TRENDS AND DYNAMICS IN THE UTILIZATION OF INSULIN IN KIAMBU LEVEL 5 HOSPITAL

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A REPORT SUBMITTED TO THE DEPARTMENT OF PUBLIC & GLOBAL HEALTH IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF MASTER OF SCIENCE IN MEDICAL STATISTICS OF THE UNIVERSITY OF NAIROBI

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DECLARATION OF ORIGINALITY FORM

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I would like to dedicate this thesis to the Almighty God.

LIST OF ABBREVIATIONS AND ACRONYMS

ACF- Autocorrelation Function

ADF- Augmented Dickey Fuller

AIDS- Acquired Immune Deficiency Syndrome

AMP- Adenosine Monophosphate

AR- Autoregressive

ARIMA- Autoregressive Integrated Moving Average

BMI- Body Mass Index

COVID-19- Corona Virus Disease

DNA- Deoxyribonucleic acid

DPP-4- Dipeptidyl Peptidase 4 Inhibitors

GAD- Glutamic Acid Decarboxylase

GLP-1- Glucagon Like Peptide 1

HIV- Human Immunodeficiency Virus

IFD- International Federation for Diabetes

IU- International Units

K-ATP- Adenosine triphosphate sensitive potassium channels

Kg/m^2 – Kilogram per meter square

Kshs- Kenya Shilling

LADA- Latent Autoimmune Disease of Adulthood

MA- Moving Average

MAPE- Mean Absolute Percentage Error

Mmol/L- Millimoles per Liter

MODY- Mature Onset Disease of the Young

PACF- Partial Autocorrelation Function

PPAR-γ- Peroxisome Proliferator Activated Receptor Gamma

SGLT-2- Sodium Glucose-Like Transporter 2

SIAPS- Systems for Improved Access to Pharmaceuticals and Services

TP- Tyrosine Phosphatases

USAID- United States Agency for International Development

US$- Unites States Dollar

WHO- World Health Organization

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ABSTRACT

The estimation of the demand for health commodities is an important aspect in the prevention of stock outs in health facilities. More so, given the numerous challenges that public health facilities in developing countries face regarding commodity procurement, accurate estimation of the commodities required is critical. Insulin therapy is a cornerstone in the management of diabetes aiding in abating diabetic complications.

This study considered the use of time series models premised on the Box-Jenkins methodology Autoregressive Integrated Moving Average (ARIMA) method to explore the trends of insulin utilisation in Kiambu Level 5 County Referral Hospital and to forecast its consumption using monthly aggregates of insulin consumption from January 2014 to June 2020, including the COVID-19 period.

The average annual consumption of insulin was 1359 ($SD = 283$) vials, with the consumption showing a generally decreasing linear trend with a maximum consumption of 2316 vials in 2014 and a minimum consumption of 661 vials in 2017. The maximum six-month forecast consumption of insulin was 103 vials in March 2019, while the minimum forecast consumption of insulin was 92 vials in January 2019 and the average forecast insulin consumption was 98 ($SD = 2$) vials.

The maximum pre-Covid consumption of insulin was 38 vials, while the minimum consumption of insulin was 19 vials, with the average insulin consumption during this period being 30 ($SD = 1$) vials. The maximum post-Covid consumption of insulin was 43 vials, while the minimum consumption of insulin was 21 vials, with the average insulin consumption during this period being 30 ($SD = 1$) vials. There was no discernible difference in the patterns of consumption during these

two time periods. The results are important to policy makers in the medical sector for planning the

purchase and inventory maintenance of insulin stock in the county.

CHAPTER ONE

INTRODUCTION

1.1 Background

Insulin replacement therapy is one of the cornerstones in the pharmacotherapy of diabetes. It is indicated when a patient has severe hyperglycemia, has Type I diabetes, or has not achieved optimal glycemic control with oral agents. A variety of insulin formulations have been developed differing with respect to source i.e., bovine insulin isolated from a cow's pancreas, porcine insulin isolated from a pig's pancreas or human insulin obtained either from recombinant deoxyribonucleic acid (DNA) technology or enzymatic modification of porcine insulin. These formulations also differ with regard to duration and onset of action i.e. short, intermediate or long acting insulins (Brogden & Heel, 1987; Heinemann & Richter, 1993).

Increasing prevalence of prediabetic and diabetic patients as well as a significant proportion of undiagnosed diabetes causing an increase in demand for insulin, availability of insulin in public health institutions is a matter of critical importance (Whiting, Guariguata, Weil, & Shaw, 2011). The catchment population of public health institutions makes this issue even more serious owing to the fact they are mostly low-income earners and solely depend on these facilities to provide insulin to them due to the price difference from private healthcare facilities. As a result, uninterrupted supply of insulin is required in these facilities if the patients are to achieve their optimum glycemic targets and abate complications arising from the disease (Lipscombe et al., 2018).

Conversely however, public health facilities are frequently plagued with stock outs of essential health commodities. More so, health commodities such as insulin that are expensive to purchase are more often affected. Several factors have been identified as reasons for frequency of stock-outs in public health care facilities. These factors include: incorrect forecast estimates of quantities

required for reordering, inadequate allocation of funds for health commodity procurement, infrastructural challenges such as lack of transport and storage facilities and sub-optimal production from health commodity manufacturers (Wagenaar et al., 2014).

Health commodity demand estimation is one of the crucial components in ensuring the security of the supply chain of health commodities. Accurate estimations result in more accurate predictions resulting in a decreased frequency of stock outs of these commodities (USAID & DELIVER, 2014). This in turn helps in the mobilization of resources where additional health commodities are required, optimal use of the available resources, development of a more responsive supply and procurement plan as well as gap identification in the existing supply chains (JSI & SIAPS, 2015). Forecasting refers to the process of estimating the future demand of a particular commodity. Typically, forecasting utilizes historical data to come up with a future estimate. However, where historical data is not available, subjective forecasts known as judgmental forecasts are employed (Papalambros & Wilde, 2018).

Time series analysis has utility not only in the determination of utilization of insulin through descriptive analysis but also in the prediction of future quantities of insulin required through time series modelling (World Health Organisation, 2018). Autoregressive (AR) models are used to forecast quantities based in correlation of a dependent variable and past values of the dependent variables. Moving average (MA) models are used to forecast quantities based on correlation of a dependent value and past error terms or random shocks. Autoregressive Integrated Moving Average (ARIMA) combines both the AR and the MA processes accounting for dependencies with past values of the variable as well as random shocks (Papalambros & Wilde, 2018).

The impact of COVID-19 on the global healthcare outlook has been quite significant. In developing countries however, the impact has been felt even more. Institution of a lockdown and

curfew hours within the country has affected the accessibility to hospitals by patients. In addition, hospitals handling COVID-19 cases, whether suspected or confirmed, have noted an aversion by other patients to their facilities due to the fear of the risk of contracting the disease (Bernstein & Stead, 2020). This has further decreased access to these facilities. This reduced access may have far reaching implications especially in chronic conditions such as diabetes that require regular visits to hospital facilities for follow-up checkups (Schaffer, 2020).

1.2 Problem Statement

Among the biggest challenges in the provision of healthcare in the public sector is that of perennial stock-outs of essential health commodities. These stock-outs in turn, worsen the health outcomes for patients due to discontinuation of treatment or alterations to harsher treatment regimens (Koomen, Burger, & Van Doorslaer, 2019). Pasquet et al. (2010) noted a direct positive correlation between non-adherence to treatment and increased frequency of stock-outs.

High stock-outs of insulin in public health care have been identified as one of the greater impediments to access of care for diabetic patients. Delayed access to insulin in these patients often leads to severe and permanent complications including ophthalmic complications resulting in blindness; cardiovascular complications; end-stage renal disease; and development of diabetic foot that may eventually lead to amputations Optimal stocking of insulin is therefore of paramount importance. However, challenges such as improper forecasting techniques result in insulin stock-outs.

1.3 Justification

A study conducted in Tanzania reported one of the interventions applied in mitigating the frequency of stock-outs was a shift to a more efficient stock forecasting technique (Wales, Tobias, Malangalila, Swai, & Wild, 2014). Leung et al. (2016) identified the need for changing the

forecasting technique to account for seasonality and variations in trend over time is critical in in getting better forecast estimates as well as having better inventory levels.

The current method being used to determine the quantity to reorder is a moving average process, with only three months of past consumption data being used in this analysis. The paucity of past consumption data limits the method's capability to capture long term seasonal and trend variations in insulin consumption. Additionally, the moving average process only typifies the relationship between a dependent variable and past random shocks or errors. Using an ARIMA model instead incorporates the relationship between a dependent variable and past value of itself into the moving average model as well (Papalambros & Wilde, 2018). A wider range of past consumption data is utilized in the development of the model. This proposal therefore seeks to address a gap in practice by exploring ARIMA time series models to forecast the insulin consumption need for Kiambu Level 5 County Referral Hospital.

1.4 Research Questions

i. What is the five-year trend and yearly insulin consumption in Kiambu Level 5 County Referral Hospital between January 2014 and December 2018?

ii. What ARIMA time series model best fits the insulin consumption in Kiambu Level 5 County Referral Hospital between January 2014 and December 2018 and what are the subsequent six-month forecasts from this model?

iii. What is the impact of onset of the COVID-19 pandemic on insulin consumption in Kiambu Level 5 Hospital?

1.5 Objectives of the Study

1.5.1 General Objective

To determine the trends and dynamics in the utilization of insulin in Kiambu Level 5 County Referral Hospital.

1.5.2 Specific Objectives

(i) To determine the five-year trend and yearly insulin consumption in Kiambu Level 5 County Referral Hospital between January 2014 and December 2018.

