**MASTERS OF MEDICINE (Paediatrics and Child Health)**

**RESEARCH THESIS**

# PREVALENCE OF VIRAL RESPIRATORY TRACT INFECTIONS AND THE RISK FACTORS ASSOCIATED WITH ICU ADMISSION AMONG CHILDREN LESS THAN 5 YEARS HOSPITALISED IN A TERTIARY HOSPITAL IN DURBAN, SOUTH AFRICA.

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As the candidate's supervisor I have/have not approved this thesis for submission.

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I.....**Preshen Ramadu**.....declare that

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## Dedication

I dedicate this thesis to my late mother, *Shirley Ramadu*, who taught me how to live beyond all life's trials, to know that everyday is a new beginning. I Love You, Forever.

## Acknowledgement

I would like to thank my supervisor, Prof Refiloe Masekela, for her amazing support, guidance and ever-willingness to assist my research journey.

## CONTENTS

## Introduction:

*What is Acute Bronchiolitis?*

Acute bronchiolitis is defined as a viral-induced inflammation of the bronchioles. The clinical manifestations occur directly as a consequence of airway inflammation and airway trapping.(1) Bronchiolitis is usually a self-limiting illness, however, the spectrum of disease ranges from mild symptomatic 'wheezers' to those with severe respiratory distress and respiratory failure requiring high care and intensive care management. Infants often feed poorly and have mild upper respiratory tract infection (URTI) signs, accompanied by a low-grade fever, hyperinflation of the chest and wheezing. Tachypnoea and lower chest wall in-drawing are symptoms of severe illness.(1) Up until 2009 in South Africa, diagnosing viral respiratory tract infections was based on symptoms, signs and radiological evidence. With the introduction of the multiplex real-time reverse transcription PCR (Polymerase chain reaction) assay test, it has provided much needed epidemiological evidence of viral aetiologies in respiratory tract infections. However, few studies have been done locally to establish the epidemiology and role of respiratory viruses in bronchiolitis, including in children with HIV-infection.

*The Problem*

Bronchiolitis is a very common childhood illness often encountered by doctors who regularly manage infants. It is one of the leading causes of presentation and admission to hospital locally and internationally. It has been reported that up to 53% of infants will have a viral respiratory tract infection in their first year of life.(2) Many of these infants will require admission to hospital for further care including admission to the intensive care unit (ICU), which means that this disease places a great burden on a resource-limited health care system, such as is the health system in Kwa-Zulu Natal. Bronchiolitis is the main cause of hospitalisation in children under two years of age in high income countries, whereas pneumonia has been reported as the most common reason for hospitalisation among human immunodeficiency virus (HIV)-infected children.(3)

Bronchiolitis is a serious cause of morbidity and mortality, especially in resource-limited settings such as South Africa. In a study published in 2013, the case fatality ratio (CFR) of *Respiratory Syncytial Virus* (RSV)-associated pneumonia among children less than five years in low income countries was said to be 2.1% (95% CI, 1.3-3.4) (4). Few studies have been done locally to establish aetiology of viral bronchiolitis in the paediatric population as well as the role HIV plays in disease outcomes.

*Aim and Objectives*

The aim of this study was to identify the viruses implicated in bronchiolitis and to assess the impact of different viral pathogens on disease outcomes in a paediatric population in the eThekwini region of KwaZulu Natal. We also explored whether known risk factors (prematurity, chronic lung disease, congenital heart disease, formula feeding and smoking exposure) were associated with more severe disease outcomes and finally the relationship between HIV-infection and bronchiolitis outcomes.

## Literature Review:

Bronchiolitis is a very common childhood illness often encountered by healthcare practitioners in the primary health care setting of low-to-middle income countries. Bronchiolitis is a viral infection of the lower airways which is often accompanied clinically by wheezing and tachypnoea.(5) Young infants and other high-risk population groups often require oxygen and supportive care during their illness including supportive ventilation. Up to 80 percent of children under two years with *Adenovirus* pneumonia may end up having severe disease requiring high-care admission.(6) Bronchiolitis is also one of the leading causes of morbidity in high income countries, whilst in low to middle income countries (LMICs) bronchiolitis is included amongst causes of pneumonia which is known to be one of the top five causes of under-5 mortality.(7)

*Viral Aetiology in Bronchiolitis*

Respiratory viruses remain the most common cause of lower respiratory infections in children.(8) With improved immunisation programmes in LMICs resulting in a lower incidence of bacterial-associated pneumonia, respiratory viruses have become an important cause of respiratory infections in children. *Rhinovirus* (RV) and *RSV* appear to be the most common viruses implicated in bronchiolitis. In a study done in Cape Town reporting prevalence among paediatric ICU admissions; *RV* and *RSV* were found in 39.0% and 27.7% of specimens, respectively.(2) The prevalence of *RSV*-related hospitalisations in the United States is reported as 48.9 per 1000 in children younger than three months.(9) *RSV* is also associated with a higher rate of ICU admission, with as much as 30% of *RSV*-associated bronchiolitis requiring ICU admission.(5)

Previously in South Africa, accurate diagnosis of the offending virus in bronchiolitis was not possible due to limited resources and diagnostic capacity. Evidence is mounting worldwide on the role of viruses in the severity of bronchiolitis and the long-term complications of these

infections. The question remains, whether the viral aetiology impacts outcomes in bronchiolitis and whether this can guide future therapeutic interventions.

