TWO-YEAR NEUROLOGICAL OUTCOMES OF VERY LOW BIRTH WEIGHT INFANTS AT KENYATTA NATIONAL HOSPITAL

BY

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DECLARATION

I declare that this thesis is my original work. It has not been submitted for a degree in any other university

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This thesis has been submitted for examination with my approval as the university supervisor.

Signed _____

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DEDICATION

This work, which I almost gave up midway, is dedicated to the one, whose passing almost shattered this dream,

My departed son KIZITO WAFULA SANYA

I have asked him in my prayers to look after the 45 little ones who joined him from this study with his traditional caring attitude that filled the 20 years and 4 months the almighty GOD allowed him to be with us on earth.

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GLOSSARY OF ABBREVIATIONS

AAP; American Academy of Paediatrics

ACOG; American College of Obstetrics and Gynaecology

AGA; Appropriate for Gestational Age

ANOVA; Analysis of Variance

APH; Ante-partum haemorrhage

BBM; Banked Breast Milk

BM; Breast Milk

CI; Confidence Intervals

CM; Centimeter(s)

EBM; Expressed Beast Milk

ELBW; Extremely Low Birth Weight

EPI INFO; Epidemiological Information

G; gram(s)

IU; International Units

IUGR; intra-uterine growth retardation

IQ; Intelligence Quotient

Kcal; Kilocalorie

KG; Kilogram

KM; Kaplan Meier

KNH; Kenyatta National Hospital

LBW; Low Birth Weight

LRA; Logistic regression analysis

MCG; Microgram

MDI; Mental Development Index

MG; Milligram

NBS; Newborn Services

NIC; Neonatal Intensive Care

NICU; Neonatal Intensive Care Unit

NU; Newborn Unit

OASDL; Ordinary Activities and Skills of Daily Life

P Value; Probability Value

PDI; Physical Development Index

PTF; Pre Term Formula

RR; Relative Risk

SD; Standard Deviation

SGA; Small for Gestational Age

SPSS; Statistical Package for Social Sciences

VLBW; Very Low Birth Weight

VVLBW; Very Very Low Birth Weight

WK; Week

WKS; Weeks

WHO, World Health Organization

GLOSSARY OF DEFINITIONS

Age corrected for gestation: Age counted from the time the child would have been delivered had the pregnancy reached the normal duration.

Ante-partum haemorrhage: Vaginal bleeding in pregnancy after 28 weeks of pregnancy.

Cerebral Palsy: Defects of neuromuscular function leading to restricted movement or activity.

Clinical Gestational Assessment: Use of infant's physical parameters to estimate the duration of pregnancy at birth.

Cognitive Delay: Neurological disorder affecting intelligence.

Expressed Breast Milk: Mothers' milk obtained by manual milking or mechanical suction.

Forty weeks post conception: Age at expected time of delivery had the pregnancy been completed.

Gestation assessment by dates: Use of mother's menstrual history to estimate the length of pregnancy.

Gestation assessment by clinical methods: Use of infant's clinical profiles to ascertain gestational age.

Long-term intact survival: Survival beyond the newborn period free of neurological disability.

Mixed feeding: Use of both breast milk and formula for feeding infants.

Neonatal Illness: Illnesses affecting babies during their first month of life.

Neuro-cognitive development: Development of the intellectual functions.

Neuro-development: Development of brain and other neurological functions.

Neuro-motor or Neuro-physical development: Development of the muscular and locomotive system.

Neurological intactness: Freedom from any neurological disability.

Newborn period: First 30 days of life.

Newborn Survival: Survival of an infant till the age of one completed month from birth.

Post-discharge mortality: All deaths occurring after discharge to the end of the follow-up.

Post-neonatal mortality: Death occurring between the end of the newborn period and the first birthday.

Preterm Formula: Infant formula milk modified by nutritional enhancement.

Re-hospitalization: Re-admission to a hospital ward after initial discharge.

Standard formula: Milk formula based on cows' milk and modified to resemble human milk.

Term: Expected time of normal delivery or a time estimated to be about 280days or 40 weeks or 9 months from conception.

ABSTRACT

Background: Determination of the long-term outcomes for high-risk newborns such as the very low birth weight should be standard practice for facilities from which such infants graduate. Centres in the developed countries have been consistently making such reviews in a systematic manner since the early 1980s. The outcome measures employed in these evaluations include quantification of neurological disabilities, post-natal growth monitoring and estimation of post-discharge morbidity and post-discharge mortality rates. Such information can be used as tools for assessing the performance of individual newborn units as well as comparison of more than one facility. The results of medical audits also provide an opportunity for evaluating the long-term effects of specific interventions in the newborn period. This study was the first of the kind to be undertaken at the Kenyatta National Hospital, a big center with more than 7000 deliveries/year.

Objectives: To estimate the prevalence of neurological disabilities, post-discharge morbidity and mortality at the age of two years for a cohort of very low birth weight infants discharged from Kenyatta National Hospital and identify some of the factors associated with these outcomes.

Design: Longitudinal cohort study with nested case control components.

Methods: One hundred and seventy five very low birth weight infants were recruited during the calendar year 2002 and scheduled for follow-up until the completed age of two years. The follow-up was terminated at the age of two years or death whichever occurred earlier. The initial documentation included recording of intra-uterine growth status, gender, neonatal morbidity and neonatal growth. The measures of neonatal growth were as follows; weight in grams/kilogram of birth weight/day and length and head circumference in centimeters/week. The type of milk consumed during the first month of life was also recorded. During follow-up, the infants' growth was monitored, re-hospitalization and mortality records obtained and detailed neurological assessments performed at the age of two years corrected for gestation. Cognitive function was determined using Egan FD's developmental examination of infants and preschool children method while functional disability employed the tool designed by Saigal, Rosenbaum, Stoskopf and Milner. Cerebral palsy was also assessed and specific lesions described.

Results: Out of the 175 infants recruited, 10 (5.6%) were lost to follow-up while 45 (25.7%) died leaving 120 (68.6%) survivors available for the neurological assessment. The male: female ratio for the whole cohort of 175 was 2:3, 64 (36.6%) had been intra-uterine growth retarded while neonatal illnesses were reported in 109 (62.3%). During the first month of life 78 (44.6%), 54 (30.8%) and 33 (18.9%) of the infants were fed on exclusive breast milk, breast milk supplemented with preterm formula and exclusive preterm formula respectively.

The mean neonatal weight gain for the 175 neonatal survivors was 13.5±3.9 g/kg/day, length 0.34±0.11 cm/week and head circumference 0.32±0.71 cm/week. By the time the infants reached the age of 40weeks from conception, term 33 (18.9%), 37 (21.1%) and 48 (28%) had attained or passed the 3rd percentile of the expected weight, length and head circumference respectively. The factors associated with better neonatal growth and growth attained at term included feeding on milk with increasing preterm formula content, P<0.001 and absence of neonatal illness, P<0.001. Infants who were appropriate for gestational age at birth showed better catch-up growth at term compared to those born intra-uterine growth retarded, P<0.001. Growth faultering in weight, head circumference and length at two years were found in 57.5, 62.5 and 60.8% of the infants respectively. Eighty-nine (53.8%), 95% CI; 25.6-73.2 of the 165 who completed the study were **re-hospitalized** during the follow-up period. Re-hospitalization was associated with; neonatal illness P=0.015, exclusive use of breast milk P=0.001, discharge weight less than two kilos P=0.041, neonatal weight gain <15grams/kilo/day P=0.001, growth faultering at the age of two years P=0.005 and the presence of functional disability P=0.001. The post-discharge mortality for the 165 infants with complete information was 27.3%, 95% CI 9.8-43.6. The factors associated with post-discharge death were; neonatal illness P=0.001, neonatal weight gain less than 15g/kg/d P=0.004, discharge weight less than two kilograms P=0.001 and history of re-hospitalization P=0.002.

Among the 120 infants who survived to the age of two years 14 (11.7%) 95% CI 6.7 - 17.1 had **Cerebral Palsy,** 11 (9.2%) 95% CI 4.8 - 16.9 were delayed in **Cognitive Scores** while 32 (26.7%) 95% CI, 9.3-381 had **Functional Disability.** The factors associated with functional disability included; neonatal illnesses P=0.005, exclusive use of breast milk during the newborn period P=0.020, neonatal weight gain less than 15g/kg/d P=0.014, growth faultering at two years P=0.019 and history of re-hospitalization P=0.001. The 88 survivors who did not have any functional disability were evaluated to determine the factors associated with low cognitive scores. There were significantly lower cognitive scores for those with neonatal weight gain less than 15g/kg/day P=0.001, neonatal illness P=0.005, increasing content of breast milk in feeds during the newborn period P=0.001 and weight less than the 3rd percentile at term P=0.001 and at two years P=0.005. The 88 infants who were alive and free of neurological disability at two years constituted 25.6% of the birth cohort of 344 and 50.3% of the 175 neonatal survivors. These are hence the estimates of intact neurological survival rates for the birth cohort and the neonatal survivors of the institution respectively.

Conclusions: The mean neonatal growth indices were all less than levels traditionally considered adequate, 15g/kg/d for weight and 0.5cm/week for both length and head circumference. Post-natal growth was poor with 80.6, 69.6 and 57.5% of the infants weighing less than the 3rd percentile of the expected at term, one and two years of age respectively.

The prevalence of cerebral palsy (11.7%), cognitive delay (9.2%) and functional disability (26.7%) were higher than expected. The predictors of neurological abnormalities at two years of age were; presence of neonatal illness, poor neonatal and post-discharge growth in weight. Post-discharge re-hospitalization (53.9%) and mortality (27.3%) were also higher than expected. Neonatal weight gain less than 15g/kg/d, history of neonatal illness and discharge weight below two kilograms were the consistent predictors of both re-hospitalization and post-discharge mortality.

Recommendations: Neonatal growth faultering was consistently associated with increased re-hospitalization, mortality and neurological disabilities. Since feeding with nutrient enriched preterm formula was also consistently associated with better neonatal growth, the preferential use of such milk or fortification of mothers' milk may be beneficial in improving these outcomes. Very Low Birth Weight infants should be discharged after attaining the weight of two kilograms, as this was associated with lower rates of re-hospitalization and post-discharge mortality.

I. INTRODUCTION

I.1 PREAMBLE

There have been tremendous developments in the field of neonatology over the past 30 years. The improvements have particularly been in the care of lower birth weight infants especially those born premature leading to their increased survival. During the 1960s, most infants weighing less than 2000 grams died soon after being born[1]. By the 1980s more than 90% of infants weighing between 1000 and 1500 grams at birth were surviving the neonatal period[2-3]. This massive improvement was brought about by the revolutionary developments in neonatal intensive care (NIC), which took place in the period following 1970.

Close to half of the few neonatal survivors in the 1960s developed major and often permanent neurological morbidity including mental retardation, cerebral palsy, deafness and blindness[1, 4-6]. These early graduates of newborn units were therefore probably merely increasing the population of disabled and dependent members in society. The rapid increase of the numbers of surviving very low birth weight (VLBW) infants that followed the neonatal intensive care revolution of the 1970s caused some anxiety regarding the possibility of an equal rise in the numbers of disabled children that may be brought about by them. It became imperative that due attention be paid to the quality of these survivors. The proportion of the graduates able to lead normal or near normal life was identified as the desired outcome to measure.

The ideal outcome was specifically identified as normal neuro-developmental and neuro-physical scores when the graduates were evaluated long after the initial care[7]. This made it essential that reliable, accurate and universally reproducible methods of such assessment be devised and used exclusively. Before 1970 such tools were not available. These have not only been developed, they have continued to be improved in recent years. Mental development can now be reproducibly estimated from as early as infancy. It is however preferred that these assessments are performed at or beyond the age of two years because developmental scores made in infancy are less sensitive compared to those performed later in life.

Assessment of high-risk newborns requires evaluations going up to school age to enhance accuracy and reliability. Such programs are expensive, tedious and need highly qualified personnel to perform. Simpler and less expensive methods for long-term assessments are required in resource poor countries with grossly insufficient budgetary allocation for health services. It would also be useful if certain simple screening measures can be used to identify the infants who need long-term follow-up most. Physical growth in the neonatal period can be such a screening tool. The use of early physical growth as a screening tool for later neurological development for VLBW infants was first suggested by results from research in the early 1980s, which revealed that early growth parameters correlated well with long-term neuro-developmental scores[8].

This implied that profiles of early growth indices could be used to identify individual infants at higher risk of later neurological deficits. Delineation of infants with disadvantageous growth patterns will not only be useful in predicting their outcomes, it will help narrow down the numbers needing more attention for longer periods and subsequently reduce the overall cost of follow-up programs. Resource constrained high-risk newborn services can adopt such screening protocols and reduce the cost of their follow-up programs.

This study quantified neurological deficits at two years for VLBW infants discharged from Kenyatta National Hospital (KNH) and identified the most suitable feeding regimen for promotion of appropriate growth and later neurological development. Some additional correctable factors that can improve neurological outcomes were also tested and their influence deduced. In addition, the study estimated the post-discharge morbidity and mortality for these high-risk infants and identified some of the predictors of these outcomes.

I.2; BACKGROUND

LONG TERM OUTCOME OF VERY LOW BIRTH WEIGHT INFANTS

Neonatal mortality has been used to measure outcomes of VLBW infants over the years[9-10]. During the period when these rates were very high it was satisfactory to use such statistics as the sole index of outcome assessment since the predominant concern then was crude survival. With improved survival of these infants, the use of neonatal mortality rate to audit outcomes became less informative. The observations needed to go beyond the newborn period because significant proportions of the increasing population of VLBW survivors were having significant residual morbidities. Neonatal survival alone was no longer a reliable reflection of the successes of NIC[11]. New measures involving post-neonatal parameters were necessary.

As more high-risk infants, especially the VLBW, survived the newborn period it was postulated that neurological intactness would become the most reliable measure of long-term outcomes of such babies. This view was supported by certain fundamental concerns of health workers, planners and financiers during the initial years of rapid NIC progression. These groups posed various questions regarding the outcomes of NIC graduates.

The first of these concerns was whether the survivors of NIC were ultimately becoming normal members of society or merely increasing the burden of caring for larger numbers of disabled members.

To answer this question longitudinal studies going into late childhood or early adulthood were essential. These studies used neurological evaluations performed beyond infancy as the main tools[3, 11-12]. The key result of such assessments was suggested as being the determination of the proportion of a birth cohort that was neurologically intact at a specific time after the newborn period. This is also called long-term intact survival rate.

High-risk newborn outcome reports are currently required to conform to universally accepted design, analysis and reporting formats. The standard models have been published in leading journals[12-14], constituted a national expert committee[15] and formed part of standard textbooks of neonatology[16-18]. Using these methods, significant decreases in disability rates despite an increasing population of VLBW infants have been realized providing evidence that NIC was indeed a worthwhile development[3]

The second question, especially asked by health planners and financiers was whether the high-risk NIC graduates had the same life expectancy and indeed quality of life as the general population. The issue of life expectancy is answered by estimating the infants' post-discharge mortality. Available information indicates that VLBW infants have five to ten times higher post-neonatal mortality compared to their normal birth weight counterparts. This is expected to significantly lower their life expectancy making it a useful audit tool[11].

Quality of life as measured by economists in adults has not been possible to estimate at the age of two years or indeed in the entire paediatric population. Attempts have been made to use perceived wellness of such children by parents and achievement of expected social and physical function to allow the construction of a comparative hierarchy against which such outcome can be assessed.[19] These methods have major difficulties when applied to a pediatric population in which functional outcome is difficult to measure. Physicians have subsequently adopted the use of neurological development as an indirect measure of quality of life. Although physical development is relatively easy to measure by observing the established motor milestones, determining mental development in young children is much more challenging. Recent developments have improved the accuracy of tools used in estimating intelligence in young children and infants[7]. For children who are two years old or younger, the Bailey's developmental scales provide the most accurate and consistently used method of cognitive assessment[20].

The final issue in the drive to find appropriate audit tools for high-risk NIC graduates involved the need to evaluate the other post-discharge factors that may modify the eventual outcomes of or increase the burden of care required for the high-risk NIC graduates. These included the post-neonatal medical and surgical morbidities whose increased incidence may be directly related to both peri-natal and post-discharge events.

Reports from industrialized countries indicate that VLBW infants endure more than three times the frequency of re-hospitalization observed among the normal birth weight infants[7]. These events also modify the infants' quality of life in addition to increasing the burden of care brought upon their families, society and government. Quantification of their occurrence hence constitutes important medical audit evaluations.

EARLY GROWTH OF VLBW INFANTS AND LATER DEVELOPMENT

Normal Early Growth in VLBW Infants

The healthy premature VLBW appropriate for gestation (AGA) infant is expected to grow at a velocity that allows them to regain their birth weights by 2-3 weeks and by term be within two standard deviations (SD) of the expected mean birth weight[1]. After regaining the birth weight subsequent increment is expected to be 15-20grams/kg/day till they reach the age of their expected time of normal delivery [16]. Head growth continues at a rate commensurate with intra uterine expectations but linier growth stagnates till about 34 weeks gestation after which it also accelerates to attain expected levels at term[1]. This growth pattern can only be achieved if adequate nutrition is provided from the earliest time possible and peri-natal and neonatal complications are avoided or effectively controlled.

Inadequate nutrition and illnesses during the neonatal period are such potent inhibitors of growth that the presence of failed growth usually indicates that one or both of these factors may be present.

The two factors lead to higher than expected initial weight loss resulting in the need for longer periods before regaining birth weight with subsequent inability to catch-up by term. Peri-natal illnesses make adequate enteral feeding difficult and where intravenous nutrition is not available inevitably lead to poor neonatal growth. The intra-uterine growth retarded (IUGR) infants of the same birth weights usually do not experience similar initial weight losses but seldom catch-up by term[21].

Importance of early events among VLBW infants

It has been observed in both humans and other mammals that there are certain periods in early life in which certain events may have effects that manifest much later in life with undesirable and often permanent consequences while the same factors have minimal effects when they affect the individual later[22-23]. For instance, intra uterine rubella infection has very severe effects on the un-born child while the disease is of trivial consequences in older children[24]. Female rats whose mothers are injected with testosterone at an early stage in pregnancy develop permanent male behaviour after birth while later injections do not manifest similar effects[22].

These observations demonstrate that an individual organism exposed to a situation at an early age, presumably of rapid development may be more likely to develop negative effects at a later age. This concept has been termed "programming" by Lucas and others[23].

In the model postulated by Lucas, programming is thought to occur in one of two ways, induction or physiological setting.

Induction: This depicts impaired growth or development of a somatic structure resulting from a stimulus or insult during a critical period as in congenital Rubella syndrome[24].

Physiological setting: This implies a specific time when an individual is most vulnerable to the effects of some stimuli or insults. Exposure to the relevant insult or stimulus at that time may then lead to untoward effects that become apparent later in the individual's life. Events that occur during the newborn period only but manifest later as neurological deficits in VLBW infants are thought to act in this way.

To test the "physiological setting" hypothesis in humans, Lucas focused his studies in VLBW infants in whom he postulated that the first month of life was a vulnerable period with inadequate nutrition, associated with poor growth, as the insults that result in impaired neuro-development[23]. The group established that infants who were inadequately fed and failed to grow normally during the first month of life had lower neuro-developmental scores when assessed in later childhood[23]. The newborn period was, therefore, presumed vulnerable and early feeding/diet regarded as a programming factor.

EARLY NUTRITION OF VLBW INFANTS

By the time of the rapid development in the care of smaller often premature infants, it was already expected that their nutritional needs would be different from those of bigger babies and had to be evaluated as well. Most of the initial concerns were exhaustively researched leading to the development of the current feeding practices in developed countries[25-29]. With this knowledge, centres in advanced countries currently employ either nutrient enriched preterm formula (PTF) or fortified breast milk (FBM) as the routine neonatal nutrients for VLBW infants.

Early Nutrition and Early Growth

In order to achieve adequate growth the specific nutritional needs of the VLBW infant must be met. Available evidence[8] indicates that early growth is an important determinant of later development, hence, newborn care units should employ neonatal feeding strategies likely to achieve adequate growth in order to promote better neurological development in future.

Mothers' milk is the sole recommended feed for normal newborns during the first months of life[30]. In Kenya, this recommendation has been extended to even the VLBW infants despite available evidence that such infants seldom receive adequate nutrition in the first month from mothers' milk alone[25-29].

It has been established that fortification of breast milk[25] or deliberate supplementation with nutrient enriched preterm formula[26] achieve better growth during the first month of life in such infants than breast milk alone. Fortification of mother's milk has the advantage of enhancing growth while preserving the other biological advantages of human milk. Published literature suggests that in identifying the appropriate diets for VLBW newborns, nutritional value and the other biological advantages of mothers' milk must be considered together and not in isolation if adequate growth is to be ensured.

Early Nutrition and Later Development

It was suggested earlier that the newborn period in VLBW infants is a vulnerable one in which nutrition may act as a programming factor for outcomes later in life. Evidence in support of this observation initially came from animal reported by McCance when he manipulated litter size in rats by feeding large litters with less milk than those from small litters during a 21day suckling period[31]. The results showed that rats originating from the large litters were substantially smaller than those that had come from the smaller litters. When he later fed both groups normally, the smaller animals originally from large litters continued to diverge in body size from the larger animals. Thus, three weeks of dietary manipulation among these rats had resulted in a lifetime programming of their growth trajectory. McCance also showed that it was only this early phase that constituted a critical period for such effects.

When McCance made identical dietary manipulation were made a few weeks later, no lasting effects were observed as the underfed animals showed catch-up growth when they resumed appropriate diets. The critical window for growth programming by early nutrition had passed.

A review of 165 animal studies by Smart[32] on the effects of early under-nutrition on later outcomes revealed that most of the studies agreed with McCance's findings. Dobbing and colleagues specifically established that animals given inadequate nutrition at early vulnerable periods ended up with various specific neurological anomalies including reduced brain size and cell numbers, behavioral changes and impaired memory and learning capacity[33].

Some observational studies had also reported the association between disruptions during certain periods and poor neurological outcomes in later life among human infants[34-36]. Randomized clinical trials with long follow-up periods have since been conducted to verify these observations. Because VLBW infant feeding was under scientific scrutiny in the final quarter of the 20th century, this group provided a window of opportunity for such studies. Using large nutritional intervention trials at a time when various milk preparations were being introduced, it was established that dietary manipulation in the neonatal period also affected later neurological development in humans especially those born VLBW[23].

I.3: LITERATURE REVIEW AND ANALYSIS.

I.3.1: LONG-TERM NEUROLOGICAL OUTCOMES OF VLBW INFANTS

Long-term neurological disabilities in LBW infants have been reported for many decades. Reports pre-dating 1970 were however very disappointing with close to 50% of neonatal survivors having significant disabilities[1]. At that time the parameters used were cerebral palsy and some crude measures of mental retardation. As neonatal care improved in the 1970s through to 1980s the situation commensurately changed. The historical progression of neurological outcomes of high-risk LBW infants is summarized in the following citations.

Johnson evaluated 66 survivors whose mean birth weight had been 2319 grams and found neurological sequelae in 30% of them. The specific handicaps in this series included deafness in ten percent, blindness in seven percent and reduced intelligence at eight years in eight percent[4]. The population included many infants over 1500 grams at birth. Brown[5] and Stahlman[6] also reported similar rates of neurological sequelae during the same period as Johnson. Brown whose group weighed less than 2000 grams at birth found 30% mental retardation measured as Intelligence Quotient <85 at eight years age while Stahlman in his series reported a 14 % mental retardation rate also at eight years using the same criteria. Stahlman's cohort included infants weighing over 2000g at birth[6].

Studies from the early 1970s including more VLBW infants reported between eight and 20% cerebral palsy and three to 15% cognitive disability rates, some improvement compared to the previous decade[36-37]. The fundamental flaw in all these earlier studies was that most of them could only recruit small numbers as the survival rates of VLBW infants was too low then to avail large groups for follow-up. They also did not use the current birth weight stratification of less than 1000grams, 1000-1499grams and 1500grams or more making comparison with present day evaluations difficult. These reports nevertheless provided the foundation for today's research. Modern reports follow strict requirements including statistically valid samples, standardized birth weight stratification and longitudinal design. As so many such reports have been published as individual papers, a selection of grouped data shall be reviewed here to show the present trends.

Escobar and colleagues[38] meta-analyzed 111 studies reported between 1960 and 1988. All 111 studies presented primary data on the outcome of all infants born weighing less than 1500grams. Each study was also required to account for all children lost to follow-up and have clear definitions of outcomes. The total number of infants involved in these studies was 26,099. Escobar utilized this large population to determine the incidence of the major outcome variables consistently reported as cerebral palsy or functional disability. Eighty-five studies reported a median cerebral palsy rate of 7.7%. The median functional disability rate from the 106 studies with this variable was 25%.

In a collaborative study involving two large centres in Australia during the late 1970s and early 1980s Kitchen et al recruited infants weighing less than 1500 grams at birth and followed them up to the age of two years from their expected date of delivery[39]. They reported 12% and 10% prevalence of cerebral palsy and cognitive developmental delay respectively. The study employed the Bailey's assessment scales for their evaluation. Some 1.3% and 1.7% of the Australian cohort were also severely deaf and blind respectively. Most of these disabilities occurred among those less than 1kg at birth, the very very low birth weight (VVLBW). This study further revealed significant differences between the two centres in various specific outcomes and concluded that the performances of different centres could be compared in this way.

Reports from industrialized countries after 1980 show only five percent significant neurological disability rates among infants born weighing 1000-1500 grams despite neonatal survival rates of over 90%. In these countries, focus has now shifted to the VVLBW group of infants. This big improvement was a result of improved understanding and intensity of the care provided to the VLBW infants in those countries in the two decades preceding 1980[2].

Though many VLBW infants are born annually in resource poor countries like Kenya, budgetary constrains have not allowed appropriate follow-up of the 50% who survive the neonatal period. This study, therefore, pioneers this area of research in Kenya.

I.3.2: POST-DISCHARGE MORTALITY

Conceptually, it is important to estimate the mortality of high-risk infants beyond the neonatal period. This is because early survival may merely postpone their death to a later time in childhood. When this occurs, then the overall goal of NIC, which is long-term survival, is undermined. Most of the available reports have been from graduates of neonatal intensive care units (NICU) in industrialized countries. Such reviews have been reported in leading journals[40-42] and are now included in standard textbooks of neonatology[7]. Some specific citations are reviewed below.

