

A Review of Children admitted to a Regional Hospital in Cape Town with Community Acquired Pneumonia

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1). Abstract:

Background: Pneumonia is a leading cause of death in children under-five. Epidemiology in our province at regional level has not been described since 2004, when HAART was rolled out and pneumococcal conjugate vaccination (PCV) was introduced.

Objectives: Describe the demographic profile, disease severity, risks for transfer and mortality and the management of children >2 months, admitted with CAP over a one year period.

Methods: Retrospective descriptive study of every second patient (>2 months to 13 years) admitted to Somerset Hospital in 2012 with the diagnosis of CAP. Demographic, clinical and outcome data were extracted from hospital records and analysed using STATA®.

Results: Of 380 cases reviewed, 90% had severe disease; the median age was 9.4 months (IQR 4.8-23). Of these 89 (23%) were LBW (<2500g) and 75 (20%) were born premature. Median age at presentation for these groups was 5.7 months compared with 10.6 months in term children ($p=0.0003$). Forty-one (12%) were severely malnourished; 34 (9%) were HIV-positive. Children below 10/12 were more likely to have incomplete immunisations (57/190, $p=0.011$). Only 15% of TB-exposed children <5 years were on Isoniazid Prevention Therapy (IPT). Prevalence of comorbid conditions was high. Median duration of stay was 3 days (IQR 2-6); this increased to 6.5 (IQR 4.5-9.5) with neurological disease and 6 (IQR4-10) with proven RSV. Seventeen patients (4.5%) required transfer to tertiary level. Mortality rate was 0.5%.

Conclusion: Preventative measures must focus on populations at risk- LBW and preterm children in first year of life, malnourished children and those with comorbidities like HIV. Immunisation and IPT rates can be improved.

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3). List of abbreviations:

ART	Antiretroviral therapy
BTS	British Thoracic Society
CAP	Community acquired pneumonia
CPT	Cotrimoxazole Prevention Therapy
CPAP	Continuous positive airway pressure
CRP	C-reactive protein
CHW	Community health workers
HAART	Highly active antiretroviral therapy
HiB	Haemophilus influenza vaccine
HIV	Human immunodeficiency virus
HEU	HIV exposed but uninfected
IPD	Invasive pneumococcal disease
IPPV	Intermittent positive pressure ventilation
IIV	Inactivated Influenza vaccine
LBW	Low birth weight (<2500g)
LRTI	Lower respiratory tract infection
NSH	New Somerset Hospital
PCT	Serum procalcitonin
PCV	Pneumococcal conjugate vaccine
PCV7	Seven-valent Pneumococcal conjugate vaccine
PCV13	Thirteen-valent pneumococcal conjugate vaccine
PJP	<i>Pneumocystis jiroveci</i> pneumonia
PMTCT	Prevention of mother to child transmission
PTB	Pulmonary tuberculosis
RCWMH	Red Cross War Memorial Hospital
RSV	Respiratory syncytial virus
SA	South Africa
SATS	South African Thoracic Society

5). CHAPTER ONE: INTRODUCTION AND LITERATURE REVIEW

5.1 Background:

Despite a thirty percent reduction in pneumonia incidence since 2010^[1], pneumonia still remains the leading cause of death in the under-five age group, excluding neonatal causes^[2]. Pneumonia accounts for approximately 15% of deaths in this age group^[3] and globally was responsible for 0.935 million deaths in children under the age of five in 2013^[2], 0.493 million of which were in Sub-Saharan Africa^[2]. Children less than two years of age are at increased risk of mortality^[1,468].

African regions are reported to have an incidence rate of 0.27 episodes per child-year^[1,9], and are over-represented in the numbers^[1,7]. A recent birth cohort study in the Western Cape estimated the incidence of severe pneumonia to be 0.06 episodes per child year^[9]. Pneumonia thus contributes significantly to both morbidity and hospital costs in Africa^[10].

Acute complications from CAP include: parapneumonic effusions, necrotising pneumonia and lung abscesses^[11], sepsis and metastatic infection^[12] and rarely haemolytic uraemic syndrome^[12].

Childhood pneumonia also has long term sequelae including chronic restrictive, obstructive and suppurative lung disease, which has been documented in up to 13.6% of children admitted to hospital^[13]. There is a significant association between CAP under three years of age and asthma and impaired lung function in adulthood. Thus childhood lower respiratory tract infection (LRTI) can lead to chronic respiratory health issues in adulthood^[14].

5.2 Objectives:

The objectives of this literature review were to describe the incidence, epidemiology and aetiology of paediatric pneumonia, and how this has been effected by the introduction of the pneumococcal conjugate vaccine. To review the risk factors for pneumonia, especially those that are considered relevant to South Africa. And lastly to review recommendations for both special investigation and management of childhood community acquired pneumonia.

5.3 Literature Search Strategy:

The literature search was done using the pubmed search engine (<http://www.ncbi.nlm.nih.gov/pubmed>) and the following search strings:

- É Childhood pneumonia incidence Africa
- É Childhood severe pneumonia risk factors
- É Childhood pneumonia mortality outcome
- É Childhood community acquired pneumonia aetiology epidemiology
- É Childhood community acquired pneumonia management

The initial search was done in 2012 and a second search was done in 2015. Articles were included if the study subjects were derived from the paediatric population, regardless of study design. Neonates were excluded as they did not form part of the group studied at New Somerset Hospital and management protocols for neonates often differ from standard paediatric practice. Only English articles were included in the review. Preference was given to articles from the developing world.

Reference lists of articles were reviewed to broaden the search strategy and additional articles were included on recommendation of either the supervisor or experts in the field.

Search Results:

The search strategy yielded 85 relevant studies; additional studies were included from reference lists of these articles and on recommendation; a total of 112 full text articles were reviewed. Fifty-four articles were eventually referenced.

The majority of the articles were from the latter part of the last decade, but one article from 2005 and two from 2002 were also included.

5.4 Pneumonia aetiology:

Childhood pneumonia can be caused by a variety of organisms, however microbiological data remains unreliable in the diagnosis of pneumonia^[15].

Streptococcus pneumoniae and *Haemophilus influenza* are vaccine preventable causes of pneumonia thought to be responsible for 33% and 17% of pneumonia deaths worldwide respectively^[1]. Influenza contributes a further 11% to pneumonia deaths^[1]. Bacterial pneumonia is most commonly caused by *Streptococcus pneumoniae*^[10]. The second most common bacterial cause of pneumonia is *Streptococcus pyogenes* and *Staphylococcus aureus*, which are responsible for substantial morbidity^[16]. *Mycoplasma pneumoniae*, which is more common in children over the age of three^[1], and to a lesser degree *Chlamydia trachomatis*, play a significant role in hospitalised children^[17].

RSV is a virus, which when detected, is consistently implicated in disease^[16]. Many studies have emphasised the role of mixed infection with either viruses or bacteria^[10,12,15,19].

HIV-positive children are more susceptible to pneumonia^[20], and are effected by additional aetiologies; these include gram-negative bacteria, *pneumocystis jiroveci* (PJP) and cytomegalovirus (CMV). PJP is more prevalent in infants and is associated with a 50% fatality rate^[20]. Rates of coinfection with PJP and CMV are high^[21].

In many cases of childhood pneumonia no causative organism will be identified^[22].

5.5 Pneumonia and vaccine prevention:

The conjugate haemophilus influenza vaccine was rolled out in South Africa in 1998. Worldwide, since introduction of the vaccine, pneumonia secondary to this organism has become rare^[10,16]. Carriage of non-vaccine serotypes remains, but these seldom cause invasive disease^[16].

The seven valent pneumococcal conjugate vaccine was introduced into the expanded programme of immunisation in 2009 and was replaced by a thirteen valent vaccine in May 2011^[23]. Doses of PCV are given at six and fourteen weeks of age, with a booster dose at nine months.

PCV-7 and PCV-13 have led to significant reductions in invasive pneumococcal disease in children under the age of five in the UK and USA (56% and 64% reduction in invasive disease from the pre-PCV7 era respectively), despite replacement disease^[6,24].

Use of pneumococcal vaccination was noted to have led to increased nasal carriage rate of non-vaccine serotypes after introduction^[6]. These serotypes, however, were not associated with a higher incidence of drug resistant strains^[6,12,16,24] and some serotypes were thought to have lower invasive potential^[6,22]. The incidence of non-vaccine serotype invasive disease in the UK has increased four years after introduction of PCV13, but the overall incidence of pneumococcal invasive disease is still on the decline^[6]. With high vaccine coverage rates, there may be a change in aetiology of pneumonia, which in turn may affect future presentations of disease and will deserve further attention^[1].

The reduction in invasive pneumococcal disease in older unvaccinated age groups is attributable to herd immunity from the serotypes included in PCV13^[6,22,24,25].

Use of PCV in South Africa has been an effective intervention against bacterial pneumonia, a recent cohort study looking at HIV uninfected children, estimated a vaccine efficiency rate of 39.2% in children (16-103 weeks of age) who had received all three doses of PCV^[23].

Worldwide PCV7 has led to a decline in all cause pneumonia admissions^[26].

Children older than six months and less than five years, those who are HIV-positive and those who have a chronic disease; are currently recommended to receive the trivalent inactivated influenza vaccine (IIV)^[27]. Pregnant women are also recommended IIV as they have a higher risk of mortality with influenza infection and to provide passive immunity to their children^[27]. IIV is less effective in children less than two years and HIV-positive children; however it does provide some protection and is thus still recommended^[28]. Vaccine efficacy is reliant on how accurately the vaccine is matched to circulating strains^[28].

New methods in preventing RSV are under development, including maternal immunisation, infant intranasal live-attenuated vaccine and passive immunisation with long lived monoclonal antibodies^[29].

