UNIVERSITY OF NAIROBI

ANALYSIS OF ADVERSE EVENTS FOLLOWING IMMUNIZATION IN KENYA

KELVIN MURIGOH KINYUA (B.PHARM)

U51/7329/2017

A thesis submitted in partial fulfilment of the requirements for the award of the Degree of Master of Pharmacy in Pharmacoepidemiology and Pharmacovigilance of the University of Nairobi

Department of Pharmacology and Pharmacognosy
School of Pharmacy, University of Nairobi.

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Registration Number: U51/7329/2017

College: Health Sciences

School: Pharmacy

Department: Department of Pharmacology and Pharmacognosy

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This thesis has been submitted with our approval as the University supervisors.

Prof Anastasia N. Guantai, PhD

Department of Pharmacology and Pharmacognosy

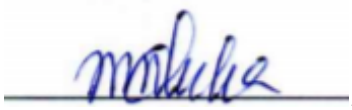
School of Pharmacy, University Of Nairobi

Signature…  30.09.2021

Dr. Margaret Oluka, PhD

Department of Pharmacology and Pharmacognosy

School of Pharmacy, University Of Nairobi

Signature  ….. Date…05-10-2021…….

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DEDICATION

I dedicate this work to all people who made it possible for me to accomplish it.

God bless you always.

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LIST OF ABBREVIATIONS

AEFI	Adverse Event Following Immunization
AKUHN	Aga Khan University Hospital Nairobi
BCG	Bacilli Calmette Guerin
DPT	Diphtheria Pertussis Tetanus
FDA	Food and Drug Administration
GCH	Gertrude's Children's Hospital
HPV	Human Papilloma Virus
ICSR	Individual Case Safety Report
ISCOMs	Immune Stimulating Complexes
KEPI	Kenya Expanded Programme on Immunization
LAVs	Live Attenuated Vaccines
MR	Measles Rubella
MMR	Measles Mumps Rubella
MMRV	Measles Mumps Rubella Varicella
NVIP	National Vaccine Immunization Programme
PPB	Pharmacy and Poisons Board
TGA	Therapeutic Goods Administration
UMC	Uppsala Monitoring Centre
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization

OPERATIONAL DEFINITIONS

Adverse event following immunization (AEFI)

Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine.

Vaccine

Substance of biological nature that is administered to healthy people to evoke an immune response against a target disease.

Vaccine-associated paralytic poliomyelitis (VAPP)

A rare event associated with OPV, which is caused by a strain of poliovirus that has genetically changed in the intestine from the original attenuated vaccine strain contained in OPV.

Uppsala Monitoring Centre (UMC)

The WHO Collaborating Centre for pharmacovigilance. UMC operates the technical and scientific aspects of the WHO's worldwide pharmacovigilance network.

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ABSTRACT

Background. As a key component of existing public healthcare programs, vaccination is considered a very important medical intervention due to its cost effectiveness. Despite their effectiveness in lowering risk of diseases that in the past caused significant mortality and morbidity, vaccines carry with them some risk. In most cases the side effects are minor and self-limiting, but there have been reports of rare but serious adverse effects associated with vaccines. In Kenya, the Pharmacy and Poisons Board (PPB) together with the National Vaccines and Immunization Programme (NVIP) maintain surveillance to monitor vaccine safety. This is mostly passive surveillance through spontaneous reporting of Adverse Events Following Immunization (AEFIs).Evaluation of the data reported is important to come up with more precise and accurate methods of assessing and minimizing the risks associated with vaccines to ensure public trust in the immunization program.

Objective. The main objective of this study was to analyze AEFI reported data at the PPB and two hospitals in Nairobi between January 2015 and December 2018.

Methods. The study was descriptive and divided into two parts. The first part involved retrospective collection of AEFI reports at the Pharmacovigilance Department of the PPB, NVIP and selected hospitals in Nairobi. Data was extracted from AEFI reports, suspected adverse drug reaction reporting forms and electronic records. The second part involved interviews of key informants at each study site.

Results: Of the 187 AEFIs reports analyzed, 93 (49.7%) were from females and 94 (50.3%) were from males. About 65 (35%) of the AEFIs occurred in persons aged between 10 to 15 years. The

median age of the vaccinated people who experienced adverse events was 9 years (IQR 3, 11). There was no statistically significant difference in the age group distribution of the people who experienced AEFIs between the two genders (p=0.795). The AEFI reporting rate was found to be approximately <0.01 per 100,000 vaccine doses distributed. A total of 105 (56.2%) of the people vaccinated experienced AEFIs due to the MR vaccine. This was followed by Oral Polio Vaccine (OPV) with 35 (18.7%) people and MMR with 26 (13.9%). Of the 224 adverse events reported, the most common adverse event was rash at 92 (41%) cases reported followed by pyrexia with 23 (10.3%) cases. Other common adverse events reported were pruritus, vomiting, diarrhoea, convulsions, anaphylactic reaction and muscular weakness.

Conclusion: The AEFI reporting rate in Kenya is low compared to other countries. Majority of the adverse events experienced were minor with serious events accounting for 7% of all adverse events reported.

CHAPTER ONE: INTRODUCTION

1.1 Background

At the beginning of the 20th century, infectious diseases posed a considerable threat to human life, well-being and were a significant cause of morbidity and mortality (1). At present, this threat has been greatly reduced due to development of vaccines and the increased immunization coverage (2). Formalization of immunization services in Kenya began after the Alma Ata declaration of 1978 by the World Health Assembly.

In 1980, the Kenya Expanded Programme on Immunization (KEPI) was set up with the mandate of conducting immunization services across the country. At that time, the main target was on the six diseases which were associated with high morbidity and mortality rates in children. These included diphtheria, poliomyelitis, whooping cough, tuberculosis, tetanus and measles.

In public health, immunization is a key concept in the prevention and eradication of infectious diseases. The continued utilization of vaccines over the years has resulted in the worldwide eradication of smallpox, decreased prevalence of poliomyelitis and significant reduction in incidence and mortality from several other diseases (3).This underscores the success, importance and cost effectiveness of vaccination as a public health intervention. Therefore, because of its widespread use which at most times is mandatory, safety and effectiveness are of key importance. There is a rigorous protocol for the evaluation of

vaccines before they are licensed. Despite this, some people still develop reactions to the antigens and ingredients in the vaccine formulation. Common signs and symptoms of reactions following vaccination include; discomfort, injection site reactions, and pain which are not considered as serious (4). However, in a few situations, more serious events can occur in susceptible individuals (5).

Following increased vaccination coverage for targeted infectious diseases, and some routine booster doses in some diseases, individuals now cumulatively receive more vaccine doses. Therefore, due to the many vaccinations received, the probability of an adverse event occurring also increases (5). In most situations, if the vaccination program is working effectively the incidence of vaccine preventable diseases decreases while that of AEFIs increases(6). In the USA, the reported AEFIs in 2001 were more than the combined incidence of common vaccine-preventable childhood morbidities (7).

For the success of any immunization program, it is necessary to continually and consistently carry out vaccine pharmacovigilance. This is important to point out real and presumed issues related to AEFI (7). Incidentally, this kind of surveillance and infrastructure required for follow-up is not at par with the development of vaccines in developed countries and is absent in many of the developing countries. To date, there is scanty data on AEFIs in Kenya .Therefore, this study seeks to analyze AEFI data reported to the Pharmacy and Poisons Board, the National Vaccines and Immunization Programme and selected hospitals in Nairobi.

1.2 Statement of the problem

Just like most pharmaceutical products, vaccines also carry some risks. Before vaccines are licensed, clinical trials are conducted; the sample size of clinical trials is not adequate to identify and characterize rare or delayed adverse effects. The clinical trials are selective and hence do not capture the different populations where the vaccine may be used. Consequently, AEFI monitoring systems are important to establish if there is an association between vaccination and an unexpected or unintended reaction to a given vaccine product. There is scanty published data on the profile of the reported AEFIs in Kenya. Therefore, this study sought to analyze and describe the profile of the reported AEFIs over a four year period (January 2015-December 2018). This period was selected because prior to 2015 just a few AEFI reports were received at both the PPB and NVIP.

1.3 Research questions

What are the types of AEFIs reported, their severity and the population affected in Kenya?

1.4 Objectives

1.4.1 Main objective

The main objective of this study was to analyze and characterize AEFIs reported to the PPB, NVIP, Gertrude's Children's Hospital (GCH), Aga Khan University Hospital Nairobi (AKUHN) and MP Shah Hospital between January 2015 and December 2018.

1.4.2 Specific objectives

The specific objectives of the study were:

1. To identify the types of AEFIs reported and the vaccines involved.
2. To describe the severity of the AEFIs reported.
3. To characterize the population affected by the reported AEFIs in Kenya.
4. To identify factors affecting the delivery of vaccine pharmacovigilance services in Kenya.

1.5 Study justification

Since vaccines are used on healthy individuals in large populations, their safety monitoring is very important. Concerns about vaccine safety by the general population, perceived or real, may cause reduction in confidence of entire vaccine programmes. Consequently this can lead to poor immunization uptake and therefore an increase in disease incidence and deaths attributable to vaccine preventable diseases (10). One of the major safety concerns that generated massive public interest in the last twenty years was the presumed association between the measles, mumps, and rubella (MMR) vaccine and autism, which was first published in *The Lancet* journal in 1998 (11).Two years later, *The Lancet* totally

withdrew the report it published in 1998, with reason that findings of the research had been intentionally falsified (13). Despite withdrawal of the report, the program experienced a major drawback; the utilization of MMR vaccine dropped in the UK from 91% in 1998 to 80% by 2004.A number of measles outbreaks occurred almost a decade after transmission of the disease had been eradicated within the UK and subsequently, in 2008 it was reported to be endemic (13).

In 2003, five northern Nigeria states directed their inhabitants to decline administration of the oral polio vaccine (OPV) to their children, with claims that the vaccines were laced with infertility causing agents in a plan by European and American governments to curb growth of the predominantly Muslim population. As a result, there was re-emergence of polio in more than 15 countries in Africa which were polio-free and the challenges to eradication of this disease remain till present (14). In February 2017, the introduction of Measles-Rubella (MR) in a mass vaccination campaign for children in 5 states in India suffered a major setback from false information on social media about adverse effects such as sterility and autism due to the MR vaccine (16). As a matter of fact, in some southern India districts where most children had already received several vaccine doses, the general opinion of well-educated people (including some pediatricians) was that parents should not accept further doses of MR vaccines in the interest of their children's safety (16).Therefore the study was aimed at improving the understanding of the AEFI pattern in Kenya and possibly inform the various stakeholders on additional measures to be taken to improve vaccines safety and minimize adverse events.

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

A vaccine is a substance of biological nature that is administered to healthy people to evoke immune response against a target disease (17). Due to their efficacy, high cost-effectiveness, and safety, vaccines are considered a very effective intervention in public health (18). Compared with other medical interventions, their impact is long-term and positive with considerably low initial costs.

Just like any medical product, no vaccine is completely safe or completely effective (19). Compared to most medicinal substances, vaccines are mostly given to healthy, young people (children) for preventing occurrence of disease and therefore monitoring for safety is paramount (18). The World Health Organization (WHO) in 1974 started its Expanded Programme on Immunization (EPI) and since then the number of children vaccinated against common diseases preventable by vaccines has risen from 5% to around 80% during their first year after birth, with a consequent reduction in the prevalence of the diseases (18).

