

**Anaemia in early childhood pneumonia –
prevalence, predictors, and associated growth in the
Drakenstein Child Health Study (DCHS)**

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Dissertation submitted in partial fulfillment of the requirements for the degree
MASTER OF PUBLIC HEALTH in Epidemiology & Biostatistics for the
School of Public Health & Family Medicine at the University of Cape Town

February 2023

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Acknowledgements

Thank you to my supervisors, Dr. Landon Myer and Dr. Heather Zar, for their guidance and patience throughout my dissertation process – I am truly grateful for the time, support, and feedback you gave me.

Thank you to the many researchers at the Red Cross Children's Hospital who collected data for the Drakenstein Child Health Study (DCHS).

And finally, thank you to the South African families who took part in the DCHS – this research is for you.

Abstract

Background: Concurrent anaemia and pneumonia in under-fives living in LMICs is a complex relationship associated with high morbidity and mortality. Ascertaining whether there is an increased prevalence of anaemia among pneumonia infected under-fives can provide valuable insights for more effective treatments. Additionally, highlighting individual and maternal risk factors of anaemia as well as associated adverse growth outcomes among under-fives can bring about findings to prioritise resource allocation for anaemia prevention and treatment.

Methods: This cross-sectional sub-study analysed data from the Drakenstein Child Health Study (DCHS), a South African population-based birth cohort which enrolled pregnant women. Mother-child pairs were followed prospectively, and a subgroup of children had additional data collected (including haemoglobin (g/dL) measurements) during episodes of LRTI/pneumonia. Prevalence ratios were used to assess the impact of LRTI/pneumonia severity on anaemia status. Binary logistic regression models were used to analyze the effects of predictors on risk of child anaemia and linear regression models were used to analyze the effect of anaemia on adverse growth outcomes (WAZ and HAZ).

Results: 28% of first LRTI/pneumonia episodes co-occurred with anaemia (95% CI, 24.9 - 31.8), and median child age was 8.4 months during the episode. When all LRTI/pneumonia episodes were included, anaemia prevalence was higher among under-fives treated in hospital compared to those treated in ambulatory care (38.9% compared to 30.3% respectively, $p=0.04$). Additionally, children who experienced recurrent LRTI/pneumonia (2+ episodes) were 1.28 times as likely to have anaemia compared to children experiencing a first episode (95% CI, 1.03 - 1.59, $p=0.023$). Overall, children aged 6-59 months, with low socioeconomic status, and were exclusively breastfed for more than 1 month were strongly associated with anaemia ($p<0.05$). Children with concurrent LRTI/pneumonia and anaemia were found to be at increased risk of wasting (WAZ) and decreased risk of stunting (HAZ).

Conclusions: This study provides evidence of a high prevalence of concurrent LRTI/pneumonia and anaemia among under-fives in South Africa. It demonstrates the complex interplay between these conditions and various risk factors including older child age, maternal anaemia, exclusive breastfeeding, low socioeconomic status, and food insecurity. These findings highlight the need for multi-sectoral approaches to address the medical treatment and underlying social determinants of health that contribute to the burden of LRTI/pneumonia and anaemia in under-fives.

Abbreviations

ANC: Antenatal care

BMI: Body Mass Index

CI: Confidence Interval

DCHS: Drakenstein Child Health Study

FBC: Full [Complete] Blood Count

HAZ: Height-for-age z-score

Hb: Haemoglobin

HIV: Human Immunodeficiency Virus

IDA: Iron Deficiency Anaemia

IQR: Interquartile Range

LMIC: Low- and Middle-income Countries

LRTI: Lower Respiratory Tract Infection

MCV: Mean Corpuscular Volume

PLT: Platelet Count

PR: Prevalence ratio

SES: Socioeconomic Status

SSA: Sub-Saharan Africa

Under-fives: Children under 5 years of age

VIF: Variance inflation factor

WAZ: Weight-for-age z-score

WCC: White Cell Count

WHO: World Health Organization

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PART A: RESEARCH PROTOCOL

1 INTRODUCTION

1.1 Background

Pneumonia (commonly referred to as a lower respiratory tract infection (LRTI)) is the single largest infectious cause of death in children worldwide, accounting for 14% of all deaths among under-fives and disproportionately affecting low- and middle-income countries (LMICs)¹. In South Africa, under-five pneumonia mortality is estimated between 8% to 22%²⁻⁴. Children who die of pneumonia ultimately die of respiratory failure and are unable to deliver sufficient oxygen to vital organs. In many cases, these children are at increased risk of respiratory failure because of underlying comorbidities or other risk factors⁴.

On the other hand, anaemia is a condition in which a deficiency in the number of red blood cells or the haemoglobin concentration within them leads to reduced oxygen flow to the body's tissues⁵. It is a global public health problem that remains a major challenge for the health and development of women and children, especially in LMICs⁶. The World Health Organization (WHO) reported that in 2019 the prevalence of anaemia among under-fives was estimated to be 39.8% globally and is highest within the African region (60.2%). South Africa's estimated burden (44.4%) is lower than other Sub-Saharan African (SSA) countries, however their prevalence of under-five anaemia has increased by 3% since 2000⁶.

The aetiology of anaemia, especially in LMICs, is multifactorial and includes complex interactions between nutritional deficiencies, genetic disorders, and infectious diseases^{7,8}. Most commonly, low consumption and absorption of iron-rich foods leads to iron deficiency anaemia (IDA) which is responsible for approximately 50% of all global anaemia cases⁹. Risk factors for anaemia among under-fives in SSA countries include age, birth order, sex, comorbidities (such as fever, diarrhoea, and respiratory infection), malnutrition or stunting, maternal age, mother's anaemia status, household wealth and place of residence^{10,30}. There are many potential health consequences of under-five anaemia, especially in the first two years of life, which include but aren't limited to, reduced cognitive development, low immunity and growth weight, fatigue, difficulty with concentration, lethargy, susceptibility to infection, and increased mortality¹¹⁻¹³. Additionally, children with anaemia are often found to have lower anthropometric indices (including height-for-age, weight-for-age, and weight-for-height z-scores)³⁰.

Anaemia is defined as a blood haemoglobin (Hb) concentration below a specified cut-off point. Per WHO guidelines, children aged ≤ 1.0 , > 1.0 to 2.0 , > 2.0 to < 6.0 , and ≥ 6.0 to 59

months with blood Hb value of ≤ 10.7 g/dL, ≤ 9.4 g/dL, ≤ 9.5 g/dL, and ≤ 11.0 g/dl respectively are considered anemic¹⁴.

Moreover, studies have shown that pneumonia affects the severity of anemia in children^{15,16} and likewise, anemia has been found to increase the risk^{17,18} and severity of pneumonia^{16,19}. Thus, concurrent anaemia and pneumonia in under-fives living in LMICs is a complex relationship associated with high morbidity and mortality rates, increased hospitalisation, and a negative effect on socioeconomic development^{15,19}. Data are limited on the prevalence, interactions and growth outcomes of concurrent anaemia and pneumonia in under-fives living in South Africa.

1.2 Rationale

Addressing under-five concurrent pneumonia and anaemia is important as South Africa focuses on reducing under-five mortality. Ascertaining whether there is an increased prevalence of anaemia among pneumonia infected under-fives can provide valuable insights for more effective treatments. Additionally, highlighting individual and maternal risk factors of anaemia as well as associated adverse growth outcomes among under-fives can bring about findings to prioritise resource allocation for anaemia prevention and treatment. This will ultimately inform policies aimed at achieving one of the 2025 Global Nutrition Targets to reduce anaemia in under-fives²⁰.

2 AIMS AND OBJECTIVES

2.1 Aim

The overall aim is to investigate the prevalence, risk factors, and associated growth outcomes of anaemia in a cohort of under-fives at the time of LRTI/pneumonia event from a Drakenstein sub-district near Cape Town, South Africa.

2.2 Objectives

1. To ascertain the prevalence of anaemia in a cohort of under-fives at the time of LRTI/pneumonia event by:
 - LRTI/pneumonia severity (hospitalisation versus ambulatory event)
 - LRTI/pneumonia recurrence (1 versus 2+ episodes)

2. Investigate underlying child and maternal risk factors associated with anaemia in a cohort of under-fives at the time of LRTI/pneumonia event.
 - Including, but not limited to prematurity, child age, HIV exposure, socioeconomic status (SES), and food security
3. To identify associations between anaemia and adverse growth outcomes in a cohort of under-fives at the time of LRTI/pneumonia event.
 - Including, but not limited to weight-for-age z-scores to determine undernutrition

3 METHODS

3.1 Study design

This proposed research will be a cross-sectional analysis of data from the Drakenstein Child Health Study (DCHS), a large prospective birth cohort study which has been described in detail and published previously²¹. The overall aim of the DCHS is to investigate the epidemiology, risk factors, aetiology, and long-term impact of LRTI/pneumonia on child health. The DCHS enrolled a cohort of pregnant women over the age of 18 from two primary health clinics over a 3-year recruitment period from March 2012 to March 2015 and followed the mother-child pairs until children were at least 5 years old. During this time, maternal and child health were investigated through longitudinal measurements of risk factors in seven areas (environmental, infectious, nutritional, genetic, psychosocial, maternal, and immunological) that may impact on child health. In addition, intensive aetiological and risk factor investigations were completed during an episode of childhood LRTI/pneumonia. This cross-sectional analysis of data from a cohort study is an appropriate design due to the ability to capture anaemia status at the time of LRTI/pneumonia diagnosis.

3.2 Study setting

The setting for the DCHS is two public health clinics (TC Newman and Mbekweni) in the Drakenstein area in Paarl, a peri-urban area, 60km outside Cape Town, South Africa. During LRTI/pneumonia episodes, continuous research surveillance is implemented at these clinics as well as Paarl Hospital, the centralized hospital that serves the entire sub-district. The community is characterized by low socioeconomic status and a high incidence of LRTI/pneumonia among infants²². Additionally, anaemia prevalence in a small subgroup of

children (n=80) enrolled in the DCHS who had presented to hospital with LRTI/pneumonia was previously estimated at 52.5%²³.

3.3 Study population and sampling

Pregnant women were recruited for DCHS while attending routine antenatal care and considered eligible if they were at least 18 years old, planned to receive antenatal care at one of the two study sites, and intended to remain in the area for over one year. Mothers were enrolled in the DCHS at 20-28 weeks' gestation and a total of 1143 live births were included and followed postnatally until at least five years of age.

Children experiencing an episode of LRTI/pneumonia were followed up in hospital or at ambulatory clinics. WHO criteria were used to define LRTI/pneumonia, as previously described²². Recurrent LRTI/pneumonia was defined as two or more episodes. Overall, there were 851 LRTI/pneumonia events (excluding 51 congenital episodes) in 453 children²⁴. For the purposes of this sub-study, only children who had a full blood count (FBC) collected that included a haemoglobin measure (g/dL) at the time of illness were included to address the objectives of this study. When investigating underlying anaemia risk factors and growth outcomes, all relevant child and maternal data collected at routine study visits and during LRTI/pneumonia episodes will be included.

3.3.1 Inclusion Criteria

The inclusion criteria for this sub-study are:

- Children 0-5 years of age (under-fives)
- LRTI/pneumonia hospital admission or ambulatory episode as defined by WHO:
 - WHO criteria to diagnose LRTI or pneumonia: “Cough and/or difficult breathing, with or without fever; pneumonia is diagnosed by the presence of either fast breathing or lower chest wall indrawing where their chest moves in or retracts during inhalation (in a healthy person, the chest expands during inhalation)¹.”
- FBC collected at time of LRTI/pneumonia event including haemoglobin measure (g/dL)

3.3.2 Exclusion Criteria

The exclusion criteria for this sub-study are:

- Congenital events: episodes of LRTI/pneumonia occurring immediately after birth or before discharge after delivery

3.4 Data Collection

Data collected during the DCHS will be used for this proposed sub-study. This includes measurements taken during LRTI/pneumonia episodes as well as child and maternal risk factor data collected at routine visits.

3.4.1 Measures taken during LRTI/pneumonia events

- Child anthropometry measurements were taken and converted to z-scores using WHO standards²⁵
- Laboratory FBCs were collected and included haemoglobin (Hb), white cell count (WCC), mean corpuscular volume (MCV), and platelet (PLT) values.
 - Anaemia was defined using WHO haemoglobin guidelines for children under-five¹⁴
 - For hospitalisations only (not applicable for ambulatory care): oximetry, hospital duration and discharge status

3.4.2 Measures taken during routine visits

- Birth information was abstracted by study staff at delivery
- A composite locally validated measure from the South African Stress and Health Study (SASH)²⁶ of socioeconomic status was used encompassing current maternal employment status, highest level of education completed, household income, and asset index.
- Perceived household food insecurity was assessed through an adapted version of the USDA Household Food Security Scale - Short Form²⁷.
- Maternal smoking in pregnancy was assessed through self-report, and alcohol use was measured using the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST). This is a retrospective questionnaire on moderate-severe alcohol use²⁸.

