RSV BRONCHIOLITIS IN 2018:
A DESCRIPTIVE STUDY OF CHILDREN ADMITTED TO TWO JOHANNESBURG TERTIARY HOSPITALS

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A Research Report submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the Discipline of Paediatrics.

Johannesburg, 20 December 2021

Declaration

I, Tannah Storm Cleak, declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine in the department of Paediatrics and Child Health, Faculty of Health Sciences, at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

Dr T S Cleak

Signature: _____

Date: 20. 12. 2021

Dedication

I dedicate this work to my family and Stephan Broich, I am eternally greatly for all of you.

Abstract

RSV Bronchiolitis in 2018: A Descriptive Study of Children Admitted to two Johannesburg Tertiary Hospitals

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Background. Respiratory Syncytial Virus (RSV) is the most common cause of severe bronchiolitis in children worldwide.

Objectives. To describe clinical characteristics and outcomes of children hospitalized with bronchiolitis and to compare those with respiratory syncytial virus (RSV) bronchiolitis to children with other viral causes of bronchiolitis.

Methods. A retrospective study of children admitted with virally screened bronchiolitis to Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Nelson Mandela Children's Hospital (NMCH) from 01 February to 31 August 2018 was conducted, where RSV positive and negative children were compared.

Results. A total of 131 children admitted with bronchiolitis from CMJAH and NMCH were compared in this study, 58 from CMJAH and 73 from NMCH. These children were identified by the National Health Laboratory Service as having undergone respiratory viral multiplex molecular assay analysis and hospital charts were retrospectively reviewed. In the sample group, 65 (49.6%) children had RSV in comparison to 66 (50.4%) children without RSV. Children with RSV consisted of 55 (42%) children with RSV only and 10 (7.6%) children with RSV in combination with another respiratory virus. Rhinovirus was the second most common virus detected in this cohort of children (n=17, 12.9%) followed by adenovirus (n= 12, 9.2%) and coronavirus (n=9, 6.9%). A statistically significant risk factor noted in children requiring hospitalisation for RSV bronchiolitis was an age of less than six months (p-value <0.001).

Conclusions. Bronchiolitis is a common disease in children. Respiratory syncytial virus is the most common cause of severe bronchiolitis in hospitalised infants less than six months of age.

Acknowledgements

I wish to express my sincere appreciation and gratitude to, Professor Debbie White and Professor Daynia Ballot for their guidance and knowledge in this research endeavour. I am grateful to Karren le Roux and her team of medical biological scientists at Infection Control for processing the initial data necessary for my study. A special thank you to Rose Bandini for her advice regarding the statistical analyses.

Table of Contents

List of Abbreviations

CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CMV	Conventional mode of Ventilation
CPAP	Continuous Positive Airway Pressure
CPR	Cardiopulmonary Resuscitation
CRP	C-reactive Protein
CSF	Cerebrospinal Fluid
CT	Computed Tomography
ECHO	Echocardiogram
ECMO	Extracorpeal Membrane Oxygenation
ELISA	Enzyme Linked Immunosorbent Assay
HFOV	High Frequency Oscillatory Ventilation
$HFNO_2$	High Flow Nasal Oxygen
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
IPPV	Intermittent Positive Pressure Ventilation
MRI	Magnetic Resonance Imaging
NHLS	National Health Laboratory Service
NIV	Non-invasive ventilation
NMCH	Nelson Mandela Children's Hospital
NPO_2	Nasal Prong Oxygen
PCR	Polymerase Chain Reaction
PHPT	Pulmonary hypertension
PICU	Paediatric Intensive Care Unit
RSV	Respiratory Syncytial Virus

List of Figures

List of Tables

1. Chapter One – Submissible Format

1.1 Background

Bronchiolitis is a lower respiratory tract infection caused by many viruses, primarily affecting children younger than two years.[1,2] In South Africa, the overall prevalence of respiratory viruses in children with a lower respiratory tract infection and under the age of five was 78%.[3] Respiratory viruses causing bronchiolitis include rhinovirus, respiratory syncytial virus (RSV), adenovirus, parainfluenza virus, influenza virus, human metapneumovirus, bocavirus, coronavirus and measles virus.[1,2] Respiratory syncytial virus is the most common cause of severe bronchiolitis.[1,2,4,5] RSV is estimated to account between 40 and 90% for all children requiring hospitalisation with bronchiolitis.[4,5] The increasing burden of RSV, particularly in infants, has been well documented worldwide.[4,5]

Several well-described risk factors have been associated with severe RSV infection.[5] Risk factors include prematurity, chronic lung disease, congenital lung malformations, haemodynamically significant congenital heart defects, neuromuscular disease, infancy (particularly infants less than six months of age), male gender, immune compromise and lack of breastfeeding.[2,6,7] Environmental risk factors attributing to severe illness include tobacco smoke exposure, overcrowding and day-care attendance.[2,7] It is possible for children to suffer from severe re-infections with RSV despite having humoral immunity from previous infections.[8] RSV infection rates are highest in the autumn and early winter months in South Africa, generally lasting four months.[1]

Signs and symptoms for all viral causes of bronchiolitis, including RSV, are non-specific and consist of nasal congestion, rhinorrhoea, cough, irritability, poor feeding and low-grade fever.[6,8,9] Bronchiolitis is a clinically diagnosed lower respiratory tract infection characterised by bilateral wheezing, hyperinflation and tachypnoea, it is generally preceded by the above mentioned upper respiratory prodrome symptoms.[7] Children with moderate and severe cases bronchiolitis are more likely to be caused by RSV rather than any of the other respiratory viruses.[1,2,4,5]. Suspected complications should undergo further investigation, such as chest radiographs.[10] There may be a role for routine viral screening for surveillance and understanding the possible contributing role of co-infection with multiple viruses.[11,12]

Management for all cases of bronchiolitis, mild to severe, remains supportive. [13,14] Treatment goals include managing hypoxia, pyrexia and optimising nutrition.[13,14]

This study aimed to determine and compare clinical characteristics, risk factors, co-infections and outcomes for children admitted with RSV positive and RSV negative bronchiolitis at two state tertiary hospital centres in Johannesburg with the necessary equipment, facilities and staff to care for moderately and severely ill children.

1.2 Methods

This study was a retrospective, descriptive analysis of children younger than two years admitted to Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Nelson Mandela Children's Hospital (NMCH) with virally screened bronchiolitis from 1 February 2018 to 31 August 2018. Children with RSV positive bronchiolitis were compared to those children with RSV negative bronchiolitis.

