META-ANALYSI ON THE RISK OF MORTALITY IN PERSON WITH EBOLA VIRUS DISEASE.
(1976-2014)

BY

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DECEMBER, 2019

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A THESIS/DISSERTATION/PROJECT SUBMITTED TO THE SCHOOL OF POSTGRADUATE STUDIES, NASARAWA STATE UNIVERSITY KEFFI, IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF DEGREE OF M.SC IN STATISTICS

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DECEMBER, 2019

DECLEARATION

I hereby declare that this thesis/ dissertation/project have been written by me and it is a report of my research work. It has not been presented in any previous application for M.Sc. Statistics. All quotations are indicated and sources of information specifically acknowledge by means of references.

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CERTIFICATION

The thesis/ dissertation/project META-ANALYSIS on the Risk of the Mortality in Person with Ebola Virus Disease: meets the regulations governing the award of Master of Science (M.Sc) in Statistics, of the school of Postgraduate Studies, Nasarawa State University, Keffi and is approved for its contribution to knowledge.

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DEDICATION

This dissertation is dedicated to Almighty God the one who has given me the basic knowledge of life situation and power to understand, and to my beloved wife Mrs Faluyi Oyenike for her care, love advice and prayer support during the period of my leaning in the university.

ACKNOWLEDGEMENTS

My greatest acknowledgement goes to the Almighty God, for granting me wisdom, knowledge and understanding and also for protecting me in the course of this study.

In the same vein, my profound gratitude goes to my amiable supervisor in person of Dr. (Mrs.) M.U Adehi for her enviable talents, prowess, maturity, motivation, motherly assistance and encouragement throughout the course of this thesis work. I am very privileged to have been supervised by her.

I wish to express my sincere gratitude to my parents, MR and MRS A.A. FALUYI for their support morally and financially. My deepest appreciation also goes to my wife MRS OYENIKE FALUYI, brothers, MR TAIWO OLAGUNJU & MR OLUSOLA OJEGBEDE, a wonderful sister MRS FOLASADE OLAGUNJU.

I must also thank my very good friends and classmates, making keffi a perfect environment all through.

Finally, my sincere appreciation also gratefully extended to all my lecturers in the department of Statistics, most especially Dr. N.O Nweze, my able course adviser Dr. Adenomon, Mr. Ibrahim, Dr. (Mrs.) Mary Adehi. May God bless them for their impact in my life?

I THANK YOU ALL.

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ABSTRACT

The Ebola virus disease outbreak that started in western Africa in 2013 was unprecedented because it spread within densely populated urban environment and affected thousands of people. As a result, previous advice and guidelines need to be critically received, especially with regard to transmission risk in different contexts. A total of 20 reports were selected from 634 found in the initial search. Data were extracted from eligible articles and summarized narratively with partial Meta-Analysis. Eight papers gave numerical odds for contracting filovirus illness;

67 further articles provided supporting anecdotal observations about how transmission probably occurred for individuals. Many forms of contact (conversation, sharing a meal, sharing a bed, direct or indirect touching) were unlikely to result in disease transmission during incubation or early illness. Among household contacts who reported directly touching a case, the attack rate was 23% [95% confidence interval (CI) 26-38%]. Risk of disease transmission between household members without direct contact was low (1%; 95% CI 0-5%). Caring for a case in the community, especially until death, and participation in traditional funeral rites were strongly associated with acquiring disease, probably due to a high degree of direct physical contact with case or cadaver. Transmission of filovirus in unlikely except through close contact, especially during the most severe stages of acute illness. More data were needed about the context, intimacy and timing of contact required to raise the odds of disease transmission. Risk of factors specific to urban settings may need to be determined.

CHAPTER ONE

INTRODUCTION

1.1 Background to the Study

The 2014 Ebola Virus Disease (EVD or “Ebola”) outbreak continues to evolve, creating challenges for the many international partners providing support. Three main affected countries, Guinea, Liberia and Sierra Leone, struggle to control the infection against a backdrop of severely compromised health systems, significant deficits in capacity and fear. WHO estimate that from six to nine months will be needed to control the outbreak and has released a ‘road map’ detailing what needs to be done to achieve this.

Ebola virus disease (EVD) has been making headlines throughout the world for most of 2014. The ongoing epidemic of Zaire Ebola virus represent the largest and deadliest known EVD outbreak and marks the first time the disease has spread outside of central and East Africa (Thomas R. Friedman, M.D., M.P.H, Inger Damon, M.D, Ph.D, Beth P. Bell, M.D., M.P.H., Thomas Kenyon, M.D., M.P.H., et al. 2014). In August of 2014, the world Health Organization (WHO) declared the outbreak to be a public health Emergency of international concern: "an extraordinary event which is determined to constitute a public health risk to other States through the international Spread of disease; and to potentially require a coordinated international response"

EVD is a contagious disease caused by an enveloped single stranded RNA virus; the illness is spread via direct contact with the body fluids of symptomatic EVD patients. When pathogens exist in an environment at a relatively constant rate, they are considered to be endemic; however, when the number of disease cases rises higher than expected, the situation is considered to be either an outbreak, epidemic, or pandemic, depending on area of impart (Institute of Medicine. EVD is sometimes referred to as Ebola hemorrhagic Fever because the disease is associated with

high fevers and vascular damage. More recently, however, this name has fallen out of favor since less than 50% of Ebola patients demonstrate appreciable hemorrhagic symptoms (Slobodan Paessler, David H Walker, 2013). The disease has an incubation period that ranges from two to twenty-one days, with symptoms typically appearing in the eight to twelve days after exposure. Early symptoms of EVD include fever, headache, muscle pain and anorexia. Prompt identification of Ebola based on these symptoms can be difficult, as they are similar to those seen in patients with Malaria, typhoid, Lassa fever, Hello fever, influenza or pneumonia (Breman JG, et al. N Engl J Med. 2014). As EVD progresses, patients often develop watery diarrhea, nausea, vomiting and abdominal pain. Hemorrhagic, hemoptysis, epistaxis and bleeding gums (Paesler &Walker, 2013; Roddy et al. 2012).

In late stages of the disease, patients demonstrated tachypnea, anuria and obtundation. Death occurs after an average of ten days of illness and it may take survivors two months to make a full recovery (Legrand, Garis, Noelle, Valleron and Flahaut, 2006).

Ebola Virus Disease (EVD) was first recognized in 1976 when two separate outbreaks occurred in Zaire and Sudan. The outbreak in Zaire began with a man who arrived at a hospital with a high fever and died a week later from a severe hemorrhagic (Feldmann H, 2011). Five days prior to his admission while on chloroquine injection at Yambuku mission hospital for malaria treatment; at the time of the outbreak, it was common syringes to be rinsed and reused between patients. Over the next three months, more than 300 people in Zaire developed symptoms of EVD. Epidemiological studies show that more than 25% of the infected EVD patients had received injections at the Yambuku mission Hospital. During the outbreak, 280 out of 318 Ebola patients died from the virus, representing a case fatality rate of approximately 88% of the 17 Hospital employees exposed to the disease, 13 individuals became ill and 11 died.

Since 1976, these have been multiple outbreak of Ebola Virus in Africa. Sudan, Gabon, Uganda and the Democratic Republic of the Congo, with a total of 1,594 deaths from the disease. Most of the outbreaks occurred in rural villages and were quickly curtain over the years, the fatality rate for EVD has varied been between 25-90% with some strains of the virus being much deadlier than others (WHO,2014). Early outbreak affected only small rural villages; however, as the disease infiltrates more populated areas, there is greater concern for disease spread speed. Fear has compounded the crisis while eroding social ties and exacerbating the impact of the epidemic, heading to the closure of schools, businesses and borders, reducing trade, halting investment and therefore reducing the prospect for growth in future years (UNDP,2014). Moreover, the EBOLA epidemic has affected key cash/export commodities, contributing to the reduction of household incomes and ultimately of purchasing power and food access of population (Magassouba N, et al. 2014)

It is on account of these that research of this nature would identify the trend and structure of Ebola outbreak and its impact on the demographic transition in Nigeria, West Africa and Africa as a whole.

1.2 Statement of the Problem

The Ebola virus disease outbreak was unprecedented, it spreads within densely populated urban environment and affects thousands of people. Given the prevalence of incidences of people infected with EVD by 2014, Africa accounting for more than 60 percent of the cumulative cases of EVD infection worldwide, (Ainsworth and over, 2014; owith regard to transmission risk in different contexts. One of the leading challenges in the West Africa Ebola virus disease (EVD) outbreak 2014/2015 was how best to quickly identify patients with Ebola, separating them from those without the disease. Since the situation varies between regions and countries, an earlier research in Nigeria indicates that there abound misconceptions as to the etiology and

transmission of the EVD. Hence, the application of meta-analysis avails data on risk of mortality in person with Ebola virus disease as predictors for Ebola causing a rise in morbidity and mortality from disease not related directly to Ebola itself.

1.3 Research question

This research will provide answers to the following questions in line with the research objectives

i. What is the risk of mortality in persons with Ebola virus?

ii. What is the heterogeneity on risk of mortality in persons with Ebola virus?

iii. Does the treatment of EVD favour survival or mortality using forest plots?

1.4 Objectives of the Study

The aim of this study is to review the risk of mortality in person with Ebola Virus Disease from 1976 – 2014 using Meta – Analysis.

The above aim is achieved through the following objectives

i. To assess the risk of mortality on person with Ebola Virus Disease.

ii. To determine whether there is heterogeneity or not on risk of mortality in the person with Ebola virus disease.

iii. To determine from the result of forest plot whether Treatment of EVD may favour survival or mortality.

1.5 Hypothesis

i. Ho; There is no risk of mortality in persons with Ebola virus

H_1; There is risk of mortality in persons with Ebola virus

ii. Ho; There is no heterogeneity on risk of mortality in persons with Ebola virus

H_1; There is heterogeneity on risk of mortality in persons with Ebola virus

iii. Ho; Treatment of EVD is of no consequence.

H_1: The treatment of EVD favours survival or mortality using forest plots.

1.6 Significance

Ebola Virus Disease (EVD) poses a significant health care challenge for a number of reasons, the first reason being that it is a virulent disease, causing significant death and illness in the affected communities. Virulence refers to the severity of a disease; it has a high mortality rate. As of April 8, 2015, the EVD epidemic in West Africa sickened over 25000 people and caused more than 10,000 deaths. Lefebure et.al (2014) performed a Meta-analysis using WHO data from 1976, different EVD outbreaks, and found an overall case mortality rate of 65.4% (C.I 95%, (54.6, 75.5)). Due to the severity of EVD symptoms caring for infected patients requires a great deal of time and resources. As a result, EVD indirectly increases morbidity and mortality among individuals with other serious health conditions by interrupting the normal provision of health care services (WHO, 2014), while the fatality numbers are clearly concerns, these are additional complicating factors associated with the disease. At this time, there is neither a vaccine for EVD, now is there any specific treatment for EVD. Therefore, care providers have limited tools available to prevent or show pathogenesis, and rely heavily on isolation and contact tracking practices. Delays in the identification of EVD greatly increase the chance of viral transmission, as one missed diagnosis can lead to a new chain of infection (Frieden et.al, 2014). The IOM (2003) points out that contact tracing is more difficult in heavily populated, mobile societies; globalization makes communicable disease management more challenging and increase the utilization of public health resources.