Table 1: Table of Variables

Variables	Type	Categories
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Child Characteristics at time of LRTI/pneumonia event			
Age	Numeric (months)	Mean (SD)/Median (IQR)	
Height	Numeric (cm)	Mean (SD)/Median (IQR)	
Weight	Numeric (kg)	Mean (SD)/Median (IQR)	
Pneumonia severity	Binary categorical	Ambulatory Hospitalisation	
Number of recurrent LRTI/pneumonia events experienced per child	Numeric (# events)	Mean (SD)/Median (IQR)	
	Binary categorical	One episode Two or more episodes	
Full Blood Count (FBC)	Haemoglobin (Hb)	Numeric (g/dL)	Mean (SD)/Median (IQR)
		Age categories with binary output	<p>≤ 1.0 month: Anaemic: ≤ 10.7 g/dL Not Anaemic: > 10.7 g/dL</p> <p>> 1.0 to 2.0 months: Anaemic: ≤ 9.4 g/dL Not Anaemic: > 9.4 g/dL</p> <p>> 2.0 to < 6.0 months: Anaemic: ≤ 9.5 g/dL Not Anaemic: > 9.5 g/dL</p> <p>≥ 6.0 to 59 months: Anaemic: ≤ 11.0 g/dl Not Anaemic: > 11.0 g/dl</p>
	White cell count (WCC)	Numeric (x 10 ⁹ /L)	Mean (SD)/Median (IQR)
	Mean Corpuscular Volume (MCV)	Numeric (fl.)	Mean (SD)/Median (IQR)
	Platelet count (PLT)	Numeric (x 10 ⁹ /L)	Mean (SD)/Median (IQR)
For Hospitalisations Only (not applicable to ambulatory cases)	Oximetry	Binary categorical	Below threshold < 95% Above threshold ≥ 95%
	Hospital duration	Numeric (days)	Mean (SD)/Median (IQR)
	Discharge status	Nominal categorical	Discharged home Died Transferred
Birth Characteristics			
Sex	Binary categorical	Female Male	
Mode of delivery	Binary categorical	Vaginal Caesarean	
Gestational age	Numeric (weeks)	Mean (SD)/Median (IQR)	
Birth weight	Numeric (grams)	Mean (SD)/Median (IQR)	

HIV exposure	Binary categorical	Unexposed Exposed Uninfected
Maternal Characteristics		
Age at enrolment	Numeric (years)	Mean (SD)/Median (IQR)
SES quartiles (sum of standardized SES components (education, income, assets and employment))	Ordinal categorical	Lowest SES Low-mod SES Mod-high SES High SES
Current smoking	Binary categorical	Yes No
Prenatal alcohol exposure	Binary categorical	Yes No
Household food insecurity	Binary categorical	Perceived food secure Perceived food insecure

3.5 Exposures

- For the first objective, looking at prevalence of concurrent anaemia and pneumonia:
 - (a) The exposure of interest will be pneumonia severity. LRTI/pneumonia episodes were treated in hospital or in ambulatory care. LRTI/pneumonia treatment in hospital is deemed ‘more severe’ than treatment in ambulatory care. Hence, the exposure will be categorised as:
 - Exposed: Hospitalised
 - Unexposed: Ambulatory
 - (b) The exposure of interest will be recurrent pneumonia.
 - Exposed: 2+ episodes
 - Unexposed: 1 episode
- For the second objective, looking at risk factors of anaemia, the exposures of interest will be child age, prematurity, HIV exposure, SES, pneumonia severity:
 - Child age (in months)
 - Prematurity:
 - Exposed: premature birth (defined as delivery ≤ 37 completed weeks of gestation)

- Unexposed: non premature birth (delivery >37 completed weeks of gestation)
 - HIV exposure:
 - Exposed: HIV child exposure but uninfected
 - Unexposed: no HIV child exposure
 - Socioeconomic Status (SES) quartiles:
 - Exposed: lowest SES
 - Unexposed: low-mod SES, mod-high SES, high SES
 - Pneumonia severity:
 - Exposed: Hospitalised
 - Unexposed: Ambulatory
- For the third objective, anaemia associated growth outcomes, the exposure of interest will be anaemia status, which was determined by FBC haemoglobin concentration (g/dL) and WHO haemoglobin guidelines for children under-five¹⁴
 - Exposed: laboratory confirmed child anaemia
 - Unexposed: laboratory confirmed no child anaemia

3.6 Outcomes

- For the first and second objectives, the outcome of interest will be anaemia status, which was determined by laboratory confirmed FBC haemoglobin concentration (g/dL) and WHO haemoglobin guidelines for children under-five¹⁴
 - Condition: child anaemia
 - No Condition: no child anaemia
- For the third objective the outcome of interest will be weight-for-age z-score as calculated by anthropometry measurements taken at the time of LRTI/pneumonia event

3.7 Data Management and Statistical Analysis

3.7.1 Data management

All data from the DCHS was entered into an online database, REDCapTM, which is overseen by a Data Manager with strictly enforced limited access, including password protection, and restricted access to any sensitive data collected. Further, all paper documents are kept in locked filing cabinets and only accessible to study staff. Specific steps to ensure confidentiality include the use of participant identifiers (PIDs) for all study data, and these PIDs are de-linked from any identifying participant information (e.g., name, address, other unique identifiers). Data being used in this sub-study will have no PIDs. The data will be stored on a password protected computer and stored as a password protected file, after which it will be deleted.

3.7.2 Statistical analysis

All analyses for this sub-study will be conducted using R Studio Version 2022.12.0 Build 353. Initially, data will be cleaned where any duplicate data is removed, and missing data identified and handled appropriately.

Summary statistics will be generated and depending on distribution these will include either mean and standard deviation or median and interquartile range for numerical variables. Proportions will be generated for categorical variables. For numerical variables, Shapiro-Wilks tests will be used to see if the data is normally distributed. If normally distributed, a t-test will be used and if not, Wilcoxon rank-sum test. Chi-squared tests will be used for categorical variables.

For the first objective, with exposure being pneumonia severity, children will be grouped by status into severe (hospitalisation) and non-severe (ambulatory). Children will then be classified as anaemic or non-anaemic based on WHO criteria and haemoglobin measurements at time of LRTI/pneumonia event. Prevalence of anaemia will then be determined by pneumonia severity and prevalence ratios will determine if there is an association between pneumonia severity and anaemia status (significance level of $p < 0.05$). The same approach will be taken with pneumonia recurrence exposure. Children will be grouped by status into 1 LRTI/pneumonia episode or 2+ LRTI/pneumonia episodes.

For the second objective, a linear regression will be used to predict haemoglobin (g/dL) (continuous dependent variable) using a set of independent variables, including child age, prematurity, HIV exposure, SES, and pneumonia severity. Initially, a univariate linear regression will be run and those variables that are statistically significant will be added to a multivariate regression to adjust for confounding. These linear regressions will generate risk ratios, for which 95% confidence intervals (CI) and p-values will be generated to assess

statistical significance. In both univariate and multivariate linear regressions, a significance level of $p < 0.05$ will be used to determine statistical significance.

Additionally, binary logistic regressions will be used to predict anaemia (categorical dependent variable) using the same independent variables. Children will be classified as anaemic or non-anaemic based on WHO criteria¹⁴ and haemoglobin measurements at time of LRTI/pneumonia event. Again, a univariate binary logistic regression will be run and those variables that are statistically significant will be added to a multivariate regression to adjust for confounding. These binary logistic regressions will generate odds ratios, for which 95% CI's and p-values will be generated to assess statistical significance. In both univariate and multivariate binary logistic regressions, a significance level of $p < 0.05$ will be used to determine statistical significance.

For the third objective, anaemic and non-anaemic groups will be assessed for associations with adverse growth outcomes, including but not limited to, weight-for-age z-scores. A significance level of $p < 0.05$ will be used to determine statistical significance of these associations.

4 ETHICAL CONSIDERATIONS

The Drakenstein Child Health Study (DCHS) received ethics approval and renewal (401/2009) from the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (UCT-HREC) (Appendix A). Ethical approval for this proposed sub-study will be sought from the UCT-HREC.

4.1 Informed Consent

For the DCHS, mothers gave written informed consent at enrolment and re-consented on an annual basis to help ensure understanding of the study time commitments. Informed consent also granted permission for abstraction of data from clinical records. This proposed sub-study will only be using data that has already been collected as part of the DCHS so no direct contact will be made with participants and therefore no additional consent is necessary.

4.2 Privacy and Confidentiality

All study staff involved in DCHS have gone through extensive Good Clinical Practice (GCP) training and on-going confidentiality training by management to ensure participant confidentiality and privacy. Specific steps to ensure confidentiality includes the use of participant identifiers (PIDs) for all study data, and these PIDs are de-linked from any

identifying participant information (e.g., name, address, other unique identifiers). Further, all documents are kept in locked filing cabinets and only accessible to study staff. Study data is collected in an online database, REDCap™, which is overseen by a Data Manager with strictly enforced limited access, including password protection, and restricted access to any sensitive data collected.

4.3 Risk and Benefits

A description of risks, benefits, and reimbursement details of the DCHS study have been provided and previously approved (HREC 401/2009).

4.3.1 Risks

There are no foreseen risks in this proposed sub-study, as confidentiality will be maintained and there will be no direct contact with patients.

4.3.2 Benefits

There are no direct benefits to this proposed sub-study. The impact of early childhood anaemia at the time of LRTI/pneumonia event has not been comprehensively studied in the South African context. This secondary analysis will contribute novel information to the understanding of anaemia among children under five with LRTI/pneumonia and help further understand burden and risk.

4.4 Reporting and Implementation

This proposed sub-study may be submitted to a peer-reviewed journal in collaboration with and upon approval from original DCHS investigators.

4.5 Logistics

Table 2: Study timeline 2022

Actions	May	June	July	Aug	Sept	Oct	Nov	Dec
Literature Review								
Protocol Development								
Ethics Review Submission								
Data Analysis								
Thesis Write-Up								
Submission to UCT for MPH								
Submission to Journal								

4.6 Budget

This proposed sub-study will be conducted as part of a Master of Public Health (MPH) degree and as such no budget or payment is required.

5 REFERENCES (Vancouver)

1. Pneumonia. Accessed August 29, 2022. <https://www.who.int/news-room/fact-sheets/detail/pneumonia>
2. von Schirnding YE, Yach D, Klein M. Acute respiratory infections as an important cause of childhood deaths in South Africa. *South Afr Med J Suid-Afr Tydskr Vir Geneeskd.* 1991;80(2):79-82.
3. Wyndham CH. Leading causes of death among children under 5 years of age in the various population groups of the RSA in 1970. *South Afr Med J Suid-Afr Tydskr Vir Geneeskd.* 1984;66(19):717-718.
4. le Roux DM, Myer L, Nicol MP, Zar HJ. Incidence and severity of childhood pneumonia in the first year of life in a South African birth cohort: the Drakenstein Child Health Study. *Lancet Glob Health.* 2015;3(2):e95-e103. doi:10.1016/S2214-109X(14)70360-2
5. Anaemia. Accessed August 29, 2022. <https://www.who.int/health-topics/anaemia>
6. Anaemia in women and children. Accessed August 29, 2022. https://www.who.int/data/gho/data/themes/topics/anaemia_in_women_and_children
7. Balarajan Y, Ramakrishnan U, Ozaltin E, Shankar AH, Subramanian SV. Anaemia in low-income and middle-income countries. *Lancet Lond Engl.* 2011;378(9809):2123-2135. doi:10.1016/S0140-6736(10)62304-5
8. Tolentino K, Friedman JF. An update on anemia in less developed countries. *Am J Trop Med Hyg.* 2007;77(1):44-51.
9. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995–2011: a systematic analysis of population-representative data - The Lancet Global Health. Accessed August 29, 2022.

[https://www.thelancet.com/journals/langlo/article/PIIS2214-109X\(13\)70001-9/fulltext](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(13)70001-9/fulltext)

10. Obasohan PE, Walters SJ, Jacques R, Khatab K. A Scoping Review of the Risk Factors Associated with Anaemia among Children Under Five Years in Sub-Saharan African Countries. *Int J Environ Res Public Health*. 2020;17(23):8829. doi:10.3390/ijerph17238829
11. WHO. The Global Prevalence of Anaemia in 2011. Published online 2015. https://apps.who.int/iris/bitstream/handle/10665/177094/9789241564960_eng.pdf?sequence=1
12. Lozoff B, Beard J, Connor J, Barbara F, Georgieff M, Schallert T. Long-lasting neural and behavioral effects of iron deficiency in infancy. *Nutr Rev*. 2006;64(5 Pt 2):S34-43; discussion S72-91. doi:10.1301/nr.2006.may.s34-s43
13. Walker SP, Wachs TD, Gardner JM, et al. Child development: risk factors for adverse outcomes in developing countries. *Lancet Lond Engl*. 2007;369(9556):145-157. doi:10.1016/S0140-6736(07)60076-2
14. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Published online 2011. https://apps.who.int/iris/bitstream/handle/10665/85839/WHO_NMH_NHD_MNM_11.1_eng.pdf
15. Dos Santos RF, Gonzalez ESC, de Albuquerque EC, et al. Prevalence of anemia in under five-year-old children in a children's hospital in Recife, Brazil. *Rev Bras Hematol E Hemoter*. 2011;33(2):100-104. doi:10.5581/1516-8484.20110028
16. Odeyemi AO, Odeyemi AO, Musa TL. Determinants of Outcome among Under-Five Children Hospitalized with Pneumonia at a Tertiary Health Facility in South-West Nigeria. *West Afr J Med*. 2021;38(2):114-119.
17. Ramakrishnan K, Harish PS. Hemoglobin level as a risk factor for lower respiratory tract infections. *Indian J Pediatr*. 2006;73(10):881-883. doi:10.1007/BF02859279
18. Savitha MR, Nandeeshwara SB, Pradeep Kumar MJ, ul-Haque F, Raju CK. Modifiable risk factors for acute lower respiratory tract infections. *Indian J Pediatr*. 2007;74(5):477-482. doi:10.1007/s12098-007-0081-3

19. Chisti MJ, Kawser CA, Rahman ASMMH, et al. Prevalence and outcome of anemia among children hospitalized for pneumonia and their risk of mortality in a developing country. *Sci Rep.* 2022;12(1):10741. doi:10.1038/s41598-022-14818-2
20. Global nutrition targets 2025: anaemia policy brief. Accessed August 29, 2022. <https://www.who.int/publications-detail-redirect/WHO-NMH-NHD-14.4>
21. Zar HJ, Barnett W, Myer L, Stein DJ, Nicol MP. Investigating the early-life determinants of illness in Africa: the Drakenstein Child Health Study. *Thorax.* 2015;70(6):592-594. doi:10.1136/thoraxjnl-2014-206242
22. Zar HJ, Barnett W, Stadler A, Gardner-Lubbe S, Myer L, Nicol MP. Aetiology of childhood pneumonia in a well vaccinated South African birth cohort: a nested case-control study of the Drakenstein Child Health Study. *Lancet Respir Med.* 2016;4(6):463-472. doi:10.1016/S2213-2600(16)00096-5
23. Wedderburn CJ, Ringshaw J, Donald K, et al. Effects of Maternal and Early-Life Anaemia on Child Brain Development: A South African Birth Cohort Study. Published online September 9, 2021. doi:10.2139/ssrn.3920258
24. Early-life respiratory syncytial virus lower respiratory tract infection in a South African birth cohort: epidemiology and effect on lung health - The Lancet Global Health. Accessed August 29, 2022. [https://www.thelancet.com/journals/langlo/article/PIIS2214-109X\(20\)30251-5/fulltext](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30251-5/fulltext)
25. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards based on length/height, weight and age. *Acta Paediatr Oslo Nor 1992 Suppl.* 2006;450:76-85. doi:10.1111/j.1651-2227.2006.tb02378.x
26. Myer L, Stein DJ, Grimsrud A, Seedat S, Williams DR. Social determinants of psychological distress in a nationally-representative sample of South African adults. *Soc Sci Med 1982.* 2008;66(8):1828-1840. doi:10.1016/j.socscimed.2008.01.025
27. Bickel, Gary, Mark Nord, Cristofer Price, William Hamilton, and John Cook. Guide to Measuring Household Food Security, Revised 2000. Published online March 2000.
28. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST). Accessed August 29, 2022. <https://www.who.int/publications-detail-redirect/978924159938-2>

29. Sandoval C. Approach to the child with anemia. In: TWP, editor. UpToDate. UpToDate Inc. (2018).
30. Moschovis PP, Wiens MO, Arlington L, et al. Individual, maternal and household risk factors for anaemia among young children in sub-Saharan Africa: a cross-sectional study. *BMJ Open* 2018;8:e019654. doi:10.1136/bmjopen-2017-019654

PART B: JOURNAL MANUSCRIPT

Anaemia in early childhood pneumonia – prevalence, predictors, and associated growth in the Drakenstein Child Health Study (DCHS)

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Keywords: anaemia, child, food insecurity, haemoglobin, lower respiratory tract infection (LRTI), pneumonia, predictors, South Africa

¹The chosen peer reviewed journal for this manuscript is the International Journal of Paediatrics. The MPH guidelines ask that co-authors are included in the acknowledgements section of the dissertation. The International Journal of Paediatrics guidelines are included in the Appendix.

