TRENDS IN SEIZURE HOSPITALISATIONS PRE AND POST ROTAVIRUS VACCINE INTRODUCTION AMONG CHILDREN IN SOWETO, SOUTH AFRICA

by

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DECLARATION

I, Joseph Omoniyi Babalola declare that this research report is my own work. It is being submitted for the degree of Master of Science in Medicine in the field of Child Health at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

Joseph O Babalola

14 September 2021

DEDICATION

I dedicate this work to all the parents who have allowed their children to participate in research towards finding a safe and effective vaccine against rotavirus. May the introduction of the rotavirus vaccine in South Africa be a major step in the fight to decrease under five mortality in this country.

I also dedicate this report to my loving and supportive family – my wife KB and my five wonderful precious children, Moyo, Tolu, Ayo, Ohunayo, and Tess. Thank you for allowing me the time to complete my Masters' degree and for supporting me during assignments, examinations, and the writing of this report.

ABSTRACT

Introduction

Reductions in childhood seizure hospitalisations following rotavirus vaccine introduction have been reported in some countries. This study evaluated the trends in seizure hospitalisation pre- and post-rotavirus vaccine introduction among children in Soweto, South Africa.

Methods

This secondary data analysis used an existing Paediatric Discharge Summary database including hospitalised children aged 6-59-months at Chris Hani Baragwanath Academic and Bheki Mlangeni District Hospitals from 1 January 2006 to 31 December 2018. International Classification of Diseases (ICD)-10 code definitions for febrile seizures (FSs), epilepsy, and unspecified seizures (collectively referred to as all-cause seizures [ACS]), acute gastroenteritis (AGE), and acute respiratory tract infections (ARI) were used. Monthly counts and incidence of ACS and FS hospitalisations pre- (2006-2008) and post-rotavirus (2010-2018) vaccine introduction in 2009 were analysed by age-group (6–11-, 12–23-, 24-35-, 36-47-, and 48-59-months).

Results

Of 74,160 hospitalisation-episodes among 57,161 children, 14,135 (19.0%) ACS hospitalisations (epilepsy, 2,993 [21.0%]; FS, 9,475 [67.0%]; unspecified seizures, 1,679 [11.9%]) occurred in children aged 6-59-months. The overall annual incidence of FS hospitalisations among children aged 6-59-months decreased by 34.2% from 4.79/1,000 (median 2006–2008) to 3.15/1,000 in 2013 but increased subsequently from 5.97/1,000 in 2015 to 7.72/1,000 in 2018. The highest incidence of FS hospitalisations of 11.29/1,000 occurred in 2018 compared to 7.59/1000 (the pre-vaccine years) among the 12-23 months age group. FS hospitalisation occurred in 8.3%, 4.9%, and 1.5% of children hospitalised with ARI, AGE, and HIV infection, respectively; and more than 50%, 60%, and 80% of the children were aged 24-59 months.

Conclusions

An un-sustained decline in ACS/FS hospitalisation was observed after rotavirus vaccine introduction but any observed changes in FS epidemiology could not be attributed to the impact

of rotavirus vaccination. There were sustained reductions in the number of AGE hospitalisations in the post-vaccination years compared to pre-vaccination.

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NOMENCLATURE

ACS: all-cause seizures

AGE: Acute gastroenteritis

ARI: Acute respiratory infection

ART: Antiretroviral therapy

ARV: Antiretrovirals

BMDH: Bheki Mlangeni District Hospital

CHBAH: Chris Hani Baragwanath Academic Hospital

CNS: Central nervous system

ED: Emergency department

ELISA: Enzyme-linked immunosorbent assay

EPI: Expanded programme on immunisation

FIRES: Febrile infection-related epilepsy syndrome

FS: Febrile seizure

GEFS+: Generalized/genetic epilepsy with febrile seizures plus

HHV: Human Herpesvirus 6

HIV: Human Immunodeficiency Virus

HIVE: HIV encephalopathy

HREC: Human Research Ethics Committee

IBE: International Bureau for Epilepsy

ICD: International Classification of Diseases

ILAE: International League Against Epilepsy

IQ: Intelligence quotient

MTCT: Mother to child transmission

NORSE: New-onset refractory status epilepticus

PCR: Polymerase chain reaction

RMPRU: Respiratory and Meningeal Pathogens Research Unit

TBM: Tuberculous meningitis

UK: United Kingdom

USA: United States of America

VPS: Viral proteins

WHO: World Health Organization

1. CHAPTER ONE- INTRODUCTION

1.1 Seizure burden and definitions

Seizures are one of the commonest reasons for paediatric emergency room attendance and hospitalisation.[1] Seizures in childhood, febrile seizures (FSs) and epilepsy inclusive, occur in about 4–5% of children under 5 years of age and are the most common neurological conditions in childhood and serious cause of anxiety for caregivers.[2,3] About 4% to 10% of children experience at least one seizure in the first 16 years of life.[2] Children are particularly susceptible to develop seizures because of the immaturity of the brain.[4] Occurrence of seizures is highest in infancy and childhood,[5] and the factors that may lead to the development of seizures in children include infection, traumatic brain injury, genetics, structural abnormality, metabolic-, immune-related-, or unknown factors.[5]

1.2. Seizure types

Seizure, as in the 2017 proposed definition in the International League Against Epilepsy (ILAE) classification, is the "transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain".[6] The recent classification has three main categorizes namely: focal, generalized, and unknown onset (including unclassified seizure) types. The classification is based on where the seizure originated in the brain, whether it affects awareness or it is accompanied with unusual movement, feeling, or sensation. It is of "focal onset" when it arises from a focus in the brain; "generalised onset" when it arises from both sides of the brain at once and it happens without warning; and of "unknown onset" if where the seizure arose is uncertain (if the seizure occurred when the person affected was asleep, alone or without a witness). A seizure is regarded as "unclassified" if it is unusual or the available information is inadequate to classify. Subcategories of seizure include those with activities that may be motor or nonmotor, and for focal seizures, awareness may be retained or impaired. The most extreme form of a seizure is described as status epilepticus, a result of failure of seizure termination process or an initiation process leading to abnormally, prolonged seizures (after 5 min, the time point t1, when treatment ought to be initiated). It can have long-term consequences (after 30 min, the time point t2), "including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of the seizures"[7]

1.2.1. Epilepsy

By consensus, the ILAE and the International Bureau for Epilepsy (IBE) defines epilepsy as a disease of the brain characterized by: "(1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; and (3) diagnosis of an epilepsy syndrome".[8,9]

1.2.2. Acute symptomatic or provoked seizures

Acute symptomatic or provoked seizures (comprising 40% of all seizures) are events, occurring in close temporal relationship with an acute central nervous system (CNS) insult, which may be metabolic, toxic, structural, infectious, or due to inflammation.[10] The interval between the insult and seizure may vary due to the underlying clinical condition. Less favoured synonyms of acute symptomatic seizures include reactive seizures, provoked seizures, or situation-related seizures.[10] The reported incidence of acute symptomatic seizures is in the range of 1,000 per 100,000 per year among hospitalised young children in Africa.[11] Common infectious conditions presenting as acute symptomatic seizures include neurocysticercosis, malaria fever, cerebral tuberculoma and brain abscess, and during acute infection or severe metabolic disturbance in human immunodeficiency virus (HIV) infection.[10]

1.2.3. Remote symptomatic seizure

A remote symptomatic seizure is a seizure that occurs longer than one week following a disorder that is known to increase the risk of developing epilepsy. The seizure may occur a long time after the disorder. These disorders may produce static or progressive brain lesions.[12]

1.3. The burden of FSs

FSs are seizures occurring in febrile children (temperature ≥ 100.4°F or 38°C by any method) aged 6 to 60 months in the absence of intracranial infection, metabolic disturbance, or history of afebrile seizure.[13] FS is a form of symptomatic or provoked seizure.[10] FS could be simple (brief, lasting <15 minutes, generalized, with one episode in a 24-hour period and no focal component) or complex (prolonged, lasting >15 minutes, focal with more than one episode in a 24-hour period).[13] FS occur in 2 to 5% of children under 5 years and are the most common seizure disorder in childhood.[13] Though simple FS, not effectively managed, can potentially result in: (1) intelligence quotient (IQ) deterioration; (2) increased risk of epilepsy; (3) risk of recurrent FSs;

and (4) death; no long-term adverse effects have been reported after simple FS except for the high rate of recurrence.[13] Varying prevalence has been reported for FS; 2–5% in the USA, 5–10% in India and about 8% in Japan.[14] Between 9–35% of FSs are complex FS.[15] During the febrile illness, seizure episode may occur before, during or after the onset of the fever.[15] About 25–40% of children with FSs have a positive family history, and in 9-22% of the siblings, FSs have been reported.[15] The risk of having a febrile seizure is higher among the male gender, those with history of antenatal complications, prolonged neonatal unit stay, developmental delay, day care attendance, viral infections, certain vaccinations, and possibly iron and zinc deficiencies.[16] In addition, it depends on the peak body temperature, the underlying cause of fever, hypocalcaemia, hyponatremia, and hypoglycaemia.[16]

Often FS need to be differentiated from mimics like shaking chills (shivering), febrile delirium, breath-holding spells, CNS infection, febrile myoclonus, generalized/genetic epilepsy with FSs plus (GEFS+), new-onset refractory status epilepticus (NORSE), and febrile infection-related epilepsy syndrome (FIRES).[15,17]

Most FSs are of multifactorial origin and are often due to viral aetiology in 80% of cases.[17] Rhinoviruses, respiratory syncytial viruses, Human Herpesvirus 6 (HHV-6), and influenza A virus, are among the most common causes.[17] The most likely aetiology differs depending on the region or setting. FSs are most often due to acute respiratory infection (ARI)[14] but episodes following gastroenteritis including rotavirus diarrhoea have been reported, and in some settings malaria (especially in the sub-Saharan Africa).[11,18,19] There have been several reports of extraintestinal manifestations of rotavirus disease including neurological presentation as seizures.[20,21] Similarly, non-rotavirus AGE-causing pathogens, for example *Shigella* and norovirus have also been associated with FSs.[18]

1.4. Rotavirus clinical presentation and childhood seizures

Rotaviruses, the causative agents of rotavirus infections, are nonenveloped, reoviridae RNA viruses with structural viral proteins (VPs), VP4 and VP7 (the two outer-capsid proteins that initiate neutralization activity) that are critical to vaccine development.[22] There are different human and animal rotavirus serotypes strains that may cause rotavirus infection.[22] Rotavirus genotype combinations found in majority of clinical isolates in most developing countries are very diverse.[23]

Prior to the introduction of rotavirus vaccines, rotavirus was the most common cause of acute severe gastroenteritis in infants and young children.[22] The rates of rotavirus detection are between 16 and 66%, with a mean of 30% in Africa and median inpatient detection rate of 24% in South Africa.[24-25]

Infected children may present with mild, watery diarrhoea of limited duration or severe diarrhoea with vomiting and fever that may be complicated with dehydration, shock, electrolyte imbalance, and at times, death.[22] The incubation period is 1–3 days, with abrupt onset and symptoms may last up to 3-7 days.[22] Infected children may have severe dehydration with a third having an accompanied high fever (>39°C).[22]

Rotaviruses are highly communicable and are transmitted by the faecal-oral route (close person-to-person contact or through fomites), by respiratory droplets, and by faecal-contaminated food and water.[22] Use of hygienic measures and improved sanitation has not had a major impact on reducing the burden of rotavirus disease, thus rotavirus vaccination has been recommended as the most cost-effective intervention to reduce the rotavirus disease burden in young children.[24] Though repeated exposures may occur throughout life, most individuals develop natural and/or vaccine-induced immunity that result in subsequent infections being mild or asymptomatic.

During the pre-vaccine years, the pattern observed for rotavirus epidemiology in South Africa showed that most diarrhoeal hospitalisations occurred among children aged <24 months and peaked during the autumn–winter months of March to May.[25,26]

Although rotavirus infection most commonly presents with gastro-intestinal symptoms, there have been some reports of neurologic manifestation, mostly afebrile or FSs, but others included encephalopathy and cerebellitis.[20, 27-29]

A proportion of Korean children with mild rotavirus gastroenteritis were reported to have also presented with febrile and afebrile seizure, 2.2% and 5.5%, respectively.[30] Other studies from Asia, Europe, and USA also reported afebrile seizure in children with mild viral gastroenteritis who had no severe dehydration, electrolyte imbalance, nor hypoglycaemia.[20,28,30] The reported prognosis for these cases is said to be benign.

