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MORTALITY IN CHILDREN <5 YEARS WITH SEVERE ACUTE RESPIRATORY ILLNESS IN URBAN AND RURAL AREAS, SOUTH AFRICA, 2009-2013.

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science in Epidemiology (Epidemiology and Biostatistics).

2016

10th February 2017

DECLARATION

I, Dr Oluwatosin Adetayo Ayeni, declare that this research report is my own work. It is being submitted in partial fulfilment of the requirements for the degree of Master of Science in Epidemiology (Epidemiology and Biostatistics), in the University of the Witwatersrand, Johannesburg. It has not been submitted for any degree or examination at this or any other University.

Signature Date: 10th February 2017.

DEDICATION

This work is dedicated to my husband Dr O. Akinwale Ayeni and my daughter Oreoluwa Ayomide Ayeni for their unrelenting support during the learning process of the entire programme.

Abstract

Background

Reducing severe acute respiratory illness (SARI)-associated mortality in African children remains a public health priority and an immense challenge. The pneumococcal conjugate vaccine (PCV) was introduced into the South African routine immunization programme in 2009. The objectives of this study were:

I. To describe the demographic characteristics, clinical presentation, respiratory pathogens of children aged <5 years hospitalized with SARI in an urban (Chris Hani-Baragwanath Hospital, Soweto) and a rural (Matikwana and Mapuleng Hospitals, Mpumalanga) setting in South Africa from 2009-2013 and

II. To compare the factors associated with mortality among children aged <5 years hospitalized with SARI in these two sites separately.

Methods

Hospitalized children with SARI were enrolled into an active, prospective sentinel surveillance program. Clinical and epidemiologic data were collected until discharge. Nasopharyngeal aspirates were tested for influenza (A and B) and eight other respiratory viruses. In-hospital case-fatality proportion (CFP) and risk factors for mortality were determined for each hospital site separately using unconditional logistic regression.

Results

The in-hospital CFP was significantly higher in the rural (6.9%, 103/1486) than the urban (1.3%, 51/3811) site ($p<0.001$). This was observed among both HIV-infected (urban: 6.6%, 17/257) vs. (rural: 12.9%, 30/233) ($p=0.019$) and HIV-uninfected children (urban: 0.6%, 13/2236) vs. (rural: 4.2% 36/857) ($p<0.001$). In the urban site the only factor that is independently associated with death on multivariate analysis was HIV infection (odds ratio (OR) 12.1, 95% confidence interval (CI) 5.8-25.2). In the rural site HIV infection (OR 3.5, 95% CI 1.7-6.9), age <1 year (OR 3.5, 95% CI 2.0-6.1) vs. 1-4 years, any respiratory virus detected (OR 0.4, 95% CI 0.2-0.6), pneumococcal infection

(OR 4.5, 95% CI 1.8-10.8) and malnutrition (OR 12.8, 95%CI 1.2-134.6) were independently associated with mortality.

Conclusion

SARI mortality was higher in the rural setting. Even in the era of PCV availability pneumococcus is still associated with mortality in rural areas. Efforts to prevent and treat HIV infections in children and reduce malnutrition may reduce SARI deaths.

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List of abbreviations

AIDS – Acquired immune deficiency syndrome

ALRI – Acute lower respiratory infection

ALRTI – Acute lower respiratory tract infection

ART – Anti-retroviral therapy

CDC – Centers for Disease Control and Prevention

CFP – Case fatality proportion

CI - Confidence interval

ELISA – Enzyme-linked immunosorbent assay

EPI – Expanded Programme on immunization

HAART – Highly active antiretroviral therapy

Hib – Haemophilus influenzae type b

HIV – Human immunodeficiency virus

ICU – Intensive care unit

IMCI - Integrated management of childhood illness

IPD – Invasive pneumococcal disease

MDGs – Millennium development goals

MTCT – Mother-to-child transmission

NICD – National institute for communicable diseases

NPA – Nasopharyngeal aspirates

OR – Odds ratio

PCR – Polymerase chain reaction

PCV – Pneumococcal conjugate vaccine

PMTCT – Prevention of mother-to-child transmission of HIV

PCP – Pneumocystis carinii pneumonia

RR – Relative risk

RSV – respiratory syncytial virus

SA – South Africa

SARI – Severe acute respiratory illness

SD – Standard deviation

SDGs – Sustainable development goals

SP – *Streptococcus pneumoniae*

WHO – World Health Organization

Chapter 1

1.0 Introduction

This chapter provides an overview of the burden of severe acute respiratory illness (SARI) in children globally and also in Africa and its public health significance with a particular focus on risk factors for mortality. This chapter also includes the problem statement, study justification, aim and objectives of the study and a literature review.

1.1 Background

Reducing the substantial public health burden of SARI in African children is still a major priority and an immense challenge(1). According to WHO's case definition, SARI is an acute respiratory infection with: history of fever or measured fever of ≥ 38 C°; and cough; with onset within the last 10 days; and requires hospitalization. (2)

Pneumonia is defined as an infection of the lungs that is caused by viruses, bacteria, fungi, or parasites. It is characterized primarily by inflammation of the alveoli in the lungs or by alveoli that are filled with fluid. Therefore SARI is a more inclusive case definition than pneumonia because it includes other non-pneumonia causes of PRTI such as bronchiolitis. For this surveillance program, a case of SARI was defined as a hospitalized person with illness onset within 7 days of hospitalization meeting age-specific inclusion criteria as follows; Children two days to under 3 months of age with a physician's diagnosis of acute lower respiratory illness (ALRTI) or sepsis, children aged 3 months to ≤ 5 years with a physician's diagnosis of ALRTI (which include pneumonia, bronchitis, pleural effusion and bronchiolitis).

Pneumonia is the major cause of death in children < 5 years of age globally, it accounts for about 1.4 million deaths annually (1) most of which are recorded in low and middle income countries, sub-Saharan Africa is disproportionately affected accounting for more than half of pneumonia deaths globally (1). Pneumonia is the commonest respiratory infection in children requiring hospitalization (3).

In South Africa, pneumonia and influenza was the second leading cause of death in children <5 years in 2013, and was responsible for about 10% of deaths in this age group. In infants, cardiorespiratory disorders specific to the perinatal period are the leading causes of death, accounting for 14% of deaths in this age group, influenza and pneumonia causes 9% of deaths in infants. (4)

Reducing mortality in children less than 5 years of age was one of the Millennium Development Goals (MDGs) which is now covered under the umbrella of good health and wellbeing in the sustainable development goals (SDGs). However, to reduce the burden of SARI remains a major challenge in Africa. (1) Possible approaches include improved access to vaccines for common causes of pneumonia, reduction in HIV, mother to child transmission (MTCT), Integrated management of childhood illness (IMCI) and indoor air pollution.(5) Preliminary studies have suggested that SARI mortality is lower in urban than in rural settings in South Africa (6).

1.2 Problem statement

Despite improvement in patient survival and the advances in the development of new antimicrobials and vaccines, pneumonia continues to carry a high morbidity and mortality rate in children especially those living with HIV. Several studies have been carried out in South Africa looking at mortality from SARI in children <5 years, but none have examined specifically the differences in risk factors for SARI-related mortality in urban and rural areas in South Africa. There have been studies describing children born in rural areas to be at greater risk of death of any cause before 5 years of age possible reason being access to care (7, 8).

1.3 Justification

This study will describe individuals at increased risk of mortality and identify risk factors for in- hospital mortality in children < 5 years of age with SARI that could be targeted for public health intervention in rural and urban settings. Studies have shown that children born in rural areas are at greater risk of death of any cause before 5 years of age possible reason being access to care (7, 8). It would be interesting to describe this in our setting and in particular to see if there is a mortality differential in patients with SARI

between rural and urban areas. If mortality is elevated in rural areas, specific interventions could potentially be targeted to address risk factors for death in these areas. Describing the risk factors for SARI-related deaths in both rural and urban settings could potentially bring about improved access to interventions to reduce pneumonia deaths in South Africa.

1.4 Literature Review

Pneumonia remains the major cause of death worldwide in children under 5 years of age (9). Pneumonia is an inflammatory lung disease affecting primarily the microscopic air sacs also known as the alveoli.(10) Children, older adults and people with chronic diseases like asthma, chronic obstructive pulmonary disease, heart failure, sickle cell anaemia and HIV are at elevated risk for pneumonia. (11) Inhaled infectious organism must bypass the host's immune and non-immune defensive mechanisms in order to cause pneumonia. (12) The symptoms and signs of pneumonia are mostly nonspecific, they can range from mild to life threatening and vary based on the infectious organisms involved, age of the patient and the general health status of the patient.(13) Typical symptoms and signs include a cough, fever, chest pain and difficulty in breathing. Pneumonia may develop in the lung or it can be from a focal complication of a systemic inflammatory process.(14) Understanding the cause of pneumonia is important because pneumonia treatment depends on its cause. Bacterial pneumonia is treated with antibiotics while viral pneumonia can be treated symptomatically and with antivirals - oseltamivir for influenza. Furthermore there is a growing need to identify respiratory pathogens that contribute to disease development because vaccines targeting specific organisms are now available to prevent infections with major pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae type b* (Hib) and influenza virus.

1.4.1 Pathogens associated with pneumonia

Pneumonia is caused mainly by viruses or bacteria and less frequently by parasites, fungi and various chemical agents. Over 100 types of infectious agents causing

pneumonia have been identified in patients, very few can be attributed to most of the cases, co-infection with both bacteria and viruses may occur in up to 45% of infections in children(15). Bacterial pathogens such as Hib, *S. pneumoniae* and *Staphylococcus aureus* remain important causes of pneumonia in African children. *S. pneumoniae* is the most important bacterial pathogen in African children, it is estimated that about 16% of cases of severe pneumonia are caused by pneumococci,(16) hence the introduction of pneumococcal conjugate vaccine (PCV) in the South African Expanded Program on Immunization (EPI) in 2009. Incidence of pneumococcus and Hib invasive disease has decreased markedly in South Africa due to the use of PCV and Hib conjugate vaccine in the EPI.(17, 18) Some other bacterial pathogens such as *Salmonella* spp and *Escherichia coli* may cause pneumonia in children, particularly in HIV-infected children.

In a recent study conducted in South Africa, the overall prevalence of respiratory viruses identified in children under 5 years of age hospitalized with SARI was 78% [rhinovirus (37%), adenovirus (26%) ,respiratory syncytial virus (RSV) accounting for 26% and enterovirus (10%)]. (6) This is similar to findings in a study conducted in children under 5 years with SARI in a densely populated urban slum in Kenya reporting 71% overall prevalence of respiratory viruses [rhinovirus/enterovirus (47.5%), adenovirus (29.5%) and RSV accounting for 20.7%]. (19) Kwofie et al while looking at respiratory viruses in children hospitalized for ALRTI in Ghana reported viruses identified as RSV (14.1%) followed by Adenoviruses (10.2%), Parainfluenza viruses type 1, 2, 3 (3.1%) and influenza B virus (0.8%). (20) In Cambodia, a study on clinical and epidemiological characteristics of acute viral lower respiratory tract infection in children reported 55% of children with documented viral infection [rhinovirus (34%), RSV (34%), parainfluenza virus (8%), human metapneumovirus (8%), influenza virus (6%), bocavirus (3%), adenovirus (3%), coronavirus (2%) and enterovirus (1%). (21)

In a nested case control study, Zar et al reported that RSV was the most frequently detected pathogen associated with pneumonia occurring in 23% of cases and 4% of controls with OR(95% CI) of 8·05 (4·21–15·38); influenza virus and *B pertussis* were also strongly associated with pneumonia.(22) This was similar to a prospective case-control study carried out by Benet et al on etiology and factors associated with

pneumonia in children under 5 years of age in Mali which reported *S. pneumoniae*, human metapneumovirus, RSV and influenza A virus as independent organisms associated with pneumonia.(23) In a similar study with healthy controls, Pretorius et al reported that Influenza virus with (attributable fraction (AF): 86.3%; 95%CI: 77.7–91.6%), RSV (AF: 83.7%; 95%CI: 77.5–88.2%) and human metapneumovirus (AF: 85.6%; 95%CI: 72.0–92.6%) infections were associated with severe disease, while adenovirus (AF: 36.4%; 95%CI: 20.6–49.0%) and rhinovirus (AF: 46.9%; 95%CI: 37.6–56.5%) were only moderately associated.(24)

However, most of these studies didn't test for bacteria. Diagnosis of bacterial pneumonia is complex as finding pneumococcus in the nasopharynx may represent colonization (25) hence the need to distinguish between *S. pneumoniae* that is simply colonizing the upper respiratory tract and *S. pneumoniae* that is causing pneumonia. Blood culture is highly specific for disease but a high percent of pneumococcal pneumonia will not be bacteraemic and thus blood culture is insensitive,(26) hence the need for better identification of *S. pneumoniae* independent of culture methods. The real-time polymerase chain reaction (PCR) targeting lytA gene on blood samples for detection of *S. pneumoniae* has been found to be highly sensitive and specific,(27, 28) and studies suggest it likely represents disease and not colonization but there is still some controversy.(27)

1.4.2 Risk factors for pneumonia

Risk factors that predispose to pneumonia in children aged under 5 are low birth weight, HIV co-infection, low socioeconomic status, being unimmunized, overcrowding, malnutrition, lack of exclusive breastfeeding in the first four months of life, parental smoking, indoor air pollution, zinc deficiency, vitamin A deficiency, co-morbidity like diarrhea, heart disease, asthma, maternal education, mother's experience as a caregiver and passive care–seeking behavior. (29) Nair et al in a study on global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis reported that disease incidence was highest in neonates aged 0-27 days (68·6 episodes per 1000 per year, 95% CI 47·8–

98·4) and infants aged 0–11 months (51·8 episodes per 1000 per year, 44·8–59·8). (3) The HIV epidemic has had a major impact on the burden and epidemiology of pneumonia in children, the increasing number of pneumonia admissions in HIV infected patients has contributed to the general increase in hospitalization and deaths due to pneumonia in South Africa. (30) There are a few studies on SARI comparing the epidemiology in rural and urban areas. Studies have shown that children born in rural areas are at greater risk of death of any cause before 5 years of age. (7, 8)

1.4.3 Risk factors for mortality

Pneumonia is the commonest cause of hospitalization and death, especially in Sub-Saharan Africa where there is high concentration of children living with HIV. HIV-infected children have a higher risk of developing pneumonia and of more severe disease than children without HIV (6, 30).

In a systemic review and meta-analysis of observational studies from 1974 to January 2014 reporting on risk factors for death from acute lower respiratory illness (ALRI) in children below five years in low- and middle income countries, the risk factors showing strong association with mortality among children with pneumonia were HIV/AIDS, diagnosis of very severe pneumonia according to WHO definition, children less than 2 months of age, low birth weight, co-morbidity with chronic diseases, severe malnutrition, *Pneumocystis carinii* (*Pneumocystis jirovecii*) diagnosis, prematurity and inadequate breastfeeding practices. (31)

In a case series study from 8 countries on SARI deaths in sub-Saharan Africa and the role of influenza, 67.9% of influenza virus–positive deaths were HIV infected (32). Furthermore, a study by Cohen et al looking at viral-associated ALRTI among children < 5 years of age in a high HIV prevalence setting in South Africa revealed that incidence of lower respiratory tract infection (LRTI) was 1.1 to 3.0-fold greater in HIV-infected children than HIV-uninfected children with a higher case fatality ratio (OR: 4.2, 95% CI: 2.6–6.8) and HIV-infection was a risk factor for death on multivariate analysis (OR: 3.7, 95% CI: 2.2–6.1) (6). This suggests that despite the availability and wide coverage of

antiretroviral therapy, HIV infection still remains a major risk factor for SARI mortality in children in sub-Saharan Africa. However, changes in prevention of mother-to-child transmission (PMTCT) and pediatric highly active antiretroviral therapy (HAART) from 2004 to 2014 in South Africa have been remarkable with the increase in HIV-PCR testing in infants less than two months old and the decreasing trend in the percentage of those testing positive. Moreover early MTCT has greatly reduced from over 20% in 2014 to less than 2% in 2015. (33-35) However, studies have shown that HIV-exposed uninfected (HIV-EU) children have a higher infectious morbidity and mortality especially in the first 2 years of life compared to the children of HIV-negative mothers (HIV-unexposed). (36-38) In a study carried out in Soweto South Africa, it was shown that HIV-EU infants aged <6 months experienced elevated incidence of LRTI hospitalization when compared with HIV unexposed uninfected (HIV-UU) infants. In addition, once hospitalized, HIV-EU infants were more likely to have a prolonged hospitalization and to die in-hospital compared with HIV-UU infants, highlighting the need for this group to be considered an at-risk group for severe pneumonia.(39) This poor health outcome may be due to infant feeding practices as infected-mothers may be less able to breastfeed or may choose replacement feeding to reduce the risk of HIV-transmission. (40) Other potential contributing factors include early maternal death, increased exposure to infections, and immune abnormalities resulting from in utero exposure to HIV and antiretroviral medications.(40)

Looking at age, 11·3 million children younger than 5 years were admitted to hospital for severe ALRI in developing countries, with an estimated case fatality ratio of 2·3% (95% CI 1·6–3·4). (41) Sonego et al in a systemic review and meta-analysis of observational studies in 2015 also reported that neonates and infants were at higher risk of mortality due to SARI compared to older children < 5 years odds ratio (OR) of 5.22 (1.70-16.03) for children below two months of age. (31)

Malnutrition and pneumonia are two of the biggest causes of death in children, in a systemic review looking at pneumonia in severely malnourished children in developing countries, Chisti et al reported that children with moderate or severe malnutrition with

pneumonia were at higher risk of death, (42) and in a score for risk of mortality among infants with pneumonia, very low weight for age and refusal to feed contributed as much to risk of mortality as hypoxia, (43) moreover Rice et al in the bulletin of the WHO reported that the most consistent and strongest relationship between malnutrition and increased risk of death was observed for children with acute respiratory infection and diarrhea. (44)

In a case–control study conducted in four healthcare centers close to Utrecht in the Netherlands, a strong male predominance of ALRTI in children < 5 years old was reported (11.2 out of 1,000 among males and 5.7 out of 1,000 among females), (45) Nair et al also reported higher incidence in boys than girls in a systematic review. (3) However despite having more males with ALRTI, several studies have shown that the female sex is associated with increased odds for mortality, (3, 46) which is also supported by Sonego et al in a meta-analysis of 23 studies on 20385 children that female sex was associated with a 15% increase in the odds for mortality, (31) possible reasons being inequality related to sex in the quality of health care provided, health seeking behavior in the community and also biological differences. A study conducted in India looking at the risk factors for death in children aged 1-59 months admitted with community acquired pneumonia however showed that the difference in mortality due to pneumonia among male and female children was not statistically significant (P=0.12). (47)

