SHORT TERM OUTCOME AND COST ANALYSIS OF CHILDREN ADMITTED WITH ROTAVIRUS GASTROENTERITIS

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DECLARATION

This dissertation is submitted as my original work and has neither been published elsewhere nor presented for a degree in any other university.

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DEDICATION

This work is dedicated to my parents and to the Catholic Church, in particular Fr Tom McDonald for the effort they put in bringing me up into who and what I am.

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ABBREVIATIONS

GE	Gastroenteritis
AGE	Acute Gastroenteritis
KNH	Kenyatta National Hospital
NHIF	National Hospital Insurance Fund
WHO	World Health Organization
WHO-CHOICE	World Health Organization – CHOosing Interventions that are Cost Effective
NEJM	New England Journal of Medicine
EPI	Expanded Programme for Immunization
KEPI	Kenya Expanded Programme for Immunization
KEMSA	Kenya Medical Supplies Agency
HIV	Human Immunodeficiency Virus.
KEMRI	Kenya Medical Research Institute.
EAMJ	East Africa Medical Journal.
PFC	Paediatric Filter Clinic.
HRV	Human Rotavirus
RVG	Rotavirus Gastroenteritis
CFR	Case Fatality rate
RVV	Rotavirus Vaccine
OPV	Oral Polio Vaccine
No.	Number.
U/E/C	Urea, electrolytes and creatinine.
LOS (d)	Length of stay to point of discharge by doctor
LOS (h)	Length of stay to point of going home
BGA	Blood gas analysis
FBC	Full Blood Count
KShs	Kenya Shillings
I$	International Dollar
ER	Emergency Room
CI	Confidence Interval
SD	Standard Deviation
IMCI	Integrated Management of Childhood Illness
GAVI	Global Alliance for Vaccines and Immunization
ORS	Oral Rehydration Solution
IV	Intravenous
IVF	Intra Venous Fluid

ABSTRACT

Background

Rotavirus infection is the single most common cause of acute gastroenteritis in children under five years of age. Rotavirus gastroenteritis (RVG) has a high morbidity and mortality in children in Kenya. The costs of care and treatment for rotavirus gastroenteritis are high. Comprehensive data on the outcomes and cost of care of RVG in Kenya are lacking.

Objective

To determine the short term clinical outcomes and compute average cost of care for children admitted to Kenyatta National Hospital (KNH) with rotavirus gastroenteritis.

Methodology

A short longitudinal survey at Kenyatta National Hospital, Nairobi, Kenya from February to May 2008. A minimum sample size of 165 was sufficient for both primary and secondary objectives of this study. This samples size was calculated using mortality as the worst outcome with a mortality rate of 11.6%. Children less than 3 years of age admitted to the paediatric wards with a diagnosis of acute gastroenteritis were tested for rotavirus in stool samples using a rapid antigen detection kit and ELISA. Those found positive for rotavirus and gave consent were recruited into the study. A full clinical evaluation was done and a pre-designed questionnaire administered. The recruited patients were followed up till discharge or death. Their outcomes, costs incurred and the bills they paid were entered into the questionnaire. The average costs were then calculated.

Results

Five hundred of the children admitted to KNH with acute gastroenteritis were screened for rotavirus. One hundred and ninety one (38.2%) of them tested positive for rotavirus in stool and 172 children were recruited into the study. Of the 172 children, 87.8% were discharged within one week, 8.1% stayed for more than 7 days while 4.1% died. The average cost of care per child admitted with rotavirus gastroenteritis was Kshs 6,505.79 to the patient, Kshs. 14,178.21 and Kshs. 16,556.08 to the hospital and economy/society respectively using the National Hospital Insurance Fund bed charge rates. Children who had co-morbidities had worse outcomes in comparison to those who did not have any co-morbidity.

Conclusion

Rotavirus gastroenteritis has a significant impact on young children and their families in terms of long hospital stay, high morbidity and mortality. It incurs considerable resource

utilization in health care settings, substantial costs for national health care and lost work days to the economy.

Recommendation

A cost benefit analysis for the whole country should be done to guide in policy making for routine rotavirus vaccination.

INTRODUCTION AND LITERATURE REVIEW

Globally gastroenteritis is a leading cause of morbidity and mortality in children under five years of age [1]. Dehydration caused by severe diarrhea is a major cause of morbidity among children in Kenya [2]. Rotavirus is the single most common cause of acute gastroenteritis (AGE) in children [1]. Rotavirus-associated gastroenteritis (GE) is often more severe than the gastroenteritis caused by other Enteropathogens [3-7]. The peak infection with rotavirus is at 3-24 months, the highest rate being between the ages of 6-11 months. In developing countries, 65-80% of children have antibodies by 12 months of age; 95% are infected by 24 months of age; and almost 100% of the children are infected by the age of five years. The incidence decreases rapidly after 24 months; this decrease in incidence has been demonstrated in all the studies done including the ones done in Africa [3-14]. In Kenya, the peak age of getting GE in children is at 6 - 24 months of age [2].

Rotavirus acute gastroenteritis (RVG) is characterized by fever, vomiting and diarrhoea that is non-inflammatory, the stools are pale, watery or loose with a characteristic milky odour. The diarrhoea last 3-8 days but it has been documented to last as long as 22 days. Fever and vomiting are most prominent in the initial few days [15]. This initial prominence of fever and diarrhoea alone may lead to increased medical costs as a result of self-medication and unnecessary tests being done to establish the cause of fever, more so, in malaria regions like Kenya before the actual diagnosis of RVG is made. Less well recognized is the association of Rotavirus-induced central nervous system dysfunction, which has been associated with seizure, encephalopathy, and death. Symptoms may vary widely, however, and children can experience short afebrile convulsions as the only manifestation of rotavirus encephalopathy [16-20].

In a study done in Brazil by Carneiro N.B et al [9] on children hospitalized with severe rotavirus-associated gastroenteritis [9], only a small proportion of the patients presented with diarrhoea at the onset of the illness and the diarrhoea rarely lasted for more than a week. Likewise, vomiting was also rare at the onset of illness, in consonance with the pathophysiology of RVG, which becomes more intense as the infected cells are replaced by immature enterocytes. The commonest symptoms in this study were diarrhea,

vomiting and fever. Early weaning was found to be an important risk factor for rotavirus gastroenteritis in this study [9].

Management is supportive with fluid replacement (ORS or IVF) and anti-pyretics for those who have a fever. Specific management of co-morbid conditions is also necessary. Hospitalization is a major cost driver in the economics of RVG. A higher rate of hospitalization will effect a significant increase in the cost of RVG management. The cost is further increased by the costs of managing nosocomial infections acquired during hospitalization. Other children admitted for different illnesses also get rotavirus infection nosocomially. The rate of nosocomial infections in South Africa is estimated to be at 20% [21]. There are no Kenyan figures for rate of rotavirus nosocomial infections.

Disease Burden

Parashar U.D et al on Global illness and deaths caused by rotavirus disease in children, estimate that, globally, rotavirus causes 111million episodes of diarrhea requiring only home care, 25million clinic visits, 2million hospitalizations and 352,000-873,000 deaths (median 520,000 deaths) in children under five years per year. In his study, by the age of five, 1 in 5 of the world's children will require a clinic visit, 1 in 65 will require hospitalization and approximately 1 in 293 will die [22-24].

Rotavirus is detected in 13-73% of children hospitalized for AGE [11,25]. The lowest rate is in a rural area in South Africa [11] and the highest rate in Korea [25]. Rotavirus is responsible for about one quarter of all GE cases identified in both hospitalized patients and outpatients [3,11,12,22,23]. Hospital based surveys have revealed that rotavirus infection is responsible for 25-73% of cases of gastroenteritis with severe dehydration [3,8,11,12,23,25,26]. The urban areas are affected more [10,14]. Diversity of strains and the deaths are more frequent in Sub-Saharan Africa where 110-155 000 rotavirus-related deaths occur per year [21,22,25]. Miller and McCain have put the figure RVG associated deaths at an average of 520,000 per year [22]. The frequency of infection with rotavirus is the same in both the developed and developing countries but there are worse outcomes in the developing countries which contribute more than 82-85% of all the rotavirus associated deaths in the world [1,23,26]. The higher mortality in developing countries is probably due to poor access to healthcare facilities, high prevalence of HIV/AIDS and higher levels of malnutrition [21-23]. However there are no studies that

have been carried out to differentiate outcomes among these different groups of children in terms of nutritional and HIV/AIDS status visa a viz the outcomes.

Cunliffe and Steele reported that rotavirus is detected in about 24% (range 13-55%) of children hospitalized for GE and is responsible for about one quarter of all GE cases identified in both in-patients and out-patients [11,12]. More recent studies have reported a higher prevalence of 13-73% [25].

If 20-25% of the deaths from diarrhea are due to rotavirus, it is estimated that an effective properly administered vaccine could potentially prevent 170,000 -210,000 or more childhood deaths every year This is equal to about 4-5% (one in twenty) deaths prevented [11,12]. These deaths are mainly in Africa and therefore, Africa would be the greatest beneficiary of routine rotavirus vaccine (RVV).

Table 1: Summary of global rotavirus morbidity and mortality.

Country or region	Av. dur. of stay (days)	RVG admissions		ER visits		Deaths		
		No. (x1000)	RVG % of AGE	%	No. (x1000)	per year	Per day	CFR %
USA [25]		55-70	33		205-272	20-70		
Europe [25]	3-5		50	40-50				
Asia [25]		1900	45 (30-73)		13500	171000		
L. America [25]			40			15000		
Africa [25]			25-40			110000 - 155000		
Nigeria [25]							80-90	
Cameroon [25]							50-60	
S. Africa [21,25]	1-49 (4.68)						10-12	2

(ER – emergency room)

The annual rotavirus associated mortality in the USA is comparable to the daily mortality in a single African country such as Nigeria or Cameroon! Even in countries where many studies of RVG have been done, average duration of stay, RVG admissions, emergency room visits and deaths have not been determined. This explains why there are many gaps in table 1.

The economic burden is high and includes direct costs of treatment and opportunity costs such as income lost due to parents or caretakers missing work during the child's illness. It includes cost of deaths which is usually not included in costing [8,21,22,26,27]. Economists define costs as the value of resources used to produce goods or services. However, the way the values of resources are measured can differ. Financial costs only include the actual expenditure on goods and services purchased. Economic or societal costs also include the opportunity costs of resources. This could, for instance, be the value of donated medications or the value of volunteers' time. Opportunity cost is the value of a product forgone to produce or obtain another product also defined as the cost of passing up the next best choice when making a decision.