(ii) To specify a model for insulin consumption using the consumption data between January 2014 and December 2018 and further forecast the insulin consumption for Kiambu Level 5 County Referral Hospital from January 2019 to June 2019

(iii)To assess the impact of COVID-19 on insulin consumption by comparing insulin consumption between April 2019-June 2019 and April 2020-June 2020

CHAPTER TWO

LITERATURE REVIEW

2.1 Social-Economic burden of diabetes

Diabetes impacts the economy in both subtle and more overt ways. Diabetes directly increases the amount of health expenditure by a household to accommodate the additional visits to healthcare facilities, medications required, and follow-up health technologies needed such as glucose test strips for routine sugar monitoring. Indirectly, the effects of the disease on the economy build on the loss of productivity by individuals afflicted with the disease. Metrics such as shrinking workforce resulting from death or incapacitation, absenteeism due to additional hospital visits, diminished work output due to decreased body functionality are estimated to give an approximate effect. The total economic burden of the disease is then a sum-total of the direct and indirect estimated costs of the disease (Bommer et al., 2018).

Bommer et al. (2017) put the approximate cost of the global economic burden of diabetes at US$1.3 trillion, with the indirect economic impact estimated at US$450 billion. The largest contribution to these costs was from the shrinking workforce, accounting for up to 48.5% of these costs, closely followed by mortality, accounting for up to 45.5% of the costs. In Africa, these costs were estimated to be in the region of US$25.52 billion (Kirigia et al., 2009).

In addition to the deleterious clinical effects diabetes has to an individual's body, the economic effects threaten to prove just as devastating. A study conducted in New Zealand concluded that the total cost of healthcare for a patient with diabetes was three times that of a patient with no diabetes (Crew, 2016). In instances where a patient with diabetes loses their gainful source of income due to effects of the disease, the indirect cost of the disease is significantly higher than the additional direct costs of healthcare due to the disease. In Indonesia, Soegondo (2016) estimated the cost of managing myocardial infarction in diabetes to be around US$22000, making it the most expensive

diabetic complication to manage clinically. Other major contributors to the direct additional costs of healthcare due to diabetes include haemodialysis costs resulting from nephropathic complications, amputation costs and costs arising from kidney transplantation.

Socially, the decrease in the quality of life of a patient afflicted with diabetes comes to the fore. Amputations arising from complications of the disease result in decreased ambulatory functioning of an individual, limiting his or her socialisation in a sense, stigma from some members of society as well as a decreased perceived sense of self-worth. Blindness resulting from the disease results in a need for additional dependence on others just to maintain the normal social functioning of an individual, significantly altering their quality of life. Nutritional freedom is also affected because of the restricted nutritional choices available to stop the normal progression of the disease, with this freedom further curtailed in cases where the patient is already undergoing dialysis. Within the family setup, the dynamic could be significantly altered in cases where patients develop erectile dysfunctions arising from autonomic neuropathic complications. Finally, the exclusion of an individual from the community in instances of hospital admission could also significantly affect the individual's social setup and quality of life involuntary.

2.2 Aetiology and classification of diabetes

One of the principal causes of Type I diabetes is the autoimmune degradation of the β-pancreatic cells where antibodies target glutamic acid decarboxylase and tyrosine phosphatase or both, in about 99% of the patients (Chowdhury, Mijovic & Barnett, 1999). The major causes of Type II diabetes are the gradual, progressive deterioration of β-pancreatic cell function and development of resistance to insulin by tissues in the body, inhibiting proper glucose uptake from the bloodstream of an individual. This arises from a multiplicity of a mix of host factors, such as the genetic predisposition of an individual and environmental factors such as the nutritional choices

of an individual. Clinical conditions that disrupt the normal functioning of the endocrine system such as somatostatinomas, hyperthyroidic states, Cushing's syndrome and glucagonomas interfere with the optimal glucose regulation in the body (Resmini, Minuto, Colao & Ferone, 2009). Infections from viruses such as Hepatitis C Virus, pancreatic disease conditions such as hereditary hemochromatosis, cystic fibrosis and inflammation of the pancreas, therapeutic drugs harmful to the pancreas and predisposing genetic states of an individual could also result in the development of diabetes by patients (O'Riordan, Robinson, Donaghue & Moran, 2009; Tattersall & Fajans, 1975).

Types I and II are the most prevalent forms of diabetes. The main difference between these two forms of diabetes is in the onset of the disease and the levels of insulin secretion by the β-pancreatic cells. In Type I, the manifestation of the disease is at a young age and the insulin secretion by the β-pancreatic cells is almost non-existent, necessitating the need for institution of insulin in the management of the disease, whereas in Type II, the manifestation of the disease is at a much older age with a diminished level of endogenous insulin being produced or development of resistance to insulin by tissues of the body (Deshpande, Harris-Hayes & Schootman, 2008). Symptomatic differentiation of these two forms of disease is difficult due to the similarity of the clinical symptoms and complications of the disease. Although there was a significant distinction between these two diseases could be drawn from the fact that insulin therapy is the mainstay therapy in Type I, this distinction is progressively growing bleaker with the increasing prevalence of insulin use in Type II diabetes. In the event of a need for clinical distinction, this can be done more conclusively by determining the presence or absence of autoantibodies against tyrosine phosphatases (TP) and glutamic acid decarboxylase (GAD) (Falorni et al., 2000).

2.3 Complications of diabetes

Untreated diabetes for protracted periods of time results in several complications in the body. There are two types of complications: microvascular and macrovascular complications. Microvascular complications arise from the damage of the endothelium by glucose molecules, increase in the vascular oxidative stress resulting from release of superoxide radicals and development of advanced glycation end products. These complications include neuropathies, retinopathies, and nephropathies (Vithian & Hurel, 2010). Macrovascular complications result from an atherogenic process triggered by an elaborate inflammatory response that causes monocytes to migrate to the sub-endothelium potentially causing conditions such as hemorrhagic stroke, cardiovascular heart disease and peripheral arterial disease (Dunn, Chan, Ng & Stocker, 2013).

Diabetic retinopathy occurs when the microvasculature of the retina is damaged. It is the commonest diabetic complication and the leading cause of blindness in the world. Diabetic nephropathy occurs when there is glomerular damage in the nephrons, resulting in microalbuminuria initially and finally progressing to proteinuria in advanced disease. Diabetic neuropathy presents as several clinical syndromes: autonomic neuropathies that include gastroparesis, postural hypotension, erectile dysfunction, and gustatory sweating; focal neuropathies such as cranial nerve palsy, entrapment syndromes and diabetic amyotrophy; symmetrical sensorimotor neuropathies (Vithian & Hurel, 2010).

Hemorrhagic stroke and ischemic heart disease contribute the most to mortality due to diabetes (Wingard & Barrett-connor, 2003). Peripheral vascular disease is characterised by the lack of pulses in the lower extremities. Unchecked, it progresses to the development of foot ulcerations that eventually lead to amputations. Other complications that result from diabetes include

increased susceptibility to infections, reduced wound healing, macrosomia where a woman gives birth to a baby with an excessive birth weight and finally increased susceptibility to dental infections (Deshpande et al., 2008).

2.4 Insulin therapy

In instances where there is an absolute lack of production of insulin in the body, such as in Type I diabetes, insulin pharmacotherapy is instituted. Insulin is derived from different sources; porcine insulin from pigs, which differs from human insulin by the presence of alanine instead of threonine in the B-chain of its insulin molecule; bovine insulin from cows, which differs from human insulin by the presence of alanine and valine in place of threonine and isoleucine in the A-chain of its insulin molecule; and human insulin derived from recombinant deoxyribonucleic acid (DNA) technology (Heinemann & Richter, 1993).

Insulin replacement therapy is intended to mimic the normal physiologic process of endogenous insulin in the body. Consequently, deficiencies in the physiologic action of regular human insulin have led to the development of human insulin analogues, altering the durations of action of the regular insulin. As such, rapid acting analogues such as insulin aspart, insulin glulisine and insulin lispro and long-acting analogues such as insulin glargine and insulin detemir have been developed (Hirsch, 2005; Siebenhofer AAS & Pieber, 2004).

Various complications arise from the regular usage of insulin. Hypoglycemia is one of the commonest complications arising from an imbalance between the levels of insulin and nutrients in the body, and a mismatch between the glucose counter-regulatory mechanisms and the action of insulin (Cryer, 2002). Lipid hypertrophy due to repeated injections has also been a common complication. However, the rotation of the injection sites has been used to resolve this complication. Another complication is immunologic reactions, especially to the animal-derived

insulins, but the increased use of human insulin and highly purified forms of insulin has decreased these reactions (Kahn & Rosenthal, 1979).

2.5 Trends in insulin use

Globally, the number of patients who require insulin has been on a steady increase due to the increasing prevalence of diabetes in the world as well as a largely remaining proportion (40–50 percent) of undiagnosed diabetes (Whiting et al., 2011). Whereas this increase in prevalence has been significantly noted with type 2 diabetes, type 1 diabetes has also been noted to increase averagely at 4 percent annually (Forlenza & Rewers, 2011). This increasing prevalence has not only been noted in developed countries, but in lower- and middle-income countries as well. The lag time between the clinical diagnosis of diabetes and the existence of the condition also contributes significantly to the increase in demand for insulin especially for type 2 diabetes patients.

Lipska et al. (2017) studied the temporal trends in the consumption of insulin between 2006 and 2013 in the United States and reported an overall incremental trend in the consumption of insulin. They however attributed this to the adoption of alternative forms of insulin, rapid and basal insulin analogues, over the intermediate acting human insulins, which they reported an actual decrease in their utilisation. The adoption of these newer analogues of insulin was however noted to be among patients who had private insurance. Xu et al. (2019) also reported a 21 percent increase in the utilisation of insulin in the state of California with a concomitant 54 percent increase in the expenditure of insulin. They however noted a decrease in the utilisation of premixed and intermediate acting insulin, in contrast to the increased use of rapid and long-acting insulins.

The global expenditure on insulin has also increased due to the increased demand for insulin as well as the emerging focus on the mitigation of non-communicable diseases. Herkert et al. (2019)

reported a threefold increase in the cost of insulin in the last decade in the United States resulting in a slight increase in the incidence of underuse of insulin by patients who needed it.