Pooled data reports a five to ten fold increase in post-discharge mortality among all graduates of the NICU during the first two years of life compared to the general infant population[7]. Yu et al in their series involving two large NICUs reported a10 fold increase in mortality during the first two post-discharge years for the VLBW infants who graduated from NICU when compared to the general population[40]. In another review by Bowman and Yu, the post-discharge mortality during the first two years was quantified at four percent for all the NICU graduates with VLBW infants reported to contribute more to these deaths[41]. In the latter study the VLBW infants had the highest mortality, more than either the total group or the VVLBW sub-group. This may have been because proportionately more VLBW survivors had severe peri-natal complication than those in the VVLBW category.

Very very low birth weight infants with severe peri-natal illness were more likely to die during the initial illness hence survivors were relatively healthier. Hack and colleagues also demonstrated increased post-neonatal death in the VLBW group when compared to either the VVLBW or all the NICU graduates[42].

The increased post-discharge mortality in the studies reported by Bowman et al and Hack et al was related to either residual peri-natal diseases or other endemic medical conditions including common infections. Sudden infant death syndrome was also a recognized cause of death in both studies. Post-discharge mortality data for high-risk infants should include the predominant causes of death whenever possible in order to help identify preventive strategies. In particular, the identification of which between residual neonatal disease and primarily post-discharge illnesses is the predominant cause will help in identifying effective interventions.

I.3.3: POST-DISCHARGE MORBIDITY

Post-discharge morbidities are observed more frequently among VLBW infants than their bigger counterparts. The specific illnesses that inflict them include respiratory tract infections, gastroenteritis, wheezing attacks and other medical illnesses. Umbilical and inguinal hernia and aural ventilation tube insertions are the common surgical problems seen in this group. These complications frequently lead to re-hospitalization after initial discharge often at a rate much higher than that expected for larger babies[7].

It has been estimated that between 22 and 53% of VLBW infants are re-hospitalized by the second birthday in developed countries. This is 3 to 5 times more than comparative groups of larger infants[7].

McCormick and colleagues[43] reviewed a random sample of 4989 one-year-old infants in the Baltimore region, USA using re-hospitalization as the dependent variable. The overall re-hospitalization rate during the first year in McCormick's study was nine percent but when the analysis was stratified in terms of birth weight, those who had weighed 1500grams or less at birth had been re-hospitalized four times more than the total group. McCormick also noted that though the subgroup of infants who had weighed 1500 grams or less at birth constituted only 6.4% of the whole group, they contributed a disproportionate 20% of all the re-hospitalization episodes. Multivariate analysis of this data established VLBW status and neurological abnormality as the best predictors for re-hospitalization in the first year of life.

Mutch, et al[44] compared the re-hospitalization experience of VLBW survivors with that of a randomly selected group of heavier infants. They found a re-hospitalization rate of 22% and 27% among the VLBW infants during the periods of 1968-1972 and 1974-1978 compared to 9.8% and 8.9% for the larger infants during these periods respectively. Both the changes over the two periods and between the birth weight categories were statistically significant.

The relative risk of re-hospitalization associated with VLBW status was computed at 2.2 and 3 during the 1968-72 and 1974-78 periods respectively. The decrease in re-hospitalization observed during these time periods occurred despite improvement of neonatal survival of the VLBW category in the region from 35% to 48%.

Hack, et al[45] prospectively observed 90 VLBW infants during their first year of life reporting 33% re-hospitalization among them. Half of the re-hospitalizations in Hack's report were due to chronic conditions related to initial neonatal complications while the other half were brought about by other acute bacterial infections. Fourteen percent were re-admitted for repair of inguinal hernia.

Combs-Orme et al suggested that socio-economic disadvantage of the family increased the risk of both morbidity and mortality in VLBW infants after discharge[46]. This group evaluated the socio-economic impact of re-hospitalization of 79 VLBW infants in a disadvantaged region of Baltimore Maryland. They found that young, single and less educated mothers accounted for up to 51% variance in re-hospitalization rates and concluded that that these features can be used to predict which infants will require re-hospitalization in their first two years of life. McCormick[43] and Mutch[44] also reported the association between low socio-economic status and post-neonatal morbidity in VLBW infants. McCormick indicated that infants using private insurance cover were more likely to be re-hospitalized compared to those on public or no support[43].

I.3.4: EARLY GROWTH AS A PREDICTOR OF LATER DEVELOPMENT

The relationship between early growth and later development has been reviewed in the background section of this thesis. In this section quantitative evidence of this association is reviewed in published literature.

Skurse and colleagues conducted a study in term infants to establish whether post-natal growth influences Bailey's mental and motor scores at the chronological age of 15 months[47]. They used weight for age less than two standard deviations (SD) of the expected mean to imply significant growth failure. The infants who fell in this disadvantaged group during their first six months of life were found to be 10 developmental points behind those with normal growth. When the growth deficit occurred during the second six months of life the developmental deficit was only 6 points. Though this study was confined to assessments performed at 15 months and involved only term infants it provided some of the early evidence that early growth may be a conditioning and hence predictive factor for later development in humans.

Hack, et al reviewed a prospective cohort of 192 VLBW infants at the age of eight months to determine the prognostic importance of post-natal growth on developmental scores[48]. The infants who failed to catch-up in growth by eight months of life corrected for gestation had lower mean Bailey's developmental scores, 89 versus 109 P= 0.001 and higher rates of neuro-physical dysfunction, 32% versus 13% P=0.01.

The group concluded that catch-up growth in early life was important in VLBW infants as well. This group further observed that intra-uterine and immediate post-natal growth failure had no prognostic significance if catch-up was achieved within infancy. They nevertheless confirmed that addition of poor growth in infancy to those who already had inadequate neonatal growth worsened the developmental outcome.

Hack and her team[49] reported on 182 VLBW infants followed up to a mean age of 21 months corrected for gestation and found that the children who had remained below two SD of the expected weight for age had significantly lower mean Bailey's developmental scores when compared to those who had grown normally, 85.3 versus 94.7 P=0.01. The cohort also reported neuro-motor deficits in 25% of the children with growth retardation and only 6% among those with normal growth. Early growth predicted later developmental scores and neuro-motor dysfunction in these non-randomized controlled trials.

A randomized controlled multi-centre trial in the1980s provided some of the most pivotal evidence of the relationship between early growth and later development in VLBW infants[8]. This nutritional intervention trial whose primary objective was to evaluate the effects of early diet on later development also hypothesized that growth in the neonatal period and early infancy could influence later development. The trial demonstrated that poor neonatal weight gain was a risk factor for reduced developmental scores at eight years.

The developmental disadvantage was particularly observed in the overall IQ and verbal scores. The trial, however, found no association between early growth and the subsequent occurrence of neuro-motor disabilities.

Quantitative analysis of the results of the multi-centretrial[8] showed improved mean overall IQ of five points P=0.01 and verbal scores of six points P= 0.003 among those who had grown at 15g/kg/day or more during the newborn period. This improvement of developmental scores at eight years for infants with better neonatal growth was only seen in male infants in this trial. The observation that females are less affected by early growth and nutritional factors has been reported from animal studies as well[50]. The developmental score advantages were enhanced further when combined neonatal weight gain above 15g/kg/d and normal weight for age at nine months were combined as one predictor. Using both parameters, all the subjects regardless of gender showed the association though the influence remained more pronounced among the males. The trial concluded that growth during the neonatal period and in the first year of life are good predictors of future cognitive performance of children born VLBW.

It is evident from these reviews that accurate observation of early growth may help identify infants more likely to have important disabilities later in childhood. Early identification of such infants will lead to more focused attention being given to them rather than the whole population and reduce the overall cost of follow-up programs.

I.3.5: EARLY NUTRITION AS A PREDICTOR OF EARLY GROWTH

Because early growth is important for ensuring normal neurological development of VLBW infants (see section 1.3.5) early feeding strategies should aim at achieving the growth patterns associated with better neurological outcomes. Evidence, in literature, shows that early nutrition intricately influences early growth (section 1.3.4) and by extension later development.

Modern enteral diets for VLBW infants consist of either fortified breast milk (FBM) or preterm formula (PTF). Preterm formula milk is standard formula modified by increasing its macro and micronutrient density. Breast milk fortifiers are powdered concentrates which when added to mothers' milk enhance its nutritional density to levels identical to PTF.

Quantitative and qualitative analysis of these modified milk products regarding their use in VLBW infants was the subject of intense research in the 1980s[25-26]. In particular their role in improving early growth was critically appraised.
A large multi-center trial evaluated growth parameters in infants fed on four different regimes; PTF, banked breast milk (BBM) and either PTF or BBM as supplements to expressed breast milk (EBM)[25]. The infants on exclusive PTF had mean neonatal weight gain of 18grams/kg/day, those on PTF+ EBM grew at a mean of 16/kg/day while infants on BBM alone achieved only 12g/kg/day growth rate. Growth in head circumference and length showed similar trends in this study.

These results invited the conclusion that enhancing nutritional density of milk used for feeding VLBW infants significantly improves their growth during the newborn period.

Brooke et al[26], compared the early growth patterns in VLBW infants fed on three different regimes, EBM, PTF and standard formula. The infants fed on PTF achieved mean neonatal weight gain of 21g/kg/day compared to 15 g/kg/d in either of the other two groups $P < 0.05$. The growth in length during the first month was 1.4 centimeters for those on PTF compared to 1.1 centimeters amongst those feed on EBM or standard formula while head growth for the infants on PTF was 0.3 centimeters better than the other two groups ($P<0.05$). Brooke and colleagues concluded that nutritionally enriched milk led to better growth of VLBW newborns. One other report while confirming the same effects of nutrient enhanced milk on early growth of VLBW infants additionally observed that infants whose diets included mothers' own milk matured faster leading to earlier hospital discharge, especially if they grew normally[27].
All the studies consistently reported the inadequacy of mothers' milk alone in ensuring expected growth velocity among VLBW infants during the first month of life.

1.3.6: EARLY NUTRITION AS A PREDICTOR OF LATER DEVELOPMENT

To establish the presence of any direct association between early diet and neurological development in infancy among preterm infants, Lucas and others in the United Kingdom (UK) followed up a cohort of 502 LBW mostly premature infants till the age of nine months[51]. The infants had during their neonatal period been randomly assigned to receive either PTF or BBM as sole diets or as supplements to EBM during their first month of life. In the primary comparison, infants on PTF averaged 2.5 Bailey's developmental points more than those on BBM. In the supplemented group, it was found that those on PTF+EBM scored about 5 points more than those on BBM+EBM especially when the BBM component was more than 50% of the total. The workers suggested that the diet used for VLBW babies over a brief but critical post-natal period has neuro-developmental consequences identifiable in that persist into infancy.

To establish whether this association between early nutrition and later development persisted beyond infancy, 424 preterm infants randomly assigned to feed on PTF or term formula during their first month of life was assessed at 18 months[52]. The infants feed on PTF had developmental score advantages of six points on motor and 15 on mental developmental.

This advantage was more than 20 points when intra-uterine growth retarded infants when analyzed alone. Nutritional enhancement continues to improve developmental outcomes into the second year of life. The latter has been confirmed by another group of reseachers[53].

Lucas, et al later reported formal IQ scores at 8 years of children who as newborns had been randomized in different nutritional regimes. They reported up to 8.3 IQ points advantage for those who received mother's milk compared to the ones who had consumed other milk preparations[54]. This IQ advantage among children previously fed on their mothers' own milk was maintained even when various socio-demographic factors were accounted for. The investigators suggested that there is an independent influence of breast milk on mental development in VLBW infants. Several other studies subsequently concurred with this finding[55-60]. None of these studies has, however, provided evidence of mothers' or any other milk's ability to achieve enhanced development without first being adequate for promotion of normal growth in early infancy. It is more likely that both parameters must coexist for normal brain development.

1.3.7: SUMMARY

The importance of post-discharge outcome audits for VLBW infants has been conclusively justified. The need to identify diverse neonatal factors that predict the undesired outcomes has also been explained in this introduction. The goal of this study was to undertake the first such audit at the KNH and identify some of the neonatal factors associated with the undesirable outcomes.

II. STUDY JUSTIFICATION, AIM AND OBJECTIVES.

JUSTIFICATION

Auditing medical services provided by specialized units is now standard practice in the developed world. It remains the best method of assessing the quantitative and qualitative performances of such units. This is particularly important in reference to high-risk categories of patients of whom eventual survival may be accompanied by significant handicaps. In case of high-risk newborns the proportion among survivors who are free of neurological disability is one of the most important measures used in the audits. Such studies are also helpful in identifying factors whose appropriate modification may lead to better and healthier survival of the infants. Since the factors frequently identified, as predictors of undesired outcomes are not uniform from region to region every health facility should identify the predominant factors in their area in order to prioritize the interventions. This has not been done at the KNH before despite over 30 years of providing care to such infants.

UTILITY

These results have identified neonatal parameters that may be used for early prediction of neurological sequelae, re-hospitalization and post-discharge mortality. The findings of the study will help the institution to narrow down on the infants who need follow-up most reducing the overall costs of the program. The study findings have also provided information regarding early interventions likely to improve later outcomes among VLBW survivors graduating from KNH.

AIM, OBJECTIVES AND HYPOTHESES

Aim: To describe the major outcomes of Very Low Birth Weight infants at the age of two years following discharge from the Kenyatta National Hospital.

Primary Objective: To determine the incidence of neurological disabilities in the VLBW infants who survive until the age of two years after discharge from KNH.

Secondary Objectives

1. Describe the growth patterns of VLBW infants during their first 24 months of life and determine the factors that influence growth failure among them.
2. Determine the factors associated with neurological disabilities among VLBW infants who survive until the age of two years at KNH.
3. Estimate the post-discharge morbidity and mortality of this cohort of VLBW infants for the first two years after initial discharge and identify some of the associated factors.

Hypotheses

Neurological disabilities, post-discharge re-hospitalization and post-discharge mortality are more prevalent among VLBW infants in this cohort than those reported from developed countries.

III. METHODOLOGY

DESIGN

This was a longitudinal follow-up of a cohort of VLBW infants who survived the neonatal period at the Kenyatta National Hospital's Newborn Unit. It involved recruitment of all eligible infants at the age of one month and subsequent follow-up until the child attained the age of two years from the time they would have been born had the mother completed the normal pregnancy duration of nine months.

The data allowed the categorization of these infants into separate exposure groups for various factors including obstetric parameters, infants' gender, intra-uterine growth status, neonatal illnesses, neonatal feeding regimens and post-natal growth indices. From this categorization, a comparative wing to ascertain predictors of neurological disability, post-discharge re-hospitalization and post-discharge mortality was done.

STUDY AREA

The study was undertaken at the Kenyatta National Hospital, the national referral health facility for Kenya and also the teaching hospital for the University of Nairobi's College of Health Sciences. It has a large maternity unit with over 7000 deliveries a year mostly from high-risk pregnancies and a level II NIC facility providing therapeutic interventions for early and intermediate morbidities affecting high-risk newborns.

The average daily population is between 70 and 100 babies. Most of these infants are born at the hospital but a few are admitted from home or other institutions.

POPULATION

Definition

Neonatal survivors among infants admitted to the Kenyatta National Hospital with birth weights of 1500 grams or less. This was a heterogeneous group consisting of both normal and intra-uterine growth retarded infants. Gestational assessment to help determine the intra-uterine status was based on Ballard's clinical scores[61].

Inclusion criteria

1. Birth weight 1500g or less.
2. Residents of Nairobi or its environs for purposes of enhancing follow-up compliance.
3. Informed, written and signed consent by parent or guardian.

Exclusion criteria

1. Non-residents of Nairobi for whom, consistent follow-up for a two-year period would have been difficult.
2. Overt congenital anomalies, which may on their own, influence growth and neurological development.

3. Infants of mothers known to have HIV infection or AIDS since such infants, if infected, are known to be independently predisposed to abnormal growth and delayed neurological development.

Sample Size

The primary objective was to describe the magnitude of neurological disorders in this cohort of VLBW babies at the age of two years corrected for gestation. The standard prevalence formula was used as described in appendix 1. A seven percent prevalence of both cerebral palsy and developmental delay found by a recent study in South Africa[62]in a population with demographic features comparable to those of the present cohort was used in the calculation. A minimum sample of 100 was required at the age of two years for statistical validity.

In order to ensure the availability of at least 100 babies at the age of two years the initial recruitment made the following assumptions;

- Loss due to attrition of about 10% of the recruited babies by the end of study.
- Loss of 22.5% due to post-discharge deaths during the first year alone because of the projected post-neonatal mortality of about 4.5%[63] and the expected five fold increase of post-neonatal mortality in VLBW infants when compared to the general population[7].

The study required a minimum of 150 neonatal survivors to ensure that100 of them would be available at the age of one year.

- Because the deaths during the second year could not be predicted, 175 infants were recruited in a blind attempt to ensure 100 survivors at the age of two years. Ultimately, 120 babies survived and were available for the neurological assessment at two years of age.

Recruitment

All infants who satisfied the above criteria were eligible for recruitment. The selection was sequential with no randomization. Recruitment was done between the 28^{th} and 30^{th} days of life since neonatal survival was the entry point into the study. All the information required at recruitment was recorded on a questionnaire (appendix 2) the same one retained for each index infant till the end of data collection.

The information recorded at recruitment included;

1. Obstetric data;

   Records of pre-natal care, pregnancy complications, place of birth, mode of delivery and menstrual history were taken. Pregnancy complications such as genito-urinary infections, pre-eclampsia, eclampsia, hypertensive disease of pregnancy and ante-partum hemorrhage were also recorded.

2. The infant records included;

   a) Birth weight measured by the MISAKI DIGITAL BABY SCALE, which is graduated at one-gram intervals. Infants were weighed immediately upon arrival at the newborn unit and this taken as their birth weight according to the study. The KNH newborn unit has a policy of only admitting infants less than 12 hours old if not born at the hospital. All the infants in this cohort were admitted within six hours of delivery. Possible underestimation of weight due to losses within six hours for infants born out off KNH was a possible source of error.

   b) Gestation was determined using menstrual history and Ballard's clinical gestational assessment method appendix 2[61]. Only the Ballard's clinical scores were used in the analysis. Clinical gestational assessments were performed only when the infants were clinically stable. This improves the accuracy of the assessment since neurological scores are influenced by the clinical state of the infant.

   c) Neonatal illnesses of interest for the study included;

   -Birth asphyxia based on five minute Apgar score less than 7 or clinical evidence of encephalopathy.

   -Neonatal infection on the basis of positive blood cultures or abnormal white blood cell features

   -Infants on intravenous fluids or oxygen for at least 3 days.

-Anaemia or shock.

-Respiratory distress syndrome defined as a patient breathing at a rate of 60 breaths/minute or more, beginning at birth and lasting for more than three days.

d) Neonatal Nutrition; A detailed history of neonatal nutrition was recorded. The feeding regimes were grouped as those on exclusive breast milk, exclusive preterm formula and mixed feeds. The latter was the case when the smaller component constituted at least 1/3 of the total daily volume of feeds. The investigators did not influence the choice and allocation of feeding regimes. They were solely determined by the guidelines in use at the hospital during the study period.

e) Identification information;

Names, physical and postal address of the families.

Fixed and/or mobile telephone numbers for the family. This identification information was also obtained and recorded for a relative or friend as an additional contact tracing channel.

POST-DISCHARGE FOLLOW-UP PROGRAM

This was done every Wednesday morning at the clinic 23 of KNH between 8:30 to 10:30. The first follow-up visit was scheduled at two weeks after discharge or about 40 weeks post conception if this had not occurred before discharge.

Thereafter normally growing infants with no other complications were seen at three monthly intervals till they attained age 2 years corrected for gestation. Those deemed to have complications were seen every month. The infants could also be brought to the clinic on any Wednesday if deemed by the mother or guardian to be unwell. This strategy was employed to enhance compliance since providing additional care beyond the study objectives was envisaged as likely to encourage the parents to maintain follow-up.

During all the scheduled reviews monitoring of growth and primary clinical evaluation were undertaken. The follow-up provided some primary health care to all the infants using the hospital resources. Gross neurological evaluations were performed at three monthly intervals and whenever any abnormality requiring occupational therapy was detected the infants received the care. Information regarding re-hospitalization or deaths was recorded.
At 24 months of age the surviving infants were subjected to the formal neurological evaluations to determine and describe disabilities among them. This was done by the investigator and separately by a senior occupational therapist with experience in gross developmental assessment of young children. The results were at 95% agreement.

MEASUREMENT METHODS

Anthropometrical Measurements

Two independent observers made each measurement and the average of the two taken as the true reading. The inter observer agreement was over 95% in these measurements. The first measurement was made and recorded by the clinic nurse. The investigator then repeated the measurement and compared with the earlier record.

Weight: The MISAKI DIGITAL BABY SCALE with one-gram graduation and an upper limit of 20 kilograms was used throughout the study. The scales were calibrated every month using standard weights. The infants were weighed without clothing.

Length: Flexible tapes were used to measure the infant's length while the infant was stretched out on a firm surface. The measurement was taken from the tip of the heel to the level of the uppermost prominence of the skull. These landmarks were identified for all those taking the observations before commencement of each clinic.

Head Circumference: This was taken as the maximum occipital-frontal circumference obtained using a flexible tape measure. This measurement was made three times for each observation and the highest of the readings recorded.

Neurological assessment

The tools used here were first tried on10 babies with no known risk of neurological disease. The agreement rate between the two examiners was 100% during the pilot run. Using this pilot the common toys likely to be identified and handled by the children were also selected. The agreement rate of about 95% was achieved during the actual study. In the case of disagreements a score midway between the independent observations was adopted.

Cognitive scores: A comprehensive neuro-developmental evaluation was performed by the principal investigator and validated by a child occupational therapist. The study used the developmental assessment designed by **Egan (appendix 3)** for pre-school children[64]. The tool uses three parameters; gross motor function, performance and language skills. In this assessment a combination of the mother's report on the baby's performance at home and the actual observation at the clinic were used. The mother's report was necessary when an infant refused to corporate fully during the evaluation. The materials used for the skills tests were selected from among implements usually present at an average Kenyan home.

The results were interpreted as follows;

- Infants who were not able to score any points in the assessment were considered as having significant cognitive delay.
- Those who scored maximum points were considered normal.

- Those with intermediate scores were classified as mildly delayed.

Functional Disability: The study used the method described by **Rosenbaum, Saigal et al (appendix 4)[65].** This tool measures the ability of a child to perform appropriately in ordinary activities and skills of daily living (OASDL) for his or her gestation corrected age. The observations used for a two-year old child include walking, feeding and ambulatory play. These parameters are determined by both cognitive and physical development. Depending on the score the child is assessed as normal or having mild, moderate or severe functional disability.

Cerebral Palsy: This was defined as the presence of abnormal tone, reduced muscle strength or poor coordination (appendix 5)[66]. Assessing resistance to passive movement around major joints, demonstrating head lag and observing truncal posture, measured muscle tone. Muscle power was estimated by assessing the motor milestones achieved by child. The information obtained led to description of the following categories;

- Generalized hypo-tonia, global reduction of muscle tone.
- Spastic lesions, increased tone with decreased muscle power;

  -Monoplegia, if only one limb was affected

  -Paraplegia, if either upper or lower limbs were affected together.

  -Diplegia, if two contra-lateral limbs were affected

  - Hemiplegia, affliction of either left or right sided limbs together.

  -Quadruplegia, if all four limbs were affected.

REPORTING RE-HOSPITALIZATION

Re-hospitalization was defined as any re-admission into a hospital ward leading to duration of stay of at least 24 hours. The parents or guardians were encouraged to bring all medical records detailing any illnesses the infants may have suffered since the previous review. From these records episodes of re-hospitalization were captured at each visit. Where such records were absent mothers'/guardians' recall was used as the source of this information. The specific diagnoses were obtained from hospital records whenever possible otherwise parents'/guardian's recollection was again used. Since re-hospitalization events were the primary focus of the study, errors in the accuracy of diagnoses were not expected to have a significant impact on the results. Accurate and reliably determined diagnoses could not have been obtained since uniform diagnostic criteria had not been employed.

REPORTING POST-DISCHARGE MORTALITY

This captured all the deaths between the initial discharge and the end of the study. At recruitment, all the parents/guardians were requested to inform the study at the next convenient Wednesday if their child died. The study reimbursed the total costs of this trip. Each parent/guardian had also been given a stamped envelope addressed to the investigator with the identification number of the child inside. They were advised to indicate in the enclosed paper if and when the child died and mail the letter to the investigator. They could also use the envelope to inform the study when and if they moved from Nairobi.

TRACING DEFAULTERS

The study recruited a contact tracer well versed with the geography of the city for this purpose. This individual made home visits to trace all the defaulters. Defaulter tracing visits were made within the month following failure to attend a scheduled follow-up clinic appointment. Some of the infants missing due to death or possible emigration were also identified by this method. Cell phone contact was the other tool used for tracing missing subjects. This new method of communication turned out to be particularly rewarding in tracing those lost due to death since self-reporting of this event was relatively rare. All subjects had provided a cell phone number through which they could be contacted and an additional one belonging to a close friend or relative who they considered appropriate to provide information regarding their children to the investigator if called upon.

STUDY DURATION

Recruitment; Twelve consecutive months from January through to December 2002

Follow-up; This started from the beginning of February 2002 when the first infant attained the age of 1 month and continued till March 2005 when the last recruit had attained the age of 2 years corrected for gestation.

ANALYSIS

Descriptive Statistics

1. Baseline characteristics presented as frequency distributions included all the obstetric and some infant data. The continuous variables were summarized as means, medians and standard deviation.
2. Neonatal growth was analyzed and presented as mean/median weight gain in grams/kilogram of birth weight / day and mean/median growth in head circumference and length in centimeters/week.
3. The proportions of infants who had not reached the 3rd percentile of the National Council for Health Statistics (NCHS) [67] mean anthropometric values by term and at one or two years after term were determined.
4. The proportion of survivors at two years with cerebral palsy including specific lesions, functional disability including severity distribution and significant delay in cognitive development were reported as percentages and 95% confidence intervals (CI).
5. The frequency of re-hospitalization and mortality after initial discharge were reported as percentages and 95% CI for all the subjects available for analysis at the end of the study.

Comparative Analysis

1. These included comparison of medians and determination of significant differences for all continuous variables. The medians were preferred because the study population was not normally distributed.