In the USA, substantial morbidity and costs are incurred in care and treatment of RVG. RVG accounts for 3-4% of all hospitalizations in children under five years of age. The economic impact in the USA exceeds $300million in medical costs and $1 billion in total costs, including indirect costs such as the loss of salary of the care giver [8,27]. In Canada, Ford-Jones et al [28], found only 20% of respondents earning less than 20,000 Canadian dollars per annum. If the caretakers who earn more than 20,000 Canadian dollars lost work days, it would translate to a large loss of income for the families.

In Taiwan, a study by Kow-Tong et al [29], the health care costs were substantial: the total annual direct medical costs for admissions associated with rotavirus infection, including medical direct costs and nonmedical direct costs (such as transportation), were US $10.4 million (NT $364 million), which was equal to $676 per child They also estimated total social costs, indirect costs, and family expenditure costs for episodes of diarrhea requiring hospital admission. These cost estimates indicated that the majority of costs associated with rotavirus infection were reflected by direct medical costs, which in turn, were mainly determined by the cost of a general pediatric bed and length of hospital stay. The direct medical and social costs in this study were US $10.4 and $13.3 million, respectively. They were also able to provide some indication of the additional costs incurred by families with children infected by rotavirus who use the highly subsidized National Health Insurance system. Their data indicated that families incur costs of US $294 when their child's admission to a hospital was associated with rotavirus infection. The average salary for unskilled and service workers in Taiwan was US $720/month; which suggested that a rotavirus-associated hospital admission could

incur costs equivalent to about 40% of their monthly salary. The study only assessed costs of episodes of rotavirus diarrhea that required hospital admission and did not include costs associated with diarrhea episodes for both outpatients [29].

In South Africa, a study was conducted by Wessel et al [21], on the economics of RVG prevention. The study was a combination of a consensus – seeking Delphi process, a retrospective literature review of RVG, data mining exercise set in the claims database of a local private sector funder and a culmination in the pharmacoeconomic modeling of the cost benefit ratio associated with rotavirus vaccination process. The costs used were local costs sourced from a claims database of a private sector funder. The average hospital cost was R13,753 (Kshs 110,026.56) per child and it ranged from R1,314 to R276,600 (Kshs 10,512 to Kshs 2,212,800 at an exchange rate of Kshs 8 to one South African Rand). These costs included clinical consultation, other clinical procedures and tests, medical devices as required and pharmacotherapy. The study determined the cost benefit ratio associated with prophylactic vaccination of infants within the first six months of their lives. It noted significant cost saving of R975 (Kshs 7,800) per patient with rotavirus vaccination. The study did not reflect out of pocket expenses, indirect costs or quality of life. There are no other studies done in Africa that have been published. It is now when the studies are being planned in Africa. However, costs in the developed countries may not be appropriate for comparison due to the very different cost of living.

Rotavirus accounted for 15.6% of the admissions related to gastroenteritis and 4.1% of all pediatric patients admitted to a tertiary hospital in Brazil, in a study by Carneiro et al [9]. A large proportion (39%) of the patients seen at the emergency room with rotavirus-associated gastroenteritis needed to be admitted to the hospital; the admission may be considered an indicator of severity.

In Canada, the mean ± SD duration of hospitalization for rotavirus was 2.4±1.7 days; it was significantly longer, 3.1±1.6 days (*P* .001), in children with an underlying medical condition [28]. This may explain partly why children in developing countries have poorer outcomes as many will have other underlying medical conditions. The mean ± SD of length of hospital stay was 4.4±3.3 days in Taiwan (a developing country) [29], almost twice that of a developed country.

While overall deaths from GE have declined in children in Bangladesh, the proportion of diarrhea deaths due to rotavirus have actually increased and this pathogen now alone accounts for about 40% of all diarrhoeal deaths. It is postulated that the proportion of admissions due to RVG are rising not because the frequency of rotavirus infection is increasing, but due to the fact that frequency of severe non-rotavirus GE has decreased as a result of improved general hygiene standards globally, leaving the RVG admissions to rise. This is probably because the rotavirus infection is not influenced by hygiene standards [26].

The RVG has been noted to have a seasonal variation worldwide [3,6-8,11,12,14,30,31]. In Kenya, it occurs throughout the year but peaks during the relatively dry months of February/March and August/September [10,30]. Gatinu found that 41% of patients with acute gastroenteritis were admitted and 59% (103) of those admitted had rotavirus infection. In Gatinu's study, 24% of patients admitted with GE died. The rotavirus infection admission case fatality rate was 11.6% [32].

Table 2: KNH case fatality rates of rotavirus gastroenteritis (from ongoing surveillance).

Month	Deaths from RV	Total RV positive patients	Percentage
August 2006	5	95	5.1
September 2006	2	82	2.4
October 2006	3	88	3.4
November 2006	2	35	5.7
December 2006	1	22	4.5
January 2007	3	9	33
February 2007	2	23	8.6
March 2007	2	69	2.8
April 2007	1	29	3.4
TOTAL	21	452	4.6

There were 1150 patients recruited from PFC and paediatric wards of KNH between August 2006 and April 2007 in the ongoing rotavirus KNH surveillance. Of the 932 stool samples examined by rotavirus ELISA, 452 (48%) of them were positive for rotavirus. The case fatality rate varied as shown in table 2. In the preliminary results of ongoing KNH rotavirus surveillance, the prevalence of RVG ranges between 25-65% and the

mortality between 2.4 to 33% in different months. The characteristics of those with the worst outcomes (long hospital stay or death) is unknown.

Table 3: KNH Paediatrics morbidity and mortality from gastroenteritis with the estimated proportion from RVG, for the year 2006.

Quarter	1	2	3	4	Total
Total paediatric admissions	2,673	3,167	2,784	2,669	11,293
GE admissions (% of total admissions)	513 (19.2%)	603 (19%)	475 (17.1)	707 (26.5%)	2,298 (20.3%)
Deaths from GE (CFR of GE admissions)	114 (22.2%)	133 (22.1%)	99 (20.8%)	87 (12.3%)	433 (18.8%)
Probable RVG admissions (39% of GE admissions [32])	200	235	185	276	896

(Data on admissions and GE deaths from KNH Medical records department)

From table 3 it can be noted that gastroenteritis alone contributes about 20% of paediatric admissions to KNH. Controlling rotavirus infections and admissions would significantly reduce childhood morbidity and mortality. To be able to intervene appropriately there is a need to better understand the rotavirus infection morbidity and mortality.

Factors associated with severity of rotavirus infection.

Immunosuppressed patients may have a more severe or prolonged disease with or without extra-intestinal infection [15]. Rotavirus infections immunocompromised children (e.g., infants with congenital immunodeficiency syndromes) can result in severe, protracted, life-threatening diarrhoea, with faecal virus excretion persisting for many months [33,34]. Extraintestinal rotavirus infections have been reported in immunodeficient children [35].

A study in Malawi by Cunliffe indicated that HIV infected children do not develop a more serious disease but are more likely to shed rotavirus during follow-up. Enrolment CD4 counts were significantly lower among HIV-infected children who died during follow-up (median 285/μL [range 33–677]) than in those who completed follow-up (830/μL [range 39–2273], p=0·005). The study did not determine whether malnutrition actually played a role in disease outcome. It was not possible to dissociate the effect of malnutrition on

RVG outcome from that of HIV infection when malnutrition and HIV were present concurrently [34]. However, there is evidence to suggest that malnourished children have a more severe disease following rotavirus infection as demonstrated in studies done in Israel and Ghana [13,14]. In a Jewish children study, compared with controls, malnourished children were more likely to be hospitalized. However, rotavirus was detected in similar proportions among well-nourished and malnourished cases with diarrhea [13]. If hospitalization is used as an indicator of disease severity, then malnutrition seems to be an important indicator of disease severity, which may explain why the toll of rotavirus-associated morbidity and mortality is particularly high among children in developing countries [13]

In Kenya according to the 2003 Kenya Demographic and Health Survey (KDHS), wasted children in Nairobi are 4.5% [2]. Could this proportion of wasted children in Kenya be contributing to the higher mortality as compared to other countries?

Co-infection with adenovirus may prolong duration of diarrhea to 10-14 days [15]. Adenovirus is found in stool in 2-31% of AGE [36]. In a private hospital in Nairobi, Forbes et al found rotavirus in 20.8% of all cases of gastroenteritis. The combination of rotavirus and adenovirus was found in 8.3% of the patients with GE [37]. The study population comprised of children aged one month to 16 years. The higher age bracket of children included in this study may have lowered the prevalence of rotavirus infection when compared to the prevalence recorded in KNH.

Vaccine

The aim of giving rotavirus vaccine is to reduce severity and case-fatality rates rather than prevent the infection. Rotavirus vaccines are currently included in Expanded Program on Immunization (EPI) programs in some countries such as Brazil, Panama, Venezuela and Oman.

In a study in Venezuela on the efficacy of the rhesus rotavirus-based quadrivalent vaccine, it was found that the vaccine was more effective in preventing severe rotavirus diarrheal illness. The vaccine achieved a protective efficacy of 75% against dehydrating rotavirus diarrheal illness, 88% protection against severe diarrhea caused by rotavirus and 70 % reduction in hospital admissions. Overall, the efficacy of the vaccine against a

first episode of rotavirus diarrhea was 48%. Horizontal transmission of vaccine virus was demonstrated in 15% of the vaccine recipients. The vaccine is particularly effective in reducing disease severity and hospitalization rate [24,38]. Moreover rotavirus vaccine may protect against nosocomial rotavirus infections as well. The protection from nosocomial infection results from the reduction of the number of children admitted for RVG. The reduction of the number of children admitted with RVG is accompanied by a reduction of nosocomial infections for those admitted suffering from other ailments. The rate of nosocomial RV infections and other infections reported in the studies in South Africa is 20% [21]

In a randomized control trial, RotaTeq™ which is a bovine – human reassortant vaccine containing 5 antigens G1, G2, G3, G4 & P1, was well tolerated with a 70% efficacy in protecting against any RVG and 100% protection against severe rotavirus GE without an increased risk of intussusceptions [39]. There is no safety or efficacy data available for the administration of RotaTeq™ to immunocompromised patients or individuals infected with HIV according to the Rotavirus Efficacy and Safety Trial (REST) by the manufacturer.

In a randomized control trial, Rotarix™, which is derived from single strain of human rotavirus (G1 [P8]), was found to have an efficacy of 62 - 73% in protecting against any RVG and a 90% protection against severe GE. Rotarix™ elicited cross-protective efficacy of 74% against severe rotavirus due to non–G1 serotypes. The uptake was not affected by polio vaccines. The trials have been done in Latin America with small trials in Asia and Africa. HRV vaccine reduced hospitalization for gastroenteritis from any cause by up to 42% [40].

Both vaccines are live, orally administered and can be administered together with the other EPI vaccines. The expected impact of rotavirus vaccine in reducing disease and death from rotavirus infection will be most evident in developing countries where rotavirus causes up to 600,000 childhood deaths annually [22].