Study Sites

CMJAH is a tertiary hospital incorporated into the academic circuit of the health science programme at the University of the Witwatersrand. The 220-bed paediatric service caters for all paediatric medical and surgical subspecialties. There are 14 beds available in the mixed paediatric and neonatal intensive care. CMJAH serves a large population including many referring clinics and hospitals. These include Bertha Gxowa Hospital, South Rand Hospital, Edenvale Hospital, Tambo Memorial Hospital, Pholosong Hospital and Far East Rand Hospital.

NMCH, a new tertiary facility in close proximity to CMJAH, opened three years ago. The hospital has both a paediatric and neonatal ICU, admitting up to 16 patients each. Paediatric cardiology and renal patients also receive care at NMCH.

Data Collection

Nasopharyngeal swab or tracheal aspirate specimens were submitted to the National Health Laboratory service (NHLS) for viral multiplex molecular assay analysis for patients admitted

with respiratory tract infections. Multiplex molecular assays detect viral nucleic acids.[15] Multiplex polymerase chain reaction (PCR)-based respiratory viral panels performed at NHLS at CMJAH tested for influenza virus, adenovirus and RSV. The NHLS outsourced full respiratory panel PCR testing on specimens from NMCH to Lancet Laboratories. The full respiratory panel tested for: adenovirus, bocavirus, coronavirus, enterovirus, influenza virus, metapneumovirus, mycoplasma pneumonia, parainfluenza, parechovirus, RSV and rhinovirus. The NHLS infection control specialists supplied lists of individuals who had undergone viral testing for bronchiolitis during the study period. These lists were reviewed and patients older than two years and from other hospitals were excluded. Hospital records of those children who were admitted with an initial diagnosis of bronchiolitis and met the specified study criteria, were reviewed. The severity of bronchiolitis was determined by the initial treating physician at the time of admission. While children from both CMJAH and NMCH's paediatric general ward and intensive care units were included in this study, all had been assessed as having either moderate or severe bronchiolitis.

Clinical, demographic, serological and radiological data were captured according to a pre-designed data collection sheet. The references ranges provided by the NHLS were used to categorise the children's results.[16] Survivors were those children who were discharged home or transferred from CMJAH or NMCH back to their base hospitals.

Statistical Analysis

An MS Excel (Microsoft, USA) spreadsheet was used to enter the data which was then imported into a statistical software package SPSS version 25 (IBM, USA). Frequencies and percentages were used to describe categorical variables. Means and standard deviations were used to describe normally distributed, continuous variables. Chi-square test and T-test were used to compare categorical and continuous variables, respectively. A p-value of <0.05 was considered significant.

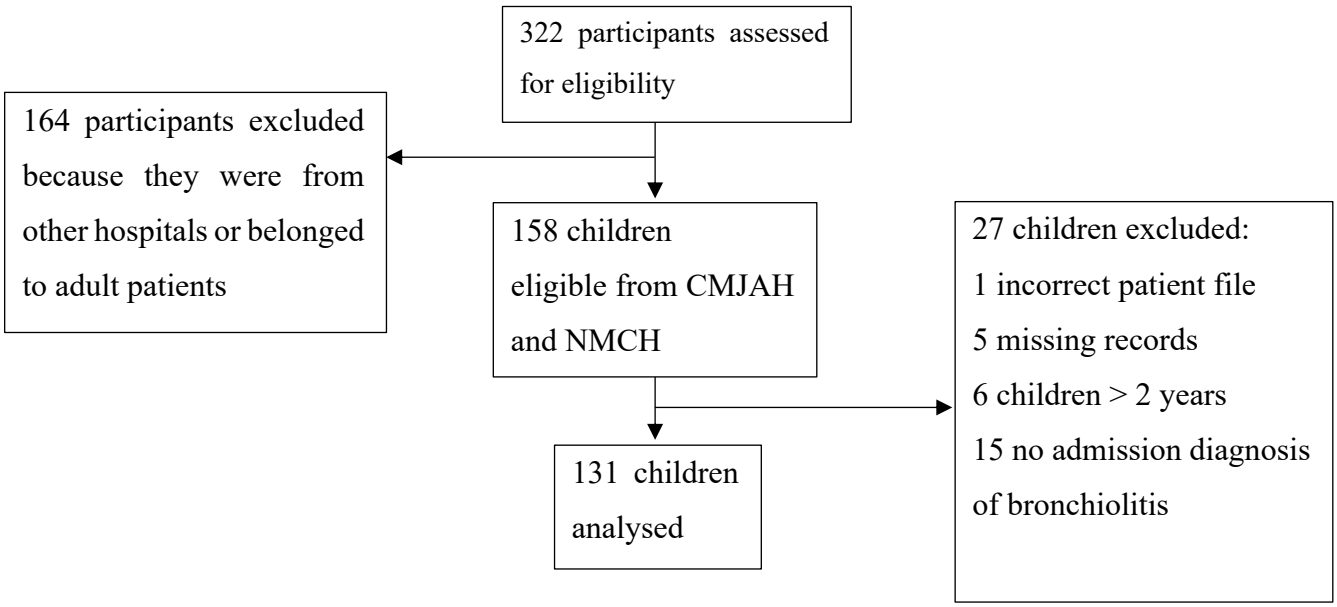
Ethics

The Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg granted ethics approval for the study (clearance certificate number M190505).

1.3 Results

During the study period, 322 participants had viral specimens submitted for testing. A total of 191 participants were excluded from further analysis, 164 participants were either adult patients or from hospitals not included in this study and remaining 27 were excluded for other reasons (see Fig. 1). The remaining cohort included 131 children, 58 from CMJAH and 73 from NMCH. It is not known the total number of children who were admitted with bronchiolitis or who underwent swabbing during the study period was not known.

Figure 1: Children with bronchiolitis included in this analysis.



The most common virus isolated in children admitted with bronchiolitis to CMJAH and NMCH was RSV (n=65, 49.6%). Rhinovirus was the second most common virus detected in children (n=17, 12.9%) followed by adenovirus (n= 12, 9.2%) and coronavirus (n=9, 6.9%). There were 17 (12.9%) children who cultured more than one respiratory virus. Table 1 demonstrates the children's viral multiplex-PCR results.

Table 1. Viral Multiplex PCR (N=131) results of children admitted with bronchiolitis.