5.6 HIV and the impact on pneumonia:

In South Africa in 2015 there were an estimated 6.19 million people (11.2 percent of the population) living with HIV/AIDS^[30]. Sub-Saharan Africa is at the epicentre of the HIV and the Tuberculosis epidemics^[31]. HIV has had a significant impact on both morbidity and mortality from pneumonia^[7].

HIV infected children have a higher incidence of lower respiratory tract infections in their lifetime^[1,18,21]. These children have a higher rate of coinfection with viruses, bacteria and opportunistic organisms^[18,21], and a greater case fatality rate compared with their HIV-uninfected counterparts^[18,20,21]. This group of children require a unique approach to management, with preventative strategies such as highly active antiretroviral therapy, immunisation and bactrim prophylaxis playing an important role^[18].

HIV exposed but uninfected (HEU) children represent a unique group with proven increased risk for hospital admission^[32], opportunistic infection^[32] and pneumonia outcomes which are intermediate between HIV infected and HIV unexposed children^[20]. This risk could be attenuated by early maternal antiretroviral therapy^[32].

Antiretrovirals were rolled out in the public sector in 2004, according to initiation criteria of a CD4 count of less than two hundred. By 2011, seventy-nine percent of adults with a CD4 of < 200 were receiving HAART^[33]. Unfortunately roll out of paediatric antiretrovirals had not attained the same success^[33].

Currently in South Africa, all children under the age of five and any child with symptomatic WHO stage three or four HIV infection, or a CD4 count of less than five hundred, qualify for antiretroviral therapy (ART) initiation^[34].

In 2013 UNAIDS reported that almost fifty percent of HIV positive children under fourteen years in South Africa, had access to antiretrovirals^[35], which is a vast improvement on previous numbers.

The roll out of prevention of mother to child transmission (PMTCT) and the subsequent improvement in PMTCT guidelines has led to a dramatic reduction in perinatal conversion rates, with only an estimated 2.7% of HIV exposed infants testing positive at eight week follow-up in 2012^[36]. There is however, a further risk of seroconversion with ongoing HIV exposure.

In December 2014 the National consolidated guidelines for prevention of mother to child transmission were published and a policy of immediate initiation of lifelong ART for all HIV-positive pregnant or breastfeeding women, regardless of CD4 count, was adopted, (Option B+)^[36].

With better access to HAART and an improved programme of PMTCT, HIV associated lung disease is expected to decline.

5.7 Tuberculosis and pneumonia:

South Africa is considered an endemic area for tuberculosis and in 2014 had the sixth highest incidence rate of tuberculosis worldwide^[31]. The incidence rate in children is suspected to be 50% of that recorded in adults^[37] and is probably underestimated in high burden areas^[38]. Factors influencing this, common to developed and developing countries, include paucibacillary disease in children^[38] and difficulty obtaining expectorated sputum samples^[38,39]. Developing countries have the additional issue of resource constraints^[38]. Globally tuberculosis is responsible for a similar mortality rate as HIV^[31].

A recent meta-analysis has emphasised the importance of Tuberculosis in acute severe pneumonia^[7], either as a direct cause or as a risk factor leading to secondary bacterial lower respiratory infection^[1,7]. The incidence rate of pulmonary tuberculosis in children under five with severe acute malnutrition or HIV infection^[37] has been documented as high as 12%.

It is postulated that with the roll out of the pneumococcal conjugate vaccine and Haemophilus influenza vaccine, tuberculosis might be more commonly isolated as a causative organism in acute pneumonia^[37].

5.8 Risk factors for pneumonia:

The risk factors for pneumonia include younger age^[1,9,12,16], with those under two years a particularly high risk group^[1]. This was recently confirmed in a study in the Western Cape, where children under six months had the highest incidence of pneumonia^[9].

Male children have a higher incidence of recorded pneumonia^[1,9], this may be secondary to biological factors^[8] or represent gender discrimination in health seeking behaviours^[8,40], with families seeking help for male children more readily than their female children. One meta-analysis reported a higher incidence of severe pneumonia in males^[8], and yet another reported male sex as a likely risk factor for severe acute LRTI^[41]. However, a more recent study, showed a fifteen percent increased risk of mortality in female children with pneumonia^[42].

Malnutrition is an established risk factor for pneumonia^[5,9]. Twenty one percent of children in Sub-Saharan Africa are underweight for age, while up to 4.9 % of South African children are wasted^[43].

Children with malnutrition are at risk of pneumonia^[9], which is likely to be severe^[41]. The risk of mortality increases for children with pneumonia and severe malnutrition^[42,44,45] (RR2.9-121.2), compared to well-nourished children^[44]. In moderate malnutrition the relative risks of mortality are also increased, (RR1.2-36.5)^[44]. This is probably explained by effects on both cellular and humoral immunity^[45]. Children with malnutrition are effected by different organisms than well-nourished children and WHO clinical signs of pneumonia may not be as reliable^[44].

Stunting reflects chronic malnutrition^[43] and is associated with an increase in pneumonia incidence and hospitalisation, as well as higher rate of treatment failure^[46]. An estimated 40% of Sub-Saharan children under the age of five are stunted^[43] and although the rate of stunting is declining, the rate of decline is slower in Sub-Saharan Africa^[43].

In HIV infected children risk factors for community acquired pneumonia include a CD4 count of

less than fifteen percent and a viral load of more than 100 000^[47]. The diagnosis of *Pneumocystis jiroveci* pneumonia in HIV infected children carries a high mortality rate^[12,42].

Other patient factors associated with severe lower respiratory tract infections or increased mortality risk include: low birth weight^[41,42], insufficient breast feeding^[41,42], comorbidity with measles^[42] and chronic diseases^[42]. Prematurity was a likely risk factor (as opposed to a definite risk factor) for severe pneumonia in one meta-analysis^[41], however it has been associated with a higher mortality rate in another recent meta-analysis^[42].

Tobacco smoke exposure^[9], weight under 2500g at birth^[5,41], lack of immunisation^[5,41] and insufficient breastfeeding^[5,41] are also associated with increased incidence and severity^[41].

Maternal factors for child mortality, are low level of education and younger age^[42].

Environmental risk factors for pneumonia (that are also associated with increased risk of mortality^[42]) include: exposure to tobacco smoke^[9] and indoor air pollution^[5,41,48] and often concomitant with this crowding^[5,41] and poverty^[48]. Lack of access to care is also linked to severity^[49].

Within South Africa many of these risk factors are applicable.

It is clear that socioeconomic and other potentially modifiable factors play an important role in incidence of severe pneumonia and in mortality from pneumonia, and that health policy needs to address all of these elements in order to make progress in improving the under-five mortality rate. Focus will need to be on children under the age of two years to have greatest effect^[1].

5.9 Investigation and management of pneumonia:

There are comprehensive local and international guidelines available for the management of childhood community acquired pneumonia, including those by the South African Thoracic Society (SATS) and the British Thoracic Society (BTS). The BTS published guidelines for the management of community acquired pneumonia in 2011 and has developed a validated paediatric audit tool to be used for evaluating case management of pneumonia^[12].

BTS guidelines do not incorporate management of HIV-infected children or children with pre-existing respiratory conditions nor do they address the management of bronchiolitis or other mild respiratory illnesses. SATS guidelines address pneumonia in both HIV infected and uninfected children^[10].

Stepwise approach to management includes clinical evaluation for presence of pneumonia and thereafter an assessment of severity, need for hospitalisation and oxygen therapy^[12].

In both guidelines routine use of chest x-ray (CXR) and inflammatory markers is discouraged^[12]. A CXR is indicated only if there is suspicion of complication, foreign body, tuberculosis or failure to respond to standard treatment^[10].

Although the CXR has commonly been used in the diagnosis of childhood pneumonia and for assessing severity^[50], it cannot distinguish viral from bacterial CAP^[51]. Currently there is no single reliable gold standard to distinguish between viral and bacterial disease^[39,51]. Leukocytosis is not helpful in distinguishing aetiology in both children and adults^[39]. A serum CRP of more

than 40mg/l has a positive predictive value of 64% for bacterial pneumonia in children^[52]. PCT is no more helpful in distinguishing severe disease than CRP^[50]. There is disagreement between studies which looked at the effectiveness of PCT in differentiating viral and bacterial causes in children^[39], PCT may be more useful in adult patients^[39].

Indicators of severe disease include signs of significant respiratory distress, apnoea, poor feeding, shock, hypoxia or cyanosis and underlying chronic disease^[12]. Severe disease should be identified and these children require admission, while children with mild to moderate pneumonias can usually be managed at outpatient community level^[12]. Any concern on the part of the medical doctor that the family will not be able to administer or access care is a further motivating factor for hospitalisation^[10].

Microbiological diagnosis is only recommended for children who have severe disease^[10] and are admitted^[10], or those that have complications of pneumonia or fail to respond to treatment within 48 hours^[12].

Recent studies have shown that the yield of positive blood culture is low in community acquired pneumonia with prevalence of just over five percent^[53] therefore a negative blood culture does not assist in making decisions related to antibiotic prescription^[53]. Limitations of the blood culture include time to result^[39], high rate of false positive and negative cultures^[39] and the invasive nature of the test itself^[51]. Urine antigen tests for *Streptococcus pneumoniae* are not recommended in making a decision about antibiotics in children, because of the high rate of false positives secondary to colonisation^[39]. PCR shows promise for organism detection, but is limited by availability^[39] and cost.

As it is difficult to differentiate viral and bacterial pneumonia, antibiotics are recommended if a clinical diagnosis of pneumonia has been made^[12]. Viruses are more common in children under two^[12]. The BTS guidelines suggest a watch and wait approach in fully vaccinated children under two years of age with mild symptoms, but antibiotics must be initiated if any concerns arise with review^[12]. High dose amoxicillin is first line therapy in children who tolerate oral therapy- higher doses overcome resistance of streptococcus pneumoniae to penicillin^[10,12]. Oral amoxicillin is equally as efficient as intravenous therapy^[10,12]. Macrolide antibiotics are added if there is suspicion for atypical organisms^[12]. If staphylococcal infection is suspected cloxacillin should be used.