The parameters included in these analyses were neonatal and post-neonatal growth compared between neonatal exposure factors like gender, feeding options, illnesses and intra-uterine growth status. Cognitive scores were analyzed in the same manner against various exposure variables. All the comparisons employed the analysis of variance (ANOVA) method for ascertaining statistical associations.

2. Cross tabulation and use of Chi-square test for categorical variables to generate significance estimates (P value), relative risk (RR) and 95% confidence intervals (CI). Exposure variables were categorized as risk or no risk and the proportional distribution of bad and good outcomes compared between them computed.
3. Logistic regression analysis was undertaken to determine the predictors of growth faultering, post-discharge re-hospitalization, post-discharge mortality and neurological dysfunction. Both the exposure and outcome variables were coded as one or two for the good and bad result respectively. For example neonatal growth faultering was bad when weight gain was less than 15g/kg/d and good when 15 or more g/kg/day growth had been achieved. Correlation coefficients were done for variables expected to have inherent association with each other. This was done during primary analysis before constructing the regression equation. Also done was exclusion of one or the other of such variables to determine their individual contribution without the influence of the competing factor.

4. The Kaplan Meier (KM)* method was used for Survival Analysis. This method generates graphs by accounting for each individual observation including those lost to follow-up in a single graphic line. The analysis is based on computing a factor called the survival time, which estimates the time from recruitment to the point of occurrence of the outcome event of interest. Those who fail to experience the outcome event will have a score equal to the duration of follow-up while the ones who experience the event score according to the time or age at which the event occurred to them. A mean of the survival observations for every risk group is then calculated with increasing numerical value signifying better survival outcome. This is then used to generate the statistical significance using the log rank statistic. Post-discharge re-hospitalization and post-discharge mortality were the appropriate outcome variables for survival analysis in this study because they are events, which occur at specific points in time. In the event of multiple re-hospitalizations the first episode was used in the KM analysis. The survival analysis was performed for the exposure variables, which demonstrated significant associations ($P<0.05$) with re-hospitalization or mortality at single variant analysis.

Statistical packages: The Statistical Package for Social Sciences (SPSS) was used for the, descriptive data, comparison of medians, regression and KM analysis.

EPI INFO version 6 was used in the analysis of grouped data.

*Kaplan Meier Survival Analysis for re-hospitalization[68],

INTERVENTIONS

- Preterm formula (described in appendix 6) was used as supplement or exclusive feed when mothers' milk was either unavailable or insufficient.
- Micronutrient supplements including, 10mg/kg/day of elemental Iron, 5mg/week of folic acid and vitamin preparations (appendix 7) were provided by the hospital. The study contributed these supplements whenever there were shortfalls at the hospital.
- The infants were provided with primary medical outpatient care in addition to the research follow-up by the principal investigator on their scheduled visits and any time they chose to come to the clinic during scheduled hours.
- All necessary laboratory or radiological investigations required for any illnesses identified during the period of follow-up were performed in the relevant departments of the hospital.
- Those requiring occupational or physical therapy were referred to these facilities within the hospital for the services.

ETHICAL ISSUES

Permission from Kenyatta National Hospital ethical committee was obtained. The parents or guardians of the study infants also gave informed and written consent before recruitment (appendix 9). The investigator explained to each parent/guardian the value of the study citing the need to know all the events surrounding the child for the two years following initial discharge.

They were informed that theirs are infants with special needs which if not observed closely and corrected as necessary may experience increased chances of death or disabilities. The invaluable importance of their participation in furthering science was also stressed.

IV: RESULTS

IV.1: BASELINE CHARACTERISTICS FOR THE 175 SUBJECTS

Obstetric Parameters

The parameters under study included antenatal clinic (ANC) attendance, history of pregnancy complications, place at which infant was born and the mode of delivery. The results are summarized in table 1.

Table 1: Obstetric Characteristics

Factor	Number	Percentage
Antenatal Clinic attendance	70	39.4
Pregnancy Complications	118	67.4
Hypertension in pregnancy	41	23.4
Acute infections	35	20.0
PROM*	24	13.7
Ante-partum hemorrhage	12	6.9
Others	6	3.4
Place of Delivery		
KNH	137	78.3
Elsewhere	38	21.7
Caesarian Section delivery		
The whole group (N=175)	33	18.9
KNH deliveries (N=137)	33	24.1

*Prolonged Rupture of Membranes

Seventy (39.4%) of the mothers had made at least one ANC visit by the time of delivery.

Pregnancy complications such as, hypertension, acute genito-urinary infections, prolonged rupture of membranes and ante-partum hemorrhage were reported in 67.4% of the mothers. Seventy eight percent of the 175 deliveries took place at KNH while 22% were occurred elsewhere. Caesarean deliveries occurred in 18.9 and 24.1% for the total and the KNH groups respectively.

Infant characteristics

Baseline characteristics of the recruited infants are summarized in table 2. Continuous variables are presented as means (SD) while the categorical ones are in percentages.

Table 2: Baseline infant characteristics

CHARACTERISTIC	MEAN	SD	RANGE
Growth at Birth			
Weight (g)	1393	103	900 - 1500
Length (cm)	43.9	1.3	41 - 46.5
Head Circumference (cm)	30.9	1.0	27 - 31.5
Gestation (wks)	32.4	2.3	28 - 36
Females N (%)		105 (60.0)	
Males N (%)		70 (40)	
AGA N (%)		111 (63.4)	
UGR N (%)		64 (36.6)	
Neonatal illnesses N (%)		109 (62.3)	
RDS*		70 (40.0)	
Sepsis		54 (30.9)	
Asphyxia		36 (20.6)	
Others		15 (8.6)	
Neonatal feeds N (%)			
Breast milk alone		78 (44.6)	
Preterm formula alone		33 (18.9)	
Mixed feeding		54 (30.8)	

*Respiratory Distress Syndrome

The mean birth weight was 1393g, gestation 32.4 wks, head circumference 30.9 cm and length 43.9 cm. The range of birth weight was 900-1500g, length 41-46.5cm, head circumference 27-31.5 and gestation 27- 36 wks. The male: female ratio was 2:3 while 36.6% of the infants were intra-uterine growth retarded. Neonatal illnesses including respiratory distress syndrome (RDS), neonatal sepsis and asphyxia were documented in 62.3%. During the first month of life 78 (44.6%), 54 (30.8%) and 33 (18.9%) of the 175 infants were fed on exclusive breast milk, breast milk supplemented with preterm formula and exclusive preterm formula respectively.

IV.2: EARLY GROWTH PATTERNS

OVERALL PROFILES

Early growth profiles for the group are summarized in table 3. They include neonatal growth and the growth status at term. Weight is presented in grams/kilogram of birth weight/day (g/kg/d) while length and head circumference are in centimeters gained/week (cm/wk). Summary measures of weight in grams, head circumference and length in centimeters at term are included.

Table 3: Early Growth Profiles

Growth Parameter	Mean	Median	SD	Range
NEONATAL GROWTH				
Weight (g /kg/d)	13.54	14.0	3.96	6.1 - 25.5
Length (cm/week)	0.34	0.30	0.11	0.2 - 0.7
Head Circum (cm/wk)	0.32	0.30	0.07	0.2 - 0.5
GROWTH AT TERM				
Weight (kg)	2.23	2.22	0.22	1.85 - 2.60
Length (cm)	46.4	46.5	1.36	42.0 - 48.5
Head Circ (cm)	32.1	32.5	1.16	29.5 - 36.5

The infants gained weight at a mean rate of 13.54 g/kg/d during the newborn period. The mean neonatal growth in head circumference and length were 0.32 and 0.34 cm/wk respectively.

The mean weight, head circumference and length at term were 2.23 kg, 32.1 cm and 46.4 cm respectively. Assuming maintenance of normal intra-uterine growth rate, VLBW infants are expected to be within two Standard Deviations of the normal infant anthropometric parameters at birth at term.

EARLY GROWTH FAULTERING

Neonatal growth faultering was defined as neonatal growth below 15 g/kg/d in weight and 0.5cm/ wk in length or head circumference. Growth faultering at term denoted measurements less than the 3rd percentile of the NCHS normograms at that time. The growth faultering rates in this cohort are presented in table 4.

Table 4: Growth faultering during the neonatal period and at term

Parameter	Total Number	Number with faultered growth	Percentage
NEONATAL FAULTERING			
Weight	175	105	60.0
Length	65	50	76.9
Head Circumference	71	50	70.4
FAULTERING AT TERM			
Weight	175	142	81.1
Length	175	138	78.9
Head Circumference	175	126	72.0

Neonatal growth faultering: In the cohort, 60, 70.4 and 76.9 of the infants did not achieve the expected neonatal growth rate in weight, head circumference and length respectively. Head circumference and length measurements at birth were not available for some of the infants, hence, the smaller denominators.

Growth faultering at term: The mean weight, length and head circumference were less than the 3rd percentile of the expected values at term in 81.1, 78.9 and 72.0% of the infants respectively.

DETERMINANTS OF NEONATAL GROWTH

Infants' gender, intra-uterine growth status, neonatal illnesses and neonatal feeding regimens were evaluated to determine their association with neonatal growth faultering. The results are summarized in table 5 as medians (SD) and compared by analysis of variance.

Table 5: Determinants of neonatal growth

Factor	Weight (g/kg/d)		Head (cm/wk)		Length (cm/wk)	
	Median (SD)	P	Median (SD)	P	Median (SD)	P
Male	13 (3.3)	0.210	0.32 (.08)	0.348	0.33 (.12)	0.572
Female	13 (4.4)		0.31 (.08)		0.33 (.11)	
AGA	13 (3.4)	0.580	0.31 (.08)	0.870	0.34 (.14)	0.125
IUGR	13 (4.7)		0.32 (.07)		0.35 (.07)	
Neonatal illness	12 (3.6)	0.001	0.29 (.06)	0.001	0.34 (.11)	0.920
No neonatal Illness	15 (3.9)		0.34 (.09)		0.34 (.11)	
PTF	17 (2.5)		0.38 (.09)		0.40 (.12)	
Mixed milk	15 (2.0)	0.001	0.33 (.08)	0.001	0.32 (.07)	0.006
BM	12 (3.9)		0.31 (.08)		0.31 (.12)	

Infants' gender: Male and female infants showed no differences in their neonatal growth patterns in all the parameters measured.

Intra-Uterine Growth: The neonatal growth rates were also similar between infants born appropriate for gestation and those born intra-uterine growth retarded.

Neonatal feeding: Infants who were exclusively fed on PTF during their neonatal period had median weight gain of 17.0 g/kg/d, two grams higher than those on PTF+ BM and 5 grams more than those on exclusive BM. This difference was statistically significant $P<0.001$. Similar trends were observed with neonatal head $P=0.001$ and linear $P=0.006$ growth. Increasing the PTF proportion in the neonatal diet was associated with improved growth in all anthropometric measures.

Neonatal illness: Infants classified as ill during the newborn period had lower median growth in weight, 12 compared to15 g/kg/d, $P<0.001$ and head circumference, 0.29 compared to 0.34 cm/wk, $P=0.001$ than those reported as having been well. Growth in length was not influenced by neonatal illness, $P=0.92$. Presence of neonatal illness was associated with neonatal weight and head growth retardation in this cohort.

LOGISTIC REGRESSION ANALYSIS (LRA) FOR PREDICTORS OF POOR NEONATAL GROWTH

Predictor variables were subjected to binary logistic regression analysis against neonatal weight gain below 15g/kg/day and head growth <0.5cm/week as the outcome variables. The predictor variables included female gender, IUGR, exclusive use of BM during the newborn period and history of neonatal illnesses. The results are summarized in table 6.

Table 6: Regression analysis for predictors of poor neonatal growth

FACTOR	Weight <15g/kg/d		Head growth <0.5cm/wk	
	P value	95% CI	P value	95% CI
Intra-uterine growth retardation	0.099	0.05-4.00	0.067	0.95-4.51
Female Sex	0.337	0.26-1.59	0.196	0.28-1.30
Neonatal Illness	0.011	1.29-7.47	0.296	0.30-1.44
Exclusive Breast Milk	0.001	3.27-18.2	0.001	0.12-0.58

Neonatal weight gain: Exclusive use of BM P<0.001 and history of neonatal illness P=0.011 were established as the independent predictors of neonatal weight gain less than 15g/kg/d.

Neonatal head growth: Exclusive use of BM was the only independent predictor of faultered head growth at term P=0.001.

DETERMINANTS OF GROWTH AT TERM

Infants' gender, intra-uterine growth status, neonatal illnesses and neonatal feeding regimens were evaluated to determine their association with growth faultering at term. The outcome variables were growth measures less than the 3rd percentile of the expected. The results are summarized in table 7 as medians (SD) and compared by analysis of variance.

Table 7: Determinants of growth at term

Factor	Weight (kg)		Head (cm)		Length (cm)	
	Median (SD)	P*	Median (SD)	P*	Median (SD)	P*
Male	2.20 (.23)	0.786	32.0 (1.25)	0.389	46.5 (1.43)	0.572
Female	2.20 (.21)		32.0 (1.09)		46.0 (1.30)	
AGA	2.25 (.22)	0.015	32.0 (0.89)	0.069	46.5 (1.15)	0.001
IUGR	2.15 (.21)		32.0 (1.50)		45.5 (1.55)	
Neonatal illness	2.15 (.18)	0.001	31.5 (1.24)	0.001	46.0 (1.43)	0.001
No neonatal Illness	2.30 (.23)		32.5 (0.94)		46.5 (1.12)	
PTF	2.40 (.19)		33.0 (0.74)		48.0 (0.53)	
Mixed milk	2.30 (.20)	0.001	32.5 (1.04)	0.001	47.0 (0.94)	0.001
BM	2.10 (.17)		31.5 (1.05)		45.5 (1.41)	

*ANOVA

Infants' gender: Male and female infants had identical median weight, head circumference and length at the time of their expected delivery. Infants' gender had no association with catch-up growth at term.

Intra-uterine growth: Infants born AGA weighed significantly more at term than those with IUGR, P=0.015. The AGA infants were also significantly longer, P=0.001 at term than those born with IUGR. This demonstrates that the lost growth opportunity during the intra-uterine period for IUGR infants was not restored after delivery.

Neonatal illness: At term, infants deemed healthy during the neonatal period were 200g heavier that those who had been ill, P<0.001. Healthy infants also had one centimeter advantage in head circumference, P=0.001 and were longer, P=0.020 at term than those who had neonatal illnesses. Neonatal illness was associated with lower median growth parameters at the expected time of delivery in this cohort.

Neonatal nutrition: Those who received exclusive PTF had a median weight of 2.4kg at term while those who had been on PTF+BM weighed 2.3. The group on exclusive BM had the lowest median weight of 2.3kg at this age. The differences were statistically significant, P<0.001. Infants feed on exclusive PTF had median head circumference of 33.0 cm compared to 32.5 and 31.5 for those on PTF+ BM and exclusive BM respectively, P value <0.001.

The median length at term was 48.0, 47.0 and 45.0 cm for the PTF, PTF+BM and BM fed infants respectively, P=0.001. Nutrient enriched PTF significantly increased all growth parameters at term.

LRA; PREDICTORS OF GROWTH FAULTERING AT TERM

All the predictor variables were subjected to binary logistic regression analysis against weight, length and head circumference < 3rd percentile of the expected as the outcome variables. A summary of the results is presented on table 8 below.

Table 8: Regression analysis for predictors of growth at term

Parameter	Weight <3rd centile		Head cir. <3rd centile		Length <3rd centile
	P value	95% CI	P value	95% CI	P value (95% CI)
IUGR	0.081	0.14-1.12	0.667	0.36-1.91	0.12 (0.82-4.95)
Male Infant	0.566	0.29-1.94	0.626	0.54-2.83	0.69 (0.52-2.74)
Neonatal Illness	0.001	0.07-0.51	0.001	0.09-0.46	0.006(1.4-7.6)
BM alone	0.002	0.03-0.46	0.001	0.08-0.53	0.001 (.07-.49)

Neonatal illness and Neonatal nutrition were both independent predictors of catch-up growth at term. Neonatal illness was predictive of failed catch-up in weight P=0.001, head circumference P=0.001 and length P=0.006. Exclusive use of BM during the newborn period was also an independent predictor of inadequate weight P=0.002, head circumference P=0.001 and length P=0.001 at term.

IV.3: POST NEONATAL GROWTH

The rates of growth faultering at term, one and two years corrected for gestation are summarized in table 9. Growth faultering was defined as failure to reach the 3rd percentile of the expected measure on the NCHS normograms.

Table 9: Post neonatal growth faultering

		Term	One year	Two years
Growth Parameter	N	175	138	120
		Percentage at or above the 3rd percentile		
Weight		80.6	69.6	57.5
Head Circumference		72.0	65.2	62.5
Length		76.4	63.8	60.8

Growth faultering rates were high but showed some improvement during the two years of follow-up. At one year 69.6, 65.2 and 63.8% of the surviving infants had less than the expected weight, head circumference and length respectively. By the age of two years this had improved to 57.5, 62.5 and 60.8% respectively. The improvement in faultering rate was highest in weight with a change from 80.6 to 57.5% between term and two years. The commensurate changes for head circumference and length were 72 to 62.5 % and 76.4 to 60.8% respectively.

DETERMINANTS OF POST NEONATAL GROWTH

The factors analyzed as predictors of post-natal growth included; infants' sex, intra-uterine growth status, post-discharge re-hospitalization and neurological dysfunction. The results are summarized in table 10.

Table 10: Predictors of growth faultering at 2 years

Factor	N (% <3rd Percentile)		Statistics* RR	(95% CI)	P value
Female, **N=70**	42	(60.0)	1.11	(0.81-1.53)	0.512
Male, **N=50**	27	(54.0)	1.00		
IUGR, **N=45**	38	(84.4)	2.04	(1.52-2.75)	0.001
AGA, **N=75**	31	(41.3)	1.00		
Neonatal illness, **N=63**	45	(71.4)	1.70	(1.20-2.39)	0.002
No neonatal illness, **N=57**	24	(42.1)	1.00		
Wt at term<3rd centile, **N=89**	59	(66.3)	2.06	(1.21-3.50)	0.001
Wt at term<3rd centile, **N=31**	10	(32.3)	1.00		
Re-hospitalization, **N=56**	48	(85.7)	2.61	(1.81-3.77)	0.001
No re-hospitalization, **N=64**	21	(32.8)	1.00		
Functional disability, **N=32**	24	(75.0)	1.47	(1.10-1.95)	0.033
No functional disability, **N=88**	45	(51.1)	1.00		

*CHI-SQUARE TEST

Infants' gender: Female babies were numerically more likely to be growth retarded at the age of two years than the male counterparts, but not to levels with statistical significance, P=0.512.

Intra-uterine growth retardation: Weight below the 3rd percentile at the age of two years was observed in 84.4% of the infants who had been born IUGR compared to only 41.3% of those born AGA. This difference was statistically significant, P=0.001. Pre-natal growth retardation was associated with sustained growth failure even after birth.

Neonatal illness: Infants who had suffered neonatal illnesses had a growth faultering rate of 71.4% while those who had been well had a rate of 42.1%, P=0.002. The growth impeding effects of neonatal illnesses persisted into the second year of life.

Growth at term: Retarded growth at term was associated with 66.3% faultered growth compared to 32.3% for the babies without growth retardation at term. The difference was statistically significant, P=0.001.

Re-hospitalization: Re-hospitalized infants were almost three times more likely to experience growth failure at two years than those not re-hospitalization, P=0.001. Re-hospitalization contributed to post-discharge growth failure.

Neurological Disability: Babies with neurological disabilities were also found to have experienced more growth retardation at two years when compared to those without neurological sequalae, P=0.033. Neurological disability predisposed to growth faultering at the age of two years.

LRA; PREDICTORS OF POST-DISCHARGE GROWTH FAILURE

Logistic regression analysis to determine the independent predictors of weight less than the 3rd percentile at the age of two years is presented in table 11.

Table 11: Regression table for predictors of growth failure at 2 years

Parameter	Weight <3rd percentile at 2 years	
	P value	95% CI
Intra-uterine growth retardation	0.007	0.08-0.68
Female Infant	0.566	0.09-2.94
Neonatal Illness	0.001	0.08-0.71
Weight <3rd percentile at term	0.095	0.05-1.98
Re-hospitalization	0.089	0.09-1.05
Neurological disability	0.002	0.03-0.46

Intra-uterine growth retardation P=0.007, neonatal illness P=0.001 and neurological disabilities P=0.001 were the independent predictors of weight below the 3rd percentile at two years of age. Growth faultering at term and IUGR were independently correlated but only IUGR was an independent predictor when both were included in the equation.

IV.4: POST-DISCHARGE RE-HOSPITALIZATION

During the two years of follow-up 89 of the165 VLBW infants whose records were complete had been re-admitted to hospital at various times. Figure 1 illustrates this distribution. The illnesses recorded as responsible for the admissions to hospital are also indicated.

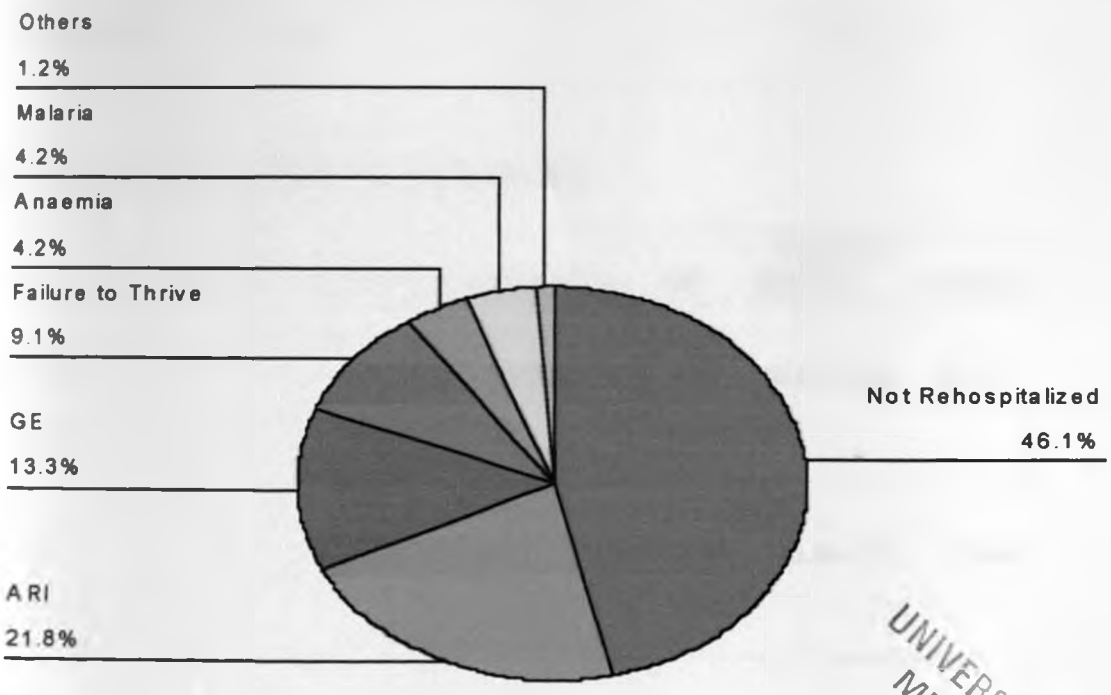

Figure 1: Re-hospitalization rates for the 165 infants

The overall re-hospitalization rate was 53.9%, 95% CI 25.6 - 73.2 with 73.0% of them occurring during the first year. The illnesses leading to re-hospitalization included acute respiratory infection (22%), gastroenteritis (13%), failure to thrive (9%), anaemia (4.2%) and malaria (4.2%).

DETERMINANTS OF RE-HOSPITALIZATION

Several factors were investigated to determine their association with re-hospitalization. Analysis used the Chi-square distribution test and was summarized as P values, RR and 95% CI. The variables evaluated included infants' gender, intra-uterine and post-natal growth, discharge weight, neonatal illness, neonatal nutrition and neurological disability status. The results are presented in tables 12 and 13.

Table 12: Determinants of re-hospitalization 1

Factor	N (% Re-hospitalized)	RR	Statistics* (95% CI)	P value
Female, **N=95**	56 (58.9)	1.25	(0.93-1.69)	0.132
Male, **N=70**	33 (47.1)	1.00		
IUGR, **N=60**	35 (58.3)	1.13	(0.85-1.51)	0.393
AGA, **N=105**	54 (51.4)	1.00		
Illness, **N=91**	57 (62.6)	1.46	(1.08-1.99)	0.015
No Illness, **N=74**	32 (43.2)	1.00		
BM alone, **N=78**	58 (74.4)	2.09	(1.53-2.85)	0.001
PTF/Mixed feeds, **N=87**	31 (35.6)	1.00		

*CHI-SQUARE TEST

Infants' gender: Re-hospitalization was reported in 47.1 and 58.9% of the males and females respectively. This marginal preponderance of re-hospitalization among the female infants was not statistically significance, P=0.132.

Status of intra-uterine growth: Re-hospitalization occurred in 58.3% of AGA and 51.4% of IUGR infants, P=0.393. Intra-uterine growth did not influence re-hospitalization.

Neonatal illnesses: History of neonatal illness was associated with 62.6% re-hospitalization during the first two post-discharge years compared to 43.2% for those who had been considered well. This difference in the frequency of re-hospitalization between neonatal illness categories was statistically significant, P=0.015. Neonatal morbidity appears to have predisposed these infants to subsequent morbidity, severe enough to warrant re-hospitalization during the first two years of their lives.

Neonatal Nutrition: Infants who were exclusively fed on BM during the newborn period were re-hospitalized twice as frequently as those fed on PTF alone or in combination with BM, P=0.001. Neonatal nutrient enrichment was associated with reduction in serious morbidity during the first two years.

Table 13 summarizes the results of discharge weight, neonatal growth, post-discharge growth and functional disability as determinants of re-hospitalization.