Many other viruses are also known to be implicated in bronchiolitis including *Parainfluenza*, *Influenza*, *Adenovirus*, *Human Metapneumovirus*, *Bocavirus* and *Coronavirus.*(1) *Adenovirus* is a frequent pathogen causing respiratory tract infections in all age groups.(10) However, it has been shown to be common in children under 5 years of age. *Adenovirus* infection is generally a self-limiting illness but a small proportion of children can develop severe disease with respiratory failure.(11) Studies have previously shown that *Adenovirus* pneumonia is associated with more severe disease often requiring ICU admission, and is also associated with a greater incidence of post-infectious complications, with up to 15% of children developing chronic lung disease.(7) Post-infectious bronchiolitis obliterans has been reported to be occurring in as high as 30% of cases.(6) It has also been shown that *Adenovirus* pneumonia in the Paediatric ICU is a significant risk factor for mortality with up to 50% associated mortality if timeous treatment is not received.(10) Risk factors for severe *Adenovirus* infection are the same as for other viral infections and include male sex and infants younger than twelve months.

*Risk factors associated with bronchiolitis*

Several known risk factors have been shown to influence hospital admission and severity of bronchiolitis in children. These include prematurity, young age, chronic lung disease, tobacco-smoke exposure, congenital heart disease and lack of breastfeeding. Prematurity on its own, has been shown to have a seven-fold increased risk for bronchiolitis and in a Brazilian study, prematurity was associated with a higher probability of ICU admission (OR 24.51; 95%CI 3.21 to 186.92).(9) A 2017 study conducted in Pretoria on children with *RSV* bronchiolitis concluded that 36% of all infants admitted to the Paediatric ICU had a background of prematurity.(5) A recent review found that passive smoking was a risk factor for supplemental oxygen and mechanical ventilation.(2) Passive tobacco smoking was associated with greater clinical severity and longer hospitalisation.(2) Children who were exposed to postnatal maternal smoking had lower levels of haemoglobin oxygen saturation than those who were not exposed.(9)

It has been well documented in the literature that the younger the child, the greater the clinical severity of acute bronchiolitis. A recent study showed that children younger than two months of age had a longer hospital stay and an increased risk of ICU admission.(9) Age was found to be inversely proportional to the time spent in ICU and the time on ventilatory support.(9) A

study at Steve Biko Academic Hospital found that almost 70% of Paediatric ICU admissions for bronchiolitis were below six months of age.(5) This corelates with data globally supporting evidence that infants less than six months age are at a greater risk for contracting bronchiolitis.(5) Lower levels of haemoglobin oxygen saturation were found in children of younger age and it was shown that for each month younger the child was, there was a reduction in oxygen saturation by 0.41%.(9) Maternal breastfeeding has been shown to be a protective factor against severe acute bronchiolitis; and duration of exclusive breastfeeding was inversely related to the duration of oxygen use and hospitalisation. For every month of exclusive breastfeeding, there was a decrease in the time of oxygen use of eleven hours.(9)

Bronchopulmonary dysplasia (BPD) is linked to more severe bronchiolitis with infants having a 6.7-fold increased risk of death from bronchiolitis if they have co-existing BPD.(9) The case-fatality-rate of *RSV* infection in children with chronic lung disease is said to be as high as 23%.(12) The presence of congenital heart disease (CHD) has also been shown to be associated with increasing severity of bronchiolitis. A retrospective study showed that the presence of CHD was associated with a 50% longer length of hospital stay than in children without CHD.(9) Children with haemodynamically significant CHD are three times more likely to succumb to *RSV* infection than those without a congenital heart lesion.(12) A study in England showed that infants with congenital heart lesions were almost four times more likely to develop severe disease from *RSV* infection that those without CHD.(13) *Adenovirus* infection is directly cardiotoxic hence predisposing to myocarditis.(14) This means that individuals with pre-existing heart disease are at greater risk of severe disease if having *Adenovirus* pneumonia.

*HIV infection and bronchiolitis*

Very few studies have been conducted in KwaZulu Natal or South Africa to explore the relationship between bronchiolitis and HIV infection. Children living with HIV in have a greater incidence of lower respiratory tract infection (LRTI), hospitalisation, duration of hospital admission as well as mortality; when compared to HIV-uninfected children.(3, 4) Children with HIV have also been found to have a more prolonged *RSV* shedding of up to 3 months when compared to HIV-negative infants.(15) This is despite the use of highly active anti-retroviral (HAART). A local study showed that children infected with HIV had a four times greater risk of death in comparison to uninfected children when admitted with bronchiolitis.(3) *RSV* and *RV* remain the main pathogens in HIV-infected children similar to its predominance in HIV-uninfected counterparts. The greatest risk of *RSV*-associated bronchiolitis is in the first year of life but also remains high in the next three years of life. Little data is available to compare

HIV viral loads and duration of ARV therapy with the severity of bronchiolitis. Bacterial co-infection is more predominant in children infected with HIV and may be an independent risk factor that contributes towards the increased mortality in this population group.(2) A Cape Town study showed co-infection with bacteria and was associated with a greater duration of mechanical ventilation.(2)

We therefore aimed in this study to assess the viral aetiologies of bronchiolitis in a population of children admitted with bronchiolitis and to explore the relationship with HIV infection and other known risk factors for severe outcomes in children admitted to a PICU at a quartenary hospital in KwaZulu-Natal.

## Methodology

*Study type*

This was a retrospective, quantitative, descriptive study done at the Paediatric ICU at Inkosi Albert Luthuli Central Hospital (IALCH) in Kwa-Zulu Natal, South Africa.

