ILLNESS EPISODES IN A COHORT OF PRETERM INFANTS IN THEIR FIRST YEAR OF LIFE

Dr Seth Muller

MLLSET001

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In fulfilment of the requirements for the degree Master of Medicine (MMed) - Paediatric Medicine

Faculty of Health Sciences

University of Cape Town

Supervisor: Dr Lloyd Tooke

Communication: mullerseth@gmail.com

TABLE OF CONTENTS

DECLARATION

I, Seth Joshua Muller, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature:

Signed by candidate

Date:

9th November 2020

PLAGIARISM DECLARATION

This thesis/dissertation has been submitted to the Turnitin module (or equivalent similarity and originality checking software) and I confirm that my supervisor has seen my report and any concerns revealed by such have been resolved with my supervisor.

Name: Seth Joshua Muller
Student number: MLLSET001

Signature:

Signed by candidate

Date: 9 November 2020

ACKNOWLEDGEMENTS

I wish to thank the following people for their input in the realisation of this dissertation:

Dr Lloyd Tooke, who has supervised this research study and edited this dissertation. His support throughout this process has been invaluable.

Prof Heather Zar, who kindly allowed us to collect data on the parent study participants, also gave instrumental input with the final drafts and data interpretation.

Elani Muller, who assisted with analysing the data with her knowledge and skills with R.

The staff at the Research Centre for Adolescents and Child Health (REACH) at Red Cross War Memorial Childrens Hosptial (RCWMCH) as well as the mothers and their infants who participated.

Contributions

Seth Muller	Collected data and wrote article
Heather Zar	Principle investigator for parent study and assisted with final editing
Lloyd Tooke	Conception of study and supervisor for Seth Muller

ILLNESS EPISODES IN A COHORT OF PRETERM INFANTS IN THEIR FIRST YEAR OF LIFE

Background: There is limited data available regarding the illness episodes and hospital admissions of preterm infants after initial discharge in low- and middle-income countries.

Objectives: To prospectively follow a cohort of HIV unexposed preterm infants (29-34 weeks) and describe their illness episodes, admissions and associated risk factors over a one-year period.

Methods: The study was nested in a parent study evaluating the efficacy of a monoclonal antibody against RSV from Jan 2017 to March 2017. 53 infants were enrolled from two government neonatal nurseries in Cape Town, South Africa. Descriptive data were collected with regards to perinatal history and socioeconomic factors of the infants' household. All infants received careful follow-up. Logistic regression was performed to assess association between hospitalisation and socio-economic factors.

Results: All 53 infants who were recruited were followed up over one year. There were 436 illness episodes of which 31 were hospital admissions. One infant died at home. The most common illnesses were respiratory (53%) and dermatological (17%) in nature. Lower respiratory tract infections accounted for 71% of all hospital admissions. There were no significant associations between socioeconomic subgroups when comparing illness episodes or hospital admissions.

Conclusion: This is one of the few studies to record all illness episodes and not just admissions over a one-year period for HIV unexposed infants. There are high rates of intercurrent respiratory infection and hospitalisation of preterm infants in their first year of life. Public health interventions to reduce the risk of LRTI must be strengthened. Larger studies need to be done to be able to report on the associations with socioeconomic determinants in developing countries.

Introduction

Preterm infants account for a large and increasing proportion of neonatal and childhood morbidity and mortality worldwide, especially in low and middle income countries (LMIC).[1] Morbidity and mortality in this population is mainly caused by respiratory tract illnesses. However, there are limited data available regarding the outcomes of preterm infants after discharge in these countries.[2,3]

The aim of this study was to provide a descriptive analysis of the illness episodes and hospitilizations of a cohort of preterm infants from two public Neonatal Intensive Care Units (NICU's) in South Africa through one year of follow-up.

Methods

This study was nested in a prospective cohort study of preterm infants born between 29- and 35-weeks gestational age at Groote Schuur Hospital (GSH) and Mowbray Maternity Hospital (MMH) in Cape Town, who were enrolled in a multicenter phase 2b novel respiratory syncytical virus (RSV) monoclonal antibody trial. This double-blinded randomised controlled trial (RCT) used a ratio of intervention to placebo of 2:1. Gestational age was determined by an ultrasound at less than 20 weeks gestation, or foot length at birth.[4]

Infants were enrolled following delivery at GSH or MMH neonatal units from 1 January 2017 to 31 March 2017. Inclusion criteria were healthy infants born between 29 weeks 0 days and 34 weeks 6 days' gestational age and maternal informed consent. Exclusion criteria for the parent study were:

1. If caregivers were unable to follow up or if there was doubt regarding follow-ups. E.g. extreme poverty, adoption, significant medical or mental illness, opioid drug addiction or maternal age <18yrs.
2. Maternal HIV infection.
3. Any acute illnesses, blood products or drug therapy two weeks prior to enrollment (except multivitamins, iron or probiotics).
4. Any known chronic illness, except for children with uncomplicated congenital heart disease (e.g. patent ductus arteriosus, small septal defect).

The reason for excluding these infants from the parent study was to remove the possible confounding effects that they could have had on the assessment of the vaccine.

All participants from the parent study were eligible for the nested study. Follow up occurred at the research center at Red Cross Hospital (RXH) on days 8, 31, 91, 151 and 361 after discharge. Clinical and socioeconomic data, feeding choice and any illness, clinic visits or hospital admission were obtained at each follow up visit. Exclusive breast milk was defined as no other food or drink, not even water. The infants' folders were also reviewed to obtain the perinatal data. Data were collected via a standardised questionnaire completed by the study staff at each follow up visit. The research team was comprised of nurses and doctors.

To ensure no illnesses were missed the following measures in addition to the routine visits were put into place:

- In case of illness, emergencies or any adverse incident, caregivers made telephonic contact (available 24hours a day) with the research team.
- These calls were logged, advice was given, and infants were followed up as either in- or outpatients, where further information was collected.
- Caregivers were phoned on a monthly basis to inquire about any symptoms or illnesses.

All diagnoses were made upon assessment by a doctor and recorded when infants followed up as either and in- or out-patients. This information was used to collect data on illness episodes and hospitalisations for the nested study.

The primary outcome for the RSV monoclonal study was medically attended RSV-LRTI. For this nested study the primary outcome was to describe maternal and infant characteristics and all infant intercurrent illness episodes through one year after discharge.

Ethical approval for the nested study was granted by the Human Research Ethics Committee, Faculty of Health Sciences, University of Cape Town (ref 886/2016). All mothers provided written consent prior to being included in the study.

Statistical analyses

Data were analysed using RStudio version 1.1.463. Continuous variables were summarised as medians with interquartile range (IQR) for non-parametric data. Categorical variables were expressed as frequencies and percentages. To assess whether there were associations between the socio-economic factors and hospital admissions, a logistic linear regression was done. Gestational age and birth weight were adjusted for in the logistic regression. A p-value of <0.05 was interpreted as statistically significant.

Results

Enrollment and follow-up

56 infants were enrolled in the RSV monoclonal study from Groote Schuur and Mowbray Maternity Hospitals; all were offered participation in the follow-up study of whom three declined. The study therefore included 53 preterm infants of which there were four sets of twins. No infant was lost to follow-up during the 1-year period, but one infant died at 130 days of age (12 weeks corrected age) at home from presumed pneumonia.

