Clinical features and outcome of patients with severe lower respiratory tract infection admitted to a Paediatric Intensive Care Unit in the Western Cape, South Africa.

Master of Medicine in Paediatrics

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Declaration

I, Hayley Kathryn Hutton, declare that the dissertation reported is based on independent work performed by myself (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree to any other university. I declare that this work has not been reported or published prior to registration for the abovementioned degree.

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Abstract

Objective: Acute lower respiratory tract infection (ALRTI) remains an important cause of childhood morbidity and mortality in low and middle income countries (LMIC). This study aims to describe the clinical features of children admitted to a Pediatric Intensive Care Unit (PICU) with severe ALRTI and to investigate risk factors, clinical course and in-hospital outcome.

Design: Retrospective cohort study

Setting: Red Cross War Memorial Children's Hospital, Cape Town, South Africa

Patients: 265 children (0-12years) admitted to the PICU during 2012 with a primary diagnosis of ALRTI.

Intervention: None.

Measurements and main results: 265 patients [median (interquartile range, IQR) age 4 months (2-12months)] were admitted with ALRTI, 157(59.3%) were male. Co-morbid disease was present in 102(38.5%) including cardiac disease in 42(15.9%) or tuberculosis in 7(6.4%) . While only 27(10.2%) were HIV infected, 87(32.8%) children were HIV exposed.

The in-hospital mortality was 34(12.8%); 24(9.1%) died in PICU and a further 10 in the medical wards following discharge from PICU. The median duration of ICU and hospital stay was 4.0 days (2.0-8.0) and 12.5 days (7.9-28.0) respectively. Most [192 (72.5%)] children required invasive ventilatory support, while 42 (15.8%) patients required cardiac inotropic support.

Risk factors for mortality included severe malnutrition (Odds ratio (OR) 8.25; 95% CI 1.47-46.21); informal housing without access to piped water and/or electricity (OR11.87; CI 1.89-20.81); or need for inotropic support (OR 44.35; CI 8.20-239.92). HIV exposure or infection was associated with a significantly longer duration of hospital stay (p=0.002).

Conclusion: Severe ALRTI occurs predominantly in young infants and is associated with a high mortality. Several sociodemographic risk factors impact on the risk of severe disease and poorer outcome.

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Abbreviations

WHO	World Health Organisation
ALRTI	Acute Lower respiratory tract infections
PICU	Paediatric Intensive care unit
RCWMCH	The Red Cross War Memorial Children's Hospital
ART	Highly Active Antiretroviral therapy
IMCI	Integrated management of childhood illness
EPI	Expanded programme of Immunization
LMIC	Lower and Middle income countries
WAZ	Weight for age z-score
PCR	Polymerase Chain reaction
PMTCT	Prevention of mother to child transmission

PART A: LITERATURE REVIEW

Introduction

Pneumonia is a leading cause of death in children under the age of five years, placing a considerable burden on health and economic resources in Low and Middle income countries (LMIC).[1] The World Health Organisation (WHO) recognises that pneumonia is the major cause of severe or very severe acute lower respiratory tract infections (ALRTI) and is responsible for up to 18% of deaths in children under the age of five years[2,3,4]. Severe ALRTI carry a substantial risk of morbidity and mortality and places a large burden on the family, the health system and the scarce resources of countries. With the development of the Millennium Development Goals there has been renewed interest and vigour in tackling some of the major burdens of childhood illness in attempt to improve childhood mortality. A better understanding of the impact of severe ALRTI as well as an understanding of the particular risk factors, aetiology and outcomes may inform improvements in intervention programmes and management strategies. The objective in this descriptive review is to determine current understanding and depth of knowledge of severe ALRTI in terms of the extent of the burden of disease; an understanding of those factors that place children at risk and the clinical features that may be helpful in understanding the outcomes and survival rates of those children admitted to hospitals with severe ALRTI.

Methods: Search Strategy

My search strategy of the literature was carried out during the months of May/June 2013 and involved computer based searches using four major search engines including Pubmed, Medline, Cochrane databases and Google Scholar. Medical subject headings(MeSH) were used to search the databases. The population of interest was children under the age of 12. Search terms used included, “child OR infant OR neonate.” ALRTI were described using the MeSH, “pneumonia OR bronchopneumonia OR respiratory tract infections OR pneumonia, viral OR bronchiolitis OR Respiratory Syncytial Virus OR CMV OR tuberculosis, pulmonology.” These articles were limited to English articles published after 1990 for practical purposes and to ensure only recent studies were included. The focus of the review included research performed in LMIC and was restricted to severe ALRTI’s.

Review of the literature

Pneumonia is the major cause of severe or very severe ALRTI and the most important cause of mortality in the paediatric population especially in Sub Saharan Africa.[5] In South Africa and the Western Cape, data from the Childhood Problem Identification Program in 2009 showed that pneumonia is one of the leading causes of death in hospital in children under the age of 5 years (29% and 18% respectively.)[6] Severe and very severe pneumonia are defined according to the WHO standards.[7] (see Appendix A). Current estimates are that pneumonia causes 1.3 million deaths in children under 5 years of age annually.[3] WHO estimated 19.2 million cases of severe acute lower respiratory tract infection (ALRTI)[4] and 3 million cases of very severe ALRTI worldwide in 2010 with 62% treated in a hospital setting. The in-hospital case fatality rate is estimated by WHO to be between 2.3 and 6% depending on severity of disease.[4] A large proportion of children with ALRTI’s still do not have access to hospitals and therefore most deaths related to ALRTI’s occur in the communities (81% of all deaths associated with respiratory tract infection occur outside of the hospital).[4]

It is not well understood what proportion of children presenting with an ALRTI will require admission to a Paediatric Intensive Care Unit (PICU) and outcomes vary substantially in different regions. A recent study in China suggested that 7% of children with ALRTI needed intensive care with an average length of stay of 5 days; 21 % of children required mechanical ventilation. The case fatality rate was 5.8%.[8] A retrospective multicentre analysis in low and middle income countries (LMIC) conducted during the peak respiratory seasons did not report an admission rate to the PICU. However, 55% of children admitted to the PICU required invasive ventilation with a median duration of PICU stay of 10 days. The case fatality rate in these children was 13%.[9]

In South Africa and the Western Cape, data from the Childhood Problem Identification Program in 2009 showed that ALRTI including pneumonia is one of the leading causes of death in hospital in children under the age of 5 years (29% and 18% respectively.)[6] A study done in 1998 at Red Cross War Memorial Children's Hospital (RCWMCH) of HIV infected and uninfected children admitted to PICU with pneumonia reported a mortality rate of 29% and 14% respectively.[10] Importantly this study preceded the roll out of antiretroviral therapy for children, so none of the HIV-infected children were on highly active antiretroviral therapy (HAART). The case fatality rate for severe pneumonia in a PICU in Pretoria was reported to be 30% a decade ago.[11] More recent work done to investigate the outcome of severe viral ALRTI in the PICU at RCWMCH reported a case fatality rate of 11%.[12] The limited South African data suggests a much higher case fatality rate than those reported by the WHO[4] and highlights the need for a better understanding of the risk factors and aetiological agents involved that influence survival.

Aetiology of severe ALRTI

Defining the aetiology of ALRTI is challenging. Blood cultures have a notoriously low yield ranging from 3-20%, with higher rates reported for HIV-infected children.[13,14] Sputum samples have a far better yield (54%) for bacteria but it is difficult to distinguish colonizing organisms from those that may be pathogenic for ALRTI.[13,14] The advent of multiplex PCR testing for respiratory viruses, bacteria and other organisms has dramatically increased the yield of potential aetiological organisms from nasopharyngeal aspirates; however it is challenging to distinguish colonizing organisms from those causing ALRTI.[15] Respiratory viruses such as Respiratory Syncytial Virus(RSV), Rhinovirus, Influenza, Adenovirus and Human Metapneumovirus in the PICU may be associated with severe disease and high mortality rates in South Africa.[12] In 2002, a report of a hospital outbreak at RCWMCH of severe ALRTI caused by Adenovirus showed that 45% of those children who contracted the virus in hospital required admission to the PICU. 39% of those patients required ventilatory support with a mean duration of stay in the PICU of 6.5 days and a PICU mortality rate of 23%.[16] RSV and Human Metapneumovirus are associated with mortality rates of 15 and 18% respectively.[17] It is important however to note that between 40-68% of asymptomatic children will have a virus detected on an upper respiratory tract swab.[18]

Other organisms such as Cytomegalovirus, *Pneumocystis jiroveci, atypical bacteria* and *Mycobacterium tuberculosis*, may also be important in the aetiology of ALRTI in the South African setting.[19,20,21,22,23,24] Accumulating evidence suggests that severe ALRTI is usually due to polymicrobial infections including bacterial-viral, bacterial-mycobacterial, viral-viral thus making aetiological diagnosis even more challenging.[22,23,24,25]