2.6 Access to insulin

A cornerstone of security of supply, as defined by the United Nation's Children Fund (UNICEF), is the uninterrupted provision of quality medicines, ensuring constant access to medicines to patients when they do need them (Kristensen, Hall & Jarrett, 2000). This in turn means that stock outs of essential commodities are reduced through a matrix of interrelated systems that include better estimation and prediction of the actual demand of the commodity, reduced lead times during the supply of the commodity and the presence of adequate buffer stock to protect from unexpected demand shocks.

Lower- and middle-income countries face various challenges in their quest to provide adequate access to insulin. Frequent disruptions in the supply chain, inefficient procurement systems and underdeveloped or nonexistent distribution systems build up the basis of the infrastructural problems limiting access to insulin in public health facilities. Consequently, the proper estimation of the accurate health demand of insulin remains a challenge bringing about inequalities in access and supply of insulin. Beran, Ewen and Laing (2016) found that while Maputo received 77.3 percent of the total insulin from the central stores in Mozambique, this only accounted for 11.3 percent of the total demand of insulin in the country. Estimation also at the central or national level is important as well. In Kyrgyzstan, stock outs of insulin were experienced at the lower facilities due to inaccurate estimations from the central stores (Beran et al., 2013).

2.7 Time series data and applications in medical research

Time series data refer to those that have been collected repeatedly over time equal or unequal intervals of time. Since these data are highly autocorrelated, conventional statistical methods that

do not adjust for this correlation are deemed inappropriate for the analysis of these data (Soyiri & Reidpath, 2013). These data have found numerous applications in medical research, where the variation of a variable over time is of interest.

In drug studies where the concentrations of a drug are measured over time to determine the pharmacodynamic and pharmacokinetic properties of the molecule, time series analysis is usually employed. In endocrinological studies where the measurement of pulsatile frequencies of secretion of hormones is desired, this data is usually critical. In comparison studies where the effect of a novel intervention is measured against a standard over time, time series analysis is usually used. In rate- determinant studies where the rate of a variable of interest is to be measured, time series analysis also comes in handy (Crabtree, Ray, Schmidt, O'Connor & Schmidt, 1990).

Kane et al. (2014) modelled influenza incidence data using ARIMA and random forest time series modelling. Although the authors concluded that Random Forest time series modelling had better predictive ability than ARIMA time series modelling for their data, they stated that the ability to incorporate exogenous variables and to automate model selection is a key advantage of ARIMA time series modelling. Reis and Mandl (2003) modelled syndromic surveillance data to forecast the expected number of visits to their emergency department. They developed a trimmed seasonal mean model, which on examining the residuals from the model, discovered strong autocorrelation of the residuals. To account for this, they subsequently fitted an ARIMA time series model to the residuals of the trimmed seasonal mean model.

Pratyaksa et al. (2017) successfully fitted an ARIMA time series model using the daily consumption data of povidone-iodine to forecast its future demand. The authors however, highlighted the need for validation and comparison of the fitted model with other forecasting models to assess its true utility as a forecasting tool. Papana, Folinas, and Fotiadis (2012) assessed

several univariate time series models to develop a forecast model for the drug rapilysin lypdinj 2x1.16g/vial (rl). The authors compared a moving average model, an exponential smoothing model, a random walk model and an autoregressive model of order one. The exponential model was found to be the most apt, with the limited range of their historical data being a reason why an ARIMA model was not fitted for their data.

Molina et al. (2016) compared the efficacy of forecasts of drug demand using Artificial Neural Networks (ARN) and ARIMA time series models and concluded that the former yielded more accurate forecasts. However, the flexibility of the latter derived from the fact that it incorporates both autoregressive and moving average processes, coupled with the complexity of developing the former model, makes a compelling case for the utilisation of ARIMA time series models in developing health demand forecasts.

2.8 ARIMA class of models

The ARIMA class of models refers to those that explain the relationship between a dependent variable and lagged values of itself together with lagged values of random errors or shocks. It is usually denoted as an ARIMA (*p, d, q*) model, where the *p* represents the autoregressive parameter, *d* is the number of times the data have been differenced to achieve stationarity, and q is the moving average parameter. It takes the following form:

$$y_t = \alpha_1 y_{t-1} + \alpha_2 y_{t-2} + \cdots + \alpha_p y_{t-p} + \varepsilon_t + \theta_1 \varepsilon_{t-1} + \theta_2 \varepsilon_{t-2} + \cdots + \theta_q \varepsilon_{t-q}$$

y_t: Dependent random variable at time (t)

y_{t-i} : Lagged values of the dependent variable

ε_t : Error term at time (t)

ε_{t-i} : Lagged error terms

α_i : Autoregressive parameters

θ_i : Moving average parameters

where the error term is independent and identically distributed and has a normal distribution with a mean of zero and a constant variance.

2.8.1 Box-Jenkins Methodology

The Box Jenkins Methodology refers to an analytical method developed by George Box and Gwilym Jenkins applied to time series models, more specifically in this case, the ARIMA class of model, to best fit past time series data to itself (Box & Jenkins, 1970). The baseline assumption of this method lies in the stationarity of the data. As such, the stationarity of the variables is the first thing to be checked. Variables that are found not to be stationary, are subsequently differenced, until stationarity is achieved.

2.8.1.1 Stationarity of Data

This is a property of time series data that states that the statistical attributes such as the mean and variance of a time series remain constant throughout the time series. Therefore, the detection of stationarity is a crucial component in the analysis of ARIMA time series models. Various methods have been used to assess for stationarity. Visual plots of autocorrelograms can be used to check for this, with a rapidly decaying to zero autocorrelogram indicating the stationarity of data and gradual decay indicating non-stationarity. Parametric measurements can be used for more rigorous estimation.

2.8.1.2 The Dickey Fuller Test

This is a parametric stationarity estimation method that assesses the presence or absence of a unit root in a stochastic process. The roots refer to the solutions of a characteristic equation of a

stochastic process and a unit root is determined whether 1 is one of the roots. The Dickey-Fuller test therefore tests for the presence or the absence of a unit root in a stochastic process, with the null hypothesis being the presence of a unit root in am autoregressive model. This test can take either form:

$\Delta x_t = \delta x_{t-1} + \varepsilon_t$ to assess for a simple AR (1) process,

$\Delta x_t = \alpha_0 + \delta x_{t-1} + \varepsilon_t$ to assess for a process with drift and finally,

$\Delta x_t = \alpha_0 + \alpha_1 t + \delta x_{t-1} + \varepsilon_t$ to test for a process with a deterministic time trend where in the above processes: x_t= variable of interest at a specified time, t, $\varepsilon_{t=}$error term of the process, $\alpha_{0=}$ represents the drift parameter, $\alpha_1 t$= represents a deterministic trend and finally δ= represents the difference between the coefficient of the original process and 1 such that the null hypothesis for the test becomes $\delta = 0$ and indicates a unit root.

2.8.1.3 The Augmented Dickey Fuller Test

This is an expansion of the Dickey Fuller Test to accommodate more variables in a stochastic process. As such, more elaborate models can be tested using this test. The general form of models tested by this statistic takes on the general form below:

$$\Delta x_t = \alpha_0 + \beta t + \gamma x_{t-1} + \delta_1 \Delta x_{t-1} + \cdots + \delta_{p-1} \Delta x_{t-p-1} + \varepsilon_t$$

Where x_t represents the timed variable, p represents the lags, α represents a constant and β represents the coefficient of the temporal trend.

Another parametric method that can be used to confirm stationarity and used adjunctively to the augmented dickey fuller (ADF) test is the KPSS test. The difference between this test and the ADF test is that the alternative hypothesis of this test is the presence of a unit root.

2.8.1.4 Model identification

This usually involves estimating the p and the q parameters in the model. The p parameter represents the autoregressive process of the model, while the q parameter represents the moving average process. This is done by plotting autocorrelograms and partial autocorrelograms and from the underlying patterns of the plots, determining the various suitable model candidates that could be used. Once the models have been run, the Akaike's Information Criterion (AIC) is used to determine the most suitable model.

The AIC is premised on maximising the likelihood from a model and reducing the number of parameters used by the model. This is used to prevent over-fitting models with many predictor variables. It takes the following form: $AIC = 2k - 2\ln(L)$ where k represents the number of parameters in the model and L represents the likelihood of the model. The model with the minimum AIC becomes the most apt model.

2.8.1.5 Diagnostic checks

This is a set of statistical tests done to validate the models chosen. Usually, this is done by the analysis of residuals of the models. The normality of the residuals and autocorrelation between the residuals is discussed.

CHAPTER THREE

METHODOLOGY

3.1 Study site

The study was conducted in Kiambu Level 5 County Referral Hospital. Kiambu County has an estimated population of 2,417,735 people and it borders Nairobi, Machakos, Murang'a and Nakuru Counties (KNBS, 2019). Owing to its proximity to the country's capital, Nairobi, the hospital serves a mix of urbanized and rural patients. The hospital serves approximately five thousand patients per month in the outpatient department with slightly more than one hundred patients requiring insulin each month. Given the hospital's proximity to Nairobi as well as its location in the administrative hub in Kiambu County, coupled with the fact it acts as a referral center for satellite rural facilities in the various sub-counties, the insulin consumption in the facility typifies both urban and rural settings.

3.2 Study design

The study design is a retrospective descriptive analysis of the temporal trends and dynamics in the consumption of insulin in Kiambu Level 5 County Referral Hospital between January 2014 and June 2020.

3.3 Sample size

The sampling interval was one month. The sample size was obtained from the frequency of the sampling interval in the duration of the study. Since the range of data used to develop the model was from January 2014 to December 2018, the sample size corresponds to the number of months during this period. Hence, the sample size for the study was sixty. Hanke & Wichern (2015) recommend that the minimum number of entries used in developing an ARIMA time series model be fifty.