Children under two months, malnourished and HIV positive children, or those with a clinical suspicion of HIV, should be covered for gram negative organisms with an aminoglycoside in addition to a beta-lactam^[10]. HIV positive children should routinely receive cotrimoxazole cover for *Pneumocystis jiroveci* and steroids if hypoxia is present^[10].

Supportive management includes oxygen, antipyretics, analgesia, fluid and nutrition^[10]. Hypoxia at presentation increases risk of mortality^[54] and improving access to saturation monitoring and oxygen therapy has been shown to decrease mortality^[54].

Studies have suggested that community case management of pneumonia, with prescription of antibiotics, may reduce acute lower respiratory tract infection mortality by up to 70%^[54]. In the Western Cape the Integrated Management of Childhood Illness (IMCI) is one such effective program^[54] which was introduced in 2009 to improve access to care^[10]. Ineffective health

systems are directly linked to an increase in pneumonia associated deaths^[22]. It is therefore important in a resource limited setting such as South Africa to streamline the management of all illnesses including pneumonia.

5.10 Summary:

Children in South Africa have a high incidence of pneumonia in early life^[9]. Pneumonia contributes significantly to the under-five mortality rate^[2] and may have lasting consequences for adult respiratory health^[14].

Routine immunisation with PCV is likely to change pneumonia aetiology and viruses and Tuberculosis may be more commonly isolated in acute pneumonia^[37].

The epidemiology in our province has not been described at regional level since 2004, when HAART was rolled out in the public sector and since routine immunisation with PCV13.

Many of the identified risk factors for CAP are prevalent in our setting with health economic factors playing an important role.

It is hoped that through further research and a greater understanding of clinical presentation, recommendations for prevention and management of CAP could be made, which in turn could improve clinical practice.

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6). Chapter Two: Publication-ready Manuscript

6.1 Title page

A review of children admitted to a regional Hospital in Cape Town with Community Acquired Pneumonia

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All analyses were performed at the paediatric wards, New Somerset Hospital, Cape Town, South Africa.

Keywords: childhood pneumonia, risk factors, epidemiology, regional hospital

1). Abstract:

Background: Pneumonia is a leading cause of death in children under-five. Epidemiology in our province at regional level has not been described since 2004, when HAART was rolled out and pneumococcal conjugate vaccination (PCV) was introduced.

Objectives: Describe the demographic profile, disease severity, risks for transfer and mortality and the management of children >2 months, admitted with CAP over a one year period.

Methods: Retrospective descriptive study of every second patient (>2 months to 13 years) admitted to Somerset Hospital in 2012 with the diagnosis of CAP. Demographic, clinical and outcome data were extracted from hospital records and analysed using STATA®.

Results: Of 380 cases reviewed, 90% had severe disease; the median age was 9.4 months (IQR 4.8-23). Of these 89 (23%) were LBW (<2500g) and 75 (20%) were born premature. Median age at presentation for these groups was 5.7 months compared with 10.6 months in term children ($p=0.0003$). Forty-one (12%) were severely malnourished; 34 (9%) were HIV-positive. Children below 10/12 were more likely to have incomplete immunisations (57/190, $p=0.011$). Only 15% of TB-exposed children <5 years were on Isoniazid Prevention Therapy (IPT). Prevalence of comorbid conditions was high. Median duration of stay was 3 days (IQR 2-6); this increased to 6.5 (IQR 4.5-9.5) with neurological disease and 6 (IQR 4-10) with proven RSV. Seventeen patients (4.5%) required transfer to tertiary level. Mortality rate was 0.5%.

Conclusion: Preventative measures must focus on populations at risk- LBW and preterm children in first year of life, malnourished children and those with comorbidities like HIV. Immunisation and IPT rates can be improved.

6.3 Introduction

Pneumonia incidence has decreased by more than 30% since 2010^[1], yet remains the leading cause of death in the under-five age group, excluding neonatal causes^[2]. Children under two years are at increased risk of mortality^[1,3,4]. African regions are reported to have an incidence rate of 0.27 episodes of pneumonia per child-year^[1,5], and are over-represented in the numbers^[1]. Community acquired pneumonia (CAP) thus contributes significantly to both morbidity and hospital costs in Africa^[6].

Children hospitalised with pneumonia have a 13.6% risk of developing subsequent chronic restrictive, obstructive or suppurative lung disease^[7]. There is an association with CAP prior to three years of age, and asthma and impaired lung function which persists into adulthood. Thus origins of some chronic adult respiratory health issues may be in childhood^[8].

Streptococcus pneumoniae and *Haemophilus influenza* are vaccine preventable causes of pneumonia, responsible for 33% and 17% of pneumonia deaths worldwide respectively^[1]. The conjugate haemophilus influenza (HiB) and seven-valent pneumococcal conjugate vaccine (PCV7) were rolled out in South Africa (SA) in 1998 and 2009 respectively, PCV 13 replaced PCV7 in May 2011^[9]. *Haemophilus influenza* disease has since become rare^[10]. Vaccination with PCV has led to significant reductions in invasive pneumococcal disease (IPD) in children under five^[11,13] and in older unvaccinated age groups^[11,13]. The latter is attributable to herd immunity^[11,13,14].

Worldwide PCV has led to a decline in all-cause pneumonia admissions^[13,14], and has shown significant efficacy in preventing bacterial pneumonia in HIV-negative children in SA^[9]. The increased incidence of non-vaccine serotype IPD^[11,12] in some age groups, has been offset by the decline in vaccine-sensitive strains, so that overall incidence is still declining^[11,12].

High vaccine coverage rates in SA may be associated with a change in aetiology of pneumonia, which in turn could affect future presentation of disease. Viral causes may become more prominent^[15] and Mycobacterium Tuberculosis may be more commonly isolated in acute pneumonia^[16].

Sub-Saharan Africa is at the epicentre of the HIV and Tuberculosis epidemics^[17]. HIV-positive children have a greater incidence of pneumonia^[15,18,19] and a higher case fatality rate^[15,18]. HIV-exposed uninfected (HEU) children are a unique group, who are at increased risk for severe pneumonia^[20] and have pneumonia outcomes which are intermediate between HIV-infected and HIV-unexposed children^[19,20].

In SA, 9% of children under-five are underweight-for-age, 5% are wasted and 24% are stunted^[21]. Malnutrition is an established risk factor for pneumonia^[5,22].

Other patient factors associated with increased risk of severe lower respiratory tract infections (LRTI) or increased mortality risk include: low birth weight (LBW)^[23,24], insufficient breast feeding^[23,24], comorbidity with measles^[23] and chronic diseases^[23]. Prematurity is a likely risk factor for severe pneumonia^[24] and has been associated with a higher mortality rate^[23].

Environmental risk factors for severe pneumonia and higher mortality rate include, passive smoking and indoor air pollution^[23,24].

Improved access to antibiotics and community case management are protective against childhood mortality^[25], while limited access is associated with severe disease^[26]. Lower socioeconomic status is linked to higher mortality^[23].

Within SA many of these risk factors are applicable and it is clear that socioeconomic and other potentially modifiable factors play an important role in incidence of severe pneumonia and in mortality from pneumonia.

There are comprehensive local and international guidelines available for the management of childhood CAP, including those written by the South African Thoracic Society (SATS)^[6] and the British Thoracic Society (BTS)^[27].

The epidemiology in our province has not been described at regional level since 2004, when HAART was rolled out in the public sector and since routine immunisation with PCV13.

Using the BTS tool we evaluated epidemiology, prevalence of risk factors for severity and transfer, hospital management and outcomes of CAP at our secondary level hospital.

6.4 Methods:

Study site:

New Somerset Hospital is a 330-bed general regional hospital that serves the Western sub-district of the Cape Metropolitan district and the West Coast. The paediatric population served is approximately 100 000^[28], mostly middle and lower socio-economic backgrounds.

Study Design and Patient Selection:

We performed a retrospective descriptive study of every second patient (>2 months to 13 years) admitted to New Somerset Hospital (NSH) between 1 January and 31 December 2012 with the diagnosis of CAP or LRTI- regardless of causative organism or severity. Transfers in for ongoing management, from both tertiary and district hospital, were included. Patients were identified through the ward admission books and clinicom database. Children with acute exacerbation of asthma, without signs and symptoms of pneumonia, were excluded.

CAP was defined according to SATS Guidelines as an acute infection of <14 days duration, acquired in the community, of the lower respiratory tract, leading to cough or difficulty breathing, tachypnoea or chest wall in drawing^[6]. BTS guidelines were used to define severe infection (Appendix 4)^[6]. These definitions would include children with probable viral bronchiolitis.

Data Collection and Analysis:

The folders of identified patients were drawn from medical records, reviewed by the principal researcher and entered on an electronic data capture sheet (Microsoft Access®). Outstanding results were followed up through the National Health Laboratory Service (NHLS).

Data collected comprised patient demographic information: HIV status, social circumstances, nutritional status and presence of comorbidity. Indicators of disease severity, results of investigations and information on management: antibiotic and oxygen use. Outcome data included: duration of stay, necessity for transfer to tertiary level and mortality. Decision to transfer was based on clinical decision that additional respiratory support was required (high flow oxygen, continuous positive airway pressure or ventilation).

Data was analysed using STATA®/IC 11.1 for Windows Data Analysis and Statistical Software (StataCorp LP, TX77845, USA). Data was tested for normality using the Shapiro-Wilks. Data was presented as medians (interquartile ranges) or means (SD) for non-normally and normally distributed data respectively. Chi-squared or Fishers exact test were used for comparison of categorical data with wilcoxon rank sum or t tests used to compare continuous data. Logistic regression analysis was conducted to determine which clinically relevant factors were associated with severity or transfer to tertiary level. For all tests a p-value <0.05 was considered significant.