Risk factors for severe ALRTI

Several factors can predispose children to ALRTI and to severe disease. Risk factors include age less than 1 year[8,26] (in South Africa, children less than 10 weeks of age are at greatest risk for respiratory tract infection.[11]); prematurity (gestational age of 32-36 week) and low birth weight of <2.5kg[27,28,29]; severe or moderate malnutrition according to WHO classification [30], micronutrient deficiency and comorbid disease (especially congenital cardiac disease[31] and immunosuppressive disease especially in the form of HIV disease[17]). A distinct seasonal variation is well described internationally.[26,32] In South Africa common respiratory viruses show distinct peaks in early winter and early spring.[12] Overcrowding, parental smoking and exposure to indoor air pollution places infants and children at higher risk of pneumonia.[26,33,34,35] In the South African context, HIV-infection or exposure may be one of the most important risk factors for severe ALRTI. Nosocomial acquired ALRTI are associated with increased severity of disease and increased mortality.[36,37]

A protective factor that was identified in many of the studies worldwide is exclusive breastfeeding for 6 months. The protection wanes as the infant gets older but in the first year of life exclusive breastfeeding can halve the risk of ALRTI.[38]

In the South African context, management of ALRTI is made more complex by a high burden of comorbidity. The incidence of malnutrition and TB, at 34% and 7% respectively[6] has a significant negative impact on the health of our children. More importantly however is the high prevalence of HIV disease and its associated complications. The high burden of HIV disease in the paediatric population severely impacts not only the outcomes of ALRTI but the incidence, aetiology, the clinical presentation, the severity and the efficacy of management of those infections.[39]

HIV-infected children have an increased risk of severe ALRTI increased incidence of opportunistic respiratory infections, and a worse outcome than HIV uninfected patients.[39] Opportunistic infections are common in children with HIV infections with diseases of the respiratory tract being the most common site of infections.[40] Children who are HIV infected are at higher risk of contracting community acquired ALRTI often with a more severe clinical course. The presentation of the ALRTI is more severe[41] or shows atypical radiological features[42] with decreased response to empiric treatment[43] The aetiological agents in HIV infected patients include a wider range of pathogens and mixed infections[44] which could contribute to the poor response to empiric treatment. Atypical and Gram negative organisms, *Pneumocystis jirovecii* and Cytomegalovirus are being recognised as more important opportunistic respiratory pathogens in LMIC countries, in keeping with international data.[20,40,43] However, use of HAART especially when initiated early in the course of HIV infection and of CTX prophylaxis has dramatically reduced the risk of pneumonia and severe pneumonia.[45] Mycobacterium tuberculosis remains an important cause of ALRTI in children in areas of high TB incidence. [24,46]

An initial study to investigate the aetiology, associated features and outcomes of pneumonia in HIV infected and uninfected children at RCWMCH highlighted the importance of *Pneumocystis jirovecii* as a pathogen.[10] Over half of the children enrolled in this were HIV infected (60,4%; 95% confidence interval 54,2-66,3%); ALRTI was the presenting clinical feature of HIV in approximately a quarter of children. The outcomes of HIV infected children were notably worse with a mortality rate of 22,5% in comparison to 8,1% of their HIV uninfected counterparts. *Pneumocystis jirovecii* made a considerable contribution to this difference in mortality and was the only significant risk factor for mortality in HIV infected children.

This study encouraged policy development with regards to *Pneumocystis jirovecii* prophylaxis, diagnostics in children with ALRTI and more aggressive treatment and preventative strategies for children suspected of being HIV infected. It also brought to question the ethical challenges of policy guidelines around the admission of HIV infected children to the PICU.

In the era of successful mother to child prevention programs, a uniquely vulnerable group, the HIV-exposed uninfected child is emerging. In the Western cape 21% of women presenting to antenatal clinics are HIV infected with mother to child transmission rates currently recorded at 3.9%, therefore there are few HIV-infected children but a considerable number of HIV-exposed uninfected children.[47] Increasing evidence suggest that HIV-exposed uninfected children may have some immune compromise with a higher risk for ALRTI and opportunistic infections than unexposed children.

Changes in the immune system of HIV-exposed uninfected infants are beginning to be described. A review article reported that in utero exposure to the HIV virus results in altered cellular immune responses.[48] The underlying mechanisms of the altered immune responses remains unclear. In Brazil, a group of HIV-exposed uninfected infants followed up for 6 months showed an overall increased incidence of infections with 1.8 infections per infant. The most common infections were skin/mucous membrane and respiratory tract infections with respiratory tract infections necessitating hospital admission in 40.7% of cases.[49] Most interestingly of the 547 HIV-exposed uninfected infants who were followed up for a period of 6 months, 18,8% experienced ALRTI (most commonly bronchiolitis).[50] Approximately half of these infants required hospital admission. They concluded that infants less than 6 months of age who were HIV exposed and whose mothers had a declining CD4 count, were at increased risk of ALRTI and severe disease.

Therefore, the HIV-exposed uninfected infant appears to be at increased risk of infectious diseases with higher associated morbidity and mortality. A study in the surgical wards at RCWMCH has shown HIV-exposed uninfected infants to be at higher risks of infections, longer hospital stays and more complications than their HIV unexposed counterparts during treatment for surgical conditions.[51] In Johannesburg, the main indicators of infant morbidity and mortality are noted to be paediatric HIV infection and maternal viraemia.[52] A higher rate of co infections with TB, herpes zoster, CMV and syphilis was seen in HIV exposed infants regardless of their HIV status/seroconversion status.[53] Case reports out of Tygerberg Hospital in Cape Town highlight the risks and vulnerability of this unique patient group with an increased infectious morbidity rate which may be attributable to a combination of factors.[54]

In the past decade, several interventions have been introduced in South Africa with potential impact on HIV-associated LRTI in children including:

1. Adoption of the Integrated Management of Childhood illness (IMCI) with adaptation to include management of HIV-infected children, aimed to target the predominant causes of childhood mortality.[55] The introduction of the IMCI strategy in many primary health care clinics in the Western Cape towards the end of the twentieth century has shown a dramatic improvement in the detection of severe disease in children as well as the early and appropriate management of common childhood illnesses.[56]

2. The South African Expanded Program of Immunization (EPI) has seen the addition of new vaccines with impact on pneumonia, namely *Haemophilus Influenzae* type B vaccine in 1999 and the 13 valent Conjugated Pneumococcal vaccine in 2012.[57,58]

3. In 2010, South Africa adopted the World Health Organisation Prevention of Mother to Child (PMTCT) guidelines. Current PMTCT coverage is reported as 91.8% either in the form of full HAART or antiretroviral prophylaxis to both mother and infant by the Department of Health. The transmission rate of HIV from mother to child in South Africa has subsequently dropped significantly and is currently recorded at 3.5%(1.4%-5.9%).[47]

4. Early initiation of highly active antiretroviral (HAART)

It is only in recent years that South Africa has introduced HAART as part of primary care. According to current national guidelines, children who are HIV positive are prioritised to initiate HAART.[59] With the marked recovery of immunological function, there is a decreased trend in the incidence of opportunistic infections.[60]

5. Chemoprophylaxis.

Pneumocystis jirovecii has been recognised as an important respiratory pathogen in the developed world but has only recently been recognised as important opportunistic infection in the South African setting. Co-trimoxazole prophylaxis should therefore be made available to all HIV-infected children as per national SA guidelines.[61]

Isoniazid prophylaxis forms part of the national Tuberculosis guidelines. INH prophylaxis is indicated for children who are exposed to a household contact with TB or for HIV-infected children older than 1 year irrespective of exposure.[62,63]

Despite the simplicity and cost effectiveness of co-trimoxazole and isoniazid prophylaxis, these strategies for preventing pneumonia remain underutilised.[64]

6. Aggressive broad spectrum antibiotic treatment.

Recent work in RCWMCH have demonstrated a 21% and 28% prevalence of *Pneumocystis jirovecii* and Cytomegalovirus pneumonia respectively in HIV infected children with severe pneumonia.[61,65] This knowledge has encouraged the use of broad spectrum empiric antibiotic and antiviral cover incorporating high dose Trimethoprim-sulphamethoxazole and Ganciclovir.

7. Improved access for HIV positive patients to ICU.

In the setting of limited resources and restricted access to health care, HIV infection places an increased demand on intensive care services in the developing world and in South Africa particularly. Previous research in this area showed that HIV children admitted to PICU had worse outcomes than their HIV negative counterparts.[66,67] Admitting HIV positive patients into the PICU therefore raised many ethical issues especially around the principle of utilitarianism. A study done in the PICU at RCWMCH in 2003-2004 showed an improvement in short and medium term outcomes in severely ill HIV infected patients admitted to the PICU with access to HAART. The PICU and hospital mortality rate in this study is shown to be a 25% and 49%

respectively. Those children established on HAART remained well after a median follow up of 350 days.[68] This study highlighted the need for further research into more aggressive management of HIV infected children with earlier initiation of HAART. With earlier access to HAART and more aggressive management of pneumonia, this group of children are gaining better access to the PICU.