Abstract

Background: Concurrent anaemia and pneumonia in under-fives living in LMICs is a complex relationship associated with high morbidity and mortality. Ascertaining whether there is an increased prevalence of anaemia among pneumonia infected under-fives can provide valuable insights for more effective treatments. Additionally, highlighting individual and maternal risk factors of anaemia as well as associated adverse growth outcomes among under-fives can bring about findings to prioritise resource allocation for anaemia prevention and treatment.

Methods: This cross-sectional sub-study analysed data from the Drakenstein Child Health Study (DCHS), a South African population-based birth cohort which enrolled pregnant women. Mother-child pairs were followed prospectively, and a subgroup of children had additional data collected (including haemoglobin (g/dL) measurements) during episodes of LRTI/pneumonia. Prevalence ratios were used to assess the impact of LRTI/pneumonia severity on anaemia status. Binary logistic regression models were used to analyze the effects of predictors on risk of child anaemia and linear regression models were used to analyze the effect of anaemia on adverse growth outcomes (WAZ and HAZ).

Results: 28% of first LRTI/pneumonia episodes co-occurred with anaemia (95% CI, 24.9 - 31.8), and median child age was 8.4 months during the episode. When all LRTI/pneumonia episodes were included, anaemia prevalence was higher among under-fives treated in hospital compared to those treated in ambulatory care (38.9% compared to 30.3% respectively, $p=0.04$). Additionally, children who experienced recurrent LRTI/pneumonia (2+ episodes) were 1.28 times as likely to have anaemia compared to children experiencing a first episode (95% CI, 1.03 - 1.59, $p=0.023$). Overall, children aged 6-59 months, with low socioeconomic status, and were exclusively breastfed for more than 1 month were strongly associated with anaemia ($p<0.05$). Children with concurrent LRTI/pneumonia and anaemia were found to be at increased risk of wasting (WAZ) and decreased risk of stunting (HAZ).

Conclusions: This study provides evidence of a high prevalence of concurrent LRTI/pneumonia and anaemia among under-fives in South Africa. It demonstrates the complex interplay between these conditions and various risk factors including older child age, maternal anaemia, exclusive breastfeeding, low socioeconomic status, and food insecurity. These findings highlight the need for multi-sectoral approaches to address the medical treatment and underlying social determinants of health that contribute to the burden of LRTI/pneumonia and anaemia in under-fives.

1.0 Introduction

Pneumonia (commonly referred to as a lower respiratory tract infection (LRTI)) is the single largest infectious cause of death in children worldwide, accounting for 14% of all deaths among under-fives and disproportionately affecting low- and middle-income countries (LMICs)¹. In South Africa, under-five pneumonia mortality is estimated between 8% to 22%²⁻⁴. Children who die of pneumonia ultimately die of respiratory failure and are unable to deliver sufficient oxygen to vital organs. In many cases, these children are at increased risk of respiratory failure because of underlying comorbidities or other risk factors⁴.

On the other hand, anaemia is a condition in which a deficiency in the number of red blood cells or the haemoglobin concentration within them leads to reduced oxygen flow to the body's tissues⁵. It is a global public health problem that remains a major challenge for the health and development of women and children, especially in LMICs⁶. The World Health Organization (WHO) reported that in 2019 the prevalence of anaemia among under-fives was estimated to be 39.8% globally and is highest within the African region (60.2%). South Africa's estimated burden (44.4%) is lower than other Sub-Saharan African (SSA) countries, however their prevalence of under-five anaemia has increased by 3% since 2000⁶.

The aetiology of anaemia, especially in LMICs, is multifactorial and includes complex interactions between nutritional deficiencies, genetic disorders, and infectious diseases^{7,8}. Most commonly, low consumption and absorption of iron-rich foods leads to iron deficiency anaemia (IDA) which is responsible for approximately 50% of all global anaemia cases⁹. Risk factors for anaemia among under-fives in SSA countries include age, birth order, sex, comorbidities (such as fever, diarrhoea, and respiratory infection), malnutrition or stunting, maternal age, mother's anaemia status, and socio-economic status (including food security)^{10,31}. There are many potential health consequences of under-five anaemia, especially in the first two years of life, which include but aren't limited to, reduced cognitive development, low immunity and growth weight, fatigue, difficulty with concentration, lethargy, susceptibility to infection, and increased mortality¹¹⁻¹³. Additionally, children with anaemia are often found to have lower anthropometric indices (including height-for-age, weight-for-age, and weight-for-height z-scores)³¹.

Anaemia is defined as a blood haemoglobin (Hb) concentration below a specified cut-off point. Children aged ≤ 1.0 , > 1.0 to 2.0 , > 2.0 to < 6.0 , and ≥ 6.0 to 59 months with blood Hb

value of ≤ 10.7 g/dL, ≤ 9.4 g/dL, ≤ 9.5 g/dL, and ≤ 11.0 g/dl respectively are considered anemic^{14,29}.

Moreover, studies have shown that pneumonia affects the severity of anemia in children^{15,16} and likewise, anemia has been found to increase the risk^{17,18} and severity of pneumonia^{16,19}. Thus, concurrent anaemia and pneumonia in under-fives living in LMICs is a complex relationship associated with high morbidity and mortality rates, increased hospitalisation, and a negative effect on socioeconomic development^{15,19}. Data are limited on the prevalence, interactions and growth outcomes of concurrent anaemia and pneumonia in under-fives living in South Africa.

Addressing under-five concurrent pneumonia and anaemia is important as South Africa focuses on reducing under-five mortality. The Drakenstein Child Health Study (DCHS)²¹ provides robust data to ascertain whether there is an increased prevalence of anaemia among LRTI/pneumonia infected under-fives. Additionally, we aimed to examine the associations between child anaemia, growth outcomes and a range of risk factors among this high-risk group. Ideally our findings can be used to prioritise resource allocation for anaemia prevention and treatment as well as inform policies aimed at achieving one of the 2025 Global Nutrition Targets to reduce anaemia in under-fives²⁰.

2.0 Methods

2.1 Study setting and design

This proposed research will be a cross-sectional analysis of data from the DCHS, a large prospective birth cohort study which has been described in detail and published previously²¹. The overall aim of the DCHS is to investigate the epidemiology, risk factors, aetiology, and long-term impact of LRTI/pneumonia on child health. A cross-sectional analysis of data from the DCHS cohort opportunely captured anaemia status at the time of LRTI/pneumonia diagnosis.

The setting for the DCHS birth cohort is two public health clinics (TC Newman and Mbekweni) in the Drakenstein area in Paarl, a peri-urban area, 60km outside Cape Town, South Africa. The community is characterized by low socioeconomic status and a high incidence of LRTI/pneumonia among infants²². Additionally, anaemia prevalence in a small subgroup of children (n=80) enrolled in the DCHS who had presented to hospital with LRTI/pneumonia was previously estimated at 52.5%²³.

2.2 Participants

Pregnant women were recruited for DCHS and considered eligible if they were at least 18 years old, planned to receive antenatal care at one of the two study sites, and intended to remain in the area for over one year. Mothers were enrolled at 20-28 weeks' gestation and a total of 1143 live births were included and followed postnatally until at least five years of age.²¹ All assessments were available in English, isiXhosa, and Afrikaans and participants chose their preferred language.

2.3 Measures

Comprehensive biomedical, environmental, psychosocial, demographic, and physical data of the mother and child were collected at routine antenatal visits. Children experiencing an episode of LRTI/pneumonia were followed up in hospital or at ambulatory clinics where additional data was collected.

2.3.1 Routine antenatal visits

Measures taken during routine visits include: (1) birth information abstracted by study staff at delivery; (2) a composite locally validated measure from the South African Stress and Health Study (SASH)²⁶ of socioeconomic status to encompass current maternal employment status, highest level of education completed, household income, and asset index; (3) maternal smoking in pregnancy assessed through self-report, and alcohol use measured using the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) as well as a retrospective questionnaire on moderate-severe alcohol use; and (4) perceived household food insecurity through an adapted version of the USDA Household Food Security Scale - Short Form²⁷.

2.3.2 LRTI/pneumonia events

WHO criteria were used to define LRTI/pneumonia, as previously described²². Recurrent LRTI/pneumonia was defined as two or more episodes. Measures taken during child LRTI/pneumonia events include: (1) child anthropometry measurements which were converted to z-scores using WHO standards²⁵; (2) laboratory FBCs which included haemoglobin (used to diagnose anaemia^{14,29}), white cell count, MCV, and platelet values and; (3) for hospitalisations only: oximetry, hospital duration and discharge status.

2.4 Statistical analysis

All analyses were conducted using R Studio Version 2022.07.1 Build 554. Initially, data was cleaned where any duplicate data was removed, and missing data identified and handled appropriately.

Sample characteristics and clinical variables are presented as means (SD) for continuous data and frequencies (%) for categorical data. When continuous data were not normally distributed, median, and interquartile range (IQR) were presented. Continuous variables with normal distribution were compared with unpaired t-tests and when distribution was skewed the Wilcoxon rank-sum test was used. Categorical variables were compared with Chi-squared tests.

The primary exposure was pneumonia severity whereby children were classified as severe (hospitalisation) or less severe (ambulatory) and the outcome was anaemia status which was classified as anaemic or non-anaemic based on haemoglobin measurements and WHO criteria^{14,29} at time of LRTI/pneumonia event. The same approach was taken with pneumonia recurrence exposure whereby children were grouped into 1 anemia episode and 2+ episodes. Prevalence ratios, 95% CI's and p-values were used to assess the measure of association between pneumonia severity or recurrence and anaemia status. A significance level of $p < 0.05$ will be used to determine statistical significance.

To assess the outcome of anaemia status, with risk factor exposures, binary logistic regressions were used to predict anaemia (binary dependent variable) using a set of independent variables, including child age groups, sex, prematurity (<37 weeks' gestation), HIV exposure uninfected, maternal anaemia status during ANC, exclusive breastfeeding for >1 month, sssum score (a sum of standardised SES components including education, income, assets, and employment), and food insecurity during ANC. Children were classified as anaemic or non-anaemic based on haemoglobin measurements at time of LRTI/pneumonia event and WHO criteria^{14,29}. An univariate binary logistic regression was run and those variables that are statistically significant ($p < 0.05$) were added to a multivariate binary regression to adjust for confounding. These binary logistic regressions generated odds ratios, for which 95% CI's and P-values were generated to assess statistical significance ($p < 0.05$). Collinearity diagnostics (variance inflation factor (VIF)) and goodness-of-fit statistics (Hosmer-Lemeshow) were calculated to test the robustness of the model.

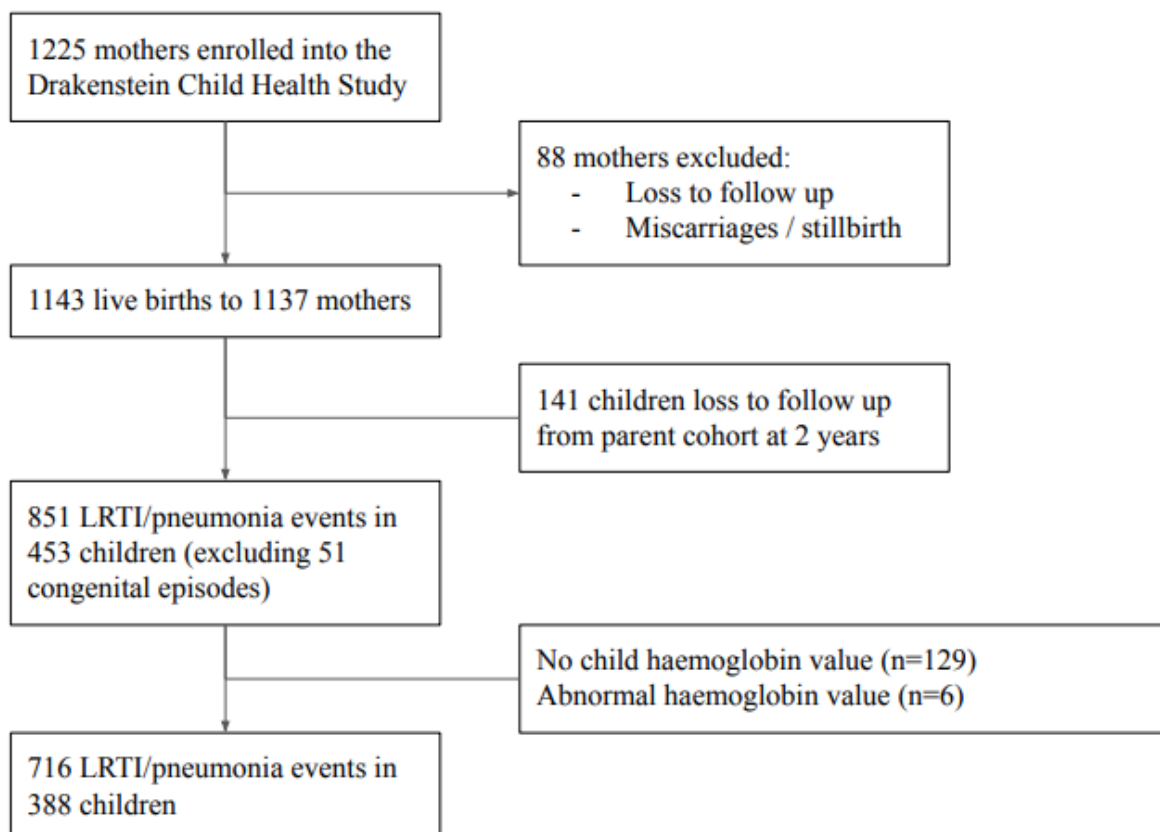
To analyze the impact of anaemia exposure on growth outcomes (WAZ and HAZ), we performed univariate and multivariate linear regression analysis with anaemia exposure as the

independent variable and WAZ and HAZ as the dependent variables. Child weight and height measurements at the time of LRTI/pneumonia event were converted to z-scores for weight-for-age (WAZ) and height-for-age (HAZ). Both univariate and multivariate linear regressions generated risk ratios, for which 95% CI's and P-values were generated to assess statistical significance ($p < 0.05$). Collinearity diagnostics (variance inflation factor (VIF)) and goodness-of-fit statistics (Hosmer-Lemeshow) were calculated to test the robustness of the multivariate models.