2.2 Types of Vaccines

Vaccines are mainly categorized according to the antigen used to prepare them. Their formulations therefore affect their usage, storage and administration. The globally recommended vaccines can be classified into four major categories as shown in Figure 2.1

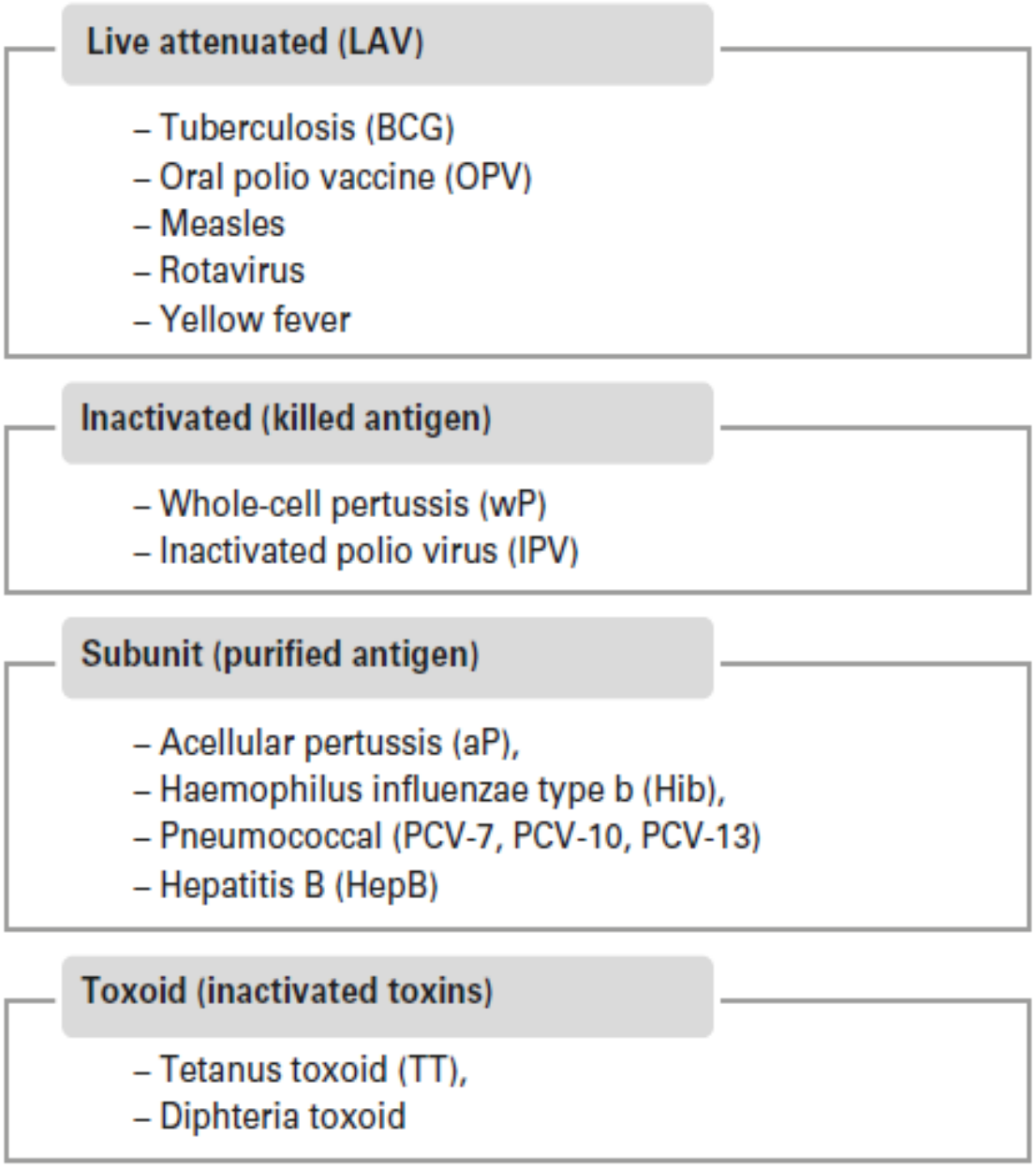


Figure 2.1: Major categories of vaccines used globally - *(WHO vaccine safety basics 2020)*

2.2.1 Live Attenuated Vaccines (LAVs)

These vaccines are obtained from viruses or bacteria which have been made weak under specified conditions. Once introduced into a healthy individual they replicate, but due to their weak nature, they will not cause disease or will result in very mild form of the disease. LAVs usually elicit a very strong immune response; close to that elicited by infection with the pathogenic form of the micro-organism. However, since LAVs are composed of living organisms they can be very unpredictable and this raises concerns about their safety and stability. In some rare cases, the weakened micro-organisms may revert to the infectious form and cause disease in vaccinated individuals (23). Therefore, as a precaution LAVs are contraindicated for use in pregnant women. LAVs recommended for use by the WHO are: OPV, measles, yellow fever, rotavirus and tuberculosis (BCG) vaccines.

2.2.2 Inactivated Whole Cell Vaccines

These vaccines are obtained from micro-organisms that have been killed using either physical or chemical means and as a result these micro-organisms cannot cause disease. Because of the killed micro-organisms, these vaccines sometimes do not stimulate immunity in the vaccinated individuals and when they do, this immunity may not be long term. They have to be administered in several doses to elicit an adequate immune response.

Inactivated whole cell vaccines generally pose zero risk of causing morbidity and are considered more stable than LAVs. Examples are Whole Cell Pertussis vaccine and Inactivated polio vaccine (24).

2.2.3 Sub Unit Vaccines

These vaccines are not made using the live components of the disease causing micro-organism, they only contain parts of the pathogen that have antigenic properties. Several potential subunits of a pathogen are carefully evaluated to establish which specific combinations will elicit an effective immune response (25). Subunit vaccines can belong to various categories including protein-based subunit, polysaccharide and conjugate subunit.

2.2.3.1 Protein-based subunit vaccines

In this type of vaccines, a specific, isolated protein of the pathogen is obtained and used to stimulate immune response. The disadvantage is that the isolated proteins by their innate nature may get denatured and therefore attach to other antibodies different from the protein of the disease causing micro-organism. Examples of these vaccines are acellular Pertussis and Hepatitis B vaccines.

2.2.3.2 Polysaccharide Vaccines

Some types of bacteria are encapsulated by a polysaccharide layer and this assists them evade the body's immune system especially in children. Polysaccharide vaccines stimulate an immune response against components in the micro-organism's capsule. Such components are small, and usually do not possess much ability to elicit an immune

response. Therefore, they are not very efficacious in young children and infants and the immunity they induce is just short term.

2.2.3.3 Conjugate subunit vaccines

These vaccines work by eliciting a reaction against the molecules in the capsule of the disease causing micro-organism. Compared to plain polysaccharide vaccines, they use a mechanism that attaches the polysaccharide to a transporter protein which stimulates immunity that is long term even in young children. Examples are *Haemophilus influenzae* type b (Hib), pneumococcal conjugate and meningococcal A vaccines.

2.2.4 Toxoid Vaccines

Some certain bacteria including tetanus and diphtheria produce toxins which invade the bloodstream and cause symptoms of the disease. Toxoid vaccines are developed from rendering the protein based toxin harmless and using it to elicit immune response (26). The vaccines are safe since they cannot cause disease in the human body. They are also fairly stable to changes in temperature light and humidity.

2.3 Components of Vaccines

Other than antigens vaccines also contain several other ingredients which include preservatives, antibiotics, stabilizers and adjuvants. They may also have some byproducts from the production process.

2.3.1 Adjuvants

A vaccine adjuvant is a substance which enhances how an individual's body responds to an immunogen (25). Aluminum was first utilized in human vaccines in 1932 and was the sole adjuvant in use for close to 70 years (27). Despite its widespread and continued usage, the immune mechanism of action of aluminum is not well understood (28). It has been postulated that adjuvants enhance immune response by coalescing the antigen close to the injection site; this enables them to be easily reached by cells of the immune system (26).

2.3.2 Stabilizers

Stabilizers help maintain the stability of the vaccine antigen together with other vaccine constituents during storage; this helps in maintaining the effectiveness of the vaccine. They also help in preventing the adherence of vaccine constituents to the walls of the vial containing the vaccine (26). Instability may result in the loss of antigenic properties and reduced efficacy of LAV. Temperature and pH are some of the factors that affect the stability of a vaccine and therefore must be monitored closely (29).

2.3.3 Antibiotics

Antibiotics are incorporated in the vaccine production process to prevent contamination (by bacteria) and appear only in little quantities in the vaccine (23). OPV and Measles Mumps Rubella (MMR) vaccine each contain trace amounts of neomycin per dose (24). Individuals with neomycin allergy should undergo close monitoring after immunization so that in case they react to neomycin, they are managed effectively.

2.3.4 Preservatives

Preservatives are generally used to prevent contamination of vaccines by either fungi and/or bacteria, and are incorporated in some vaccine preparations. There are a variety of agents used as preservatives for example thimerosal, formaldehyde, and phenol derivatives.

2.4 Adverse Events Following Immunization

An Adverse event following immunization (AEFI) is any unexpected medical event following immunization and which may or may not have a causal relationship with the use of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease (30).

AEFIs can be classified into five categories namely; vaccine product-related event, vaccine quality defect related event, immunization error-related event, immunization anxiety-related event and coincidental event.

2.4.1 Vaccine reactions

A vaccine reaction is one that occurs when a person reacts to the intrinsic features of a vaccine, despite the vaccine being formulated, handled and given in the right way (31). These include reactions related to the vaccine product and its quality defect. The vaccine reactions may be categorized as either severe or minor.

2.4.1.1 Minor Reactions

They typically occur within a few hours of the vaccine administration, have a short resolution time and usually pose minimal risk. Their local effects include erythema, pain and injection site swelling. Systemic effects include fever, nausea, general body weakness, myalgia, headache and loss of appetite. They may be due to the vaccine antigen or other components e.g. stabilizers, preservatives and adjuvants (32). A quality and safe vaccine is one that keeps these reactions at minimal level while producing the best possible immunity (30).

2.4.1.2 Severe Reactions

Severe reactions are usually short term. They can cause disabilities but are not usually life threatening. They include seizures and anaphylactic reactions as a result of the body's reaction to certain vaccine components.

2.4.2 Immunization error-related reaction

This refers to a preventable AEFI that occurs when a vaccine is not handled appropriately during its prescription or administration (30). It is therefore important to identify and correct these incorrect immunization practices.

Immunization errors may lead to a conglomerate of events, defined as two or more cases of the same adverse event related in place, time or vaccine given. The conglomerates are normally attributable to a healthcare worker, facility, or an improperly constituted or

contaminated vaccine vial. A number of vials may also be affected by immunization errors, for example, frozen vaccines during transportation may lead to increased local reactions.

2.4.3 Immunization anxiety-related reactions

During the immunization process some individuals may develop anxiety from fear of injections. The most common reactions are fainting, hyperventilation, vomiting and convulsions (33). These reactions are mostly short term, resolve on their own and rarely life threatening. Clear explanations by the healthcare provider concerning the immunization process and calm, confident administration decreases anxiety levels regarding the (vaccine) injection process and thus lower the incidence of these reactions (30).