Conclusions

The overall mortality of severe pneumonia and ALRTI of children admitted to intensive care units or hospital in LMIC remains high in comparison to WHO standards. The scarcity of resources and the limited availability of intensive care units in LMIC make it even more important to understand the factors that place children at risk of severe disease. A better understanding of these factors may assist in mobilising primary health care strategies targeted specifically at health promotion and disease prevention in order to improve case fatality and overall childhood mortality.

From the review of current literature, we can conclude that there are certain factors that distinctly place children at higher risk for acquiring ALRTI and predispose to increased disease severity and worsened outcomes. Modifiable factors that increase the risk of severe ALRTI and poorer outcomes include malnutrition, low birth weight and prematurity, poor socioeconomic status with overcrowding and poverty, exposure to indoor air pollution related to unprocessed solid fuel use and tobacco smoke, comorbid disease and HIV infection. Of note there is a growing awareness and understanding that HIV exposure is as much of a risk as HIV infection and disease placing HIV exposed and negative infants at increased risk of severe disease and poorer outcomes.

Certain factors such as age and seasonal variation are difficult to modify but perhaps with the knowledge that younger children are at risk at certain times of the year it may be prudent to increase our surveillance of this age group and develop strategies to offer seasonal immunisations to at risk groups of children.

Although a lot of the above mentioned risk factors reflect an overall need to address greater health issues and span multiple sectors, there are definitely factors that can be addressed at relatively low cost. It is important to highlight that exclusive breastfeeding for a period of 6 months is the only protective factor in reducing the incidence and improving the outcomes of those admitted with ALRTI revealed in this review. Breastfeeding needs to be encouraged and promoted at all levels of health care to have a greater protective impact on the outcomes of severe ALRTI.

If we can reduce the incidence of ALRTI and the severity of disease on presentation, we will be able to avoid admission to the PICU and the added morbidity and mortality risks. Unfortunately, despite global advances in the management of HIV and pneumonia and despite renewed international commitment to decreasing childhood mortality as evidenced by the Millennium Development Goals of 2015, ALRTI remain a significant cause of childhood morbidity and mortality in LMIC.

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PART B: STUDY PROTOCOL

Definitions

"patient" is defined as any child less than the age of 12 years of age presenting to RCWMCH in need of medical care.

"acute lower respiratory tract infection" includes clinical diagnoses in keeping with pneumonia; bronchopneumonia; bronchitis; bronchiolitis; or respiratory infection. It is defined according to World Health Organisation as an infection that affects the lungs resulting in the symptoms of cough, difficulty breathing and tachypnoea.

"outcomes" will be defined as: PICU mortality; hospital mortality; duration of invasive ventilatory support in days; length of ICU stay in days; length of hospital stay in days.

"length of stay" for the purpose of this study a day is defined as a 24hour period. Day one is considered to be the first 24 hours or any part thereof. Thereafter each day will be calculated as multiples of 24.

"ventilatory support" will be considered to be non-invasive (nasal cannula, high flow nasal cannula oxygen or non-invasive CPAP) or invasive (positive pressure ventilation or high frequency oscillatory ventilation.)

"cardiac support" will be considered the use of or the administration of inotropic agents.

"community acquired" is defined as a positive culture from a sample taken within 48hrs of hospital admission.

"nosocomial" is defined as a suspected new sepsis or culture positive sample obtained 48hrs after hospital admission.

"nutritional status" is determined by the WHO classification of malnutrition using Z score cut-offs of <-2 and <-3 for moderate and severe malnutrition respectively. In this study, we will look at markers for wasting, stunting and underweight. We will rely on clinical and dietetics assessment on nutritional status for final classification.

“WAZ” the weight for age Z-score of between -2 and -3 indicates a patient who is moderately underweight. A weight for age Z-score <-3 indicates a patient who is severely underweight.

“sociodemographic status” is determined on the basis of geographical localisation, income bracket and home language.

“income bracket” is determined by the monthly household income. It is classified according to the provincial government hospital biling department.

Study Aim

The aim of this study is to describe the clinical features and outcome of patients admitted to a Paediatric Intensive Care Unit (PICU) in a tertiary hospital in Cape Town with severe ALRTI and to identify risk factors associated with outcome. The study will include investigation of HIV infection or exposure as a risk factor for poor outcome.

Study Objectives

Primary Objective

1. To describe the clinical characteristics, course and outcome of patients admitted to a PICU with severe lower respiratory tract disease.
2. To identify factors associated with worse outcomes.

Secondary objectives

1. To establish the impact of specific risk factors on outcomes including:
    - HIV infection or exposure
    - Nutritional status
    - Age

- Season of admission
- Prematurity or history of Low birth weight
- Comorbidities (Congenital cardiac lesions, genetic syndromes and non-HIV immunosuppression)
- Immunisation status
- Breastfeeding
- Recent admission to hospital
- Socioeconomic status
- Exposure to indoor air pollution

2 To describe the aetiology of severe ALRTI in children admitted to a PICU.

3 To identify key areas for further research and make recommendations.

Methodology

Study Design

This is a retrospective descriptive study of the medical records of patients who were admitted to the PICU of the Red Cross War Memorial Children's Hospital from 1st January 2012 - 31st December 2012 inclusive with a diagnosis of a ALRTI.
The estimated sample size is 350 over the study period.

Study setting

This study will take place at the RCWMCH in Cape Town, South Africa. This is a tertiary, referral hospital with 300 beds which offers comprehensive specialist and sub-specialist care to the paediatric population in the Western Cape. The study will investigate admission to the Paediatric Intensive Care Unit, a 20 bedded multidisciplinary unit with an annual of 7300 PICU bed nights. The unit had 1259 admission during 2012 with an average length of stay for medical admissions of 4 days. The PICU mortality rate for 2012 was 6.5%. (Personal communication Prof Andrew Argent)

Study population

Children admitted with a confirmed diagnosis of ALRTI from 1st January 2012 - 31 December 2012 will be included in the study.

The PICU database will be screened for any patients with a primary or secondary diagnosis of ALRTI. Each folder will be assessed and data extracted from the patients meeting inclusion criteria.

Inclusion criteria

1. Children will be included in the study if they were admitted to the PICU with a diagnosis of “pneumonia” or “lower respiratory tract infection” or “bronchopneumonia” or “bronchiolitis” or “pulmonary tuberculosis” during the time period from the 1st January 2012 - 31st December 2012.
2. Age between 0-12years

Exclusion criteria

1. A patient who developed a nosocomial ALRTI while admitted in the PICU.
2. Medical records of patient not obtainable from the RCWMCH records department.

Research procedures and data collection

The PICU database (Ethics approval number 139/2011) will be used as the primary source of information. The PICU database will be searched for patients using the search terms “pneumonia” or “lower respiratory tract infection” or “bronchopneumonia” or “pulmonary tuberculosis” or “bronchiolitis” in either the “primary diagnosis” or “secondary diagnosis” category. Any child who is admitted to the PICU with these diagnoses from the 1st January 2012 - 31st December 2012 will be screened for enrolment on the study. A list of patients meeting the study criteria will be generated. The folders of the list of patients will be requested from medical records to verify information. The baseline patient characteristics and admission details will be obtained from the PICU database. Information regarding the aetiology, clinical severity and outcome of the pneumonia will be obtained from the medical folders. If a full set of data is not obtainable from the medical records, results of investigations performed while in the PICU will be sought from the National Health Laboratory Service (NHLS). Chest radiographs performed on admission to the PICU will be reviewed on the electronic Paxim system. The X-rays will be reread and analysed by two readers with a third reader for discrepant results using the WHO standardised definitions of interpretation of chest radiographs for the diagnosis of pneumonia.

Patient information from the PICU database, the medical records and NHLS will be carefully reviewed in a confidential manner by the primary investigator. Relevant data will be extracted from the medical records.

The data will be collected by the primary investigator and abstracted to an electronic data capture sheet (See Appendix C). Once collected, the data will be entered into an Epidata spread sheet. Restricted access by means of an account username and password for the database held by the primary investigator will ensure patient privacy at all times. Identification of patients will be by means of a unique ICU admission number to further ensure patient confidentiality.

Data Analysis

The data once captured on an Epidata Database will be analysed descriptively using appropriate statistical methods using the Stata program. Continuous variables will be assessed for normality by drawing histograms and formally tested using the Shapiro-Wilks test and the appropriate parametric and nonparametric statistics applied. Proportions will be described with a 95% confidence interval. Associations between categorical variables will be assessed using the Chi-Square test or Fisher's exact test if the expected frequency in any cell is less than five. Logistical regression analysis will be performed on risk factors identified by the current literature review and defined by the list of risk factors in the objective above. Any factor in the univariate analysis which show a trend towards statistical importance with a $p<0.26$ as well as any other factor chosen by virtue of clinical reasoning will be included in the multivariate logistic regression analysis.

The assistance of a statistician will be sought to ensure accurate results.

Time frame

Following ethics and departmental approval, the study will commence and will run over a 6-month period allowing for complete data capturing and analysis.

Description of risks and benefits

<u>Risks:</u>

There are no risks to the patients or attending clinicians.

The study will not incur any additional cost to neither the patient, patient care nor the PICU.