The personal protective equipment (PPE) needed for EVD management poses yet another hurdle for health care workers. Initial guidance from the CDC stated that health care workers should use standard contact and droplet precautions when caring for infected patients. However, when health care workers continued to become ill, it became apparent that (PPE) modifications were needed.

In October 2014, the CDC issued updated EVD PPE guidelines stating that individuals working with EVD patients must receive thorough training on EVD infection control practices, that PPE should cover all skin, and that a trained observer should oversea the process of donning and doffing PPE (2014g). These updated guidelines require a great level of PPE training and vigilance, and the purchasing of new supplier.

The cost of EVD- both financially and in terms of human suffering is significant. EVD is imparting impoverished countries, such as areas of the African continent that are already struggling economically. The World Bank estimates that West Africa could lose billions in loss gross domestic product (the World Bank Group, 2014).in addition to economic burdens;it's even difficult to measure the mental and physical pain of human suffering. Families have been separated and possessions destroyed in an effort to halt transmission of the virus; the psychological impact of the outbreak is severe enough that WHO has developed 60-page training document on the provision of psychological first aid (WHO, 2014c). Among Ebola survivors, the physical suffering also continues, as there are reports of lingering physical symptoms, including visual loss, muscle aches and fatigue (WHO, 2014d). One final reason that EVD poses a challenge to health care communities is because there is a significant amount of fear associated with the disease.

Many members of the general public know several things about EVD that it has an enormous and devastating effect on affected communities, that it has a high mortality rate, and currently there is no vaccine to prevent EVD. The newness of the illness, in conjunction with the high mortality rate and lack of preventive measures, generates considerable fear and anxiety. Research suggests that feelings, rather than statistical likelihood, often dictate one's perception of perceived risk. Slovic (2014) states that people perceive themselves to be at greater risk for

any disease that is unfamiliar, thought to be uncontrolled, considered to be poorly-understood by experts, and has fatal outcomes.

The excitement and media coverage of Ebola begs the question: does this outbreak pose a health risk for people outside the African continents? EVD is an emerging infectious disease (EID), an illness that has only recently been recognized as a threat to humans in a particular area. In this regard, it falls into the same category as other relatively new illness such as human immune deficiency virus (HIV), severe acute respiratory syndrome (SARS), or the swine flu. The impact of EIDs on a community can be enormous. For example, in 2013 SARS sickened approximately 8000 people, with a mortality rate of less than ten percent.

Emerging infectious disease can appear unexpectedly due to drug resistance, population changes, and international travel or alterations in human-animal contact (Henry J. Kaiser family foundation 2014). According to the institute of medicine (IOM), there is a need for an integrated system of networks aimed at preparing for, identifying and responding to disease outbreak (2003). Organization must have basic response capabilities in order to respond quickly and effectively. The IOM report states that EIDs will continue to be identified and there must be leaders ready to protect human against microbial threats.

Although the international community is making every effort to halt the spread of EVD, one cannot be certain where the disease may appear again. It's interesting to note that Sanchez et.al wrote a paper in 1995 calling on providers and public health agencies to be aware of the re-emergency of EVD. The warning was largely ignored, but serves as a reminder that one does not know when the next big public health threat will develop.

The primary reservoir of the Ebola virus is believed to be fruits bats. However, non-human primates, including chimpanzees, gorillas, and cynomolgus monkeys, and forest antelopes have been reported as possible vectors in transmission to humans, and EVD has caused devastating mortality in non-human-primate populations. Once infected, the symptoms of human EVD are

non-specific and typically include fever, headache, joint or muscle pains, sore throat, vomiting and / or diarrhea.

At the start of an infectious disease outbreak, it is critical to understand the transmission dynamics of the pathogen and to determine those at highest risk for infection or severe outcomes in the population(s) affected. This information is needed to develop interventions to reduce the spread of disease and to reduce morbidity and mortality in the affected populations. Real time analysis of any ongoing outbreak by analyzing detailed information collected on the confirmed, probable and suspected cases and deaths provides an opportunity to determine the stages of disease and areas where control measures can be applied. For example, knowledge of the incubation period distribution of the pathogen will inform the duration of time requires following up the contacts of cases to evaluate whether or not they become secondary cases. Additionally, information on the timing of symptom onset, isolation, hospitalization and outcome (either death or recovery) are important to understand EVD progression. Mathematical models which make use of available data early in an outbreak to estimate the outbreaks potential impact are increasingly used by public health policy makers to inform decision making around emerging and re-emerging pathogens. The purpose of the review was to collect all published epidemiological parameter estimates (reprinted in detailed tables containing estimates, and corresponding confidence intervals) estimated from past EVD outbreaks

1.7 Scope of the Study

This research work covers application of Meta-analysis on Ebola Virus Disease (EVD) in West Africa from (1976-2014).

1.8 Limitation of study

The research work supposed to cover all the African countries but due to inadequate materials, financial and time constraint the study shall cover West Africa

1.9 Definition of Terms

Mortality**:** is the rate of being mortal, or susceptible to deaths due to a specific cause.

Meta –Analysis: is the statistical procedure for combining data from multiple studies on particular studies.

Effect size: is a quantitative measure of the magnitude of a phenomenon.

Survival: is the act or fact of living or continuing longer than another person or things.

1.9.1 NOMENCLATURE

i. EVD: Ebola Virus Disease

ii. WHO: World Health Organization

iii. SUVD: Sudan Virus Disease

iv. IOM : Institute of Medicine

v. EID : Emerging Infectious Disease

vi. RESTV: Reston virus

vii. HIV : Human Immune Deficiency Virus

CHAPTER TWO

LITERATURE REVIEW

2.1 Conceptual Framework of Ebola Virus Outbreaks

The earliest described outbreak of a filovirus (Marburg (MBG) virus) was in 1976 in Germany and Yugoslavia. Cases of MBG virus infection occurred in South Africa in 1975 in Kenya in 1980, and again in Kenya in 1987. Epidemiologic surveys did not identify a reservoir; however, a bitting insect was suspected in South Africa (WHO, 2014).

Ebola (EBO) epidemics were recorded in the Democratic Republic of the Congo (DRC) and Sudan in 1976; investigation did not discover the virus in insects or Mammals. Ebo re-emerge with a single lethal case in Tandala, DRC, in 1977 and a new outbreak in Sudan in 1979. An outbreak due to a new subtype of the virus, EBO (Subtype Reston (EBO- R)) has occurred in a colony of cynomolgusmon - keys (Macacafascicularis) in a quarantine facility in Reston, Virginia in 1989 .The same virus was responsible for three further epizootics among monkeys in the united states in 1990,as well as one outbreak in Italy in 1992 . Investigation traced the source of all EBO -R outbreaks to a primate exports facility in the Philippines, but the mode of Contamination of this facility was not determined. Although African Green Monkeys (Cercopithecusaethiops) from Uganda where the first animals known to be infected with filovirus, the cycle of these viruses in nature remains a mystery.

In November 1994, ethologists studying the behavior of a community of chimpanzees (pan trolodytesverus) in the Tai national park, cote d'ivoire, found 8 dead chimpanzees and noted the absence of their individuals. An epidemiologic survey was done to elucidate the cause of these deaths Herein, we report the results of investigations that led to the identification of a new subtype of the virus, EBO (subtype Co'te d'ivoire (EBO- Cl)), in the blood of a researcher who was probably infected during a chimpanzee necropsy.

2.2 Signs and Symptoms of Ebola

Signs and symptoms of Ebola usually begin suddenly with influenza- like stage characterized by fatigue, fever, headaches, joint, muscles and abdominal pains, vomiting, diarrhea and loss of appetite are also common. Less common symptoms include the following: sore throat, chest pain, hiccups, breath and trouble swallowing. The average time between contracting the infections and the start of symptoms (incubation period) is 8 to 10 days but it varies between 2 and 21 days (George et al. 1999).

2.3 Theoretical Framework

Causes, Transmission, Reservoir and Virology of Ebola

EVD is caused by four or five viruses classified in the genus Ebola virus, family Filoviridae, and order Mononegaviral. The four disease causing viruses are Bundibugyo virus (BDBV), Sudan virus (SUDV), Tai forest virus (TAFV), and one called simply, Ebola Virus (EBOV, formerly Zaire Ebola Virus). Ebola virus is the sole member of the Zaire Ebola virus species, and the most dangerous of the known Ebola disease causing viruses, as well as being responsible for the largest number of outbreaks. The fifth virus, Reston virus (RESTV), is not thought to be disease- causing in humans (Fedmann H, Geisbert TW. 2011). The five Ebola viruses are closely related to the Marburg viruses.

In addition, it is not entirely clear how Ebola is spread. EVD is believed to occur after an Ebola virus is transmitted to an initial human by contact with infected animal's body fluids. Human to human transmission can occur via direct contact with blood or bodily fluids from an infected person (including embalming of an infected dead person) or by contact with contaminated medical equipment, particularly needle and springs. The potential for widespread EVD infections is considered low as the disease is only spread by direct contact with the secretions from someone

who is showing signs of infection. The quick onset of symptoms makes it easier to identity sick individuals and limits a person's ability to spread the disease by traveling. Because dead bodies are still infectious local traditional burial ritual may spread the disease. Semen may be infectious in survivors for up to 50 days; Medical workers who do not wear appropriate protective clothing may also contract the disease. In the past hospital - acquired transmission has occurred in African hospitals due to the reuse of needles and lack of universal precautions. Airborne transmission has not been documented during EVD outbreaks. They are, however, infectious as breathable 0.8−1.2Nm laboratory - generated droplets (Nkoghe D, Leroy EM, Toury-Mve M, et al. 2012). The virus has been shown to travel without contact from pigs to nonhuman primates, although the same study failed to achieve transmission in that manner between primates. Consequently, Bats drop partially eaten fruits and pulp, then land mammals such as gorillas and duikers feed on these fallen fruits.

This chain of events forms a possible indirect means of transmission from the natural host to animal populations, which has led to research towards viral shedding in the saliva of bats. Fruit production, animal behavior, and other factors vary at different times and places that may trigger outbreaks among animal populations. Moreover, Bats are considered the most likely natural reservoir of the EBOV plants, arthropods, and birds have also been considered. Bats were known to reside in the gotten factory, in which the first cases for the 1996 and 1979 outbreaks were employed, and they have also been implicated in Marburg virus infectious in 1975 and 1980.of 24plants species and 19 vertebrate species experimentally inoculated with EBOV, only bats became infected. The absence of clinical signs in these bats is characteristics of a reservoir species.