2.4.5 Coincidental events

These are events that have a temporal association to the immunization process but are not causally related (30).Vaccines are normally administered in infancy and childhood, and usually in this period some infections and diseases occur often. Some underlying congenital or neurological conditions also manifest during this period. Therefore, it is possible to falsely attribute a number of events including mortalities to the vaccines through temporal association. The estimated number of coincidental events can be estimated by obtaining the normal morbidity and mortality incidence in these age groups and the period when the vaccines were administered (34).

2.5 Severe Adverse Event

Although the terms ‘serious’ and ‘severe’ adverse events are often used interchangeably, they do not have the same meaning (30). A serious adverse event or reaction is a regulatory term, which, as defined by the Uppsala Monitoring Centre (UMC), is any unexpected medical event that occurs at any dose and may result in death, requires inpatient hospital admission or extension of existing hospitalization, results in significant disability, or is life-threatening. Severe reaction is not a regulatory term and includes serious reactions and other severe reaction (29).

2.6 Reporting Adverse Events Following Immunization

In AEFI surveillance, the most important first step is case identification. The person to report an AEFI may be a health worker working in the field or a health facility, volunteer, caregiver or any other person who suspects it (31). Usually, reporting is based on suspicion of an AEFI and the primary reporter does not have to be certain or carry out causality assessment. In many jurisdictions the person who reports first submits a report (using a standard reporting form) to the local authority in charge of public health. This report is then transmitted upwards, through the intermediary level to the national immunization programme or national regulatory authority (31). To improve reporting and case detection it is important for the regulatory authority or immunization programme to regularly conduct training and sensitization programmes. These are essential in updating skills and knowledge and also improving the capacity of the primary reporters.

Events to be reported include; AEFIs considered as serious, unusual occurrences associated with a recently introduced vaccine, events attributed to an immunization error, unexplainable significant events that occur within 30 days of immunization and events that elicit considerable parental or public concerns (31).

2.7 Analysis of AEFI Data

In vaccines surveillance, it is essential to carry out data analysis on an epidemiological basis and share the findings with the various stakeholders. During analysis, the first step is to line list all reported AEFIs**.** This helps to identify clustering or any events that are significant and unusual and therefore require further analysis (31). The AEFI data is then arranged by place of occurrence, person, time, vaccine antigens and nature of events. The AEFI rates are then calculated using the number of doses administered for each antigen as the denominator for calculating reported AEFI rates for each antigen in a specified time period (31).

Selection of a proper denominator usually poses a major challenge with just a few options available as shown below in table 2.2.

Table 1.2: Options for selecting a denominator in analysis of AEFI data

Options for selecting a denominator

Denominator	Limitations
Administered doses of vaccines	Most reliable, but not often available
Distributed doses	Greater than administered doses, thus may reduce rate (underestimate)
Coverage x population	May be less accurate because of variability in coverage estimates
Target population	Proxy measure for vaccine population (may also underestimate)

The last step is comparison and interpretation of AEFI rates based on each event per antigen. The observed events are compared to the background rates of medical events reported in the country. The background rates are unrelated to the vaccines and are therefore independent. Observed (reported) rates comprise both vaccine related rates and background rates as shown in Figure 2.2

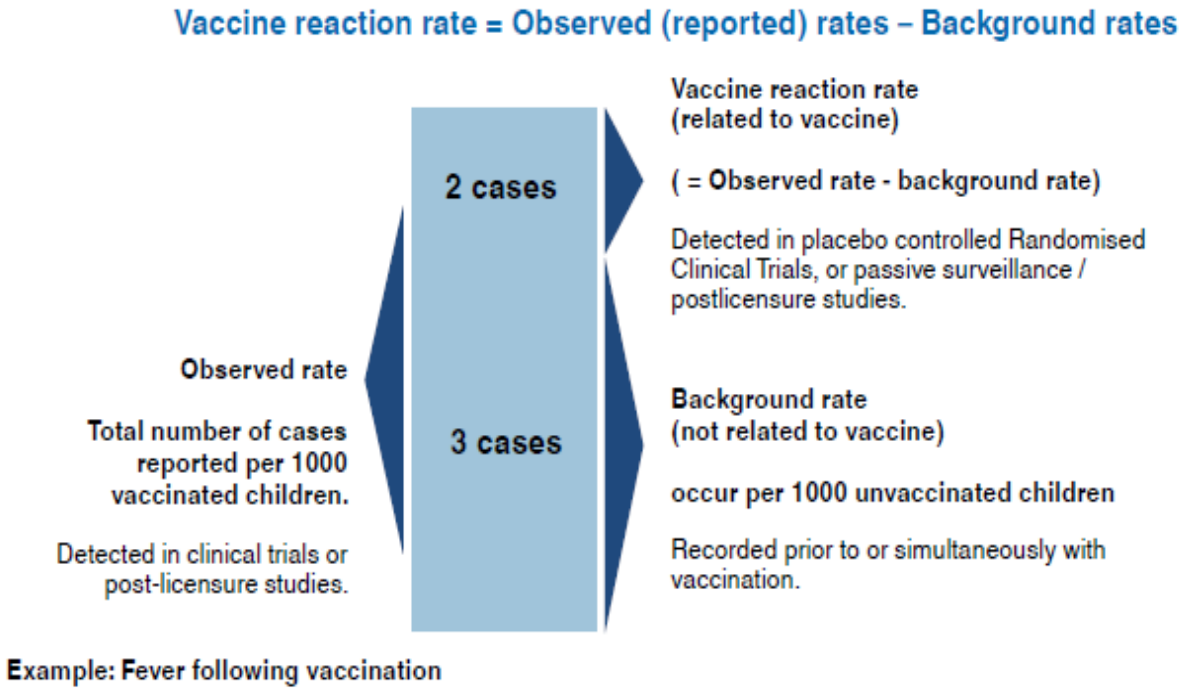


Figure 2.2: Illustration of Vaccine reaction rate, Observed rate and Background rates-

CHAPTER THREE: METHODOLOGY

3.1 Study site

The study was conducted at the pharmacovigilance departments of the Pharmacy and Poisons Board (PPB), National Vaccines and Immunization Programme (NVIP) and immunization clinics of GCH and AKUHN. The Department of Pharmacovigilance at PPB was set up in 2004 and serves as the national pharmacovigilance centre. The immunization programme in Kenya is managed by the NVIP. The programme has been in existence since 1980 when it was established as Kenya Expanded Program on Immunization (KEPI).

3.2 Study design

The study was in two parts; the first part was a quantitative retrospective descriptive cross sectional study of AEFI reports. The second part was a qualitative key informant interview which was done prospectively.

3.3 Study population

The study population for the retrospective quantitative study included all AEFI reports received at the PPB, NVIP, GCH and AKUHN between January 2015 and December 2018. For the qualitative part, the study population was a maximum of two key informants at each study site, specifically those involved in pharmacovigilance activities.

3.4 Eligibility criteria

a) Inclusion and Exclusion criteria

All AEFI reports received between January 2015 and December 2018 with all data elements completed were included in the study. Reports with some missing key data elements such as age, sex, suspected vaccine and nature of AEFI were excluded.

3.5 Sample size and Sampling techniques

3.5.1 Quantitative retrospective study

Most of the data available on AEFIs is through passive surveillance systems such as spontaneous reporting (32). The shortcomings of passive surveillance systems include underreporting, inconsistent quality of reports, incomplete reports, unavailable denominator data, and possible reporting bias. Therefore, universal sampling was done. Similar studies conducted in Valencia, Spain (33), India (34) and Brazil (35) utilized all reported cases during the respective study periods. This was meant to eliminate sampling error and provide data on all the reported AEFIs during the study period that met the inclusion criteria.

3.5.2 Participant recruitment strategy for the key informant interview

Purposive sampling technique was used to recruit a maximum of two key informants from each study site. The heads of pharmacovigilance at each of the study sites were consulted to help identify these informants.

3.6 Data Collection instruments and procedures

Data on AEFIs was extracted from both manual and electronic pharmacovigilance reports using a structured Data Collection Form (Appendix 4).

An interview guide in form of a questionnaire (Appendix1) was used to conduct open ended interviews to the key informants. 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 (Appendix 5). The proceedings of the interviews were captured using a recording device and transcription done as soon as an interview was over.

In each study site the key informants were interviewed separately to avoid any form of external influence to their responses.

3.7 Variables

For the retrospective data, the primary outcomes of interest were the most common AEFIs reported and the vaccines involved, and frequency of the AEFIs among the various age groups. Another outcome of interest was the severity proportion of the reported AEFIs. The predictor variables were the age and gender of the patient.

For the qualitative study, the primary outcomes of interest were the factors affecting the delivery of vaccine pharmacovigilance services at both national and facility level.

3.8 Quality assurance and data management

The data collection tools were pre-tested and improved appropriately by the researcher. All the raw data collected was entered into Epi-Info version 7(2007-2010) software and a database created. The information in the database was backed up on a daily basis by the researcher using an external flash drive. Hard copies of the data collection forms and the external flash drive were stored in a lockable cabinet to restrict access and enhance confidentiality. Data cleaning and validation was done before being exported into STATA (version 13) for analysis.

3.9 Data analysis

Data analysis was both qualitative and quantitative. Descriptive statistics were used to analyze patient AEFI data on sex, age, and suspected vaccine antigen; this was presented as proportions and percentages. Data analysis was done using STATA® (version 13.0) software. The responses from the questionnaires were extracted and reported according to the following themes: (i) AEFI structures, systems and stakeholder coordination (ii) Risk management and communication.

3.10 Ethical consideration

Approval to carry out this study was granted by the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UoN-ERC), PPB, GCH Ethics Committee and AKUHN Research Committee (Appendix 6, 7, 8 and 9). Individual participant identifier information was omitted and instead, codes were used. The data

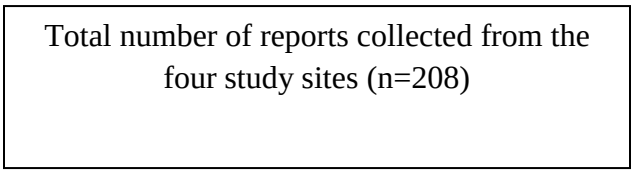
collection tools and any other materials that were used during the study were kept in a lockable cabinet only accessible to the researcher.

CHAPTER FOUR: RESULTS

Review of submitted reports following immunization

A total of 208 AEFI reports were collected from four study sites namely PPB, NVIP, GCH and AKUHN. These reports covered the period from January 2015 to December 2018. All the AEFI reports received at NVIP are later submitted to PPB for entry into VigiFlow®. VigiFlow® is a web-based Individual Case Safety Report (ICSR) management system that is available for use by national pharmacovigilance centers of the WHO Programme for International Drug Monitoring.

Out of the 208 reports collected, 21 (10%) had some missing key data elements hence were excluded from the analysis. Figure 4.1 shows the total number of AEFI reports collected, excluded and analyzed.