Permission to conduct this study was obtained from the Human Research Ethics Committee (HREC REF: 543/2013) and the need for informed consent was waived owing to the retrospective nature of the study.

6.5 Results:

In the period 01 January to 31 December 2012, 970 cases were initially identified. Of these 209 cases were excluded: 54 folders did not meet criteria for CAP or were double entries, 13 folders could not be located and 142 were excluded based on age <2 months. We reviewed 380 admissions, (half of the remaining 761).

Demographics and Prevalence of Risk Factors:

Table 1 shows the population characteristics. In this study 87% (332/380) of children were under-five years of age, median age of 9.4 months (IQR 4.8-23), with a slight male preponderance (p=0.48).

There was a high percentage of ex-premature (22%) and LBW (25%) children. The median age of admission was 5.7 months for both these groups; significantly lower than the median age of the group of children born at term, (10.6 months, p=0.0003).

HIV-positive children constituted 9% of the study group; of which 4% were newly diagnosed and 2% defaulted treatment. Of the children admitted 17% were documented as HEU and 14% were HIV untested.

Of the studied group; 1% were obese (BMI>30), 9% were moderately- and 12% were severely-malnourished (WHO child growth standards). Excluding HIV, prematurity and LBW; 22% of children had another chronic illness. Respiratory comorbidity was the most common (Table1).

Immunisation was incomplete in 25%, this number increased to 30% in children Öten months of age.

Of those under-five years 16% were recently exposed to household tuberculosis, only 15% of this group were on IPT. Previous Pulmonary Tuberculosis (PTB) was recorded in 6% of the overall group; however 27% of the HIV-positive group had previous PTB.

One 4 month old HIV-positive child who had defaulted ART had proven PJP; while 5 children (4 newly diagnosed and one who had defaulted ART) had a *Cytomegalovirus* (CMV) viral load > 5000 and were treated for CMV disease.

Management:

Table 2 shows investigations performed. The most common was a chest radiograph (91%); 80% had a white cell count (WCC) and 51% had a C-reactive protein (CRP).

Of those children who had severe disease 27% (55/202) had a WCC>18 x10⁹/l, while of those with mild/moderate disease 5% (1/21) had a WCC >18x10⁹/l, (p=0.024). A CRP of × 40mg/l did not correlate with disease severity.

Blood culture was taken in 57%; 24 cases cultured an organism, 88% of these were skin commensals. There was one proven case of penicillin-sensitive IPD in an unimmunised child. Two cases cultured gram-negative organisms, sensitive to either ampicillin or gentamicin.

Antibiotics were issued in 96% of cases; 54% received ampicillin or amoxicillin, whilst 37% received ampicillin and gentamicin.

Of the HIV positive children 71.4% (20/28) received ampicillin and gentamicin, while 71.4% (137/242) of the HIV negative children received ampicillin/amoxicillin ($p < 0.0001$). Of the children who were severely malnourished 69.7% (23/33) received ampicillin and gentamicin, while 63.3% (143/246) of the well-nourished children received ampicillin/amoxicillin ($p = 0.001$).

Excluding the children who were HIV positive and severely malnourished, 34.6% (93/269) received treatment with an aminoglycoside.

Tuberculosis treatment was initiated in 14%; but in only 7% was decision to treat based on positive microscopy, culture or PCR results.

In 54% of cases supplemental oxygen was used.

Severity of disease, duration of stay and mortality:

Of the children admitted 90% had severe disease (BTS definition), while 10% had mild or moderate disease. Hypoxia was recorded in 37% of cases. Table 3 shows possible risk factors for severe disease in the studied children.

Informal housing, malnutrition and HIV status were not significantly associated with severe disease. Of the LBW children, 83% were classified as having severe disease, whilst 91% of children with birth weight $> 2500g$ had severe disease, this difference was significant ($p = 0.042$).

The median duration of stay was 3 days (IQR 2-6). Younger age at admission and isolation of adenovirus were not associated with longer duration. Isolation of *Respiratory syncytial Virus* (RSV), with or without other viruses (20%), increased the median stay to six days (IQR 4-10, $p < 0.0001$). Children with neurological comorbidity had a mean stay of 6.5 days (IQR 4.5-9.5, $p = 0.008$).

Transfer rate for disease requiring assisted ventilation (CPAP or IPPV) was 4.5%. The mortality rate of CAP at NSH was (2/380) 0.5%.

Univariate analysis did not reveal an association between need to transfer and mortality; with either age, gender, LBW, prematurity or HIV status. However children with malnutrition were 3.1 times more likely to be transferred or demise ($p = 0.069$).

6.6 Discussion:

The median age at admission of nine months is in keeping with findings of previous studies, including a recent study from the Western Cape, which prove a high incidence of pneumonia in the first year of life^[1,4,5]. The majority of pneumonia deaths occur in children under two years, suggesting that interventions should focus on these children^[1].

In this study the high incidence of LBW and prematurity and younger age at admission of both of these groups, suggests that they are at risk for developing pneumonia. The LBW incidence in our study is higher than the background LBW rate of 16.4% and 16.8% for the Metro West district for January-June 2013 and 2014 respectively (Prof Anthony Westwood; Head of Metro West; personal communication).

LBW children may have an impaired immune response which predisposes to infectious disease^[29]. Healthy preterm children in the first few months have reduced lung function compared to well term children^[30] and are at proven risk for RSV infection and hospitalisation for both RSV and community acquired alveolar pneumonia^[31].

The protective effect from severity in LBW children could be a result of excluding children Ö two months, who have high potential for severe disease^[23] or perhaps these results reflect bias on the part of the admitting physician; who may be more likely to admit a child with a significant neonatal history.

In a study in 2001 of hospitalised children with pneumonia in Cape Town, up to 20% were related to HIV disease^[32], whereas only 9% of the children in our study were HIV-positive. The decreased prevalence of HIV-positive children in South Africa is a direct reflection of improved PMTCT guidelines and access^[33]. In 1998 9.9% of HIV-positive children admitted with pneumonia were diagnosed with PJP^[32], while we had only one proven case of PJP. This is to be expected with improved access to antiretrovirals for children^[34] and standard provision of cotrimoxazole prevention therapy (CPT).

A high proportion of children were HEU, however we could not prove increased incidence of severity for this group, this risk could be attenuated by early maternal ART^[20].

The high prevalence of malnutrition and association with transfer and mortality (although not significant) is unsurprising. These children are known to be at increased risk of pneumonia^[5] which is more likely to be severe^[24]. The risk of mortality from CAP is increased with both severe^[23,35,36] and moderate malnutrition^[35], secondary to changes in cellular and humoral immunity^[36]. Stunting reflects chronic malnutrition^[21] and is associated with an increase in pneumonia incidence and hospitalisation and with higher rate of treatment failure^[37].

Children with chronic underlying conditions are at increased risk of mortality from CAP^[23], although we could not prove an increased risk for transfer in these children, both of the children who demised with CAP at our hospital had significant genetic comorbidities. The high prevalence of comorbidity with CAP admissions and the increased duration of stay with neurological comorbidity, suggests that focused preventative strategies and case management is necessary in these children.

South Africa is considered an endemic area for tuberculosis^[17], which is reflected in the high number of Tuberculosis-exposed children. Tuberculosis in children is likely underestimated in

high burden areas^[38]. We diagnosed 14% with PTB, most of which were classified as probable or possible cases. Recent studies have emphasised the importance of Tuberculosis in acute severe pneumonia^[39], either as a direct cause or as a risk factor leading to secondary bacterial LRTI^[1,39]. It is postulated that with successful implementation of PCV and Hib, Tuberculosis might be more commonly isolated as a causative organism in acute pneumonia^[16]. IPT is an effective method of preventing progression to TB disease in exposed children under five^[38].

Lack of immunisation is a known risk for severe CAP^[24], the only child with proven IPD was unimmunised.

Currently there is no single reliable gold standard to distinguish between viral and bacterial causes of CAP^[40,41]. Leukocytosis is proven unhelpful in distinguishing aetiology^[41]; 20% of cases in this study did not have a WCC; it is reasonable to assume that severe cases were more likely to have blood investigation. Therefore, despite a significant result, correlating leukocytosis with severity would be inaccurate. A serum CRP of > 40-60 mg/l is considered weakly predictive for bacterial pneumonia in children^[42], we did not demonstrate this.

Blood culture is currently recommended for children with severe disease^[6]. However limitations include low yield (<10% positive in cases of CAP)^[43], long duration to result and high percentage of false positives and negatives^[41]. This is reflected in our findings. Improvements in culture technique and possibly selection of patients, who are most likely to benefit from culture, may be necessary.

A high proportion of children had special investigations including chest radiograph and acute phase reactants, these are not routinely recommended in the investigation of CAP by BTS and SATS^[6,27]. Adherence to peer-reviewed guidelines would reduce cost (and radiation exposure) among admitted children.

Our hospital protocols recommend addition of gentamicin to amoxicillin/ampicillin in children over 2 months who are severely malnourished or HIV-infected. In accordance with this protocol, both HIV positive and malnourished children were significantly more likely to receive both ampicillin and gentamicin. However, a large proportion of children who were well-nourished and HIV negative received an aminoglycoside, which suggests inappropriate aminoglycoside prescription

Despite the fact that only 30% of children had a NPA sent for respiratory viruses, detection of RSV led to longer duration in hospital and therefore significant cost burden. RSV is the leading cause of viral pneumonia in children under two^[44] and is linked to the development of paediatric asthma^[45] and wheezing in infancy^[44]. New preventative strategies against RSV include maternal immunisation, infant intranasal live-vaccines and passive immunisation with antibodies^[45]. These measures could serve to reduce morbidity and the high cost burden associated with this illness. The public sector currently does not have access to any RSV preventative strategy.