1.5. Rotavirus vaccination and impact on diarrhoeal disease

Vaccines are biological preparations, that are products from living organisms (whole or component part), with the ability to enhance immunity against disease. They are protective while not producing the disease in the vaccine recipients. Thus, they are used to prevent (prophylactic vaccines) or treat diseases (therapeutic vaccines). Vaccines are prepared in liquid form, to be administered as injection, orally, or intranasally.[31] Four oral, live-attenuated rotavirus vaccines are World Health Organisation (WHO)-prequalified and currently in use, the two initial ones which are licenced globally; Rotarix (GlaxoSmithKline, GSK Vaccines, Rixensart, Belgium) and RotaTeq (Merck Research Laboratories, Philadelphia, PA, USA), and the recently introduced thermostable Rotavac (Bharat Biotech, Hyderabad, India) and Rotasiil (Serum Institute of India, Pune, India). When rotavirus vaccine is administered to children, it promotes an immune response to the attenuated rotavirus strain before natural exposure to a virulent wild-type rotavirus.[22] Both Rotarix vaccine and RotaTeq vaccine are orally delivered, live, attenuated of human strain, and human-bovine reassortant strains, respectively.[22] The two types of rotavirus vaccines are quite different in structure, although they have similar safety profiles and protective efficacy. The overall rotavirus vaccine efficacy in high-income countries against the severe rotavirus disease was above 90% but lower efficacy of 40–60% have been reported in studies from low-middle income countries including South Africa, Malawi, Bangladesh, and Vietnam.[22,32,33]

Rotavirus vaccine introduction in many countries worldwide has led to significant reduction in rotavirus hospitalisations and mortality, although rotavirus still remains a leading cause of severe acute gastroenteritis (AGE) among under-fives globally.[34] The annual global rotavirus childhood mortality has reduced to 215,000 (2013) from about half a million (2,000).[31,32] Before rotavirus vaccine introduction, about 40% of diarrhoea hospitalisations world-wide was caused by rotavirus infection but this has declined to about 20% with vaccination.[35,36]

Regardless of the over 100 countries that have introduced rotavirus vaccine into their national immunization program, about 53% of all children globally (>70 million) remain unvaccinated.[37] Before the introduction of the national rotavirus vaccination in August 2009[38] in South Africa, diarrhoeal mortality in the under-five age group accounted for about 20% of all-cause mortality, and it has currently declined to about 10%.[39-41] A significant incidence reduction (40-65%) in the overall all-cause diarrhoeal hospitalisations has been observed since vaccine introduction.[39]

Among children aged <12 months a reduction in all-cause diarrhoeal hospitalisations incidence was achieved; from 54.4/1,000 pre-vaccine to 18.9/1,000 in the postvaccine years 2008 and 2014, respectively.[39] The second dose coverage rates of the two-dose public funded Rotarix given, at 6 and 14 weeks has risen from 67% in 2010 to 96% in 2011.[39] The seasonal pattern of diarrhoeal hospitalisations post–vaccine introduction, was also altered, with flattening of the autumn–winter peaks seen before rotavirus vaccine introduction.[39]

1.6. Impact of rotavirus vaccination on seizure hospitalisation

Some studies have found a protective association between full rotavirus vaccination and childhood seizures. Among children in the US, there was a 18-21% reduction of emergency department (ED) presentation or hospital admission for childhood seizures (defined using the International Classification of Diseases [ICD], ninth revision, codes) in the year after rotavirus vaccine introduction.[42,43] Similarly reports of all-seizure hospitalisation reductions following rotavirus vaccine introduction were obtained from Spain (16-34%); and Australia (35%–38%).[20,44] However, other studies have shown no impact of rotavirus vaccination on seizure hospitalisations, for example a population-level study from the United Kingdom (UK) by Biggart et al., 2018 using an interrupted time series analysis, and a population-based, ecological study in Spain by Orrico-Sánchez et al., 2018.[45,46]

While acknowledging that the contribution of seizures associated with laboratory-confirmed rotavirus infection to all seizures among hospitalised children may be small, a UK population-level study of the impact of rotavirus vaccination on hospitalised seizures in association with AGE observed reductions in seizure incidence that were higher during the rotavirus season (49%, during season and 13% out-of-season).[28]

While rotavirus vaccine introduction in most countries has led to reductions in severe AGE hospitalisation, the impact on extra-intestinal manifestations including seizure hospitalisation remains unclear.

1.7. Rotavirus-associated seizures in HIV-infected children

Prior to the advent of the adoption of universal antiretroviral treatment (ART) of HIV infected mothers to avert mother to child transmission (MTCT), paediatric HIV transmission in many sub-Saharan African countries, including South Africa, was very high, with a prevalence of 8-

28% reported among hospitalised children.[47, 48] Similarly, a systematic review of 17 studies exploring HIV prevalence and mortality among children treated for severe malnutrition in sub-Saharan Africa in 2008, reported an overall HIV prevalence of 29.2%.[49] The national prevalence of HIV infection among mothers attending antenatal clinic remains stable at about 30% but the transmission of HIV to their infants has been reduced from 23% in 2003 to <1% by 2019.[50] This was accounted for by the improved access to highly active ART in South Africa's public health sector since 2010. The overall estimated ART coverage in HIV-infected children has subsequently increased to 63% by 2018.[51]

Children with HIV infection are often immunocompromised and are at higher risk of contracting rotavirus infection, including severe gastroenteritis and seizures.[52] HIV infected and exposed children were more likely to be poorly nourished, hospitalised, and respond poorly/had poorer outcome to diarrhoeal care/treatment when compared with HIV-uninfected children.[53, 54] Groome et al., 2012 in a study on the incidence of AGE hospitalisation in HIV-infected and HIV-uninfected children from Soweto, South Africa, reported that HIV-infected children accounted for 26% of AGE hospitalisations.[55] Prevalence of seizures in HIV positive children has been reported to be between 2%-14% depending on the regional risk of infection.[56]

A retrospective case-control study in South Africa in 2019 reported seizure rate of 23% among HIV-infected children.[57] Most of the HIV-infected children had generalized tonic-clonic seizures (64%) that were of infectious aetiology (62%).[57] Children with HIV may have seizures due to opportunistic infections, tumours, medications, metabolic and electrolyte derangements, or from HIV encephalopathy.[58] Although confirmed rotavirus-associated seizures in HIV-infected children are rarely reported, Acácio et al., 2018, reported among 0–59 months aged children with moderate-to-severe diarrhoea, convulsion in 8% of HIV-infected children, as compared to 6% of HIV-uninfected children.[58] In a separate study in 2021, Acácio et al., further reported convulsion in HIV-infected children with moderate-to-severe diarrhoea associated with confirmed rotavirus.[59]

1.8. Management of seizures

The sight of a child presenting with a seizure could be frightening to parents and caregivers, therefore, they should be assured that the condition is benign if it is a simple FS and should be educated (verbally, in writing, and through support groups) about the cause and prognosis of the

disorder to alleviate their anxiety.[2,60] The immediate care prior to hospital visit includes placing the child having seizure on his or her side on a protected or safe surface and carefully noting the presenting features.[60] The duration of the seizure should also be noted by the witness. For the child with a persisting seizure of >5 min that presents at the hospital, seizure is confirmed; the airway, breathing, and circulation are assessed; and treatment is initiated immediately with a potent benzodiazepine to terminate or arrest the seizure.[2,60] A second-line treatment with non-benzodiazepine anti-seizure medications such as valproate, fosphenytoin, or levetiracetam may be required. Identifiable and correctable precipitating cause is determined concurrently with a workup.[60] A brief history to exclude CNS infection/trauma and examination (including a record of the respiratory rate, blood pressure, temperature, and oxygen saturation) and potential co-morbidities are established based on local disease epidemiology.[60]

1.9. Justification and study objectives

The positive impact of rotavirus vaccination has been confirmed against hospitalisation for severe rotavirus diarrhoeal disease in Sowetan children, [61,62] but the possible impact on hospitalisation for childhood seizures in South Africa is yet to be explored. Encephalitis and seizures could result from natural rotavirus infection.[27] The impact and effectiveness of rotavirus vaccine introduction on childhood seizures have been reported in some settings but not all findings are consistent. Among US children, a protective association between full rotavirus vaccination and childhood seizures was found, resulting in 18-21% reduction of ED presentation or hospital admission in the year after vaccination.[42, 43] Similarly, reductions were shown from studies in Spain and Australia.[20,44] No impact of rotavirus vaccination on seizure hospitalisations was found with population-level studies from the UK by Biggart et al., 2018 and in Spain by Orrico-Sánchez et al., 2018.[45,46]

Knowing the impact or effect that the introduction of rotavirus vaccination has on all seizures hospitalisation in South Africa will help us understand whether it has added benefit in this regard. The evaluation of the cost-effectiveness of the introduction of rotavirus vaccine into the expanded programme on immunisation (EPI), the guidance in decision making on future use of these vaccines in South Africa, and the value of their potential introduction into other African countries are reasons to examine the trends in the incidence for seizure hospitalisation to guide policy.

1.10. Objectives

1.10.1. Primary objectives:

1. To describe the incidence of seizures (all-cause seizures [FSs, epilepsy, and unspecified seizures] and FSs) among children aged between 6 months and 59 months from 2006-2018, stratifying by age group (6-11 months, 12-23 months, 24-35 months, 36-47 months, and 48-59 months) and HIV status.
2. To evaluate the temporal association of the introduction of oral rotavirus vaccine into the childhood immunization program on the incidence of childhood seizures (all-cause seizures [ACS] and FSs) in hospitalised children aged between 6 months and 59 months.
3. To investigate risk factors (age, sex, HIV status, season of admission) associated with FS in children aged between 6 months and 59 months.

1.10.2. Exploratory objectives:

To describe trends in the incidence of acute gastroenteritis (AGE) -seizures and acute respiratory infection (ARI)-seizures.

2. CHAPTER TWO- MATERIALS AND METHODS

2.1. Study design

This was a descriptive secondary data analysis of an existing Paediatric Discharge Summary database (derived from the hospital admission registries and patient discharge summaries) for the period 2006 to 2018 for Chris Hani Baragwanath Academic Hospital (CHBAH) and 2014 to 2018 for Bheki Mlangeni District Hospital (BMDH). The Paediatric Discharge Summary database is a record-based system containing demographic and clinical information on all paediatric hospital admissions and is administered by the Respiratory and Meningeal Pathogens Research Unit (RMPRU), University of the Witwatersrand, based on the CHBAH premises, on behalf of the Paediatric Departments of CHBAH and BMDH. Trends in number and incidence of hospitalisations for childhood seizures were evaluated over time and compared before and after the introduction of the oral rotavirus vaccine into routine use in South Africa. In addition, a cross-sectional study design was used to evaluate risk factors associated with FS at the time of hospitalisation. This study did not involve collection of any additional data over and above that which was collected as part of standard-of-care by the attending medical doctors, as captured in the database.

2.2. Study population

Until 2014 CHBAH was the only public hospital which served the population of Soweto, and it was estimated that 90% of all hospitalisations in children from the area occurred in this hospital. Since 2014, children residing in Soweto may also have been admitted at BMDH, a new district hospital in Jabulani. The population of Soweto included an estimated 1.3 million people, including 125 000 children under five years of age by 2019.[63]

Children presenting to CHBAH or BMDH were assessed in the paediatric casualty. Depending on the diagnosis and severity of the illness they were discharged home with medication, sent to the “short -stay” ward for observation overnight (CHBAH only) or admitted to the general paediatric ward. Those with less severe illness but who were not well enough to go home were sent to the “short- stay” ward for observation. These patients were reassessed the following morning and the majority were discharged. They did not receive oxygen supplementation, intravenous fluids, or intravenous antibiotics in this ward. Children with more severe illness requiring oxygen supplementation, and intravenous fluids or antibiotics would be admitted to

one of the general paediatric wards. Patient ages in all paediatric wards ranged from neonates to approximately 12 years of age.

Children infected with or exposed to HIV and antiretrovirals (ARV) are at risk for impaired growth, neurodevelopmental, behavioural, and cognitive functions and may experience health conditions for which they may be hospitalised for specialised care.[53]

In South Africa, routine HIV PCR testing in HIV–exposed infants at six weeks of age started in 2004. This progressed to include testing symptomatic infants prior to six weeks of age, and then routine birth testing for all HIV–exposed infants by 2015 (to make certain that intra–uterine infected infants were detected early).[64] By 2019, 18-month rapid test/ ELISA for all children regardless of HIV exposure (the universal testing) became standard practice.[64,65] Therefore, there was a low threshold for HIV testing and all children with a repeat admission had HIV tests done as per standard of care by the attending physicians. HIV enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) tests were performed as appropriate.

All paediatric patients admitted to the general paediatric wards had a discharge summary (in paper form) completed by the attending physician on discharge from the hospital or death of the patient. Children admitted to the short stay ward did not have a discharge summary completed on discharge but basic information including patient demographics and diagnosis were recorded in the ward admission registry. Discharge summaries were collected by staff from RMPRU on a regular basis. In the short stay ward, information from the admission registers were collected by RMPRU staff.

