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DEPARTMENT OF PEDIATRICS AND CHILD HEALTH

EFFECT OF CUE-BASED FEEDING ON WEIGHT GAIN AMONG PRETERM NEONATES BORN AT 28 TO 34 WEEKS OF GESTATION AT KIWOKO HOSPITAL: A RETROSPECTIVE COHORT STUDY

BY

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A DISSERTATION PREPARED FOR SUBMISSION TO THE DIRECTORATE OF RESEARCH AND GRADUATE TRAINING IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF MASTER OF MEDICINE IN PEDIATRICS AND CHILD HEALTH OF MAKERERE UNIVERSITY

JULY, 2026

DECLARATION

I, Odong Paul Eric, affirm that this dissertation titled "**Effect of cue-based feeding on weight gain among preterm neonates born at 28 to 34 weeks of gestation at Kiwoko Hospital**" is my original work and has not been submitted to any university or institution for any academic qualification. All literature used in this study has been cited for acknowledgment.

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APPROVAL

We endorse this dissertation titled " **Effect of cue-based feeding on weight gain among pre-term neonates born at 28 to 34 weeks of gestation at Kiwoko Hospital**" conducted under our close supervision. We recommend its submission to Makerere University for the partial fulfillment of the award of a Master's Degree of Medicine in Pediatrics and Child Health.

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DEDICATION

This research is dedicated to my beloved family for their unconditional love and support, and to all caregivers, healthcare workers, and researchers striving to improve health outcomes among newborns. May this work contribute to the advancement of knowledge and the betterment of neonatal outcomes in Uganda.

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LIST OF ABBREVIATIONS/ACRONYMS

bCPAP	**:**	Bubble Continuous Positive Airway Pressure
CBF	**:**	Cue-Based Feeding
CI	**:**	Confidence Interval
GA	**:**	Gestational Age
KH	**:**	Kiwoko Hospital
LBW	**:**	Low Birth Weight
LHS	**:**	Length of Hospital Stay
NICU	**:**	Neonatal Intensive Care Unit
PMA	**:**	Post Menstrual Age
SCU	**:**	Special Care Unit
SDG	**:**	Sustainable Development Goals
SGA	**:**	Small for Gestational Age
SSA	**:**	Sub-Saharan Africa
TFOF	**:**	Time to Full Oral Feeding
UBOS	**:**	Uganda Bureau of Statistics
WHO	**:**	World Health Organization

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OPERATIONAL DEFINITIONS

Effect: Weight status measured as weight for age Z score (WAZ) on day 21 of life

Weight gain: Operationalized as the weight-for-age Z-score (WAZ) at 21 days of life, calculated using the Fenton 2025 third-generation preterm growth charts based on gestational age and sex. The feeding approach with a higher WAZ at day 21 was interpreted as having achieved better weight gain.

Weight velocity: Weight velocity was defined as the average daily weight gain per kilogram of body weight during hospitalization. It was calculated as:

Weight velocity (g/kg/day) = Discharge weight (g) − Admission weight (g)) ÷ [Length of stay (days) × (Admission weight (g)/1000)]

Feeding practices in preterm infants: Encompass a range of strategies and protocols designed to meet the unique nutritional needs of these infants. These include feeding methods, type of feed, timing of initiation, frequency and advancement of feeds and feeding regime, including supportive strategies.

Cue-based feeding: A responsive approach to infant feeding that involves observing and responding to the baby's feeding cues, such as sucking and rooting behavior, wakefulness, tone, and stability of vital signs to determine oral feeding readiness or the need to pause or stop the oral feeding.

Volume-based feeding: A traditional approach to feeding infants that emphasizes achieving a specific volume of milk intake within a prescribed time frame, often overlooking individual feeding readiness cues.

Time to full oral feeding: Time in days from the initiation of cup feeding to the achievement of full cup feeding when the preterm infant receives all nutrition orally without gavage feeds or intravenous fluids

Preterm neonate: Refers to an infant born before 37 completed weeks of gestation as measured from the first day of the last normal menstrual period OR determined by the clinician within the first 30 minutes of delivery using modified Ballard score OR using first-trimester ultrasound scan gestation estimate.

Low birth weight: Refers to an infant whose birth weight is between 1500 grams and 2499 grams, irrespective of gestational age, as recorded at birth.

Very low birth weight: Refers to an infant whose birth weight is less than 1500 grams at birth, irrespective of gestational age.

Low gestational age: Preterm infants born at 28 to 31 weeks and 6 days of gestation

High gestational age: Preterm infants born at 32 to 34 weeks and 6 days of gestation

Special Care Unit: Also known as a Level II Nursery is a hospital unit that provides care for sick or premature newborns who require short-term respiratory support such as continuous positive airway pressure (CPAP)**,** intravenous therapy, phototherapy, or feeding support but do not need intensive care

Level III Neonatal Intensive Care Unit: A neonatal unit that provides comprehensive care for critically ill term and preterm neonates, including sustained invasive mechanical ventilation, surfactant administration, and other advanced intensive care services for as long as clinically indicated, but does not offer complex neonatal surgical services requiring on-site pediatric surgical subspecialists

Sepsis: Clinical diagnosis with abnormal axillary temperature (> 38.5° or < 36 °C), fast respirations (above 60 breaths per minute) with refusal to breastfeed or new apnea/ oxygen requirement in one who was previously stable and in the absence of anemia. Blood cultures are not available

Maternal chronic illness: Is defined as any serious illness that requires ongoing medical attention for more than 1 year and limits maternal activities of daily living. This will include hypertension, diabetes, HIV

Admission hypothermia: Axillary temperature below 36.5℃ at admission

Admission hypoglycemia: Blood glucose level below 2.6 mmol/L or less than 47mg/dl at admission

Hypoxic ischemic encephalopathy: Clinically defined as failure to initiate or sustain breathing at birth and a low APGAR score of less than 7 in 5 minutes with neurological signs of encephalopathy

Post-menstrual age (PMA): PMA was calculated as gestational age at birth plus postnatal age in weeks

Major congenital anomaly: Any major structural malformation present at birth that was identified on newborn physical examination and/or explicitly documented in the Kiwoko Hospital medical record and is likely to independently compromise feeding, growth, or survival e.g, cleft lip/palate; spina bifida/anencephaly; omphalocele/gastroschisis; anorectal malformation; or clinically significant cardiac disease**,** defined as any congenital heart defect other than an isolated small Patent Ductus Arteriosus(PDA)**,** or a PDA documented as moderate/large or hemodynamically significant (e.g symptomatic/heart failure, left heart dilation on echo, or need for medical/procedural closure)**.**

ABSTRACT

Background: In Uganda, preterm birth contributes significantly to neonatal morbidity and mortality**,** affecting an estimated 10–15% of all live births**.** Feeding difficulties due to immature sucking and swallowing mechanisms often hinder growth and recovery in these infants. Cue-based feeding, an individualized approach that relies on infant readiness cues rather than fixed feeding schedules, is increasingly recognized as a promising strategy for enhancing feeding efficiency, physiological stability, and growth outcomes in preterm infants. This study aimed to assess the effect of cue-based feeding on weight gain, measured by weight-for-age Z-scores (WAZ), among preterm neonates aged 28-34 weeks at Kiwoko Hospital.

Methods: A facility-based retrospective cohort study was conducted at Kiwoko Hospital Special Care Unit, Uganda, using records of preterm neonates aged 28-34 weeks admitted between April 2017 and February 2022. Cohorts managed with volume-driven feeding (2017-2019) and those with cue-based feeding (2020-2022), separated by a nine-month washout period to prevent overlap were analyzed. Eligible neonates were admitted within 48 hours of birth and hospitalized for at least 21 days. Data were extracted from the hospital's electronic neonatal database and verified against physical files. The primary outcome was weight-for-age z-score (WAZ) at day 21; secondary outcomes included weight velocity, change in WAZ, time to full oral feeds, and length of stay. Data were analyzed in Stata 19 using descriptive statistics, t-tests, chi-square tests, and multivariable linear regression adjusting for key maternal and neonatal covariates.

Results: A total of 343 preterm infants were analyzed, 160 managed with volume-driven feeding and 183 with cue-based feeding. Infants in the cue-based group had significantly higher mean weight-for-age z-scores at day 21 (adjusted mean difference = 0.22; 95% CI: 0.07–0.38; $p = 0.005$) and greater weight velocity (adjusted mean difference = 2.06 g/kg/day; 95% CI: 1.12–3.00; $p < 0.001$). Although crude analyses showed a shorter hospital stay in the cue-based group (35.9 vs. 39.9 days; mean difference = –4.0; 95% CI: –7.1 to –1.0; $p = 0.011$), this difference was not significant after adjustment (adjusted $p = 0.118$). Time to full feeds did not differ between groups (mean difference = 0.3 days; 95% CI: –1.7 to 2.3; $p = 0.777$).

Conclusion: Cue-based feeding significantly improved weight gain among preterm infants within the first three weeks of life. There was no significant difference in hospital stay and time to full feeds. Despite this, these findings suggest that, when implemented with trained staff and caregiver involvement, cue-based feeding promotes more effective weight gain and improved early growth outcomes among preterm infants, supporting its potential as a beneficial feeding approach in resource-limited neonatal care settings.

CHAPTER ONE: INTRODUCTION

1.0 Introduction

Preterm birth remains the leading cause of death among children under five worldwide (1). The preterm infant survival rates vary greatly between countries, more likely in high income than low income countries. Studies conducted in low-income settings indicate that up to half of infants born at or before 32 weeks of gestation die**,** primarily due to the lack of affordable and effective interventions for thermoregulation, infection control, respiratory support, and nutritional care (1). These infants often find challenges in sucking, swallowing and breathing, which are vital for effective and safe feeding for growth (2, 3). Traditional feeding approaches tend to emphasize the volume of milk intake over the quality and safety of the feeding experience, often leading to adverse outcomes such as aspiration and feeding aversion (4-6).

Cue-based feeding (CBF), a responsive feeding approach that emphasizes observing and responding to an infant's feeding cues, has emerged as a promising strategy to address challenges relating to feeding among preterm babies (7). By prioritizing the infant's readiness and ability to feed, rather than merely on the volume consumed, CBF aims to improve feeding experiences and outcomes among preterm infants. This approach was implemented at Kiwoko Hospital to enhance individualized feeding and promote optimal growth among preterm neonates. This study therefore aimed to determine the effect of cue-based feeding on weight gain among preterm neonates born at 28 to 34 weeks of gestation at Kiwoko Hospital.

1.1 Background

Preterm birth is a significant global public health concern. According to the World Health Organization (WHO), an estimated 13.4 million babies were born preterm in 2022, with preterm birth rates ranging from 4% to 16% of all births in 2020 (1). Sub-Saharan Africa (SSA) and Asia carry the highest burden, with over 60% of preterm births and 80% of the world's 1.1 million deaths due to preterm birth complications occurring in these regions (8). In SSA, a recent analysis of demographic and health survey data reported a preterm birth prevalence of 5.33% (9). Although prematurity is a major contributor to under-five mortality, most deaths and complications can be reduced through cost-effective interventions, including appropriate feeding support for preterm infants (1).

Feeding is central to the survival, growth, and recovery of preterm infants. At birth, many preterm infants lack mature sucking, swallowing, and breathing coordination, which limits their ability to feed safely and effectively. Oral-motor function develops progressively with advancing postmenstrual age (PMA), neurological integration, and maturation of motor pathways (10, 11). The ability to coordinate sucking, swallowing, and breathing generally emerges between 32 and 34 weeks of gestation (12). Feeding before this coordination is adequately developed may increase the risk of aspiration, hypoxia, apnea, bradycardia, and feeding intolerance (13, 14). However, studies suggest that some preterm infants may feed safely at earlier gestational ages when feeding is guided by their behavioral and physiological cues(15, 16).

The World Health Organization emphasizes the need to improve feeding practices for preterm infants in order to enhance growth and development and reduce morbidity and mortality associated with poor infant feeding (1). In many SSA neonatal units, feeding practices remain largely volume-driven. This approach focuses on ensuring that infants consume a prescribed volume of milk within a set timeframe, often based on gestational age and weight. Although volume-driven feeding supports nutritional planning, it may not fully account for infant readiness, feeding endurance, or physiological stability. As a result, oral feeds may be initiated before the infant is developmentally prepared, increasing feeding stress and the risk of adverse feeding-related events (17, 18). Volume-based feeding has also been associated with aspiration, poor weight gain, and readmission (4).

Cue-based feeding is an infant-centered approach that focuses on feeding readiness and tolerance rather than milk volume alone (2). It involves observing cues such as rooting, sucking motions, wakefulness, muscle tone, facial expression, and physiological stability to determine whether an infant is ready to feed, needs a pause, or should stop feeding (2, 19, 20). By responding to these cues, caregivers may create a safer and less stressful feeding environment, improve feeding efficiency, and support better growth outcomes.

Studies from high-resource settings have shown that cue-based feeding may improve feeding and growth outcomes among preterm infants. Cue-based feeding has been associated with earlier attainment of full oral feeding, reduced feeding-related stress, improved weight gain, shorter hospital stay, and fewer feeding complications (19, 21, 22). These findings suggest that cue-based feeding may support both the physiological stability and feeding competence of preterm infants.

However, most of this evidence comes from high-income settings, and there remains limited evidence on its implementation and effectiveness in SSA.

In Uganda, prematurity remains a major cause of neonatal morbidity and mortality, with approximately 10-15% of live births estimated to be preterm (23). Preterm birth complications contribute to 8 to 27 neonatal deaths per 1,000 live births and are among the top three causes of neonatal mortality in Uganda (24). At Kiwoko Hospital Special Care Unit, prematurity is one of the commonest reasons for neonatal admission. The unit admits over 1,200 newborns annually and provides feeding support to many preterm infants who are not yet developmentally ready for independent oral feeding. This local burden highlights the need to evaluate feeding approaches that may improve weight gain and early growth outcomes among preterm neonates admitted to the unit.

Weight gain among preterm neonates is influenced by several factors beyond feeding strategy, including gestational age at birth, birth weight, medical complications, Kangaroo Mother Care (KMC), maternal health status, socioeconomic factors, and the quality of neonatal care (25). In Uganda, additional challenges such as infection risk, limited access to breast milk, and inconsistent care practices due to workforce shortages in NICUs may further affect neonatal growth outcomes (26). Therefore, evaluating the effect of cue-based feeding on weight gain among preterm neonates born at 28 to 34 weeks of gestation at Kiwoko Hospital is important for informing feeding practices and improving neonatal growth outcomes in this setting.