Table 13: Determinants of re-hospitalization 2

Factor	N (% Re-hospitalized)	RR	Statistics* (95% CI)	P value
Discharge at <2kg, **N=110**	66 (60.0)	1.43	(1.01-2.03)	0.041
Discharge at 2kg+, **N=55**	23 (41.8)	1.00		
Neon wt gain<15g/kg/d, **N=99**	68 (68.7)	2.16	(1.48-3.15)	0.001
Neon wt gain 15g/kg/d+, **N=66**	21 (31.8)	1.00		
Wt at term <3rd centile, **N=133**	83 (62.4)	3.33	(1.60-6.90)	0.001
Wt at term, 3rdcentile+, **N=32**	6 (18.8)	1.00		
Wt at 2yrs<3rd centile, **N=69**	35 (50.7)	1.99	(1.18-3.36)	0.005
Wt at 2yrs, 3rd centile+, **N=51**	13 (25.5)	1.00		
Functional disability, **N=32**	22 (68.8)	2.33	(1.56-3.47)	0.001
No functional disability, **N=88**	26 (29.5)	1.00		

*CHI-SQUARE TEST

Discharge Weight: Infants discharged weighing less than 2kg recorded 60% re-hospitalizations while those discharged after attaining the weight of 2kg had 41.8%. Discharge before attainment of 2kg significantly increased the chances of subsequent re-hospitalization, P=0.041.

Mean neonatal weight gain: Infants with neonatal growth less than 15g/kg/d had 68.7% re-hospitalization frequency compared to 31.8% for those who had grown faster. Neonatal weight gain was associated with a significant decrease in subsequent re-hospitalization, P=0.001.

Weight at 40 weeks: The frequency of re-hospitalization in infants who weighed less than the 3rd percentile of the expected at term was 62.4% compared to 18.8% for those who equaled or passed this mark. Growth faultering at term was significantly associated with increased re-hospitalization after initial discharge, P=0.001.

Post-discharge growth: Infants who had caught up in weight by the age of two years had a re-hospitalization rate of 25.5% compared to 50.7% for those still below the 3rd percentile. This difference was statistically significant, P=0.005, demonstrating that inadequate post-discharge growth doubled the risk of re-hospitalization in this cohort.

Functional Disability: Re-hospitalization rates were more than two times higher among infants with neurological sequelae when compared to the normal group, 68.8 versus 29.5% respectively, P=0.001. Presence of neurological disability significantly increased the risk of re-hospitalization.

KAPLAN MEIER SURVIVAL ANALYSIS FOR RE-HOSPITALIZATION*

Neonatal illness

Survival curves comparing the re-hospitalization episodes between infants who had been ill during the newborn period and those deemed well are presented in figure 2. The mean survival statistics and P values are included within the figure.

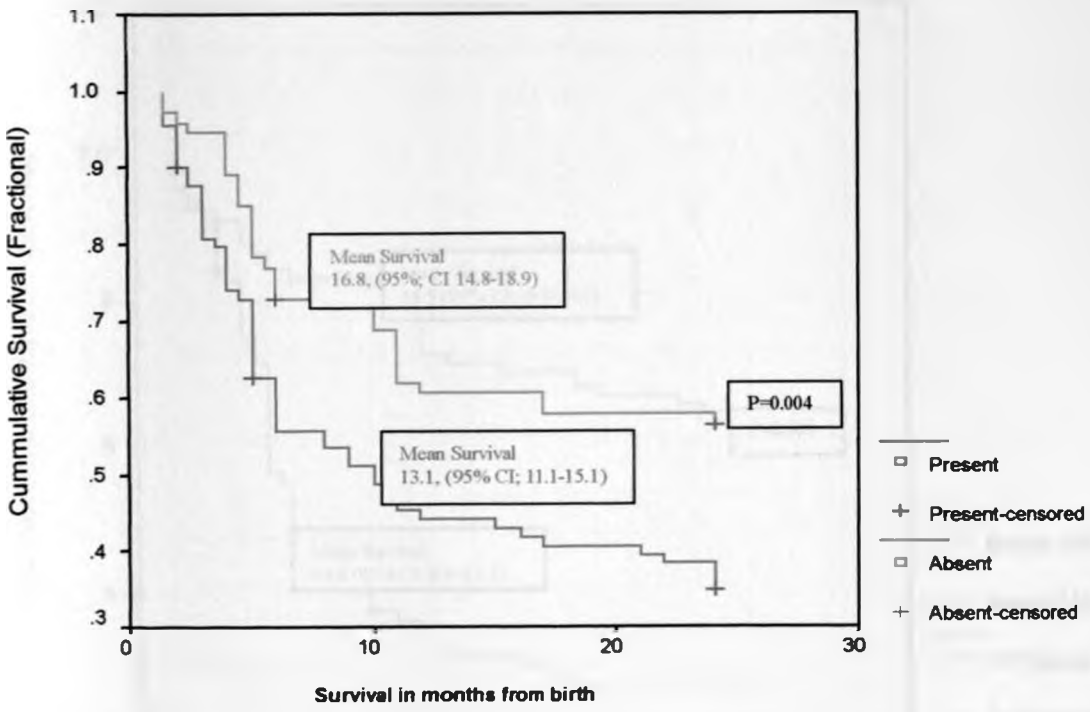

Figure 2: Survival Graph: Neonatal illness and re-hospitalization

The graph for infants deemed healthy during the newborn period remained significantly above the one describing the sick ones throughout the follow-up period. The mean survival value was 3.7 months higher for infants who had been well during the neonatal period, a difference found statistically significant, P=0.004.

*Kaplan Meier Survival Analysis for re-hospitalization[68],

Neonatal feeding

The survival curves were constructed for re-hospitalization with neonatal feeding regimens as the exposure variables. The results are presented in figure 3 including mean survival statistics.

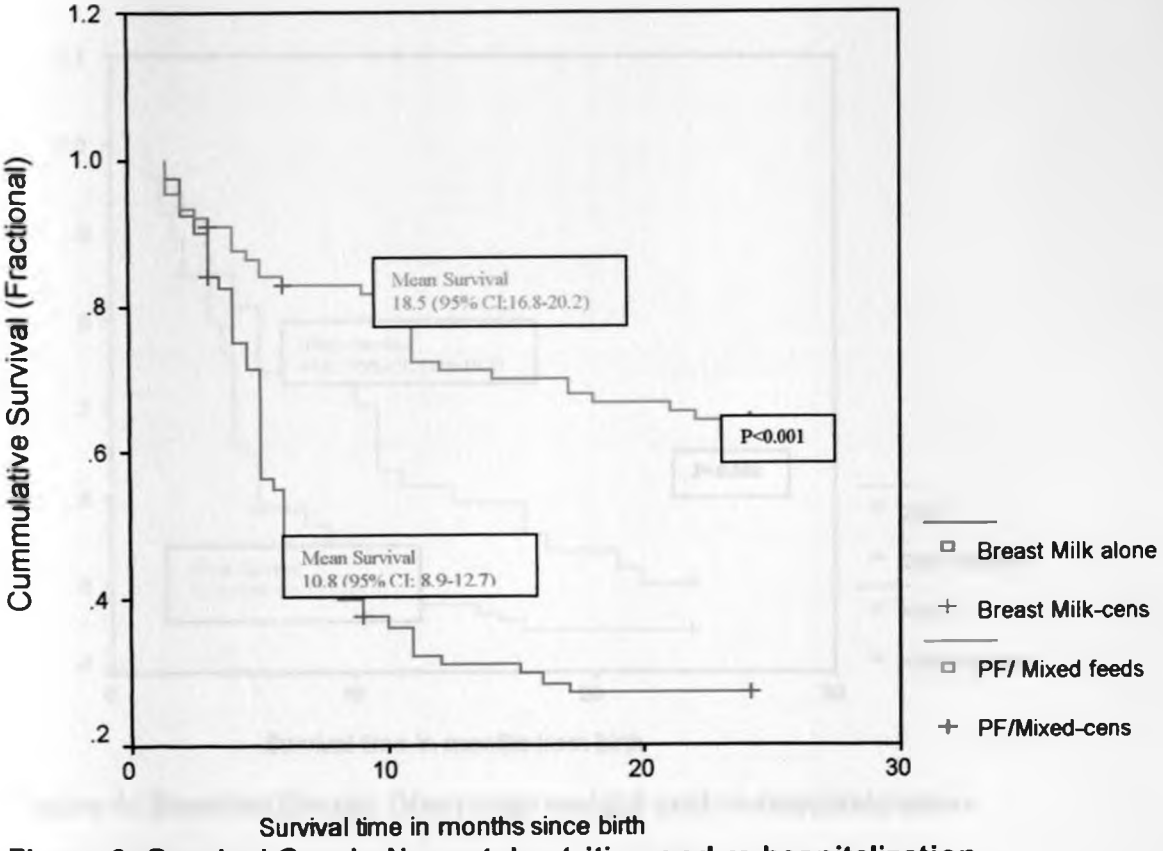

Figure 3: Survival Graph: Neonatal nutrition and re-hospitalization

The graph representing the infants who were nursed on PTF alone or combined with BM was consistently above the one for those on exclusive BM with a mean survival difference of 7.7 months. Inclusion of PTF in the diets of these infants led to significantly better re-hospitalization profiles, P<0.001.

Discharge weight

With re-hospitalization as the outcome, discharge weight less than 2kg was compared with that of 2kg or more as predictor variables generating the survival curves plotted in figure 4. The mean survival statistics are included for each graph.

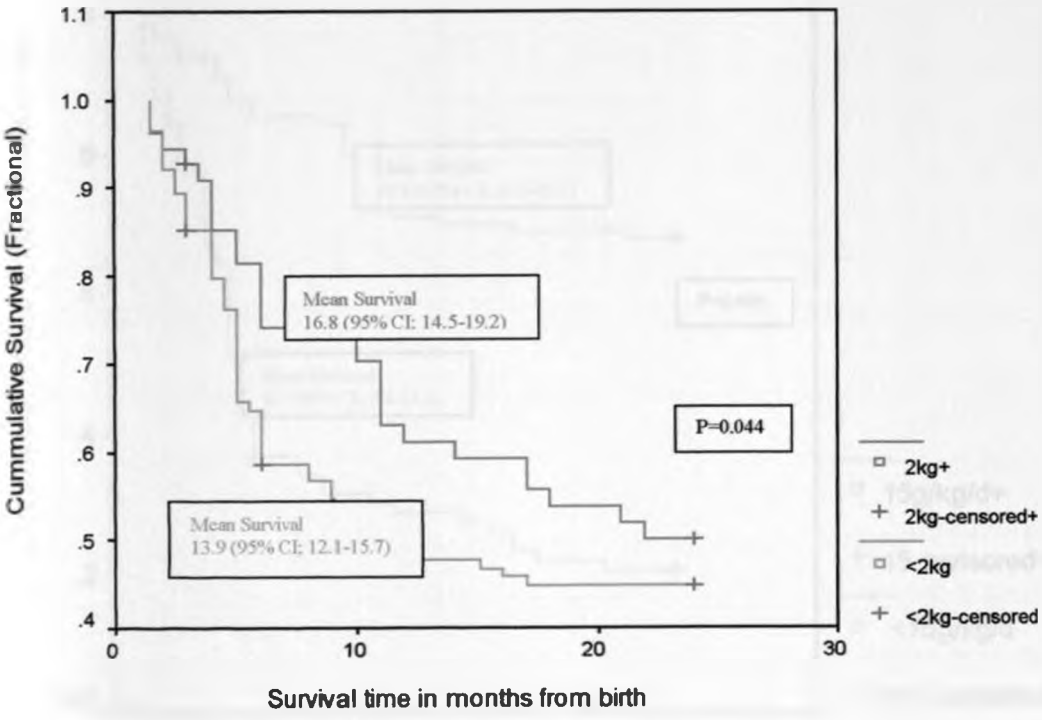

Figure 4: Survival Graph: Discharge weight and re-hospitalization

Infants discharged weighing less than 2kg had a mean survival value of 13.9 months compared to 16.8 for those who had attained 2kg at discharge. The 2.9 months difference was statistically significant, P=0.044. Discharging VLBW infants before attaining the weight of two kilograms worsened their re-hospitalization profiles.

Neonatal weight gain

Survival analysis for re-hospitalization with neonatal weight gain as the exposure variable including mean survival statistics is presented in figure 5.

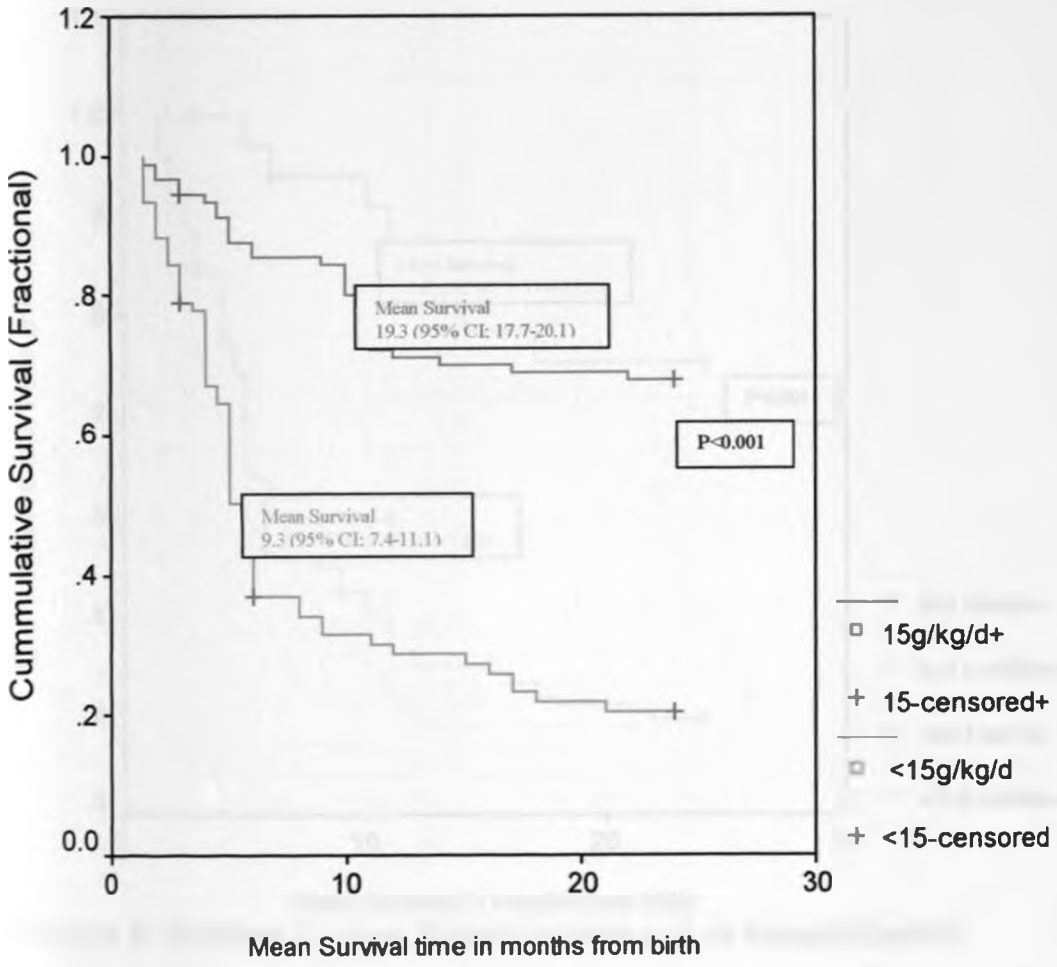

Figure 5: Survival Graph: Neonatal weight gain and re-hospitalization

The Mean survival value for the infants who grew at a rate of 15g/kg/day or more was 19.3 compared to 9.3 months for the slower growing group. The difference was statistically significant, P<0.001 indicating that re-hospitalization profiles were improved by better neonatal growth.

Weight at term

Catch-up in weight at term was also established as a predictor for re-hospitalization at single variable comparison. The survival analysis of this association is presented in figure 6.

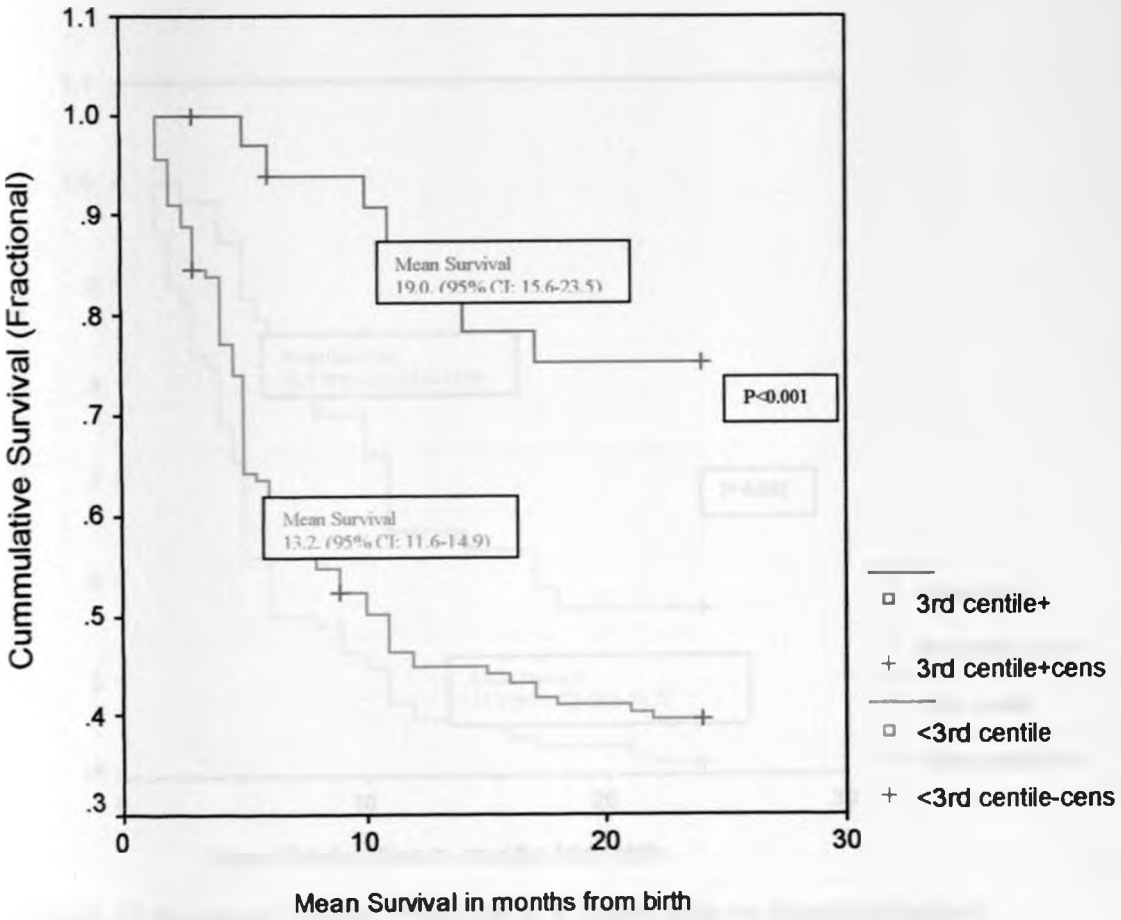

Figure 6: Survival Curves: Weight at term and re-hospitalization

There was a large gap between the curves of the infants with faultered growth at term and that of the ones with adequate growth. The mean survival difference was 5.8 months, $P < 0.001$. Somatic growth faultering at term negatively affected re-hospitalization profiles.

Weight at 2 years

Survival analysis for growth faultering at two years with re-hospitalization as the outcome was performed. The results, including the statistical output are presented in figure 7.

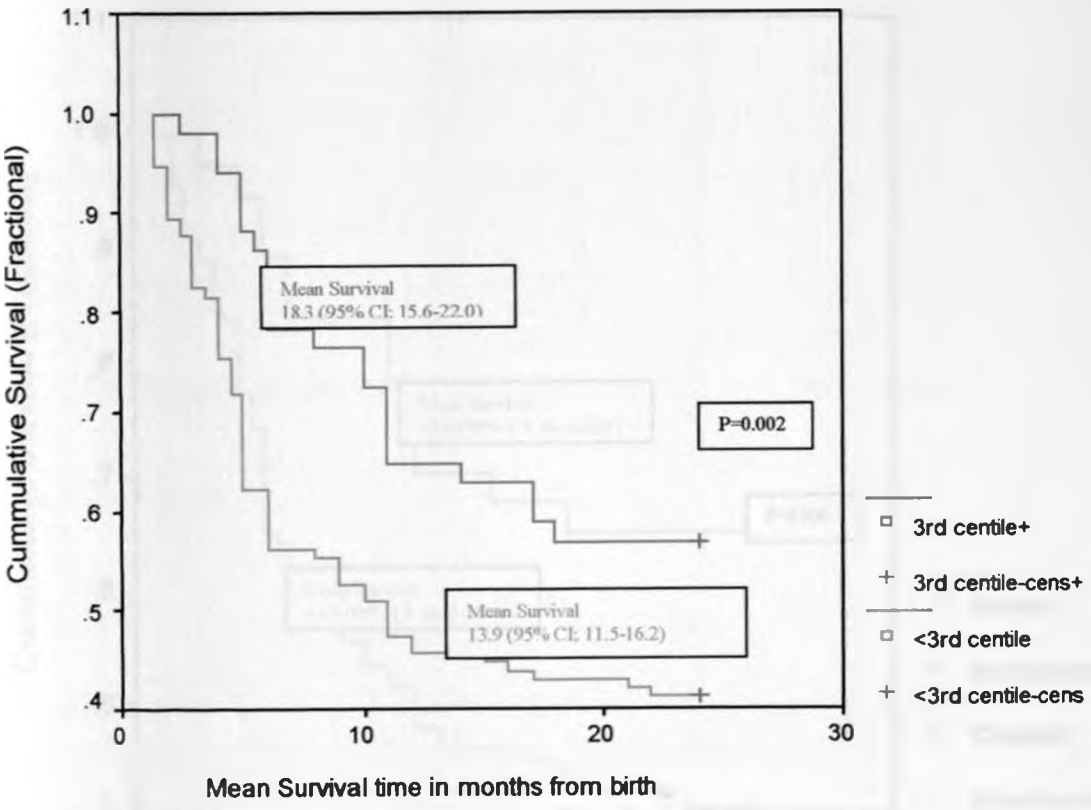

Figure 7: Survival Curves: Weight at 2 years and re-hospitalization

Those who had reached the expected weight at the age of two years had better survival profiles with mean survival value 4.4 months higher than that of the ones who were lighter, P=0.002. Lower weight than expected at the age of two years was associated with poorer re-hospitalization profiles.

Functional disability

The survival curve for re-hospitalization episodes was constructed to compare the profiles for neurologically disabled infants with the normal counterparts. The results are presented in figure 8.

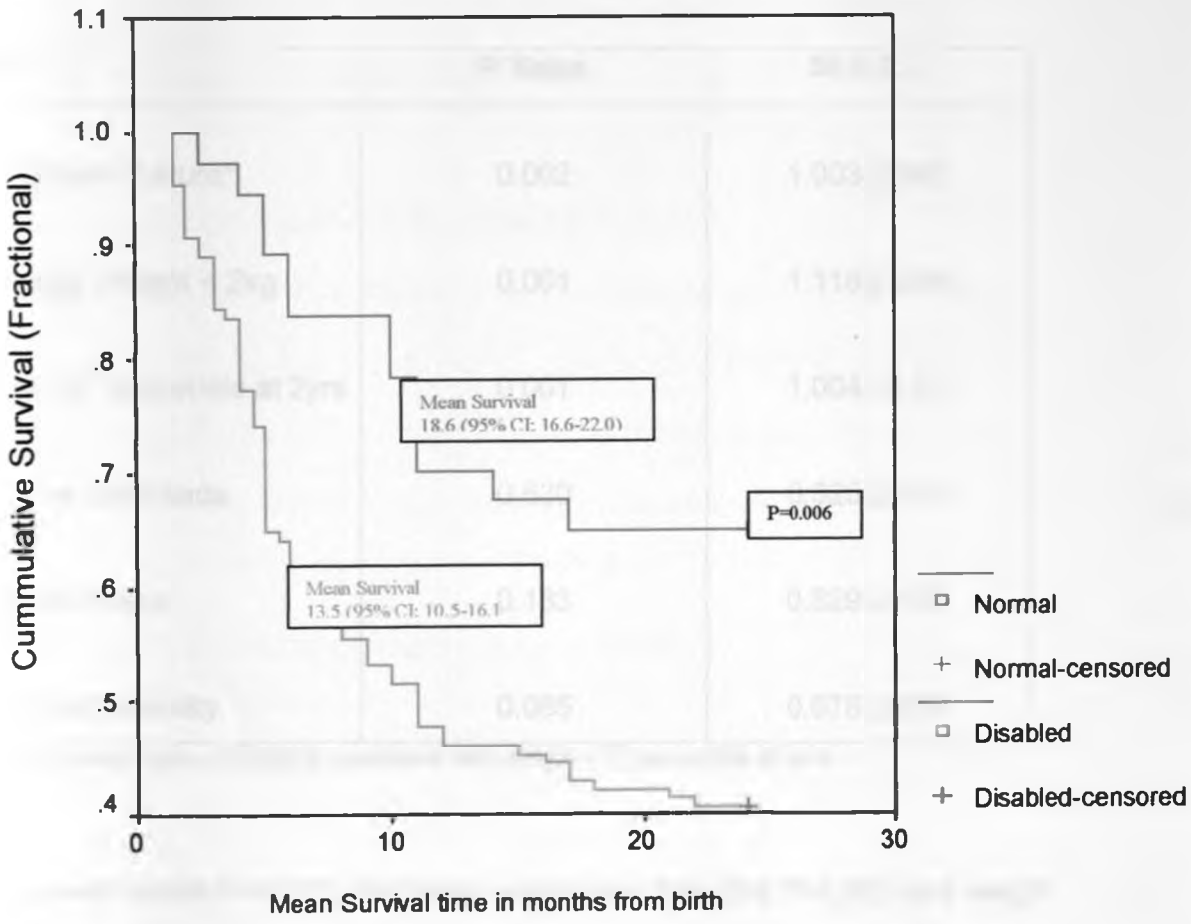

Figure 8: Survival curves: Functional disability and re-hospitalization

Despite an initial proximity of the two curves, disabled infants digressed from the normal group beginning at the age of 6 months. There was a difference of 5.1 months in mean survival values between the two groups, P=0.006.

LOGISTIC REGRESSION FOR PREDICTORS OF RE-HOSPITALIZATION

A binary logistic regression equation was constructed with re-hospitalization as the outcome variable to determine its independent predictors. The results are presented in table 14.