Table 4: Percentages of rotavirus morbidity and mortality without vaccination

Reference number	21	23	9	11
Author, Setting, Year	Wessel et al South Africa, 2006.	Parashar et al Global 2003	Carneiro et al, Brazil, 2005	Cunliffe et al, Africa, 1998
Design, Subjects/Studies (n)	Retrospective, Review	Review	Retrospective 218 patients	Review, 43 studies
% Children infected by RVG by 5yrs of age	80%	100%		
Hospital visits (% of RVG infections)	20%	41 - 86%		
Severe disease (% of RVG infections) to warrant admission	10%	20 – 34%	39%	13 - 55% (24%)
Mortality rate	<2%	0.34%		

Table 4 is a summary of the findings from some studies. If no vaccine is given, 80-100% of all children will have a rotavirus infection by the age of 5 years while 20-86% will visit a hospital. If a vaccine is given, infections would be reduced by 62-77% depending on vaccine type [39,40]. Of those seeking medical help in hospital, 13-73% [25] get admitted, a percentage which may be brought down by between 78-99.9% if the vaccine is given. Rotavirus alone causes 4-5% of all childhood deaths [23,32], which would be drastically reduced by vaccination. Hypothetically, there would be significant benefits if the same percentages were to apply in Kenya. In our set-up where HRV accounts for 39-65% of the AGE admissions, the Rotarix™ vaccine would reduce the admissions by 78-90% and Rotateq™ would reduce admissions by up-to 100%. There would also be a possible reduction of 42% in AGE admissions due to other aetiologies. However there are differences in efficacy between countries, the highest efficacy being in Europe and lowest in developing countries [21].

Reducing infections and severity in those infected would have a significant saving in costs incurred in the management of these patients. A reduction in HRV infections and subsequent admissions not only from RVG but also from non-HRV gastroenteritis would translate into a significant reduction of costs of health care provision and decongestion of paediatric wards.

STUDY JUSTIFICATION

Rotavirus is a major cause of diarrhoea in children in both the developed and developing countries. Advances in hygiene standards do not seem to help in its prevention [1].

Several studies in Kenya, (Gatinu [32] Gatheru [10,30] and ongoing KNH surveillance), have described the prevalence, circulating RV strains and case fatality of patients with rotavirus gastroenteritis. However, little is known about the outcome of children admitted with RVG and the determinants of the clinical outcomes of the severe cases of rotavirus gastroenteritis. The attributes of those who die or with long hospital stay are not known. Understanding the clinical outcomes and their determinants would help to prioritize those at the greatest risk of poor outcome and also guide in improving management or in targeted vaccination should this be an option.

As effective rotavirus vaccines become available, policy makers will need to make decisions regarding the relative cost and benefit of routine vaccination. In doing so, they should systematically consider the economic burden of disease, the potential impact of vaccination on health, net cost of vaccination and compare the costs of vaccination to health benefits. The vaccines are available in Kenya albeit costly. There is no local data on costs incurred in the management of RVG patients. A cost analysis of the care and treatment for these patients would provide preliminary data that can be used in cost benefit analysis of routine rotavirus vaccination in Kenya.

The data from this study will form part of the body of knowledge to help policy makers in arriving at decisions regarding routine rotavirus vaccination in this country. It would also be useful in monitoring and evaluation of the impact on outcome of RVG patients after routine RVV is started. It provides pre-vaccination outcome comparison data to the one that would be obtained after vaccination is started.

OBJECTIVES

Primary objectives

1. To determine short term clinical outcomes of children admitted to KNH with rotavirus gastroenteritis.

2. To compute the average cost of hospitalization attributable to rotavirus gastroenteritis.

Secondary objective

1. To determine correlates of poor outcomes due to acute rotavirus infection in children at KNH. Potential correlates include age and co-morbidities such as HIV, severe malnutrition and adenovirus co-infection.

METHODOLOGY

Study design

Short longitudinal survey.

Study area

The study was carried out in Kenyatta National Hospital's Paediatric wards. KNH is the national referral hospital as well as a primary care hospital for patients in Nairobi and its suburbs. The hospital has four general paediatric wards where children aged between 0-12 years with non-surgical medical illnesses are admitted. The average number of children admitted per day is about 30 patients of whom, 5-7 are due to gastroenteritis. *(Data on admissions from KNH Medical records department)*

Study period

This study was carried out from February 2008 to May 2008.

Study population

Children aged 0 to 35 months admitted to KNH paediatric wards with RV gastroenteritis. This age cut off was selected as most children, more than 95%, get infected by the age of three years [3-14].

Inclusion criteria

1. Children aged within 0-35 months.
2. Parent/guardian's written informed consent.
3. Availability of stool sample within 48 hours of admission.
4. Stool tested positive for RV antigen by rapid antigen detection test and confirmed by ELISA or stool positive for RV antigen by ELISA only.

Exclusion criteria

1. If the parent/guardian withdrew their consent after enrollment.
2. Patients for whom cost data was not obtained were excluded from cost analysis.

Definitions

Gastroenteritis was defined as one of the following: passage of three or more loose or semi solid stools in 24 hours; three or more vomiting episodes in 24 hours; diarrhea with at least two additional symptoms; or vomiting with at least two additional symptoms. Additional symptoms were abdominal pain, abdominal cramps, nausea, mucus in stool, fever, diarrhea, or vomiting.

Acute gastroenteritis is gastroenteritis lasting less than fourteen days.

Severe gastroenteritis due to rotavirus infection in this context means gastroenteritis that has warranted admission in the paediatric wards of KNH.

Outcome in this study is mortality or length of hospital stay.

Time of discharge in this study is when the primary clinician makes the decision to discharge the patient from the hospital. There is an assumption that standards of care by all the clinicians are uniform and appropriate.

Short term in this study refers to a period of up to a maximum of thirty (30) days.

Poor outcome in this study refers to long hospital stay or death from a rotavirus gastroenteritis admission.

Long duration of hospital stay in this study refers to a hospitalization lasting more than seven days. Seven days were taken as the cut-off in this is because diarrhoea from rotavirus commonly lasts 3-8 days [9,15]. A study by Kow Tong in a developing country reported a mean ± SD hospital stay of 4.4±3.3 days [29].

Cost benefit is the cost associated with decreased risk.

Sample size

The worst primary outcome variable of the study was death during the time of admission. The expected proportion of deaths (mortality rate) of children during the admission period with Rota virus in KNH is 11.6% [32]. With 95% desired confidence interval and power of 80%, the formula for the sample size for estimation of a single proportion is given as:-

$$n = 2[A + B]^2 \times p \times (1\text{-}p)/D^2$$

Where n = the required sample size

A = depends on desired significance level - here 1.96 that corresponds to 95% confidence,

B = depends on desired power - here 0.84 corresponding at 80% power.

P = the expected proportion - here 0.116

D = Precision or width of confidence interval - here 0.10.

Using the above formula, a sample of 165 children with Rota virus admitted was required to obtain a 95 % confidence with a margin of error of +/- 5% around a prevalence estimate of 11.6 % [32].

The secondary aim is determine correlates of poor outcome such as long hospital stay or mortality, this can be done by comparing the mean duration of admission for the

children with RVG who are HIV positive and those with RVG who are HIV negative. The formula for the sample size of a study with two groups is given as;

$$n = [A + B]^2 \times 2 \times SD^2 / D^2$$

Where n = the sample size required,

S = pooled standard deviation for two groups, of the primary outcome variable,

D = difference between the means.

A = depends on desired significance level - here 1.96 that corresponds to 95% confidence,

B = depends on desired power - here 0.84 corresponding at 80% power.

Using the values (mean=2.4, SD=1.7) and (mean=4.1, SD=1.6) from Ford-Jones study in Canada [28] to represent the mean and SD and for those without and with co-morbidities like HIV respectively, we required a sample size of 50 (40 and 10) assuming a prevalence of 20% of those with a co-morbid illness to have a power of 80%. The study from Canada had the same age group of patients.

The overall sample size of 165 used in this study is sufficient for both primary and secondary objectives.

Sampling method

Sequential sampling of patients who met the inclusion criteria.

Demographic data

Demographic data was obtained during administration of the questionnaire. All those who came from informal settlements within industrial area of Nairobi such as Mukuru kwa Njenga and Mukuru kwa Rueben were lumped together as coming from industrial area. Those from other areas of Nairobi or its suburbs were listed independently. Age of weaning was taken as when other feeds or water were introduced into infant's diet, anything less than a month was taken as zero; and rounding off was done to the lower full month.

Clinical procedure

Patients admitted with gastroenteritis were screened for rotavirus in stool after obtaining an informed consent from the care giver. Stool sample was obtained as soon as possible and taken to the laboratory for rotavirus detection. Those found to have rotavirus in stool were recruited into the study and followed up daily till they went home or died. Demographic data, purposeful and focused history and examination of patients found to have rotavirus antigens in stool was taken. Examination was done to assess the nutritional status; weight and height were taken as per clinical examination guidelines. Z score of less than minus three (-3) was taken as severe malnutrition. Co-morbid conditions in patients were sought from patient records and examination. The primary clinicians were assumed to be following standard clinical practice in diagnosis and in giving prompt and appropriate care. For a co-morbid condition to qualify there had to be evidence from the patients' medical records. The evidence was in form of laboratory test reports such as for rickets, meningitis, urinary tract infections and malaria. Adenoid hypertrophy was confirmed by post nasal space radiograph reports. While in others the diagnosis was made by clinical signs and symptoms observed and documented such as pneumonia, asthma and/or bronchospasms. In case of pneumonia, other clinical signs (other than fast breathing) were sought from the records. This is because dehydration or acidosis from RVG could also cause fast breathing. The co-morbid conditions so obtained were entered into the questionnaire. If the child was HIV exposed by a HIV infected mother, PCR using RNA for HIV was done and WHO clinical and immunological staging was done.