1.2 Statement of the problem

Preterm birth remains a major contributor to neonatal morbidity and mortality, especially in low-resource settings such as sub-Saharan Africa and South Asia, where health system constraints limit optimal neonatal care (8). In Uganda, prematurity accounts for an estimated 10-15% of live births, and its complications are among the leading causes of neonatal deaths (23). Many preterm infants have immature sucking, swallowing, and breathing coordination, which affects their ability to feed safely and gain weight adequately (27).

Feeding difficulties among preterm neonates may lead to feeding intolerance, aspiration, poor weight gain, delayed attainment of full oral feeds, prolonged hospitalization, and increased vulnerability to adverse neonatal outcomes (6). In many Ugandan neonatal units, feeding practices remain largely volume-driven, with emphasis on prescribed milk volumes and scheduled feeding rather than infant readiness and physiological stability (28). Local studies have also documented suboptimal feeding practices among preterm and very low birth weight infants, including delayed initiation of enteral feeds and poor early weight gain, which contribute to postnatal growth failure and poor neonatal outcomes (3, 29).

Cue-based feeding is a responsive feeding approach that uses infant behavioral and physiological cues to guide feeding readiness and progression. Studies, mainly from high-income countries, have associated cue-based feeding with better weight gain, earlier attainment of full oral feeding, shorter hospital stay, and fewer feeding-related complications (19, 30).

At Kiwoko Hospital, cue-based feeding was introduced to improve feeding practices among preterm neonates, however, there is limited evidence on its effectiveness in Uganda, where neonatal units face different resource constraints, staffing patterns, and feeding support systems. This study therefore aimed to determine the effect of cue-based feeding on weight gain among preterm neonates born at 28 to 34 weeks of gestation at Kiwoko Hospital.

1.3 Justification

Preterm infants, born before 37 weeks of gestation, often struggle with safe and effective oral feeding due to underdeveloped neurologic and physiological systems (7). Traditional volume-driven feeding methods, which focus on the amount of milk intake, can pose risks such as aspiration and prolonged hospital stays, often leading to negative feeding experiences and developmental delays (19, 30).

Cue-based feeding offers a promising alternative by focusing on the infant's readiness and feeding cues, leading to safer and more positive feeding outcomes (2). Despite its potential benefits, the implementation of cue-based feeding in NICUs is limited due to cultural resistance among nurses and clinicians, lack of healthcare worker-caregiver training, and insufficient local experience and evidence (20, 31) and therefore the WHO, in the recent guidelines for feeding of preterm and low birth weight neonates in health centers has maintained use of a traditional scheduled approach over responsive feeding(32). This being the first study in Uganda aims to fill these gaps by evaluating the effectiveness of cue-based feeding and providing evidence to support its broader adoption especially in resource limited settings.

The anticipated benefit of this study is the generation of local evidence on whether cue-based feeding improves weight gain among preterm neonates. The study also provides evidence on related outcomes, including weight velocity, time to full oral feeds, and length of hospital stay. These findings may inform neonatal feeding practices and guide future research on individualized and developmentally appropriate feeding approaches for preterm infants in resource-limited settings.

1.4 Research Question

1. What is the difference in weight gain among preterm neonates born at 28 to 34 weeks of gestation before and after the introduction of cue-based feeding at Kiwoko Hospital (KH)?

1.5 Study Objectives

1.5.1 General Objective

To determine the effect of cue-based feeding on weight gain among preterm neonates born at 28 to 34 weeks of gestation at KH.

1.5.2 Specific Objectives

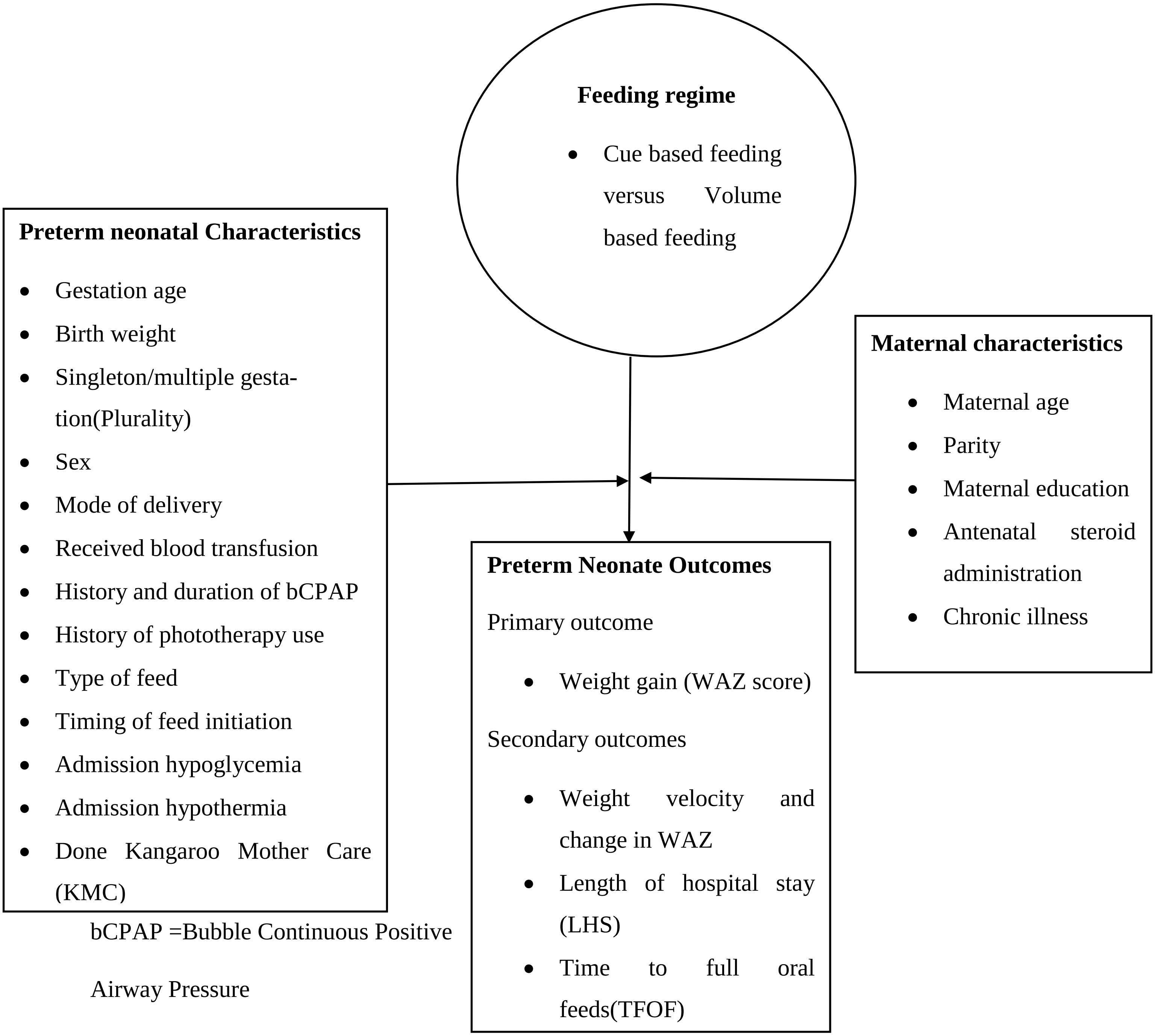
Primary objective

1. To compare weight measured as WAZ on day 21 among preterm neonates born at 28 to 34 weeks of gestation before and after the introduction of cue-based feeding at KH.

Secondary objectives

2. To compare weight gain velocity in grams/kilogram/day (g/kg/d) and change in mean WAZ from day 14 and day 21 among preterm neonates born at 28 to 34 weeks of gestation before and after the introduction of cue-based feeding at KH.
3. To compare the length of hospital stay among preterm neonates born at 28 to 34 weeks of gestation at before and after introduction of cue-based feeding at KH.
4. To compare the time to full oral feeds among preterm neonates born at 28 to 34 weeks of gestation before and after introduction of cue-based feeding at KH.

1.6 Conceptual framework



bCPAP =Bubble Continuous Positive Airway Pressure

Figure 1**:** The Conceptual Framework showing the relationship between feeding regime and other variables.

1.7 Narrative

This study aimed to assess the effect of cue-based feeding (CBF) on weight gain among preterm neonates born at 28 to 34 weeks of gestation. The conceptual framework is structured around the premise that feeding regime (Cue-based feeding vs. Volume-based feeding) directly influences the primary outcome, weight gain measured by Weight-for-Age Z-score (WAZ) between birth and day 21. However, this relationship is mediated by multiple maternal and neonatal characteristics, which serve as intervening variables.

The feeding regime represents the key exposure. In the cue-based approach, infants are fed based on observable readiness cues rather than on fixed schedules or volumes. This is hypothesized to enhance feeding tolerance and promote more efficient weight gain.

Maternal characteristics such as maternal age, education level, parity, presence of chronic illnesses (e.g. hypertension or diabetes), and use of antenatal corticosteroids can affect neonatal health at birth, feeding initiation, and overall recovery trajectory. These variables may indirectly influence how an infant responds to a given feeding method. Neonatal characteristics including gestational age, birth weight, presence of comorbidities like sepsis, hypothermia, and hypoglycemia, as well as interventions such as Kangaroo Mother Care (KMC) also significantly influence the neonate's capacity to tolerate and benefit from a feeding strategy. These factors may act as effect modifiers or confounders in the relationship between feeding type and weight gain.

By positioning maternal and neonatal factors as intervening variables, the framework acknowledges the complex interplay of influences on neonatal growth. It guides both the analysis and interpretation of outcomes, ensuring that the effect of feeding type is evaluated within the broader clinical context that shapes preterm infants' growth and recovery.

CHAPTER 2: LITERATURE REVIEW

2.0 Introduction

This literature review presents information regarding burden of prematurity, feeding practices for preterm infants and the effect of cue-based feeding and factors influencing weight gain among preterm neonates. Information was obtained from articles, and reports from PubMed, Google Scholar, BMC, and other online search engines.

2.1 Burden of Prematurity

Preterm birth rates have been reported to range from 5% to 7% of live births in some developed countries, but are estimated to be substantially higher in developing countries (33). In developing countries, accurate and complete population data and medical records usually do not exist. In 2005, it is estimated that over 9.6% of all births were preterm, which translates to over 12.9 million births. Over 85% of this burden was however reported to occur in Africa and Asia (33).

Preterm birth complications are the leading cause of childhood mortality worldwide, accounting for approximately 1 million deaths annually (34). Of these, 965,000 deaths occur in the neonatal period due to complications of prematurity with an additional 125,000 deaths in children aged one to five years (35, 36). In 2019, complications from preterm births caused around 900,000 deaths among children under five. Three-quarters of these deaths could have been prevented with cost-effective interventions including achieving independent oral feeding, often hindered by underdeveloped feeding skills and associated health issues like respiratory distress and feeding intolerance (37).

Uganda is the 28th country worldwide with a high preterm births rate of 13.6 per 1000 live births (8), with the risk of preterm birth estimated at 10 to 15%. Deaths in preterm infants make up 30% of all neonatal deaths(38) and remains among the top three causes of death during the neonatal period(39).

Preterm birth underlies neonatal complications such as poor feeding, immature lungs, slow weight gain, infections and regulating body temperature which lead to death, longer or more intense nursery care and imposes a high financial burden to families and healthcare facilities (40, 41).

2.2 Feeding practices for Preterm neonates

Optimal feeding practices are among major strategies for enhancing the prognosis, growth, and development of preterm and low birth weight (LBW) infants (27). Feeding practices in preterm neonates encompass a range of strategies and protocols designed to meet the unique nutritional needs of these infants. These include feeding methods, type of feed, timing of initiation, frequency and advancement of feeds and feeding regimen, including supportive strategies. The overarching goal of these feeding practices is to promote gestation-equivalent fetal growth rate in terms of weight, length, and head circumference, organ size, tissue components including cell number and structure, concentrations of blood and tissue nutrients, and developmental outcomes (42). Inadequate intake of recommended nutrients leads to suboptimal growth and is linked to heightened short-term risks including growth failure, while also increasing the likelihood of long-term consequences such as neurodevelopmental impairments and adult onset metabolic and cardiovascular disease (43, 44).

Most evidence regarding feeding practices for hospitalized preterm infants recommended by the WHO comes from high-income countries, with limited data from sub-Saharan Africa, where resource constraints pose significant challenges to implementing these recommended practices (45).

2.2.1 Feeding Methods

2.2.1.1 Parenteral nutrition

This involves providing nutrition intravenously, bypassing the gastrointestinal tract. The goal of early intravenous feeding is to maintain normal cellular energy and amino acid supplies. For several proven reasons, IV nutrition is fundamental in all infants who cannot tolerate full enteral feedings (46). The Current recommendations are that IV nutrition should be initiated within a few hours of birth (47). However, it may be associated with catheter-related complications, including sepsis (48) and not widely used in resource constrained settings like Uganda.

2.2.1.2 Enteral nutrition

This involves delivering nutrients directly into the gastrointestinal tract through use of Nasogastric/Orogastric or very rarely naso-jejunal tube. Formula or expressed breast milk (EBM) is delivered through a tube passed through the nose or mouth into the stomach. This method is widely used globally and in Ugandan NICUs due to its practicality, safety and relatively non-invasive nature. Also, it has been found that enteral feeding aids the development of the gut and reduces the risk of infections and sepsis (49). However, there is a reported risk of developing Necrotizing enterocolitis (NEC).

2.2.1.3 Oral Feeding

This is the ultimate goal for preterm infants, involving sucking from breast or bottle, cup or spoon feeding. Breastfeeding, recommended by the WHO is the gold standard for infant nutrition and provides numerous health benefits such as better feed tolerance, lower risk of NEC, shorter hospital stay, promotes intestinal adaptation and maturation (50-53). However, breastfeeding of small, sick and/ or preterm infants on the neonatal ward may present multiple challenges due to maternal and neonatal physiology and the environment (54). Also, breast milk alone may not be sufficient to comprehensively provide proteins, energy, minerals, vitamins, and trace elements requirements of the preterm infant (55). Bottle feeding is another method used in oral feeding of preterm neonates however, it requires selection of special teats for preterm neonates, causes nipple confusion and rapid milk flow (56). Use of cup feeding is another alternative method of oral feeding recommended by the WHO with studies showing stable heart rate and oxygen saturation and higher maintenance rates of breastfeeding post discharge compared to bottle feeding for preterm infants (57).