1.4.3.1 Respiratory pathogens as a risk factor for mortality

In a case series study from 8 Countries on SARI deaths in Sub-Saharan Africa and the role of influenza surveillance from 2009–2012, McMorrow et al reported that rhinovirus (14.2%), RSV (13.4%), adenovirus (13%), parainfluenza virus 3 (5.3%) were observed amongst those that died from SARI in children < 5 years old.(32)

In HIV-infected persons the incidence of influenza-associated ALRTI was 4-8 times greater than the incidence in HIV-uninfected persons and those with HIV are more likely to die (OR 3.9, 95% CI 1.1–14.1) (48), this is in keeping with a study conducted by Schnell et al looking at risk factors for pneumonia in immunocompromised patients with

influenza which reported that immunocompromised patients with influenza are at higher risk of death from pneumonia (49). Several studies have described a high burden of RSV-associated pneumonia with HIV-infected children having a higher risk of hospitalization with RSV-associated ALRTI and a poorer outcome than HIV-uninfected children (50, 51)

Bacterial pneumonia is associated with higher mortality than viral pneumonia. In 2009, in a study on global burden of disease caused by *S. pneumoniae* in children younger than 5 years, O'Brien et al reported approximately 826,000 deaths in children < 5 years of which about 91,000 occurred in HIV-positive and approximately 735,000 in HIV-negative children.(52) Rudan et al in 2010 in a systematic review looking at etiology and epidemiology of childhood pneumonia for 192 countries reported that 33% of pneumonia death were caused by *S. pneumoniae* with *Haemophilus influenzae* accounting for 16% of death (53). In India, Farooqui et al in 2010 estimated about 560,000 severe episodes of pneumococcal pneumonia with about 105,000 pneumococcal deaths.(54) In South Africa, pneumococcal co-infection was identified by Cohen et al as a risk factor for mortality among patients with influenza associated severe acute respiratory illness (OR 4.1, 95% CI 1.5–11.2). (55) PCP is an important pathogen independent of patient's HIV status. It has been reported in both HIV–infected and HIV-uninfected children (especially those that are immunocompromised).(56) In 2000, Zar et al reported that 9.9% of HIV-infected had PCP.(57) Furthermore, in 2014 Morrow et al in a study on pneumocystis pneumonia in South African children diagnosed by molecular methods reported that children with PCP had a higher case fatality proportion (CFP) (32.1%) compared to those without PCP (17.2%), relative risk (RR) 1.87: 95% confidence interval (CI) 1.11-3.15. (58)

1.4.4 Vaccines for prevention of pneumonia

S. pneumoniae has been identified as the leading bacterial cause of pneumonia in children, it is also recognized as a common cause of super-imposed bacterial infection in children with respiratory virus-associated pneumonia (59, 60). According to Madhi et al in 2004, in a double-blinded, randomized, placebo-controlled clinical trial in 37,107

infants that were fully immunized in Soweto, South Africa, it was reported that the 9-valent pneumococcal conjugate vaccine prevented 31% (95% CI: 15−43%) of viral pneumonias in hospitalized children. (60) However, vaccines are now available to prevent infections with pathogens like *S. pneumoniae*, Hib and influenza virus, while RSV vaccine is being actively pursued (61, 62).

In South Africa, Hib was introduced into the EPI in 2000, PCV-7 in April 2009 and with the 13-valent PCV (PCV-13) replacing PCV-7 in May 2011. (63) Influenza vaccine is available in South Africa but coverage is exceptionally low, (64) ±1 million doses of influenza vaccines are distributed each year but there are ±20 million individuals in the risk groups targeted (65) In South Africa in 2009, pertussis vaccine changed from whole cell to acellular pertussis vaccine in the EPI. (66)

In a multi-center study carried out in South Africa it was reported that PCV vaccination was associated with a 69% (95% CI 7-90) reduced odds of hospitalization for vaccine–serotype invasive pneumococcal disease (IPD).(67) In 2014, von Gottberg et al also reported that IPD rates among South African children reduced remarkably by 2012. (68) A case-control study was conducted by Madhi et al in 2014 to establish the effectiveness of PCV vaccine looking at the endpoint of clinical pneumonia in South Africa.(63) These studies are helpful in quantifying the direct effectiveness in routine use of these vaccines, however the public health impact of these vaccines is yet to be fully quantified.

1.4.5 In-Hospital death

Nair et al in the systemic review of global and regional burden of hospital admission for severe ALRTI in young children reported that about 62% of children with severe ALRI were admitted into the hospital and amongst these admissions about 19% died in hospital. Nearly 99% of deaths outside the hospital take place in developing countries (3, 32).

1.5 Research Question

What are the demographic, clinical and pathogen specific factors associated with in-hospital mortality among children aged < 5 years of age with SARI in urban and rural settings in South Africa?

1.6 Aim

This study aims to compare the in-hospital mortality and factors associated with mortality among children < 5 years hospitalized with SARI in a rural and an urban area in South Africa from 2009 to 2013.

1.6.1 Specific Objectives

The specific objectives of this study are:

1. To describe the demographic characteristics, clinical presentation and respiratory pathogens of children < 5 years of age hospitalized with SARI in hospital sites in an urban and a rural area of South Africa.
2. To identify the risk factors for mortality among children < 5 years of age hospitalized with SARI in an urban and a rural area of South Africa separately.

CHAPTER 2

2.0 MATERIALS AND METHODS

The study design, study population and setting, selection of study site, data sources, case definition and study procedure are reviewed in detail in this chapter. The exposure and outcome variables are defined; data management, statistical methods, data analysis and ethical considerations are also discussed.

2.1 Study design

This study is a cross sectional study through secondary analysis of data derived from SARI surveillance conducted by the National Institute for Communicable Diseases (NICD). The SARI surveillance data could potentially be described as a cohort data because patients are enrolled at presentation to hospital due to their exposure to SARI and followed for the period of their hospital stay to record the outcome; hence it is a prospectively collected cohort data. But for this study, data on both exposure and outcome are collected at the same point in time, and the period from admission to outcome was very short hence the assessment was a cross-sectional study design. Data collected from February 2009 to December 2013 will be used for this study.

2.2 Study Setting

The data came from prospective, active, hospital-based sentinel surveillance for SARI which was implemented in February 2009 in three provinces of South Africa. Urban hospital data from Chris Hani-Baragwanath Academic Hospital (CHBAH) of Gauteng Province, and rural hospital data from Matikwana and Mapulaneng Hospitals of Mpumalanga Province in South Africa was used for this study. The two peri-urban sites were excluded from this study in order to allow comparison between the rural and urban settings.

The Chris Hani Baragwanath Hospital was established in 1941 and it is the 3rd largest hospital in the world and the largest hospital in the southern hemisphere in terms of hospital beds with approximately 3'200 beds and about 6'760 staff members. (69) Located in the Soweto area of Johannesburg, it is a tertiary level academic hospital serving a population of ±1.3 million people. It is a highly specialized hospital with about 70% of all admissions being emergencies.(69)

The Mapulaneng (Bushbuckridge) and Matikwana (Mkhuhlu) hospitals are in a rural area of Mpumalanga province, South Africa. Matikwana hospital is located adjacent to the Agincourt demographic surveillance site; therefore population surveys on demographic data are captured annually. Mapulaneng have high care facilities with 3 ICU beds. Matikwana have no ICU. These hospitals service a population of ±450,000 people.

These sites were selected for the SARI surveillance based on their geographical location; urban and rural sites with different climatic zones, capacity at the sites for specimen storage and transport, interested and committed clinicians and where routine evaluation of SARI cases can be accompanied by some investigations such as blood culture and HIV serology testing which enhances case evaluation.

2.3 Surveillance program - Primary data source

Surveillance for SARI was established in February 2009 because there was a global concern that an influenza pandemic could occur which led to the establishment of sentinel hospital-based surveillance of severe acute respiratory infections (SARI) in some countries.(70) The April 2009 H1N1 pandemic further supported the need to routinely monitor severe influenza. The South African SARI surveillance was already in place before this pandemic. Hospital-based, active, prospective sentinel surveillance [SARI program] was implemented in 3 of the 9 provinces of South Africa in 2009. Matikwana and Mapulaneng hospitals in rural area of Mpumalanga and Chris Hani-Baragwanath Academic Hospital (CHBAH) in an urban area of Gauteng Province in February and Edendale Hospital in a peri-urban area of KwaZulu-Natal Province in

September 2009. A surveillance site was introduced in June 2010 at Klerksdorp/Tshepong hospital complex located in a peri-urban area of the Northwest Province. For the study described in this report, only data from the CHBAH and Matikwana and Mapulaneng hospitals were included. The other sites will not be discussed further.

The aim of the primary study was to determine trends in number of SARI cases at sentinel surveillance sites and determine the relative association of influenza and other respiratory viruses such as adenovirus, human metapneumovirus, RSV, rhinovirus, enterovirus and parainfluenza virus 1, 2 and 3 to this disease presentation in a setting with a high HIV prevalence.

2.4 Case definition

A case of SARI was defined as a hospitalized person with illness onset within 7 days of hospitalization meeting age-specific inclusion criteria as follows; Children two days to under 3 months of age with a physician's diagnosis of ALRTI or sepsis, children aged 3 months to ≤ 5 years with a physician's diagnosis of ALRTI (which include pneumonia, bronchitis, pleural effusion and bronchiolitis).

2.5 Inclusion criteria for this study:

Children < 5 years of age hospitalized in either the rural or urban hospital site meeting the SARI case definition.

2.6 Study procedures

All individuals hospitalized from Monday through Friday were eligible for enrollment in the surveillance. Weekend admissions were excluded because surveillance officers were not screening during weekends. In 2013, enrolment was down-scaled at CHBAH, pediatric patients were subsequently enrolled on 2 working days per week. In 2012 routine collection of information on the children's weight was commenced in both study sites. Total number of children hospitalized meeting study case definition were documented throughout the period. Informed consent was obtained from parents or

legal guardian to the children before enrollment. History taking on demographic, socioeconomic factors, clinical presentation and outcome were documented by means of hospital record review and structured interviews. Case report forms were completed by study staff, information on patient management was collected and patients were followed for in-hospital outcome. Whole blood specimen and nasopharyngeal aspirates (NPA) were collected from consenting patients.

Patient management decisions, admission into the hospital and the intensive care unit (ICU), collection of specimens for culture were performed according to attending physician's discretion. In the event that data on patient HIV status was not available through record review of results of routine HIV testing by attending physician as part of patient management, anonymised linked HIV ELISA or PCR testing was performed using a dried blood spot or whole blood specimen if patient consented to this. HIV data was anonymised and linked; it is anonymous to the people who receive and hold the information such as a research team but contains information or codes that would allow others such as physicians responsible for the individual's care to identify an individual from it.(69) Monitoring of patients that were enrolled into SARI surveillance was carried out until discharge or death to determine in-hospital outcome.

2.6.1 Laboratory Methods

NPA in viral transport medium and blood specimens were transported to the NICD of the National Health Laboratory Services (NHLS) within 72 hours of collection at 4–8°C. Multiplex real-time reverse-transcription PCR (RT-PCR) assay was used to test the respiratory specimens for 10 respiratory viruses (influenza A and B viruses, adenovirus, parainfluenza virus 1, 2 and 3, enterovirus, RSV, human metapneumovirus and rhinovirus).(71) RT-PCR has been shown to be significantly more sensitive than Fluorescent-Antibody Assays (FA) for the detection of respiratory viruses in clinical specimens from children. (71, 72)

Blood was tested for *S. pneumoniae* using a single-target (lytA) quantitative RT-PCR assay and culture was also carried out by clinicians where indicated according to standard practice in the hospital. HIV was tested through anonymised linked dried blood spot specimen testing using HIV PCR assay for children aged <18 months and ELISA

for individuals aged ≥18months. CD4+ T-cell counts were determined by flow cytometry. (73) Tuberculosis was initially tested for using sputum smear microscopy and culture. In addition, in 2011 GeneXpert was introduced for the diagnosis of pulmonary tuberculosis at some of the sites. (74) Tuberculosis testing was carried out by clinicians where indicated according to standard practice in the hospital.

2.7 Study Population and Study sampling

All patients (children and adults) meeting the SARI case definitions were enrolled into the SARI surveillance. For this analysis, the study population comprised all children less than 5 years of age hospitalized and enrolled into the SARI surveillance program in hospitals from the rural and urban sentinel sites in South Africa from February 2009 to December 2013. Children aged 5 years and above and adults were excluded from this secondary analysis. Children that were admitted as sleepovers (children in the short stay ward that spent less than 48 hours in the hospital) were not included in the analysis dataset for CHBAH because the rural site did not have a comparable sleepover ward.

2.8 Explanatory and outcome variables

The following variables studied for each objective are described below.

Objective 1: The characteristics were described for patients enrolled at the rural and urban sites separately.

Demographic: Age, sex, race, year, 2 or more doses of pneumococcal vaccine, type of housing, number of rooms used for sleeping, number of people sleeping in a room.

Clinical presentation and in-hospital management: Duration of symptoms, antibiotics prescribed on admission, difficulty in breathing, unable to feed and drink, use of oxygen, admission into ICU, mechanical ventilation, duration of hospitalization, tuberculosis therapy started on admission and in-hospital death.

Underlying Medical conditions: HIV, tuberculosis, prematurity, reported malnutrition, malnutrition (weight for age), chronic lung diseases, asthma, renal disease, heart diseases, diabetes and neurological diseases.

Respiratory pathogens: Influenza, adenovirus, enterovirus, rhinovirus, RSV, human metapneumovirus, parainfluenza virus 1, parainfluenza virus 2, parainfluenza virus 3, parainfluenza virus 1, 2 or 3, any respiratory virus, more than 1 respiratory virus, pneumococcal infection on lytA PCR, blood culture, relevant bacterial infection on blood culture, co-infection with pneumococcus and influenza.

Objective 2:

A separate analysis was conducted to evaluate factors associated with mortality in rural and urban settings.

Outcome Variable: In-hospital death vs. no in-hospital death

Explanatory Variables:

Demographic: Age, sex, race, year, 2 or more doses of pneumococcal vaccine, type of housing, number of rooms used for sleeping, number of people sleeping in a room.

Clinical presentation and in-hospital management: Duration of symptoms, antibiotics prescribed on admission, difficulty in breathing, unable to feed and drink, use of oxygen, admission into ICU, mechanical ventilation, duration of hospitalization, tuberculosis therapy started on admission.

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Underlying Medical conditions: HIV, tuberculosis, prematurity, malnutrition (reported), malnutrition (weight for age), chronic lung diseases, asthma, renal disease, heart diseases, diabetes and neurological diseases.

Respiratory pathogens: Influenza, adenovirus, enterovirus, rhinovirus, RSV, human metapneumovirus, parainfluenza virus 1, parainfluenza virus 2, parainfluenza virus 3, parainfluenza virus 1, 2 or 3, any respiratory virus, more than 1 respiratory virus, pneumococcal infection on lytA PCR, blood culture, relevant bacterial infection on blood culture, co-infection with pneumococcus and influenza.

2.9 Data management

2.9.1 Data Processing

Surveillance data of patients with SARI from the rural and urban hospitals was obtained from the NICD. Demographic information, clinical evaluation and laboratory results of each patient were captured into Microsoft access database by laboratory and data clerks at the NICD. Data was extracted into Microsoft Excel and imported into Stata 14 for analysis. Those not meeting the eligibility criteria were excluded (see flow chart Figure.1), for each variable missing data were checked.

Prior to data analysis, all variables were defined.

- The outcome of interest was in-hospital death. In-hospital death was generated from the variable final outcome which could be death, discharge, query, referred to step down facility, transferred or unresolved. In-hospital death was defined as a categorical variable with 2 levels; “Yes” if the patient died during admission and “No” for those that were discharged. Those with final outcome recorded as query, referred to step down facility, transferred or unresolved were categorized as survived (No) as they did not die in the hospital. All individuals with missing outcomes were excluded from the logistic regression analysis.
- All continuous variables were recoded into categories
- Variable age was generated from the date of birth and date of presentation at the hospital. Age was categorized into 2 groups which are <1 year and 1-4 years.
- Number of rooms used for sleeping in the patients’ house was categorized into < 2 rooms and ≥ 2 rooms. This variable was included to reflect crowding and possibility of exposure to respiratory viruses.
- The number of people sleeping in a room was also categorized into ≤ 2 people in a room or > 2 people in a room. This variable was included to reflect crowding and possibility of exposure to respiratory viruses.
- Duration of symptoms was generated from date of presentation and date of onset of symptoms and categorized into < 2 days and ≥ 2 days prior to admission. It is the number of days from onset to admission to hospital.

- Duration of hospitalization: This variable was generated from the date of presentation and date of final outcome. It was then categorized into < 2 days, 2-7 days and > 7 days.

Some categorical variables were redefined while others were utilized as it was defined in the database.

- Sex was defined as either male or female.
- Race was defined as blacks and others, others being white, colored or asian.
- Year was based on the year that the data was collected which was 2009, 2010, 2011, 2012 and 2013.
- Type of housing was categorized as brick, iron sheeting, mud and others.
- 2 or more doses of pneumococcal vaccine was labeled as “Yes” or “No” based on the number of doses of pneumococcal vaccine received. Yes “2 or more doses” while No “<2 doses”. One dose is not effective while 2 doses are highly effective.(67)
- HIV status was defined as positive or negative documented from medical records of tests done during current or prior admission documented by a clinician.
- The variable tuberculosis was generated from AFB result, tuberculosis PCR site result or tuberculosis culture site result. A positive result from any test was considered positive.
- Parainfluenza virus 1, 2 or 3 was generated from results of each of the parainfluenza viruses.
- More than 1 respiratory virus was generated from the result of the entire respiratory viruses.
- Pneumococcal infection on lytA PCR was defined as the presence of *S. pneumonia* in the blood sample of the patient.
- Co-infection with pneumococcus and influenza was generated from the results of pneumococcal infection and influenza.
- Invasive bacterial infection on blood culture and relevant invasive bacterial infection on culture were recoded from the blood culture result.