Laboratory

Stool sample was collected in a stool container for rotavirus and adenovirus detection. Caregivers were given a stool container in which to put collected stool using a spatula. They were instructed on how to collect and the amount (5 mls) to collect by the principal investigator. The stool sample was collected as soon as it was voided. The stool was only collected from the children who were able to void within 48 hours of admission. If not collected within that time, the child was not enrolled into the study. This is because the child may have acquired nosocomial RVG after 48 hours of admission. The caretaker was requested to deliver the stool sample within five minutes of sample collection. The caretaker was asked to deliver the collected stool sample to a central collection point for each ward. The central collection points had a cooler box or a

refrigerator in which the stool sample was put. The cooler boxes were uniform in design and location for three wards while the fourth ward had a refrigerator. Each of the three wards had its own cooler box whose ice packs were changed every day at 8.00am by the principal investigator. The cooler boxes were maintained at a temperature range of 2^0 - 8^0 Celsius while the refrigerator was maintained at 4^0 - 8^0 Celsius. A well trained assistant collected the stool samples from the wards and delivered them to the laboratory for analysis in a portable cooler box. During the day the samples were taken to the laboratory at three hour intervals. The transport of samples from the wards to the laboratory took about 10 -15 minutes for each trip. At night the samples were collected at three hour intervals from the cooler boxes and kept in the refrigerator till morning. In the immunology laboratory, rapid antigen detection Rota/Adeno Combistick test kits were used for rotavirus and adenovirus detection. The Rota/Adeno CombiStick has a 96% sensitivity and specificity, does not cross react with other intestinal pathogens and detects specific hexon adenovirus antigen present in all human serotypes - as per the manufacturer (Novamed Ltd, Israel). The remaining stool sample was further analyzed for rotavirus group A by the ongoing KNH rotavirus surveillance. Rotavirus-associated illness was diagnosed only in patients who had rotavirus antigens detected in the stools by ELISA.

The reports of HIV test done before admission into the study were obtained from the patient's file. In patients with no previous HIV test, pre-test counseling was carried out and rapid HIV antibody testing done in collaboration with the HIV counselors already assigned to the wards. For those patients whose results were positive or inconclusive, a blood sample was taken for further HIV staging and confirmatory tests respectively. ELISA test result was used for children over 18 months and a PCR for those aged 18 months and below.

Costing

The cost of treatment and managing the illness was determined to as much detail as possible. All costs that could be attributed to this illness were sought; these were obtained through a pre-designed schedule and from the fee notes/invoices from KNH. The costing included both direct and indirect costs of care.

The cost elements were calculated up to the point of discharge and also up to the point of going home. This is because there were patients who were discharged but were unable to go home on day of discharge as they waited to clear the hospital bill or to obtain credit or waiver. This two level costing was necessary to bring out the economic burden incurred when patients are retained in the hospital after the clinician discharges them

The patient, hospital and societal or economic costing perspective were done.

Patient perspective costing:

The patient perspective has two types of costs; direct and indirect costs. Direct costs are those costs incurred in diagnosis and treatment of illness. Direct costs include such costs as the costs the patients incurred as outpatient fees, bills paid to KNH and costs for medication during the illness prior to seeking medical help in KNH. Indirect costs are those costs incurred because of cost of time and cost of other inputs. The indirect costs include the income lost by the family during the child's illness and the cost of travelling to the hospital. These costs were entered into the questionnaire.

The bills paid by the patient to KNH may not necessarily be what the actual hospital cost of their care was. This is due to government subsidies and waiving of hospital fee. The bills paid were obtained from KNH records; the fee notes and receipts from the hospital cash office. The pre-KNH treatment costs include out-of-pocket costs to both formal and informal private health facilities incurred by the patients prior to seeking care in KNH. These costs were obtained by asking the caretakers what they were.

Travel costs were obtained by the investigator from the caretaker. The caretaker was asked to document the immediate family members who visited the patient and how

much they paid as fare for each visit. These travel costs were collected each day by the investigator and summed up when the patient was going home. Transport cost was calculated at two levels, up to the point of discharge and up to the point the patients actually went home. The transport costs included the amount they were likely to pay to get home depending on means of travelling and where they stay. All patients said they would use public means to go home.

The caretakers had foregone some activities to be in the ward with the patient. The caretakers would have been undertaking some income generating activities. These foregone activities have an economic value. The value of the foregone activity was their opportunity cost, which cannot be known with certainty. The opportunity cost, though not a real financial cost, is important in economic decision making. The daily value of the foregone daily activity was taken as the daily lost income in this study. The families' lost income is that which would have been earned by the caretakers had the caretakers been in their routine duties. The income lost as a consequence of being in hospital was calculated using the caretaker's daily income. This amount was obtained by asking the caretakers what their average daily pay or daily net income or net profit was. The total lost income per patient was then calculated as the product of daily lost income multiplied by the duration of hospital stay in days to the day of discharge and to the day of going home. This was done to get the total lost income at the two levels; to the time of discharge and time of going home. For those who were paid while off-duty, the value of the time spent in the ward was taken as the opportunity cost (lost income in this study).

The lost income was calculated for the caretakers who were engaged in income generating activities for which a monetary value could directly be ascertained. Some caretakers such as housewives' daily activities did not have a directly ascertainable monetary value. These families were assumed not to be losing income. The complexity of attaching a monetary value for such activities was beyond the limited scope of this study. This is recognized as a limitation in this study. Only the caretakers' lost income was included and not the lost income by other family members. It was assumed that most of the visitors visited the patient during their free time and not during working hours; hence they did not lose income. It was outside the scope of this study to ascertain lost income for those who lost working hours when they visited the patient. Again this is recognized as a limitation in this study.

The total patient cost for each patient was then calculated using the following formula:

$$C_p = BP + (PKC) + (TC) + (LI)$$

Where for each patient;

C_p	Total patient cost
BP	Bill paid by the patient
PKC	Pre –KNH treatment costs
TC	Travel costs
LI	Lost income

In cases where there were twins, the shared costs such as travel costs and lost income were divided by two to arrive at each child's fraction of it.

The mean cost of the total patient costs and its components was calculated.

Hospital perspective costing:

This includes total treatment costs incurred at KNH. Hospital costs are classified according to pharmaceuticals, investigations and non-curative care (overhead) costs. This latter category includes the costs of staff, laundry, catering, building maintenance, utilities, cleaning, transport for hospital functions and capital assets usually lumped together as a daily bed costs. Cost per bed-day does not include the patient-specific costs of diagnostic tests, medications and medical supplies. In reality the amount of time staffs spend on patients can vary considerably, it is difficult and time consuming to allocate staff costs on a patient-specific basis, as this would involve physically observing how much time staff spend on different patients through time-and-motion studies.

A list was generated including all pharmaceuticals and the different diagnostic tests used in these patients and their prices (appendix 3). The cost of items was sought from the office of the hospital pharmacist for pharmaceuticals. The costs used were those which the hospital purchased the pharmaceuticals as from the supplier prices for that period. Hospital bed day cost was obtained from the hospital finance office at KShs 600.00 per day for the general wards in KNH. Cost of laboratory tests was from the head of the laboratory services in KNH. The cost of tests used is the one that is used for amenity

patients who are charged at cost without the cost-sharing. These costs were set in 1994 and as per the WHO recommendations; they were discounted at 3% per annum to get the current price [40].

The discounting formula to get value to use was:

$$A = P\ (1+.03)^n$$

Where;

A – Current value of the amount from when the figures were arrived at.

P – Initial figure set for the test or service

n – Number of years since the figure was set

The lists for tests and other consumables/supplies are as per appendix 3. The cost of tests was calculated based on the tests done up to the point where the patients were discharged. None of the patients had any more tests after the clinician had discharged them from the ward.

To include such items not usually charged by the hospital like electricity, rent or buildings, the WHO-CHOICE (World Health Organization – CHOosing Interventions that are Cost Effective) estimates guidelines for costing were used [41]. These advocate for national figures to be used before international figures are used. The closest figure for this is the National Hospital Insurance Fund (NHIF) values for hospitals in Kenya. KNH would then be in the category of 2,000.00 Kshs per day. WHO-CHOICE values were used too for purposes of comparison. Kenya is in region AFR mortality strata E according to the WHO-CHOICE grouping. KNH being a tertiary hospital; the values for bed charges per day for tertiary hospitals was used which is 26.06 International dollars (2000) [41-43]. All costs are in Kenya shillings and conversion from US dollars using the average rate from the Central Bank of Kenya at 65.00 KShs per dollar for that period. Discounting rates used are the standard approach as proposed by WHO-CHOICE, with both costs and health effects discounted at 3% per annum [42]. In addition to using the WHO figures for the bed-day charges, the figures that were provided by the KNH finance office for these charges were also used and a comparison done using both values.

Cost-sharing in KNH consists of nominal fee rates for services in the form of an outpatient and inpatient treatment fee, a dispensing fee depending on the drug prescribed, and investigation fees. The fees aim to achieve a degree of cost-recovery, and are set according to a combination of direct costs of supplies and patients' perceived willingness and ability to pay. In a study by Bhatt et al on costs of care of HIV positive and HIV negative patients in KNH, they found that only the investigation fee is set at the level of the direct cost of supplies [44].

The cost of drugs prescribed to maintain long-term chronically ill patients after discharge or to treat another confirmed illness was excluded. For example, the cost of the long-term prescription of anti-convulsants for a patient with epilepsy or cost of anti-malarials for a confirmed malaria patient was excluded. For the same reason, the cost of antibiotic was excluded in the patients in whom pneumonia was diagnosed as a co-morbid condition as noted by primary clinician with supportive evidence. For those patients whose records did not show amount of intravenous fluids given in the Paediatric Filter clinic (the paediatric emergency unit), the clinical evaluation and classification of dehydration by the clinician was used to calculate amount of fluids given if the caretaker of the child acknowledged that intravenous fluids were given. Drug consumed by a patient was calculated for his/her total dose and rounded up to the nearest issuable amount. This also took into account the normal expected wastage or losses. Drugs' cost was the sum of cost of drugs used up to the point of discharge and those prescribed on discharge by the clinician.

The total hospital cost for each patient was then calculated using the following formula:

$$TC_h = (LoS \times HC) + (I) + (D) + (S) + (CF)$$

Where for each patient;

TC_h	total hospital cost
LoS	length of stay
HC	hospital bed-day cost or non-curative care cost per day
I	investigation cost
D	drug/pharmaceutical cost
S	Other Supplies/Consumables
CF	Consultation fee (paid at casualty on the day of admission)

For patients who absconded, the day they absconded was treated as the day they went home if they had been discharged already, and if not discharged, it was treated as the day of both discharge and going home. Their costs were treated as if waived by the hospital.

Economic perspective costing:

This is the sum of the hospital perspective cost and patient perspective cost excluding any double costing. The economic or societal cost was obtained from the information available or the best estimate available.

The total economic cost of each patient was calculated using the following formula:

$$C_s = (LoS \times HC) + (I) + (D) + (S) + (CF) + (PKC) + (TC) + (LI)$$

Where for each patient;

C_s	total societal or economy cost
LoS	length of stay
HC	hospital bed-day charge or non-curative care cost per day
I	investigation cost
D	drug/pharmaceutical cost
S	Other Supplies/Consumables
CF	Consultation fee
PKC	Pre –KNH treatment costs
TC	Travel costs
LI	Lost income

There was an expected difference in the mean costs to discharge and up to the point of going home due to the difference in extra bed charges, extra lost income and extra transport costs incurred when patients are discharged and do not go home on the day of discharge.