Table 14: Regression analysis for the predictors of re-hospitalization

Factor	P Value	95% C.I.
Early Growth Failure*	0.002	1.003-5.980
Discharge Weight < 2kg	0.001	1.118-6.098
Weight <3rd percentile at 2yrs	0.001	1.004-18.01
Exclusive BM Feeds	0.530	0.325-2.654
Neonatal Illness	0.183	0.829-2.675
Functional Disability	0.085	0.678-2.989

*Neonatal weight gain <15g/kg/d combined with weight <3rd percentile at term

Early growth failure P=0.001, discharge weight less than 2kg P=0.002 and weight less than the 3rd percentile at two years P=0.001 were the independent predictors of post-discharge re-hospitalization.

IV.5: POST-DISCHARGE MORTALITY

MAGNITUDE

One hundred and sixty five infants with complete information at the end of the study were available for this analysis. This group excluded the 10 infants who were lost to follow-up. Of these 165 subjects 45 had been reported dead giving a two-year post-discharge mortality of 27.3%, 95% CI 9.8-43.6. Thirty-three, (73.3%) of the deaths occurred in the first year.

DETERMINANTS OF POST-DISCHARGE MORTALITY

The factors investigated for association with post-discharge mortality included infants' gender, intra-uterine growth status, early feeding regimes, growth profiles, neonatal illness and re-hospitalization as summarized in tables 15 and 16. The Chi-square distribution test was used in the analysis.

Table 15: Determinants of post-discharge mortality 1

Factor	N (%)Deaths		Statistics* RR	95% CI)	P value
Males, **N=70**	20	(28.6)	1.25	(0.60-1.79)	0.747
Females, **N=95**	25	(26.3)	1.00		
AGA, **N=105**	30	(28.6)	1.17	(0.67-1.95)	0.620
IUGR, **N=60**	15	(25.0)	1.00		
BM alone, **N=78**	24	(30.8)	1.27	(0.77-2.10)	0.339
PTF/Mixed feeds, **N=87**	21	(24.1)	1.00		
Illness, **N=91**	34	(37.4)	2.51	(1.37-4.61)	0.001
No Illness, **N=74**	11	(14.9)	1.00		

*CHI-SQUARE TEST

Infants' gender: The post-discharge mortality was 28.6% and 26.3% for male and female infants respectively, P=0.747. Infants' sex did not influence post-discharge mortality in this cohort.

Intra-uterine growth: Mortality was marginally higher among the appropriate for gestation infants, 28.6% when compared to the intra-uterine growth retarded group at 25%. This difference was not statistically significant, P=0.620. Intra-uterine growth status had no influence on post-discharge mortality.

Nutrition: Infants fed on BM alone had a post-discharge mortality of 30.8% compared to 24.1% for those on PTF or PTF+BM. Feeding regime did not significantly influence post-discharge mortality, P=0.339.

Neonatal Illness: Infants who had been ill during the newborn period had 37.4% mortality compared to 14.9% for those who had been well, P=0.001. There was increased post-discharge mortality among infants with neonatal illnesses.

Table 16 presents the results of discharge weight, neonatal weight gain, weight attained at term and history of re-hospitalization as predictors of post-discharge mortality in the cohort.

Table 16: Determinants of post-discharge mortality

Factor	N (%)Deaths	Statistics* RR 95% CI)	P value
Discharge at <2kg, **N=110**	37 (33.6)	2.90 (1.24-4.38)	0.001
Discharge at 2kg+ **N=55**	8 (14.5)	1.00	
Neon[1] wt gain<15g/kg/d, **N=99**	35 (35.4)	2.33 (1.24-4.38)	0.004
Neon wt gain 15g/kg/d+, **N=66**	10 (15.2)	1.00	
Wt at term <3rd centile[2], **N=133**	40 (30.1)	1.92 (0.83-4.48)	0.091
Wt at term at 3rd centile+, **N=32**	5 (15.6)	1.00	
Re-hospitalized, **N=89**	33 (37.1)	2.40 (1.34-4.31)	0.002
Not re-hospitalized, **N=76**	12 (15.8)	1.00	

[1]NEONATAL, 2PERCENTILE *CHI-SQUARE TEST

Discharge Weight: Thirty seven (33.6%) of the 110 infants discharged weighing less than 2kg died compared to eight (14.5%) of the 55 who had reached 2kg at the time of discharge, P=0.001. Infants discharged before attaining 2kg were at an increased risk of subsequent mortality.

Neonatal Weight Gain: Infants with neonatal growth less than 15g/kg/d had post-discharge mortality of 35.4% compared to 15.2% for those who had grown at15g/kg/d or more, P=0.004. Better neonatal weight gain was associated with reduced post-discharge mortality.

Weight at term: Weight less than the 3rd percentile of the expected at term was associated with 30.1% post-discharge mortality while infants who were equal to or more than this growth parameter had 15.6%. This difference, however, did not attain statistical significance, P=0.091.

Re-hospitalization and mortality: The re-hospitalized infants had a post-discharge mortality of 37.1% compared to 15.8% in those who had not been re-hospitalized. This difference was statistically significant, P=0.002. Re-hospitalization increased the post-discharge mortality in the cohort.

KAPLAN MEIER ANALYSIS FOR POST-DISCHARGE MORTALITY*

Neonatal illness

The survival analysis for mortality and neonatal illness was performed. The results are presented in figure 9. The mean survival values, 95% CI and P values are included.

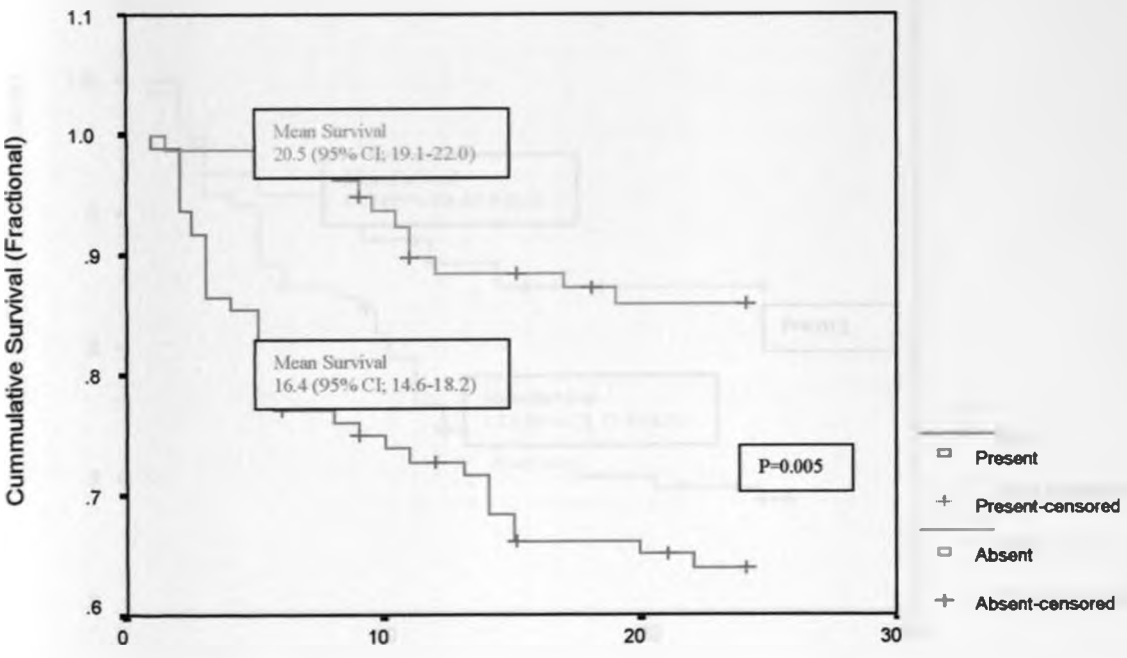

Figure 9: Survival Graphs: Neonatal illness and mortality

The graph generated by the infants without neonatal illnesses remained above the one by those classified as ill. Infants who were well during the neonatal period had a mean survival value of 20.5 months compared to 16.4 for those with history of neonatal morbidity, P=0.005. Absence of neonatal illness was associated with better post-discharge survival profiles.

*Kaplan Meier Survival Analysis for re-hospitalization[68],

Discharge weight

The survival curves for discharge weight including mean survival statistics are presented in figure 10

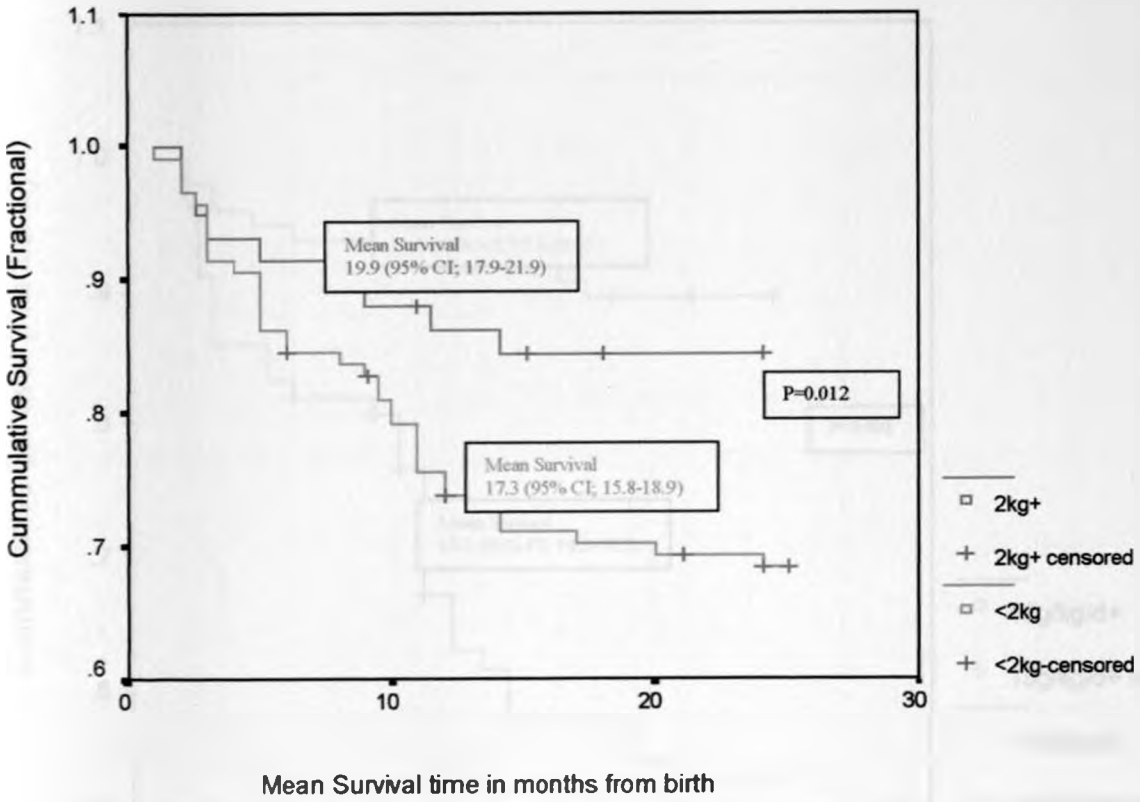

Figure 10: Survival graphs: Discharge weight and mortality

The survival graph for infants discharged after attaining 2kg was above that of the ones discharged lighter demonstrating better survival profiles for those discharged heavier. The 2.6 months mean survival difference observed between the two groups was statistically significant, P=0.0128. Lower discharge weight significantly worsened post-discharge mortality profiles.

Neonatal weight gain

The survival curves for neonatal weight gain are presented in figure 11 together with the relevant statistical calculations.

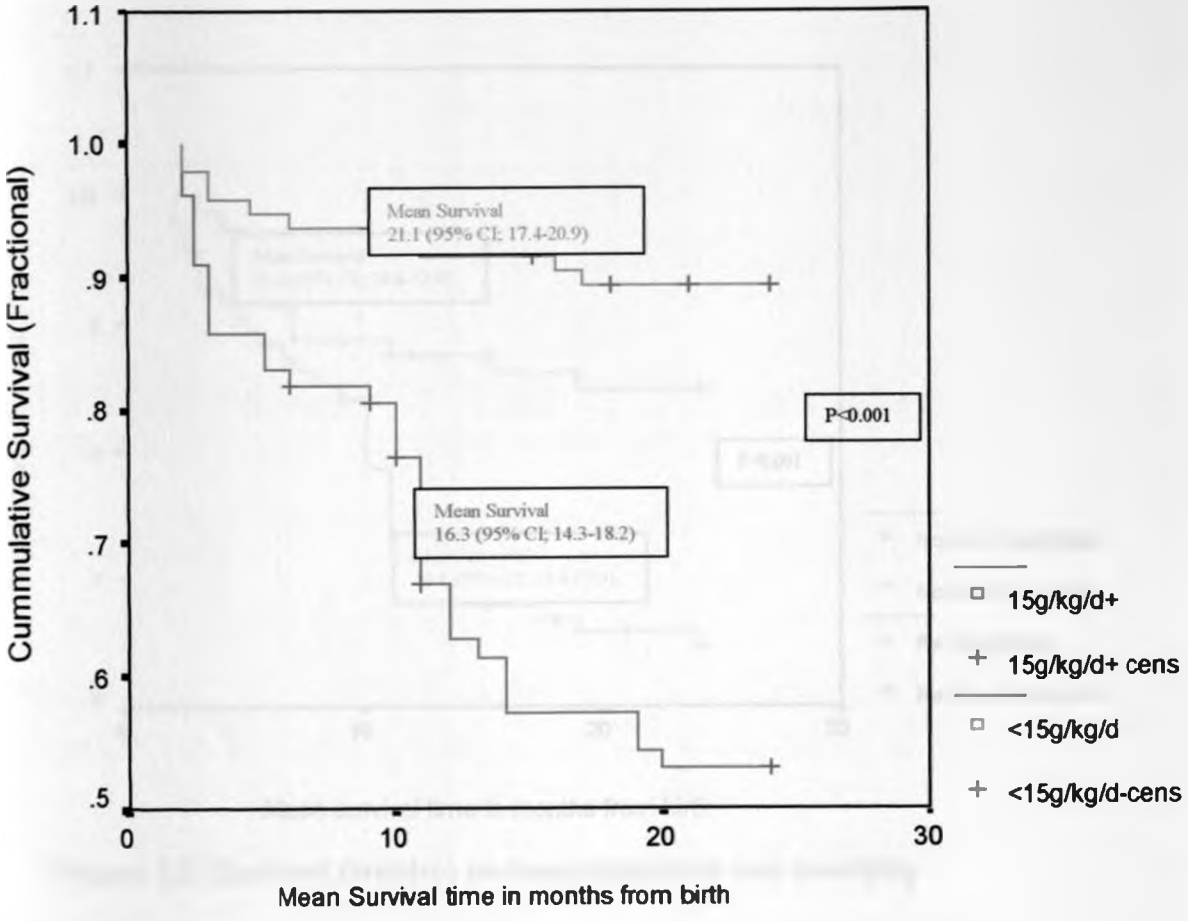

Figure 11: Survival Graphs: Neonatal weight gain and mortality

Infants who gained weight at 15g/kg/day or more during the neonatal period had a curve indicating better survival profiles compared to those with slower growth. The difference in their mean survival was 4.8 months, P<0.001. Better neonatal weight gain improved post-discharge mortality profiles.

Re-hospitalization

The survival curves for post-discharge re-hospitalization against post-discharge mortality as the outcome together with the relevant statistics are presented in figure 12.

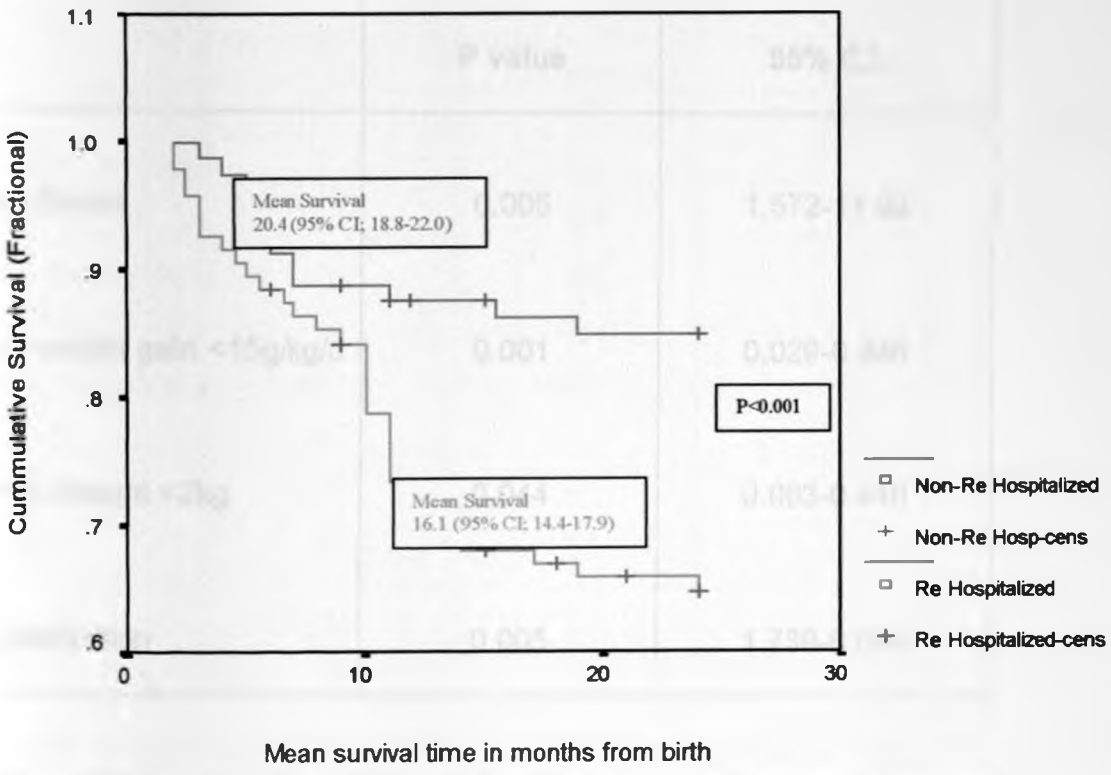

Figure 12: Survival Graphs: re-hospitalization and mortality

The re-hospitalized infants' survival curve remained lower than that for the group not re-hospitalized throughout the period of follow-up. Infants who were not re-hospitalized had a mean survival value of 20.4 months, 4.3 months higher than the re-hospitalized group, P<0.001. Re-hospitalization, therefore, worsened post-discharge mortality profiles.

LOGISTIC REGRESSION; PREDICTORS OF POST-DISCHARGE MORTALITY

The variables with statistical significance of 0.05 or less were subjected to binary logistic regression analysis to determine the independent predictors of death in the cohort. Table 17 summarizes the results

Table 17: Regression analysis for predictors of post-discharge mortality

Factor	P value	95% C.I.
Neonatal Illness	0.005	1.572-11.92
Neonatal weight gain <15g/kg/d	0.001	0.029-0.346
Discharge Weight <2kg	0.044	0.063-0.410
Re-hospitalization	0.005	1.739-8.044

Neonatal weight gain less than 15g/kg/d, P=0.001, history of neonatal illnesses P=0.005, post-discharge re-hospitalization P=0.005 and discharge weight less than 2kg P=0.044 were the independent predictors of death during the first two years of life.

IV.6: NEUOROLOGICAL OUTCOMES

MAGNITUDE

From the neurological evaluation done at the age of two years corrected for gestation, cerebral palsy, cognitive delay and functional disabilities rates were determined. The results are presented on table 18.

Table 18: prevalence of neurological sequelae

Two-year neurological Outcomes for the 120 survivors			
	Number	Percentage	95% CI
Cerebral Palsy	**14**	**11.7**	**6.2 - 17.1**
Spastic hemiplegia	4	3.3	
Spastic diplegia	3	2.5	
Spastic quadriplegia	1	0.8	
Hypo-tonia	6	5.0	
Functional Disability	**32**	**26.7**	**9.3 - 38.1**
Mild	14	11.7	
Moderate	11	9.2	
Severe	7	5.8	
Cognitive Delay	**11**	**9.2**	**4.8 - 16.9**

Fourteen (11.7%) of the 120 survivors had various forms of cerebral palsy, 11 (9.2%) had cognitive delay while 32 (26.7%) were diagnosed with functional disability. Most of the infants with cerebral palsy had the generalized hypotonic and spastic hemiplegic types. The functional disabilities were further classified as mild in 4 (11.7%), moderate in 11 (9.2%) and severe in 7 (5.8%) of the infants.

DETERMINANTS OF FUNCTIONAL DISABILITY

Various parameters were analyzed to determine their association with the presence of functional disability as detailed in tables 19 and 20. Neonatal illness, nutrition and weight gain, weight at term and at two years and re-hospitalization are presented in table 19 while table 20 has the obstetric and some baseline infant factors.

Table 19: Determinants of functional disability 1

Factor	N (%With disability)		Statistics RR	(95% CI)	P value
Illness, **N=57**	22	(38.6)	2.42	(1.26-4.69)	0.005
No Illness, **N=63**	10	(15.9)	1.00		
BM alone, **N=54**	20	(37.0)	2.04	(1.10-3.78)	0.020
PTF+/-BM, **N=66**	12	(18.2)	1.00		
Neon wt gain<15g/kg/d, **N=64**	23	(35.9)	2.24	(1.13-4.42)	0.014
Neon wt gain 15g/kg/d+, **N=56**	9	(15.2)	1.00		
Wt at term <3rd centile, **N=89**	27	(30.3)	1.88	(0.79-4.45)	0.120
Wt at term at 3rd centile+, **N=31**	5	(16.1)	1.00		
Re-hospitalized, **N=48**	22	(45.8)	3.30	(1.72-6.34)	0.001
Not re-hospitalized, **N=72**	10	(13.9)	1.00		
Wt at 2yrs<3rd centile, **N=69**	24	(34.8)	2.20	(1.09-4.53)	0.019
Wt at 2yrs 3rd centile+, **N=51**	8	(15.7)	1.00		

*CHI-SQUARE TEST

Neonatal illness: The proportion of infants with functional disability was more than twice among those who had suffered significant neonatal morbidity when compared to those who had been well, 38.6 and 15.9% respectively.

Surviving infants who suffered neonatal morbidity had more than twice the risk of developing functional disability when assessed at two years, RR 2.42, P=0.005.

Neonatal nutrition: The 54 infants exclusively fed on BM during the newborn period had 37.0% functional disability rate while the 66 who had been fed on PTF alone or in combination with BM had 18.2%. Exclusive use of BM during the neonatal period had statistically significant association with occurrence of functional disability, RR2.04, P=0.020.

Neonatal Weight Gain: Fifty-six surviving infants who had grown at 15g/kg/d or more had15.2% disability rates compared to 35.9% for the 64 who grew at less than 15g/kg/d. Infants who grew poorly during the newborn period had more than twice the risk of developing functional disability at two years, RR 2.24, P=0.014.

Weight at Term: Functional disabilities were seen in 30.3% of infants who weighed less than the 3rd percentile of the expected compared to 16.1% of the group more than the 3rd percentile at the same age. The difference was, however, not statistically significant, P=0.12.

Re-hospitalization: There were significantly more disabilities among infants who had been re-hospitalized during follow-up period, RR 3.3, P=0.001. Re-hospitalization increased the occurrence of functional disabilities.

Weight at 2 years: Functional disabilities were identified in 34.8% of the 69 survivors who had not reached the 3rd percentile of the expected weight at the age of two years compared to 15.7% of the 51 who had. Growth faultering at the age of two years was associated with more than twice the risk of functional disabilities, RR 2.2, P=0.019.

Table 20 comprises the results of the obstetric and baseline infant parameters evaluated as possible determinants of functional disability in the study.

Table 20: Determinants of functional disability 2

Factor	N (%With disability)		RR	Statistics* (95% CI)	P value
No ANC, **N=39**	14	(35.9)	1.62	(0.09-2.90)	0.110
ANC attended, **N=81**	18	(22.2)	1.00		
#Preg. Complications. **N=84**	25	(29.8)	1.53	(0.73-3.21)	0.240
No preg complications, **N=36**	7	(19.4)	1.00		
Born elsewhere, **N=22**	8	(36.4)	1.61	(0.77-2.85)	0.250
Born at KNH, **N=98**	24	(24.5)	1.00		
Caesarian Section, **N=25**	9	(36.0)	1.49	(0.79-2.80)	0.240
Vaginal Delivery, **N=95**	23	(24.2)	1.00		
Males, **N=50**	14	(28.0)	1.09	(0.66-1.98)	0.780
Females, **N=70**	18	(26.3)	1.00		
AGA, **N=75**	22	(29.3)	1.32	(0.69-2.53)	0.393
IUGR, **N=45**	10	(22.2)	1.00		

*CHI-SQUARE TEST # PREGNANCY

Antenatal Clinic Attendance: Infants whose mothers had attended ANC had a lower disability rate (22.2%) compared to those whose mothers had not attended (35.9%). This difference was not statistically significant, P=0.11, hence, ANC attendance had no influence on the development of functional disabilities.

Pregnancy Complications: Seven (19.4%) of the 36 infants born following un-complicated pregnancies had disabilities compared to 25 (29.8%) of the 84 delivered from complicated pregnancies. Functional disability was more prevalent among babies born following complicated pregnancy, though the association was not statistically significant, P=0.24.

Place of Delivery: Twenty-four (24.5%) of the 98 infants born at KNH were found to have disabilities compared to eight (36.4%) of the 22 admitted from elsewhere. The marginal advantage of hospital delivery in the functional disability rate was not statistically significant, P = 0.25.

Mode of Delivery: Nine (36%) of the 25 infants born by caesarian section had functional disabilities compared to 23 (24.2%) of the 95 born through the vaginal route. This difference was not significant on statistical analysis, P=0.061.

Intra-uterine growth Status: Functional disabilities were found in 22 (29.3%) of the 75 AGA infants compared to 10 (22.2%) in the IUGR group. This difference was not statistically significant, P=0.393.

Infants' gender: Male and female infants had almost identical disability rates of 28 and 26.3% respectively, P=0.780. Infants' gender had no significant influence on the occurrence of functional disability at the age of two years.

LOGISTIC REGRESSION FOR PREDICTORS OF FUNCTIONAL DISABILITY

All the parameters significantly associated with the occurrence of functional disability during single variable analysis were included in a binary logistic regression equation to determine its independent predictors. The results are summarized in table 21.

Table 21: Regression table for predictors of functional disability

Predictor Variable	P Value	95% C.I.
Re-hospitalization	0.084	0.57-3.14
Weight <3rd percentile at 2years	0.041	1.88-9.23
Exclusive use of Breast Milk	0.242	0.43-9.51
Neonatal Illness	0.011	1.06-4.14
Neonatal weight gain <15g/kg/d	0.039	1.07-1.94

Neonatal illness, P=0.011, neonatal weight gain less than 15g/kg/d, P=0.039 and growth faultering at the age of two years, P=0.041 were the independent predictors of functional disability.