Participants with RSV	*n (%)*	Participants without RSV	*n (%)*
RSV	55 (42)	No virus present	25 (19.1)
RSV and Rhinovirus	3 (2.3)	Rhinovirus	13 (9.9)
RSV and Adenovirus	2 (1.5)	Adenovirus	5 (3.8)
RSV and Bocavirus	1 (0.8)	Influenza A virus	5 (3.8)
RSV and Coronavirus	1 (0.8)	Coronavirus	4 (3.1)
RSV and Influenza A virus	1 (0.8)	Human Metapneumovirus	3 (2.3)
RSV, Bocavirus and Coronavirus	1 (0.8)	Parainfluenza	2 (1.5)
RSV, Coronavirus and Parainfluenza	1 (0.8)	Enterovirus	2 (1.5)
		Influenza B virus	1 (0.8)
		Adenovirus and Parainfluenza	3 (2.3)
		Adenovirus and Coronavirus	1 (0.8)
		Adenovirus and Influenza B	1 (0.8)
		Rhinovirus and Coronavirus	1 (0.8)
Total	**65 (49.6)**	**Total**	**66 (50.4)**

The majority of children in this study were aged six months and younger (n=74, 56.5%), with more than half of these children having RSV positive bronchiolitis (n=47/75, 62.7%). The remaining children consisted of 45 (34.3%) between the ages of 7 to 11 months and 12 (9.1%) older than one year. Only 42 (32%) children were born prematurely, i.e. than 37 weeks gestation, with the majority of these children (n=24/42, 57,1%) having RSV positive bronchiolitis. However, prematurity was not a statistically significant risk factor for children having RSV positive bronchiolitis compared to children with non-RSV bronchiolitis. Children in this study were predominantly not exposed to HIV at birth (n=81, 61,8%). Only three children with HIV exposure were confirmed to be HIV positive with further testing. HIV did not demonstrate any statistical difference in children presenting with RSV positive bronchiolitis. There was not enough data for the following risk factors: feeding choice, other immunodeficiency states, siblings attending crèche or tobacco smoke exposure to compare and comment on in the context of this study. Table 2 compares other risk factors between RSV

positive and negative bronchiolitis participants. The only statistically significant risk factor for RSV bronchiolitis was an age of less than six months (p-value <0.001).

Table 2. Comparison of risk factors for children with and without RSV infection

Risk Factor	**RSV Positive** *N 65, n (%)*	**RSV Negative** *N (66), n (%)*	**p-value**
HIV Exposed	29 (44.6)	21 (31.8)	0.09
HIV Unexposed	36 (55.4)	45 (68.2)	
HIV PCR Positive	2 (3)	1 (1.5)	0.49
HIV ELISA/PCR Negative	63 (97)	65 (98.5)	
Premature	24 (36.9)	18 (27.3)	0.16
Congenital Heart Disease*	9 (13.8)	18 (27.3)	0.053
Chronic Lung Disease†	26 (40)	22 (33.3)	0.27
<6 months in age	47 (72.3)	27 (40.9)	**<0.001**

* Congenital heart disease with increased blood flow, consisting of: ventricular septal defects, atrial septal defects, atrioventricular septal defects and patent ductus arteriosus.

† Chronic lung disease was predominantly secondary to bronchopulmonary dysplasia (n=21/48), when specified in the respective children's hospital records, however, the remaining children's records did not specify the underlying cause for their chronic lung disease.

There was no statistically significant difference between both laboratory and radiological investigations performed on RSV positive and RSV negative children with bronchiolitis. A multivariable regression analysis showed that none of the above listed risk factors were found to be dependently associated with RSV, as evidenced by a p-value of greater than 0.05 for each variable. The majority of initial chest radiographs for children with RSV positive bronchiolitis were hyperinflated with infiltrates (n=33/65, 50.7%). Children with RSV negative bronchiolitis generally had infiltrates only on their chest radiographs (n=38/66, 57.6%). There were eight positive admission blood cultures for children with RSV and seven for children without RSV bronchiolitis. No clinically significant organisms were cultured for children with RSV bronchiolitis. While, two children without RSV grew Staphylococcus aureus and one Escherichia coli, the remaining cultures were clinically insignificant.

Complications, outcomes, oxygen therapy and length of admission is summarised in Table 3. A total of 103 (78.6%) children required admission to CMJAH and NMCH's ICU facilities for invasive methods of ventilation, during the study, 54 children with RSV and 49 without RSV. The remaining 28 (21.4%) children were cared for in the general wards. More than half of children from this study were investigated for nosocomial sepsis, 49 with RSV bronchiolitis and 43 without RSV. There were 11 children with RSV and 15 without RSV who had evidence of nosocomial sepsis on blood cultures. Children with RSV cultured the following organisms: one *Acinetobacter baumannii*, one *Candida albicans*, one *Escherichia coli*, two *Klebsiella pneumoniae*, two *Staphylococcus aureus* and four clinically insignificant organisms (*Coagulase negative staphylococcus)*. Children without RSV cultured the following organisms: one *Acinetobacter baumannii*, one *Candida albicans*, one *Escherichia coli*, one *Methicillin-resistant staphylococcus aureus*, one *Pseudomonas aeruginosa*, two *Staphylococcus aureus* and eight clinically insignificant organisms. Seven children experienced seizures during their admissions and underwent neuroimaging. Four of these children had features in keeping with hypoxic brain injury, three of whom had RSV positive bronchiolitis and one child without RSV. The three remaining children had normal neuroimaging. Seventeen children died in this study: three children had no virus isolated, seven children did not have RSV, and the remaining seven children had RSV. Three of the seven children with RSV who died had RSV in combination with another virus. However, there were no statistical differences demonstrated for outcomes or complications for either group of children.