All discharge summaries were taken to the RMPRU where a designated study doctor reviewed the discharge summaries and admission register entries and assigned one or more ICD-10 codes based on the physician diagnoses recorded in the discharge summary or admission register. The discharge summary and admission register data including the RMPRU-assigned ICD-10 codes were entered onto a database maintained at RMPRU. Children presenting to the paediatric casualty and outpatient department were not included in the database.

In order to ensure that all patients who were admitted in the general paediatric wards had a discharge summary entered on the database, standard procedure involved that all entries in the general ward registries were cross-checked against the database entries. Hospitalisations

appearing in the admission registries, but which did not have a discharge summary record completed were identified and attempts were made to locate the discharge summary. If the discharge summary could not be located, information was abstracted from the admission registries. In addition, the death registries in each of the wards were cross-checked with the discharge summary database to identify any deaths for which a discharge diagnosis may not have been completed, and relevant information was abstracted for inclusion into the database as required by an assigned qualified medical doctor from RMPRU.

2.3. Study sample and definitions

This secondary data analysis included all children aged 6 to 59 months hospitalised at the Paediatrics General and Short stay wards of CHBAH and the BMDH from 1 January 2006 to 31 December 2018. Those with missing age and ICD-10 diagnosis code were excluded from the analysis. Patients may have had more than one hospitalisation during the study period, so there could have been more than one observation per patient but with different admission dates reflecting separate admissions. Hospitalisations within 14 days of a previous hospitalisation for an individual patient were considered as part of the same event and excluded from the analysis.

a. FSs were defined by the ICD-10 code R56.0 in any diagnosis.
b. Unspecified seizures were defined by the following ICD-10 codes: R56.8, and R56.9. These included seizures with inadequate information or that cannot be placed in other categories which are referred to as unclassified convulsion (seizures of unknown onset or "unclassified" or with additional features, including motor, nonmotor, tonic–clonic, epileptic spasms, and behaviour arrest).
c. Epilepsy was defined by the following ICD-10 codes: G40–G41.
d. All- cause seizures were defined by the following ICD-10 codes in any diagnosis field: R56.0; R56.8, R56.9 and G40–G41.

e. Acute gastroenteritis (AGE) was defined by the following ICD-10 codes: A00–A05, A06.0–A06.3, A06.9, A07.0–A07.2, A07.9, and A08–A09.

f. Acute respiratory tract infections were defined by the following ICD-10 codes: J00-, J01.4, J01.8, J01.9, J02, J02.9 , J03.1, J03.6, J03.9, J04.0- J04.2, J04.9, J05.0, J05.1, J05.6, J05.9, J06.0- J06.5, J06.9, J08.0, J08.9, J1.3, J10- J15.5, J15.8, J15.9, J16.8, J17.1, J17.3, J18.0, J18.1, J18.2, J18.8, J18.9, J20-J23, and J27.9.

2.4. Data management

2.4.1. Data sources

The dataset was made available in two Excel spreadsheets containing data for each of CHABH and BMDH. The data provided to the investigator were de-identified of patient name and hospital number but contained clinico-demographic information relevant to the study including date of admission, date of birth, sex, HIV status, and up to five diagnosis fields containing the ICD-10 codes and text.

2.4.1. Data processing methods

The de-identified data spreadsheets were imported into STATA 14.2 and merged after ensuring similarity of the variables and storage types. Existing variables were recoded, and new variables were created as required.

2.4. 2. Data analysis

The outcome (dependent variables) measures analysed were hospitalisations for 1) ACS (including FSs, unspecified convulsion, and epilepsy) and 2) FSs only. Risk factors (independent variables) measured were age, sex, HIV infection status, seasonality, and co-diagnosis of ARI and AGE. Age at hospitalisation was calculated as date of hospitalisation minus date of birth and categorised into the following age groups: 6-11 months, 12-23 months, 24-35 months, 36-47 months, and 48-59 months. Children with a reactive HIV ELISA test (≥18 months of age) or a positive HIV PCR test (<18 months of age) or an ICD-10 diagnosis code of HIV disease were regarded to be HIV-infected. Not all the participants had HIV testing performed at admission. When the HIV result was missing or indeterminate, the HIV result was regarded as being unknown. A sensitivity analysis was also conducted, where those with an unknown HIV infection status were assumed to be HIV-uninfected on the assumption that a child would eventually present with clinical signs or symptoms of HIV disease and be tested during the current or a subsequent hospitalisation. To calculate the mortality rate, the discharge outcome was categorised into alive (0) or dead (1); all transferred patients were categorised as alive along with those discharged home.

Monthly counts of ACS and FS hospitalisations were plotted against time for age groups 6–11, 12–23, 24-35 months, 36-47 months, and 48-59 months for the period 2006–2018. The incidence of ACS and FS hospitalisations (per 1,000 population) were estimated using the number of children hospitalised for seizures in the numerator and the midyear population estimate in the denominator. The population estimates for Soweto (subdistrict D and G, Johannesburg) obtained from Statistics South Africa were used as denominators.[66] The population estimate for 2014 was used for 2015-2018 as data beyond was unavailable, despite numerous attempts to access the updated population estimates. The population estimates used as the denominator for the 6-11 months age category was estimated at 50% for the under 1 year age population category. The median annual incidence during the pre-vaccine years (2006–2008) was compared to the incidence in the rotavirus vaccine era, post-vaccine years (2010–2018), and this was stratified by age group. As vaccine was introduced in August 2009, the year of vaccine introduction (2009) was excluded in the comparative analysis.

Categorical variables were presented as count and percentages and compared using the chi-squared test. Continuous variables were presented as mean ± standard deviation (if normally distributed) or median and interquartile range (IQR) and compared using an independent t-test (if normally distributed) or Mann-Whitney U test (if non-normally distributed).

For the investigation of risk factors associated with FS, available risk factor variables were compared between those diagnosed with FSs and those without any seizures. Other seizures and epilepsy hospitalisations were excluded from this analysis. Risk factors examined included age, sex, HIV infection status, season and year of admission, vaccination period (pre and post) and co-morbidities. To identify the risk factors associated with FS hospitalisations, a logistic regression analysis was conducted in two levels. The first part included a univariate unadjusted analysis where each potential risk factor was included individually in a model with the outcome (FS hospitalisation) one after another. In building the multivariate model, all explanatory variables theoretically known to be important and those with p-value of <0.05 (a commonly used cut off) were included in the model. Then using a forward selection technique, all the variables that were significant in the model ($p<0.05$) were retained. Level of statistical significance was reported at the 95% confidence interval (CI). Odds ratios were used to interpret the strength of association between FS hospitalisation and the explanatory variables. All statistical analyses

were performed using STATA Version 14 (College Station, TX: StatCorp LP) and P value <0.05 was set as the significance level.

2.5. Ethics approval

The ethics approval for the study was obtained from the Human Research Ethics Committee (HREC), University of the Witwatersrand, Johannesburg (M1911170). The gatekeepers of the database at RMPRU gave permission for the use of data from the database.

This analysis involved the use of administrative data records which were collected as part of standard-of-care and were anonymised of personal patient identifiers. The analysis posed no risk to the participants as it was conducted retrospectively. The requirements of written informed consent from the participants were waived by the HREC, University of the Witwatersrand.

3. CHAPTER THREE- RESULTS

3.1. Clinical and demographics of children with seizure hospitalisation-episodes

Overall, there were 74,160 hospitalisations episodes among 57,161 children aged between 6 and 59 months from 2006 to 2018: 71,345 (96.2%) at CHBAH and 2,815 (3.8%) at BMDH (Appendix A). Of the hospitalised children, 26.8% and 33.8% were aged 6-11 months and 12-23 months respectively (Appendix B). An ICD-10 diagnosis was available for 73,769 of the hospitalisation-episodes (99.5%). A total of 14,135 (19.1%) ACS hospitalisations (epilepsy, 2,993 [21.2%]; FS, 9,466 [67.0%]; unspecified seizures, 1,676 [11.9%]) occurred in children aged between 6 and 59 months from 1 January 2006 to 31 December 2018 (Appendix A).

The average hospital admissions per year in the pre-vaccine year was 6,343 while during the post-vaccine years it was 5,347. During the pre-vaccine years, 31.0% and 33.8% of admissions were among children aged 6-11 and 12-23 months, while 24.8% and 34.0% occurred in the same age groups in the post-vaccination years, respectively (Table 3.1).

Table 3.1: Age group and average admissions per year (pre and post vaccine periods)

	Vaccination period		
Age group (months)	Pre (2006-2008) n; (%)	Post (2010-2018) n; (%)	Total
6-11	5,906 (31.0)	11,945 (24.8)	17,851
12-23	6,426 (33.8)	16,360 (34.0)	22,786
24-35	3,370 (17.7)	9,490 (19.7)	12,860
36-47	1,955 (10.3)	6,038 (12.6)	7,993
48-59	1,373 (7.2)	4,289 (8.9)	5,662
Av. admissions/year	6,343	5,347	

NB. The year of vaccine introduction was excluded from the above

3.2. ACS hospitalisation count

There was no remarkable decline in the ACS hospitalisation count after rotavirus vaccine introduction (Figure 3.1) Before rotavirus vaccine introduction (2006-2008), 9.9%, 33.7%, 27.7%, 17.4%**,** and 11.3% of ACS hospitalisations occurred in children aged 6–11, 12–23, 24-35, 36-47, and 48-59 months, respectively, compared to the post-vaccine era (2010-2018) with 9.2%, 32.0%, 27.8%, 18.4%, and 12.6% of hospitalisations in these respective age groups (Table 3.2). There was no significant difference between the pre and post vaccination period in ACS hospitalisation by age group (p=0.107).

Table 3.2: Proportion of all-cause seizures hospitalisation by age group pre- and post-vaccination

Pre- vaccination						
Age categories (months)	6-11 (N, %)	12-23 (N, %)	24-35 (N, %)	36-47 (N, %)	48-59 (N, %)	Total (100%)
Admission year						
2006	110 (9.5)	397 (34.3)	317 (27.4)	199 (17.2)	136 (11.7)	1,159
2007	73 (9.6)	245 (32.2)	214 (28.1)	141 (18.5)	89 (11.7)	762
2008	110 (10.7)	351 (34.2)	285 (27.8)	173 (16.9)	107 (10.4)	1,026
Total	293 (9.9)	993 (33.7)	816 (27.7)	513 (17.4)	332 (11.3)	2,947
Average count/year	97.7	331	272	171	110.7	982.3
Post- vaccination						
Age categories	6-11 months (N, %)	12-23 months (N, %)	24-35 months (N, %)	36-47 months (N, %)	48-59 months (N, %)	Total (100%)
Admission year						
2010	99 (9.6)	348 (33.7)	264 (25.5)	187 (18.1)	136 (13.2)	1,034
2011	82 (8.8)	273 (29.3)	294 (31.6)	162 (17.4)	120 (12.9)	931
2012	102 (9.4)	313 (28.7)	301 (27.6)	230 (21.1)	143 (13.1)	1,089
2013	76 (10.3)	208 (28.2)	207 (28.0)	144 (19.5)	104 (14.1)	739
2014	104 (10.6)	314 (32.1)	260 (26.6)	167 (17.1)	134 (13.7)	979
2015	113 (9.2)	424 (34.4)	351 (28.4)	211 (17.1)	135 (10.9)	1,234
2016	120 (8.9)	428 (31.8)	393 (29.2)	246 (18.3)	158 (11.8)	1,345
2017	96 (7.4)	427 (32.8)	386 (29.7)	243 (18.7)	149 (11.5)	1,301
2018	148 (9.7)	517 (34.0)	376 (24.8)	280 (18.4)	198 (13.0)	1,519
Total	940 (9.2)	3,252 (32.0)	2,832 (27.8)	1,870 (18.4)	1,277 (12.6)	10,171
Average count/year	104.4	361.33	314.66	207.8	141.9	1,130.1

3.3. FS hospitalisation count

A similar pattern of initial count reduction for FS hospitalisation in the immediate post-vaccine era were observed from 2010-2012 before a gradual increase in hospitalisation count (Figure 3.2). FS hospitalisation occurred in 9.7%, 37.7%, 28.0%, 15.7%, and 8.8% of children aged 6–11 months, 12–23 months, 24-35 months, 36-47 months, and 48-59 months of age, respectively (pre

-vaccination); and 8.6%, 35.6%, 29.5%, 16.4% and 9.9% (post-vaccination) in the respective age groups (Table 3.3). There was no statistically significant difference in the pre- and post-vaccination FS hospitalisations (p=0.165).

