TRENDS IN DIARRHOEAL DISEASE HOSPITALISATIONS TO A SHORT STAY PAEDIATRIC WARD AT THE CHRIS HANI BARAGWANATH HOSPITAL FROM 2002 TO 2016

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Masters of Medicine

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Declaration

I, Euphrasia Makgatho declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Masters of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

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Euphrasia Makgatho

18th day of August 2019 in Johannesburg

Dedication

I would like to dedicate this research report to my husband, Adolf Tapelo and our daughters Gabriella Lerato and Zoe Lesedi and thank them for their understanding, support, love and encouragement. I would also like to extend my gratitude to my friends and family who stepped in to look after my girls while mhamhi was working.

Presentations arising from this study

1. Makgatho E, Patel F, Solomon F, Groome MJ, Lala SG, Vallabh P and Dangor Z. The burden of acute diarrhoeal disease in young hospitalised urban South African children five years after rotavirus vaccine introduction: a retrospective descriptive study. University of the Witwatersrand, Faculty of Health Sciences Research Day, 6 September 2018 (Poster presentation-ID-P-16).
2. Makgatho E, Patel F, Solomon F, Groome MJ, Lala SG, Vallabh P and Dangor Z. The burden of acute diarrhoeal disease in young hospitalised urban South African children five years after rotavirus vaccine introduction: a retrospective descriptive study. University of the Witwatersrand, Paediatric Research Day, 26 October 2018 (Oral presentation).
3. Makgatho E, Patel F, Izu A, Groome MJ, Lala SG, Vallabh P and Dangor Z. Trends in diarrhoeal disease hospitalisation to a paediatric short-stay ward at a tertiary-level hospital in Soweto: 2002-2016. University of the Witwatersrand, Paediatric Research Day, 26 October 2018 (e-poster presentation).

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- the co-authors: Doctors Firuzan Patel, Fatima Solomon, Alane Izu, Michelle Groome and Prof. Sanjay Lala.

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List of Abbreviations and Symbols

AIDS	Acquired Immune Deficiency Syndrome
aLRTI	Acute Lower Respiratory Tract Infection
aOR	Adjusted Odds Ratio
ART	Antiretroviral Therapy
ARV	Antiretroviral
BMDH	Bheki Mlangeni District Hospital
CD	Cluster of Differentiation
CHBAH	Chris Hani Baragwanath Academic Hospital
CI	Confidence Interval
CPA	Change Point Analysis
^{o}C	Degrees Celsius
DALYs	Disability-Adjusted Life-Years
EPI	Expanded Programme on Immunisation
HAZ	Height-for-Age Z-Score
HIV	Human Immunodeficiency Virus
HU	HIV-Unexposed
HE	HIV-Exposed
HREC	Human Research Ethics Committee
IQR	Interquartile Range
IMCI	Integrated Management of Childhood Illness
mL	Millilitres
PCR	Polymerase Chain Reaction
PMEAD	Paediatric Medical Emergency and Ambulatory Department
PMTCT	Prevention of Mother-To-Child Transmission
RMPRU	Respiratory and Meningeal Pathogens Research Unit
StatsSA	Statistics South Africa
SSW	Short Stay Ward
WASH	Water, Sanitation and Hygiene
WAZ	Weight-for-Age Z-Score
WHO	World Health Organisation

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Preface

Acute diarrheal disease remains a leading cause of morbidity and mortality worldwide, mostly affecting young children from low and middle income countries. Since the implementation of the rotavirus vaccine in South Africa, the burden of rotavirus-associated and all-cause diarrhoeal disease has significantly declined. The effectiveness of rotavirus vaccination has however been better for severe forms of rotavirus-specific diarrhoeal disease. Over the past few years, however, health care workers have anecdotally observed a reduction in diarrhoeal admissions to the short stay ward at the Chris Hani Baragwanath Academic Hospital. We therefore sought to determine factors contributing to the perceived decline of hospital admissions to the short stay ward. In addition, we looked at the overall burden of diarrhoeal disease hospitalizations (to all wards) five years after rotavirus vaccine introduction, and with vaccine coverage rates above 85%, in a setting with a high HIV exposure prevalence and improved access of antiretroviral therapy for HIV infected mothers and children. In-order to meet the above objectives, two independent manuscripts have been submitted to two different journals.

Manuscript 1 is entitled: 'Trends in diarrhoeal disease hospitalisation to a paediatric short-stay ward at a tertiary-level hospital in Soweto: 2002-2016' and was accepted for publication in the *South African Journal of Child Health*. Author guidelines for this manuscript are available at: http://www.sajch.org.za/index.php/sajch/about/submissions#authorGuidelines.
The authors for this manuscript are Euphrasia Makgatho, Firuzan Patel, Alane Izu, Michelle J. Groome, Sanjay G. Lala, Preeteeben Vallabh and Ziyaad Dangor.

Manuscript 2 is entitled: 'The burden of acute diarrhoeal disease in young hospitalised urban South African children five years after rotavirus vaccine introduction: a retrospective descriptive study' and was published in July 2019 in *The Pediatric Infectious Disease*

Journal. Author guidelines for this manuscript are available at:

http://edmgr.ovid.com/pidj/accounts/ifauth.htm.

The authors for this manuscript are Euphrasia Makgatho, Firuzan Patel, Fatima Solomon, Michelle J. Groome, Sanjay G. Lala, Preeteeben Vallabh and Ziyaad Dangor.

The research report is therefore being submitted in the 'Submissible Format' in line with the University of the Witwatersrand Faculty of Health Sciences accepted formats for a research report. The formatting for both manuscripts differ slightly; for readability, we have formatted both manuscripts in UK English using double line spacing and 12-point Times New Roman font.

We have also attached the plagiarism declaration and the Turnitin report which has a similarity index of 12% (Appendix 1), the Human Research Ethics Committee approval certificate (Appendix 2) and the postgraduate committee approved protocol (Appendix 3).

MANUSCRIPT 1

TRENDS IN DIARRHOEAL DISEASE HOSPITALISATION TO A PAEDIATRIC SHORT-STAY WARD AT A TERTIARY-LEVEL HOSPITAL IN SOWETO: 2002-2016

Abstract

Globally, a decline in diarrhoeal disease has been observed over the last two decades. This may be attributable to several interventions, including rotavirus vaccination since 2009 in South Africa. From January 2002 to December 2016, we conducted a retrospective trend analysis of diarrhoeal hospitalisations with mild or moderate dehydration to a short stay ward (SSW) in children less than 14-years of age. We found that diarrhoeal hospitalisation to the SSW accounted for 29.3% of the 53 717 children that presented with diarrhoea to the emergency department. A significant decline in disease incidence was noted after 2009/ 2010, coinciding with rotavirus vaccine implementation into the Expanded Programme on Immunisation. The yearly incidence (per 100 000) declined from 307 (95%CI: 277- 337) over the 2002-2008 period to 141 (95%CI: 120- 161) from 2011-2016; $p<0.001$. In conclusion, we report a temporal association between rotavirus vaccination and diarrhoeal disease hospitalisations to the SSW at this hospital.

Introduction

Diarrhoeal disease is a leading cause of disability-adjusted life-years (DALYs), morbidity and mortality worldwide, with an estimated 957 million cases reported in children less than five years of age in 2015.[1] Since the implementation of the rotavirus vaccine, the global burden of rotavirus-associated and all-cause diarrhoeal disease has declined.[2] The effectiveness of rotavirus vaccination has been better for severe forms of rotavirus-specific diarrhoeal disease,[2] and marked reductions in diarrhoeal disease mortality rates (39.2%) and rotavirus-specific mortality rates (59.3%) have been observed worldwide.[1,3] In addition to introduction of rotavirus vaccination into the Expanded Programme of Immunisation (EPI) to reduce the burden of diarrhoeal disease since 2009 in South Africa, there have been other interventions such as: improved access to anti-retroviral therapy (ART), the promotion of breastfeeding, safe Water Sanitation and Hygiene (WASH) initiatives, Vitamin A supplementation and the Integrated Management of Childhood Illness (IMCI) program (Supplementary Table 1). The aim of this study was to determine the trends and highlight time point changes to diarrhoeal disease hospitalisations, with mild and moderate dehydration, to a Short Stay Ward (SSW) at the Chris Hani Baragwanath Academic Hospital (CHBAH) over a 15-year period.

Methods

A retrospective review of children 6-weeks to less than 14-years of age with diarrhoea, hospitalised to a SSW at CHBAH from January 2002 to December 2016 was conducted. The CHBAH is the third largest hospital in the world with 164 general paediatric beds and 40 short stay paediatric beds. Until April 2014, when the primary-level Bheki Mlangeni District Hospital became operational, CHBAH was the only state funded paediatric hospital in Soweto. The population of Soweto was estimated at 1.27 million in 2011 with approximately 314 000 children less than 14 years of age. The population comprises mainly of black-Africans from low to middle income formal and informal households.

Children presenting at the CHBAH with a diarrhoeal disease are managed as per the IMCI protocol. The standard-of-care for triage and management of children with a diarrhoeal disease at CHBAH has been mostly consistent over the study period, and the senior Paediatric Medical Emergency and Ambulatory Department (PMEAD) medical staff has remained unchanged. Children older than six weeks of age and less than 14-years of age with mild or moderate dehydration are admitted to the SSW. Children less than 6 weeks of age are not routinely admitted to the SSW on the premise that they may have possible severe bacterial infection and require further investigation. Mild dehydration is defined as a child who is alert, drinks eagerly and has a normal to slightly reduced urine volume (as reported by the caregiver and based on a reduced number of nappies changed or passing dark/concentrated urine). These children are hospitalised only if they are not tolerating oral fluids. Moderate dehydration is defined as a child with at least two of the following signs: sunken eyes, depressed anterior fontanelle, absent tears, thirst/ drinks eagerly, restless/ irritable, a slow skin pinch but <2 seconds and sticky mucosa. Excluded from admission to the SSW are those children with: shock, suspected or proven electrolyte imbalances, decreased level of consciousness, a surgical cause of diarrhoea, chronic diarrhoea, the presence of other

significant co-morbidities (e.g. severe malnutrition, oncology patients, renal and cardiac disease) and those with no available caregiver as the presence of a caregiver is mandatory in the SSW.