*Inclusion criteria*

The study population included all children with a clinical diagnosis of bronchiolitis, as determined by the attending Paediatric Physician. Children were included if they were below the age of five years and were admitted to the Paediatric ICU between1$^{st}$ January 2017 till 31$^{st}$ March 2018.

*Exclusion criteria*

Participants were excluded if they had a previous admission of bronchiolitis, if they had a prior diagnosis of asthma or atopy.

*Study definitions*

These participants were classified as presumed bronchiolitis if they had clinical symptoms (i.e. cough, wheezing and hyperinflation), and chest x-ray picture of hyperinflation without a positive viral PCR; whilst those with a confirmed viral pathogen on PCR were classified as confirmed bronchiolitis.

*Data collection*

Purposive consecutive sampling was done from the electronic records of the hospital, records were searched for the study duration till the required sample size was met. Demographic data

included age and gender. Clinical variables included; date of admission and discharge, weight, height, HIV status, history of prematurity; the presence of TB co-infection, congenital heart disease and chronic lung disease. Laboratory markers included respiratory virus PCR and bacterial culture. Outcomes variables were duration of ventilation, discharge and death.

## Statistics

*Sample size calculation*

The following statistical parameters were used to arrive at a sample size with a minimum statistical power of 80 (%); effect size = 0.56, type 1 (α) error = 0.05 (i.e. probability of falsely rejecting the null hypothesis), type 2 (β) error = 0.2 (i.e. probability of falsely failing to reject the null hypothesis) and statistical power = 1 – β = 0.8. On the basis of the above statistical parameters, a minimum sample size of 104 was determined.

*Statistical analysis*

Descriptive statistics were presented as frequencies and percentages for categorical variables and expressed as mean ± SD, or median and interquartile range for continuous variables. Comparisons of duration of ventilation and ICU stay according to patient and risk factors were performed using the Mann-Whitney U and the Kruskal-Wallis tests. Proportions on categorical variables were compared using Pearson's chi-squared test and the Fishers exact test as appropriate. Binary logistic regression modelling was performed to determine mortality odds ratios associated with the risk factors. The level of significance was set at $p < 0.05$. Statistical analysis was performed using IBM SPSS version 25.

*Ethics*

Ethics approval was obtained from the University of Kwa-Zulu Natal's Biomedical Research Ethics Committee (BREC Number: BE214/18). Research permission was also obtained from KZN Department of Health and Inkosi Albert Luthuli Central Hospital, respectively.

## Results:

*Baseline characteristics*

A total of 104 participants were selected as initial study cohort. Two of these participants were excluded as both had been admitted with bronchiolitis in the preceding year. Of the 102 participants who met inclusion criteria, 59 (57.8%) were female, Table 1. The majority of these participants were under the age of six months (76.5%) with a median (IQR) age of 3 (IQR=3.0) months. The nutritional status was adequate in three quarters (75.0%) who were well

nourished, with 18.0% with moderate acute malnutrition and 7.0% with severe acute malnutrition. The majority were HIV negative (81.4%), with 17.6% being HIV positive and 1.0% unknown. Of the 18 participants who were HIV positive, the majority of these were newly diagnosed (83.3%), whilst all of the HIV positive participants were not virologically suppressed.

The majority of the participants (81.4%) had a virus positively identified on their endotracheal aspirate. Of those who had a virus positively identified, *RSV* was the most common virus found with a prevalence 52% in this group, Figure 1. This was followed by Adenovirus (22%) and ParaInfluenza-3 virus (12%), respectively. With regards to co-morbidities, 15% had a congenital cardiac lesion, 11% had chronic lung disease whilst 4.9% had concurrent tuberculosis (TB) infections.