2.2.2 Type of feed

Currently, the enteral nutrition options available for preterm infants may include expressed breast milk (EBM) that can be mother's own milk or donor milk, formula milk or fortified EBM (58). However, although human milk has several known proven benefits, this may not be sufficient to provide all preterm infants' nutritional requirements (59). Thus fortifying breast milk may help to provide additional nutrients to preterm infants whose needs are not met by EBM alone. Also, there is formula milk designed for preterms on the market which can be used as an alternative as it contains all essential nutrients (51) although it may be associated with an increased risk of NEC(60). Pasteurized donor milk is another option recommended when mother's own milk is not available, or when mothers milk is insufficient or contraindicated (61).

In Uganda and other resource limited settings, the lack of facilities for pasteurizing milk, the cost of human milk fortifiers and preterm formulas has significantly hindered their adoption in NI-

CUs and therefore provision of mother's own milk is the primary nutrition option in these setting.

2.2.3 Feeding Frequency

There are two approaches used, continuous and intermittent bolus milk feeding. Although there are few studies that have reveal comparable outcomes with the two feeding methods, continuous feeding technique has been shown to cause significantly faster growth rate and achievement of full enteral feeding than bolus feeding (62, 63). Bolus feeding however remains a commonly used method in most Ugandan NICUs, administered every 2 to 3 hours depending on institutional preferences, as there is no concrete evidence to support the exclusive use of either 2-hour or 3-hour feeding intervals(64).

2.2.4 Time of initiation and advancement of feeds

The early initiation of enteral feeding within 72 hours of birth as opposed to delayed initiation after 72 hours, has been found to reduce the time required to regain birth weight, it shortens the duration of parenteral nutrition and decreases the length of hospital stay (3, 65). This has also been shown to reduce the risk of developing feeding complication (3, 65). Moreover, rapid advancement of enteral feeding, as compared to slower feeding approach has been linked to a significantly shorter time to achieve full enteral feeding and regain birth weight, a reduced hospital stay, enhance feed tolerance and reduce the risk of NEC (66-68).

2.2.5 Feeding Regime

Feeding protocols for transitioning from tube feeding to oral feeding that are outlined in the literature are often inconsistent(69). There are two major approaches of determining when to feed an infant, that is volume based feeding and responsive or cue-based feeding. Traditionally, NICUs have used volume-based scheduled feeding criteria, where clinicians determine feeding volumes based on the infant's weight and gestational age. Success is measured by the infant consuming the predetermined amount at specific times, without considering the overall state of the infant (70). Consequently, bottle or cup feeding was introduced as preliminary step to breastfeeding, enabling quantifiable nutritional intake by tracking the volume consumed. This approach helps ensure adequate nourishment to support postnatal growth rate as compared to that of the normal fetus with the same gestational age(71). However, these criteria have been shown to compromise the infant and may lead to increased levels of anxiety and frustration for parents and caregivers (72).

On the other hand, cue-based feeding, also known as responsive feeding is another approach used in NICUs in some countries. This seems to be more comprehensive than other approaches and involves all domains of feeding (18). As stated in the cue-based feeding protocol, the infant's behavioral cues are the key feeding readiness determinant. Successful feeding under this protocol maybe characterized by being safe, functional, nurturing, individualized and developmentally appropriate for each neonate (18).

It is well known that cue-based feeding is collaborative and infant-led method in which caregivers initiate and end feeds based on infant's behavioral cues. These cues may include disengagement, physiological instability, distress, satiety or sleep (2, 31). As a result, the infant autonomously determines the timing, duration and volume of feeds to take. At each stage during transition to oral feeding, by understanding and interpretation of their cues, infants maybe supported in such a way that they can attain all they are capable of with regards to oral feeding. The cue-based feeding method is often integrated with supplementary tube feeding by recognizing that, many preterm infants are not yet developmentally mature enough to sustain adequate nutrition solely through oral feeding. However, modifications of cue-based feeding, caregivers may pre-set a maximum permitted duration of inactivity or sleep between feeds or a maximum volume of intake or modify feeding plans to consider the reduced endurance levels of preterm infants.

Current available evidence from high resource settings showed decreased hospital stay, shorter transition to oral feeds and parental satisfaction for infants on cue-based feeding compared to those on scheduled feeding(72-74). Despite these benefits, the WHO, following a systematic review maintains use of scheduled feeding approach for hospitalized preterm infants due to limited evidence in resource limited settings and a very low quality evidence showing a slightly low rate of weight gain among infants receiving responsive/ cue based feeding (75).

2.2.6 Supportive strategies

Kangaroo Mother Care: Skin-to-skin contact between the infant and caregiver recommended by the WHO for every preterm infant, promotes breastfeeding, temperature regulation, bonding, weight gain and many other physiologic benefits.(76-78)

2.3 Feeding practices before and after cue-based feeding at Kiwoko Hospital

Table 1: Table showing feeding practices

Practice	**Before cue-based feeding**	**After cue-based feeding**
Timing of introduction of any feeds in LBW infants	Trophic (low volume) feeds started on day one	Same
Goal volume of feeds by 7 days of age	160ml/kg/day	Same
Criteria for type of feeds		
Mother's own milk	Default	Same
preterm/term formula	If mother's milk not expected (these include maternal death or abandonment)	Same
Fortified mother's milk	Not available	Smallest babies (<*1kg*) without weight gain after week one
Criteria for use of feeding routes		
Breastfeeding	Anyone not on CPAP	CBF score 1 or 2
Cup feeding	Anyone not on CPAP	CBF score 1 or 2
Nasogastric feeds	CPAP treatment or inability to feed orally	CBF score 3, 4 and 5
Orogastric feeds	CPAP treatment or inability to feed orally	CBF score 3, 4 and 5
Other interventions for weight gain	KMC	KMC Neurodevelopmental care including nesting, lactation support via trained staff family centered care staff and family education including videos

Discharge criteria	• Stable cardiorespiratory status/physiologically mature • >1.5kg with consistent weight gain • Maintaining normal temperature in a cot • Discharge education for the family complete • No clinical signs of convulsions • HIV care plan if applicable • Received appropriate immunizations	• Stable cardiorespiratory status/physiologically mature • >1.5kg with consistent weight gain • Maintaining normal temperature in a cot • Discharge education for the family complete • No clinical signs of convulsions • Family contact information documented for follow up plan for CHW visit • HIV care plan if applicable • Received appropriate immunizations

2.4 Effect of cue-based feeding on weight gain

It has been shown that weight gain in preterm neonates can be an important indicator of health and developmental progress. Suboptimal weight gain in the neonates maybe correlated with increased mortality and long term cognitive and physical deficits(79).

It has also been shown that cue-based feeding can improve weight gain in preterm infants compared to scheduled based feeding as revealed by three studies (19, 20, 80). This improvement in weight gain can be attributed to the fact that CBF allows for more efficient feeding, with infants consuming the amount they are physiologically ready for, thus minimizing fatigue and feeding intolerance (16).

However, findings across studies remain inconsistent. Ofek-Shlomai et al. (2024) in Israel, in a retrospective cohort of 240 preterm infants, found that while cue-based feeding facilitated earlier transition to full oral feeds and shorter hospital stay, it was associated with declining Weight-for-Age Z-scores at discharge compared to the volume-driven epoch (81). Similarly, the SINC Trial conducted in Turkey, which implemented the Cue based feeding protocol, reported modest improvements in Z-score trajectories and oral-feeding efficiency but no statistically significant advantage in overall weight gain velocity(82)

Three other studies have also reported low-certainty evidence of a slight decrease in weight at hospital discharge of approximately 22g (72, 83, 84). These findings align with the WHO (2016) Cochrane review which reported low quality evidence suggesting that infants randomized to responsive feeding had a marginally low daily weight gain rate(85).

2.5 Effect of Cue-based feeding on the time taken to full oral feeds

The duration taken by preterm neonates to transition to full oral feeds is an important milestone for their development and generally a point at which a neonate can be discharged home.

Studies exploring cue-based feeding (CBF) in preterm infants consistently demonstrate a reduction in the time needed to achieve full oral feeds compared to traditional scheduled feeding approaches. A study implementing a cue-based oral feeding clinical pathway found that premature infants reached full oral feeding approximately six days earlier than those in a control group, with an average postmenstrual age (PMA) of 36 weeks as compared to 36 weeks and 6 days for the control group (86). Similarly, in a study from perinatal centres in the U.S. Northeast, cue-based feeding shortened the time to full oral feeding by seven days in infants born between 23- and 27-weeks gestation, and by approximately 6.6 days for those born between 28 and 31 weeks (87).

In Iran, research found that preterm infants reached full oral feeds three days sooner with cue-based feeding (17 days versus 20 days in the control group)(19). A study done by Spagnoli showed that very low birth weight infants achieved full oral feeds at a median PMA of 247 days after cue-based feeding was implemented, younger than the median of 250 days before the intervention(20).

Further, a prospective trial study showed that infants in the CBF intervention group may reach full oral feeding and maybe discharged slightly earlier, with an average post-conceptual age (PCA) of 35.8 weeks as compared to 36.5 weeks in the control group. The study also observed fewer adverse feeding-related events in the CBF group (72). Lastly, a hospital-based study done in Tehran showed that infants in the cue-based group achieved full oral feeding in just over three days, which is almost half the time required by the scheduled feeding group. This highlights the efficiency of cue-based approaches in promoting timely feeding progression in preterm infants (83).

Collectively, these findings indicate that cue-based feeding may significantly reduce the time to full oral feeds, which can potentially accelerate discharge and reduce the feeding-related complications among preterm infants.

2.6 Effect of Cue-based feeding on the length of hospital stay

It has been shown that preterm neonates on cue-based feeding protocols have a shorter length of hospital stay compared to those on scheduled feeds. In a study conducted across regional perinatal centers in the U.S. Northeast, infants born at 23 to 27 weeks gestation experienced a 4.4-day reduction in hospital stay with cue-based feeding, while those born at 28 to 31 weeks showed a 2.7-day decrease (87).

In a clinical trial conducted in Tehran's NICU, it was found out that preterm infants in the cue-based group had a substantially shorter hospital stay with an average hospital stay of 15.6 days, as compared to 27.1 days for those on scheduled feeding (83). Similarly, an Indian study demonstrated that neonates on cue-based feeding had a median hospital stay of 5 days, in contrast to 8 days for those on scheduled, volume-driven feeding every two hours(88).

Further analysis in a separate study, adjusting for gestational age at birth, found that preterm infants on cue-based feeding averaged 10.0 days in the hospital, compared to 14.5 days in the control group(72). Also, a retrospective study conducted in USA among very low birth weight neonates reported hospital stay decreased from a median stay of 55 to 48 days after cue-based feeding implementation. This demonstrates that cue-based feeding may improve care efficiency and facilitate earlier discharge, enhancing NICU resource use and potentially patient outcomes(20).

2.7 Factors influencing weight gain among preterm neonates

Weight changes in the neonatal period begins with a transient period of weight loss, which is considered a period of physiological weight loss. Results of a systematic review conducted among breastfed preterm neonates showed that weight loss of up to 12% of birth weight was experienced by about 95% of the neonates in the first week of life (89). These neonates may however begin to exhibit significant weight gain provided all conditions are optimal. In a study conducted by Hoffman, it was revealed preterm neonates gained an average of 16.7 g/kg per day with a mean duration of 10.6 days following attainment of their birth weight (90). Nevertheless, multiple factors may influence this weight trajectory, with some facilitating and others impeding the rate of gain.

One of the key factors influencing weight gain among preterm neonates is the feeding protocol employed. While parenteral nutrition is commonly initiated shortly used after birth to meet the nutritional needs of extremely preterm neonates, evidence suggests that an early transition to enteral feeding has been linked to better growth outcomes. Studies have also shown that human milk plays a critical role in supporting the growth and development of preterm infants especially the fortified breast milk. This was for example demonstrated in a randomized control trial (91) which found that preterm infants receiving fortified human milk showed higher rates of weight gain as compared to those fed unfortified milk. According to this study, fortification compensates caloric and nutritional deficiencies that are always observed in preterm infants, leading to improved weight gain and developmental outcomes.

Moreover, specific feeding methods impact weight gain in preterm neonates. The use of orogastric or nasogastric tubes allows for consistent nutrient delivery and supports weight gain by accommodating frequent feeding schedules suited to the neonates' limited digestive capacities(92). Further research by (93) suggests that feeding strategies that involve smaller, more frequent feedings can lead improve feeding tolerance and enhance weight gain by minimizing the risk of feeding intolerance and related complications.

Health complications such as including necrotizing enterocolitis (NEC) and infections are common among preterm neonates and pose significant barriers to optimal weight gain. NEC, in particular, compromises intestinal integrity and impairs nutrient absorption often necessitating prolonged reliance on parenteral nutrition, which can delay optimal weight gain (94). Studies have shown that the risk of NEC maybe lower in infants receiving human milk, which can support better growth outcomes of the neonate. Also, the risk of respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD) maybe high preterm neonates, often requiring interventions like mechanical ventilation that may contribute to metabolic stress, ultimately hindering weight gain (95).

Parental involvement and support are also crucial in the weight gain of preterm neonates. In a systematic review and meta-analysis study done by Chan et al, it was showed that parents who are actively involved in the routine care of hospitalized preterm or low-birth weight infants; there are notable improvements in outcomes such as enhanced weight gain and shorter durations of hospital stays(96).

2.8 Summary of the literature review

The literature explores the feeding practices for preterm infants and the impact of cue-based feeding on several health metrics for preterm neonates, especially weight gain, achievement of full oral feeds, and the length of hospital stay. The literature shows that current recommended feeding practices are based on studies conducted in high-income countries. However, the adoption of these practices in resource-limited countries is constrained by unique challenges such as inadequate infrastructure, limited staffing, and a high patient burden, among others.

Also, literature shows that CBF can reduce hospital stays and time to full oral feeds as seen in studies conducted in the USA, Iran, and India and Canada. However, there have been mixed findings regarding its impact on weight gain as some studies have reported a slight decrease in weight gain among preterm infants fed using CBF.

The review underscores the pressing need for CBF in preterm infants. Despite the recognition of this need, there is a notable scarcity of research on CBF in African and Ugandan preterm neonates. This gap in the literature demonstrates the urgent need for further studies to examine the effect of cue-based feeding on weight gain, length of stay and time to full oral feeds among preterm neonates aged 28 to 34 weeks gestation age at birth. Such research is essential to develop targeted interventions that can significantly improve the health and survival of these infants.