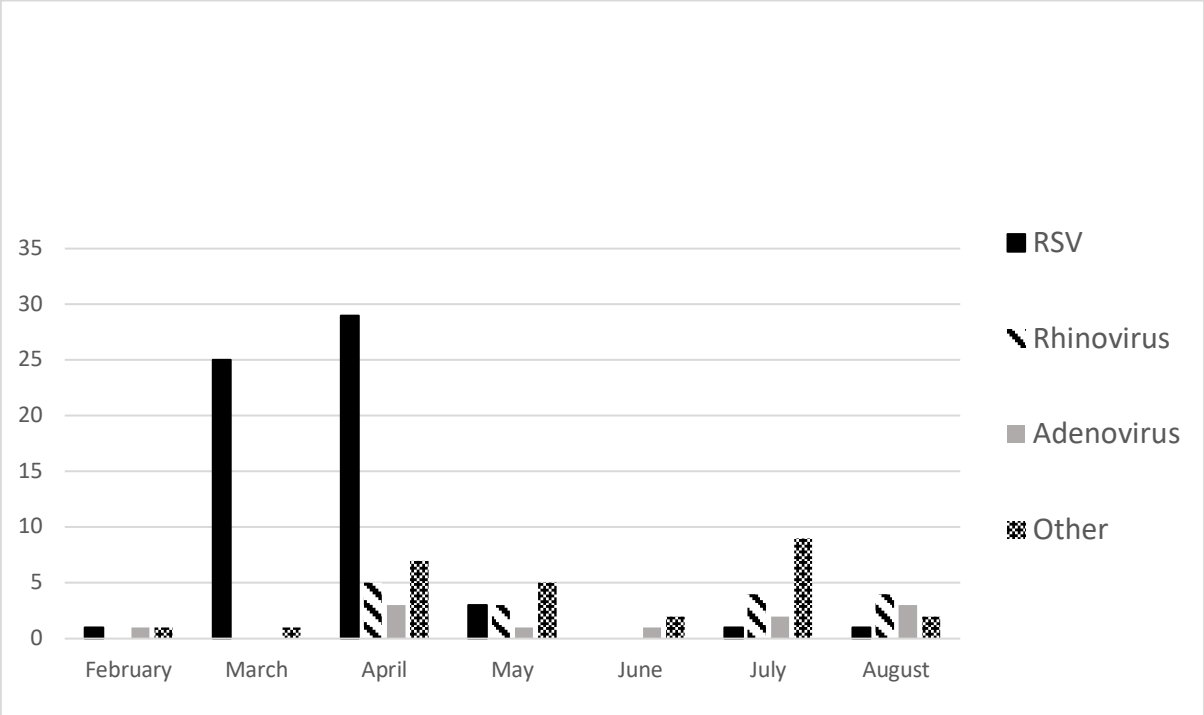
Table 3. Comparison of complications, outcomes and oxygen therapy for children with and without RSV infection

Complications and Outcomes		**RSV Positive** *n/N (%)*	**RSV Negative** *n/N (%)*	**p-Value**
Nosocomial Sepsis		49/65 (75.4)	43/66 (65.2)	0.18
Apnoea		35/65 (53.4)	30/66 (45.5)	0.38
Cardiopulmonary Resuscitation		9/65 (13.8)	14/66 (21.2)	0.35
Hypotension requiring inotropes		9/65 (13.8)	18/66 (27.3)	0.8
Seizures		5/65 (7.7)	2/66 (3)	0.27
Pulmonary Hypertension		3/65 (4.6)	7/66 (10.6)	0.61
Myocarditis		4/65 (6.2)	5/66 (7.6)	0.78
Ventilation Acquired Pneumonia		13/65 (20)	11/66 (16.7)	0.78
Outcomes	**Death**	7/65 (5.3)	10/66 (7.6)	0.64
	Discharge	58/65 (44.3)	56/66 (42.3)	
Days on oxygen	NPO_2	216/883 (24.5)	264/844 (31.3)	0.67
	$HFNO_2$	106/883 (12)	138/844 (16.4)	
	CPAP	16/883 (1.8)	4/844 (0.4)	
	CMV	429/883 (48.6)	319/844 (37.8)	
	HFOV	116/883 (13.1)	86/844 (10.2)	
	ECMO	0/883 (0)	33/844 (3.9)	
Length of admission (days)		945 (52)	873 (48)	0.27

In this study, children stayed at CMJAH and NMCH for an average of 14.5 days (s=10.3 days), admissions to ICU averaged 10.1 days (s=8.1 days). Children required oxygen therapy for approximately 13.4 days (s= 9.7days).

Children with RSV bronchiolitis were predominantly admitted in March and April of 2018, with some later admissions in July and August as shown in Figure 2. Rhinovirus was the second most common virus found from April to August.

Figure 2: A Bar graph demonstrating the epidemiology of Respiratory Viruses from February 2018 to August 2018.



Other: Human metapneumovirus, Coronavirus, Bocavirus, Parainfluenza virus, Influenza A, Influenza B and Enterovirus.

1.4 Discussion

This present study, conducted at two large academic referral centres in Johannesburg, South Africa, demonstrated that RSV was the most common virus detected in children hospitalised with moderate and severe bronchiolitis in the season of 2018 (n=65, 49.6%). In the present study, it was demonstrated that RSV was the most common virus detected in children hospitalised with severe bronchiolitis in the season of 2018 (n=65, 49.6% Table 1). Seventeen children had more than one virus identified on their respective viral swabs but the implications, i.e. determining if one specifically or the combination of all the viruses determined the severity of illness, duration of illness and subsequent outcomes for those respective children, cannot be determined in the context of this study. The next most common viruses identified in this study were adenovirus (n= 12, 9.2%) and coronavirus (n=9, 6.9%). The nine children with coronavirus all survived to discharge. These children had coronaviruses other than the newly identified SARS-CoV-2 in 2020 , responsible for the COVID-19 pandemic. The clinical presentation of children admitted with bronchiolitis with coronavirus were all respiratory in

nature with a well-documented prodrome of upper respiratory tract infection symptoms followed by unproductive coughing and tachypnoea. None of them had any of the following documented at the time of their presentations or preceding their arrival to hospital: erythematous maculopapular rash, conjunctivitis, gastrointestinal symptoms, myalgia, severe headache or confusion or loss of taste or smell, however, some of these symptoms would be difficult to illicit in a toddler.

Children with RSV presented mostly in March and April, with fewer RSV cases from May to August of 2018 (Figure 2). This is keeping with the seasonality described for RSV in Gauteng, with a peak around Autumn.[1,2] However, this specific seasonality of RSV may remarkably differ in the forthcoming years in view of the Covid-19 pandemic and our global fight to curb the infection rate. This international goal has caused our general behaviour to be modified through the implementation various levels of lockdown by each country, the mandatory wearing of face masks, better hand hygiene practices and many more individuals, including parents, working from home with fewer younger children needing to go to day-care. All of these factors contributed to an almost non-existent RSV season in 2020. However, in America during their summer months of 2021 they experienced unprecedented high levels of RSV, this was out of keeping with their typical winter season of RSV. This new pattern raises the concern that there may be a possibility of differing seasons of RSV in the not too distant future.

A number of well described risk factors have been associated with increased frequency and severity of RSV bronchiolitis.[5] In this study, infants under six months of age were more likely to be admitted with RSV positive bronchiolitis compared to other viruses ($p < 0,001$). More children with RSV bronchiolitis were premature and had chronic lung disease in comparison to RSV negative children, but these factors were not statistically significant in this study, which was unexpected when reviewing the data in comparison to other local and international studies. HIV-infected children are more likely to have pneumonia rather than bronchiolitis and HIV has been postulated to possibly be protective against RSV.[2] This was not the case in our study as more participants with RSV bronchiolitis were HIV exposed or positive, although this did not reach statistical significance. There was not enough data available to comment on impact of environmental risk factors on the children from this study.