Monthly statistics using ward registries from the SSW and the PMEAD are routinely collected by senior medical staff. All children admitted to the SSW with a diagnosis of diarrhoea or having a discharge diagnosis of diarrhoea and /or dysentery were included in the study. The incidence trends of diarrhoea with mild or moderate dehydration was estimated as the number of cases with diarrhoea admitted to the SSW over the median population estimates of children less than 14-years of age in Soweto and its surrounding areas as per StatsSA.[4] A non-parametric change point analysis (CPA) was undertaken to highlight changes to public health practices at various time points.[5] Unlike an intervention analysis, a CPA identifies points in time where a change in trend occurs, These points are referred to as change points. The change points are then associated with the public health intervention or strategies occurring around that change point. Average monthly minimum and maximum temperatures and rainfall patterns were obtained from weather SA and seasonal patterns mapped out to determine associations between these parameters and diarrhoeal disease trends.[6] Permission to conduct the study was obtained from the University of the Witwatersrand Human Research Ethics Committee (M170501).

Results

Over half a million (n= 503 512) children presented to the PMEAD over the 15-year period, and diarrhoeal disease occurred in 11.6% (n=53 717) (Supplementary Table 2). We observed a 27.1% (12.5% in 2002 vs. 9.1% in 2016) decline in the proportion of diarrhoeal disease consultations at the PMEAD. Although the number of children admitted with diarrhoeal illness to the SSW declined, the proportion to overall consultations remained unchanged (Supplementary Table 2). Of the 17 057 children admitted to the SSW, 860 (5.0 %) had dysentery. There was a 51.8% decline in the use of intravenous fluids for rehydration from 28.3% in 2002 to 13.6% in 2016. There was no difference in the formal or informal housing of patients over the 15 years; 31.1% of parents reported living in informal settlements in 2002 compared to 28.2% in 2016, p= 0.447 (data not shown).

The CPA identified change points in monthly diarrhoeal incidence in May 2009 and July 2010. We then sought to determine the most likely intervention/s that may have been associated with that change point- rotavirus vaccine introduction into the EPI and changes to the prevention of mother to child transmission (PMTCT) programme were the that began just prior to the change points identified (Figure 1). Based on these results, we then compared the 2002-2008 (pre-rotavirus) with the 2011-2016 (post rotavirus) vaccine period; and considered 2009 and 2010 as a transition period. Rotavirus vaccine coverage was estimated as 85% in 2011 and 91% in 2016.[7] During the 2002-2008 period, the average yearly incidence (per 100 000) was estimated at 307 (95% CI: 227-337), and declined to 141 (95% CI: 120-161) over the 2011-2016 period ($p<0.001$) (Figure 1). No other significant declines in relation to public health interventions (as listed in the Supplementary Table 1) were observed.

Average temperatures and rainfall patterns were plotted against the monthly diarrhoeal incidence rates (Figure 2 and 3). Higher maximum and minimum temperatures were closely

followed by peaks in diarrhoeal hospitalisations. Similarly, increased rainfall was associated with peaks in hospital admissions. These patterns were less distinct in the post-rotavirus vaccine era.

Discussion

To our knowledge, this was the first study to report long-term trends of hospitalisation for diarrhoeal disease with mild and moderate dehydration in South Africa. Previously, a study conducted at CHBAH looked at trends in hospitalisations for more severe diarrhoeal disease.[8] We report a significant temporal decline in incidence of "milder" diarrhoeal disease that followed the introduction of the rotavirus vaccine into the EPI in 2009 and persisted with vaccine coverage rates above 85%. Although other interventions, such as improved access to ART, PMTCT, WASH, IMCI, breastfeeding practices, and Vitamin A supplementation have likely contributed to this decline, the most marked change was observed after rotavirus vaccine implementation.

Numerous studies have reported the effectiveness of rotavirus vaccination on rotavirus associated and all-cause diarrhoea in both high and low income settings.[2, 8] The effectiveness has reportedly been less for milder forms of diarrhoeal disease.[2] Despite the 27% decline in the number of diarrhoeal cases seeking medical care at this PMEAD, our study was unable to tease out the effect of rotavirus vaccination on community managed diarrhoeal disease. We were however able to show an effect on a specific subgroup of children with diarrhoeal disease that require primary or secondary level care for mild or moderate dehydration and importantly, this once busy "gastroenteritis" unit in a high burden setting may soon be redundant. Nonetheless, diarrhoeal disease remains a high disease burden in Africa with marked variations in incidence and mortality,[9] and interventions to further reduce the burden of disease should continue.

Diarrhoeal hospitalisations to the SSW occurred mainly in the late summer months following peaks of temperature increases and rainfall patterns. However, we observed less effect of the above weather patterns after the implementation of the rotavirus vaccine. Similar findings have been reported elsewhere.[10]

This study was a retrospective review and therefore had some limitations. The aforementioned public health initiatives may have had minor impacts that occurred at other time points or masked by the large impact of rotavirus vaccination, and therefore not identified in the CPA. Additionally, improvements to the PMTCT and ART programmes may have impacted on diarrhoeal disease hospitalisation in HIV-infected and HIV-exposed children; however, we did not have data on HIV-status to determine the impact of these changes. We were unable to obtain all registries to verify the captured statistics because registration books were destroyed or misplaced over the years; however, statistics were consistently captured by the same senior medical staff over the entire study period.

In conclusion, rotavirus vaccination has likely made this significant decline to the burden of diarrhoeal disease hospitalisations to a SSW in this setting, and questions the relevance of such units in an era of widespread rotavirus vaccination.

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Figures and Tables

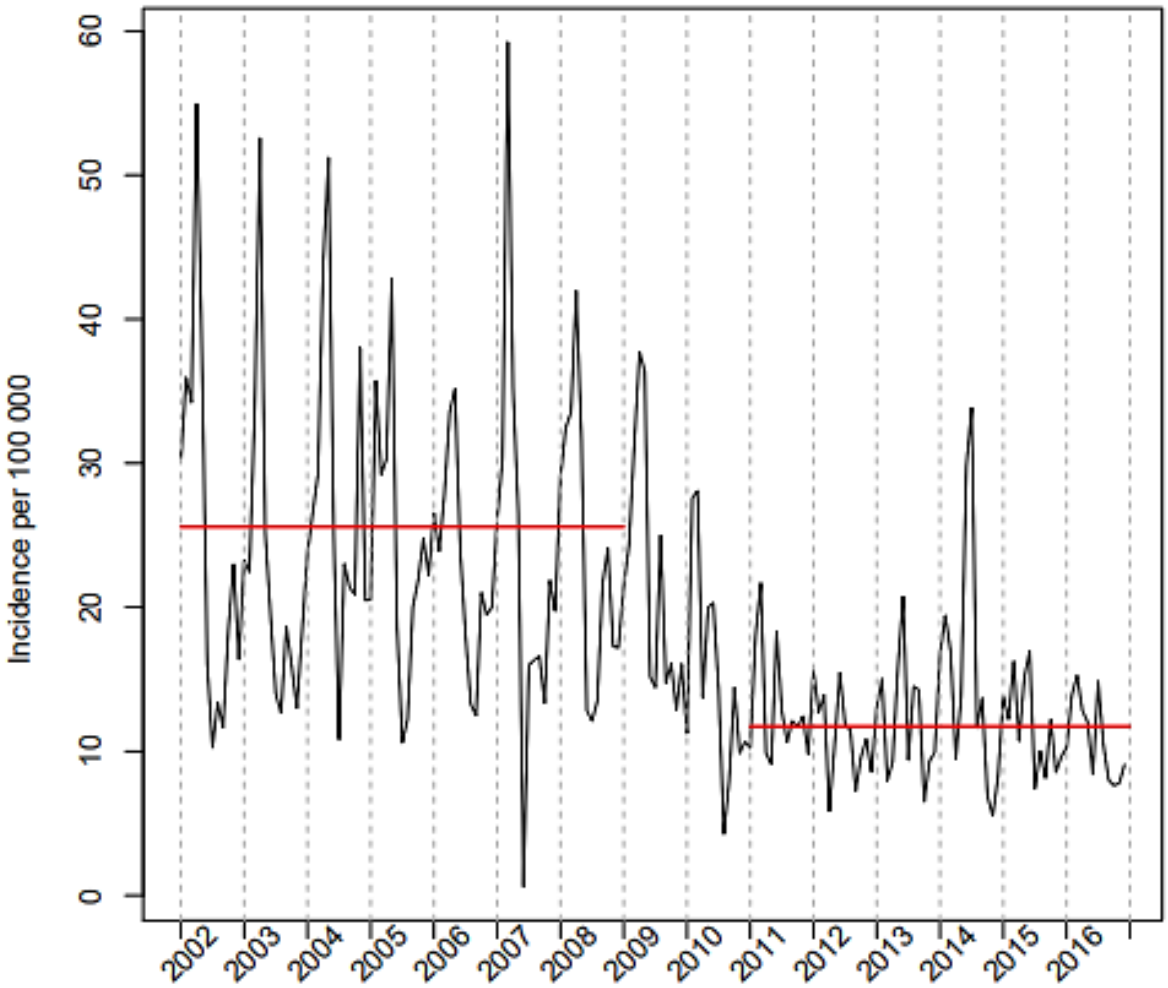

Figure 1: Monthly incidence (per 100 000) of diarrhoeal disease hospitalisations to the short stay ward