DETERMINANTS OF COGNITIVE DEVELOPMENT

The median overall developmental scores for the 88 infants who did not have functional disabilities were used to identify the determinants of cognitive scores. Neonatal illness, neonatal feeding regimes and some growth parameters are included in table 22 while the rest of the variables are presented in table 23.

Table 22: Determinants of cognitive delay 1

Factor	Developmental Scores Mean	Median	(SD)	P value*
Illness	5.28	5.00	(2.48)	0.005
No Illness	6.95	6.50	(1.56)	
BM alone	4.33	4.00	(2.44)	
PTF+BM	6.33	6.00	(1.85)	0.001
PTF alone	6.60	7.00	(1.76)	
Neonatal wt gain<15g/kg/d	4.87	4.00	(1.92)	0.001
Neonatal wt gain 15g/kg/d+	6.98	7.00	(2.01)	
Wt at term <3rd percentile	5.33	5.00	(2.67)	0.001
Wt at term at 3rd percentile+	8.21	8.00	(1.85)	
Re-hospitalized	5.65	6.00	(2.17)	0.056
Not re-hospitalized	6.35	6.00	(1.89)	
Wt at 2years<3rd percentile	5.83	5.00	(2.67)	0.005
Wt at 2years 3rd percentile+	6.75	7.00	(1.85)	

*ANOVA

Neonatal Illness: Infants who had been healthy during the newborn period had a two points advantage in median overall cognitive scores over those who had been ill, P=0.005. Neonatal illness was associated with reduced cognitive scores at the age of two years.

Nutrition: Infants exclusively fed on PTF during the newborn period had a median overall score of seven, one point higher than those on mixed feeds and three points more than those who had been fed on exclusive BM, P=0.001. Early nutrient enrichment improved later cognitive scores.

Neonatal weight gain: Infants who grew at 15g/kg/day or more had a two point advantage in median cognitive scores when compared to those who grew at less than 15g/kg/d, P=0.001. Faster neonatal weight gain improved cognitive scores in this cohort.

Weight at term: Infants whose weights were within the 3rd percentile of the normal at term had a median cognitive score of eight while those less than the 3rd percentile scored only five, P<0.001. Catch-up growth at term was associated with improved cognitive scores at the age of two years.

Post-discharge Growth: Babies who had achieved catch-up growth in weight at the age of two years had a two point advantage in overall cognitive scores over the faultered group at the same age, P=0.005.

Re-hospitalization: The re-hospitalized and the non re-hospitalized infants had identical median cognitive scores of six. Re-hospitalization did not influence cognitive scores in the cohort.

Table 23 contains the summary of the obstetric and baseline infant predictors of cognitive scores that were included in the analysis.

Table 23: Determinants of cognitive delay 2

Factor	Developmental Scores Mean	Median	(SD)	P value (ANOVA)
No ANC	6.03	6.00	(2.42)	0.898
ANC attended	6.12	6.00	(1.64)	
Pregnancy complications	5.73	6.00	(2.44)	0.396
No pregnancy complications	6.34	6.00	(1.74)	
Born elsewhere	5.40	5.00	(2.56)	0.485
Born at KNH	6.24	6.00	(1.94)	
Vaginal Delivery	5.96	6.00	(2.45)	0.772
Caesarian Section	6.47	6.00	(2.60)	
Males	6.00	6.00	(2.38)	0.890
Females	6.10	6.00	(2.92)	
AGA	6.29	6.00	(2.47)	0.550
IUGR	5.79	6.00	(2.50)	

Antenatal clinic attendance: Infants born of mothers who had received some pre-natal care had the same median cognitive scores as those who had not had any. ANC attendance did not influence cognitive scores, P=0.898.

Pregnancy complications: Those born from complicated pregnancies had similar scores as the ones whose mothers had reported no complications, P=0.396. Complications in pregnancy did not influence subsequent cognitive scores.

Place of birth: Infants born at KNH scored one point higher than the ones born elsewhere in this assessment though the difference was not statistically significant, P=0.485. There was no association between cognitive scores and place of delivery.

Mode of Delivery: Babies born vaginally or by caesarian section had identical median cognitive scores indicating no association between mode of delivery and cognitive scores at the age of two years, P=0.772.

Infants' gender and intra-uterine growth status: There were no numerical or statistical differences in overall median cognitive scores attributable to infants' gender, P=0.890, or intra-uterine growth status, P=0.550.

LOGISTIC REGRESSION: PREDICTORS OF COGNITIVE DELAY

A regression equation was constructed to determine the predictors of cognitive delay in the cohort. The outcome variable was a score of zero, which comprised of the 11 infants diagnosed to have cognitive delay. The predictor variables included in the equation were, neonatal illness, early growth (combined neonatal and catch-up growth at term), neonatal feeding (BM alone versus the rest), weight at two years and re-hospitalization. The results are presented in table 24.

Table 24: Regression analysis for predictors of cognitive delay

Predictor variable	P Value	95% C.I.
Neonatal Illness	0.014	1.37-4.14
Exclusive breast milk	0.214	0.04-3.99
Early growth failure*	0.017	1.06-6.24
Re-hospitalization	0.081	0.35-7.76
Growth failure at 2 years	0.043	1.38-7.23

***Neonatal weight gain <15g/kg/d combined with weight at term <the 3rd percentile**

Neonatal illness, P=0.014, early growth failure, P=0.017 and growth failure at the age of two years, P=0.043 were the independent predictors of cognitive delay in that order.

Neonatal nutrition was a predictor when early growth was removed from the equation but lost the power when both variables were included. Early growth remained a predictor even when analyzed together with early nutrition in the same equation.

TWO-YEAR INTACT NEUROLOGICAL SURVIVAL RATE

This is the proportion of a cohort of children alive and free neurological sequelae at the age of two years. The value in this study was 50% (88/175) when confined to the neonatal survivors and 25% (88/344) if the entire birth cohort was taken as the denominator.

V: DISCUSSION

V.1: BASELINE CHARECTERISTICS

OBSTETRIC CHARACTERISTICS

Antenatal clinic visits provide an opportunity for identification and possible correction of pre-natal events that may increase peri-natal, neonatal and probably post-neonatal morbidity, mortality and other diverse outcomes. This should be even more important for those born VLBW who are at higher risk of preventable or treatable conditions, which can be alleviated if identified early. In this group, 61% of the mothers had not attended any antenatal clinic. Only 39% of them had benefited from this important service by the time of delivery. This constitutes inadequate obstetric care. Olel, in his thesis found 36% ANC booking rates in mothers who delivered before 36 weeks gestation in the same institution[69]. The most recent estimate of the national average of ANC booking was above 80% indicating that most mothers commence their antenatal clinic visits late[70].

Pregnancy complications are associated with increased peri-natal and neonatal morbidity and mortality[71] though their effects on long-term outcomes have not been frequently reported. In this series, only two-thirds of the deliveries came from pregnancies in which complications such as hypertension, acute genitor-urinary infections, prolonged rupture of membranes and ante-partum hemorrhage had been reported. This level of pregnancy complications is expected at a referral center such as KNH with predominantly for high-risk patients.

Previous reports from this unit[72] and elsewhere[73] have shown increased neonatal morbidity and mortality for VLBW infants born out of the hospitals from which they eventually receive their NIC. This is usually due to the risks of transporting such infants. The long-term effects of birth away from the provider hospital have not been reported in recent years. More than 20% of the infants were admitted following delivery elsewhere and referred to Kenyatta National Hospital.

The 35% caesarian section rate for those born at the hospital was within the usual range at the facility for all deliveries[69].

INFANT CHARACTERISTICS

The male: female ratio of 2:3 was quite different from the 1:1 ratio observed for the total birth cohort indicating disproportionately higher neonatal deaths among the male infants in the cohort. The phenomenon is now established in literature, male infants regardless of birth weight have more neonatal mortality than their female counterparts[72].

Sixty-four (36.6%) of the infants were intra-uterine growth retarded. Only 89 (25.9%) of the 344 VLBW infants from whom this study population was selected were intra-uterine growth retarded. This suggests a smaller attrition of IUGR infants compared to those born AGA during the initial hospitalization period. This may have been due to better neonatal survival expected among IUGR infants who are more mature than the AGA group.

The mean birth weight of the recruited infants was 1393g with a range between 900 and 1500g. The distribution was skewed towards the upper end of the VLBW category. In the source population the mean birth weight had been 1280g suggesting that there were more neonatal deaths among the smaller infants. In fact, only four out of 56 infants less than 1000g at birth were alive by the end of the first month. A recent study at KNH also reported neonatal survival less than 5% for infants born less than 1000grams[72]. The lack of properly equipped level 2 and 3 intensive care facilities is responsible for early losses of smaller and/or less mature infants.

The mean gestation for the recruited infants was 32.4 weeks. The large number of intra-uterine growth retarded infants in the surviving cohort was responsible for the mean being above 32weeks, the expected gestation for infants weighing 1.5 kilograms with normal intra-uterine growth. Like the smaller infants, the less mature ones may have contributed disproportionately to neonatal deaths.

V.2. EARLY GROWTH PROFILES

EARLY GROWTH

The mean neonatal weight gain for the whole group was 13.54± 3.96 g/kg/day, length 0.34±0.3 cm/week and head circumference 0.32± 0.3 cm/week. All these were lower than the expected post-natal growth in VLBW infants of 15g/kg/day in weight and 0.5cm/wk for head and length[74-76]. When the infants were classified in terms of neonatal growth, 60, 76.9 and 70.4% were found to have grown at rates slower than the cut off points in weight, length and head circumference respectively. Studies have shown that poor neonatal weight gain, in particular that less than 15g/kg/day is associated with lower developmental scores when the infants are evaluated later[8]. During this early period of development, normal growth signifies appropriate conditioning which predicts better neurological development later in life.

It has been postulated that the newborn period is vulnerable in VLBW infants regarding brain growth and development[23]. Inability to achieve the adequate growth in a large proportion of the infants in this cohort is, therefore, considered a precursor for poor neuro-development that may manifest at a later stage. The goal of post-natal growth for VLBW infants is to maintain the predicted intra-uterine growth rate. If that is achieved, it is expected that such infants will reach the expected anthropometric measures when they attain the age of expected delivery with normal pregnancy duration.

The mean weight, head circumference and length at term were 2.23±0.22 kg, 32.1±1.2 cm and 46.4±1.36 cm respectively. The expected values at term are 2.5kg, 33cm and 50cm for weight, head circumference and length respectively[67]. Catch-up growth in weight, length and head circumference had not occurred at term in 81.1, 78.9 and 72% of the infants respectively. Somatic growth failure rate of 81.1% observed in this cohort was almost twice the 45% reported by Hack, et al[48]. The latter, reporting from an advanced country, probably owes the superior post-natal growth rate to better medical care and use of modern nutritional strategies for VLBW infants. Failure to catch-up in growth by the expected date of delivery has also been reported as detrimental to later development[47-48].

From these results, it is concluded that both neonatal growth and anthropometric parameters at term were below the expected norms in most of the infants. Growth in weight and head circumference is particularly important indices for prediction of neurological outcomes. Since many of these infants did not grow well during the vulnerable period, they were at risk of subsequent neurological disabilities. The next section will explore the factors found causally related to poor growth in the present study.

DETERMINANTS OF EARLY GROWTH

Some of the factors previously reported to be associated with decreased neonatal growth include intra-uterine growth retardation, use of un-fortified mothers' milk and neonatal illness[8]. The effects of these factors on the early growth indices in this cohort are discussed in this section.

Intra-uterine Growth: The median neonatal growth indices of infants born IUGR was similar to that of the AGA group in weight P=0.058, length P=0.127 and head circumference P=0.087. When evaluated at term, however, IUGR infants were significantly lighter P=0.015 and shorter P<0.001 than the AGA group. Though daily post-delivery growth was similar between the two groups the weight attained at term was significantly lower among IUGR infants. This was not surprising since in order to achieve catch-up growth, IUGR infants have to grow at rates faster than their AGA counterparts. Only then will they be able to bridge the "lost time before delivery", when they grew inadequately. In addition, IUGR infants may continue to suffer the growth suppressing effects of the disruptive pre-natal events even after birth. Hack and colleagues also found more catch-up growth at term for AGA infants when compared to those who had suffered IUGR suggesting that the negative effects of intra-uterine growth retardation on post-natal growth appear to be unaffected by differences in resource base.

Neonatal Illness: The infants who had been classified as having neonatal illnesses had significantly slower neonatal growth in weight P<0.001, head circumference P=0.001 and length P=0.001 than those deemed well. When evaluated at term, the previously ill infants still had significantly lower weight P<0.001, and head circumference P<0.001. Neonatal illness impacted negatively on both neonatal growth and catch-up in anthropometric measures at term. Infants who suffer significant illness during the newborn period are expected to have some impairment of their growth. This is because neonatal illnesses not only make feeding difficult they also modify the infant's metabolic functions in ways that may be unfavorable for normal growth. In situations where intravenous nutrition is not available neonatal illness will have a profound effect on feeding and growth. Infants in such situations depend on long periods of intravenous fluids with no actual nutritional value, a practice that has been found detrimental to early growth of VLBW infants[8].

Logistic regression analysis performed to determine the independent predictors of inadequate growth identified neonatal illness as a predictor of poor growth in all the measured indices in this cohort except neonatal head growth. This strengthens the observation that illnesses were an important deterrent of early growth. The care provided to sick VLBW infants needs to be reviewed as this may improve early growth among them at KNH.

Neonatal Feeding: Infants fed on BM alone had poorer growth parameters than those on mixed feeds or exclusive PTF. This was expected because the BM provided at KNH during the period was not fortified, hence, not likely to satisfy the macro-nutritional needs of these infants. The improved growth brought about by PTF was statistically significant for all the anthropometric parameters measured, $P<0.001$. Exclusive BM in the neonatal period retarded growth in all the anthropometric parameters evaluated. Other workers have reported this association between nutrient enriched milk with improved growth of VLBW infants during the first month of life[25-26, 77].

Brooke and colleagues reported mean neonatal growth for infants on PTF of 21.5g/kg/d, 1.4cm/wk and1.13cm/wk in weight, length and head circumference compared to 15.6, 0.84 and 0.93 respectively for infants fed on BM alone in their study which had 40 patients[26]. In a randomized multi-centre clinical trial Lucas and colleagues in the United Kingdom later established the superiority of PTF over un-fortified BM on the early growth of VLBW infants[25]. In this large series, VLBW infants on PTF had the best neonatal growth followed by those on PTF mixed with BM while those on BM alone had the lowest growth parameters. These finding of Brooke and Lucas are confirmed by the present study.

The national infant feeding policy in use at KNH has no birth weight stratification. As long as it is available, BM is used exclusively for even the smallest infants regardless of the growth patterns observed.

Nutrient enriched PTF is only used to supplement inadequate BM production or as replacement when maternal health or other circumstances preclude use of mothers' milk. This study suggests that this practice constitutes inadequate feeding for the VLBW infants. Since exclusive BM was an independent predictor of poor growth during the newborn period and at term, the need to enrich it for use in VLBW infants at KNH is confirmed by this study. There is ample literature supporting modification of feeding regimes for VLBW infants[25,26,77].

The national infant feeding policy of exclusive breast milk for the first six months of life, as practiced at KNH, is not appropriate for VLBW infants. It is necessary for KNH to optimize the value of breast milk for VLBW infants by introducing universal fortification for this high-risk group. Breast milk fortification has been practiced for several decades with conclusive evidence that it produces neonatal growth comparable to that achieved by PTF[77]. According to the 2003 Kenya demographic health study 96% of mothers in Kenya routinely breastfeed their infants[70] making breast milk fortification the logical and practical recommendation for early feeding of all VLBW infants.

In this study, there were some marginal differences between the growth patterns of males and females with the former seeming to grow better. Yu and colleagues reported significantly better growth among male VLBW infants in their cohort[71]. The design of the present study is likely to have been responsible for the inability to detect this difference.

V.3. POST-DISCHARGE GROWTH

PROFILES

Inadequate growth after the newborn period has also been found to be a bad prognostic sign for neurological development in VLBW infants[49]. There post-discharge growth faltering rate was high in this cohort with over 60% of the infants having retarded growth at one and two years in all growth parameters. The Kenyan average rate of growth faultering defined as, weight less than 2SD of the expected is 26% for children under five years[70]. The infants in this cohort appear to have suffered more growth retardation than the general under population. The growth failure rate reported here is also higher than that from developed countries. Hack and colleagues[49] in their cohort of VLBW infants reported rates of 31 and 27% at the ages of 8 and 21 months respectively. The rate found by the present study was, therefore, more than double what is expected in developed regions.

DETERMINANTS OF POST-DISCHARGE GROWTH

The study hypothesized that IUGR, neonatal illness, re-hospitalization and functional disability are associated with reduced post-discharge growth. Intra-uterine growth retardation P=0.001, neonatal illness P=0.002, growth faultering at term P=0.001, re-hospitalization P=0.001 and presence of functional disability P=0.033 were all associated with growth failure at the age of two years.

Logistic regression analysis found IUGR P=0.007, neonatal illnesses P=0.001 and functional disability P=0.033 as the independent predictors of poor growth at the age of two years.

Many of the intra-uterine growth retarded infants did not recover even after two years. This is in agreement with the findings of Hack and colleagues[49]. Since post-natal recovery for IUGR infants seems difficult, attention should be focused on strategies for reducing its occurrence.

Neonatal illness appears to have sustained its negative impact on growth into the second year. This may be due to the effects of neonatal illness as a destructive programming factor leading to sustained growth failure.

Neurologically impaired infants are expected to have difficult post-discharge adjustments including feeding and morbidity. These may explain the disturbed post-natal growth observed in neurologically impaired infants. An appropriately designed study will be helpful in identifying post-natal factors contributing to poor growth during the first two years of life among VLBW infants.

V.4: RE-HOSPITALIZATION

MAGNITUDE

Re-hospitalization is considered an important parameter in outcome audits for VLBW infants because it indicates increased burden of care by the society for this high-risk population[7]. It was defined, in this study, as any episode of hospital admission after the initial discharge from the newborn unit. The study hypothesis was "re-hospitalization was more frequent in this cohort than reported from more affluent regions". Among the 165 infants who completed the study 89 (53.9%) 95% CI: 25.6-73.2 had been re-hospitalized on at least one occasion during the follow-up period. Because of the different dynamics that may govern re-hospitalization, its reported frequency is markedly varied, 22 - 53%[7]. The rate reported in this cohort is high but still within the range hence the hypothesis as stated above is rejected. The clinical diagnoses of the re-hospitalized infants in this group were included acute lower respiratory and gastrointestinal infections, malaria, failure to thrive and anaemia.

One of the most important factors that contribute to re-hospitalization of VLBW infants is the neonatal risk category of the infant. Very low birth weight infants are not a homogeneous group and additional risks factors like initial disease severity may vary greatly. The reports cited in the reference above[7] involved many infants who had required level three NIC. Such infants would have been of higher risk category than those in this group who at most required level two lower dependency (non-invasive monitoring) care.

The observed re-hospitalization rate in this group was, hence, higher than should have been predicted by their neonatal risk classification. Low socio-economic disadvantage has also been identified as a contributory factor to post-discharge re-hospitalization of VLBW infants[43-44]. This may have played a part in this group since the hospital's source population is mainly the low socio-economic groups in Nairobi and its environs. This group was poorer than those in affluent societies, which register rates closer to 30%[45].

Hack et al, reported a 33% re-hospitalization [45], with [the] majority being re-admitted due to acute respiratory and gastro-intestinal infections. The next most important cause of morbidity in Hack's study was complications emanating from neonatal morbidity such as chronic lung disease. A few were re-admitted for correction of surgical complications like inguinal hernia from the effects of increased intra abdominal pressure during mechanical ventilation. The causes of re-hospitalization vary according to different neonatal risk situations and probably geographic disparities.

Re-hospitalization of VLBW infants is now regarded as an audit tool for assessing their long-term outcomes because not only does it increase the cost of health care, it also contributes to increased post-discharge mortality decreasing the life expectancy of these infants. The American Academy of Paediatrics (AAP) has estimated that it costs about 50,000 United States Dollars for medical care of VLBW infants in the first year post-discharge year[78]. It has also been

reported that each graduate of the NICU regardless of birth weight needs US$ 10,000 for re-hospitalization costs during the first post-discharge year[79]. The cost of post-discharge re-hospitalization of VLBW infants is likely to constrain already marginal budgets in most developing countries, which have more of such infants than the richer nations. The AAP has recommended increased efforts to identify simpler measures to reduce post-discharge re-hospitalization for VLBW infants. The group estimated that every infant who is made to reach term at the expected weight saves the health care system an average of up to 50,000$ in medical costs during their first year of life[78]. They further assert that this can be achieved, in many cases, by simple and cheap pre-natal care technologies.

DETERMINANTS OF RE-HOSPITALIZATION

It is important to identify the factors associated with re-hospitalization as this will help in formulating strategies necessary for reducing its occurrence. Neonatal illness P=0.015, exclusive BM during the newborn period P=0.001, discharge before attaining two kilograms P<0.001, inadequate neonatal growth P<0.001, growth faultering at two years P=0.005 and neurological disability P<0.001 were found to be associated with later re-hospitalization. Regression analysis established that inadequate neonatal growth P=0.002, discharge weight less than two kilograms P=0.001 and growth faultering at the age of two years P< 0.001 were independent predictors of post-discharge re-hospitalization.

These three factors should provide opportunities for interventions aimed at reducing post-discharge re-hospitalization.

Infants having normal somatic growth are more likely to develop defenses against common illnesses better than those not growing well. As the predominant illnesses leading to re-hospitalization in this group were infections, probably in the background of reduced immunity, the finding is not surprising. Poor growth is associated with reduced immunity in children[83]. The results of the present study suggest that the negative effects of poor growth in the newborn period persist into the second year of life. Ensuring normal neonatal growth may have protective effects on major morbidities in VLBW infants that continue into the second year of life.

Before the commencement of the study, the recommended discharge weight for VLBW infants at KNH was two kilograms. Due to the introduction of the kangaroo mother care technique, this practice had been liberalized allowing lower discharge weights. This situation allowed the study to test the hypothesis that "discharge weight below two kilograms was associated with increased post-discharge re-hospitalization". The results of the study proved this hypothesis. Infants discharged smaller than two kilograms were more vulnerable to re-hospitalization, especially in the immediate post-discharge period as shown in figure 4.

In order to successfully discharge VLBW infants at smaller weights, an intensive follow-up program including home support is essential. Where such a program is not guaranteed, it is advisable to maintain the practice of discharging VLBW infants after attaining the weight of 2kg. The kangaroo mother care technology allows for the discharge of smaller babies than the usual 2KG[80-82]. In this cheap technology infants are continuously nursed in contact with their mothers' skin for adequate thermo-regulation. The success of the technology depends, in part, on intensive supervision by health workers, which was not available for the subjects of the study.

The hypothesis stating that, "growth failure at two years was associated with increased post-discharge re-hospitalization", was also proved by results of the study. These being infants with chronic failure to thrive, it was not surprising when they suffered more illnesses than the normally growing counterparts. Improving post-discharge growth may decrease re-hospitalization in VLBW infants.

Exclusive use of breast milk during the newborn period was also associated with re-hospitalization as had been hypothesized but only at single variable analysis. Nutrient enrichment of the diets of these infants during their first month of life was associated with decreased chances of re-hospitalization. This is likely to have been a manifestation of better growth brought about by nutrient enrichment.

Infants who are fed on nutritionally richer diets and follow better growth patterns are expected to cope better with environmental hazards like infections, which were responsible for the majority of re-hospitalizations in this group. Their immune systems and physical developments are better equipped for such situations[83]. When normal growth is been achieved, infants predominantly fed on mothers' milk suffer less morbidity during infancy than those on artificial feeds[26]. The findings of this study show that it is essential for the feeding regime adopted to ensure normal growth in VLBW infants since their growth was a better predictor of re-hospitalization than nutrition at regression analysis. HIV/AIDS was not controlled for in the study hence its contribution to morbidity among infants feed on possibly infected mothers' milk was not known. This was an important confounder to be considered when interpreting the results of this study.

Neonatal illnesses were also hypothesized to be associated with increased post-discharge re-hospitalization. Sixty two percent of the infants who had suffered significant neonatal illnesses were later re-hospitalized compared to 42% of those deemed well, P=0.015. The relative risk of re-hospitalization for previously sick infants was 1.46. This hypothesis could, however, only be confirmed on the basis of single variable analysis. It is postulated that such illnesses have effects, which either directly or through impaired growth, disturb the adaptation of the immune system and other physical mechanisms required for protection against post-discharge morbidity.

This is particularly so, when infants are discharged with residual diseases like peri-natal asphyxia, chronic lung disease and anaemia, extending from the newborn period[7, 43-45]. There was no reliable documentation of residual illness at discharge for most the infants in the study making its contribution to re-hospitalization in this study un-determinable. Re-hospitalization was more frequent among infants with neurological sequelae confirming the study hypothesis regarding this association. Very low birth weight infants with neurological disorders have been previously reported to be more prone to childhood illnesses than is expected for their neurologically normal counterparts[43, 45]. They have also been found to suffer traumatic injuries, accidental or otherwise, more frequently than neurologically intact children of the same age[84]. McCormick and others[43] reported significantly increased risk of re-hospitalization for VLBW infants with neurological deficits while Hack, et al[45] specifically reported re-hospitalization in 40% of very low birth weight infants with neurological delay at two years compared to 30% for those who were normal, a 33% risk. Continuing medical care was part of the increased burden on society brought about by improved survival of VLBW infants. This justified its inclusion among long-term medical audit statistics for these infants[7]. Since the hospitalization rate for normal birth weight or all Kenyan children has not been established, it is not possible to estimate the disparity between the findings of this study and the general population. It is likely, however, that the infants in this study were re-hospitalized more frequently than expected for the general population.