Maternal characteristics

The median age of the mothers at time of delivery was 28 years with five mothers being less than 20 years of age. Table 1 describes the maternal characteristics

Table 1: Characteristics of mothers (n=49)

Outcome	***Median (IQR)***	***Frequency (%)***
Maternal age at time of delivery	28 (23, 32)	
Attended antenatal care		43 (88)
Booking bloods		
Positive rapid plasma reagin		1 (2)
Rhesus negative		3 (6)
Gravidity	1 (1, 2)	
Antenatal treatment		
None		20 (41)
Steroids		18 (37)
Magnesium sulphate		6 (12)
Steroids and Magnesium sulphate		5 (10)
Maternal illnesses during pregnancy		
Pre eclampsia / Eclampsia		8 (16)
Sepsis / Infection		7 (14)
Maternal illnesses known prior to pregnancy		
Cardiac		2 (4)
Lung disease		3 (6)
Endocrine		2 (4)
Other		4 (8)
Housing		
Shack		10 (21)

Wendy house	4 (8)
Apartment	8 (16)
Free standing house	27 (55)
Access to water	
Piped inside the house	36 (73)
Piped outside the house	9 (18)
Communal tap outside the yard	4 (9)
Level of education of mother	
Grade 0 to 7	4 (8)
Grade 8 to 12	40 (82)
Diploma / Degree	5 (10)
Yearly income of household	
< R 99 999	44 (90)
R 100 000 to R 350 000	1 (2)
> R 350 001	4 (8)
Smoking in the home	
No	33 (67)
Yes	16 (33)
*Substance abuse in the home**	7 (14)

*Opioids, marijuana and amphetamines

The majority of mothers (35, 71%) were living in formal housing and all mothers had access to electricity. 43 mothers (88%) had some high school education and in four (8%) the highest level of education was primary school. The median number of people living in the same dwelling, including the infants, was 7 (IQR 5, 8). Refer to table 1 for maternal medical and socio-economic background.

A third of mothers reported household smoke exposure and 14% reported substance abuse during pregnancy.

Infant characteristics

Most infants (35 (66%) were born by emergency Caesarian section with a median birth weight of 1500 grams, table 2. The median length of stay after birth was 27 days.

There were two infants with congenital abnormalities; one infant had upper limb dysgenesis and another had a ventricular septal defect (VSD). Three infants were diagnosed with patent ductus arteriosis (PDA) via echocardiogram all of which spontaneously closed.

Table 2: Infant characteristics (n = 53)

Outcome	***Median (IQR)***	***Frequency (%)***
Mode of delivery		
Caesarian section		35 (66)
Vaginal delivery		18 (34)
Length of stay after birth	27 (23, 31)	
Male		32 (60)
Birth weight (in grams)	1500 (1300, 1840)	
Gestational age at birth (in weeks^{+days})	32 weeks (30^{+3}, 33^{+2})	
Head circumference for age at birth (Z-score)	0.04 (-1.07, 0.61)	
Apgar scores		
1 minutes	7 (5, 8)	
5 minutes	9 (8, 10)	
Initial resuscitation required		
None		27 (51)
Oxygen		1 (2)
Facemask ventilation		17 (32)

Cardiopulmonary resuscitation (CPR)		5 (9)
Intubation		2 (4)
Epinephrine		1 (2)
Surfactant required		2 (4)
Temperature at admission	36.1 (35.9, 36.4)	
Congenital abnormalities		2 (4)
Highest level of respiratory support		
Room air		18 (34)
Nasal prong oxygen		3 (6)
High flow nasal cannulas		7 (13)
Nasal CPAP		22 (42)
Mechanical ventilation		3 (6)
Feeding at discharge		
Exclusive breast milk (EBM)		50 (94)
Breast milk substitute		2 (4)
Mixed		1 (2)
Twins		4 (8)

The number of infants who had fathers that provided financially was 43 (81%) at Day 8 and gradually declined to 37 (70%) by Day 361. Fathers lived in the same dwelling at birth for 31 (58%) of the infants, with a gradual decline to 27 (51%). Substance misuse (opioids, marijuana and amphetamines) fluctuated between 2 and 9% of the households.

At 1 year, only four infants were attending crèche and all the others were cared for by family members.

There was a high proportion of infants that received EBM from birth until discharge (50, 94%) with a gradual reduction over time (Fig. 1). By day 151, 9 infants (17%) received EBM

and 19 infants (37%) received any breast milk. By day 361, there were still 19 infants (37%) receiving any breast milk.

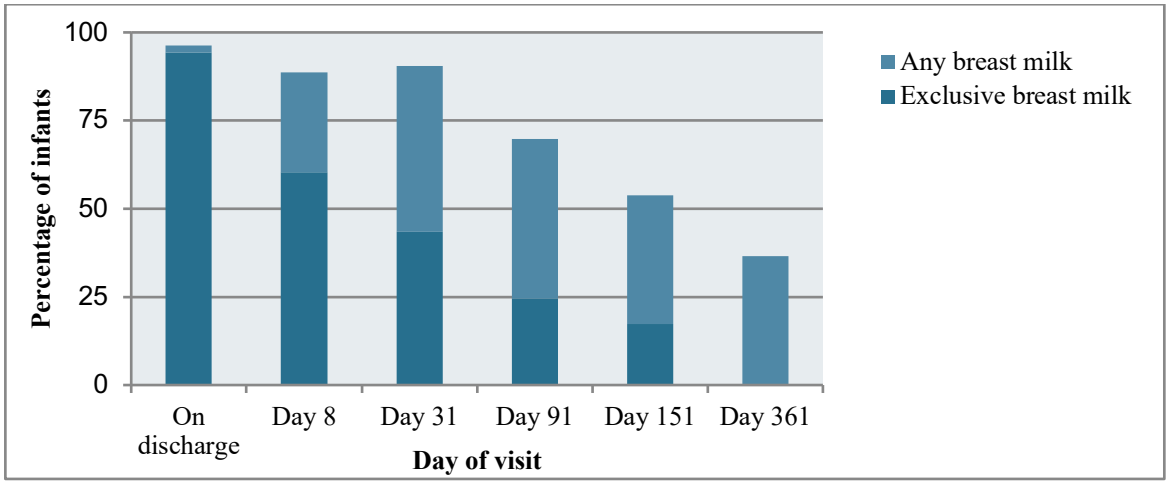

Figure 1: Percentage of infants that received exclusive and any breast milk over one year

Weight for corrected age (median, IQR) Z scores were day 31: -0,58 (-1,52, 0,08); day 91: -021 (-0,85, 0,29) and day 151: -0,49 (-1,08, 0,07). One infant had failure to thrive at 4 months of age. Another infant was admitted with severe acute malnutrition at 10 months of age.

By day 361, 91% of infants had received all their vaccines including the 9 months measles and pneumococcal vaccines.

Intercurrent illness episodes and hospital admissions

The total number of illness episodes reported over the study period was 436 with a median of 7 (IQR 5, 11) illness episodes per infant per year (e/iy). The most common illness (170, 39%) was upper respiratory tract infections (URTI) with a rate of 3.2 e/iy. 72 (17%) illness episodes were attributed to dermatological conditions with a rate of 1.4 e/iy and 59 (14%) illness episodes with a rate of 1.1 e/iy for both LRTI and gastrointestinal disorders.