In a 2002- 2003 survey of 1,030 animals including 679 bats from Gabon and the Republic of the Congo, 13 fruits bats were found to contain EBOV, RNA fragments. As of 2005, three types of fruit bats (Hypsiqnathusmonstronus, Epomossfranqueti, and Myonycteristorquata) have been identified as being in contact with EBOV (Hoenen T. Safronetz D. Groseth A. et al. 2015). They are now

suspected to represent the EBOV reservoir hosts. Antibodies against Ebola Zaire and Reston viruses have been found in fruit bats in Bangladesh, thus identifying potential virus hosts and signs of the filoviruses in Asia. Between 1976 and 1998, in 30,000 mammals, birds, reptiles, amphibians and arthropods sampled from outbreak regions , no Ebola virus was detected apart from some genetic traces found in six rodents (Mussetulosus and praomys) and one shrew (Sylvisorexollula) collected from the central African Republic Traces of EBOV were detected in the carcasses of gorillas and chimpanzees during the outbreaks in 2001and 2003 ,which later became the source of human infections .However , the high lethality from infection in these species makes them unlikely as a natural reservoir. Transmission between natural reservoir and humans is rare, and outbreaks are usually traceable to a single case where an individual has handled the carcass of gorilla, chimpanzees or duiker. Fruits bats are also eaten by people in parts of West Africa where they are smoked, grilled or made into a spicy soup (Barrette RW, Metwally SA, Rowland JM, et al. 2009).

Like all mononegaviruses, Ebola virions contain linear non-segmented, single- strand ,noninfectious RNA genomes of negative polarity that possesses inverse -- complementary 3'and 5' termini do not possess a 5 cap, are not polyadenylated ,and are nor covalently linked to a protein .Ebola virus genomes are approximately 19 kilobase pairs long and contain seven genes in the order 3'UTR-Np-VP35-Vp40-- Gp-Vp30-- Vp24- L-5'UTR.The genomes of the fire different Ebola virus (BDBV, EBOV, RESTV,SUDV and TAFV) differ in sequence and the number and location of gene overlaps(WHO 2014). Also like all filoviruses, Ebola virions are filamentous particles that may appear in the shape of a shepherd’s crook or in the shape of a"U"or a "6", and they may be coiled, toroid, or branched.

In general, Ebola virions are 80nm in width, but vary somewhat in length. In general, the median particles of Ebola viruses range from 974 to 1,086nm (in contrast to Marburgvirus, whose median particle length was measured at 795-828nm) but particle as long as 14,000nm have been detected in tissueculture.Finally, Ebola Virus life cycle begins with virion attachment to specific cell- surface

receptors, followed by fusion of the virion envelope with cellular membranes and the concomitant release of the virus nude capsid into the cytosol. The viral RNA polymerase, encoded by the L gene, partially uncast the nucleocapsid and transcribes the genes to positive-strand MRN As, which are then translated into structural problems. Ebovirus RNA polymerase (L) bonds to a single promoter located at the 3' end of the genome. Transcription either terminates after a gene or continues to the next gene downstream. This means that genes close to the 3' end of genome are transcribed in the greatest abundance, whereas those toward the 5' end are least likely to be transcribed. the gene order is, therefore a simple but effective form of transcriptional regulation. The most abundant protein produced is the nucleoprotein, whose concentration in the cell determines when in switches from gene transcription to genome replication (Korte peter MG, Bausch DG Bray M. 2011). Replication results in full- length ,positive strand antigenomes that are, in turn, transcribed into negative -strand antigenomes that are, in turn, transcribed into negative-strand virus progeny genome copy .Newly synthesized structural proteins and genome self - assemble and accumulate near the inside of the cell membrane .virions bad off from the cell ,gaining their envelopes from the cellular membrane they bud from ,The mature progeny particles then affect other cells to repeat the cycle .The Ebola virus genetic are difficult to study due to its virulent nature.

2.4 Pathophysiology and Diagnosis

Endothelial cells, mononuclear phagocytes and hepatocytes are the main target of infection. After infection ,a secreted glycoprotein (SGP) known as the Ebola virus glycoprotein (GP) is synthesized .Ebola replication overwhelms protein synthesis of infected cells and host immune defense .The GP form a trimesic complex ,which binds the virus to the endothelial cells living the interiors surface of blood vessels .The SGP forms a dimeric protein that interferes with the signaling of neutrophils ,a type of white blood cell ,which allows the virus to evade the immune system by inhibiting early steps of neutrophil activation. These white blood cells also serve as carries to transport the virus

throughout the entire body to places such as the lymph nodes, liver, lungs and spleen (Lo TQ. Marston BJ. Dahl BA. De Cock KM 2017).

The presence of viral particles and cell damage resulting from budding causes the release of cytokines (to be specific, TNF- x, IL-6 IL-8, etc) which are the signaling molecules for fever and inflammation the cytopathic effect, from infection in the endothelial.

Cells results in a loss of vascular integrity. This loss in vascular integrity responsible for cells adhesion to the inter - cellular structure, and damage to the lived, which leads tocoagulopathy (Briand S; Bertherat E; Cox P; & et al. 2014).

The medical history ,especially travel and work history along with exposure to wildlife are important to suspect the diagnosis of EVD .The diagnosis is confirmed by isolating the virus ,detecting its RNA or proteins or detecting antibodies against the virus in a person 's blood isolating the virus by cell culture detecting the viral RNA by polymerase chain reaction (PCR) and detecting proteins by enzymes linked immunosorbent assay (ELISA) is effective early and in those who have died from the disease and in those who recover .During an outbreak ,virus isolation is often not feasible .the most common diagnostic methods are therefore real time PCR and ELISA detection of proteins which can be performed in field of mobile hospitals filovirus's can be seen and identified In cell culture by electron microscopy due to their unique filamentous shapes, but electron microscopy cannot tell the difference between the various fila virions despite there being some length differences.

The general Ebola virus and Marburgvirus were originally classified as the species of the now - obsolete filovirus genus. on march 1998, the vertebrate virus subcommittee proposed in the international committee on Taxonomy of viruses (lCTV) to change the filoviridae family with two specific general Ebola - like viruses and Marburg - like viruses. This proposal was implemented in Washington, DC on April 2001 and in Paris on July 2002 on 2000, another proposal was made in

Washington DC, to charge the “like viruses “to" viruses" resulting in today's Ebola virus and Marburg virus.

Rates of genetic change are 100 times slower than influenza A in humans, but on the same magnitude as those of hepatitis B. Extrapolating backwards using these rates indicates that Ebolavirus and Marburgvirus diverged several thousand years ago.

However, paleoviruses (genomic fossils) of filoviruses (Filoviridae) found in mammals indicate that the family itself is at least tens of millions of years old. Fossilized viruses that are closely related to Ebolaviruses have been found in the genome of the Chinese hamster (Bogoch II. Creatore MI. Cetron MS. Et al. 2015).

The symptoms of EVD are similar to those of Marburg virus disease. It can also easily be confused with many other diseases common in Equatorial Africa such as other viral hemorrhagic fevers, falciparum malaria, typhoid fever, shigellosis, rickettsia diseases such as typhus, cholera, gram-negative septicemia, borreliosis such as relapsing fever or EHEC enteritis. Other infectious diseases that should be included in the differential diagnosis include the following: leptospirosis, scrub typhus, plague, Q fever, candidiasis, histoplasmosis, trypanosomiasis, visceral leishmaniasis, hemorrhagic smallpox, measles, and fulminant viral hepatitis. Non-infectious diseases that can be confused with EVD are acute promyelocytic leukemia, hemolytic uremic syndrome, snake envenomation, clotting factor deficiencies/platelet disorders, thrombotic thrombocytopenic purpura, hereditary hemorrhagic telangiectasia, Kawasaki disease and even warfarin poisoning.

2.5 Epidemiology

The disease typically occurs in outbreaks in tropical regions of Sub-Saharan Africa. From 1976 (when it was first identified) through 2013, the World Health Organization reported 1,716 confirmed cases. The largest outbreak to date is the ongoing 2014 West Africa Ebola virus

outbreak, which is affecting Guinea, Sierra Leone, Liberia and Nigeria as of 13 August, 2,127 cases have been identified, with 1,145 deaths.

The first identified case of Ebola was on 26 August 1976, in Yambuku, a small rural village in Mongala District in northern Democratic Republic of the Congo (then known as Zaire). The first victim, and the index case for the disease, was village school headmaster Mabalo Lokela, who had toured an area near the Central African Republic border along the Ebola River between 12–22 Augusts. On 8 September he died of what would become known as the Ebola virus species of the Ebolavirus. Subsequently a number of other cases were reported, almost all centered on the Yambuku mission hospital or having close contact with another case. 318 cases and 280 deaths occurred in the DRC. The Ebola outbreak was contained with the help of the World Health Organization and transport from the Congolese air force, by quarantining villagers, sterilizing medical equipment, and providing protective clothing. The virus responsible for the initial outbreak, first thought to be Marburg virus was later identified as a new type of virus related to Marburg, and named after the nearby Ebola River. Another Ebola virus, the Sudan virus species, was also identified that same year when an outbreak occurred in Sudan, affecting 284 people and killed 151 (Feldmann H, Geisbert TW. 2011).

The second major outbreak occurred in 1995 in the Democratic Republic of Congo, affecting 315 and killed 254. The next major outbreak occurred in Uganda in 2000, affecting 425 and killed 224; in this case the Sudan virus was found to be the Ebolavirus species responsible for the outbreak. In 2003 there was an outbreak in the Republic of Congo that affected 143 and killed 128, a death rate of 90%, the largest to date.

In August 2007, 103 people were infected by a suspected hemorrhagic fever outbreak in the village of Kampungu, Democratic Republic of the Congo. The outbreak started after the funerals of two

village chiefs, and 217 people in four villages fell ill. The 2007 outbreak eventually affected 264 individuals and resulted in the deaths of 187.

On 30 November 2007, the Uganda Ministry of Health confirmed an outbreak of Ebola in the Bundibugyo District in Western Uganda. After confirmation of samples tested by the United States National Reference Laboratories and the Centers for Disease Control, the World Health Organization confirmed the presence of a new species of Ebolavirus, which was tentatively named Bundibugyo. The WHO reported 149 cases of this new strain and 37 of those led to deaths.

The WHO confirmed two small outbreaks in Uganda in 2012. The first outbreak affected 7 people and resulted in the death of 4 and the second affected 24, resulting in the death of 17. The Sudan variant was responsible for both outbreaks.

On 17 August 2012, the Ministry of Health of the Democratic Republic of the Congo reported an outbreak of the Ebola-Bundibugyo variant in the eastern region. Other than its discovery in 2007, this was the only time that this variant has been identified as the Ebola virus responsible for an outbreak. The WHO revealed that the virus had sickened 57 people and claimed 29 lives. The probable cause of the outbreak was tainted bush meat hunted by local villagers around the towns of Isiro and Viadana.

Ebola virus was first isolated in 1976 during outbreaks of Ebola hemorrhagic fever in the Democratic Republic of the Congo (then Zaire) and Sudan. The strain of Ebola that broke out in the Democratic Republic of the Congo had one of the highest case fatality rates of any human virus, 88%.