3.4 Data analysis

Descriptive time series analysis was used for the analysis of temporal trends. For forecasting, an ARIMA model was developed using the Box Jenkins Methodology. The model was as follows:

$$y_t = \alpha_1 y_{t-1} + \alpha_2 y_{t-2} + \cdots + \alpha_p y_{t-p} + \varepsilon_t + \theta_1 \varepsilon_{t-1} + \theta_2 \varepsilon_{t-2} + \cdots + \theta_q \varepsilon_{t-q}$$

Where: y_t is the insulin consumption in month (t)

y_{t-i} : Lagged monthly consumption of insulin

ε_t : Error term at month (t) where $\varepsilon \sim N\ (0, \sigma^2)$

ε_{t-i} : Lagged monthly error terms

α_i : Autoregressive parameters

θ_i : Moving average

p: Order of the autoregressive process

q: Order of the moving average process

d: Number of times the data has been differenced to make it stationary

The data was drawn from the Ministry of Health Mixtard 70/30 Daily Activity Register with the daily insulin consumption aggregated into monthly summaries. The data extracted from January 2014 to June 2019 was divided into training data used to develop the model and test data that was used to assess the validity of the model. The training data was the monthly insulin consumption in vials from January 2014 to December 2018 while test data was the monthly insulin consumption in vials from January 2019 to June 2019. The consumption of insulin between April 2019 and June 2019 was compared against that between April 2020 and June 2020 to assess for the effect of the

COVID-19 pandemic on insulin consumption. The software used for data management and analysis was R version 4.0.3. (R: A language and environment for statistical computing, 2020)

3.4.1 Box-Jenkins Methodology

The Box-Jenkins Methodology consists of three components: Model Identification; Parameter Estimation and Diagnostic Checks. However, the data was first checked for stationarity using the Augmented Dickey Fuller (ADF) test with a p-value lower than 0.05 (p-value < 0.05) indicating the data is stationary. Differencing was used to make the data stationary.

3.4.1.1 Model Identification

The autocorrelation function (ACF) and partial autocorrelation function (PACF) plots were used to identify the values of p and q in the ARIMA (*p, d, q*) model and subsequently produce a list of potential models.

3.4.1.2 Parameter estimation

The maximum likelihood estimation method was applied in the estimation of the parameters of the potential models. The Akaike's Information Criterion (AIC) was used to select the most apt model, with the model with the least AIC score being the most apt model.

3.4.1.3 Diagnostic checks

Finally, diagnostic checks such as normality and independence of residuals, homogeneity of variance, and presence or absence of outliers were performed on the chosen model and if it failed any check, the next best apt model was selected and checked.

3.5 Ethical consideration

Data was de-identified during the extraction of daily records of patient insulin consumption thereby ensuring the confidentiality of patients' records. The identity of the patients' records was in any way re-identified during the analysis and subsequent publication of the study results. The

data was stored in encrypted, and password protected files to prevent unapproved access to it.

Ethical approval was sought from the KNH-UoN Ethical Review Committee.

CHAPTER FOUR

RESULTS

4.1 Time series characteristics

The monthly insulin consumption decreased gradually from 2014 to 2018. The maximum peak consumption of insulin was 252 vials in March and June 2014 while the minimum consumption of insulin was 0 vials in July 2017 as well as July and August 2018 as shown in Figure 1. The general trend of the insulin consumption was linear. The average annual consumption of insulin was 1359 ± 283 vials while the average monthly insulin consumption was 113 ± 8 vials.

|	2014	2015	2016	2017	2018
January	221	148	162	99	100
February	207	134	54	73	52
March	252	157	47	70	65
April	217	133	120	94	111
May	202	150	144	66	134
June	252	155	149	1	17
July	183	75	29	0	0
August	165	90	15	2	0
September	177	134	169	1	100
October	146	131	128	48	116
November	139	150	169	79	137
December	155	145	70	128	128
Total	2316	1602	1256	661	960

Table 1

Monthly Insulin Consumption from 2014 to 2018 in Kiambu Level 5 Hospital
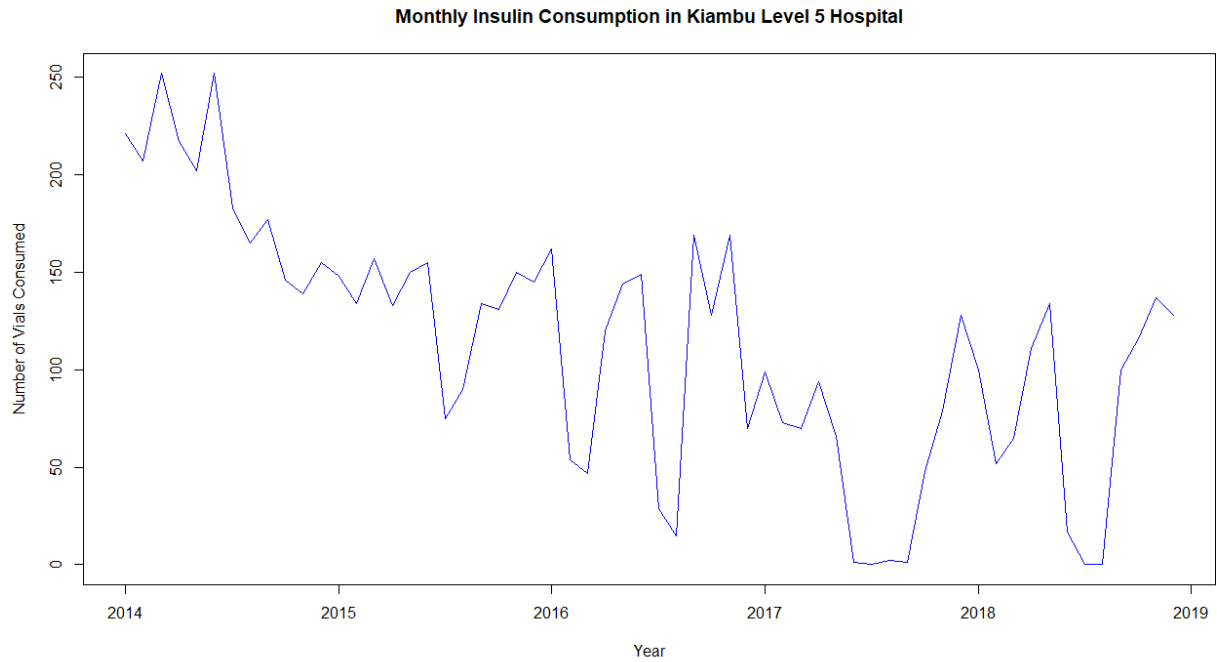
Figure 1

Graph of the Monthly Insulin Consumption in Kiambu Level 5 Hospital

Decomposing the time series revealed more clearly the inherent trends of the time series. The trend component was seen to be linearly decreasing from 2014 to 2017 with a slight linear increase in trend from 2017 to 2018. There was a seasonal component spotted in the series most likely since the data is annual monthly summaries. The random component of the time series was shown in Figure 2.
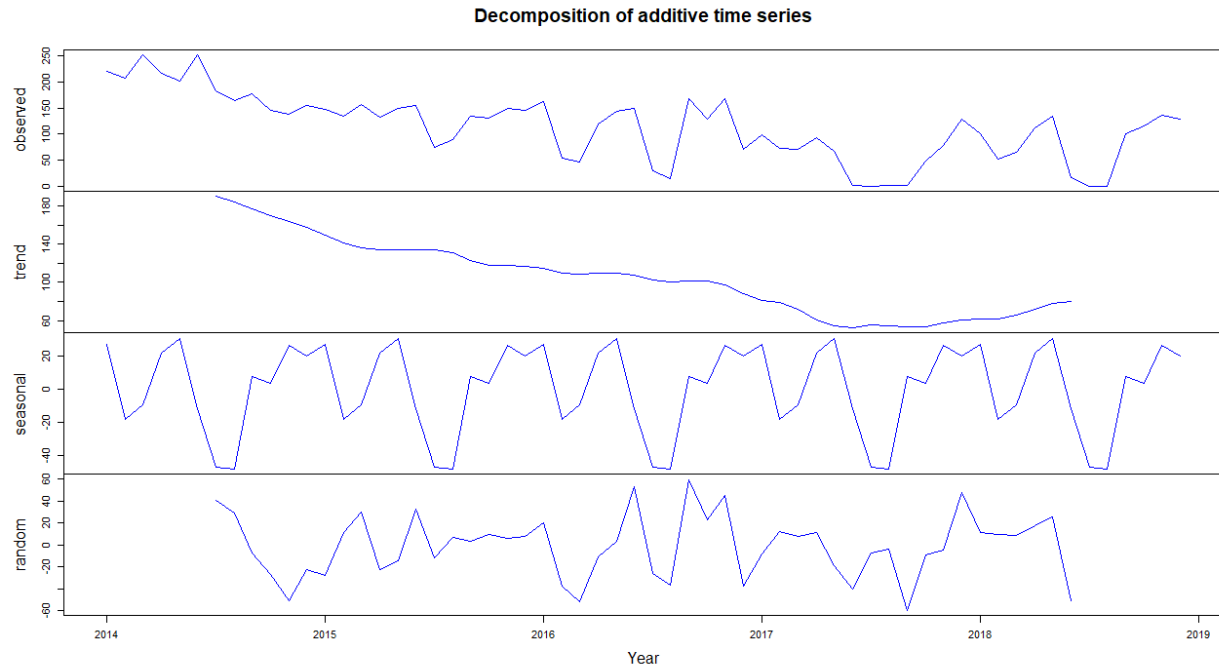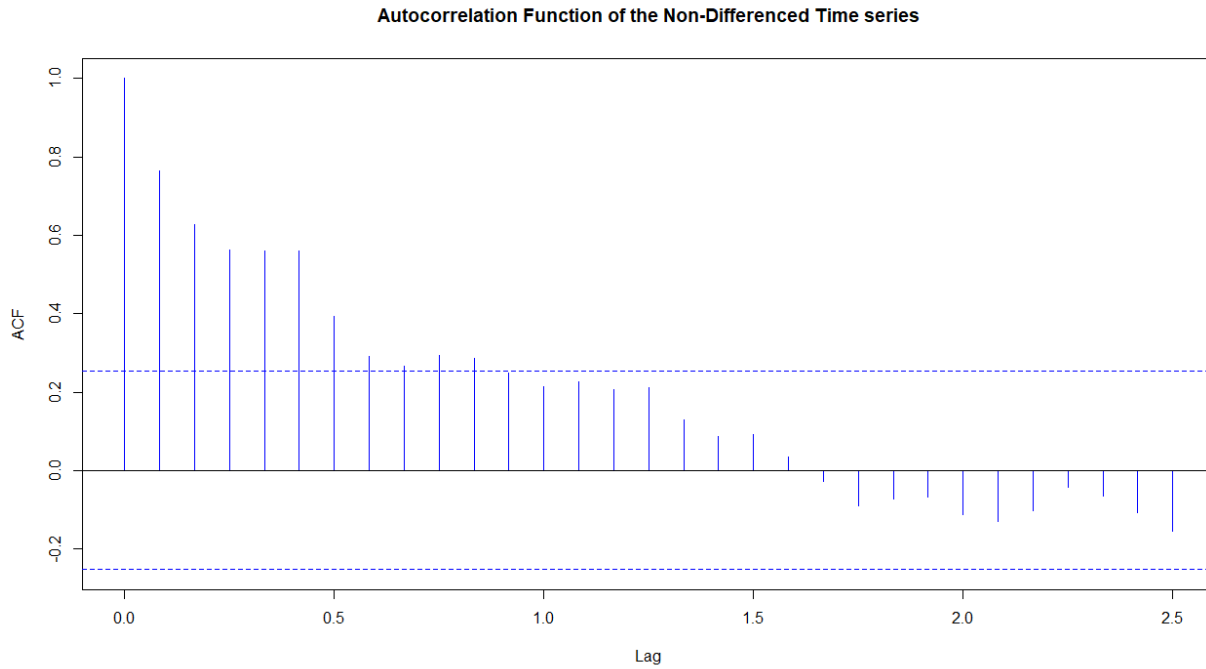
Figure 2