Table 3: Illness episodes in infants through 1 year of age

Type of illness	***Total number of illness episodes n = 436 (%)***
Respiratory	*229 (53%)*

URTI	170
LRTI	59
Dermatological	*72 (17%)*
Napkin dermatitis	12
Viral exanthem	12
Other	11
Falliculitis / Impetigo	9
Fungal	7
Scabies	7
Papular urticuria	7
Tinea	4
Mouth ulcers	3
Gastrointestinal	*59 (14%)*
Gastroenteritis	43
Reflux	5
Oral thrush	5
Constipation	2
Dysentery	2
Abdominal cramps	2
Ears, nose and throat	*15 (3%)*
Otitis media	13
Tonsilitis	1
Laryngomalacia	1
Haematological	*12 (3%)*
Aneamia	9
Jaundice	3

Ophthalmological	*10 (2%)*
Conjunctivitis	7
Blocked duct	3
Other	*10 (2%)*
Fever	5
Colic	3
Lymphadenopathy	2
Surgical	*9 (2%)*
Burn	2
Umbilical hernia	2
Abscess	2
Undescended testes	1
Surgical complications	1
Cardiac	*6 (1%)*
Allergy	*5 (1%)*
Eczema	3
Allergic rhinitis	2
Central nervous system	*3 (1%)*
Meningitis	1
Torticollis	1
Macrocephaly	1
Urology	*3 (1%)*
*Malnutrition**	*2 (1%)*

*Defined by WHO as severe and moderate acute malnutrition[5]

Over the one-year of follow-up, 20 (38%) infants were admitted to hospital, with a total of 31 admissions. Of the 31 admissions, 29 were managed medically and two required surgical interventions (repair of a VSD and drainage of an abscess). Four required admission to ICU. Lower respiratory tract infection accounted for 22 (71%) of all hospital admissions (Fig. 2) with a rate of 0.4 e/iy. The median corrected age of hospital admissions was 12 weeks$^{+3\ days}$ (IQR 5^{+2}, 28^{+2}) and the median length of hospital stay was 5 days (IQR 3, 7). There was no association between corrected gestational age and timing of hospital admissions.

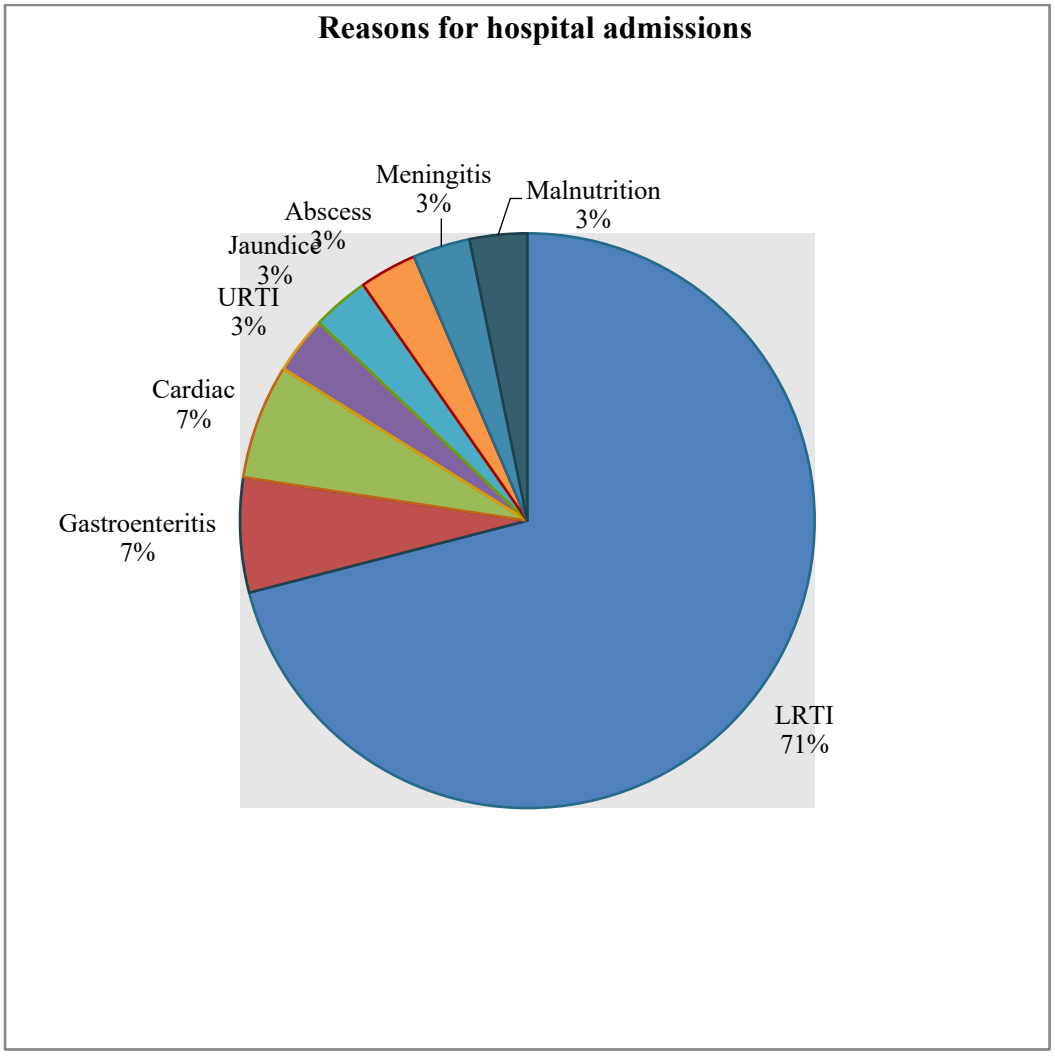

Figure 2: Reasons for hospital admissions

One infant with presumed pneumonia died at home, giving an overall mortality rate of 1 in 53 (2%); no postmortem was permitted.

Factors associated with hospitalisation

Table 4 shows the multivariate logistic regression of factors associated with hospital admission. One infant with a VSD had a large number of illness episodes and hospital admissions unrelated to prematurity, so this infant was excluded from the multivariate analysis. Gestation age and birth weight were adjusted for as these are known confounders to the outcomes in this population group. None of the variables showed statistically significant associations.

Table 4: Multivariate logistic regression of the association between hospital admission and socio-economic factors, adjusted for gestational age and birth weight

Variable	***Estimated OR (95% CI)***	***p-value***
Smoking in the home		
Yes	1.0	
No	2.760 (0.773 - 11.703)	0.135
Maternal drug abuse during pregnancy		
Yes	1.0	
No	1.624 (0.275 - 9.300)	0.575
Drug abuse in the home		
Yes	1.0	
No	1.52 (0.16 - 33.26)	0.73
Number of people sleeping in the same dwelling	0.94 (0.70 - 1.23)	0.64
Father living in the same dwelling at Day 361		
Yes	1.0	
No	0.63 (0.19 - 2.07)	0.45
Father providing support at Day 361		
Yes	1.0	
No	1.90 (0.53 - 6.81)	0.32
Feeding at Day 31		

Breast milk	1.0	
Any breast milk	0.60 (0.16 - 2.07)	0.42
Breast milk substitutes	2.90 (0.38 - 29.67)	0.32
Housing		
Shack	1.0	
Wendy house	0.55 (0.02 - 6.32)	0.65
Apartment	0.31 (0.01 - 3.13)	0.37
Freestanding house	1.21 (0.29 - 5.56)	0.80
Access to water		
Piped inside dwelling	1.0	
Piped inside the yard	1.77 (0.37 - 8.44)	0.46
Communal tap	1.36 (0.15 - 10.15)	0.76
Immunisation up to date at Day 361		
Yes	1.0	
No	1.14 (0.28 - 4.30)	0.85

CI: Confidence interval

Discussion

This study has shown a high prevalence of poor socioeconomic factors and smoke exposure as well as a high number of hospitalisations in this group of South African preterm infants, but low mortality. There were no associations between hospital admissions and socioeconomic factors, but this may partly be due to the relatively poor socioeconomic status of all participants with no participants from high socioeconomic groups. Further, the small sample size limits the power of the analyses to detect such associations.

Due to the rigorous follow-up, this is one of the few studies to accurately record all illness episodes and not just admissions to hospital. Respiratory tract infections (URTI and LRTI) contributed just over half of all illness episodes. Of the 229 respiratory tract infections recorded, only 23 (10%) required admission to hospital.

More than a third of infants were admitted to hospital over the one-year follow-up. These results are higher than those from a systematic review[6], in which 25% of low or very low birth weight infants required hospitalisation in the first year of life, however the studies included in the systematic review were done in high income countries. The reason for the higher rate of hospital admissions in this population could be due to a higher burden of infectious diseases in LMICs and higher exposure to risk factors. This is especially true for severe LRTIs as a major cause of hospitalisation, which is consistent with studies from other settings.[7,8] The high burden of respiratory conditions highlights the need to strengthen preventative interventions and new strategies to tackle this burden on the health sector.