3.0 Results

A total of 1143 live births were enrolled in to the DCHS and followed postnatally until at least five years of age.²¹ Overall, there were 851 LRTI/pneumonia events (excluding 51 congenital episodes) in 453 children²⁴. For the purposes of this sub-study analysis, only children who had a full blood count (FBC) collected that included a haemoglobin measure (g/dL) at the time of LRTI/pneumonia event were included to address the objectives of this study. Once missing or unpalusible haemoglobin data were removed, the final analysis for this cross-sectional sub-study included 716 LRTI/pneumonia events from 388 children (*Figure 1*).

Figure 1. Drakenstein Child Health Study (DCHS) flowchart



3.1 Baseline characteristics at first LRTI/pneumonia episode

Table 1 shows characteristics of children at the time of first LRTI/pneumonia episode with and without anaemia. Twenty-eight percent of first LRTI/pneumonia episodes co-occurred with anaemia (of which median child age at episode was 8.38 months). Most anemic children were ≥ 6.0 to 59 months old (63.06%) and when broken down by age categories (≤ 1.0 , > 1.0 to 2.0 , > 2.0 to < 6.0 , and ≥ 6.0 to 59 months), anaemic children were older than non-anaemic children ($p < 0.001$). In terms of overall LRTI/pneumonia severity, 68.47% of first LRTI/pneumonia episodes were treated in ambulatory care. Overall, the WAZ and HAZ scores were below average when compared to the reference population.

In terms of birth characteristics, there were no differences between groups for sex, premature birth (< 37 weeks' gestation), birth delivery type or HIV exposure (uninfected). Due to a highly effective antenatal antiretroviral therapy programme, there was a low prevalence of HIV exposure uninfected amongst children.

Maternal characteristics were similar between groups including age, smoking and alcohol use in pregnancy or maternal anaemia during ANC. Interestingly, a higher proportion of anemic children were exclusively breastfed for more than 1 month ($p = 0.047$). Childhood anaemia has been found to be worse as the duration of breastfeeding increases due to the limited iron content in breast milk from anaemic mothers exposed to poor nutrition and low food security³⁰.

Sociodemographic characteristics were different between groups as calculated by the overall sessum score which is the sum of standardised SES components from SASH²⁶ including current maternal employment status, highest level of education completed, household income, and asset index. Anaemic children had statistically significantly lower sessum scores ($p = 0.035$) compared to non-anaemic children. There were no differences between groups for food security at ANC or 14 weeks post-delivery.

Table 1. Characteristics of anaemic versus non-anaemic children at the time of first LRTI/pneumonia episode

Variable	Overall (n=388)	Anaemia (n=111)	No Anaemia (n=277)	P-value
Child characteristics				
Child age, months (median (IQR))	5.57 (2.66-15.68)	8.38 (2.66-16.14)	5.03 (2.66-15.16)	0.13
Age categories, months				
≤ 1.0	10 (2.58%)	2 (1.80%)	8 (2.89%)	
> 1.0 to 2.0	52 (13.40%)	14 (12.61%)	38 (13.72%)	
> 2.0 to < 6.0	141 (36.34%)	25 (22.52%)	116 (41.88%)	< 0.001

≥ 6.0 to 59	185 (47.68%)	70 (63.06%)	115 (41.52%)	
LRTI Severity				
Ambulatory	285 (73.45%)	76 (68.47%)	209 (75.45%)	0.20
Hospitalisation	103 (26.55%)	35 (31.53%)	68 (24.55%)	
WAZ	-0.48 (1.62)	-0.63 (1.87)	-0.42 (1.50)	0.63
HAZ	-1.07 (1.98)	-1.43 (2.29)	-0.92 (1.82)	0.20
Birth characteristics				
Sex (male)	218 (56.19%)	60 (54.05%)	158 (57.04%)	0.67
Premature (<37 weeks' gestation)	71 (18.30%)	24 (21.62%)	47 (16.97%)	0.35
Caesarean delivery	69 (17.78%)	23 (20.72%)	46 (16.61%)	0.40
HIV exposed uninfected	87 (22.42%)	29 (26.13%)	58 (20.94%)	0.33
Maternal and socio-economic characteristics				
Site (Mbekweni)	218 (56.19%)	67 (60.36%)	151 (54.51%)	0.34
Maternal age at birth, years (median (IQR))	26.0 (21.8-31.2)	25.3 (22.0-31.2)	26.4 (21.7-31.2)	0.64
Maternal anaemia during ANC	137 (35.31%)	40 (36.04%)	97 (35.02%)	0.73
Exclusive breastfeeding for >1mo	209 (53.87%)	69 (62.16%)	140 (50.54%)	0.047
Maternal smoking during pregnancy	97 (25.00%)	28 (25.91%)	69 (24.91%)	0.90
Maternal alcohol use during pregnancy	65 (16.75%)	18 (16.22%)	47 (16.97%)	0.93
Sessum score (median (IQR))	-0.12 (-1.21 - 1.40)	-0.20 (-1.58 - 0.86)	-0.11 (-1.13 - 1.72)	0.035
Food insecurity (ANC)	110 (28.35%)	39 (35.14%)	71 (25.61%)	0.15
Food insecurity (14 wks)	40 (10.31%)	10 (9.01%)	30 (10.83%)	0.67

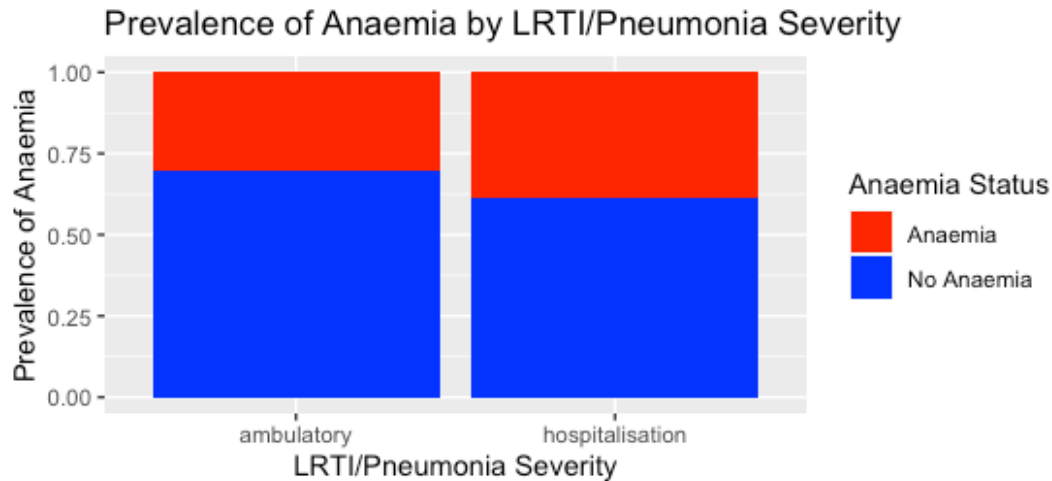
Footnote: Data are n/N(%) or mean (SD) unless otherwise indicated. Continuous variables with normal distribution were compared with unpaired t-tests and when distribution was skewed the Wilcoxon rank-sum test was used. Categorical variables were compared with Chi-squared tests. Anaemia was classified per the WHO recommendations for women and children^{14,29}. Child weight and height measurements were converted to z-scores for weight-for-age (WAZ) and height-for-age (HAZ). Sessum score is a sum of standardised SES components from SASH²⁶ including current maternal employment status, highest level of education completed, household income, and asset index. Other components of the variables displayed in 1 x 1 contingency cells were not shown (including sex (female), full-term (≥37 weeks' gestation), vaginal delivery, HIV unexposed, Site TC Newman, maternal no anaemia during ANC, not exclusively breastfeeding for >1mo, no maternal smoking during pregnancy, no maternal alcohol use during pregnancy, Food secure (ANC), and Food secure (14 wks)).

3.2 LRTI/pneumonia severity and child anaemia

In this cross-sectional sub-study, the overall prevalence of anaemia among under-fives at the time of any LRTI/pneumonia episode was 32.3% (95% CI, 28.9-35.9). The prevalence of anaemia among under-fives treated in hospital was 38.9% (95% CI, 31.4-46.9) and 30.3% (95% CI, 26.6-34.4) among under-fives treated in ambulatory care (*Figure 2*). The prevalence ratio (PR) between hospitalised and ambulatory cases was 1.28 (95% CI, 1.02 - 1.61, p=0.040),

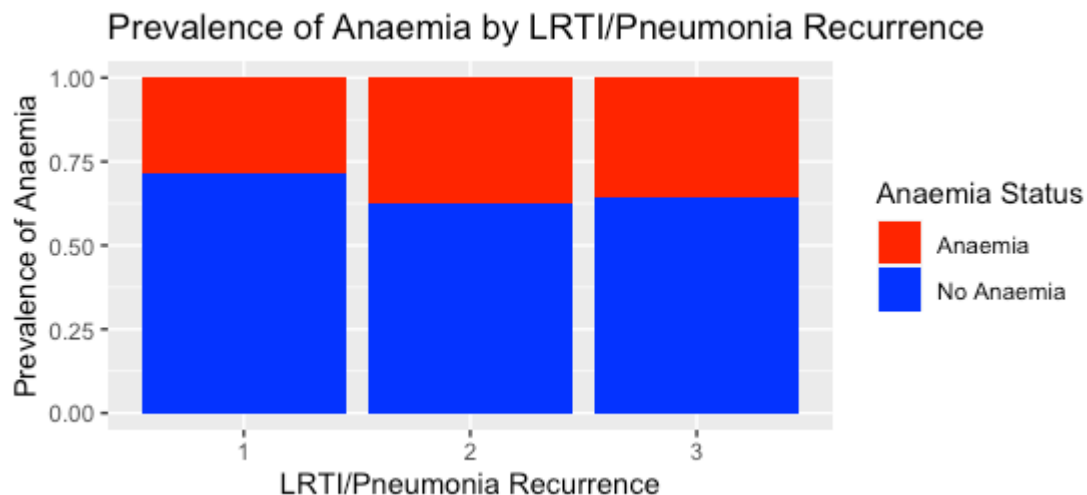
indicating that under-fives with hospitalised LRTI/pneumonia were 1.28 times as likely to have anaemia compared to under-fives with ambulatory LRTI/pneumonia.

Figure 2. Prevalence of Anaemia by LRTI/Pneumonia Severity



Additionally, we assessed the association between pneumonia recurrence and anaemia status, using prevalence ratios and associated 95% CIs. The results showed that 28.6% (95% CI, 24.2 - 33.4) of under-fives who experienced their first LRTI/pneumonia episode had anaemia, while 36.6% (95% CI, 31.4 - 42.1) of under-fives who experienced 2 or more LRTI/pneumonia episodes had anaemia (Figure 3). Therefore, under-fives who experienced 2 or more LRTI/pneumonia episodes were 1.28 times as likely (95% CI, 1.03 - 1.59, p=0.023) to have anaemia compared to under-fives who experienced their first LRTI/pneumonia episode.

Figure 3. Prevalence of Anaemia by LRTI/Pneumonia Recurrence



3.3 Predictors and child anaemia

A binary logistic regression model was conducted to predict the outcome of anaemia status in children with various risk factor exposures. In the initial univariate binary logistic regression models (*Table 2*), eight variables were included: age category, sex, premature birth (<37 weeks' gestation), HIV exposure uninfected, maternal anaemia during ANC, exclusively breastfed for >1 month, sessum score, and food insecurity during ANC. Again, sessum score is a sum of standardised SES components from SASH²⁶ including current maternal employment status, highest level of education completed, household income, and asset index.

Out of these eight variables, four were found to have a p-value of <0.05 and were included in the multivariate analysis: age category, exclusively breastfed for >1 month, sessum score, and food insecure during ANC. Maternal anaemia during ANC was also included in the multivariate analysis despite not having a statistically significant p-value (p=0.13), but due to its known clinical significance as a predictor of child anaemia^{10,15}.

A multivariate binary logistic regression model (*Table 2*) was used to predict the binary outcome of anaemia status based on five risk factor variables as discussed above. The analysis revealed that three variables were significantly associated with the risk of anaemia when controlled for other predictors in the model, with p-value less than 0.05. These were child age category, exclusive breastfeeding for >1 month, and sessum score. The child age category of >2.0 to <6.0 months was compared with the reference category of ≥ 6.0 to 59 months, resulting in an odds ratio of 0.33 (95% CI, 0.21-0.52), indicating that children in the >2.0 to <6.0 months age group had a 67% reduced risk of developing anaemia compared to those in the ≥ 6.0 to 59 months age group. Exclusive breastfeeding for more than 1 month was found to increase the risk of anaemia, with an odds ratio of 1.45 (95% CI: 1.02-2.07) compared to children who were not exclusively breastfed for more than one month. The sessum score, a composite measure of socioeconomic status, was also found to be a significant predictor of anaemia with an odds ratio of 0.99 (95% CI: 0.99-1.00), indicating a 1% decrease in the odds of developing anaemia for each unit increase in the sessum score (*Figure 3*).