The relevant invasive bacterial infections were *S. pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae, S. aureus, Neisseria meningitidis, E. coli, Streptococcus agalactiae or group b streptococcus, Pseudomonas aerugenosa and Salmonella* species.

- All other variables were defined as the presence “Yes” or absence “No” of the attribute.

Consistency checks were carried out to further affirm the validity and integrity of the data; some of the consistency checks done include:

- Date of admission must be after date of birth
- Date of admission must be before date of final outcome.
- Ensure that duration of symptoms meet case definition
- Ensure that there were results for samples collected.

Variables with missing data were explored and described.

2.10 Statistical Analysis plan

The analysis of the data involved three stages which were descriptive analysis, univariate analysis and multivariate analysis using binary logistic regression. All available data were used for each analysis.

2.10.1 Data Analysis

Objective 1: Descriptive statistics such as frequencies and percentages was reported by means of tables for categorical variables in each hospital site based on the demographic characteristics, clinical presentation, underlying medical conditions and respiratory pathogens. This was done using the Pearson’s Chi Square test. The expected cell number was checked to determine if the Fisher’s exact test was more appropriate. The P-value was reported with the descriptive analysis in order to determine if the differences in the above listed characteristics between the urban and rural hospital sites were significant.

Objective 2: Risk factors associated with mortality in each hospital site were determined using univariate and multivariate logistic regression analyses. This analysis was carried out separately for each hospital site.

On univariate analysis, binary logistic regression was used to determine factors associated with in-hospital mortality. In-hospital death was coded “1” while no in-hospital death was coded “0”. Crude odds ratio (OR) was reported (with 95% confidence Interval (CI) and p-values). For each univariate analysis, we used all available case information. In the multivariate model, patients with missing data for included variables were dropped from the model. All variables that were significant at $p<0.1$ in univariate analysis were evaluated in the multivariate analysis and non-significant factors were dropped with stepwise backward regression. A two-sided p-value of <0.05 was considered significant throughout. A goodness of fit test was carried out on the final model to determine how well the model fits into the set of variables.

A similar analysis was carried out restricted to children that died to assess the characteristics they presented with. Descriptive statistics such as frequencies and percentages were reported for children who died in each hospital site based on the demographic characteristics, clinical presentation, underlying medical conditions and respiratory pathogens using the Pearson’s Chi Square test or the Fisher’s exact. Univariate and multivariate logistic regression analysis were carried out using the hospital site as the outcome variable in order to determine factors associated with each hospital site. The rural hospital site was coded “1” while the urban was coded “0”. Crude odds ratio (OR) was reported (with 95% confidence Interval (CI) and p-values). All variables that were significant at $p<0.1$ on univariate analysis were evaluated in the multivariate analysis and non-significant factors were dropped with stepwise backward regression. A two-sided p-value of <0.05 was considered significant throughout. A goodness of fit test was carried out on the final model to determine how the variables fit into the model.

Survival estimates were compared amongst those who died looking at duration of symptoms to hospitalization (onset of symptoms to date of hospitalization), duration of symptoms to death (onset of symptoms to date of death) and duration of hospitalization

to time of death (date of hospitalization to date of death) in the rural and urban sites using the Kaplan-Meier survival estimates with a log-rank test for equality of survival function amongst children that died.

Analysis was performed using Stata version14 (StataCorp Limited, Texas, United States of America).

2.11 Ethical consideration

The study was approved by the University of the Witwatersrand Human Research Ethics Committee (Medical) in December 2015. Ethics approval certificate is attached (Appendix 2). Permission to use the NICD data was granted (Appendix 3). The protocol for the original study was approved by Ethics committee of University of the Witwatersrand. Annual recertification was obtained from the Ethics committee (Appendix 4).

CHAPTER 3

3.0 RESULTS

The results presented in this chapter were based on the study objectives and the data analysis plan. The demographic characteristics, clinical presentation and respiratory pathogens in children < 5 years of age hospitalized with SARI in each hospital site were compared and reported.

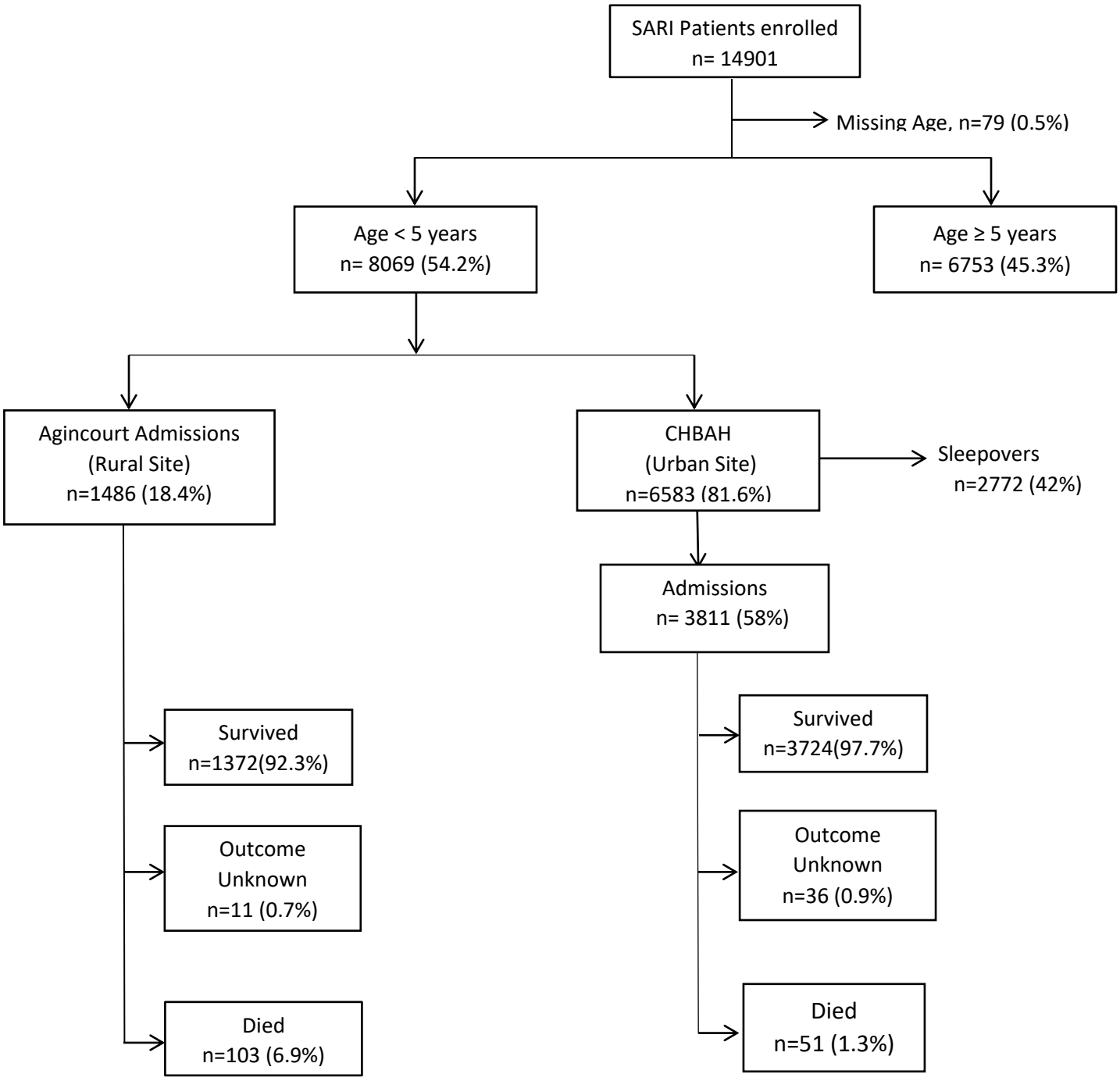
The risk factors for mortality were reported based on the results from the univariate and multivariate analysis.

3.1 Overview

From February 2009 through December 2013, 14901 patients with SARI were enrolled in the rural and urban hospital sites. Of these, 14822 (95.5%) patients had their ages known of which 8069 (54.2%) were children < 5 years old (**Figure 1**). 6583 (81.6%) of these patients presented at the urban hospital site while 1486 (18.4%) presented at the rural hospital site. In the urban site 2772/6583 (42%) were classified as sleepovers and were excluded from further analysis while 3811/6583 (58%) were pediatric admissions.

A total of 5297 children < 5 years were included in the final analysis, 3811(72%) from the urban site and 1486 (28%) from the rural site. In the urban site, 3724 (97.7%) of these patients survived, 36 (0.9%) patient's outcome were unknown and 51 (1.3%) died. From the rural site1372 (92.3%) survived, 11 (0.7%) had unknown outcome while 103 (6.9%) died (Figure 1).

Figure 1: Flow chart of patients enrolled in the South African Severe Acute Respiratory Illness (SARI) surveillance program in urban and rural sites in South Africa, 2009 to 2013.



*CHBAH (Chris Hani Baragwanath Hospital)

3.1.1 Demographic Characteristic

The proportion of children aged <1 year was significantly higher in the urban (74.9%, 2855/3811) as compared to the rural site (58.8%, 874/1486) p<0.001. In both urban and rural site, majority of the children with SARI were males (57.5% urban vs. 56.9% rural) p=0.666. The majority of patients were black at both urban (3724/3811, 97.7%) and rural (1479/1486, 99.5%) sites.

The highest number of SARI admissions was in 2009 in both the urban (1031/3811, 27.0%) and the rural (330/1486, 22.2%) sites, however, they decreased sharply in 2010 in the urban hospital while they decreased slightly and stabilized in rural hospitals. Of all patients in the urban site 1386/3811 (36.4%) had record of pneumococcal vaccination of which 1032/1386 (74.5%) had received 2 or more doses of pneumococcal vaccine while in the rural site 855/1486 (57.6%) had record of pneumococcal vaccination of which 551/855 (64.4%) had received 2 or more doses of the vaccine which is significantly different p<0.001. Most of the children lived in brick houses in both urban 2680/3811 (70.3%) and rural 1419/1486 (95.5%) sites, in the urban site 1079/3811 (28.3%) of the patients lived in houses with iron sheeting while only 7/1486 (0.5%) patients were recorded living in housing with iron sheeting in the rural site. (Table 1)

3.1.2 Clinical Presentation

The proportion of patients reporting symptoms for ≥ 2 days before hospitalization was higher in the urban (2217/3784, 58.6%) than in the rural (668/1474, 45.3%) site (p<0.001). The majority of patients were administered antibiotics on admission in both urban (3446/3687, 93.5%) and rural (1469/1479, 99.3%) sites (p<0.001). A high percentage of the patients reported difficulty in breathing in both study sites 2813/3801 (74%) in urban and 1207/1477 (81.7%) in rural (p<0.001). In the urban site 712/3800 (18.7%) were unable to feed and drink vs. 345/1477 (23.4%) in the rural site (p<0.001). A higher proportion of patients in the urban site 2025/3772 (53.7%) required oxygen therapy compared to 312/1474 (21.2%) in the rural site (p<0.001).

Patients in the rural site were significantly more likely to be hospitalized for 2-7 days than < 2 days (1083/1466, 73.9%) compared to patients in the urban site (2305/3768, 61.2%) p<0.001. The median duration of hospitalization in the urban site was 5 days (interquartile range (IQR) 1-60) while it is 5 days (IQR 0-27) in the rural site, p=0.018. (Table 1)

TABLE 1

Comparison of the demographic characteristics, clinical presentation and respiratory pathogens agents of children aged < 5 years with SARI in urban and rural hospital sites, South Africa 2009-2013.

Characteristics	Urban site N=3811 n (%)	Rural site N= 1486 n (%)	P value
Demographic			
Age group			
< 1 year	2855/3811 (74.9)	874/1486 (58.8)	<0.001
1 – 4 years	956/3811 (25.1)	612/1486 (41.2)	
Sex			
Female	1619/3811 (42.5)	641/1486 (43.1)	0.666
Male	2192/3811 (57.5)	835/1486 (56.9)	
Race			
Black	3724/3811 (97.7)	1479/1486 (99.5)	<0.001
Other	87/3811 (2.3)	7/1486 (0.5)	
Year			
2009	1031/3811 (27.0)	330/1486 (22.2)	<0.001
2010	791/3811 (20.8)	303/1486 (20.4)	
2011	795/3811 (20.9)	252/1486 (17.0)	
2012	793/3811 (20.8)	306/1486 (20.6)	
2013	401/3811 (10.5)	295/1486 (19.8)	
2 or more doses of pneumococcal vaccine			
Yes	1032/1386 (74.5)	551/855 (64.4)	<0.001
No	354/1386 (26.5)	304/855 (35.6)	
Missing	2425	631	

Type of housing			
Brick	2680/3811 (70.3)	1419/1484 (95.5)	<0.001
Iron Sheeting	1079/3811 (28.3)	7/1486 (0.5)	
Mud	8/3811 (0.2)	32/1486 (2.1)	
Others	44/3811 (1.2)	28/1486 (1.9)	
Number of rooms used for sleeping			
<2 Rooms	1452/3777 (38.4)	169/1467 (11.5)	<0.001
≥2 Rooms	2325/3777 (61.6)	1298/1467 (88.5)	
Missing	34	19	
Number of people sleeping in a room			
≤ 2 people	256/3767 (6.8)	15/1466 (1.0)	<0.001
>2 people	3511/3767 (93.2)	1450/1465 (99.0)	
Missing	44	21	
Clinical presentation			
Duration of symptoms			
<2 days prior to admission	1567/3784 (41.4)	806/1474 (54.7)	<0.001
≥2 days prior to admission	2217/3784 (58.6)	668/1474 (45.3)	
Missing	27	12	
	Median=2 days, *IQR(0-10)	Median=1 days, *IQR(0-7)	<0.001
Antibiotics prescribed on admission			
Yes	3446/3687 (93.5)	1469/1479 (99.3)	<0.001
No	241/3687 (6.5)	10/1479 (0.7)	
Missing	124	7	
Difficulty breathing			
Yes	2813/3801 (74.0)	1207/1477 (81.7)	<0.001
No	988/3801 (26.0	270/1477 (18.3)	
Missing	10	9	
Unable to drink or feed			
Yes	712/3800 (18.7)	345/1477 (23.4)	<0.001
No	3088/3800 (81.3)	1132/1477 (76.6)	
Missing	11	9	
Use of oxygen			

Yes	2025/3772 (53.7)	312/1474 (21.2)	<0.001
No	1747/3772 (46.3)	1162/1474 (78.8)	
Missing	39	12	
Admission into ICU			
Yes	37/3772 (1.0)	0/1473 (0.0)	<0.001
No	3735/3772 (99.0)	1473/1473 (100.0)	
Missing	39	13	
Mechanical ventilation			
Yes	39/3772 (1.0)	23/1474 (1.6)	0.113
No	3733/3772 (99.0)	1451/1474 (98.4)	
Missing	39	12	
Duration of hospitalization			
<2 days	406/3768 (10.8)	129/1466 (8.8)	<0.001
2-7 days	2305/3768 (61.2)	1083/1466 (73.9)	
>7 days	1057/3768 (28.0)	254/1466 (17.3)	
Missing	43	20	
	Median=5 days, *IQR(1-40)	Median=5 days, *IQR(0-27)	0.018
TB therapy started on admission	123/3763 (3.3)	60/1474 (4.1)	0.155
Yes	3640/3763 (96.7)	1414/1474 (95.9)	
No	48	12	
Missing			
In-hospital death			
Yes	51/3811 (1.3)	103/1486 (6.9)	<0.001
No	3760/3811 (98.7)	1383/1486 (93.1)	
Underlying Medical Conditions			
HIV			
Positive	257/2493 (10.3)	233/1126 (20.7)	<0.001
Negative	2236/2493 (89.7)	893/1126 (79.3)	
Missing	1318	360	
Tuberculosis			
Yes	85/815 (10.4)	7/123 (5.7)	0.100
No	730/815 (89.6)	116/123 (94.3)	

Missing	2996	1363	
Prematurity			
Yes	58/3806 (1.5)	3/1482 (0.2)	<0.001
No	3748/3806 (98.5)	1479/1482 (99.8)	
Missing	5	4	
Malnutrition (reported)			
Yes	26/3806 (0.7)	7/1482 (0.5)	0.382
No	3780/380 (99.3)	1475/1482 (99.5)	
Missing	5	4	
Malnutrition (weight for age)			
Yes	209/758 (27.6)	99/451 (22.0)	0.030
No	549/758 (72.4)	352/451 (78.0)	
Missing	3053	1035	
Chronic lung diseases			
Yes	3/3806 (0.1)	0/1482 (0.0)	0.564
No	3803/3806 (99.9)	1482/1482 (100.0)	
Missing	5	4	
Asthma			
Yes	17/3806 (0.5)	12/1482 (0.8)	0.108
No	3789/3806 (99.5)	1470/1482 (99.2)	
Missing	5	4	
Renal diseases			
Yes	3/3806 (0.1)	0/1482 (0.0)	0.564
No	3803/3806 (99.9)	1482/1482 (100.0)	
Missing	5	4	
Heart diseases			
Yes	27/3806 (0.7)	0/1482 (0.0)	<0.001
No	3779/3806 (99.3)	1482/1482 (100.0)	
Missing	5	4	
Diabetes			
Yes	4/3806 (0.1)	0/1482 (0.0)	0.582
No	3802/3806 (99.9)	1482/1482 (100.0)	
Missing	5	4	

Neurological diseases			0.171
Yes	11/3806 (0.3)	8/1482 (0.5)	
No	3795/3806 (99.7)	1474/1482 (99.5)	
Missing	5	4	
Respiratory pathogens			
Influenza			
Yes	227/3709 (6.1)	118/1426 (8.3)	0.006
No	3482/3709 (93.9)	1308/1426 (91.7)	
Missing	102	60	
Adenovirus			
Yes	779/3461 (22.5)	323/1304 (24.8)	0.099
No	2682/3461 (77.5)	981/1304 (75.2)	
Missing	350	182	
Enterovirus			
Yes	344/3708 (9.3)	139/1426 (9.4)	0.605
No	3364/3708 (90.7)	1287/1426 (90.6)	
Missing	103	60	
Rhinovirus			
Yes	1219/3708 (32.9)	495/1426 (34.7)	0.211
No	2489/3708 (67.1)	931/1426 (65.3)	
Missing	103	60	
Respiratory syncytial virus			
Yes	1010/3708 (27.2)	246/1426 (17.3)	<0.001
No	2698/3708 (72.8)	1180/1426 (82.7)	
Missing	103	60	
Human metapneumovirus			
Yes	209/3708 (5.6)	75/1426 (5.3)	0.597
No	3499/3708 (94.4)	1351/1426 (94.7)	
Missing	103	60	
Parainfluenza virus 1			
Yes	64/3708 (1.7)	17/1426 (1.2)	0.169
No	3644/3708 (98.3)	1409/1426 (98.8)	
Missing	103	60	
Parainfluenza virus 2			
Yes	40/3708 (1.1)	23/1426 (1.6)	0.119

No	3668/3708 (98.9)	1403/1426 (98.4)	
Missing	103	60	
Parainfluenza virus 3			
Yes	230/3708 (6.2)	90/1426 (6.3)	0.885
No	3478/3708 (93.8)	1336/1426 (93.7)	
Missing	103	60	
Parainfluenza virus 1,2 or 3			
Yes	327/3708 (8.8)	127/1426 (8.9)	0.921
No	3381/3708 (91.2)	1299/1426 (91.1)	
Missing	103	60	
Any respiratory virus			
Yes	2878/3709 (77.6)	1082/1426 (75.9)	0.189
No	831/3709 (22.4)	344/1426 (24.1)	
Missing	102	60	
More than 1 respiratory virus			
Yes	1253/3709 (33.8)	467/1426 (32.7)	0.482
No	2456/3709 (66.2)	959/1426 (67.3)	
Missing	102	60	
Pneumococcal infection on lytA PCR			
Yes	113/1592 (7.1)	53/1211 (4.4)	0.002
No	1479/1592 (92.9)	1158/1211 (95.6)	
Missing	2219	275	
Blood culture done			
Yes	2189/3811 (57.4)	39/1486 (2.6)	<0.001
No	1622/3811 (42.6)	1447/1486 (97.4)	
**Relevant bacterial infection on blood culture			
Yes	50/2189 (2.3)	0/39 (0.0)	1.000
No	2139/2189 (97.7)	39/39 (100.0)	
Missing	1622	1447	
Co-infection with pneumococcus and influenza			
Yes	17/1393 (1.2)	3/1063 (0.3)	0.011
No	1375/1393 (98.8)	1060/1063 (99.7)	

Missing	2419	423

*** IQR=interquartile range**

** Column percentage were calculated as a percent of all those with available data for the variable (i.e. not including missing)

****** The relevant invasive bacterial infections are *Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae, Staphylococcus aureus, Neisseria meningitidis, Escherichia coli, Streptococcus agalactiae or group b streptococcus, Pseudomonas aerugenosa and Salmonella* species.