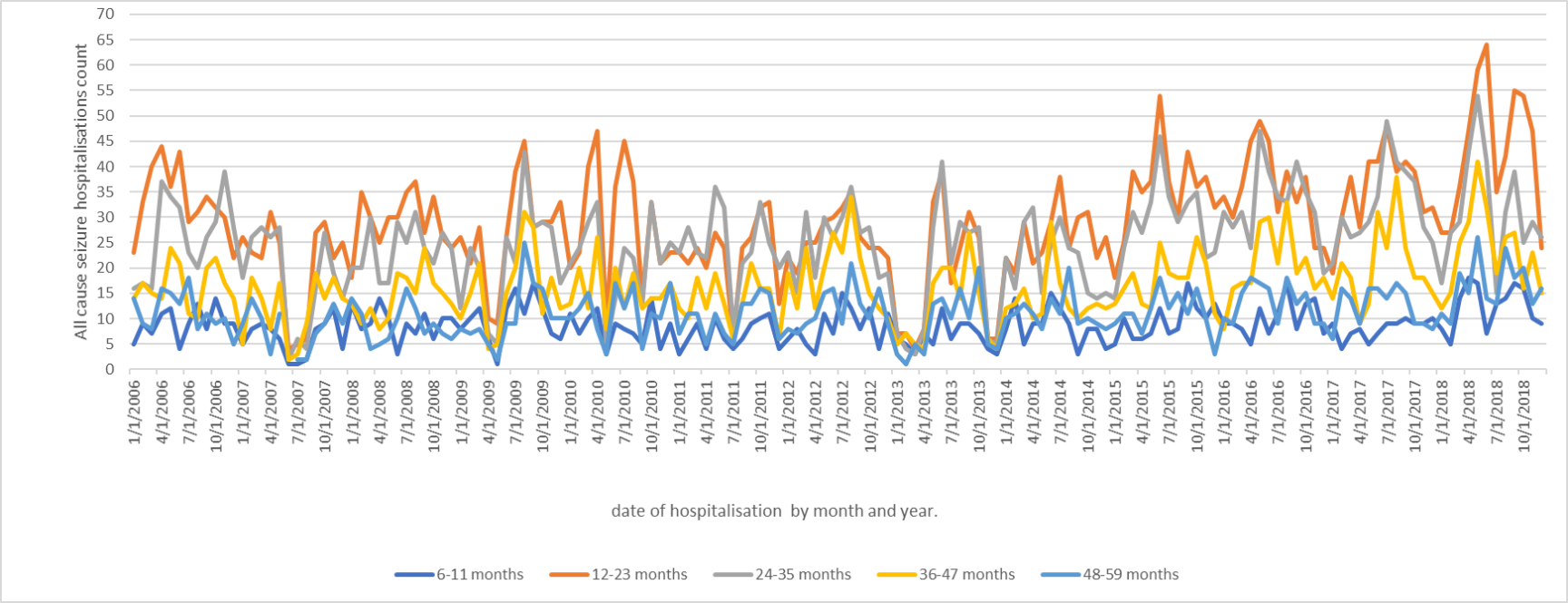


Figure 3.1:

Monthly count of all-cause seizure hospitalisations in children 6-59 months years of age at CHBAH and BMDH, Soweto, South Africa, 2006–2018.

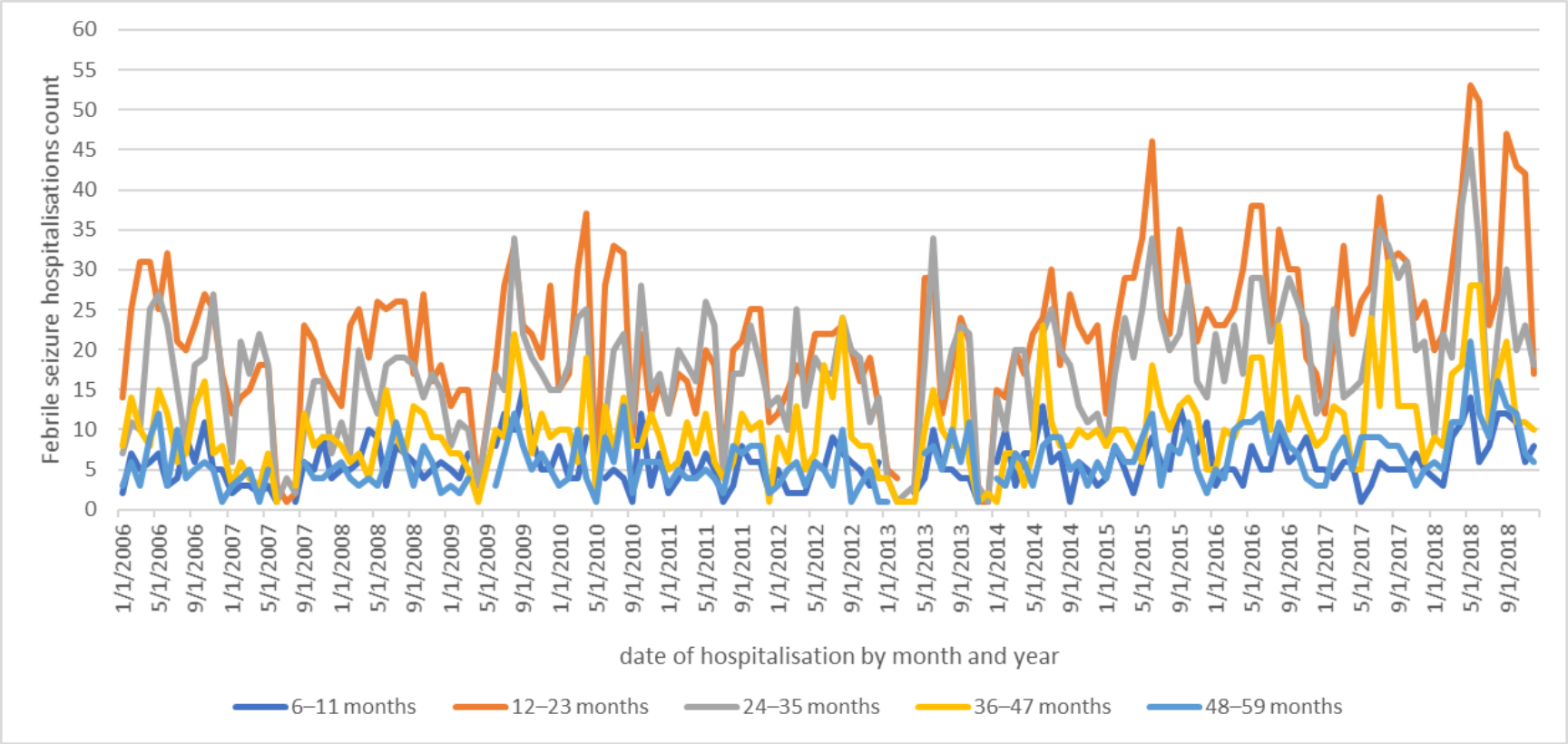


Figure 3.2:

Monthly count of febrile seizure hospitalisations in children aged between 6 and 59 months at CHBAH and BMDH, Soweto, South Africa, 2006–2018.

Table 3.3: Proportion of febrile seizures hospitalisation by age group pre- and post-vaccination

Pre- vaccination						
	Age group					
Admission year	6-11 months (N, %)	12-23 months (N, %)	24-35 months (N, %)	36-47 months (N, %)	48-59 months (N, %)	Total (100%)
2006	71 (9.3)	293 (38.5)	206 (27.1)	124 (16.3)	67 (8.8)	761
2007	39 (8.9)	159 (36.1)	140 (31.8)	65 (14.8)	37 (8.4)	440
2008	74 (10.7)	261 (37.7)	185 (26.7)	109 (15.8)	63 (9.1)	692
Total	184 (9.7)	713 (37.7)	531 (28.1)	298 (15.7)	167 (8.8)	1,893
Average count/year	61.3	237.7	177.0	99.3	55.7	631
Post- vaccination						
			Age group			
Admission year	6-11 months (N, %)	12-23 months (N, %)	24-35 months (N, %)	36-47 months (N, %)	48-59 months (N, %)	Total (100%)
2010	61 (8.6)	255 (35.8)	208 (29.2)	118 (16.6)	70 (9.8)	712
2011	55 (8.9)	202 (32.8)	208 (33.8)	91 (14.8)	60 (9.7)	616
2012	58 (8.8)	218 (33.2)	204 (31.1)	125 (19.1)	51 (7.8)	656
2013	36 (7.8)	147 (32.0)	145 (31.5)	81 (17.6)	51 (11.1)	460
2014	74 (10.6)	254 (36.5)	195 (28.0)	104 (14.9)	69 (9.9)	696
2015	85 (9.8)	328 (37.6)	251 (28.8)	127 (14.6)	81 (9.3)	872
2016	71 (7.8)	329 (4)	271 (29.7)	150 (16.4)	93 (10.2)	914
2017	58 (6.5)	325 (36.2)	276 (30.8)	157 (17.5)	81 (9.0)	897
2018	104 (9.2)	415 (36.8)	290 (25.7)	189 (11.5)	130 (11.5)	1,128
Total	602 (8.7)	2,473 (35.6)	2,048 (29.5)	1,142 (16.4)	686 (9.9)	6,951
Average count/year	66.9	274.8	227.6	126.9	76.2	772.3

Table 3.4: Febrile seizures hospitalisation pre- and post-vaccination

	Vaccination period		
	Pre-	Post-	Total
No seizure	16,087 (29.8)	37,954 (70.2)	54,041
Febrile seizure	1,889 (21.4)	6,948 (78.6)	8,837
Total	17,976 (28.6)	44,902 (71.4)	62,878

3.4. Annual FS hospitalisation rates

The estimated annual incidence (per 1,000 population) of FS hospitalisations among children aged between 6 months and 59 months decreased from 4.79 per 1,000 population (median 2006–2008) to 3.15 per 1,000 population in 2013 (maximal reduction of 34.2% reduction) [Table 3.5]. By 2015, the overall FS hospitalisation had increased (5.97 per 1,000 population), the incidence changes peaked at 61.1% but the annual incidence peaked at 7.72 per 1,000 in 2018 (Table 3.5). While the maximal incidence-change reduction of 55.6% (2.46 per 1,000) occurred in 2013 among the 6-11 months age category, the incidence change increase was most remarkable in 2018 in the 24-59 months age group category which was 71.6% (5.57 per 1,000 [pre-vaccine, 3.25 per 1,000]) (Table 3.5). The highest incidence of 11.29 per 1,000 occurred in 2018 in the 12-23 months age group category compared to the pre-vaccine incidence of 7.59 per 1,000 (Appendix C).

Table 3.5: Incidence of febrile seizures hospitalisations pre–vaccine introduction (2006–2008) compared with post-vaccine era (2010–2018) among children aged between 6 and 59 months in Soweto, South Africa

Age group and Year	Incidence per 1,000	Incidence difference[a]	Change in incidence[b], %
6-59 months			
Median 2006-2008	4.79		
2010	4.93	0.14	2.9
2011	4.22	-0.57	-12.0
2012	4.50	-0.29	-6.1
2013	3.15	-1.64	-34.2
2014	4.77	-0.03	-0.6
2015	5.97	1.18	24.6
2016	6.26	1.46	30.5
2017	6.14	1.35	28.1
2018	7.72	2.93	61.1

NB. [a]Incidence difference: the difference in incidence between post-vaccine year and the median pre-vaccine year.

[b] Change in incidence: Incidence difference as a proportion of the median pre-vaccine value

3.5. ARI trend and FS Hospitalisations

Of 74,160 hospitalisations of children aged between 6 and 59 months from 2006-2018, 31,179 had ARI, with an overall co-diagnosis of FSs in 8.3% (2,579). The proportion with a co-diagnosis of FSs with ARI reached a peak at 11.3%, 13.4%, and 16.3% for the year 2015, 2016, and 2017, respectively (Appendix D). More than 50% of children hospitalised with ARI and FSs were aged 24-59 months (Table 3.6). The peak hospitalisation count of ARI occurred in the pre-vaccine era (Figure 3.3). Throughout the pre- and post-vaccine years, ARI hospitalisation trend among children aged 48-59 months had the least count fluctuations (Figure 3.3).