To check for model robustness, we checked for collinearity between predictors to ensure that the estimates for each predictor are not confounded by the presence of other highly correlated predictors. We calculated the variance inflation factor (VIF) for each predictor in the regression model. All predictors had a VIF close to 1 which indicates no collinearity and thus no predictors were removed from the model.

Additionally, we calculated Hosmer-Lemeshow goodness-of-fit statistics to evaluate the fit of the model. The model had chi-square statistic of 3.24 with a p-value 0.92 which indicates the test did not find evidence of a lack of fit in the regression model. Therefore, the model's predicted probabilities match the observed outcomes well.

Table 2. Binary logistic regression models for risk factors associated with anaemia status during any LRTI/pneumonia episode (binary outcome)

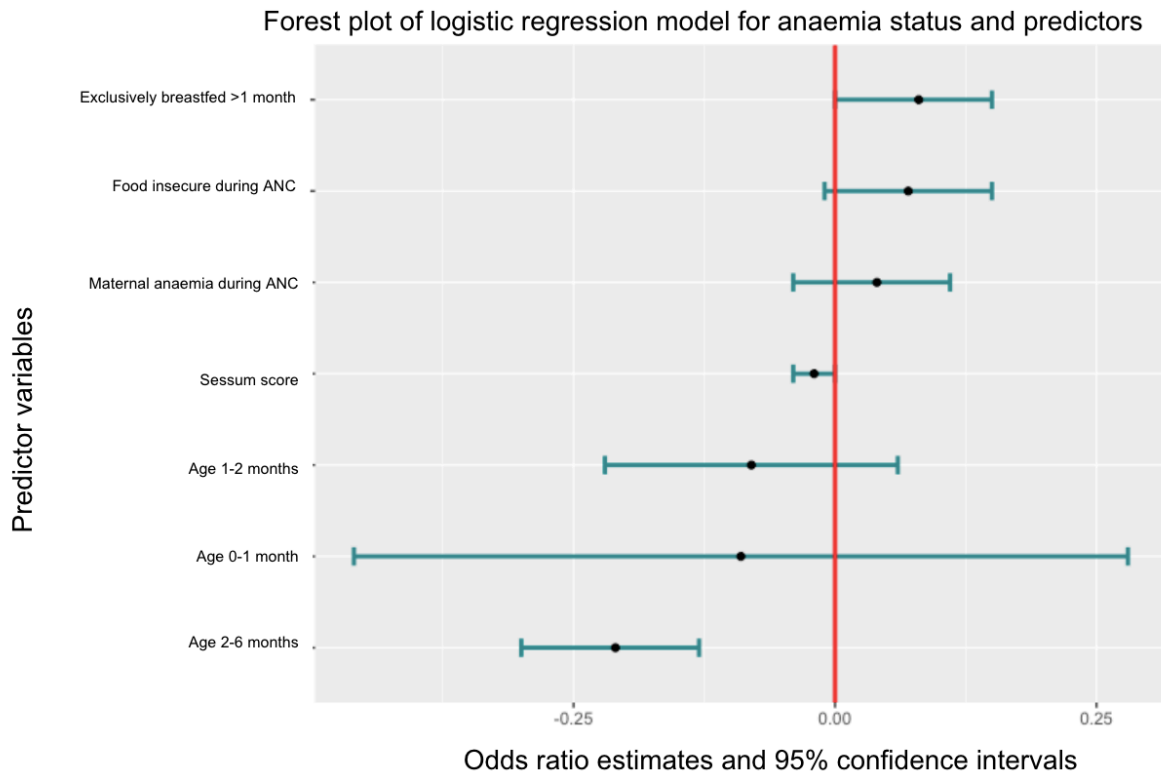
Model	Coefficients		95% Confidence Interval	
	Estimated Odds ratio	P-value	Lower Bound	Upper Bound
Univariate binary logistic regressions^a				
Child age groups (months) ^b				
≤ 1.0	0.38	0.23	0.06	1.54
> 1.0 to 2.0	0.52	0.045	0.27	0.96
> 2.0 to < 6.0	0.32	<0.001	0.21	0.48
Sex (female)	0.83	0.24	0.60	1.14
Premature (<37 weeks' gestation)	1.41	0.07	0.97	2.05
HIV exposed uninfected	1.13	0.51	0.78	1.62
Maternal anaemia during ANC	1.29	0.13	0.93	1.80
Exclusive breastfeeding for >1mo	1.49	0.015	1.08	2.06
Sessum ^c score	0.99	0.0034	0.99	1.00
Food insecure during ANC	1.47	0.025	1.05	2.05
Multivariate binary logistic regressions^a				
Child age groups (months) ^b				
≤ 1.0	0.66	0.64	0.09	3.53
> 1.0 to 2.0	0.68	0.26	0.34	1.30
> 2.0 to < 6.0	0.33	<0.001	0.21	0.52
Maternal anaemia during ANC	1.20	0.30	0.85	1.72
Exclusive breastfeeding for >1mo	1.45	0.042	1.02	2.07
Sessum ^c score	0.99	0.030	0.99	1.00
Food insecure during ANC	1.38	0.093	0.95	2.02

a. Dependent variable: anaemia status

b. Reference category: ≥ 6.0 to 59 months

c. Sessum score is a sum of standardised SES components from SASH²⁶ including current maternal employment status, highest level of education completed, household income, and asset index

Figure 4. Forest plot of multivariate binary logistic regression model for anaemia status and predictors



*Reference category for age is ≥ 6.0 to 59 months

3.4 Growth outcomes

Two initial univariate linear regression models (*Table 3*) were conducted to predict weight-for-age z-scores (WAZ) and height-for-age z-scores (HAZ) in children with anaemia. Both models did not find a significant p-value of <0.05

Two multivariate linear regression models were conducted to predict weight-for-age z-scores (WAZ) and height-for-age z-scores (HAZ) in children with anaemia while adjusting for other confounding risk factors. The results of the multivariate linear regression models showed that child anaemia status was a significant predictor of both growth outcomes when controlling for confounding variables (*Table 3*). Children with anaemia had a 23% higher risk of having a lower WAZ (95% CI 1.02-1.47, $p=0.026$) compared to children without anaemia (*Figure 4*). On the other hand, children with anaemia had a 24% reduced risk of having a lower HAZ (95% CI 0.62-0.95, $p=0.015$) compared to children without anaemia (*Figure 5*). Confounding variables included in the models were: sex, sessum score, and severity of LRTI/pneumonia (hospitalisation).

Both models showed good fit with adjusted R-squared values of 0.50 for the WAZ model and 0.49 for the HAZ model and p-values <0.001 . Collinearity was checked by calculating the

variance inflation factor (VIF) for each predictor, and all VIF values were around 1.00 to 1.10, indicating no multicollinearity and no need to remove predictors.

Table 3. Linear regression models for growth outcomes

Model	Coefficients		95% Confidence Interval	
	Estimated Odds ratio	P-value	Lower Bound	Upper Bound
Univariate linear regression				
WAZ	0.99	0.84	0.90	1.09
Univariate linear regression				
HAZ	0.93	0.097	0.85	1.01
Multivariate linear regression – WAZ				
Child anaemia	1.23	0.026	1.02	1.47
Sex (female)	1.17	0.08	0.98	1.39
Sessum ^a score	1.00	0.42	1.00	1.00
HAZ	1.78	<0.001	1.70	1.86
Hospitalised	0.61	<0.001	0.50	0.75
Multivariate linear regression - HAZ				
Child anaemia	0.76	0.015	0.62	0.95
Sex (female)	1.09	0.42	0.88	1.34
Sessum ^a score	1.00	0.014	1.00	1.01
WAZ	2.26	<0.001	2.11	2.41
Hospitalised	1.03	0.86	0.80	1.31

a. Sessum score is a sum of standardised SES components from SASH²⁶ including current maternal employment status, highest level of education completed, household income, and asset index

Figure 5. Forest plot of linear regression model for WAZ and predictors



Figure 6. Forest plot of linear regression model for HAZ and predictors



4.0 Discussion

In this South African birth cohort sub-study, the overall prevalence of anaemia among under-fives at the time of any LRTI/pneumonia episode was 32.3% (95% CI, 28.9 - 35.9), with higher prevalence among children treated in hospital compared to those treated in ambulatory care (38.9% compared to 30.3% respectively, $p=0.04$). This indicates that the severity of pneumonia, as indicated by hospitalisation, is positively associated with a higher prevalence of anaemia in early childhood. It is important to note that these estimations are lower than South Africa's overall estimated anaemia burden for children aged 6-59 months (44.4%)⁶ and lower than the previous estimations among hospitalised children (no ambulatory care) aged 24-48 months from this cohort (52.5%)²³. However, results are consistent with previous studies that have found pneumonia can affect the severity of anaemia in children, and conversely, anaemia can increase the risk and severity of pneumonia¹⁵⁻¹⁹. Additionally, under-fives who experienced 2 or more LRTI/pneumonia episodes were 1.28 times as likely to have anaemia compared to under-fives who experienced their first LRTI/pneumonia episode (95% CI, 1.03 - 1.59, $p=0.023$). This suggests that repeated episodes of LRTI/pneumonia may be a risk factor for anaemia in under-fives and thus children admitted for a recurrent episode of LRTI/pneumonia should be assessed for anaemia.

One of the key findings of this study was the strong risk factor associations between anaemia and child age (6-59 months), exclusively breastfed for more than 1-month, low sessum score (a measure of socioeconomic status), and food insecurity during ANC ($p<0.05$). These findings

suggest that older children from socioeconomically disadvantaged families and those with inadequate nutrition are at higher risk of developing anaemia in the context of LRTI/pneumonia.

In terms of breastfeeding, our results are in line with previous studies³⁰ that found childhood anaemia worsens as the duration of breastfeeding increases due to the limited iron content in breast milk from anaemic mothers exposed to poor nutrition and food insecurity. Although not statistically significant, children of mothers with anaemia in our sample were more likely to be anaemic themselves (OR 1.30, $p=0.30$), which highlights the importance of maternal health and alternative feeding interventions to combat child anaemia risk. An important limitation to note is that this data lacked consistent maternal haemoglobin measures (g/dL) which may have affected our ability to see a strong association.

Another key finding was the differing growth outcomes among anaemic children. Children with anaemia had a 23% increased risk of low WAZ (95% CI 1.02-1.47, $p=0.026$) and a 24% reduced risk of low HAZ (95% CI 0.62-0.95, $p=0.015$). A WAZ score less than -2 indicates wasting which is a form of acute malnutrition. Whereas a HAZ score less than -2 indicates stunting, which is a form of chronic malnutrition that can have long term effects on a child health and development. Thus, the anaemic children in our sample were at higher risk of wasting and lower risk of stunting compared to non-anaemic children. These results may be due to our sample not being chronically malnourished, which would lead to stunting and instead having decreased energy levels leading to weight loss and higher risks of wasting.

The cross-sectional study design is a limitation to address. Due to this design, the direction of causality between LRTI/pneumonia, anaemia, and risk factors cannot be determined. The study was conducted in a peri-urban area 60km outside Cape Town, South Africa and thus results may not be generalizable to other populations.

Due to low levels of literacy among respondents, fieldworkers provide help in administering questionnaires that are ordinarily self-administered. This may have led to respondents feeling reluctant to disclose personal or embarrassing information. However, the benefits of proper completion of questionnaires outweighs the potential costs of bias, especially given that the longitudinal study design allows for increased rapport between participants and members of the research team.

Further studies should examine the causal relationships between LRTI/pneumonia and anaemia to better understand temporality and determine effective interventions to prevent co-occurrence.

5.0 Conclusions

In conclusion, this cross-sectional sub-study that used data from the DCHS provides evidence of high prevalence of concurrent pneumonia and anaemia among under-fives in South Africa. The results of this study demonstrate the complex interplay between these conditions and various risk factors including, child age (ages 6-59 months), maternal anaemia, exclusive breastfeeding for more than 1-month, low socioeconomic status, and food insecurity. These findings highlight the need for multi-sectoral approaches to address not only medical treatment and interventions among children hospitalised for LRTI/pneumonia with anaemia, but also the underlying social determinants of health (including poverty and food insecurity) that contribute to the burden of these conditions in SSA countries. The results of this study can inform policies and programs aimed at reducing the burden of LRTI/pneumonia and anaemia among under-fives in South Africa and contribute to global efforts to achieve the 2025 Global Nutrition Targets to reduce anaemia in this population²⁰.

6.0 Declarations

Ethics approvals and consent to participate:

- Written informed consent obtained from all study participants, for participation and data abstraction from routine clinical records during study period.
- DCHS received ethical approval from: University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (UCT HREC 401/2009) (Appendix 1).
- This study received ethical approval from the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (662/2022) (Appendix 2).