3.1.3 Underlying Medical Conditions

Information on HIV infection status was available for 3619 (68.3%) children overall with 1678 (31.7%) missing. The HIV prevalence in the urban site was significantly lower 10.3% (257/2493) than in the rural site 20.7% (233/1126), p<0.001. In the urban site more children were newly diagnosed with tuberculosis 85/815 (10.4%) compared to the rural site of 7/123 (5.7%). Prematurity (58/3806 (1.5%) in urban with 3/1482 (0.2%) in rural p<0.001) and underlying heart disease (27/3802 (0.7%) in the urban site and none in the rural site, p<0.001) were more commonly reported in the urban site. A similar percent of children were reported malnourished in the urban and rural sites (26/3806 (0.7%) in urban with 7/1482 (0.5%) in rural, p=0.382). Malnutrition was further assessed by estimating the weight for age which was calculated using the WHO z score chart for 1209/5297 (22.8%) of individuals for whom weight data were available. A significant higher proportion were assessed to be malnourished in the urban site (209/758, 27.6%) as compared to the rural site (99/451, 22.0%) (p=0.03). (Table 1)

3.1.4 Respiratory pathogens

Overall 5135/5297 (96.9%) of children were tested for respiratory viruses, influenza was detected more commonly in the rural (118/1426, 8.3%) than in the urban (227/3709, 6.1%) (p=0.006).

RSV was detected more in the urban (1010/3708, 27.2%) than in the rural (246/1426, 17.3%) p < 0.001. A similar percentage of children had at least one respiratory virus in

both study sites (2878/3709, (77.6%) in urban with 1082/1426, (75.9%) in rural, p=0.189).

Overall 2803/5297 (52.9%) children were tested for blood pneumococcal on lytA PCR of which a significantly higher proportion of those positive were recorded in urban (113/1592, 7.1%) compared to rural (53/1211, 4.4%), (p=0.002). Total number of children that had blood culture were 2189/3811 (35.9%) in urban vs. 39/1486 (2.6%) in rural, (p<0.001), with 50/2189 (2.3%) testing positive for relevant bacterial infection in urban and 0/39 (0%) testing positive in the rural site, (p=1.000). (Table 1)

3.2 Case-fatality proportion (CFP)

The overall CFP in this study was 2.9% (154/5297).The CFP was significantly higher in the rural (103/1486, 6.9%) than the urban (51/3811, 1.3%) p< 0.001. This was observed among both HIV-infected [urban 6.6% (17/257) vs. rural 12.9% (30/233), (p=0.019)] and HIV-uninfected [urban 0.6% (13/2236) vs. rural 4.2% (36/857), (p<0.001)] children. (Tables 2 and 3)

3.3.1 Univariate analysis of risk factors associated with mortality in the urban site

The variables found to be significantly associated with in-hospital mortality in the urban site on univariate analysis using binary logistic regression at p<0.1 were HIV, race, year, difficulty in breathing, use of oxygen, duration of hospitalization, chronic lung disease, rhino virus, RSV, any respiratory virus, blood culture and invasive relevant bacterial infection on culture (Table 2).

3.3.2 Multivariate analysis of variables associated with in-hospital mortality in the urban site

A total of 2475 children from urban site with complete data were included in the multivariable analysis. In the urban site the only factor independently associated with death on multivariate analysis was HIV infection (OR 12.1, 95% CI 5.8-25.2). (Table 2)

Table 2: Factors associated with In-Hospital death in children < 5 years of age with SARI, in Urban Hospital Site, South Africa, 2009–2013.

Characteristics	Hospitalized Case Fatality Proportion	Univariate analysis OR (95%CI)	P value	Multivariable analysis OR (95%CI)	P value
Demographic					
Age group					
< 1 year	42/2855 (1.5%)	1.6 (0.8-3.2)	0.200	-	-
1 – 4 years	9/956 (0.94%)	Reference			
Sex					
Female	26/1619 (1.6%)	1.4 (0.8-2.5)	0.219	-	-
Male	25/2192 (1.1%)	Reference			
Race					
Black	45/3724 (1.2%)	Reference	**0.020**	NS	NS
Other	6/87 (6.9%)	6.1 (2.5-14.6)			
Year					
2009	15/1031 (1.5%)	Reference	**0.005**	NS	NS
2010	21/791 (2.7%)	1.8 (0.9-3.6)			
2011	7/795 (0.9%)	0.6 (0.2-1.5)			
2012	6/793 (0.8%)	0.5 (0.2-1.3)			
2013	2/401 (0.5%)	0.3 (0.1-1.5)			
2 or more doses of pneumococcal vaccine					
Yes	18/1032 (1.7%)	Reference	0.778	-	-
No	7/354 (2%)	1.1 (0.5-2.7)			
Type of housing					
Brick	35/2680 (1.3%)	Reference	0.341	-	-
Iron Sheeting	14/1079 (1.3%)	1.0 (0.5-1.9)			
Mud	0/8 (0%)	Undefined			
Others	2/44 (4.6%)	3.6 (0.8-15.5)			
Number of rooms used for sleeping					
<2 Rooms	22/1452 (1.5%)	1.3 (0.7-2.2)	0.420	-	-
≥2 Rooms	28/2325 (1.2%)	Reference			

Number of people sleeping in a room					
≤2 people	4/256 (1.6%)	1.2 (0.4-3.3)	0.739	-	-
>2 people	46/3511 (1.3%)	Reference			
Clinical presentation					
Duration of symptoms					
<2 days prior to admission	17/1567 (1.1%)	Reference	0.279	-	-
≥2 days prior to admission	33/2217 (1.5%)	1.4 (0.8-2.5)			
Difficulty breathing					
Yes	43/2813 (1.5%)	2.2 (1.0-4.9)	**0.04**	NS	NS
No	7/988 (0.7%)	Reference			
Unable to drink or feed					
Yes	13/712 (1.8%)	1.5 (0.8-2.9)	0.204	-	-
No	37/3088 (1.2%)	Reference			
Antibiotics prescribed on admission					
Yes	48/3446 (0.8%)	Reference	0.352	-	-
No	5/241 (0.8%)	1.6 (0.6-4.1)			
Use of oxygen					
Yes	43/2025 (2.1%)	5.4 (2.4-12.0)	**<0.0001**	NE	NE
No	7/1747 (0.4%)	Reference			
Admission into ICU					
Yes	0/37 (0%)	Undefined	-	-	-
No	50/3735 (1.3%)	Reference			
Mechanical ventilation					
Yes	0/39 (0%)	Undefined	-	-	-
No	50/3733 (1.3%)	Reference			
Duration of hospitalization					
<2 days	4/406 (1%)	Reference	**0.07**	NS	NS
2-7 days	25/2305 (1.1%)	1.1 (0.4-3.2)			
>7 days	22/1057 (2.1%)	2.1 (0.7-6.2)			
TB therapy started on admission					

Yes	3/123 (2.4%)	1.9 (0.6-6.2)	0.325	-	-
No	47/3640 (1.3%)	Reference			
Underlying medical conditions					
HIV					
Positive	17/257 (6.6%)	12.1 (5.8-25.2)	**<0.0001**	**12.1 (5.8-25.2)**	**<0.001**
Negative	13/2236 (0.6%)	Reference		**Reference**	
Tuberculosis					
Yes	2/85 (2.4%)	1.3 (0.3-6.0)	0.720	-	-
No	13/730 (1.8%)	Reference			
Prematurity	1/58 (1.7%)	1.3 (0.2-9.8)	0.792	-	-
Yes	49/3748 (1.3%)	Reference			
No					
Malnutrition (reported)	1/26 (3.9%)	3.0 (0.4-22.9)	0.354	-	-
Yes	49/3780 (1.3%)	Reference			
No					
Malnutrition					
(weight for age)	3/209 (1.4%)	3.0 (0.4-22.9)	0.279	-	-
Yes	1/548 (0.2%)	Reference			
No					
Chronic lung diseases	1/3 (33.3%)	38.3 (3.4-429.4)	**0.027**	NS	NS
Yes	49/3803 (1.3%)	Reference			
No					
Asthma	0/17 (0%)	Undefined	-	-	-
Yes	50/3789 (1.3%)	Reference			
No					
Renal diseases	0/3 (0%)	Undefined	-	-	-
Yes	50/3803 (1.3%)	Reference			
No					
Heart diseases	0/32 (0%)	Undefined	-	-	-
Yes	50/3779 (1.3%)				
No					
Diabetes	0/4 (0%)	Undefined	-	-	-
Yes	53/3802 (1.3%)				

No					
Neurological diseases	1/11 (9.1%)	7.6 (1.0-60.9)	0.134	-	-
Yes	49/3795 (1.3%)	Reference			
No					
Respiratory pathogen					
Influenza					
Yes	4/227 (1.8%)	1.3(0.5-3.8)	0.593	-	-
No	46/3482 (1.3%)	Reference			
Adenovirus					
Yes	12/779 (1.5%)	Reference	0.681	-	-
No	36/2682 (1.3%)	0.9 (0.5-1.7)			
Enterovirus					
Yes	5/344 (1.5%)	1.1 (0.4-2.8)	0.861	-	-
No	45/3364 (1.3%)	Reference			
Rhinovirus					
Yes	11/1219 (0.9%)	Reference	**0.09**	NS	NS
No	39/2489 (1.6%)	1.7 (0.9-3.4)			
Respiratory syncytial virus					
Yes	8/1010 (0.8%)	Reference	**0.058**	NS	NS
No	42/2698 (1.6%)	2.0 (0.9-4.2)			
Human metapneumovirus					
Yes	2/209 (1.0%)	Reference	0.595	-	-
No	48/3499 (1.4%)	1.4 (0.3-6.0)			
Parainfluenza virus 1					
Yes	1/64 (1.6%)	1.2 (0.2-8.6)	0.8838	-	-
No	49/3644 (1.3%)	Reference			
Parainfluenza virus 2					
Yes	1/40 (2.5%)	1.9 (0.3-14.1)	0.570	-	-
No	49/3668 (1.3%)	Reference			
Parainfluenza virus 3					
Yes	4/230 (1.7%)	1.3(0.5-3.7)	0.611	-	-
No	46/3478 (1.3%)	Reference			
Parainfluenza virus 1,2					

or 3					
Yes	5/327 (1.5%)	1.2 (0.5-2.9)	0.771	-	-
No	45/3381 (1.3%)	Reference			
Any respiratory virus					
Yes	33/2878 (1.2%)	Reference	**0.060**	NS	NS
No	17/831 (2.1%)	1.8 (1.0-3.2)			
More than 1 respiratory virus					
Yes	19/1253 (1.5%)	Reference	0.529	-	-
No	31/2456 (1.3%)	0.8(0.5-1.5)			
Pneumococcal infection on lytA PCR					
Yes	1/113 (0.9%)	0.9(0.1-6.7)	0.892	-	-
No	15/1479 (1.0%)	Reference			
Blood culture done					
Yes	36/2189 (1.6%)	1.8 (1.0-3.3)	**0.05**	NE	NE
No	15/1622 (0.9%)	Reference			
****R**elevant bacterial infection on blood culture					
Yes	1/50 (2%)	1.2 (0.2-9.1)	**0.04**	NE	NE
No	35/2139 (1.6%)	Reference			
Co-infection with pneumococcus and influenza					
Yes	0/17 (0%)	Undefined	-	-	-
No	15/1375 (1.1%)				

- Variables statistically significant on univariate and multivariate logistic regression analysis presented in boldface.
- Variables not statistically significant on univariate logistic regression ($p>0.1$) were omitted from the multivariable logistic regression model.
- NE (Not evaluated): variables statistically significant on univariate analysis but omitted in the multivariate analysis.
- NS (Not significant): variables not statistically significant on multivariate analysis ($p\geq0.05$)

** The relevant invasive bacterial infections are *Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae, Staphylococcus aureus, Neisseria meningitidis, Escherichia coli, Streptococcus agalactiae or group b streptococcus, Pseudomonas aerugenosa and Salmonella* species.

3.3.3 Univariate analysis of risk factors associated with mortality in the rural site

The variables found to be significantly associated with in-hospital mortality in the rural site on univariate analysis using binary logistic regression at p<0.1 were HIV, age-group, sex, unable to drink or feed, use of oxygen, mechanical ventilation, duration of hospitalization, malnutrition (weight for age), adenovirus, RSV, any respiratory virus, more than 1 respiratory virus, pneumococcal infection and blood culture. (Table 3)

3.3.4 Multivariate analysis of variables associated with in-hospital mortality in the rural site

A total of 1029 from the rural site with complete data were included in multivariable analysis. In the rural site HIV infection (OR 3.5, 95%CI 1.7-6.9), age <1 year (OR 3.5, 95% CI 2.0-6.1) vs. 1-4 years, malnutrition (OR 12.8, 95%CI 1.2-134.6) and pneumococcal infection on *lytA* PCR (OR 4.5, 95% CI 1.8-10.8) were independently associated with increased risk of mortality. Individuals with respiratory virus detected were less likely to die (OR 0.4, 95%CI 0.2-0.6). (Table 3)

Table 3:

Factors associated with In-Hospital death in children < 5 years of age with SARI, in Rural Hospital Site, South Africa, 2009–2013.

Characteristics	Hospitalized Case Fatality Proportion	Univariate analysis OR (95%CI)	P value	Multivariable analysis OR (95%CI)	P value
Demographic					
Age group					
< 1 year	82/874 (9.4%)	2.9 (1.8-4.8)	**<0.0001**	**3.5 (2.0-6.1)**	**<0.001**
1 – 4 years	21/612 (3.4%)	Reference		**Reference**	
Sex					
Female	60/641 (9.3%)	1.9 (1.3-2.9)	**0.002**	NS	NS
Male	43/845 (5.1%)	Reference			
Race					
Black	102/1377 (7.4%)	Reference	0.497	-	-
Other	1/7 (14.3%)	2.3 (0.3-18.9)			
Year					

2009	18/330 (5.5%)	Reference	0.193	-	-
2010	29/303 (9.6%)	1.8 (1.0-3.4)			
2011	21/252 (8.3%)	1.6 (0.8-3.0)			
2012	18/306 (5.9%)	1.1 (0.6-2.1)			
2013	17/295 (5.8%)	1.1 (0.5-2.1)			
2 or more doses of pneumococcal vaccine					
Yes	31/551 (5.6%)	Reference			
No	26/304 (8.6%)	1.6 (0.9-2.7)	0.106	-	-
Type of housing					
Brick	97/1419 (6.8%)	Reference	0.391	-	-
Iron Sheeting	0/7 (0%)	Undefined			
Mud	2/32 (6.3%)	0.9 (0.2-3.9)			
Others	4/28 (14.3%)	2.2 (0.05-0.1)			
Number of rooms used for sleeping					
<2 Rooms	17/169 (1.0%)	1.6 (0.9-2.8)	0.100	-	-
≥2 Rooms	84/1298 (6.5%)	Reference			
Number of people sleeping in a room					
≤2 people	1/15 (6.7%)	1.0(0.1-7.4)	0.972	-	-
>2 people	100/1450 (6.9%)	Reference			
Clinical presentation					
Duration of symptoms					
<2 days prior to admission	51/806 (6.3%)	Reference	0.326	-	-
≥2 days prior to admission	51/668 (7.6%)	1.2 (0.8-1.8)			
Difficulty breathing					
Yes	90/1207 (7.5%)	1.6 (0.9-2.9)	0.108	-	-
No	13/270 (4.8%)	Reference			
Unable to drink or feed					
Yes	34/345 (9.9%)	1.7 (1.1-2.6)	**0.021**	NS	NS
No	69/1132 (6.1%)	Reference			
Antibiotics prescribed on admission					