Table 3.6: Age distribution of children with febrile seizures hospitalisations with co-diagnosis of ARI by year

	ARI & FS by Age group (months)					
year	6-11	12-23	24-35	36-47	48-59	Total
2006	20 (8.2)	98 (40)	67(27.4)	38 (15.5)	22 (9.0)	245
2007	6 (5.0)	52 (43.7)	31 (26.1)	21 (17.7)	9 (7.6)	119
2008	20 (10.4)	70 (36.3)	46 (23.8)	36 (18.7)	21 (10.9)	193
2009	19 (12.7)	48 (32.0)	45 (30.0)	21(14.0)	17 (11.3)	150
2010	11 (6.5)	59 (34.9)	57 (33.7)	30 (17.8)	12 (7.1)	169
2011	10 (9.3)	41 (38.0)	34 (31.5)	13 (12.0)	10 (9.3)	108
2012	16 (12.9)	36 (29.0)	41 (33.1)	18 (14.5)	13 (10.5)	124
2013	6 (8.2)	17 (23.3)	30 (41.1)	11 (15.1)	9 (12.3)	73
2014	14 (11.1)	42 (33.3)	39 (31.0)	19 (15.1)	12 (9.5)	126
2015	32 (10.7)	115 (38.6)	94 (31.5)	33 (11.1)	24 (8.1)	298
2016	30 (8.8)	116 (34.0)	95 (27.9)	59 (17.3)	41 (12.0)	341
2017	19 (4.6)	157 (38.3)	128 (31.2)	69 (16.8)	37 (9.0)	410
2018	26 (11.7)	88 (39.5)	56 (25.1)	32 (14.4)	21 (9.4)	223
Total	229 (8.9)	939 (36.4)	763 (29.6)	400 (15.5)	248 (9.6)	2,579

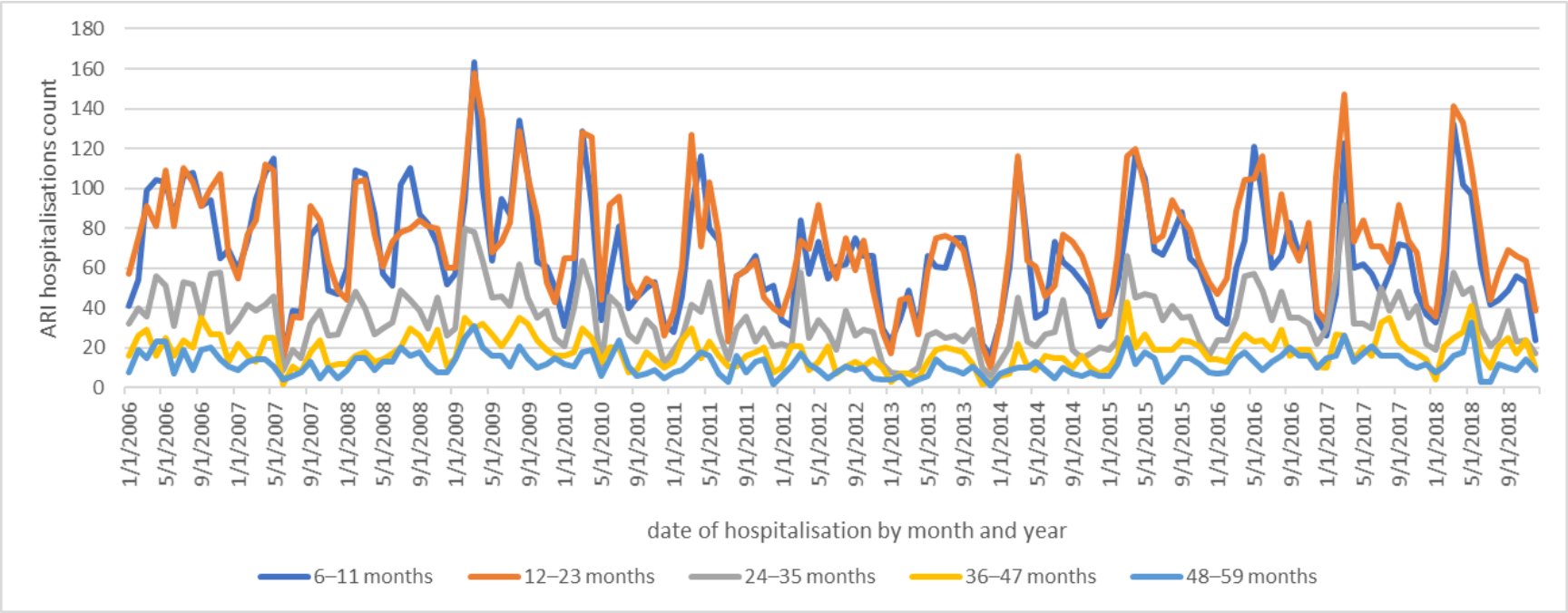


Figure 3.3:

Monthly count of Acute respiratory infection (ARI) hospitalisations in children aged between 6 and 59 months at CHBAH and BMDH, Soweto, South Africa, 2006–2018.

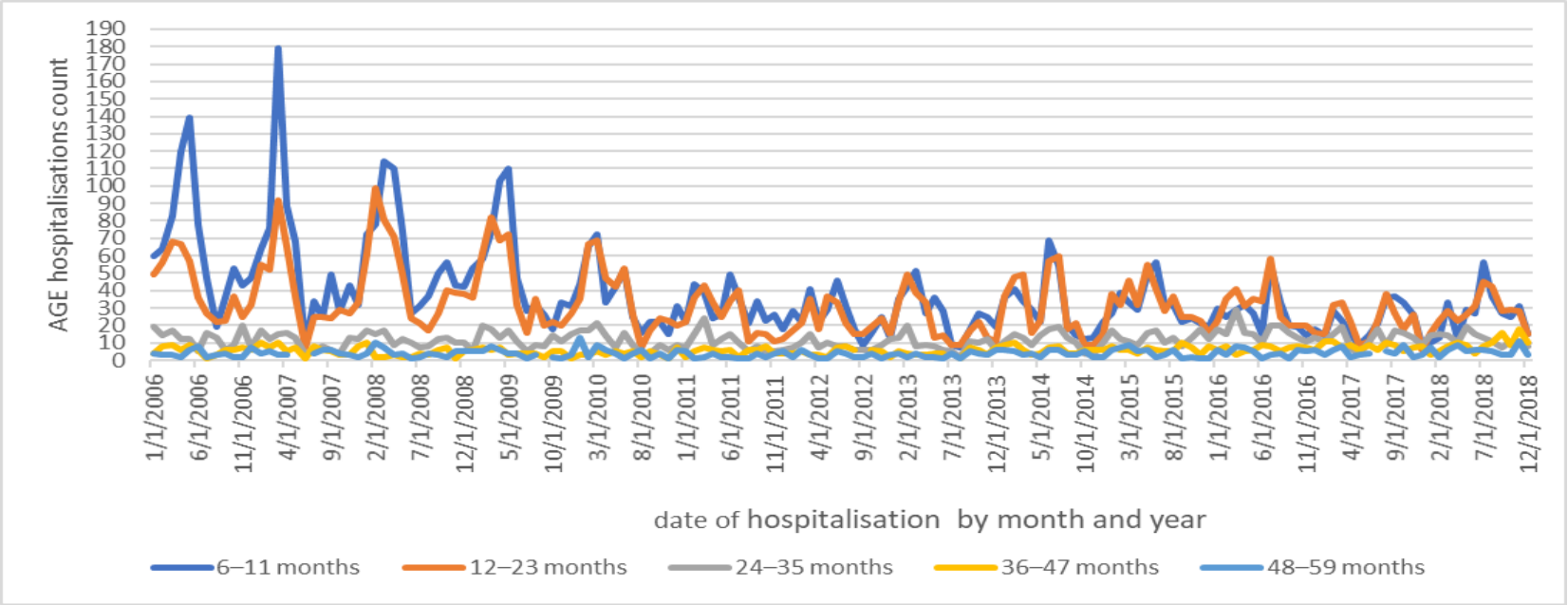


Figure 3.4:

Monthly count of acute gastroenteritis (AGE) hospitalisations in children aged between 6 and 59 months at CHBAH and BMDH, Soweto, South Africa, 2006–2018.

3.6. AGE trend and FS hospitalisations

Of the 14,000 children aged between 6 and 59 months hospitalised for AGE from 2006 to 2018, 692 (4.9%) had a co-diagnosis of FSs (Appendix E). The AGE trend indicated a decline of monthly AGE in the post-vaccine era (Figure 3.4). The overall proportion with a co-diagnosis of FS hospitalisations was 4.9%, and a peak was reached from 2014 to 2017 (6.4%, 9.0%, 10.6%, and 14.8%, respectively) [Appendix E]. More than 60% of children hospitalised with AGE and FSs were aged 24-59 months in the post-vaccine era (Table 3.7; Figure 3.4). In the post-vaccination period, there were more co-diagnoses of FS episodes among children hospitalised for AGE (Table 3.8). Throughout the pre- and post-vaccine years AGE hospitalisation trend among children aged 48-59 months had the least hospitalisation count fluctuation (Figure 3.4).

Table 3.7: Age distribution of children with febrile seizures hospitalisations with co-diagnosis of AGE by year

	AGE & FS by Age group (months) Total n=					
Year	6-11	12-23	24-35	36-47	48-59	Total (100.0%)
2006	3 (10.3)	6 (20.7)	8 (27.6)	7 (24.1)	5 (17.2)	29
2007	0 (0.0)	12 (44.4)	7 (25.9)	6 (22.2)	2 (7.4)	27
2008	6 (19.4)	7 (22.6)	7 (22.6)	7 (22.6)	4 (12.9)	31
2009	1 (4.6)	7 (31.8)	8 (36.4)	6 (27.3)	0 (0.0)	22
2010	2 (5.3)	9 (23.7)	12 (31.6)	8 (21.1)	7 (18.4)	38
2011	4 (18.2)	5 (23.7)	8 (36.4)	2 (9.09)	3 (13.6)	22
2012	1 (2.63)	12 (31.6)	12 (31.6)	8 (21.1)	5 (13.2)	38
2013	0 (0.0)	11 (29.7)	15 (40.5)	6 (16.2)	5 (13.5)	37
2014	5 (8.1)	18 (30.7)	19 (30.7)	13 (21.0)	7 (11.3)	62
2015	6 (6.4)	35 (37.2)	31 (33.0)	15 (16.0)	7 (7.5)	94
2016	1 (1.0)	30 (28.6)	39 (37.1)	21 (20.0)	14 (13.3)	105
2017	4 (3.4)	34 (28.8)	39 (33.1)	30 (25.4)	11 (9.3)	118
2018	3 (4.4)	21 (30.4)	21 (30.4)	15 (21.7)	9 (13.0)	69
Total	36 (5.2)	207 (29.9)	226 (32.7)	144 (20.8)	79 (11.4)	692

Table 3.8: Proportion of febrile seizures among AGE Pre- and post-vaccination

	Febrile seizure		Total	p-value
	Vaccination period			
	Pre	Post		
No seizure	4,348 (98.0)	7,652 (92.9)	12, 000	<0.001
febrile seizure	87 (2.0)	583 (7.1)	670	
Total	4,435	8,235	12,670	

3.5. HIV-infected and HIV-uninfected children

Of ACS hospitalisations from 2006 to 2018 among children aged between 6 months and 59 months, 305 (2.2%) were HIV positive (142, 1.5% among FS hospitalisations) [Table 3.9]. The prevalence of HIV infection among children aged between 6 months and 59 months hospitalised for FSs reached a peak of 3.3% in 2013 and declined to 0.8% by 2018 (Table 3.9).

Table 3.9: Prevalence of HIV among children aged between 6 months and 59 months with all-cause seizures and febrile seizures

	All-cause seizures			Febrile seizures		
year	HIV status		Total (100%)	HIV status		Total (100%)
	Negative	Positive		Negative	Positive	
2006	1,127 (97.24)	32 (2.76)	1,159	744 (97.77)	17 (2.23)	761
2007	737 (96.72)	25 (3.28)	762	433 (98.41)	7 (1.59)	440
2008	1,008 (98.25)	18 (1.75)	1,026	682 (98.55)	10 (1.45)	692
2009	996 (97.94)	21 (2.06)	1,017	623 (98.73)	8 (1.27)	631
2010	1,010 (97.68)	24 (2.32)	1,034	697 (97.89)	15 (2.11)	712
2011	916 (98.39)	15 (1.61)	931	611 (99.19)	5 (0.81)	616
2012	1,052 (96.6)	37 (3.4)	1,089	643 (98.02)	13 (1.98)	656
2013	698 (94.45)	41 (5.55)	739	445 (96.74)	15 (3.26)	460
2014	955 (97.55)	24 (2.45)	979	687 (98.71)	9 (1.29)	696
2015	1,220 (98.87)	14 (1.13)	1,234	864 (99.08)	8 (0.92)	872
2016	1,326 (98.59)	19 (1.41)	1,345	899 (98.36)	15 (1.64)	914
2017	1,280 (98.39)	21 (1.61)	1,301	886 (98.77)	11 (1.23)	897
2018	1,505 (99.08)	14 (0.92)	1,519	1,119 (99.2)	9 (0.8)	1,128
Total	13,830 (97.84)	305 (2.16)	14,135	9,333 (98.5)	142 (1.5)	9,475

3.5. Risk factors associated with FSs

Seven risk factors identified to be significantly associated with FSs were age, sex, HIV status, season of admission, co-diagnoses of ARI and AGE and vaccination period (Table 3.10).