The high proportion of severe pneumonia could be explained as children are pre-selected to be hospitalised at a regional hospital.

Despite high levels of LBW, comorbid chronic illness, malnutrition and poor immunisation rates; mortality at NSH was low. On further review, the two children who demised had significant comorbidity and established limitation of intervention, which precluded them from further escalation of support.

As this was a retrospective descriptive study it was limited by the data recorded in the admission notes- there was thus insufficient data to reliably analyse the effect of breast versus formula feeding and exposures like indoor air pollution and passive smoking- which are known to effect CAP presentation^[23,24].

We chose to look at children > two months of age, as management and causative organisms differ in the younger age groups. However exclusion of the younger group may have missed significant severe disease.

Collecting every second admission meant that we could not analyse seasonality or identify children with repeat admissions accurately. The small number of transfers made analysis of risk factors in that group difficult, further studies looking at risk factors at tertiary level may be helpful.

6.7 Conclusion and recommendations:

To improve the under-five mortality rate preventative measures need to focus on at risk populations; LBW and preterm children in first year of life, those with co-morbidities like HIV and malnourished children.

HIV remains a risk factor and strong PMTCT policies and provision of ART must remain a priority.

The low rate of immunisation reflects a need to strengthen primary health care approaches. The poor provision of IPT is particularly alarming in view of the current TB epidemic. Community health workers may be helpful in identifying at risk children and providing accessible care, prior to hospital admission becoming necessary.

We are concerned about the lack of adherence to peer reviewed guidelines in terms of unnecessary special investigations and aminoglycoside use, and this can be improved. The high false positive blood culture rate also requires attention.

Proven RSV and concomitant neurological disease lead to longer duration of admission, new strategies in RSV prevention are in development but not equally accessible.

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TABLE 1: Features of study population

<u>Demographic data</u>	No/No known	%
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Hospital of origin:		
From RCWMH*	103/380	27
RCWMH from Informal settlement	39/102	38
NSH admission ^A	277/380	73
NSH from Informal settlement	111/270	41
Gender:		
Male	210/380	55
Female	170/380	45
Age:		
Age (months) median, IQR	10.6 (4.8-23)	
Age males median IQR	10.6 (4.8-23)	
Age females median IQR	9 (4.8-24)	
Age LBW median IQR	5.7 (3.8-12)	
Age >2500g BW median IQR	10.6 (5.3-24)	
Age Ex-prem median IQR	5.7 (3.8-14.8)	
Age term median IQR	10.6 (5.7-24)	
Age HIV positive median IQR	35.4 (9-67)	
LBW babies	89/355	23
Ex-premature babies	75/341	20
HIV status:		
Exposed negative	65/380	17
Exposed unknown	1/380	0.3
Negative	226/380	60
Positive default ART	7/380	2
Positive on ART	11/380	3
Positive preART	16/380	4
Unknown	54/380	14

Immunisation:		
Immunisation incomplete (total)	87/354	25
Immunisation incomplete (<10/12)	57/190	30
Malnutrition:		
Moderate malnutrition	32/342	9
Severe Malnutrition	41/342	12
Obese	3/342	1
Breastfed (at least 2/12 exclusively):	181/380	48
Chronic illness:	84/380	22
Cardiac	14/84	17
Genetic	12/84	14
Neurological	5/84	6
Renal	1/84	1
Respiratory	52/84	62
Previous admission (last 6 months)	111/362	31
Tuberculosis:		
TB exposed<5 years	53/332	16
TB exposed <5 years on INH	8/53	15
Previous PTB	21/380	5.5

* RCWMH (Specialist centre) down-refers children to NSH (Regional level); this includes children who originate from NSH drainage area and/or require further secondary level care.

ÄNSH admissions are from the clinics within the Metro West District and includes those referred in from Westfleur and Vredenberg Hospital

TABLE 2: Special investigations

Special investigations and management		
Special investigations:	No/No known	%

Chest radiograph	348/380	92
WCC	303/380	80
CRP	195/380	51
Blood culture	218/380	57
Nasopharyngeal aspirate	101/380	27
Induced sputum	115/380	30

TABLE 3: Risk factors for severe disease

No of severe cases/no of mild or moderate cases= %			p-value
Informal	Formal housing		
124/142 (87.3%)	190/208 (91.3%)		p=0.422
Ex-premature babies	Term babies		
60/72 (83.3%)	227/252 (90%)		p=0.112
LBW babies	BW>2500g		
68/82 (82.9%)	232/255 (91%)		P=0.042
Severe malnutrition	Moderate malnutrition	Normal nutrition	
35/37 (94.6%)	24/27 (89%)	227/258 (88%)	p=0.720
HEU	HIV positive preART	HIV negative	
59/65 (89.7%)	14/14 (100%)	181/209 (86.6%)	p=0.127

TABLE 4: Special investigations and relation to severity

Severe disease: (CRP>40/Total) ☒	Mild/moderate disease: (CRP>40/Total) ☒	
48/168 (29%)	3/19 (16%)	p=0.236
Severe disease: (WCC>18/Total) §	Mild/moderate disease: (WCC<18/Total) §	
55/202 (27%)	1/21 (5%)	P=0.024

☒CRP reported as milligram per litre (mg/l)

§ Reported as WCC per microliter (x10⁹/l)

TABLE 5: Use of Ampicillin and Gentamicin versus Amoxil/Ampicillin ¶

	Received Ampicillin and Gentamicin	%	Received Ampicillin/Amoxil	%
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	TOTAL 40.3% (129/320)		TOTAL (191/320) 59.7%	
HIV negative	105/242	43.4%	137/242	56.6%
HIV positive	20/28	71.4%	8/28	28.6%
HIV unknown	4/50	8%	46/50	92%
≥Normal nutrition	83/226	36.6%	143/226	63.3%
Moderate Malnutrition	14/28	50%	14/28	50%
Severe Malnutrition	23/33	69.7%	10/33	30.3%
HIV and ≥Normal nutrition	93/269	34.6%	176/269	65.4%

¶ Children who received nil/other antibiotics excluded (60/380, 15.8%)

Supplementary Table 1: Respiratory Virus Panel Results

Respiratory Virus Panel Results- Nasopharyngeal aspirates

RSV only	22/101 (22%)
RSV±other viruses	7/101 (6.9%)
Adenovirus only	11/101 (10.9%)
Adenovirus±other viruses	4/101 (4%)
Pertussis only	0
Pertussis±other viruses	1/101 (1%)
Parainfluenzae	4/101 (4%)
Parainfluenzae±other viruses	3/101 (3%)
Influenzae	3/101 (3%)
Influenzae±other viruses	0
Metapneumovirus	5/101 (5%)
Metapneumovirus±other viruses	1/101 (1%)
Rhinovirus	11/101 (10.9%)
Rhinovirus ±other viruses	7/101 (6.9%)

Supplementary list 1: Diagnosis of children with neurological comorbidity

1. Spinal Muscular Atrophy
2. Dravet Syndrome with severe developmental delay
3. Spastic Cerebral Palsy
4. Dystonic Cerebral Palsy
5. Cerebral palsy (unspecified)

7) APPENDICES

APPENDIX 1: THE PROTOCOL

MMED Proposal:

A review of children admitted to a regional Hospital in Cape
Town with Community Acquired Pneumonia

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Introduction:

Pneumonia is the leading cause of mortality worldwide contributing 1.575 million deaths to the under-five mortality rate in 2008 (1) and an estimated 18% to the worldwide under 5 mortality rate annually (2). In South Africa in 2007 lower respiratory tract infections were responsible for 15.1% of child deaths (1-4 years of age), only ranked below diarrhoeal diseases and ill-defined natural causes. (4)

A quarter of children from the developing world will have one episode of pneumonia a year (5), therefore pneumonia contributes significantly to morbidity and hospital costs in Africa. (6)

Although it is often difficult to isolate specific pathogens in childhood pneumonia, vaccine trial studies have been used to estimate the incidence of bacterial causes (7). In developing countries bacterial causes contribute significantly to both hospitalisation and mortality from pneumonia. (8). Viral isolates were found in 30-40% of children admitted to hospital in Cape Town with pneumonia (8), while respiratory syncytial virus is the leading viral cause of pneumonia in developing countries (7). Tuberculosis (TB) contributes to disease in both HIV (Human immunodeficiency virus) infected and uninfected children (7). South Africa is classified as a high TB burden country; in 2011 tuberculosis had an incidence rate of 993 per 100000 population. (9). Eight percent of pneumonia cases are reported secondary to tuberculosis in high TB/HIV prevalence areas (8, 10).

Co-infection with viruses and bacteria is not uncommon occurring in as many as two thirds of childhood pneumonia cases. (8)

In 2008 an estimated 23-320 000 children between 1-14 years were suffering from HIV/AIDS (11). This is a population at greater risk for infectious disease, including opportunistic infections such as pneumocystis jirovecii (PJP), as well as a group at higher risk for adverse outcomes.(6,12,13). PJP was the causative organism in 20% of newly diagnosed HIV positive children hospitalised for severe pneumonia (12) and Mycobacterium tuberculosis also contributed (8). HIV positive patients hospitalized with PJP have a reported mortality between 20 and 63 percent. (10). CMV pneumonitis was noted as a cofactor in 30-40% of postmortem studies in HIV positive children.

Antiretrovirals were rolled out in the public sector in South Africa in 2004 and according to initiation criteria of CD4 <200, 80% coverage of adults was attained in 2011 (14). Lower rates of initiation were recorded in children; but in 2011, 152000 children were receiving highly active antiretrovirals (HAART) as compared to 4200 in 2004. (14) The ratio of new children enrolled on HAART to number of newly diagnosed HIV positive children was 1.13 (95% CI 0.74-1.48) from mid-2010 to mid-2011 (14). With better access to HAART and programmes for Prevention of Mother to Child Transmission (PMTCT) of HIV for mothers, HIV associated lung disease would be expected to decline.