For hospital and economic perspective KNH, NHIF and WHO-CHOICE bed charge rates were used. The KNH bed charge rate was used to bring out the difference in costs as a result of government subsidy. This is in comparison to the costs obtained using the NHIF bed charge rate. The NHIF daily bed charge rate was taken as the figure that is not

subsidized for such a facility. WHO-CHOICE rate is used to make it easier to compare with other countries with a similar setting.

Statistical analysis

The data was collected using a well structured questionnaire. The filled questionnaire was kept in a safe place ready for the data entry and for confidentially of the patients' details. After cross checking the questionnaires for any missing entries, a data base was designed in MS excel. On completion of the data entry exercise, the data was exported onto a Statistical Package (SPSS – Version 13.0) for analysis.

Since the expected outcome of the rotavirus patients is grouped into two broad categories of whether the patient had a good or bad outcome, univariate and logistic regression were used to get the significant factors explaining the outcome of rotavirus patients. Wald statistics was used to get the most significant factors which are important in explaining the outcome of the patient. The equation below was used;

$$\dot{Y} = \alpha + \beta i Xij + \varepsilon ij$$

From the above general equation, it can be expanded into a more specific equation

$$\dot{Y} = \alpha + \beta 1 Xi1 + \beta 2 Xi2 + \beta 3 Xi3 + \beta 4 Xi4 + \beta 5 Xi5 + \beta 6 Xi6 + \ldots + \varepsilon ij$$

Where;

$\dot{Y}$ = response variable (Outcome of the rotavirus, Survived/Died)

α = Constant

βi = the coefficient

Xij = the factors to be considered for the logistic regression such as age of patient, breastfeeding, having co-morbidities, shock on admission.

For factor which assumes a qualitative measure dummy matrices were used. E.g. for variable with three levels, this dummy table was as follows-

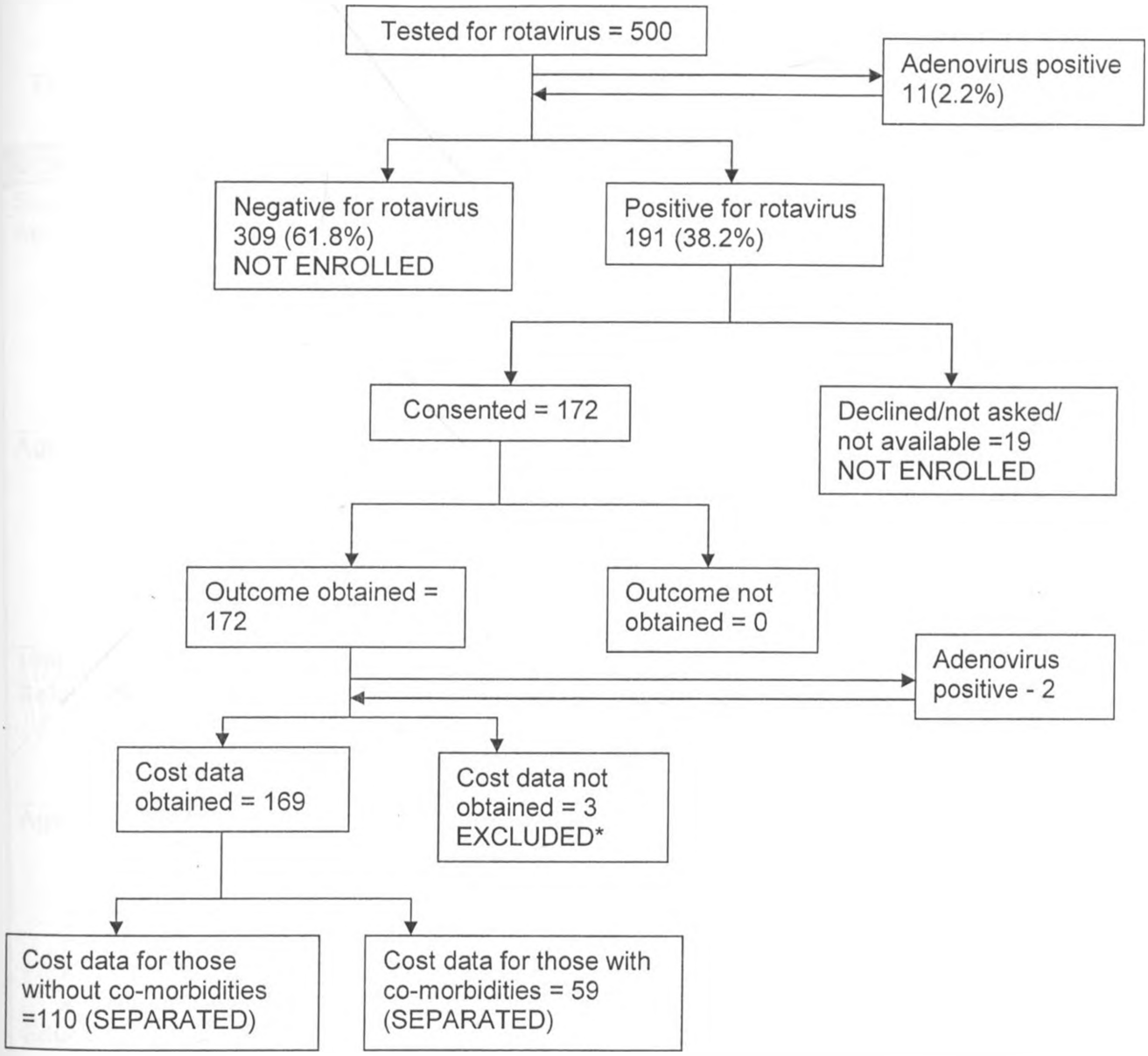
$$\begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \begin{bmatrix} X1 \\ X2 \\ X3 \end{bmatrix}$$

Odds Ratios (OR) and their associated 95% Confidence interval (CI) were employed to determine the factors that are more likely to explain the explanatory variable. P-value of less than 5% was considered statistically significant.

Ethical considerations

1. Approval was sought from the KNH Ethics and Research Committee and University of Nairobi, Department of Paediatrics and Child Health.
2. Informed consent was obtained from parents/guardians of children.
3. All test results were availed to the primary clinician(s) as soon as they were ready and to the parent or guardian of the child.
4. Emergency care and resuscitation of patient took priority where the need arose.
5. After HIV testing by DTC, those found to be exposed were counseled further and then referred to the KNH comprehensive care center after samples being taken for further confirmatory testing and for staging.
6. Confidentiality of the patient's details was observed.

Figure 1: Flow Chart of the Patients



** Although four patients absonded, cost data for one of them was obtained up to the day.the caretaker absonded with the child. Hence three of the four who absonded were not included in the second primary objective of cost analysis. However,since outcomes in terms of duration of stay to discharge or going home were known for all who absconded, they were included in the first primary objective of outcome.*

A total of 4,034 patients were admitted to the general paediatric wards during the study period. Of these admissions, 668 (16.6%) children aged 0-12 years were admitted due to gastroenteritis. Five hundred (74.9%) of those admitted with gastroenteritis were

tested for rotavirus and adenovirus. The prevalence of rotavirus and adenovirus was 38.2% and 2.2% of children admitted with acute gastroenteritis in KNH respectively. The prevalence of co-infection with both rotavirus and adenovirus was 0.4%.

Table 5: Socio-demographic characteristics of the patients (n = 172)

Characteristic	Frequency (%) or Mean (SD)
Sex (male)	99 (58)
Age (in Months)	
Mean age (SD)	8.7 (5)
Age categories (%)	
• ≤ 6	58 (34)
• 7 – 12	86 (50)
• 13 – 18	23 (13)
• 18 +	5 (3)
Age of weaning (in Months)	
Mean weaning age (SD)	2(2)
Weaning age categories (%)	
• 0 – 2	106 (62)
• 3 – 4	43 (25)
• 5 – 6	21 (12)
• > 6	2 (1)
Still breastfeeding	155 (90)
Relationship of caretaker	
• Mother	170(99)
• Father	1(0.5)
• Grandmother	1(0.5)
Age of caretaker (Years)	
Mean age of caretaker (SD)	25.6(4.9)
Caretaker age categories (%)	
• ≤ 20	16(9)
• 21 – 30	127(74)
• 31 – 40	26(15)
• 40 +	3(2)
Education of caretaker	
• None	2(1)
• Primary	55(32)
• Secondary	86(50)
• Post Secondary	29(17)
Occupation of caretaker	
• No formal employment/Housewife	123(72)
• Business	18(10)
• Casual labourer	18(10)
• Salaried Employment	12(7)
• Other	1(1)

There were slightly more males than females, ratio of 1.4:1.The youngest patient was one month old. Eighty four percent of the patients were infants. A third of the patients were weaned within the first month of life. Only 8% of the patients were weaned at six months while two children were weaned after six months. Majority were still breastfeeding. Almost all of the children were under the care of the mother, 155 (98.8%), one was under the care of the maternal grandmother because the mother had abandoned her while one was under the care of the father since the mother was at home with a neonate. Most (87%) of the caretakers were young, under the age of 30 years. More than half, 67%, of the caretakers had secondary school education and above. A majority of the caretakers 123 (72%) were not formally employed.