The results of univariate and multivariate analyses of risk factors associated with hospitalisation for FSs are shown in Table 3.11. In the univariate analysis, the age group category had significant effect on hospitalisation for FSs. The odds of hospitalisation for FS when compared to the age 6-11 months, was high in the 24-35 months age category (OR, 5.7; CI 95%, 5.3-6.2; $p<0.001$). Males had significant effect on hospitalisation for FSs with OR, 1.2 (CI 95%, 1.2-1.3; $p<0.001$). Autumn (OR, 1.6; CI 95%, 1.5-1.7; $p<0.001$) and Winter (OR, 1.5; CI 95%, 1.4-1.6; $p<0.001$) had significant effect on hospitalisation for FSs as did post-vaccination period (OR, 1.56; CI 95%, 1.48-1.65; $p<0.001$). Being positive for HIV as well as ARI and AGE were less likely associated with hospitalisation for FSs (OR, 0.16; CI 95%, 0.14-0.19; $p<0.001$), (OR, 0.4; CI 95%, 0.39-0.43; $p<0.001$), and (OR, 0.28; CI 95%, 0.26-0.30; $p<0.001$), respectively.

For the multivariate analysis variables, the most significant associated factors influencing the occurrence of FSs were selected; and included age, sex, season, and vaccination period. HIV status, ARI, and AGE were not included because they were less associated with hospitalisation for FSs in the univariate analysis. The results of the multivariate analysis are shown in Table 3.10.

Table 3.10: Risk factors for febrile seizures

Risk factor	Febrile seizures N (%)	No Seizures, N (%)	p- value
Age group (months)			
6-11	865 (4.5)	18,549 (95.5)	<0.001
12-23	3,400 (14.2)	20,536 (85.8)	
24-35	2,749 (21.1)	10,257 (78.9)	
36-47	1,544 (19.9)	6,215 (80.1)	
48-59	908 (16.9)	4,477 (83.1)	
Sex			
Male	5,854 (14.8)	33,811 (85.2)	
Female	3,550 (12.4)	25,143 (87.6)	<0.001
Season			
Autumn	2,351 (11.1)	21,134 (88.9)	<0.001
Winter	2,752 (16.7)	16,452 (83.3)	
Spring	2,612 (15.7)	16,645 (84.3)	
Summer	1,751 (11.5)	15,269 (88.5)	
HIV status			
Positive	142 (2.7)	5085 (97.3)	<0.001
Negative	9324 (14.5)	54949 (85.5)	
Vaccination period			
Pre	1,889 (10.5)	16,087 (89.5)	<0.001
post	6,948 (15.5)	37,954 (84.5)	
ARI			
Positive	2577 (8.3)	28602 (91.7)	<0.001
Negative	6889 (18.0)	31432 (82.0)	
AGE			
Positive	692 (4.94)	13308 (95.06)	<0.001
Negative	8774 (15.8)	46726 (84.2)	

Table 3.11: Logistic regression of risk factors for febrile seizures

	Univariate				Multivariate			
Risk factor	OR (95% CI)	[95% Conf. Interval]		p- value	OR (95% CI)	p- value	[95% Conf. Interval]	
Age group (months)								
6-11	Reference				Reference			
12-23	3.6	3.3	3.8	<0.001	3.6	<0.001	3.32	3.90
24-35	5.7	5.3	6.2	<0.001	5.8	<0.001	5.36	6.34
36-47	5.3	4.9	5.8	<0.001	5.3	<0.001	4.82	5.80
48-59	4.3	3.9	4.8	<0.001	4.3	<0.001	3.90	4.79
Sex								
Male	1.2	1.2	1.3	<0.001	1.2	<0.001	1.17	1.29
Female	Reference				Reference			
missing					0.5		0.37	0.65
Season								
Autumn	Reference				Reference			
Winter	1.6	1.5	1.7	<0.001	1.4	<0.001	1.35	1.53
Spring	1.5	1.4	1.6	<0.001	1.3	<0.001	1.26	1.43
Summer	1.0	0.97	1.1	0.3	0.9	<0.001	0.86	0.99
HIV status								
Positive	0.16	0.14	0.19	<0.001	-	-	-	-
Negative	Reference							
Vaccination period								
Pre	Reference				Reference			
post	1.56 (1.5-1.6)	1.48	1.65	<0.001	1.4	<0.001	1.35	1.51
ARI								
Positive	0.4	0.39	0.43	<0.001	-	-	-	-
Negative	Reference							
AGE								
Positive	0.28	0.26	0.30	<0.001	-	-	-	-
Negative	Reference							

NB. HIV status, AGE and ARI were not included in the multivariate analysis. These were deliberately left out as this analysis was performed after excluding the less significant risk factors (The relative risks are hereby reported).

4. CHAPTER FOUR- DISCUSSION

This study evaluated the trends in seizure hospitalisation pre- and post-rotavirus vaccine introduction among children in Soweto, South Africa. In South Africa, the introduction of an oral live attenuated rotavirus vaccine into the national immunisation programme in August 2009 was not associated with a sustained reduction in the incidence of ACS and FS hospitalisations among children aged between 6 and 59 months in the urban setting of Soweto, Johannesburg, accounting for 19.0% and 12.8%, respectively, during the study period.

Following rotavirus vaccine introduction, the transient downward trend in ACS and FS hospitalisation count was observed from 2010-2012. The overall annual incidence of FS hospitalisations among children aged between 6 and 59 months initially decreased by 34.2%; however, there was subsequent an increase from 2015 to 2018. The highest incidence of 11.29 per 1,000 population occurred in 2018 among the 12-23 months age group; the pre-vaccine incidence for the same age group was 7.59 per 1,000 population. The maximum incidence-change reduction of 55.6% (-2.46 per 1,000 population) occurred in 2013 among the 6-11 months age group. During the pre- (31.0% and 33.8%) and post-vaccine years (24.8% and 34.0%), admissions among children aged 6-11 months and 12-23 months, respectively, were not significantly different.

Among all hospitalised children with ARI, 8.3% had a co-diagnosis of FSs, and more than 50% were aged 24-59 months. Amidst all hospitalised children with AGE, 4.94% had a co-diagnosis of FS and more than 60.0% of them were aged 24-59 months. In the post-vaccination period, there were more co-existing FS episodes in children hospitalised for AGE. Among FS hospitalised children, 1.5% had an overall co-diagnosis of positive HIV infection and more than 80% were aged 24-59 months, but the proportion of FS hospitalisation with a co-diagnosis of HIV declined to 0.8% by 2018.

Similar to our finding of un-sustained reduction in seizure hospitalisation following rotavirus vaccine introduction, Biggart et al. 2018 found no impact on seizure hospitalizations in a UK population-level study.[45] Orrico-Sánchez et al. 2018 in Spain also found no impact in a population-based ecological study.[46] The Spanish study reported rotavirus vaccine coverage of 42% at the time of study, different from the >90% vaccine coverage achieved in our setting.[61]

On the contrary, other studies observed a reduction in seizure hospitalisation (either for afebrile seizure or FS) in the post-rotavirus vaccine introduction years, compared to the pre-vaccination periods.[42, 44] Payne et al., 2013 and Burke et al., 2018, in two different studies in the US, reported risk reduction in childhood seizures admission /hospitalization between 18-24%, the effect of which lasted up to five years after vaccination introduction.[42,43] Similarly, in the UK, Hungerford, et al. 2019 reported a 23% and 31% reduction in the incidence of any seizures and FSs, respectively, with AGE among under 5 hospital admissions.[28]

There are several possible reasons for the observed lack of reduction in FS hospitalisation counts and incidence post-rotavirus vaccine introduction in South Africa. Firstly, this might be related to the lower efficacy and effectiveness of oral rotavirus vaccines against the severe rotavirus diseases observed in low- and middle-income countries, compared to high-income countries.[23,32,33] If the overall effectiveness of the vaccines against rotavirus diarrhoea is lower, we might expect the impact on FS to be reduced compared to high income countries; this might explain the lack of effect on FS hospitalisation as observed in our study.

Secondly, rotavirus diarrhoea occurs at a younger age in low- and middle-income countries, compared to high income ones, with the incidence of severe rotavirus diarrhoea prior to vaccine introduction in South Africa being highest in the first year of life.[26] In contrast, this study showed that the incidence of FS hospitalisation was highest in the 12-23 months age group, in both the pre- and post-vaccination periods. This is in keeping with results from the secondary analysis of a cohort study conducted in Soweto from 1998-2005, where the incidence of FS hospitalisation was highest in children aged 12-23 months and this age group was five times more likely to be hospitalised for FSs compared to those in the 6-11 month age group.[67] Thus, the contribution of rotavirus to the occurrence of FS in South Africa may be reduced as the peak of the rotavirus disease occurs prior to 12-23 months of age, when FSs are more common.

Thirdly, due to the seasonal nature of rotavirus diarrhoea, which most commonly occurs during the dry, winter months in South Africa, respiratory pathogens might play more important roles in the aetiology of FS, and might, thus, mask any possible effects of the rotavirus vaccine on FS incidence. In the study by Sheridan et al., the possibility of the influence of influenza vaccination rates was unclear on the observed reduction in seizure hospitalisation.[44] Tebeila et al, in the same setting recently demonstrated an association between influenza A detection and FSs among

hospitalized children, and found that the detection of influenza A in the nasopharynx doubled the odds of hospitalisation for FSs in children in Soweto.[67] This might have impacted any visible effect of the rotavirus vaccine on seizure hospitalisation reduction in our setting.

Fourthly, considering the possible mechanisms of action of rotavirus infection causing convulsions, the dominance of rotavirus genotypes which are less inciting to convulsions in some settings may account for the lack of reduction in seizure hospitalisation in the post-vaccination era.[21]

Lastly, the present analysis used data from a routine paediatric discharge summary database, which mostly would have captured the severe cases requiring hospitalisation. Finding from the various studies on rotavirus-associated seizure hospitalisation reduction are impacted by the type of study design, level of vaccine coverage, case definition, and analysis methods. Rotavirus testing was not routinely performed on all children hospitalised with AGE at CHBAH and BMDH. Therefore, the direct impact of rotavirus vaccine introduction on rotavirus-specific ACS hospitalisations could not be assessed; thus, ACS (with focus on FSs) hospitalisations were used as a proxy measure. According to the WHO definition, a single episode of AGE occurs when ≥ three loose stools are passed in any 24-hour period with a duration of <14 days, but not less than 30 days after a previous episode of diarrhoea. For this study, the ICD codes for diarrhoeal disease were adopted as we did not have detailed clinical information. In addition, detailed information on other potential confounders, for example, family history of FS, was not available in the dataset.

Encouragingly, we observed a sustained reduction in the number of hospitalisations for AGE in the post-vaccination period, compared to the pre-vaccination period. A previous evaluation by Groome et al., 2016 showed a reduction in all-cause diarrhoeal hospitalisations during the post-vaccination period (2010-2014).[39] This study shows that this trend continued in the post-vaccination period (2015-2018), with reduced numbers of AGE hospitalisations compared to pre-vaccination, particularly in children under the age of 2 years.

Our results show a slight increase in the number and incidence of hospitalisations for FSs during the period from 2015 to 2018. One possible explanation might be that the completeness of the data collection improved over this time period. In particular, BMDH was opened in 2014 and steadily saw an increase in admissions from this time onwards. It is possible that patients that

might have accessed a hospital other than CHBAH prior to the opening of BMDH, accessed this new hospital once it was opened, and thus contributed to the numerator in the incidence calculations. However, the sustained reductions in AGE hospitalisations in the period from 2015-2018 suggest that this was most likely not the case.

The increase in FSs might indicate an increase in another pathogen associated with the occurrence of FSs, for example, influenza A or non-rotavirus AGE-causing pathogens, for example *Shigella* and norovirus, which have also been associated with FSs.[18] Data from the National Institute for Communicable Diseases respiratory surveillance programme shows a possible trend towards higher influenza positivity between the years 2015-2018 (Appendix F page 17). Thus, the role of respiratory viruses, in particular the influenza virus, in the aetiology of FSs in South Africa needs further investigation, especially as effective vaccines against the influenza virus are licenced for use within the country.[68] Despite this, remarkable reduction in AGE hospitalisation has been reported from our setting.[39]

Limitations

This ecological study, with de-identified data, has inherent limitations, including its inability to assess causality. The use of ACS hospitalisation meant that trends in rotavirus-associated seizure hospitalisations could not be accurately assessed, as pathogen-specific testing was not available. The potential differential recording of data over the study period may have introduced errors, including misclassification of the diagnosis and missing data. Data for the earlier years may not have been as clean or as accurate as the later years. However, if diagnoses of FSs were more accurately recorded post-vaccination, compared to pre-vaccination, then this would, in fact, bias any finding towards the null. Information available in the database did not allow for classifying seizure type, first and recurrent FSs were not specified, and simple and complex FSs were not differentiated. Due to the limitation of the secondary data, other relevant risk factors, such as height of the temperature, positive family history of seizures in first-degree relatives, developmental delay, and day care attendance history could not be assessed.