Yes	101/1469 (6.9%)	Reference	0.177	-	-
No	2/10 (20%)	3.4 (0.7-16.2)			
Use of oxygen					
Yes	83/312 (26.6%)	20.7(12.4-34.4)	**<0.0001**	NE	NE
No	20/1162 (1.7%)	Reference			
Admission into ICU					
Yes	0/0 (0%)	Undefined	-	-	-
No	103/1473 (7%)	Omitted			
Mechanical ventilation					
Yes	19/23 (82.6%)	77.3(25.7-232.3)	**<0.0001**	NE	NE
No	84/1451 (5.8%)	Reference			
Duration of hospitalization					
<2 days	18/129 (14%)	Reference	**0.003**	NS	NS
2-7 days	62/1083 (5.7%)	0.4 (0.2-0.7)			
>7 days	22/254 (8.7%)	0.6 (0.3-1.1)			
Tuberculosis therapy started on admission					
Yes	4/60 (6.7%)	0.9 (0.3-2.7)	0.9201	-	-
No	99/1414 (7%)	Reference			
Underlying medical conditions					
HIV					
Positive	30/233 (12.9%)	3.5 (2.1-5.8)	**<0.0001**	**3.5 (1.7-6.9)**	**<0.001**
Negative	36/857 (4.2%)	Reference		**Reference**	
Tuberculosis					
Yes	2/7 (28.6%)	7.3 (1.2-45.9)	**0.058**	NS	NS
No	6/116 (5.2%)	Reference			
Prematurity					
Yes	0/3 (0%)	Undefined	-	-	-
No	102/1479 (6.9%)	Reference			
Malnutrition (reported)					
Yes	3/7 (42.9%)	10.4 (2.3-47.2)	**0.008**	**12.8 (1.2-134.6)**	**0.034**
No	99/1475 (6.7%)	Reference		**Reference**	
Malnutrition (weight for age)					
Yes	12/99 (12.1%)	1.2 (0.4-2.0)	**0.005**	NE	NE
No	14/352 (4.0%)	Reference			

Chronic lung diseases					
Yes	0/0 (0%)	Undefined			
No	102/1380 (7.4%)	Reference	-	-	-
Asthma					
Yes	0/12 (0%)	Undefined	-	-	-
No	102/1470 (6.9%)	Reference			
Renal diseases					
Yes	0/0 (0%)	Undefined	-	-	-
No	102/1482 (6.9%)	Reference			
Heart diseases					
Yes	0/0 (0%)	Undefined	-	-	-
No	102/1482 (6.9%)	Reference			
Diabetes					
Yes	0/0 (0%)	Undefined	-	-	-
No	102/1482 (6.9%)	Reference			
Neurological diseases					
Yes	1/8 (12.5%)	1.9 (0.2-15.9)	0.569	-	-
No	101/1474 (6.9%)	Reference			
Respiratory pathogens					
Influenza					
Yes	4/118 (3.4%)	0.5 (0.2-1.4)	0.140	-	-
No	86/1308 (6.6%)	Reference			
Adenovirus					
Yes	12/323 (3.7%)	Reference	**0.032**	NS	NS
No	67/981 (6.8%)	1.9 (1.0-3.6)			
Enterovirus					
Yes	9/139 (6.5%)	1.0 (0.5-2.1)	0.934	-	-
No	81/1287 (6.3%)	Reference			
Rhinovirus					
Yes	30/495 (6.1%)	Reference	0.776	-	-
No	60/931 (6.4%)	1.1 (0.7-1.7)			
Respiratory syncytial virus					
Yes	5/246 (2.0%)	Reference	**0.001**	NS	NS

No	85/1180 (7.2%)	3.7 (1.5-9.3)			
Human metapneumovirus					
Yes	2/75 (2.75)	Reference	0.136	-	-
No	88/1351 (6.5%)	2.5 (0.6-10.5)			
Parainfluenza virus 1					
Yes	1/17 (5.9%)	0.9 (0.1-7.1)	0.941	-	-
No	89/1409 (6.3%)	Reference			
Parainfluenza virus 2					
Yes	1/23 (4.3%)	0.7 (0.1-5.0)	0.680	-	-
No	89/1403 (6.3%)	Reference			
Parainfluenza virus 3					
Yes	5/90 (5.6%)	0.9 (0.3-2.2)	0.756	-	-
No	85/1336 (6.4%)	Reference			
Parainfluenza virus 1,2 or 3					
Yes	7/127 (5.5%)	0.9 (0.4-1.9)	0.692	-	-
No	83/1299 (6.4%)	Reference			
Any respiratory virus					
Yes	55/1082 (5.1%)	0.5 (0.3-0.8)	**0.001**	**0.4 (0.2-0.6)**	**<0.001**
No	35/344 (10.2%)	Reference		**Reference**	
More than one respiratory virus					
Yes	20/467 (4.3%)	Reference	**0.023**	NS	NS
No	70/959 (7.3%)	1.8 (1.1-2.9)			
Pneumococcal infection on lytA PCR					
Yes	8/53 (15.1%)	2.9 (1.3-6.5)	**0.016**	**4.5 (1.8-10.8)**	**0.001**
No	66/1158 (5.7%)	Reference		**Reference**	
Blood culture done					
Yes	11/39 (28.2%)	5.8 (2.8-12.0)	**<0.0001**	NE	NE
No	92/1447 (6.4%)	Reference			
**Relevant bacterial infection on blood culture					

Yes	Empty	Omitted	-	-	-
No	11/39 (28.2%)	Reference			
Co-infection with pneumococcus and influenza					
Yes	0/3 (0%)	Undefined	-	-	-
No	64/1060 (6%)	Reference			

* Variables statistically significant on univariate and multivariate logistic regression analysis presented in boldface.
* Variables not statistically significant on univariate logistic regression (p>0.1) were omitted from the multivariable logistic regression model.
* NE (Not evaluated): variables statistically significant on univariate analysis but omitted in the multivariate analysis.
* NS (Not significant): variables not statistically significant on multivariate analysis (p≥0.05)

** The relevant invasive bacterial infections are *Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae, Staphylococcus aureus, Neisseria meningitidis, Escherichia coli, Streptococcus agalactiae or group b streptococcus, Pseudomonas aerugenosa and Salmonella* species

3.4.1 Characteristics of children who died

Amongst children who died, the proportion of children aged <1 year was not significantly different in both hospital sites (42/51 (82.4%) in urban and 82/103 (79.6%) in rural, p=0.686. In both urban and rural sites majority of the children who died were females (26/51 (51.0%) urban vs. 60/103 (58.3%) rural, p=0.392). The highest number of children that died was recorded in 2010 in both urban (21/51, 41.2%) and rural (29/103, 28.1%) sites. Of all the children that died in the urban site 18/25 (72.0%) had received 2 or more doses of pneumococcal vaccine while in the rural site (31/57 (54.4%) p=0.134) had received PCV. Most of the children who died lived in brick houses in both urban 35/51 (68.6%) and rural 97/103 (94.2%) sites, p<0.001. (Table 4)

The proportion of children that died reporting symptoms for ≥ 2 days before hospitalization was higher in the urban (33/50, 66.0%) than in the rural (51/102, 50.0%) site, (p=0.062). The majority of the children that died were administered antibiotics on admission in both urban (45/50, 90.0%) and rural (101/102, 98.1%) sites, but significantly higher in the rural site (p=0.025). A high percentage of children who died reported difficulty in breathing in both study sites 43/50 (86.0%) in urban and 90/103

(87.4%) in rural (p=0.812). Children that died in the rural site were significantly more likely to be hospitalized for 2-7 days (62/102, 60.8%) compared to those in the urban site (25/51, 49.0%) p=0.014. The average time of hospitalization was shorter for children who died in the rural site 3 days (IQR 0-26) than in the urban site (5 days (IQR 1-59), p=0.013). (Table 4)

The HIV prevalence in the urban site amongst children who died was higher in urban than in rural site although this was not statistically significant, 57.7% (17/30) vs. 45.5% (30/66), p=0.308. A similar percent of children who died were reported malnourished in the urban and rural sites (1/50 (2.0%) in urban with 3/102 (2.9%) in rural, p=0.733). Assessing malnutrition by calculating the weight for age there was no significant difference in both sites for children that died (urban 3/4 (75.0%) and rural 12/26 (46.2%), p=0.598. (Table 4)

Overall 140/154 (90.9%) of children who died were tested for respiratory viruses, influenza was detected more commonly in the urban (4/50, 8.0%) than in the rural (4/90, 4.4%) (p=0.385). RSV was detected more in the urban (8/50, 16.0%) than in the rural (5/90, 5.6%) (p=0.041). More than one respiratory virus was detected more amongst children who died in the urban (19/50, 38.0%) than in the rural (20/90, 22.2%) (p=0.046), (Table 4). Amongst children who died, 90/154 (58.4%) were tested for blood pneumococcal on lytA PCR of which a higher proportion of those positive were recorded in rural (8/74, 10.8%) compared to urban (1/16, 6.3%), (p=0.581).

Table 4: Demographic characteristics, clinical presentation and respiratory pathogens with factors associated with hospital site (rural vs. urban) among children < 5 years of age with SARI who died in hospital, South Africa, 2009–2013.

Characteristics	Urban site N=51 n (%)	Rural Site N= 103 n (%)	Univariate analysis OR (95%CI)	P value	Multivariable analysis OR (95%CI)	P value
Demographic						
Age Group < 1 year	42/51 (82)	82/103 (80)	0.8 (0.4-2.0)	0.686	-	-
Female gender	26/51 (51)	60/103 (58)	0.7 (0.4-1.5)	0.392	-	-
Black race	45/51 (88)	102/103 (99)	13.6 (1.6-116.3)	**0.002**	NS	NS
Year						
2009	15/51 (29)	18/103 (18)	Reference	**0.041**	NS	NS
2010	21/51 (41)	29/103 (28)	1.2 (0.4-2.8)			
2011	7/51 (14)	21/103 (20)	2.5 (0.8-7.5)			
2012	6/51 (12)	18/103 (18)	2.5 (0.8-7.9)			
2013	2/51 (4)	17/103 (16)	7.1 (1.4-35.7)			
2 or more doses of pneumococcal vaccine	18/25 (72)	31/57 (54)	0.5 (0.2-1.3)	0.134	-	-
Type of housing						
Brick	35/51 (69)	97/103 (94)	Reference	**<0.001**	NS	NS
Iron Sheeting	14/51 (27)	0/103 (0)	Undefined			
Mud	0/51 (0)	2/103 (2)	Undefined			
Others	2/51 (4)	4/103 (4)	1.4 (0.2-7.9)			
≥2 Rooms for sleeping	28/50 (56)	84/101 (83)	3.9 (1.8-8.3)	**<0.001**	**4.9 (2.1-11.3)**	**<0.001**
>2 people sleeping in a room	46/50 (92)	100/101 (99)	8.7 (0.9-80.0)	**0.023**	NS	NS
Clinical presentation						
Symptoms <2 days prior to admission	17/50 (34)	51/102 (50)	1.9 (1.0-3.9)	**0.062**	NS	NS
Antibiotics prescribed on admission	45/50 (90)	101/102 (98)	5.6 (1.0-30.0)	**0.025**	**12.5 (1.3-119.4)**	**0.028**

Difficulty breathing	43/50 (86)	90/103 (87)	0.9 (0.3-2.3)	0.812	-	-
Unable to drink or feed	13/50 (26)	34/103 (33)	0.7 (0.3-1.5)	0.378	-	-
Use of oxygen	43/50 (86)	83/103 (81)	0.7 (0.3-1.7)	0.402	-	-
Admission into ICU	0/50 (0)	0/103 (0)	Undefined	-	-	-
Mechanical ventilation	0/50 (0)	19/103 (18)	Undefined	**0.001**	NE	NE
Duration of hospitalization	4/51 (8)	18/102 (18)	4.5 (1.3-15.5)	**0.014**	NS	NS
<2 days	25/51 (49)	62/102 (61)	2.5 (1.2-5.3)			
2-7 days	22/51 (43)	22/102 (21)	Reference			
>7 days	Median=5 days, IQR(1-59)	Median=3 days, IQR(0-26)		0.013		
TB therapy started on admission	3/50 (6)	4/103 (4)	0.6 (0.1-2.9)	0.557	-	-
HIV infection	17/30 (57)	30/66 (46)	0.6 (0.3-1.5)	0.308	-	-
Tuberculosis	2/50 (13)	2/103 (25)	0.5 (0.1-4.1)	0.482	-	-
Prematurity	1/50 (2)	0/102 (0)	Undefined	-	-	-
Malnutrition (reported)	1/50 (2)	3/102 (3)	0.7 (0.1-6.6)	0.733	-	-
Malnutrition (weight for age)	3/4 (75)	12/26 (46)	0.3 (0.03-3.1)	0.283	-	-
Chronic lung diseases	1/50 (2)	0/102 (0)	Undefined	-	-	-
Asthma	0/50 (0)	0/102 (0)	Undefined	-	-	-
Renal diseases	0/50 (0)	0/102 (0)	Undefined	-	-	-
Heart diseases	0/50 (0)	0/102 (0)	Undefined	-	-	-
Diabetes	0/50 (0)	0/102 (0)	Undefined	-	-	-
Neurological diseases	1/50 (2)	1/102 (1)	0.5 (0.03-7.9)	0.604	-	-
Respiratory pathogens identified						
Influenza	4/50 (8)	4/90 (4)	0.5 (0.1-2.2)	0.385	-	-
Adenovirus	12/48 (25)	12/79 (15)	0.5 (0.2-1.3)	0.171	-	-

Enterovirus	5/50 (10)	9/90 (10)	1.0 (0.3-3.2)	1.000	-	-
Rhinovirus	11/50 (22)	30/90 (33)	1.8 (0.8-3.9)	0.152	-	-
Respiratory syncytial virus	8/50 (16)	5/90 (6)	0.3 (0.1-1.0)	**0.047**	NS	NS
Human metapneumovirus	2/50 (4)	2/90 (2)	0.5 (0.1-4.0)	0.545	-	-
Parainfluenza virus 1	1/50 (2)	1/90 (1)	0.6 (0.03-9.0)	0.671	-	-
Parainfluenza virus 2	1/50 (2)	1/90 (1)	0.6 (0.03-9.0)	0.671	-	-
Parainfluenza virus 3	4/50 (8)	5/90 (6)	0.7 (0.2-2.6)	0.572	-	-
Parainfluenza virus 1,2 or 3	5/50 (10)	7/90 (8)	0.8 (0.2-92.5)	0.653	-	-
Any respiratory virus	33/50 (66)	55/90 (61)	0.8 (0.4-91.7)	0.565	-	-
More than 1 respiratory virus	19/50 (38)	20/90 (22)	0.5 (0.2-1.0)	**0.049**	**0.4 (0.1-0.9)**	**0.032**
Pneumococcal infection on lytA PCR	1/16 (6)	8/74 (11)	0.5 (0.1-4.7)	0.581	-	-
Blood culture	36/51 (71)	11/103 (11)	0.05 (0.02-0.1)	**<0.001**	NE	NE
Relevant bacterial infection on blood culture	1/36 (3)	0/11 (0)	Undefined	-	-	-

- Variables statistically significant on univariate and multivariate logistic regression analysis presented in boldface.
- Variables not statistically significant on univariate logistic regression (p>0.1) were omitted from the multivariable logistic regression model.
- NE (Not evaluated): variables statistically significant on univariate analysis but omitted in the multivariate analysis.
- NS (Not significant): variables not statistically significant on multivariate analysis (p≥0.05)
- ***IQR: Interquartile range**
- **The relevant invasive bacterial infections are *Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae, Staphylococcus aureus, Neisseria meningitidis, Escherichia coli, Streptococcus agalactiae or group b streptococcus, Pseudomonas aerugenosa and Salmonella* species
- *** The organism that was relevant on bacterial culture in the child who died in the urban site is *Klebsiella pneumoniae.*

3.4.2 Univariate and multivariate analysis of factors associated with rural hospital site amongst children who died

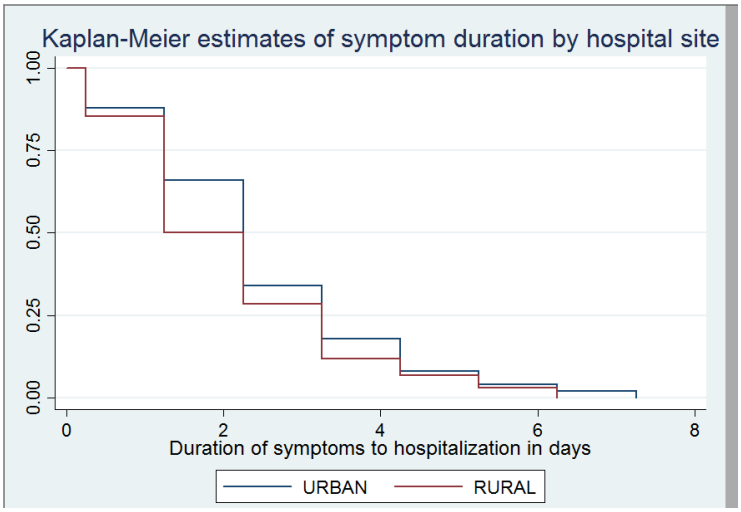
The variables found to be significantly associated with rural hospital site on univariate analysis using binary logistic regression at p<0.1 were black race, year, type of housing, 2 or more rooms for sleeping, more than 2 people sleeping in a room, symptoms < 2 days prior to admission, mechanical ventilation, duration of hospitalization, RSV, more than 1 respiratory virus and blood culture. (Table 4)

On multivariate analysis, the factors independently associated with the rural site were >2 rooms for sleeping (OR 4.9, 95%CI 2.1-11.3), antibiotics prescribed on admission (OR 12.5, 95% CI 1.3-119.8) and individuals with more than one respiratory virus detected were less likely to be from the rural site (OR 0.4, 95%CI 0.1-0.9). (Table 4)

3.5 Survival estimates in both rural and urban sites

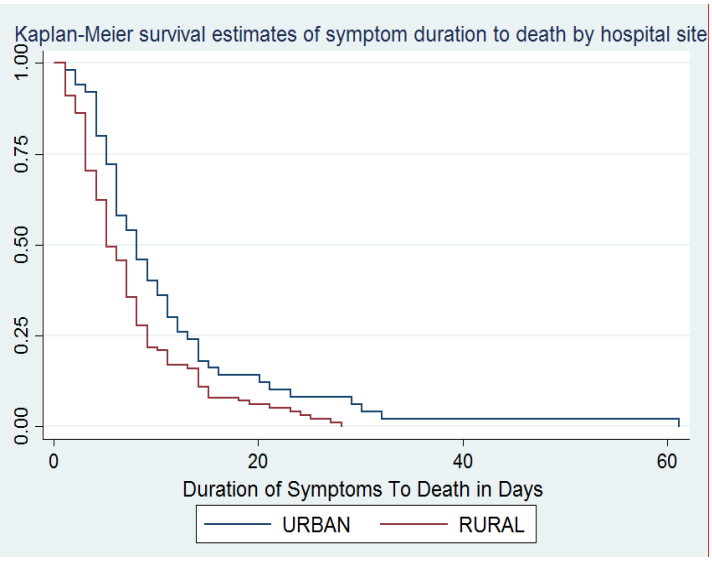
Amongst those that died, the median duration of reported onset of symptoms to admission was similar in both hospital sites, 2 days (IQR 0-7days) in the urban site and 2 days (IQR 0-6 days) in the rural site, p=0.194. (Figure 2A)

Figure 2A: Duration of symptoms (onset of symptoms to date of hospitalization) amongst those who died from SARI in urban and rural sites in South Africa, 2009 to 2013.