Table 6: Residence of patients

Residence	Frequency
• Within Nairobi	146 (84.9)
• Nairobi suburbs	26 (15.1)
Further Grouping	
• Industrial Area	18 (10.5)
• Huruma	14 (8.1)
• Kayole	21 (12.2)
• Rongai	11 (6.4)
• Mathare	6 (3.6)
• Pipeline/Embakasi	15 (8.7)
• Kariobangi South & North	10 (5.8)
• Dandora	19 (11.0)
• Eastleigh	15 (8.7)
• Kasarani/Githurai	15 (8.7)
• Dagoretti/Waithaka/Other	28 (16.3)

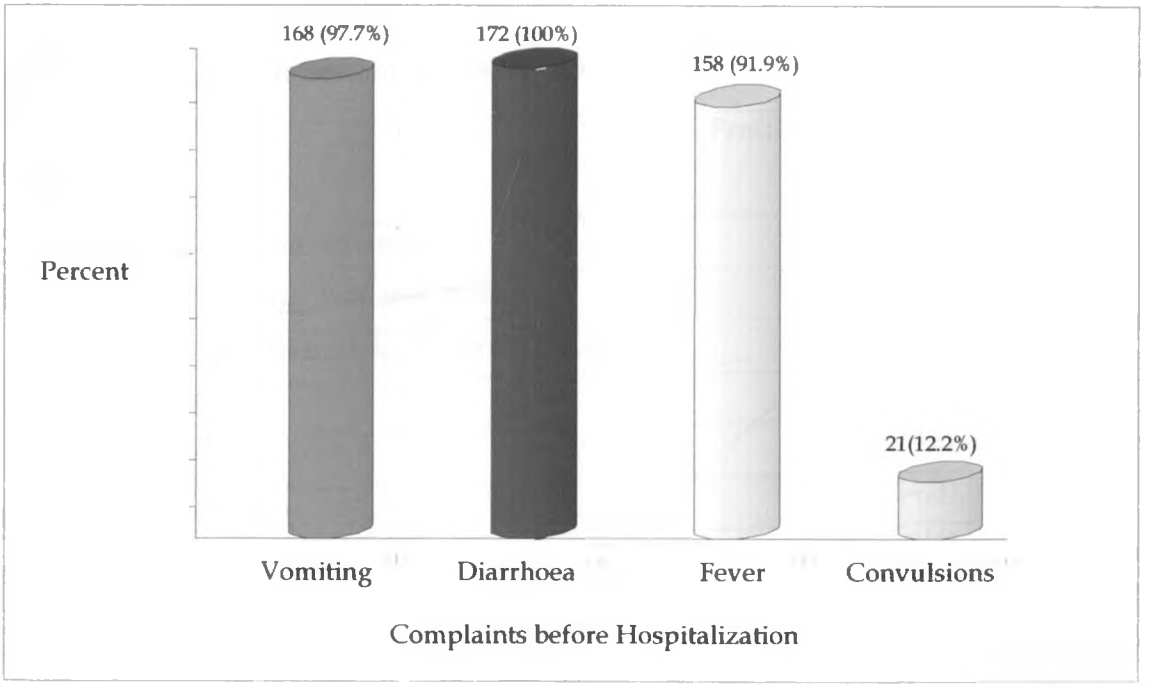
The patients came from all geographical areas of Nairobi and a few of its suburbs. The patients were from low and mid socioeconomic status.

Table 7: Presenting complaints: episodes per day and duration before admission.

Complaint	Mean (SD)	Median (IQR)
Vomiting		
• No. of vomiting episodes per day	4.6 (2.6)	4 (3-6)
• Duration of vomiting in days	3.3 (2.2)	3 (2-4)
Diarrhoea		
• No. of diarrhoeal episodes per day	5.6 (2.4)	5 (4-7)
• Duration of diarrhoea in days	3.4 (2.2)	3 (2-4)
Fever		
• Duration of fever in days	3.4 (2.3)	3 (2-4)
Convulsions		
• No. of convulsion episodes per day	1.9 (1.4)	1 (1-2.5)
• Duration of convulsions in days	1.3 (0.6)	1 (1-1)

The mean duration of symptoms before admission was three days except for convulsions which was shorter.

Figure 2: Presenting complaints (n = 172)



All patients had diarrhoea which was an inclusion criterion. The other symptoms were not present in all the patients. However, all the patients presented with two or more complaints. The vomiting and diarrhoea were the most frequent in 168 (97.7%) patients.

The combination of fever, vomiting and diarrhoea was in 154 (90%) patients. Nineteen (11%) patients had all the four symptoms.

Table 8: Facility where patients received prior care

Facility	Frequency	Percentage
Private Clinic/Hospital	67	39.0
None	57	33.1
Health Centre/Nairobi City Council clinic	17	9.9
Mission Clinic/Hospital	15	8.7
Over The Counter/Chemist drugs	10	5.8
District Hospital	3	1.7
Traditional Healer	2	1.2
Armed Forces Memorial Hospital	1	0.6
Total	172	100.0

A third of the patients sought health services at KNH as the first contact with a clinician. Sixty seven (39%) patients had sought services in private clinics. Only two patients acknowledged having taken herbal or traditional medications.

Table 9: Clinical evaluation on admission (n = 172)

Characteristic	Frequency (%) or Mean (SD)
Duration of illness before admission	3.85(2)
Other household member with diarrhoea	25(15)
Had sought care elsewhere prior to coming to KNH	115(67)
Referred to KNH	76(44)
Shock on admission	24 (14)
Any co-morbidity	59(34.3)
Adenovirus	2(1)
Rapid test positive for HIV-1	12(7)
Co-morbidities other than PEM, HIV and adenovirus.	40(23)

Table 9 gives additional details of the patients as noted by the primary clinicians. Fourteen percent of the patients were in shock on admission while 34.3% had co-morbidities.

Table 10: Nutritional status among the patients: Frequency (%) of Z scores

Z score	Weight for age	Height for age	Weight for Height
<-3	13 (7.6)	5 (2.9)	11(5.8)
-3 to -2	29 (16.9)	10 (5.8)	38 (22.1)
>-2	130 (75.6)	157 (91.3)	123 (71.5)

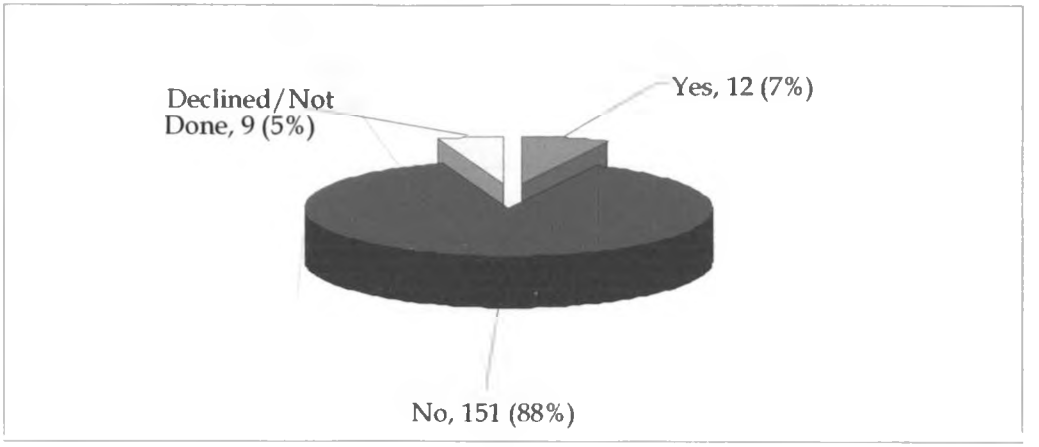
Severe malnutrition with Z scores of less than minus three was in thirteen (7.6%) weight for age, five (2.9%) height for age and in eleven (5.8%) weight for height.

Table 11: Co-morbidities among patients besides PEM, HIV and Adenovirus

Co-Morbid	Frequency	Percent
Rickets	15	8.7
UTI	6	3.5
Pneumonia	11	6.4
Asthma/Bronchospasm	7	4.0
Meningitis/Meningoencephalitis	3	1.7
Malaria	1	0.6
Adenoid Hypertrophy/Tonsillitis	2	1.2
Ascariasis	1	0.6
Epilepsy	1	0.6
NNS	1	0.6
Otitis Media	1	0.6
Anaemia	1	0.6

There were forty patients who had co-morbidities besides PEM, HIV exposure and adenovirus as listed in table 11. There were some patients who had more than one co-morbid illness.

Figure 3: HIV exposure status among study subjects (n = 172)



Ninety five percent of the study children were subjected to a rapid HIV test. Rapid HIV test was positive in twelve (7%) of the patients. Of these twelve children, one child was over 18 months of age. This child did not require further testing for diagnosis of HIV and was clinically in WHO stage IV with severe immunosuppresion (CD4 percentage of 10% at 2 years).

Table 12: HIV status of the Exposed (n = 11)

Status	Count	Percent
PCR negative	4	36.4
PCR positive (III/IV)	2	18.1
Declined/Not Done	5	45.5

Those who declined further testing for HIV by PCR were also not breastfeeding for prevention of mother to child transmission of HIV. Of the eleven children who were subjected to PCR testing, two were positive for HIV. These two children were in WHO stage II but with severe immunosuppresion (CD4 percentage of 14% in both) according to the revised WHO version of HIV 2006 classification. The overall HIV positive with AIDS were 3 (1.7%). The children who were HIV positive with AIDS had other underlying/co-morbid illnesses.

Table 13: Investigations done.

Test	Frequency	Percent
Haemogram	45	26.2
BGA	19	11.0
U/E/C	33	19.2
MPS	77	44.8
Blood culture	16	9.3
PCV	5	2.9
LFTs	2	1.2
VDRL	1	0.6
Urine Culture	1	0.6
Urinalysis	3	1.7
RBS	7	4.1
LP Biochemistry	19	11.0
LP M/C/S	19	11.0
Widal test	1	0.6
GXM	1	0.6
Chest x-ray	5	2.9
Wrist X-ray	8	4.7
CT scan head	2	1.2

Table 13 gives a breakdown of the investigations done on the study patients. Malaria parasite slide, Haemogram and U/E/Cr were the most requested investigations. These tests may have been done as baseline investigations, to rule out other illnesses that have the same presenting complaints and to look for complications of gastroenteritis.

Table 14: Medications given

Medications Given	Frequency	Percent
Antibiotics	132	76.7
Paracetamol	70	40.7
Anti-malarials	19	11.0
10% dextrose	9	5.2
50% Dextrose	4	2.3
ReSoMal	8	4.7
ORS	86	50.0
HSD	2	1.2
N/Saline	3	1.7
R/Lactate	158	91.9
Multivitamins	19	11.0
Phenobarbitone	4	2.3

More than 75% of the patients were given antibiotics. Ringer's lactate was used in a majority of the patients while only 50% of the patients were documented to have been given ORS. All patients had some form of fluid replacement (either intravenous or oral).

OUTCOMES:

PRIMARY OBJECTIVE

Table 15a: Duration of stay (days) in hospital – mean and SD

Duration of stay	All patients n = 172	Any co-morbidity n =59	No co-morbidity n =113	P value
To discharge/death	4.2(5.3)	6.7(8.2)	2.9(1.8)	**<0.001**
To going home	5.9(7.5)	8.8(11.1)	4.4(4.0)	**<0.001**
Extra days after discharge	1.7(3.6)	2.1(4.2)	1.5(3.3)	0.302

Table 15a gives mean and SD duration of stay (in days) to discharge, to time of going home and the extra days from discharge to going home. It is divided into rows for all patients admitted with RVG, those with and those without any co-morbidity.