Components of the Time Series

4.2 Determination of Stationarity

There were several positive significant lags from figure 3 other than the first lag beyond the 95%
confidence limits. This is indicative of the highly correlated nature of the original time series.
There was a slight element of the lags being sinusoidal in nature due to a general progressive
decrease in the initial positive lags till lag 20 and a subsequent slight increase in the negative lags
thereafter.

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Autocorrelation Function of the Non-Differenced Time series

Figure 3

Autocorrelation Function Plot of the Non-Differenced Time Series

The original time series had an Augmented Dickey-Fuller test statistic of -1.8099 (p-value=0.6516) indicating the non-stationarity of the original time series while that of the first difference of the original time series was -6.2541 (p-value=0.01) indicating the stationarity of the first difference of the original time series as shown in table 1. The null hypothesis was tested at a 5% level of significance.

Original Time Series	First Difference of Original Time Series
Dickey-Fuller = -1.8099, Lag order = 3, (p-value = 0.6516)	Dickey-Fuller = -6.2541, Lag order = 3, (p-value = 0.01)
alternative hypothesis: stationary	alternative hypothesis: stationary

Table 2

Augmented Dickey-Fuller Test of the Original and First-Differenced Time Series

4.3 Model Selection

There was only one positive significant lag, lag 5, other than the first lag beyond the 95% confidence limits as shown in figure 4. The rest of the lags fell within the 95% confidence limits indicative of the non-correlated nature of the differenced time series. There was no apparent pattern in the non-significant lags within the bound limits.
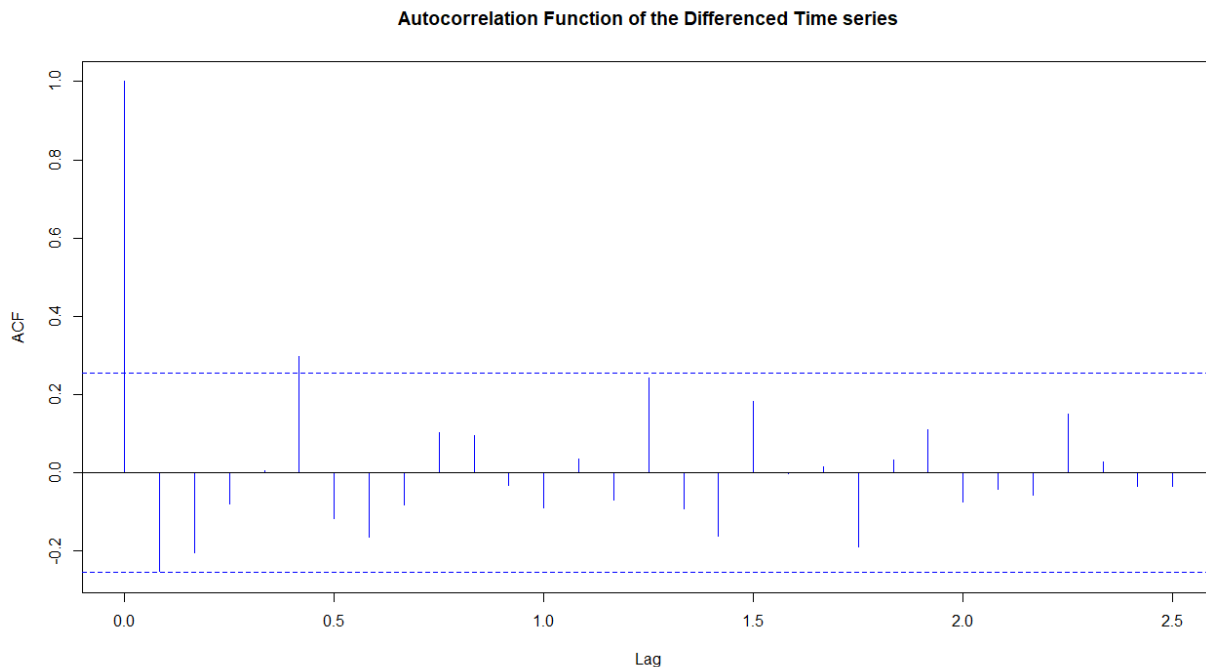
Figure 4

Autocorrelation Function Plot of the Differenced Time Series

There was only one positive significant lag, lag 2, beyond the 95% confidence limits as shown in figure 5. The rest of the lags fell within the 95% confidence limits indicative of the non-correlated nature of the differenced time series. There was no apparent pattern in the non-significant lags within the bound limits of significance.

Partial Autocorrelation Function of the Differenced Time series
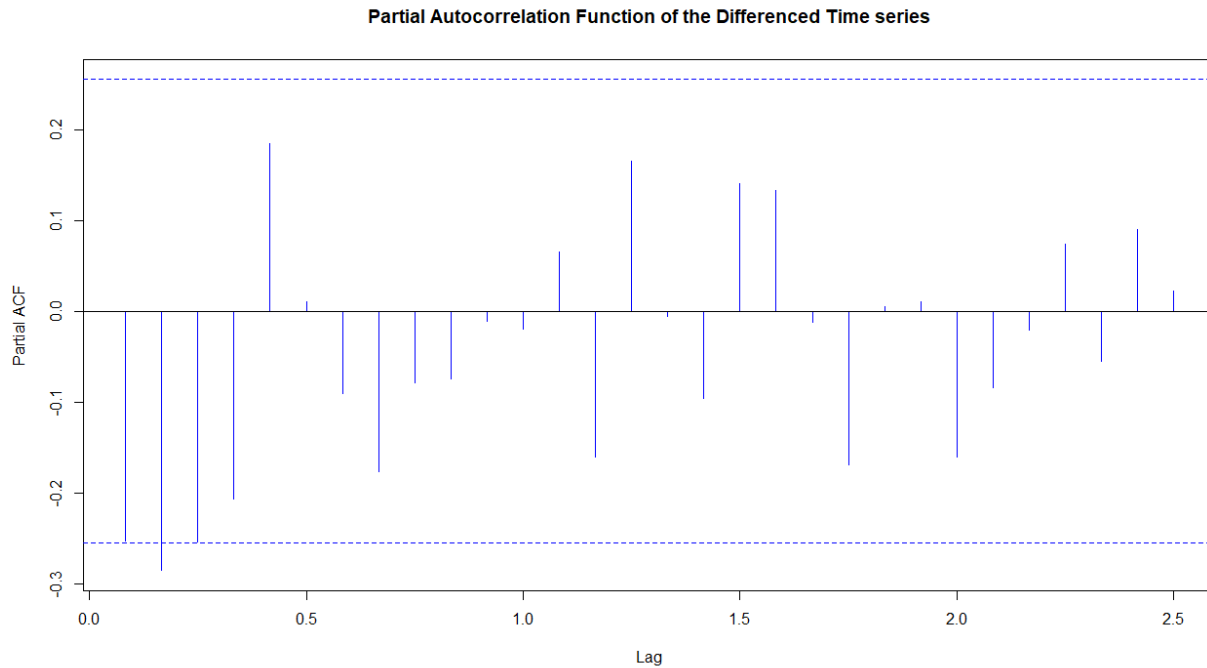
Figure 5

Partial Autocorrelation Function Plot of the Differenced Time Series

The AIC values of the fifteen empirical models ranged between 599.54 and 593.26. The model that had the largest AIC score was ARIMA (*1,1,0*) while the model that had the least score was ARIMA (*2,1,3*) as shown in table 2. The model with the least score was thereby selected for further assessment of its validity.