CHAPTER THREE: METHODOLOGY

3.1 Study design

This was a facility-based retrospective comparative cohort study utilizing quantitative data collection methods.

3.2 Study duration

The study was conducted over three months, from August 2025 to October 2025

3.3 Study period

The study included records of all eligible preterm neonates admitted to Kiwoko Hospital Special Care Unit between April 2017 and February 2022. The study period was divided into two distinct timeframes based on the implementation timeline of feeding strategies at Kiwoko Hospital. From April 2017 to April 2019, scheduled or volume-based feeding constituted the standard practice. To ensure a clear transition and minimize contamination between feeding approaches, a washout period from May 2019 to January 2020 was included. This 9-month interval allowed staff to adapt to the upcoming changes and ensured consistency in the new protocol. From February 2020 to 2022, cue-based feeding (CBF) was formally implemented and became the routine practice. This separation ensured that each cohort distinctly reflected its respective feeding approach.

3.4 Study setting

The study was conducted at Kiwoko Hospital in Uganda, a private, not-for-profit secondary care facility established in 2001 which primarily serves as a referral center for three districts of Nakaseke, Luwero and Nakasongola with an estimated catchment population of 1,000,000 inhabitants.

The Special Care Unit (SCU) at Kiwoko Hospital is a well-developed level two newborn care unit, renowned in the region as a center of excellence in the care of small and sick newborns(97). With a bed capacity of 35, the SCU admits over 1200 babies annually, accommodating neonates with gestational ages ranging from 24 to 44 weeks, with prematurity being the most common reason for admission. Approximately half of these neonates are born at Kiwoko Hospital, while the rest are referred from home or other facilities. Overall unit mortality was 12% in 2023, predominantly from birth asphyxia, prematurity, and infection. The mortality rates per 1,000 admissions for each diagnosis in 2023 were as follows: birth asphyxia at 206 per 1,000, prematurity at 96 per 1,000, and infection at 68 per 1,000(98).

There are 5-7 nurses per shift with a nurse-to-infant ratio of 1:5, one designated medical officer, and a pediatrician who conducts daily rounds and remains on call. Most staff members reside on site. The Special Care Unit operates 24 hours a day, seven days a week. Both in-born neonates and out-born neonates referred from home or other health facilities are admitted and managed within the same neonatal unit. The unit has separate designated partitions for in-born and out-born neonates to facilitate infection prevention and control (IPC) practices and reduce the risk of healthcare-associated transmission of infections. Referral status is documented in the neonatal database and was included as a covariate during analysis.

Various forms of care are provided in the SCU, including thermoregulatory support through radiant warmers, incubators, and kangaroo mother care; infection control and treatment; nasogastric and cup feeding; intravenous hydration; phototherapy; blood transfusion; basic laboratory services; oxygen therapy; and pulse oximetry. Improvised bubble Continuous Airway Pressure (bCPAP) remains the standard of care for respiratory failure in the unit. As the neonatal unit does not provide surfactant therapy, invasive mechanical ventilation, or total parenteral nutrition, with bCPAP representing the highest level of respiratory support available, preterm infants requiring more advanced neonatal intensive care are identified promptly, stabilized with the available respiratory and supportive care, and referred to higher-level neonatal intensive care units. Referrals are coordinated through prior communication with the receiving facility, parental/caregiver counseling and consent, and transfer by a hospital ambulance equipped for neonatal transport and accompanied by a nurse trained in neonatal stabilization. Most referrals are made to the public level III NICUs at Kawempe National Referral Hospital and Mulago Specialized Women and Neonatal Hospital, although referral to private level III NICUs may also be arranged based on parental/caregiver preference. This referral pathway is consistent with Uganda's tiered neonatal referral system, whereby lower-level neonatal units stabilize infants within their available capacity and refer those requiring advanced neonatal intensive care to higher-level facilities.

3.4.1 Implementation of CBF in Kiwoko Hospital

Cue-based feeding (CBF) was formally introduced at Kiwoko Hospital between April 2019 and January 2020, with full implementation starting in February 2020. The CBF protocol was introduced gradually, preceded by staff training and formation of a multidisciplinary feeding committee. Staff are trained in feeding readiness assessments and caregivers, including mothers, are educated on how to interpret and respond to feeding cues. A designated nurse educator conducts daily CBF education sessions for 2 hours from 10:00am to 12:00pm, Monday to Friday. Feeding readiness and quality are monitored using adapted tools, and feeding assessments are recorded in patient charts. To initiate cue-based feeding, Kiwoko Hospital adopted the Oral Feeding Readiness Assessment Scale (OFRS) derived with modifications from a study by Ludwig et al, Lubbe et al, Dodril et al and Pirelli et al(2, 99, 100) and described in appendix II.

This five-point scale ranges from 1, indicating the most optimal and mature infant response, to 5, indicating the least optimal as described below in section 3.4.2.

3.4.2 Description of the CBF protocol used for Oral Feeding Assessment and Management of Preterm Infants Admitted to the Kiwoko Hospital Neonatal Unit Based on a Standardized 1–5 Feeding Readiness Score Incorporating Behavioural Feeding Cues and Physiological Stability.

Table 2: Description of the CBF feeding protocol

Feeding readiness score	**Infant Cues**	**Offer oral feedings?**
1	• Beginning to wake up, or awake before caregiver interaction • Rooting and/or bringing hands to mouth, sucking on fingers • Good muscle tone, respirations are normal with activity	YES
2	• Begins to wake up, or is awake with caregiver interaction • Shows some rooting behavior • Adequate muscle tone, respirations are normal with activity	YES

3	• Briefly awake with caregiver interaction, but falls asleep again • No hunger behaviors • No increase in muscle tone	NO
4	• Sleeps throughout caregiver interaction • Shows no hunger signals • No change in muscle tone	NO
5	• May be asleep or awake and showing cues, but vital signs are unstable - signs of physiological instability are: o Decrease in oxygen saturations o Apnea and/or bradycardia with care o Respirations increase above normal range with caregiver interaction	NO

Before each feeding, the nurse assesses and categorizes the baby's current state, recording the score on the flow sheet under the column labeled "feeding assessment score". Likewise, the nurse continuously evaluates the quality of preterm infants' oral feeding using the Oral Feeding Quality Scale (appendix), which considers sucking, spilling, vomiting, presence of choking, apnea, and duration of feeding.

Caregivers pay attention to the "cues" or signs the infant provides throughout feeding. Based on these cues, caregivers can adjust how the infant is being fed. If the infant demonstrates distress cues, such as changes in heart rate, respiratory rate, or oxygen saturation levels, oral feeding is stopped, and the remainder of the feed is given by nasogastric tube.

3.4.3 Electronic neonatal database description

Kiwoko Hospital has maintained an electronic database of all neonatal admissions since late 2012. On admission, nursing staff document essential neonatal and maternal information using a standardized bedside paper form. After discharge, a trained data entry team extracts additional details from the medical file, including interventions received, final diagnoses made by the attending doctor, feeding records, and outcomes (discharge, death, or referral). This information is entered into a secure electronic system. The database provides a reliable source for retrospective data collection and enables cross-verification with physical records to ensure data completeness and accuracy. Daily weight measurements are routinely recorded for all preterm infants, with the weight on day 21 of life serving as the primary outcome for this study. All weights are obtained using calibrated Seca weighing scales, with infants fully undressed to ensure accuracy and consistency.

3.4.4 Maternal awareness of CBF

As part of the CBF implementation, mothers and caregivers receive structured education on cue recognition and appropriate feeding responses. These sessions are conducted routinely by trained nurse educators and involve practical demonstrations and use of visual aids. Each session lasts approximately two hours and is held daily from Monday to Friday, between 10:00 a.m. and 12:00 midday. This initiative ensures that caregivers are not only aware of but actively engaged in CBF practices.

3.5 Study population.

3.5.1 Target population

Preterm neonates in Uganda born at 28 to 34 weeks of gestation.

3.5.2 Accessible population

Preterm neonates born at 28 to 34 weeks of gestation admitted at Kiwoko Hospital with records available in the database within 2 days of birth during the period of study with admission lasting at least 21 days.

3.5.3 Study population

Pre-CBF implementation Group: Preterm neonates born at 28 to 34 weeks of gestation who were admitted at KH two years prior to the introduction of cue-based feeding (from April 2017 to April 2019).

Post CBF implementation Group: This comprised of preterm neonates born at 28 to 34 weeks of gestation who were admitted at KH during the two years following the introduction of cue-based feeding (from February 2020 to February 2022).

3.6 Eligibility criteria

3.6.1 Inclusion criteria

The study included records of all preterm neonates born at 28 to 34 weeks of gestation 2 years after and before the initiation of cue-based feeding protocol at Kiwoko Hospital (documented by first-trimester ultrasound, Maternal last normal menstrual period (LMP) or New Ballard Score). Eligible neonates were those admitted within the first 48 hours of life and who remained hospitalized for a minimum of 21 days at Kiwoko Hospital, the period generally considered as an appropriate duration to observe meaningful weight changes (101).

3.6.2 Exclusion criteria

All preterm neonates born between 28 and 34 weeks of gestation who had major congenital anomalies documented in the clinical records were excluded. Major congenital anomalies referred to visible or clinically documented structural abnormalities likely to independently affect feeding, growth, or survival, including major congenital heart disease, gastrointestinal malformations, major neurological abnormalities, and craniofacial anomalies affecting oral feeding.

Neonates whose oral feeding was discontinued due to necrotizing enterocolitis (NEC) were also excluded. In addition, records with incomplete key data required for outcome assessment, including missing birth weight, gestational age, day 21 weight, discharge weight, admission date, or discharge date, were excluded. Neonates who died before discharge or were referred to other facilities before completion of outcome assessment were also excluded from the study.

3.7 Sample size estimation

The sample size was estimated using the formula for comparing two independent means:

$$n = (Z\alpha/2 + Z\beta)^2 \times 2\sigma^2 / d^2$$

where $Z_{\alpha/2}$ is the critical value of the Normal distribution at $\alpha/2$ (e.g. for a confidence level of 95%, α is 0.05 and the critical value is 1.96), Z_β is the critical value of the Normal distribution at β (e.g. for a power of 80%, β is 0.2 and the critical value is 0.84), σ^2 is the population variance, and d is the difference you would like to detect. Based on this formula, an initial sample of 286 participants was required to detect a mean difference of 0.2 in weight-for-age z-score (WAZ) at 21 days of age or larger, assuming a standard deviation (SD) of 0.6 (equivalent to a

Cohen's d of 0.33). This effect size was selected for its moderate magnitude and meaningful clinical and public health significance in neonatal growth assessment (Valerie,(102). To compensate for potential missing or incomplete records (10%), the calculated sample size was adjusted upward to a target of 316 preterm neonates. The minimum calculated sample size was therefore 316.

However, during data extraction and screening, a total of 343 eligible preterm neonate records met the study inclusion criteria, 160 from the volume-based feeding group (pre-CBF) and 183 from the cue-based feeding group (post-CBF). This actual sample size exceeded the minimum required estimate, thereby enhancing the statistical power and precision of the study's comparisons between the two feeding approaches.

3.8 Sampling Procedure

A two-stage sampling approach was used. First, total enumeration of all preterm neonatal records admitted during the two study periods was conducted using the Special Care Unit electronic neonatal database. These included records from the volume-driven feeding period, April 2017 to April 2019, and the cue-based feeding period, February 2020 to February 2022. A total of 635 medical records were initially identified and screened for eligibility.

After applying the inclusion and exclusion criteria, 481 records were eligible for inclusion in either the volume-driven feeding or cue-based feeding cohort. Since the number of eligible records exceeded the required sample size, stratified simple random sampling was then conducted separately within each feeding cohort. Random numbers were generated in Microsoft Excel and assigned to eligible records in each group. The final sample included 343 records, comprising 160 neonates managed with volume-driven feeding and 183 neonates managed with cue-based feeding. This approach ensured that each eligible record within the respective feeding cohort had an equal chance of selection.

3.9 Study Variables

Dependent variable

The primary outcome variable was weight for age Z-scores **(**WAZ) at day 21, a standardized measure of relative weight status used to compare growth outcomes between feeding regimens.

Independent variables

Key variables captured included:

- Infant identifiers and demographics: study ID, sex, plurality (singleton/multiple birth).
- Perinatal characteristics: gestational age (weeks and days) at birth, mode of delivery, referral status.
- Anthropometry: birth weight, admission weight with weights of interest at birth, day 14, and day 21.
- Feeding regime: cue-based or volume-based feeding as recorded in the clinical documentation.
- Comorbidities and therapies: hypoxic-ischaemic encephalopathy (HIE), respiratory support (bCPAP), phototherapy, antibiotic duration.
- Maternal characteristics: age, parity, chronic illnesses, education level, and antenatal corticosteroid administration.
- Admission physiology: admission temperature (°C) and random blood sugar (RBS).

3.10 Data Collection tool

A pretested semi-structured questionnaire was used to collect data from physical files consisting key variables pertinent to the study objectives. It included fields for recording neonatal gestational age, birth weight, admission weight, day 14 weight and weight at 21 days of life, dates of admission and discharge, and time to full oral feeds (including initiation of oral feeds and achievement of full oral feeds), maternal age, maternal education, maternal chronic illnesses, antenatal steroid use, therapies received like blood transfusion, CPAP, antibiotic use, phototherapy use.

3.11 Data collection and abstraction procedure

Data was collected from both the KH electronic neonatal database and the corresponding physical files. The electronic database was used as the primary source of information. However, in cases where specific data points were incomplete, missing, or unclear, the physical files were consulted to supplement the required information. This dual-source strategy ensured comprehensive and accurate data abstraction.

We reviewed 635 records of preterm neonates (28 to 34 weeks' gestation) admitted to the Kiwoko Hospital Special Care Unit from April 2017 to February 2022. Because feeding practices changed during the study period, a prespecified nine month washout interval (May 2019 to January 2020) was excluded to allow complete protocol transition and reduce exposure contamination. Records were screened using predefined eligibility criteria, excluding charts with missing anthropometry required for weight gain computation, incomplete admission or discharge documentation, and infants with major congenital anomalies or necrotizing enterocolitis, yielding 481 eligible records. Because the eligible pool exceeded the required sample size and full manual retrieval and verification of all eligible physical files was not feasible, we selected the final cohort using computer generated simple random sampling without replacement from the 481 eligible records, performed after eligibility screening and independent of feeding protocol and outcomes, to preserve representativeness while reducing chart review workload. This resulted in the exclusion of 138 otherwise eligible records and a final analytical sample of 343 neonates. This selection ensured that each participant had reliable serial measurements suitable for evaluating weight-for-age Z-score trajectories and feeding outcomes. A study flow chart (Figure 2) was developed to illustrate the screening and selection process, highlighting the initial record pool, excluded cases, and final analytic sample.