Although there is a global reduction in the prevalence of children who are stunted and wasted, in South Africa an estimated 10-19.9% of children are underweight for age (weight for age <-2SD) and 20- 29-9% of children are stunted (Ht for age <-2SD) (15). Malnutrition (wt for age <-2SD) contributes 35% to overall childhood under 5 mortality rate (15), this is again a group of children who are at high risk for

morbidity and mortality from many infections, including pneumonia (7,13). Hypoxia and malnutrition are the strongest predictors for mortality in both HIV infected and uninfected children (16).

There were 25929 low birth weight babies (1 kg to 2,5 kg) born in the Western Cape for the period 2010 to 2011 (17). The low birth weight rate in the Western Cape is 16.66 % (14.7% for South Africa) (17). Low birth weight is a definite risk factor for the incidence of pneumonia in developing countries (7).

Community case management and prescription of antibiotics in childhood pneumonia has proven to be beneficial in reducing acute lower respiratory tract infection mortality by 35% (6). In the Western Cape the Integrated Management of Childhood Illness (IMCI) is one such effective programme (18).

Ineffective health systems are directly linked with an increase in pneumonia associated deaths (5), it is therefore important in a resource limited setting such as South Africa to streamline the management of all illnesses including pneumonia.

The South African Extended Programme of Immunisation (EPI) includes immunization against Bortadella pertussis, Haemophilus influenza, measles and the pneumococcal conjugate vaccine. Immunization has had a significant effect on mortality and pneumonia rates (19). The pneumococcal vaccine was introduced into the expanded immunization programme in April 2009 and the Haemophilus conjugate vaccine introduced in 1998. The pneumococcal vaccine has the potential to decrease the incidence of pneumonia by 13-20% (10) and the Haemophilus influenza vaccine reduces invasive disease by as much as 93%, although it is not as effective in HIV positive children not on HAART. Vaccination rates are directly related to strength of health systems in the area as well as socioeconomic circumstances (13).

There are comprehensive local and international guidelines available for the management of community acquired pneumonia (CAP), including those by the South African Thoracic Society (SATS) and the British Thoracic Society (BTS). The BTS has published guidelines for the management of community acquired pneumonia in 2011 and has developed a validated paediatric audit tool to be used for evaluating case management of pneumonia. Steps include clinical evaluation for presence of pneumonia and thereafter assessing severity and need for hospitalisation and oxygen therapy. Radiological diagnosis is only required in children to screen for complications, in suspected pulmonary tuberculosis or foreign body aspiration or in children unresponsive to standard treatments. In hospitalized children there should be an attempt to establish the causative organism, but this should not interfere with initiation of empirical therapy. The first choice antibiotic is amoxicillin but children less than two months of age should also receive aminoglycosides and HIV exposed children under six months of age, unless confirmed negative, should receive clotrimoxazole. Suspected staphylococcal pneumonia should be treated with cloxacillin. Supportive management includes oxygen, antipyretics and analgesic, fluids and nutrition. Preventative measures include immunization, micronutrient supplementation, optimisation of nutrition, promotion of breast feeding as well as tuberculosis prophylaxis (16,20)

In view of this common presentation, we decided to utilize the BTS tool to evaluate in hospital management at our secondary level hospital. Due to our unique patient population and the SATS guidelines we modified this to include additional aetiologies and management relevant to our setting

(see appendices 1 and 2). The epidemiology in our province has not been described since 2004 when HAART was rolled out in the public sector.

Our hypothesis is that at our a secondary hospital many of our admissions will have underlying risk factors, the exact aetiology will often not be identified, and we anticipate a high incidence of TB and possibly a reduction in PJP considering the improved PMTCT programme, chemoprophylaxis for PJP and HIV rollout over the past 9 years.

Methodology

Objectives:

Primary:

1. To describe the demographic profile, clinical presentation, severity , and investigation results (including aetiology where available), of children admitted with a diagnosis of CAP over a 1 year period
2. To describe management including antibiotic use
3. To describe outcome including any mortality
4. To determine the presence of co- morbidities, such as malnutrition, HIV infection, LBW, prematurity, lack of breast feeding that may be as associated with a higher incidence of severe pneumonia

Secondary:

1. To compare management to standard guidelines
2. To compare aetiology with other studies in a similar setting
3. To identify any potential need to modify local guidelines specific to our setting and findings

Study design:

Retrospective descriptive study

Study identification or selection:

All paediatric patients (>2 months to 13 years of age) admitted to New Somerset Hospital between January and December 2011 with the diagnosis of pneumonia or lower respiratory tract infection- regardless of causative organism or severity.

Patients transferred in from tertiary level with the above diagnosis, would also be included and the photocopied notes from the admitting doctor used for data entry.

Every second folder of patients who meet the above criteria will be reviewed.

Measurement:

Instruments: Data will be captured directly onto an Access® data capture sheet, based on the BTS Pneumonia audit tool, but modified to include criteria significant to the South African population.

Definitions:

1. Paediatric: any patient under the age of 13 years, and within this study context, more than two months of age.
2. Community acquired pneumonia: Acute infection of <14 days duration, acquired in the community, of the lower respiratory tract, leading to cough or difficulty breathing, tachypnoea or chest wall in drawing (20).
3. Pneumonia: The WHO defines pneumonia as acute episode of cough or difficulty breathing associated with an increased respiratory rate, the underlying cause being viral or bacterial. (WHO)
4. HIV positive: HIV PCR + <18 months of age with a confirmatory VL; or two positive HIV elisas on a child >18 months old.
5. HIV exposed and negative: Mother positive in pregnancy and child tests PCR negative
6. HIV exposed: Mom tested HIV positive, child's status is unknown
7. HIV negative: HIV unexposed child with a negative HIV test (Elisa or PCR)
8. Unknown: No information on child or mothers status available
9. Breast fed: Child under six months of age, breast fed exclusively for at least two months.
10. Low birth weight: Less than 2500g at birth
11. Preterm: Less than 37 weeks completed gestation at delivery
12. Tachypnoeic for age: > 50 breaths per minute in a child 2-12 months of age and >40 breaths per minute for child 1-5 years of age. (20)
13. Definite TB: Culture positive Mycobacterium Tuberculosis or MTB PCR positive

Patient identification:

Using the ward admission books from the two general admission paediatric wards, the names and folder numbers of all the children between 2 months and 13 years of age admitted to New Somerset Hospital over the period from January to December 2012 with a diagnosis of CAP/lower respiratory tract infection will be identified. The hospital clinicom database will also be searched for any children with the final discharge diagnosis of pneumonia or lower respiratory tract infection, to ensure no cases are missed. Children with an acute exacerbation of asthma, without signs and symptoms of pneumonia will

be excluded. The diagnosis of bronchiolitis would not qualify as exclusion criteria, but if the diagnosis was 'likely bronchiolitis' then this will be captured on the data capture sheet.

The expected number of children to be included in this study is 808 (as per New Somerset Hospital admission book from 2012). However some of these children may be under the age of two months of age and therefore would not be included and other folders will not be included should records be incomplete.

Data collection:

The folders of the identified patients will be requested and drawn from medical records at New Somerset Hospital and will be reviewed by the principal researcher.

Any culture results or blood results that are outstanding will be followed up by the principal researcher through the NHLS computer system and telephonically should it be necessary.

This data will be directly entered on an electronic data collection (Microsoft Access®) database (see Appendix). Each entry will record patient details: demographics, HIV status, social circumstances, nutritional status; indicators of disease severity; results of investigations and look at how the patient was managed and treated; as well as determine outcomes based on re-admission and adverse events.

Data will be analysed by a University of Cape Town (UCT) statistician using appropriate descriptive and comparative statistics. Analysis will be using STATA®

Ethics:

In order to maintain confidentiality each admission will receive a study number and the data collated onto the data collection forms will only bear this study number. The principal researcher however, will retain a copy of folder numbers correlated with study numbers so that a folder could be located again through medical records should it be necessary. This will be an electronic list, kept in a password encrypted folder. No published data will be linked to any specific patient.

HIV results will be obtained from the folders, for which consent (as per hospital guidelines) will have been obtained by the clinician involved in care and management and the parents duly counselled.

It will not be possible to obtain individual consent from the parents of each child involved because of the retrospective design, but management is not influenced or altered by the study. Consent for the use of medical records will be obtained from the hospital CEO with application to waive individual consent (see Appendix 3).

Risks to participants: There are no risks to the participants as this is a retrospective study.

Benefits to participants: There are no direct benefits to the patients in this study. However management guidelines at the local institution may be improved depending on results

Reporting and implementation:

All results of data analysis will be reported back to the paediatric department of New Somerset hospital with the potential to improve future management.

Budget:

The study will be undertaken by the principal researcher as part of her MMED project under the University of Cape Town. There will be no personal compensation for the principal researcher or the supervisor. Only routine existing equipment available at New Somerset Hospital will be required.

Expenses related to printing and internet will be covered by funding through the postgraduate committee allocated to training registrars research projects (R5000/student). This will be managed from the supervisors entity for incidental costs. Statistical support will be from the University allocated statistician at no additional cost

Strengths and limitations:

The study is limited by its retrospective nature -the accuracy of recorded notes and the availability of the required folders from medical records may impact on data collection and validity.

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ACCESS DOCUMENT:

Patient Information:

Folder number

Date of birth: In format: date/month/year

Gender: Drop down boxes for male and female

Housing: Drop down boxes for Formal/Informal/Unknown

Low birth weight: Drop down boxes for Yes/No/Unknown

Exprem: Drop down boxes for Yes/No/Unknown

Feeds: Breastfed/Formula/Unknown

Nutrition: Drop down boxes for normal, moderate malnutrition, severe malnutrition and unknown.