The name of the disease originates from the first recorded outbreak in 1976 in Yambuku, Democratic Republic of the Congo, which lies on the Ebola River. In late 1989, Hazelton Research Products' Reston Quarantine Unit in Reston, Virginia suffered a mysterious outbreak of fatal illness (initially diagnosed as Simian hemorrhagic fever virus (SHFV)) among a shipment of crab-eating

macaque monkeys imported from the Philippines. Hazelton's veterinary pathologist sent tissue samples from dead animals to the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) at Fort Detrick, Maryland, where a laboratory test known as an ELISA assay showed antibodies to Ebola virus. An electron microscopist from USAMRIID discovered filovirusessimilar in appearance to Ebola in the tissue samples sent from Hazelton Research Products' Reston Quarantine Unit (WHO 2014).

Shortly afterward, a US Army team headquartered at USAMRIID went into action to euthanize the monkeys which had not yet died, bringing those monkeys and those which had already died of the disease to Ft. Detrick for study by the Army's veterinary pathologists and virologists, and eventual disposal under safe conditions.

Blood samples were taken from 178 animal handlers during the incident. Of those six animal handlers eventually reconverted. When the handlers did not become ill, the CDC concluded that the virus had a very low pathogenicity to humans. The Philippines and the United States had no previous cases of Ebola infection, and upon further isolation, researchers concluded it was another strain of Ebola, or a new filovirus of Asian origin, which they named Reston ebolavirus (REBOV) after the location of the incident.

The research has therefore been undertaken purposely to fill methodological and empirical review gap. This provides literature that could be useful to policy makers and academics in explaining the relationship between Ebola outbreak in Nigeria, West Africa and Africa and its impact on demographic transition in Africa (Bray M. 2005).

2.6 Empirical Literature of Ebola Virus outbreaks

As of April 8, 2015, the EVD epidemic in West Africa sickened over 25000 people and caused more than 10,000 deaths (CDC, 2014c). Lefebure et.al (2014) performed a Meta-analysis using WHO data from 1976, different EVD outbreaks, and found an overall case mortality rate of 65.4%

(C.I 95%, (54.6, 75.5)). Due to the severity of EVD symptoms caring for infected patients requires a great deal of time and resources. As a result, EVD indirectly increases morbidity and mortality among individuals with other serious health conditions by interrupting the normal provision of health care services (WHO, 2014), while the fatality numbers are clearly concerns, these are additional complicating factors associated with the disease. At this time, there is neither a vaccine for EVD, now is there any specific treatment for EVD. Therefore, care providers have limited tools available to prevent or show pathogenesis, and rely heavily on isolation and contact tracking practices. Delays in the identification of EVD greatly increase the chance of viral transmission, as one missed diagnosis can lead to a new chain of infection (Frieden et al. 2014). The IOM (2003) points out that contact tracing is more difficult in heavily populated, mobile societies; globalization makes communicable disease management more challenging and increase the utilization of public health resources.

The personal protective equipment (PPE) needed for EVD management poses yet another hurdle for health care workers. Initial guidance from the CDC stated that health care workers should use standard contact and droplet precautions when caring for infected patients. However, when health care workers continued to become ill, it became apparent that (PPE) modifications were needed. In October 2014, the CDC issued updated EVD PPE guidelines stating that individuals working with EVD patients must receive thorough training on EVD infection control practices, that PPE should cover all skin, and that a trained observer should oversea the process of donning and doffing PPE (2014). These updated guidelines require a great level of PPE training and vigilance, and the purchasing of new supplier.

The cost of EVD- both financially and in terms of human suffering is significant. EVD is imparting impoverished countries, such as areas of the African continent that are already struggling economically. The World Bank estimates that West Africa could lose billions in loss gross domestic product (WHO 2014). In addition to economic burdens; it’s even difficult to measure the

mental and physical pain of human suffering. Families have been separated and possessions destroyed in an effort to halt transmission of the virus; the psychological impact of the outbreak is severe enough that WHO has developed 60-page training document on the provision of psychological first aid (WHO, 2014c). Among Ebola survivors, the physical suffering also continues, as there are reports of lingering physical symptoms, including visual loss, muscle aches and fatigue (WHO, 2014). One final reason that EVD poses a challenge to health care communities is because there is a significant amount of fear associated with the disease.

Many members of the general public know several things about EVD that it has an enormous and devastating effect on affected communities, that it has a high mortality rate, and currently there is no vaccine to prevent EVD. The newness of the illness, in conjunction with the high mortality rate and lack of preventive measures, generates considerable fear and anxiety. Research suggests that feelings, rather than statistical likelihood, often dictate one's perception of perceived risk. Slovic (2014) states that people perceive themselves to be at greater risk for any disease that is unfamiliar, thought to be uncontrolled, considered to be poorly-understood by experts, and has fatal outcomes.

The excitement and media coverage of Ebola begs the question: does this outbreak pose a health risk for people outside the African continents? EVD is an emerging infectious disease (EVD), an illness that has only recently been recognized as a threat to humans in a particular area. In this regard, it falls into the same category as other relatively new illness such as human immune deficiency virus (HIV), severe acute respiratory syndrome (SARS), or the swine flu. The impact of EIDs on a community can be enormous. For example, in 2013 SARS sickened approximately 8000 people, with a mortality rate of less than ten percent.

Emerging infectious disease can appear unexpectedly due to drug resistance, population changes, and international travel or alterations in human-animal contact (Henry J. Kaiser family foundation

2014). According to the institute of medicine (IOM), there is a need for an integrated system of networks aimed at preparing for, identifying and responding to disease outbreak (2003). Organization must have basic response capabilities in order to respond quickly and effectively. The IOM report states that EIDs will continue to be identified and there must be leaders ready to protect human against microbial threats.

Although the international community is making every effort to halt the spread of EVD, one cannot be certain where the disease may appear again. It's interesting to note that Sanchez et al. wrote a paper in 1995 calling on providers and public health agencies to be aware of the re-emergency of EVD. The warning was largely ignored, but serves as a reminder that one does not know when the next big public health threat will develop. The purpose of the review was to collect all published epidemiological parameter estimates (reprinted in detailed tables containing estimates, and corresponding confidence intervals) estimated from past EVD outbreaks.

(Hilary *et* al.2017) Asymptomatic Ebola virus infection could greatly influence transmission dynamics, but there is little consensus on how frequently it occurs or even if it exists. These research summaries the available evidence on seroprevalence of Ebola, Sudan and Bundibugyo virus IgG in people without known Ebolavirus disease. Through systematic review, we identified 51 studies with seroprevalence results in sera collected from 1961 to 2016. We tabulated findings by study population, contact, assay, antigen and positivity threshold used, and present seroprevalence point estimates and 95% confidence intervals. We classified sampled populations in three groups: those with household or known case-contact; those living in outbreak or epidemic areas but without reported case-contact; and those living in areas with no recorded cases of ebolavirus disease. Meta-Analysis was performed only in the known case-contact group since this is the only group with comparable exposures between studies. Eight contact studies fitted our inclusion criteria, giving an overall estimate of seroprevalence in contacts with no reported symptoms of 3.3% (95% CI 2.4–4.4, $P<0.001$), but with substantial heterogeneity.

Meta-analysis was performed using the Freeman Turkey arcsine square root transformation method and ‘fixed effects’ (weighted average) inverse variance (*metaprop,* STATA) on the eight study populations with known-case contact. ‘fixed effects’ (weighted average) model as contact should give similar risks in different contexts, and because random effects models give too much weight to small studies pooled summary estimate was present for the group with known contact exposure. Base on the review the researcher does not show summary estimates for the groups covering subjects living in outbreak areas but without reported case-contact, or drawn from general populations in locations without known EVD as these populations are likely to have very different exposure levels so an overall summary estimate of prevalence would be meaningless.

CHAPTER THREE

3.1 Research Design

Methods and Materials:

Identification of relevant existing literature was performed by an online search in MEDLINE, Google Scholar and relevant Journals for studies published. The MESH headings (keywords) included “Ebola” and “symptom” or “clinical” or “Suspect”.

Statistical approach to analysis of data involves review of meta- analysis

3.2 Method of Data Collection

The data for this study are secondary in nature. The data were collected from World Health Statistical data base from the year 1976-2014. Subsequently the data would be analyzed using Meta-Analysis

3.3 Model Specification

There are two models used in Meta-Analysis, the fixed effect model and the random effects model. The two make different assumptions about the nature of the studies, and these assumptions lead to different definitions for the combined effect, and different mechanisms for assigning weights.

Under the fixed effect model, we assume that there is one true effect size which is shared by all the included studies. It follows that the combined effect is our estimate of this common effect size.

By contrast, under the random effects model we allow that the true effect could vary from study to study. For example, the effect size might be little higher if the subjects are older, or more educated, or healthier, and so on. The studies included in the Meta-Analysis are assumed to be a random sample of the relevant distribution of effects, and the combined effect estimates the mean effect in this distribution.

Computing a Combined Effect

Under the fixed effect model all studies are estimating the same effect size, and so we can assign weights to all studies based entirely on the amount of information captured by that study. A large study would be given the lion's share of the weight, and a small study could be largely ignored.

By contrast, under the random effects model we are trying to estimate the mean of a distribution of true effects. Large studies may yield more precise estimates than small studies, but each study is estimating a different effect size, and we want to be sure that all of these effect sizes are included in our estimate of the mean. Therefore, as compared with the fixed effect model, the weights assigned under random effects are more balanced. Large studies are less likely to dominate the analysis and small studies are less likely to be trivialized.

Precision of the Combined Effect

Under the fixed effect model the only source of error in our estimate of the combined effect is the random error within studies. Therefore, with a large enough sample size the error will tend toward zero. This holds true whether the large sample size is confined to one study or distributed across many studies (Hedgs, L.V. 1982).

By contrast, under the random effects model there are two levels of sampling and two levels of error. First, each study is used to estimate the true effect in a specific population. Second, all of the true effects are used to estimate the mean of the true effects. Therefore, our ability to estimate the combined effect precisely will depend on both the number of subjects within studies (which addresses the first source of error) and also the total number of studies (which addresses the second).