Data extraction was conducted using a standardized structured tool developed by the PI in Microsoft Excel specifically for this study. The tool was designed to promote consistency and completeness, and it is organized into two major sections: (A) Preterm Neonate Characteristics and Clinical Course, and (B) Maternal Characteristics.

The preterm neonate section captured variables extracted from the electronic neonatal database and corresponding physical files. These included unique study ID, date of birth, sex, mode of delivery, gestation type, admission blood sugar and temperature, weight indicators at birth, admission, day 14, day 21, and discharge, feeding timeline including dates and gestational ages at first and full oral feeds, length of hospital stay, feeding type (cue-based or volume-driven), type of feed (mother's milk, formula, or fortified expressed breast milk), and therapeutic interventions such as bCPAP, antibiotics, phototherapy, blood transfusion, and kangaroo mother care (KMC). During routine clinical care in the Special Care Unit, neonatal weights were measured using calibrated Seca weighing scales, with infants weighed fully undressed to improve accuracy and consistency. The study team did not directly measure participants' weights; recorded weights were abstracted for this study because they were required for calculating WAZ and weight velocity.

The maternal section included maternal education level, chronic illnesses (e.g, hypertension, diabetes), use of antenatal corticosteroids, and parity. Each field in the tool was structured with corresponding response formats, such as checkboxes and dropdowns, to minimize entry errors. Fields indicating the data source either database or physical file is included to maintain traceability. The Z-score at day 21 was used to determine weight gain and to compare the two feeding approaches, with a higher Z-score indicating a higher weight gain**.** The trajectory of mean weight-for-age Z-scores from birth, day 14, and day 21 was also assessed to monitor overall growth patterns. Weight-for-age Z-scores were derived using the Fenton 2025 third-generation preterm growth standards. For each infant, we entered gestational age at birth, weight at birth, day-14 weight, day-21 weight, and post-menstrual age (PMA) for each postnatal time point into a validated Fenton 2025 Z-score calculator (103). The feeding regimen (cue-based or volume-based) was also recorded. PMA was calculated as gestational age at birth plus postnatal age in weeks to align postnatal measurements with the appropriate reference percentiles. Outputs were exported to the master dataset as WAZ birth, WAZ_14, and WAZ_21.

The primary outcome was mean WAZ at day 21. Secondary outcomes included: (i) Change in WAZ from day 14 to day 21 (ΔWAZ_{14-21}) (ii) Weight velocity in grams per kilogram per day (g/kg/day), (iii) time to full oral feeds, and (iv) length of hospital stay (days).

Weight velocity (g/kg/day) as one of the secondary outcomes was calculated using the standard formula:

Weight velocity = (Discharge weight (g) − Admission weight (g)) ÷ [Length of stay (days) × (Admission weight (g)/1000)].

Study flow Chart

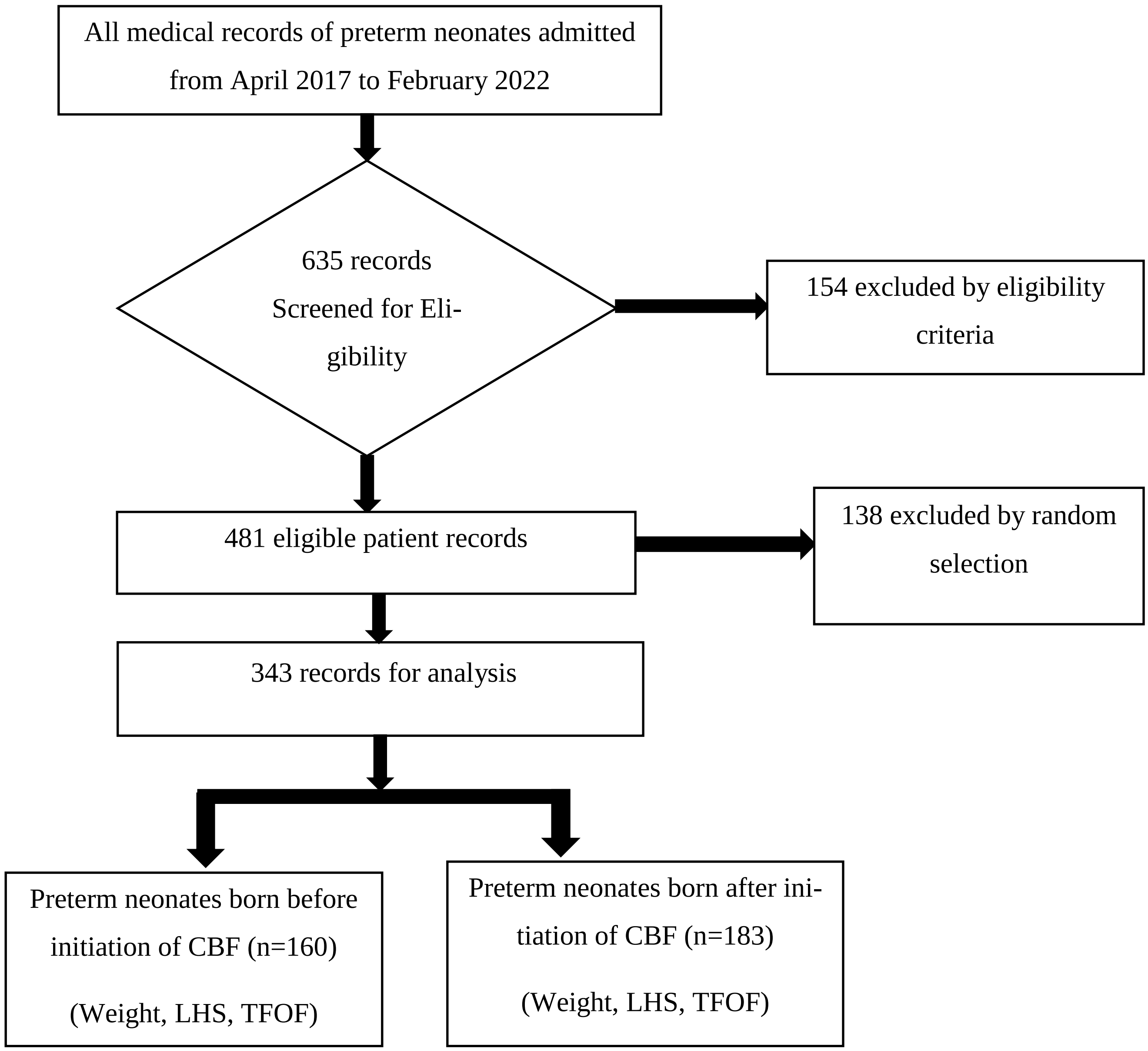


Figure 2: Showing the study flow chart

3.12 Data management

Data were extracted from medical records (files and electronic database) of preterm neonates. The data was entered electronically into excel and the PI performed data quality checks for accuracy and completeness. The data was then exported to Stata Version 19.0(StataCorp; College Station, TX, USA) for cleaning and analysis. To protect confidentiality, no direct identifiers (e.g., names, hospital numbers, addresses, telephone contacts) were recorded in the analysis dataset; instead, each record was assigned a unique study code, and any linkage document (if needed for verification) was stored separately with access restricted to the Principal Investigator (PI). Data abstraction was conducted within the Records Department in a designated secure area under staff supervision, and no patient files were removed from the department. Completed paper-based data collection tools were stored in a locked cabinet accessible only to the PI. Electronic study data were stored on password-protected devices with access limited to authorized study personnel, and an encrypted backup was maintained on a password-protected external drive kept in the custody of the PI, consistent with recommended technical and organizational measures for protecting sensitive health data. All results were presented in aggregate form, and no potentially identifying information was included in tables, figures, or text, in line with confidentiality reporting expectations. Study data was retained and securely destroyed in accordance with institutional and ethics committee requirements after completion of the study and dissemination of findings.

3.13 Data analysis

Analyses were conducted in Stata 19.0 (StataCorp LLC, College Station, TX, USA). Continuous variables are summarized as means with standard deviations or medians with interquartile ranges, as appropriate; categorical variables are summarized as counts and percentages. Bivariable comparisons between CBF and VBF were performed using independent t-tests for continuous variables and chi-squared tests for categorical variables.

We fit multivariable linear regression models for continuous outcomes, including WAZ at day 14, WAZ at day 21, Change in WAZ over time, weight velocity (g/kg/day), time to full feeds, and length of stay. Primary analysis compared mean WAZ scores at day 21 between infants that used cue-based feeding and those that used scheduled or volume-based feeding. All models adjusted for pre-specified covariates: infant sex; gestational age at birth; mode of delivery; plurality; maternal education; antenatal corticosteroids; duration of antibiotics; history of HIE; referral status; phototherapy; bCPAP use; maternal age (years); parity; birth weight (g); admission temperature (°C); and admission RBS. Model assumptions were assessed—linearity, normality of residuals, heteroskedasticity, multicollinearity, and influential outliers—and were not violated.

For longitudinal trajectories, mixed-effects linear models were specified to account for repeated measures within infants. Models included fixed effects for feeding group (CBF vs. VBF), time (birth, day 14, day 21), and their interaction, with random intercepts for infant and random slopes for time. An unstructured covariance matrix was used to model within-subject correlation. Estimates are presented as beta coefficients with 95% confidence intervals, and statistical significance was evaluated at $\alpha = 0.05$. Post-estimation contrasts (marginal means and average marginal effects) were derived using the margins framework to compare groups at each time point.

Planned subgroup and sensitivity analyses

To examine potential effect modification, analyses were stratified by birth-weight category and by gestational-age strata. Where relevant, trajectories and adjusted contrasts were compared within strata to contextualize findings across clinically meaningful subgroups.

3.14 Quality control

Data quality assurance was rigorously maintained throughout the study. Three research assistants, all trained in Good Clinical Practice (GCP), confidentiality, and the use of the data abstraction tool, conducted data extraction from eligible records. Identifiable information such as names, hospital numbers, and addresses was excluded to preserve participant anonymity. Access to physical and electronic records was restricted to authorized study personnel only, with the Records Department maintaining a log of all accessed files for accountability.

Prior to commencement of full data collection, the data abstraction tool underwent a pre-test using ten files (five from the cue-based feeding period and five from the volume-based feeding period) to assess clarity, completeness, and consistency. The pre-test results were used to refine the tool, and data from this phase were excluded from the final analysis. The Principal Investigator (PI) developed Standard Operating Procedures (SOPs) to guide the data collection process and conducted a one-day training session for the research assistants on standardized data abstraction procedures, use of the tool, and ethical data handling. Continuous supervision was provided by the PI during the data collection phase to ensure adherence to study protocols.

To enhance reliability and validity of the data, the PI independently verified a random sample (10–20%) of the collected data for completeness and accuracy. Any discrepancies or inconsistencies identified were corrected in consultation with the research assistants, and feedback was provided to improve subsequent abstraction. The analytic dataset was subjected to iterative cleaning involving automated range and logic checks. Records with implausible or inconsistent dates, weights, or corrected gestational ages (CGA) were flagged and cross-checked against source documents. Extreme or biologically implausible Z-scores were re-evaluated by verifying corresponding raw weight and CGA entries.

The final anonymized dataset was stored in a secure, password-protected electronic file. Access was limited to the PI in accordance with institutional data protection and ethical guidelines. These comprehensive quality control measures ensured the accuracy, integrity, and confidentiality of the study data, consistent with best practices for retrospective cohort research.

3.15 Ethical considerations

The study received ethical approval from Makerere University School of Medicine Research and Ethics Committee (SOMREC) and the Department of Pediatrics and Child Health at Makerere University, and administrative clearance was obtained from Kiwoko Hospital before any records were accessed. Because this investigation was a retrospective review of existing medical records with no direct participant contact and minimal risk to participants, a waiver of individual informed consent was granted by the ethics committee, consistent with accepted ethics and data-governance approaches for secondary use of anonymized clinical data. All study procedures were conducted strictly within the scope of the approvals obtained. Participant confidentiality and privacy were safeguarded through de-identification, restricted access to records and datasets, secure storage, and anonymized reporting as described in the Data management section, and findings are reported only in aggregate form such that no individual neonate can be identified from the dissertation or any resulting publications.

3.16 Dissemination of results

The findings from this study were consolidated into a dissertation to meet the requirement for the award of Master of Medicine in Pediatrics and Child Health. A copy will be submitted to the Albert Cook Library, Department of Pediatrics and Child Health, Directorate of Research and Graduate Training, and to KH. Furthermore, the findings will be disseminated through presentations at scientific gatherings such as conferences, workshops, and seminars, and will also be published in peer-reviewed journals.

CHAPTER FOUR: RESULTS

4.1 Baseline maternal and neonatal characteristics of preterm neonates by feeding group

A total of 343 preterm neonates were analyzed, with 160 (46.6%) in the volume-driven feeding group and 183 (53.4%) in the cue-based feeding group. The sex distribution was similar between the two groups, with 48.1% males in the volume-driven feeding group compared to 52.5% in the cue-based feeding group ($p=0.423$). The groups were also comparable in mode of delivery, gestation type, timing of feed initiation, maternal age, chronic maternal illness, referral status, kangaroo mother care, phototherapy, bCPAP use, admission temperature, and admission random blood sugar ($p>0.05$).

However, there were significant baseline differences in selected maternal and neonatal characteristics. The cue-based feeding group had a higher mean birth weight compared to the volume-driven feeding group (1355.1 ± 256.4 g versus 1269.4 ± 213.8 g, $p<0.001$). Similarly, the mean gestational age was higher in the cue-based feeding group than in the volume-driven feeding group (31.05 ± 1.83 weeks versus 30.34 ± 1.71 weeks, $p<0.001$). Maternal education was also higher in the cue-based feeding group, with 58.5% having attained secondary education or above compared to 35.0% in the volume-driven feeding group ($p<0.001$). Antenatal steroid use was more common in the cue-based feeding group (94.0% versus 82.5%, $p<0.001$), while antibiotic use for more than seven days was more common in the volume-driven feeding group (33.8% versus 7.1%, $p<0.001$). Most infants in both groups received mothers' own expressed breast milk (Table 3).