7.0 References (Vancouver)

1. Pneumonia. Accessed August 29, 2022. <https://www.who.int/news-room/fact-sheets/detail/pneumonia>

2. von Schirnding YE, Yach D, Klein M. Acute respiratory infections as an important cause of childhood deaths in South Africa. *South Afr Med J Suid-Afr Tydskr Vir Geneeskd.* 1991;80(2):79-82.
3. Wyndham CH. Leading causes of death among children under 5 years of age in the various population groups of the RSA in 1970. *South Afr Med J Suid-Afr Tydskr Vir Geneeskd.* 1984;66(19):717-718.
4. le Roux DM, Myer L, Nicol MP, Zar HJ. Incidence and severity of childhood pneumonia in the first year of life in a South African birth cohort: the Drakenstein Child Health Study. *Lancet Glob Health.* 2015;3(2):e95-e103. doi:10.1016/S2214-109X(14)70360-2
5. Anaemia. Accessed August 29, 2022. <https://www.who.int/health-topics/anaemia>
6. Anaemia in women and children. Accessed August 29, 2022. https://www.who.int/data/gho/data/themes/topics/anaemia_in_women_and_children
7. Balarajan Y, Ramakrishnan U, Ozaltin E, Shankar AH, Subramanian SV. Anaemia in low-income and middle-income countries. *Lancet Lond Engl.* 2011;378(9809):2123-2135. doi:10.1016/S0140-6736(10)62304-5
8. Tolentino K, Friedman JF. An update on anemia in less developed countries. *Am J Trop Med Hyg.* 2007;77(1):44-51.
9. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995–2011: a systematic analysis of population-representative data - The Lancet Global Health. Accessed August 29, 2022. [https://www.thelancet.com/journals/langlo/article/PIIS2214-109X\(13\)70001-9/fulltext](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(13)70001-9/fulltext)
10. Obasohan PE, Walters SJ, Jacques R, Khatab K. A Scoping Review of the Risk Factors Associated with Anaemia among Children Under Five Years in Sub-Saharan African Countries. *Int J Environ Res Public Health.* 2020;17(23):8829. doi:10.3390/ijerph17238829
11. WHO. The Global Prevalence of Anaemia in 2011. Published online 2015. https://apps.who.int/iris/bitstream/handle/10665/177094/9789241564960_eng.pdf?sequence=1

12. Lozoff B, Beard J, Connor J, Barbara F, Georgieff M, Schallert T. Long-lasting neural and behavioral effects of iron deficiency in infancy. *Nutr Rev.* 2006;64(5 Pt 2):S34-43; discussion S72-91. doi:10.1301/nr.2006.may.s34-s43
13. Walker SP, Wachs TD, Gardner JM, et al. Child development: risk factors for adverse outcomes in developing countries. *Lancet Lond Engl.* 2007;369(9556):145-157. doi:10.1016/S0140-6736(07)60076-2
14. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Published online 2011. https://apps.who.int/iris/bitstream/handle/10665/85839/WHO_NMH_NHD_MNM_11.1_eng.pdf
15. Dos Santos RF, Gonzalez ESC, de Albuquerque EC, et al. Prevalence of anemia in under five-year-old children in a children's hospital in Recife, Brazil. *Rev Bras Hematol E Hemoter.* 2011;33(2):100-104. doi:10.5581/1516-8484.20110028
16. Odeyemi AO, Odeyemi AO, Musa TL. Determinants of Outcome among Under-Five Children Hospitalized with Pneumonia at a Tertiary Health Facility in South-West Nigeria. *West Afr J Med.* 2021;38(2):114-119.
17. Ramakrishnan K, Harish PS. Hemoglobin level as a risk factor for lower respiratory tract infections. *Indian J Pediatr.* 2006;73(10):881-883. doi:10.1007/BF02859279
18. Savitha MR, Nandeeshwara SB, Pradeep Kumar MJ, ul-Haque F, Raju CK. Modifiable risk factors for acute lower respiratory tract infections. *Indian J Pediatr.* 2007;74(5):477-482. doi:10.1007/s12098-007-0081-3
19. Chisti MJ, Kawser CA, Rahman ASMMH, et al. Prevalence and outcome of anemia among children hospitalized for pneumonia and their risk of mortality in a developing country. *Sci Rep.* 2022;12(1):10741. doi:10.1038/s41598-022-14818-2
20. Global nutrition targets 2025: anaemia policy brief. Accessed August 29, 2022. <https://www.who.int/publications-detail-redirect/WHO-NMH-NHD-14.4>
21. Zar HJ, Barnett W, Myer L, Stein DJ, Nicol MP. Investigating the early-life determinants of illness in Africa: the Drakenstein Child Health Study. *Thorax.* 2015;70(6):592-594. doi:10.1136/thoraxjnl-2014-206242
22. Zar HJ, Barnett W, Stadler A, Gardner-Lubbe S, Myer L, Nicol MP. Aetiology of childhood pneumonia in a well vaccinated South African birth cohort: a nested case-

- control study of the Drakenstein Child Health Study. *Lancet Respir Med*. 2016;4(6):463-472. doi:10.1016/S2213-2600(16)00096-5
23. Wedderburn CJ, Ringshaw J, Donald K, et al. Effects of Maternal and Early-Life Anaemia on Child Brain Development: A South African Birth Cohort Study. Published online September 9, 2021. doi:10.2139/ssrn.3920258
24. Early-life respiratory syncytial virus lower respiratory tract infection in a South African birth cohort: epidemiology and effect on lung health - The Lancet Global Health. Accessed August 29, 2022. [https://www.thelancet.com/journals/langlo/article/PIIS2214-109X\(20\)30251-5/fulltext](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30251-5/fulltext)
25. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards based on length/height, weight and age. *Acta Paediatr Oslo Nor 1992 Suppl*. 2006;450:76-85. doi:10.1111/j.1651-2227.2006.tb02378.x
26. Myer L, Stein DJ, Grimsrud A, Seedat S, Williams DR. Social determinants of psychological distress in a nationally-representative sample of South African adults. *Soc Sci Med 1982*. 2008;66(8):1828-1840. doi:10.1016/j.socscimed.2008.01.025
27. Bickel, Gary, Mark Nord, Cristofer Price, William Hamilton, and John Cook. Guide to Measuring Household Food Security, Revised 2000. Published online March 2000.
28. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST). Accessed August 29, 2022. <https://www.who.int/publications-detail-redirect/978924159938-2>
29. Sandoval C. Approach to the child with anemia. In: TWP, editor. UpToDate. UpToDate Inc. (2018).
30. Buck S, Rolnick K, Nwaba AA, Eickhoff J, Mezu-Nnabue K, Esenwah E, Mezu-Ndubuisi OJ. Longer breastfeeding associated with childhood anemia in rural south-eastern Nigeria. *International Journal of Pediatrics*. 2019 Jun 10;2019.
31. Moschovis PP, Wiens MO, Arlington L, et al. Individual, maternal and household risk factors for anaemia among young children in sub-Saharan Africa: a cross-sectional study. *BMJ Open* 2018;8:e019654. doi:10.1136/bmjopen-2017-019654

PART C: APPENDICES

Appendix 1: DCHS HREC Renewal (401/2009; 03AUG2022)



FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee



FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
<input checked="" type="checkbox"/> Approved	Annual progress report	Approved until/next renewal date	30-8-23
<input type="checkbox"/> Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	4/8/2022

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
<http://www.health.uct.ac.za/fhs/research/humanethics/forms>



Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	27 July 2022		
HREC REF Number	401/2009	Current Ethics Approval was granted until	30 August 2022
Protocol title	Drakenstein Child Health Study		
Protocol number (if applicable)	Version 1.21		
Are there any sub-studies linked to this study?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	
If yes, could you please provide the HREC Reference number for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.	Details can be found in the appendix attached.		
Principal Investigator	Prof Heather Zar		



Department / Office	Department of Paediatrics and Child Health
Internal Mail Address	Red Cross War Children's Hospital

1.1 Does this protocol receive US Federal funding?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval? Note: Any annual approvals for Full Committee review MUST be submitted on the monthly HREC submission dates. (Please send electronic copy for full committee review to hrec-submission@uct.ac.za)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

If yes in 1.2 please complete section 1.3 below for invoicing purposes

1.3 Ethics Renewal Fee

Please (tick ✓) appropriate box for billing purposes:

Submission Type	Description	New fee /Vat Incl.	tick ✓
Research funded solely from UCT departmental/divisional/group budget	Annual evaluation of research progress report for re-certification	R0,00	<input type="checkbox"/>
Non-sponsored student research for degree purposes at UCT/Other Universities & Colleges	Annual evaluation of research progress report for re-certification	R0,00	<input type="checkbox"/>
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Full Committee Approval	R7000,00	<input type="checkbox"/>
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Expedited review	R3 710,00	<input type="checkbox"/>
Annual re-certification / Progress report (FHS016 Form)	National grant funded research - Annual evaluation of research progress report for re-certification for Full Committee Approval	R6000,00	<input type="checkbox"/>
Annual re-certification / Progress report (FHS016 Form)	National Grant funded research for Annual evaluation of research progress report for re-certification for Expedited review	R1 500,00	<input type="checkbox"/>

NB: Protocols funded by UCT (e.g. departmental funding / student research) and by certain grant funding organizations (e.g. MRC, NRF, CANSAs) are exempt from these charges.

Please provide details for invoicing, either complete section 1 or 2 :

1. Invoice billing – Directly to Sponsor

Sponsor's name	MRC unit funding
Billing Address of Sponsor:	
Vat Number:	



Contact person	
Telephone number	
Email Address	
2. Internal Journal Billing:	
Fund Number:	
Cost Centre Number:	
Account Holder Name:	
Division of Account Holder:	

2. List of documentation for approval

FHS016 Annual Renewal FHS006 Amendment

3. Protocol status (tick ✓)

<input type="checkbox"/>	Open Enrolment
<input checked="" type="checkbox"/>	Closed to enrolment (tick ✓)
<input checked="" type="checkbox"/>	Research-related activities are ongoing
<input type="checkbox"/>	Research-related activities are complete, long-term follow-up only
<input type="checkbox"/>	Research-related activities are complete, data analysis only
<input type="checkbox"/>	Main study is complete but sub-study research-related activities are ongoing
<input type="checkbox"/>	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date	1232
Number of participants enrolled, since last HREC Progress report (continuing review)	0
Additional number of participants still required	0

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	605
---------------------------------------------------------------------------------------------	-----

6. Cumulative summary of participants



Total number of participants who provided consent	1232												
Number of participants determined to be ineligible (i.e. after screening)	1471												
Number of participants currently active on the study	980												
Number of participants completed study (without events leading to withdrawal)	0												
Number of participants withdrawn at participants' request (i.e. changed their mind)	33												
Number of participants withdrawn by PI due to toxicity or adverse events	0												
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	0												
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	239												
<table border="0" style="width: 100%;"> <tr> <td style="padding-left: 100px;">Unable to contact</td> <td style="text-align: right;">37</td> </tr> <tr> <td style="padding-left: 100px;">Relocated</td> <td style="text-align: right;">82</td> </tr> <tr> <td style="padding-left: 100px;">Pregnancy losses/Child died</td> <td style="text-align: right;">67</td> </tr> <tr> <td style="padding-left: 100px;">Mother/ guardian unable to attend visits</td> <td style="text-align: right;">33</td> </tr> <tr> <td style="padding-left: 100px;">Other</td> <td style="text-align: right;">20</td> </tr> <tr> <td style="padding-left: 100px;">TOTAL</td> <td style="text-align: right;">239</td> </tr> </table>	Unable to contact	37	Relocated	82	Pregnancy losses/Child died	67	Mother/ guardian unable to attend visits	33	Other	20	TOTAL	239	
Unable to contact	37												
Relocated	82												
Pregnancy losses/Child died	67												
Mother/ guardian unable to attend visits	33												
Other	20												
TOTAL	239												
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	0												

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:



The Drakenstein Child Health study aims to provide data on the early life exposures and risk factors that impact on child health including long-term illness. A key focus is on the aetiology, risk factors and long term outcome of pneumonia in children who are well vaccinated (including PCV13) in a low-middle income country setting. As the cohort enters adolescence, there will be less focus on pneumonia and more focus on development of NCDs including asthma, obesity, neurocognition and cardiometabolic health with follow-up of participants through age 15.

Substantial progress has been made towards achieving the objectives and outcomes of the Drakenstein Child Health Study. Enrolment (n=1232) and births (n=1137) were completed in 2015. Currently, all children have completed follow-up visits through 78 months of age. Cohort retention, specimen collection and attendance has been high and consistent with the study objectives (average overall attendance for study visits is 89%); this has been achieved through engagement with participants, families and communities, a consistent experienced study team, community health workers and a dedicated study telephone for participants to call whenever needed. Feedback from participants has indicated high levels of satisfaction with study participation. Staff teams and infrastructure are well established; there is ongoing staff training and careful attention to quality control of clinical procedures as well as laboratory aspects. Additional surveillance for COVID illness or for SARS-CoV-2 infection has been implemented and approved by HREC and the Biosafety committees.

The study currently accommodates 16 PhD students (and a further 13 graduated), 14 masters students (further 16 graduated) and 7 post-doctoral students (further 12 graduated). Data has been presented at or accepted to 132 conferences and 138 manuscripts have been published or submitted to journals.

8. Protocol violations and exceptions (tick ✓ all that apply)

<input checked="" type="checkbox"/>	No prior violations or exceptions have occurred since the original approval
<input type="checkbox"/>	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved
<input type="checkbox"/>	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

9. Amendments (tick ✓ all that apply)

<input checked="" type="checkbox"/>	No Prior amendments have been made since the original approval
<input type="checkbox"/>	Prior amendments have been reported since the last review and have already been approved
<input type="checkbox"/>	New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).

Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.



N/A

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?

Yes No Not applicable

If yes, please describe:

Mothers who have screened for mental health issues or illness have been referred. Children on the study found to have illnesses have been referred to appropriate clinic or hospital staff for follow up.

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)?

Yes No Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?

Yes No Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.

Agency Name		Report attached	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Not applicable
		DSMB report attached	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Not applicable

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?

Yes No

If yes, please explain:

12. Level of risk (tick ✓)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:

Increased

Decreased

Shown no change

If there has been a change, please explain:



--

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk. No new relevant literature available as yet. The study continues to work closely with the PERCH Study (Pneumonia Etiology Research for Child Health), which was launched in 2011 to investigate the risk factors for severe pneumonia through a multi-country case control study and hope to be privy to PERCH's preliminary analysis and publications.

13. Insurance

Please confirm that valid no fault insurance is still in place? (tick ✓)			
<input checked="" type="checkbox"/> Yes		<input type="checkbox"/> No	
If yes, please complete the following:			
Insurer's name:	UCT Indemnity Insurance		
Policy no.		*Coverage Period:	
<i>For UCT sponsored studies please liaise the Insurance office via fhs_sponsorship@uct.ac.za regarding the required documentation and information required obtain a renewed UCT No-fault Insurance Certificate.</i>			

14. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
If yes, please explain and if necessary, attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form EHS013):	

15. Signature

My signature certifies that the above is complete and correct.			
Signature of PI		Date	27 July 2022

Appendix 2: Sub-Study HREC Approval (662/2022; 28OCT2022)



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za

Website: <https://health.uct.ac.za/home/human-research-ethics>

28 October 2022

HREC REF: 662/2022

Prof L Myer

Division of Epidemiology & Biostatistics
Public Health & Family Medicine-FHS
Email: Landon_myer@uct.ac.za
Student: prncar014@myuct.ac.za

Dear Prof Myer

PROJECT TITLE: ANAEMIA IN EARLY CHILDHOOD PNEUMONIA - PREVALENCE, PREDICTORS, AND ASSOCIATED GROWTH IN THE DRAKENSTEIN CHILD HEALTH STUDY (DCHS)-SUB-STUDY LINKED TO 401/2009- (MASTERS CANDIDATE-CARLEY PRENTICE)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 October 2023.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Ms Carley Prentice will also be involved in this study.