<u>Benefits:</u>

The potential benefits of the study are a better awareness and understanding of the outcomes of patients admitted to the PICU with ALRTI and therefore the opportunity to explore strategies for improved patient care.

Dissemination of Data

A written report of all data and findings will be made available to the Departmental Research Committee and the clinical staff of the PICU at RCWMCH. Findings will be presented to the clinical staff of RCWMCH at paediatric academic meetings and at national congresses.
I will endeavour to publish the results in a major international journal.
An abstract will be submitted for conferences.

Ethical considerations

This is a low risk study.

Approval for the study will be obtained by the Departmental Research Committee, School of Child and Adolescent Health as well as the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town.
As the study is a retrospective review of medical records informed consent will not be obtained.
No interventions are planned and no risks are foreseen.

Patient confidentiality will be maintained at all times by means of a unique ICU admission number use as identification and all data being kept in a restricted access setting. All patient identifying data including date of birth and physical address have been excluded from the study. The database will be destroyed after a period of 10 years following completion of the study.

There are no known conflicts of interest.

The research will adhere to the requirements of the Declaration of Helsinki (2008).

CHAPTER 3: PUBLICATION READY MANUSCRIPT

Clinical features and outcome of patients with severe lower respiratory tract infection admitted to a Pediatric Intensive Care Unit in the Western Cape, South Africa.

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*Keywords R*espiratory tract infection, intensive care unit, pediatric, survival, risk factor

Word count: 3722 (abstract=310)

Abstract

Objective: Acute lower respiratory tract infection (ALRTI) remains an important cause of childhood morbidity and mortality in low and middle income countries (LMIC). This study aims to describe the clinical features of children admitted to a Pediatric Intensive Care Unit (PICU) with severe ALRTI and to investigate risk factors, clinical course and in-hospital outcome.

Design: Retrospective cohort study

Setting: Red Cross War Memorial Children's Hospital, Cape Town, South Africa

Patients: 265 children (0-12years) admitted to the PICU during 2012 with a primary diagnosis of ALRTI.

Intervention: None.

Measurements and main results: 265 patients [median (interquartile range, IQR) age 4 months (2-12months)] were admitted with ALRTI, 157(59.3%) were male. Co-morbid disease was present in 102(38.5%) including cardiac disease in 42(15.9%) or tuberculosis in 7(6.4%) . While only 27(10.2%) were HIV infected, 87(32.8%) children were HIV exposed.

The in-hospital mortality was 34(12.8%); 24(9.1%) died in PICU and a further 10 in the medical wards following discharge from PICU. The median duration of ICU and hospital stay was 4.0 days (2.0-8.0) and 12.5 days (7.9-28.0) respectively. Most [192 (72.5%)] children required invasive ventilatory support, while 42 (15.8%) patients required cardiac inotropic support.

Risk factors for mortality included severe malnutrition (Odds ratio (OR) 8.25; 95% CI 1.47-46.21); informal housing without access to piped water and/or electricity (OR11.87; CI 1.89-20.81); or need for inotropic support (OR 44.35; CI 8.20-239.92). HIV exposure or infection was associated with a significantly longer duration of hospital stay (p=0.002).

Conclusion: Severe ALRTI occurs predominantly in young infants and is associated with a high mortality. Several sociodemographic risk factors impact on the risk of severe disease and poorer outcome.

Introduction

Acute lower respiratory tract infection (ALRTI), primarily pneumonia is a leading cause of death in children under the age of five years, placing a considerable burden on health and economic resources particularly in low and middle income countries (LMICs)(1). The World Health Organisation (WHO) recognises that pneumonia alone is responsible for up to 15% of deaths in children under the age of five years(2). In Sub Saharan Africa, pneumonia is the most important cause of under 5-year mortality outside the neonatal period(3). In South Africa and the Western Cape, pneumonia accounts for 9.1-15.2% and 23% of all under 5 year deaths respectively(4,5). Data from the Medical Research Council Burden of disease report 2015 found that pneumonia remains one of the leading causes of death in hospital in South African children under 5 years(4).

In South Africa there is very little data on outcome of severe ALRTI. WHO estimated 19.2 million cases of severe ALRTI in 2010 with the majority of those (62%) being treated in a hospital setting(6). The in-hospital case fatality rate estimated by WHO is between 2.3 and 6% depending on severity of disease(6). A study done in 1998 at Red Cross War Memorial Children's Hospital (RCWMCH) of HIV infected and uninfected children admitted to PICU with ALRTI reported a mortality rate of 29% and 14% respectively(7). Importantly this study preceded the roll out of highly active antiretroviral therapy (ART) for children, thus giving an explanation for the marked discrepancy in survival. The limited South African data suggests a much higher case fatality rate than that reported by the WHO(6) and highlights the need for further research into the causes, risk factors and outcome of severe ALRTI in this setting.

Several factors may predispose children to ALRTI and to severe disease. Reported risk factors include age less than 1 year(8,9) in South Africa, children less than 10 weeks of age are at greatest risk for respiratory tract infection(10); prematurity (gestational age < 36 weeks) or low birth weight of <2.5kg(11,12,13); severe or moderate malnutrition according to WHO classification(14), micronutrient deficiency or comorbid disease (especially congenital cardiac disease(15) and immunosuppressive disease especially HIV infection(16)). Increasing evidence suggests that HIV-exposed uninfected children have a higher risk for ALRTI or opportunistic infections than unexposed children(17,18). A protective factor that was identified in many studies is exclusive breastfeeding for 6 months(19,20,21); protection wanes with age but exclusive breastfeeding may halve the risk of ALRTI in infancy.

This study aims to describe the clinical characteristics and outcomes of children with severe ALRTI admitted to a Paediatric Intensive Care Unit (PICU) in a tertiary hospital in South Africa and to identify risk factors associated with in-hospital mortality.

Methods

Study Design and setting

This was a retrospective, descriptive cohort study of patients admitted to the PICU at Red Cross War Memorial Children's Hospital (RCWMCH) with a diagnosis of ALRTI.

RCWMCH in Cape Town is a tertiary, referral hospital with 300 beds, which offers comprehensive specialist and sub-specialist care to the paediatric population in the Western Cape. The PICU is a 20-bedded multidisciplinary unit with 7300 annual bed nights available.

Study Population

Children up to 12 years who were admitted with a confirmed diagnosis of ALRTI from January 2012 - December 2012 inclusive were included in the study.

Children who developed an ALRTI while already admitted in the PICU or those for which the medical records were not obtainable were excluded from the study.

Data source

The PICU database (Ethics approval 139/2011) was used to identify patients with a primary or secondary diagnosis of lower respiratory tract disease using medical subheadings “pneumonia” or “lower respiratory tract infection” or “bronchopneumonia” or “bronchiolitis” or “pulmonary tuberculosis”.

Details of the PICU stay were obtained from the database. The medical records and National Health Laboratory service records were used to gain further clinical information regarding risk factors and results of investigations performed during the admission.

All data were collected on electronic data capture forms and held by the primary investigator using password protected computer software namely EpiData Entry version 2.0 (The EpiData Association, Denmark, Europe) and Tap Forms organiser version 4.0.5 (Tap Zapp Software Inc, Calgary, Canada). A database was generated in Microsoft Excel from the collective data preserving patient confidentiality by means of a unique ICU admission number.

Study variables

For the purpose of this study, the following terms needed to be defined:

“Acute lower respiratory tract infection” includes clinical diagnoses in keeping with pneumonia; bronchopneumonia; bronchitis; bronchiolitis; or respiratory infection. It is defined according to World Health Organisation as an infection that affects the lungs resulting in the symptoms of cough, difficulty breathing and tachypnea.

“Outcomes” will be defined as PICU mortality and in-hospital mortality.

“Length of stay” for the purpose of this study a day is defined as a 24hour period. Day one is considered to be the first 24 hours or any part thereof. Thereafter each day will be calculated as multiples of 24.

"Ventilatory support" will be considered to be non-invasive (nasal cannula, high flow nasal cannula oxygen or non-invasive CPAP) or invasive (positive pressure ventilation or high frequency oscillatory ventilation.)

"Cardiac support" will be considered the use of or the administration of inotropic agents.

"Nosocomial" is defined as a suspected new sepsis or culture positive sample obtained 48hrs after hospital admission.

"Nutritional status" is determined by the WHO classification of malnutrition using Z score cut-offs of <-2 and <-3 for moderate and severe malnutrition respectively (looking at markers for wasting, stunting and underweight.) The specialist PICU dietician's clinical assessment was used as the final classification.

"Prematurity" was defined as birth prior to 37 completed weeks of gestation.

"Birthweight" was categorised as low birthweight <2.5kg; very low birth weight 1.00-1.49kg and extremely low birthweight <1.0kgs. Fenton's correction scale was used to adjust for gestational age in ex premature patients when assessing birthweight and current weight in terms of z-scores(23).

"**Socioeconomic status"** is determined on the basis of type of housing with/without access to piped water and electricity and income bracket classified according to the provincial government hospital billing department.

"Feeding choice" Choices recorded were based on maternal self-report (exclusive breast, exclusive formula or mixed feeding) up to and including admission to hospital; mixed feeding was considered any child who had a mixture of breast and formula milk or any other oral substance used for nutrition purposes prior to admission.

"HIV status" was confirmed using results accessed via the National Health Laboratory Services (NHLS).

"HIV exposure" was recorded from the notes and not verified via the NHLS due to ethical concerns obtaining parent's health information retrospectively.

"Prevention of mother to child transmission (PMTCT)" data was defined according to current applicable Department of Health guidelines, which have subsequently been updated. For the purpose of this study, antenatal PMTCT included mothers who received antiretroviral therapy (either Zidovudine or combination drug therapy) prior to the start of labour; perinatal PMTCT included Zidovudine and Nevirapine therapy given to the mother during labour as well as a dose of Nevirapine administered to the infant; Post-natal PMTCT included 6 weeks of Nevirapine to the infant (or longer if breastfeeding.)

"Paediatric index of mortality score (PIM2)" this score is a composite of clinical factors, biochemical markers, ventilatory requirements as well as underlying risk factors at the time of PICU admission. It has been well validated for use in LMIC and is a useful predictor of mortality(24,25).

Statistical analysis

The data was analysed using STATA 13 statistical software (STATA Corporation, College Station, TX, USA).

Exploratory data analysis of categorical and continuous variables included frequency tables and histograms to determine distribution. Simple descriptive statistics were used to characterise the study population. Normally distributed continuous data were summarised by mean and standard deviations (SD); non-normally distributed continuous data by median and interquartile range (IQR). Categorical data were summarised as number and proportion. Statistical tests included Chi-square test (adjusted if number less than 5) and Kruskal-Wallis comparison of medians and Student's t-test for comparison of means. Risk factors that tended towards statistical significance ($p<0.26$) or those specifically chosen based on clinical reasoning were included in a multivariate cox regression analysis, which included both forward and backward regression. Factors considered to be competing risk factors for mortality were excluded namely duration of PICU stay and invasive ventilatory requirements. HIV infection and breastfeeding were treated as potential confounding variables. Statistical tests were two sided at α = 0.05.

Ethical considerations

Ethical approval for the research was granted by the University of Cape Town Faculty of Health Science Human Research Ethics Committee. (HREC 435/2013)

Results

Figure 1: Summary of patients included in study

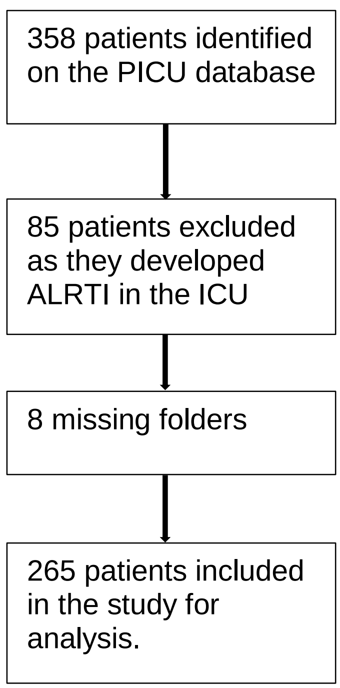

Table 1. Baseline characteristics of children admitted with a diagnosis of ALRTI, by hospital outcome (survived/died)

Characteristic	All N (%)	Survived N (%)	Died N (%)	OR[1] (95% CI[2])	P value
Gender N (%) male	157 (59.3%)	133 (57.6%)	24 (70.6%)	1.76 (0.80-3.86)	0.153
Age in months Median (IQR)	4 (2 – 12)	4 (2 – 12)	6.5 (2.5 – 12)	1.00 (0.98-1.01)	1.00
Age category					
< 10 weeks	84 (31.7%)	75 (89.3%)	9 (10.7%)	1.31 (0.58-2.96)	0.505
< 6 months	155 (58.5%)	139 (89.7%)	16 (10.3%)	0.59 (0.29-1.21)	0.150
Birthweight WAZ[3] Median (IQR)	-0.8 (-1.4; 0)	-0.8 (-1.4; 0.1)	-0.9 (-1.5-0.5)	0.88 (0.63; 1.23)	0.458
Preterm (< 37 weeks)	60 (22.6%)	53 (22.9%)	7 (20.6%)	0.87 (0.36-2.11)	0.759
HIV status N (%)					
Exposed; not infected	60 (22.6%)	52 (22.5%)	8 (23.5%)	1.04 (0.44-2.45)	0.935
Exposed; Infected	27 (10.2%)	24 (10.4%)	3 (8.8%)	0.84 (0.23-3.02)	0.792
Unexposed	178 (67.2%)	155 (67.1%)	23 (67.7%)	reference	
PMTCT[4] N (%)					
Antenatal received	44 (50.6%)	36 (47.4%)	8 (72.7%)	1.14 (0.90-1.43)	0.281
Perinatal received	50 (57.5%)	41 (54.0%)	9 (81.8%)	1.14 (0.90-1.44)	0.285
Postnatal - correct	54 (62.1%)	45 (59.2%)	9 (81.8%)	0.96 (0.73-1.27)	0.781
Postnatal - incorrect dose	18 (20.7%)	17 (22.4%)	1 (9.1%)		
Infant feeding N (%)					
Exclusive breast fed	121 (46.2%)	99 (43.0%)	22 (68.8%)	reference	
Exclusive formula	61 (23.3%)	57 (24.8)	4 (12.5%)	0.31 (0.10-0.96)	0.043
Mixed feeding	80 (30.5%)	74 (32.2%)	6 (18.8%)	0.36 (0.14-0.94)	0.038
Nutritional status					
None/mild	202 (76.5%)	185 (80.1%)	17 (51.5%)	reference	
Moderate	27 (10.2%)	22 (9.5%)	5 (15.2%)	2.47 (0.83-7.36)	0.104
Severe	35 (13.3%)	35 (13.3%)	11 (33.1%)	4.99(2.90-11.90)	<0.001

[1] Odds ratio
[2] Confidence interval
[3] Adjusted for gestation using Fenton's calculation
[4] HIV exposed N=87

Income bracket < R4000 per month >/= R4000 per month	 245 (92.5%) 20 (7.5%)	 213 (92.2%) 18 (7.8%)	 32 (94.1%) 2 (5.9%)	 1.35 (0.30-6.10 reference	 0.695
Housing Formal Informal	 136 (52.3%) 124 (47.7%)	 126 (55.5%) 101 (30.3%)	 10 (44.5%) 23 (69.7%)	 reference 2.87 (1.30-6.30)	 0.009
Tobacco Smoke exposure (self-report)	59 (25.1%)	56 (26.8%)	3 (11.5%)	0.36 (0.10-1.23)	0.103
TB disease[5]	17 (6.4%)	14 (6.1%)	3 (8.8%)	1.50 (0.41-5.52)	0.542
Hospital acquired infection (suspected)	72 (27.2%)	60 (25.9%)	12 (35.3%)	1.56 (0.73-3.33)	0.257
No comorbid disease Cardiac diagnosis Other	164 (61.9%) 42 (15.9%) 59 (22.3%)	148 (64.1%) 32 (13.9%) 51 (22.1%)	16 (47.1%) 10 (29.4%) 8 (23.5%)	Reference 2.89 (1.20-6.95) 1.45 (0.59-3.59)	 0.018 0.421
Bacterial isolate	27 (13.1)	19 (10.5)	8 (32.0)	4.01 (1.53-10.54)	0.005
Inotropic support	42 (15.7%)	18 (7.8%)	23(67.7%)	24.7 (10.4-58.7)	<0.001
Length of time to start antibiotics (hours)	1 (1-3)	2 (1-3)	1 (1-2)	1.29 (0.98-1.70)	0.068
At least one dose of prevenar administered	180 (67.9%)	155 (67.1%)	25 (73.5%)	1.36 (0.61-3.06)	0.455
Duration in PICU (days)	4.0 (2.0-8.0)	4 (2.0-7.0)	5.0 (2.0-12)	1.00 (1.00 – 1.01)	0.053
Duration in hospital (days)	12.5 (7.9-28.0)	12.9 (8.1-27.0)	8.35 (2-48)	1.01 (1.00 – 1.02)	0.008
Invasive ventilation N (%)	155 (58.4%)	126 (81.3%)	29 (18.7%)	5.75 (2.24-14.98)	<0.001

[5] Includes previous and current infection

Outcomes

Of 265 patients admitted to PICU, 34(12.8%) died in-hospital; 24(9.1%) died in PICU and a further 10 in the medical wards following discharge from PICU. The median duration of hospital stay was 12.5 days (7.9-28.0). The median duration of ICU stay was 4.0 days (2.0-8.0). Ventilatory support was required by 250(94.3%) of patients with a mean duration of all forms of ventilatory support of 3.5 days (1.5-6.9). Many children required more than one form of respiratory support during their PICU stay as they recovered or deteriorated. Overall, invasive ventilatory support (Conventional mechanical ventilation or High frequency oscillatory ventilation) was necessary in 192(72.5%) patients. Inotropic support for haemodynamic instability or cardiac failure was necessary in 42(15.7%) of patients.

The 265 patients used a total of 1544 PICU days which is approximately 21% of the annual available bed days. The mean PIM2 score was 0.134 (SD 0.192) indicating a risk of mortality on admission of 13.4%. The PIM2 score can be used to calculate the Standardised mortality rate (SMR) by dividing the actual mortality by the mean predicted mortality score. The SMR can then be a useful marker of the quality of care or performance in the unit. In this study the calculated SMR in the PICU and overall in-hospital following PICU discharge was 0.70 and 0.99 respectively.

When evaluating for causes of mortality in the PICU the main causes were multi-organ failure (16(47.1%)), respiratory failure (4(11.8%)) or those associated with complex congenital cardiac disease who died from cardiac failure (3(8.8%)). Of the deaths that occurred in the ward following discharge from the PICU, only 1 out of the 10 was unexpected and related to a cardiac arrest caused by electrolyte disturbances. The other patients were discharged from the

PICU for palliation due to either severe hypoxic brain damage or significant lung disease occurring during the PICU stay.

Risk factors for Death

On univariate analysis the following factors showed a statistically significant effect on outcome: exclusive formula feeding (OR 0.31 95% CI 0.10-0.96); mixed feeding (OR 0.36 95% CI 0.14-0.94); severe malnutrition (OR 4.99 95% CI 2.90-11.90); informal housing (OR 2.87 95% CI 1.30-6.30); associated cardiac disease (OR 2.89 95% CI 1.20-6.95); bacteria isolated from a normally sterile site (OR 4.01 95% CI 1.53-10.54); need for inotropic support (OR 24.7 95% CI 10.4-58.7) and duration in hospital (OR 1.01 95% CI 1.00-1.02). These variables as well as age, prematurity, HIV status, time to first dose of antibiotics and duration in PICU were included in the multivariate analysis as they were considered clinically important factors both in the literature and in personal clinical practice. The multivariate analysis with adjusted odds ratios showed significance of the following factors: severe malnutrition; informal housing; inotropic support and duration of hospital stay. These factors were associated with a statistically significant higher risk of in hospital mortality, after adjusting for HIV infection, prematurity, age at admission and method of feeding (table 2). Age, birthweight, prematurity, feeding choice, HIV status or comorbid disease, time to start antibiotics, seasonal variability, nosocomial infection and tobacco smoke exposure were not associated with survival in this study (table 2).

Table 2. Multivariate analysis of risk factors for children admitted with a diagnosis of ALRTI, by hospital outcome (survived/died)

	Univariate association		Multivariate association	
	OR (95% CI)	P value	OR (95% CI)	P value
Age category < 6 months	0.59 (0.29-1.21)	0.150	0.82 (0.19-3.56	0.794
HIV status N (%)				
Exposed; not infected	1.04 (0.44-2.45)	0.935	0.49 (0.03-8.05)	0.619
Exposed; Infected	0.84 (0.23-3.02)	0.792	2.85 (0.55-14.86)	0.213
Unexposed	reference			
Preterm (< 37 weeks)	0.87 (0.36-2.11)	0.759	1.62 (0.31-8.33)	0.565
Infant feeding N (%) Exclusive breast fed			4.38 (0.92-20.82)	0.063
Nutritional status				
None/mild	reference			
Moderate	2.47 (0.83-7.36)	0.104	0.81 (0.12-5.32)	0.822
Severe	4.99 (2.90-11.90)	<0.001	8.25 (1.47-46.2)	0.016
Housing				
Formal	reference			
Informal	2.87 (1.30-6.30)	0.009	11.87 (1.89-20.8)	0.008
Bacterial isolate	4.01 (1.52-10.54)	0.005	3.61 (0.65-20.00)	0.141
No comorbid disease	Reference			
Cardiac diagnosis	2.89 (1.20-6.95)	0.018	1.05 (0.19-5.80)	0.957
Other	1.45 (0.59-3.59)	0.421	1.97 (0.30-12.81)	0.480
Inotropic support	24.7 (10.4-58.7)	<0.001	44.35 (8.20-239-9)	<0.001
Length of time to start antibiotics (hours)	1.29 (0.98-1.70)	0.068	0.71 (0.37-1.35)	0.294
Duration in hospital	1.01 (1.00 – 1.02)	0.008	1.04 (.01-1.06)	0.007
Duration in PICU	1.00 (1.00 – 1.01)	0.053	1.00 (0.99-1.00)	0.789

Impact of HIV exposure and infection on outcomes.

In this study sample, 87 (32.8%) of patients were HIV exposed and 25 (10.2%) were confirmed to be HIV infected. The Mother to Child HIV transmission rate in this study is 31.0%. Details of PMTCT as follows reveals low coverage in the HIV exposed group and less than would be expected for a successfully PMTCT program: antenatal coverage 44(50.6%); perinatal coverage 50(57.5%) and postnatal coverage 54(62.1%). Only 6 infants received full PMTCT including all three components at the correct dosing, of these patients 3 were breastfed; 1 was formula fed and 2 received mixed feeding. 9 patients did not receive any PMTCT at all prior to admission. 4 patients received incomplete PMTCT. These infants only received postnatal PMTCT. The assumption is that these mothers were diagnosed in labour or at the delivery of the infant. 2 of the patients had all the components of PMTCT but the dosing of Nevirapine was incorrect. In 6 patients who were tested HIV positive on this admission, the medical records did not contain any information about PMTCT.

Of the HIV infected group, 22 patients were newly diagnosed on the current admission with a mean viral load of 2 660 254 (log 6.4); mean CD4 count of 23% and mean WHO clinical stage of 3.75. Of the 5 patients known to be HIV infected, 4 were on first line ART, one was on second line ART but only two patients were virally suppressed on therapy.

HIV exposure or infection did not significantly affect mortality however HIV infection was associated with a higher PIM2 score on admission and longer duration of PICU and hospital stay (table 3).

TABLE 3: Impact of HIV exposure/infection on outcomes

Characteristic	HIV unexposed	HIV exposed, not infected	HIV exposed and infected	P value
Survival rate	0.87	0.87	0.89	0.740
Case fatality rate In hospital:	0.13 (24/178)	0.13 (8/60)	0.11 (3/27)	-
Duration hospital stay in days (median/IQR)	11.0 (7.2-27.0)	11.0 (7.9-24.4)	23.0 (16.1-43.0)	0.002
Duration ICU stay in days (median/IQR)	4.0 (2.0-8.0)	4.0 (2.0-7.0)	6.0 (4.0-10.0)	0.131
PIM2 score (mean)	0.115	0.116	0.315	<0.001

Aetiology

Overall 960 investigations in total were done to try identity a potential cause of the ALRTI. Tests performed included culture of blood, induced sputum, tracheal aspirate, broncho-alveolar lavage and pleural fluid for bacteria and fungi; viral polymerase chain reaction (PCR) panel testing for 7 respiratory viruses on nasopharyngeal aspirate and TB microscopy and culture as well as PCR on induced sputum and gastric washings. Of the 265 patients admitted to PICU, 206(77.7%) patients had at least one organism identified on investigations and 86(32.5%) patients had more than one organism identified (table 4). Viruses were most commonly identified 117(44.2%) with a frequency of Respiratory Syncytial virus, Rhinovirus and Adenovirus of 9.3%, 7.2% and 4.7% respectively.

CMV was tested by means of a quantitative viral load with a log >4 considered to be positive for disease. 18 patients out of 27 who were tested had a CMV log > 4 (66.7%). CMV testing was only done in patients known to be HIV-infected. There was no significant difference in aetiology between the HIV unexposed, HIV exposed-negative and HIV infected groups (p-value=0.2).

Children who had a bacteria isolated from blood culture, broncho-alveolar lavage, sputum or histology were three times more likely to die compared to viral, fungal or mixed causes for ALRTI (OR 3.61 95% CI 0.65-20.00) (table 2).

TABLE 4: Organism type isolated from investigations in the PICU

Organism isolated	Number	Proportion	Odds ratio (95% CI)	P value
None	59	22.3%	-	-
Bacteria[1]			4.01(1.53-10.57)	0.005
1x bacterium isolated	25	9.2%		
>1 bacteria isolated	2	1.0%		
Virus:			0.43(0.15-1.21)	0.112
1x virus isolated	91	34.2%		
>1 virus isolated	26	10.0%		
Fungal (P. jirovecii)[2]	4	1.5%	-	-
Mixed infections:			1.07(0.38-3.03)	0.885
Bacterial/Viral	45	17.0%		
Bacterial/Fungal	3	1.1%		
Viral/Fungal	7	2.6%		
Bacterial/Viral/Fungal	3	1.1%		
TOTAL	**203**	**100**		

[1]Bacteria were isolated from blood culture, broncho-alveolar lavages, culture of tracheal aspirates or pleural fluid.
[2]No deaths in children who cultured fungal organisms

Discussion

This study provides new data on the risk factors and outcome of South African children with severe ALRTI admitted to a PICU and reflects a much larger burden of childhood disease(1,6,26). The severity of illness in this population was extremely high as evidenced by the high PIM2 scores and requirement for mechanical ventilation, with almost all children receiving ventilatory support, mostly conventional or high frequency oscillatory ventilation. The requirement for mechanical ventilation (72.5%) was much higher than in other LMICs such as South America or China where rates of mechanical ventilation in children admitted to PICU with severe ALRTI are reported as 55% and 21% respectively(8,27). The PIM2 score on admission to PICU predicted a mortality of 13%, but the mortality rate in the PICU was 9%. This affirms the high quality of care received by children admitted to this unit and can be attributed to strategies used including broad spectrum antibiotics, lung protection ventilator strategies and preventative interventions to decrease the risk of nosocomial infection or other complications all of which may be important factors resulting in better than expected outcomes. The further ten patients who died following discharge from the PICU increase the overall mortality to 13%, but all of these deaths, except one, were anticipated and palliation had begun within the PICU or shortly after discharge. These outcomes are especially encouraging in comparison to other LMICs such as South America or China who report PICU mortality rates from severe ALTRI of 13% and 5.8% respectively(8,27).

Several factors were identified as influencing in-hospital mortality. Of these, socioeconomic factors were a key determinant associated with both admissions to PICU and of survival. Children from impoverished backgrounds living in informal housing without access to electricity and running water on their property had almost four times the rate of mortality. The PIM2 score on admission to the PICU was significantly higher for children living in informal housing. Lack of access to basic amenities such as running water, adequate sanitation or electricity were associated with higher mortality as well as with a higher PIM2 score on admission. A recent study in this geographical area reflects that children from informal housing are more severely ill at PICU admission, possibly reflecting higher prevalence of risk factors for illness as well as poorer access to healthcare, unnecessary delays in diagnosis or referral patterns(26). Our study corroborates these findings and although children from poorer socioeconomic backgrounds received the same treatment as those from richer backgrounds, the higher mortality of the former may be a result of their greater severity of illness or underlying co-morbidity.

This study does not seem to show that exclusive breastfeeding for a duration of 6 months is a protective factor when it comes to severity or survival. This is in contradiction to the current literature and clinical understanding. A possible explanation for this may be the very young age of the study sample population (median age 4 months) with almost half of the deaths (15 out of 34) occurring before the age of 6 months. If the deaths are scrutinised, even though there was no statistical significance to verify this fact, 7 of the deaths had complex congenital cardiac disease, 3 had HIV disease and 3 had other comorbidities so even though they were breastfeeding, as a single protective factor it may not have made enough of a difference. The sizes of the samples and groups of survivors versus deaths may also not be large enough to show a true protective effect.

HIV infection has long been recognised as a risk factor for more severe disease and worse outcome from ALRTI. The mortality rate of HIV infected children in the current study was 11%, substantially lower than that predicted by the PIM2 score (mean PIM2 score of 31.5%). Further, this was much lower than previously reported in a study done at RCWMCH in 1998 which reported a mortality rate in HIV infected and uninfected children admitted to PICU with pneumonia of 29% and 14% respectively(28). However, other intensive units in South Africa continue to report mortality rates for HIV infected children of approximately 30%(29). The success of early detection of HIV infection with timely initiation of HAART as well as aggressive broad spectrum management of ALRTI with HIV infected children in a PICU setting may explain these impressive reductions in mortality. Such outcomes support the decision to accept HIV infected children into the PICU for supportive treatment which in the era before ART was perhaps not justified(30,31). However, the duration of PICU and hospital stay of HIV infected children were almost double that of HIV uninfected children, confirming that this is a vulnerable population who are still at substantial risk for severe disease and who still constitute a large burden on the health system.

Recently, HIV exposure has also been associated with a higher risk of pneumonia, as shown by a South African study in which HIV negative children born to HIV-infected mothers had a higher rate of pneumonia in the first year of life compared to those born to HIV-negative women(32). Just over 30 % of this study population were HIV exposed which is in keeping with antenatal HIV positive rates in 2012 of approximately 29% in this geographical area. However, the documented transmission rate in the Western Cape in the setting of fully implemented and effective PMTCT is 1.4%(33).   Of the 25 children who were HIV infected, 17 either had no documented PMTCT, incomplete PMTCT or incorrect PMTCT dosages, highlighting that implementation of effective PMTCT programs may still be problematic. As PMTCT programs are strengthened, so increasing attention must be given to HIV exposed but uninfected children who represent an emerging, important vulnerable group.

Study limitations

This study has several limitations. As the study was retrospective, there was limited ability to have complete, detailed data records and standardised measures of certain tests and investigations. Nevertheless, the abstracted clinical data was consistent for all children and comprehensive, given the strong PICU data base. Factors that relied on medical records and documentation had a completeness of approximately 76-96% which was deemed suitable for data analysis.

In terms of outcomes, it has to be acknowledged that certain factors can be seen to be competing risk factors for outcome e.g. duration of ventilation was used as a risk factor for outcome but could also be referred to as an outcome in and of itself. This complex relationship between risk factors and outcomes makes the interpretation difficult. It was therefore decided to focus on survival as the only outcome of this study. All other outcomes including length of hospital stay, length of PICU stay and duration of ventilation are important and warrant further in depth analysis in future publications.

Further, the ability to attribute aetiology was limited as aetiological investigations were highly variable and attributing aetiology in childhood ALRTI may be especially difficult. The sample of patients in the PICU represent the sickest children, therefore these results may not be generalizable to children with lesser severity of illness. Further, the sample size was relatively small, but representative of a full year of PICU admissions for LRTI, thus accounting for seasonal variation.

In conclusion, children admitted for ALRTI to the PICU at RCWMCH in 2012 had severe disease on admission but despite this had fairly good outcomes in terms of survival, better than predicted and much improved from a decade earlier. Several risk factors for poor outcome were shown, which require broad interventions to effectively address these. Future research should investigate the morbidity related to severe ALRTI and the long term outcomes such as development of chronic lung disease, reactive airway disease or neurodevelopmental sequelae.

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Appendix A: Definitions

Classification of the severity of pneumonia by World Health Organisation

Sign or symptom	Classification
1 Fast breathing 2 Definite crackles on auscultation	Pneumonia
As above plus: 1 Chest in drawing	Severe pneumonia
As above plus: 1 Central cyanosis 2 Severe respiratory distress (e.g. head nodding) 3 Not able to drink	Very severe pneumonia

Reference ranges for fast breathing:
≥60 breaths/minute in a child aged <2 months
≥50 breaths/ minute in a child aged 2–11 months
≥40 breaths/minute in a child aged 1–5 years

Definitions

"**patient**" is defined as any child less than the age of 12 years of age presenting to RCWMCH in need of medical care.

"acute lower respiratory tract infection" includes clinical diagnoses in keeping with pneumonia; bronchopneumonia; bronchitis; bronchiolitis; or respiratory infection. It is defined according to World Health Organisation as an infection that affects the lungs resulting in the symptoms of cough, difficulty breathing and tachypnoea.

“outcomes” will be defined as: PICU mortality; hospital mortality; duration of invasive ventilatory support in days; length of ICU stay in days; length of hospital stay in days.

“**length of stay”** for the purpose of this study a day is defined as a 24hour period. Day one is considered to be the first 24 hours or any part thereof. Thereafter each day will be calculated as multiples of 24.

“**ventilatory support**” will be considered to be non-invasive (nasal cannula, high flow nasal cannula oxygen or non-invasive CPAP) or invasive (positive pressure ventilation or high frequency oscillatory ventilation.)

“**cardiac support”** will be considered the use of or the administration of inotropic agents.

“**community acquired”** is defined as a positive culture from a sample taken within 48hrs of hospital admission.

“**nosocomia**l” is defined as a suspected new sepsis or culture positive sample obtained 48hrs after hospital admission.

“**Nutritional status”** is determined by the WHO classification of malnutrition using Z score cut-offs of <-2 and <-3 for moderate and severe malnutrition respectively. In this study, we will look at markers for wasting, stunting and underweight.

“WAZ” the weight for age Z-score of between -2 and -3 indicates a patient who is moderately underweight. A weight for age Z-score <-3 indicates a patient who is severely underweight.

“**Sociodemographic status”** is determined on the basis of geographical localisation, income bracket and home language.

“Income bracket” is determined by the monthly household income. It is classified according to the provincial government hospital biling department.

Appendix B: Standardised interpretation of paediatric chest radiographs

	FINDING	DEFINITION
Film quality	Uninterpretable	Features of the image are not interpretable with respect to presence or absence of “primary end-point” without additional images
	Suboptimal	Features allow interpretation of primary end-point, but not of other infiltrates or findings; no entries were made for “other infiltrates” for such images
	Adequate	Features allow confident interpretation of end-point as well as other infiltrates
Classification of findings	Significant pathology	Refers specifically to the presence of consolidation, infiltrates or effusion of findings
	End-point consolidation	A dense or fluffy opacity that occupies a portion or whole of a lobe or of the entire lung, that may or may not contain air-bronchograms
	Other (non-end-point) infiltrate	Linear and patchy densities (interstitial infiltrate) in a lacy pattern involving both lungs, featuring peribronchial thickening and multiple areas of atelectasis; it also includes minor patchy infiltrates that are not of sufficient magnitude to constitute primary end-point consolidation, and small areas of atelectasis which in children may be difficult to distinguish from consolidation
	Pleural effusion	Presence of fluid in the lateral pleural space between the lung and chest wall; in most cases, this will be seen at the costo-phrenic angle or as a layer of fluid adjacent to the lateral chest wall; this does not include fluid seen in the horizontal or oblique fissures
Conclusion	Primary end-point pneumonia	The presence of end-point consolidation (as defined above) or pleural effusion that is in the lateral pleural space (and not just in the minor or oblique fissure) and was spatially associated with a pulmonary parenchymal infiltrate (including other infiltrate) OR if the effusion obliterated enough of the hemithorax to obscure an opacity
	Other infiltrate	The presence of other (non-end-point) infiltrate as defined above in the absence of a pleural effusion
	No consolidation/infiltrate/ effusion	Absence of end-point consolidation, other infiltrate or pleural effusion

Appendix C: Data Capture form

	ICU Admission number
Patient details:	
Hospital number	
Age in months	_ _ _ months
Sex	☐ Male ☐ Female
Race	☐ African ☐ Caucasian ☐ Coloured ☐ Other
Geographical area of residence	
Home language	☐ English ☐ Afrikaans ☐ Xhosa ☐ Other
Income bracket	☐ H0 ☐ H1 ☐ H2 ☐ H3
Hospital details	
Date of admission to RCWMCH	_ _/_ _/2012
Date of admission to PICU	_ _/_ _/2012
Date of discharge from PICU	_ _/_ _/2012
Date of discharge from RCWMCH	_ _/_ _/2012
Duration of PICU stay(hours)	
Duration of hospital stay (hours)	
Morbidity or mortality in PICU	☐ Survived ☐ Died

Morbidity or mortality in RCWMCH	☐ Survived ☐ Died
Details of PICU stay:	
Primary diagnosis	☐ Lower respiratory tract infection ☐ Pneumonia ☐ Bronchopneumonia ☐ Pulmonary Tuberculosis ☐ Bronchiolitis
Secondary diagnosis	
PIMMS score on admission	
Need for ventilatory support	☐ No ☐ Yes
Need for High flow nasal cannula oxygen	☐ No ☐ Yes
Need for non-invasive CPAP	☐ No ☐ Yes
Need for invasive positive pressure ventilation	☐ No ☐ Yes
Need for High frequency oscillatory ventilation	☐ No ☐ Yes
Duration of ventilatory support (hours)	
Need for inotropic support	☐ No ☐ Yes
Duration of inotropic support (hours)	
Risk factors:	
Weight of the child	_ , _ _kg
Length of the child	_ _ _ cm
Nutritional status	☐ Normal ☐ Mildly malnourished

	☐ Moderately malnourished ☐ Severely malnourished ☐ Unknown
Infant feeding for 1st 6 months	☐ Breast ☐ Formula ☐ Mixed ☐ Unknown
Gestational age at birth	_ _ weeks
Birth weight	_ , _ _ kg
Any respiratory complications at birth	☐ No ☐ Yes
Immunisation status	☐ Birth immunisations Date: _ _/_ _/_ _ _ _ ☐ 6 week Date: _ _/_ _/_ _ _ _ ☐ 10 week Date: _ _/_ _/_ _ _ _ ☐ 14 week Date: _ _/_ _/_ _ _ _ ☐ 9 months Date: _ _/_ _/_ _ _ _ ☐ 18 months Date: _ _/_ _/_ _ _ _ ☐ 6 years Date: _ _/_ _/_ _ _ _ ☐ Unknown
No. of pneumococcal vaccines received	☐ 0 ☐ 1 ☐ 2 ☐ 3
Mother's age	_ _ years
Number of siblings	
Type of housing	☐ Formal ☐ Informal
Exposure to TB within last 6 months	☐ No ☐ Yes
Is child currently on INH prophylaxis	☐ No ☐ Yes
Ever diagnosed with TB	☐ No ☐ Yes Previously ☐ Yes Currently

Ever treated for TB	☐ No ☐ Past ☐ Current – New treatment ☐ Current – Retreatment ☐ Defaulted
Clinical suspicion of TB	☐ No ☐ Yes
Congenital cardiac disease	☐ No ☐ Yes
Other comorbid condition present	☐ No ☐ Yes Specify:______________________________
Recent admission to hospital (within 2 weeks)	☐ No ☐ Yes
Suspected nosocomial infection	☐ No ☐ Yes
HIV status:	
Is the child HIV exposed?	☐ No ☐ Yes
Mom received ARVs in pregnancy?	☐ No ☐ Yes ☐ Not recorded ☐ Not applicable
Perinatal PMTCT	☐ No ☐ Yes ☐ Not recorded ☐ Not applicable
Did infant receive Nevirapine	☐ No ☐ Yes – Dose correct ☐ Yes – Dose incorrect ☐ Not recorded ☐ Not applicable
Infant feeding choice	☐ Breast ☐ Formula ☐ Mixed ☐ Unknown

Is the child HIV infected	☐ No ☐ Yes ☐ Still to be confirmed ☐ Not recorded
Baseline CD4	_ _ %
Baseline Viral load	Log _ , _ _
Clinical stage at diagnosis	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ Not applicable
Is the child on HAART	☐ No ☐ Yes ☐ Not recorded ☐ Not applicable
What line	☐ 1st ☐ 2nd ☐ 3rd
Duration of HAART in months	
Compliance	☐ No ☐ Yes ☐ Not recorded ☐ Not applicable
Bactrim prophylaxis	☐ No ☐ Yes ☐ Not recorded ☐ Not applicable
Details of ALRTI:	
Classification of aetiology	☐ Unknown ☐ Bacterial ☐ Viral ☐ Fungal ☐ Mycobacterial

	☐ Mixed
Organism identified: Viral: Bacterial: Fungal: Mycobacterium:	☐ RSV ☐ Influenza A and B ☐ Parainfluenza ☐ Human Metapneumovirus ☐ Adenovirus ☐ Rhinovirus ☐ Staph Aureus ☐ Strep pneumoniae ☐ H. influenzae ☐ Klebsiella pneumoniae ☐ Acinetobactor ☐ Candida ☐ Other ☐ Mycobacterium TB ☐ MOTT
By which test	☐ Blood culture ☐ NPA ☐ Induced sputum ☐ Gastric washing ☐ BAL
Was a nasopharyngeal aspirate done?	☐ No ☐ Yes Date _ _/_ _/_ _ _ _ Result:
Was a BAL done? Results	☐ No ☐ Yes Date _ _/_ _/_ _ _ _ Result:
Was a sputum done? Result	☐ No ☐ Yes Date _ _/_ _/_ _ _ _ Result:
Was a gastric washing done? Result	☐ No

	☐ Yes Date _ _/_ _/_ _ _ _ Result:
Was a blood culture done? Result	☐ No ☐ Yes Date _ _/_ _/_ _ _ _ Result:
Chest radiograph done on admission	☐ No ☐ Yes Date _ _/_ _/_ _ _ _
Reader 1:	Film quality: ☐ Uninterpretable ☐ Suboptimal ☐ Adequate Classification of findings: ☐ Significant pathology ☐ End point consolidation ☐ Other infiltrate ☐ Pleural effusion Conclusion of CXR findings: ☐ Primary end point pneumonia ☐ Other infiltrate ☐ No abnormality
Reader 2	Film quality: ☐ Uninterpretable ☐ Suboptimal ☐ Adequate Classification of findings: ☐ Significant pathology ☐ End point consolidation ☐ Other infiltrate ☐ Pleural effusion Conclusion of CXR findings: ☐ Primary end point pneumonia ☐ Other infiltrate ☐ No abnormality

Reader 3	Film quality: ☐ Uninterpretable ☐ Suboptimal ☐ Adequate Classification of findings: ☐ Significant pathology ☐ End point consolidation ☐ Other infiltrate ☐ Pleural effusion Conclusion of CXR findings: ☐ Primary end point pneumonia ☐ Other infiltrate ☐ No abnormality ☐ Not applicable
Management of ALRTI:	
Were antibiotics prescribed?	☐ No ☐ Yes
Choice of antibiotics	☐ Ampicillin ☐ Gentamycin ☐ Ceftriaxone ☐ Ertapenem ☐ Piptazobactum ☐ Amikacin ☐ Other
Time to first dose in hours	
Were antivirals prescribed?	☐ No ☐ Yes
Choice of antivirals	☐ Aciclovir ☐ Gangciclovir ☐ Other
Time to first dose in hours	
Were antifungals prescribed?	☐ No ☐ Yes
Choice of antifungals	☐ Fluconazole

	☐ Amphotericin B ☐ Other
Time to first dose in hours	
Was TB treatment started on diagnosis?	☐ No ☐ Yes

Appendix D: Ethics Approval (see attached PDF)

Appendix E: Instruction to Authors – Pediatric Critical Care Medicine (see attached PDF)