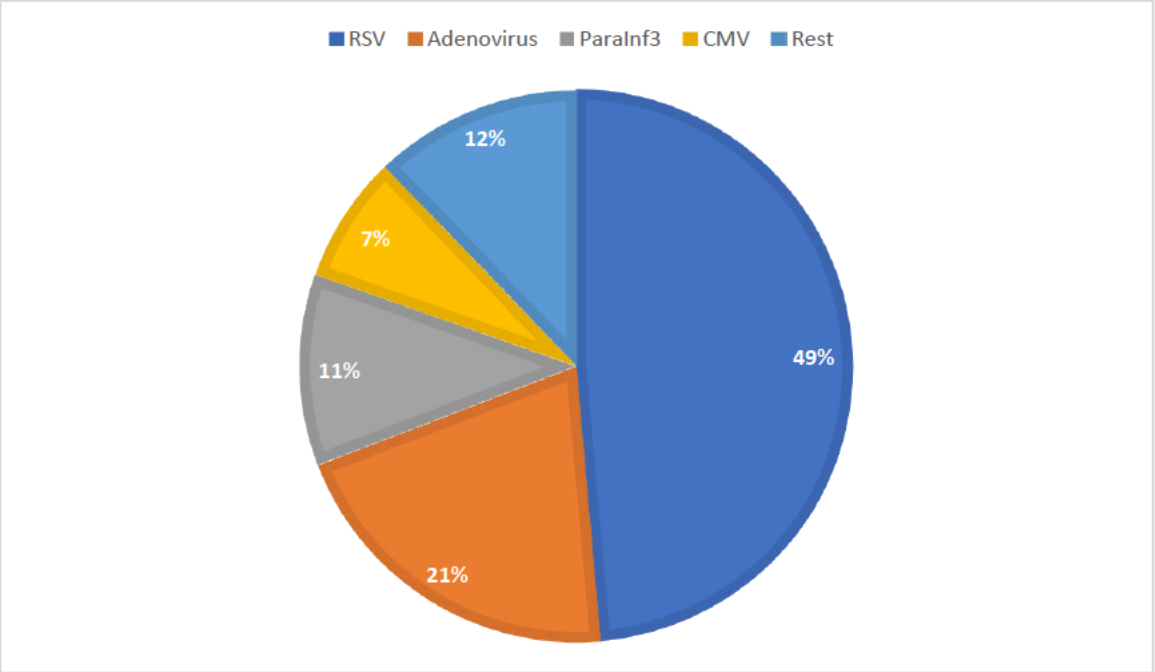


Figure 1. Distribution of viral aetiologies for bronchiolitis in children, N=83

*Table 1. Baseline characteristics and outcomes by gender, age and nutrition of children with bronchiolitis*

| Demographic/ Baseline Data | N | Duration of ventilation (days) | | | Duration of ICU admission (days) | | | Mortality | |
|---|---|---|---|---|---|---|---|---|---|
| | | *Median* | *IQR* | *P* | *Median* | *IQR* | *p* | *N* | *p* |
| **Gender** | | | | | | | | | |
| Male | 43 (42%) | 10.0 | 10.0 | 0.89 | 11.0 | 13.0 | 0.76 | 8 (18.6%) | 0.13 |
| Female | 59 (58%) | 11.0 | 17.0 | | 12.0 | 19.0 | | 5 (8.5%) | |
| **Age Group** | | | | | | | | | |
| <6 months | 78 (77%) | 12.0 | 15.0 | **0.01** | 13.0 | 16.0 | **0.01** | 9 (11.5%) | 0.51 |
| ≥6 months | 24 (23%) | 6.5 | 10.0 | | 6.5 | 10.0 | | 4 (16.7%) | |
| **HIV Status** | | | | | | | | | |
| Negative | 83 (81%) | 10.0 | 16.0 | 0.60 | 11.0 | 17.0 | 0.59 | 10 (12.0%) | 0.60 |
| Positive | 18 (18%) | 12.0 | 13.0 | | 13.0 | 15.0 | | 3 (16.7%) | |
| Unknown | 1 (1%) | | | | | | | | |
| **Nutritional Status** | | | | | | | | | |
| NAM | 77 (76%) | 10.0 | 15.0 | **0.03** | 11.0 | 15.0 | **0.02** | 10 (13.0%) | 0.65 |
| MAM | 18 (17%) | 14.5 | 13.0 | | 19.0 | 15.0 | | 1 (5.6%) | |
| SAM | 7 (7%) | 6.0 | 6.0 | | 8.0 | 8.0 | | 2 (28.6%) | |
| **TB Co-infection** | | | | | | | | | |
| Yes | 5 (5%) | 15.0 | 19.0 | 0.55 | 15.0 | 20.0 | 0.57 | 1 (20.0%) | 0.62 |
| No | 97 (95%) | 10.0 | 15.0 | | 11.0 | 15.0 | | 12 (12.4%) | |
| **Bronchiolitis** | | | | | | | | | |
| Presumed | 19 (19%) | | | | | | | | |
| Confirmed | 83 (81%) | | | | | | | | |

*Comparison of outcomes by age, gender and nutrition*

There were no statistically significant gender differences in duration of ventilation (p=0.89) or duration of stay in ICU (p=0.76). Males had a median ICU admission stay of 10 days whilst females had a median ICU admission stay of 11 days. Male infants were shown to have a higher mortality rate (18.6%) versus their female counterparts (8.5%) but this difference was shown not to be statistically significant (p=0.13). Infants younger than 6 months had a significantly longer duration of ventilation, Median (IQR) (12.0;15.0) vs. (6.5;10.0), p=0.01 and longer hospital of stay Median (IQR) (13.0;16.0) vs. (6.5;10.0), p=0.01. The moderate acutely malnourished group were shown to be ventilated for more days Median (IQR) (14.5;13.0) when compared to well-nourished infants, p=0.03. The moderate acutely malnourished group were also shown to have a longer ICU stay in days Median (IQR) (19.0;15.0) vs. well nourished (11.0;15.0) and severe acutely malnourished groups (8.0;8.0), p=0.02. Mortality was shown to be highest within the severe acutely malnourished group with 28.6% of these participants having demised.

*Comparison of outcomes by HIV and TB status*

HIV negative infants had a marginally shorter duration of ventilation in days when compared to the HIV positive group although this did not reach statistical significance Median (IQR) (10.0;16.0) vs. (12.0;13.0), p=0.6. HIV positive infants had a higher rate mortality (16.7%) compared to the HIV negative group (12.0%) but this difference was also not statistically significant (p=0.60). Those with concurrent TB infection did not have a longer hospital stay nor increased mortality compared to those without TB, both p>0.05.

*Outcomes by known risk factors*

*Previous prematurity*

More than a quarter (26.5%) of infants were premature and this was associated with more prolonged ventilation, (15.0;17.0) days vs. (10.0;12.0) days, p=0.05, Table 2. Prematurity was also associate with longer ICU stay, (18.0;18.0) vs (11.0;13.0), p=0.03. This group did not however show to have an increased mortality rate when compared to term infants. A virus was positively identified in 85% of infants with a background of prematurity with *RSV* making up 65% of these infections.