Survival function in terms of symptom duration to death amongst those who died differed in both hospital sites (8 days (IQR 1-61) in urban and 5 days (IQR 1-28) in rural, p=0.009). The children in the rural site who died did so sooner after onset of symptoms than urban children. (Figure 2B)

Figure 2B: Duration of symptoms to death (onset of symptoms to date of death) amongst those who died from SARI in urban and rural sites in South Africa, 2009 to 2013.



Survival function in terms of duration of hospitalization to death amongst those that died differed in urban and rural sites, (5 days (IQR 1-59) in urban and 3 days (IQR 1-27) in rural, p=0.0127). The rural children who died did so sooner after hospitalization compared with urban children. (Figure 2C)

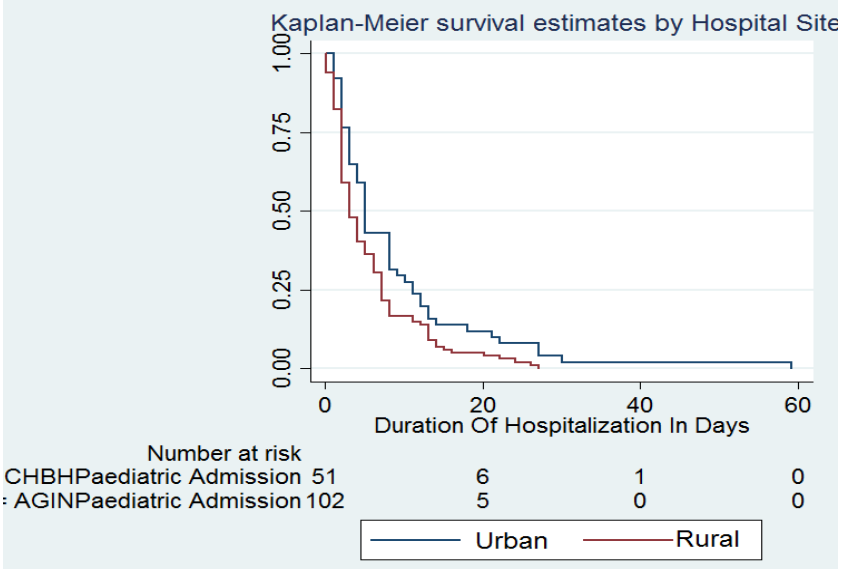


Figure 2C: Duration of hospitalization to death (date of hospitalization to date of death) amongst those who died from SARI in urban and rural sites in South Africa, 2009 to 2013.

Although time from onset of symptoms to admission was the same in both sites (p=0.194), time from onset of symptoms to death differed (p=0.009) in both sites which supports our finding that duration of hospitalization to death differed at both sites (p=0.0127).

3.6 HIV-infected children and HAART

HIV prevalence amongst hospitalized SARI cases decreased over the study period at both sites; however the prevalence was consistently higher at the rural site compared to the urban site. Similarly the percentage of HIV positive children on HAART increased over the study period in the rural site and was consistently higher in the urban site initially. However, by 2013 the percentage of children on HAART was similar between the sites. (Table 5a)

Table 5a: Percentage of children that are HIV-infected and those receiving HAART by year amongst children <5 years hospitalized with SARI in urban and rural hospital sites, South Africa, 2009-2012.

	HIV-infected			**HIV-infected children on HAART**		
Year	**Urban site N=3811**	**Rural site N=1486**	**P value**	**Urban site N=257**	**Rural site N=233**	**P value**
	n/N (%)	**n/N (%)**		**n/N (%)**	**n/N (%)**	
2009	102/655 (16)	53/166 (32)	<0.001	34/78 (44)	5/26 (19)	0.637
2010	62/503 (12)	73/262 (28)		16/37 (43)	9/28 (32)	
2011	37/513 (7)	35/220 (16)		7/23 (30)	7/13 (54)	
2012	44/559 (8)	46/259 (18)		13/26 (50)	13/23 (57)	
2013	12/263 (5)	26/219 (12)		5/8 (63)	10/18 (56)	
Overall	257/2493 (10)	233/1126 (21)		75/172 (44)	44/108 (41)	
Missing Data	1318	360		85	125	

On sensitivity analysis, assuming that all the children with missing data on HIV status were HIV-uninfected, the prevalence of HIV amongst hospitalized SARI cases also decreased over the study period at both sites and was consistently higher at the rural site compared to the urban site. (Table 5b)

Table 5b: Percentage of children HIV-infected by year compared with sensitivity analysis (assuming all those with missing data were HIV-uninfected) amongst children <5 years hospitalized with SARI in urban and rural hospital sites, South Africa, 2009-2012.

	HIV-infected		HIV-infected (sensitivity analysis)	
Year	**Urban site N=2493**	**Rural site N=1126**	**Urban site N=3811**	**Rural site N=1486**
	n/N (%)	**n/N (%)**	**n/N (%)**	**n/N (%)**
2009	102/655 (16)	53/166 (32)	102/1031 (10)	53/330 (16)
2010	62/503 (12)	73/262 (28)	62/791 (8)	73/303 (24)
2011	37/513 (7)	35/220 (16)	37/795 (5)	35/252 (14)
2012	44/559 (8)	46/259 (18)	44/793 (6)	46/306 (15)
2013	12/263 (5)	26/219 (12)	12/401 (3)	26/295 (9)
Overall	257/2493 (10)	233/1126 (21)	257/3811 (7)	233/1486 (16)

Only 26% (129/490) of HIV-infected children had available CD4+ T-lymphocyte data, of whom 75% (83/110) in urban and 47% (9/19) in rural site had severe immunosuppression. Ninety percent (18/20) in urban and 10% (2/20) in rural of those with available CD4+ T-lymphocyte data reported receiving HAART. (Table 5c)

Table 5c: Percentage of children with severe immunosuppression by year amongst children <5 years with CD4 count hospitalized with SARI in urban and rural hospital sites, South Africa, 2009-2013.

	Low CD4 count		
Year	**Urban site N=110** **n/N (%)**	**Rural site N=19** **n/N (%)**	**P value**
2009	31/40 (78)	1/1 (100)	0.162
2010	20/26 (77)	2/4 (50)	
2011	9/15 (60)	0/2 (0)	
2012	16/20 (80)	4/7 (57)	
2013	7/9 (78)	2/5 (40)	
Overall	83/110 (75)	9/19 (47)	

CHAPTER 4

4.0 DISCUSSION

4.1 Overview of study findings

In this study, we described the demographic characteristics, clinical presentation and respiratory pathogens of children < 5 years of age hospitalized with SARI from rural and urban sites in South Africa and also identified the risk factors for mortality amongst these children in these 2 sites separately.

The CFP was 1.3% in the urban site and 6.9% in the rural site. HIV infection was associated with death in the urban site. In the rural site HIV infection, children aged less than 1 year, malnutrition, pneumococcal infection on lytA PCR were associated with increased mortality while individuals with respiratory virus detected were less likely to die. This study serves as an important benchmark in addressing areas in which to intervene for reducing mortality in children less than 5 years of age in different parts of South Africa.

4.2 Case fatality proportion

Our result shows that SARI causes substantially higher mortality in the rural area (6.9%) than in the urban site (1.3%), this is similar to findings recorded in China and Bangladesh from their national demographic surveillance system which recorded mortality that is 4.9 and 1.4 fold higher respectively in the rural area compared to urban area.(75, 76) However 7% mortality from the rural site in this study is similar to but slightly lower than 9% mortality that was reported from rural Thailand.(77) A case series study from 8 countries in Africa reported 2.8% (country range 0.1-5.3%) SARI deaths overall which is very similar to the overall mortality in this study (2.9%), this finding is however much lower than the mortality rate from our rural site.(32) The higher CPF recorded in the rural hospital site could possibly be that rural children present with more

severe form of illness, it could also be that the quality of in-hospital care might not be as good as in the urban hospital and IMCI guidelines not strictly enforced. Another possibility is data issues e.g. bias. Some children could have been too sick to be enrolled and died soon after presentation leading to underestimation of mortality which could have occurred in either site. Although the highest proportion of patients in the urban site required oxygen therapy compared to the rural site, possible reason could be that oxygen was more readily available and not necessarily because they had a more severe presentation. Moreover, CHBAH is a highly specialized hospital with 12 neonatal ICU beds and paediatric subspecialties such as oncology, renal, cardiac, haematology and neurology units. (78) CHBAH strives to achieve the highest level of patient care based on sound scientific principles and administered with empathy and insight: (69) therefore the quality of in-hospital care may be able to mitigate against the risk posed by other factors.

It is therefore important to analyze mortality in rural and urban settings separately in order to define the problems facing each site and also the specific intervention that will be required by each site.

4.3.1 HIV as a risk factor for mortality

In both sites HIV was a risk factor for death. Almost 21% of children admitted with SARI in the rural area were HIV-infected while in the urban area over 10% were HIV-infected. HIV-infected individuals had 11 times greater mortality rate than HIV-uninfected children in the urban site (CFR for HIV-infected children was 6.6% and for HIV-uninfected children 0.6%) while in the rural site HIV-infected individuals had 3 times greater mortality rate than HIV-uninfected children (CFR for HIV-infected children was 12.9% and for HIV-uninfected children 4.2%), moreover there was a real difference in the OR of death in HIV-infected children by site [urban 12.1 (5.8-25.2) and rural 3.5 (2.1-5.58)]. This finding from our urban site was consistent with other studies carried out in South Africa which estimated approximately 10 times elevated mortality risk in HIV-infected children and also globally.(30, 79) Amongst those that died in the urban site 57.7% were HIV-infected while in the rural area 45.5% were HIV-infected. There have been studies showing that reduction in SARI is associated with availability of HAART but despite this,

high incidence of SARI is still reported in HIV-infected children on HAART, (80-83) hence the impact of HIV as an underlying risk factor for SARI mortality despite the widespread availability of HAART cannot be over emphasized. Of the 13.5% HIV infected children overall, 67% and 27% of these children had data on HIV treatment and CD4 count respectively. Only about a quarter of HIV-infected children were on treatment with HAART while even fewer had available CD4+ T-lymphocyte data, of whom majority had severe immunosuppression.(84) Stratifying the HIV prevalence by year, the prevalence was seen to be reducing at both sites but the prevalence at the rural site was consistently double than that of the urban site. (Table 5a).This could be driven by the fact that underlying HIV prevalence differ in both communities, according to Shisana et al in the South African National HIV prevalence, incidence and behaviour survey of 2012, the HIV prevalence amongst children < 14 years in 2008 was 2.2% and 3.8% in Gauteng and Mpumalanga province respectively while in 2012 it was 2.1% and 1.7% in Gauteng and Mpumalanga province respectively.(35) In infants the HIV prevalence was higher in Mpumalanga province (3.0%) compared to 1.1% in Gauteng province.(85) From the 2012 National antenatal sentinel HIV & Herpes simplex type-2 prevalence survey in South Africa, the HIV prevalence amongst pregnant women was consistently higher in Mpumalanga province (rural) [2010 (35%), 2011(37%), 2012 (36%)] compared to Gauteng province (urban) [2010 (30%), 2011(29%), 2012 (30%)].(86) MTCT of HIV infection could also contribute to this, the MTCT in 2012 was much higher in Mpumalanga province 5.7% (CI 4.1-7.3) while in our urban site (Gauteng) it was 2.5% (CI 1.5-3.6).(85) However, the magnitude of the difference in community prevalence seems unlikely to fully explain why the prevalence of HIV was consistently doubled in the rural site compared to the urban site.

Looking at the percentage of children on HAART by year, an increased trend was observed with children on HAART from 2009-2012 in the rural site (Table 5a). In this study data on HAART was not analyzed in our multivariate model because of missing data. On sensitivity analysis, assuming that all the children not tested for HIV were HIV-uninfected the trend towards a reduction in prevalence at both sites except in 2012 and doubled prevalence in the rural site remained in all years (Table 5b).

In the rural site several factors were associated with mortality apart from HIV including; age, malnutrition, pneumococcal infection on lytA PCR and identification of any respiratory virus. The difference in risk factors between urban and rural sites could be due to lower power to detect a significant difference for some factors in the urban area because of the fewer deaths recorded. Alternatively, it is possible that perhaps in the urban site patients have earlier access to high quality care and antibiotics even before admission and so this reduces impact of some other factors leaving only HIV as a risk factor for death.

4.3.2 Age as a risk factor for mortality

We found that age is an important risk factor for SARI-mortality in the rural site. Children aged < 12 months have a higher CFP (9.4%) and also a higher risk of death (OR 3.5, 95% CI 2.0-6.1) compared to children aged 1-4 years with CFP of 3.4% in the rural site. This is similar to studies from Africa and the USA where mortality is higher in children < 1 year compared to older children < 5 years of age.(41, 55, 87, 88) Sonego et al in a systematic review and meta-analysis of observational studies from low and middle income countries also reported age below 2 months as a risk factor for mortality in children with ALRTI (OR 5.22, 1.70-16.0).(31) This could be due to lower immunity experienced by the younger age group (new born and infants) making them more susceptible to severe forms of infections and hence increased mortality. (89)

4.3.3 Malnutrition as a risk factor for mortality

Malnutrition was significantly associated with mortality in the rural area (OR=12.8, 95% CI 1.2-134.6). This is similar to estimates from a systemic review on pneumonia in severely malnourished children in developing countries (OR ranged from 2.5-15.1 and relative risk (RR) ranged from 2.9-121.2) and also corroborates the study by Caulfield et al that reported malnutrition as a risk factor for mortality in children with pneumonia (OR=8.1, 95%CI 4.4-15.0). (42, 90) Furthermore in a review of findings from cohort and case-control studies by Rice et al, a strong and consistent relationship was observed between malnutrition and increased risk of death from ARI.(44) These suggest that

malnutrition in children contribute significantly towards the burden of SARI. A child's immune system may be weakened by malnutrition or undernourishment, especially in infants who are not exclusively breastfed.(91)

4.3.4 Detection of respiratory virus as being associated with lower mortality

Any respiratory virus was significantly protective against mortality in this study in the rural site. The CFR in those without any respiratory virus was twice those with any respiratory virus. This could be that amongst children hospitalized with SARI who do not die, viral etiologies are more implicated compared to bacterial etiologies, however amongst children who die bacterial etiologies are more implicated as these are often more severe and more likely to result in death.(92) This could potentially be more marked in rural setting where access to antibiotics could be delayed, although we did not have data on timing of antibiotic administration to assess this and time from symptom onset to death was shorter in the rural than the urban site.

This is similar to what McMorrow reported with influenza-associated SARI deaths in Sub-Saharan Africa (CFP was 1.8% (57/3091) for influenza positive cases, compared with 2.9% (1016/34 623) for influenza virus-negative cases and also support study from South Africa, using the same dataset, that reported that children with RSV-associated ALRTI are less likely to die compared to those testing RSV-negative.(32, 51) Nair et al in a systematic review concluded that RSV is a major cause of mortality in children because of its huge burden, however case fatality ratio (CFR) for RSV in developing countries is 2.1% in children with ALRTI which is higher compared to CFR for RSV in children with ALRTI in industrialized countries. (41)

4.3.5 Pneumococcal infection as a risk factor for mortality

Overall, 52.9% of the children were tested for pneumococcal infection on lytA PCR; pneumococcal infection was significantly associated with mortality in the rural site in this study. Those who tested positive for pneumococcal infection were more likely to die compared to those who tested negative for pneumococcus. This study is consistent with

studies from South Africa, India, global estimates and systemic reviews which reported pneumococcal infection being associated with death in children with SARI, (6, 52-54) Cohen et al reported pneumococcal co-infection as a risk factor for death amongst children with viral associated ALRTI (OR: 2.4, 95% CI 1.1-5.6) using the same data.(6) In our study vaccination with 2 or more doses of PCV was significantly higher in the urban site compared to the rural site. Despite advances in preventing SARI caused by *S. pneumoniae* with the introduction of pneumococcal conjugate vaccine, pneumococcus is still implicated in some of SARI deaths. Diagnostic tests for pneumococcal pneumonia have low sensitivity and so the contribution of pneumococcus is likely greater than the 6% of individuals testing lytA positive in our study.(93)

Delay in presentation to the hospital as a possibility for increased mortality in the rural site was not supported by data because rural patients reported shorter interval between symptom onset and hospitalization and death. Other factors like underlying medical conditions and quality of care that's delivered at each site could affect the mortality rate in each site.

4.3.6 Variables not significantly associated with mortality

This study does not show sex as a significant risk factor for death in either study sites, which also support results from one study, (47) but there are studies which have shown the female sex having increased odds of dying. (31, 46) Some studies have also reported disease duration of more than 21 days from onset of illness to presentation as a risk factor for mortality,(46) however we could not explain this because we only included patients with symptoms less than 7 days in our study.

The CFP was low in 2009 and peaked in 2010 at both sites with a gradual decline in the CFP trend from 2011-2013. This could be attributed to improved health care system in the last few years, PCV introduction, widespread availability of HAART and prevention PMTCT.

4.4 Residual confounding

Data on some variables that could be possible confounders like indoor air pollution, socio-economic status, type of feeding, were not collected, therefore there could still be residual confounders which we did not measure and could not include. Result of pneumococcal infection was used in the multivariate analysis instead of bacterial culture result to prevent multicollinearity and we had more children that were tested for pneumococcal infection on lytA PCR than those that had blood culture especially in the rural site where very few of the children had a blood culture.

4.5 Study strengths

The strength of this study is the use of active surveillance data on SARI. The data include large number of cases over 5 year period which powered the study to be able to determine the risk factors for mortality in children with SARI. Data from the urban and rural sites were systematically collected over a long and similar period with a consistent protocol and methodology making the data comparable and allowing comparison between the urban and rural sites.