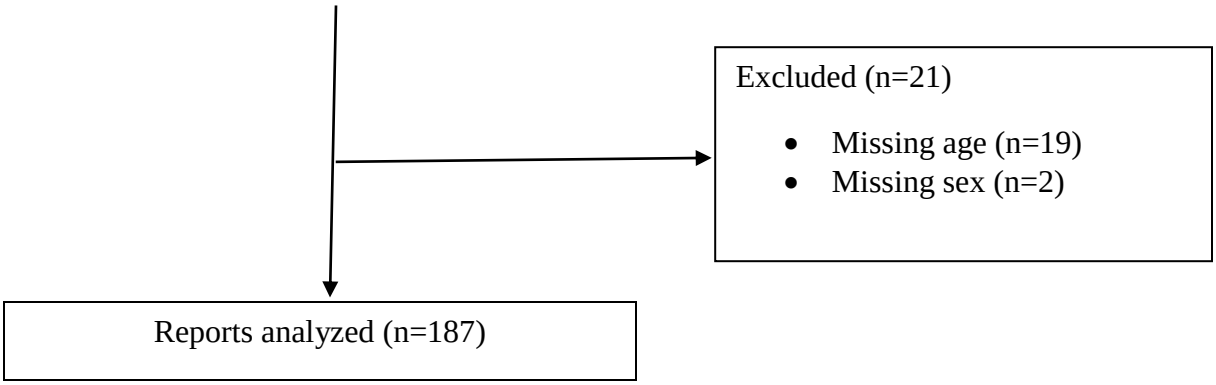


Figure 4.1: Number of AEFI reports analyzed between 2015 and 2018.

The PPB/NVIP had the highest number of reports each year and a cumulative total of 175 (94%) reports followed by GCH with 10 (5%) and AKUHN with 2 (1%).The highest number of AEFIs across the three study sites were reported in 2016 (n=128) with the least number of reports (n=5) being reported in 2017.There were no reports from any of the institutions in 2015. Table 4.1 shows the number of AEFI reports collected from each institution between 2015 and 2018.

Table 4.1: AEFIs reported per year in each institution between 2015 and 2018

	Institution			
Year	AKUHN	GCH	PPB/NVIP	**Total**
2015	0	0	0	**0**
2016	1	1	126	**128**
2017	0	3	2	**5**
2018	1	6	47	**54**
Total	**2**	**10**	**175**	**187**

4.1: Characteristics of patients affected by the AEFIs

Of the 187 AEFIs reports analyzed, 93 (49.7%) were from females and 94 (50.3%) were from males. About 65 (35%) of the AEFIs occurred in patients aged between 10 years to ≤15 years. The median age of the participants was 9 years [IQR 3, 11]. The youngest patient to experience an AEFI was 18 days while the oldest was 35 years. There was no statistically significant difference in the age group distribution of the people who experienced AEFIs between the two genders (p=0.795). Table 4.2 shows the distribution of AEFIs reported between 2015 and 2018 by gender and age group.

Table 4.2: Distribution of AEFIs reported between 2015 and 2018 by gender and age group

	Frequency of AEFIs Reported		
Age Group	**Male**	**Female**	**Total**
≤1 Year	14	16	30
1-5 Years	27	17	44
5-10 Years	21	23	44
10-15 Years	29	36	65
>15 Years	3	1	4
Total	**94**	**93**	**187**

4.2 Vaccines implicated in adverse events

The total number of study participants whose AEFI data was analyzed for period 2015-2018 were 187. A total of 105 (56.2%) of the participants experienced AEFIs due to the MR vaccine. This was followed by OPV with 35 (18.7%) participants and MMR with 26 (13.9%) as shown in table 4.3

Table 4.3: Frequencies of adverse events associated with vaccines

Suspected vaccine	Number of individuals Frequency (n)	Percent (%)
MR	105	56.2
OPV	35	18.7
MMR	26	13.9
Influenza	4	2
Pentavalent	3	1.6
Tetanus	2	1
Measles	2	1
Meningococcal	2	1
Rotavirus	2	1
Cholera	2	1
BCG	1	0.5
Pneumococcal	1	0.5
DPT	1	0.5
HPV	1	0.5
Total	**187**	**100**

4.3 Distribution of AEFI reports by vaccine and age group

The MR vaccine was responsible for 9 (30%) of the AEFI cases reported in children aged ≤1 Year and about 53 (82%) of the cases in those aged 10 to 15 Years. MR therefore accounted for the majority of AEFI reports among individuals aged in this age group.

OPV was responsible for 10 (33%) of the AEFI cases in children aged ≤ 1 year and 25 (57%) of the cases in those aged 1to 5 years. OPV accounted for the majority of AEFI cases among individuals aged below 1 year. Figure 4.2 shows the number of AEFI cases per vaccine in each age group.

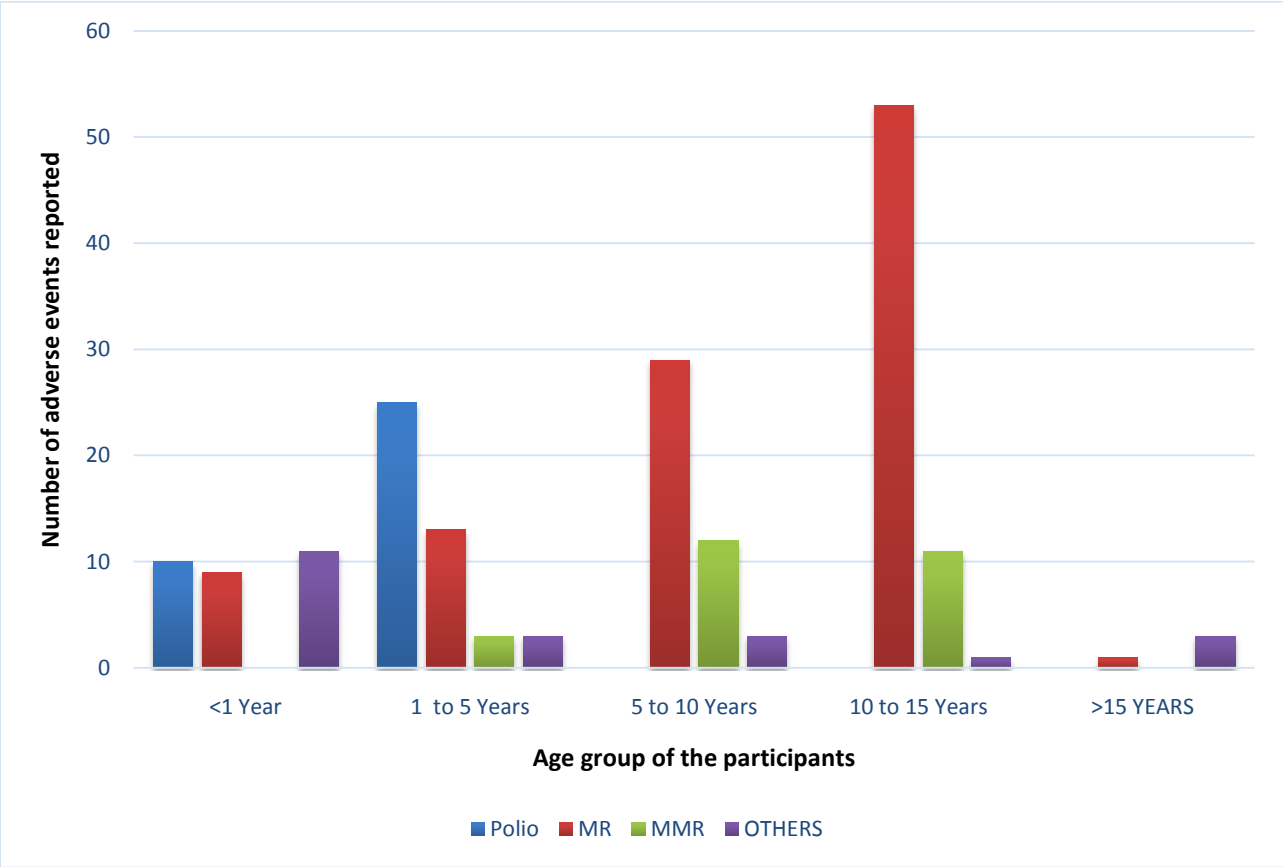


Figure 4.2: Number of reported AEFI cases per vaccine in each age group

4.4 Number of adverse events per individual

A total of 224 adverse events were reported among the 187 participants in the study. This was because 26 (14%) individuals experienced more than one adverse event. Of these, 8 (31%) were female while 18 (69%) were male. There were 17 individuals who experienced two adverse events, 7 who experienced three adverse events and 2 who experienced four adverse events. Of the 26 individuals 10 (38%) were in the age group ≤1 year, 14 (54%) in the age group 1-5 years and 2 (8%) in the age group >15 years. The vaccine most responsible for causing more than one adverse event was OPV with 15 (60%) cases reported followed by MR with 5 (20%) cases. Table 4.4 shows the vaccines that caused more than one adverse event.

Table 4.4: Vaccines that caused more than one AEFI

Vaccine	**Individuals with >1 AEFI *(n)***	**Percentage *(%)***
OPV	15	57
MR	6	23
Tetanus	1	4
Meningococcal	1	4
Rotavirus	1	4
BCG	1	4
Pneumococcal	1	4
Total	**25**	**100**

4.5 Types of adverse events reported

Of the 224 adverse events reported, the most common adverse event was rash at 92 (41%) cases reported followed by pyrexia with 23 (10.3%) cases. Other common adverse events reported were pruritus, vomiting, diarrhoea, convulsions, anaphylactic reaction, cough and muscular weakness as shown in table 4.5.

Table 4.5: Nature of adverse events reported and their frequency

Nature of AEFI	Frequency (n)	Percent (%)
Rash	92	41
Pyrexia	23	10.3
Pruritus	9	4
Vomiting	8	3.6
Diarrhoea	7	3
Convulsion	7	3
Anaphylactic reaction	7	3
Cough	7	3
Muscular weakness	6	2.7
Injection site cellulitis	5	2.2
Dizziness	4	1.8
Limb discomfort	4	1.8
Syncope	4	1.8
Peripheral swelling	3	1.3
Injection site swelling	4	1.8
Abdominal pain	2	0.9
Death	2	0.9
Dyspnoea	2	0.9
Eye pain	2	0.9
Headache	2	0.9
Lethargy	2	0.9

Pain	2	0.9
Others*	20	8.9
Total	**224**	**100**

**This represents adverse events that had a frequency of 1. They include anxiety, bacterial sepsis, bradycardia, cerebral vasoconstriction, chest pain, conjunctivitis, dysstasia, haematemesis, haematochezia, hypotension, hypersomnia, jaundice, myalgia, skin reaction, Stevens-Johnsons syndrome, apathy, somnolence, diplegia, decreased appetite and rhinitis.*

4.6 Distribution of the common types of adverse events reported per vaccine

MR vaccine was responsible for 61 (66%) cases of rash, followed by MMR vaccine with 20 (22%) cases. Of the 23 cases of pyrexia reported, 10 (44%) of them were due to the OPV, 8 (35%) of them due to MR vaccine and 5 (22%) due to the other vaccines. MR vaccine was also responsible for every 9 out of every 10 cases (89%) of pruritus reported. OPV was responsible for majority of the gastrointestinal adverse events namely diarrhoea and vomiting. It accounted for 6 out 8 (75 %) of the vomiting cases and 5 out of 7 (71 %) of the diarrhoea cases reported. Table 4.6 shows the nature of AEFIs and the number of adverse events per vaccine.