*Chronic lung disease and congenital heart disease*

Those participants with established chronic lung disease were shown to have a longer duration of ventilation in days versus those infants without evidence of chronic lung disease, (20.0;23.0) vs. (10.0;12.0), p=0.02. These infants were also shown to have a significantly longer duration of ICU stay in days versus those infants without chronic lung disease, (23.0;25.0) vs. (11.0;12.0), p=0.01.

Infants with congenital heart disease spent a longer duration on ventilatory support when compared to infants without congenital heart disease, (18.0;15.0) vs. (10.0,12.0), p=0.09. CHD was also associated with a prolonged ICU stay (20.0;15.0) vs. (11.0;14.0), p=0.09. Mortality in those with CHD was marginally significant 26.7% vs 10.3%, p=0.08. There was insufficient data collected on both breastfeeding practices and smoking exposure in the participant group to comment on these risk factors.

*Table 2. Bronchiolitis severity by prematurity, chronic lung disease and congenital heart disease.*

| **Risk Factors** | N (%) | **Duration of ventilation (days)** | | | **Duration of ICU admission (days)** | | | **Mortality** | |
|---|---|---|---|---|---|---|---|---|---|
| | | *Median* | *IQR* | *P* | *Median* | *IQR* | *p* | *n* | *p* |
| **Prematurity** | | | | | | | | | |
| Yes | 27(26%) | 15.0 | 17.0 | **0.05** | 18.0 | 18.0 | **0.03** | 1 (3.7%) | 0.10 |
| No | 75 (74%) | 10.0 | 12.0 | | 11.0 | 13.0 | | 12 (16.0%) | |
| **CLD** | | | | | | | | | |
| Yes | 11(11%) | 20.0 | 23.0 | **0.02** | 23.0 | 25.0 | **0.01** | 1 (9.1%) | 0.70 |
| No | 91 (89%) | 10.0 | 12.0 | | 11.0 | 12.0 | | 12 (13.2%) | |
| **CHD** | | | | | | | | | |
| Yes | 15(15%) | 18.0 | 15.0 | 0.09 | 20.0 | 15.0 | 0.09 | 4 (26.7%) | 0.08 |
| No | 87 (85%) | 10.0 | 12.0 | | 11.0 | 14.0 | | 9 (10.3%) | |

*Outcome by viral pathogen*

Those participants who had a virus positively identified on PCR testing were shown to have a significantly longer duration of ventilation in days than those participants in whom a virus was not identified, Median (IQR) (12.0;16.0) vs. (5.0;5.0), p=0.00,Table 3. These participants also had a longer duration of ICU stay in days, Median (IQR) (13.0;17.0) vs. (6.0;6.0), p=0.00.

All of the eligible participants who demised in the study (n=13) had a virus positive PCR (100%). Of those participants that demised, *Adenovirus* was shown to be the dominant factor being found in 54%(n=7) of this group. *Adenovirus* infection also conferred a higher mortality 38.9% vs.7.1%; p=0.00; and was a significant predictor of mortality (p=0.00). Infants who are *Adenovirus* positive are eight times more likely to demise compared to those who are *Adenovirus* negative (OR=8.3, 95% CI = 2.3-29.2).

Those participants who were virus-positive also occupied a much longer stay in ICU, occupying on average 17.3 days versus the virus-negative group whose average ICU stay was 7.8 days, p=0.00. Among the viruses, those with *Influenza A*, had the longest median duration of ICU admission at 24.5 days, p=0.15, but the interpretation of this is limited by the fact that only two children had *Influenza A* infection. RSV infection was associated with the longest duration of ventilation Median (IQR) (15.0;17.0) vs. (9.0;10.0), p=0.03.

*Table 3. Viral Aetiology and Outcomes*

| Virus | n | Duration of ventilation (days) | | | Duration of ICU admission (days) | | | Mortality | |
|---|---|---|---|---|---|---|---|---|---|
| | | *Median* | *IQR* | *p* | *Median* | *IQR* | *P* | *n* | *p* |
| **Virus** | | | | | | | | | |
| Positive | 83 (81%) | 12.0 | 16.0 | **0.00** | 13.0 | 17.0 | **0.00** | 13 (15.7%) | 0.07 |
| Negative | 19 (19%) | 5.0 | 5.0 | | 6.0 | 6.0 | | 0 (0.0%) | |
| **Adenovirus** | | | | | | | | | |
| Yes | 18 (18%) | 10.5 | 9.5 | 0.81 | 11.5 | 10.3 | 0.83 | 7 (38.9%) | **0.00** |
| No | 84 (82%) | 10.5 | 16.0 | | 11.5 | 17.0 | | 6 (7.1%) | |
| **CMV** | | | | | | | | | |
| Yes | 7 (7%) | 12.0 | 17.0 | 0.57 | 13.0 | 14.0 | 0.45 | 1 (14.3%) | 0.92 |
| No | 95 (93%) | 10.0 | 15.0 | | 11.0 | 15.0 | | 12 (12.6%) | |
| **RSV** | | | | | | | | | |
| Yes | 43 (42%) | 15.0 | 17.0 | **0.03** | 15.0 | 18.0 | **0.03** | 4 (9.3%) | 0.38 |
| No | 59 (58%) | 9.0 | 11.0 | | 10.0 | 12.0 | | 9 (15.3%) | |
| **Influenza A** | | | | | | | | | |
| Yes | 2 (2%) | 23.0 | - | 0.18 | 24.5 | - | 0.15 | 0 (0.0%) | 0.59 |
| No | 100 (98%) | 10.0 | 14.8 | | 11.0 | 15.0 | | 13 (13.0%) | |
| **Influenza B** | | | | | | | | | |
| Yes | 4 (4%) | 9.5 | 23.3 | 0.90 | 10.0 | 22.8 | 0.86 | 0 (0.0%) | 0.86 |
| No | 98 (96%) | 10.5 | 15.3 | | 11.5 | 15.5 | | 13 (13.3%) | |
| **Parainfluenza 1** | | | | | | | | | |
| Yes | 4 (4%) | 6.0 | 8.8 | 0.16 | 6.5 | 13.0 | 0.24 | 0 (0.0%) | 0.38 |
| No | 98 (96%) | 11.0 | 16.0 | | 12.0 | 17.0 | | 13 (13.3%) | |
| **Parainfluenza 2** | | | | | | | | | |
| Yes | 1 (1%) | 30.0 | - | 0.17 | 31.0 | - | 0.17 | 0 (0.0%) | 0.22 |
| No | 101 (99%) | 10.0 | 14.5 | | 11.0 | 15.0 | | 13 (12.9%) | |
| **Parainfluenza 3** | | | | | | | | | |
| Yes | 10 (10%) | 16.5 | 16.5 | 0.48 | 17.5 | 18.3 | 0.48 | 1 (10.0%) | 0.79 |
| No | 92 (90%) | 10.0 | 13.8 | | 11.0 | 15.0 | | 12 (13.0%) | |