Please quote the HREC REF 662/2022 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN

CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number:

IRB00001938 NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix 3: International Journal of Paediatrics Author Guidelines

Guide for Authors

Instruction for Authors

All papers submitted will be blinded of authors' names and origins and subject to screening before being peer-reviewed by Editorial Board members. Authors are requested to ensure that they comply with the following instructions when submitting papers (online submission system).

***Cover letter:** The cover letter should be submitted via website to the editor and indicated the reasons that the paper are suitable to be published in this journal and comprised the e-mail address and telephone of the author responsible for correspondence.

***Conflict of Interest & Copyright Transfer Form:** Authors must state all possible conflicts of interest in the manuscript, including financial, consultant, institutional and other relationships that might lead to bias or a conflict of interest. If there is no conflict of interest, this should also be explicitly stated as none declared. In addition, copyright transfer form is to be completed by corresponding author submitting manuscripts to the International Journal of Pediatrics. This form should be printed and signed by the corresponding author and then submitted via website to the Editor. The corresponding author is responsible for the accuracy and completeness of the submitted information. Please submit both forms via the website.

After the article is accepted in the scientific review stage, the costs related to the editing of English texts will be announced to the corresponding author.

Format of Manuscripts:

1. Aims and scope: International Journal of Pediatrics is a peer-reviewed, open access journal that publishes original research articles, review articles, and clinical studies in all areas of pediatric research.

2. Submissions: The journal accepts submissions presented as an original article, short communication, case report, review article(solicited), or letter to the editor. Manuscript must be accompanied by a covering letter to the editor-in-chief, including title and author(s) name and undertaking that it has not been published or submitted elsewhere. All authors should review the submitted manuscript and the corresponding author should sign the covering letter on their behalf. In case the manuscript was earlier submitted to some other journals and was rejected, the authors must provide full information for proper analysis. Manuscripts submitted in English, must be type written, double-spaced on one side of the A-4 size paper with clear margins on both sides. Tables as well as illustrations should be typed and drawn on a separate paper. Authors are requested to reserve margins of at least 2 cm all around the paper. The figures should be sent in JPEG or GIF format which will produce high quality images in the online edition of the journal.

3. The manuscript should include: Title page, Structured Abstract and Keywords, Text (Introduction, Materials and Methods, Results, Discussion, Conclusion), Acknowledgment and References.

4. Title pages: Title page must be submitted as part of manuscript. This should contain: article title (not to exceed 75 characters, including spaces); authors' names with full first name, their degrees and affiliations (dept., institution, city, state); institution where the work was done

(indicate which author is in which department); a short running title of no more than 45 letters and spaces, with complete address (including e-mail address and postal codes) and telephone and fax numbers.

5. Structured Abstract and Keywords:

Abstract: All manuscripts must include a brief Abstract intelligible without reference to the main text. Formats and word limits for abstracts are summarized below according to the type of article submitted.

Keywords: 3-7 key words or phrases should be provided which should be selected from the body of the text and not duplicate title words. Key words should be provided below the Abstract to assist with indexing of the article.

6. Introduction: This should summarize the purpose and the rationale for the study. It should neither review the subject extensively nor should it have data or conclusions of the study.

7. Materials and Methods: This should include exact method or observation or experiment. If the method is established, give reference but if the method is new, give enough information so that another author is able to perform it. If a drug is used, its generic name, dose and route of administration must be given. For patients, age, sex with mean age \pm standard deviation must be given. Statistical method must be mentioned and specify any general computer program used. The Info system used should be clearly mentioned.

8. Results: It must be presented in the form of text, tables and illustrations. The contents of the tables should not be all repeated in the text. Instead, a reference to the table number may be given.

9. Discussion: This should emphasize the present findings and the variations or similarities with other works in the field of study. The detailed data should not be repeated again.

10. Conclusion: Conclusions should be based on the results.

11. Acknowledgement: All contributors who do not meet the criteria for authorship should be covered. It should include persons who provided technical help, writing assistance and departmental head that only provided general support. Financial and material support and conflict of interests must be written in this section.

12. Tables: Tables should be self-contained and complement, but not duplicate, information contained in the text. Tables should be numbered consecutively in Arabic numerals. Each table should be presented on a separate page with a comprehensive but concise legend above the table. Tables should be double-spaced and vertical lines should not be used to separate columns. Column headings should be brief, with units of measurement in parentheses; all abbreviations should be defined in footnotes. Use superscript letters (not numbers) for footnotes and keep footnotes to a minimum. *, †, ‡ should be reserved for P values. The table and its legend/footnotes should be understandable without reference to the text.

13. Figures: Only scientifically necessary illustrations should be included. All illustrations (line drawings and photographs) are classified as figures. Figures should be cited in consecutive order in the text. Color photographs should be submitted as good quality. Authors have to bear the cost of color printing. Figures and other graphic material sent electronically: May be sent in any common file format, such as TIFF, GIF, JPG, or BMP) as long as quality and resolution are borne in mind.

14. References: Resources should be based on Vancouver style and enter the **Endnote** software. The authors are responsible for the accuracy of the references. For abbreviations of journal names, refer to list of journals indexed in Index Medicus.

Sample references are given below (according to Vancouver style):

Article: Author(s) name (more than 6 names use et al). Title of article. Abbreviation of title of journal Year; Volume (Issue): Page. Example:

Vakili R, Baradran – Heravi A, Barid – Fatehi B, Gholamin M, Ghaemi N, Abbaszadegan M.R. Molecular Analysis of the CYP21 Gene and Prenatal Diagnosis in Families with 21-Hydroxylase Deficiency in Northeastern Iran. *Horm Res* 2005; 63(3): 119 – 124. (Persian)

Chapter: Author(s) name. Chapter. In: Editor(s) name. Book. Edition. Place: Publisher; Year: Page.

Example: Goadsby PJ. Pathophysiology of headache. **In:** Silberstein SD, Lipton RB, Dalessio DJ, et al. *Wolff's headache and other head pain*. 7th ed. Oxford, England: Oxford University Press; 2001: 57 – 72.

Book: Author(s) name. Book. Edition. Place: Publisher; Year: Page. Example: Stillman RJ. Endometriosis. In: Scott RJ, Disaia PhJ, Hammond chB, et al. *Danforth's obstetrics & gynecology*. 8th ed. Philadelphia: Lippincott Williams & willkins; 1999: 669-676.

Dissertation: Author(s) name. Title. Degree. Dissertation. Place: University, College, Year: Page. Example: Abdullahi S. [Study of epidemiologic aspects of otosclerosis in patients with otosclerosis in Ghaem Hospital since 1993 to 2003]. MD. Dissertation. Mashhad: Mashhad University of Medical Sciences, Faculty of Medicine, 2003: 20-35. (Persian)

Electronic Article: Morse SS. Factors in the emergence of infectious diseases. *Emerg Infect Dis* (derail online) 1995 Jan-Mar [cited 1996 Jun 5], 1(1): [24 screens]. Available from: URL; <http://www.cdc.gov/ncidod/EID/eid.htm>

Best regards

International Journal of Pediatrics

TABLES/FIGURES

PART A: RESEARCH PROTOCOL

Table 1: Table of Variables

Variables		Type	Categories
Child Characteristics at time of LRTI/pneumonia episode			
Age		Numeric (months)	Mean (SD)/Median (IQR)
Height		Numeric (cm)	Mean (SD)/Median (IQR)
Weight		Numeric (kg)	Mean (SD)/Median (IQR)
Pneumonia severity		Binary categorical	Ambulatory Hospitalisation
Number of recurrent LRTI/pneumonia episodes experienced per child		Numeric (# episodes)	Mean (SD)/Median (IQR)
		Binary categorical	One episode Two or more episodes
Full Blood Count (FBC)	Haemoglobin (Hb)	Numeric (g/dL)	Mean (SD)/Median (IQR)
		Age categories with binary output	<p>≤ 1.0 month: Anaemic: ≤ 10.7 g/dL Not Anaemic: > 10.7 g/dL</p> <p>> 1.0 to 2.0 months: Anaemic: ≤ 9.4 g/dL Not Anaemic: > 9.4 g/dL</p> <p>> 2.0 to < 6.0 months: Anaemic: ≤ 9.5 g/dL Not Anaemic: > 9.5 g/dL</p> <p>≥ 6.0 to 59 months: Anaemic: ≤ 11.0 g/dl Not Anaemic: > 11.0 g/dl</p>
	White cell count (WCC)	Numeric (x 10 ⁹ /L)	Mean (SD)/Median (IQR)
	Mean Corpuscular Volume (MCV)	Numeric (fl.)	Mean (SD)/Median (IQR)
	Platelet count (PLT)	Numeric (x 10 ⁹ /L)	Mean (SD)/Median (IQR)
For Hospitalisations Only	Oximetry	Binary categorical	Below threshold < 95% Above threshold ≥ 95%
	Hospital duration	Numeric (days)	Mean (SD)/Median (IQR)
	Discharge status	Nominal categorical	Discharged home Died Transferred

(not applicable to ambulatory cases)			
Birth Characteristics			
Sex	Binary categorical	Female Male	
Mode of delivery	Binary categorical	Vaginal Caesarean	
Gestational age	Numeric (weeks)	Mean (SD)/Median (IQR)	
Birth weight	Numeric (grams)	Mean (SD)/Median (IQR)	
HIV exposure	Binary categorical	Unexposed Exposed Uninfected	
Maternal Characteristics			
Age at enrolment	Numeric (years)	Mean (SD)/Median (IQR)	
SES quartiles (sum of standardized SES components (education, income, assets and employment))	Ordinal categorical	Lowest SES Low-mod SES Mod-high SES High SES	
Current smoking	Binary categorical	Yes No	
Prenatal alcohol exposure	Binary categorical	Yes No	
Household food insecurity	Binary categorical	Perceived food secure Perceived food insecure	

Table 2: Study timeline 2022

Actions	May	June	July	Aug	Sept	Oct	Nov	Dec
Literature Review								
Protocol Development								
Ethics Review Submission								
Data Analysis								
Thesis Write-Up								
Submission to UCT for MPH								
Submission to Journal								

PART B: JOURNAL MANUSCRIPT

Figure 1. Drakenstein Child Health Study (DCHS) flowchart

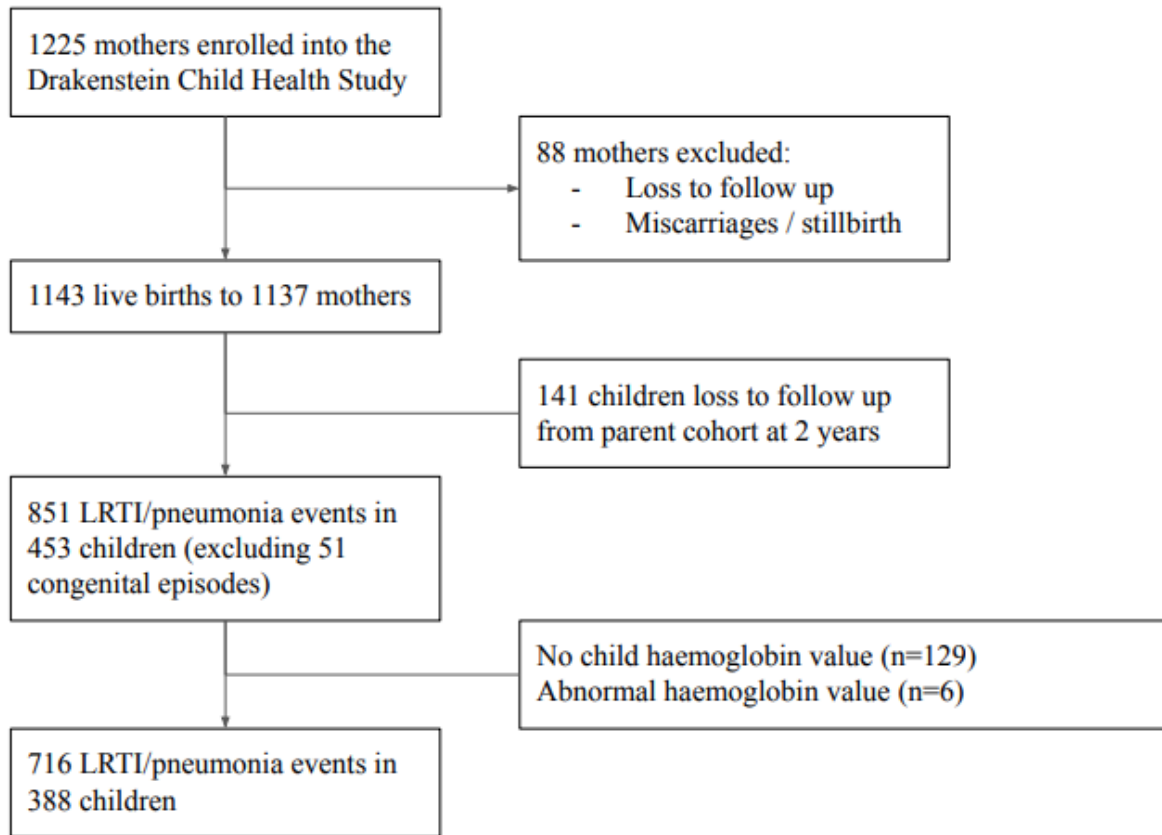


Table 1. Characteristics of anaemic versus non-anaemic children at the time of first LRTI/pneumonia episode