Table 15b: Duration of stay (days) in hospital – median and IQR

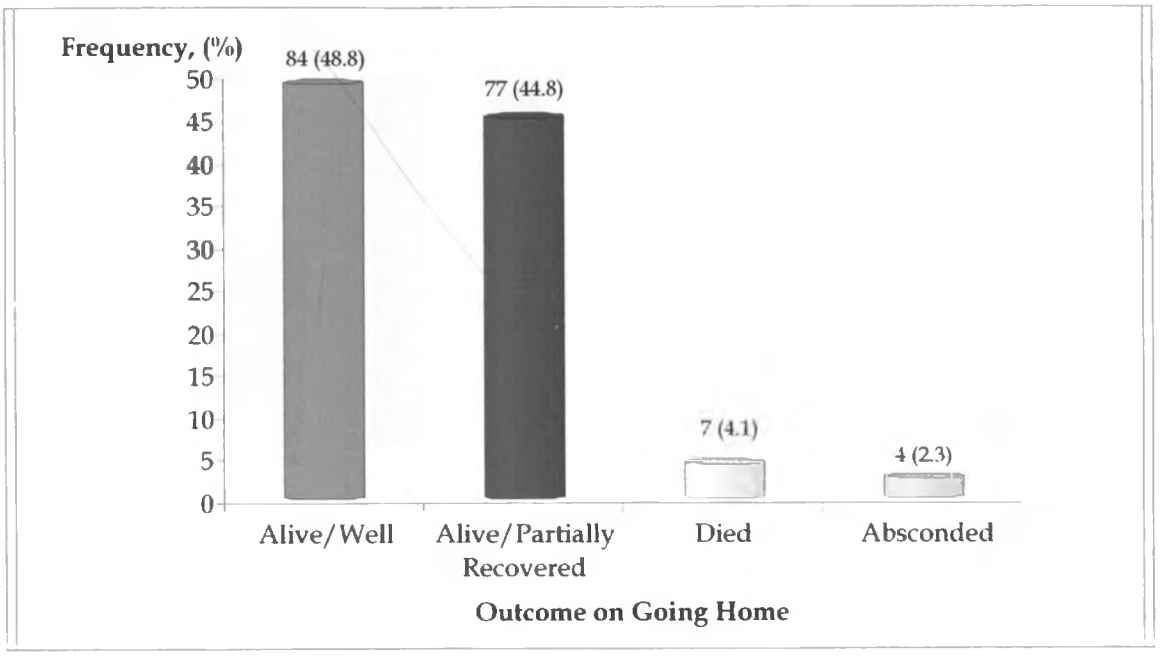
Duration of stay	All patients n = 172	Any co-morbidity n =59	No co-morbidity n =113	P value
To discharge/death	3(2-5)	5 (3-7)	3 (2-3)	**<0.001**
To going home	4(2-7)	6 (3-13)	3 (2-5)	**<0.001**
Extra days after discharge	0(0-1)	0 (0-2)	0 (0-1)	0.725

Table 15b gives median and inter quartile ranges for duration of stay (in days) to discharge, to time of going home and the extra days from discharge to going home. It is divided into rows for all patients admitted with RVG, those with and those without any co-morbidity

Those with a good outcome were 151 (87.8%) while poor outcome were 21 (12.2%). The number of children who died was 7(4.1% deaths, 95% CI 1.2-6.9). The number of children with long hospital stay, more than 7 days, was 14 (8.1%).

There were 77(44.8%) patients who stayed for extra days after discharge.

Figure 4: Outcomes on going home



A total of 163(95.9%) patients went home alive: 84(48.8%) had completely recovered, 77(44.8%) were partially recovered while 4(2.3%) absconded. Partial recovery group consisted of the children who were discharged because they were stable but they had not stopped having diarrhoea and went home on oral rehydration fluids. Those who absconded went home alive as per the hospital records.

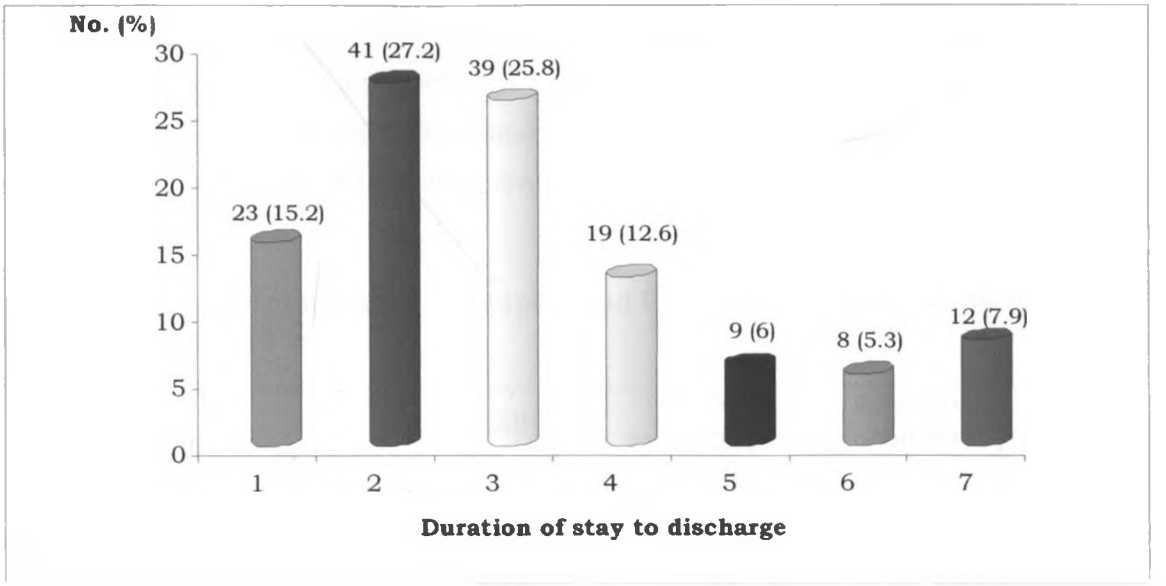
Table 16: Poor Outcome patients on discharge in frequency (%)

Outcome	All patients n= 172	Any co-morbidity n =59	No co-morbidity n =113	P value
Death - Freq (%)	7(4.1)	5(8.5)	2(1.8)	**0.038**
Length of stay >7days	14(19)	11(18.6)	3(2.7)	**<0.001**

Table 16 summarizes the patients who died and those who stayed for more than seven days in all the patients, those with and without co-morbidities. Co-morbidities were significantly associated with poor outcomes.

Of the children who died, the mean stay in the ward before death was 4 days, SD of 3.2.

Figure 5: Duration of stay to discharge for patients with good outcomes



Most children with good outcomes were discharged within three days. The median (IQR) in days for those with a good outcome was 3(2-4) to the time of discharge and 4(2-6) to the point of going home after discharge.

AVERAGE COSTS

Out of the 172 patients who were followed up for outcomes, 22 (12%) had an insurance cover (NHIF). Costs for three patients (1.7%) out of the four who absconded could not be ascertained. The three absconded patients whose costs could not be obtained were excluded from analysis for the second primary objective.

Table 17: Means of Total costs for Hospital and Economic perspective up to the time of discharge (KShs)

Perspective	All n = 169	No co-morbidity n =110	Any co-morbidity n =59	P value
Hospital perspective				
KNH bed charge rats	4,853.95	2,969.18	8,367.91	**<0.001**
NHIF bed charge rate	10,627.91	7,067.37	17,266.21	**<0.001**
WHO-CHOICE bed charge rate	11,229.15	7,494.10	18,192.78	**<0.001**
Economic perspective				
KNH bed charge rate	7,019.80	5,010.23	10,766.47	**<0.001**
NHIF bed charge rate	12,793.77	9,108.41	19,664.77	**<0.001**
WHO-CHOICE bed charge rate	13,395.00	9,535.15	20,591.34	**<0.001**

The patients with co-morbidities incur significantly more costs compared to those patients with no co-morbidity.

Table 18: Mean Total Costs up to the time of going home (KShs)

Perspective	All n = 169	No co-morbidity n =110	Any co-morbidity n = 59	P value
Patient perspective	6,505.79	5,645.39	8,057.20	**0.010**
Hospital perspective				
KNH bed charge rates	5,919.03	3,896.71	9,845.87	**<0.001**
NHIF bed charge rates	14,178.21	10,171.25	22,184.86	**<0.001**
WHO-CHOICE bed charge rates	15,038.22	10,824.61	23,469.70	**<0.001**
Economic perspective				
KNH bed charge rates	8,296.90	6,101.94	12,348.67	**<0.001**
NHIF bed charge rates	16,556.08	12,376.48	24,260.53	**<0.001**
WHO-CHOICE bed charge rates	17,416.09	13,029.84	25,500.90	**<0.001**

Mean total cost for the patient at the point of going home is KShs. 6,505.79. It is less if they have no co-morbidity and significantly more if they have co-morbidities. In the hospital perspective, the mean cost using the NHIF or WHO-CHOICE bed charge rate is almost three times the subsidized mean cost.

Table 19: Summary of mean costs up to the time of going home for non-changing costs (KShs)

Cost element	All n = 169	No co-morbidity n = 110	Any co-morbidity n = 59	P value
Pre KNH costs	430.14	553.18	195.68	0.058
KNH bills paid	4,127.92	3,440.16	5,367.97	**0.008**
KNH bills waived	1,824.56	1,141.55	3,097.97	**0.030**
KNH total billing	5,952.47	4,581.71	8,465.93	**<0.001**
Cost of tests	1,624.09	586.90	3,555.28	**0.002**
Cost of drugs	423.18	315.70	621.24	**0.049**
Other consumables	132.11	105.01	181.22	**<0.001**

Table 19 summarizes the patients' costs before being admitted in KNH and the other costs incurred at KNH with the bills paid by patient including the bills waived by the hospital per patient admitted. Most of the costs significantly differ between those with and those without co-morbidities. The average cost of tests per patient is slightly more than a quarter of average KNH total bill at the subsidized rates. The average cost of tests for the patients admitted with co-morbidities is slightly more than a third of total average KNH bill for the same group at the subsidized rates.

Table 20: Summary of changing costs from point of discharge to time of going home (KShs).

Cost	All n = 169	No co-morbidity n =110	Any co-morbidity n = 59	P value
To discharge				
Lost income	541.21	361.73	875.85	**0.027**
Transport costs	1,191.54	1,054.50	1,455.51	**0.028**
Bed charges				
KNH rate	2,478.11	1,925.45	3,498.31	**0.002**
NHIF rate	8,260.36	6,418.18	11,661.02	**0.002**
WHO-CHOICE rate	8,862.45	6,886.00	12,510.99	**0.002**
To going home				
Lost income	643.58	443.55	1,016.53	**0.037**
Transport costs	1,304.14	1,157.68	1,577.20	**0.027**
Bed charges				
KNH rate	3,539.65	3,054.55	4,454.24	0.054
NHIF rate	11,798.82	10,181.82	14,847.46	0.054
WHO-CHOICE rate	12,658.83	10,923.97	15,929.69	0.054
Extra costs (From time of discharge to going home)				
Lost income	102.37	81.82	140.67	0.308
Transport costs	112.60	103.18	121.69	0.207
Bed charges				
KNH rate	1,061.54	1,129.09	955.93	0.621
NHIF rate	3,538.46	3,763.64	3,186.44	0.621
WHO-CHOICE rate	3,796.38	4,037.96	3,418.70	0.621

Table 20 summarizes the averages for lost income, transport costs and bed charges to the time of discharge and to time of going home and the extra costs from time of discharge to time of going home. It further categorizes in columns the mean total of these costs for all the patients, those with and without co-morbidities.