*Bacterial Co-infection*

Overall, 42.0% percent of participants had a positive culture on admission. The most common organisms identified were Candida Albicans (17%) and Klebsiella Pneumoniae (12%). Those participants who were culture positive, had a significantly longer duration of ventilation versus those participants that were culture negative, Median (IQR)(15.0;18.0) vs, (9.0;10.0), p=0.00. The culture positive participants also had a significantly longer duration of ICU stay in days than the culture negative participants, Median (IQR) (17.0;20.0) vs. (10.0;12.0), p=0.01. Klebsiella Pneumoniae infection was associated with a significantly greater duration of ventilation in days than those that were Klebsiella negative, Median (IQR) (22.5;29.5) vs. (10.0;12.0), p=0.00. No significant difference in mortality outcomes were shown amongst those with bacterial co-infections versus the culture negative group (14.0% vs 11.9%, p=0.70).

## Discussion

The majority of our participants and patients admitted to the ICU with severe bronchiolitis were under six months of age with a median age of 3 months. Moderate and severe malnutrition conferred prolonged ventilation and ICU stay but not a greater mortality risk. *RSV* was found to be the most common virus causing severe bronchiolitis contributing to the greatest morbidity whereas *Adenovi*rus was found to be associated with the highest mortality. More severe disease with prolonged ventilation was also found in children with chronic lung disease and prematurity. Of interest children with congenital cardiac lesions and HIV infection did not significantly impact need for ventilation and ICU stay.

In the current study, there were more females than males, this is contrary to previous data showing male gender to be a risk factor for severe bronchiolitis.(8) Two factors that could have influenced this was both a higher incidence of malnutrition (22% versus 11.6%) and HIV infection rate (24% versus 9%) among the female group as compared to the males in the current study. Although proportionally more females were admitted to ICU, the mortality was proportionally higher in the males compared to females (18.6% versus 8.5%) although this did not reach statistically significance, possibly due to the low mortality in the study.(9)

The majority of the participants were also found to be under six months old (76.5%) which supports data that young infants are at a higher risk of contracting bronchiolitis especially RSV.(8) These infants also had longer duration of ventilation and ICU stay compared to older infants. This finding underscores the need for targeted prevention strategies including RSV Immunoglobulin in these high-risk groups.

Poor nutrition and increasing severity of malnutrition also resulted in prolonged ventilation and ICU stay. Results show that the moderate acutely malnourished group were shown to have the longest duration of ventilation with a median duration of 14.5 days. This is likely due to the severe acute malnourished group having the highest mortality rate amongst the nutritional groups, thus shortening their duration of ventilation but we did not reach statistical significance likely due to low number of overall deaths ($p=0.65$). Severe acute malnutrition may thus be an independent risk factor for poor outcomes in bronchiolitis which has implications for eligibility criteria for ICU admission in a resource limited setting. Although in the current study we could not assess outcomes by breastfeeding, this finding further supports the need to support breastfeeding and encourage breastfeeding for at least 6 months in young infants to prevent bronchiolitis as well as to limit morbidity associated with bronchiolitis.(9)

Despite the relatively high prevalence of HIV in the current study, HIV infection did not confer a higher risk of more severe disease nor need for ventilation. The majority of HIV positive participants were newly diagnosed, suggesting a failure in the prevention of mother to child program.

More than a quarter (26.5%) of our participants were found to have previous prematurity as a risk factor for severe bronchiolitis. This supports previous evidence linking prematurity with severe bronchiolitis, with infants with a background of prematurity having a seven-fold increased risk of *RSV*-bronchiolitis. *RSV* infection in this subgroup has also been associated with an increased risk of type 1 respiratory failure and need for ventilation.(9) Our study showed that a virus was positively identified in 85% of infants with a background of prematurity; furthermore *RSV* proving to be the predominant aetiology, found in 65% of these positive cases. This data overwhelmingly shows that previous prematurity is a significant risk factor for *RSV* infection in the first year of life and strategies aimed at preventing this is imperative to decrease the burden on the health care system.