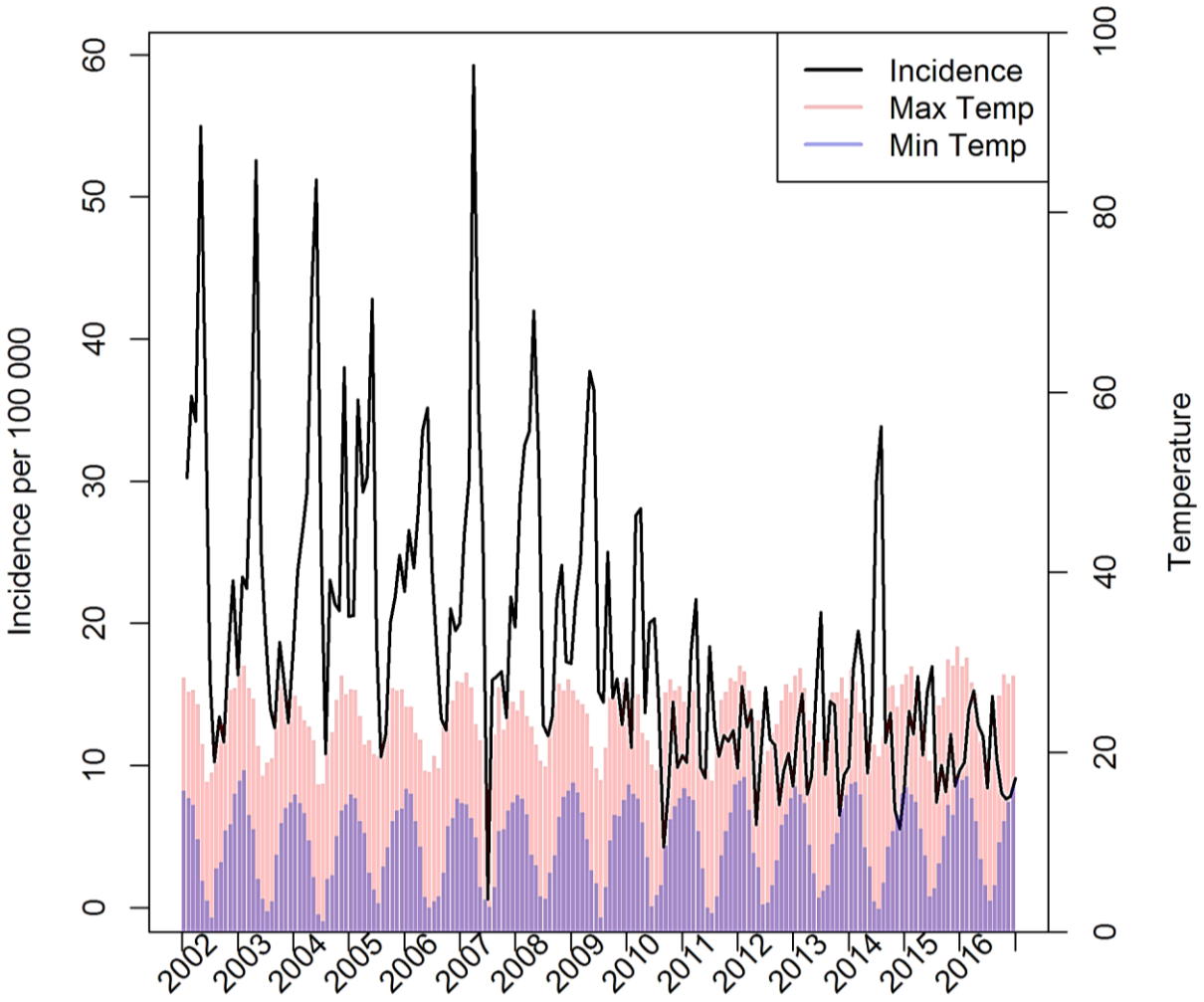

Figure 2: Monthly incidence (per 100 000) of diarrhoeal disease hospitalisations to the short stay ward, with maximum and minimum temperature (ºC)

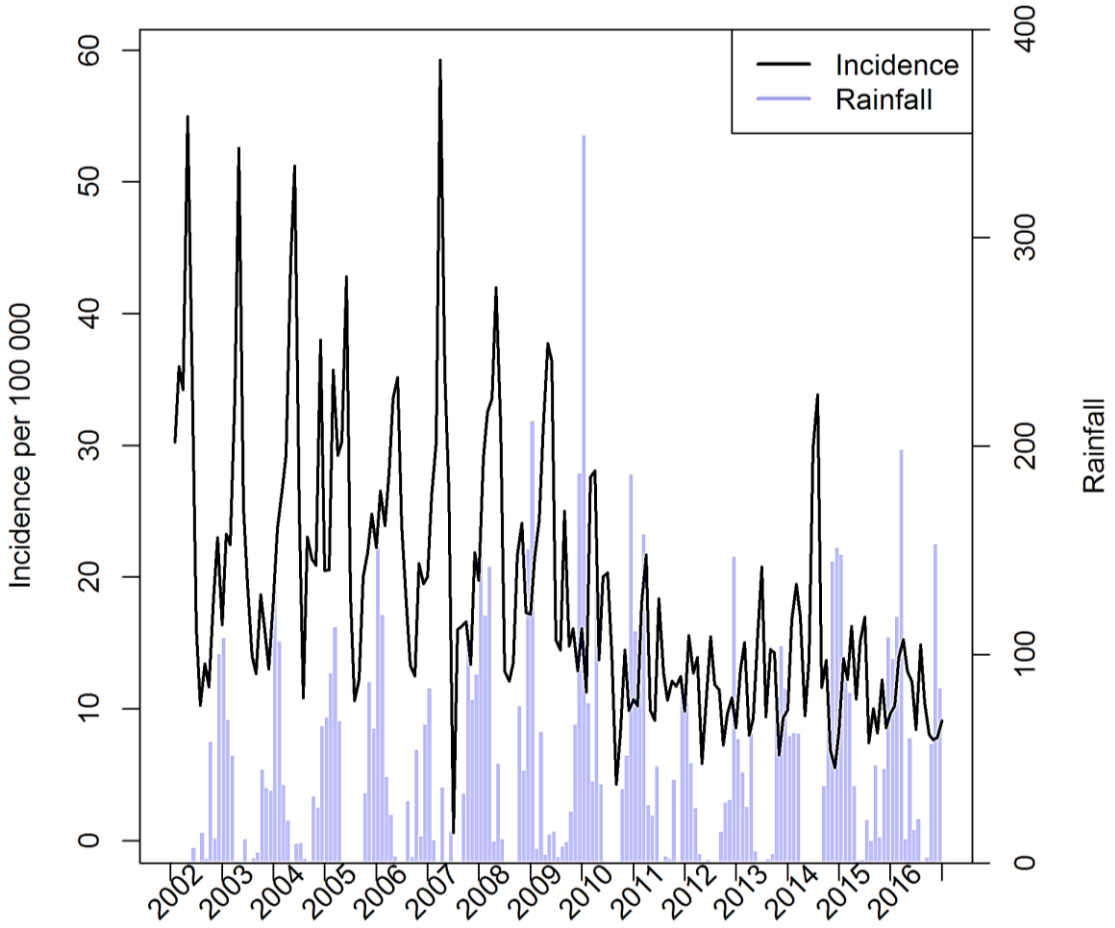

Figure 3: Monthly incidence (per 100 000) of diarrhoeal disease hospitalisations to the short stay ward, with rainfall patterns (mL)

Supplementary Table 1: Public Health initiatives introduced into South Africa over the study period that may have influenced diarrhoeal disease trends

Year	Public health initiatives/strategies
1998	Introduction of Integrated Management of Childhood Illness (IMCI) programme
2000	HIV/AIDS life skills education introduced in schools
2001	Prevention of Mother to Child Transmission (PMTCT) pilot sites established – Nevirapine given to women in labour and to neonates Breastfeeding discouraged in place of formula Water Sanitation and Hygiene (WASH) initiative Vitamin A supplementation added to the Expanded Programme on Immunisation (EPI)
2004	Free antiretroviral therapy (ART) to children with CD4+ counts of <15% in >18 months old, or less than 20% in <18months old and /or modified WHO stage 3 and 4 disease Oral rehydration therapy introduced
2008	Change to the PMTCT programme -Zidovudine and Nevirapine from 28 weeks of pregnancy, Nevirapine during labour and to the neonate (72hrs)
2009	ROTAVIRUS vaccine introduced into the EPI
2010	ART to all children less than 1year of age and all pregnant women
2011	Breastfeeding policy revised and exclusive breastfeeding recommended, and actively promoted until six-months of age regardless of HIV exposure status, and free formula phased out for HIV-exposed babies
2013	ART for pregnant and breastfeeding mothers regardless of CD4+ count, daily nevirapine throughout breastfeeding, and ART to all children less than 5 years of age.
2014	Birth PCR test for HIV-exposed infants.
2015	Test and treat approach and pre-exposure prophylaxis ART for high risk populations.

Supplementary Table 2: Demographic characteristics of children hospitalised to the short stay ward (SSW) with diarrhoeal disease

Year	Number seen at PMEAD*	Number with diarrhoea seen at PMEAD	Hospitalised in SSW	Receiving IVF† in SSW	Demised in SSW
2002	41 032	5 120 (12.5%)	1 475 (28.8%)	418 (28.3%)	1
2003	41 973	‡	1333	419 (31.4%)	0
2004	42 040	5 579 (13.3%)	1 713 (30.7%)	678 (39.6%)	1
2005	36 404	5 406 (14.9%)	1 476 (23.9%)	562 (38.1%)	1
2006	37 344	4 895 (13.1%)	1 419 (29.0%)	472 (33.4%)	1
2007	34 883	4 926 (14.1%)	1 379 (28.0%)	341 (24.7%)	0
2008	38 882	5 443 (14.0%)	1 435 (26.4%)	570 (39.7%)	1
2009	41 372	5 014 (12.1%)	1 360 (27.1%)	365 (26.9%)	0
2010	30 244	3 417 (11.3%)	937 (27.4%)	113 (12.2%)	0
2011	29 609	2 579 (8.7%)	811 (31.4%)	239 (29.5%)	0
2012	25 398	1 901 (7.5%)	660 (34.7%)	149 (22.6%)	0
2013	26 491	2 538 (9.6%)	724 (28.5%)	163 (22.5%)	0
2014	28 119	2 566 (9.1%)	938 (36.6%)	182 (19.4%)	1
2015	25 835	2 159 (8.4%)	723 (33.5%)	153 (21.2%)	0
2016	23 886	2 174 (9.1%)	674 (31.0%)	92 (13.6%)	0
Overall	**503 512**	**53 717 (11.6%)**§	**17 057 (29.3%)**§	**4 916 (28.8%)**	**6 (0.04%)**

*paediatric medical emergency and ambulatory department, †intravenous fluids, ‡data missing, § 2003 values were excluded from the calculation

MANUSCRIPT 2

THE BURDEN OF ACUTE DIARRHOEAL DISEASE IN YOUNG HOSPITALISED URBAN SOUTH AFRICAN CHILDREN FIVE YEARS AFTER ROTAVIRUS VACCINE INTRODUCTION: A RETROSPECTIVE DESCRIPTIVE STUDY

Abstract

Background

Diarrhoeal disease is a leading cause of childhood morbidity and mortality worldwide. Multiple interventions, including rotavirus vaccination to infants since 2009, have reduced the incidence of diarrhoeal disease in South African children. Our study aimed to determine the burden of diarrhoeal disease five years after rotavirus vaccine introduction at a tertiary-level hospital.