Variable	Overall (n=388)	Anaemia (n=111)	No Anaemia (n=277)	P-value
Child characteristics				
Child age, months (median (IQR))	5.57 (2.66-15.68)	8.38 (2.66-16.14)	5.03 (2.66-15.16)	0.13
Age categories, months				
≤ 1.0	10 (2.58%)	2 (1.80%)	8 (2.89%)	
> 1.0 to 2.0	52 (13.40%)	14 (12.61%)	38 (13.72%)	<0.001
> 2.0 to < 6.0	141 (36.34%)	25 (22.52%)	116 (41.88%)	
≥ 6.0 to 59	185 (47.68%)	70 (63.06%)	115 (41.52%)	
LRTI Severity				
Ambulatory	285 (73.45%)	76 (68.47%)	209 (75.45%)	0.20
Hospitalisation	103 (26.55%)	35 (31.53%)	68 (24.55%)	
WAZ	-0.48 (1.62)	-0.63 (1.87)	-0.42 (1.50)	0.63
HAZ	-1.07 (1.98)	-1.43 (2.29)	-0.92 (1.82)	0.20
Birth characteristics				
Sex (male)	218 (56.19%)	60 (54.05%)	158 (57.04%)	0.67
Premature (<37 weeks' gestation)	71 (18.30%)	24 (21.62%)	47 (16.97%)	0.35
Caesarean delivery	69 (17.78%)	23 (20.72%)	46 (16.61%)	0.40
HIV exposed uninfected	87 (22.42%)	29 (26.13%)	58 (20.94%)	0.33
Maternal and socio-economic characteristics				
Site (Mbekweni)	218 (56.19%)	67 (60.36%)	151 (54.51%)	0.34
Maternal age at birth, years (median (IQR))	26.0 (21.8-31.2)	25.3 (22.0-31.2)	26.4 (21.7-31.2)	0.64
Maternal anaemia during ANC	137 (35.31%)	40 (36.04%)	97 (35.02%)	0.73
Exclusive breastfeeding for >1mo	209 (53.87%)	69 (62.16%)	140 (50.54%)	0.047
Maternal smoking during pregnancy	97 (25.00%)	28 (25.91%)	69 (24.91%)	0.90
Maternal alcohol use during pregnancy	65 (16.75%)	18 (16.22%)	47 (16.97%)	0.93
Sessum score (median (IQR))	-0.12 (-1.21 - 1.40)	-0.20 (-1.58 - 0.86)	-0.11 (-1.13 - 1.72)	0.035
Food insecurity (ANC)	110 (28.35%)	39 (35.14%)	71 (25.61%)	0.15
Food insecurity (14 wks)	40 (10.31%)	10 (9.01%)	30 (10.83%)	0.67

Footnote: Data are n/N(%) or mean (SD) unless otherwise indicated. Continuous variables with normal distribution were compared with unpaired t-tests and when distribution was skewed the Wilcoxon rank-sum test was used. Categorical variables were compared with Chi-squared tests. Anaemia was classified per the WHO recommendations for women and children^{14,29}. Child weight and height measurements were converted to z-scores for weight-for-age (WAZ) and height-for-age (HAZ). Sessum score is a sum of standardised SES components from SASH²⁶ including current maternal employment status, highest level of education completed, household income, and asset index. Other components of the variables displayed in 1 x 1 contingency cells were not shown (including sex (female), full-term (≥37 weeks' gestation), vaginal delivery, HIV unexposed, Site TC

Newman, maternal no anaemia during ANC, not exclusively breastfeeding for >1mo, no maternal smoking during pregnancy, no maternal alcohol use during pregnancy, Food secure (ANC), and Food secure (14 wks)).

Figure 2. Prevalence of Anaemia by LRTI/Pneumonia Severity

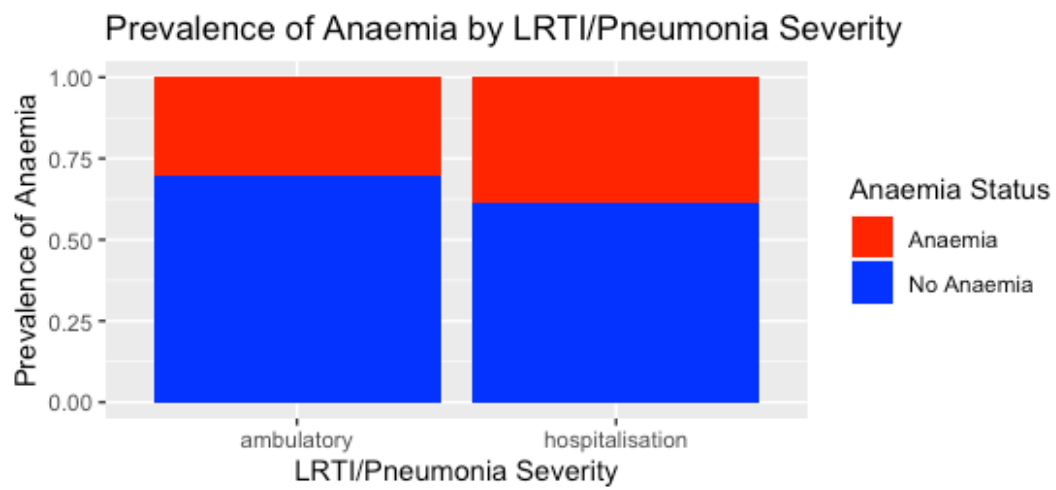


Figure 3. Prevalence of Anaemia by LRTI/Pneumonia Recurrence

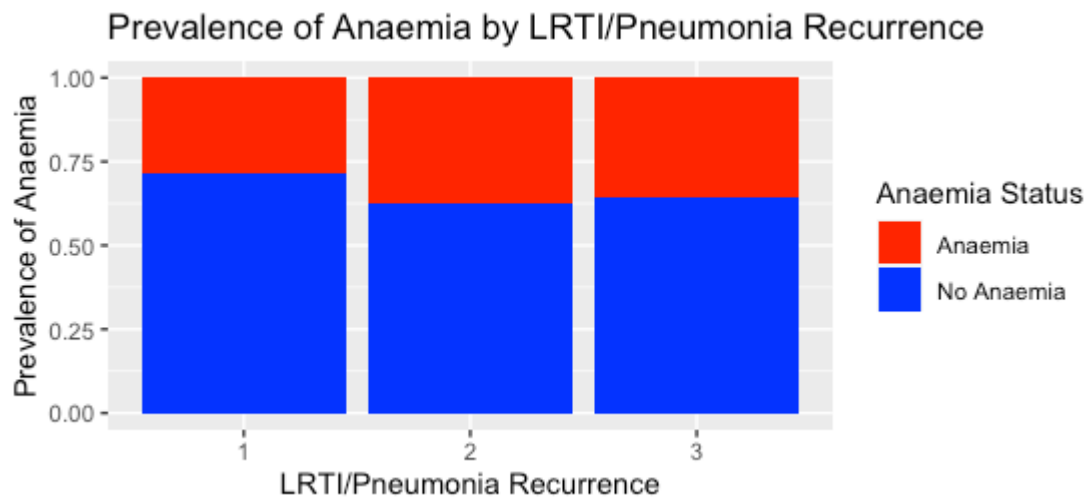


Table 2. Binary logistic regression models for risk factors associated with anaemia status during any LRTI/pneumonia episode (binary outcome)

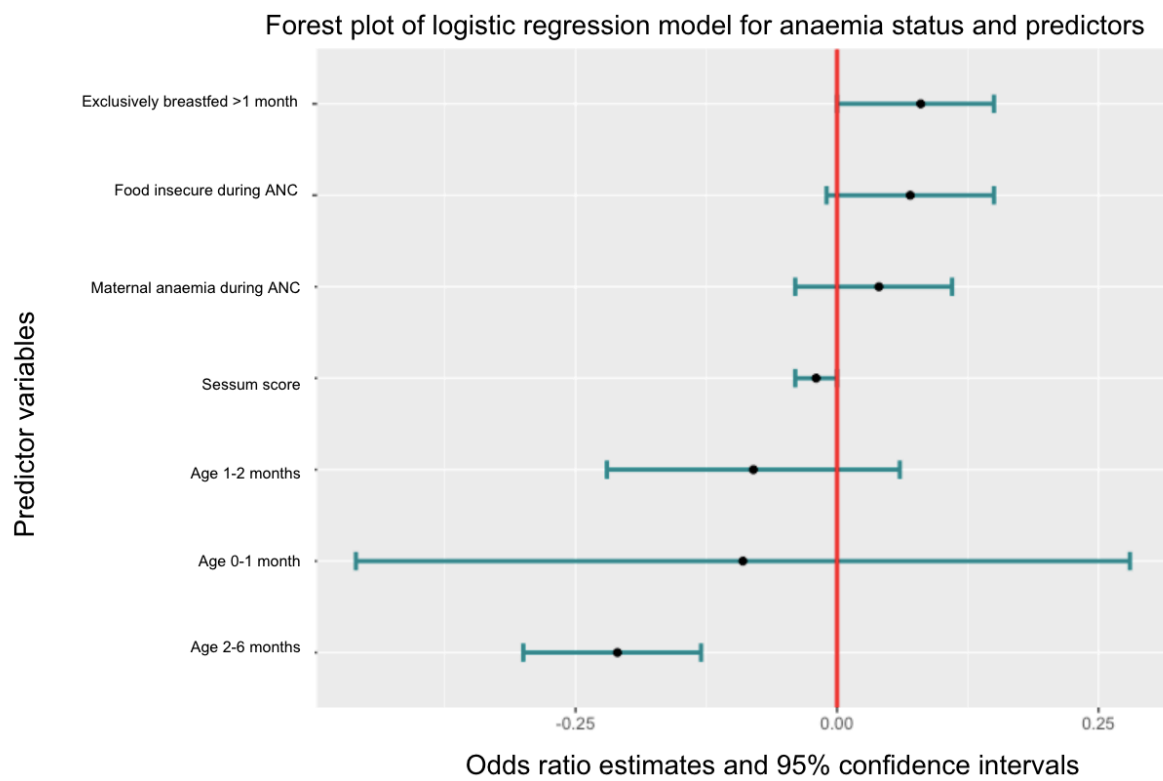
Model	Coefficients		95% Confidence Interval	
	Estimated Odds ratio	P-value	Lower Bound	Upper Bound
Univariate binary logistic regressions ^a				
Child age groups (months) ^b				
≤ 1.0	0.38	0.23	0.06	1.54
> 1.0 to 2.0	0.52	0.045	0.27	0.96
> 2.0 to < 6.0	0.32	<0.001	0.21	0.48
Sex (female)	0.83	0.24	0.60	1.14
Premature (<37 weeks' gestation)	1.41	0.07	0.97	2.05
HIV exposed uninfected	1.13	0.51	0.78	1.62
Maternal anaemia during ANC	1.29	0.13	0.93	1.80
Exclusive breastfeeding for >1mo	1.49	0.015	1.08	2.06
Sessum ^c score	0.99	0.0034	0.99	1.00
Food insecure during ANC	1.47	0.025	1.05	2.05
Multivariate binary logistic regressions ^a				
Child age groups (months) ^b				
≤ 1.0	0.66	0.64	0.09	3.53
> 1.0 to 2.0	0.68	0.26	0.34	1.30
> 2.0 to < 6.0	0.33	<0.001	0.21	0.52
Maternal anaemia during ANC	1.20	0.30	0.85	1.72
Exclusive breastfeeding for >1mo	1.45	0.042	1.02	2.07
Sessum ^c score	0.99	0.030	0.99	1.00
Food insecure during ANC	1.38	0.093	0.95	2.02

a. Dependent variable: anaemia status

b. Reference category: ≥ 6.0 to 59 months

c. Sessum score is a sum of standardised SES components from SASH²⁶ including current maternal employment status, highest level of education completed, household income, and asset index

Figure 4. Forest plot of multivariate binary logistic regression model for anaemia status and predictors



*Reference category for age is ≥ 6.0 to 59 months

Table 3. Linear regression models for growth outcomes

Model	Coefficients		95% Confidence Interval	
	Estimated Odds ratio	P-value	Lower Bound	Upper Bound
Univariate linear regression				
WAZ	0.99	0.84	0.90	1.09
Univariate linear regression				
HAZ	0.93	0.097	0.85	1.01
Multivariate linear regression – WAZ				
Child anaemia	1.23	0.026	1.02	1.47
Sex (female)	1.17	0.08	0.98	1.39
Sessum ^a score	1.00	0.42	1.00	1.00
HAZ	1.78	<0.001	1.70	1.86
Hospitalised	0.61	<0.001	0.50	0.75
Multivariate linear regression - HAZ				
Child anaemia	0.76	0.015	0.62	0.95
Sex (female)	1.09	0.42	0.88	1.34
Sessum ^a score	1.00	0.014	1.00	1.01
WAZ	2.26	<0.001	2.11	2.41
Hospitalised	1.03	0.86	0.80	1.31

a. Sessum score is a sum of standardised SES components from SASH²⁶ including current maternal employment status, highest level of education completed, household income, and asset index

Figure 5. Forest plot of linear regression model for WAZ and predictors

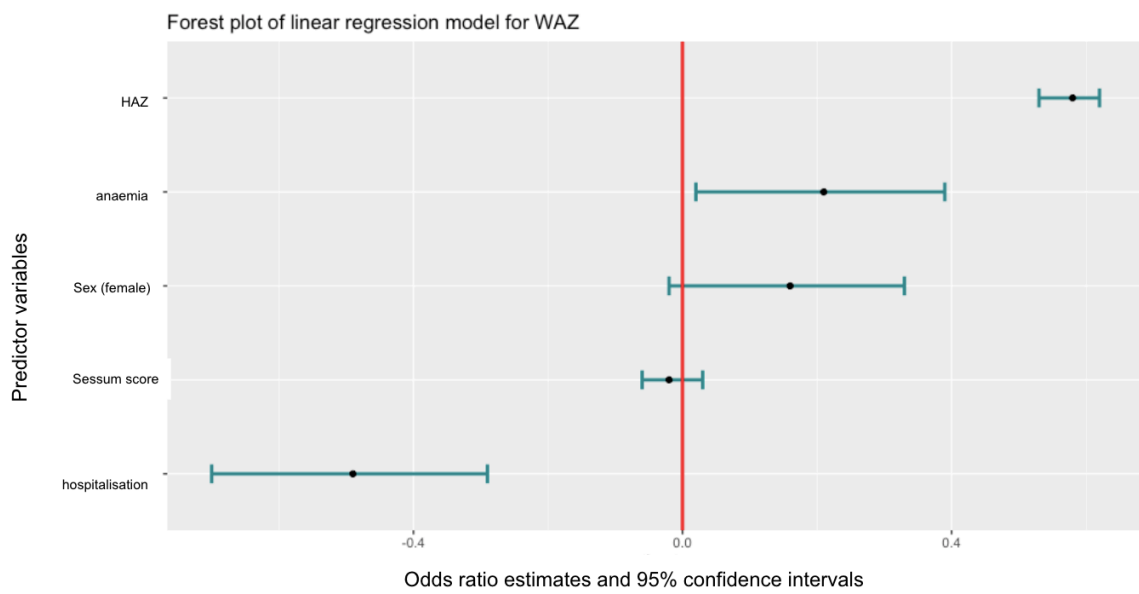


Figure 6. Forest plot of linear regression model for HAZ and predictors