About 1 out of every 10 infants admitted to the ICU had a background of chronic lung disease. This group was shown to require a longer duration of ventilation, with an average of ten days more than those infants without a background of chronic lung disease. Bronchopulmonary dysplasia is a known risk factor for readmission to hospital in the first year of life due to respiratory tract infections.(16) Chronic lung disease is a risk factor for *RSV* infection and severity of bronchiolitis with infants having a 6.7-fold increased risk of death from bronchiolitis if they have co-existing chronic lung disease.(9) This may be secondary to viral respiratory infections which alter pulmonary blood flow and decrease lung capacity in children with CLD thus altering the pathophysiological response to disease.(16)

Congenital heart disease made up a significant proportion of children in the current study (15%). We found no differences in duration of ICU stay nor ventilation in children with CHD compared to those without CHD. This is contrary to previous studies that found that CHD was associated with a 50% longer duration of hospital stay than in children.(9) The mortality rate is also not higher in these infants with CHD unlike that reported by Simon and colleagues in Germany where they found a 3.7-fold increased risk of death among infants hospitalized for

*RSV* with co-existing CHD.(17) Our study may be limited by the low numbers of children with CHD and stricter admission criteria.

More than four-fifths (81.4%) of participants had a positive virus PCR sample. Ghani et al. reported a prevalence of 63% in a study done at a Cape Town Paediatric ICU whilst Famoroti et al. reported a prevalence of 46% in a mixed setting in Kwa-zulu Natal.(2, 18) One of the reasons for the high positivity rate could be attributed to infants that have viral respiratory infections often end up having more severe disease, hence needing ICU care..

*RSV* was the most common virus identified with a prevalence of 52%, followed by Adenovirus at 22%. This supports previous studies which showed *RSV* to be the dominant viral pathogen in children with prevalence in the under-1 year age group as high as 75%.(12) This prevalence of *RSV* was much higher than previous local studies which showed *RSV* prevalence ranging from 26% to 32%.(2, 18) Our study period overlapped two rainy seasons in Kwa-Zulu Natal (January to March), and this may have contributed to the higher prevalence of *RSV* in our study group. *RSV* seasonality is known to peak during the summer months, notably from February to April every year.(18) Previous studies have shown that at-risk infants with *RSV*-associated respiratory tract infections are more likely to have a longer duration of ICU stay than an otherwise-normal infant.(5) Those participants who had *RSV* infection in the study were shown to have on average one week longer duration of mechanical ventilation than those without *RSV* infection (p=0.03).

All of the eligible participants who demised in the study (n=13) had a virus positively identified (100%). Of those participants that demised, *Adenovirus* was shown to be the predominant factor being found in 54% of those who died and increased the mortality by eight times. Previous studies have shown *Adenovirus* pneumonia to cause significant morbidity with up to half (52%) of cases having post-infectious bronchiolitis obliterans and a quarter (26%) needing non-invasive home respiratory support.(6) Certain strains of *Adenovirus* are known to cause more severe disease and a necrotising pneumonia.(14) This could explain why a very high percentage of *Adenovirus*-infected infants demised in our study. However, current laboratory testing does not account for the specific subtype of Adenovirus on a viral PCR test. There are no antiviral treatments currently licensed for treatment of severe *Adenovirus* disease. Takahashi et al. reported that use of pulse methylprednisolone (25mg/kg/day) for 3 days, in a case of severe Adenovirus pneumonia (type 3) with hypercytokinemia, which resulted in relief

of respiratory distress. Cidofivir is occasionally used in immunocompromised children with severe Adenovirus disease. It has been shown to lower the viraemia present in blood, however it has not shown to reduce mortality and is also a nephrotoxic agent. More studies are needed to look at treatment strategies in severe Adenovirus disease to improve disease outcomes.

Overall, forty-two percent of participants had a positive bacterial or fungal culture on admission, which correlates to a Cape Town study. Ghani et al. showed that 39% of infants admitted to the Paediatric ICU with viral pneumonia's had a bacterial co-infection, with these infants having twice as long ICU stay than those without a bacterial co-infection.(2) The most common organisms identified were Candida Albicans (39.5%) and Klebsiella Pneumoniae (27.9%). Those participants who had a positive culture spent on average 7 days longer on mechanical ventilation than those who were culture negative (p=0.00). Klebsiella Pneumoniae infection was associated with a significantly longer duration of ventilation in days than those that were Klebsiella negative. This means they cause more severe disease and require longer recovery times. Aims at preventing nosocomial infections pre-transfer of patient to ICU as well as in the ICU are necessary and require continuous infection control strategies at all levels of hospital care. We observed no significant difference in mortality outcomes amongst those with bacterial co-infections versus the culture negative group (14.0% vs 11.9%).

**Strengths of study**

The strength of the current study was this was in a cohort of children admitted to an ICU which has a protocolised diagnostic and management of children with lower respiratory tract infections, where on admission samples are sent for viral PCR, this provided data from two RSV seasons on the outcomes of children admitted in the ICU. We also identified common risk factors in our setting that lead to severe disease. These include malnutrition, previous prematurity, chronic lung disease and HIV infection, these groups require prioritising for RSV prophylaxis in our population.