Methods

A retrospective review of a discharge summary database of children less than five years of age hospitalised with acute diarrhoeal illness from 2015 to 2016 at the Chris Hani Baragwanath Academic Hospital.

Results

Diarrhoeal disease accounted for 14.8% of hospital admissions. The incidence (per 100,000 population) was 675.8 (95%CI: 638.8-714.3) in 2015 and 612.2 (95%CI: 577.0-648.9) in 2016. The case fatality ratio was 2.9% over the study period. The median age at diagnosis was 12 months (IQR: 6.2-21.4) and 50.4% of cases occurred during infancy. A third of cases were underweight and/or stunted. In a multivariable analysis using logistic regression, the adjusted

odds ratio (aOR) for death was higher in children with an associated acute lower respiratory tract infection (aOR: 3.7, 95%CI: 1.2-11.5; p=0.021), HIV-infection (aOR: 9.1, 95%CI: 2.6-31.6; p=0.001), and an age of less than six months (aOR: 6.9, 95%CI: 2.1-22.9; p=0.002).

Conclusions

Sustained reductions in diarrhoeal disease incidence were observed five years post rotavirus vaccine implementation. In children hospitalised with an acute diarrhoeal illness, an increased risk of mortality occurs in young infants, children that are HIV-infected, and those with an associated acute lower respiratory tract infection.

Introduction

Diarrhoea is a leading cause of childhood mortality and morbidity worldwide (1). In 2015, diarrhoeal deaths accounted for 8.6% of under-5 mortality, and an estimated 957.5 million cases occurred in children less than five years of age globally (1); additionally, the burden of diarrhoeal disease is disproportionately higher in low and low-middle income countries (2, 3, 4, 5). In South Africa, diarrhoeal disease is the second leading cause of premature death after HIV/AIDS (6). Children less than two years of age, those who are malnourished, and HIV-infected are at a higher risk of morbidity and mortality due to diarrhoeal disease (1, 2, 4, 7).

Rotavirus infection is the leading cause of severe diarrhoea in young children, accounting for approximately 29.3% of diarrhoeal deaths in children less than five years, globally (1). The rotavirus vaccine was introduced at 6 and 14 weeks into the South African Expanded Programme on Immunisation (EPI) in 2009 (8). The coverage of the second dose of rotavirus vaccine has been above 85% in South Africa since 2011 (9). Since the introduction of the rotavirus vaccine, studies have shown significant reductions in severe rotavirus-associated diarrhoea, and more importantly, a 38% decline in all-cause diarrhoeal illness in both high income and low-middle income countries (10). Studies in South Africa have reported a 33-57% reduction in all-cause diarrhoea (11, 12, 13). Five years into the era of high rotavirus vaccine coverage (>85%), we determined whether the reductions in acute diarrhoeal disease burden were maintained in young children hospitalised with a diarrhoeal illness; additionally, we determined predictors of mortality in these children.

Methods

This was a retrospective review of a discharge summary database of children less than five years of age hospitalised with an acute diarrhoeal illness at the Chris Hani Baragwanath Academic Hospital (CHBAH) from January 2015 to December 2016. Until April 2014, when the primary-level Bheki Mlangeni District Hospital (BMDH) became operational, CHBAH was the only state funded paediatric hospital that served the population of Soweto and neighbouring suburbs. The under-five population served by CHBAH was estimated at 183 497 in 2015 and 183 764 in 2016 by Statistics South Africa (14). This population comprises of mainly black Africans from low to middle income households (15).

The standard-of-care for the management of children presenting with diarrhoea in this hospital has remained unchanged over the study period. Children seen at primary health care clinics with diarrhoea are managed according to the Integrated Management of Childhood Illness (IMCI) protocol, which includes use of oral rehydration solution (ORS) and zinc supplementation. The national rate of use of ORS and Zinc is however only 51% and 37% respectively, with only 28% of under-fives with diarrhoea receiving both (16). Those children with dehydration and/or those who do not tolerate oral rehydration at the primary health care clinics are referred to CHBAH or BMDH for further management and/or hospitalisation. BMDH is however, a primary level hospital and there are only 32 paediatric beds and with only a third bed occupancy (17). In addition BMDH refers all complicated cases to CHBAH. In addition to the clinic and BMDH referrals, some children with diarrhoeal disease may present directly to CHBAH. The degree of dehydration, as assessed by the attending physician is the main criteria used to decide whether the child will be hospitalised; the hospital protocol describes the degree of dehydration as: (1) mild dehydration - the child is alert with few clinical signs of dehydration: thirst, drinks eagerly and has a normal to decreased urine output (as reported by the mother), (2) moderate dehydration - the child has two of the following

signs: sunken eyes, depressed anterior fontanelle, absent tears, thirst/ drinks eagerly, restless/ irritable, a slow skin pinch but <2 seconds and sticky mucosa, and (3) severe dehydration - the child has worsening of symptoms, reduced level of consciousness, markedly reduced urine output and may be in shock with barely palpable pulses, capillary refill time >=3 seconds, cold mottled limbs. Children with moderate or severe dehydration are hospitalised.

The provision of anti-retroviral therapy (ART) and the prevention of mother to child transmission (PMTCT) programme in South Africa has led to a reduction in HIV transmission rates from 3.6% in 2011 to 1.5% in 2016 (18). Amongst women attending antenatal clinics, however, the prevalence of HIV has remained at approximately 30% and therefore almost a third of newborns in Soweto are HIV-exposed (18).

Statistical analysis

Data was extracted from a discharge summary database captured by the Respiratory and Meningeal Pathogens Research Unit (RMPRU). Children less than five years of age with any ICD 10 (A00-A09) discharge diagnosis of a diarrhoeal illness were included in the study. We excluded a discharge diagnosis of nosocomial diarrhoea, chronic non-infective gastroenteritis, and other specified non-infective gastroenteritis and/or colitis. Data was stratified by age, gender, HIV status and presence of a co-existing acute lower respiratory tract infection (aLRTI) (ICD10 codes: B25.0, B20.6, J13-J18, J21 and J22).

The HIV status of cases was confirmed using RMPRU database and National Health Laboratory Service TrakCare^{TM} system. HIV-exposure was defined as children born to HIV-infected women with either a negative HIV PCR result, or if the HIV PCR test result was unavailable.

The incidence was calculated as the number of diarrhoea cases per 100,000 population estimates (14). Case fatality rates were reported as a proportion of the total number of diarrhoeal cases. Anthropometry software (WHO AnthroPlus, version 1.0.4) was used to calculate weight-for-age and length/ height-for-age Z-Scores (19). The Mann-Whitney test was used to compare continuous variables, and the Chi-squared or Fisher's exact test was used to compare categorical variables. A p-value <0.05 was considered statistically significant. Variables which were found to have a p-value <0.20 in a univariate analysis were then included into a multivariable logistic regression analysis, and adjusted odds ratios and 95% confidence interval were reported.

STATA version 13.0 and STATISTICA version 13.2 were employed for statistical analysis. Permission to conduct the study was obtained from The University of the Witwatersrand Human Research Ethics Committee (M170501).

Results

Over the two-year period, 15 942 children less than five years were admitted to the paediatric wards at CHBAH; of these, 2365 (14.8%) had diarrhoeal disease (Figure 1). Approximately 50.4% (n=1193) of all diarrhoeal hospitalisation occurred in infants (Table 1). More than a third of the study population were underweight for their age (826/2260 =36.5%) and/or stunted (629/1801=34.9%). The median length of hospitalisation was 2 days (IQR: 1-5) and the case fatality ratio was 2.9% (n=68). The HIV status was known in 2 015 (85.2%) of children, of these, 147 (7.4%) were HIV-infected. The yearly incidence of diarrhoeal disease was 675.8 per 100 000 (95%CI: 638.8-714.3) in 2015 and 612.2 per 100 000 (95%CI: 577.0-648.9) in 2016. Most of the admissions (58.0%) occurred during the autumn and winter seasons (from May to August) (Figure 2). Fewer admissions (n=450; 19.0%) were observed during spring (September to November).

Children who died were younger (median age: 8.6 months; IQR: 3.6-15.1) than those who were discharged (12.2 months; IQR: 6.3-22.0; p= 0.002) (Table 2). Children less than six months of age were 6.9 (95%CI: 2.1-22.9) times more likely to die from diarrhoeal illness than older children (p<0.002). Two thirds of children who demised were underweight (41/62; 66.1%) and/or stunted (13/19; 68.4%), but these anthropometric parameters were not significantly different when compared to survivors. Children diagnosed with a co-existing aLRTI had 3.7 (95% CI: 1.2-11.5; p=0.021) fold greater odds of death. HIV-infected children had an increased odds of death (adjusted odds ratio: 9.1, 95% CI: 2.6-31.6; p=0.001) (Table 2), but HIV-exposed (HE) infants did not (p=0.398).

We further compared clinical characteristics between HE and HIV-unexposed (HU) infants less than six months of age because these infants were at highest risk of diarrhoeal disease. Of 578 infants less than 6 months of age, 45 (7.8%) were HIV-infected, 211 (36.5%) were HE,

293 (50.7%) were HU, and 29 (5.0%) were unknown. The median weight-for-age (WAZ) and height-for-age (HAZ) z-scores were lower in HE compared to HU infants; $p<0.001$ and $p=0.046$ respectively (Supplementary Table 1). HE infants, however, did not have a more prolonged hospital stay or more co-existent aLRTI compared to HU infants.