ARIMA MODEL	AIC VALUE
ARIMA (*0,1,1*)	594.16
ARIMA (*0,1,2*)	593.45
ARIMA (*0,1,3*)	595.30
ARIMA (*1,1,0*)	599.54
ARIMA (*1,1,1*)	594.14
ARIMA (*1,1,2*)	594.91
ARIMA (*1,1,3*)	597.20
ARIMA (*2,1,0*)	596.53

ARIMA (*2*,*1*,*1*)	594.94
ARIMA (*2*,*1*,*2*)	594.32
ARIMA (*2*,*1*,*3*)	593.26
ARIMA (*3*,*1*,*0*)	594.92
ARIMA (*3*,*1*,*1*)	596.10
ARIMA (*3*,*1*,*2*)	594.69
ARIMA (*3*,*1*,*3*)	595.24

Table 3

Table of Candidate Models and Their Corresponding AIC values

4.4 Model Diagnostics for Selected Model ARIMA (*2, 1, 3*)

The Q-Q plot revealed that most of the data points were aligned very close to or along the line depicting the expected values of a normal distribution as shown in Figure 6. This is lack of departure from the reference line is indicative of the fact that the residuals have a normal distribution.
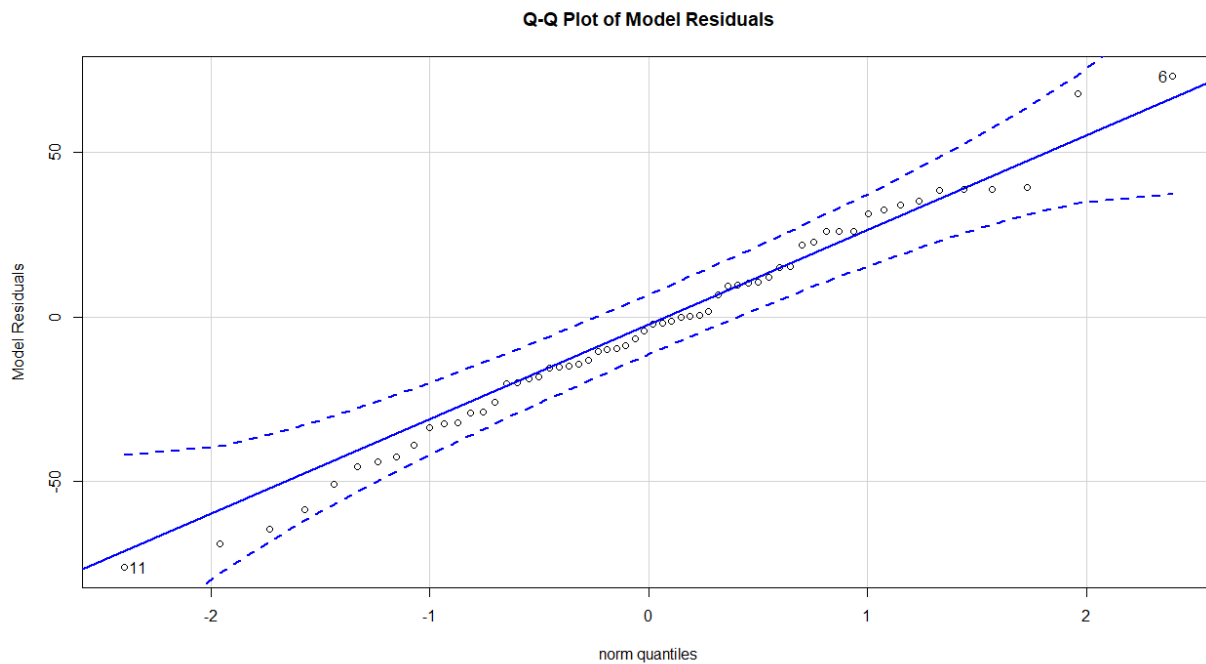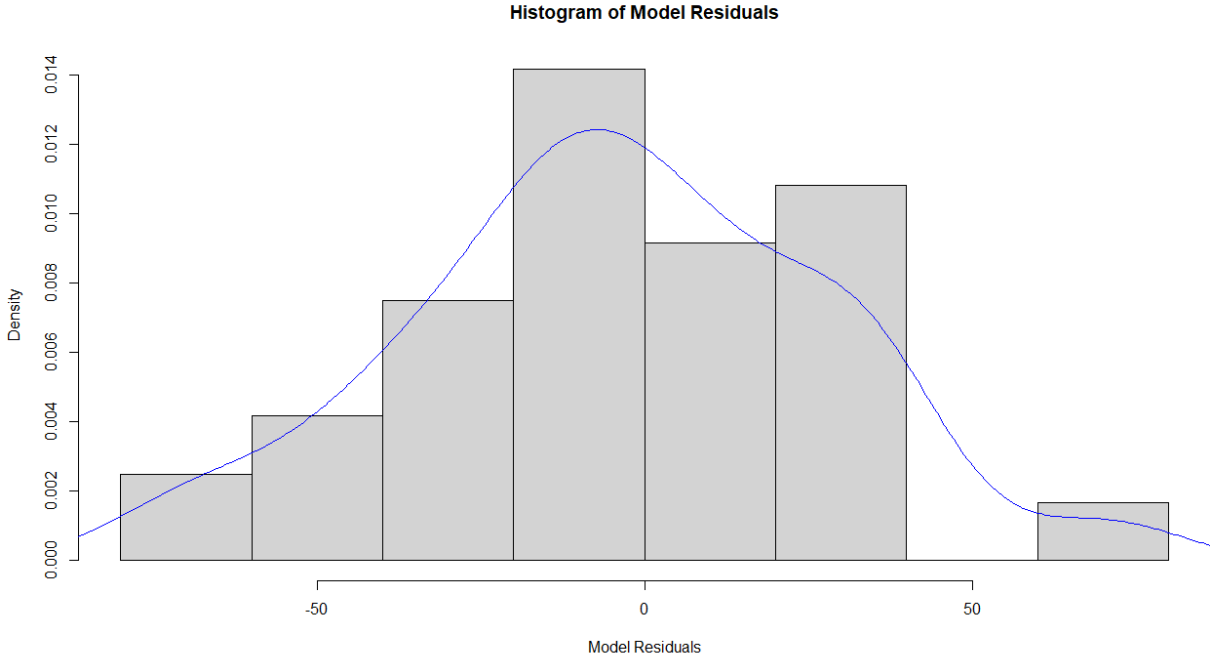

Figure 6

QQ- Plot of the model residuals

The histogram of the residuals indicate that the distribution of the residuals is unimodal and there is no distinctly apparent pattern of skewness of the residuals as seen in Figure 7. The Shapiro-Wilks test resulted in a test statistic of 0.99 and a corresponding p-value of 0.91, confirming the normal distribution of the residuals by failing to reject the null hypothesis of the Shapiro-Wilks test. The coefficient of skewness was -0.01, confirming the lack of skewness in the distribution of the residuals.

Histogram of Model Residuals

Figure 7

Histogram of Model Residuals

There were no significant lags from figure 7 other than the first lag beyond the 95% confidence limits. This is indicative of the independence of the residuals. There was no apparent pattern of the non-significant lags. The Box-Ljung test resulted in a test statistic of 37.30 with a p-value of 0.87, further confirming the independence of the residuals.

Autocorrelation Function of Model Residuals
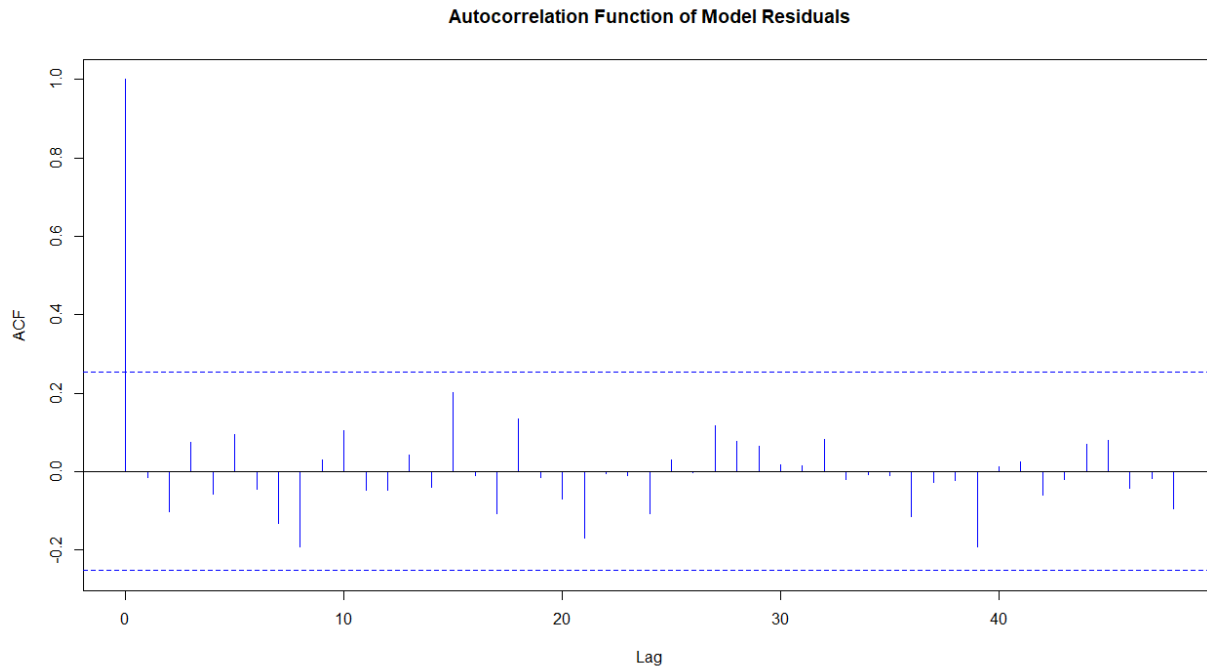
Figure 8

Autocorrelation Function of Model Residuals

4.5 Model Forecasts

The maximum six-month forecast consumption of insulin was 103 vials in March 2019 while the minimum forecast consumption of insulin was 92 vials in January 2019 as shown in Figure 9 whereas the average insulin consumption 98 ± 2 vials. The maximum actual consumption of insulin was 107 vials in January 2019 while the minimum consumption of insulin was 107 vials in June 2019 as shown in Figure 9 whereas the average insulin consumption was 119 ± 4 vials. The general trend line for the actual consumption of insulin was higher than that of the forecasted consumption indicating generally higher levels of insulin consumed than those predicted.