4.6 Study limitations

There are several limitations in this study. This study used cases from specific surveillance sites which could have introduced selection bias and therefore the results might not be generalizable to other sites. This study population includes hospitalized children alone, some children could have died at home; others may have died soon after presentation and children who die are less likely to be enrolled as they may be too sick or die quickly before enrolment which might lead to underestimation of mortality.

Malnutrition was significantly associated with mortality in the rural site. Initially in the study malnutrition was collected from clinical records or clinician reported so there could be the possibility of information bias. More robust data including weight and height was collected from 2012, but these data were not included in multivariate models due to

large amount of missing data. Other factors outside the hospital like use of coal/wood or natural gas for cooking, indoor air pollution, type of feeding, low socio-economic status would have been considered but these were not in the original data collected.

Another limitation is missing information. Systematic testing for bacterial agents was limited to *Streptococcus pneumoniae* which had lots of missing data and for viruses (10 viruses were tested). Blood culture was only done on a minority of cases, some blood culture data were available, but only few from rural site. Tachypnoea variable seems to have been systematically incorrectly recorded at the rural site; hence we did not include it in our analysis. HIV data were incomplete and data on CD4 count and ARV use were very scanty, also data on HIV exposure was not collected.

4.7 CONCLUSION AND RECOMMENDATION

In conclusion, we have demonstrated a higher SARI mortality in the rural site than in the urban site. This was observed among both HIV-infected and HIV-uninfected children. We have also demonstrated HIV as a significant risk factor for SARI mortality in both urban and rural South African settings. There was a higher CFP amongst children <1 year at both sites compared to children aged 1-4 years and we also found age <1 year vs. 1-4 years as a significant risk factor for SARI death in the rural site. Other risk factors significantly associated with death in the rural sites were reported malnutrition, absence of any respiratory virus detected and pneumococcal infection on lytA PCR. HIV still plays a huge role in SARI mortality in children less than 5 years old even in the era of widespread availability of PMTCT and HAART as 49% of those that died overall were HIV positive.

Recommendations

The results presented in this study suggest that more focus still needs to be put on HIV prevention and treatment. Increase in campaign on HIV prevention by providing more information and education on HIV prevention, further reduction in MTCT by advocating

for pregnant women to present to the hospital as early as possible for antenatal care, voluntary counseling and testing, prophylactic anti-retroviral therapy to reduce transmission, ensuring safe delivery practices, increased counseling and improved support for safer infant feeding practices. These preventive methods need more attention in order to further reduce the burden of HIV in the communities.

Improving adherence to IMCI guidelines in South Africa which involves case management skills of health care workers, improving overall health systems, improving family and community health practices and effective pneumonia management has been found to play a major role in reducing the burden of SARI,(94) although there may be differences in how this is applied between the rural and urban areas. Introduction of the IMCI strategy has also helped to develop and update national policies in the management of sick children. (95)

Assisting those that are poor and do not have easy accessibility to health care especially those in the rural site even though health care is free for children < 5 years old. Making more clinics available in the rural sites and closer to their homes and bringing the hospitals closer to the communities can improve accessibility to health care. Access to effective health care for children can go a long way in improving health outcomes.

The malnutrition challenge is multifactorial; some factors like promotion of breastfeeding, food-aid programs and supplemental programs with iron and vitamin A, maternal education and alleviation of poverty could be addressed.

Efforts to prevent and treat HIV infections in children and reduce malnutrition may also reduce SARI deaths.

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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I OLUWATOSIN AYENI (Student number: 966440) am a student

registered for the degree of M.SC EPIDEMIOLOGY (EPIDEMIOLOGY AND BIOSTATISTICS) in the academic year 2016.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.

Signature: _____ Date: 10th February 2017

NATIONAL HEALTH LABORATORY SERVICE
NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES

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Case Investigation Form (CIF)

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SO Initials: ☐☐☐
Date completed: ☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)

SARI Study ID:

TSAP Study ID:

Note: For Edendale Hospital only if patient co-enrolled in TSAP study.

Patient Hospitalised at: CHBH ☐ Selby ☐ Mapulaneng ☐ Matikwana ☐
Edendale ☐ Klerksdorp ☐ Tshepong ☐

Note: surveillance officer to review criteria for all case definitions before making a decision about the case definition/s met

SARI* ☐ SRI** (severe respiratory illness not SARI) ☐ Febrile illness*** (enrolled on TSAP) ☐

**SARI with duration of symptoms ≤ 7 days.*
*** SARI with duration of symptoms > 7 days, SARI/TB or TB (for Edendale and Klerksdorp-Tshepong Hospital Complex only).*
****If patient co-enrolled in the TSAP study (for Edendale Hospital only).*

NB: For Edendale and Klerksdorp-Tshepong Hospital Complex only

Enrolled in shedding study Yes ☐ No ☐

1. Date of birth (DOB): ☐☐/☐☐/☐☐☐☐ If DOB unknown, please enter age:_____Years ☐ Months ☐ Days ☐
2. Gender: Male ☐ Female ☐
3. Race: Asian/Indian ☐ Black ☐ Coloured ☐ White ☐ Other ☐ (Specify) _____
4. What is your house made of: Bricks ☐ Iron sheeting ☐ Mud ☐ Other ☐ (Specify) _____
5. Number of rooms used for sleeping? _____ 5.1 Number of people living in the house? _____
6. What is the interviewee's relationship to the participant? Self ☐ Parent/Caregiver ☐ Other ☐ (Specify) _____
7. Date of admission: ☐☐/☐☐/☐☐☐☐
8. Admission diagnosis: (Tick all that apply) Neonatal Sepsis ☐ Bronchiolitis ☐ Bronchopneumonia/Pneumonia/Lower Respiratory Tract Infection ☐
   TB ☐ Bronchitis ☐ Diarrhoea ☐ Febrile seizures ☐ Meningitis ☐ Sepsis (not neonatal) ☐
   Other ☐ (Specify) _____
9. Date of onset of symptoms: ☐☐/☐☐/☐☐☐☐
9.1 Duration of symptoms: 0-7days ☐ 8-14days ☐ >14days

Note: Complete the signs and symptoms at the time of admission, some of the signs or symptoms may have resolved by the time you interview the patient. This information should be available in the patient records.

10. Maximum recorded temperature within 24hours of admission ____.____C° (##.#C°)
Note: Record the maximum temperature recorded in the clinical notes or a temperature taken by the surveillance officer within 24 hours of admission if no temperature in the file.
11. Date of maximum temperature recorded: ☐☐/☐☐/☐☐☐☐ Temperature not recorded ☐
12. History of fever? Yes ☐ No ☐ Unk ☐ If yes, date of fever onset: ☐☐/☐☐/☐☐☐☐
13. Respiratory Rate: _____breaths per minute Not recorded ☐
14. Oxygen saturation (room air): _____% Date of O_2 Saturation: ☐☐/☐☐/☐☐☐☐
    Recorded on file ☐ Measure by Surveillance Officer within 24h of admission ☐
    Not recorded on file and not measured by Surveillance Officer within 24h of admission ☐
15. Patient length (if not recorded, surveillance officer to measure): _____.____cm Percentile (if patient < 5 years) _____ Unk ☐
15.1 Patient weight (if not recorded, surveillance officer to measure): _____.____kg Percentile (if patient < 5 years) _____ Unk ☐
15.2 Mid upper arm circumference (MUAC) (for patients < 5 years of age only) _____cm

16. Blood pressure on day of admission: _____/_____ Not recorded ☐

17. Mental status of the patient (based on AVPU), within 24 hours of admission

Alert ☐ Disorientated ☐ (responds to verbal commands) Stuporous ☐ (responds to painful stimuli) Comatose ☐ Sedated ☐ Unknown ☐

Note: If patient is alert report 15/15.

18. Glasgow Coma Score (GCS) _____/15 GCS from medical records: Yes ☐ No ☐

GCS Unk ☐ (if patient not alert and GCS not recorded on medical records)

Note: Complete for patients ≥ 12 years, if patient < 12 years skip to Q 20.

19. Patient oriented to:

Person: Yes ☐ No ☐ Unk ☐ Place: Yes ☐ No ☐ Unk ☐ Time: Yes ☐ No ☐ Unk ☐

Note: Complete the table below for children < 5 years, if patient ≥ 5 years skip to Q 21.

20. Were any of the following signs and symptoms present?

Cough	Y	N	Difficulty breathing	Y	N	Chest in drawing (retraction)	Y	N
Stridor in a calm child	Y	N	Tachypnoea/respiratory distress (2mnth-1yr RR>50, 1-5 RR>40)	Y	N	Diarrhoea (>3 loose stools per day)	Y	N
Unable to drink or breast feed	Y	N	Vomits everything	Y	N	Convulsions	Y	N
Lethargy	Y	N	Unconsciousness	Y	N	Any vomiting	Y	N
Wheezing	Y	N						

Note: Complete the table below for patients ≥ 5 years, if patient < 5 years skip to Q 22.

21. Were any of the following signs and symptoms present?

Sore throat	Y	N	Cough	Y	N	Chest pain	Y	N
Shortness of breath/difficulty breathing	Y	N	Diarrhoea (>3 loose stools per day)	Y	N	Wheezing	Y	N

Note: Complete the table below for all patients.

22. Were any of the following signs and symptoms present?

Chronic cough for 2 weeks or more	Y	N	Fever for more than 2 weeks (14 days)	Y	N	Cough up blood (Hemoptysis)	Y	N
Loss of appetite	Y	N	Night sweats	Y	N	Loss of weight	Y	N
Painless enlarged lymph glands	Y	N	History of close contact with a person with recently active TB (diagnosis ≤ 12 months ago)	Y	N	If yes, is the patient staying in the same house with the TB contact	Y	N

Note: Complete the following questions for patients ≥ 18 years, if patient < 18 years skip to Q 26.

23. Do you drink alcohol? Yes ☐ No ☐ If yes, how many units per week? _____

24. Do you currently smoke? Yes ☐ No ☐ If yes, how many cigarettes do you smoke per day? _____

24.1 If no, have you smoked in the past? Yes ☐ No ☐ If yes, date stopped smoking: ☐☐/☐☐/☐☐☐☐

25. Do you currently or have you ever worked in a mine before? Yes ☐ No ☐ Unk ☐
Note: If no or unknown, skip to Q 26)

25.1 If yes, date started working in the mine: ☐☐/☐☐/☐☐☐☐ Date unknown ☐

25.2 If working in a mine or worked in a mine before, when did you stop working in the mine? ☐☐/☐☐/☐☐☐☐ Ongoing ☐

Date Unknown ☐

25.3 If currently or worked in mine before, what type of mine/s? (tick all that apply)

Gold ☐ Coal ☐ Platinum ☐ Asbestos ☐ Other ☐ (Specify) _____

26. Do you have any underlying illness or condition at the moment? Yes ☐ No ☐
Note: Check patient's notes for details if necessary. If no skip to Q 27

Asthma	Y	N	Other chronic lung disease	Y	N	CVA/Stroke	Y	N
Cirrhosis/Liver failure	Y	N	Chronic renal failure	Y	N	Heart failure	Y	N
Valvular heart disease	Y	N	Coronary artery disease (except H/T)	Y	N	Pregnancy	Y	N
Organ transplant	Y	N	Any immunosuppressive therapy, cortisone, chemotherapy, radiation therapy	Y	N	Sickle cell	Y	N
Splenectomy	Y	N	Diabetes	Y	N	Burns	Y	N
Immunoglobulin deficiency	Y	N	Autoimmune disease, SLE	Y	N	Kwashiorkor/ Marasmus	Y	N
Nephrotic syndrome	Y	N	Spinal cord injury	Y	N	Seizure disorder	Y	N
Prematurity	Y	N	Obesity / BMI >=30	Y	N	COPD/Emphysema	Y	N
Malignancy/Cancer	Y	N	If yes, specify:					
Other	Y	N	If yes, specify:					
Does the patient live in an institution/care facility	Y	N	If yes, name of institution:					

27. Has the patient been admitted to hospital in the last 12months? (prior to this admission) Yes ☐ No ☐ Unk ☐
Note: If no or unknown, skip to Q 28.

27.1 If yes, what was the date that you were discharged from your last hospital admission? ☐☐/☐☐/☐☐☐☐ Date Unk ☐

27.2 Was the patient admitted more than once in the past year? Yes ☐ No ☐ Unk ☐ If yes, how many times? _____

Note: Complete for patients < 5 years, if patient ≥ 5 years skip to Q 29.

28. HIV result during pregnancy (mother of patient): Yes ☐ No ☐ Unk ☐
Note: If no or unk skip to Q 29

28.1 If yes, what was the result? Positive ☐ Negative ☐

28.2 What was the source of the results? RTHC ☐ Laboratory report ☐ Medical records ☐ Verbal ☐ Other ☐ Specify _____

28.3 Was the child exposed to HIV (yes if the mother tested HIV positive during pregnancy) Yes ☐ No ☐ Unk ☐ N/A ☐

29. Has the patient been tested for HIV prior to this admission? Yes ☐ No ☐ Unk ☐
Note: If no or unknown skip to Q 30

29.1 If yes, what was the result? Positive ☐ Negative ☐ Unk ☐
Note: If negative or unknown skip to Q 30

29.2 Currently on ART? Yes ☐ No ☐ Unknown ☐ If yes, date of initiation of ART: ☐☐/☐☐/☐☐☐☐

29.3 Bactrim (contrimoxazole/trimethoprim) prophylaxis taken currently? Yes ☐ No ☐ Unk ☐
Note: If no or unknown skip to Q 29.5

29.4 If yes, how long have you taken Bactrim? _____Years _____Months _____Weeks _____Days

29.5 What is the patient's clinical HIV stage according to WHO criteria (refer to WHO clinical staging information and HIV staging tick box document)

1 ☐ 2 ☐ 3 ☐ 4 ☐

30. Have you ever taken TB prophylaxis? Yes ☐ No ☐ Unk ☐ If yes, date TB prophylaxis initiated: ☐☐/☐☐/☐☐☐☐
Note: If no or unknown skip to Q 31

30.1 Are you still taking TB prophylaxis? Yes ☐ No ☐ Unk ☐ If no, date TB prophylaxis stopped: ☐☐/☐☐/☐☐☐☐
Note: If yes skip to Q 32

31. TB treatment in the last 12 months? Yes ☐ No ☐ Unk ☐ If yes, date TB treatment initiated: ☐☐/☐☐/☐☐☐☐
Note: If no or unknown skip to Q 32

31.1 Are you still taking TB treatment? Yes ☐ No ☐ Unk ☐ If no, date TB treatment stopped: ☐☐/☐☐/☐☐☐☐

Note: Ask patients and check medical records for PCP diagnosis and/or treatment

32. Have you ever been diagnosed with PCP before this admission? (check from medical records) Yes ☐ No ☐ Unk ☐
Note: If no or unknown skip to Q 33

32.1 If yes, date last treatment started: ☐☐/☐☐/☐☐☐☐ Date Unk ☐

32.2 If yes, date last treatment stopped: ☐☐/☐☐/☐☐☐☐ Date Unk ☐ Ongoing ☐

32.3 If yes, treatment started with steroid therapy? Yes ☐ No ☐ Unk ☐

33. Has the patient been prescribed and taken antibiotics in the 24 hours before this admission? Yes ☐ No ☐ Unk ☐
Note: If no or unknown skip to Q 34

33.1 If yes, what is the name of the antibiotic? 1. _____ 2. _____ 3. _____

AMO Amoxicillin; AMP Ampicillin; AUG Augmentin; CEF Cefuroxime, CIP Ciprofloxacin; CLI Clindamycin; CTX Ceftriaxone; DOX Doxycycline; ERY Erythromycin, PEN Penicillin, TMX/SMX Contrimoxazole, VAN Vancomycin. If other, specify _____

34. Vaccination history. Complete for patients < 5 years, if patient ≥ 5 years skip to Q 35

34.1 Is the person being interviewed the primary caregiver of the child? Yes ☐ No ☐
Note: If no skip to Q 34.3

34.2 If yes, has the child ever been vaccinated? Yes ☐ No ☐ Unk ☐
Note: Excluding the vaccines given at birth

34.3 Was the Road to Health Card seen? Yes ☐ No ☐ 34.4 Was a copy of the Road to Health Card made? Yes ☐ No ☐
Note: If no skip to Q 35

34.5 If copy was not made, state reason: Mother refused ☐ Other ☐ (specify) _____

If Road to Health Card seen, please copy the following information from the card:

34.6 What is patients' gestational age: Term ☐ Pre-term ☐ Not recorded on Road to Health Card ☐

If pre-term, record gestational age: _____weeks

34.7 If Road to Health Card seen, please complete the details on the following vaccines for all children < 5 years old

Note: Tick no for vaccines that are not yet due according to the schedule. At 18 months if only the DTP was given tick DTP only and N/A for the combined DTP/HIB, if a combined DTP/HIB was given tick yes under combined and N/A under DTP only

Vaccine	Dose due	Given			Date given
BCG	Birth	Y	N		☐☐/☐☐/☐☐☐☐
DTP + HIB vaccine	Dose 1 (6 weeks)	Y	N		☐☐/☐☐/☐☐☐☐
	Dose 2 (10 weeks)	Y	N		☐☐/☐☐/☐☐☐☐
	Dose 3 (14 weeks)	Y	N		☐☐/☐☐/☐☐☐☐
	Dose 4 (18 months)	Y	N	N/A	☐☐/☐☐/☐☐☐☐
DTP only (tick N/A if DTP+HIB)	Dose 4 (18 months)	Y	N	N/A	☐☐/☐☐/☐☐☐☐
S.pneumoniae conjugate vaccine ($PCV_{7/13}$/Prevenar)	Dose 1 (6 weeks)	Y Batch N°_____ Unk ☐	N		☐☐/☐☐/☐☐☐☐
	Dose 2 (14 weeks)	Y Batch N°_____ Unk ☐	N		☐☐/☐☐/☐☐☐☐
	Dose 3 (9 months)	Y Batch N°_____ Unk ☐	N		☐☐/☐☐/☐☐☐☐
	Catch up	Y Batch N°_____ Unk ☐	N		☐☐/☐☐/☐☐☐☐
Measles	Dose 1 (9 months)	Y	N		☐☐/☐☐/☐☐☐☐
	Dose 2 (18 months)	Y	N		☐☐/☐☐/☐☐☐☐

Hepatitis B	Dose 1 (6 weeks)	Y	N	☐☐/☐☐/☐☐☐☐
	Dose 2 (10 weeks)	Y	N	☐☐/☐☐/☐☐☐☐
	Dose 3 (14 weeks)	Y	N	☐☐/☐☐/☐☐☐☐
Rotavirus	Dose 1 (6 weeks)	Y	N	☐☐/☐☐/☐☐☐☐
	Dose 2 (14 weeks)	Y	N	☐☐/☐☐/☐☐☐☐

Note: Complete for patients ≥ 5 years, if patient < 5 years skip to Q 36

35. Did the patient receive pneumococcal polysaccharide vaccine?

Vaccine	Dose given			Date given	
Pneumococcal Vaccine (Pneumovax)	Y	N	UNK	☐☐/☐☐/☐☐☐☐	**Date unknown** ☐

36. Did the patient receive an influenza vaccine in the past 12 months (For all patients)

Vaccine		Dose given			Date given	
Influenza vaccine	Dose 1	Y	N	UNK	☐☐/☐☐/☐☐☐☐	**Date unknown** ☐
	Dose 2	Y	N	UNK	☐☐/☐☐/☐☐☐☐	**Date unknown** ☐

QC Performed by: Initials: ☐☐☐ Date: ☐☐/☐☐/☐☐☐☐

NATIONAL HEALTH LABORATORY SERVICE
NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES

Severe Acute Respiratory Illness (SARI) Surveillance
Hospital Results Form (HRF)

Centre for Respiratory Diseases and Meningitis (CRDM)
TEL: 011 386 6410 or 011 386 6434
FAX: 086 723 3569

SO Initials: ☐☐☐
Date completed: ☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)

SARI Study ID

TSAP Study ID

Note: For Edendale Hospital only if patient co-enrolled in TSAP study.