Co-existing aLRTI was diagnosed in 405 (17.1%) children with diarrhoeal illness (Supplementary Table 2). Children with aLRTI had a longer duration of hospitalisation: median stay of 3 (IQR: 1-7) vs. 1 (IQR: 1-4) day, $p <0.001$. Children with aLRTI were significantly more underweight and stunted, $p= 0.010$ and 0.030 respectively. Overall, HIV co-infection was commoner in children with an aLRTI (10.9% vs. 5.3%, $p <0.001$).

Discussion

Five years into an era of high-coverage rotavirus vaccination, acute diarrhoeal disease hospitalisation is a major cause of hospital admissions (14.8% of total admissions) in children less than five years of age at this tertiary hospital. The incidence estimates for 2016 (612 per 100,000) are however, 58% lower than the 2006-2008 pre-vaccine rates (1470 per 100,000) and, 37% lower than reported in 2010 (970 per 100,000), the year after rotavirus vaccine introduction (13). Nonetheless, despite the declining trends, the incidence of diarrhoeal disease is two-fold higher than in high-income countries (13, 20). In our setting, the overall case fatality ratio from acute diarrhoeal cases (2.9%) was lower than the pre-rotavirus vaccine rate (3.5%) but higher than comparative global and South African estimates (2.0% and 2.2% respectively) over the same period (2, 7, 21).

Rotavirus vaccination, together with other interventions (e.g. ORS, Zinc supplementation, improved sanitation, access to improved water, upscaling of PMTCT and ART), are likely to have reduced the burden of disease in our setting. Nonetheless, in children with diarrhoeal disease, those who are young, HIV-infected and those with a co-existing aLRTI have an increased risk of death; these findings are similar to reports from other low and low-middle income settings (5). In non-severely malnourished Kenyan children with diarrhoeal disease, those who were younger or had abnormal respiratory signs were found to have a 1.7 and 3.6 fold higher risk of death respectively (22).

Approximately a third of our patients were underweight and/or stunted, which is higher than the rates observed in other South African studies (23). In our study, however, we did not have access to the pre-illness weight and therefore some children may have been misclassified as being underweight. More importantly, however, a third were also stunted and two thirds of

deaths occurred in children who were stunted, and these findings are consistent with reports describing increased mortality rates in malnourished children with diarrhoea (24-26).

This rate of HIV-infection in our study was higher than the national HIV prevalence rate in children less than 5 years (27), and most likely represents a referral bias to a tertiary care hospital. Historically, HIV-infection increases the risk of death from diarrhoea eleven-fold, and despite improved access to ART in our setting, we found a 9.1 increased odds of death in HIV-infected children (7, 28). We were unable to correlate HIV viral loads and CD4+ lymphocyte counts in HIV-infected children with acute diarrhoeal disease – a study limitation – but this is an important area for further research. Of the children less than six months of age, over a third were HE, an observation consistent with antenatal HIV prevalence rates (18). An increased risk of mortality and morbidity is reported in HE compared to HU infants (29, 30), and a number of reasons are postulated to account for the increased vulnerability in HE infants, including a lack of protective maternal antibody transfer to foetus, and an altered immune system in the infant (30, 31). In our study, however, there were no significant differences in terms of length of stay (LOS), death, age at admission, and co-existing aLRTI between the HE and HU infants. This observation could be attributed to the improved maternal access to early antiretroviral therapy (> 95% of pregnant women with HIV accessed antiretroviral treatment in 2016) (32).

Children with co-existing aLRTI were 3.7 (95% CI 1.2-11.5) times more likely to die (Table 2 and Supplementary Table 2). These children were younger ($p=0.002$) and had longer length of stay ($p<0.001$) than those without an aLRTI. Children who were HIV-infected were also more likely to have an aLRTI. Several reports from low and middle-income countries report an increase in aLRTI incidence with or following a diarrhoeal illness (33, 34), possibly because

diarrhoeal disease and LRTI share common risk factors such as immunodeficiency, HIV-infection, malnutrition, and young age.

The vast majority of admissions occurred in the autumn-winter months with fewer admissions occurring in spring. Previous South African and international studies confirm winter peaks in diarrhoeal hospitalisations in children less than five years of age (13, 20, 35, 36). These winter peaks were more pronounced in the pre-rotavirus vaccine era while in the post vaccine era, the diarrhoeal disease season appears to start later with less pronounced peaks (13, 20).

This was a retrospective study and had several limitations. We were unable to determine the aetiological agents responsible for acute diarrhoeal disease because stool samples are not routinely collected. The percentage of underweight children may have been over-estimated because pre-illness and post-recovery (i.e. discharge) weights are not routinely recorded; nonetheless, the large proportion of stunting indicates that malnutrition is a significant problem in our study population. The duration and use of antiretroviral therapy, HIV viral loads, level of maternal education, vaccination status and breastfeeding practices are not recorded in the database.

In conclusion, diarrhoeal disease is a significant cause of morbidity and mortality in our setting and measures aimed at preventing diarrhoeal illnesses should continue. Our study indicates higher mortality rates in children hospitalised with diarrhoea who are less than six months of age, HIV-infected and have co-existing aLRTI: decreasing the mortality rates in these high-risk children should be the focus of further studies.

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Figures and Tables

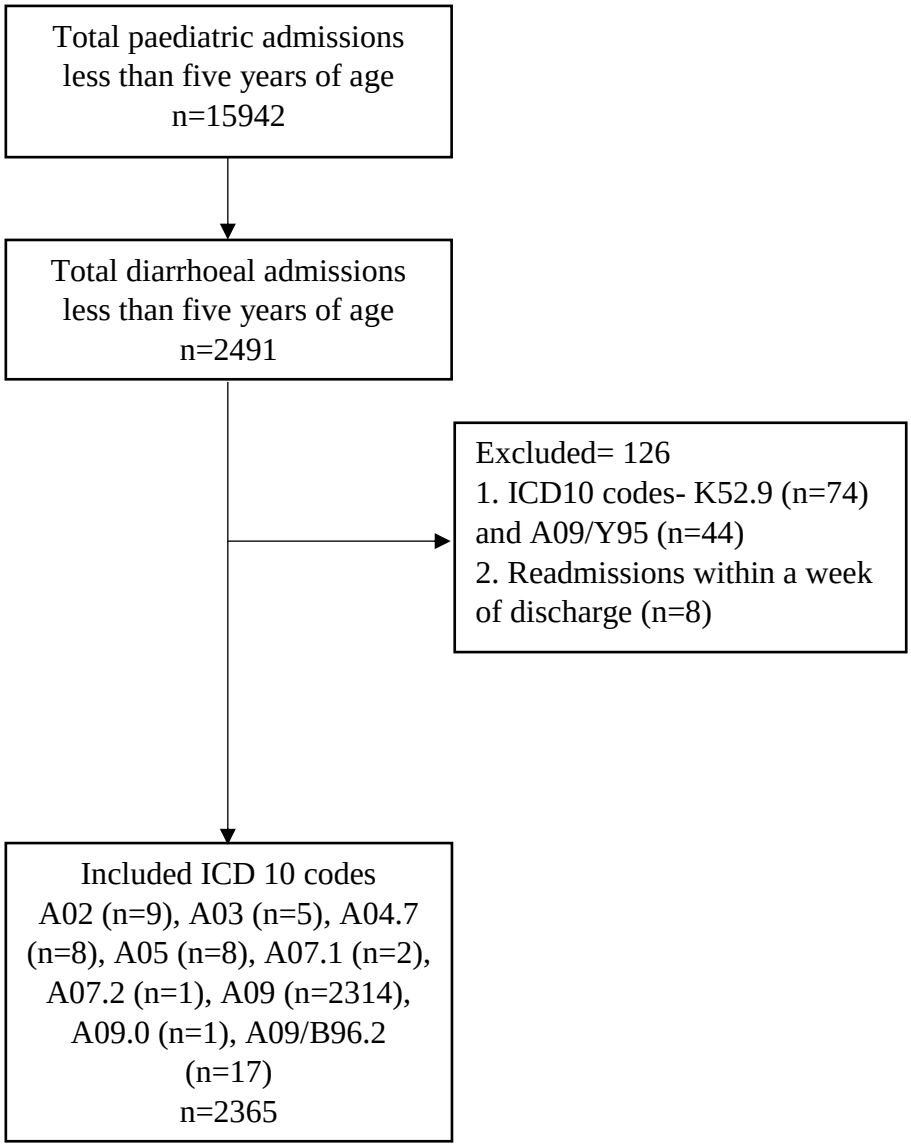

Figure 1: Flow diagram of children hospitalised with diarrhoea

Footnote detailing ICD10 codes: A02- other salmonella infections, A03-shigellosis, A04.7-enterocolitis due to *clostridium difficile*, A05- other bacterial food-borne intoxication, not elsewhere specified, A07.1-giardiasis (lamliasis), A07.2- cryptosporidiosis, A09- diarrhoea and gastroenteritis of presumed infectious origin, A09.0-, A09/B96.2- diarrhoea and gastroenteritis due to *Escherichia Coli*, K52.8- other specified non-infective gastroenteritis and colitis, K52.9- non-infective gastroenteritis and colitis unspecified, A09/Y95- nosocomial infection.