Table 3: Comparison of Baseline Maternal and Neonatal Characteristics of preterm neonates by feeding group

Variable	**Volume-Driven Feeding N (%) 160(46.6)**	**Cue-Based Feeding N (%) 183(53.4)**	**P-value**
Sex			
Male	77 (48.1)	96 (52.5)	0.423
Female	83 (51.9)	87 (47.5)	
Birth Weight (g)			
ELBW 750-999	14 (8.8)	11 (6.0)	**0.007**
VLBW 1000-1499	120 (75.0)	116 (63.4)	
LBW 1500-2170	26 (16.2)	56 (30.6)	
Gestation Age			
28-31 weeks	113 (70.6)	102 (55.7)	**0.004**
32-34 weeks	47 (29.4)	81 (44.3)	
Mode of Delivery			
Cesarean Section	22 (13.8)	32 (17.5)	0.343
Spontaneous Vaginal Delivery	138 (86.2)	151 (82.5)	
Gestation Type			
Singleton	99 (61.9)	110 (60.1)	0.738
Multiple	61 (38.1)	73 (39.9)	
Type of Feed			
Mothers' own milk(EBM)	153 (95.6)	176 (96.2)	**0.005**
Fortified EBM	0 (0.0)	6 (3.3)	
Formula	7 (4.4)	1 (0.5)	
Timing of Feed Initiation (hours)			
24	13 (8.1)	11 (6.0)	0.718
48	141 (88.1)	166 (90.7)	
72	6 (3.8)	6 (3.3)	
Maternal Age (mean ± SD)	25.1(6.3)	25.4 (6.3)	0.643
Maternal Education			
None	28 (17.5)	13 (7.1)	**<0.001**
Primary	76 (47.5)	63 (34.4)	
Secondary+	56 (35.0)	107 (58.5)	
Antenatal Steroids			
No	28 (17.5)	11 (6.0)	**<0.001**
Yes	132 (82.5)	172 (94.0)	
Chronic Illness			
Diabetes Mellitus	0 (0.0)	1 (0.5)	0.381
HIV	16 (10.0)	11 (6.0)	
Hypertension	6 (3.8)	5 (2.7)	
None	138 (86.2)	166 (90.7)	
Antibiotic Duration			
≤7 days	106 (66.2)	170 (92.9)	**<0.001**

>7 days	54 (33.8)	13 (7.1)	
HIE diagnosis			
No	134 (83.8)	146 (80.2)	0.398
Yes	26 (16.2)	36 (19.8)	
Referral status			
In-Born	124 (77.5)	155 (84.7)	0.088
Referral	36 (22.5)	28 (15.3)	
Kangaroo Mother Care Done			
No	2 (1.2)	2 (1.1)	0.892
Yes	158 (98.8)	181 (98.9)	
Phototherapy			
No	20 (12.5%)	29 (15.8)	0.377
Yes	140 (87.5%)	154 (84.2)	
bCPAP Used			
No bCPAP	60 (37.5)	72 (39.3)	0.726
bCPAP	100 (62.5)	111 (60.7)	
Admission Temp (°C) (mean ± SD)	35.3 (1.1)	35.3 (1.2)	0.569
Admission RBS (mean ± SD)	4.4 (2.32)	4.2 (1.73)	0.356
GA first feeds weeks (mean ± SD)	31.4 (1.7)	32.7 (1.7)	<**0.001**
GA full feeds weeks (mean ± SD)	33.0 (1.8)	34.3 (1.6)	<**0.001**

4.2 Bivariable Analysis of the effect of cue-based feeding on study outcomes

Infants on cue-based feeding showed better weight outcomes than those on volume-based feeding. By day 14, there was no significant difference in mean WAZ between the two groups (-1.42 vs. -1.51; CI -0.13 to 0.31, p = 0.415). However, by day 21, infants on cue-based feeding had significantly higher mean WAZ (-0.78 vs. -1.02; CI 0.01 to 0.46, p = 0.037). The change in WAZ from day 14 to day 21 was also greater in the cue-based group (0.64 vs. 0.49; CI 0.04 to 0.25, p = 0.006). The mean length of hospital stay was significantly reduced in the cue-based group compared to the volume-based group (35.87 days vs. 39.89 days, p = 0.011). Cue-based feeding resulted in a significantly higher mean weight velocity compared to volume-based feeding, p = 0.001). There was no statistically significant difference in the mean time to full feeds between preterm infants on cue-based feeding and those on volume-based feeding (p=0.777). (Table 4)

Table 4: Bivariable Linear Regression showing crude mean differences in WAZ, WAZ change, weight velocity, time to full feeds and length of hospital stay by feeding group

Outcome variable	**Feeding group**	**Mean**	**Crude mean difference (95% CI)**	**P-value**
WAZ day 14	VBF	-1.51	1	
	Cue	-1.42	0.09 (-0.13 to 0.31)	0.415
WAZ day 21	VBF	-1.02	1	
	Cue	-0.78	0.24 (0.01 to 0.46)	**0.037**
WAZ change	VBF	0.49	1	
(waz_d21 - waz_d14)	Cue	0.64	0.15 (0.04 to 0.25)	**0.006**
Length of hospital stay,	VBF	39.89	1	
days	Cue	35.87	-4.02 (-7.11 to -0.93)	**0.011**
Weight velocity,	VBF	6.35	1	
g/kg/day	Cue	7.99	1.64 (0.70 to 2.59)	**0.001**
Time to full feeds, days	VBF	11.43	1	
	Cue	11.15	-0.28 (-2.20 to 1.65)	0.777

4.3 Adjusted effect of cue-based feeding on day 21 WAZ stratified by birth weight and gestational age

Stratified analysis demonstrated variation in the effect of cue-based feeding across subgroups. Among infants of higher gestational age (32–34 weeks), cue-based feeding was associated with significantly higher WAZ at day 21 ($\beta = 0.28$; CI 0.003 to 0.56, $p = 0.047$), whereas the effect was smaller and non-significant among lower gestational-age infants ($\beta = 0.04$; CI -0.25 to 0.32, $p = 0.808$). Similarly, when stratified by birth weight, the effect was higher among low birth weight (LBW; 1500–2170 g) infants ($\beta = 0.28$; CI -0.09 to 0.66, $p = 0.136$) compared to very low birth weight (VLBW; 750–1499 g) infants ($\beta = 0.20$; CI -0.05 to 0.45, $p = 0.108$), although the differences were not statistically significant (Table 5). The forest plots (Figures 3 and 4) visually depict these subgroup differences, with the horizontal bars representing 95 % confidence intervals around each adjusted mean difference.

Table 5: Adjusted effect of cue-based feeding on day 21 WAZ stratified by birth weight and gestational age

Outcome Variable	**Subgroup**	**Adjusted Mean Difference (95% CI)**	**P-value**
WAZ Day 21	**LBW** (1500-2170 g)	0.28 (-0.09 to 0.66)	0.136
	VLBW (750-1499 g)	0.20 (-0.05 to 0.45)	0.108
	Low Gestational Age (28-31 weeks)	0.04 (-0.25 to 0.32)	0.808
	High Gestational Age (32-34 weeks)	0.28 (0.003 to 0.56)	0.047

Adjusted for: Sex, Gestational age, Mode of delivery, Multiple births, Maternal education, Antenatal steroids, Antibiotic duration, History of HIE, Referral status, Phototherapy, BCPAP used, Maternal age (years), Parity, Birth weight (g), Admission temperature (°C), Admission RBS.

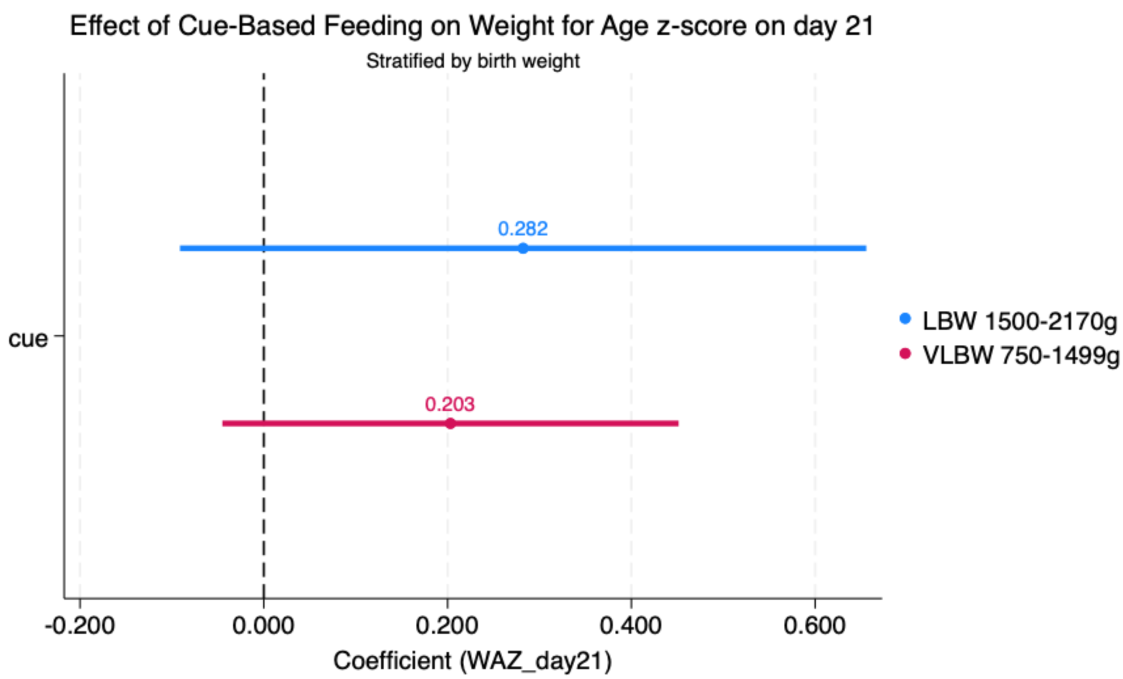


Figure 3: Effect of cue-based feeding on day 21 WAZ stratified by birth weight category

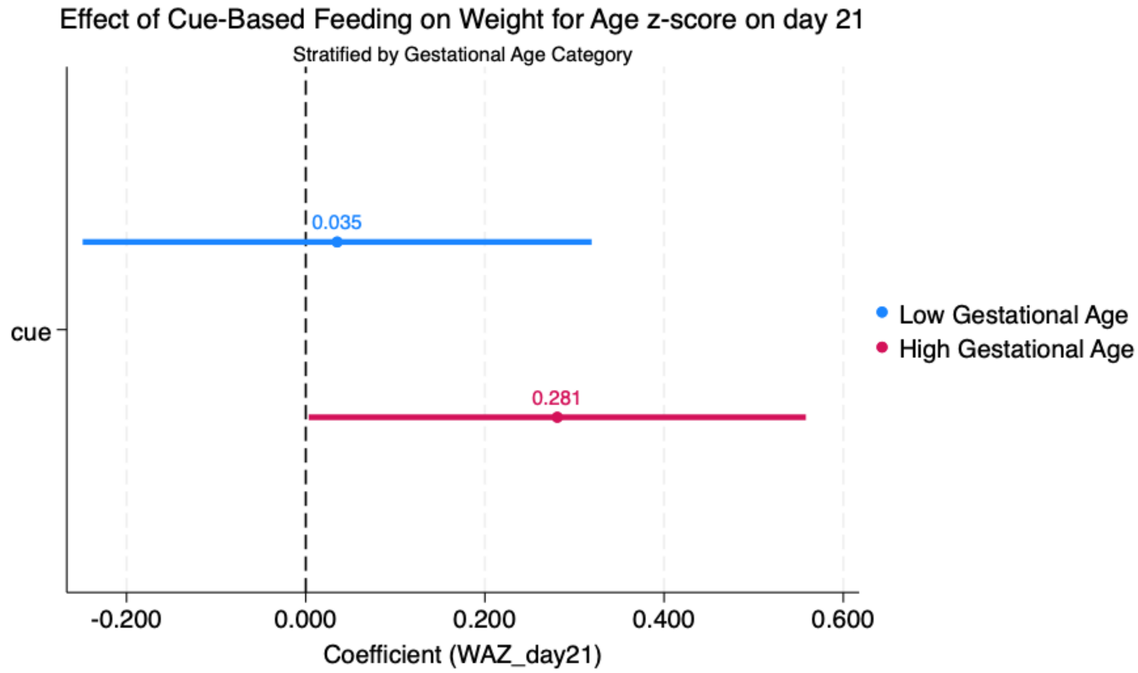


Figure 4: Effect of cue-based feeding on day 21 WAZ stratified by gestational age category

4.4 Adjusted effect of cue-based feeding on weight velocity stratified by birth weight and gestational age

Stratified analysis of weight velocity showed that cue-based feeding was associated with higher daily weight gain across all subgroups, with the greatest effects observed among very low birth weight (2.02 g/kg/day; CI 1.14 to 2.91, $p < 0.001$) and lower gestational-age infants (1.61 g/kg/day; CI 0.80 to 2.41, $p < 0.001$). A significant benefit was also seen in the higher gestational-age group (2.14 g/kg/day; CI 0.72 to 3.57, $p = 0.003$), whereas the effect among low birth weight infants was smaller and not statistically significant (1.64 g/kg/day; $p = 0.078$) (Table 6). The box plots and Heat plot (Figures 5 and 6) visually depict these differences.