3.4 Flow Diagram on the Risk of mortality in Ebola Virus Disease Patients

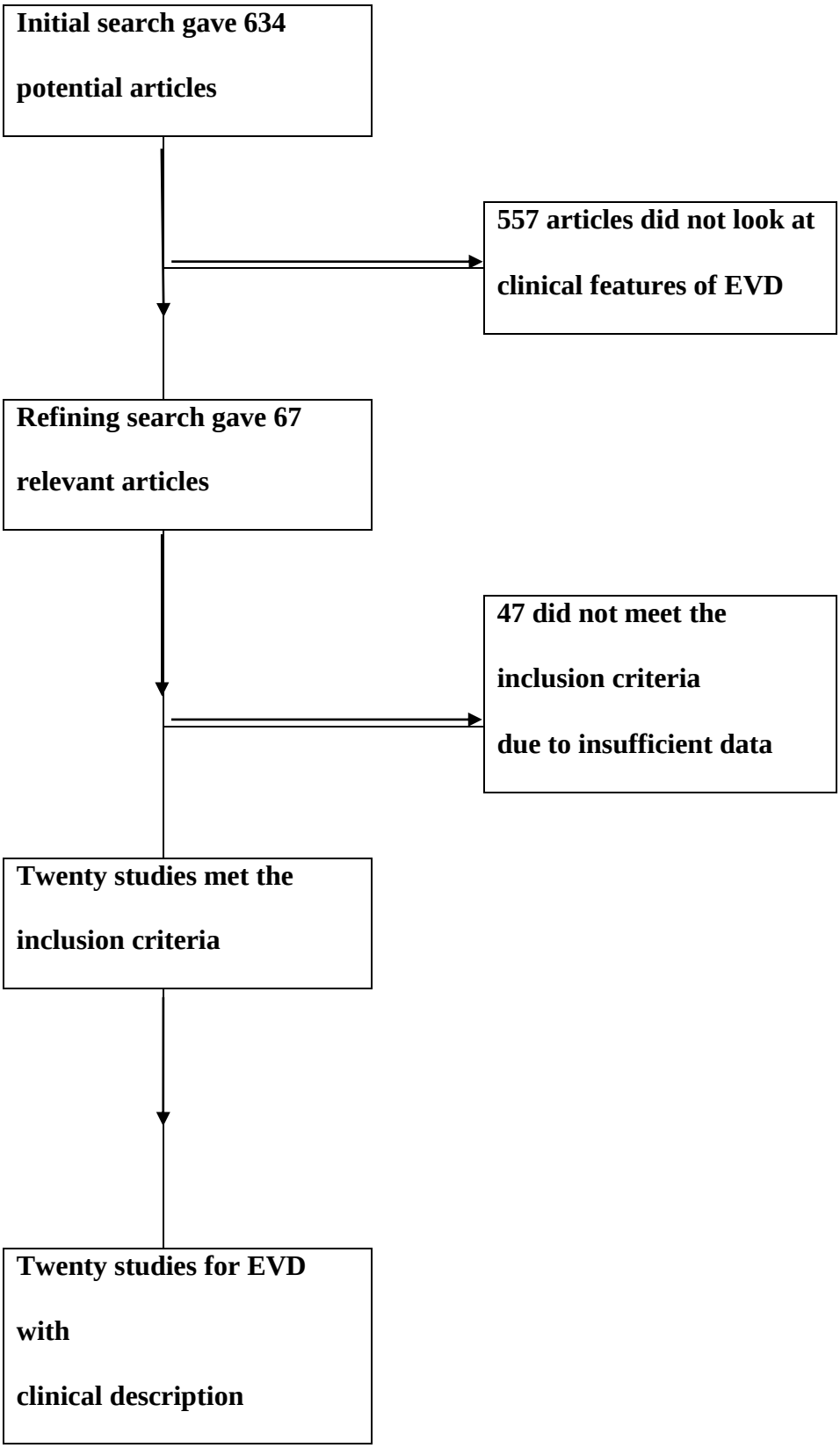
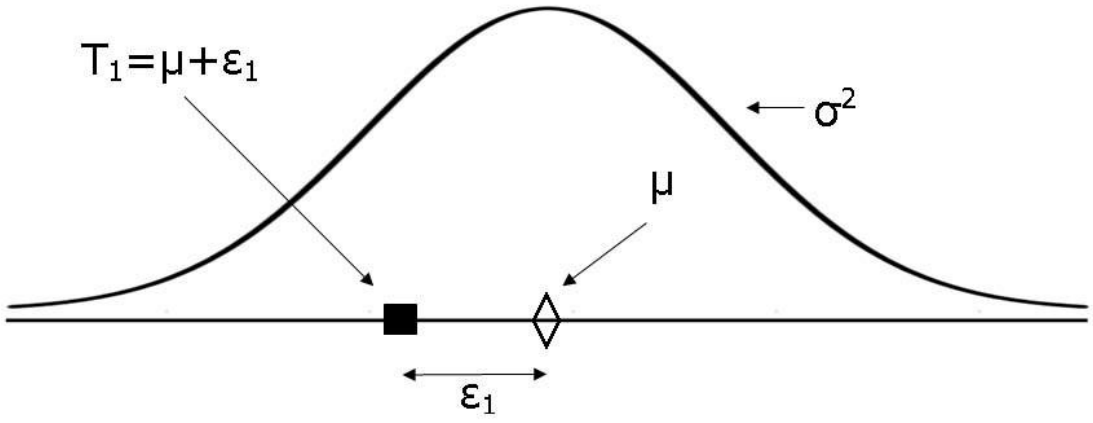


Fig 3.4: Flow diagram for selected 20 studies for review and Meta-Analysis

3.5 Fixed effect model

Definition of a combined effect

In a fixed effect analysis, we assume that all the included studies share a common effect size, μ. The observed effects will be distributed about μ, with a variance σ2 that depends primarily on the sample size for each study.



Fixed effect model. The observed effects are sampled from a 2 distribution with true effect μ, and variance σ. The observed effect T_1 is equal to $+\varepsilon_i$

In this schematic the observed effect in Study 1, T_1, is a determined by the common effect μ plus the within-study error ε_1. More generally, for any observed effect T_i,

$$T_i=\mu+e_i \qquad (3.1)$$

3.5.1 Assigning weights to the studies

In the fixed effect model there is only one level of sampling, since all studies are sampled from a population with effect size μ. Therefore, we need to deal with only one source of sampling error within studies.

Since our goal is to assign more weight to the studies that carry more information, we might propose to weight each study by its sample size, so that a study with 1000 subjects would get 10 times the weight of a study with 100 subjects. This is basically the approach used, except that we assign weights based on the inverse of the variance rather than sample size. The inverse variance is roughly proportional to sample size, but is a more nuanced measure (see notes), and serves to minimize the variance of the combined effect.

Concretely, the weight assigned to each study is

$$w_i = \frac{1}{w_i} \tag{3.2}$$

Where vi is the within-study variance for study (i). The weighted mean (T •) is then computed

$$\overline{T}. = \frac{\sum_{i=1}^{k} w_i T_i}{\sum_{i=1}^{k} w_i} \tag{3.3}$$

That is, the sum of the products $w_i T_i$ (effect size multiplied by weight) divided by the sum of the weights. The variance of the combined effect is defined as the reciprocal of the sum of the weights, or

$$V. = \frac{1}{\sum_{I=1}^{K} w_i} \tag{3.4}$$

and the standard error of the combined effect is then the square root of the variance,

$$SE(\overline{T}.) = \sqrt{V}. \tag{3.5}$$

The 95% confidence interval for the combined effect would be computed as

$$\text{Lower Limit } \overline{T}. - 1.96 \times SE(\overline{T}.) \tag{3.6}$$

$$\text{Upper Limit } \overline{T}. + 1.96 \times SE(\overline{T}.) \tag{3.6}$$

Finally, if one were so inclined, the Z-value could be computed using

$$Z = \frac{\overline{T}.}{SE(\overline{T}.)} \tag{3.7}$$

For a one-tailed test the p-value would be given by

$$p = 1 - \Phi(|Z|) \tag{3.8}$$

(Assuming that the effect is in the hypothesized direction), and for a two-tailed test by

$$P^* = 2[1 - \Phi|Z^*|] \tag{3.9}$$

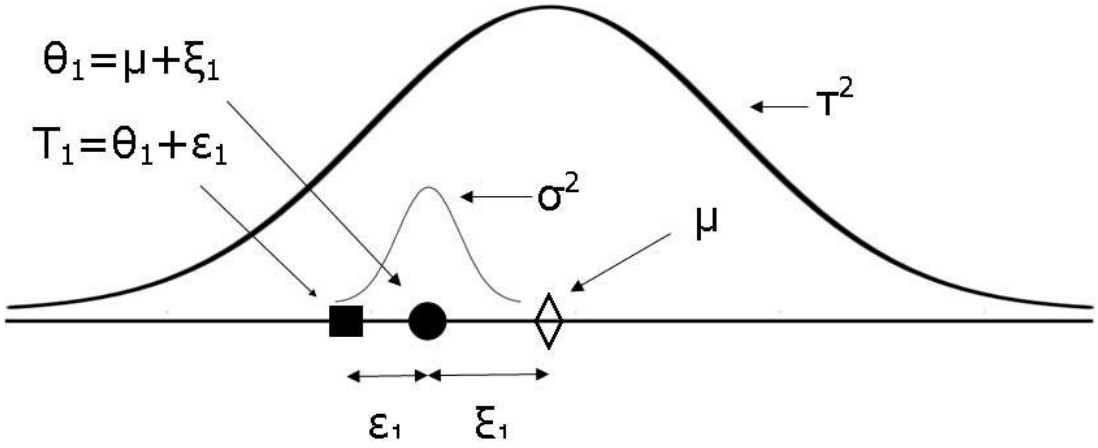
Where Φ is the standard normal cumulative distribution function.

3.6 Random Effects Model

The fixed effect model, discussed above, starts with the assumption that the true effect is the same in all studies. However, this is a difficult assumption to make in many (or most) systematic reviews. When we decide to incorporate a group of studies in a meta-analysis, we assume that the studies have enough in common that it makes sense to synthesize the information. However, there is generally no reason to assume that they are "identical" in the sense that the true effect size is exactly the same in all the studies.

3.6.1 Definition of a Combined Effect

Rather than assume that there is one true effect, we allow that there is a distribution of true effect sizes. The combined effect therefore cannot represent the one common effect, but instead represents the mean of the population of true effects.



Random effects model. The observed effect T_2 is a sampled from a distribution with true effect θ_1, and variance σ. The true effect $\theta_{1,}$ in turn, is sampled from a distribution with mean μ and variance τ_2.

In this schematic the observed effect in Study 1, T_1, is a determined by the true effect θ_1 plus the within-study error ε_1. In turn, θ_1, is determined by the mean of all true effects, μ and the between-study error ξ_1. More generally, for any observed effect T_i,