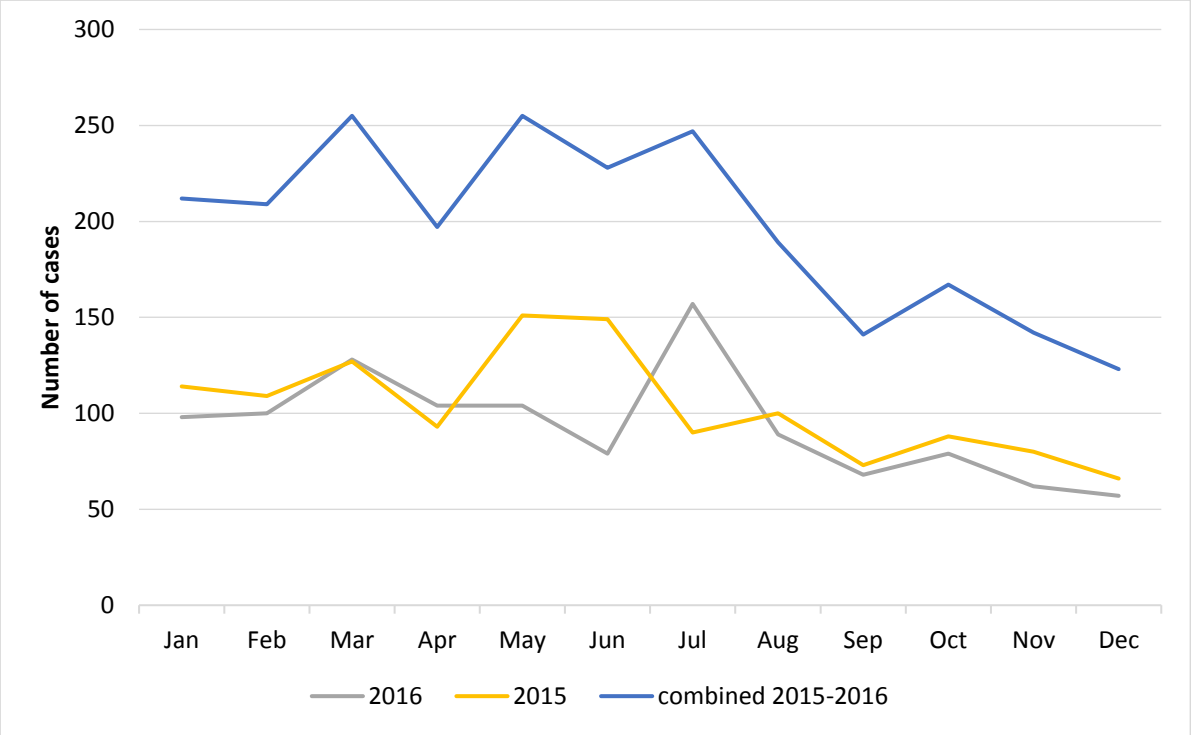

Figure 2: Seasonal pattern of diarrhoeal disease hospitalisations over the study period

Table 1: Demographic characteristics of children (n= 2365) hospitalised with diarrhoeal illness

Variables	**Total n=2365 (%)**
Male gender	1327 (56.1)
Age in months	
<6	578 (24.4)
6-<12	615 (26.0)
12-<24	653 (27.6)
24-<60	519 (21.9)
Median length of stay (IQR)	2 (1-5)
Outcomes	
Discharged home	2260 (95.6)
Death in hospital	68 (2.9)
Transferred to other hospital	35 (1.5)
Refusal of hospital treatment	2 (0.1)
Anthropometry[1]	
Median weight-for-age Z-score (IQR)	-1.41 (-2.56 to -0.44)
Median length/ height-for-age Z-score (IQR)	-1.33 (-2.57 to -0.18)
Associated LRTI	405 (17.1)
HIV status	
<18 months old (n=1621)	
Exposed[2]	543 (33.5)
Unexposed	805 (49.7)
Infected	115 (7.1)
Unknown	158 (9.7)
>18 months old (n=744)	
Uninfected[3]	520 (69.9)
Infected	32 (4.3)
Unknown	192 (25.8)

[1]Weight and length values were available for 2260 and 1809 patients respectively. [2]Includes HIV-exposed infants whose PCR result was unavailable/unknown (n=97). [3]Includes children whose mothers tested negative and therefore the child was presumed negative (n=242), and those who tested ELISA-negative (n=278).

Table 2: Predictors of mortality in children hospitalised with diarrhoeal illness

Variable	Demised n=68 (%)	Discharged n=2260 (%)	p-value[1]	aOR[2] (95% CI)	p-value[2]
Male gender	37 (54.4)	1271 (56.2)	0.765		
Age <6 months	29 (42.6)	532 (23.5)	<0.001	6.9 (2.1-22.9)	0.002
Median length of stay (IQR)	1 (0-5)	2 (1-4)	0.001	0.9 (0.8-1.0)	0.134
Underweight[3]	41 (66.1)	763 (35.3)	<0.001	3.3 (0.7-14.8)	0.118
Stunted[4]	13 (68.4)	604 (34.5)	0.002	1.4 (0.4-5.1)	0.604
Associated aLRTI[5]	20 (30.9)	378 (17.1)	0.006	3.7 (1.2-11.5)	0.021
HIV-Infected	17 (25.0)	125 (5.5)	<0.001	9.1 (2.6-31.6)	0.001

[1]p-value for univariate analysis, [2]Only variables which with a p-value <0.20 in the univariate analysis were included in the regression model, [3]defined as a weight-for-age z-score <-2, [4]defined as a length/height-for-age z-score <-2, [5]aLRTI- acute lower respiratory tract infection.

Supplementary Table 1: Demographic characteristics of children under six months of age with diarrhoeal disease stratified by HIV exposure status

Variable	HIV-exposed[1] n=211 (%)	HIV-unexposed n=293 (%)	p-value
Male gender	122 (57.8)	154 (52.6)	0.242
Median age (IQR)	3.3 (1.87-4.7)	3.4 (1.9-5.0)	0.418
Median length of stay (IQR)	4 (1-7)	4 (2-7)	0.910
Outcome			
Discharged home	196 (92.9)	272 (92.8)	0.740
Death in hospital	10 (4.7)	12 (4.1)	
Transferred to other hospital	5 (2.4)	9 (3.1)	
Anthropometry			
Weight/age Z-score median (IQR)[2]	-2.40 (-3.66 to -1.18)	-1.58 (-3.01 to -0.49)	<0.001
Length/age Z-score median(IQR)[3]	-1.93 (-3.63 to -0.48)	-1.41 (-3.03 to -0.28)	0.046
Associated with aLRTI[4]	41 (19.8)	61 (21.0)	0.702

[1]Excludes HIV-infected infants, [2]weight measurements were available for 202 (95.7%) HIV-exposed and 278 (94.9%) HIV-unexposed infants; [3]length measurements were available for 146 (69.2%) HIV-exposed and 213 (72.7%) HIV-unexposed infants, [4]aLRTI- acute lower respiratory tract infection.

Supplementary Table 2: Demographics of children with diarrhoea and associated acute Lower Respiratory Tract Infection (aLRTI)

Variable	aLRTI n=405 (%)	no aLRTI n=1960 (%)	p-value
Male gender	230 (56.8)	1097 (56.0)	0.762
Length of stay, median (IQR)	3 (1-7)	1 (1-4)	<0.001
Age			
<6 months	124 (30.6)	454 (23.2)	0.002
Anthropometry[1]			
Weight/age Z-score median (IQR)	-1.37 (-2.49 to -0.41)	-1.60 (-2.99 to -0.55)	0.010
Length/age Z-score median(IQR)	-1.28 (-2.47 to -0.16)	-1.50 (-2.88 to -0.28)	0.030
Outcome			
Death in hospital	20 (5.0)	48 (2.4)	0.006
HIV-infected	44 (10.9%)	103 (5.3%)	<0.001

[1]weight and length measurements were available for 396 (97.8%) and 315 (77.8%) for those with aLRTI, and weight and length measurements were available for 1864 (95.1%) and 1486 (75.8%) for those without LRTI, respectively.

APPENDIX 1, Plagiarism Declaration and Turnitin Report

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I, Euphrasia Makgatho (Student number: 1727748) am a student registered for the degree of

Masters of Medicine (Paediatrics) in the academic year 2016.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.

- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.

- I have followed the required conventions in referencing the thoughts and ideas of others.

- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.

- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

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APPENDIX 2, Ethics Clearance Certificate

R14/49 Dr Euphrasia Makgatho

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170501

NAME: (Principal Investigator)	Dr Euphrasia Makgatho
DEPARTMENT:	Paediatrics Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Trends in Diarrhoeal Disease Hospitalisations to Short Stay Paediatric Ward at the Chris Hani Baragwanath Hospital from 2002-2016
DATE CONSIDERED:	26/05/2017
DECISION:	Approved unconditionally
CONDITIONS:	Title Change (03/11/2017)
SUPERVISOR:	Dr Ziyaad Dangor and Dr Preeteeben Vallabh
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	26/06/2017

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 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the conditions under which I am/we are authorised 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 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 review 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 06/11/2017

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 3, MMed Research Protocol

TITLE: TRENDS IN DIARRHOEAL DISEASE HOSPITALISATIONS TO A SHORT STAY PAEDIATRIC WARD AT THE CHRIS HANI BARAGWANATH HOSPITAL FROM 2002 TO 2016

STUDENT	Dr Euphrasia Makgatho
STUDENT NUMBER	1727748
SUPERVISORS	Dr Ziyaad Dangor Dr Preeteeben Vallabh
COLLABORATORS	Prof Sanjay Lala Dr Firuzan Patel Dr Michelle Groome

Acronyms

ART	Antiretroviral Therapy
ARV	Antiretroviral
CHBAH	Chris Hani Baragwanath Academic Hospital
EPI	Expanded Programme on Immunisation
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
IMCI	Integrated Management of Childhood Illness
MEAD	Medical Emergency and Ambulatory Department
PCR	Polymerase Chain Reaction
PMTCT	Prevention of Mother-To-Child Transmission
RMPRU	Respiratory and Meningeal Pathogens Research Unit
SSW	Short Stay Ward
WASH	Water, Sanitation and Hygiene
WHO	World Health Organisation

Introduction and background

Diarrhoea is a leading cause of childhood mortality and morbidity accounting for 9% of the deaths worldwide (which amounts to 525 000 deaths) in 2015 (1), and over 1.7 billion cases estimated annually in children less than 5 years (2). The burden of diarrhoea is higher in African countries, including South Africa (3, 4). In 2015 more than 50% of global diarrhoeal deaths occurred in Africa (5, 6). South Africa lost 3600 children under 5 years of age (8.5% of total under five deaths) due to diarrhoea in 2015 (5). Diarrhoea has also been associated with malnutrition, stunting and thus reduced cognitive function and impaired school performance (7) and is a risk factor for pneumonia (8).