Forecasts of Insulin Consumption from the Arima (2,1,3) Model
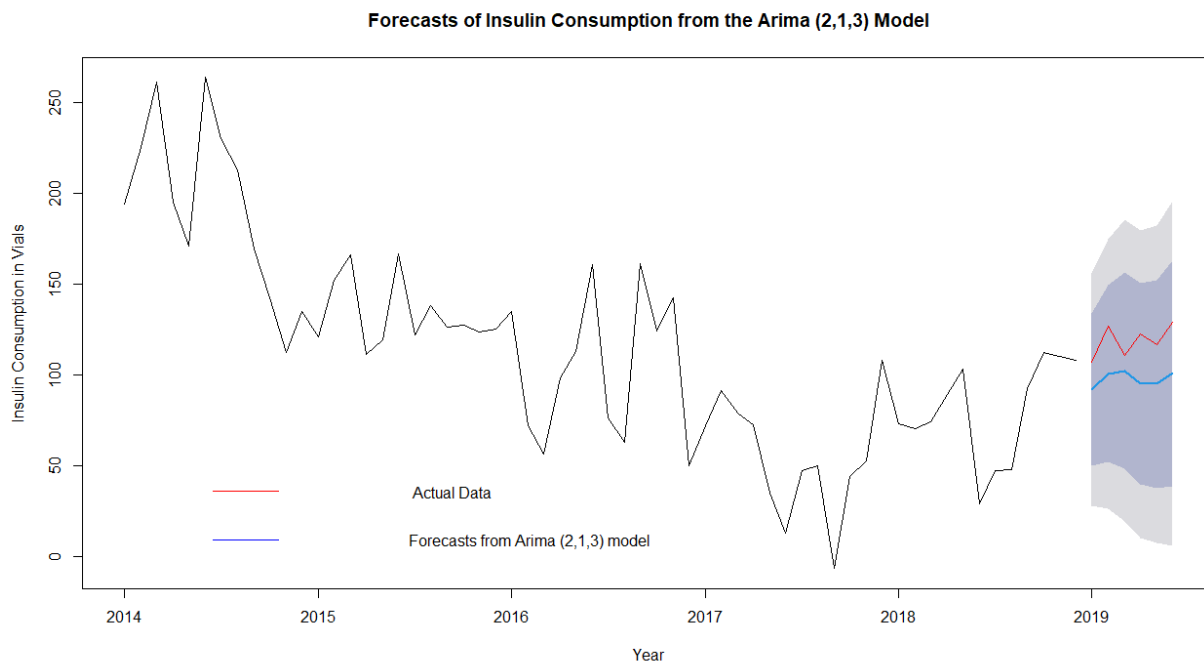
Figure 9

Graph of Comparison between Model Forecasts and Actual Values of Insulin Consumption

4.6 Comparison of Insulin Utilization between April to June 2019 (Pre-Covid) and April to June 2020 (Post-Covid)

The maximum pre-Covid consumption of insulin was 38 vials while the minimum consumption of insulin was 19 vials with the average insulin consumption during this period being 30 ($SD = 1$) vials. The maximum post-Covid consumption of insulin was 43 vials while the minimum consumption of insulin was 21 vials with the average insulin consumption during this period being 30 ($SD = 1$) vials. There was no discernible difference in the patterns of consumption during these two time periods as seen in figure 10.

Weekly Insulin Consumption Between April-June 2019 (Pre-Covid) and April-June 2020 (Post-Covid)
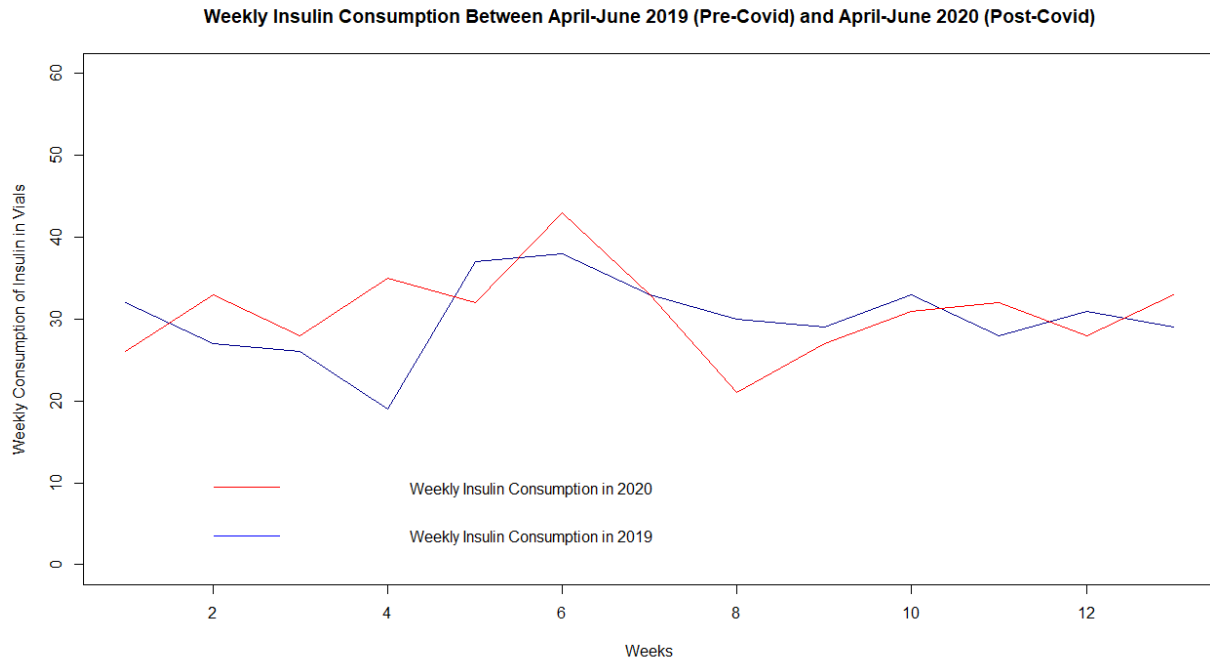
Figure 10

Graph of Insulin Consumption between April to June 2019 (Pre-Covid) and April to June 2020 (Post-Covid)

CHAPTER FIVE

DISCUSSION

5.1 Discussion

This study intended to characterize the monthly insulin consumption at Kiambu Level 5 Hospital and fit an appropriate time series model to the data. Visual inspection of the plotted time series revealed the series to have a general downward trend that appeared linear. While this could be directly attributable to a decrease in the number of patients requiring insulin visiting the hospital, the decrease in the insulin available and stockouts in the subsequent years contribute significantly to this downward trend in consumption.

Peltzer (2009) cited low patient satisfaction arising from stock-outs of essential health commodities as a cause for decreased patient visits to public health facilities. This could explain the general linear decrease where in insulin consumption due to the various stockouts of the commodities experienced in the facility.

Additionally, this reduced insulin consumption could be due to reduced insulin supply due to budgetary allocation constraints occasioning the purchase of more-perceived emergency drugs. This results in the capping of the vials of insulin given to the patient, not as per their actual need, but as per the amount available in the hospital. These budgetary allocations force the facilities to shift their purchasing priorities from routine drugs to only drugs used during emergencies or those likely to cause public uproar when they stock out (Hodes et al., 2017).

The minimum number of insulin vials consumed was noted in 2017. This could be attributed to the budgetary constraints due to deficient hospital allocations caused by a shift in priorities during the electioneering periods by the political administration. There was a general dip in insulin

consumption during the half-year months across the various years, with stockouts also occurring around the same time.

Whereas this has a budgetary root as well, the budgetary reason attributable to this could be the transitioning between the financial government years where there is a protracted delay in the disbursement of funds from the national government to the county governments, forestalling critical services within the county level, such as healthcare allocations.

There was no obvious seasonality or outliers observed in the series. The constancy of variance was difficult to assess by visual inspection. However, no visible increase in variance and as such, no logarithmic or square root transformation of the original time series was required. Differencing was used to transform a non-stationary time series into a stationary time series. A stationary time series is one with constancy of variance and mean.

The ACF plot of the original time series had several significant positive correlations between lags close to one that tailed off with slow linear decay over seven lags, indicating an element of non-stationarity of the series. Differencing strongly reduces these positive correlations (Identifying the order of differencing in ARIMA models, 2021). Upon differencing this time series, only one significant positive lag was observed. This is a strong indication of stationarity. The more formal ADF test was performed to compare the two time series. The original time series was found to be non-stationary (p-value=0.3277) while the first difference of the series was found to be stationary (p-value=0.01).

Because of the progressive reduction in autocorrelation due to differencing, strongly negative correlation values indicate over-differencing. In our case however, the largest negative lag was at-

0.2, a good indicator that the model was not over-differenced. Over-differencing leads to excess

dependencies that would increase the standard deviation of a model (Solo, 1984). Since the

first difference of the series was stationary, the value of the d parameter in the ARIMA (p, d, q)

model became 1. The model therefore became first order differenced and is denoted as follows:

$$y'_t = y_t - y_{t-1}$$

To estimate the remaining parameters in the model, the ACF and PACF were plotted for the

differenced series. The patterns of the lags can be used to identify various candidate p and q

parameters. Non-significant ACF and PACF lags indicate white noise. The p and q parameters can

be estimated where the PACF and the ACF lags cut off, respectively (Ukpata & Waterman, 2012).