Table 4.6: Distribution of the various adverse events by vaccine

Nature of AEFI	**Number of adverse events per vaccine**				
	OPV	**MR**	**MMR**	**Others**	**Total**
Rash	8	61	20	3	**92**
Pyrexia	10	8	0	5	**23**
Pruritus	0	8	1	0	**9**
Vomiting	6	2	0	0	**8**
Anaphylaxis	0	3	4	0	**7**
Convulsions	3	4	0	0	**7**

Cough	6	1	0	0	**7**
Diarrhoea	5	1	0	1	**7**

4.7 Seriousness of the Adverse Events Following Immunization

Out of the 224 adverse events reported between 2015 and 2018, 7% (n=16) of them were classified as serious. Of these 16 cases, 12 of them required inpatient hospitalization while 4 of them resulted in death. About 8 (50%) of the serious adverse events were due to MR with 7 (58%) of the hospitalizations attributed to it. OPV was suspected to have caused the 2 deaths with MR and rotavirus vaccines causing 1 death each. This is shown in table 4.7

Table 4.7: Serious adverse events caused by vaccines between 2015 and 2018 in Kenya

	Serious adverse event		
Vaccine	**Hospitalization**	**Death**	**Total**
OPV	2	2	**4**
MR	7	1	**8**
HPV	1	0	**1**
Meningococcal	0	0	**0**
Rotavirus	0	1	**1**
Pneumococcal	1	0	**1**
DPT	1	0	**1**
Total	**12**	**4**	**16**

About 19 (73%) of the adverse events reported were not serious. However, a total of 5 (19%) individuals who experienced more than one adverse event were hospitalized while 2 (8%) of them died. The vaccines suspected to have caused the two deaths were OPV and Rotavirus.

The four mortalities occurred in children aged 18 days, 1 month, 1 year and 12 years. Children in the age group ≤1 year accounted for the highest number of hospitalizations with 6 (37.5%) cases followed by those in the age group 1 to 5 years with 4 (25%) of them getting hospitalized after vaccination. This is shown figure 4.3.

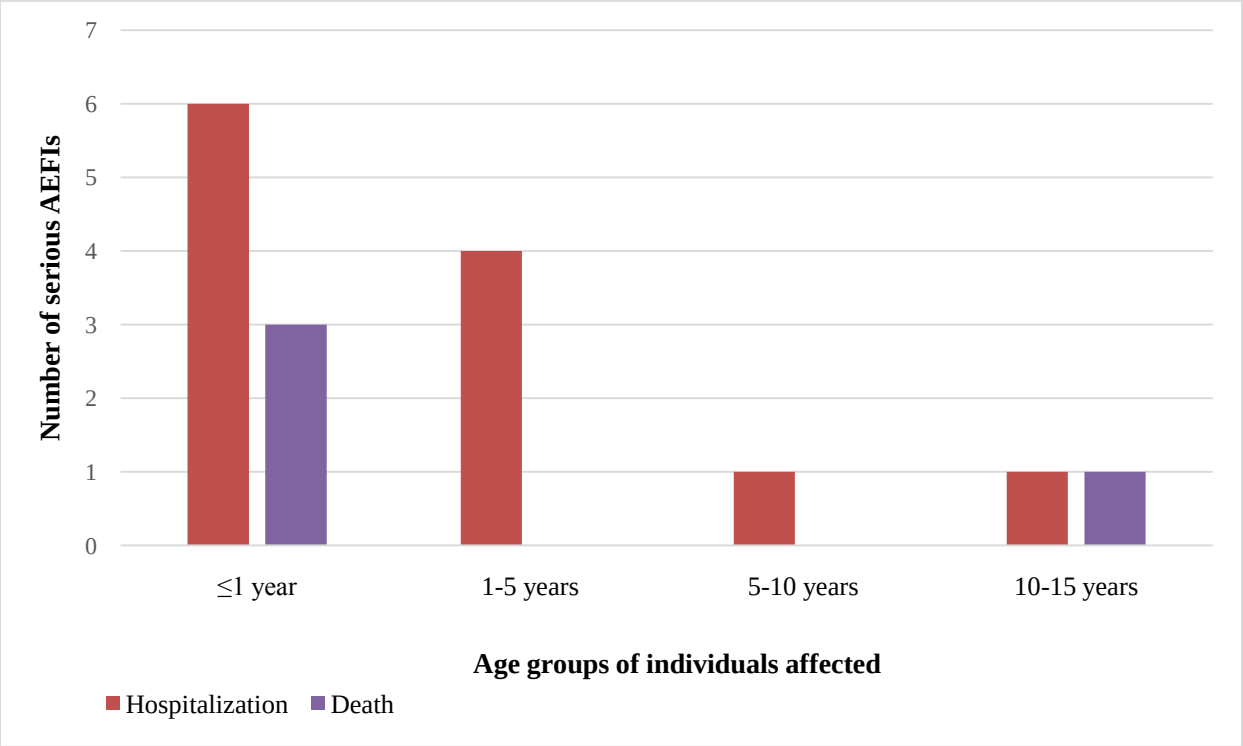


Figure 4.3: Distribution of serious AEFIs in by age-group.

Qualitative Data

4.8 Key Informants

Table 4.8 below gives a brief description of the key informants interviewed. Two informants were from the PPB, two from NVIP and one from GCH.

Table 4.8: Description of key informants interviewed

Unit	Cadre	Number of informants	Job designation
PPB	Pharmacist	2	Pharmacovigilance
NVIP	Pharmacist	2	Vaccine pharmacovigilance
GCH	Nursing Officer	1	Paediatric Nursing

4.9 AEFI structures, systems and stakeholder coordination

From the assessment it was established that the PPB being the national pharmacovigilance center had the overall responsibility for AEFI surveillance in Kenya. This is done by the pharmacovigilance department which also maintains surveillance for the other medical products. There is a defined framework of sharing of information between PPB and NVIP;

most of the AEFI reports are collected by NVIP which then transmits them to PPB. However, the PPB also receives some of the AEFI reports direct through the suspected adverse drug reaction reporting form (appendix 2) and the pharmacovigilance electronic reporting system (36). There are currently no national AEFI surveillance guidelines; they are currently in draft stage. There has been a gap in AEFI training for health workers across the country, the pharmacovigilance training curriculum has mostly concentrated on adverse event reporting and post marketing surveillance for other medical products. However, a few trainings on vaccine pharmacovigilance have been conducted to members of staff at GCH through the Ministry of Health. PPB and NVIP are currently working together to revise the training curriculum to include vaccine training for health workers. Both institutions take advantage of mass vaccination campaigns and roll out of new vaccines (for example, the rollout of the malaria vaccine in 2019) to conduct trainings and sensitizations on vaccines handling and pharmacovigilance.

4.10 Risk Assessment, Evaluation and Communication

The AEFI reporting rate is very low in the country. Out of approximately 91 million vaccine doses distributed only 187 AEFI reports were made. After an AEFI report is received at either NVIP or PPB it is checked for validity using the data variables on the standard reporting form, these include the date, age and sex of the patient, nature of event, suspected vaccine, details of the reporter and outcome of the event. Events that lead to either death or hospitalization are termed serious and are investigated for causality and outcome. The investigating team present their findings to the National Vaccines Safety

Advisory Committee who conduct an expert review. This committee consists of various experts including immunologists, pediatricians, pathologists, pharmacologists and epidemiologists. The final findings are then presented to the heads of PPB and NVIP who in consultation with the Director of Medical Services give feedback to the concerned parties and the general public. All reports received are entered into the WHO global database, VigiBase and quarterly adverse reports are generated. However, the quarterly reports generated are a compilation of adverse events from vaccines and other medical products. At GCH, any suspected vaccine adverse event is documented and reported to the PPB. A follow up is routinely done at institutional level for any vaccine adverse event that occurs, whether serious or not. This follow up enables the institutions to as far as possible establish the cause of the adverse event and take corrective action to minimize future occurrence. The hospital also carries out educational activities touching on vaccine safety, risks and benefits to clients before vaccinations are carried out. This has helped address various client concerns on vaccine safety and has also reduced vaccine hesitancy.

CHAPTER 5: DISCUSSION

Vaccine clinical trials often utilize a small number of study participants and therefore it is not possible to detect all potential adverse events. Consequently, surveillance of AEFIs after vaccines are licensed is always important to continuously monitor their safety during their use in the general population. Passive surveillance systems though commonly used in many settings have several short comings. These include low reporting rates, incomplete data on events reported, lack of denominators (i.e. number of vaccine doses administered in a given population), inconsistent diagnoses due to lack of standardized case definitions, and insufficient information on differential diagnoses or diagnoses excluded, which would be important for proper causality assessment. In spite of these weaknesses, passive surveillance systems still provide vital information because signals and trends can still be detected even with incomplete reporting (37).

In this study, AEFI reports obtained from 187 participants over a four year period (2015-2018) were analyzed. This is against approximately 91 million number vaccine doses

distributed over that period of time, translating to an average of 1 report per every 500,000 vaccine doses distributed.

In the field of vaccine pharmacovigilance, Africa has not been very proactive as brought to the fore by an analysis of data in the World Health Organization (WHO) vaccine safety database, VigiBase, in June 2015. The analysis showed that less than 1% of all the AEFIs reported globally were from Africa. The analysis further revealed that about 97% of these AEFI reports from Africa came from 10 countries, which were Senegal, South Africa, Egypt, Zimbabwe, Ghana, Democratic Republic of Congo, Nigeria, Morocco, Sierra Leone and Tunisia (38). There were no AEFI reports from Kenya entered into VigiBase prior to 2016. Between 2016 and 2018 about 6.5 million AEFI reports were reported globally according to data extracted from VigiBase, out of this just about 10,324 (0.2%) of the reports were from Africa. Of the 10,324 reports from Africa, approximately 2% were from Kenya (39).

5.1 Characteristics of patients affected by the AEFIs

In this study, comparable numbers of males and females experienced AEFIs. There was no statistically significant difference in the age group distribution of AEFIs between the two genders ($p=0.795$). This compares to a study done in Canada which reported minimal differences in the number of males and females that experienced AEFIs for vaccines administered from 2005 through 2012 (40). A study conducted in Oman reported a significantly higher number of adverse events in males than in females (41). Conversely, in

another study in Australia there were more events in females than males (42). In this study, most of the AEFIs occurred to individuals in the age group >10 years to ≤15 years; representing 65 (35%) of all the cases. This is contrast to a study done in Oman which reported that the highest proportion of AEFI reports was among children aged < 1 year (80.5%) (41). In a study done in Canada, most of the AEFIs occurred in children aged 1 to <2 years followed closely by infants <1 year old (40).