Immunisation: Drop down boxes for up to date, not up to date, unknown.

TB exposed: Drop down boxes for exposed, unexposed and unknown.

Isoniazid prophylaxis therapy (IPT): Drop down boxes for yes, no, unknown and not applicable.

Previous PTB: Drop down boxes for yes, no and unknown.

HIV status: Drop down boxes for positive on HAART, positive pre-HAART, positive defaulted ARV's, exposed but HIV status unknown, negative and unknown.

Chronic illness: Drop down boxes for yes, no and unknown and then a block to include specific chronic illness.

Preadmission antibiotic: Drop down boxes for yes, no and unknown.

Admitted in last six months: Drop down boxes for yes, no and unknown.

Transfer from RXH: In format yes/no

Box for date of arrival at Red Cross: In format day/month/year

Box for date of arrival NSH: In format day/month/year

Box for date of discharge: In format day/month/year

Transfer in to NSH from tertiary level: Drop down boxes for yes/no

Clinical:**Signs of CAP:**

Box for respiratory rate: (To be recorded as breaths per minute)

Tachynoeic for age: Drop down boxes for yes or no

O2 saturation: Drop down boxes for <92 or >92

Nasal flaring: Drop down boxes for yes, no and unknown.

Recessions: Drop down boxes for yes, no and unknown.

Apnoea: Drop down boxes for yes, no and unknown.

Grunting: Drop down boxes for yes, no and unknown.

Not feeding in an infant: Drop down boxes for yes, unknown an not applicable.

Wheezing: Drop down boxes for yes, no and unknown.

Highest temperature recorded: Box for value in degrees celsius

Likely bronchiolitis: Drop down boxes for yes/no

Work up:

CXR:_Drop down boxes for: not done, normal, abnormal, lobar pneumonia, not recorded:

WCC: Drop down boxes for yes and no. Box for value to be recorded.

CRP: Drop down boxes for yes and no. Box for value to be recorded.

Blood culture done: Drop down boxes for yes and no.

Organism cultured from blood culture: Drop down boxes for yes and no.

Organism cultured from blood culture number 1: Drop down boxes for nil, streptococcus pneumonia, Haemophilus influenza, staphylococcus aureus MRSA, staphylococcus aureus non-MRSA, mycoplasma pneumonia, chlamydia pneumonia, moraxhella catarrahlis, mycobacterium tuberculosis, skin commensal.

Organism cultured from blood culture number 2: Drop down boxes for nil, streptococcus pneumonia, Haemophilus influenza, staphylococcus aureus MRSA, staphylococcus aureus non-MRSA, mycoplasma pneumonia, chlamydia pneumonia, moraxhella catarrahlis, mycobacterium tuberculosis, skin commensal.

NPA: Drop down boxes for done or not done.

NPA 1 organism recovered: Drop down boxes for nil, RSV, corona virus, rhinovirus, influenza, parainfluenza, CMV, PJP, bocavirus, human metapneumovirus.

NPA 2 organism recovered: Drop down boxes for nil, RSV, corona virus, rhinovirus, influenza, parainfluenza, CMV, PJP, bocavirus, human metapneumovirus.

Induced sputum: Drop down boxes for done or not done.

Induced sputum 'number one' results: Drop down boxes for RSV, metapneumovirus, rhinovirus, parainfluenza, influenza, CMV, PJP, bocavirus, Group A streptococcus, Haemophilus influenza, Staph aureus (MRSA), Staph aureus (non-MRSA), mycoplasma and chlamydia, moraxhella catarrhalis, MTB, commensal.

Induced sputum 'number two' results: Drop down boxes for RSV, metapneumovirus, rhinovirus, parainfluenza, influenza, CMV, PJP, bocavirus, Group A streptococcus, Haemophilus influenza, Staph aureus (MRSA), Staph aureus (non-MRSA), mycoplasma and chlamydia, moraxhella catarrhalis, MTB, commensal.

Gastric washing: Drop down boxes for done or not done.

Gastric washing 'number one' results: AFB positive and culture positive, AFB negative and culture positive, AFB and culture negative.

Gastric washing 'number one' results: AFB positive and culture positive, AFB negative and culture positive, AFB and culture negative.

CMV viral load: Drop down boxes for <5000, >5000, not done.

Management:

O2 given- (Given anytime): Drop down boxes for yes, no and not recorded.

Bronchodilators given: Drop down boxes for yes, no and not recorded.

Hypertonic saline nebs given: Drop down boxes for yes, no and not recorded.

Antibiotics used:

1 Antibiotic: First line antibiotics: Drop down boxes for amoxicillin, augmentin, erythromycin, flucloxacillin, cefalexin, cefuroxime, oseltamavir, bactrim oral, antituberculous medication, oseltamavir, ampicillin, gentamycin, amikacin, piptazobactem, cloxacillin, ceftriaxone, cefotaxime, cefuroxime, vancomycin, ertapenem, meropenem, iv bactrim, gangcyclovir. (Four options of drugs as first line: 1Antibiotic1, 1Antibiotic2,1Antibiotic3, 1Antibiotic4)

2 Antibiotic: Second line antibiotics: Drop down boxes for amoxicillin, augmentin, erythromycin, flucloxacillin, cefalexin, cefuroxime, oseltamavir, bactrim oral, antituberculous medication, oseltamavir, ampicillin, gentamycin, amikacin, piptazobactem, cloxacillin, ceftriaxone, cefotaxime, cefuroxime, vancomycin, ertapenem, meropenem, iv bactrim, gangcyclovir. (Four options of drugs as second line: 2Antibiotic1, 2Antibiotic2,2Antibiotic3, 2Antibiotic4)

Duration of therapy?

Complications of Therapy:

Drop down boxes for yes, no or not recorded.

Drop down boxes for complications: Transfer to tertiary centre for further management or cpap, no response to therapy within 48-72 hours, pulmonary abscess, empyema, osteomyelitis/septic arthritis, necrotizing pneumonia.

Follow up:

Hospital follow up: Drop down boxes for yes, no and no data.

Clinic follow up: Drop down boxes for yes, no and no data.

APPENDIX 2: HREC APPROVAL LETTER AND PROOF OF EXTENSION UNTIL 2016

UNIVERSITY OF CAPE TOWN



Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
e-mail: shucella.thomps@uct.ac.za
Website: www.health.uct.ac.za/research/humanethics/forms

10 September 2013

HREC REF: 543/2013

Dr M Meyer
c/o Dr M Cooke
Paediatrics
Red Cross War Memorial Children's Hospital

Dear Dr Meyer

PROJECT TITLE: A REVIEW OF CHILDREN ADMITTED TO A REGIONAL HOSPITAL IN CAPE TOWN WITH COMMUNITY ACQUIRED PNEUMONIA

Thank you for your email to the Faculty of Health Sciences Human Research Ethics Committee received 5th September 2013.

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

Approval is granted for one year until the 30th September 2014

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

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

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 312.56 and 312.57.

s.thomps



FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FMA00001837; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
<input checked="" type="checkbox"/> Approved	Annual progress report	Approved until next renewal date	30/09/2016
<input type="checkbox"/> Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed: 21/9/15	

Principal Investigator to complete the following:

1. Protocol Information

Date (when submitting this form)	13-2015		
HREC REF Number	EH2-2015	Current Ethics Approval was granted by	HUMAN RESEARCH ETHICS COMMITTEE
Protocol title	A Review of Children admitted to Cape Town with congenitally acquired Malaria		28 SEP 2015
Principal Investigator	Mandylyn Meyer		
Department / Office Internal Mail Address	Mandylyn.meyer@uct.ac.za		
HEALTH SCIENCES FACULTY UNIVERSITY OF CAPE TOWN			
1.1 Does this protocol receive US/Federal funding?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	

2. Protocol status (tick ✓)

<input type="checkbox"/> Research-related activities are ongoing
<input checked="" type="checkbox"/> Data collection is complete; data analysis only
Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.
N/A

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval	390 total
Total number of records or specimens collected, reviewed or stored since last progress report	340 total
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

4. Signature

Signature of PI		Date	10/09/2015
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APPENDIX 3: BRITISH THORACIC SOCIETY AUDIT TOOL



BTS Paediatric Pneumonia Audit Tool Patient Data Collection Sheet

please complete one form for each patient before entering data on the audit tool system

https://audits.brit-thoracic.org.uk/
audittools@brit-thoracic.org.uk

Minimum inpatient paediatric data set for children > 12 months admitted with a final diagnostic coding label of pneumonia, into a paediatric unit and under paediatric care

SECTION 3. CONTINUED
3.4* Viral Serology: No Acute only Acute + convalescent Convalescent only
No data / not recorded

SECTION 1. PATIENT INFORMATION

1.1* Hospital Number
 1.2* Gender Male Female
 1.3* Date of Birth DD / MM / YYYY
 1.4* Admission Date DD / MM / YYYY
 1.5* Discharge Date DD / MM / YYYY
 1.6* Antibiotics pre-admission
 Yes No No Data / Not Recorded
 1.7* Days of antibiotics
 1.8 Length of Stay
 (This is automatically calculated by the system)
 1.9 Age of Patient
 (This is automatically calculated by the system)

3.5* CXR? No No data / not recorded
 3.6* Abnormal? Yes No No data / not recorded
 3.7* Lobar consolidation? lobar patchy none No data / not recorded
 3.8* Causative organism found? Yes No No data / not recorded
 3.9 Causative Organism: Streptococcus pneumoniae
 Co. A beta haemolytic streptococci
 Methicillin resistant Staphylococcus aureus
 Pseudomonas species
 Chlamydia pneumoniae
 Influenza A
 Influenza B
 Influenza H1N1
 Parainfluenza
 Adenovirus
 Other
 Mycoplasma pneumoniae
 Moraxella catarrhalis
 Respiratory syncytial virus
 Haemophilus influenzae
 Staphylococcus aureus
 Streptococcus pneumoniae