Table 6: Adjusted effect of cue-based feeding on weight velocity stratified by birth weight and gestational age

Outcome Variable	Subgroup	Adjusted Mean Difference (95% CI)	P-value
Weight Velocity (g/kg/day)	**LBW** (1500–2170 g)	1.64 (–0.19 to 3.48)	0.078
	VLBW (750–1499 g)	2.02 (1.14 to 2.91)	<0.001
	Low Gestational Age (28–31 weeks)	1.61 (0.80 to 2.41)	<0.001
	High Gestational Age (32–34 weeks)	2.14 (0.72 to 3.57)	0.003

**Adjusted for: Sex, Gestational age, Mode of delivery, Multiple births, Maternal education, Antenatal steroids, Antibiotic duration, History of HIE, Referral status, Phototherapy, BCPAP used, Maternal age (years), Parity, Birth weight (g), Admission temperature (°C), Admission RBS.*

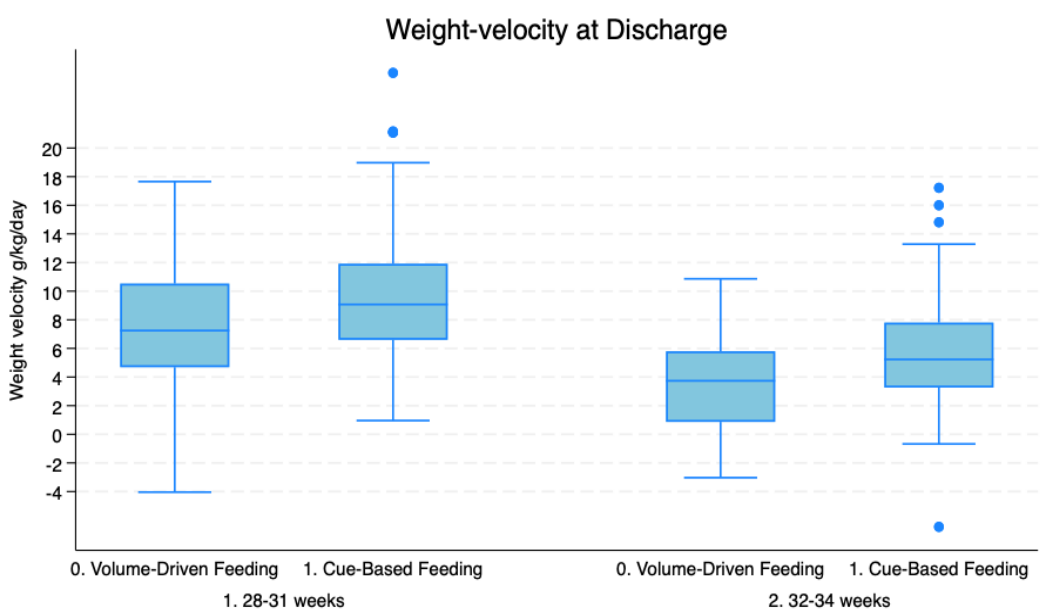


Figure 5: Box plot showing distribution of weight velocity by feeding group across gestational age categories

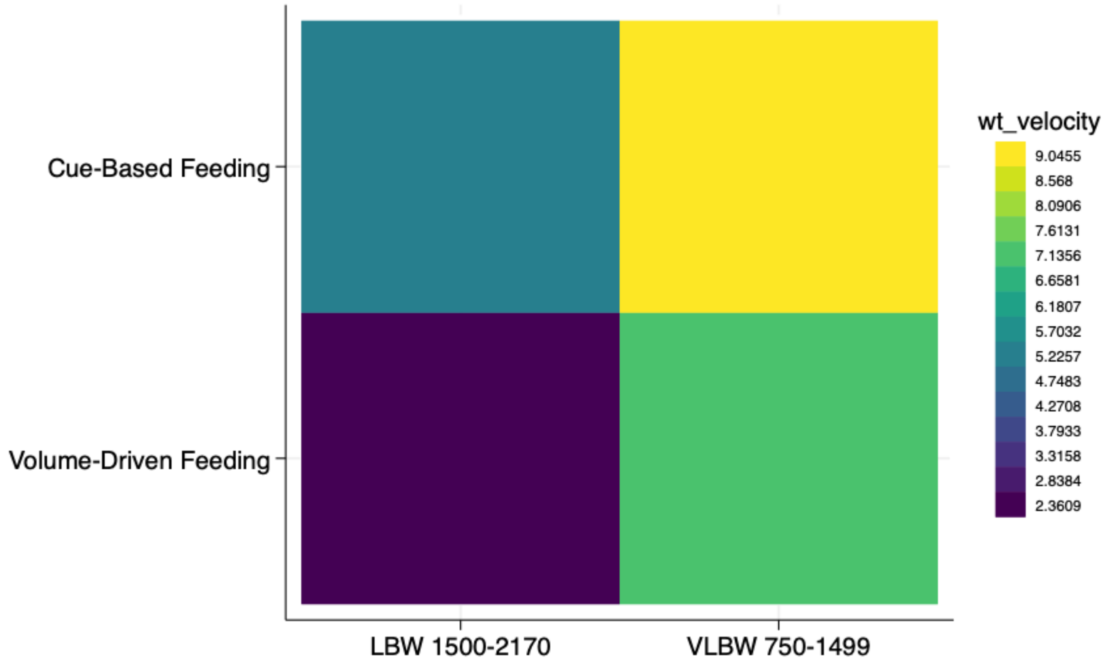


Figure 6: Heat plot showing weight velocity by feeding group across birth weight categories

4.5 Multivariable Analysis of the effect of cue-based feeding on study outcomes

After adjusting for potential confounders, infants on cue-based feeding showed a significantly higher weight-for-age z-score (WAZ) at day 21 compared to those on volume-based feeding (adjusted mean difference = 0.22, 95% CI: 0.07-0.38, $p = 0.005$). They also had a significantly higher weight velocity (adjusted mean difference = 2.06 g/kg/day, 95% CI: 1.35-2.76, $p < 0.001$). However, there were no significant differences between the two feeding approaches in WAZ at day 14, change in WAZ from day 14 to 21, time to full feeds, or length of hospital stay (all $p > 0.05$). (Table 7).

Table 7: Multivariable Linear Regression showing adjusted mean differences in WAZ, WAZ change, weight gain velocity, Time to full feeds and length of hospital stay for cue based versus volume driven feeding.

Outcome variable	Feeding group	Adjusted Mean Difference	P-value
WAZ day14			
	VBF	1	
	Cue	0.13(-0.04 to 0.30)	0.126
WAZ day21			
	VBF	1	
	Cue	0.22(0.07 to 0.38)	**0.005**
WAZ change (waz_d21 - waz_d14)			
	VBF	1	
	Cue	0.09(-0.02 to 0.21)	0.116
Weight velocity (g/kg/day)			
	VBF	1	
	Cue	2.06(1.35 to 2.76)	**<0.001**
Time to full feeds			
	VBF	1	
	Cue	1.11(-1.02 to 3.24)	0.304
Length of Hospital Stay			
	VBF	1	
	Cue	2.17(-0.25 to 4.60)	0.079

**Adjusted for: Sex, Gestational age, mode of delivery, multiple births, maternal education, Antenatal Steroids, Antibiotic duration, History of HIE, Referral status, Phototherapy, BCPAP used, Maternal Age, Parity, Birth Weight in grams, Admission Temp, Admission RBS.*

4.6 Adjusted marginal mean WAZ across time points by feeding group

Simple effects analysis showed that the cue-based feeding group had significantly higher weight velocity z-scores compared to the volume based feeding group on day 14 ($\beta = 0.19$, 95% CI [0.06, 0.32], $p = 0.003$) and day 21 ($\beta = 0.34$, 95% CI [0.17, 0.51], $p < 0.001$), but not on day 1 ($\beta = -0.04$, 95% CI [-0.11, 0.04], $p = 0.309$). These findings are consistent with the pattern illustrated in Figure 7, which presents the adjusted marginal predictions of weight-for-age z-scores (WAZ) over time from the linear mixed-effects model. At baseline (day 1), both feeding groups had comparable adjusted WAZ values. A modest separation emerged by day 14, corresponding to the statistically significant advantage observed in weight-velocity z-scores. By day 21, infants managed with cue-based feeding exhibited a markedly higher adjusted WAZ compared with those receiving volume-driven feeding.

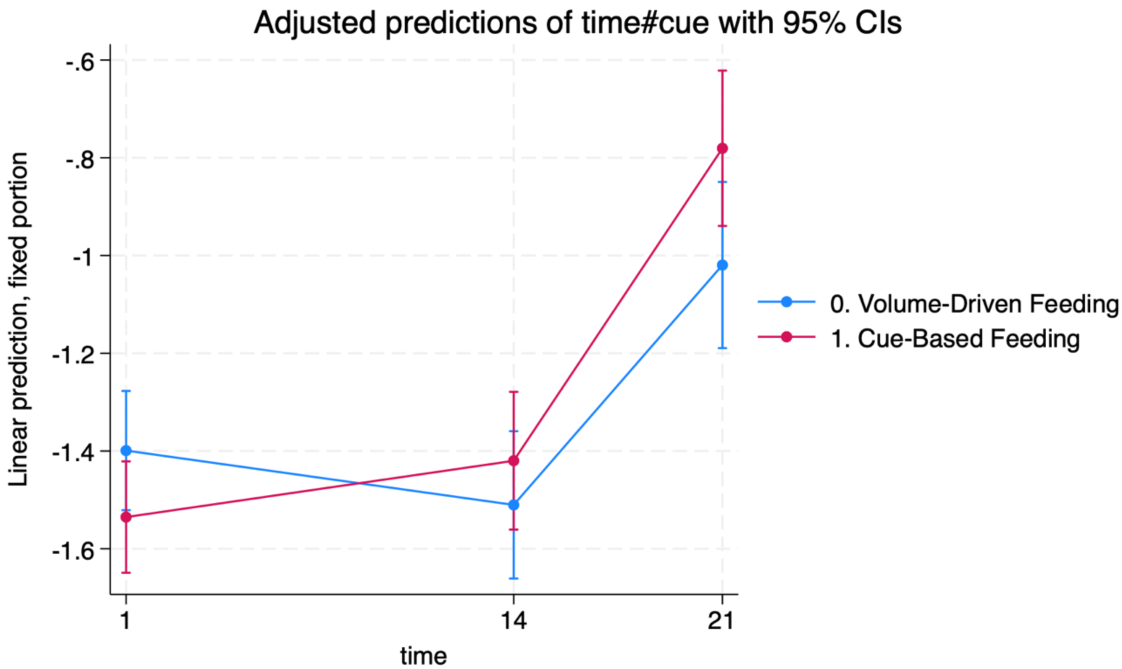


Figure 7: Adjusted marginal mean WAZ across time points by feeding group

CHAPTER FIVE: DISCUSSION

5.0 Overview

This study compared cue-based feeding with volume-driven feeding among preterm neonates born at 28-34 weeks of gestation at Kiwoko Hospital. Cue-based feeding was associated with higher WAZ at day 21 and higher weight velocity after adjustment for relevant maternal and neonatal factors. However, there were no significant adjusted differences in length of hospital stay, time to full feeds, or change in WAZ from day 14 to day 21. The discussion presents these findings in relation to existing literature and the local neonatal care context.

5.1 Comparison of weight measured as WAZ on day 21 before and after introduction of cue-based feeding.

In this study, preterm infants managed with cue-based feeding had a significantly higher weight-for-age z-score (WAZ) at day 21 compared to those managed by volume-driven feeding, even after adjusting for potential confounders. This implies that cue-based feeding independently contributes to a meaningful improvement in short-term growth by three weeks of age. A plausible mechanism is that cue-based feeding promotes better coordination of sucking-swallowing-breathing, reduces feeding stress, and encourages feeding when the infant is physiologically ready, leading to more efficient and effective oral intake and therefore improved accrual of weight over days to weeks (16). Additionally, implementation features may have also contributed to the observed effect as the cue-based feeding at Kiwoko hospital included structured staff training, a feeding committee, caregiver education and systematic feeding assessment (OFRS), which may have improved feeding quality and caregiver engagement and hence nutritional intake.

Several studies have also reported improved short-term weight outcomes with cue-based feeding, largely when implemented alongside structured nurse training and close intake monitoring. In an Iranian cohort, cue-based feeding enhanced early weight gain and feeding milestones (104), while Pucket B et al, 2008, similarly demonstrated that cue-based feeding was feasible and achieved comparable or better weight gain with fewer adverse events through improved cue recognition and meticulous intake tracking (105). Other reports corroborate these findings, showing faster or greater weight gain compared with scheduled feeding (20, 87, 106). These positive findings are however, linked to high implementation fidelity and integration of cue-based protocols with nutritional safeguards that ensure adequate energy delivery while supporting developmental readiness.

Conversely, higher-level syntheses show more variable results. The Cochrane review by Watson and McGuire (107) found that while cue-based feeding hastened transition to oral feeding in some trials, pooled analyses suggested slightly slower in-hospital weight gain in others, mainly due to small sample sizes, methodological heterogeneity, and differences in how "full feeds" were defined. The CUBS mixed-methods feasibility study McFadden, Fitzpatrick (108) similarly reported inconsistent weight outcomes across sites and attributed this to variation in staff training, case-mix, and local feeding policies such as use of fortifiers or fixed-volume schedules. The 2022 American Academy of Paediatrics (AAP) evidence summary and the WHO guidance likewise noted that responsive feeding may lower in-hospital weight velocity in units managing more immature or very-low-birth-weight infants, where physiological cue expression is limited (109). Differences in population maturity, feeding composition (breastmilk versus formula), and how rigorously cues are interpreted may explain the observed heterogeneity as compared to the present study.

In a recent retrospective cohort from a high-resource setting by Ofek Shlomai et al, 2024, a decline in weight-for-age z-scores was observed from admission to discharge among preterm infants managed with cue-based feeding, particularly among those with higher birth weights, suggesting that prioritizing cue responsiveness without adequate caloric oversight may transiently slow growth (81). By contrast, the present study found overall higher WAZ by Day 21 among preterm infants 28–34 weeks' gestation on cue-based feeding, with the greatest gains in those of higher gestation age. These more mature infants were developmentally better equipped for oral feeding, displayed clearer feeding cues, and responded more efficiently to responsive feeding routines(13, 100). The contrast with the Shlomai study likely reflects contextual and methodological differences in timing of measurement (fixed early time-points versus discharge), population maturity, and degree of nutritional oversight, underscoring that cue-based feeding yields optimal growth when balanced with structured intake monitoring and timely escalation for suboptimal feeding

Overall, the present study and previous studies showing improved weight gain typically ensured close intake monitoring, staff competency, and escalation protocols for inadequate feeds, whereas those reporting no change or reduced gains often lacked such safeguards or included more immature infants.

The findings of this study therefore imply that cue-based feeding appears beneficial when implemented within a structured system that preserves nutritional adequacy while promoting behavioral readiness, but its impact varies with design, population, and fidelity of practice.