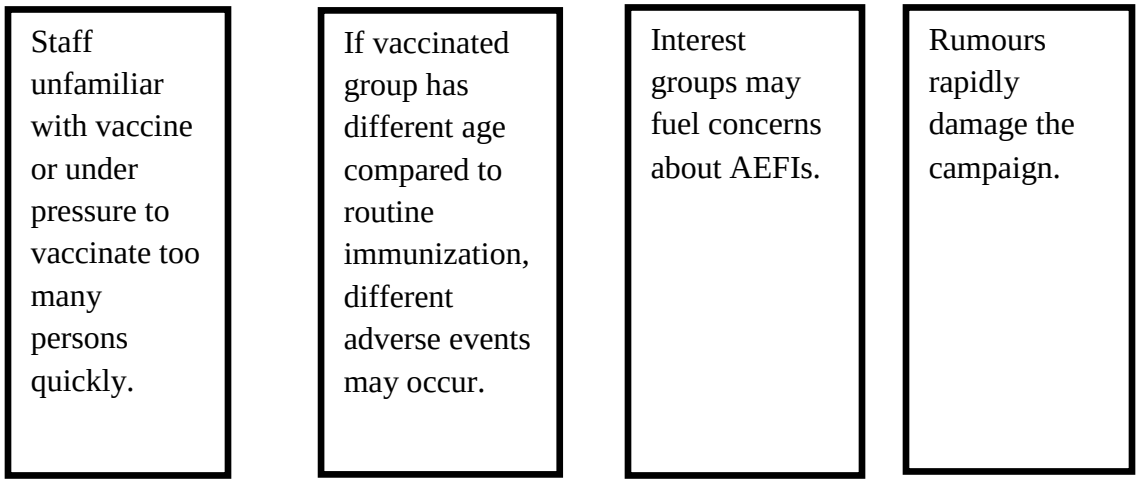
5.2 Vaccines implicated in adverse events

MR vaccine accounted for the highest number of reports with 105 (56.2%). This was followed by OPV with 35 (18.7%) adverse event reports and MMR vaccine with 26 (13.9%) adverse event reports. Measles-containing vaccines (MR and MMR) accounted for 131(70.1%) AEFI reports, while MR, OPV and MMR together accounted for 166 (88.8%) AEFI reports.

The occurrence of the high number of AEFIs related to the MR and OPV vaccines may have been due to the increased number of doses administered during mass vaccination campaigns during the study period. There was a countrywide mass vaccination campaign for OPV in 2017 and for MR in 2016. Usually the main objective of mass immunization campaigns is to vaccinate a large proportion of the population in a short period; this has been shown to present safety challenges and a consequent increase in AEFI rates.(45), (29).

AEFIs sometimes differ according to how the vaccine was formulated or manufactured, the age of the vaccine recipient, and country (vaccination scheme in use, adverse event reporting systems and policies for adverse events compensation); hence it is challenging to compare outcomes of AEFIs within a country and between different countries. Because of such challenges, this is an area that has not been studied comprehensively (7).

Commonly encountered issues regarding safety in vaccination campaigns include the following points as shown in fig 5.1



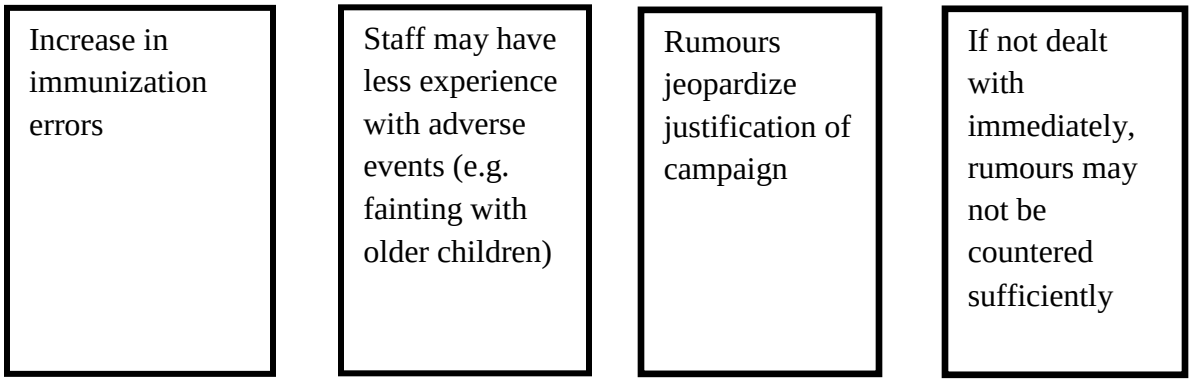


Figure 5.1:Common safety issues or concerns in vaccination campaigns globally (45).

5.3 Types of adverse events reported

Of the 224 adverse events reported, the most common was rash at (n=92, 41%) followed by pyrexia (n=23, 10.3%). Other common adverse events reported were pruritus (n=9), vomiting (n=8), diarrhoea (n=7), convulsions (n=7), anaphylactic reaction (n=7) and muscular weakness (n=6). This is similar to a study conducted in Australia in 2017 which found reaction on the injection site, fever, rash, vomiting and pain as the most common adverse events reported to the Therapeutic Goods Administration (TGA) (46).

MR vaccine was responsible for every two out three (66%) of rash cases reported, followed by MMR vaccine accounting for about 22% of the cases. This is much higher than studies that have been conducted in the past. MCVs have been known to cause rashes in about 2% - 6% of vaccinees. The rash usually occurs approximately 1 week after

vaccination and lasts about 48 hours (47). In their study, Gillet et al (2009) found that skin rash following Measles-Mumps-Rubella (MMR) immunization was 1-7% (48). This is similar to the 1-5% rate observed among Iranian children (49). Other less common adverse events associated with MCVs are lymphadenopathy (8.7%), pain and swelling at injection site (2.6% - 13.0%) (48) (49).

MR vaccine was also responsible for every 9 out of every 10 cases (89%) of pruritus reported. The use of MCVs can result in arthritis, rash, malaise, sore throat, pyrexia, headache, joint pain and mild lymphadenopathy (47). Of the 23 cases of pyrexia reported, 35% (n=8) of them were due to MR vaccine. Systemic reactions following administration of MCVs includes fever (>39.4 ºC) which occurs in about 5 to 15% of vaccine recipients. In some cases, the fever may occur coincidentally, as a result of other infections (47). In a study by Fan-Ya Meng et al (2017) the most common AEFIs reported in Anhui Province following administration of MCVs from 2009 through 2014 were fever (106.9 per million doses), rash (48.3 per million doses), and local reaction (29.3 per million doses) (50). Analysis of China's AEFI surveillance data by Hu et al (2013) between 2008 and 2011 showed that fever was the commonest adverse event associated with MCVs with a 25.6% occurrence (51). In another study, Halperin (2009) found that incidence of fever following administration of measles-mumps-rubella-varicella (MMRV) vaccine was between 16 and 19% (52).

OPV was responsible for majority of the gastrointestinal adverse events namely diarrhoea and vomiting. It accounted for 6 out 8 (75 %) of the vomiting cases and 5 out of 7 (71 %) of the diarrhoea cases reported. These findings are comparable to a study by Nzolo et al (2013) and the WHO guidance document on vaccine background rates. In the study by Nzolo et al (2013) conducted in Congo the most common AEFIs following vaccination with OPV were; headache (22.4%), abdominal pain (17.2%), fever (11.7%), diarrhea (9.9%), and asthenia (7.5%) (53). According to the WHO, common minor vaccine reactions associated with OPV are fever, irritability, malaise, and non-specific symptoms, such as diarrhea, headache, and/or muscle pain (47).

5.4 Severity of AEFIs

Between 2015 and 2018 a total of 16 serious adverse events were reported; this accounted for about 7% of all adverse events reported. Of these 16 cases, 12 of them required inpatient hospitalization while 4 of them resulted in death. This is consistent with a study conducted in Australia which found that most of the reported AEFIs in 2017 were classified as non-serious (88%) with 12% classified as serious.(46). The observed 7% of AEFIs defined as serious is in concurrence with findings from AEFI surveillance systems in; Australia (11%), and the United States of America (14.2%), but it differs remarkably from the findings in Germany (19%) Croatia (3%) and Zhejiang province, China (1%). The observed differences may be as a result of different reporting practices of the various countries. These differences point to a bias in reporting of serious AEFIs, which in most

cases have been observed to be significantly lower in active surveillance systems and in clinical trials compared to passive surveillance systems (54).

OPV was suspected to have caused the 2 deaths with MR and rotavirus vaccines causing 1 death each. MR vaccine was responsible for 6 out every 10 (58%) hospitalizations due to AEFIs. The four mortalities occurred in children aged 18 days, 1 month, 1 year and 12 years. AEFI investigations of the deaths that occurred showed there was no causal relationship with the vaccines administered. There was no conclusive information on the hospitalizations regarding the duration and outcome.

A study by Singh et al (2018) found that, 32% of the fatal AEFIs occurred following three vaccines used together (OPV,DPT and Hep B), and 22% followed two vaccines used together (OPV and pentavalent). Yu et a l(2016) found that 91.9% of the serious AEFIs occurred in patients <7 years of age, and 8.1% occurred in patients >7 years of age. Fatal events accounted for 0.2% of all reported AEFIs; all cases were infants (<1 year of age) with 60% being females and 40% male (51).

In the USA, a review by the Institute of Medicine (IOM) on deaths reported post vaccination in children in the early 1990s showed that most of deaths reported were coincidental and there was no causal relationship to vaccination (55).

Several other published reviews of data from VAERS for various vaccines and vaccine types have not found significant patterns that would indicate a causality between vaccination and deaths following vaccination (56) (57) (58) (59) (60).

5.2 Vaccines pharmacovigilance and stakeholder coordination

A robust pharmacovigilance system involves not just adverse events data collection but also effective mechanisms to enable adequate communication of medical products safety information to health care professionals and the public, and incorporation of pharmacovigilance activities into the various levels of the health system and public health programs (61).

When a pharmacovigilance system is not comprehensive, adverse events still occur but it becomes very difficult to estimate or compute the size and magnitude of the problem. In addition to the impact of adverse events on morbidity and mortality and the resultant costs to health systems, vaccine adverse events are also associated with reduced confidence in the health system and vaccine hesitancy (61).

National pharmacovigilance guidelines offer guidance on how pharmacovigilance should be conducted in a country. The *"Guidelines for the National Pharmacovigilance System in Kenya"* mainly focus on drugs without any mention of vaccines (62). The country is in the process of developing guidelines on immunization safety surveillance but at present they do not exist. Development and implementation of guidelines will serve as a basis for coordination of activities among various stakeholders.

Training is a critical component of the vaccine safety surveillance system and its follow-up activity (64). Trainings and sensitizations for health workers across the country on vaccines pharmacovigilance have been few and intermittent. According to the WHO,

HCWs are the primary reporters of AEFI across the globe (64). It is therefore important to empower them on matters related to AEFIs through regular trainings and provision of relevant reference materials. Masika et al, 2014 found that only 29.2% of nurses working in Nairobi city council hospitals had good knowledge on AEFI surveillance and only about a third of them had good practice towards AEFI surveillance (65). Lack of training may be a big contributor to the low number of AEFI reports received at the NVIP and PPB. For example, in the year 2015 there was no single AEFI report received at both institutions.

To continuously build vaccine safety capacity among staff in countries, an online platform that offers training to the various people involved in vaccination safety issues at various levels was developed by WHO in 2012. The e-learning course is free, self-guided and user-friendly therefore can be taken in any setting and over any period of time (64).