Despite the significant reduction in mortality (more than 50%) and reduction in hospitalisations due to severe diarrhoeal disease (after rotavirus vaccine introduction), the overall incidence in diarrhoeal disease has remained largely unchanged (8). For over three decades, an average of three episodes per child per year has been recorded worldwide (8). The South African incidence of diarrhoea is 3.4 episodes per child per year (9), with studies reporting an increase in prevalence over the last few years (9). This may be due to a limited effect of rotavirus vaccination on milder forms of diarrhoea. Trends of diarrhoeal disease incidence/prevalence have been inconsistent. In a pre-vaccine era, a study conducted in the Democratic Republic of Congo, in spite of poor living conditions, reported a reduction of community diarrhoea from 22% to 16% (10). A study conducted in Ghana, however, showed an increase in the prevalence from 3.5% in 2008 to 4.5% in 2012 (11).

The World Health Organisation (WHO) defines diarrhoea as a passage of three or more loose or watery stools per day or more frequent passage than is normal for the individual. Infective diarrhoea is caused by viruses, bacteria and protozoa (12). In children, rotavirus is the leading cause of diarrhoea, accounting for about 40% of hospitalisations and 37% of deaths due

diarrhoea worldwide and nearly all children would have been infected by rotavirus by their 5th birthday (13). The incidence of diarrhoeal disease varies with age. Higher incidence rates and mortality rates are seen in children under the age of two, and also in HIV infected children (8, 14). Diarrhoeal incidence is seasonal (14, 15), in South Africa peaks occur in summer for bacterial infection and in winter for rotavirus infection (16, 17). An increase in ambient temperature has also been associated with an increase in diarrhoeal disease incidence in recent years (18).

Interventions/strategies that may have influenced the burden of diarrhoeal illness in South Africa (Protocol Appendix 1)

Rotavirus vaccination was introduced to the South African Expanded Programme on Immunisation (EPI) in 2009. Vaccine effectiveness of about 57% against rotavirus confirmed diarrhoea and 30%-57%against all cause diarrhoea has been reported in South Africa (19, 20). Effectiveness was seen more in children less than 2 years of age. The studies however only focused on children less than 5 years of age.

The Human Immunodeficiency Virus, (HIV) prevalence rate in South Africa is high (12.8%) (21). HIV increases diarrhoeal mortality 11-fold (22). In South Africa, HIV positive children showed a five times greater chance of being hospitalised with diarrhoea (14). The Anti-Retroviral therapy (ART) and the prevention of mother to child transmission of HIV (PMTCT) programme in South Africa reduced the prevalence of HIV-infected children from 5% in 2006 to 3.8 % in 2013 (23). Mother-to-child transmission rates fell from 3.6% in 2011 to 1.5% in 2016 (21), and the proportion of children initiated on ART has increased from 54% in 2009 to 75% in 2014 (23).

Breastfeeding recommendations have changed, especially for HIV-exposed babies. Since 2011 exclusive breastfeeding was recommended for all infants under 6 months in South Africa. Breastfeeding reduces the incidence of diarrhoeal disease by half (1). The rate of exclusive breastfeeding, however, was only 54% at 4-8 weeks and 8% at 6 months in 2012 (24).

The Water Sanitation and Hygiene (WASH) initiative was launched in 2001 and advocates water and sanitation for all. According to the StatsSA, in 2016 89.9% of households had access to clean water (25). Handwashing with soap is reported to reduce the incidence of diarrhoeal illness by approximately 40% (1).

The Integrated Management of Childhood Illness (IMCI) program, a WHO and UNICEF initiative, was launched in 1998 in various primary health care facilities in South Africa, and focuses on assessing the level of dehydration and instituting appropriate management and referral. The use of oral rehydration solution (ORS) was recommended by the WHO in 2004, but only 40% of children with diarrhoea receive ORS in Sub-Saharan Africa (1).

Vitamin A supplementation leads to a 24% reduction in mortality and 15% reduction in diarrhoeal illness (1). Since 2001 Vitamin A supplementation is standard of care practice at 6-months of age and coverage was 52% in 2016 (26). Zinc supplementation is not routine in the community management of diarrhoeal illness even though studies have reported a significant reduction in mortality (1).

Justification of the study

This study is a retrospective review of patient data at the Paediatric Medical Emergency and Ambulatory Department (PMEAD) and Short Stay Ward (SSW) at Chris Hani Baragwanath Academic Hospital (CHBAH). The CHBAH is the third largest hospital in the world with 164 general paediatric beds and 40 short stay paediatric beds (27). The CHBAH serves population of Soweto (a low to middle income population) (28) and the southern and western regions of Johannesburg. Until April 2014, when Bheki Mlangeni District Hospital became operational, CHBAH was the only paediatric hospital in Soweto.

Although the burden of severe diarrhoea and hospitalisations due to severe diarrhoea has declined, to our knowledge there are no current studies that have reported the prevalence and outcomes of children hospitalised with milder forms of dehydration. In addition, studies elsewhere in Africa have reported an increase in prevalence of diarrhoea in the community (11). At CHBAH, children with mild and moderate dehydration, meeting specific admission criteria, are hospitalised specifically to the SSW rather than the general paediatric ward. Therefore undertaking a study over a lengthy period of time evaluating the prevalence and outcomes of children with diarrhoea and mild and moderate dehydration will allow us to highlight trends of milder forms of diarrhoea in this setting. We may be able to demonstrate the effect of multiple strategies that occurred during this study period on diarrhoeal disease trends. Furthermore, the study may influence future policy decisions regarding the need for a SSW in this hospital.

Therefore the aim of this study, in partial fulfillment of the Masters of Medicine in Paediatrics (MMed) degree is to determine the trends in diarrhoeal disease admissions to the SSW at CHBAH over a 15year period.

Objectives

1. To describe hospitalisation trends for diarrhoea with mild and moderate dehydration over a 15-year period to the SSW at CHBAH
2. To determine seasonal variations of diarrhoeal hospitalisations with mild and moderate dehydration over a 15-year period to the SSW at CHBAH
3. To determine outcomes of children admitted with diarrhoea and mild and moderate dehydration over a 15-year period to the SSW at CHBAH
4. To determine the clinical and demographic characteristics of all children less than 5 years of age hospitalised with diarrhoea at the CHBAH from January 2015 to December 2016

Standard of care protocol for the management of diarrhoea at CHBAH

All children presenting at the Paediatric MEAD with a complaint of loose/watery/bloody stools of any duration and frequency as described by the caregiver is labeled as having diarrhoea, (this may be in contrary to the WHO case definition of diarrhoea). Children seen at local clinics with diarrhoea are managed as per IMCI protocol. Those children with dehydration and /or not tolerating oral rehydration are referred to CHBAH for further management. The standard-of-care protocol for the management of children presenting with diarrhoea in this hospital has remained unchanged over the study period. Additionally, the senior Paediatric MEAD medical staff has remained the same over the study period. The degree of dehydration, as assessed by the attending physician is the main criteria used to decide whether the child will be discharged home, admitted to the SSW or to the general paediatric ward. The degree of dehydration is classified as:

- "No dehydration"- no visible signs of dehydration. If the child is tolerating ORS and not vomiting the child can be discharged home and continue ORS as instructed by the attending physician.
- "Mild dehydration" - the child is alert with few clinical signs of dehydration: thirst, drinks eagerly and has a normal urine output. The child is either discharged home or admitted to SSW for oral rehydration. A child who is not tolerating oral fluids is admitted to the SSW for intravenous rehydration and monitoring.
- "Moderate dehydration" - the child has two of the following signs: sunken eyes, depressed anterior fontanelle, absent tears, thirst/ drinks eagerly, restless/ irritable, a slow skin pinch but <2 seconds and sticky mucosa; the child is admitted to the SSW for rehydration (ORS or IV) and further monitoring.
- "Severe dehydration" –the child has worsening of symptoms, reduced level of consciousness, markedly reduced urine output and may be in shock. These children

have initial IVF resuscitation and once out of shock are admitted to the general paediatric ward and not the SSW.

The following conditions exclude patients from SSW admission:

- Less than six weeks of age
- Age of 14 years or older
- Children with “severe dehydration / requiring resuscitation for shock
- Children with suspected significant electrolyte imbalances
- Children with decreased level of consciousness
- Caregiver unavailable (presence of a caregiver is mandatory in SSW)
- Children with a surgical cause for their diarrhoea
- Children with other co-morbidities (e.g. severe malnutrition, oncology diagnoses, renal disease, cardiac disease)

Study inclusion criteria:

- In phase 1 of the study all children admitted to the SSW with a diagnosis of diarrhoea as per SSW criteria stipulated above will be included
- In phase 2 of the study all children admitted to the Chris Hani Baragwanath Hospital Paediatric Wards (SSW and general paediatric wards),with diarrhoea will be included

Methods

Study design

This study is a retrospective descriptive review of children less than 14 years of age with diarrhoea admitted to CHBAH over a 15-year period, from January 2002 to December 2016.

Study Methods

Data will be collected in two phases.

Phase1: (Protocol Appendix 2)

The monthly captured patient data from the SSW and the Paediatric MEAD will be used to meet the first three objectives. This data was collected by the senior paediatricians in the department (Dr Patel and Dr Vallabh) using the registries in the SSW and Paediatric MEAD. The ward clerks enter the patient information in these registries on arrival and discharge from the ward. These registries record demographic information including name, age, gender, address, contact details, diagnosis, HIV status, nutritional status, management with intravenous fluids or oral rehydration only and outcome of patients. Identifiers (the Name and Contact details of participants) were not captured. The above captured data will be transcribed into an excel spread sheet and imported into a statistical program. The results will then be stratified by age, sex, year and month of presentation. Trends in hospitalisation will be described and seasonal variations will be determined. In order to show trends over the fifteen year period data may be represented annually.