Initial investigations, including haematological and radiological studies, yielded no statistical differences between children who were RSV positive or negative. This is in keeping with

current literature that bronchiolitis should be diagnosed clinically, assessing the disease severity from history and examination findings.[9] There may be some value in performing routine viral screening for all children presenting with bronchiolitis as it would contribute to epidemiological data as well as to cohort children with specific viruses. However, routine viral testing may not be viable in resource limited setting, especially as treatment for children with bronchiolitis remains supportive regardless of the infecting organism. However, in light of the Covid-19 pandemic, other treatment modalities have been tried and tested in the management of children admitted with coronavirus, which supports routine viral screening for children admitted with any presentation of respiratory illness.

The majority of children in this study required admission to CMJAH and NMCH's intensive care units (n=103, 78.6%). More than half of these children (n=54/103, 52.4%) had RSV bronchiolitis. This finding is comparable to other studies that have been conducted globally with regard to the large number of children of children needing hospitalisation for moderate or severe bronchiolitis having confirmed RSV. [4]

More children from the RSV positive group were investigated for nosocomial sepsis in comparison to the RSV negative group of children. This may be due to the fact that children with RSV were admitted for longer than children who did not have RSV, but this was not found to be statistically significant. Almost all the children admitted with bronchiolitis were discharged (n=114, 87.0%) home or back to their base hospital, despite the large number of children needing ICU admission and care. A total of 17 children demised, 10 (7.6%) from the RSV negative group of children and seven (5.3%) from the RSV positive group. It is difficult to compare this finding to international mortality estimations as the total number of cases of bronchiolitis and all possible causative organisms were not known in this study.

Conclusion

In keeping with international literature, RSV was the commonest virus isolated in this cohort of hospitalised children (65/131, 49.6%) with bronchiolitis.[1,2,4,5] The majority of children were under 6 months of age (75/131, 57.3%) and infants less than six months of age were more likely to have RSV confirmed bronchiolitis than those without (p-value <0.001). Respiratory syncytial virus cases peaked around Autumn in 2018, in keeping with the described local

seasonality of RSV.[1] Despite requiring hospitalisation, 114 of the 131 children in this study survived to discharge.

Study Limitations

As this was a retrospective study reviewing only the files of children screened for bronchiolitis the true prevalence of RSV bronchiolitis cannot be determined from this analysis. Not all data was available from participants' files, which limited accurate comparisons between children with and without RSV. Another limitation is that the number viruses screened for at each hospital was not standardised.

Author contributions. TSC: protocol, data collection, write-up, this article was submitted in fulfilment of the degree of Masters of Medicine in the discipline of Paediatrics at the University of the Witwatersrand; TT: supplied the NHLS raw data, review and advice; NMM and LC review and advice; DEB and DAW: oversight, advice and editing.
Funding. None.
Conflict of Interests. None.

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Chapter Two – Author Guidelines

Author Guidelines: SAJCH

Please view the Author Tutorial for guidance on how to submit on Editorial Manager.

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There is currently a backlog of articles in production. Authors submitting new articles should note that the earliest date for publication will be in the second quarter of 2022.

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Submitted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction prior to being sent for review, which will delay publication.

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- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
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If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAJCH is a Journal on child health, therefore for articles involving genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones arenot.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

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- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

Research

Guideline word limit: 3 000 words (excluding abstract and bibliography)

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Where appropriate, sample size calculations should be included to demonstrate that the study

is not underpowered. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

- May include up to 3 illustrations or tables.
- A max of 20 - 25references

Structured abstract

- This should be no more than 250words, with the following recommended headings:
    - **Background:** why the study is being done and how it relates to other published work.
    - **Objectives:** what the study intends to find out
    - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
    - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
    - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
    - Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors. It should be able to be intelligible to the reader without referral to the main body of the article.
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Here is an example of a good abstract.

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These include case reports, side effects of drugs and brief or negative research findings.

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- Must include a correspondence address.

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- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

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- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author.
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Rather: Combine into one column, *n* (%).

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- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
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- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx/doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references
- Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.

NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
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From submission to acceptance

Submission and peer-review

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- All submissions should be submitted via Editorial Manager

- The following are required for your submission to be complete:
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Errata

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Send an email to publishing@hmpg.co.za, including the following details:

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- Article title and authors
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Chapter Three: Approved Protocol

RSV BRONCHIOLITIS IN 2018:

A DESCRIPTIVE STUDY OF CHILDREN ADMITTED TO TWO JOHANNESBURG TERTIARY HOSPITALS

Tannah Storm Cleak MBChB (UKZN)

Student Number:
304291

DEGREE: MASTERS OF MEDICINE IN THE DISCIPLINE OF PAEDIATRICS

RESEARCH PROTOCOL 2018

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Co-supervisor:
Prof. D. Ballot
MBChB, FC Paed (SA), PhD

Justification for study

Respiratory syncytial virus (RSV) is a common cause of moderate and severe bronchiolitis in infants. There are a number of risk factors associated with RSV infection; of these prematurity poses the greatest risk. Moderate and severe RSV bronchiolitis is associated with high morbidity and mortality rates. No effective vaccine or cure has been developed to prevent or treat RSV infection. The only form of prevention available currently is Palivizumab, a form of passive immunoprophylaxis. Palivizumab is costly and therefore strict guidelines for administration exist. However, in view of the number of cases of moderate and severe RSV bronchiolitis treated at Charlotte Maxeke Johannesburg Academic Hospital and Nelson Mandela Children's Hospital in 2018 the cost of prevention may be warranted not only in the best interests of high-risk patients but for cost effectiveness too.

List of Abbreviations

CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CPAP	Continuous Positive Airway Pressure
CPR	Cardiopulmonary Resuscitation
CRP	C-reactive Protein
CSF	Cerebrospinal Fluid
CT	Computed Tomography
ECHO	Echocardiogram
ECMO	Extracorpeal Membrane Oxygenation
ELISA	Enzyme Linked Immunosorbent Assay
HFOV	High Frequency Oscillatory Ventilation
$HFNPO_2$	High Flow Nasal Prong Oxygen
HIV	Human Immunodeficiency Virus
IPPV	Intermittent Positive Pressure Ventilation
MRI	Magnetic Resonance Imaging
NICU	Neonatal Intensive Care Unit
NIV	Non-invasive ventilation
NMCH	Nelson Mandela Children's Hospital
NPO_2	Nasal Prong Oxygen
PCR	Polymerase Chain Reaction
PHPT	Pulmonary hypertension
PICU	Paediatric Intensive Care Unit
RSV	Respiratory Syncytial Virus

Glossary

Bronchiolitis: Bronchiolitis is a viral-induced lower respiratory tract infection that occurs predominantly in children younger than two years of age, particularly infants.