$$T_i = \theta_i + e_i = \mu_i + \varepsilon_i + e_i \qquad (3.10)$$

3.6.2 Assigning Weights to the Studies

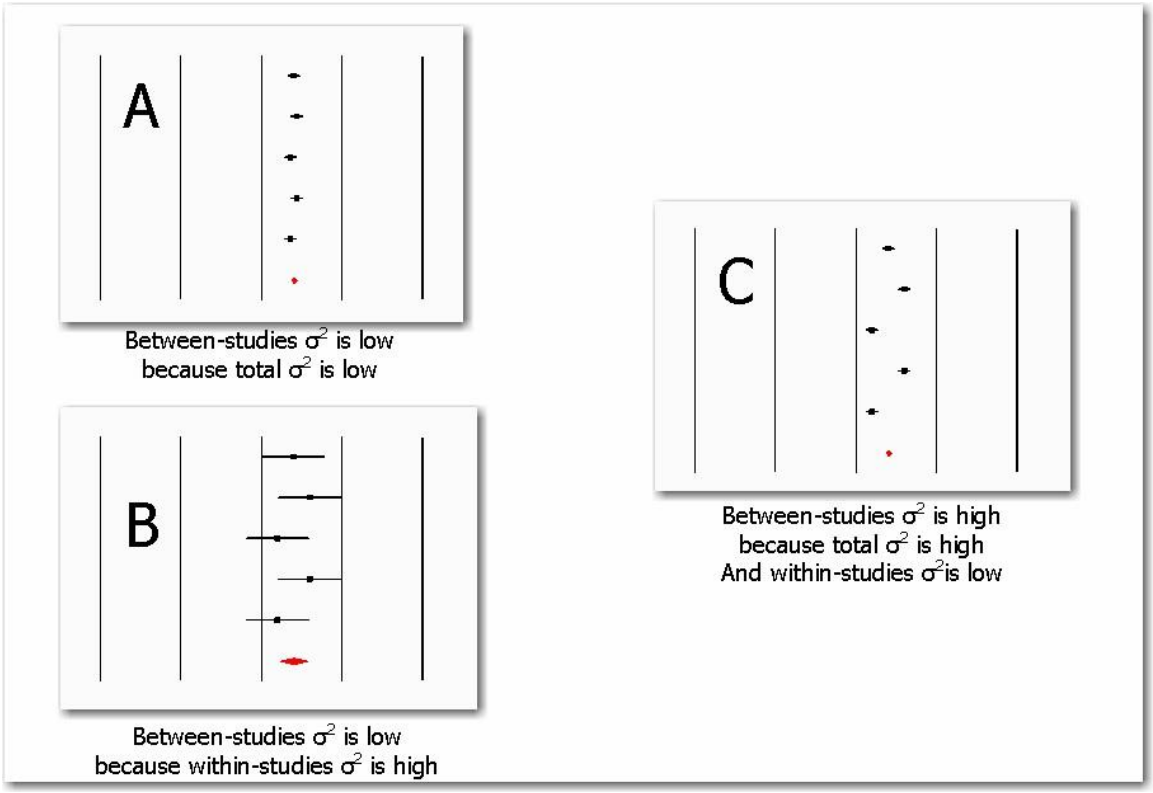
Under the random effects model, we need to take account of two levels of sampling, and two sources of error. First, the true effect sizes θ are distributed about μ with a variance τ^2 that reflects the actual distribution of the true effects about their mean. Second, the observed effect T for any given θ will be distributed about that θ with a variance σ^2 that depends primarily on the sample size for that study. Therefore, in assigning weights to estimate μ, we need to deal with both sources of sampling error – within studies (e), and between studies (ε).

Decomposing the Variance

The approach of a random effects analysis is to decompose the observed variance into its two component parts, within-studies and between-studies, and then use both parts when assigning the weights. The goal will be to reduce both sources of imprecision.

The mechanism used to decompose the variance is to compute the total variance (which is observed) and then to isolate the within-studies variance. The difference between these two values will give us the variance between-studies, which is called Tau-squared (τ^2).

Consider the three graphs in the following figure.



In (A), the studies all line up pretty much in a row. There is no variance between studies, and therefore tau-squared is low (or zero).

In (B) there is variance between studies, but it is fully explained by the variance within studies. Put another way, given the imprecision of the studies, we would expect the effect size to vary

somewhat from one study to the next. Therefore, the between-studies variance is again low (or zero).

In (C) there is variance between studies. And, it cannot be fully explained by the variance within studies, since the within-study variance is minimal. The excess variation (between-studies variance), will be reflected in the value of tau-squared.

It follows that tau-squared will increase as either the variance within-studies decreases and/or the observed variance increases.

This logic is operationalized in a series of formulas. We will compute Q, which represents the total variance, and df, which represents the expected variance if all studies have the same true effect. The difference, Q - df, will give us the excess variance. Finally, this value will be transformed, to put it into the same scale as the within-study variance. This last value is called Tau-squared.

The Q statistic represents the total variance and is defined as

$$Q = \sum_{i=1}^{k} \mathrm{W}_i(\mathrm{T}_i - \overline{\mathrm{T}}_i)^2 \qquad (3.11)$$

That is, the sum of the squared deviations of each study (*Ti*) from the combined mean (*T.*). Note the "w_i" in the formula, which indicates that each of the squared deviations is weighted by the study's inverse variance. A large study that falls far from the mean will have more impact on *Q* than would a small study in the same location. An equivalent formula, useful for computations, is this allows us to compute the between-studies variance, τ^2, as

$$Q = \sum_{\mathrm{i}=1}^{k} w_i \mathrm{T}_i^2 - \frac{\left(\sum_{i=1}^{k} w_i T_i\right)^2}{w_i} \qquad (3.12)$$

Since *Q* reflects the total variance, it must now be broken down into its component parts. If the only source of variance was within-study error, then the expected value of

Q would be the degrees of freedom for the meta-analysis (*df*) where

$$df = (Number\ Studies) - 1 \tag{3.13}$$

This allows us to compute the between-studies variance, $\tau 2$, as

$$\tau^2 = \begin{cases} \frac{Q-df}{C} & \text{if } Q > df \\ 0 & \text{if } Q \leq df \end{cases} \tag{3.14}$$

Where

$$C = \sum w_i - \frac{\sum w_i^2}{\sum w_i} \tag{3.15}$$

The numerator, *Q - df*, is the excess (observed minus expected) variance. The

Denominator, *C*, is a scaling factor that has to do with the fact that *Q* is a weighted sum of squares. By applying this scaling factor, we ensure that tau-squared is in the same metric as the variance within-studies.

Assigning weights under the random effects model

In the fixed effect analysis each study was weighted by the inverse of its variance. In the random effect's analysis, too, each study will be weighted by the inverse of its variance. The difference is that the variance now includes the original (within-studies) variance plus the between-studies variance, tau-squared. Note the correspondence between the formulas here and those in the previous chapter. We use the same notations, but add a (*) to represent the random effects version. Concretely, under the random effects model the weight assigned to each study is

Note the correspondence between the formulas here and those in the previous chapter. We use the same notations, but add a (*) to represent the random effects version. Concretely, under the random effects model the weight assigned to each study is

$$W_i^* = \frac{1}{W_i^*} \tag{3.16}$$

Where v_i* is the within-study variance for study (i) plus the between-studies variance, tau-squared. The weighted mean ($T\bullet$ *) is then computed as

$$\overline{\mathrm{T}}_{i}^{*} = \frac{\sum_{i=1}^{\mathrm{k}} w_i^{*}\mathrm{T}_i}{\sum_{i=1}^{k} w_i^{*}} \tag{3.17}$$

That is, the sum of the products (effect size multiplied by weight) divided by the sum of the weights.

The variance of the combined effect is defined as the reciprocal of the sum of the weights, or

$$V^{*} = \frac{1}{\sum_{i=1}^{k} w_i^{*}} \tag{3.18}$$

and the standard error of the combined effect is then the square root of the variance,

$$\mathrm{SE}(\overline{\mathrm{T}}_{\cdot}^{*}) = \sqrt{\mathrm{V}_{\cdot}^{*}} \tag{3.19}$$

The 95% confidence interval for the combined effect would be computed as

$$\text{Lower Limit}^{*} = \overline{T}_{\cdot}^{*} - 1.96 \times \mathrm{SE}(\overline{\mathrm{T}}_{\cdot}^{*}) \tag{3.20}$$

$$\text{Lower Limit}^{*} = \overline{T}_{\cdot}^{*} + 1.96 \times \mathrm{SE}(\overline{\mathrm{T}}_{\cdot}^{*}) \tag{3.21}$$

Finally, if one were so inclined, the Z-value could be computed using

$$\mathrm{Z}^{*} = \frac{\overline{\mathrm{T}}_{\cdot}^{*}}{\mathrm{SE}\overline{\mathrm{T}}_{\cdot}^{*}} \tag{3.22}$$

The one-tailed p-value (assuming an effect in the hypothesized direction) is given

$$\mathrm{P}^{*} = 1 - \Phi(|\mathrm{Z}^{*}|) \tag{3.13}$$

and the two-tailed p-value by

$$\mathrm{P}^{*} = 2[1 - \Phi|\mathrm{Z}^{*}|] \tag{3.24}$$

Where Φ is the standard normal cumulative distribution function.

3.7 Techniques for Data Collection

The fixed effect and random effects models represent two conceptually different approaches.

Fixed Effect

The fixed effect model assumes that all studies in the meta-analysis are drawn from a common population. Put another way, all factors which could influence the effect size are the same in all the study populations, and therefore the effect size is the same in all the study populations. It follows that the observed effect size varies from one study to the next only because of the random error inherent in each study.

Random Effects

By contrast, the random effects model assumes that the studies were drawn from populations that differ from each other in ways that could impact on the treatment effect. For example, the intensity of the intervention or the age of the subjects may have varied from one study to the next. It follows that the effect size will vary from one study to the next for two reasons. The first is random error within studies, as in the fixed effect model. The second is true variation in effect size from one study to the next.

Definition of a combined effect

The meaning of the "combined effect" is different for fixed effect vs. Random effects analyses.

Fixed effect

Under the fixed effect model there is one true effect size. It follows that the combined effect is our estimate of this value.

Random Effects

Under the random effects model there is not one true effect size, but a distribution of effect sizes. It follows that the combined estimate is not an estimate of one value, but rather is meant to be the average of a distribution of values.

Computing the Combined Effect

These differences in the definition of the combined effect lead to differences in the way the combined effect is computed.

Fixed effect

Under the fixed effect model, we assume that the true effect size for all studies is identical, and the only reason the effect size varies between studies is random error. Therefore, when assigning weights to the different studies we can largely ignore the information in the smaller studies since we have better information about the same effect size in the larger studies.

3.8 Estimation of Parameters for Meta-Analysis

To compute meta-analysis, the following parameters must be computed from each study

The effect size (ES) is computed as

$$ES = \frac{\mu 1+\mu 2}{(\sigma 1+\sigma 2)/_2} \text{For i = 1,2, 3……...} \quad (3.25)$$

Where $\mu 1$ and $\mu 2$ are the study$i$ mean, and $\sigma 1$ and $\sigma 2$ are the study$i$ standard deviation

The study effect size from response variable by the following formula;

The study weight or inverse of variance computed as in equations (1.2) and (2.6)

$W_i = \frac{1}{V_i}$ where V_i is the within-study variance for each study$i$. (3.26)

of the sum of the weights

V. = $\frac{1}{W_i}$ where W_i is the weight of the study i. (3.27)

The Variance (V_y) is computed as

$$V_y = \frac{n1+n2}{n1+n2} + \frac{ES^2}{2(n1+n2)} V_y \quad (3.28)$$

Where n_i is the sample of the study i.

And the standard error of the combined effect is then the square root of the variance.

Moderators/covariates (independent variables) of interest in percentage from each study as M = $\frac{Xi}{N} \times 100$ (3.29)

The weighted mean ($\bar{T}_\bullet$) is then computed as

$$\bar{T}_\bullet = \frac{\sum_{i=1}^{k} W_i T_i}{\sum_{i=1}^{k} W_i} \quad (3.30)$$

That is, the sum of products $W_i T_i$ (effect size multiply by weight) divided by the sum of weights.

The variance of the combined effect is defined as the reciprocal of the sum

$$SE(\bar{T}) = \sqrt{V} \quad (3.31)$$

Standard Error is computed as of the summary mean is given by

$$SE_M = \sqrt{\frac{\sigma^2}{k \times n}} \quad (3.32)$$

Where σ^2 is the standard deviation, n is the sample size, and k population?