Environmental exposures that may be associated with LRTI include smoke exposure.[9–11] Of concern is that a third of infants (33%) in this study were exposed to household smoke. Crowding may be another factor; the household size in this study was higher than the 4.9 mean household size for people living with children in South Africa in 2018[12]. Lack of breastfeeding may be an additional risk factor. Despite the WHO recommendations for EBM until six months of age, this study again demonstrates the low rates of EBM in South Africa. By day 151 only 9 (17%) of the infants received EBM which is similar to another local study where only 12% received EBM.[13,14] Encouragingly, most of the infants were transitioned to solid feeds after 6 months. In a Lancet systematic review from 2016, it was found that breastfeeding reduced diarrhoea episodes by approximately 50% and further reduced hospital admissions for diarrhoea by 72%. Breastfeeding also reduced 33% of respiratory infections and 57% of hospital admissions due to respiratory infections.[15] Even though exclusive breastfeeding is the ideal, any breastfeeding should be encouraged as there is a modest protective dose response effect with partial breastfeeding when compared to nonbreastfeeding.[16]

Lack of immunisations make a child more vulnerable to LRTI and preterm infants should be vaccinated according to their chronological and not corrected age.[17] Only 9% of infants in this study were not up to date with their vaccines, which is lower than the average of 19% of infants with incomplete vaccination reported in the Western Cape province.[14]

Poor levels of parental education have shown to be associated with worse outcomes and an increased risk for preterm infant mortality.[18] Only six of the infants' mothers in this study had a form of post school qualification. There was however a low mortality rate of 2% in this study. In contrast, a study in 1997, following very low birth weight (VLBW) infants in South Africa over eighteen months, reported a 13% mortality rate.[19] The lower mortality rate in this study may reflect improvements in care due to advances in technology and maternal and infant management. Further, the high coverage of childhood immunisations, exclusion of

HIV-infected mothers and regular follow-up through the study may all have contributed to improved outcomes.

No association was shown for infant morbidity in those families where substance abuse was reported, however there may have been under reporting due to the fluctuating reported numbers and the prevalence being well below the nation average of 13%.[20]

It is surprising that in such a closely monitored group two infants developed severe malnutrition, but this highlights the constant threat of food security in many of our communities.

Due to the nature of the infants included in the parent study this sample was expected to be healthier than the ones excluded. It is therefore assumed that the true results of the general population could be even worse.

Strengths and limitations

A strength of the study is the comprehensive follow-up and the ability to identify all intercurrent illness episodes and not only hospital admissions over a year for each infant.

This study was nested in a much larger funded study and whilst this resulted in excellent follow-up, there are three important limitations which hinder the generalization of the results.

The first limitation is that all babies were HIV unexposed (HU). It has been shown that HIV exposed uninfected (HEU) infants have an increased infectious morbidity when compared to HU infants.[21] There has been debate that many of the earlier studies were done before the move to early universal maternal ART and exclusive breastfeeding which may ameliorate some of the mechanisms responsible for these earlier findings. Le Roux et al[22] showed that even with maternal ART and universal breastfeeding (HEU) infants have an increased incidence rate ratio of infection-related hospitalisations when compared to HU infants but this was significant only in the first three months of life.

Although the efficacy of the monoclonal antibody in the parent study is still unknown (results have not yet been published) it is possible that those infants who received the antibody would have been less likely to consult or be admitted for complications of RSV. Other RSV monoclonal antibodies such as palivizumab and motavizumab have been shown to decrease hospital admissions for RSV by 50% as well as decrease outpatient visits for LRTI.[23,24]

Finally, the ‘most as risk infants’ could have been excluded due to inclusion criteria ruling out mothers who were unlikely to come to follow-up visits. Linked to this is that because participants were part of a study follow-up and had access to care, the outcomes could differ from those patients without such access.

Despite these limitations, this study remains important as it shows not only hospital admissions but also the high number of illness episodes in this cohort of preterm infants. It is probably that these results are an under-representation of what could be anticipated in the general population, especially if the higher risk infants are included and monoclonal antibodies are not available.

Conclusion

There are high rates of intercurrent infection and hospitalisation in HU preterm infants in their first year of life. Public health interventions to reduce the risk of LRTI must be strengthened, including promoting exclusive breastfeeding, avoidance of tobacco smoke exposure and improvements in living conditions. Larger studies are needed to investigate the association between various socioeconomic determinants and intercurrent illnesses in preterm infants.

Disclosure

The parent study received research funding from MedImmune, LLC, a wholly owned subsidiary of AstraZeneca PLC.

Acknowledgements

The authors would like to thank the staff in Research Centre for Adolescents and Child Health (REACH) as well as the mothers and their infants who participated.

References

1. Grisaru-Granovsky S, Reichman B, Lerner-Geva L, Boyko V. Mortality and morbidity in preterm small-for-gestational-age infants : a population-based study. Am J Obstet Gynocology. Elsevier Inc.; 2012;206(2):150.e1-150.e7.
2. Cooper PA, Rothberg AD, Thomson PD, Cohn RJ. The spectrum of clinical problems and outcome in infants in a neonatal unit. South African Med J. 1983;64(15):574–7.

3. Campbell A, Rudan I. Systematic review of birth cohort studies in Africa. J Glob Health. 2011;1(1):46–58.
4. Drey EA, Kang M, Mcfarland W, Darney PD. Improving the accuracy of fetal foot length to confirm gestational duration. Obstet Gynecol. 2005;105(4):773–8.
5. World Health Organization, United Nations Children's Fund. WHO child growth standards and the identification of severe acute malnutrition in infants and children. 2009.
6. Petrou S, Sach T, Davidson L. The long-term costs of preterm birth and low birth weight: Results of a systematic review. Child Care Heal Dev. 2000;27(2):97–115.
7. Le Roux DM, Nicol MP, Myer L, Vanker A, Stadler JAM, Delft E Von, et al. Lower respiratory tract infections in children in a well-vaccinated South African birth cohort: Spectrum of disease and risk factors. CID. 2019;69(9):1588–96.
8. Martens P, Dersen S, Gupta S. Predictors of hospital readmission of Manitoba newborns within six weeks postbirth discharge- a population-based study.PDF. Pediatrics. 2004;114(3):708–13.
9. Vanker A, Barnett W, Workman L, Nduru PM, Sly PD, Gie RP, et al. Early-life exposure to indoor air pollution or tobacco smoke and lower respiratory tract illness and wheezing in African infants: a longitudinal birth cohort study. Lancet Planet Heal. The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license; 2017;1(8):e328–36.
10. Li JSM, Peat JK, Xuan W, Berry G. Meta-analysis on the association between environmental tobacco smoke (ETS) exposure and the prevalence of lower respiratory tract infection in early childhood. Pediatr Pulmonol. 1999;27:5–13.
11. Reddy P, Zuma K, Shisana O, Jonas K, Sewpaul R, Town C, et al. Prevalence of tobacco use among adults in South Africa : Results from the first South African National Health and Nutrition Examination Survey. 2015;105(8):648–55.
12. Hall K. Children's access to housing. In: Shung-king M, Lake L, Saunders D, Hendricks M, editors. South African Child Gauge 2019: Child and adolescent health. Cape Town: Children's Institute, University of Cape Town; 2019. p. 248–51.
13. Siziba, LPJerling J. Low rates of exclusive breastfeeding are still evident in four South African provinces. South African J Clin Nutr. 2015;28(4):170–9.
14. Shung-king M, Lake L, Sanders D, Hendricks M. Child gauge 2019. Cape Town: Children's Institute, University of Cape Town; 2019.
15. Victora CG, Bahl R, Barros AJD, França GVA, Horton S, Krasevec J, et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. Lancet. Elsevier Ltd; 2016;387:475–90.
16. Sankar MJ, Sinha B, Chowdhury R, Bhandari N, Taneja S, Martines J, et al. Optimal breastfeeding practices and infant and child mortality: a systematic review and