Bronchopulmonary Dysplasia (BPD) or Chronic lung disease (CLD): Is as a result of prolonged oxygen therapy in infants of 36 weeks postmenstrual age plus a total duration of 28 days of supplemental oxygen.

Congenital heart disease: Defect in the heart's structure and function present from birth.

Intermittent Positive Pressure Ventilation (IPPV): A form of manual or mechanical ventilation providing a breath sequence independent to the patient's inspiratory pattern.

Neuromuscular disease: A broad term encompassing all diseases affecting the muscles, nerves or neuromuscular junctions all resulting in impaired function of muscles.

Non-invasive Ventilation: is ventilatory support without the use of an artificial airway in the form of an endotracheal tube. Examples of which are continuous positive airway pressure (CPAP) and high flow nasal prong oxygen (HFOV).

Pulmonary hypertension: Hypertension in the pulmonary circuit, may be primary or secondary to pulmonary or cardiac disease.

Table of Contents

1.0 Introduction

1.1 Background Information

Definition

Bronchiolitis is a viral-induced lower respiratory tract infection that occurs predominantly in children younger than two years of age, particularly infants. [1]

Causative Organisms of Bronchiolitis

Bronchiolitis is caused by a number of different viruses, all leading to a similar clinical syndrome. [2] In South Africa, the overall prevalence of respiratory viruses in children presenting with a lower respiratory tract infection was 78%.[3] Causative viruses include respiratory syncytial virus (RSV), rhinovirus, adenovirus, parainfluenza virus, influenza virus, human metapneumovirus, bocavirus, coronavirus and measles virus.[1,2]

Respiratory syncytial virus causes approximately 60% of all lower respiratory tract infections in pre-school aged children worldwide.[4] Respiratory syncytial virus affects infants 2-3 times more than children younger than five years.[1] Moderate and severe cases of bronchiolitis are most commonly caused by RSV.[1]

Pathophysiology

Respiratory syncytial virus, a pneumovirus, is composed of a single strand of ribonucleic acid (RNA) surrounded by an 11-protein nucleocapsid and lipid envelope.[4] Respiratory syncytial virus derives its name from the syncytia formed during the invasion of the host's respiratory epithelium.[4] Respiratory syncytial virus is part of the paramyxoviridae family and is subdivided into two major subsets RSV-A and RSV-B.[1,4] These are further classified into several genotypes according to variations of the surface fusion glycoprotein G.[1,4]

Respiratory syncytial virus is acquired either through the inspiration of large virus-containing respiratory droplets or contamination of the nasal or conjunctival mucosa.[5] Viral replication takes place in the nasal epithelium with progression to the ciliated epithelial cells of the lower respiratory tract.[5] Virus invasion induces the host's innate immune response causing an influx of numerous inflammatory cells resulting in oedema of the cells, increased mucosal secretions, sloughing of necrotic tissue and reduction of ciliary movement, all of which contributes to bronchiolar narrowing.[5,6] Humoral immunity is also activated during the course of the infection to produce memory cells, however, these appear to be ineffective as evidenced by

subsequent re-infections.[6] Immune responses to RSV infection are exaggerated and this too contributes to the pathogenesis of the illness.[5,6] Respiratory syncytial virus appears to elude or impede host immune systems, but this is not completely understood and is further confounded by the fact that there is no antigenic change of RSV's surface glycoproteins.[5,6]

Seasonality of RSV

Specific RSV seasons are well documented around the world, with outbreaks lasting approximately four months.[1] In temperate climates, epidemics occur during winter months while in more tropical regions the incidence is higher during the hot, rainy seasons.[1] The cause of this temporal course of RSV, in comparison to other viruses, is not completely understood; but the geographical location and associated climate factors are thought to contribute to outbreaks.[1,2] In South Africa, RSV season varies marginally from province to province.[1] In Gauteng, RSV onset is in February and lasts until June.[1]

Risk Factors for developing RSV

A number of well-described risk factors have been associated with severe RSV infection. Risk factors include prematurity, chronic lung disease, congenital lung malformations, haemodynamically significant congenital heart defects, neuromuscular disease, infancy (particularly those younger than six months), male gender, immune compromise and lack of breastfeeding.[2,5,7] Environmental risk factors attributing to severe illness include tobacco smoke exposure, siblings living in the same household, overcrowding and day-care attendance.[2,7]

The most significant predictor associated with severe RSV infection is prematurity, with susceptibility increasing as the gestational age decreases.[5] The absence of transplacental transference of maternal immunoglobulins, which only occurs in the third trimester, may explain prematurity as a risk factor.[4] Chronological age is also an important predictor of severe disease as a large portion of hospitalizations occur in infants less than five months.[5] Infection in this age group coincides with the natural reduction of circulating immunoglobulins, as they are progressively removed by the infant's liver.[4] Immunodeficient states, including malignancy and primary immunodeficiency, have been noted to contribute to increased risk, however, in some studies conducted in South Africa, it is postulated that human immunodeficiency virus (HIV) may be protective against RSV infection, the reasons for this is not known.[2]

Clinical Course of RSV Bronchiolitis

Clinical features of bronchiolitis manifest after 4-6 days post inoculation with RSV.[5] Symptoms of RSV infection are non-specific and may consist of nasal congestion, rhinorrhoea, cough, irritability, poor feeding and low-grade fever.[5,7,8] Two days later, as a consequence of the airway inflammation and air trapping, tachypnoea, wheezing and hyperinflation develop.[7] Bronchiolitis is usually self-limiting but may progress to become severe as evidenced clinically by nasal flaring, intercostal or subcostal recessions, grunting and hypoxia.[7,8] Severe bronchiolitis usually results in hypoxia requiring hospitalisation for supplemental oxygen therapy and may even require intermittent positive pressure ventilation.