According to Nicole Vigelzengs Old Ratio is computed as

$$OR = \frac{p}{1-p} \quad (3.34)$$

Where P is the proportion of study

3.8.1 Test for Heterogeneity (Q-Test)

The usual way of assessing whether there is true heterogeneity in a meta-analysis has been touse the *Q* test, a statistical test defined by Cochran (1954). The *Q* test is computed by summing the squared deviations of each study's effect estimate from the overall effect estimate, weighting the contribution of each study by its inverse variance. Under the hypothesis of homogeneity among the effect sizes, the *Q* statistic follows a chi-square distribution with $k - 1$ degrees of freedom, k being the number of studies.

The test (Q) is not powerful when number of studies is small or within-study variance is large, hence cannot be used to estimate the magnitude of true variance

$$Q = \sum_{i=1}^{k} W_i(Y_i - M)^2 \quad (3.35)$$

Where W_i is the individual study weight?

y_i the individual effect sizes and M is the Moderators

3.8.2 I square (I^2)

The I^2 index measures the extent of true heterogeneity dividing the difference between the result of the *Q* test and its degrees of freedom ($k - 1$) by the *Q* value itself, and multiplied by 100.

The I^2 index can be interpreted as the percentage of the total variability in a set of effect sizes due to true heterogeneity, that is, to between-studies variability. For example, a meta-analysis with $I^2 = 0$ means that all variability in effect size estimates is due to sampling error within studies. On the other hand, a meta-analysis with *I2* = 50 means that half of the total variability among effect sizes is caused not by sampling error, but by true heterogeneity between studies.

I square is computed as $I^2 = \frac{(Q-df)}{Q} \times 100$ (3.35)

3.9 **Justification of Method**

In Metal Analysis, there are two models that are available to statistician/ researchers. But choosing a particular model is based on reality, effectiveness and adequacy of the model. Hence among these models we choose Fixed Effect model. The choice of these model is informed by the fact that it helps to assume that there is only one true effect size which is share by all the included studies and also, that all studies in the Metal Analysis are drawn for a common population.

CHAPTER FOUR

4.1 DATA PRESENTATION AND ANALYSIS

This section aimed at presenting and interpreting the result and the data, which will be used for the statistical analysis. The data used were collected from world hearth statistical data base from the year 1976-2014; subsequently, the data would be analyzed using Meta-Analysis stated in the previous chapter. It will do justice to the highlighted objectives of the research; it will also help in validating the inferences and conclusion to be drawn in the subsequent chapter.

4.1.1 Table 1: Reported Case of Ebola Virus Disease

S/N	Year	Country	Species	FT	CT	DT
1	1976	Zaire	EBOV	88	318	280
2	1976	Sudan	SUDV	53	284	151
3	1977	Zaire	EBOV	100	1	1
4	1979	Sudan	SUDV	65	34	22
5	1994	Gabon	EBOV	60	52	31
6	1994	Ivory coast	TAFV	0	1	0
7	1995	Zaire	EBOV	79	315	250
8	1996	Gabon	EBOV	57	37	21
9	1996	South Africa	EBOV	50	2	1
10	1997	Gabon	EBOV	75	60	45
11	2000-2001	Uganda	SUDV	53	425	224
12	2001-2002	Dr Congo	EBOV	79	122	96
13	2002-2003	Congo	EBOV	90	143	128
14	2003	Congo	BDBV	83	35	29
15	2004	Sudan	SUDV	41	17	7
16	2007	Congo	EBOV	71	246	187

17	2007-2008	Uganda	BDBV	25	149	37
18	2012-2013	Dr Congo	BDBV	47	77	36
19	2012-2013	Uganda	SUDV	71	24	17
20	2013-2014	Guinea	EBOV	55	2615	1427

CT = Number of Cases of Reported Human Virulence

FT = Fatality of Reported Human Virulence

DT = Death of Reported Human Virulence

4.1.2 Descriptive Statistics

Below shows the descriptive statistics of all the variables used in the study

	CT	**DT**	**FT**
Mean	247.8532	149.5098	62.1034
Median	35.00000	22.00000	53.00000
Maximum	2615.000	1427.000	100.0000
Minimum	1.000000	0.000000	0.000000
Std. Dev.	571.5274	313.8495	23.5372
Mean Dev.	4.461408	4.216077	0.350831
Probability	0.000000	0.000000	0.351755
Observation	20	20	20

The table above presents the descriptive statistics used in the study. Where the mean value of fatality is 62.10, case is 247.85 and death is 149.50

4.1.3. Table 2: Converted Parameter for Meta-Analysis

Study ID	Year	Country	ES	Weight	LCI	UCI
1	1976	Zaire	280	2.44	107.523	452.477
2	1976	Sudan	151	6.71	47.122	254.878
3	1977	Zaire	231	1.89	35.004	426.996
4	1979	Sudan	22	4.46	-105.398	149.398
5	1994	Gabon	31	5.24	-86.598	148.598
6	1994	Ivory coast	121	5.24	3.402	238.598
7	1995	Zaire	250	3.02	95.163	404.837
8	1996	Gabon	21	5.81	-90.718	132.718
9	1996	South Africa	83	7.54	-14.998	180.998
10	1997	Gabon	45	3.35	-101.997	191.997
11	2000-2001	Uganda	224	6.71	120.122	327.878
12	2001-2002	Dr Congo	96	3.02	-58.837	250.837
13	2002-2003	Congo	128	2.33	-48.397	304.397
14	2003	Congo	29	2.74	-133.677	191.677
15	2004	Sudan	32	11.22	-48.359	112.359
16	2007	Congo	187	3.74	47.843	326.157
17	2007-2008	Uganda	37	6.01	-72.758	146.758
18	2012-2013	Dr Congo	36	8.54	-56.118	128.118
19	2012-2013	Uganda	31	3.74	-108.157	170.157
20	2013-2014	Guinea	231	6.24	123.202	338.798

LCL = Lower Confidence Interval

UCL = Upper Confidence Interval

4.2 Table 3: Result of Analysis

Study	ES	[95% Conf.	Interval]	% Weight
Zaire (1976)	280.000	107.523	452.477	2.44
Sudan (1976)	151.000	47.122	254.878	6.71
Zaire (1977)	231.000	35.004	426.996	1.89
Sudan (1979)	22.000	-105.398	149.398	4.46
Gabon (1994)	31.000	-86.598	148.598	5.24
Ivory Coast (1994)	121.000	3.402	238.598	5.24
Zaire (1995)	250.000	95.163	404.837	3.02
Gabon (1996)	21.000	-90.718	132.718	5.81
South Africa (1996)	83.000	-14.998	180.998	7.54
Gabon (1997)	45.000	-101.997	191.997	3.35
Uganda (2000-2001)	224.000	120.122	327.878	6.71
Dr Congo (2001-2002)	96.000	-58.837	250.837	3.02
Congo (2002-2003)	128.000	-48.397	304.397	2.33
Congo (2003)	29.000	-133.677	191.677	2.74
Sudan (2004)	32.000	-48.359	112.359	11.22
Congo (2007)	187.000	47.843	326.157	3.74
Uganda (2007-2008)	37.000	-72.758	146.758	6.01
Dr Congo (2012-2013)	36.000	-56.118	128.118	8.54
Uganda (2012-2013)	31.000	-108.157	170.157	3.74
Guinea (2013-2014)	231.000	123.202	338.798	6.24

I-V pooled ES | 99.974 73.056 126.892 100.00

Heterogeneity chi-squared = 36.18 (d.f. = 19) p = 0.010

I-squared (variation in ES attributable to heterogeneity) = 47.5%

Test of ES=0: z= 7.28 p = 0.000

In table 4.2, the first column of the output table gives the country of study and publication year. The next column is labeled “ES”, the effect size, which stands for Standardized Mean Difference. The next two columns give the 95% confidence interval around the estimate of the effect size. The last column gives the “% Weight”. The sum of the % Weight column is 100. At the bottom of the table, we see the pooled ES, which is 99.974, with a 95% confidence interval of Lower 73.056, 105.688 to Upper 126.892, 143.927 for Fixed and Random effect. The Test of ES = 0 is given in the very last line of the output, and it indicates that the z test statistic equals 7.28 with a p-value of 0.00, which is statistically significant at the alpha = 0.05 level. The first two lines of the output below the table give estimates of the heterogeneity. The Heterogeneity chi-squared or Q-test equals 36.18 on 19 degrees of freedom, with a p-value of 0.010, which is not statistically significant. The I-squared is estimate 47.5%which means there is no biasness in the analysis.

4.2.1 Table 4: Overall association of clinical symptoms and signs with EVD

Symptom/sign	**% of pooled proportion of patients with this symptom/sign**
Fever	92.9 (95% CI=87.3–96.9)
Headache	73.4 (95% CI=52.9–89.7)
Diarrhea	73.3 (95% CI=66.4–79.7)
Fatigue	68.6 (95% CI=58.6–77.8)

Symptom/sign	% of pooled proportion of patients with this symptom/sign
Myalgia/arthralgia	65.7 (95% CI=37.9–88.7)
Vomiting	61.3 (95% CI=53.9–68.4)
Abdominal pain	44.1 (95% CI=29.3–59.4)
Bleeding events[a]	42.5 (95% CI=26.9–58.9)
Sore throat	40.3 (95% CI=18.6–64.2)
Conjunctivitis	38.8 (95% CI=19.9–60.1)
Cough	33.3 (95% CI=24.4–42.8)

Bleeding events include melena, bright red bleed per rectum, epistaxis, hemoptysis, hematemesis, petechiae, conjunctival hemorrhage, gingival hemorrhage, unexplained bleeding, bleeding per vagina, hematuria, and bleeding under skin.