**Limitations of study**

Due to this study being a retrospective design, convenience sampling was used, and are therefore not representative of the general population and are therefore prone to selection bias. The study period overlapped two summer months and hence seasonal variability of virus predominance could have affected the results. Sampling of infants was done at a Tertiary ICU where the most severe disease is prevalent and may not be a reflection of the viral prevalence in the general population. There was insufficient data was available to collect regarding

tobacco smoke exposure and previous breastfeeding practices of the participants, which are possible risk factors for severe bronchiolitis. This and other confounding factors could not be measured to ascertain effect on the study group. Lastly, we were unable to identify *Adenovirus* serotypes in this study, as testing for serotype is not routinely offered in our setting.

## Conclusion

Young infants with malnutrition, premature infants and those with chronic lung disease are high risk for severe bronchiolitis disease. *RSV* remains a significant cause of viral bronchiolitis in children and RSV immunoglobulin for these high-risk groups should be targeted as a public health strategy. Adenovirus-associated bronchiolitis is associated with increased morbidity and mortality.

## References:


1. Green RJ, Zar HJ, Jeena PM, Madhi SA, Lewis H. South African guideline for the diagnosis, management and prevention of acute viral bronchiolitis in children. S Afr Med J. 2010;100(5):320, 2-5.
2. Ghani AS, Morrow BM, Hardie DR, Argent AC. An investigation into the prevalence and outcome of patients admitted to a pediatric intensive care unit with viral respiratory tract infections in Cape Town, South Africa. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2012;13(5):e275-81.
3. Cohen C, Walaza S, Moyes J, Groome M, Tempia S, Pretorius M, et al. Epidemiology of viral-associated acute lower respiratory tract infection among children <5 years of age in a high HIV prevalence setting, South Africa, 2009-2012. Pediatr Infect Dis J. 2015;34(1):66-72.
4. Moyes J, Cohen C, Pretorius M, Groome M, von Gottberg A, Wolter N, et al. Epidemiology of respiratory syncytial virus-associated acute lower respiratory tract infection hospitalizations among HIV-infected and HIV-uninfected South African children, 2010-2011. J Infect Dis. 2013;208 Suppl 3:S217-26.
5. Dearden CX JA, Havinga J, Green RJ. The epidemiology of respiratory syncytial virus: A retrospective review from Steve Biko Academic Hospital 2013-2016. African Journal of Thoracic Critical Care Medicine. 2017;24(1):30-4.
6. Li Min Lim YYW, Jessie Anne de Bruyne, et al. Epidemiology, clinical presentation and respiratory sequelae of adenovirus pneumonia in children in Kuala Lumpur. PloS one. 2018:1-19.
7. Zampoli M, Mukuddem-Sablay Z. Adenovirus-associated pneumonia in South African children: Presentation, clinical course and outcome. S Afr Med J. 2017;107(2):123-6.
8. Annamalay AA, Abbott S, Sikazwe C, Khoo SK, Bizzintino J, Zhang G, et al. Respiratory viruses in young South African children with acute lower respiratory infections and interactions with HIV. J Clin Virol. 2016;81:58-63.
9. Alvarez AE, Marson FAL, Bertuzzo CS, Arns CW, Ribeiro JD. Epidemiological and genetic characteristics associated with the severity of acute viral bronchiolitis by respiratory syncytial virus. Jornal de Pediatria (Versão em Português). 2013;89(6):531-43.
10. Shi J, Zhou Y, Wang F, Wang C, Miao H, Sun T, et al. A case series of children with adenovirus pneumonia: three-year experiences in a tertiary PICU. BMC Pediatr. 2020;20(1):375.
11. Pei-Qiong Wu S-QZ, et al. Clinical manifestations and risk factors of adenovirus respiratory infection in hospitalized children in Guangzhou, China during the 2011–2014 period. Medicine. 2020;99:4:1-6.
12. Zar HJ, Madhi SA, White DA, Masekela R, Risenga S, Lewis H, et al. Acute viral bronchiolitis in South Africa: Strategies for management and prevention. S Afr Med J. 2016;106(4):27-9.
13. Murray J, Bottle A, Sharland M, Modi N, Aylin P, Majeed A, et al. Risk factors for hospital admission with RSV bronchiolitis in England: a population-based birth cohort study. PloS one. 2014;9(2):e89186.
14. Zampoli M M-SZ. Adenovirus-associated pneumonia in South African children: Presentation, clinical course and outcome. SAMJ. 2017;107(2):4.
15. King JC, Jr., Burke AR, Clemens JD, Nair P, Farley JJ, Vink PE, et al. Respiratory syncytial virus illnesses in human immunodeficiency virus- and noninfected children. Pediatr Infect Dis J. 1993;12(9):733-9.
16. Cecilie Revhaug MB-M, Magdalena Zasada, et al. Immune system regulation affected by murine experimental model of Bronchopulmonary Dysplasia: Genomic and Epigenetic Findings. Journal of Neonatology. 2019;2019;116(3):269-277.

17. Simon A, Ammann RA, Wilkesmann A, Eis-Hubinger AM, Schildgen O, Weimann E, et al. Respiratory syncytial virus infection in 406 hospitalized premature infants: results from a prospective German multicentre database. Eur J Pediatr. 2007;166(12):1273-83.
18. Famoroti T, Sibanda W, Ndung'u T. Prevalence and seasonality of common viral respiratory pathogens, including Cytomegalovirus in children, between 0-5 years of age in KwaZulu-Natal, an HIV endemic province in South Africa. BMC Pediatr. 2018;18(1):240.