Please record these results from the laboratory if they are available.
Note: Only results from this admission except for Q 4, 5 and 8 where the most recent available result should be entered and Q 7 where results before admission must be recorded.

Test			Date of test	Result
1. CRP on admission	Done ☐	Not done ☐	☐☐/☐☐/☐☐☐☐	_____mg/l
2. ESR on admission	Done ☐	Not done ☐	☐☐/☐☐/☐☐☐☐	_____mm/Hr
3. Urea on admission	Done ☐	Not done ☐	☐☐/☐☐/☐☐☐☐	_____mmol/l
4. Documented HIV Antibody Result (ELISA or rapid)	Yes ☐	No ☐	☐☐/☐☐/☐☐☐☐ ***Note: Enter date of most recent result available***	Reactive ☐ Non reactive ☐ ***Note: Enter most recent result available***
5. Documented HIV PCR Result	Yes ☐	No ☐	☐☐/☐☐/☐☐☐☐ ***Note: Enter date of most recent result available***	Positive ☐ Negative ☐ ***Note: Enter most recent result available***
6. Based on all the information available to you, what is the current HIV status of the patient				Positive ☐ Negative ☐ Pending ☐ Unknown ☐
6.1 If current HIV status unknown, why was the patient not tested? Refused consent ☐ Patient died ☐ No guardian ☐ Other ☐ specify_____				
6.2 What was the source of the results? RTHC ☐ Laboratory report ☐ Medical records ☐ Verbal ☐ Other ☐ Specify _____				
6.3 if patient < 5 years, was the child exposed to HIV : N/A ☐ Yes ☐ No ☐ Unk ☐				
7. CD4 count on admission	Done ☐	Not done ☐	☐☐/☐☐/☐☐☐☐	_____ Absolute CD4 ____.____%
8. CD4 count collected before this admission	Done ☐	Not done ☐	☐☐/☐☐/☐☐☐☐	_____ Absolute CD4 ____.____%
9. HIV viral load	Done ☐	Not done ☐	☐☐/☐☐/☐☐☐☐ ***Note: Enter date of most recent result available***	_____ HIV RNA copies/ml ____.____ Viral load log ***Note: Enter most recent result available***

10. Was a CXR done on the patient? Yes ☐ No ☐
Note :If not done go to Q 11

10.1. If X-ray done record X- ray number here: _____

Note: For Klerksdorp Tshepong Hospital Complex only
10.2 Copy of X-ray downloaded? Yes ☐ No ☐

10.3 if yes, date X-ray copy downloaded ☐☐/☐☐/☐☐☐☐

11. Bacterial Culture, done **within 48 hours** of admission? Yes ☐ No ☐
Note: If yes, complete the table below, if no skip to Q11

Date of culture	Site			Organism Isolated	If other (99), specify
	Blood	CSF	Pleural fluid		
☐☐/☐☐/☐☐☐☐					
☐☐/☐☐/☐☐☐☐					
☐☐/☐☐/☐☐☐☐					
☐☐/☐☐/☐☐☐☐					

Organism codes:			
01 = No growth	02 = *Streptococcus pneumoniae*	03 = *Haemophilus influenzae*	04 = *Klebsiella pneumoniae*
05 = *Staphylococcus aureus / MRSA*	06 = *Neiserria meningitides*	07 = *Coagulase negative staphylococcus / Staphylococcus epidermidis*	08 = *Bacillus Species*
09 = *Corynebacterium species*	11 = *Cryptococcus neoformans*	12 = *Escherichia coli*	13 = *Salmonella species*
14 = *Streptococcus agalactiae / Group B Streptococcus*	15 = *Acinetobacter baumanii*	16 = *Pseudomonas aeruginosa*	17 = *Enterococcus faecalis*
18 = *Streptococcus viridans*	19 = *Micrococcus species*	20 = *Salmonella enterica_ Non-Typhodial* (NTS)	*21 = Salmonella enterica- Typhi*
22 = Salmonella parathyphi	99 = Other		

11.1 Blood Specimen and Culture taken by ☐ SO ☐ Clinician

11.2. Blood Culture Specimen requested by clinician ☐ Yes ☐ No

12. TB testing done during this admission? Yes ☐ No ☐

Date of Test	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐
Specimen*				
AFB's present (Yes/No/Not Applicable)	Y N N/A	Y N N/A	Y N N/A	Y N N/A
Culture Done (Yes/No)	Y N	Y N	Y N	Y N
Culture Results (Positive/Negative/ Contaminated)	POS NEG CONT Date of final results report ☐☐/☐☐/☐☐☐☐	POS NEG CONT Date of final results report ☐☐/☐☐/☐☐☐☐	POS NEG CONT Date of final results report ☐☐/☐☐/☐☐☐☐	POS NEG CONT Date of final results report ☐☐/☐☐/☐☐☐☐
GeneXpert Done	Y N	Y N	Y N	Y N
GeneXpert Results (Positive/ Negative/ Inconclusive)	POS NEG INC	POS NEG INC	POS NEG INC	POS NEG INC

***Specimen codes:**
1 = Sputum 2 = Gastric Washing 3 = Bone Marrow 4 = Pleural Aspirate 5 = Lymph Node 6 = Other (if other, write in full)

Note: Culture results will be reviewed at a later date.
Do not delay submission of CIF and Result Form while waiting for TB culture results.

Note: complete the table below for TSAP (For Edendale Hospital KZN Only):

13. Was a blood count done during this admission? Yes ☐ No ☐

Note: If not done end; if yes, complete table below

WBC	☐☐☐.☐ (1000/µl)	**Platelets**	☐☐☐.☐ (1000/µl) ☐ Not recorded
RBC	☐☐.☐ (10^6/ µl)	**Neutrophils**	☐☐.☐ (%WBC) ☐ Not recorded
Hb	☐☐.☐ (g/dl)	**Monocytes**	☐☐.☐ (%WBC) ☐ Not recorded
Hct	☐☐.☐ (%)	**Lympocytes**	☐☐.☐ (%WBC) ☐ Not recorded
MCV	☐☐☐.☐ (fl)	**Eosinophils**	☐☐.☐ (%WBC) ☐ Not recorded
MCH	☐☐☐.☐ (pg)	**Basophils**	☐☐.☐ (%WBC) ☐ Not recorded
MCHC	☐☐.☐ (g/dl)		

QC perfomed by: Initials ☐☐☐ **Date:** ☐☐/☐☐/☐☐☐☐

NATIONAL HEALTH LABORATORY SERVICE
NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES

Severe Acute Respiratory Illness (SARI) Surveillance
Final Outcome Form (FOF)

Centre for Respiratory Diseases and Meningitis (CRDM)
TEL: 011 386 6410 or 011 386 6434
FAX: 086 723 3569

SO Initials: ☐☐☐ SARI Study ID: Date of admission: ☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)

Did any of the following occur during admission?

1. Was TB therapy started?	Yes ☐	No ☐
2. Did the patient receive oxygen?	Yes ☐	No ☐
3. Did the patient receive mechanical ventilation?	Yes ☐	No ☐
4. Did the patient have a cardiac arrest?	Yes ☐	No ☐
5. Was the patient admitted to ICU?	Yes ☐	No ☐
6. Did the patient go into shock (Systolic BP < 90mmHg) or require inotropes?	Yes ☐	No ☐

7. Antibiotics prescribed during this admission: Yes ☐ No ☐ Unk ☐
Note: If yes, complete the table below. If no/unknown, skip to Q 8

	PO	IVI	IMI	Date started (enter date prescribed)	Total number of days
Amoxicillin				☐☐/☐☐/☐☐☐☐	
Augmentin				☐☐/☐☐/☐☐☐☐	
Ceftriaxone (Rocephin)				☐☐/☐☐/☐☐☐☐	
Ciprofloxacin (Ciprobay)				☐☐/☐☐/☐☐☐☐	
Contrimoxazole (Bactrim)				☐☐/☐☐/☐☐☐☐	
Erythromycin				☐☐/☐☐/☐☐☐☐	
Penicillin G				☐☐/☐☐/☐☐☐☐	
Ampiclox				☐☐/☐☐/☐☐☐☐	
Ampicillin				☐☐/☐☐/☐☐☐☐	
Cefotaxime				☐☐/☐☐/☐☐☐☐	
Cefuroxime (Zinnat)				☐☐/☐☐/☐☐☐☐	
Clindamycin				☐☐/☐☐/☐☐☐☐	
Doxycycline				☐☐/☐☐/☐☐☐☐	

Gentamycin				☐☐/☐☐/☐☐☐☐	
Vancomycin				☐☐/☐☐/☐☐☐☐	
Metronidazole				☐☐/☐☐/☐☐☐☐	
Other (Specify):				☐☐/☐☐/☐☐☐☐	

8. Was Oseltamivir (Tamiflu®) prescribed during this admission? Yes ☐ No ☐ Unk ☐

8.1 If yes, date prescribed: ☐☐/☐☐/☐☐☐☐

9. Was *Pneumocystis jirovecii* pneumonia (PCP) treatment prescribed during this admission? Yes ☐ No ☐ Unk ☐
Note: If yes, complete table below, if no or unknown skip to Final Outcome of Patient

	Dose (Specify quantity and unit)	Oral	IMI	IVI	Frequency	Date started (enter date prescribed)	Total number of days
Cotrimoxazole						☐☐/☐☐/☐☐☐☐	
Dapsone						☐☐/☐☐/☐☐☐☐	
Prednisone						☐☐/☐☐/☐☐☐☐	
Hydrocortisone						☐☐/☐☐/☐☐☐☐	
Other (specify) _____						☐☐/☐☐/☐☐☐☐	

Final outcomes of patient (for this admission)

10.1 What was the final outcome (for this admission)?

Discharge ☐ Death ☐ Refused hospital treatment/absconded ☐

Referred to step down ☐ Name of facility: _____

Transferred ☐ Name of facility: _____

10.2 Date of final outcome: ☐☐/☐☐/☐☐☐☐

11.Discharge/final diagnosis or diagnosis on transfer/referral
Neonatal Sepsis ☐ Bronchiolitis ☐ Bronchopneumonia/Pneumonia/Lower Respiratory Tract Infection ☐
Suspected TB ☐ Confirmed TB ☐ Bronchitis ☐ Diarrhoea ☐ Febrile seizures ☐
Meningitis ☐ Sepsis (not neonatal) ☐ Not recorded ☐ Other ☐ (Specify) _____

Outcome follow up *(for all SARI and SRI cases enrolled at Edendale, Klerksdorp and Tshepong Hospitals only)*

12. Date of follow up: ☐☐/☐☐/☐☐☐☐ Not done ☐

12.1 What was the follow up outcome? Death ☐ If died, date of death ☐☐/☐☐/☐☐☐☐ Date Unk ☐
Alive ☐ Unknown (not possible to determine) ☐

QC performed by: Initials: ☐☐☐ Date: ☐☐/☐☐/☐☐☐☐

SARI/ILI SURVEILLANCE

Location Code: M8012
Test Code: RVPCR

☐ SARI (☐ PERCH) ☐ SRI ☐ ILI
☐ Febrile Illness ☐ Control ☐ Shedding

SARI/ILI/Control Study ID:

TSAP Study ID

Note: For Edendale Hospital only if patient co-enrolled in TSAP study.

TCD Number:

Note: For lab use only.

CRDM Number (Virology)

Note: For lab use only.

Ward: Paediatric Admission ☐ Adult Admission ☐
Short Stay/Sleepover: *Child* ☐ Short Stay/Sleepover: *Adult* ☐
Antenatal ☐ Postnatal ☐ ICU ☐ Selby ☐ Clinic ☐

Date of birth: ☐☐/☐☐/☐☐☐☐ **Gender:** Female ☐ Male ☐

Specimen Collection: Date: ☐☐/☐☐/☐☐☐☐
Time: ☐☐:☐☐ SO initials: ☐☐☐

HIV consent: Yes ☐ No ☐ **Consent for storage:** Yes ☐ No ☐

Specimen Type	Anatomic site of origin	No of specimens (indicate 0 if not collected)
☐ Swab	Oro-pharyngeal ☐ Naso-pharyngeal ☐	
☐ Aspirate		
☐ Blood		
☐ Dry blood spot		
☐ TB Sample for site testing	Expectorated Sputum ☐ Induced Sputum ☐ Gastric Washing ☐ Bronchial aspirate ☐	
☐ PCP/TB Sample for testing at NICD	Induced Sputum ☐ Bronchial aspirate ☐ Oral rinse ☐	

Time of delivery to site laboratory: ☐☐:☐☐

Storage at site: Refrigerator ☐ Dry Shipper ☐

SARI/ILI SURVEILLANCE

Location Code: M8012
Test Code: RVPCR

☐ SARI (☐ PERCH) ☐ SRI ☐ ILI
☐ Febrile Illness ☐ Control ☐ Shedding

SARI/ILI/Control Study ID:

TSAP Study ID

Note: For Edendale Hospital only if patient co-enrolled in TSAP study.

03/07/2012

Note: For lab use only.

Note: For lab use only.

Ward: Paediatric Admission ☐ Adult Admission ☐
Short Stay/Sleepover: *Child* ☐ Short Stay/Sleepover: *Adult* ☐
Antenatal ☐ Postnatal ☐ ICU ☐ Selby ☐ Clinic ☐

Date of birth: ☐☐/☐☐/☐☐☐☐ **Gender:** Female ☐ Male ☐

Specimen Collection: Date: ☐☐/☐☐/☐☐☐☐
Time: ☐☐:☐☐ SO initials: ☐☐☐

HIV consent: Yes ☐ No ☐ **Consent for storage:** Yes ☐ No ☐

Specimen Type	Anatomic site of origin	No of specimens (indicate 0 if not collected)
☐ Swab	Oro-pharyngeal ☐ Naso-pharyngeal ☐	
☐ Aspirate		
☐ Blood		
☐ Dry blood spot		
☐ TB Sample for site testing	Expectorated Sputum ☐ Induced Sputum ☐ Gastric Washing ☐ Bronchial aspirate ☐	
☐ PCP/TB Sample for testing at NICD	Induced Sputum ☐ Bronchial aspirate ☐ Oral rinse ☐	

Time of delivery to site laboratory: ☐☐:☐☐

Storage at site: Refrigerator ☐ Dry Shipper ☐

R14/49 Dr Oluwatosin Ayeni

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M151030

NAME: (Principal Investigator) Dr Oluwatosin Ayeni

DEPARTMENT: Public Health
University of the Witwatersrand

PROJECT TITLE: Mortality in Children <5 Years With Severe Acute Respiratory Illness in Urban and Rural Areas of South Africa, 2009 - 2013

DATE CONSIDERED: 30/10/2015

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Dr Cheryl Cohen

APPROVED BY: Professor P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 07/12/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature

Date 10th December 2015.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Centre for Respiratory Diseases and Meningitis
1 Modderfontein Road, Sandringham, 2031
Tel: +27 (0)11 386 6593 Fax: +27 (0)11 882

31 July 2015
Oluwatosin Ayeni
Student Number: 966440

RE: Permission to use Data

STUDY TITLE: Mortality in children <5 years with severe acute respiratory illness in urban and rural areas of South Africa, 2009-2013.

This is to confirm that permission to conduct the above mentioned retrospective study for your M.Sc (Epidemiology) research at the University of the Witwatersrand with existing data collected as part of Severe Acute Respiratory illness (SARI) surveillance programme is hereby granted. The data should be used for the purposes of meeting requirements for your MSc and should not be shared with others unless cleared with your supervisor/s from National Institute for Communicable Diseases (NICD).

Regards

Dr Cheryl Cohen
Centre Head: Epidemiology
Centre for Respiratory Diseases and Meningitis (CRDM)
National Institute for Communicable Diseases, a division of the National Health Laboratory Service
1 Modderfontein Rd Sandringham,
Johannesburg 2193
Telephone: +27 11 386 6593 Fax:+27 11 882 9979 Mobile: +27 82 803 8093

Chairperson: Prof Barry Schoub Interim CEO: Ms Joyce Mogale

R14/49 Dr Cheryl Cohen et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140824

NAME: (Principal Investigator)	Dr Cheryl Cohen et al
DEPARTMENT:	School of Public Health Rahima Moosa Mother and Child Hospital, Klerksdorp-Tshepong Hospital Complex, Helen Joseph Hospital and Edendale Hospital
PROJECT TITLE:	National Syndromic Surveillance for Pneumonia in South Africa
DATE CONSIDERED:	29/08/2014
DECISION:	Approved unconditionally
CONDITIONS:	Futher hospitals will be approved on receipt of permission
SUPERVISOR:	Prof Shabir Madhi

APPROVED BY:

Professor P Cleaton-Jones Chairperson, HREC (Medical)

DATE OF APPROVAL: 09/01/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature

Date 9/01/2015

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES