Risk factors associated with the severity of pneumonia in a cohort of hospitalised children in a rural setting

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Declaration

I declare that this thesis and the content contained herein is of my own original work. Unless stated otherwise in the thesis, I am the owner and author of its content. I have not, in part nor in its entirety, submitted this work previously for obtaining any qualification.

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Abstract

Title

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Background

Pneumonia remains a leading cause of death in South African children under 5 years of age. Known risk factors have been the focus of public health strategies to mitigate disease. This study aimed to determine adverse household environmental factors associated with severe pneumonia in children admitted to Worcester Provincial Hospital (WPH). We compared the odds of adverse household environmental factors with severe pneumonia to non-severe pneumonia in children under 5 years admitted to WPH.

Methods

We conducted a prospective case control study at WPH from the 1st of January 2019 to 31 December 2019 including children aged 0-59 months admitted with pneumonia. Using the WHO definition, children were categorised as having severe or non-severe pneumonia. Structured interviews with consenting primary caregivers were conducted in both groups on weekdays throughout the year. We compared demographic, social, maternal, infant, and household factors in children with severe pneumonia and non-severe pneumonia using multivariable logistic regression.

Results

A total of 305 children were assessed, comprising of 134 (43.9%) cases with severe pneumonia and 171 (56.1%) controls with non-severe pneumonia. Baseline characteristics of children including a median age of 6.9 months (IQR 2.5-17.5), exclusive breastfeeding practice (51.5%; n=157), term gestation at birth (65%; n=199), appropriate nutritional status (81.6%; n=249), appropriate immunisation status (86.9%; n=265), and HIV unexposed uninfected status (81.3%; n=248) were similar between groups. Caregiver characteristics were also comparable between groups including a median age of 28 years (IQR 23-33), South African citizenship (94.7%; n=288), some secondary schooling education (71.2%, n=217), and reported HIV negative status (81%; n=247). Univariable regression analysis did not demonstrate an association between severe pneumonia and adverse household environmental factors including indoor tobacco smoke exposure (unadjusted odds ratio (uOR) 0.73; 95% confidence interval (CI) 0.46-1.16), overcrowding (uOR 0.72; 95% CI 0.45-1.15) or indoor biomass fuel exposure (uOR 1.49; 95% CI 0.91-2.43). Multivariable analysis, adjusting for factors known to be associated with severe pneumonia in children (including age <3 months, birth weight <1500g, any breastfeeding, complete immunisation status, child's HIV infection status, young maternal age, and caregiver education less than matric), did not demonstrate an association between severe pneumonia and adverse household environmental factors. However, children with severe pneumonia had at least a five

times greater odds (aOR 5.42; 95% CI 1.10-26.65) of living in a household with a pit latrine toilet compared to any other toilet than children with non-severe pneumonia.

Conclusion

Within a fairly homogenous group of children admitted with pneumonia, few factors were found to be associated with pneumonia severity, except for living in a household with pit latrine toilet . Broadly, this may represent socioeconomic vulnerability and the risk associated with developing severe pneumonia and should be further explored in this setting. We did not identify any specific modifiable household environmental factors to be associated with severe pneumonia, however these factors could still be important risk factors for incident pneumonia, even if not associated with the severity of the pneumonia episode.

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Dedication

To my parents, Zainab Chickte Barday and Mohammed Hanief Barday.

Thank you for your strength, the value you place in education, and its application in the pursuit of caring for others.

Definitions

Asthma	Recurrent and reversible episodes of bronchial obstruction manifesting in shortness of breath and wheeze that responds to bronchodilators[1,2]
Biomass fuel	Solid fuels – wood, coal, animals dung, agricultural products Liquid fuels – Liquid petroleum gas (LPG), paraffin, naphtha, ethanol Gas fuels – methane, butane, propane
Breastfeeding	No breastfeeding – exclusive formula feeding Partial breastfeeding – breastfeeding for less than 6 months with the introduction of alternative feeds Predominantly breastfeeding – breastfeeding is the predominant source of nutrition (including breast milk expressed from a wet nurse) in addition to other liquids (water/tea/juice) Exclusive breastfeeding – breastfeeding (including breast milk expressed from a wet nurse) for 6 months to the exclusion of any other sources of fluids/ feeds[3]
Bronchiolitis	Respiratory disorder caused by an infective agent resulting in inflammation of the bronchioles and manifesting as cough and wheeze[1,2]
Bronchopneumonia	Subtype of pneumonia characterised by suppurative inflammation localised in patches around bronchi which may or may not be localised to a single lobe of the lung[4]
Cerebral palsy	Neurological disorder caused by non-progressive brain injury or malformation during brain development[1]
Care Dependency Grant	The Care Dependency Grant (CDG) is a monetary social grant intended to provide support to parents, primary care-givers or foster parents of any child with severe mental and/or physical disabilities[5,6]
Child Support Grant	The Child Support Grant (CSG) is a monetary aid intended to provide for the basic needs of South African children whose primary-care givers are not able to provide sufficient support due to unemployment or poverty[5,7]
Community Health Centre	The Community Health Centre (CHC) functions as a primary health care centre that also provides 24-hour emergency maternity care, casualty care, and short stay ward. CHCs refer to district hospitals for higher level care[8]
Complete vaccinations	Vaccinations received in accordance with the South African Expanded Program on Immunisations or scheduled for within 2 weeks
Confirmed tuberculosis	Bacteriological confirmation of tuberculosis obtained from at least one respiratory specimen[9]
Congenital heart disease	Malformation of the heart, aorta, or other large blood vessels present at birth and presenting as cyanotic or acyanotic heart disease[1]
Constitutional symptoms	Clinical signs or symptoms suggestive of tuberculosis: a) Persistent or unremitting cough for > 2 weeks b) Failure to thrive c) Persistent unexplained fever d) Persistent unexplained lethargy or reduced playfulness e) Additional signs or symptoms in neonate or infant: i) Neonatal pneumonia ii) Unexplained hepatosplenomegaly iii) Sepsis like illness[9]
Croup	Respiratory disorder caused by an infective agent resulting in inflammation of the larynx and manifesting as cough and inspiratory stridor[1,2]
District Hospital	The district hospital provides primary level care services to in-patients and outpatients (ideally on referral from a community health centre or clinic). The

	hospital has between 30 and 200 beds, a 24-hour emergency service and an operating theatre. Generalists from a range of clinical disciplines provide these services including surgery, obstetric and gynaecology, medicine, paediatric, metal health, geriatrics, and casualty care. District hospitals refer to level 2 hospitals[10]
Failure to thrive	a) Clear deviation from previous growth trajectory b) Documented crossing of the percentile lines in preceding 3 months c) Weight for age Z-score <-2 OR weight for height Z-score <-2 in the absence of previous/recent growth trajectory d) Not responding to nutritional rehabilitation[9]
General danger signs	Not able to breastfeed or drink, lethargic or reduced level of consciousness, severe malnutrition[2]
HIV exposed	Child born to a woman living with human immunodeficiency virus (HIV), including children living with and without HIV
HIV exposed uninfected	Child born to a woman living with human immunodeficiency virus (HIV) and confirmed HIV uninfected during hospital stay
Incomplete vaccinations	Vaccinations not done within 2 weeks of it being scheduled, in accordance with South African Expanded Program on Immunisation
Indoor air pollution	Use of biomass fuels for cooking and heating OR indoor smoking. Organic matter that is used to generate energy for purposes of cooking, heating, and lighting[11]
Level of education	The highest level of education that a person has successfully completed based on South African Education Structure Foundation: Grade R – Grade 3 Intermediate: Grade 4 – Grade 6 Senior phase: Grade 7 – Grade 9 Further Education and Training: Grade 10 – Grade 12 Higher education and training: Diplomas and Degrees[12]
Low birth weight	Birth weight of < 2.5kg irrespective of gestational age
Moderate acute malnutrition	Weight for height Z-score < -2 standard deviations (SD) and > -3 SD OR mid-upper arm circumference (MUAC) between 11.5cm and 12.5cm[13]
Non-severe pneumonia	Cough or difficulty breathing AND age appropriate threshold for tachypnoea or chest indrawing AND not meeting the criteria for severe pneumonia[2,14]
Overcrowding	More than two people per room (excluding bathrooms and including kitchen and living room)[15]
Pneumonia	Cough or difficulty breathing **AND** age appropriate threshold for tachypnoea or chest indrawing[2,14]
Preterm birth	Gestational age of < 37 weeks gestation Early preterm birth: less than 34 weeks gestation Late preterm birth: less than 37 weeks but greater than or equal to 34 weeks gestation
Primary level hospital	Primary level hospitals provide basic medical services including internal medicine, obstetrics and gynaecology, paediatrics, and general surgery; limited laboratory services available for general pathological analysis. Alternative terms that fall under primary level care include district hospitals, rural hospitals, and community hospitals[16]
Secondary level hospital	Secondary level hospitals provide highly differentiated clinical specialities and ranges from 200-800 beds. Often referred to as provincial hospitals or regional hospitals[16]
Severe acute malnutrition	Weight for height Z-score of <-3 SD OR the presence of nutritional oedema OR mid-upper arm circumference (MUAC) of less than 11.5cm[13]

Severe pneumonia	Cough or difficulty breathing **AND** age appropriate threshold for tachypnoea or chest indrawing **AND** Hypoxaemia (oxygen saturation of < 92% in room air) OR Requiring high flow nasal oxygen or continuous positive airway pressure (CPAP) or ventilation support OR General danger signs[2]
Small for gestational age	Weight < 10th centile for gestational age
Stunting	Height for age Z-score of < -2 SD[13]
Tachypnoea	Respiratory rate of > 60 (<2 month of age) Respiratory rate of > 50 (2 months – 11 months) Respiratory rate > 40 (12 months – 59 months)[2]
Tertiary level hospital	Tertiary level hospitals consist of highly specialised healthcare personnel with technical equipment. They include cardiology, intensive care units, and specialised imaging units; clinical services are highly differentiated by function; could have teaching activities; ranges from 300-1500 beds. Could be referred to as national hospital or academic hospital[16]
Tobacco smoke exposure	Exposure to tobacco smoke; includes maternal smoking and secondary smoke exposure
Tuberculosis exposure	Reported exposure to a case of tuberculosis (household/ close contact) within the preceding 12 months with documented or verbal report of smear positive and/ culture positive tuberculosis, or on tuberculosis treatment[9]
Unconfirmed tuberculosis	Bacteriological confirmation NOT obtained AND at least 2 of the following: 1) Constitutional symptoms of tuberculosis 2) Chest radiograph consistent with tuberculosis 3) Close tuberculosis exposure or immunological evidence of *M. tuberculosis* infection 4) Positive response to tuberculosis treatment with *M tuberculosis* infection (immunological evidence of *M. tuberculosis*) or without *M. tuberculosis* infection (no immunological evidence of *M. tuberculosis* infection)[9]
Underweight	Weight for age Z-score < -2 SD
Unlikely tuberculosis	Bacteriological confirmation NOT obtained AND criteria for "unconfirmed tuberculosis" NOT met with *M. tuberculosis* infection (immunological evidence of *M. tuberculosis*) or without *M. tuberculosis* infection (no immunological evidence of *M. tuberculosis* infection)[9]
Wasting	Weight for height Z-score of <-2 SD OR mid-upper arm circumference (MUAC) of less than 12.5cm[13] Subclassified as moderate acute malnutrition and severe acute malnutrition (see definitions elsewhere)

Abbreviations

ALRI	Acute Lower Respiratory Infection
ARDS	Acute Respiratory Distress Syndrome
CDG	Care Dependency Grant
ChPIP	Child Healthcare Problem Identification Programme
PPIP	Perinatal Problem Identification Programme
CI	Confidence Interval
CMV	Cytomegalovirus
CPAP	Continuous Positive Airway Pressure
CrI	Credible Interval
CSG	Child Support Grant
DALY	Disability Adjusted Life Years
EBF	Exclusive Breast Feeding
eCCR	Electronic Continuity of Care Record
HAP	Household Air Pollution
HICs	High income countries
HIV	Human Immunodeficiency Virus
HREC	Health Research Ethics Committee
ICU	Intensive Care Unit
IQR	Interquartile range
LMICs	Low- and Middle-Income Countries
LPG	Liquid petroleum gas
LRTI	Lower Respiratory Tract Infection
MAM	Moderate Acute Malnutrition
OR	Odds Ratio
PCR	Polymerase chain reaction
QALY	Quality-Adjusted Life Years
REDCap	Research Electronic Data Capture
RSV	Respiratory Syncytial Virus
SAM	Severe Acute Malnutrition
SD	Standard Deviation

TB	Tuberculosis
UI	Uncertainty Interval
UR	Uncertainty Range
SU	Stellenbosch University
WHO	World Health Organization
WPH	Worcester Provincial Hospital

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Chapter 1

Introduction and Extended Literature Review

Introduction

Pneumonia is a major contributor of childhood mortality and morbidity in developing countries[17,18]. The past decade has seen important declines in pneumonia related mortality and to a lesser extent pneumonia related incidence[17]. From 2005 to 2015 the total number of under-5 deaths globally due to pneumonia decreased by 36.9% (95% uncertainty interval (UI) 31.6-42.0) from an estimated 1.11 million (95% UI 1.03-1.20 million) to 0.703 million (95% UI 0.651-0.763 million)[17]. However, the incidence of pneumonia only declined from 0.18 episodes per child year (95% UI 0.61-0.20) in 2005 to 0.15 episodes per child year (95% UI 0.13-0.20) in 2015[17]. In South Africa, pneumonia is the leading single cause of death in children under five years of age accounting for 8.6% of child deaths[19]. This literature review will discuss the definition of pneumonia and its classification, the burden of disease, aetiology and pathophysiology, and the related risk factors. The review will conclude with a South African context and the community in which this study was conducted.

Pathophysiology of pneumonia

Pneumonia refers to an inflammatory process that involves the lung parenchyma[1] and results from the overgrowth of pathogenic micro-organisms combined with loss of local defence mechanisms[20]. Pathogenesis may include surrounding structures such as the visceral pleura, connective tissue and vascular structures. Disease severity is determined by host-related factors such as sex, age, comorbidities and pathogen related factors such as virulence and inoculum size[21]. Pathogenic organisms spread most frequently by aerosolised droplets[21]. Particles up to 5 µm can transport up to 100 micro-organisms and theoretically bypass respiratory host defences[21]. Index cases can potentially transfer disease to susceptible hosts through the expulsion of respiratory droplets in the form of sneezing and coughing[21]. Micro-aspiration is another possible route of infection; however, an innate or acquired defect bypassing protective barriers is required to initiate lung disease through this mechanism, such as an altered level of consciousness, impaired mucociliary escalator system and immunosuppression[21]. Haematogenous spread is a less frequent route of infection and may result from right sided infective endocarditis or translocation of organisms from the gut to the blood stream[21].

Definition of pneumonia

To simplify case management in resource limited settings, the World Health Organization (WHO) has defined pneumonia using clinical manifestations of disease and not according to its pathophysiological presentation. Demonstrating evidence of lung parenchymal inflammation or micro-organism overgrowth is challenging and relies on investigations that are not readily available in resource limited settings. In the 1990s the WHO examined the sensitivity and specificity of deriving the clinical diagnosis of pneumonia by evaluating clinical signs and symptoms of disease[22,23]. Available evidence at the time was used to assimilate a clinical definition of pneumonia. This definition is based on a series of studies undertaken in low and middle income countries (LMICs) and adapted into the current definition of pneumonia[22,23]. Pneumonia is defined by the WHO as coughing or difficulty breathing and age appropriate threshold for tachypnoea or subcostal recessions[14]. With time, this definition was incorporated into the Integrated Management of Childhood Illnesses (IMCI) strategy which included ''danger signs'' to further describe the severity of the illness. The primary objective of the WHO clinical case definition was to capture as many cases of pneumonia with the aim of providing timeous and appropriate management and reduce mortality.

There is a global trend toward the use of lower respiratory tract infections (LRTI's) to describe airway disease including pneumonia. LRTIs and the WHO clinical definition of pneumonia differ in that the former uses the anatomical location of infection and the latter uses clinical criteria[22]. Both descriptions cast broad diagnostic nets and have inherent limitations. This study adopted the WHO definition of pneumonia as it provides a highly sensitive means of capturing pneumonia cases and allows for comparisons to be made with previously published research[22,23]. It is however recognised that children classified in this way include those not only with pathophysiologically defined pneumonia but also other clinical conditions such as bronchiolitis and reactive airway disease[14,22,23].

Classification of pneumonia

WHO has classified pneumonia severity into three broad clinical entities namely, no pneumonia, pneumonia (that in this study for clarity we have termed “non-severe pneumonia”) and severe pneumonia[14]. This classification serves to direct case management in the form of antibiotic use, appropriate referral, and the need for supplemental oxygen. No pneumonia refers to clinical cases of isolated coughing or difficulty breathing in the absence of age appropriate threshold for tachypnoea or subcostal recessions. This clinical entity can only be assessed in the absence of danger signs including inability to feed, lethargy or reduced level of consciousness. Management involves symptomatic treatment, advice on when to return and when

tuberculosis (TB) screening is indicated[2,14]. Non-severe pneumonia is defined by the WHO as coughing or difficulty breathing AND age appropriate threshold for tachypnoea or subcostal recessions[2,14]. This clinical diagnosis is made in the absence of any danger signs and can be managed as an out-patient with oral antibiotics[14]. Severe pneumonia is defined by the WHO as coughing or difficulty breathing AND age appropriate threshold for tachypnoea or subcostal recessions in the presence of hypoxia (oxygen saturations less than 92% in room air), or severe respiratory distress manifesting as severe subcostal recessions and grunting, or general danger signs that include inability to feed, lethargy or reduced level of consciousness[14]. Severe pneumonia requires admission to hospital, supplemental oxygen if saturations are below 92%, and the administration of antibiotics[2,14].

Aetiology

Pneumonia can be caused by a number of viruses, bacteria, and fungi. Determining the aetiology of pneumonia is challenged by distinguishing colonising organisms of the respiratory tract from pathogenic organisms and this can be further complicated by co-infections[24]. Identifying the aetiological agent of a pneumonia episode is further complicated by the fact that few children develop bacteraemic illness and that there is a high prevalence of nasopharyngeal colonisation by pathogenic bacteria that renders interpretation of respiratory tract samples challenging[25]. Interventions of the past decade, including preventative strategies and case management of pneumonia have been influenced by changes in the aetiological causes of pneumonia. The increased coverage of pneumococcal conjugate vaccine (PCV) and haemophilus influenzae type B (Hib) vaccine has seen a shift in micro-organism aetiology. The reduction of *Streptococcus pneumoniae* and *Haemophilus influenzae type B* has led to the emergence of viruses and other bacteria such as *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Mycobacterium tuberculosis* (in endemic areas) playing prominent aetiological roles[24,25]. In an international case-control study conducted in seven LMICs that investigated the aetiology of severe pneumonia in HIV negative children requiring hospitalisation (PERCH study), viruses accounted for 61·4% (95% credible interval [CrI] 57·3–65·6) of cases, bacteria 27·3% (95% CrI 23·3–31·6) and *Mycobacterium tuberculosis* 5·9% (95% CrI 3·9–8·3)[26]. In South African children, important aetiological bacterial organisms included *Haemophilus influenzae type B*, *Mycobacterium tuberculosis*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and other *Streptococci* and *Enterococci*[26]. Important viral agents included respiratory syncytial virus (RSV), para-influenza virus, adenovirus, rhinovirus (RV), and human metapneumonvirus (HMPV)[24,26].

Burden of disease

Globally, LRTIs remain the leading cause of under-5 mortality and an important healthcare burden[17,18,27]. In 2015, an estimated 0·921 million (UR 0·812 –1·117) children under-5 years old died from LRTI with sub-Saharan Africa accounting for the largest proportion of mortality 16.6% (UR 14.8-19.1), 0·49 million (UR 0·417–0·631)[18]. This was the second most important cause of mortality in this age distribution surpassed only by preterm birth complications (1·055 million [95% uncertainty range (UR) 0·935–1·179])[18]. From 2005 to 2015, the estimated global burden of LRTIs in children under 5 years decreased by 36.9%, disability adjusted life years (DALYs) caused by LRTI fell by 8.9% globally and mortality rates for pneumonia and pneumonia incidence declined in most regions of the world[17].

In 2015, South African mortality due to LRTIs in children under 5 years had declined by 63.5% compared to 2005, with an estimated 62.1 deaths per hundred thousand population (95% UI 49.7 – 77.7)[17]. Similarly the disability adjusted life years (DALYs) from LRTIs declined by 63.4% over the same period and was 2.85 per 100 000 in 2015[17].

The global and national trend toward reduced burden of disease caused by LRTIs in children under 5 years highlights the important progress made in preventative strategies. Of note are interventions such as decreased indoor and ambient air pollution, improved childhood nutrition, greater coverage of childhood vaccines, progress made in HIV treatment, and case management of pneumonia[17,18].

Risk factors for pneumonia and pneumonia associated morbidity and mortality

There are many well recognized risk factors for pneumonia including adverse birth outcomes (being born preterm, low birth weight or small for gestational age), young age, incomplete vaccination status and malnutrition. Additionally chronic infectious diseases including TB and HIV as well as non-infectious diseases such as congenital heart disease, asthma, and cerebral palsy can all predispose to acute pneumonia episodes. Less well recognised is the impact of the geographic location, vulnerable immigration status and seasonal migration on childhood pneumonia incidence and outcomes. Patients with severe pneumonia may have multiple risk factors acting in synergy resulting in a more severe disease manifestation. In LMICs there is limited information regarding the role of risk factors and the severity of pneumonia.

Young age and preterm birth

Young patient age and preterm birth are well known risk factors for pneumonia, often working in concert with a number of other risk factors[28]. Age related factors are predominantly due to differences in immunity

and lung development[28,29]. As children grow, immune maturity and lung development result in improved capacity to manage pathogens and allergens.

Multiple studies have reported a larger proportion of pneumonia cases, both ambulatory and inpatient, in children less than 12 months[26,30,31]. Preterm birth additionally predisposes to more severe viral LRTI and mortality in both low- and high-income countries[32,33]. A number of factors contribute to the vulnerability of developing pneumonia in neonates and infants. Impaired neutrophil function, immature adaptive immunity, dampened expression of pro-inflammatory cytokines and impaired clearance of pathogens increases disease susceptibility in this population[34–36]. Preterm birth poses an additional risk as preterm infants receive limited passive immunity from their mothers compared to term counterparts[36]. In addition to immunologic deficiencies in preterm neonates, complications also arise due to differences in lung development compared to term neonates[29]. Bronchopulmonary dysplasia, a complication of preterm birth and compromised lung development, is associated with a higher incidence of hospital admissions for RSV[37].

Biological sex

Biological sex may play a small role in developing pneumonia with males being affected more often than females. Some studies have demonstrated no risk between biological sex[17,38] while others have demonstrated male predominance[31,39,40]. The under-5 year mortality on a global level is approximately the same in males and females, however in South Asia it was 1.2 times higher in females[17]. The Drakenstein Child Health Study, conducted in South Africa and looking at children younger than 2 years between 2012-2014, demonstrated that male sex was associated with increased risk of pneumonia (odds ratio (OR) 1.67, 95% CI 1.21 – 2.31)[24]. In contrast, a retrospective cohort study conducted in Kenya demonstrated that female sex was associated with increased risk of inpatient mortality due to pneumonia (OR 1.52, 95% CI 1.17-1.96)[40]. When considering biological sex as a risk factor for pneumonia, these studies demonstrate varying and different degrees of risk that may be context specific to particular geographic locations. Currently, presiding evidence does not suggest that a particular biological sex is universally associated with differential pneumonia risk.

Malnutrition

Childhood malnutrition is an important public health challenge affecting millions of people worldwide. It is observed most frequently in developing countries amongst children less than 5 years of age[41]. Malnutrition affects host immunity through a number of mechanisms including protein and micronutrient deficiencies

that impact the haematopoietic and lymphoid organs and compromise both innate and adaptive immune functions[41]. Additionally, changes in intestinal microbiota also contribute to growth faltering and dysregulated inflammation and immune function[41]. Several studies in LMICs including South Africa have demonstrated that malnutrition, whether moderate or severe, increases the risk of pneumonia[3,42–47].

HIV infection and exposure

Pneumonia often occurs as a co-infection in the context of a number of chronic diseases including HIV. HIV affects both innate and adaptive immune responses through its effects on macrophages and T-lymphocytes at different stages of the disease[48]. The inability of T-lymphocytes to activate B-cells that facilitate the production of antibodies, as well as the loss of macrophages that serve as an initial defence, predisposes the body to opportunistic and severe infections[48]. These opportunistic infectious agents often form part of the normal body flora and the immune system's ability to keep them in check is compromised by HIV co-infection[48]. Infants with HIV experience four times greater risk of hospitalisation and three times greater in-hospital mortality compared with infants HIV unexposed and uninfected[49]. Numerous studies have demonstrated that children with HIV develop severe forms of pneumonia, have a higher risk of mortality and are predisposed to developing opportunistic infections[25,46,49]. Managing HIV infection with antiretroviral therapy has dramatically altered the natural course of disease and has reduced mortality caused by pneumonia and opportunistic infections.

Exposure to HIV even in the absence of HIV infection is a significant independent risk factor for developing pneumonia[31,49]. Studies have demonstrated that children HIV exposed but uninfected (HEU) not only have an increased risk of developing pneumonia but also an increased risk of admission to hospital, prolonged hospital stay, and increased hospital mortality when compared to children HIV unexposed uninfected (HUU)[31,49]. It is hypothesised that this increased risk is due to impaired immunity, limited protection due to reduced maternal antibodies, diminished response to some vaccines and increased exposure to infectious diseases from living in a household with a member who has HIV[31,49,50].

Vaccinations

Vaccinations have played an instrumental role in reducing the number of hospital admissions and childhood mortality associated with pneumonia. Following the introduction of Haemophilus influenzae type B, pneumococcal and measles vaccinations, pneumonia incidence and mortality have reduced substantially[51].

Immunisations have reduced the risk of pneumonia related mortality, decreased the risk of developing severe disease, and demonstrated a decline in radiologically confirmed pneumonia[52–58].

In South Africa, from 2009 to 2012 the District Heath Information Systems (DHIS) estimated improved vaccination coverage in consecutive years throughout all South African provinces[59]. The DHIS and the Child Healthcare Problem Identification Programme (Child PIP) which analysed data collected from 41 South African hospitals demonstrated a decline in in-hospital pneumonia deaths[59]. This reduction of in-hospital mortality was further demonstrated in a study conducted in Red Cross War Memorial Children's Hospital between 2004 – 2013[60]. The third report of the committee on morbidity and mortality in children under five years, which assessed data from Statistics South Africa and the DHIS from 2011 to 2015 has demonstrated further decline in national pneumonia deaths[61]. Although not the only contributor to the reduction of mortality or hospitalisation for childhood pneumonia and other infections, vaccinations have played an important role in reducing the burden of disease.

Household air pollution

Household air pollution (HAP) is estimated to cause a high burden of morbidity and mortality globally, and of importance is the associated risk of LRTIs[62]. HAP refers to indoor by-products that are released following combustion of solid fuels for the purposes of cooking, heating, and lighting[63]. Solid fuel is a broad term that includes biomass fuels (derived from plant sources) or coal, animal dung, domestic rubbish and plant residues for combustion. Products used for heating and cooking such as paraffin, kerosene, and candles also produce particulate matter that can contribute to HAP. These fuels result in the release of by-products such as carbon monoxide and particulate matter (PM)[63]. Exposure to these by-products are associated with adverse health events. The duration of exposure, the type(s) of fuels burned, and PM threshold that confer risk are unknown[63,64]. The WHO however recommends interim targets for PM that are associated with improved health outcomes[64,65].

A large proportion of the world's population, mostly in LMICs, use solid biomass fuel as a primary cooking source[66]. The largest number of households utilising solid fuel occur in sub-Saharan Africa and South Asia[62] predisposing these populations to adverse health events. Several studies have summarised the relationship between HAP from solid fuels and risk of acute respiratory infection in children[62,67,68]. However, studies demonstrate differences in effect estimates which may be due to the heterogeneous definitions of exposures and outcomes in these studies. A meta-analysis of 24 studies reported a summary OR of HAP and

LRTIs of 1·78 (95% CI 1·45–2·18)[67]. In comparison, a different meta-analysis of 24 studies demonstrated a summary risk ratio for LRTIs of 3·53 (95% CI 1·93– 6·43)[68]. An estimate of the global disease burden of HAP suggests that every year household solid fuel use causes ±455 000 LRTIs deaths, the loss of 39 100 000 DALYs, and an LRTI population attributable fraction of 52%[62].

Overcrowding

A number of studies have described pneumonia and its association with overcrowding[44,45,69]. Crowding is defined as more than two people per room (excluding bathrooms but including kitchen and living room)[15] and is often associated with lower socioeconomic status. There is also evidence that bed sharing and having a household member that coughs are associated with an increased probability of severe pneumonia[43]. Close contact and frequent (direct and indirect) exchanges with potential sources of respiratory disease coupled with confined and poorly ventilated dwellings predispose household members to disease.

Maternal smoking

Maternal smoking antenatally and postnatally is associated with increased incidence of infant pneumonia[31]. Several studies have demonstrated an association of developing pneumonia and severe disease with tobacco smoke exposure[38,44,58,70–72]. Tobacco smoke exposure may predispose to pneumonia by means of suppression or modulation of the immune system, reduced plasma levels of antioxidant factors, impaired mucociliary apparatus of the respiratory tract, and via certain toxins that are not easily detected by conventional means[73–75].

Hygiene

Strategies involving improved hygiene have also been investigated. Infectious agents of pneumonia, including bacteria, viruses and fungi, are transferable by a number of means including droplet spread, fomite transmission, and direct contact. Good hygiene serves to curb these transferable states and prevent transmission.

Hand washing with soap has been described as one of the most cost-effective means of preventing pneumonia in children[76]. There is some evidence that hand hygiene interventions delivered in childcare, school, and domestic settings in LMICs can reduce respiratory infections[76]. The effectiveness depends on the setting, intervention target and compliance. Previous meta-analyses have estimated that community-based hygiene interventions may reduce acute respiratory tract infection transmission by 16%–21%; however,

these estimates were primarily based on studies performed in high-income settings[77,78]. Hygiene behaviour is influenced by a number of factors such as wealth, education and access to water, which is limited in LMICs[79]. It is postulated that the potential impact of hygiene and water quality interventions in LMIC settings may be greater due to higher LRTI rates[79]. More studies are required to determine the impact of hygiene and its effect on disease prevention in LMICs[76].

Breastfeeding

Breastfeeding is one of the few interventions where the survival benefits span the entire continuum of childhood[80]. Both the WHO and United Nations Children's Fund (UNICEF) recommend early initiation of breastfeeding, exclusive breastfeeding during the first six months of life and continued breastfeeding until 24 months of age[81]. Breastfeeding offers a protective mechanism against all-cause mortality including pneumonia[80]. In a systematic review of infants aged 0-59 months a graded increased all-cause mortality risk was demonstrated for predominant, partial and no breastfeeding compared to exclusive breastfeeding[80]. When comparing infants that have breastfed for less than 23 months to those who were breast fed for a longer period an increased risk of mortality was also demonstrated[80]. A meta-analysis assessing the epidemiology and aetiology of childhood pneumonia also concluded that non-exclusive breastfeeding was associated with childhood pneumonia[45].

The health benefits of breastfeeding include its optimal nutritional components and bioactive molecules that protect against infection, inflammation and contribute to immune maturation, organ development, and healthy microbial colonisation[82,83].

Maternal Age, education, and socio-economic factors

In 2016, adolescent women aged 15–19 years in developing regions accounted for an estimated 21 million pregnancies, of which about 12 million resulted in a birth[84]. Young maternal age has been associated with adverse health outcomes in mothers and infants[85]. There is limited supporting evidence that young maternal age is a risk factor for childhood pneumonia with studies demonstrating no association and others demonstrating an increased probability of developing disease[38,86]. A cross-sectional study looking at risk factors for acute respiratory tract infections in Cameroonian children did not demonstrate an association with young maternal age. In contrast, a study conducted in Burma in 2007 that followed a cohort of refugee infants found that young maternal age was a risk factor for their children developing pneumonia[86]. These

two studies describe two very different populations. More evidence, however, is required to determine the role that young maternal age may play in risk for pneumonia and severity of disease.

Several studies have demonstrated an association with low maternal education and severe pneumonia in their children[44,87–89]. These studies, however, have defined different thresholds for lower education and interpreting them collectively is challenging due to this heterogeneity.

Socioeconomic factors pose several health challenges that predispose to disease. A number of studies have described links between worse health outcomes and poor socioeconomic status[88,90]. A study that used the Demographic and Health Surveys between 2000 and 2011 in 52 LMICs, demonstrated that household wealth inequality positively correlated with a higher prevalence of anaemia and childhood mortality[90]. Poorer socioeconomic factors are often coupled to more specific risks including food insecurity, overcrowding, and HAP. Alleviating poverty by increasing wealth among the poor would improve health outcomes and help address associated factors[90].

Pneumonia in South Africa

Over the past decade, access to basic services has progressively improved throughout South Africa. Better access to healthcare has included increases in antiretroviral clinics, TB clinic sites, and improved ambulance coverage[91]. A number of South African observational studies, DHIS and the Child PIP have demonstrated a decline in pneumonia incidence following the introduction of a number of preventative strategies including the management of HIV, malnutrition and immunisation against *Streptococcus pneumoniae* and *Haemophilus influenzae type b* [53,59,60].

Between 2011 and 2016, the Cape Winelands has demonstrated increased access to formal housing (average annual growth of 3.2%), water (average annual growth of 3.4%), sanitation (average annual growth of 4.7%), electricity (average annual growth of 3.5%), and refuse removal (average annual growth of 4.0%)[91]. The Breede Valley which forms part of the Cape Winelands, however; remains a vulnerable population. Comparative data between 2014 and 2016 demonstrated a decline in immunisation coverage (86.1% in 2014 to 61.4% in 2016) and an increased malnutrition prevalence (2.6% in 2014 to 7.5% in 2016) in the Breede Valley municipality[91]. These factors coupled with high HIV and TB prevalence compound the risk of a number of communicable diseases including pneumonia[91,92].

Evidence relating to household risk factors for pneumonia remains sparse in the South African context. Combustion of biomass fuels resulting in household air pollution, overcrowding, and maternal smoking are associated with increased risk of pneumonia[31,44,45,62,69]. These household risk factors, independently or synergistically, may play a significant role in the development of pneumonia. Whether they are associated with the severity of pneumonia in this population remains unknown.

Study Context

Worcester Provincial Hospital (WPH) is a secondary level hospital located in the Breede Valley, approximately 110km from Cape Town. The hospital drains the areas of Worcester, Breede Valley, Cape Winelands East and Overberg districts and serves a population of predominantly low socio-economic status. The Breede Valley Municipality covers an area of 3833 km² extending from Du Toitskloof Mountains in the southwest to Kwadousberg in the southeast[92]. It includes Rawsonville, Worcester, De Doorns, Touws River and adjacent rural areas[92]. The health facilities in the Breede Valley comprise of one community day centre, six fixed primary healthcare clinics, nine mobile or satellite clinics, one regional hospital (WPH), eight antiretroviral treatment sites and 19 TB clinics treatment sites[91,92]. There are currently no community health centres nor district hospitals within the municipal area. WPH not only serves as a drainage hospital to seven District Hospitals outside the Breede Valley area but also provides district hospital service to this municipal area.

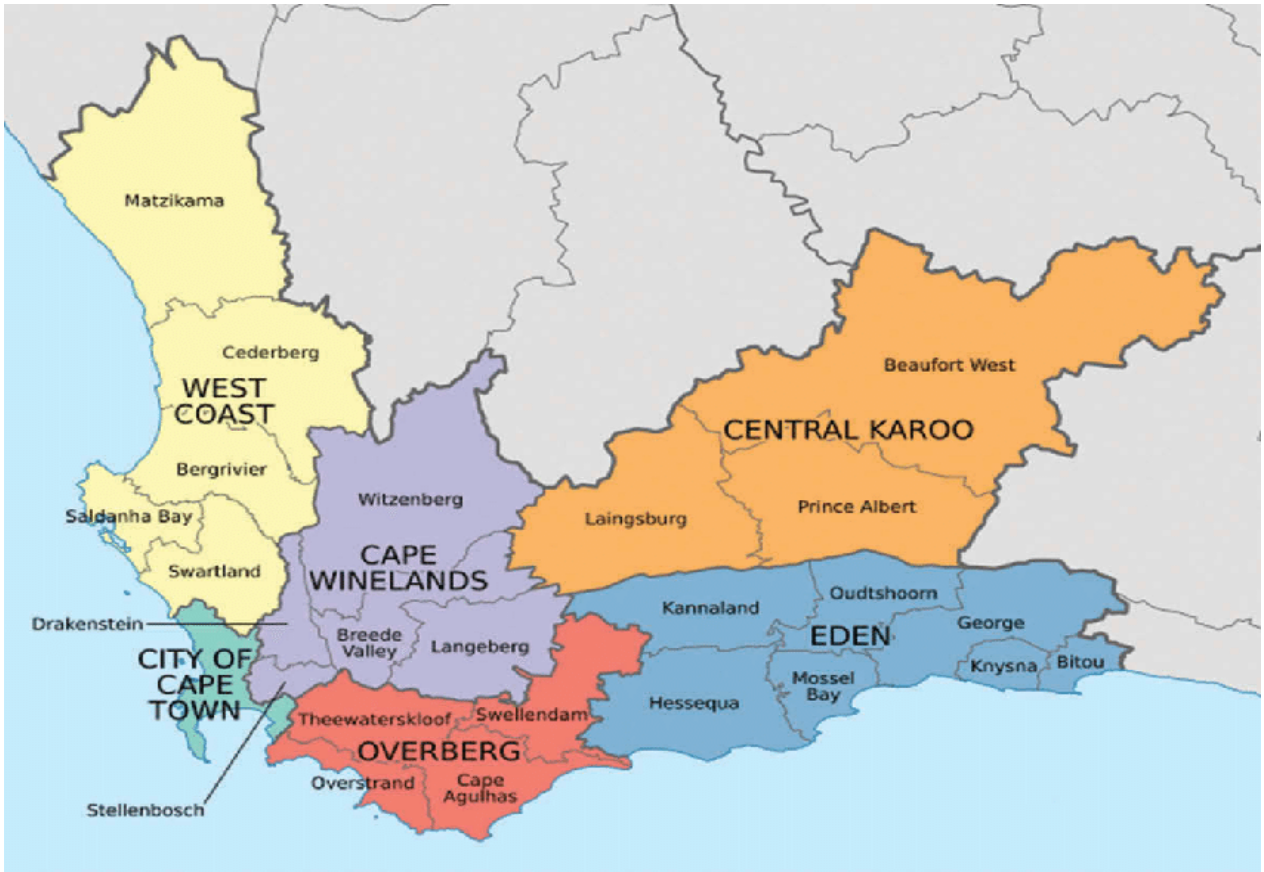

Figure 1. District and sub-district level map of Western Cape Province, South Africa[93]

The Breede Valley has the second largest population density in the Cape Winelands District with 176578 residents according to Community Survey 2016 data and a projected population of more than 182 938 in 2020[92]. Sectors of this population experience extreme poverty characterised by seasonal migration driven by employment for economic subsistence in the agricultural sector. Other major economic sectors coupled to job opportunities include tourism and manufacturing which are also subject to seasonal peaks and troughs. Over the period of 2014 to 2015, the Breede Valley economy grew by 3.4% and 1.5% respectively. However, the Gini Coefficient, a measure of economic inequality, has increased over the same period from 0.57 in 2014 to 0.58 in 2015. This highlights a growing economic disparity in this region[92].

The Breede Valley region consists of ±47 569 households of which 14.7% are classified as indigent[92]. According to the Community Survey 2016, 20% of households live in informal dwellings (n = 9 679) and 1.5% in traditional dwellings[92]. Households reported having 94.8% flush/chemical toilet, 96.8% access to piped water inside the household, and 90% access to electricity[92].

The Breede Valley has the second highest number of people living with HIV (March 2015, n=4 584) in the Cape Winelands District[92]. The Cape Winelands accounts for 50% of people living with HIV in the Western Cape. The Breede Valley also has the second highest number of TB cases in the Cape Winelands District and accounts for 13.8% (2014) of TB cases in the Western Cape[92]. Over the same period, the reported severe malnutrition rate per 100 000 population was 2.6% which is higher than the Western Cape average of 2.43%[92]. Other important health issues include immunisation coverage[92]. For children less than 1 year old, the Western Cape Department of Health reported an immunisation coverage of 86% in the Breede Valley (2016), less than the Western Cape average of 90% coverage.

The Breede Valley houses a population with a unique risk profile that predisposes children to a number of illnesses. There is limited information regarding the risk factors related to childhood pneumonia in this population and this has not previously been studied in detail. This study aims to determine factors in this community associated with the severity of pneumonia by analysing admissions to WPH. The information gathered may allow identification of modifiable factors prevalent in this population and inform policy makers where efforts should be focused to reduce the burden of disease and mortality.

Chapter 2

Aims and objectives

Aims of the study

The aim of this study was to determine factors associated with the severity of pneumonia, particularly household environmental factors, in children admitted with pneumonia to WPH during 2019.

Hypothesis

Children (0-59 months) admitted to WPH with severe pneumonia have a higher odds of exposure to adverse household environmental factors including indoor smoking, overcrowding and indoor use of biomass fuels compared to children with non-severe pneumonia.

Research Question

Do children with severe pneumonia compared to those with non-severe pneumonia have a higher odds of exposure to household environmental factors including indoor smoking, overcrowding and indoor use of biomass fuels?

Primary Objective

To compare the odds of adverse household environmental factors including indoor smoking, overcrowding, or indoor use of biomass fuels in children aged 0 – 59 months with severe pneumonia compared with non-severe pneumonia admitted to WPH.

Secondary Objective

1. To compare the odds of childhood related factors (including seasonal migration status, nationality, neighbourhood, adverse birth outcomes, age, sex, vaccination status, nutritional status, and chronic infections specifically TB, HIV, and chronic non-infectious diseases such as congenital heart disease, asthma, and cerebral palsy) in children with severe pneumonia compared to non-severe pneumonia.
2. To compare the odds of maternal or primary caregiver risk factors (including age, level of education, employment status, application for social grants, and the presence of chronic infections specifically TB and HIV) in children with severe pneumonia compared to non-severe pneumonia.

3. To categorise severe and non-severe pneumonia and disaggregate conditions with similar clinical presentations such as bronchiolitis, asthma, and intrathoracic TB.

Chapter 3

Methods

Study design, setting and sample

We conducted an unmatched case-control study of children aged 0-59 months admitted with severe pneumonia compared to those with non-severe pneumonia. The study took place at WPH (Worcester, South Africa) between 1st of January 2019 and 31st of December 2019. WPH is a regional public hospital, which provides specialist support to district hospitals and is located in the Breede Valley, approximately 110km from Cape Town. The hospital drains the areas of Worcester, Breede Valley, Cape Winelands East and Overberg districts and serves a population of predominantly low socio-economic status.

Eligible participants were children aged 0-59 months who were admitted to WPH with respiratory symptoms suggestive of clinical pneumonia. Children older than sixty months were excluded from the study as the incidence of childhood pneumonia is lower beyond this age group. We excluded patients admitted immediately post-delivery that presented with respiratory distress of the newborn and children referred back from tertiary hospitals for step-down care of pneumonia. The admissions register in A1 (Paediatric Ward) and intensive care unit (ICU) were reviewed daily for eligible candidates. This was conducted from Monday to Friday excluding weekends and public holidays. Primary caregivers of eligible participants were approached and interviewed after having consented to study participation.

Data collection and management

Written informed consent was obtained from the primary caregiver of all enrolled participants in English, Afrikaans, Xhosa or seSotho (Appendix A). We conducted a structured interview (Appendix B) with the primary caregiver detailing information related to the child, primary caregiver, and household risk factors. The interview was conducted within 48 hours of admission in a language of the caregivers' choice (English, Afrikaans, isiXhosa, or seSotho) by the principal investigator (MMB) or with the aid of a translator when necessary. The primary and secondary outcomes were based on information recalled by the primary caregiver during the interview.

Medical information related to pneumonia, anthropometric data and HIV status were collected from the admission notes. The medical history was supplemented with the aid of the Road to Health Booklet (RTHB) which contained the birth history, immunisation status, growth trajectory, previous admissions and chronic

medical conditions. Laboratory investigations or chest x-rays were performed at the discretion of the treating clinical team and no additional study-specific investigations were requested.

Pneumonia classification

The primary outcome of pneumonia was classified as severe or non-severe following review of the admission notes shortly after admission as well as at the time of discharge. Pneumonia was classified according to the WHO clinical definition of pneumonia[14]. Non-severe pneumonia is defined as coughing or difficulty breathing and age appropriate threshold for tachypnoea or chest indrawing. Severe pneumonia is defined as cough or difficulty breathing and age appropriate threshold for tachypnoea or chest indrawing AND any one of the following features: hypoxaemia (oxygen saturation of < 92% in room air), respiratory support (including high flow oxygen, continuous positive airway pressure (CPAP), and ventilation), OR any IMCI general danger signs. General danger signs include not being able to breastfeed or drink, lethargy or reduced level of consciousness, and severe malnutrition.

The discharge diagnosis was based on cumulative information during the admission. This included clinical presentation, inpatient records and additional investigations made at the discretion of the treating clinician. The discharge diagnosis was supported by information from the electronic continuity of care record (eCCR), a software application used to digitise and integrated medical records in patients being discharge from public health facilities.

Due to the broad definition of clinical pneumonia we sub-categorised this group according to five main diagnoses that fulfilled the WHO clinical definition of pneumonia: pneumonia, bronchopneumonia, asthma, bronchiolitis, pulmonary TB and other. The category ‘other’ refers to conditions that did not satisfy any of the five main diagnoses made at discharge but did meet the WHO definition for pneumonia. This included and was not limited to conditions such as pertussis, unspecified LRTIs, reflux disease, and cardiac failure. It was possible for a participant to be classified into more than one of these diagnostic sub-categories.

Data was analysed based on the admission diagnosis as opposed to the discharge diagnosis as disease severity was more relevant at presentation. Further analysis of the discharge diagnoses was not conducted.

HIV classification

The RTHB and when available clinical records were used to determine HIV status in children. Using these resources children were categorised into HIV unexposed and uninfected, HIV exposed uninfected, HIV infected, and unknown status. All children with an unknown HIV status received an HIV rapid test on admission as part of routine care. Children who tested negative and who were older than 24 months were classified as HIV uninfected. Children with a positive HIV rapid test and who were older than 24 months were classified as HIV infected. This was confirmed with a repeat rapid test or HIV ELISA following indeterminate results. Children with a positive HIV rapid test or who were HIV exposed and younger than 24 months had an HIV polymerase chain reaction (PCR) test performed. The HIV PCR tests were performed in accordance with provincial testing guidelines[94]. Omission of appropriate testing or invalid laboratory samples were repeated at WPH. If the HIV PCR was negative and the patient was HIV exposed (born to a mother with HIV) they were classified as HIV exposed uninfected and if HIV the PCR was positive they were classified as HIV infected. A positive HIV PCR was confirmed with a repeat HIV PCR.

Indoor smoke exposure

Indoor smoke exposure was determined by data collected from the structured interview with the study participant's caregiver and his or her reported use of household biomass fuel. Biomass fuel refers to any organic matter used to generate energy for the purposes of cooking, heating, and lighting. These fuels could be solid (e.g. wood, coal, animal dung, and agricultural products), liquid (e.g. liquid petroleum gas (LPG), paraffin, naphtha, and ethanol) or gas (methane, butane, and propane).

Household crowding

Household crowding was determined by data collected from the structured interview and the reported number of people living in the household including the number of rooms. Household crowding was defined as more than two people per household room[15]. This excluded bathrooms but included kitchen and living room areas.

Indoor tobacco smoke exposure

Tobacco smoke exposure was determined by data collected from the structured interview and the reported number of household members that smoked. Indoor tobacco smoke exposure refers to all household members that smoked including caregivers. Tobacco smoke exposure was further described in terms of

reported areas of smoking, namely: outside the household, inside the household and in the same bedroom that the child (participant) slept.

Breastfeeding

Breastfeeding was determined by data collected from the structured interview and the reported breastfeeding practiced. The WHO classification of breastfeeding was used to categorise patients. Patients were categorised as either not breastfed, partially breastfed, predominantly breastfed, or exclusively breastfeed. No breast feeding describes patients that were never breast fed and received exclusive formula feeding. Partial breast feeding refers to patients that receive some breast feeds and some artificial feeds, either milk or cereal, or other food or water. Predominantly breastfed refers to breastfeeding as the predominant source of nutrition (including breast milk expressed from a wet nurse) in addition to other liquids (water/juice/tea). Exclusive breastfeeding refers to patients that received only breast milk for six months with no additional feeds or liquids.

Nutrition

Nutritional assessment of children was performed using anthropometric data obtained from the recorded admission weight and height. Children were classified using sex appropriate WHO child growth charts as appropriate weight for height, underweight for age, stunted, or wasted which was subclassified as moderate or severe wasting. Appropriate weight for height was defined as age and sex appropriate weight for height between -2 and +2 z-score[13]. Underweight for age was defined as age and sex appropriate weight for age less than -2 z-score. Stunting was defined as age and sex appropriate height less than -2 z-score[13]. Wasting was defined as age and sex appropriate weight for height less then -2 z-score with moderate wasting between -2 and -3 z-score or mid-upper arm circumference (MUAC) between 11.5cm and 12.5cm (moderate acute malnutrition) and severe wasting less than -3 z-score or MUAC less than 11.5cm (severe acute malnutrition)[13]. Patients with nutritional oedema were classified as severe acute malnutrition irrespective of their weight for height[13]. Consistent with the WHO definition of severe pneumonia, children with severe acute malnutrition and nutritional oedema were classified into the severe pneumonia group irrespective of the degree of distress or seriousness of pneumonia. Thus, severe acute malnutrition and nutritional oedema were defining features of severe pneumonia and could not be compared across groups.

Data management

All data were entered into a primary data collection tool developed in Research Electronic Data Capture (REDCap). This is a secure application for building and managing online surveys and databases supported by Stellenbosch University and housed on secure Stellenbosch University servers with a dual authentication process for access. The study data were only accessible to the principal investigator, supervisors and supporting biostatistician. Confidentiality was maintained by assigning study participants unique identifiers. No personal information or hospital folder numbers were captured in the data capturing sheet. These identifiers and their corresponding patient information are kept in a secure location at the Worcester Campus of Stellenbosch University.

Analytic Methods – sample size and statistical analysis

Excluding weekends and public holidays during the 2019 calendar year, 252 days were available to collect data. We estimated 302 pneumonia cases would be admitted in 2019 and estimating a participation rate of 80%, approximately 241 cases could be included during the study period. These estimates were determined based on ward admission data from April 2015 to August 2018, where an average admission rate of 1.2 admissions per day for pneumonia or LRTI in children under 5 years of age was observed. Estimating that two-thirds of the admissions would meet the study definition of severe pneumonia and one-third the study definition of non-severe pneumonia, with an alpha-level of 0.05 a study sample of 240 cases would have 80% power to detect an absolute increase of 20% or an odds ratio of 2.2 for adverse household environmental factors in children with severe compared to non-severe pneumonia.

Statistical analysis was conducted in consultation with the Biostatistics Unit at the Faculty of Medicine and Health Sciences. Basic descriptive statistics were conducted using IBM SPSS Statistics (Version 27) for all factors of interest. The association between severe pneumonia and adverse household environmental factors – tobacco smoke exposure, indoor smoke exposure, and overcrowding - was evaluated using the parametric Chi-square test if assumptions were met or the parametric Fishers Exact test when assumptions for the Chi-square test were not met. Unadjusted ORs for the primary and secondary exposures were calculated comparing children with severe and non-severe pneumonia using univariable logistic regression. We additionally conducted multivariable logistic regression to estimate adjusted ORs including *a priori* identified confounders of age, sex, preterm birth, breastfeeding, nutrition status, HIV infection and exposure, participant co-morbidities, immunisation status, caregiver age and level of education, and additional factors associated with an outcome at p-value of < 0.1.

Ethical considerations

Ethics approval was obtained from the Health Research Ethics Committee of Stellenbosch University (reference number: S18/10/253) (Appendix C), as well as from the Provincial Government of the Western Cape Health Impact Assessment Committee (reference number: WC_201812_011) (Appendix D). Informed consent was obtained from the participant's primary caregiver in a language of their preference. All data were anonymised to ensure privacy and confidentiality of patients' personal information, with each participant assigned a unique identifier.

Chapter 4
Results

During the study period a total of 427 cases of pneumonia or LRTI were admitted to WPH. Three hundred and ninety-six children reviewed during the weekday periods were eligible for enrolment and 335 consented to study enrolment. Following review of admission notes 30 participants were excluded on the basis of not fulfilling the WHO criteria for pneumonia. Between the 1st of January and 31st of December 2019 we enrolled 305 children of which 134 (43.9%) were categorised as severe pneumonia and 171 (56.1%) as non-severe pneumonia. Sixty one percent (n=186) of cases were admitted between March and August 2019, consistent with autumn and winter months in South Africa.

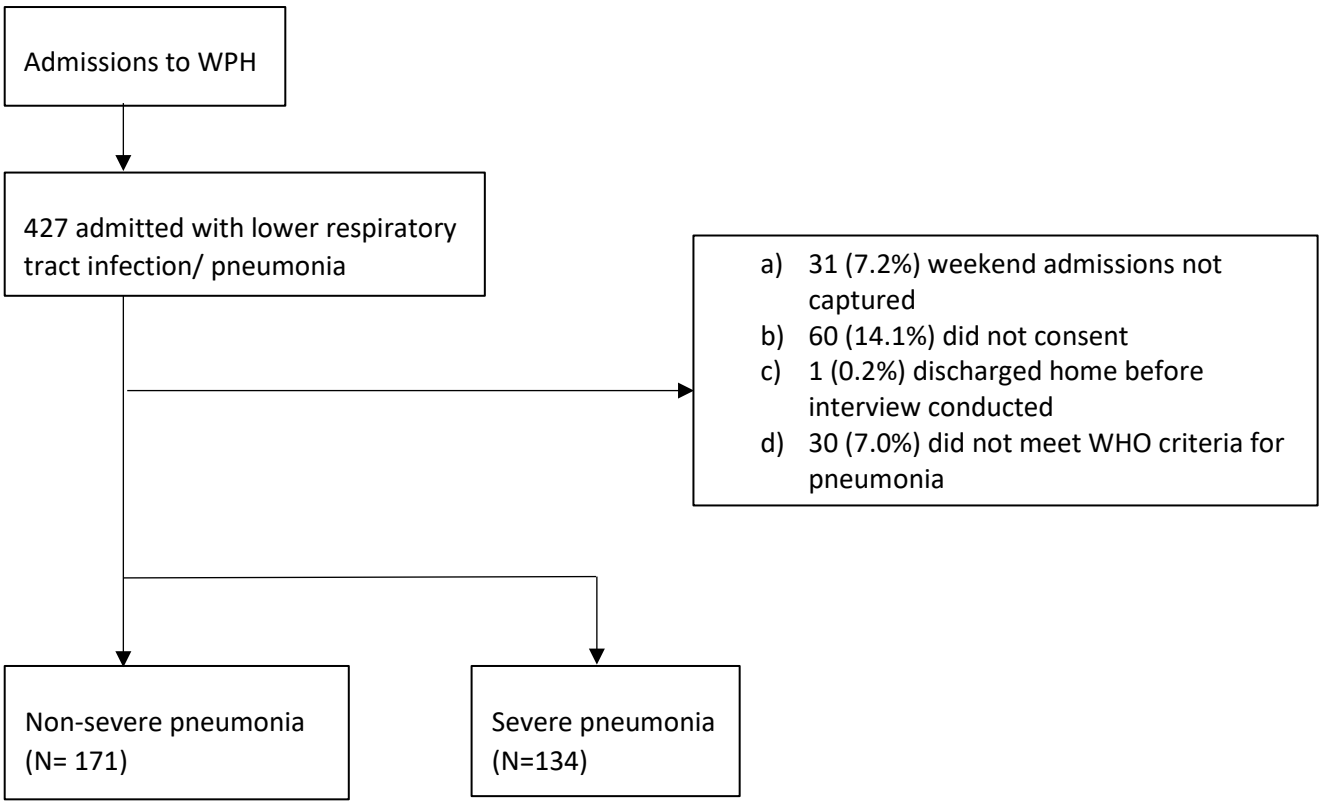

Figure 2 Flow diagram of participant inclusion

Child Characteristics

Baseline characteristics of children (Table 1) were similar in both groups of participants with severe pneumonia and non-severe pneumonia. Of the 305 study participants with pneumonia, the median age at admission was 6.9 months (IQR 2.5-17.5). More than three quarters of the participants (75.7%; n=231) were younger than 18 months with 66.9% (n=204) younger than 12 months of age. Exclusive breastfeeding was practiced by 51.5% (n=157) of participants with no significant difference between groups. Most children

were born term (65.5%; n=200) with appropriate weight for gestation (75.4%; n=230). The median gestational age of both groups was 38 weeks (IQR 36-40) with a median birth weight of 2.88kg (IQR 2.38-3.21). Participants that were preterm at birth made up 28.1% (n=86) of study participants. Late preterm deliveries accounted for most preterm births (60.9%, n=53, p=0.8) compared to early preterm deliveries (37.9%, n=33, p=0.11). Out of home care was reported in 29.5% (n=90) of participants and of these 25.6% (n=23) reported out of home care in informal dwellings. Regarding anthropometry and nutritional assessment, 14.1% (n=43) of participants were classified as underweight for age, 18.4% (n=56) stunted, and 9.8% (n=30) assessed as moderate acute malnutrition with no significant differences between groups. Severe acute malnutrition, including the presentation of nutritional oedema, were defining criteria for severe pneumonia and thus all six children with these characteristics were classified in the severe pneumonia group.

Age-appropriate immunisation coverage was recorded in 86.9% (n=265) of children. Slightly less coverage was found in the severe pneumonia compared to the non-severe pneumonia group (84.3% versus 88.9%), however this was not significantly different. Of all participants, 10.2% (n=31) had TB household contacts and of those only 25.8% (8/31) were on appropriate TB prophylaxis. Over 20% (n=63) of all participants were diagnosed with pulmonary TB at admission with 6.3% (4/63) of those cases confirmed microbiologically. Tuberculosis therapy was discontinued in some patients (15.8%, n=10) at discharge following review of case information. Children who were HIV exposed or HIV infected made up 18.6% (n=57) of all participants of which 75.4% (43/57) were on appropriate cotrimoxazole prophylaxis.

The final diagnosis in 78.3% (n=239) of cases was pneumonia or bronchopneumonia (Table 2). The final diagnosis of bronchiolitis or pulmonary TB was made in 10.5% (n=32) and 17.4% (n=53) respectively. Bronchiolitis was diagnosed less often in the severe pneumonia group (7.5%, n=10) than the non-severe pneumonia group (12.9%, n=22). Asthma was not a frequent diagnosis in this cohort accounting for 3.3% (n=10) of the diagnoses. In 18.1% (2/11) of asthma cases and 56.6% (30/53) of pulmonary TB cases a concomitant diagnosis of pneumonia and bronchopneumonia were made. A number of concomitant and co-morbid conditions (“other” diagnoses) were noted in some participants (15.1%; n=46). Four participants had diagnoses other than the five sub-categories of diagnoses for clinical pneumonia. These included two patients with unspecified LRTIs, one case of laryngotracheobronchitis, and one case of pertussis. The most prevalent co-morbidity was congenital heart disease occurring in 4.6% (n=14) of all children with pneumonia. The most prevalent concomitant diagnoses included anaemia (3.9%; n=12), failure to thrive (3.3%; n=10), acute gastroenteritis (3.0%; n=9) and urinary tract infection (2.6%; n=8).

The average length of stay was greater in the severe pneumonia group with a median stay of 4 days (IQR 2.3-6.0) versus the non-severe pneumonia group with a median stay of 3 days (IQR 1.3-4.0) ($p < 0.01$). Only one patient death occurred in this cohort with most children being discharged home (86.2% ; n=263) following hospital admission. A smaller proportion of children (12.7%, n=39) were transferred to step-down facilities, either Brewelskloof TB Hospital or the appropriate district level hospital. Two patients (0.7%) required transfer for tertiary level hospital care.

Caregiver characteristics

Maternal characteristics were comparable amongst both groups of children with severe pneumonia and non-severe pneumonia (Table 3). Mothers accounted for the majority (94.7%, n=288) of caregivers with a median age of 28 years (IQR 23.2-33.8). More than 90% (n=277) of caregivers were South African citizens with the remainder from Lesotho (5.6%, n=17), Zimbabwe (3.3%, n=10), and Malawi (0.3%, n=1). A large proportion (88.5%, n=270) of caregivers, irrespective of citizenship, resided permanently in the areas they dwelt and 11.1% (n=34) reported that their area of dwelling was only temporary or seasonal. The majority of caregivers had received some secondary schooling (71.1%, n=217) however only 20.7% (n=63) matriculated with no differences between groups. Forty-five percent (n=138) of caregivers reported being employed and 68.8% (n=95/138) of this group were primary breadwinners. Seasonal or temporary work accounted for 49.5% (n=47/95) of employed caregivers who were primary breadwinners. Additional sources of household income included government pension (20.3%, n=62) and child support grants (53.1%, n=162). Eighteen percent (n=57) of caregivers were known to have HIV, which was slightly higher in the severe pneumonia group (20.1%, n=27) compared to the non-severe pneumonia group (17.5%, n=30, p=0.53). Overall, 30% (n=93) of caregivers reported current smoking, with slightly fewer smokers in the severe pneumonia group compared to the non-severe pneumonia group, 26.9% (n=36) and 33.3% (n=57) respectively (p=0.22). The number of pack years was also less in the severe pneumonia group compared to the non-severe pneumonia group, median pack years of 1.0 (IQR 0.48-1.9) and 1.8 (IQR 0.70-3.50) respectively.

Household risk factors

The majority of participants (58.7%, n=179) lived in formal dwellings; 93.1% (n=284) had access to electricity and 62.6% (n=191) reported water piped into the dwelling (Table 4). Flush toilets were available to 88.2% (n=269) of participants and 25.9% (n=79) reported use of communal toilets. Household kitchens were predominantly reported as separate household rooms (64.1%, n=195) and areas without partitions (35.5%, n=108). Eighty-six percent (n=263) of households utilised electric stoves (including hotplates), followed by gas stoves (14.8%, n=45) and paraffin stoves (7.9%, n=24). Household wall material was reported as bricks

in 175 (57.4%), tin or iron sheeting in 98 (32.1%), and wood in 32 (10.5%) participants. More than 90% (n=277) of households reported tin or iron sheeting as household roof material.

Exposure to household tobacco, in household members other than the primary caregiver, was assessed in 269 participants of whom 55% (n=148) reported household members that smoked (Table 5). Open fires were reported in 40.6% (124/305) of households with wood (97.6%, 121/124) followed by coal (12.1%, 15/124) being the most frequently used biomass fuel. There was no association between severe pneumonia and non-severe pneumonia in households that made open fires versus those that did not. There tended to be more households that burned coal in the severe pneumonia (20.0%, n=10) compared to the non-severe pneumonia group (6.8%, n=5), however there was no statistical difference between groups. Most households that reported open fires made these less than once per week (46.0%, n=57) or only once per week (37.1%, n=46). The majority of households (88.5%, n=270) reported no additional items burned. Of the 11.8% (n=36) of participants that reported burning additional items, incense and imphepho (*helichrysum petiolare* – liquorice plant) were most frequently used. Almost two thirds of households (63.3%, n=193) reported no pesticide use. In those that did utilise pesticides, *Doom* was reported as the most frequently used (27.2%, n=83). A median of 5 (IQR 4.0-6.0) household members were reported living together with a median of 3 members (IQR 3.0-4.0) sleeping in the same room as the participant. Overcrowding was reported in 120 households (39.3%) with no significant difference between groups.

To answer the primary study objective of whether adverse household environmental factors including indoor smoking, overcrowding and indoor use of biomass fuels are associated with severe pneumonia in children we conducted unadjusted and adjusted logistic regression analyses. We evaluated the association between severe pneumonia and each of the adverse household environmental factors (indoor tobacco smoke exposure, overcrowding and indoor biomass fuel exposure) individually and in a combined model. In the unadjusted analyses there was no association between indoor tobacco smoke exposure, overcrowding or indoor biomass fuel exposure and severe pneumonia. Adjusting for factors known to be associated with severe pneumonia in children (including age <3 months, birth weight <1500g, any breastfeeding, immunisations status, child's HIV status, maternal age <20 years, and caregiver education less than matric) there was still no association between our hypothesised adverse household environmental factors and the odds of severe pneumonia. However, children with severe pneumonia had at least a five times greater odds (aOR 5.42; 95% CI 1.10-26.65) of living in a household with a pit latrine toilet compared to any other toilet than children with non-severe pneumonia.

Tables

Table 1. Baseline characteristics of children with non-severe compared to severe pneumonia

	Total (n= 305)	**Non-severe pneumonia (n= 171)**	**Severe pneumonia (n= 134)**	**p-value**
Age (months) - median (IQR)	6.9 (2.5 - 17.5)	6.9 (2.8-16.0)	6.9 (2.3-18.4)	0.82
Male sex – N(%)	164 (53.8%)	90 (52.6%)	74 (55.2%)	0.65
Admission duration (days) – median (IQR)	3.0 (2.0-5.0)	3.0 (1.4-4.0)	4.0 (2.3-6.0)	<0.01
Gestation at birth in weeks – median (IQR)	38.0 (36.0-40.0)	38.0 (35.0-40.0)	38.0 (36.0-40.0)	0.94
Gestational category – N(%)				
Preterm	86 (28.1%)	52 (30.4%)	34 (25.3%)	0.31
Term	200 (65.5%)	110 (64.3%)	90 (67.1%)	
Postdates	16 (5.2%)	8 (4.7)	8 (6.0%)	
Unknown	3 (1.0%)	1 (0.6%)	2 (1.5%)	
Birth weight in kg – median (IQR)	2.88 (2.38-3.21)	2.85 (2.35-3.20)	2.93 (2.50-3.22)	0.37
Gestation for weight – N(%)				
Appropriate for gestational age	230 (75.4%)	127 (74.3%)	103 (76.9%)	0.53
Small for gestational age	52 (17.0%)	31 (18.1%)	21 (15.7%)	
Large for gestational age	16 (5.2%)	10 (5.8%)	6 (4.5%)	
Unknown	7 (2.3%)	2 (1.2%)	5 (3.7%)	
Nutritional status – N(%)				
Underweight	43 (14.1%)	24 (14.0%)	19 (14.2%)	0.97
Stunted	56 (18.4%)	28 (16.4%)	28 (20.9%)	0.31
Nutritional oedema	3 (1.0%)	0 (0.0%)	3 (2.2%)	0.04
Malnutrition Status – N(%)				
No malnutrition	249 (81.6%)	144 (84.2%)	105 (78.4%)	0.19
Moderate acute malnutrition	30 (9.8%)	17 (9.9%)	13 (9.7%)	0.94
Severe acute malnutrition	6 (2.0%)	0 (0.0%)	6 (4.5%)	<0.01
Immunisation up to date – N(%)	265 (86.9%)	152 (88.9%)	113 (84.3%)	0.50
Feeding practice – N(%)				
Exclusive breast feeding	157 (51.5%)	90 (52.6%)	67 (50.0%)	0.95
Predominantly breast feeding	38 (12.5%)	20 (11.7%)	18 (13.4%)	
Partial breast feeding	78 (25.6%)	43 (25.1%)	35 (26.1%)	
No breast feeding	32 (10.5%)	18 (10.5%)	14 (10.4%)	
Out of home care – N(%)	90 (29.5%)	55 (32.2%)	35 (20.5%)	0.25
HIV status – N(%)				
Unexposed uninfected	248 (81.3%)	141 (82.5%)	107 (79.9%)	0.55
Exposed uninfected	47 (15.4%)	27 (15.8%)	20 (14.9%)	
Exposed but not confirmed negative	6 (1.9%)	2 (1.2%)	4 (3.0%)	
HIV infected	4 (1.3%)	1 (0.6%)	3 (2.2%)	

IQR, interquartile range; HIV, Human Immunodeficiency Virus

Table 2. Diagnosis at discharge and co-morbidities of children admitted with non-severe compared to severe pneumonia

Diagnosis	**Total (n=305)**	**Non-severe pneumonia (n=171)**	**Severe Pneumonia (n=134)**	**p-value**
Diagnostic classification – N(%)*				
Pneumonia	107 (35.1%)	54 (31.6%)	53 (39.6%)	0.14
Bronchopneumonia	132 (43.3%)	77 (45.0%)	55 (41.0%)	0.48
Asthma	11 (3.6%)	5 (2.9%)	6 (4.5%)	0.69
Bronchiolitis	32 (10.5%)	22 (12.9%)	10 (7.5%)	0.24
Pulmonary tuberculosis	53 (17.4%)	33 (19.3%)	20 (14.9%)	0.45
Other	46 (15.1%)	18 (10.5%)	28 (20.9%)	-
Concomitant diagnoses and Co-morbidities – N(%)*				
None	258 (84.6%)	149 (87.1%)	109 (81.3%)	0.16
Congenital heart disease	14 (4.6%)	6 (3.5%)	8 (6.0%)	0.45
Anaemia	12 (3.9%)	6 (3.5%)	6 (4.5%)	0.66
Failure to thrive	10 (3.3%)	4 (2.3%)	6 (4.5%)	0.29
Urinary tract infection	8 (2.6%)	1 (0.6%)	7 (5.2%)	0.01
Acute gastroenteritis	9 (3.0%)	6 (3.5%)	3 (2.2%)	0.51

*Patients could be assigned to more than one diagnosis at discharge and could experience more than one co-morbidity, therefore categories sum to more than 100%

Table 3. Characteristics of caregivers of children with non-severe compared to severe pneumonia

	Total n=305	**Non-severe pneumonia (n=171)**	**Severe pneumonia (n=134)**	**p-value**
*Primary caregiver** – N(%)				
Mother	288 (94.7%)	162 (94.7%)	126 (94.7%)	0.57
Other	16 (5.3%)	9 (5.3%)	7 (5.3%)	
Age of primary caregiver – median (IQR)	28.1 (23.2-33.9)	27.8 (23.3-34.2)	29.3 (23.0-33.7)	0.98
Permanence of residence – N(%)				
Permanent	270 (88.5%)	151 (88.3%)	119 (88.8%)	
Temporary/ seasonal	34 (11.1%)	19 (11.1%)	15 (11.2%)	
Unknown	1 (0.3%)	1 (0.6%)	0 (0.0%)	0.67
Country of origin – N(%)				
South African	277 (90.8%)	155 (90.6%)	122 (91.0%)	0.90
Lesotho	17 (5.6%)	10 (5.8%)	7 (5.2%)	
Zimbabwe	10 (3.3%)	5 (2.9%)	5 (3.7%)	0.61
Malawi	1 (0.3%)	1 (0.6%)	0 (0.0%)	
Highest level of education – N(%)				
≤ Grade 6	17 (5.6%)	13 (7.6%)	4 (3.0%)	
Some secondary	217 (71.1%)	114 (66.7%)	103 (76.9%)	
Matriculated	63 (20.7%)	40 (23.4%)	23 (17.2%)	
Tertiary education	7 (2.3%)	4 (2.3%)	3 (2.2%)	0.35
Employed – N(%)	138 (45.2%)	80 (46.8%)	58 (43.3%)	0.54
Primary caregiver breadwinner – N(%)	95 (31.1%)	56 (32.7%)	39 (29.1%)	0.49
Employment status – N(%)				
Unemployed – N(%)	12 (4.8%)	8 (5.6%)	4 (3.8%)	
Seasonal/ temporary work – N(%)	47 (18.9%)	27 (18.8%)	20 (19.0%)	
Permanent work – N(%)	36 (14.5%)	21 (14.6%)	15 (14.3%)	0.84
Other sources of household income - (N(%)				
Pensioner grant	62 (20.3%)	32 (18.7%)	30 (22.4%)	0.42
CSG	162 (53.1%)	90 (52.6%)	72 (53.7%)	0.84
CDG	2 (0.7%)	1 (0.6%)	1 (0.7%)	0.86
Caregiver smoker – N(%)	93 (30.5%)	57 (33.3%)	36 (26.9%)	0.22
Caregiver with HIV – N(%)	57 (18.7%)	30 (17.5%)	27 (20.1%)	0.58

IQR, interquartile range; CSG, Child Support Grant; CDG, Care Dependency Grant; HIV, Human immunodeficiency virus.
** Unknown variable in one participant with severe pneumonia*

Table 4. Structural household risk factors in children with non-severe compared to severe pneumonia

	Total (n=305)	**Non-severe pneumonia (n = 171)**	**Severe pneumonia (n = 134)**	**p-value**
Formal dwelling – *N(%)*	179 (58.7%)	106 (62.0%)	73 (54.5%)	0.18
Electricity present – N(%)	284 (93.1%)	160 (93.6%)	124 (72.5%)	0.58
Drinking water – N(%)				
Public tap	55 (18.0%)	30 (17.5%)	25 (14.6%)	0.80
Piped into yard	56 (18.4%)	30 (17.5%)	26 (15.2%)	0.67
Piped into dwelling	191 (62.6%)	109 (63.7%)	82 (48.0%)	0.64
Toilet type – N(%)				
Flush toilet	269 (88.2%)	153 (89.5%)	116 (86.6%)	0.43
Pit toilet	**11 (3.6%)**	**2 (1.2%)**	**9 (6.7%)**	**0.01**
No facility	14 (4.6%)	8 (4.7%)	6 (4.5%)	0.93
Mobile toilet	10 (3.3%)	8 (4.7%)	2 (1.5%)	0.12
Communal toilet – *N(%)*	79 (25.9%)	41 (24.0%)	38 (28.4%)	0.38
Kitchen type – N(%)*				
Inside without partitions	108 (35.5%)	60 (35.3%)	48 (35.8%)	0.52
Separate room inside house	195 (64.1%)	110 (64.7%)	85 (63.4%)	
Outside kitchen	1 (0.3%)	0 (0.0%)	1 (0.7%)	
Stove type – N(%)				
Electric	263 (86.2%)	148 (86.5%)	115 (85.8%)	0.85
Wood	5 (1.6%)	2 (1.2%)	3 (2.2%)	0.46
Gas	45 (14.8%)	28 (16.4%)	17 (12.7%)	0.36
Paraffin	24 (7.9%)	12 (7.0%)	12 (9.0%)	0.53
Microwave	17 (5.6%)	13 (7.6%)	4 (3.0%)	0.08
None	2 (0.7%)	1 (0.6%)	1 (0.7%)	0.86
Wall material – N(%)				
Bricks	175 (57.4%)	105 (61.4%)	70 (52.2%)	0.10
Tin/iron sheeting	98 (32.1%)	50 (29.2%)	48 (35.8%)	0.22
Wood	32 (10.5%)	16 (9.4%)	16 (11.9%)	0.46
Roof material – N(%)				
Tin/iron sheeting	277 (90.8%)	153.0 (89.5%)	124.0 (92.5%)	0.35
Tiled	24 (7.9%)	16.0 (9.4%)	8.0 (6.0%)	0.27
Other	1 (0.3%)	1.0 (0.6%)	0.0 (0.0%)	-

** Unknown in one participant with non-severe pneumonia*

Table 5. Indoor household exposures in children with non-severe compared to severe pneumonia

*Indoor household exposures**	**Total N=305**	**Non-severe pneumonia (n = 171)**	**Severe Pneumonia (n = 134)**	**p-value**
Household members – median (IQR)	5.00 (4.0-6.0)	5.0 (4.0-6.0)	4.0 (4.0-6.0)	0.04
Number of rooms – median (IQR)	3.00 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	0.88
Members/room – median (IQR)	1.5 (1.3-2.3)	1.7 (1.3-2.5)	1.5 (1.3-2.0)	0.17
Members sleeping in same room – median (IQR)	3.00 (3.0-4.0)	3.0 (3.0-4.0)	3.0 (3.0-4.0)	0.04
Members sleeping in same bed – median (IQR)	3.00 (2.0-3.0)	3.0 (2.0-3.0)	3.0 (2.0-3.0)	0.53
Overcrowding – N(%)	120 (39.3%)	73 (42.7%)	47 (35.1%)	0.17
Household smokers** – N(%)	148 (55.0%)	90 (58.8%)	58 (50.0%)	0.28
Smoking area				
Bedroom	14 (9.5%)	9 (10.0%)	5 (8.6%)	0.52
Inside	23 (15.5%)	10 (11.1%)	13 (22.4%)	0.20
Outside	128 (86.5%)	78 (86.7%)	50 (86.2%)	0.14
Open household fires – N(%)	124 (40.6%)	74 (43.3%)	50 (37.3%)	0.29
Open household fire material	**N=124**	**n = 74**	**n = 50**	
Wood (subgroup)	121 (97.6%)	71 (95.9%)	50 (100.0%)	0.45
Coal (subgroup)	15 (12.1%)	5 (6.8%)	10 (20.0%)	0.06
Additional items burned – N(%)	36 (11.8%)	17 (9.9%)	19 (14.2%)	
Plants	1 (0.3%)	1 (0.6%)	0 (0.0%)	0.37
Incense	11 (3.6%)	8 (4.7%)	3 (2.2%)	0.25
Imphepho	21 (6.9%)	8 (4.7%)	13 (9.7%)	0.08
Other	3 (1.0%)	0 (0.0%)	3 (2.2%)	0.04
Nothing	270 (88.5%)	154 (90.1%)	116 (86.6%)	0.34
Pesticides in household – N(%)				
Doom	83 (27.2%)	44 (25.7%)	39 (29.1%)	0.51
Mortein target	12 (3.9%)	9 (5.3%)	3 (2.2%)	0.17
Other spray pesticide	11 (3.6%)	4 (2.3%)	7 (5.2%)	0.18
None	193 (63.3%)	112 (65.5%)	81 (60.4%)	0.36

IQR, interquartile range.
*Unknown variable in one participant in the severe pneumonia group.
**Household smoking unknown in 18 participants in non-severe pneumonia group and 17 participants in severe pneumonia group

Table 6. Unadjusted and adjusted logistic regression models of the primary exposures and the outcome of severe relative to non-severe pneumonia

	ur (95% CI)	Model 1: Indoor Smoking aOR (95% CI)	Model 2: Overcrowding aOR (95% CI)	Model 3: Indoor Smoke Exposure aOR (95% CI)	Model 4: Combined aOR (95% CI)
Indoor tobacco smoking – any (reference none)	0.73 (0.46-1.16)	0.68 (0.42-1.11)	----------	----------	0.73 (0.44-1.21)
Overcrowding* - yes (reference no)	0.72 (0.45-1.15)	----------	0.63 (0.38-1.03)	----------	0.65 (0.39-1.08)
Indoor coal biomass fuel burned (reference no biomass burned)	2.31 (0.75-7.02)	----------	----------	2.58 (0.83-8.00)	2.85 (0.89-9.09)
Indoor non-coal biomass fuel burned (reference no biomass burned)	1.49 (0.91-2.43)	----------	----------	0.64 (0.392-1.07)	0.71 (0.423-1.19)
Child age < 3 months (reference ≥ 3 months)	1.41 (0.86-2.32)	1.39 (0.82-2.36)	1.32 (0.78-2.23)	1.35 (0.79-2.29)	1.31 (0.77-2.25)
Birth weight <1500g (reference ≥ 1500g)	1.14 (0.42-3.04)	1.10 (0.40-3.01)	1.19 (0.43-3.27)	1.25 (0.46-3.41)	1.27 (0.46-3.51)
Any breastfeeding (reference no breastfeeding)	1.00 (0.48-2.11)	1.02 (0.48-2.18)	1.00 (0.47-2.13)	1.08 (0.50-2.33)	1.08 (0.50-2.34)
Immunisations not up to date (reference up to date)	1.49 (0.75-2.94)	1.46 (0.72-2.96)	1.42 (0.70-2.88)	1.49 (0.73-3.03)	1.43 (0.70-2.93)
Child with HIV (reference without HIV)	3.89 (0.40-37.85)	3.43 (0.34-34.05)	4.23 (0.42-42.54)	3.67 (0.36-36.92)	4.18 (0.41-42.73)
Maternal age < 20 years (reference ≥ 20 years)	1.04 (0.52-2.07)	1.08 (0.53-2.23)	0.98 (0.48-2.01)	1.01 (0.49-2.07)	1.06 (0.51-2.23)
Caregiver education less than matric (reference at least matric)	0.70 (0.40-1.21)	0.75 (0.42-1.32)	0.72 (0.40-1.28)	0.73 (0.41-1.30)	0.64 (0.38-1.16)
Household toilet pit latrine (reference any other toilet)	6.08 (1.29-28.65)	5.01 (1.02-24.62)	5.18 (1.05-25.41)	5.21 (1.06-25.57)	5.42 (1.10-26.65)

aOR – adjusted odds ratio; CI – confidence interval; ur – unadjusted odds ratio; HIV – Human Immunodeficiency Virus

Chapter 5

Discussion

Pneumonia remains an important public health burden and determining factors that may mitigate severe disease has beneficial implications in resource limited settings. These factors may help inform interventions and policy decisions in an already constrained health care system.

This case-control study compared risk factors of cases with severe pneumonia to unmatched controls with non-severe pneumonia admitted to a regional secondary level rural hospital in the Western Cape Province of South Africa between 1st of January 2019 and 31st of December 2019. We compared infant, caregiver and household risk factors and found a predominantly homogenous group of participants with few significant variations between cases with severe pneumonia and controls with non-severe pneumonia. These similarities were noted in baseline characteristics including a mean caregiver age, similar education level with most caregivers having achieved some secondary education or matriculated. While less than half of caregivers were employed, participants mostly resided in formal dwellings with similar structural characteristics, including wall and roofing material, in both groups. Participants were predominantly South African citizens living permanently in the various areas they reported. Established risk factors for pneumonia were also similar between groups, with the majority of children being less than seven months of age at the time of admission, almost a quarter born preterm, 87% appropriately immunised and just over half having been exclusively breastfed for six months. It should be noted that in the first 35 participants data relating to household smokers was missing due to an initial data capturing error that was corrected following identification. Despite this error, similar exposure profiles were reported in both groups. Open household fires, household smokers, caregiver smokers and household overcrowding were prevalent exposures in both groups. The distinguishing feature amongst these groups related to children with severe pneumonia having a greater odds of living in a household with a pit latrine toilet compared to children with non-severe pneumonia.

As expected a large proportion of participants were infants in the first year of their life. Severe pneumonia and non-severe pneumonia in the early months of life reflects the vulnerability of this young age group which is consistent with studies in LMICs[26,30,31]. Our study however did not demonstrate group differences related to age, indicating that young age, though a known risk factor for pneumonia, was not a factor associated with the severity of pneumonia in this study. Similarly, more than a quarter of participants were preterm with the majority of participants appropriate for gestational age. Prematurity is associated with immature immune function, reduced production of pro-inflammatory cytokines, and reduced passive

immunity conferred by transplacental maternal antibodies[28,34,36]. Despite prematurity being a known risk factor for pneumonia[28], it was not associated with greater odds of severe disease when comparing severe pneumonia with non-severe pneumonia. This was demonstrated in both late and early preterm births.

Adequate nutrition plays a pivotal role in disease prevention and children that are malnourished have secondary immunodeficiency due to compromised innate and adaptive immune responses[41]. According to the WHO definition of pneumonia all children with evidence of severe acute malnutrition with respiratory tract infection features are considered to have severe pneumonia, thus we could not evaluate severe acute malnutrition as an independent risk factor for severe pneumonia. Although the majority of children had appropriate weight for height, more than 40% were assessed as moderately malnourished, underweight or stunted. Despite evidence to support the importance of malnutrition as a risk factor for pneumonia[42,95] there was no observable association with the severity of disease. This observation may be skewed due to assigning severely malnourished children automatically to the severe pneumonia group and essentially excluding them from analysis.

Prevention of childhood communicable diseases through immunisation plays an important role in reducing pneumonia mortality, morbidity and burden of disease[51,59]. This important preventative strategy, however; was not associated with severe pneumonia in this study with similar and fairly good immunisation coverage reported in the severe pneumonia and non-severe pneumonia groups.

While HIV-infection was low (1.3%), HIV exposure without infection was fairly prevalent (17.3%) in this study. HIV compromises host innate and adaptive immune responses predisposing to infective and inflammatory processes[46]. HIV exposed infants also develop abnormalities of the innate and adaptive immune systems which is compounded by limited protection due to reduced maternal antibodies, impaired response to some vaccines and increased exposure to infectious diseases from living in a household with a member who is HIV infected[31,49,50]. Our study, however, did not demonstrate an association with HIV infection or HIV exposure without infection and severe pneumonia.

Cotrimoxazole prophylaxis is recommended to prevent pneumocystis jirovecii pneumonia (PJP) in children with HIV[96,97]. Despite more than 20% of children with HIV or HIV exposed not being on appropriate cotrimoxazole prophylaxis, this was not associated with a greater odds of severe pneumonia. A larger sample of children with HIV or HIV exposed and uninfected (HEU) would be needed to assess any increased risk for severe pneumonia associated with not receiving cotrimoxazole prophylaxis. Interestingly, two studies conducted in Botswana and South Africa looking at cotrimoxazole prophylaxis amongst children who are

HEU did not demonstrate improvement in the 18 month survival among children who are HEU on prophylaxis compared to placebo or evidence of inferiority in children not on prophylaxis compared to those on cotrimoxazole[98,99]. These studies were conducted in comparable settings to WPH where caregivers had access to vertical HIV transmission prevention interventions and malaria was not endemic.

Whether mutually exclusive or found in concert, maternal age and education have been observed as risk factors for childhood pneumonia. Maternal age less than 20 years of age has been described as a risk factor for pneumonia[38,86]. We did not find an association between young maternal age and the development of severe pneumonia. Our median caregiver age was similar between the two groups with no increased odds of developing severe disease. In addition, higher maternal education often associated with lower risk of pneumonia[88,90] was not a demonstratable protective factor against developing more severe disease. Although young maternal age and lower education levels are associated with the risk of developing pneumonia, these factors, independently or synergistically, are not drivers of severe disease in this study context.

Tobacco smoke exposure is a well described risk factor for pneumonia in studies conducted in South Africa and Cameroon[31,38,44]. The Drakenstein Child Health Study, a birth cohort study conducted outside of Cape Town, demonstrated in regression models that maternal smoking was an independent risk factor for pneumonia. The Drakenstein Study included ambulatory and hospitalised LRTIs and was conducted at two separate clinics. This study used WHO criteria to define pneumonia similar to our study but the clinic setting and ambulatory LRTI was a noted difference[70]. A case control study conducted at Chris Hani Baragwanath Academic Hospital also observed that a primary caregiver who smoked was a risk factor for pneumonia (aOR: 5.15, 95% CI: 2.94–9.03)[44]. This study however did not use the WHO criteria for pneumonia and was conducted in a tertiary hospital. The study conducted in Cameroon assessed pneumonia risk factors using a cross sectional study at a secondary hospital. This study included both ambulatory and hospitalised acute respiratory tract infections and found that passive smoking was associated with acute respiratory tract infections. Both the Drakenstein and Cameroon studies used WHO case definitions for pneumonia; however, both studies included ambulatory cases of pneumonia. None of the three studies looked at severe and non-severe pneumonia and comparison groups were matched differently. The Drakenstein Study was a birth cohort that followed up mother and infant pairs, the study conducted in Chris Hani Baragwanath Hospital used age matched community controls, and the study in Cameroon recruited participants that presented to their institution without a control arm. These differences in study design and sample selection may represent

different populations with different risk factors and disease severity compared to the cohort admitted to WPH and included in our study.

Our study reflected less smoking in caregivers in the severe pneumonia group than the non-severe pneumonia group. This unexpected observation may have been due to reverse causality bias implicated in the study design and behaviour change following hospital admission of participants. Our study examined risk factors after the outcomes (severe pneumonia and non-severe pneumonia) were assessed and we hypothesize that severe disease may have caused a change in smoking behaviour or social desirability bias reporting rather than that increased tobacco smoke exposure may be protective.

Combustion of biomass fuels result in by-products such as carbon monoxide and particulate matter, both of which cause household air pollution. Household air pollution is estimated to cause a high burden of morbidity and mortality globally, and of importance is the associated risk of pneumonia[62]. Our study did not demonstrate an observable difference between the two groups and found that household smoke exposure was not associated with the severity of pneumonia. Our study, however, was not designed to determine factors that cause incident pneumonia, where combustion biomass fuels may be an important risk factor. The burning of coal for household, cooking, heating, or light demonstrated increased odds of developing severe pneumonia but this was not statistically significant and the study may have been under-powered to identify this difference. Other items such as *imphepho* that is burned in households was not associated with an increased odds of severe pneumonia compared to non-severe pneumonia.

Overcrowding is an established risk factor for childhood pneumonia. It is often associated with lower socioeconomic status which represents an inherently vulnerable child population. Close contact and frequent (direct and indirect) exchanges with potential sources of respiratory disease coupled with confined and poorly ventilated dwellings predispose members to disease and is a risk factor for pneumonia[44,45] . Our study, however, did not demonstrate this factor to be associated with the severity of pneumonia. In contrast, our study demonstrated that having a greater number of household members was associated with a reduced odds of developing severe disease. This may be due to larger households being able to provide more childhood monitoring, stimulation, caregiving, education, and financial support in this generally socioeconomically vulnerable population.

In relation to the primary study objective no association was demonstrated in univariable or multivariable analysis between adverse household environmental factors and severe pneumonia. Overcrowding, indoor smoke exposure and tobacco smoke exposure were comparable between groups and in this vulnerable study

population there may have been limited heterogeneity in these risk factors to identify differences. Severe pneumonia was only associated with greater odds in households that reported use of pit latrine toilets. This association may be more representative of the most marginalized families and increased risk of developing disease in a vulnerable population. Further analysis of socioeconomic disparities may be helpful in assigning risk to other adverse household environmental factors and the detection of protective factors.

In an attempt to help inform interventions and policy decisions to mitigate pneumonia severity we continue to advocate for primary health interventions. Primary interventions such as childhood immunisations, maternal education relating to smoking and smoke exposure, exclusive breast feeding, appropriate education on nutrition, and compliance with vertical HIV transmission prevention guidelines remain important strategies to reduce community disease burden. Of equal importance are parallel strategies to improve living conditions and alleviate poverty through appropriate housing, access to sustainable energy, clean water, sanitation, and appropriate sewerage disposal.

Limitations

Notable limitations that deserve consideration include the method of data capturing, the broad pneumonia case definition, assessing the severity of pneumonia and quantifying household environmental factors.

The method of data collection was dependent on information recalled by the primary caregiver and some elements may have been inaccurate. This may have influenced certain questions related to past events such as the duration of breastfeeding or previous hospital admissions. Participants may also have been reluctant to answer sensitive questions relating to HIV, smoking or home circumstances and may have refrained from answering or may have offered socially desirable responses. These elements were addressed by being sensitive to certain impressions or insinuations, refraining from leading questions and phrasing questions in a nonthreatening manner. Confidentiality played a large role and was impressed upon and reinforced with those conducting the interviews. A strength of this study however is the prospectively collected detailed socioeconomic, household and environmental information that would not ordinarily be available in routine clinical records.

Another important limitation related to the study design and feasibility of conducting the study was the exclusion of outpatient pneumonia cases. A large number of district hospitals and community clinics diagnose clinical pneumonia daily and depending on their assessment, may offer ambulatory treatment. Although not part of the study design, this group of patients represents an important source of information

related to pneumonia and risk factors for developing pneumonia as opposed to risk factors driving the severity of disease.

A larger study cohort would be better powered to detect smaller but still clinically meaningful differences between population groups. This was not feasible within the time and study resources available.

The diagnosis of pneumonia was based on clinical findings in children that were documented by the attending clinician. This element may have varied amongst the attending doctors when assessing the severity of pneumonia. This element was addressed to some extent by standardising the clinical criteria, however, this subjectivity may have influenced the data captured. Use of dedicated physicians recording the clinical features on presentation and during admission as opposed to different physicians with different experience levels may have improved the accuracy of classifying pneumonia.

The WHO definition of pneumonia casts a broad diagnostic net. Respiratory tract infections that imitate pneumonia include asthma and bronchiolitis. These share the same clinical manifestations as the pneumonia case definition. Although these are not pneumonia events (i.e. lung parenchymal disease) they were not excluded from the study which may have marginally affected our results related to risk factors. Despite separating cases into pneumonia, bronchiolitis, and asthma these cases were included in the analysis of the two groups. Other studies have used different definitions of pneumonia in an attempt to provide more robust criteria for defining the diagnosis. These definitions include radiological and biochemical supporting evidence. Using the WHO definition of pneumonia, however allows us to compare findings with studies that have utilised this definition and may be more applicable in resource limited settings[70].

Household air pollution and tobacco smoke exposure were not quantified in terms of particulate matter concentrations, carbon monoxide levels and the duration of indoor smoke exposure. Confounding factors including indoor ventilation, population density, and environmental air pollution which may be a biproduct of biomass fuels were not measured. Although these factors did not fall into the scope of this study, this information may have been of value when comparing severe pneumonia and non-severe pneumonia.

Conclusion

This cohort provides a comparison of risk factors in children admitted with severe pneumonia and non-severe pneumonia in a rural setting in South Africa. We compared child, caregiver and household risk factors and found a predominantly homogenous group of participants with few significant variations. These similarities were noted in both baseline characteristics and risk factors. The distinguishing feature amongst these groups related to children with severe pneumonia having a greater odds of living in a household with

pit latrine toilet compared to children with non-severe pneumonia. This may represent the socioeconomic differences of this cohort and the risk associated with developing severe pneumonia.

Our study did not demonstrate risk factors associated with developing severe compared to non-severe pneumonia. The factors measured are well known protective and adverse factors that are associated with the development of pneumonia. Their effects, independently and combined, were not indicators or predictive of disease severity in hospitalised patients in this setting.

Chapter 6

Recommendations

Our study aimed to determine risk factors that are associated with developing severe pneumonia. We compared severe pneumonia with non-severe pneumonia; however, we did not observe major differences between the two groups. Although we could not identify a specific risk factor associated with severe pneumonia and non-severe pneumonia, the factors studied remain agents that pose public health risks. In an attempt to help inform interventions and policy decisions to mitigate disease severity we continue to advocate for primary health interventions.

Primary interventions such as childhood immunisations, maternal education relating to smoking and smoke exposure, exclusive breast feeding, appropriate education on nutrition, and compliance with vertical HIV transmission prevention guidelines remain important strategies to reduce community disease burden. Of equal importance are parallel strategies to improve living conditions and alleviate poverty through appropriate housing, access to sustainable energy, clean water, sanitation, and appropriate sewerage disposal. These are basic human rights and strategies to address these challenges have been outlined in the Sustainable Development Goals[100]. These serve as a guideline with appropriate implementation remaining the responsibility of communities, municipalities, and government working concurrently.

Healthcare workers of all levels remain important advocates for the impoverished and disenfranchised. They play an important role in the interface with communities and health. Children are a vulnerable population that require ongoing support and continued re-evaluation to address problems unique to their communities. Ensuring that primary care interventions are appropriately implemented, ongoing education related to nutrition and tobacco smoke exposure and providing oversight of interventions at clinic visits remain important responsibilities.

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Conflict of interest

The authors declare that they have no competing interests.

References

1. Kliegman, R., Stanton, B., St. Geme, J. W., Schor, N. F., & Behrman RE. *Nelson Textbook of Pediatrics*. 20th ed. Phialdelphia: Elsevier Ltd; 2016.

2. World Health Organization. *Pocket Book of Hospital Care for Children WHO (Second Edition)*. Vol 1.; 2013. doi:10.1111/j.1553-2712.1996.tb03308.x

3. Black RE, Allen LH, Bhutta ZA, et al. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet*. 2008;371(9608):243-260. doi:10.1016/S0140-6736(07)61690-0

4. Jain V, Vashisht R, Yilmaz G, Bhardwaj A. Pneumonia Pathology. 2021. http://www.ncbi.nlm.nih.gov/pubmed/30252372 (accessed 31.01.2022).

5. May J, Witten C, Lake L. *South African Child Gauge: Food and Nutrition Security*. Vol 23.; 2020.

6. South African Social Security Agency. Care dependecy grant boolet. http://www.sassa.gov.za/index.php/social-grants/care-dependency-grant (accessed 20.01.2022).

7. DSD S and U. The South African Child Support Grant Impact Assessment: Evidence from a survey of children, adolescents and there households. 2012:117. http://www.unicef.org/southafrica; http://www.dsd.gov.za and http://www.sassa.gov.za (accessed 20.01.2022).

8. Health ND of. *NATIONAL HEALTH ACT 61 OF 2003*.; 2013:1-88. https://www.hpcsa.co.za/Uploads/Legal/legislation/nati_heal_act_61_2003.pdf(accessed 23.01.2022).

9. Graham SM, Cuevas LE, Jean-Philippe P, et al. Clinical Case Definitions for Classification of Intrathoracic Tuberculosis in Children: An Update. *Clin Infect Dis*. 2015;61(Suppl 3):S179-S187. doi:10.1093/cid/civ581

10. Health ND of. *A District Hospital Service Package for South Africa*.; 2002. http://www.kznhealth.gov.za/norms.pdf(accessed 23.01.2022).

11. Adaji EE, Ekezie W, Clifford M, Phalkey R. Understanding the effect of indoor air pollution on pneumonia in children under 5 in low- and middle-income countries: a systematic review of evidence. *Environ Sci Pollut Res*. 2019;26(4):3208-3225. doi:10.1007/s11356-018-3769-1

12. Education D of basic. *National Protocol for Assessment Grades r – 12*.; 2012. https://www.education.gov.za/Portals/0/Documents/Policies/NatProtAssess.pdf (accessed 21.01.2022).

13. World Health Organisation G. *Training Course on Child Growth Assessment*. Vol 7.; 2008. https://apps.who.int/iris/bitstream/handle/10665/43601/9789241595070_C_eng.pdf?sequence=3&isAllowed=y (accessed 19.01.2022).

14. World Health Organization, Department of Maternal NC and AH, World Health Organization. *Revised Who Classification and Treatment of Pneumonia in Children at Health Facilities: Evidence Summaries*.; 2014.

15. Hall K. Children ' s access to housing. 2015;28(1):2015-2017. http://www.ci.uct.ac.za/sites/default/files/image_tool/images/367/Child_Gauge/2006/Child_Gauge_2016-children_count_housing.pdf.

16. Hensher M, Price M, Adomakoh S. *Disease Control Priorities in Developing Countries, Chapter 66, Referral Hospitals*. Second Edi. New York NY 10016: The World Bank and Oxford University Press; 2006. https://dcp-3.org/sites/default/files/dcp2/DCP66.pdf (accessed 19.01.2022).

17. Troeger C, Forouzanfar M, Rao PC, et al. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory tract infections in 195 countries: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Infect Dis*. 2017;17(11):1133-1161. doi:10.1016/S1473-3099(17)30396-1

18. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals. *Lancet*. 2016;388(10063):3027-3035. doi:10.1016/S0140-6736(16)31593-8

19. Statistics South Africa. Statistical release Mortality and causes of death in South Africa, 2008: Findings from death notification. *Stats Sa*. 2016;(November). doi:Statistical release P0309.3

20. Alcón A, Fàbregas N, Torres A. Pathophysiology of pneumonia. *Clin Chest Med*. 2005;26(1):39-46. doi:10.1016/j.ccm.2004.10.013

21. Cillóniz C, Cardozo C, García-Vidal C. Epidemiology, pathophysiology, and microbiology of community-acquired pneumonia. *Ann Res Hosp*. 2018;2:1-1. doi:10.21037/arh.2017.12.03

22. Lanata CF, Rudan I, Boschi-Pinto C, et al. Methodological and quality issues in epidemiological studies of acute lower respiratory infections in children in developing countries. *Int J Epidemiol*. 2004;33(6):1362-1372. doi:10.1093/ije/dyh229

23. Scott JAG, Wonodi C, Moïsi JC, et al. The definition of pneumonia, the assessment of severity, and clinical standardization in the pneumonia etiology research for child health study. *Clin Infect Dis*. 2012;54(SUPPL. 2). doi:10.1093/cid/cir1065

24. Marangu D, Zar HJ. Childhood pneumonia in low-and-middle-income countries: An update. *Paediatr Respir Rev*. 2019;(xxxx). doi:10.1016/j.prrv.2019.06.001

25. Zar HJ, Madhi SA, Aston SJ, Gordon SB. Pneumonia in low and middle income countries : progress and challenges. 2013:1052-1056. doi:10.1136/thoraxjnl-2013-204247

26. O'Brien KL, Baggett HC, Brooks WA, et al. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. *Lancet*. 2019;394(10200):757-779. doi:10.1016/s0140-6736(19)30721-4

27. Kassebaum NJ, Reiner RC, Olsen HE, et al. Diseases, Injuries, and Risk Factors in Child and Adolescent Health, 1990 to 2017: Findings from the Global Burden of Diseases, Injuries, and Risk Factors 2017 Study. *JAMA Pediatr*. 2019;173(6). doi:10.1001/jamapediatrics.2019.0337

28. Carvajal JJ, Avellaneda AM, Salazar-ardiles C, Maya JE. Host Components Contributing to Respiratory Syncytial Virus Pathogenesis. 2019;10(September):1-19. doi:10.3389/fimmu.2019.02152

29. Fonseca W, Lukacs NW, Ptaschinski C. Factors affecting the immunity to respiratory syncytial virus: From epigenetics to microbiome. *Front Immunol*. 2018;9(FEB):1-15. doi:10.3389/fimmu.2018.00226

30. Gallagher KE, Knoll MD, Prosperi C, et al. The Predictive Performance of a Pneumonia Severity Score in Human Immunodeficiency Virus–negative Children Presenting to Hospital in 7 Low- and Middle-income Countries. *Clin Infect Dis*. 2019. doi:10.1093/cid/ciz350

31. 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 Heal*. 2015;3(2):e95-e103. doi:10.1016/S2214-109X(14)70360-2

32. Scheltema NM, Gentile A, Lucion F, et al. Global respiratory syncytial virus-associated mortality in young children (RSV GOLD): a retrospective case series. *Lancet Glob Heal*. 2017;5(10):e984-e991. doi:10.1016/S2214-109X(17)30344-3

33. Shi T, Balsells E, Wastnedge E, et al. Risk factors for respiratory syncytial virus associated with acute lower respiratory infection in children under five years: Systematic review and meta-analysis. *J Glob Health*. 2015;5(2). doi:10.7189/jogh.05.020416

34. Bermick JR, Lambrecht NJ, denDekker AD, et al. Neonatal monocytes exhibit a unique histone modification landscape. *Clin Epigenetics*. 2016;8(1):1-15. doi:10.1186/s13148-016-0265-7

35. Carr R, Pumford D, Davies JM. Neutrophil chemotaxis and adhesion in preterm babies. 1992;(December 1991):813-817. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1590408/.

36. Simister NE. Placental transport of immunoglobulin G. 2003;21:3365-3369. doi:10.1016/S0264-410X(03)00334-7

37. Boyce TG, Mellen BG, Mitchel EF, Wright PF, Griffin MR. Rates of hospitalization for respiratory syncytial virus infection among children in Medicaid. *J Pediatr*. 2000;137(6):865-870. doi:10.1067/mpd.2000.110531

38. Tazinya AA, Halle-Ekane GE, Mbuagbaw LT, Abanda M, Atashili J, Obama MT. Risk factors for acute respiratory infections in children under five years attending the Bamenda Regional Hospital in Cameroon. *BMC Pulm Med*. 2018;18(1):1-8. doi:10.1186/s12890-018-0579-7

39. Dembele BPP, Kamigaki T, Dapat C, et al. Aetiology and risks factors associated with the fatal outcomes of childhood pneumonia among hospitalised children in the Philippines from 2008 to 2016: A case series study. *BMJ Open*. 2019;9(3). doi:10.1136/bmjopen-2018-026895

40. Tuti T, Agweyu A, Mwaniki P, Peek N, English M. An exploration of mortality risk factors in non-severe pneumonia in children using clinical data from Kenya. *BMC Med*. 2017;15(1):1-12. doi:10.1186/s12916-017-0963-9

41. Ibrahim MK, Zambruni M, Melby CL, Melby PC. Impact of childhood malnutrition on host defense and infection. *Clin Microbiol Rev*. 2017;30(4):919-971. doi:10.1128/CMR.00119-16

42. Chisti MJ, Tebruegge M, La Vincente S, Graham SM, Duke T. Pneumonia in severely malnourished children in developing countries - Mortality risk, aetiology and validity of WHO clinical signs: A systematic review. *Trop Med Int Heal*. 2009;14(10):1173-1189. doi:10.1111/j.1365-3156.2009.02364.x

43. Howie SRC, Schellenberg J, Chimah O, et al. Childhood pneumonia and crowding, bed-sharing and nutrition: A case-control study from The Gambia. *Int J Tuberc Lung Dis*. 2016;20(10):1405-1415. doi:10.5588/ijtld.15.0993

44. Verani JR, Groome MJ, Zar HJ, et al. Risk Factors for Presumed Bacterial Pneumonia among HIV-uninfected Children Hospitalized in Soweto, South Africa. *Pediatr Infect Dis J*. 2016;35(11):1169-1174. doi:10.1097/INF.0000000000001264

45. Rudan I, O'Brien KL, Nair H, et al. Epidemiology and etiology of childhood pneumonia in 2010: Estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. *J Glob Health*. 2013;3(1). doi:10.7189/jogh.03.010401

46. Sonego M, Pellegrin MC, Becker G, Lazzerini M. Risk factors for mortality from acute lower respiratory infections (ALRI) in children under five years of age in low and middle-income countries: A systematic review and meta-analysis of observational studies. *PLoS One*. 2015;10(1):1-17. doi:10.1371/journal.pone.0116380

47. Jackson S, Mathews KH, Pulanić D, et al. Risk factors for severe acute lower respiratory infections in children – a systematic review and meta-analysis. *Croat Med J*. 2013;54(2):110-121. doi:10.3325/cmj.2013.54.110

48. Pasman L. the complication of coinfection. *Yale J Biol Med*. 2012;85:127-132. https://europepmc.org/article/PMC/3313527 (accessed 12.01.2022).

49. Cohen C, Moyes J, Tempia S, et al. Epidemiology of Acute Lower Respiratory Tract Infection in HIV-Exposed Uninfected Infants. *Pediatrics*. 2016;137(4):e20153272-e20153272. doi:10.1542/peds.2015-3272

50. Afran L, Garcia Knight M, Nduati E, Urban BC, Heyderman RS, Rowland-Jones SL. HIV-exposed uninfected children: A growing population with a vulnerable immune system? *Clin Exp Immunol*. 2014;176(1):11-22. doi:10.1111/cei.12251

51. Wardlaw T, Salama P, Johansson EW, Mason E. Pneumonia: the leading killer of children. *Lancet*. 2006;368(9541):1048-1050. doi:10.1016/S0140-6736(06)69334-3

52. Theodoratou E, Johnson S, Jhass A, et al. The effect of Haemophilus influenzae type b and pneumococcal conjugate vaccines on childhood pneumonia incidence, severe morbidity and mortality. *Int J Epidemiol*. 2010;39(SUPPL. 1). doi:10.1093/ije/dyq033

53. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N Engl J Med*. 2003;349(14):1341-1348. doi:10.1056/NEJMoa035060

54. Lucero MG, Nohynek H, Williams G, et al. Efficacy of an 11-valent pneumococcal conjugate vaccine against radiologically confirmed pneumonia among children less than 2 years of age in the Philippines: A randomized, double-blind, placebo-controlled trial. *Pediatr Infect Dis J*. 2009;28(6):455-462. doi:10.1097/INF.0b013e31819637af

55. Ngocho JS, Magoma B, Olomi GA, et al. Effectiveness of pneumococcal conjugate vaccines against invasive pneumococcal disease among children under five years of age in Africa: A systematic review. *PLoS One*. 2019;14(2):1-14. doi:10.1371/journal.pone.0212295

56. Gothankar J, Doke P, Dhumale G, et al. Reported incidence and risk factors of childhood pneumonia in India: a community-based cross-sectional study. *BMC Public Health*. 2018;18(1):1111. doi:10.1186/s12889-018-5996-2

57. Kasundriya SK, Dhaneria M, Mathur A, Pathak A. Incidence and risk factors for severe pneumonia in children hospitalized with Pneumonia in Ujjain, India. *Int J Environ Res Public Health*. 2020;17(13):1-15. doi:10.3390/ijerph17134637

58. Hoang VT, Dao TL, Minodier P, et al. Risk factors for severe pneumonia according to WHO 2005

criteria definition among children <5 years of age in thai binh, vietnam: A case-control study. *J Epidemiol Glob Health*. 2019;9(4):274-280. doi:10.2991/jegh.k.191009.001

59. Madhi SA, Bamford L, Ngcobo N. Effectiveness of pneumococcal conjugate vaccine and rotavirus vaccine introduction into the South African public immunisation programme. *South African Med J*. 2014;104(3):228-234. doi:10.7196/SAMJ.7597

60. Isaacs-Long Y, Myer L, Zar HJ. Trends in admissions, morbidity and outcomes at Red Cross war memorial children's hospital, Cape Town, 2004 - 2013. *South African Med J*. 2017;107(3):219-226. doi:10.7196/SAMJ.2017.v107i3.11364

61. Mackerow ND of H. *THIRD TRIENNIAL REPORT OF THE COMMITTEE ON MORBIDITY AND MORTALITY IN CHILDREN UNDER 5 YEARS (COMMIC): 2015 - 2017*. Pretoria; 2017. Provided by Dr Thandi Wessels, Department of Paediatrics and Child Health, Tygerberg Hospital.

62. Smith KR, Bruce N, Balakrishnan K, et al. Millions Dead: How Do We Know and What Does it Mean? Methods Used in the Comparative Risk Assessment of Household Air Pollution. *Ssrn*. 2014. doi:10.1146/annurev-publhealth-032013-182356

63. Gordon, Prof Stephen B; Bruce, Prof Nigel; Grigg, Prof Jonathan; Hibberd, Prof Patricia; Kurmi O. Respiratory risks from household air pollution in low and middle income countries. *Lancet Respir Med*. 2016;2(10):823-860. doi:10.1016/S2213-2600(14)70168-7

64. World Health Organization. *WHO Air Quality Guidelines for Particulate Matter, Ozone, Notrogen Dioxide, and Sufur Dioxide*. Vol 1. Geneva; 2006. doi:10.1007/s12011-019-01864-7

65. World Health Organization. *WHO Global Air Quality Guidelines*. Geneva; 2021. https://apps.who.int/iris/handle/10665/345329 (accessed 02.04.2022).

66. Thakur M, Nuyts PAW, Boudewijns EA, et al. Impact of improved cookstoves on women's and child health in low and middle income countries: a systematic review and meta-analysis. *Thorax*. 2018:thoraxjnl-2017-210952. doi:10.1136/thoraxjnl-2017-210952

67. Dherani M, Pope D, Mascarenhas M, Smith KR, Weber M, Bruce N. Indoor air pollution from unprocessed solid fuel use and pneumonia risk in children aged under five years: A systematic review and meta-analysis. *Bull World Health Organ*. 2008;86(5):390-394. doi:10.2471/BLT.07.044529

68. Po JYT, FitzGerald JM, Carlsten C. Respiratory disease associated with solid biomass fuel exposure in rural women and children: Systematic review and meta-analysis. *Thorax*. 2011;66(3):232-239. doi:10.1136/thx.2010.147884

69. Ram PK, Dutt D, Silk BJ, et al. Household air quality risk factors associated with childhood pneumonia in urban Dhaka, Bangladesh. *Am J Trop Med Hyg*. 2014;90(5):968-975. doi:10.4269/ajtmh.13-0532

70. le Roux DM, Nicol MP, Myer L, et al. Lower Respiratory Tract Infections in Children in a Well-vaccinated South African Birth Cohort: Spectrum of Disease and Risk Factors. *Clin Infect Dis*. 2019;(Xx):1-9. doi:10.1093/cid/ciz017

71. Suzuki M, Thiem VD, Yanai H, et al. Association of environmental tobacco smoking exposure with an increased risk of hospital admissions for pneumonia in children under 5 years of age in Vietnam. *Thorax*. 2009;64(6):484-489. doi:10.1136/thx.2008.106385

72. Salih KEMA, Salih A, El Samani EFZE, Hussien KE, Ibrahim SA. Characteristics associated with severe pneumonia in under-five children admitted to emergency units of two teaching hospitals in Khartoum, Sudan. *Sudan J Paediatr*. 2011;11(2):25-31. http://www.ncbi.nlm.nih.gov/pubmed/27493316%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4949831 (accessed 12.01.2022).

73. Al-Sayed EM, Ibrahim KS. Second-hand tobacco smoke and children. *Toxicol Ind Health*. 2014;30(7):635-644. doi:10.1177/0748233712462473

74. Kum-Nji P, Meloy L, Herrod HG. Environmental tobacco smoke exposure: Prevalence and mechanisms of causation of infections in children. *Pediatrics*. 2006;117(5):1745-1754. doi:10.1542/peds.2005-1886

75. Eyuboglu TS, Aslan AT, Kose M, et al. Passive smoking and disease severity in childhood pneumonia under 5 years of age. *J Trop Pediatr*. 2021;66(4):412-418. doi:10.1093/TROPEJ/FMZ081

76. Mcguinness SL, Barker SF, O'Toole J, et al. Effect of hygiene interventions on acute respiratory infections in childcare, school and domestic settings in low- and middle-income countries: A systematic review. *Trop Med Int Heal*. 2018;23(8):816-833. doi:10.1111/tmi.13080

77. Rabie T, Curtis V. Handwashing and risk of respiratory infections: A quantitative systematic review. *Trop Med Int Heal*. 2006;11(3):258-267. doi:10.1111/j.1365-3156.2006.01568.x

78. Aiello AE, Coulborn RM, Perez V, Larson EL. Effect of hand hygiene on infectious disease risk in the community setting: A meta-analysis. *Am J Public Health*. 2008;98(8):1372-1381. doi:10.2105/AJPH.2007.124610

79. Curtis, val; Schmidt, Wolf; Luby, Stephenl Florez, Rocio; Toure, Ousmane; Biran A. Hygiene: new hopes, new horizons. *Lancet Infect Dis*. 2011;11(January):312-321.

80. Sankar MJ, Sinha B, Chowdhury R, et al. Optimal breastfeeding practices and infant and child mortality: a systematic review and meta-analysis. *Acta Paediatr*. 2015;104:3-13. doi:10.1111/apa.13147

81. WHO. *Guideline: Counselling of Women to Improve Breastfeeding Practices*. Geneva: World Health Organization; 2018. https://www.who.int/publications-detail-redirect/9789241550468 (accessed 29.11.2021).

82. Eidelman AI, Schanler RJ. Breastfeeding and the use of human milk. *Pediatrics*. 2012;129(3). doi:10.1542/peds.2011-3552

83. Ballard, Olivia JD; Morrow AL. Human Milk Composition: Nutrients and Bioactive Factor. *Peadiatrics Clin North Am*. 2012:49-74. doi:10.1016/j.pcl.2012.10.002

84. Darroch JE, Woog V, Bankole A. Costs and Benefits of Meeting the Contraceptive Needs of Adolescents. *New York Guttmacher Inst*. 2016;(May):1-16. https://www.guttmacher.org/adding-it-up (accessed 15.12.2021).

85. Organization WH. Adolescent pregnancy fact sheet. *Adolesc Pregnancy Fact Sheet*. 2014:1. https://www.who.int/news-room/fact-sheets/detail/adolescent-pregnancy (accessed 15.12.2021).

86. Turner C, Turner P, Carrara V, et al. High Rates of Pneumonia in Children under Two Years of Age in a South East Asian Refugee Population. *PLoS One*. 2013;8(1). doi:10.1371/journal.pone.0054026

87. Gupta N, Hirschhorn LR, Rwabukwisi FC, et al. Causes of death and predictors of childhood mortality in Rwanda: A matched case-control study using verbal social autopsy. *BMC Public Health*. 2018;18(1):1-9. doi:10.1186/s12889-018-6282-z

88. Lu SSM, Stewart Williams J, Sommar JN. Inequalities in early childhood mortality in Myanmar - Association between parents' socioeconomic status and early childhood mortality. *Glob Health Action*. 2019;12(1):1-12. doi:10.1080/16549716.2019.1603516

89. Nirmolia N, Mahanta TG, Boruah M, Rasaily R, Kotoky RP, Bora R. Prevalence and risk factors of pneumonia in under five children living in slums of Dibrugarh town. *Clin Epidemiol Glob Heal*. 2018;6(1):1-4. doi:10.1016/j.cegh.2017.07.004

90. Van Deurzen I, Van Oorschot W, Van Ingen E. The link between inequality and population health in low and middle income countries: Policy myth or social reality? *PLoS One*. 2014;9(12):1-22. doi:10.1371/journal.pone.0115109

91. Western Cape Government. Breede Valley Municipality Socio-Economic Profile. 2017:1-38. https://www.westerncape.gov.za/provincial-treasury/files/atoms/files/WC025 Breede Valley 2018 Socio-economic Profile %28SEP-LG%29 F.pdf (accessed 15.12.2021).

92. Municipality BV. *FINAL FIVE-YEAR Intergrated Development Plan 2017-2022*.; 2017. http://mfma.treasury.gov.za/Documents/01. Integrated Development Plans/2017-18/02. Final/02. Local municipalities/WC025 Breede Valley/WC025 Breede Valley Final IDP 2017-18.pdf (accessed 07.08.2019).

93. Mlotshwa M, Smit S, Williams S, Reddy C, Medina-Marino A. Evaluating the electronic tuberculosis register surveillance system in Eden District, Western Cape, South Africa, 2015. *Glob Health Action*. 2017;10(1). doi:10.1080/16549716.2017.1360560

94. The Western Cape Consolidated Guidelines for HIV Treatment: Prevention of Mother- to- Child Transmission of HIV (PMTCT), Children, Adolescents and Adults. 2018 (Amended Version). 2018. https://www.westerncape.gov.za/assets/departments/health/hiv_treatment_2018_-_western_cape_consolidated_guidelines_for_hiv_treatment_2018.pdf (accessed 20.11.2021)).

95. Black RE, Victora CG, Walker SP, et al. Maternal and Child Nutrition: Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet*. 2013;382:427-451. http://dx.doi.org/10.1016/ S0140-6736(13)60937-X%0Aof.

96. World Health Organization. Guidelines on Co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults in resource-limited settings. 2006:1-68. papers2://publication/uuid/6EA80890-45B4-4B65-BF48-E4C6504C21E1 (accessed 01.06.2021).

97. Shibata S, Kikuchi T. Pneumocystis pneumonia in HIV-1-infected patients. *Respir Investig*. 2019;57(3):213-219. doi:10.1016/j.resinv.2019.01.009

98. Lockman S, Hughes M, Powis K, et al. Effect of co-trimoxazole on mortality in HIV-exposed but uninfected children in Botswana (the Mpepu Study): a double-blind, randomised, placebo-controlled trial. *Lancet Glob Heal*. 2017;5(5):e491-e500. doi:10.1016/S2214-109X(17)30143-2

99. Daniels B, Coutsoudis A, Moodley-Govender E, et al. Effect of co-trimoxazole prophylaxis on morbidity and mortality of HIV-exposed, HIV-uninfected infants in South Africa: a randomised controlled, non-inferiority trial. *Lancet Glob Heal*. 2019;7(12):e1717-e1727. doi:10.1016/S2214-

109X(19)30422-X

100. ONU. The sustainable development goals report 2019. *United Nations Publ issued by Dep Econ Soc Aff*. 2019:64. https://unstats.un.org/sdgs/report/2019/The-Sustainable-Development-Goals-Report-2019_Spanish.pdf%0Ahttps://undocs.org/E/2019/68.

APPENDIX

Appendix A – Consent form (English)

Participant information and Consent Form

Title of the research project:

Risk factors associated with the severity of pneumonia in a cohort of hospitalised children in a rural setting

Reference number: _____

Principal investigator: Dr MM Barday

Address: Department of Paediatrics and Child Health

Worcester Hospital

Murray Street

Worcester

Contact Number: 023 3481100

Dear potential participant

Please take time to read the information concerning this study. Feel free to ask the study investigator or interpreter questions about this study in the event that you do not fully understand or some part is not clear. It is important that you fully understand what the research is about and how your participation will be valued. Your participation is completely voluntary and you may decide not to participate at any point in the study. Should you not want to participate, it will not negatively affect you or your child's treatment.

The study has been approved by the Health Research Ethics Committee at Stellenbosch University. It will be conducted in accordance to ethical guidelines and principles of the International Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is the study all about?

This study will be done at Worcester Provincial Hospital in the Children's Ward (Ward A1) and intensive care unit (ICU). By participating in this study, you will be helping us research the field of childhood pneumonia/ chest infections. You will be helping us find factors that exist in the community that may increase the chances of children getting pneumonia/ chest infection. This information can be used to help prevent pneumonia/ chest infections in children in the future.

The information I need will be gathered from information you share with me as well as information from the Road to Health Booklet (clinic book) and hospital notes. These questions are fairly simple like the age of the child, what you fed your child as an infant, and information regarding your household.

Why have you been invited to participate?

You have been asked to participate as your child has been admitted to Worcester Hospital with pneumonia/ a chest infection.

What are your responsibilities?

If you are prepared to participate in this study, we will have a few expectations from you including the answering of questions as honestly and as carefully as possible. There are no correct or incorrect answers and no matter what you answer your child's care will continue. These questions will take about 10min and for me to review the file and Road to Health Booklet (clinic book) will take 5min

Will you benefit from taking part in this research?

By assisting us with this study you will help us understand some of the reasons why children get pneumonia/ chest infections in this community. This information will help us put in place plans to try and prevent future cases of pneumonia/ chest infection.