In addition, there was inadequate data regarding the nutritional status of the children, thus, the impact of malnutrition and trace element deficiencies, and their effect on the immune response following rotavirus vaccination and possibly the seizure pattern could not be assessed.[23] Some reports indicate that the efficacy of vaccination is impaired by malnutrition especially zinc

deficiency and avitaminoses, gut microbiota, other concurrent infections, and maternal antibodies.

To calculate the incidence, population estimates based on census data (2001 and 2011)[66] were only available for years 2006-2014. Numerous attempts were made to get access to updated Region D and G mid-population estimates, without success. Thus, the estimate for year 2014 was applied for years 2015-2018. Any increase in population estimates during these years would not have been taken into account in our calculations, and thus, we might have overestimated the true incidence of FSs in these years.

FSs are most often due to ARI [14] and episodes following AGE, including rotavirus diarrhoea, have been reported; in some settings, malaria (especially in sub-Saharan Africa) contributes significantly to morbidity and mortality.[11,18,19] Information on testing of respiratory and other pathogens were not available and could thus not be assessed. A prospective study, including testing for respiratory, diarrhoeal, and other pathogens would be needed to accurately assess the aetiology of FSs in South Africa.

Our study focused on seizure hospitalisations (likely the most severe form) and may not truly reflect the severity of seizure incidence in the community. Future studies might need to quantify the absolute population impact of rotavirus vaccination on FSs for all severity, since the proportion of children hospitalised for rotavirus-associated seizures are only a subset of the less severe presentations in the community. Finally, we studied, Soweto, one urban community in South Africa; thus, the results may not be generalizable to other South African and African settings.

Potential confounders

There may be annual temporal changes in the severity and incidence of ARI and AGE hospitalisation, which needs to be accounted for. Other potential factors that were not adjusted for included ARV rollout, maternal prevalence of HIV infection, HIV mother to child transmission rate (these parameters were recorded relatively well in the postvaccination period but not in the pre-vaccination period).

The study period in South Africa witnessed challenges to ART access- and usage-monitoring; this included the approach to reporting, inadequate data on the age of patients, the transition in

the treatment guidelines, and the lack of consensus on the best measures for assessing coverage. So, it is difficult to discern the contribution of ART when evaluating the impact of rotavirus vaccination on FS hospitalisations.

Recommendations

A prospective, multicentre observational study could be performed to investigate the role of rotavirus vaccination on the prevalence and incidence of ACS/FS hospitalisations. However, if the effect size is expected to be small, this would necessitate a large sample size, which is a limitation. Rotavirus testing would need to be incorporated to validate any potential correlation with FS hospitalisation. The role of respiratory viruses, in particular the influenza virus, in the aetiology of FSs in South Africa also needs further investigation.

APPENDICES

Appendix A: Total hospitalisations and seizure hospitalisations stratified by hospital

	Hospital		
	CHBAH (n, %)	BMDH (n, %)	Total
No of children hospitalised	54,666 (95.6)	2,495 (4.4)	57,161
No of hospitalisations	71,345 **(**96.2**)**	2,815 **(**3.8**)**	74,160
Seizure types			
Epilepsy	2,887 (96.5)	106 (3.5)	2,993 (21.2)
FSs	8,754(92.5)	712 (7.5)	9,466 (67.0%)
Unspecified convulsions	1,541 (92.0)	135 (8.0)	1,676 (11.9%)
All-cause seizures	13,182 (93.3)	953 (6.7)	14,135

Appendix B: Age distribution of hospitalised children at CHBAH and BMDH from 2006-2018

Age group (months)	Freq.	Percent	Cum.
6-11	19,899	26.8	26.8
12-23	25,099	33.8	60.7
24-35	14,164	19.1	79.8
36-47	8,787	11.9	91.6
48-59	6,211	8.38	100.0
Total	74,160	100.0	

Appendix C: Incidence of febrile seizures hospitalisations pre–vaccine introduction (2006–2008) compared with post-vaccine era (2010–2018) among children aged between 6 and 59 months (stratified age groups) in Soweto, South Africa

Age group and Year	Incidence per 1,000	Incidence difference[a]	Change in incidence[b], %
6-59 months			
6-11 months			
Median 2006-2008	4.42		
2010	3.57	-0.85	-19.1
2011	3.07	-1.35	-30.5
2012	3.20	-1.22	-27.7

2013	1.96	-2.46	-55.6
2014	3.99	-0.43	-9.7
2015	4.58	0.16	3.7
2016	3.83	-0.59	-13.3
2017	3.13	-1.29	-29.2
2018	5.61	1.19	26.9
12-23 months			
Median 2006-2008	7.59		
2010	7.25	-0.34	-4.4
2011	5.58	-2.00	-26.4
2012	6.00	-1.59	-20.9
2013	4.02	-3.57	-47.**0**
2014	6.91	-0.68	-9.0
2015	8.92	1.33	17.6
2016	8.95	1.36	17.9
2017	8.84	1.25	16.5
2018	11.29	3.70	48.8
24-59 months			
Median 2006-2008	3.25		
2010	3.63	0.38	11.8
2011	3.27	0.02	0.7
2012	3.48	0.23	7.0
2013	2.53	-0.71	-22.0
2014	3.37	0.12	3.7
2015	4.20	0.95	29.4
2016	4.70	1.46	44.9
2017	4.70	1.46	44.9
2018	5.57	2.33	71.6

NB. [a]Incidence difference: the difference in incidence between post-vaccine year and the median pre-vaccine year.

[b] Change in incidence: Incidence difference as a proportion of the median pre-vaccine value

Appendix D: Febrile seizures hospitalisations among children with ARI by year

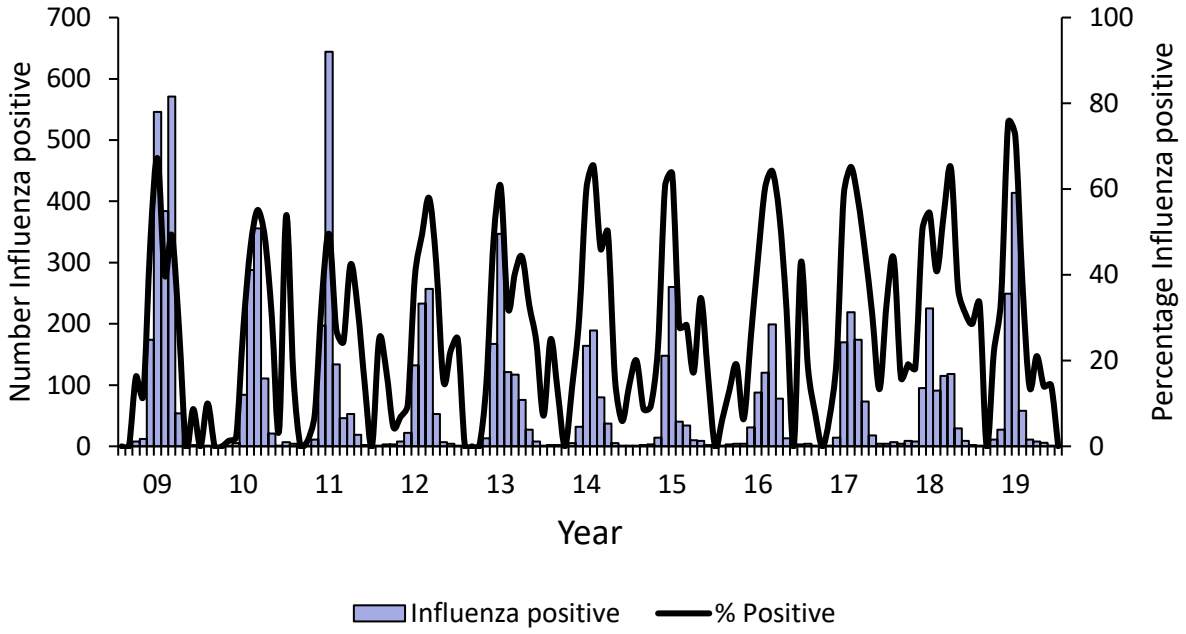
	Febrile seizures		
year	No	Yes	Total
2006	2,790 (91.9)	245 (8.1)	3,035
2007	2,126 (94.7)	119 (5.3)	2,245
2008	2,493 (92.8)	193 (7.2)	2,686
2009	3,100 (95.4)	150 (4.6)	3,250
2010	2,083 (92.5)	169 (7.5)	2,252
2011	2,075 (95.1)	108 (5.0)	2,183
2012	1,875 (93.8)	124 (6.2)	1,999
2013	1,443 (95.2)	73 (4.82)	1,516
2014	1,796 (93.4)	126 (6.6)	1,922
2015	2,332 (88.7)	298 (11.3)	2,630
2016	2,198 (86.6)	341 (13.4)	2,539
2017	2,112 (83.7)	410 (16.3)	2,522
2018	2,177 (90.7)	223 (9.3)	2,400
Total	28,600 (91.7)	2,579 (8.3)	31,179

Appendix E: Febrile seizures hospitalisations among children with AGE by year

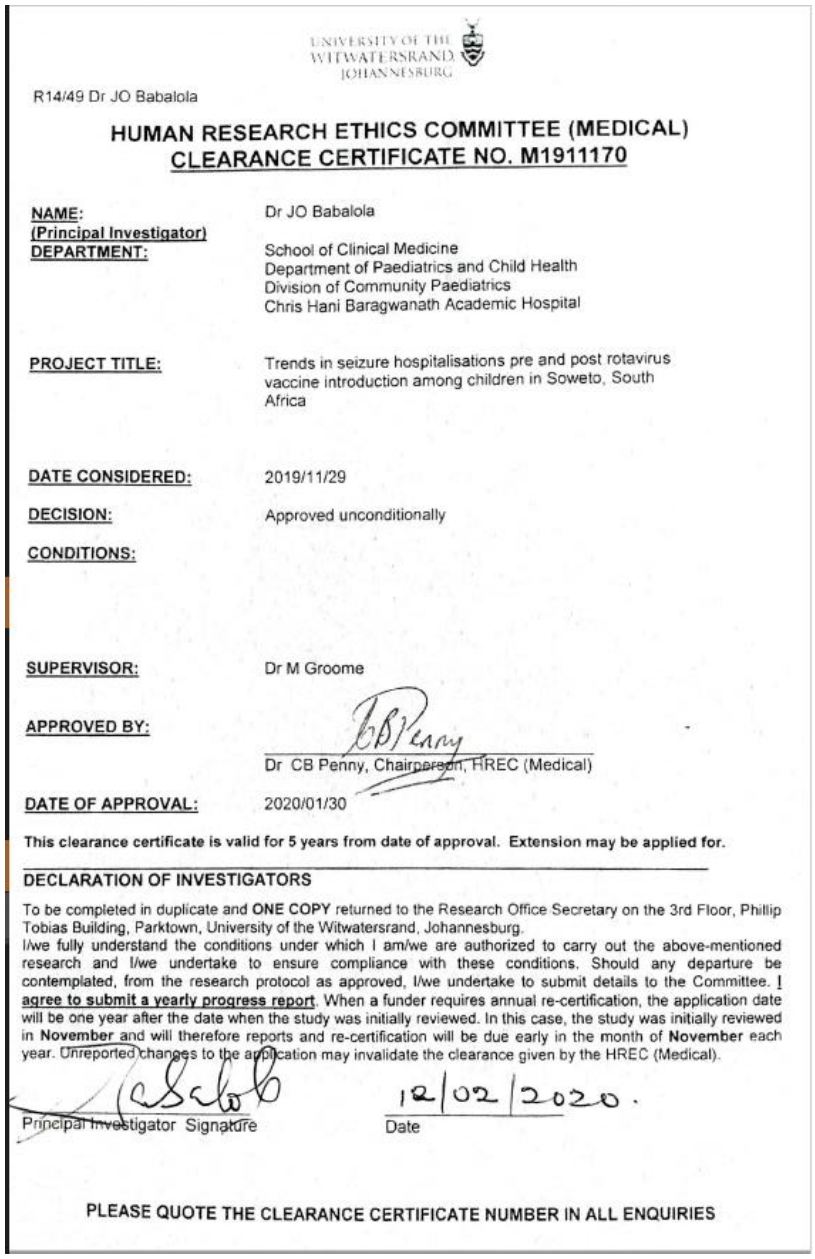
	Febrile seizures		
Year	Negative	Positive	Total admissions
2006	1,512 (98.12)	29 (1.88)	1,541
2007	1,345 (98.03)	27 (1.97)	1,372
2008	1,491 (97.96)	31 (2.04)	1,522
2009	1,308 (98.35)	22 (1.65)	1,330
2010	1,052 (96.51)	38 (3.49)	1,090
2011	845 (97.46)	22 (2.54)	867
2012	707 (94.9)	38 (5.1)	745
2013	730 (95.18)	37 (4.82)	767
2014	909 (93.61)	62 (6.39)	971
2015	952 (91.01)	94 (8.99)	1,046
2016	886 (89.4)	105 (10.6)	991
2017	681 (85.23)	118 (14.77)	799

2018	890 (92.81)	69 (7.19)	959
Total	13,308 (95.06)	692 (4.94)	14 000

Appendix F: 2009-2019_Influenza trend (Courtesy NICD)



Appendix G: Ethics clearance certificate



UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr JO Babalola

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M1911170

NAME: (Principal Investigator)	Dr JO Babalola
DEPARTMENT:	School of Clinical Medicine Department of Paediatrics and Child Health Division of Community Paediatrics Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Trends in seizure hospitalisations pre and post rotavirus vaccine introduction among children in Soweto, South Africa
DATE CONSIDERED:	2019/11/29
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr M Groome
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/01/30

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, Johannesburg.