V.5: POST-DISCHARGE MORTALITY

MAGNITUDE

Post-discharge mortality directly determines the life expectancy of high-risk newborns such the VLBW. It is a pivotal outcome audit tool for VLBW infants. The post-discharge mortality was 27.3%, 95% CI, 9.8 - 43.6 for the two-year period, with 73% of the deaths occurring in the first year. This was seven times the rate reported from a typical center in an industrialized country[40] confirming the study's hypothesis that "post-discharge mortality for VLBW infants is higher in this cohort than reported from developed regions". The post-neonatal mortality was 19.9% or 199/1000, which is almost 4 times the national average for all infants in Kenya[70]. Reports from industrialized countries also indicate that the post-neonatal mortality of VLBW infants is between 3 and 5 times that of the normal population[7].

In Australia, a developed country, Yu et al[40] reported 3.9% post-discharge mortality at two years for a cohort of VLBW infants; seven times lower than the one seen in the present study despite the fact that most of the infants in the Australian series had required higher levels of neonatal intensive care. The Australian infants were in a higher risk category than the group in the present series. Based on neonatal illness risk category, this cohort should have lower mortality than the Australian group.

The disparity in economic power and possibly post-discharge care between Kenya and Australia may have contributed towards the observed differences in post-discharge mortality between the two groups. The survival analysis showed that the peak period of death was during the first 6 months of life. This may imply that the immediate post-discharge adjustments are of particular importance. The increased vulnerability of VLBW infants to post-discharge complications makes them require more intensive post-discharge care if this mortality is to be monitored and reduced.

The reports from developed countries show that VLBW infants dying during the first two years of life succumb to illnesses emanating from the neonatal complications, community acquired respiratory and intestinal infections and the sudden infant death syndrome [7, 39-42]. As most of the infants in this cohort were relatively well during the newborn period, neonatal complications were not expected to be a major factor in causation of post-discharge deaths. The majority of the deaths in this group are likely to have followed the trends of the normal population. From these findings, it is concluded that VLBW infants warrant special attention as they may significantly contribute to the national infant mortality. The factors associated with post-discharge mortality in this study are discussed below.

DETERMINANTS OF POST-DISCHARGE MORTALITY

The factors that have been consistently identified as contributory to increased post-discharge mortality among LBW infants include birth weight[85-87] and severity of neonatal illnesses[7]. The study hypothesized that neonatal illness, discharge weight, neonatal growth and re-hospitalization were associated with post-discharge mortality. In this study, neonatal illnesses P=0.001, discharge weight less than two kilograms P=0.001, neonatal weight gain below 15g/kg/day P=0.004 and re-hospitalization P=0.002 were associated with increased post-discharge mortality. The hypotheses that these factors increased post-discharge re-hospitalization are accepted.

The increased post-discharge mortality found in this study among infants who had been ill during the neonatal period is consistent with previous reports, which also identified early illness as a risk for later death among VLBW infants[7, 40]. In the previous reports, the specific issues implicated in causation of these deaths are related to the complications of neonatal illnesses that continue beyond discharge such as chronic lung disease. In a report by Yu et al, 70% of post-discharge deaths were related to neonatal disorders, particularly those related to respiratory distress syndrome[40]. Residual disease at discharge was, in Yu's study, a vital factor in increasing post-discharge death among VLBW infants. Infants in the present study had less severe neonatal morbidity and no reported residual complications at discharge yet they had more post-discharge deaths than Yu's group.

The post-discharge mortality was significantly higher among infants who had been discharged weighing less than two kilograms. Discharge of VLBW infants before they reach this weight probably exposed them to a less controlled environment before they are ready.
As most of the infants were from poor family backgrounds, it is unlikely that they could afford either additional warmth or even adequate clothing for their infants. This is particularly dangerous in an area with low ambient temperatures and high levels of acute respiratory infection such as the one most of these infants were discharged to, the lower class suburbs of Nairobi.

Discharge of smaller infants reduces overcrowding in the newborn facility but must be done in a more selective way. At the time this study undertook its recruitment, KNH had introduced the kangaroo mother care program allowing discharge of VLBW infants as early as they could be kept warm by round the clock contact with the mother's skin. This method of care has been successfully tested and used before[80-82]. Its implementation, however, requires rigorous follow-up programs that are difficult to ensure in resource poor communities. Discharge weight should remain at a minimum of two kilograms until this new technology, kangaroo mother care, can be implemented properly.

Somatic growth in the neonatal period had a significant impact on post-discharge mortality providing further justification for ensuring normal growth for VLBW newborn infants.

The advantages of better growth in the newborn period seem to last into the second year. At regression analysis neonatal weight gain was one of the independent predictors of post-discharge death. Poor growth is known to affect health negatively during childhood[83]. It is, therefore, not surprising that VLBW infants are also affected. The fact that the advantageous effects of normal growth in the in the newborn period can last for two years in VLBW infants offers an opportunity for an effective intervention strategy.

Post-discharge mortality was significantly higher among infants who had been re-hospitalized after the initial discharge. At regression analysis, re-hospitalization was an independent predictor of death. Re-hospitalization signifies severe morbidity, which may act together with inadequate medical facilities to bring about increased mortality. Due to their vulnerable state, VLBW infants are likely to require more intensive attention whenever they are re-hospitalized compared to the bigger ones. Areas with less equipped health facilities are therefore expected to experience more post-discharge deaths among such infants.

V.6: NEUROLOGICAL OUTCOMES

MAGNITUDE

The gold standard, long-term, outcome measure for VLBW infants is estimation of neurological intactness. Neurological intactness not only affects important parameters like quality of life, it is also influences other important outcomes like post-discharge morbidity and mortality. The neurological outcome measures evaluated in this study were cerebral palsy, cognitive dysfunction and functional disability. The latter is contributed by both physical and cognitive development. The hypotheses were, "the rates of occurrence of these outcomes are higher than those reported in recent literature from more advanced countries".

Cerebral palsy: Fourteen of the 120 survivors assessed at two years were found to have cerebral palsy giving a rate of 11.7%, 95% CI 6.2 – 17.1. This being more than double what is presently reported in western literature, the hypothesis is accepted[2]. In a comparable environment of Soweto in South Africa[61] and a more advanced one in Malaysian[88], cerebral palsy rates of seven and five percent respectively, were reported in the late 1990s. The cerebral palsy rate in this cohort is higher than found in regions economically closer to Kenya. The KNH rate falls closer to the level by Escobar and colleagues of 8.3% 95% CI of 5.7 -10.1 in a meta-analysis of pooled data[38]. This suggests that the performance of the newborn unit at KNH today compares with the expectations in the advanced countries 20 years earlier.

A proportion of cerebral palsy lesions are known to resolve with time[89-90]. It is possible that the Soweto findings would have been better had the evaluation also been performed at the age of two years instead of 18 months as was the case. Nelson and colleagues, reported reversal to normality of up to 50% of VLBW infants who had been found to have cerebral palsy at two years when they were reassessed five years later[89]. Kitchen et al, also reported 50% remission in physical disabilities between two and five years among VVLBW infants[90].

If the present cohort were to emulate this recovery, the cerebral palsy rates would probably drop below 6% in later years. This would be nearer the rates reported from developed countries[2]. Such recovery necessarily depends on the availability and intensity of re-habilitation measures provided during the intervening period, which are unlikely to be as good in KNH as the facilities in the richer countries. Fifty percent remission will be less likely to be realized in the KNH group. If any remission occurs here, it will probably be to a lesser degree in comparison with that reported by Nelson[89] and Kitchen[90].

Functional Disability: Functional disability was found in 26.7%, 95% CI 9.3 - 38.1 of the 120 survivors at the age of two years. This was almost twice the 14.2% rate found by Saigal and Rosenbaum's original study involving 147 infants of born weighing between 1000 and 1500g[65]. The hypothesis, "functional disability was higher in the KNH than reported in western literature" is accepted.

The functional disability rate reported in this study was similar to the median rate of pooled data by Escobar and colleagues, 22.6%, 95% CI 17.1-32.9 for VLBW infants more than 15 years earlier[38].

The functional disability tool tests the ambulatory and other activities essential for independent life. The test is influenced by both physical and cognitive development, hence, measuring global neurological function. Unfortunately, it may also be affected by factors that are independent of brain function such as poor muscle development. It is the simplest tool available for neurological assessment of young children.

Cognitive delay

Eleven (9.2%) 95% CI 4.8-16.9 of the 120 survivors had cognitive delay. This was twice the rate reported by western rearchers[2-3] and those recently reported in South Africa[62] and Malaysia[88]. The South African group was expected to be comparable to the present study since the patient population and the economic profiles of the areas are closer to each other. These findings confirmed the hypothesis that "cognitive delay is more frequent here than reported in more developed countries".

The developmental scoring system used in this study was a screening method modified to provide semi-quantitative measurement. It can be used to identify developmentally delayed infants who need help.

The test was modified by quantification of each component as described in appendix 3. The infants who were not able to successfully perform any of the tasks included in the evaluation were regarded as significantly delayed. The cited studies including the Malaysian and South African groups used the more accurate Bailey's assessment tool posing some limitation when comparing their findings with those of the present study.

By the end of the 1980s Sells et al, in Australia, reported over 90% two-year survival with less than 10% neurological impairment for infants with birth weights of 1-1.5kg [3]. This means, for any birth cohort of such babies, over 80% are expected to celebrate the second birthday as normal young children. The present study had only 88 (25.9%) of the birth cohort of 344 alive and neurologically normal at the age of two years. Not withstanding the 10 infants lost due to selection criteria and another 10 who did not complete the study, the two-year intact neurological survival rate was significantly lower at KNH than reported from developed countries[2-3].

There are some important confounding factors that may have influenced the neurological development of these infants but were not controlled for in the design of this study. The socio-economic status of a family is known to influence children's cognitive development with the poor being less advantaged. This was not controlled for in the study and may have influenced the disability rates and some of the differences in the comparative analysis.

Anecdotally, it is unlikely that these families, mostly from the lower class residential areas of Nairobi were significantly different in this respect. The inability to specifically control for HIV/AIDS in the study may also have an unknown contribution of this disease towards abnormal neurological development in the cohort.

DETERMINANTS OF NEUROLOGICAL OUTCOMES

In pursuit of possible interventions that may improve the neurological outcomes in this population, several parameters were scrutinized to determine their role in possible causation of or association with developmental delays or defects. The factors found to be associated with occurrence of neuro-developmental deficits in this study were; neonatal illness, exclusive use breast milk during the first month of life, history of re-hospitalization, poor neonatal growth and growth faultering at two years corrected for gestation.

The study hypothesized that, "presence of neonatal illness was associated with increased occurrence of neurological deficits". At single variant analysis, this was indeed the case for both functional disabilities $P=0.005$ and cognitive scores $P<0.001$. Neonatal illness was indeed, an independent predictor of functional disability $P=0.011$ and cognitive delay $P=0.014$ at regression analysis. The hypothesis as stated above is confirmed.

Neonatal illness, an event occurring early in life, was associated with disturbed neurological development detected at the age of two years. The first month of life appears to have been a specifically vulnerable period for neurological damage in these infants.

In the introduction section, the concept of programming in animals and humans was discussed in detail. This is a biological concept, which hypothesizes that there are brief periods during early life when it is particularly easy to cause changes with everlasting effects to a living organism. The events that cause such changes are referred to as programming factors. This concept projects that the period when such programming is most likely to occur is amenable to both destructive and constructive forces. Programming is most potent during times of rapid growth and development of organisms. Lucas and his group identified the first month of life in VLBW human infants as a vulnerable period in their randomized controlled trial of the 1980s[23]. The findings of the present study indicate that neonatal illness may have been a destructive programming factor taking advantage of the VLBW infants during their vulnerable period.

The major neonatal illnesses seen in this cohort were; respiratory distress syndrome, asphyxia and infection. They are all known to induce brain damage through reduction of oxygen supply, causation of abnormal patterns of blood flow or both. Studies have also reported negative effects of neonatal illnesses on later development[91-94].

Hunt et al, showed that VLBW infants who had milder disease ratings during the neonatal period had better developmental scores at 8 and 11 years[91] than the sicker ones. Namasivayan made similar observations in his study[92]. Van De Bor, et al found that VLBW infants with lower developmental scores at two years had significantly higher peak bilirubin levels than those who had normal scores[93]. In a longitudinal study, McGrath and others found that neonatal morbidity among preterm infants exerted significant effects on cognitive development later in life and concluded that neonatal medical status is an important variable for predicting neuro-cognitive outcomes and school performance[94].

Many studies have specifically indicated that the level of intensive care needed in the newborn period is of prognostic importance regarding neurological development[39, 62, 88]. In the South African study, VLBW infants who had been sick enough to require life support had 20% cerebral palsy frequency while those not ventilated had only 7%[62] demonstrating that even in poor environments, VLBW infants who escape major neonatal morbidity should enjoy favorable neurological outcomes. None of the subjects in the KNH study were sick enough to require life support as such infants would not have survived the newborn period in this level I/II care centre. The infants in the KNH group were not exposed to the same neonatal illness risk level as those in the developed countries or the South Africa cohorts suggesting that KNH graduates of NIC had poorer performance in neurological outcomes than reported elsewhere.

Another hypothesis put forward by the study was that the type of milk used during the neonatal period would influence the occurrence of neurological deficits. At single variant analysis, infants fed on exclusive BM had significantly more functional disabilities P=0.020 and lower cognitive scores P<0.001 than those fed on PTF alone or in combination with BM.

The type of milk was, however, not an independent predictor of either outcome at regression analysis when analyzed together with early growth. When early growth was removed from the regression equation then exclusive use of BM was a significant predictor of both functional disability and cognitive delay. This means that infants exclusively fed on mothers' milk had poorer neurological outcomes at two years if they failed to grow adequately during the newborn period. Though the hypothesis stating that type of milk given to VLBW infants during their first month of life affects later neurological development is rejected on the basis of regression analysis, the single variant association is noted.

These findings were contrary to current views that mothers' milk is associated with improved neurological development in humans. The study demonstrated that this might not be the case in VLBW infants. Exclusive use of breast milk during the vulnerable first month of life was a potential destructive programming factor in this group. A likely explanation of the present findings is that infants fed on breast milk alone had significantly poorer neonatal and catch-up growth profiles than those on preterm formula containing feeds.

The breast milk provided to these infants was not commensurate with their macro-nutritional needs because it was not fortified. The apparent negative effect of breast milk on subsequent neurological development in this group may have been related to its quantitative rather than qualitative properties. There was also the possible confounding effect of HIV/AIDS among infants on breast milk. Some of them may have been infected from their mothers' milk and developed neurological illness as a consequence.

Researchers in the 1980s and 1990s established the superiority of nutrient enriched PTF over un-fortified breast or standard formula milk in VLBW infants. Lucas and colleagues reported better developmental scores in infancy[51] and at 18 months[52]. Lucas and colleagues[54] also reported a definite advantage of mothers' milk on developmental scores if VLBW infants were fed on enriched breast milk during the newborn period. Subsequent reports have agreed that when mothers' milk is fortified to enhance its nutritional value, the advantage of preterm formula over breast milk in later neurological development is lost[28, 54]. The apparent disadvantage of breast milk observed in this series regarding neurological outcomes will probably be erased by fortification of such milk.

Other studies comparing un-fortified breast milk with various formula options also reported definite advantages in developmental scores for infants fed on preterm formula over those on standard formula or un-fortified breast milk[51-52].

The differences persisted even when the formulae were used as supplements to mother's milk. It seems paramount that neonatal feeding regimes ensure normal growth in order to achieve the beneficial effects on subsequent neurological development.

The World Health Organization policy of exclusive breast milk for the first six months of life, as formulated by an expert committee in 2002[30], is practiced in KNH on the recommendation of the Ministry of Health. Very Low Birth Weight infants have been assimilated into the practice without regard to the established inadequacy of un-fortified human milk in promotion of early growth[25-26] and improvement of neurological outcome among them[27-29, 51-52, 54]. Human milk fortification should be recommended for all VLBW infants, at least during the first month of life. The benefits of fortification far outweigh the costs.

The results of this study suggest that the extensively reported advantages of breast milk in improving neurological development of young infants are lost for VLBW infants if the milk is not nutritionally enriched. As there was a strong association between early nutrition and early growth with an equally strong one between early growth and later neurological outcomes, nutritional regimes in the first month of life for VLBW infants should ensure adequate growth for later developmental advantages to be realized.

It was hypothesized that "early growth failure was associated with cognitive delay and increased frequency of functional disability in these infants at the age of two years". Infants who had grown at less than 15g/kg/day had a significantly higher frequency of functional disabilities P=0.014 at single variant analysis. The median overall cognitive score was also lower among infants who grew at less than 15g/kg/d P=0.001 or weighed below the 3rd percentile at term P<0.001. At regression analysis, inadequate neonatal growth was an independent predictor of functional disability P=0.039 and cognitive delay P=0.017, hence, the hypothesis stated above is accepted.

Growth in infants is determined by a combination of adequate nutrition and good health. Adequate nutrition and proper treatment of or absence of growth deterring illnesses is essential for optimum growth during early life. The intricate association between early growth and later development makes early growth parameters important markers for later neuro-developmental expectations. Using the vulnerable period-programming theory abnormal growth during early life can be considered a manifestation of harmful programming at that vulnerable period in VLBW infants.

Since early nutrition has also been identified as an important intervention in the care of VLBW infants and adequate growth is associated with appropriate nutrition, early growth monitoring should assume as much importance as nutrition itself.

Measurements of growth indirectly tell us about the successes of this important programming factor, nutrition. Early growth patterns can be used to sub-classify VLBW neonatal survivors into those at high and low risk of unwanted neuro-developmental sequelae allowing prioritization for prolonged re-evaluation with subsequent reduction of the cost of follow-up programs.

The advantages of early growth for better neurological development have been extensively reported in literature from centres in more advanced countries. Morley and others found that neonatal growth better than 15g/kg/day was associated with statistically significant improvement in developmental scores at 8 years[8]. Hack and colleagues specifically reported two-year developmental advantages when catch-up growth was achieved at term for VLBW infants in their series[49]. The study by Hack and colleagues also reported significant increments of cerebral palsy frequency among VLBW infants with inadequate growth early in life. This study supports earlier findings in confirming that early growth is a predictor of later development. Measures to optimize early growth of VLBW infants are necessary at KNH.

The hypothesis that "inadequate post-discharge growth was associated with increased chances of both functional disability and cognitive delay" was tested. Infants who were less than the 3rd percentile of the expected weight at two years were more likely to have functional disabilities P=0.019 and lower mean overall cognitive scores P=0.005 than those who had grown better.

When subjected to regression analysis, weight less than the 3rd percentile of the expected at two years was an independent predictor of both functional disability P=0.041 and cognitive delay P=0.043. The hypothesis is accepted. Continuing growth failure beyond the infancy had negative effects on neurological development in this cohort.

This phenomenon has been reported previously. Hack, et al found mean± SD developmental quotient of 94.7±15.9 for well-grown 21-month-old VLBW infants compared to 85.3±18.9 for the growth retarded, P<0.05[49]. In a large national study involving almost 500 infants Bucher and colleagues reported that infants who had not caught up in growth during infancy developed motor milestones significantly later than those who had[95]. In the work reported by Morley and others growth failure at nine months was significantly predictive of lower developmental scores at eight years[8]. Normal post-natal growth needs to be ensured in order to maintain neurological development.

The hypothesis, "post-discharge re-hospitalization increased the chances of neurological sequelae" was tested. Re-hospitalization predicted functional disability P<0.001 but not with cognitive delay P=0.056 at single variable but not at regression analysis. The hypothesis is rejected but the association of re-hospitalization with functional disability at single variable analysis is noted.

V.7.CONCLUSIONS

The findings of this study clearly lead to a number of conclusions;

1. The mean neonatal increments in weight, length and head growth were lower than the expected intra-uterine rates for the same period in-utero. Lower nutrient density breast milk and neonatal illnesses were associated with reduced neonatal growth
2. All the mean anthropometric parameters were lower than expected at term. Lower nutrient density BM and neonatal illnesses were also associated with growth faultering at term.
3. Sixty percent of survivors at two years had faultered growth. IUGR status and history of re-hospitalization were the predictors of growth failure at the age of two years.
4. Fifty four percent of the infants were re-hospitalized within the two years of follow-up, equaling the highest figures reported in literature. Neonatal growth failure, discharge weight below two kilos and failure to thrive at the age of two years were the established predictors of re-hospitalization.
5. The post-discharge mortality was 27.3% most of the deaths occurring in the first post-discharge year. This was 5 times more than the national average and 7 times that reported from advanced countries. Neonatal Illness, poor neonatal weight gain, lower discharge weight and re-hospitalization were the predictors of mortality.

6. Cerebral palsy (11.7%), cognitive delay (9.2%) and functional disability (26.7%) were found in more infants than has been reported in recent studies. Inadequate growth and neonatal illnesses were the predictors of neurological disability.

V.8. RECOMMENDATIONS

Based on the results of this study it is recommended that KNH newborn unit;

1. Introduces routine breast milk fortification for all VLBW infants to improve early growth, reduce post-discharge re-hospitalization and indirectly promote better neurological development.
2. Improves the medical care given to these newborns when they are sick as this may bring about improvement of neurological development, early growth and subsequent morbidity and mortality.
3. Identifies through an appropriately designed study, the post-discharge factors associated with poor growth, as this was associated with re-hospitalization and increased neurological sequelae.

VI: REFERENCES

1. Fitzhardinge P M. Follow-up studies of the low birth weight infant. Clinics in Perinatology. 1976; 3: 503-515.
2. Orgill AA, Asbury J, Baja B, and Yu VYH. Early neuro-development outcomes of very low birth weight infants. Australian Pediatric Journal. 1982; 18:193-196.
3. Sells, CJ. Outcome of very very low birth weight infants. Clinics in perinatology. 1986; 13:451-459.
4. Johnson JD, Malachowski NC, Grobstein R et al. Prognosis of children surviving with the aid of mechanical ventilation in the newborn period. Journal of Paediatrics . 1974; 84:272-280.
5. Brown JK, Cockburn F, and Forfar JO, Marshall RL and Stephen RL. Problems in the management of assisted ventilation in the newborn period and follow-up of treated cases. British Journal of Anaesthesia. 1973; 45:808-813.
6. Stahlman M, Hedvall G, Dolanski E, Faxelius G, Burko H and Kirk V. Six year follow-up of clinical hyaline membrane disease. Pediatric Clinics of North America. 1973; 20: 433-443
7. Yu VHY. After care of high-risk infants and long-term outcome. Schaffer and Avery's DISEASES OF THE NEWBORN. Tauscher, Ballard, Avery (eds), 6th edition, SAUNDERS, Philadelphia 1991, pp 293-299

8. Morley R. Early growth and later Development. Nutrition of the very low birth weight infant. Nestle nutrition workshop series pediatric program, Lippincott Williams and Wilkins Philadelphia 1999; number 43: pp19-32.
9. Rothstein P, Johnson P. Pediatric intensive care: factors that influence outcome. Critical Care Medicine 1982; 10: 34-37.
10. Schroeder SA. Outcome assessment 70 years later; are we ready? New England Journal of Medicine, 1987; 316:160-168.
11. Pollack MM, Putimann VE, Geston PR. Accurate measurement of the outcome of pediatric intensive care. A new quantitative method. New England Journal of Medicine 1987; 316: 134-139.
12. Kelly JL, Paneth N. Follow-up studies of low birth weight infants: suggestions for design analysis and reporting. Developmental Medicine, Child Neurology 1981; 23:96-100.
13. Davies PA. Follow-up of low birth weight children. Archives of Diseases of Childhood 1984; 59:794-797.
14. Bhat R, RajuTNK, Vidyasagar D. Immediate and long-term outcome of infants less 1000grams. Critical Care medicine, 1978;6:147-150
15. American Academy of Paediatrics and American College of Obstetricians and Gynecologists. Guidelines for peri-natal care. AAP/ACOG, Evanson 1983; 97-105.
16. Stewart AL, Follow-up studies. In; Roberton NRC (Ed) Textbook of Neonatology, 2nd edition, Churchill Livingstone, Edinburgh 1992; pp 49-74.

17. Yu VYH. After care of high-risk infants and long-term outcomes. In: Schaffer and Avery's Diseases of the newborn, 6th edition. WB Saunders, Philadelphia 1991:pp 293-299

18. Hack M, Amiel-Tison C. The outcome of neonatal intensive care. In: Klaus and Fanaroff are Care of the High-risk Neonate, 3rd edition, W.B. Saunders Company, Philadelphia. 1986: pp 378-382.

19. Donabedian A. The quality of care; How can it be assessed? Journal of American Medical Association, 1988; 260:1943-8.

20. Bailey DB. Assessing infants and preschoolers with special needs. In: McLean M, Bailey DB, Wolery M (Eds). Columbus, Ohio: Merril. 2nd Edition, 1996, pp203-233.

21. Kliegman RM, King KC. Intra-uterine growth: determinants of aberrant fetal growth. Neonatal - Peri-natal Medicine, 3rd edition. Fanaroff AA and Martin JR (eds), the C.V. Mosby Company, St Louis. Toronto 1983, pp49-80.

22. Angelbeck JH Dubrul EF. The effect of neonatal testosterone on specific male and female patterns of phosphorylated cystosolic proteins in the rat preoptic-hypothalamus, cortex and amygdala. Brain Residence. 1983; 264:277-283.

23. Lucas A. Early nutrition and later outcome. Nutrition of the Very Low Birth Weight Infant. Nestle Nutrition Workshop Series, Lippincott Williams and Wilkins, Philadelphia, 1999; number 43: pp2-18.

24. Behrman RE, Vaughan VC. Nelsons textbook of paediatrics. 12th ed. WB Saunders 1983, pp 412-413 and pp 747-750.

25. Lucas A, Gore SM, Cole TJ, Bam ford MF, Dissector JFB, Barr I, Diablo L, Cork S and Lucas PJ. Multi-centre trial on feeding the low birth weight infants: effects of diet on early growth. Archives of Diseases of Childhood, 1984, 59: 722-730.

26. Brooke OG, Wood C and Barley J. Energy balance, nitrogen balance, and growth in preterm infants feed on expressed milk, a preterm infant formula, and two low-salute adapted formulae. Archives of Diseases of Childhood; 1982, 57: 898-904.

27. Schanler RJ, Shulman RJ and Lau C. Feeding strategies for premature infants: Beneficial outcomes of feeding fortified human milk versus preterm formula. Paediatrics, 1999, 103: 1150-1157.

28. Lucas A, Morley R, Cole TJ and Gore SM. A randomized multi-centre study of human milk versus formula and later development in preterm infants. Archives of Diseases of Childhood. 1994; 70: 141-148.