What are the risks involved in your taking part in this research?

There is minimal risk involved in the participation of this study. No discomfort will be made to either you or your child as only questions with voluntary answers will be needed from you. Questions relating to sensitive issues including HIV or household smoking will be asked and should you feel uncomfortable you may decline to answer. All information that you give will be kept securely and under no circumstances will we reveal any of your personal details.

If you do not agree to take part, what alternatives do you have?

Should you not wish to participate in this study there will be no impact or changes to your child's treatment. Study participation is voluntary and valued; in no way do we wish to impose or force you to participate.

Who will have access to your medical records?

Some of the questions related to the study require us to look at your child's hospital notes and Road to Health Book (clinic book). All this information will be kept in a safe location and we will not reveal any personal information. Only the doctors that are doing the study will have access to this information. Once we have collected enough information from a number of participants we will analyse the information and present it in a journal article. This article will not mention any details of you or your child.

What compensation will be available?

No money or incentive will be provided for participation. Your child, irrespective of you agreeing to participate or not, will receive all the care he/she requires.

Is there anything else that you wish to know?

- Contact Dr MM Barday at 023 348 1100 for further enquiries or problems encountered
- You can also contact the Health Research Ethics Committee at 021 938 9207 if you have any concerns or complaints that have not been adequately addressed by the primary investigator
- You will receive a copy of this information and consent form for your own record

Declaration of the Participant

By signing below, I ..... agree to take part in a research study entitled: *Risk factors associated with the severity of pneumonia in a cohort of hospitalised children in a rural setting*

I declare that:

- I have read or been informed about the study information and consent form and it is written in a language that that I am comfortable with and I understand
- I have had a chance to ask questions and all my queries have been adequately answered
- I understand that taking part in this study is voluntary and I have not been pressurised into participating
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way
- I may be asked to leave the study before it has finished in the event that the investigator/ researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) ..... on (*date*) ..... 2019.

....

Signature of participant Signature of witness

Declaration by investigator

I *(name)* ..... declare that:

- I explained the information in this document to .....
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use an interpreter. (*If an interpreter is used then the interpreter must sign the declaration below.*

Signed at (*place*) ..... on (*date*) ..... 2005.

....

Signature of investigator Signature of witness

Declaration by interpreter

I *(name)* …… declare that:

- I assisted the investigator (*name*) …… to explain the information in this document to (*name of participant*) …….. using the language medium of Afrikaans/Xhosa/sesSotho.

- We encouraged him/her to ask questions and took adequate time to answer them.
- I conveyed a factually correct version of what was related to me.
- I am satisfied that the participant fully understands the content of this informed consent document and has had all his/her question were satisfactorily answered.

Signed at (*place*) …….. on (*date*) ……..

…….. ……..

Signature of interpreter Signature of witness

Appendix B – Structured Interview (Data capturing form)

REDcap data collection form – adapted for dissertation

My First Instrument

1) Record ID
2) Date of data capturing?
3) Date of admission and time?
4) Date of discharge?
5) Type of Hospital exit:
    a. Discharged form Worcester Hospital
    b. Transferred to base for continuation of care
    c. Transferred to Brewelskloof TB Hospital
    d. Transferred to tertiary level care
    e. Death
6) Duration of admission?
7) Consent – yes/no?

Caregiver Factors

1) Who is the primary caregiver? e.g. mother/ grandmother/ aunt
2) Date of birth of the primary caregiver?
3) Age of the primary caregiver?
4) What area do you currently reside? e.g. Avian Park/ Zwelethemba
5) Do you reside in this area throughout the entire year? Yes/no/unknown
6) If you do not reside in this area for the entire year, do you reside in this area only for a period of the year? Yes/no/unknown
7) Do you or your family live in this area only for work during the harvesting season? Yes/no / unknown
8) Where does the child reside?
    a. Exclusively with the caregiver?
    b. Resides in different residence?
        i. If not exclusively with caregiver, where does the child reside? (area)
9) For what period has the child resided here [months]?
10) What is your country of origin? e.g. South Africa/ Lesotho/ Swaziland
11) What is the highest level of education for the primary caregiver?
    a. No education
    b. Grade R – Grade 3
    c. Grade 4 – Grade 6
    d. Grade 7 – Grade 9
    e. Grade 10 – Grade 12
    f. Matriculated
    g. Completed a diploma
    h. Completed an undergraduate degree
    i. Completed postgraduate studies
12) Are you currently employed? Yes/ no/ unknown
13) Are you the main provider for the child? Yes/ no/ unknown
    a. If you are the main provider for the child, what type of employment is held?
        i. Seasonal/ temporary work
        ii. Permanent work

iii. Unknown
iv. Unemployed

b. If you are not the main provider for the child, who provides the main monetary support for the child?
c. If you are not the main provider for the child, what type of employment is held by the individual providing the main monetary support for the child?

14) Does anyone in the household receive a pension? Yes/no
15) Do you receive a Child Support Grant (CSG) for this child? Yes/no
16) Do you receive a Child Dependency Grant (CDG) for this child? Yes/no
17) Do you (caregiver) smoke? Yes/no
    a. How many cigarettes did you smoke yesterday?
    b. For how many years have you been smoking?
    c. Pack years (calculate)
18) Where do you (caregiver) smoke?
    a. Inside the household
    b. Outside the household
    c. Inside the same bedroom as the child
19) Do you (caregiver) have HIV? Yes/no/ decline to answer
    a. When did you initiate treatment?
20) Do you (caregiver) have tuberculosis? Yes/no/ decline to answer
    a. When did you initiate treatment?
21) Have you ever had previous tuberculosis? Yes/no/ decline to answer
    a. Did you complete treatment for tuberculosis? Yes/ no
    b. When did you complete treatment for tuberculosis?

Infant Factors

1) What type of household does the caregiver live in?
    a. Formal dwelling
    b. Informal dwelling
    c. Traditional dwelling
    d. Unknown
2) Are there members of the household that smoke (excluding the primary caregiver)? Yes/no/unknown
3) If there are household members that smoke, other than the primary caregiver, where do they smoke?
    a. Inside including the participants bedroom
    b. Inside excluding the participants bedroom
    c. Outside the household
4) What type of kitchen is in the home?
    a. Inside without participations/ open plan
    b. Inside excluding the participants bedroom
    c. Outside the household
5) Does the household use as electric stove? Yes/no/unknow
6) What type of stove is present?
    a. Wood burning stove
    b. Gas stove
    c. Paraffin stove
    d. Electric stoves
    e. Microwave stove
    f. Coal stove
    g. Other

   h. None
7) Does the household make open fires for heating, lighting or social occasions? Yes/no
   a. If so, how many times a week?
   b. What type of biomass fuel is used?
      i. Wood
      ii. Spirits
      iii. Coal
      iv. Rubbish
      v. Candles
      vi. Other
8) Do you ever burn any of the following items in your home?
   a. Herbs
   b. Plants
   c. Incense
   d. Imphepho
   e. Other
   f. Nothing burned that gives off smoke
9) How often are these items burned inside your house?
   a. Weekly
   b. Monthly
   c. A few times each year
10) Is any of the following kept in the home?
   a. Doom
   b. Rat-ex
   c. Raid
   d. Mortein Target
   e. Other spray pesticide
   f. None
11) What are the walls in the home primarily made of?
   a. Bricks
   b. Tin/iron sheeting
   c. Mud/ traditional
   d. Cement/ concrete
   e. Wood
   f. Plaster
   g. Stone
   h. Other
12) How many household members sleep in the house as least 4 nights of the weeks?
13) How many rooms does the household consist of (excluding bathrooms but including kitchen and living room)?
14) How many rooms does the household consist of (excluding bathrooms but including kitchen and living room)?
15) How many people (adults and children) usually sleep in the same room as the child, including the study child?
16) How many people (adults and children) share the child's bed, including the study child?
17) What kind of toilet facilities does the home have?
   a. Flush toilet
   b. Pit toilet
   c. No facility/bush/field
   d. Mobile toilet
18) Is the toilet a communal toilet? Yes/no
19) What of the following items does the house have?

a. Fridge/freezer
b. Polisher/ vacuum cleaner
c. Television
d. Hi-fi or music centre
e. Washing machine
f. Video cassette recorder/ DVD player
g. None

20) Which of the following are present in the home?
    a. Running water
    b. Domestic worker
    c. At least one car/truck
    d. Built in kitchen sink
    e. Working telephone or cell phone
    f. Cupboard
    g. Radio
    h. Bicycle
    i. Motorcycle/ scooter
21) Is there electricity at home? Yes/no
22) What is the main source of drinking water in the household for most of the year (more than 6 months)?
    a. Pond/ river/ stream
    b. Natural spring
    c. Rainwater
    d. Borehole
    e. Public tap
    f. Piped into yard/ plot
    g. Piped into dwelling
    h. Other
23) Doe the child attend out of home care e.g. nursery/ preschool/ family care/ creche
    a. Does this facility have a name?
    b. What type of building is the care facility?
        i. Formal dwelling
        ii. Stand alone building
        iii. Informal dwelling
        iv. Traditional dwelling
    c. On average, how many hours/ week does your child spend at the creche?
    d. On average, how many other children are there at the creche?
        i. 1-5 children
        ii. 6-10 children
        iii. 11-15 children
        iv. 16-20 children
        v. > 20 children

Medical records

1) Date of birth of the participant?
2) Age of the participant?
3) Sex of the participant? Male/Female
4) Participant gestation when born? (weeks)
5) Gestational category?
    a. Preterm

   b. Term
   c. Postdates
   d. Unknown
6) Birth weight category (weight in grams)?
7) Gestational age category?
   a. Appropriate for age
   b. Small for gestational age
   c. Large for gestational age
   d. Unknown
8) History of cough? Yes/no
9) Subcostal recessions at admission? Yes/no
10) Respiratory rate at admission (number)?
11) Oxygen saturation in room air (percentage)?
12) Respiratory support required?
   a. None
   b. Nasal prong
   c. High flow oxygen
   d. Continuous positive airway pressure
   e. Ventilation
13) General danger signs
   a. Unable to feed
   b. Presence of lethargy or reduced level of consciousness
   c. Prescence of severe malnutrition
   d. None
14) Significant co-morbidities?
   a. Cerebral Palsy
   b. Congenital heart disease
   c. Acquired heart disease
   d. Gastro-oesophageal reflux disease
   e. Asthma
   f. Trisomy 21
   g. None
   h. Other
15) What is the final diagnosis made prior to discharge/transfer/ death?
   a. Pneumonia
   b. Bronchopneumonia
   c. Asthma
   d. Bronchiolitis
   e. Pulmonary TB
   f. Other
16) Is there a tuberculosis household contact present? Yes/no
17) Is the participant on INH prophylaxis? Yes/no
18) Tuberculosis status?
   a. Unlikely TB
   b. Unconfirmed Tuberculosis
   c. Confirmed Tuberculosis
19) If yes to confirmed or unconfirmed pulmonary TB, was treatment initiated? Yes/no
20) If on treatment for TB, when was treatment initiated (date)?
21) How was the diagnosis of TB made?

   a. Clinical signs/ features suggestive of tuberculosis
   b. Mantoux positive
   c. Chest x-ray features suggestive of TB
   d. Sputum/ gastric washings suggestive of tuberculosis
22) HIV status on admission?
   a. Unexposed uninfected
   b. Unexposed but not confirmed uninfected
   c. Exposed uninfected
   d. Exposed but not confirmed uninfected
   e. Infected
   f. Unknown
23) If HIV infected, is the participant on HAART?
24) If HIV infected, when did he/she start treatment?
25) If HIV exposed/ positive, is he/she on cotrimoxazole therapy?
   a. Qualifies for cotrimoxazole prophylaxis but not on treatment
   b. Qualifies for cotrimoxazole prophylaxis and on treatment
   c. Does not qualify for cotrimoxazole treatment and not on treatment
   d. Does not qualify for cotrimoxazole treatment and on treatment
26) Nutritional status: admission weight (kilograms)?
27) Nutritional status: admission height (centimetres)?
28) Nutritional status: (if applicable) admission MUAC (centimetres)?
29) Nutritional category?
   a. Underweight
   b. Stunted
   c. Wasted
   d. Presence of nutritional oedema
   e. Appropriate wright for height (NAM)
   f. MAM
   g. SAM
30) Immunisation status?
   a. Up to date
   b. Not up to date
   c. Unknown

Appendix C – HREC Approval Notice and Amendment

Health Research Ethics Committee (HREC)

Approval Notice

New Application

10/12/2018

Project ID :8658

HREC Reference # S18/10/253

Title: Hospitalisation for pneumonia and associated risk factors

Dear Dr Mohammed Barday

The Response to Modifications received on 02/12/2018 22:28 was reviewed by members of **Health Research Ethics Committee via expedited** review
procedures on 10/12/2018 and was approved.

Please note the following information about your approved research protocol:

Protocol Approval Period: 10 December 2018 - 9 December 2019

Please remember to use your project ID (8658) on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review

Translation of the informed consent document(s) to the language(s) applicable to your study participants should now be submitted to the HREC.

Please note you can submit your progress report through the online ethics application process, available at: Links Application Form Direct Link and the
application should be submitted to the HREC before the year has expired. Please see Forms and Instructions on our HREC website (www.sun.ac.za/healthresearchethics) for guidance on how to submit a progress report.

The HREC will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility, permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Please consult the Western Cape Government website for access to the online Health Research Approval Process, see: https://www.westerncape.gov.za/general-publication/health-research-approval-process.
Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.

For standard HREC forms and instructions, please visit: Forms and Instructions on our HREC website https://applyethics.sun.ac.za/ProjectView/Index/8658

If you have any questions or need further assistance, please contact the HREC office at 021 938 9677.

Yours sincerely,

Mrs. Ashleen Fortuin,
Health Research Ethics Committee 2 (HREC2)

National Health Research Ethics Council (NHREC) Registration Number:

REC-130408-012 (HREC1)·REC-230208-010 (HREC2)

Federal Wide Assurance Number: 00001372
Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number:
IRB0005240 (HREC1)·IRB0005239 (HREC2)

Approval Letter
Amendment

04/07/2019

Project ID: 8658

Ethics Reference No: S18/10/253

Project Title: Risk factors associated with the severity of pneumonia in a cohort of hospitalised children in a rural setting

Dear Dr Mohammed Barday

Your amendment request # 1 dated 27 June 2019 refers.

The Health Research Ethics Committee (HREC) reviewed and approved the amended documentation through an expedited review process.

The following amendment was reviewed and approved:

1. Extension of data collection period for an additional 6 months ending 31/12/2019
2. Protocol version 2.0

Where to submit any documentation

Kindly note that the HREC uses an electronic ethics review management system, Infonetica, to manage ethics applications and ethics review process. Tosubmit any documentation to HREC, please click on the following link: https://applyethics.sun.ac.za.

Please remember to use your project ID 8658 and ethics reference number S18/10/253 on any documents or correspondence with the HREC concerningbyour research protocol.

Yours sincerely,
Mrs. Ashleen Fortuin
Health Research Ethics Committee 2 (HREC2)

National Health Research Ethics Council (NHREC) Registration Number:

REC-130408-012 (HREC1)·REC-230208-010 (HREC2)

Federal Wide Assurance Number: 00001372
Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number:
IRB0005240 (HREC1)·IRB0005239 (HREC2)

The Health Research Ethics Committee (HREC) complies with the SA National Health Act No. 61 of 2003 as it pertains to health research. The HREC abides by the ethical norms and principles for research, established by the World Medical Association (2013). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects;the South African Department of Health(2006). Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2nd edition); as well as the Department of Health (2015). Ethics in Health Research: Principles, Processes and Structures (2nd edition).

The Health Research Ethics Committee reviews research involving human subjects conducted or supported by the Department of Health and Human Services, or other federaldepartments or agencies that apply the Federal Policy for the Protection of Human Subjects to such research (United States Code of Federal Regulations Title 45 Part 46); and/or clinical investigations regulated by the Food and Drug Administration (FDA) of the Department of Health and Human Services.

Appendix D – Provincial Ethics Approval

Health Impact Assessment
Health Research sub-directorate
Health.Research@westerncape.gov.za
tel: +27 21 483 0866: fax: +27 21 483 9895
5th Floor, Norton Rose House, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za

REFERENCE: WC 201812 011

ENQUIRIES: Dr Sabela Petros

Stellenbosch University

Faculty of Medicine and Health Sciences

Francie Van Zijl drive

Parow Valley

Cape Town

7505

For attention: Dr Mohammed Barday, Dr Amy Slogrove, Prof Sharon Kling, Dr Arnoldus Engelbrecht

Re: **Risk factors associated with the severity of pneumonia in a cohort of hospitalised children in a rural setting**

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.

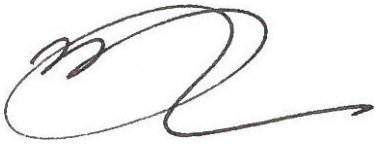
Please contact the following person to assist you with any further enquiries in accessing the following sites:

Worcester Hospital: Dr M Kunneke 023 348 1218

Kindly ensure that the following are adhered to:

1) Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2) By being granted access to provincial health facilities, you are expressing consent to provide the department with an electronic copy of the final feedback (annexure 9) within six months of completion of your project. This can be submitted to the provincial Research Co-ordinator Health.Research@westerncape.gov.za).
3) In the event where the research project goes beyond the estimated completion date which was submitted, researchers are expected to complete and submit a progress report **(Annexure 8)** to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).
4) The reference number above should be quoted in all future correspondence.

Yours sincerely



DR M MOODLEY

DIRECTOR: HEALTH IMPACT ASSESSMENT

DATE: 13.02.2019