5.4 Risk assessment, evaluation and communication

Risk assessment is dependent on signal generation; Nwokike & Eghan, 2010 emphasize on the need of constantly assessing and evaluating signals, especially those that are of public health importance (66). The procedure involves confirming the signal's validity, searching the relevant databases and literature, gathering and compiling expert opinions, then making decisions, and implementing appropriate measures to lower the risks. Signals can be generated only when adverse events are reported. In Kenya, approximately 91 million vaccine doses were distributed between 2015 and 2018 with 187 AEFI reports analyzed; this translates to a reporting rate of <0.01/100,000 vaccine doses. A similar analysis carried

out in Zimbabwe over a 10 year period found an annual reporting rate of 0.58 per 100,000 vaccine doses (68). A study by Alguacil-Ramos et al (2016) found that out of the more than 13 million vaccines doses administered to the Valencian community in Spain during 2005 through 2011,the reporting rate of adverse events was 12.4/100,000 doses administered with the highest value in 2009 (27.4/100,000) (33). This shows that the AEFI reporting rate in Kenya is very low.

According to WHO, vaccine hesitancy was one of the top ten threats to global health in 2019; vaccine hesitancy is the reluctance or refusal to vaccinate despite the availability of vaccines (69). There are several reasons why people shy away from vaccinations; a vaccines advisory group to WHO identified complacency, inconvenience in access to vaccines, and lack of confidence as major reasons for hesitancy. Health workers, especially those in communities, have been shown to be the most trusted informants and influencers of vaccination related decisions. Therefore it is important to continuously support them to convey the right, relevant and credible information on vaccines (70).

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

In this study, comparable numbers of males and females experienced AEFIs. The AEFI reporting rate is very low; it stands at <0.01 per 100,000 vaccine doses distributed. MR vaccine accounted for more than half of the AEFI reports followed by OPV. Measles-containing vaccines (MR and MMR) accounted for 70.1% of the AEFI reports, while MR, OPV and MMR together accounted for 88.8% of the AEFI reports. The occurrence of the high number of AEFIs related to the MR and OPV vaccines may have been due to the increased number of doses administered during mass vaccination campaigns during the study period.

The most common adverse event was rash followed by pyrexia. Other common adverse events reported were pruritus, vomiting, diarrhoea, convulsions, anaphylactic reaction and muscular weakness.

Majority of the adverse events experienced were minor with serious events accounting for 7% of all adverse events reported.

There are currently no national AEFI surveillance guidelines; they are currently in draft stage. There has been a gap in AEFI training for health workers across the country, the

pharmacovigilance training curriculum has mostly concentrated on adverse event reporting and post marketing surveillance for other medical products. Trainings and sensitizations for health workers across the country on vaccines pharmacovigilance have been few and intermittent .This may be a big contributor to the low number of AEFI reports received at the NVIP and PPB.

6.2 Recommendations

Based on the findings of the study the following recommendations were made:

- The development of AEFI surveillance guidelines should be finalized and once complete they should be disseminated widely to health workers across the country.
- Health workers should be sensitized and encouraged to take up the free online vaccine pharmacovigilance courses offered by WHO. This will greatly improve their knowledge and possibly increase the vaccine adverse events reporting rate and quality of reports.
- The PPB should develop an online reporting platform specifically for vaccine adverse events. This may increase the reporting rate and also the quality of reports submitted.

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APPENDICES:

Appendix 1: Key Informant Questionnaire
STUDY TITLE: ANALYSIS OF ADVERSE EVENTS FOLLOWING IMMUNIZATION IN KENYA

Part A:

Questions to the personnel involved in AEFI surveillance at PPB and NVIP:

1. Are there national guidelines for AEFI surveillance in Kenya? Yes___ NO___
   If yes, how accessible are they by health workers?
   …….
   …….
   …….
   ……..

2. Which institution between PPB and NVIP has the overall responsibility in AEFI surveillance? **.....**

   Is there a defined framework for sharing of information between the two institutions?
   …….
   …….

3. Since health is a devolved function as per the constitution of Kenya 2010, how does the NVIP/PPB ensure that health workers under the devolved units receive adequate training on AEFI surveillance and reporting?
   …….
   …….
   …….

……

……..

……..

4. How would you rate the reporting rate of AEFIs in public, faith based and private health facilities across the country? (i) Low____ (i) Average_____ (ii) Above Average_____ (iii) High____

   For responses i, ii and iii above, what measures has the PPB/NVIP taken to improve this?

   ……..

   ……

   ……

5. a) What happens after an AEFI report has been submitted?

   ……

   ……

   ……..

   ……

   b) Is there regular analysis of the data reported on AEFIs?

   ……

   …….....

   c) How are reports on serious AEFIs handled?

   ……

   ……..

   ……...

   ……

6. Is there a national AEFI expert review committee? Yes___ No____

   If yes, who are the members and what is their mandate?

   ……

……

……..

……..

……

……

Part B:

Questions to staff responsible for pharmacovigilance in private hospitals

1. Who is responsible for reporting of AEFIs in this institution?

……

……

……

……

……

2. Has any member of staff received training received training on pharmacovigilance of vaccines and reporting of AEFIs? If yes how many and what are their cadres?

……..…….

……

……

……

3. What happens when a suspected AEFI case occurs following vaccination:

(i) In this facility?

……

……

……

……

(ii) In another facility but the person presents to this facility

……
……
……
……

4. What are some of the challenges encountered in identification and reporting of AEFIs?

……..
……..
……..
……..
……..
……

5. Is the data reported on AEFIs utilized at institution level? If yes, please indicate how?

……..
……...
……
……

6. Are there any client education activities regarding vaccine safety issues that this institution carries out? Do they help reduce vaccine hesitancy?

……
……
……
……
……
……..

Appendix 2: Suspected Adverse Drug Reaction Reporting Form

PV 1

MINISTRY OF HEALTH
THE PHARMACY AND POISONS BOARD
P. O. Box 27663-00506 NAIROBI
Tel: (020)-2716905 / 6 Ext 114 Fax: (020) 2713431/2713409.
Email: pv@pharmacyboardkenya.org

IN CONFIDENCE

☐ Initial Report
☐ Follow-up Report

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

NAME OF INSTITUTION: ..... **INSTITUTION CODE:** .....

ADDRESS: ..... **CONTACT:** .....

****

PATIENT'S NAME/ INITIALS: ..... **IP/OP. NO.:** ..... **D.O.B:** .....

PATIENT'S ADDRESS: ..... **WARD/CLINIC:** ..... **GENDER:** ☐ Male ☐ Female
(Name/Number)

ANY KNOWN ALLERGY: ☐ No ☐ Yes (specify) .....

PREGNANCY STATUS: ☐ Not Pregnant ☐ 1st Trimester ☐ 2nd Trimester ☐ 3rd Trimester

WEIGHT (kg): .....

HEIGHT (cm): .....

DIAGNOSIS: (What was the patient treated for)..... .....

BRIEF DESCRIPTION OF REACTION: ....

LIST OF *ALL* DRUGS USED IN THE LAST 3 MONTHS PRIOR TO REACTION (include OTC and herbals) {use rear side of this form for additional drugs}	DOSE	ROUTE AND FREQUENCY	DATE STARTED	DATE STOPPED	INDICATION	TICK (√) SUSPECTED DRUG(S)
1						
2						
3						
4						
5						

SEVERITY OF THE REACTION: (Refer to scale overleaf)
☐ Mild
☐ Moderate
☐ Severe
☐ Fatal
☐ Unknown

ACTION TAKEN:
☐ Drug withdrawn
☐ Dose increased
☐ Dose reduced
☐ Dose not changed
☐ Unknown

OUTCOME:
☐ Recovering / resolving
☐ Recovered / resolved
☐ Requires or prolongs hospitalization
☐ Causes a congenital anomaly
☐ Requires intervention to prevent permanent damage
☐ Unknown

CAUSALITY OF REACTION: (Refer to scale overleaf)
☐ Certain
☐ Probable / Likely
☐ Possible
☐ Unlikely
☐ Conditional / Unclassified
☐ Unassessable / Unclassifiable

ANY OTHER COMMENT: ....

NAME OF PERSON REPORTING: .....**DATE:** .....

E-MAIL ADDRESS: .....**PHONE NO.** .....

DESIGNATION: .....**SIGNATURE:** .....

You need not be certain ... just be suspicious !

Your support in this Pharmacovigilance program is appreciated.
Submission of a complaint does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the event.
Patient's identity is held in strict confidence and programme staff is not expected to and will not disclose reporter's identity in response to any public request.
Information supplied by you will contribute to the improvement of drug safety and therapy in Kenya. Once completed please send to:
The Pharmacy and Poisons Board on the above address

EXPLANATORY NOTES

CONFIDENTIALITY
All information collected in this form, identities of the reporter and patient, will remain confidential

WHAT TO REPORT
An Adverse Drug Reaction (ADR) is defined as a reaction that is noxious and unintended, and occurs at doses normally used in man for prophylaxis, diagnosis or treatment of a disease, or for modification of physiological function.

Report all suspected adverse experiences with medications,
especially those where the patient outcome is:

- Death
- Life-threatening (real risk of dying)
- Hospitalization (initial or prolonged)
- Disability (significant, persistent or permanent)
- Congenital anomaly
- Required intervention to prevent permanent impairment or damage

Report even if:

- You are not certain if the drug caused the reaction
- You do not have all the details

WHO CAN REPORT
All healthcare professionals (clinicians, dentists, nurses, pharmacists, physiotherapists, community health workers etc) are encouraged to report. Patients (or their next of kin) may also report.

WHAT HAPPENS TO THE SUBMITTED INFORMATION
All information submitted is handled in strict confidence. The Pharmacy and Poisons Board will assess causality and statistical analysis on each form. Data will periodically be used for review and suggest any interventions that may be required to the Ministry of Health. Data will also be submitted periodically to the Uppsala Monitoring Centre - the WHO Collaborating Center for International Drug Monitoring in Sweden.

SUBMISSION OF INITIAL OR FOLLOW-UP REPORTS
It is important to tick the appropriate box on the top-right corner of the front page to indicate whether the report is an initial (original) report or is a follow-up (subsequent) report.
It is very important that follow-up reports are identified and linked to the original report.

WHERE TO REPORT
After completing this form, please forward the same to your Pharmacy Department for onward submission, or mail directly, to:

THE PHARMACY AND POISONS BOARD
Lenana Road.
P. O. Box 27663-00506 NAIROBI
Tel: (020)-2716905 / 6 Ext 114 Fax: (020)-2713431/2713409
E-mail: pv@pharmacyboardkenya.org

Please use the space provided below for any further information. You may attach more pages to this form if required.