meta-analysis. Acta Paediatr. 2015;104:3–13.
17. Tooke L, Louw B. A successful preterm vaccination program in a neonatal unit in a developing country. Heliyon. 2019;5(11):1–3.
18. Ko Y, Shin S, Park SM, Kim H, Lee J, Kim KH, et al. Effects of employment and education on preterm and full-term infant mortality in Korea. Public Health. 2014;128:254–61.
19. Cooper PA, Sandler DL. Outcome of very low birth weight infants at 12 to 18 months of age in Soweto, South Africa. Pediatrics. 1997;99(4):537–44.
20. Myers B, Petersen P, Govender R, Manderscheid R, Koch JR. Substance abuse treatment engagement , completion and short-term outcomes in the Western Cape province , South Africa : Findings from the Service Quality Measures Initiative. Drug Alcohol Depend. Elsevier; 2019;185(February 2018):278–84.
21. Slogrove AL, Goetghebuer T, Cotton MF, Singer J, Bettinger JA. Pattern of infectious morbidity in HIV-exposed uninfected infants and children. Front Immunol. 2016;7(164).
22. Le Roux SM, Abrams EJ, Donald KA, Brittain K, Phillips TK, Zerbe A, et al. Infectious morbidity of breastfed, HIV-exposed uninfected infants under conditions of universal antiretroviral therapy in South Africa: a prospective cohort study. Lancet Child Adolesc Heal. Elsevier Ltd; 2020;4(3):220–31.
23. The IMpact-RSV Study Group. Palivizumab, a Humanized Respiratory Syncytial Virus monoclonal antibody, reduces hospitalization from Respiratory Syncytial Virus infection in high-risk infants. Pediatrics. 1998;102(3):531–7.
24. Carbonell-estrany AX, Eric AF. Motavizumab for prophylaxis of Respiratory Syncytial Virus in high-risk children: A noninferiority trial. Pediatrics. 2010;125(1):e35–51.

APPENDICES

APPENDIX A: INFORMED CONSENT FORM

Research nr

INFORMED CONSENT FORM

TITLE OF STUDY: The outcome of well preterm infants (29-35 weeks) admitted to two Neonatal Intensive Care Units in state institutions in Cape Town followed up over a one year period

Date

Dear Ms

You are already involved in a study where you may be receiving medication to prevent lung infections in your preterm baby. This study is called:
A Phase 2b Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897, a Monoclonal Antibody with an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Preterm Infants

We want to do an additional study to try and understand more about what happens to our premature babies. During the study you have already signed for, your baby will be followed-up five times during the next year. We would like to ask you an additional set of questions at each follow up. These questions will mainly be about your living conditions and your baby's health. We will also weigh, measure the length and head size of your baby at each follow up. There will be no additional samples taken or procedures done for this study.

There are no risks to participating in this study and you may at any time withdraw from this study and anonymity will be respected always. No compensation will be offered for participation in the study but the study may help other babies in the future by helping our understanding of the management.

Should any participant have any further queries concerning this study, the investigator can be contacted:

Seth Muller
Telephone number: 021 658 5111
Email: mullerseth@gmail.com

I have read and I understand the above information. I hereby volunteer to take part in this study.

Participant	Date
Research nurse	Date

Witness	Date

Research nr

INFANT AND MATERNAL HISTORY FORM

Infant information:

Patient details / Patient sticker

Date of birth	dd	mm	cccc
Date of initial discharge	dd	mm	cccc

Gender	Male	Female

Birth weight	g

Gestational age	Weeks	Days

Head circumference at birth	cm

Length at birth	cm

APGAR scores	1 min	5min	10 min

Initial resuscitation	None	Oxygen	Face mask / Neopuff
	Endotracheal tube	Cardiac compression	Epinephrine

Surfactant required	Yes	No

Temperature within first hour of admission	Degrees

Congenital abnormalities	Yes	No
If yes, describe		

Cranial ultrasound	**Left:**	IVH 1	IVH 2	IVH 3	IVH 4
	Right:	IVH 1	IVH 2	IVH 3	IVH 4
	PVL		Not done		

Highest level of respiratory support during initial admission	Room air	Nasal Prongs	High Flow Nasal Canulas

	Nasal CPAP	Conventional ventilation	High frequency ventilation
Neonatal sepsis	Yes		No
Oxygen required at 36 weeks gestational age	Yes		No
HIV Birth PCR	Not applicable	Negative	Positive
Feeding at discharge	Breast milk	Formula	Mixed

MATERNAL INFORMATION:

Patient details / Patient sticker

Household income	H0	H1	H2	H3	P

Maternal age at delivery	Years

Pre-natal care	Booked	Unbooked

Booking bloods	RPR	Rhesus	HIV

Parity	

Maternal hypertension	None	Chronic	Pregnancy-induced

Antenatal treatment	None	Steroids	$MgSO_4$

Maternal illnesses	None	Diabetes	Other
If other, elaborate			

Maternal substance abuse	Yes	No
If yes, elaborate		

Mode of delivery	NVD	Forceps	Vacuum	Caesarian section

Prolonged rupture of membrane	Yes	No

Research nr

FOLLOW-UP FORM: DAY 8

Patient details / Patient sticker

Infant address	

Race	African	Coloured	Caucasian	Indian	Asian

Highest level of education of mother	Gr. 0 - 7	Gr. 8 - 12	Post-school training	Diploma / Degree

Number of people living in same dwelling	

Drug abuse in the same dwelling	Yes	No

Primary caregiver	

Father living in the same dwelling	Yes	No

Father providing financial support	Yes	No

Person looking after infant for most the day	

Travel outside of Western Province	Yes	No
If yes, elaborate		

Grants	None	Child support	Foster care	Care dependency

Feeding choice	Breast milk	Formula	Mixed

Introduction to solid food initiated	Yes	No
If yes, when?		

KMC at present	Yes	No

Weight	g

Head circumference	cm

Length	cm

Any hospital admissions from the last visit	Yes	No
If yes, where		
If yes, why		

Immunisation:

Birth	BCG	Yes	No
	OPV (1)	Yes	No
Six weeks	OPV (2)	Yes	No
	RV (1)	Yes	No
	DTaPIPV / HiB (1)	Yes	No
	HepB (1)	Yes	No
	PCV 13 (1)	Yes	No
Ten weeks	DTaPIPV / HiB (2)	Yes	No
	HepB (2)	Yes	No
Fourteen weeks	RV (2)	Yes	No
	DTaPIPV / HiB (3)	Yes	No
	HepB (3)	Yes	No
	PCV 13 (2)	Yes	No
Six months	Measles Vaccine (1)	Yes	No
Nine months	PCV 13 (3)	Yes	No
Twelve months	Measles Vaccine (2)	Yes	No
Eighteen months	DTaPIPV / HiB (4)	Yes	No

Research nr

FOLLOW-UP FORM - DAY 31

Patient details / Patient sticker

Infant address	

Type of dwelling	Flat	Free standing house	Shack	Wendy house	Room in a house

Access to electricity in dwelling	Yes	No

Access to water	Communal tap	Piped onto property	Piped inside dwelling

Number of people living in same dwelling	

Smokers living in same dwelling	Yes	No

Drug abuse in the same dwelling	Yes	No

Primary caregiver	

Father living in the same dwelling	Yes	No

Father providing financial support	Yes	No

Person looking after infant for the majority of the day	

Attending crèche	Yes	No

Travel outside of Western Province	Yes	No
If yes, elaborate		

Grants	None	Child support	Foster care	Care dependency

Feeding choice	Breast milk	Formula	Mixed

Introduction to solid food initiated	Yes	No
If yes, when?		