SECTION 2. SEVERITY

2.1* Highest recorded respiratory rate:
 < 50 /min 50-70 /min > 70 /min No data / not recorded
 2.2* Costal recession: Present Absent No data / not recorded
 2.3* Wheeze Yes No No data / not recorded
 2.4* O₂ Saturation in air: < 92 /min ≥ 92 /min No data / not recorded
 2.5* Apnoeas noted? Yes No No data / not recorded
 2.6* Grunting noted? Present Absent No data / not recorded
 2.7* Feeding poorly? Yes No No data / not recorded
 2.8* Highest temperature recorded:
 < 38 degC 38-39 degC > 39 degC No data / not recorded

SECTION 4. MANAGEMENT

4.1* Oxygen
 Given at any time during admission Not given during admission No data / not recorded
 4.2 Oxygen given by
 Via head box Via face mask
 Via face mask and nasal cannula Not given No data / not recorded
 4.3 Chest physiotherapy Yes No No data / not recorded
 4.4 Assisted ventilation Yes No No data / not recorded
 4.5 Nasogastric feeding Yes No No data / not recorded
 4.6 IV Fluids Yes No No data / not recorded
 4.7 Antipyretics given Yes No No data / not recorded
 4.8 Bronchodilators given Yes No No data / not recorded

SECTION 3. ADMISSION TESTS

3.1* B blood cultures drawn? Yes No No data / not recorded
 3.2* Cough Swab/Sputum Culture Yes No No data / not recorded
 3.3* NPA: Yes No No data / not recorded

October 2010
continued over...

* indicates required field

SECTION 5. ANTIBIOTICS

5.1 Antibiotics

5.2 Route IV/Oral

Tick all prescribed:

	IV	Oral
Amoxicillin	<input type="checkbox"/>	<input type="checkbox"/>
Augmentin	<input type="checkbox"/>	<input type="checkbox"/>
Azithromycin	<input type="checkbox"/>	<input type="checkbox"/>
Cefotaxime	<input type="checkbox"/>	<input type="checkbox"/>
Cefuroxime	<input type="checkbox"/>	<input type="checkbox"/>
Cephador	<input type="checkbox"/>	<input type="checkbox"/>
Clarithromycin	<input type="checkbox"/>	<input type="checkbox"/>
Erythromycin	<input type="checkbox"/>	<input type="checkbox"/>
Flucloxacillin	<input type="checkbox"/>	<input type="checkbox"/>
Penicillin	<input type="checkbox"/>	<input type="checkbox"/>
Other	<input type="checkbox"/>	<input type="checkbox"/>

SECTION 6. COMPLICATIONS + FOLLOW-UP

- 6.1* Empyema Yes No No data / not recorded
- 6.2* Lung Abscess Yes No No data / not recorded
- 6.3* Osteomyelitis / Septic Arthritis
 Yes No Other No data / not recorded
- 6.4 Other complication (if answered other in 6.3)
- 6.5* Co-morbidities Yes No No data / not recorded
- 6.5.1* Asthma Yes No No data / not recorded
- 6.5.2* Cystic Fibrosis Yes No No data / not recorded
- 6.5.3* Immuno-Compromise Yes No No data / not recorded
- 6.5.4 Other Disease (please specify)
- 6.6* Hospital Follow Up Arranged Not arranged No data / not recorded
- 6.7* Chest X-Ray at follow-up Yes No No data / not recorded

* indicates required field

APPENDIX 4: Definition of severe pneumonia (BTS guidelines)

BTS guidelines

Table 6 Severity assessment

	Mild to moderate	Severe
Infants	Temperature <38.5°C Respiratory rate <50 breaths/min Mild recession Taking full feeds	Temperature >38.5°C Respiratory rate >70 breaths/min Moderate to severe recession Nasal flaring Cyanosis Intermittent apnoea Grunting respiration Not feeding Tachycardia* Capillary refill time ≥2 s
Older children	Temperature <38.5°C Respiratory rate <50 breaths/min Mild breathlessness No vomiting	Temperature >38.5°C Respiratory rate >50 breaths/min Severe difficulty in breathing Nasal flaring Cyanosis Grunting respiration Signs of dehydration Tachycardia* Capillary refill time ≥2 s

*Values to define tachycardia vary with age and with temperature.^{67/68}

APPENDIX 5: Database data collection form

RTI data entry

(New) FN

DOB

Gender

Housing

LBW

Exprem

Feeds

Nutrition

Immunization

TBexp

IPT

Previous TB

HIVstatus

Chronic illness

Chronic illness specify

Pre-admission antibiotic

Admitted in past 6 mo

Admit via RXH?

Current DOA RXH

Current DOA NSH

Current DOD

RR

Tachpnoeic

Sats

Flare

Recessions

Apnoea

Grunting

Poor feeding

Wheeze

Highest temp

Bronchiolitis likely?

CXR	<input type="text"/>	<input type="text"/>	<input type="text"/>
wcc done	<input type="text"/>	<input type="text"/>	<input type="text"/>
CRP done	<input type="text"/>	<input type="text"/>	<input type="text"/>
Bld culture done	<input type="text"/>	<input type="text"/>	<input type="text"/>
organism cultured	<input type="text"/>	<input type="text"/>	<input type="text"/>
Bld organism1	<input type="text"/>	<input type="text"/>	<input type="text"/>
Bld organism2	<input type="text"/>	<input type="text"/>	<input type="text"/>
NPA done	<input type="text"/>	<input type="text"/>	<input type="text"/>
NPA pos1	<input type="text"/>	<input type="text"/>	<input type="text"/>
NPA pos2	<input type="text"/>	<input type="text"/>	<input type="text"/>
I/S done	<input type="text"/>	<input type="text"/>	<input type="text"/>
I/Sputum1	<input type="text"/>	<input type="text"/>	<input type="text"/>
I/Sputum2	<input type="text"/>	<input type="text"/>	<input type="text"/>
GW done	<input type="text"/>	<input type="text"/>	<input type="text"/>
GW result1	<input type="text"/>	<input type="text"/>	<input type="text"/>
GW result2	<input type="text"/>	<input type="text"/>	<input type="text"/>
CMV VL	<input type="text"/>	<input type="text"/>	<input type="text"/>

Supplemental O2	<input type="text"/>	<input type="text"/>
Bronchodilator	<input type="text"/>	<input type="text"/>
Hypertonic saline	<input type="text"/>	<input type="text"/>

1Antibiotic 1	<input type="text"/>	<input type="text"/>
1Antibiotic 2	<input type="text"/>	<input type="text"/>
1Antibiotic 3	<input type="text"/>	<input type="text"/>
1Antibiotic 4	<input type="text"/>	<input type="text"/>
1Antibiotic 5	<input type="text"/>	<input type="text"/>
2Antibiotic 1	<input type="text"/>	<input type="text"/>
2Antibiotic 2	<input type="text"/>	<input type="text"/>
2Antibiotic 3	<input type="text"/>	<input type="text"/>
2Antibiotic 4	<input type="text"/>	<input type="text"/>
2Antibiotic 5	<input type="text"/>	<input type="text"/>

Complication	<input type="text"/>
Follow-up	<input type="text"/>

APPENDIX 6: Instructions to authors of chosen journal

SAJCH AUTHOR GUIDELINES

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, and will delay publication.

AUTHORSHIP

Named authors must consent to publication. Authorship should be based on substantial contribution to: (i) conception, design, analysis and interpretation of data; (ii) drafting or critical revision for important intellectual content; and (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org).

CONFLICT OF INTEREST

Authors must declare all sources of support for the research and any association with a product or subject that may constitute conflict of interest.

RESEARCH ETHICS COMMITTEE APPROVAL

Provide evidence of Research Ethics Committee approval of the research where relevant.

PROTECTION OF PATIENT'S RIGHTS TO PRIVACY

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to www.icmje.org.

ETHNIC CLASSIFICATION

References to ethnic classification must indicate the rationale for this.

MANUSCRIPTS

Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences. Original articles not exceeding 3 000 words, with up to 6 tables or illustrations, are usually observations or research of relevance to child health. References should preferably be limited to no more than 15.

Please provide a structured abstract not exceeding 250 words, with the following recommended headings: Background, Objectives, Methods, Results, and Conclusion.

Scientific letters/short reports, which include case reports, side effects of drugs and brief or negative research findings should preferably be 1500 words or less, with 1 table or illustration and no more than 6 references. Please provide an accompanying abstract not exceeding 150 words.

Editorials, Opinions, etc. should be about 1000 words and are welcome, but unless invited, will be subjected to the SAJCH peer review process. Review articles are rarely accepted unless invited. Letters to the editor, for publication, should be about 400 words with only one illustration or table, and must include a correspondence address.

Obituaries should be about 400 words and may be accompanied by a photograph.

MANUSCRIPT PREPARATION

Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - www.icmje.org.

Manuscripts must be provided in UK English. Qualification, affiliation and contact details of ALL authors must be provided in the manuscript and in the online submission process.

Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'. Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and <) should be followed by a space (e.g. '> 40 years of age'). The same applies to \pm and $^{\circ}$, i.e. '35 \pm 6' and '19 $^{\circ}$ C'. Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'

Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

General formatting

The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, with the exception of Tables).

ILLUSTRATIONS AND TABLES

If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder. Tables may be embedded in the manuscript file or provided as 'supplementary files'. They must be numbered in Arabic numerals (1,2,3...) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed

carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes or tabs), and accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: * ÅŒ¶ ¶ || then ** ÄÄŒEtc.

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Book references: Jeffcoate N. *Principles of Gynaecology*. 4th ed. London: Butterworth, 1975:96-101. Chapter/section in a book: Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. *Pathologic Physiology: Mechanisms of Disease*. Philadelphia: WB Saunders, 1974:457-472.

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