LIST OF ALL DRUGS USED IN THE LAST 3 MONTHS PRIOR TO REACTION (include OTC and herbals)	DOSE	ROUTE AND FREQUENCY	DATE STARTED	DATE STOPPED	INDICATION	TICK (✓) SUSPECTED DRUG(S)
6						
7						
8						
9						
10						

Criteria for Assessment of Severity of an ADR

Mild	• The ADR requires no change in treatment with the suspected drug • The ADR requires that the suspected drug be withheld, discontinued or otherwise changed. No antidote or other treatment is required • No increase in length of stay.
Moderate	• The ADR requires that the suspected drug be withheld, discontinued or otherwise changed, and/or an antidote or other treatment is required. • Increases length of stay by at least one day • The ADR is the reason for admission.
Severe	• The ADR requires intensive medical care • The ADR causes permanent harm to the patient
Fatal	• The ADR either directly or indirectly leads to the death of the patient

WHO-UMC Causality Assessment Scale

Causality Term	Assessment
Certain	• Event of laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically *(i.e an objective and specific medical disorder or a recognized pharmacological phenomenon)* • Rechallenge satisfactory , if necessary.
Probable / Likely	• Event or laboratory tests abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory tests abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drugs withdrawal lacking or unclear
Unlikely	• Event or laboratory tests abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper, assessment needed or • Additional data under examination
Unassessable/ unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because of insufficient or contradictory information • Data cannot be supplemented or verified.

Your support in this Pharmacovigilance program is appreciated.
Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the event.
Patient's identity is held in strict confidence and programme staff is not expected to and will not disclose reporter's identity in response to any public request.
Information supplied by you will contribute to the improvement of drug safety and therapy in Kenya.
Once completed please send to: The Pharmacy and Poisons Board on the above address

Appendix 3: 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 any)

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.

Appendix 4: Data capture form

Name of Institution…….. Year of Reports……..

	Age			Sex		Type of AEFI*											Suspected Vaccine										
Report No	0-11 Months	1-4 Years	5-9 Years	Male	Female	A	B	C	D	E	F	G	H	I	J	K	1	2	3	4	5	6	7	8	9	10	11
TOTAL																											

*Type of AEFI	Suspected Vaccine
A=BCG Lymphadenitis	1=BCG
B=Convulsion	2=OPV
C=Generalised Urticaria	3=Hep B
D=High Fever	4=DPT
E=Injection Site Abscess	5=HIB
F=Severe Local Reaction	6=Pneumococcal
G=Anaphylaxis	7=Rotavirus
H=Encephalopathy,Encephalitis/Meningitis	8=Measles
I=Paralysis	9=Yellow Fever
J=Toxic Shock	10=MR
K=Others	11=Others

Appendix 5: Written Informed Consent
STUDY TITLE: ANALYSIS OF ADVERSE EVENTS FOLLOWING IMMUNIZATION IN KENYA

Introduction

My name is Dr.Kelvin Murigoh, a postgraduate student in the School of Pharmacy at the University of Nairobi. I am currently pursuing Masters of Pharmacy in Pharmacovigilance and Pharmacoepidemiology. I would like to seek your consent to participate in this study.

Kindly read the consent form below and feel free to ask any questions you may have.

Purpose of the study: The purpose of this study is to analyze and characterize adverse events following immunization in Kenya.

Study Procedures: The study is divided into two parts; the first part involves collection and analysis of all AEFI reports reported between 2015 and 2018 in four study sites. The second part involves an interview to key informants at each of the study sites. The interview will take approximately 40 minutes. It will be an open discussion on your knowledge and experience regarding the study

Benefits of participation: There might be no direct benefits from your participation in the study but your contribution will lead to improvement in the field of vaccine pharmacovigilance with regard to reporting of AEFIs.

Risks and Discomforts: The study has minimal risks as it involves retrospective collection of AEFI reports and filling out questionnaires. The nature of questions asked will not in any way elicit discomfort or psycho-social harm to you.

Confidentiality: To protect your privacy, your name will not be filled on the data collection instrument. For this study, you will be assigned a unique number that i will use to identify you in a password protected database. With your approval the interview will be recorded and whatever information you provide will be held in strict confidence. The voices recorded will be masked to protect the identity of the interviewees. The results from this study may be published or presented at professional meetings but your name will not be used or associated with the findings.

Ethics approval for this study was sought from the KNH/UoN ethics committee.

Compensation: You will not receive any form of payment for taking part in the study.

Voluntary participation: Your participation in this study is voluntary and refusal to participate will not result in any penalties.

Contacts: If you have any question about this study feel free to contact the principal investigator, Dr.Kelvin Murigoh (Tel. 0722551648) at the School of Pharmacy, University of Nairobi.

You may also contact the secretary/chairperson, **Kenyatta National Hospital/University of Nairobi Ethics Review Committee (KNH-UoN ERC) Tel 2726300 Ext 44355 and 44102, Nairobi-Kenya, or E-mail:uonknh_erc@uonbi.ac.ke**

Statement of Consent

I have and understood the information provided the study and any questions regarding the study have been answered. I willingly consent to participate in this study.

Name of Participant……..

Signature……

Date……

Researcher's Statement

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and responded adequately to questions raised.

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

Researcher's Name……

Signature……

Date……

You can contact any of the following researchers:

- The Principal Investigator Dr.Kelvin Murigoh; 0722551648,
- The lead supervisor Prof A.N Guantai; 0722636427 or,
- Dr. Margaret Oluka; 0722604216

Appendix 6: KNH/UoN ERC approval letter

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://www.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/ Mod&SAE/355

August 21, 2019

Kelvin Murigoh Kinyua
Reg. No.U51/7329/2017
Dept. of Pharmacology & Pharmacology
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Kelvin

Re: Approval of modifications– study titled "Analysis of Adverse Events Following Immunization in Kenya (P871/12/2018)

Your communication dated 25th July 2019 refers.

Upon review the KNH-UoN ERC has **approved** the following amendments:

1. Approval granted for change of methodology to include a descriptive cross sectional method to enable use of questionnaires for qualitative data collection.
2. Approval granted for change of 'Unit of Vaccines and Immunization Services (UVIS) to 'National Vaccines and Immunization Programme(NVIP)' .
3. Approval for inclusion of key informant Questionnaire (Appendix I, page 31) for collection of data.

All the changes are reflected in the revised proposal and are acceptable.

The study stool is hereby endorsed and stamped for use.

Yours sincerely

PROF. M.L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Director CS, KNH
The Chair, KNH- UoN ERC
The Dean, School of Pharmacy, UON
The Chair, Dept.of Pharmacology and Pharmacognosy,UoN
Supervisors: Prof.A.N. Guantai, Dr.Margaret Oluka

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

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.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

KENYATTA NATIONAL HOSPITAL APPROVED 09 JAN 2019 KNH/UoN-ERC P. O. BOX 20723 - 00202 NAIROBI

Ref: KNH-ERC/A/7

9th January 2019

Kelvin Murigoh Kinyua
Reg.No.U51/7329/2017
Dept. of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Kelvin

RESEARCH PROPOSAL – ANALYSIS OF ADVERSE EVENTS FOLLOWING IMMUNIZATION IN KENYA (P871/12/2018)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 9th January 2019 – 8th January 2020.

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) Death and life threatening problems and serious 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.
d) 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.
e) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
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) 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 **http://www.erc.uonbi.ac.ke**

Appendix 7: PPB Student Confidentiality Agreement

REPUBLIC OF KENYA

MINISTRY OF HEALTH

PHARMACY AND POISONS BOARD

STUDENT CONFIDENTIALITY AGREEMENT

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

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

(a) Not to use the Information for any purpose other than discharging my 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 any 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 to maintain confidentiality in my study could be grounds for immediate suspension of attachment with PPB and/or possible liability in any legal action arising from such breach.

I confirm that I 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.

I shall promptly notify the Chief Executive Officer, PPB of any change in the above circumstances, including if an issue arises during the course of my work.

All documents supplied to me 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

KELVIN MURIGOH KINYUA
(Student Name)

(Signature)

14/02/2019
(Date)

Appendix 8: Aga Khan University Hospital research approval

THE AGA KHAN UNIVERSITY

Ref: 2019/REC-28 (v1)
May 20, 2019

Mr. Kelvin Murigoh Kinyua– Principal Investigator,
Pharmacology and Pharmacognosy,
University Of Nairobi.

Dear Mr. Kinyua and team,

Re: Analysis of Adverse Events Following Immunization in Kenya

The Aga Khan University, Nairobi, Research Office is in receipt of your proposal and request to include the Aga Khan University Hospital, Nairobi (AKUHN) as a research site for the above study. We note that the study has local ethics approval from KNH-UON ERC, letter Ref: KNH-ERC/A/7.

The Institutional Ethics Review Committee (IERC) and Research Committee (RC) in consultation with relevant internal departments have reviewed your request and granted authorization to conduct this study (*{as per attached official stamped protocol - version 2019/REC-28 (v1)}* at AKUHN from **May 20, 2019.** Prior to commencing the study, you will be expected to obtain a research permit from the National Commission for Science, Technology and Innovation (NACOSTI) and also obtain an approval from Gertrude's Hospital and MP Shah Hospital indicated as your study sites. Copies of these approvals should be submitted to the AKU Research Office for record purpose. This approval is valid up to **8th January 2020.** While at AKUHN, please liaise with Ms. Irene Wesonga. Ms. Wesonga is the ANC Unit Supervisor. You will be expected to adhere to specific applicable hospital protocol for the duration of data collection.

In implementing the study, you are expected to ensure the protocol complies with relevant institutional administrative regulations and applicable sections of the IERC guidelines. You should notify the IERC immediately of any changes that may affect your research project. You must immediately report any unanticipated problems involving risks to the participants. You must provide an interim report before expiration of the validity of this approval and request extension if additional time is required for study completion. You must advise the IERC when this study is finished or discontinued and a final report submitted to the Research Office. **De-identification** of the hospital must be adhered in your study discussion/reports. Further approval from the AKUHN management should be sought before publishing the results. In addition to the final report, an in-depth analysis of the specific findings at AKUHN should be submitted. If you have any questions please contact Research Office research.supportea@aku.edu or call 020-366 2148.

Sincerely,

R Adam

.....

Prof. Rodney Adam
Chair, Research Committee, AKU (Nairobi)

Copies:
Chief of Staff & Associate Dean Clinical Affairs, Hospital Administration, AKUH, N
Chair, Institutional Ethics Review Committee (IERC) AKU
Chief Pharmacist – AKUH, N
Program Administrator, Maternal and Child Health, AKUH, N
ANC Unit Supervisor, AKUH, N

Appendix 9: Gertrude's Children's Hospital Ethical Approval Letter

Gertrude's
CHILDREN'S HOSPITAL
Quality Healthcare for Children

April 30, 2019

REF: GCH/ERB/VOLMMIX/195

Kelvin Murigoh Kinyua (B.PHARM)
U51/7329/2017

Dear Mr. Kinyua,

RE: REQUEST TO UNDERTAKE RESEARCH IN GERTRUDE'S CHLDREN'S HOSPITAL

We are in receipt of your revised proposal requesting to conduct a study: "**Analysis of Adverse Events Following Immunization in Kenya".**

The Hospital's Ethical Review Board has reviewed and **approved** your request to now commence the study.

Please note that this approval is only to conduct the study and is not an approval for publication or presentation of findings. A separate approval will be required for this purpose.

The Hospital will require the write up of your study findings upon completion as this will form part of our database for future references. **Meeting this requirement will be a condition for granting approvals for publications or presentations of research findings in the future.**

On behalf of the Hospital I wish you a fruitful research.

Regards,

Dr. Thomas Ngwiri
Secretary - Ethical Review Board

Dr. Vankwa Indeche
Chair-Ethical Review Board

ANALYSIS OF ADVERSE EVENTS FOLLOWING IMMUNIZATION IN KENYA

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