Investigations for Bronchiolitis

All patients presenting with bronchiolitis require measurement of their peripheral oxygen saturation levels in order to determine the presence of hypoxia.[7] Saturation levels of less than 92% at sea level and 90% inland indicate the need for supplemental oxygen. Other investigations, such as chest radiographs and blood studies, are generally not warranted unless severe illness or complications are suspected.[7] However, it has been recommended in a retrospective study conducted from 1995-2006, that chest radiographs be performed routinely on all hospitalized children with bronchiolitis.[9] Chest radiographs may demonstrate radiological features of Mycobacterium tuberculosis, possible congenital malformations, lung complications or be used for prognostication.[9]

Viral testing using nasopharyngeal aspirates and nasal swabs does not change routine management of bronchiolitis but may help tailor therapy, inform surveillance and measure frequency of disease.[4,7] The detection rates of viruses using nasopharyngeal aspirates versus nasal swabs are comparable for most viruses including rhinovirus, influenza type A or B, Parainfluenza virus 1, 2 or 3, adenovirus, enterovirus and herpes simplex virus.[10] However, nasopharyngeal aspirates have a higher RSV detection rate in comparison to nasal swabs.[10] In a study on the prevalence of viruses in patients hospitalised with pneumonia, viral detection rates using multiplex real-time polymerase chain reaction assay were found to be highest in patients between 2 and 4 years (83,9%) followed by those between 0 and 1 years (76,5%).[11] 17% were co-infected with other viruses, the following combinations of viruses, in order of frequency, were found in specimens tested using the 10-plex real-time reverse-transcription polymerase chain reaction assay: rhinovirus and adenovirus (24,9%), rhinovirus and RSV (22,4%), and RSV and adenovirus (14,8%).[11]

Other bacterial coinfections should be considered in complicated cases of bronchiolitis.[1] However, it may be difficult to isolate bacterial agents as blood culture yield rates are only between 3 and 18%.[1] C-reactive protein (CRP) of more than 40mg/dl has been described as a possible screening tool to differentiate between bacterial and viral infections.[4]

Management of Respiratory Syncytial Virus Bronchiolitis

Management of bronchiolitis is supportive.[11] No other adjunctive therapy, other than supplemental oxygen for hypoxia, has been shown to have any clinical benefit.[8,12] The following therapies including short-acting bronchodilator therapy, ipratropium bromide, systemic or inhaled corticosteroids, chest physiotherapy and antibiotics have been shown to have no effect on reducing hospital admissions after outpatient treatment, duration of admission or in time to full recovery at home.[8,12]

A small portion of children admitted with bronchiolitis will have severe disease needing ventilatory support.[13] An estimated 20% of admissions to paediatric intensive care units (PICU) in South Africa have positive respiratory viral isolates, particularly RSV.[13] Treatment in PICU remains supportive and is directed at managing hypoxia with either invasive or non-invasive methods, fluids and antipyretics.[13]

Prevention of Respiratory Syncytial Virus Bronchiolitis

There is no effective vaccine or antiviral available against RSV infection.[12] Passive immunoprophylaxis is the only form of prevention against RSV infection currently, an example of which is palivizumab, an intramuscular monoclonal antibody.[11] A course of five 15mg/kg intramuscular injections of Palivizumab one month apart for five months is required to treat a susceptible individual. In order to prevent one hospitalization of RSV disease in a premature infant or children with chronic lung disease or congenital heart defects between 16 and 23 need to be treated with Palivizumab.[11] A Palivizumab course costs approximately R55 000 and is hence, unaffordable in resource-limited settings. The duration of Palivizumab courses also contributes further limitation to administration in susceptible individuals.

Parents and carers, therefore, need to be counselled on other preventative measures such as hand hygiene and reducing environmental risk factors.[6]

Mortality

RSV has a case fatality rate globally of approximately 6.6%.[2] The incidence of severe RSV associated illness is found to be similar in both developing and developed countries, however, case mortality rates are higher in developing countries.[1]

1.2 Rationale

Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) is a large tertiary hospital incorporated into the academic circuit of the health science programme offered at the University of the Witwatersrand. The 220-bed paediatric service caters for all paediatric medical and surgical subspecialties. There are 14 beds available in the mixed paediatric and neonatal intensive care. Charlotte Maxeke Johannesburg Academic Hospital serves a large population including many referring clinics and hospitals. These include Natalspruit Hospital, South Rand Hospital, Edenvale Hospital, Tambo Memorial Hospital, Pholosong Hospital and Far East Rand Hospital.

Nelson Mandela Children's Hospital (NMCH), a brand new tertiary facility, has begun admitting and managing patients in their paediatric and neonatal intensive care facilities as part of their opening phase this year. NMCH will have the capacity to admit 48 patients to their PICU and NICU facilities but these units currently admit between 14 and 16 patients.

Microbiological services of the National Health Laboratory Service, provided to both CMJAH and NMCH, uses the multiplex real-time reverse-transcription polymerase chain reaction assays to process nasopharyngeal specimens for respiratory viruses.

In view of the above, CMJAH and NMCH's have been selected to describe the course of paediatric RSV infections and compare to current literature

2.0 Study Aims and Objectives:

2.1 Principal Aim

To determine the profile of paediatric patients diagnosed with bronchiolitis presenting to Charlotte Maxeke Johannesburg Academic Hospital and Nelson Mandela Children's Hospital from 01 February to 31 August 2018 and compare the profile of RSV positive to RSV negative patients.

2.2 Study Objectives

i. To describe characteristics and basic clinical information of all paediatric patients screened for bronchiolitis

ii. To compare RSV positive and negative patients in terms of risk factors, co-infections, complications and outcomes

3.0 Methodology

3.1 Study Design

A retrospective descriptive study of children admitted to Charlotte Maxeke Johannesburg Academic Hospital and Nelson Mandela Children's Hospital between 1 February and 31 August 2018, who were screened for bronchiolitis, comparing RSV positive and RSV negative patients.

3.2 Study Population and Sampling

i. Inclusion Criteria

-Any child <2 years admitted with bronchiolitis and screened using either a nasopharyngeal aspirate or nasal swab. This will be obtained from infection control records.

ii. Exclusion Criteria

-A patient treated for bronchiolitis with missing or indeterminate results.

3.3 Data collection and Handling

Files will be obtained from the record departments at CMJAH and NMCH according to the list of patients provided by the infection control team, for each hospital, who were screened for viral causes of bronchiolitis. Data will be entered onto a prepared data collection sheet (Appendix A). Each participant will be allocated a data collection number in sequential and rising order. The author will only know the participant's data collection number. Data will be entered into an Excel spreadsheet.

4.0 Data

4.1 Sample Size

A total number of approximately 110 patients were tested for bronchiolitis at Charlotte Maxeke Johannesburg Academic Hospital and Nelson Mandela Children's Hospital during the study time period.

4.2 Data Analysis

Data will be captured using Microsoft Excel spreadsheets. Statistical analysis will be carried out using means and standard deviations for continuous variables with a normal distribution. Categorical variables will be described using frequency and percentages. Medians, ranges and interquartile percentages will be used for ordinal variables not having a normal distribution. Comparisons will be carried out with the aid of chi-square tables for categorical variables and Student t-test for continuous variables. SPSS version 25 will be employed to analyze data.