4.2.2 Table 5: Association of clinical signs and symptoms of EVD patients with fatal outcome versus survivors

Symptom/sign	% of pooled proportion of dead patients with this symptom/sign	% of pooled proportion of EVD survivors with this symptom/sign
Diarrhea	69.9 (95% CI=60.7–78.4)	37.8 (95% CI=13.8–65.6)
Bleeding events	64.5 (95% CI=14.8–99.0)	25.1 (95% CI=5.3–53.4)
Vomiting	60.8 (95% CI=49.9–71.2)	31.7 (95% CI=3.8–70.8)
Abdominal pain	58.3 (95% CI=30.8–83.3)	37.5 (95% CI=20.7–55.9)
Sore throat	47.7 (95% CI=11.6–85.3)	19.8 (95% CI=11.4–29.7)

Symptom/sign	% of pooled proportion of dead patients with this symptom/sign	% of pooled proportion of EVD survivors with this symptom/sign
Conjunctivitis	39.3 (95% CI=16.1–65.4)	20.3 (95% CI=10.2–32.7)
Cough	31.6 (95% CI=26.1–37.4)	22.3 (95% CI=20.4–25.1)

4.2.3 Table 6: Heterogeneity data and risk of bias associated with individual symptoms in pooled patient population

Symptom/sign	I^2 (inconsistency)	Harbord bias
Fever	99.2% (95% CI=99–99.4)	2.33 (92.5% CI=−0.85–5.51), *P*=0.17
Headache	99.1% (95% CI=99–99.2)	6.46 (92.5% CI=−1.69–14.6), *P*=0.14
Diarrhea	92.4% (95% CI=87.9–94.7)	2.02 (92.5% CI=−1.66–5.69), *P*=0.28
Fatigue	99% (95% CI=99–99.1)	−2.37 (92.5% CI=−7.91–3.17), *P*=0.37
Myalgia/arthralgia	99.5% (95% CI=99.4–99.5)	9.99 (92.5% CI=−3.05–23.03), *P*=0.14
Vomiting	92.1% (95% CI=87.3–94.5)	−2.40 (92.5% CI=−6.29–1.49), *P*=0.23
Abdominal pain	97.6% (95% CI=96.7–98.2)	1.59 (92.5% CI=−11.04–14.23), *P*=0.76
Bleeding events	98.8% (95% CI=98.5–99)	10.50 (92.5% CI=2.36–18.63), *P*=0.03
Sore throat	99% (95% CI=98.8–99.2)	9.43 (92.5% CI=−8.01–26.87), *P*=0.24
Conjunctivitis	98.2% (95% CI=97.4–98.6)	8.09 (92.5% CI=−7.89–24.07), *P*=0.22
Cough	93.2% (95% CI=86.1–95.9)	2.06 (92.5% CI=−10.18–14.29), *P*=0.62

In table 4.2.2; initial search identified 634 reference articles, of which 67 were selected and reviewed. Data were extracted from 20 articles (N= 5,792) of EVD which met the inclusion criteria. Bleeding event (64% vs 25.1%), abdominal pain (58.3% vs 37.5%), vomiting (60.8% vs 31.6%), diarrhea (69.9% vs 37.8%), cough (31.6% vs 22.3%), sore throat (47.7% vs 19.8%), and conjunctivitis (39.3% vs 20.3%) were more often present in pooled proportion of fatal cases as compared to EVD survivors. All the pooled proportions given are the estimate calculated by the random effect model. Random effect model was preferred due to heterogeneity of the result.

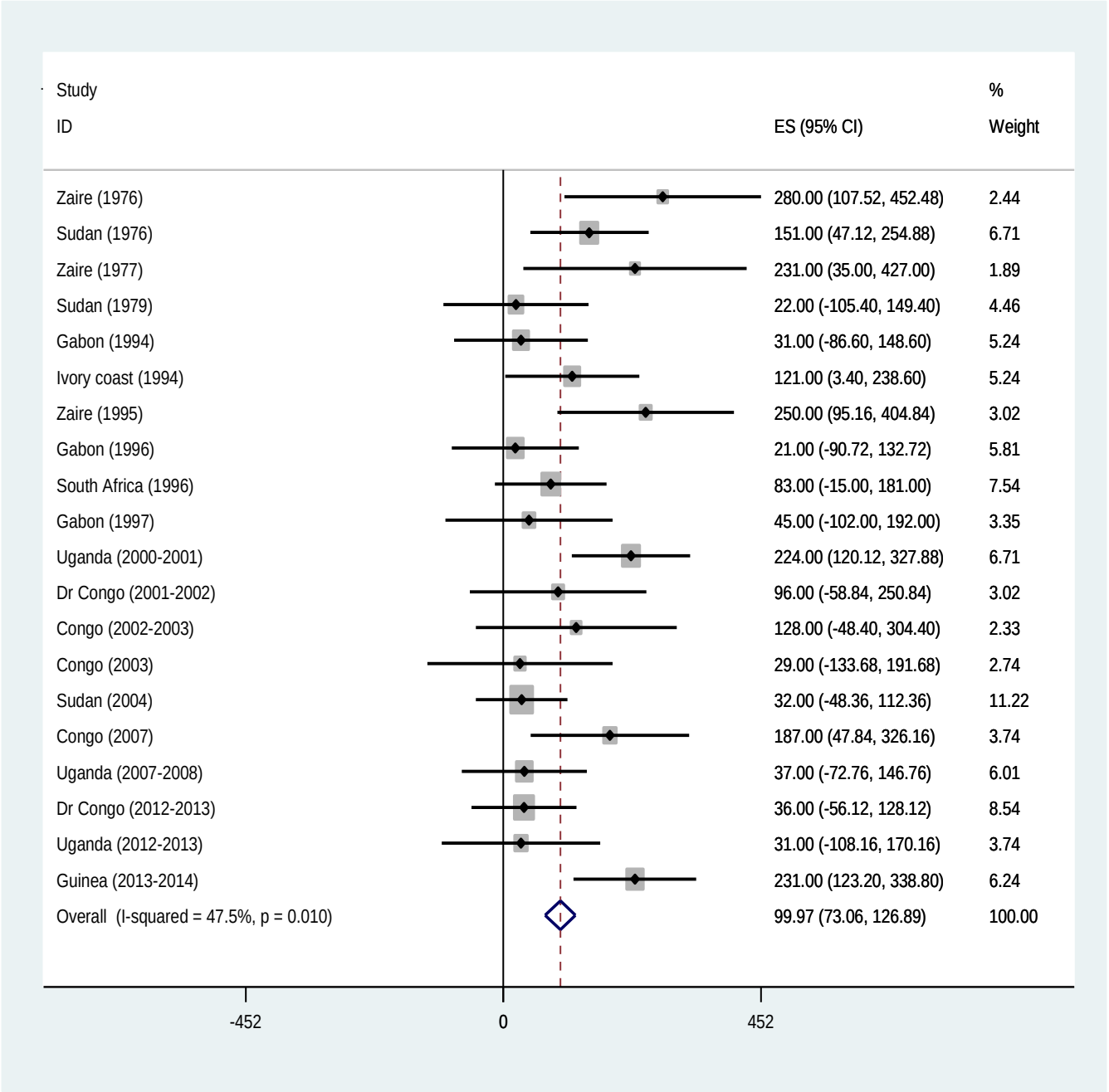


Fig 1; Forest plot of Fatality of Ebola Outbreak

From fig 1, the forest plot shows essentially the same information as the table. The left-hand side of the horizontal line is Mortality and the right-hand side is survival. The summary effect of 99.974 is shown with the red dotted line and the blue rectangle at the bottom of the graph. Each horizontal line on a forest plot represents an individual study with the result plotted as a box and

the 95% confidence interval of the result is displayed as in. The vertical line is known as the "line of null effect". Since all the individual studies cross the vertical line, it means the null value lies within the 95% confidence interval. This implies the study result is in fact the null value and therefore the study did not observe statistically significant difference between mortality and survival. The $I^2 = 47.5\%$ less than 50% means the studies are inconsistent due to a reason or other chance. The diamond shapes at the bottom of the forest plot shows the result when all the individual studies are combined together and averaged. The horizontal points of diamond shape are limits of the 95% confidence intervals and are subject to the same interpretation as any other individual studies on the plot.

4.3 Discussion of Result

From the result above, it can be seen that introducing fatality into the model causes the establishment of a relationship between cases of reported human virulence and death of reported human virulence. It indicated that one per cent increase in cases of reported human virulence will lead to 0.23 decreases in fatality of reported human virulence. This means that the ability for cases to be reported to the hospital leads to the reduction of fatal human virulence; this means that cases of Ebola virus outbreak should be reported if any victim is suspected in the neighborhood. Also, the result indicated one percent increase in the death of reported human virulence will lead to 0.42 increases in fatality of reported human virulence. This means that death caused by victims infected by their loved ones or during burial as there is a positive relationship between death reported human virulence and fatality of reported human virulence. Finally, one per cent increase in the Forest plot of Ebola virus will lead to 55.60 per cent increase in fatality of reported human virulence.

CHAPTER FIVE

SUMMARY, CONCLUSION AND RECOMMENDATIONS

5.1 Summary

This research has examined the relationship between the determinants of Ebola outbreak and meta-Analysis on the risk of mortality of Africa using annual time series data between 1976 - 2014.

It is carried out under the theoretical construct that if Ebola outbreak causes cases of reported human virulence and cases of reported human virulence causes fatality of reported human virulence, then by inference, a developed education and health sector will definitely bring about reduction of the Ebola virus outbreak and economic growth in Nigeria and Africa as a whole. In the research, the empirical continental relationship among the variables is examined using a meta-Analysis tool known as Effect size.

The forest plot of the Ebola outbreak showed that there is massive fluctuation of the fatality of outbreak. The forest plot also showed that the increase in the number of deaths as a result of the outbreak was noticeable between 2013 and 2014 in West Africa. In the same vein, the number of cases of the outbreak increase sharply between 2013 and 2014 in West Africa.

The effect size result showed that in Africa, about 75.04% of the total variation in the number of fatalities is jointly explained by the variations in the number of cases, number of deaths (occurrence of Ebola in West Africa). In all, number of cases contributes significantly to the fatality of the Ebola outbreak.

1.2 Conclusion

Clinical features of EVD that may be associated with higher mortality include bleeding events, vomiting, diarrhea, abdominal pains, cough, sore throat and conjunctivitis. These patients should be identified promptly, and appropriate management should be instituted immediately.

There is little evidence that more distant contact or that contact with people incubating the disease poses any risks. More studies are needed that correlate context, timing and intimacy of contact with days after disease onset and external symptoms or severity of illness. There is evidence that transmission from non-intimate contact is low during early illness, but there is no simple indicator for the transition to late illness when disease transmission is highly likely from any contact without adequate protective measures. Meta-analysis showed that transmission is very unlikely without direct physical contact. Once an outbreak has been identified, care for patients in well-equipped health care facilities cuts transmission rates. There is wide variation in the confidence intervals and magnitude, in many suggested risk factors even when adjusted for confounders, suggesting that understanding of community filovirus transmission could be greatly improved.

5.3 Recommendations

Sequel to the above findings, the research recommends the following key issues for policy consideration:

i. Government should adopt modern security technologies and infrastructures in the health sector by establishing the Ebola healthcare center for the manufacturing of vaccines and treatment of affected persons which will help to combat Ebola outbreak.

ii. Put suspected or confirmed cases in single isolation room with an adjoining dedicated toilet or latrine, showers, sink equipped with running water, soap and single-use towels, alcohol-based hand rub dispensers.

iii. Ensure that clinical and non-clinical personnel are assigned exclusively to HF patient care areas and that members of staff do not move freely between the HF isolation areas and other clinical areas during the outbreak.

iv. Restrict all non-essential staff from heart failure (HF) patient care areas.

v. Stopping visitor access to the patient is preferred, but if this is not possible, limit their number to include only those necessary for the patient's well-being and care, such as a child's parent.

vi. Do not allow other visitors to enter the isolation rooms/areas and ensure that any visitors wishing to observe the patient do so from an adequate distance (approximately 15 m or 50 feet). Before allowing visitors to enter the HCF, screen them for signs and symptoms of HF.

vii. Antibiotics: I strongly recommend, with moderate confidence, prompt administration of board- spectrum antibiotics to patients with suspect, probable, or confirmed Ebola virus disease and high severity of illness

viii. Parental administration of fluids: I strongly recommend, with moderate confidence, parental administration of fluids rather than no parental administration for patients who are unable to drink or whose volume are larger than oral volume intake

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