There was a significant spike at lag 5 in the ACF plot, whereas the rest of the lags fell within the

significance limits. This spike could either have represented a significant MA term in the model

or could have been because of random chance (Identifying and Estimating ARIMA models; Using

ARIMA models to forecast future values, 2021). Assuming the former, this became the value of

the q parameter in the model became 5.

There was a significant spike at lag 2 in the PACF plot, whereas the rest of the lags fell within the

significance limits. The value of the p parameter in the model became 2. The resulting empirical

model therefore became ARIMA ($2,1,5$). A set of 15 candidate models around the ARIMA ($2,1,5$)

model were assessed for their AIC scores. The AIC score determines the most suitable model as a

function of the likelihood and the number of parameters of the model (Takane & Bozdogan, 1987).

The lower the AIC score, the better the model fits the data. The model that emerged with the lowest

AIC score was the ARIMA ($2,1,3$) model with an AIC score of 593. This model was then assessed

for its validity.

A Q-Q plot of the residuals of the model revealed an almost linear pattern inferring a normal distribution of the residuals. The histogram corroborated this inference as it showed that the residuals had an approximate normal distribution with a mean of about zero. The more formal Shapiro Wilks test for normality also indicated a normal distribution (p-value=0.9144) as we failed to reject the null hypothesis of the test (Royston, 1992).

The coefficient of skewness was found to be -0.01. The model residuals were then assessed for correlation by plotting the ACF and PACF plots. All the lags were found to be within the significance limits, implying no correlation of the residuals in the model. The more formal test for the independence of the residuals, Ljung-Box test, indicated that the residuals were independent (p-value=0.8679) as we failed to reject the null hypothesis (Lobato, Nankervis and Savin, 2001).

Since the model passed the various checks, the ARIMA (*2,1,3*) became the most appropriate model to fit the insulin consumption data in Kiambu Level 5 Hospital. The model fit therefore became:

$$y_t = -0.18y_t - 0.80y_{t-1} - 0.22\varepsilon_{t-1} + 0.73\varepsilon_{t-2} - 0.64\varepsilon_{t-3} + \varepsilon_t$$

The fitted model was then used to make a forecast for the insulin consumption in the next 6 months (January 2019- June 2019). The forecasts from the model were generally lower than the observed values for the same period. This could have been a result of forecast errors (Alabdulrazzaq et al., 2021). An assessment of the accuracy of the model fit revealed that the Mean Absolute Percentage Error (MAPE) of the model was 17.5%. This could explain the differences in the values between the observed and the forecasted values.

The effects of access to healthcare posed by the emergence of COVID-19 remain an issue of interest in the public healthcare framework. WHO (2020) posited that there has been a disruption in the supply chain of essential health commodities, in part due to the shift of focus towards

combatting the pandemic. Further, the redistribution of available personnel in an already thin and severely stretched out workforce further worsens access to health in our set-up. Individual perceptions of risk towards healthcare workers and healthcare institutions have as well decreased access to healthcare (Núñez, Sreeganga & Ramaprasad, 2021).

The study set out to measure this aspect of access to healthcare using the number of insulin vials consumed within the facility. Drug usage within hospitals and documented health outcomes are some of the quantifiable indicators used to measure access to healthcare (Arueira Chaves, de Souza Serio dos Santos, Rodrigues Campos & Luiza, 2019). The study revealed that there was a slight increase in the number of insulin vials consumed in 2020 compared to in 2019, however, there was no statistically significant difference in the utilisation of insulin across this period (p-value>0.05).

This could be attributed to the chronic nature of the disease and the dependency of insulin for its management. Additionally, the cost incentives laid out in public healthcare facilities for insulin could insulate it against emerging demand disruptions.

A limitation of the study was the paucity of data used to create the training data for the model. While the sample size was greater than the minimum number of observations required to develop an ARIMA model, more data when available would make the model fit better and in essence reduce the forecast errors. The study only fitted an ARIMA model. However, more time series models could be fit to the data and their performance assessed as to the most apt model for the data. The model was also univariate and fitting exogenous variables could improve the performance of the model. Finally, the duration of comparison of utilisation of insulin was just 3 months. This was due to the availability of the data.

CHAPTER SIX

CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

The total number of insulin vials consumed was 6795, with the average annual consumption of insulin being 1359 (SD =283) vials and the maximum consumption of insulin being 2316 vials in 2014, with the minimum consumption being 661 vials in 2017 during the period between 2014 and 2018. There was a general linear decrease in the annual insulin consumption during this period and notable stock-outs of the commodity or dips in utilisation during the mid-year period.

An appropriate ARIMA time series model was successfully fitted for the consumption of insulin, indicating the viability of these models as suitable alternative health commodity demand estimation techniques. The model fitted had an accuracy of 82.5% with a MAPE of 17.5%.

The average weekly pre-COVID (April 2019- June 2019) consumption of insulin was 30 ($SD = 1$) vials with a maximum consumption of 38 vials and a minimum consumption of 19 vials, while the weekly post-COVID (April 2020-June 2020) was 30 ($SD = 1$) vials with a maximum consumption of 43 vials and a minimum consumption of 21 vials. There was no significant difference in the weekly consumption of insulin between the first 3 months of the pandemic and a similar period the previous year.

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6.2 Recommendations

At a policy level, budgetary allocations to health facilities need to be buffed up especially during the mid-year months when there is a transitioning between two government fiscal years and during

the electioneering periods to avert stock-outs of critical health commodities during these periods. While routine monitoring and evaluation of essential health commodities is critical, additional monitoring should be conducted during these periods noted to be plagued by stock-outs or decreased insulin utilisation. Further studies on trends of insulin consumption need to be conducted to shed more light on the noted decreasing annual consumption of insulin despite increasing prevalence of diabetes and largely high prevalence of undiagnosed prevalence in the country. The study also forms a basis for additional ARIMA model fits to be developed based on newer insulin consumption data and adoption of these models as alternative methods of demand estimation. Expanding the currently available dataset, Mixtard 70/30 Daily Activity Register, to capture additional variables will help form exogenous variables that could also be fit to newer ARIMA models that could maybe better characterise insulin consumption or reduce the forecast errors

Additionally, different time series models should be fitted to the data and their performances assessed against each other to determine whether further insights into modelling this data exist and which time series model is the most apt for modelling this data. More data is required to assess the effects of the pandemic on the insulin consumption. Since the data used was only for 3 months, longer term trends have not been captured and this remains an important aspect to explore to understand the true effects of the emergence of COVID-19 on access to healthcare.

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Ref: KNH-ERC/A/13

17th January 2021

George Mwangi Kiragu
Reg. No.W62/10967/2018
Institute of Tropical and Infectious Diseases(UNITID)
College of Health Sciences
University of Nairobi

APPROVED
17 JAN 2021
KNH/UoN-ERC

Dear George

RESEARCH PROPOSAL – TRENDS AND DYNAMICS IN THE UTILIZATION OF INSULIN IN KIAMBU LEVEL 5 HOSPITAL
(P433/08/2020)

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 17th January 2021 – 16th January 2022.

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.

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

Yours sincerely,

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

c.c.   The Principal, College of Health Sciences, UoN
          The Senior Director, CS, KNH
          The Chairperson, KNH- UoN ERC
          The Assistant Director, Health Information Dept, KNH
          The Director, Institute of Tropical and Infectious Diseases (UNITID) UoN
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                    Dr. Ann Wang'ombe, School of Mathematics/UNITID, UoN
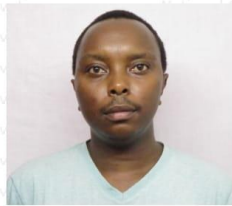
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REPUBLIC OF KENYA

**NATIONAL COMMISSION FOR
SCIENCE,TECHNOLOGY & INNOVATION**

Ref No: **631123**

Date of Issue: **18/October/2021**

RESEARCH LICENSE

This is to Certify that Dr.. George Mwangi Kiragu of University of Nairobi, has been licensed to conduct research in Kiambu on the topic: TRENDS AND DYNAMICS IN THE UTILIZATION OF INSULIN IN KIAMBU LEVEL 5 HOSPITAL for the period ending : 18/October/2022.

License No: **NACOSTI/P/21/13393**

631123
Applicant Identification Number

Director General
NATIONAL COMMISSION FOR
SCIENCE,TECHNOLOGY &
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THE SCIENCE, TECHNOLOGY AND INNOVATION ACT, 2013

The Grant of Research Licenses is Guided by the Science, Technology and Innovation (Research Licensing) Regulations, 2014

CONDITIONS

1. The License is valid for the proposed research, location and specified period
2. The License any rights thereunder are non-transferable
3. The Licensee shall inform the relevant County Director of Education, County Commissioner and County Governor before commencement of the research
4. Excavation, filming and collection of specimens are subject to further necessary clearence from relevant Government Agencies
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All correspondence should be addressed to HEAD
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HEALTH RESEARCH AND DEVELOPMENT
UNIT
P. O. BOX 2344 – 00900
KIAMBU

Ref. No.: KIAMBU/HRDU/21/10/19/RA_KIRAGU   Date: 19th Oct 2021

TO WHOM IT MAY CONCERN

RE: CLEARANCE TO CONDUCT RESEARCH IN KIAMBU COUNTY

Kindly note that we have received a request by Mr. George Mwangi Kiragu of University of Nairobi to carry out research in Kiambu County, the research topic being on **"Trends And Dynamics In The Utilisation Of Insulin In Kiambu Level 5 Hospital"**

We have duly inspected his documents and found that he has been cleared by NACOSTI to carry out the research for a period ending **18th October 2022**. He thus does not need any further clearance with another regulatory body in order to conduct research within the county of Kiambu.

However, it is incumbent upon the institution where he is carrying out research to ensure that he receives adequate supervision during the process of conducting the research. This note also accords him the duty to provide a feedback on his research to the county at the conclusion of his research.

DR. MWANCHA KWASA
COUNTY CLINICAL RESEARCH OFFICER
KIAMBU COUNTY