29. Lucas A, Petrel MS, Morley R, Lucas PJ, Baker BA, Lister G and Bishop NJ. Randomized outcome trial on human milk fortification and developmental outcome in preterm infants. American Journal of Clinical Nutrition, 1996, 64: 142-151

30. Report of an expert consultative group. On optimal period of exclusive breast feeding, Geneva 2002; WHO/NHD/01.09: 1-10

31. McCance RA. Food growth and time. Lancet, 1962; ii: 271-272.

32. Smart J. Under nutrition, learning and memory: review of experimental studies. In: Tailor TG, Jenkins NK, Eds. Proceedings of XIII International congress of nutrition. London: John Libbey; 1986:pp74-78.

33. Dobbing J, Sands J. Vulnerability of developing brain. IX. The effect of nutritional growth retardation on the timing of the brain growth spurt. Biology of the Neonate 1971; 19: 363-378.

34. Drillien CM. The incidence of mental and physical handicaps in school age children of very low birth weight. Paediatrics, 1967; 39: 238-248.

35. Lubchenco LO, Delivoria-Papadopoulos M, Butterfield LJ et al. Long term follow-up studies of prematurely born infants. I. Relationship of handicaps to nursery routines. Journal of Paediatrics, 1972; 80:501-508.

36. Reynolds EOR and Taghizadeh A. Improved prognosis of infants mechanically ventilated for hyaline membrane disease. Archives of Diseases of Childhood. 1974; 49:505-512.

37. Outerbridge EW, Ramsay M, Stein L. Developmental follow-up of survivors of neonatal respiratory failure. Critical Care Medicine. 1974; 2:23-31.

38. Escobar GJ, Littenberg B and Pettit DB. Outcome among surviving very low birth weight infants: a Meta analysis. Archives of Diseases of Childhood, 1991; 66:204-211.

39. Kitchen WH, Yu VY, Lissenden JV and Bajuk B. Collaborative study of very low birth weight infants. Outcome of two-year-old survivors. Lancet, 1982; 1(8287):1454-1457.

40. Yu, VYH, Watkins A, and Bajuk B. Neonatal and post-neonatal mortality in very low birth weight infants. Archives of Diseases of Childhood, 1984; 59: 987-989.

41. Bowman E and Yu VYH, Continuing morbidity in extremely low birth weight infants. Early Human Development. 1988; 18: 165-172

42. Hack M, Merkatz IR, Jones PK and Fanaroff AA. Changing trends of neonatal and post-neonatal deaths in very low birth weight infants. American Journal of Obstetrics and Gynecology, 1980; 137: 797-800.

43. McCormick, MC, Shapiro S and Stanfield BH. Re-hospitalization in the first year of life for high-risk survivors. Paediatrics 1980; 66:991-999.

44. Mutch L, Newdick M, Lodwick A and Chalmers. Secular changes in re-hospitalization of very low birth weight infants. Paediatrics 1986; 78:164-171.

45. Hack M, DeMonterise RN, Merkatz PJ, Jones P and Fanaroff A. Re-hospitalization of the VLBW infant. American Journal of Diseases of Children, 1981; 135: 263-266.

46. Combs-Orme T, Fishbein J, Summerville C and Evans MG. Re-hospitalization of very low birth weight infants. American Journal of Diseases of Children, 1988; 142:1109-1116.

47. Skurse D Pickles a, Wolke D, Reilly S. Post-natal growth and mental development: evidence for a sensitive period. Journal of Clinical Psychology and Psychiatry 1994; 35: 521-545.

48. Hack M, Merkatz IR, Gordon D, Jones PK and Fanaroff AA, The prognostic significance of post-natal growth in VLBW infants. American Journal Obstetrics Gynecology. 1982; 143: 693-699.

49. Hack M. Merkatz IR, McGrath SK, Jones PK and Fanaroff AA. Catch-up growth in VLBW infants. American Journal of Diseases of Children, 1984; 138: 370-375.

50. Smart J. Under nutrition, learning and memory; review of experimental studies. In: Tailor TG, Jenkins NK, Eds. Proceedings of xiii international congress on nutrition. London, John Libbey; 1986:74-78.

51. Lucas A, Morley R, Cole TJ, Gore SM, Davis JA, Bamford MF and Dosetor JF. Early diet in preterm babies and developmental status in infancy. Archives of Diseases of Childhood, 1989; 64:1570-1578.

52. Lucas A, Morley R, Cole TJ, Gore SM, Lucas PJ, Crowke P, Pearse R, Boon AJ, Powell R. Early diet in preterm babies and developmental status at 18 months. The Lancet 1990; 335:1477-1481.

53. Grantham-McGregor S. Field studies in early nutrition and later achievement. In: Dobbing J, Ed; Early nutrition and later achievement. London: Academic press. 1987; pp128-174.

54. Lucas A, Morley M, Cole TJ, Lister G and Leeson-Payne. Breast milk and subsequent intelligence quotient in children born preterm. The Lancet, 1992; 339: 261-264.

55. Hoefer A, Hardy MC. Later development of breast-fed and artificially fed infants. Journal of American Medical Associations, 1929; 92:615-619.

56. Rogerson BFC, Rogerson CH. Feeding in infancy and subsequent psychological difficulties. Journal of Mental Sciences 1939; 85: 1163-1182.

57. Broad B. The effect of infant feeding on speech quality. New Zealand Medical Journal 1972; 76:28-31.

58. Tailor B. Breast versus bottle-feeding. New Zealand Medical Journal, 1977; 85:235-238.

59. Morley R, Cole TJ, Lucas A, Powell R. Mother's choice to provide breast milk and developmental outcome. Archives of Diseases of Childhood, 1988; 63:1382-1385.

60. Rodgers B. Feeding in infancy and later ability and attainment: a longitudinal study. Developmental Medicine and Child Neurology. 1978; 20:421-426.

61. Ballard J, Norak KC, Driver M. A simplified score for assessment of foetal maturity on newly born infants. Journal of Pediatrics , 1979; 95:769-774

62. Cooper PA, Sandler DL. Outcome of VLBW infants at 12 and 18 months of age in Soweto Township, South Africa. Paediatrics , 1997; 99:537-544

63. Kichamu G. Early childhood mortality. In The 1998 Kenya Demographic and Health Study. Macro International Inc. Calverton, Maryland USA. 1999: 89-94

64. Egan FD, Developmental examination of infants and preschool children. Clinics in developmental medicine No 112, Mac Keith Press, Oxford, Blackwell Scientific Publications Limited, Philadelphia, 1990:pp52-81.

65. Saigal S, Rosenbaum P, Stoskopf B and Milner R. Follow-up of infant's 501 to 1500 gm birth weight delivered to residents of a geographically defined region with peri-natal intensive care facilities. Journal of Paediatrics, 1982; 100: 606-613.

66. Huttenlocher PR. Cerebral Palsy. In Nelson's Textbook of Paediatrics, 13th Edition. WB Saunders Company, Philadelphia, 1987; 1307-1309.

67. Vaughan VC and Litt IF, Developmental paediatrics: growth and development. In Nelson's Textbook of Paediatrics, 13th Edition. WB Saunders Company, Philadelphia, 1987; pp 6-19.

68. Bland JM, Altman DG, Survival Probabilities (The Kaplan Meier Method). British Medical Journal, 1998: 317; 1572-1580

69. Olel MK, Quality of antenatal and pregnancy care at Kenyatta national hospital. A Masters of medicine thesis in the Department of Obstetrics and Gynaecology, University of Nairobi, PO Box 19676, 00202 Nairobi, Kenya.

70. Preliminary Report of the Kenya demographic health study 2003. Central Bureau of Statistics, Ministry of Planning, e mail, director@cbs.go.ke, PO Box 30266 Nairobi, KDHS 2003

71. Yu VY, Downe L, Astbury J, Banjuk B. Peri-natal factors and adverse outcome. Archives of Diseases of Childhood, 1986: 61; 554-8.

72. Were F, Mukhwana RO, and Musoke RN. Neonatal survival of newborn infants less than 2kg at birth at Kenyatta National Hospital. East African Medical Journal, 2000; 79:77-79

73. Blackmon LR. The role of hospital of birth on survival of ELBW infants. Neonatology Reviews, 2003; 4(6):149-155

74. Babson SG. Growth of LBW infants. Journal of Paediatrics , 1970;77:11-20

75. Casey PH, Kraemar HC, Bernbaum J, Yogman MW, Sells JC. Growth status and growth rates of a varied sample of LBW infants. Journal of Paediatrics ,1991;119: 599-605

76. Gardner D and Pearson J. A growth chart for premature and other infants. Archives of Diseases of Childhood, 1971;46:783-787

77. Guido EM, Iolanda M. Fortification of human milk. Nestle nutrition workshop series pediatric program, Lippincott Williams and Wilkins Philadelphia 1999; 43: pp81-93.

78. Rogowski J. Cost effectiveness of care for Very Low Birth Weight Infants. Paediarics 1998:102:35-43

79. Shankaran S, Cohen SN, Linver M, Zonia S. Medical Care Costs of High-risk Infants after Neonatal Intensive Care: A Controlled Study. Paediatrics 1988; 81:372-378

80. Cattaneo A, Davanzo R, Worku B. Kangaroo mother care: A randomized controlled trial in different settings. Acta Paediatrica Scandinavica, 1998;87:976-85

81. Collona F, Uxa F, Da Grac AM, De Vonderweld V. The "kangaroo mother" care method. An evaluation of an alternative method for the care of low birth weight infants in developing countries. International Journal of Gynecology and Obstetrics, 1990; 31: 335-9.

82. Kambarani RA, Chidede O, Kowo DT. Kangaroo care for well low birth weight infants in Harare central hospital maternity unit-Zimbabwe. Central African Medical Journal 1999; 4:56-65

83. Katz M, Stiehm ER, Host defense in malnutrition. Paediatrics, 1977;59:490-496

84. McCormick MC, Shapiro S, Stanfield BH. Injury and Its Correlates among 1-Year-Old Children. American Journal of Diseases of Children. 1981;135:159-163

85. Chase CH, Infant mortality and weight at birth. American Journal of Public Health, 1969; 59:1618-28.

86. Bedor DE, Chang C, Fisher R, Belloc B. Factors affecting post-discharge mortality. Health Reports 1971; 49:33-57

87. Shapiro S, McComick MC, Starfield B, Krischer JP, Bross D. Relevance of correlates of infant death for significant morbidity at 1 year of age. American Journal of Obstetrics and gynecology. 1980;136:363-73

88. Ho JJ, Amar HSS, Mohan AJ and Hon TH. Neuro-developmental outcome of very low birth weight babies admitted to a Malaysian nursery. Journal of Paediatrics and Child health, 1999; 35: 175-180

89. Nelson KB, Ellenbberg JH. Children who outgrew cerebral palsy. Paediatrics, 1982; 69:529-536.

90. Kitchen WH, Ford GW, Richards A, Lissenden JV, Ryan MM. Children of birth weight<1000g: Changing outcome between 2 and 5 years. Journal of Paediatrics 1987;110:283-288

91. Hunt JV, Bruce A.B. Cooper and William H. Tooley, Very Low Birth Weight Infants at 8 and 11 Years of Age: Role of Neonatal Illness and Family Status. Paediatrics , 1988; 82:596-603

92. Namsivayan A, Nelson GK, Alexander G, Johnson SE, Biasini F, Carlo WA. Prediction of Neurological Morbidity in Extremely Low Birth Weight Infants. Journal of Perinatology, 2000; 20: 496-503

93. Van De Bor M, Van-Zeben TM, Verloove-Vanhorick SP, Brand RR, Hyperbilirubinemia in Preterm Infants and Neuro-developmental Outcome at 2 Years of Age: Results of a National Collaborative Study, Paediatrics 1989; 83: 915-920

94. McGrath MM, Sullivan MC, Barry ML and William Oh. Longitudinal Neurological Follow-up in Neonatal Intensive Unit Survivors With various Neonatal Morbidities. Paediatrics 2000; 106: 1397-1405

95. Bucher HU, Killer C, Ochsner Y, Vaihinger S, Fauchere J. Growth, developmental milestones and health problems in the first 2 years in very preterm infants compared to term infants: a population based study. European Journal of Paediatrics , 2002; 161: 131-136

VII: APPENDICES

VI.1: APPENDIX 1; SAMPLE SIZE CALCULATION

We used the standard prevalence determination formula described here;

$$N = Z2\frac{P\,(1-P)}{C^2}$$

Where;

N = the minimum sample required.

P = an estimate of the expected prevalence of the condition(s) under Study. Traditionally a prevalence determined by a previous study Based in a similar environment is used. Seven percent from the South African by Cooper et al[62] report was used in this study.

Z = A constant which corresponds to the desired power of the study. When the desired power is 95% confidence (alpha) then Z=1.96.

C = 1-alpha = 0.05 when 95% confidence is desired.

Therefore $N = \frac{1.96^2\ (0.07X0.93)}{0.05^2} = 100$

VI.2: APPENDIX 2; QUESTIONAIRE

IDENTITY DATA

Study number _____

Hospital number _____

Name of baby_____

Infant's Sex; male=1 female=2 _____

Date of birth _____

Parents' name; Mother_____

Father_____

Family's address, PO BOX _____

Telephone No; Mother_____

Father_____

Relative/friend_____

Street name_____

Estate name _____Hse No _____

OBSTETRIC DATA

Last menstrual period _____Gestation_____weeks.

Antenatal clinic attendance Yes=1, No=2

Pregnancy complications Yes=1, No=2

If yes specify _____

Place of delivery Inborn=1, Out-born=2

NEONATAL INFORMATION

Gestation; *by dates*_____ *wks, clinical assessment*_____wks

Status of intra-uterine growth; AGA=1, SGA=2 _____

Anthropometric measurements

Birth; Weight _____g. Length _____cm. H. Circ. _____cm

Discharge; Weight _____g. Length _____cm. H. Circ. _____cm

40 weeks; Weight_____ g. Length _____cm. H. Circ. _____cm

Mean gain till discharge

Weight _____g/kg/day, Length ____cm/week, H. Circ. ____ cm/week

Mean parameters till 40 weeks

Weight _____g/kg/day, Length _____cm/week, H. Circ. ___cm/week

Neonatal Illnesses; Absent=1 Present=2 _____

Actual diagnosis_____

Early nutrition

Type of milk used; PTF alone=1, EBM+PTF=2, EBM alone=3 _____

FOLLOW-UP PROFILES

Three months

Weight _____kg. Length _____cm. Head cir. _____Cm.

Neurological assessment

Muscle tone, Normal=1 Hyper/Hypo-tonia =2 ____

Deep tendon reflexes, Normal =1 Hyper/Hypo-reflexia=2 ____

Muscle strength; is the child able to support their neck?

Yes=1 No=2 ____

If the answer is 2 for any of these, child was sent for occupational therapy

Illnesses and re-hospitalization

Has the child had any significant illnesses leading to hospital admission since the last visit? Yes=1, No=2 _____

If yes what was the illness? _____

Six months

Weight_____Kgs, Length _____Cm H.Cir. _____Cm

Neurological evaluation

Muscle tone, Normal=1 Hyper/Hypo-tonia =2 _____

Deep tendon reflexes, Normal =1 Hyper/Hypo-reflexia=2 _____

Muscle strength; is the child able to sit with support? Yes=1 No=2 _____

If the answer is 2 for any of these, child was sent for occupational therapy

Re-hospitalization

Has baby been hospitalized since last review? Yes=1, No=2 ____

If yes what was the nature of illness? _____

Nine months

Weight _____Kg Length _____cm H. Cir. _____Cm

Neurological assessment

Muscle tone, Normal=1 Hyper-tonia or hypo-tonia =2 _____

Deep tendon reflexes, Normal =1 hyper/hypo-reflexia=2 _____

Muscle strength, is the child able to sit without support or stand with support?

Yes=1 No=2 _____

If the answer is 2 for any of these, child was sent for occupational therapy

Re-hospitalization

Has baby been hospitalized since last review? Yes=1, No=2 _____

If yes what was the nature of illness? _____

One year

Growth; Weight; _____ Kg, Length; _____ cm, H. Cir. _____ cm

Neurological evaluation

Muscle tone, Normal=1 Hype/hypo-tonia =2 _____

Deep tendon reflexes, Normal =1 hype/hypo-reflexia=2 _____

Muscle strength; is the child able to stand without support? Yes=1 No=2 _____

If the answer is 2 for any of these, child was sent for occupational therapy

Illness and re-hospitalization

Has baby been hospitalized since the last review? Yes=1, No=2 _____

If yes what was the nature of illness? _____

Fifteen months

Growth; Weight _____Kg, Length _____ cm, H. Circ._____ cm

Neurological evaluation

Muscle tone, Normal=1 Hyper/hypo-tonia =2 _____

Deep tendon reflexes, Normal =1 hyper/hypo-reflexia=2 _____

Muscle strength; is the child able to walk with support? Yes=1 No=2 _____

If the answer is 2 for any of these, child was sent for occupational therapy

Illnesses and re-hospitalization

Has baby been hospitalized since last review? Yes=1, No=2 _____

If yes what was the nature of illness? _____

Eighteen Months

Growth; Weight; _____Kg, Length/Height; _____cm, H. cir. _____Cm

Neurological evaluation

Muscle tone, Normal=1 Hyper/hypo-tonia =2 _____

Deep tendon reflexes, Normal =1 hyper/hypo-reflexia=2 _____

Muscle strength; is the child able to walk without support? Yes=1 No=2 _____

If the answer is 2 for any of these, child was sent for occupational therapy

Illnesses and re-hospitalization

Has baby been hospitalized since last review? Yes=1, No=2 _____

If yes what was the nature of illness? _____

Twenty-one months

Growth; Weight; _____Kg, Length; _____cm, H. cir. _____Cm

Neurological evaluation

Muscle tone, Normal=1 Hyper/hypo-tonia =2 _____

Deep tendon reflexes, Normal =1 hyper/hypo-reflexia=2 _____

Muscle strength; is the child able to walk steadily on its own? Yes=1 No=2 ____

If the answer is 2 for any of these, child was sent for occupational therapy

Illnesses and re-hospitalization

Has baby been hospitalized since last review? Yes=1, No=2 _____

If yes what was the nature of illness? _____

Two-year

Growth; Weight; _____Kg, Height/Length; _____cm, H. cir. _____cm

Illnesses and re-hospitalization

Has baby been hospitalized since last review? Yes=1, No=2 _____

If yes what was the nature of illness? _____

Neurological assessment

Cerebral palsy; absent=1 Present=2. _____

If present describe the lesion_____

Functional disability; absent=1 Present=2 _____

If present grade; Mild=1, Moderate=2, Severe=3 _____

Developmental score

Gross Motor Skills_____ Performance Skills_____

Language Skills _____ TOTAL SCORE_____

If child is reported dead, Date_____ corrected age_____ months

VI.3: APPENDIX 3; TEST FOR COGNITIVE DEVELOPENT AT 2 YEARS

Based on the Dorothy F. Egan model

This is a semi qualitative method of developmental assessment. It is used for children 0 to 5 years old. The parameters used in the model include; Gross motor skills, Performance skills and Language skills. The examination is based on both history and actual physical evaluation. The skills evaluated are based on what average infants or children are expected to have achieved by the given age.

Gross Motor Skills

The "play ball" test

In a sufficiently spacious office the child is observed while moving about freely. A small ball is placed within the vicinity. The examiner issues specific instructions if necessary.

The Score	
Child easily walks towards the ball, holds it above the head or kicks it	*2*
Child performs these task with difficulty	*1*
Child is unable to perform any of the task	*0*

Performance skills

Test 1: Building Cube Test

The Child is given several small rectangular blocks and asked to lay them on top of each other to form a bigger structure.

This may be demonstrated to the child by the examiner if verbal command is not understood.

Result

Mounts at least 5 cubes	*2*
Mounts less than 5 cubes	*1*
Unable to mount any cubes	*0*

Test 2: Symbolic play test

The child is observed while playing with toys of commonly used household implements or things the child is known to have been exposed to previously. Examples; putting a spoon into a tea cup, propelling a car, putting cup on a saucer or table and positioning chairs on or next to the table.

Result

Task achieved easily and completely	*2*
Task achieved with difficulty or incompletely	*1*
Task not achieved at all	*0*

Language

The test 1; Expressive Verbal Labels or "What Is It" Test

Child asked to identify miniature toys of common household objects. These should include things that should have been encountered by the child in their

natural environment. The commonly used toys include; cup, chair, table, spoon, glass, kettle, bed, car, shoes and dolly. These are retrieved by the examiner one at a time from a concealed position and exposed to the child as the question; what is this is asked?.

Result

Child identifies at least 4 toys	*2*
Child identifies less than 4 toys	*1*
Child not able to identify any toys	*0*

Test 2: Comprehension test

Now the child is asked to put a dolly on the sit or the bed, put a spoon in a cup or put cup on the table or any other simple logical tasks involving the available toys.

Result;	*Able to perform at least one task with ease*	*2*
	Performs at least one task but with difficulty	*1*
	No task not performed even with difficulty	*0*

TOTAL SCORE _____

VI.4: APPENDIX 4; ROSENBAUM AND SAIGAL'S TEST[66]

From observation of the child, neurological examination and interview of the guardian information is gathered to be able to classify the child into one of the categories below.

Normal; A healthy child able to perform appropriately in ordinary activities and skills of daily living (OASDL) for his or her corrected age. No additional or unusual care taking burden. A two-year old child should be able to walk steadily, feed himself and undertake normal ambulatory play.

Mild dysfunction; A child who was able to perform appropriately in OASDL for corrected age despite developmental or structural abnormalities. These were children who while performing normally but had identifiable physical anomalies.

Moderate dysfunction; A child who required some additional adult care taking or help in OASDL beyond what is normally expected for corrected age. This referred to one not able to walk steadily, requiring some help when feeding, sluggish on ambulatory playing in this study.

Severe dysfunction; A child who required constant additional adult care or help in OASDL. Unable to walk without support, feed him or herself or undertake ambulatory playing at the evaluation age of 2 years.

APPENDIX 5. CEREBRAL PALSY ASSESSMENT

Muscle tone

- Passive movements of; Elbow, Shoulder, Hip and Knee joints. These joints are gently moved through their anatomical range noting the degree of resistance or restriction of movement. Resistance to passive movement around any of the joints or flaccidity constituted increased or decreased tone respectively.
- Head lag; this is done by holding both wrists and gently lifting the child from the prone position. If the child is not able to keep the neck straight they are considered hypo-tonic.
- Posture; Presence of fixed limb positions indicate hyper-tonia while inability to sit or stand steadily implies reduced tone

Muscle Power;

A two-year old child should be able to sit, stand or walk while maintaining the normal posture.

Interpretation

Generalized hypo-tonia; decreased tone affecting the trunk and/or limbs

Hyper-tonia; increased tone with loss muscle strength;

- One limb, spastic mon-oplegia.
- Both lower and upper limbs, spastic para-plegia.
- Diagonal limbs, spastic di-plegia.
- All limbs affected, spastic quadri-plegia.

APPENDIX 6; the composition of each 100 mls of preterm formula

Component	Amount	Component	Amount
Fat	3.9g	Vitamin D	79.9 IU
Protein	2.3g	Vitamin E	1.6 IU
Carbohydrates	9.1g	Vitamin K	9.6 mcg
Energy	80kcal	Vitamin C	12.9 mg
Sodium	49.3mg	Biotin	1.8mcg
Chloride	49.6mg	Folic acid	47.3mcg
Potassium	86.4mg	Choline	6.0mg
Calcium	79.9mg	Inositol	3.6mg
Phosphorus	52.2mg	Camitine	1.3mg
Vitamin A	244.5 IU	Copper	0.1mg
Cadmium	79.9mg	Magnesium	8.8mg
Iodine	8.0 mcg	Iron	1.2mg
Manganese	5.5mg	Zinc	0.6mg
Vitamin B_{12}	0.2mcg	Niacin	0.8mg

APPENDIX 7; COMPOSITION OF VITAMIN PREPARATION

Multivitamin supplements pre-packed as concentrate in which every 0.6mls contained;

- Vitamin A; 5000 International Units
- Vitamin D; 400 International Units
- Vitamin C; 50mgs
- Vitamin B1; 1.5mgs
- Vitamin B2; 1.2mgs
- Vitamin B6; 0.5mgs
- Nicotinamide; 10mgs

VI.8: **APPENDIX 8;** CONSENT FORM FOR STUDY PARTICIPATION

Investigator's Statement

We are asking you to be in a research study. The purpose of this consent form is to give you the information you will need to help you decide whether to be in the study. Please read it carefully or let the investigator explain its contents to you in a language you can understand if you can't read. You may ask any questions regarding the study.

Introduction

Babies born smaller than expected are now known to be at increased risk of many problems later in life. They are more likely to develop childhood illnesses, die and fail to attain normal development than bigger babies. There are ways of reducing these undesired outcomes. This can however only be achieved if such infants are regularly and methodically followed up for long periods. As this has not been reliably performed here in the past the study intends to act as pioneer.

Study procedures

During the follow-up there will be no painful procedures performed on your baby. In most cases we will mainly ask questions regarding the health of the child and make the usual clinical examination to determine the wellness of your child.
On two occasions your child will be subjected to a longer evaluation to determine his developmental status. The only rather complicated that will be performed your child are those related to assessment of hearing and vision.

Your child will receive treatment for all ailments discovered during follow-up and specific treatment for any developmental delays identified. We may visit you at home if we have not seen you at the clinic during your appointment. This is because it is important for us to know the final outcome of all the infants including your child.

Benefits of being in the study

In addition to receiving the care you actually need since your child is considered be at more risk than normal children, you will help us determine the long-term needs of small infants. We will be able to find out the later effects of some of earlier events or interventions on babies as small as yours. This is the same method that helped other countries to improve the outcomes of their similar children.

Risks of the study

We foresee no risks from this study as it is actually based on what should be a routine practice that we have simply not been routinely doing due to financial constrains.

Confidentiality.

Your participation in this study will be part of your child's routine healthcare. Nevertheless the usual confidentiality enshrined in medical ethics will be upheld. We will hold your participation in utmost secrecy.

If you agree to participate in the study please sign bellow

I _____being the parent/guardian of baby _____ hereby give consent for full and voluntary participation in 2 year follow-up of my child in Kenyatta National Hospital as part of research program.

I am also aware that the investigators may visit me and my child at home in the course of the study. The investigators have explained the importance of this study to me and I freely allow my baby to participate in it.

Signature of guardian

_____Name_____

Signature of investigator_____