Phase 2:

The registries and discharge summaries from the SSW and general paediatric ward are entered into a database by the Respiratory and Meningeal Pathogens Research Unit (RMPRU) and this database will be used to meet the fourth objective. A discharge summary is completed by the treating physician on discharge or death of a patient. The database will be used to identify all children admitted to CHBAH with a diagnosis of diarrhoea from January 2015 to December 2016. The data obtained from the RMPRU database will imported onto a Microsoft

spread sheet, identifiers will be removed and a numerical value will be assigned per entry. The student and supervisors alone will have access to the password protected data sheet. The database captures similar variables as is captured in the registries at PMEAD and SSW. Variables not captured on the RMPRU database will be supplemented using the registries. Phase 2 of the study will allow exploration of the demographic characteristics of diarrhoea in the later years of the study (for which data is available), and the overall diarrhoeal disease trends at CHBAH in the SSW as well as the general paediatric wards.

An estimated 60 children per month are admitted to the SSW with diarrhoeal disease and this will equate to at least 10,000 cases over the study period. In phase 2 of the study an estimated 2000 patients were admitted with diarrhoea at CHBAH.

Variables to be collected for the study:

- Number of children presenting with diarrhoea regardless of dehydration status at the Paediatric MEAD
- Number of children hospitalised with diarrhoea to SSW and/or general paediatric ward
- Number of children presenting to the Paediatric MEAD
- Number of children hospitalised in the SSW with any other non diarrhoeal illness
- Outcomes of children admitted with diarrhoea to SSW
    - Death, discharge home, transferred to the general ward or other (e.g. absconding, refusal of hospital treatment)
- Number of children receiving intravenous versus oral rehydration at the SSW
- Gender of children with diarrhoea admitted to the SSW
- Ages of children with diarrhoea admitted to the SSW
- HIV status of children with diarrhoea admitted to the SSW and general paediatric wards (from 2015 onwards)
- Nutrition status of children with diarrhoea admitted to the SSW and general paediatric wards (from 2015 onwards)

- Type of residence: formal or informal settlements- (dwellings that are described as shacks or refugee camps will be classified as informal settlements)

Statistical analysis

Demographic characteristics will be reported per year over the study period (Appendix 2); continuous variables will be reported as means, standard deviations or medians depending whether the data is parametric or non-parametric. Categorical variable will be reported as proportions. A p-value of <0.05 will be considered as statistically significant.

Phase1: To determine the trends in the prevalence of diarrhoea with mild and moderate dehydration, the prevalence/point incidence will be estimated as the number of cases with diarrhoea with mild and moderate dehydration over the (i) total number of children presenting with any illness, and (ii) number of children admitted with diarrhoea. Furthermore, a trend analysis will be undertaken by mapping the prevalence of diarrhoea over the study period to highlight seasonal patterns and the possible influences of public health interventions introduced at various time points. Weather and rainfall patterns will be obtained from weather SA and monthly rainfall will be used to classify month as being dry, average or wet.

Phase 2: In order to evaluate the prevalence and clinical characteristics of all children hospitalised with diarrhoea for the last 2 years of the study the prevalence/point incidence will be estimated as the number of cases admitted with diarrhoea regardless of dehydration status over the (i) total number of children presenting with any illness, and (ii) number of children seen at Paediatric MEAD with diarrhoea. Mortality rates will be reported as a proportion of the total number of cases. Data will be used to compare children based on their nutrition status and HIV status using the t-test or Mann-Whitney for continuous variables and the Chi-squared or Fischer exact test for categorical variables.

Protection of human research participants

Risks

As the trial is retrospective, there are no risks for participants

Confidentiality

Participants will not be identified by name or hospital numbers or date of birth and numerical numbers only will be used for the second phase of the study.

Costs to participants

Participants will incur no extra costs based on participation in the study.

Permissions

Permission obtained from Professor Madhi (director) to use the RMPRU database.

Permission obtained from Dr Patel and Dr Vallabh to use the Paediatric MEAD and SSW statistics

Review board approval

Permission will be sought from the Human Research Ethics committee (HREC) at the University of the Witwatersrand, prior to initiation of the study. In addition, the CHBAH Medical Advisory Committee granted us permission to conduct the study.

Disseminating results to the public:

A summary of results will be reported to the HREC on completion of the study. Results may be presented at professional clinical meetings and national or international scientific meetings. Results will be submitted for publication in a peer-reviewed journal.

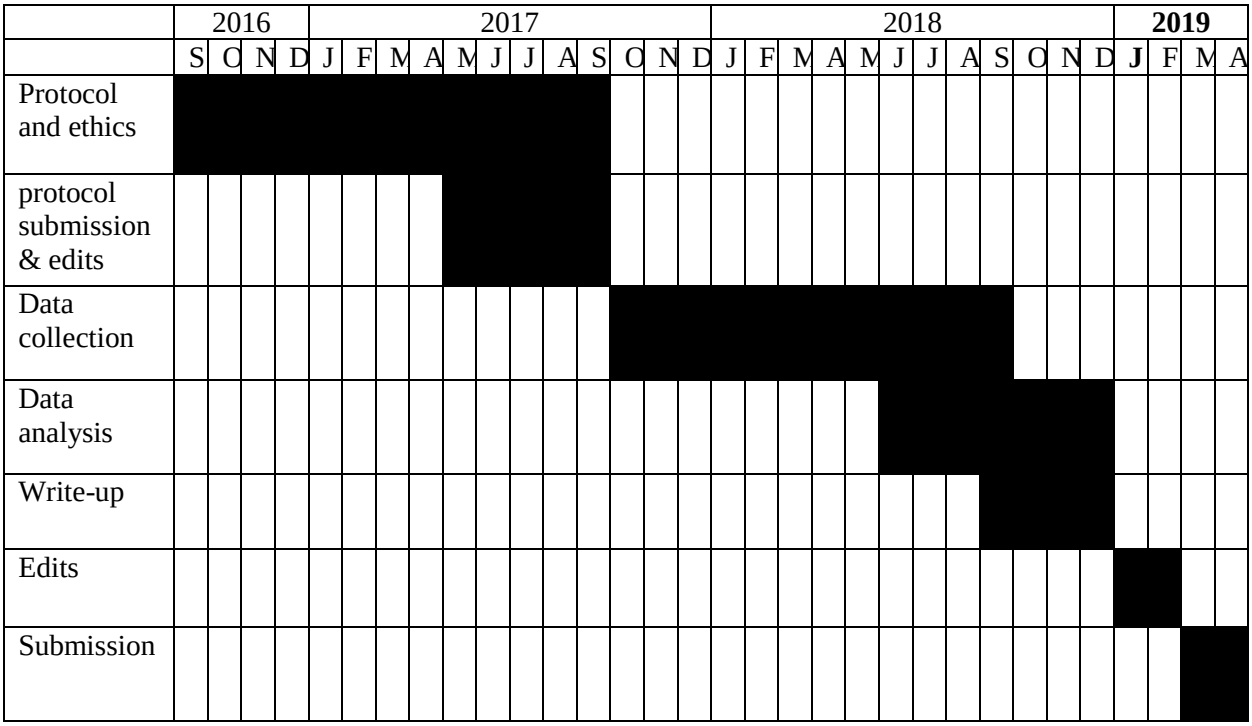
Funding

There is no cost implication to the study patients or hospital, and the student will cover the small cost of printing and stationery.

Anticipated limitations

- Important information pertaining to diarrhoea (e.g. breast feeding and immunisation status) is not routinely captured in the Paediatric MEAD monthly statistics and registries.
- The admission criteria to SSW, though stipulated, are at the discretion of the admitting physician.
- The opening of Bheki Mlangeni District Hospital in April 2014 may contribute to a reduction, if any in diarrhoeal disease cases seen at CHBAH.
- The number of patients referred to CHBAH is dependent on external factors e.g. behavioural changes in the community, referral practices at local clinics and experience and effectiveness of staff at local clinics to manage dehydration. Our study will not be able to account for this.
- Some data may be missing as most of the earlier data was not captured electronically at the Paediatric MEAD and SSW.

Study Timeline (Gantt chart)



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Protocol Appendices

Protocol Appendix 1, Public health initiatives introduced in South Africa over the study period that may influence diarrhoeal disease trends (29, 30)

Year	Public health initiatives/strategies
1998	Introduction of IMCI
2000	HIV/AIDS life skills education introduced in schools
2001	PMTCT pilot sites established –Nevirapine given to women in labour and to neonate), breastfeeding discouraged in place of formula, WASH initiative and Vitamin A supplementation added to the EPI.
2004	Free HAART to children with CD4+ counts of <15% in >18 months old, or less than 20% in <18months old and /or modified WHO stage 3 and 4 disease and ORS introduced.
2008	Change to the PMTCT programme -Zidovudine and Nevirapine from 28 weeks of pregnancy, Nevirapine during labour and to the neonate (72hrs).
2009	**ROTAVIRUS** vaccine introduced into the EPI.
2010	HAART to all children less than 1year of age and all pregnant women.
2011	Breastfeeding policy revised and exclusive breastfeeding recommended, and actively promoted until six-months of age regardless of HIV exposure status, and free formula phased out for HIV-exposed babies.
2013	HAART for pregnant and breastfeeding mothers regardless of CD4+ count, daily nevirapine throughout breastfeeding, and HAART to all children less than 5 years of age.
2014	Birth PCR test for HIV-exposed infants.
2015	Test and treat approach and pre exposure prophylaxis ARVS for high risk populations.

Protocol Appendix 2, **DATA COLLECTION SHEET, Phase 1**

	2002	*2003*	*2004*	*2005*	*2006*	*2007*	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*	*2016*
Total number seen at PMEAD (all acute illnesses)															
Total number of diarrhoeal cases seen at PMEAD															
Outcomes of diarrhoeal cases seen in PMEAD • Discharged home • Admitted to general paediatric ward • Admitted to SSW • Died • Other															
Total number admitted to SSW(regardless of diagnosis)															
Outcomes of diarrhoeal cases admitted to SSW • Discharged home • Admitted to general paediatric ward • Admitted to surgical ward • Died • Other															
Rehydration fluid used • IVF +/- ORS • ORS only															
Gender • Female • Male															
HIV status • Exposed • Negative • Positive • Unknown															
Nutritional status • NWFA • OWFA • UWFA															
Settlement • Formal • Informal															
Ages • 5-14 years • 2-4 years • 12-23 months • <12 months															