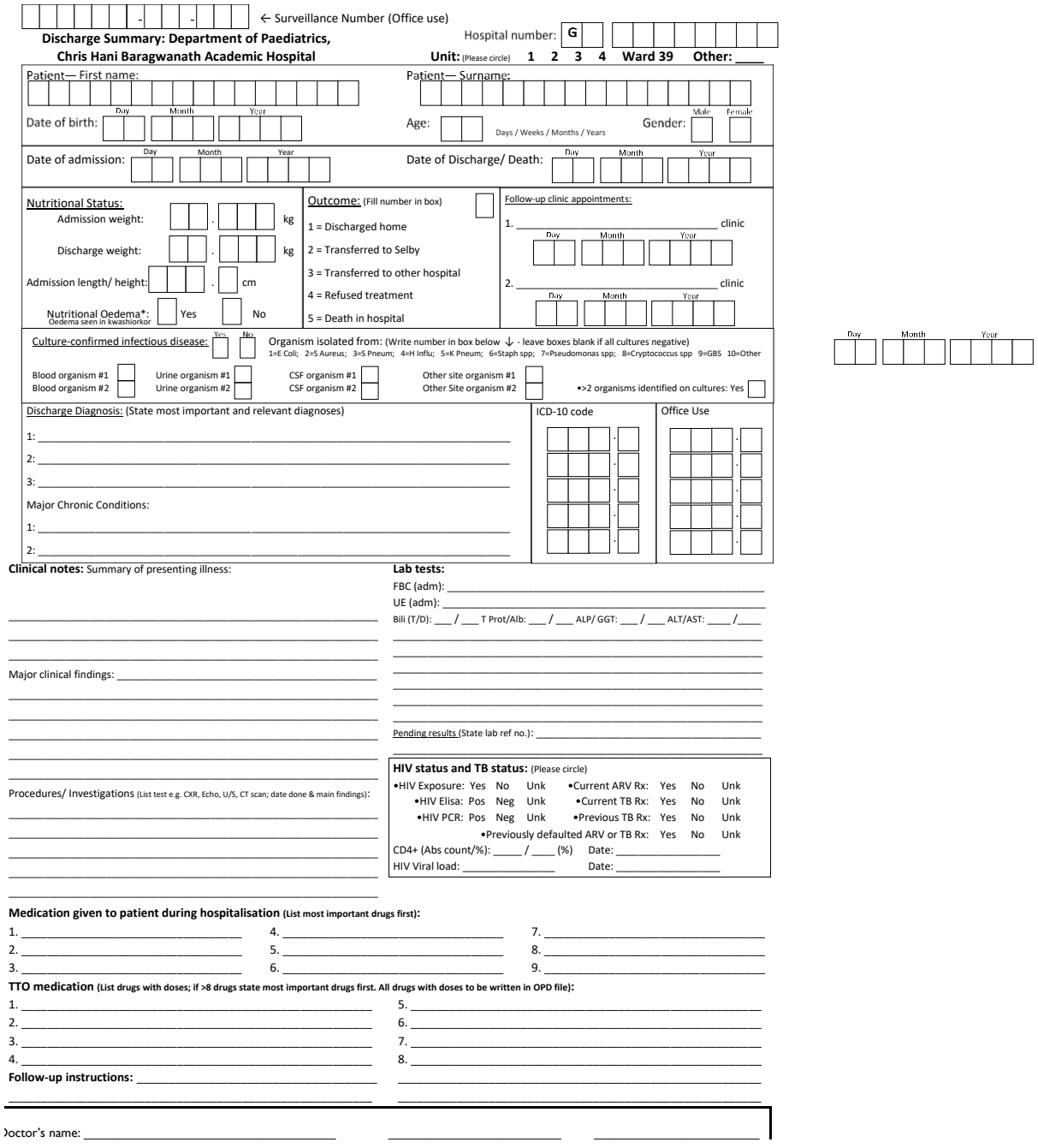
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **November** and will therefore reports and re-certification will be due early in the month of **November** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

12/02/2020.
Date

PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES

Appendix H: Discharge summary form



← Surveillance Number (Office use)

Hospital number: G

Discharge Summary: Department of Paediatrics,
Chris Hani Baragwanath Academic Hospital

Unit: (Please circle) **1 2 3 4 Ward 39 Other: ____**

Patient— First name:

Patient— Surname:

Date of birth: Day Month Year

Age: Days / Weeks / Months / Years

Gender: Male Female

Date of admission: Day Month Year

Date of Discharge/ Death: Day Month Year

Nutritional Status:
Admission weight: . kg
Discharge weight: . kg
Admission length/ height: . cm
Nutritional Oedema*: Yes No
*Oedema seen in kwashiorkor

Outcome: (Fill number in box)
1 = Discharged home
2 = Transferred to Selby
3 = Transferred to other hospital
4 = Refused treatment
5 = Death in hospital

Follow-up clinic appointments:
1. _____ clinic Day Month Year
2. _____ clinic Day Month Year

Culture-confirmed infectious disease: Yes No

Organism isolated from: (Write number in box below ↓ - leave boxes blank if all cultures negative)
1=E Coli; 2=S Aureus; 3=S Pneum; 4=H Influ; 5=K Pneum; 6=Staph spp; 7=Pseudomonas spp; 8=Cryptococcus spp 9=GBS 10=Other

Blood organism #1 / #2
Urine organism #1 / #2
CSF organism #1 / #2
Other site organism #1 / #2
•>2 organisms identified on cultures: Yes

Discharge Diagnosis: (State most important and relevant diagnoses)
1: _____
2: _____
3: _____

Major Chronic Conditions:
1: _____
2: _____

ICD-10 code

Office Use

Clinical notes: Summary of presenting illness:

Major clinical findings: _____

Procedures/ Investigations (List test e.g. CXR, Echo, U/S, CT scan; date done & main findings):

Lab tests:
FBC (adm): _____
UE (adm): _____
Bili (T/D): ___ / ___ T Prot/Alb: ___ / ___ ALP/ GGT: ___ / ___ ALT/AST: ____ /____

Pending results (State lab ref no.): _____

HIV status and TB status: (Please circle)
•HIV Exposure: Yes No Unk
•HIV Elisa: Pos Neg Unk
•HIV PCR: Pos Neg Unk
•Current ARV Rx: Yes No Unk
•Current TB Rx: Yes No Unk
•Previous TB Rx: Yes No Unk
•Previously defaulted ARV or TB Rx: Yes No Unk
CD4+ (Abs count/%): _____ / ____ (%) Date: _____
HIV Viral load: _____ Date: _____

Medication given to patient during hospitalisation (List most important drugs first):
1. _____ 4. _____ 7. _____
2. _____ 5. _____ 8. _____
3. _____ 6. _____ 9. _____

TTO medication (List drugs with doses; if >8 drugs state most important drugs first. All drugs with doses to be written in OPD file):
1. _____ 5. _____
2. _____ 6. _____
3. _____ 7. _____
4. _____ 8. _____

Follow-up instructions: _____

Doctor's name: _____

Day Month Year

DISCHARGE SUMMARY: Department of Paediatrics, Chris Hani Baragwanath Hospital **Unit: 1 2 3 4**

Patient Details: First name(s): Surname:

Hospital Number: Date of birth: Day Month Year Age: _____ Male Female

Admission details:

Date of admission: Date of discharge / death: Previous admission:

Admission weight: . kg Discharge weight: . kg Admission Length/Height: . cm Oedema:

Nutritional Status:
1= Normal 2= Underweight 3= Obese
4= Kwash 5= Marasmus 6= Marasmic-Kwash

Outcome:
Discharged home Transferred to Selby Transferred to other Hosp. Refused treatment Patient died

Diagnosis: Acute disease(s) or condition(s)	ICD-10 code	Office Use
1.		
2.		
3.		
4.		
5.		

Diagnosis: Chronic disease(s) or condition(s)	ICD-10 code	Office Use
1.		
2.		
3.		

Mother HIV Status:
Positive Negative Status Unknown

Mother received PMTCT? Yes

Child HIV ELISA:
Pos Neg Not done Pending

Child HIV PCR:
Pos Neg Not done Pending

ART: On treatment No ART treatment

Treatment started this admission? Yes

Previously defaulted treatment? Yes

Referral to HIV clinic:
Harriet Shezi PHRU Other

TB Status:
Mantoux Positive Mantoux Negative Mantoux Not done

Size of Mantoux induration: mm

Tests for microscopy & culture:
Induced Sputum Gastric Washings Blood / Other Not done

Chest X-ray:
Suggestive of TB Not suggestive of TB Not done

Circle radiological findings (see key):

1= Hilar adenopathy
2= Miliary TB
3= Bronchopneumonia
4= Consolidation
5= Pleural effusion
6= Cavitation
7= Other: _____

Microbiology:

Blood Culture #1 Blood Culture #2 Blood Culture #3

More than 3 blood cultures drawn? Yes

CSF Culture #1 CSF Culture #2

More than 2 CSF specimens drawn? Yes

Urine Culture #1 Urine Culture #2

More than 2 urine cultures sent? Yes

1= Negative
2= E Coli
3= S Aureus
4= S Pneumoniae
5= H Influenzae
6= K Pneumoniae
7= Staph spp
8= Pseudomonas spp
9= Cryptococcus spp
10= Other: _____

CD4: (Date: _____)
Absolute Percentage

Nosocomial sepsis: Suspected: Proven:

≥ 2 episodes of suspected / proven nosocomial sepsis? Yes

Special Investigations: (Done this admission; please write results in OPD file)

CT Scan: _____
Done Booked Date: _____

MRI Scan: _____
Done Booked Date: _____

Ultrasound: _____
Done Booked Date: _____

Other investigation(s):

DISCHARGE SUMMARY: Department of Paediatrics, Chris Hani Baragwanath Hospital

No.	Other problems not listed before as diagnosis:	Date first identified	Resolved:	
			Yes (date)	Ongoing
1.				
2.				
3.				
4.				

Clinical notes / Progress in ward:

Laboratory results:

TTO medication (List drugs; formal TTO to be written in OPD file):

Follow-up plan:

Follow-up clinic (1): **Follow-up date (1):**

Follow-up clinic (2): **Follow-up date (2):**

Doctor's name: _____ (Please print name legibly) _____ (Signature) _____ (Date)

Appendix I: Clinico-demographic characteristics of hospitalised children aged 6-59 months at CHBAH and BMDH, Soweto, South Africa, 2006–2018

	Admissions	Percentage	Cum.
Variables			
Study ID			
Gender (N= 74,160)			
Male	42,440	57.23	57.23
Female	30,545	41.19	98.42
Missing data	1,175	1.58	100.00
Age (months) (N= 74,160)			
6-11 months	19,899	26.83	26.83
12-23 months	25,099	33.84	60.68
24-35 months	14,164	19.1	79.78
36-47 months	8,787	11.85	91.62
48-59 months	6,211	8.38	100
History			
AGE (N=74,160)			
positive	14,209	19.16	19.16
negative	59,951	80.84	100.00
ARI (N=74,160)			
positive	31,666	42.70	42.70
negative	42,494	57.30	100.00
HIV status(N=74,160)			
HIV negative	68,770	92.73	92.73
HIV positive	5,390	7.27	100.00
Seizures (N=74,160)			
No seizure	60,025	80.94	80.94
Epilepsy	2,993	0.04	80.98
Febrile	9,466	12.76	99.98
Unspecified convulsion	1,676	0.02	100.00
Outcome (N=74,160)			

Alive	58,658	79.10	79.10
Died	959	1.29	80.39
Missing data	14,543	19.61	100.00

Abbreviations: AGE, severe acute gastroenteritis; PCV, pneumococcal vaccine; ARI, acute respiratory infection; Study ID; study identification, HIV, human immunodeficiency virus

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