KMC at present	Yes	No

Weight	g

Head circumference	cm

Length	cm

Any hospital admissions from the last visit	Yes	No
If yes, where		
If yes, why		

Immunisation:

Birth	BCG	Yes	No
	OPV (1)	Yes	No
Six weeks	OPV (2)	Yes	No
	RV (1)	Yes	No
	DTaPIPV / HiB (1)	Yes	No
	HepB (1)	Yes	No
	PCV 13 (1)	Yes	No
Ten weeks	DTaPIPV / HiB (2)	Yes	No
	HepB (2)	Yes	No
Fourteen weeks	RV (2)	Yes	No
	DTaPIPV / HiB (3)	Yes	No
	HepB (3)	Yes	No
	PCV 13 (2)	Yes	No
Six months	Measles Vaccine (1)	Yes	No
Nine months	PCV 13 (3)	Yes	No
Twelve months	Measles Vaccine (2)	Yes	No
Eighteen months	DTaPIPV / HiB (4)	Yes	No

Research nr

FOLLOW-UP FORM - DAY 91

Patient details / Patient sticker

Number of people living in same dwelling		
Drug abuse in the same dwelling	Yes	No
Father living in the same dwelling	Yes	No
Father providing financial support	Yes	No
Person looking after infant for the majority of the day		
Attending crèche	Yes	No
Travel outside of Western Province	Yes	No
If yes, elaborate		

Feeding choice	Breast milk	Formula	Mixed

Introduction to solid food initiated	Yes	No
If yes, when?		
KMC at present	Yes	No

Developmental milestones	**Date**
Rolling	
Neck control	
Sitting without support	
Crawling	
Standing with assistance	
Standing alone	
Walking with assistance	
Walking alone	

Weight	g
Head circumference	cm
Length	cm

Any hospital admissions from the last visit	Yes	No
If yes, where		

If yes, why	

Immunisation:

Birth	BCG	Yes	No
	OPV (1)	Yes	No
Six weeks	OPV (2)	Yes	No
	RV (1)	Yes	No
	DTaPIPV / HiB (1)	Yes	No
	HepB (1)	Yes	No
	PCV 13 (1)	Yes	No
Ten weeks	DTaPIPV / HiB (2)	Yes	No
	HepB (2)	Yes	No
Fourteen weeks	RV (2)	Yes	No
	DTaPIPV / HiB (3)	Yes	No
	HepB (3)	Yes	No
	PCV 13 (2)	Yes	No
Six months	Measles Vaccine (1)	Yes	No
Nine months	PCV 13 (3)	Yes	No
Twelve months	Measles Vaccine (2)	Yes	No
Eighteen months	DTaPIPV / HiB (4)	Yes	No

Research nr

FOLLOW-UP FORM - DAY 151

Patient details / Patient sticker

Number of people living in same dwelling		
Smokers living in same dwelling	Yes	No
Drug abuse in the same dwelling	Yes	No
Primary caregiver		
Father living in the same dwelling	Yes	No
Father providing financial support	Yes	No
Person looking after infant for most the day		
Attending crèche	Yes	No
Travel outside of Western Province	Yes	No
If yes, elaborate		

Grants	None	Child support	Foster care	Care dependency

Feeding choice	Breast milk	Formula	Mixed

Introduction to solid food initiated	Yes	No
If yes, when?		
KMC at present	Yes	No

Developmental milestones	**Date**
Rolling	
Neck control	
Sitting without support	
Crawling	
Standing with assistance	
Standing alone	
Walking with assistance	
Walking alone	

Weight	g

Head circumference	cm

Length	cm

Any hospital admissions from the last visit	Yes	No
If yes, where		
If yes, why		

Immunisation:

Birth	BCG	Yes	No
	OPV (1)	Yes	No
Six weeks	OPV (2)	Yes	No
	RV (1)	Yes	No
	DTaPIPV / HiB (1)	Yes	No
	HepB (1)	Yes	No
	PCV 13 (1)	Yes	No
Ten weeks	DTaPIPV / HiB (2)	Yes	No
	HepB (2)	Yes	No
Fourteen weeks	RV (2)	Yes	No
	DTaPIPV / HiB (3)	Yes	No
	HepB (3)	Yes	No
	PCV 13 (2)	Yes	No
Six months	Measles Vaccine (1)	Yes	No
Nine months	PCV 13 (3)	Yes	No
Twelve months	Measles Vaccine (2)	Yes	No
Eighteen months	DTaPIPV / HiB (4)	Yes	No

Research nr

FOLLOW-UP FORM - DAY 361

Patient details / Patient sticker

Infant address	

Number of people living in same dwelling	

Drug abuse in the same dwelling	Yes	No

Primary caregiver	

Father living in the same dwelling	Yes	No

Father providing financial support	Yes	No

Person looking after infant for most the day	

Attending crèche	Yes	No

Travel outside of Western Province	Yes	No
If yes, elaborate		

Grants	None	Child support	Foster care	Care dependency

Feeding choice at present	Breast milk	Formula	Mixed

Introduction to solid food initiated	Yes	No
If yes, when?		

KMC at present	Yes	No

Any hospital admissions from the last visit	Yes	No
If yes, where		
If yes, why		

Developmental milestones	**Date**
Rolling	
Neck control	
Sitting without support	
Crawling	
Standing with assistance	
Standing alone	
Walking with assistance	
Walking alone	

Weight	g

Head circumference	cm

Length	cm

Immunisation:

Birth	BCG	Yes	No
	OPV (1)	Yes	No
Six weeks	OPV (2)	Yes	No
	RV (1)	Yes	No
	DTaPIPV / HiB (1)	Yes	No
	HepB (1)	Yes	No
	PCV 13 (1)	Yes	No
Ten weeks	DTaPIPV / HiB (2)	Yes	No
	HepB (2)	Yes	No
Fourteen weeks	RV (2)	Yes	No
	DTaPIPV / HiB (3)	Yes	No
	HepB (3)	Yes	No
	PCV 13 (2)	Yes	No
Six months	Measles Vaccine (1)	Yes	No
Nine months	PCV 13 (3)	Yes	No
Twelve months	Measles Vaccine (2)	Yes	No
Eighteen months	DTaPIPV / HiB (4)	Yes	No

HUMAN RESEARCH ETHICS COMMITTEE
15 AUG 2019
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30·08·2020
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	16/8/19

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	13 August 2019		
HREC REF Number	886/2016	Current Ethics Approval was granted until	14/8/19
Protocol title	THE OUTCOME OF WELL PRETERM INFANTS (29-35 WEEKS) ADMITTED TO NEONATAL INTENSIVE CARE UNITS IN STATE INSTITUITIONS IN CAPE TOWN, FOLLOWED UP OVER A ONE YEAR PERIOD		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes X ☐ No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Lloyd Tooke		
Department / Office Internal Mail Address	Neonatal Department, H-floor, Old Main Building		

1.1 Does this protocol receive US Federal funding?	☐ Yes	X ☐ No

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Author Guidelines

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

To submit a manuscript, please proceed to the SAJCH Editorial Manager website: Editorial Manager

To access and submit an article already in production, please see the guidelines here.

Author Guidelines

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: submissions@hmpg.co.za).

Article Processing Charges

All articles published in the South African Journal of Child Health are open access and freely available online upon publication. This is made possible by applying a business model to offset the costs of peer review management, copyediting, design and production, by charging an article-processing charge (APC) of R3 180 (ex Vat) for all articles published. The charge applies only to Research articles submitted after 1 Jan 2019. The APC is standard and does not vary based on length, colour, figures, or other elements.

When submitting a Research article to the SAJCH, the submitting author must agree to pay the APC should the article be accepted for publication. The APC is payable when your manuscript is editorially accepted and before production commences for publication. The submitting author will be notified that payment is due and given details on the available methods of payment. Prompt payment is advised; the article will not enter into production until payment is received.