5.2 Comparison the length of hospital stay before and after introduction of cue-based feeding

In this study, preterm infants on cue-based feeding had a shorter mean hospital stay than those on volume-driven feeding, although the difference lost statistical significance after adjustment. This suggests that while cue-based feeding may facilitate earlier discharge, much of the crude difference reflects baseline advantages in gestational age and birth weight rather than feeding strategy alone. The cue-based group had slightly higher gestational age and birth weight, which naturally predispose to faster physiological stabilization and earlier discharge. In addition, many infants in both groups were likely subject to similar discharge criteria focused on clinical stability rather than feeding readiness, limiting the visible effect of cue-based feeding on length of stay (LOS).

Similarly, several quality improvement (QI) and observational studies show reduced LOS after cue-based feeding implementation. A study by Spagnoli, Dhanireddy (20) reported significantly shorter hospitalization among infants on cue-based feeding, attributing this to fewer feeding-related stress events and earlier feeding competence. Other studies likewise found shorter LOS associated with cue-based programs that emphasized dedicated staff training and parental engagement (105, 110).

However, the CUBS feasibility study and the Cochrane review found inconsistent LOS benefits across sites (107, 108). The differences may be explained by discharge criteria, staff adherence, and patient case-mix. In settings where discharge depends on medical stability rather than feeding readiness, the impact of cue-based feeding on LOS may be minimal. Similarly, very-low-birth-weight infants who require extended respiratory or nutritional support may not experience shorter stays despite improved feeding coordination. The findings of this study therefore suggests that cue-based feeding can modestly shorten hospital stay when implemented in mature preterm populations with consistent discharge practices and strong nursing support, but results may vary depending on baseline characteristics, discharge protocols, and unit culture.

5.3 Comparison of Weight velocity and change in WAZ on day 14 and 21 before and after cue-based feeding

Cue-based feeding was associated with significantly higher weight velocity (+2.06 g/kg/day) compared to volume-driven feeding, though the adjusted change in WAZ between day 14 and 21 was not statistically significant. This indicates that while infants on cue-based feeding accrued daily weight faster, their short-term z-score change remained trivial, possibly due to initial differences in birth weight and gestational maturity. However, the positive effect may be attributed to reduced feeding stress, more efficient milk transfer, and feeding when infants are physiologically ready, enhancing metabolic efficiency and nutrient retention (16)

These findings align with multiple studies showing improved short-term growth under cue-based protocols. A retrospective review reported that most units adopting cue-based feeding observed faster weight velocity and earlier transition to full oral feeds (81). Similarly, a prospective study found improved growth efficiency and reduced feeding-related instability following cue-based interventions (105).

In contrast, the Cochrane review and the AAP evidence summary by the World Health Organization noted that some trials reported slower in-hospital weight gain with responsive feeding, likely due to reduced enforced volumes or suboptimal cue interpretation in very preterm infants (107, 109). The CUBS feasibility study also documented site-level variability linked to implementation fidelity and nutritional oversight (108).The differences with the current study may be attributed to differences in monitoring of intake and fortification, inconsistent feeding supervision, or enrollment of less mature neonates. Therefore, cue-based feeding has shown potential to improve early growth in preterm infants, though evidence from resource-limited settings remains scarce and outcomes depend on infant maturity, staff training, and consistent nutritional monitoring.

5.4 Comparison of time to full oral feeds before and after cue-based feeding

In this study, there was no significant difference in the time taken to reach full feeds between preterm infants managed with cue-based feeding and those under volume-driven feeding. This indicates that, although cue-based feeding improved weight velocity and WAZ, it did not accelerate the attainment of full enteral or oral feeding. The similarity suggests that both groups achieved feeding milestones at comparable rates, possibly due to uniform clinical protocols defining “full feeds” or limited variation in feeding readiness criteria among staff.

Similarly, the Cochrane review reported that while some randomized trials showed faster transition to oral feeds, pooled results revealed no consistent overall advantage for cue-based feeding (107). Similarly, in the CUBS mixed-methods feasibility study, there was wide variability in time-to-full-feeds across hospitals implementing cue-based feeding, concluding that differences in how “full feeds” were defined (volume vs. frequency or oral intake) and staff adherence to cue recognition largely explained the inconsistencies (108).

Conversely, Quality improvement (QI) projects and single-center trials have demonstrated earlier feeding milestones with cue-based approaches. For instance, Spagnoli, Dhanireddy (20) reported reduced time to full oral feeding and fewer adverse feeding events after introducing cue-based protocols in a tertiary NICU, linking success to improved staff competency and individualized readiness assessment. Similarly, Kamran, Khatoonabadi (110) observed earlier achievement of oral feeding in Iranian preterm infants following structured cue-based training for nurses and parents. These differences highlight the importance of implementation fidelity, when staff are adequately trained to interpret and respond to cues, feeding progression tends to improve. Therefore, without consistent cue assessment, benefits may be attenuated. The variation across studies can also be attributed to differences in gestational age and feeding composition. Trials enrolling more mature preterm infants, who have better-developed sucking and swallowing coordination, often report faster feeding milestones, while those dominated by very-low-birth-weight or extremely preterm infants tend to show minimal or no difference because these infants are less capable of expressing reliable feeding cues. In the current study, the inclusion of infants from 28-34 weeks’ gestation may have minimized contrast between groups, as both were physiologically ready for progressive feeding by the same postnatal window.

5.5 Study Strengths and Limitations

The study utilized a large, high-quality neonatal database with clearly defined feeding cohorts separated by a washout period, reducing contamination. Use of standardized tools, consistent weight measurements, and adjustment for confounders strengthened the validity of findings. Rigorous data verification and pretested extraction tools enhanced reliability and accuracy. However, being retrospective, the study depended on existing records, which may have missing or incomplete data. Gestational age was mainly estimated using the last normal menstrual period (LNMP), modified Ballard score, or first-trimester ultrasound where available. However, LNMP is less accurate than first-trimester ultrasound and may have introduced gestational age misclassification. In addition, foot length, which can be used as an additional tool for assessing gestational age in very small preterm infants, particularly those weighing less than 1000 g, was not routinely documented in the records and could therefore not be used. This may have affected gestational age classification, especially because preterm infants born at 28 to 34 weeks may present variably. Unmeasured factors such as illness severity, electrolyte disturbances, staff experience, and parental involvement could also have influenced outcomes, limiting the ability to fully attribute differences to the feeding approach alone. Furthermore, conducted at a single hospital, results may not be fully generalizable, especially to very preterm neonates in other settings.

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

This study demonstrates that cue-based feeding offers a meaningful advantage over traditional volume-driven feeding in promoting early growth among preterm infants. Infants managed with cue-based feeding achieved higher weight-for-age z-scores by day 21 and faster weight velocity at discharge, highlighting its effectiveness in supporting physiologic and developmentally appropriate nutrition. While its impact on hospital stay and time to full oral feeds was not statistically significant, the overall trend suggests that cue-based feeding fosters better feeding efficiency and readiness. These findings suggest that cue-based feeding may improve short-term weight-related growth outcomes among preterm neonates in this setting.

6.2 Recommendations

1. The Ministry of Health should consider a phased review of existing neonatal feeding guidelines to evaluate the feasibility of incorporating cue-based feeding principles. Adoption should be informed by additional evidence from multi-Centre studies within resource-limited settings to ensure contextual applicability and safety before widespread implementation as a standard of care for preterm neonates.
2. The Ministry of Health and Kiwoko hospital administration should develop quality improvement (QI) initiatives in neonatal units to evaluate and refine cue-based implementation fidelity, feeding safety, and outcomes.
3. Future research should undertake randomized controlled trials with larger and more diverse preterm populations, including extremely low-birth-weight infants, to validate generalizability.
4. Future studies should prospectively assess length, head circumference, and feeding-related adverse events in addition to weight to provide a more comprehensive evaluation of cue-based feeding effects on overall growth and safety.
5. Kiwoko Hospital should embed a minimal feasible feeding and growth monitoring package in routine documentation

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APPENDICES

APPENDIX I: DATA COLLECTION TOOL

Participant Information:

1. Participant ID: __________

2. Date of Birth: __________

3. Gestation age: ____________

A PRETERM NEONATE CHARACTERISTICS

3. Sex:

☐ Male

☐ Female

4 Mode of delivery

☐ Vaginal birth

☐ cesarean section

5 Gestation type

☐ Singleton

☐ multiple

6 Admission RBS

☐ less than 2.6 mmol/l

☐ more than 2.6 mmol/l

7 Admission axillary temperature

☐ less than 36.5℃

☐ more than 36.5℃

Section 1: Weight Gain

1. Birth Weight (grams): ___________

2. Weight at admission (grams): ___________

3. Weight at discharge (grams): ___________

4. Weight on day 14_________________________

4. Weight on day 21_________________________

Section 2: Feeding Details

1. Date of first oral feed: ___________

2. Date of full oral feeds: ___________

3. Gestation age at first oral feed: ______________

4. Gestation age at full oral feeds: ______________

5. Timing of feeding

☐ 24 hours

☐ 48 hours

☐ 72 hours

☐ more than 72 hours(write value)

Section 3: Hospital Stay

1. Date of admission: ___________

2. Date of discharge: ___________

Section 4: Feeding practice

1. Feeding regime

☐ Cue-based feeding

☐ Volume/scheduled based-driven feeding

2. Type of feed

☐ Mother's own milk

☐ formula

☐ fortified EBM

Section 5: Therapeutic Interventions

1. Respiratory support

☐ bCPAP

☐ No bCPAP

☐ duration of bCPAP use

2. Blood transfusion

☐ yes

☐ No

3. Antibiotic use

☐ Yes

☐ No

4.Duration of antibiotic use

☐ <3 days ☐ 3-7days ☐ 7days

5Phototherapy use

☐ Yes

☐ No

6. KMC done

☐ Yes

☐ No

B MATERNAL CHARACTERISTICS

1 Maternal education

Completed level of education

☐ Primary

☐ Secondary

☐ Post-secondary

☐ Tertiary

☐ None

2Maternal chronic illness

☐ hypertension

☐ Diabetes Mellitus

☐ other______________________

3Maternal antenatal steroid use

☐ yes

☐ No

4 Parity_________

APPENDIX II: CUE BASED FEEDING PROTOCOL

ASSESSMENT FOR SAFE FEEDING

This scale will be used to help you decide if a baby is physiologically stable and showing adequate hunger signs for safe breastfeeding or cup feeding. Before each feeding, decide which category best describes the baby's current state and record the score on the flowsheet under the column labeled "feeding assessment score".

1 Beginning to wake up, or awake before caregiver interaction
Rooting and/or bringing hands to mouth, sucking on fingers
Good muscle tone, respirations are normal with activity

2 Begins to wake up, or is awake with caregiver interaction
Shows some rooting behavior
Adequate muscle tone, respirations are normal with activity

3 Briefly awake with caregiver interaction, but falls asleep again
No hunger behaviors
No increase in muscle tone

4 Sleeps throughout caregiver interaction
Shows no hunger signals
No change in muscle tone

5 May be asleep or awake and showing cues, but vital signs are unstable - signs of physiological instability are:

- Decrease in oxygen saturations
- Apnea and/or bradycardia with care
- Respirations increase above normal range with caregiver interaction

The baby's feeding score will determine if that baby is ready to eat.

Baby scores a 1 or 2:

- These babies are ready to eat by breastfeeding or cup feeding

- Supportive measures should be provided
- During the process of feeding, continue to monitor the baby. When the baby falls asleep or shows signs of physiological instability (as noted above), document on the feeding chart, oral feeding should be stopped feeding given by gavage through NG tube.

Baby scores a 3, 4 or 5

- These babies are not ready to participate in breastfeeding or cup feeding
- The feeding should be given by gavage tube through the NG tube
- KMC during the gavage feeding will promote positive feeding experiences and help the baby advance to better oral feeding

ORAL QUALITY FEEDING SCALE

Feeding evaluation	Breastfeeding evaluation
Well = W Choke/Coughing = C Fell Asleep = SL Refused feeding = R Spilling = SP Vomiting = V Apnoea = A	Well = W (good attachment, suckling, swallowing 15” or longer) Good = G (good attachment, suckling, swallowing, less than 15”) Fair = F (off and on attachment, some suckling, no swallowing, less than 10”) Nil – N (no attachment, no suckling, asleep)

APPENDIX III: STUDY BUDGET

Study Title: Effect of Cue-Based Feeding on Weight Gain Among Preterm Neonates Born at 28 to 34 Weeks at Kiwoko Hospital

Institution: Kiwoko Hospital

Country: Uganda

Category	Description	Amount (UGX)
Personnel	Research Assistant 1	277,500
Personnel	Research Assistant 2	277,500
Personnel	Research Assistant 3	277,500
Personnel	Research Assistant 4	500,000
Travel	-	740,000
Administration	-	555,000
Results dissemination	-	555,000
Contingency	-	555,000
Other	-	1,110,000
Materials and Supplies	Pens, highlighters; Printing of 350 data extraction sheets; Stapler; Folders (2); Flash disk for backup, Calculator	475,500
TOTAL	-	5,323,000

APPENDIX IV: STUDY WORK PLAN

Study Title: Effect of Cue-Based Feeding on Weight Gain among Preterm neonates Born at 28 to 34 Weeks at Kiwoko Hospital, Uganda.

Study Type: Retrospective study involving review of medical records from Kiwoko Hospital neonatal database and Physical files

Study Period: 25th August – 25th October 2025

Activity	Description	Responsible Person(s)	Timeframe
Study preparation and ethical approval	Finalize protocol and obtain ethical and administrative approvals	Principal Investigator (PI), Supervisor	Aug 25–31
Stakeholder engagement	Meet with hospital administration and NICU staff to introduce the study	PI	Aug 26–30
Database access and setup	Coordinate access to neonatal database and prepare data extraction tools	PI, Data Manager	Sep 1–5
Data extraction	Retrieve relevant records from April 2017–April 2019 and Feb 2020–Feb 2022	Research Assistant, PI	Sep 6–20
Data cleaning and	Check for completeness, con-	PI, Statistician	Sep 21–25

validation	sistency, and remove duplicates		
Data analysis	Analyze extracted data to assess weight gain patterns and feeding method impact	Statistician, PI	Sep 26–Oct 5
Drafting of report	Prepare initial findings and interpretation	PI	Oct 6–12
Review and finalize report	Incorporate supervisor feedback and finalize report	PI, Supervisor	Oct 13–17
Presentation to Department of Paediatrics, Makerere University	Present findings for academic review and feedback	PI	Oct 18–20
Dissemination of findings	Present findings to hospital staff and stakeholders	PI	Oct 21–23
Submission for publication	Submit to academic journals or Makerere University	PI	Oct 24–25