check "Yes" if at least one active surveillance study is on-going or was
4.6	Percentage of patients in the immunization program for whom vaccine-related adverse events were reported in the last year (disaggregated by type of adverse	Core	Check "Yes" if at least 1% of vaccinees are documented to have experienced AEFI
4.7	Percentage of vaccinees who experienced vaccination failure	Core	Enter "Yes" if the value is at least 1 %
4.8	Percentage of patients in the immunization program for whom vaccine-related, serious "unexpected adverse events" were	Supplementary	Check "Yes" if the immunization program has a register or documentation for recording new, unexpected adverse events. The value may range from 0 to 0.1%

Component 5. Risk Management and Communication

5.2	Prequalification schemes (e.g., WHO prequalification program and Pharmaceutical Inspection Co-operation Scheme) used in	Supplementary	Enter "Yes" if key informant confims that pre-qualification reports are used

5.3	Number of vaccine safety information requests received and addressed in the last year	Supplementary	Check the number of requests that were addressed and logged in the last year and enter "**Yes**" if 100 requests per million population received per year.
5.4	Percentage of planned issues of the medicine safety bulletin (or any other health-related newsletter that routinely features AEFI or vaccine safety issues)	Supplementary	If key informant confirms that a publication schedule exists, enter "Yes" if the number of issues published in the last year is more than 70% of the total number planned for publication
5.5	Number of vaccine safety issues of local relevance identified from outside sources (e.g., from another country, or from regional or international sources) and acted on locally in the last year	Supplementary	Enter value if : • Key informant confirms that a system exists for monitoring new safety reports from outside sources. • A register exists that confirms the type and number of actions or steps taken locally to address the safety issues in
5.6	Number of "Dear health care professional" letters or other safety alerts developed and distributed in the last year	Supplementary	Key informants confirm that vaccine regulatory alert letters were sent to health care professionals within the last year and it can be verified
5.7	Average time lag between identification of safety signal of a serious ADR or significant medicine safety issue and communication to health care workers and the public	Core	Enter value if the following are true— • Key informant confirms that vaccine safety signals and significant safety issues are promptly communicated to health workers. • A register or some other form of documentation on vaccine safety signalswith dates is available. Compute the value as follows— • Using a *list of recent safety warnings* with dates, identify when in-country warnings were communicated. • (Average time lag from receipt to communication of safety report/Total number of reports communicated) ×

5.9	Number of public or community education activities relating to vaccine safety carried out in the	Supplementary	Enter "**Yes**" if at least one community education activity was carried out.

Appendix VII

AEFI Reporting form

Ministry of Health
Unit of Vaccines and Immunization Services

AEFI
REPORTING FORM

A. Reporting Facility

To be filled in Duplicate

1. Name of Facility:	3. District:
2. Division:	4. Province:

B. Patient details

5. Name of Patient.....
6. OPD Number.....
7. Guardian Name *(If patient is a child)*.....
8. Address.....
9. Landmark .....
10. Village .....
11. Division.....
12. District.....
13. Province.....
14. Gender: Male [ ] Female [ ]
15. Date of Birth (DOB) *(dd/mm/yyyy)*.....
16. Age *(If DOB not known)* Yrs [ ] Months [ ]
17. Immunization Center.....
18. Date of Immunization.....
19. Type of vaccination service: /_/ Static, /_/ Outreach,/_/ Mass *(Tick where appropriate)*
20. Date of Onset.....
21. Date of notification.....
22. Date of Investigation.....
23. Interval of symptoms Day [ ] hr. [ ]

C. Type of AEFI

Please tick:

24. Injection site abscess	Yes ☐	No ☐	27. Anaphylaxis	Yes ☐	No ☐
25. BCG Lymphadenitis	Yes ☐	No ☐	28. High Fever	Yes ☐	No ☐
26. Severe Local Reaction	Yes ☐	No ☐	29. Toxic shock	Yes ☐	No ☐

30. Others (specify) .....
.....

D. CNS

Please tick:

31. Acute flaccid paralysis	Yes ☐	No ☐
32. Encephalopathy, Encephalitis/Meningitis	Yes ☐	No ☐
33. Convulsion	Yes ☐	No ☐

E. Suspected vaccine(s)

34. Name of Vaccine *(BCG, DPT-Hib-HeB, Pneumo, OPV, Measles, YF,Rot Vaccine))*	Dose Number	Details of Vaccine			Details of Diluents		
		Batch No.	Manufacturer's Name	Expiry Date	Batch No.	Manufacturer's Name	Expiry Date

35. Did the patient receive any form of treatment when the event occurred? Yes ☐ No ☐ (If yes), describe treatment .....

36. Where was the treatment given? *(Specify)*.....

37. AEFI Outcome: Recovered ☐ Death ☐

38. Specimen Collection and dispatch (If any0

Type of Specimen Collected	Dispatched to	Date Of Dispatch

39. Final Classification of AEFI:

Name of Investigating Officer: ..... Signature .....Date.....

(See Measles Campaign guidelines and behind this form on how to complete the AEFI form)

WHEN TO COMPLETE THIS FORM

Complete this form when any of the following AEFI occurs:

1. Serious Events
2. Any Uncommon Or Unexpected Events
3. Injection Site Abscesses
4. BCG Lymphadenitis (Lumps In The Armpit Following BCG Vaccination)
5. Severe Local Reaction (Swelling, redness or inability to move the limb)

GUIDELINES ON THE COMPLETION OF FORM

Section A

Please complete the particulars of the Reporting Institutions

Section B

Please complete the particulars of the client and details of the Immunization.

- Record Date of Birth (DOB) as follows: 10th June 2000 as 10/06/2000. If the DOB is unknown indicate the approximate age in years or where client is less than a year old records it in months.
- Where the client is a child, please indicate the name of the Mother (7).
- Address of the client should be a traceable address. For example "P.O. Box 21, Keta" is not helpful in case tracing. Use street names, house numbers, village names and landmarks where available and applicable.
- Immunization facility (17) means name of Vaccination point (e.g. Mbalambala Health Center) where the "offending" vaccination was given.
- Interval to Symptoms (23), is the time interval between the Date of Immunization (18) and Date of Onset of Symptoms and signs (20)

Section C

- Please **TICK** only the correct answers in (24) to (30).
- Do not tick both **Yes** and **No** or fail to tick either of them.
- Please note that toxic shock follows septicemia and is distinct from Anaphylactic shock.

Section D

- Please **TICK** only the appropriate answers in (31) to (33).
- Do not tick both Yes and No or fail to tick either of them.

Section E

- Fill in the information on the Vaccine(s) to which the client reacted.
- The "Dose Number" refers to that which triggered the reaction. For example dose 3rd dose of DPT-Hib-HeB or 2nd dose of TT will be dose number 3 and 2 respectively.
- Information on the Manufacturer and Expiry dates of the Vaccine and/or diluents may be obtained from the label of its container. If multiple vaccines are suspected, provide the required information on each of them.
- Treatment in (35) refers to both orthodox and herbal treatment. AEFI outcome (37) refers to the ultimate outcomes – recovery (partial of full) and death.

Section F

- Provide information on any specimen collected as part of the investigation of this unusual event.
- Indicate the Type of Specimen taken e.g. Blood, stool, etc.
- The specimen may be dispatched to, for example, KEMRI, National Public Health Reference Laboratory e.t.c.
- The Final Classification of AEFI is made at the National Level and feedback is provided through this column.
- The Investigator should remember to write his/her name and sign the form.