Queries can be directed to claudian@hmpg.co.za.

Please refer to the section on ‘Sponsored Supplements’ regarding the publication of supplements, where a charge is applicable. Queries can be directed to dianes@hmpg.co.za or claudian@hmpg.co.za

Authorship

Named authors must consent to publication. Authorship should be based on: (I) substantial contribution to conceptualisation, design, analysis and interpretation of data; (II) drafting or critical revision of important scientific content; or (III) approval of the version to be published. These conditions must all be met for an individual to be included as an author (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.

Author contributions should be listed/described in the manuscript.

Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.

If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on Ethics in Health research: principles, processes and structures to ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchers have been adhered to.

Clinical trials

Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The SAJCH therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Protection of rights to privacy

Patient

Information that would enable identification of individual patients should not be published in written descriptions, photographs, radiographs and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has given informed written consent for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to Protection of Research Participants. The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

Other individuals

Any individual who is identifiable in an image must provide written agreement that the image may be used in that context in the SAJCH.

Copyright notice

Copyright remains in the Author's name. The work is licensed under a Creative Commons Attribution - Noncommercial Works License. Authors are required to complete and sign an Author Agreement form that outlines Author and Publisher rights and terms of publication. The Agreement form should be uploaded along with other submissions files and any submission will be considered incomplete without it [FORTHCOMING].

Material submitted for publication in the SAJCH is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement. The SAJCH does not hold itself responsible for statements made by the authors. The corresponding author should also indicate if the research forms part of a postgraduate short report, dissertation or thesis.

Previously published images

If an image/figure has been previously published, permission to reproduce or alter it must be obtained by the authors from the original publisher and the figure legend must give full credit to the original source. This credit should be accompanied by a letter indicating that permission to reproduce the image has been granted to the author/s. This letter should be uploaded as a supplementary file during submission.

Privacy statement

The SAJCH is committed to protecting the privacy of its website and submission system users. The names, personal particulars and email addresses entered in the website or submission system will not be made available to any third party without the user's permission or due process. By registering to use the website or submission system, users consent to receive communication from the SAJCH or its publisher HMPG on matters relating to the journal or associated publications. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

Ethnic/race classification

Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note thatit is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

Continuing Professional Development (CPD)

SAJCH is an HPCSA-accredited service provider of CPD materials. Principal authors can earn up to 15 CPD continuing education units (CEUs) for publishing an article; co-authors are eligible to earn up to 5 CEUs; and reviewers of articles can earn 3 CEUs. Each month, SAJCH also publishes a CPD-accredited questionnaire relating to the academic content of the journal. Successful completion of the questionnaire with a pass rate of 70% will earn the reader 3 CEUs. Administration of our CPD programme is managed by Medical Practice Consulting. To complete questionnaires and obtain certificates, please visit MRP Consulting

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this requirement are Editorials, Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.

Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.

Mask self-citations by referring to your own work in third person.

General article format/layout

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.

General:

Manuscripts must be written in UK English (this includes spelling).

The manuscript must be in Microsoft Word or RTF document format. Text must be 1.5 line spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes). Pages and lines should be numbered consecutively.

Please make your article concise, even if it is below the word limit.

Qualifications, **FULL** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.

Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).

Litres is denoted with an uppercase L e.g. 'mL' for millilitres).

Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.

Please be sure to insert proper symbols e.g. μ not u for micro, a not a for alpha, b not B for beta, etc.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.

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

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

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 are not.

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

** NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- 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 6 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.

Do not include any references in the abstracts.

Here is an example of a good abstract.

SCIENTIFIC LETTERS/short reports

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

GUIDELINE WORD LIMIT: 1500 WORDS

Abstract: unstructured, of about 100-150 words

May include only one illustration or table

A maximum of 6 references

Editorials

GUIDELINE WORD LIMIT: 1 000 WORDS

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

expert opinion

personal clinical experience

observational studies

trials

systematic reviews.

Review articles

Review articlesshould always be discussed with the Editor prior to submission.

GUIDELINE WORD LIMIT: 4 000 WORDS

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners. They should be aligned to practice in South and/or sub-Saharan Africa and not a precis of reviews published in the international literature

Please ensure that your article includes:

Abstract: unstructured, of about 100-150 words, explaining the review and why it is important

Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.

When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have

to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.

Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

GUIDELINE WORD LIMIT: 400 WORDS

Letters to the editor should relate either to a paper or article published by the SAJCH or to a topical issue of particular relevance to the journal's readership

May include only one illustration or table

Must include a correspondence address.

Obituaries

GUIDELINE WORD LIMIT: 400 WORDS

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Illustrations/photos/scans

If illustrations submitted have been published elsewhere, the author(s) should provide evidence of consent to republication obtained from the copyright holder.

Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.

Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).

All images must be of high enough resolution/quality for print.

All illustrations (graphs, diagrams, charts, etc.) must be in PDF form.

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.

Tables

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.

Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.

Number each table in Arabic numerals (Table 1, Table 2, etc.) consecutively as they are referred to in the text.

Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.

Ensure each table has a concise title and column headings, and include units where necessary.

Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

RATHER:

Each row of data must have its own proper row:

Do not: use separate columns for N and %:

RATHER:

Combine into one column, N (%):

Do not: have overlapping categories, e.g.:

RATHER:

Use <> symbols or numbers that don't overlap:

References

NB: Only complete, correctly formatted reference lists in Vancouver style will be accepted. If reference manager software is used, the reference list and citationS IN TEXT ARE TO BE UNFORMATTED TO PLAIN TEXT BEFORE SUBMITTING..

Authors must verify references from original sources.

Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]

All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).

Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.

Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.

Volume and issue numbers should be given.

First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.

Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:

On the Crossref homepage, paste the article title into the 'Metadata search' box.

Look for the correct, matching article in the list of results.

Click Actions > Cite

Alongside 'url =' copy the URL between { }.

Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

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.

Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.

Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

From submission to acceptance

Submission and peer-review

To submit an article:

Please ensure that you have prepared your manuscript in line with the SAJCH requirements.

All submissions should be submitted via Editorial Manager

The following are required for your submission to be complete:

Anonymous manuscript (unless otherwise stated)

Author Agreement form [forthcoming]

Manuscript

Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.

Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer Review Process

All manuscripts are reviewed initially by the Editor-in-Chief and only those that meet the scientific and editorial standards of the journal, and fit within the aims and scope of the journal, will be sent for external peer review. Each manuscript is reviewed by either one or two reviewers selected on the basis of their expertise in the field. A double blind review process is followed at SAJCH.

Authors are expected to receive feedback from reviewers and an editorial decision within approximately 6 weeks of submission. The time period of the entire review process may vary however depending upon the quality of the manuscript submitted, reviewers' responses and the time taken by the authors to submit the revised manuscript.

Manuscripts from review may be accepted, rejected or returned to the author for revision or resubmission for review. Authors will be directed to submit revised manuscripts within two months of receiving the editor's decision, and are requested to submit a point by point response to the reviewers' comments. Manuscripts which authors are requested to revise and resubmit will be sent for a second round of peer

review, often to the original set of reviewers. All final decisions on a manuscript are at the Editor's discretion.

Production process

An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).

The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.

If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.

The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.

The CE will finalise the article and then it will be typeset.

Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.

The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.

The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

Errata and retractions

Errata

Should you become aware of an error or inaccuracy in yours or someone else's contribution after it has been published, please inform us as soon as possible via an email to publishing@hmpg.co.za,including the following details:

Journal, volume and issue in which published

Article title and authors

Description of error and details of where it appears in the published article

Full detail of proposed correction and rationale

We will investigate the issue and provide feedback. If appropriate, we will correct the web version immediately, and will publish anerratum in the next issue. All investigations will be conducted in accordance with guidelines provided by the Committee on Publication Ethics (COPE).