5.0 Ethics and Confidentiality

Ethical clearance will be obtained from the Human Research Ethics Committee, University of Witwatersrand. Permission will be obtained from the respective chief executive officers at Charlotte Maxeke Johannesburg Academic Hospital and Nelson Mandela Children's Hospital. The study will be registered on the National Health Research Database. Furthermore, in view of it being a retrospective descriptive study with data obtained from existing records and the maintenance of patient confidentiality, consent will not be required from patients, parents or primary caregivers involved.

6.0 Timeline

Table 1. Timeline

	Sep 2018	Oct 2018	Jan 2019	Feb 2019	Mar 2019	Jun 2019	Jul 2019	Sep 2019	Oct 2019	Nov 2019	Nov 2019	Dec 2019
Literature Review												
Preparation of Protocol												

Protocol Assessment												
Ethics Approval												
Post Graduate Approval												
Data Collection												
Data Analysis												
Writing up of Research Report												
Supervisor Review												
Writing up of Paper												

7.0 Costs and Funding

Costs involved would include stationery, photocopying, printing and binding as well as the purchase of software from the University ofWitwatersrand (namely statistical and referencing packages). All costs incurred will be borne by the principal investigator. Costs are expected to total to the amount of R3000.

8.0 Limitations

In view of this study being a retrospective audit, it relies on both on the confirmed diagnosis of RSV and the existing records obtained during the period of analysis. Patients who have incomplete records may weaken the study. Assessing the presence of pulmonary hypertension will be limited to those patients who had echocardiograms undertaken, as this is not a routine investigation in children with bronchiolitis this data will be limited.

9.0 Authorship

Table 2. Authorship Table

Name	**Department/ Institution**	**Involvement**	**Contribution to Study**
Dr T. Cleak	Department of Paediatrics, University of Witwatersrand, CMJAH	Principle Investigator First Author	Principle Investigator
Prof D. White	Department of Paediatrics, University of Witwatersrand, CMJAH	Co-supervisor, Co-author	Co-supervisor
Prof D. Ballot	Department of Paediatrics, University of Witwatersrand, CMJAH	Co-supervisor, Co-author	Co-supervisor
Dr P. Moshesh	Department of Paediatrics, University of Witwatersrand, NMCH	Collaborator, Co-author	Patient data collection
Dr P. Chirwa	Department of Paediatrics, University of Witwatersrand, NMCH	Collaborator, Co-author	Patient data collection
Dr T. Thomas	Infection control Lab (NHLS) Department of Clinical Microbiology and Infectious Diseases University of Witwatersrand, CMJAH	Collaborator, Co-author	Patient data collection

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Appendix A

Study Identifier number: _____

Data Collection Sheet

Age: _____

Date of admission: _____

Date of discharge/death: _____

Length of stay: _____ days

Outcome: Discharge: ☐☐

Death: ☐

☐

HIV: Unexposed: ☐ Exposed: ☐

HIV PCR/ELISA Result: Positive: ☐ Negative: ☐

Risk Factors for RSV:

Ex-premature: Yes: ☐ No: ☐☐

Gestational Age: _____ weeks

Congenital heart disease: Yes: ☐ No: ☐

Congenital lung disease: Yes: ☐ No: ☐

Neuromuscular disease: Yes: ☐ No: ☐

Age <6months: Yes: ☐ No: ☐

Exclusive Formula Feeding: Yes: ☐ No: ☐

Immune compromise: Yes: ☐ No: ☐

(Malignancy, primary immunodeficiency)

Siblings in household: Yes: ☐ No: ☐

Age of siblings: _____

Attending day-care: Yes: ☐ No: ☐

Exposure to tobacco smoke: Yes: ☐ No: ☐

Unknown: Yes: ☐ No: ☐

Investigation:

Nasopharyngeal specimen: RSV: Yes: ☐ No: ☐

Indeterminant: Yes: ☐ No: ☐

If RSV negative; what virus was found:

Virus:_____

Initial Chest Radiograph:

Hyperinflation:	Yes:	□	No:	□
Patchy infiltrates:	Yes:	□	No:	□
Pneumothorax:	Yes:	□	No:	□
Atelectasis:	Yes:	□	No:	□
Other:	Yes:	□	No:	□

Describe:_____

Serology:

Admission:

Haemoglobin: _____

Platelets: _____

White cell count: _____

Lymphocytes (%): _____

Neutrophil (%): _____

CRP: _____

Blood culture:

Initial: Positive: □ Negative: □

Organism:_____

Subsequent: Positive: □ Negative: □

Organism:_____

CSF:

Cell count: Normal: □ Abnormal: □

Culture: Positive: □ Negative: □

Organism:_____

CT Scan: Yes: □ No: □

Findings:_____

_____

MRI Scan: Yes: □ No: □

Findings:_____

_____

ECHO: Yes: □ No: □

PHPT: Yes: □ No: □

Cardiac anomaly: Yes: □ No: □

Findings:_____

_____

Supplemental oxygen: Yes: □ No: □□ Number of days:_____

Ventilation

NIV: CPAP: Yes: □ No: □ Number of days:_____

HFNP$O_{2:}$ Yes: □ No: □ Number of days:_____

IPPV: CMV: Yes: □ No: □ Number of days:_____

HFOV: Yes: □ No: □ Number of days:_____

ECMO: Yes: □ No: □ Number of days:_____

Complications:

Nosocomial sepsis: Yes: □ No: □

Apnoea: Yes: □ No: □

CPR: Yes: □ No: □

Number of episodes:_____

Hypotension needing Inotrope support: Yes: □ No: □

Seizures: Yes: □ No: □

Pulmonology Hypertension: Yes: □ No: □

Other: Yes: □ No: □

Details:_____

Appendix A: Ethics

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Tannah Storm Cleak

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M190505

NAME: (Principal Investigator)	Dr Tannah Storm Cleak
DEPARTMENT:	Paediatrics Charlotte Maxeke Johannesburg Academic Hospital: Paediatric and Neonatal Intensive Care Unit, General Paediatric Wards, Nelson Mandela Children's Hospital: Paediatric and Neonatal Intensive Care Units
PROJECT TITLE:	RSV Bronchiolitis in 2018: A descriptive study of children admitted to two Johannesburg tertiary hospitals
DATE CONSIDERED:	31/05/2019
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Debbie White and Prof Daynia Ballot
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	03/09/2019

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 Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **May** and will therefore be due in the month of **May** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B: Turnitin Report

00100697:Tannah_Cleak.docx

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