Retractions

Retraction of an article is the prerogative of either the original authors or the editorial team of HMPG. Should you wish to withdraw your article before publication, we need a signed statement from all the authors.

Should you wish to retract your published article, all authors have to agree in writing before publication of the retraction.

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

Journal, volume and issue to which article was submitted/in which article was published

Article title and authors

Description of reason for withdrawal/retraction.

We will make a decision on a case-by-case basis upon review by the editorial committee in line with international best practices. Comprehensive feedback will be communicated with the authors with regard to the process. In case where there is any suspected fraud or professional misconduct, we will follow due process as recommended by the Committee on Publication Ethics (COPE), and in liaison with any relevant institutions.

When a retraction is published, it will be linked to the original article.

Indexing

Published articles are covered by the following major indexing services. As such articles published in the SAJCH are immediately available to all users of these databases, guaranteed a global and African audience:

DOAJ

AIM

AJOL

Crossref

Sabinet

Scielo

EBSCO

EMBASE

Sponsored supplements

Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

Named authors consent to publication and meet the requirements of authorship as set out by the journal.

The submission has not been previously published, nor is it before another journal for consideration.

The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.

The manuscript is in Microsoft Word or RTF document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.

Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (preferably TIFF or PNG). These must be submitted as 'supplementary files' (not in the manuscript).

For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.

Where possible, references are accompanied by a digital object identifier (DOI) and PubMed ID (PMID)/PubMed Central ID (PMCID).

An abstract has been included where applicable.

The research was approved by a Research Ethics Committee (if applicable)

Any conflict of interest (or competing interests) is indicated by the author(s).

Copyright Notice

Authors are free to copy, print and distribute their articles, in full or in part, for teaching activities, and to deposit or include their work in their own personal or institutional database or on-line website. Authors are requested to inform the Journal/Publishers of their desire/intention to include their work in a thesis or dissertation or to republish their work in any derivative form (but not for commercial use).

Material submitted for publication in the SAJCH is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement.

Privacy Statement

The SAJCH is committed to protecting the privacy of the users of this journal website. The names, personal particulars and email addresses entered in this website will be used only for the stated purposes of this journal and will not be made available to third parties without the user's permission or due process. Users consent to receive communication from the SAJCH for the stated purposes of the journal. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

Reviewer 1
This is a prospective observational study nested in a cohort of preterm infants enrolled in a RCT to determine the efficacy of a RSV monoclonal antibody. The study enrolled 53 infants who had been followed up very closely for a year after premature birth between 29 - 35 wGA. The study describes the rate of illness episodes and hospitalisations in this group of children and explores associations between illness episodes and socioeconomic factors. The conclusion of the study, supported by the data, is that there are high rates of illness episodes and hospitalisation in this group of patients. This is a relevant article that describes not only the hospitalisation of premature children but also the illness episodes that did not require hospitalisation, which makes it more novel and informative. The article is well written and the results are mostly well presented.
Thank you for taking the time to review this manuscript. We appreciate the comments and made changes as explained below.
There are two methodological issues with this study. The first being that HIV exposed children were excluded. This is unfortunate, but was a prerequisite of the parent study. The exclusion of these children should be highlighted in the abstract, the results and the conclusion, so that it does not seem that the results can be generalized to all children.
This is an excellent suggestion. We have incorporated this suggestion throughout the manuscript. We have also included a short paragraph in the strengths and limitations section elaborating the potential effect on this sample of infants with reference to two large local studies.
The second issue is much more important. The parent study was a study looking at the efficacy of a RSV monoclonal antibody. This was a randomized controlled trial. As previous literature on palivizumab and motavizumab have shown us, these treatments have a huge effect on the incidence of wheezing and hospitalisations in the first year of life. The fact that some of these children received a treatment that actively decreases illness episodes and hospitalisations in this exact group is a major flaw in this study and makes the reader wonder if the results are not an under-representation of the actual rates found in this subgroup. The fact that roughly half

the patients would have received the treatment and the other half did not means that we are dealing with two very different groups of patients, but describing them as a single unit. This problem needs to be addressed by the authors before i would consider this manuscript for publication. The results need to be presented as a whole group as well as divided into treatment and placebo groups. This would included the demographic data as well as the clinical data. If this is not possible, there should at a minimum be a very strongly worded admission and explanation regarding this issue, before a final decision can be reached on the acceptance of the manuscript.
This is a valid point, which we reconsidered. This is a novel monoclonal antibody so the efficacy is unknown. However, we have included further references to highlight the point that Palivuzimab and Motavizumab decrease outpatient visits and admissions for RSV. This means that our study possibly underestimated the number of illness episodes and hospital admissions. We have amended the 'methods' and 'strengths and limitations' sections to describe this more clearly. We are still blinded to intervention/placebo but even if we were not, the sample size would be too small to compare groups for our local study. Despite the risk of underestimating the number of infections and admission in the general population, we feel that this is still important information to be placed in the public domain. The message that there are a large number of infectious episodes (rarely reported) and admissions is important and the fact that this is probably an underestimation is we feel (now) well explained.
Abstract: Background: Please change 'after discharge' to 'after initial discharge'
We made the changes accordingly.
Abstract: Objectives: Add HIV unexposed before 'preterm infants'
We made the changes accordingly.
Abstract: Objectives: Add risk before 'factors' in 'associated factors'
We made the changes accordingly.
Abstract: Results: Remove 'with one death' and add it add end of sentence 'of which 31 were hospital admissions'
Instead of adding it to the end of the sentence, which may imply that this infant died in hospital, we amended it to 'One infant died at home' in a separate sentence.

Abstract: Conclusion: Need to highlight that these findings were only in HIV unexposed children and can not be generalized to all children
The first sentence in ‘conclusion’ was changed to ‘This is one of the few studies to record all illness episodes and not just admissions over a one-year period for HIV unexposed infants’.
Introduction: Please change 'increasing and large' to 'large and increasing'
We made the changes accordingly.
Introduction: Accepted abbreviation is LMIC. If plural needed, then LMICs
We noted this error and changed it to ‘LMIC’.
Results: Page 5, line 37. There is to much repetition of results here. I would combine all these first 3 paragraphs into one as a quick summary and then refer to the table for more detail.
We agree that most of the data is represented by the table and was repeated in writing. We have amalgamated three paragraphs into one.
Results: Under infant characteristics, the first paragraph should be moved down this section, after the next paragraph.
We moved the paragraph as suggested.
Results: Not sure if figure 1 adds much more than the text and could be used as a supplementary table.
Thank you for this suggestion. We compared the use of a graph and a table and feel that this graph represents the data easily in a strong visual way and that a table would not demonstrate the rapid decline in exclusive breast feeding over time as vividly as a graph. We are also within the guidelines of the number of tables and figures one can use for an article.

Results: Table 3: impetigo is misspelled
We corrected the spelling error.
Results: Table 5 in the text describes the actual Table 4.
We have labeled the tables correctly.
Discussion: In the discussion, please add a paragraph explaining how HIV infection and exposure may influence childhood health and the incidence of infections. Also, reiterate that this study only included HIV unexposed children and that the results cannot be generalized to the whole population.
Thank you once again for pointing this out. We have made changes throughout the paper to draw attention to this important part of our study. In the 'strengths and limitations' section we added an extensive paragraph with two large South African studies, looking at the outcomes of HIV exposed and HIV unexposed infants. The findings of these two studies are noted in the changes to alert the reader that there is an effect on illness episodes in infants of HIV exposed mothers. This effect appears to be greatest in the first six months and then the effect is ameliorated.
Conclusion: Mention only in HIV unexposed children.
The opening sentence of the conclusion now reads 'There are high rates of intercurrent infection and hospitalisation in HU preterm infants in their first year of life.' with the addition of HU (HIV unexposed infants) as referenced in the strengths and limitations by Le Roux and Slogrove.