The mean total lost income and transport costs per RVG admission is higher for those patients who had co-morbidities up to the time of discharge and to the time of going home.

SECONDARY OBJECTIVE

Table 21: Association between outcome and patient's characteristics (n = 172)

Factors	Outcome		OR 95%CI	P-value
	Good, (%) n=151	Poor, (%) n=21		
HIV Exposed	9 (6.0)	3 (14.3)	0.38(0.09-1.54)	0.161
Z_WA (<-3)	9 (6.0)	4 (19.0)	0.23 (0.08-0.97)	***0.034***
Z_WH (<-3)	9 (6.0)	2 (9.5)	0.60 (0.1-3.0)	0.532
Z_HA (<-3)	4 (2.6)	2 (9.5)	0.23 (0.04-1.50)	0.108
Co-Morbid other than above*	30 (19.9)	10 (47.6)	0.27(0.11-0.70)	***0.005***
Rickets	11 (7.3)	4 (19.0)	0.33 (0.10-1.17)	0.073
Pneumonia	8 (5.3)	3 (14.3)	0.34 (0.08-1.38)	0.115
Sex (male)	88 (58.3)	11 (52.4)	1.27 (0.51-3.17)	0.688
Age (≤ 6 month)	47 (31.1)	11 (52.4)	0.41 (0.16-1.03)	0.054
Not Breastfeeding	14 (9.3)	3 (14.3)	0.61 (0.16-2.34)	0.471
Duration before ADMN (≥ 4 days)	63 (41.7)	11 (52.4)	0.65 (0.26-1.63)	0.355
Referred	64 (42.4)	12 (57.1)	0.55 (0.22-1.39)	0.202
No Prior Care Received	52 (34.4)	5 (23.8)	1.68 (0.58-4.85)	0.332
Severity • Shock	14 (9.3)	10 (47.6)	0.11 (0.14-0.31)	***<0.001***

** Co-morbid conditions are as listed in table 11.*

Severe malnutrition (Z score weight for age less than minus three), patients with co-morbidities and shock on admission were the significant predictors of poor outcome. Patients aged six months or less showed a trend of having poor outcomes.

Table 22: Association between outcome and caretaker baseline characteristics (n = 172)

Factors	Outcome		OR 95%CI	P-value
	Good, n=151 (%)	Poor, n=21 (%)		
Age (in Years)				
• < 26	69 (45.7)	9 (42.9)	1.12 (0.45 – 2.82)	0.807
• ≥ 26	82 (54.3)	12 (57.1)		
Education				
• Primary & Below	50 (33.1)	7 (33.3)	0.99 (0.38 – 2.61)	0.984
• Secondary & Above	101 (66.9)	14 (66.7)		
Occupation				
• Employed/Working	43 (28.5)	6 (28.6)	1.0 (0.36-2.73)	0.993
• Un-employed	108(71.5)	15 (71.4)		

Caretaker characteristics did not have an association with poor outcome of the patients.

Table 23: Logistic regression between outcome and patient characteristics

Factor	ODDs	P-value
Z_WA	1.09	0.003
Age (≤ 6 months)	1.26	0.016
Co-morbid (other than HIV and PEM)*	1.26	0.010
Shock (on admission)	1.07	<0.001

* Co-morbid conditions as listed in table 11.

On multivariate analysis, shock was the strongest predictor of poor outcome. A young age of six months or less was a significant predictor of poor outcome on multivariate analysis.

DISCUSSION

Among the children admitted with acute gastroenteritis, 38.2% had rotavirus. This is within the range noted in most hospital studies done so far. A study in Canada by Ford-Jones reported an RVG prevalence of 37% [28], Cunliffe and Steele in Africa and South Africa respectively, estimated that rotavirus was detected in about 24% (range 13-55%) [11,12] and in Brazil, Carneiro reported an RVG prevalence of 39% [9]. The RVG prevalence in this study is less than the 59% as was reported by Gatinu [32]. This difference could be attributed to the seasonality of rotavirus. This study was conducted from February to May past the peak episodes which ends in March in Kenya while Gatinu's study was conducted from June to August, a different peak season.

The adenovirus prevalence of 2.2% in this study is comparable to the 2% prevalence reported by Basu et al [45] in Botswana, 2.8% prevalence reported by Jarecki-Khan et al [46] among infants with diarrhea in rural Bangladesh and the 2.5% prevalence reported by Kow-Tong et al in Taiwan [29]. In this study, the co-infection of rotavirus and adenovirus was in less than 2% of the study patients. This is much lower than the one noted by Forbes et al in a private hospital in Nairobi where the co-infection of rotavirus and adenovirus was 8.3% [37]. The latter study by Forbes [37] had a population of children aged from one month to 16 years while the studies by Kow Tong [29], Basu [45], and Jarecki-Khan [46] had an upper age limit of 5 years. This study had an upper age limit of 36 months.

More than 80% of the children with rotavirus were below 12 months of age. This finding is comparable to the findings from other studies, including those from Africa [3-14]. However, in this study, the fraction of those under six months was high at 34% compared to other studies where it was about 10% or less [9,14,28,47]. Less than 10% of the children were exclussively breastfed for 6 months. This is in contrast to the KDHS [2], where 13% were found to be exclusively breastfed up to 6 months. The 90% of the study children who were still breastfeeding is comparable to the 97% of KDHS among children in Kenya [2]. The differences in breastfeeding rates, higher on the national average, could be attributed to higher breastfeeding practices in the rural areas than in the urban setting of this study. Some of the study patients in this study, less than 3%, were not breastfeeding for prevention of mother to child transmission of HIV. Early

weaning or introduction of alternate feeds may predispose the infants to acquiring RVG early.

The children came from all geographical areas of Nairobi, although the number from the Lang'ata and Kibera areas, listed as others, was low considering the high population of the people in that area. The low number of patients with RVG from Lang'ata and Kibera may partly be explained by the presence of another governement health facility, Mbagathi District Hospital, in this region unlike the other areas of Nairobi that do not have a district hospital. Although the children were from all geographical areas of Nairobi, they were mainly from low socioeconomic status. KNH mainly serves patients from low economic status, hence the high numbers from such background.

Almost 70% had sought some form of medical help from another health facility prior to coming to KNH, mostly in private clinics, 39%. This is likely to increase the cost of care for rotavirus gastroenteritis. Almost 50% of the children who came to KNH were referred. The patients admitted had the common symptoms of rotavirus; all had diarrhea (100%), 97.7% had vomiting and 91.9 % had fever. These were also the common symptoms in a study in Brazil by Carneiro [9], while in the Canada study by Ford-Jones, 97% reported vomiting and 89% reported fever [28]. In this study all the patients had diarrhoea as a symptom, it was an entry criterion for the patients to be classified as having gastroenteritis. However, children may have rotavirus gastroenteritis without having diarrhoea but present with vomiting and the other symptoms of gastroenteritis.

The co-morbidities were lumped together for analysis as the individual illnesses were too few to be analyzed independently. Rickets was diagnosed as the single leading co-morbidity in about 9% of the study patients. In the Canada study by Ford-Jones [28] respiratory tract illness was the leading co-morbidity that was found in 38% of the subjects. In the management of the patients, various tests were done and medication given. These tests, as the clinicians investigate any other causes of the patients' illness, and drugs, given form part of the costs of care for rotavirus gastroenteritis. The most common tests were malaria parasite slide, haemogram, urea and electrolytes, blood gas analysis and cerebrospinal fluid analysis. These tests were probably done to rule out other illnesses that have the same presenting complaints with rotavirus gastroenteritis

such as malaria and meningitis. The tests may also have been done to look for the complications associated with gastroenteritis, in this case, electrolyte imbalances and acidosis. While the haemogram test is considered a baseline investigation for most children admitted with infection in KNH. The patients with co-morbidities may have had more tests. They thus had higher costs for the tests. This might have driven their mean costs higher.

All children (100%) received some form of fluids, either intravenous or oral, to restore and/or replace losses, whereas only 94% received fluids in the study by Ford-Jones [28]. More than 75% of the patients received antibiotics even though less than 35% were documented to have co-morbidities. These patients may have had a high respiratory rate secondary to dehydration or metabolic acidosis. The high respiratory rate may have led to a wrong diagnosis and treatment for pneumonia even though other evidence for pneumonia was not documented. The high respiratory rate may have led to a diagnosis of pneumonia which is in keeping with the Integrated Management of Childhood Illness (IMCI) guidelines on diagnosis of pneumonia.

The rotavirus infection admission case fatality rate was 4.1% in this study. This is much lower than that reported by Gatinu at 11.6% [32] but closer to the average of the ongoing surveillance in KNH by April 2007 of 4.6%. It is much higher than in other more developed countries like South Africa and the USA [21,25]. The case fatality rate from rotavirus gastroenteritis may have decreased from the time Gatinu did his study as there has been a lot of staff training on emergency care of children presenting in the emergency room in KNH. This Emergency Triage and Treatment (ETAT) training might have improved care of patients presenting in KNH. This might have lowered the case fatality rate of RVG. The mean ± SD duration of hospitalization before death in this study was 4±3.2 days. This is longer than mean duration of hospitalization before death of 1.8 days reported by Gatinu [32]. This could also be due to improved emergency care as noted above.

The mean ±SD of length of stay to discharge was 4.2±5.3 for all the patients. This length of stay is comparable to a mean (± SD) of length of hospital stay of 4.4±3.3 days reported by Kow Tong in Taiwan [29], 5.5±4.5 days as reported by Noel et al [48], 5.3

days as reported by Matson [49] and 5.2 days reported by Nokes in a study in Kilifi, Kenya [50]. In this study, of the children with a good outcome, those who stayed in the hospital for less than a week, a majority (68%) were discharged within 3 days.

The mean total cost per RVG admission was Kshs. 6,505.79 to the patient. Most of the patients were from low socioeconomic status as evidenced by their residential areas. These people live on an income of less than a dollar per day (Exchange rate of Kshs. 65 per one dollar). Thus the cost of RVG admission to these families is almost up to 300% their average monthly income, while it was only 40% of the monthly income in Taiwan [29]. The patient perspective cost is helpful to the patient to decide whether or not they can incur the cost of vaccination. This is by comparing the benefit of the vaccine viz a viz the cost of the vaccine and the cost of hospitalisation should they get admitted. Most of the caretakers are in informal employment and they do not get any income for the time they are in hospital. The high cost to the patient can be used to create awareness and advocacy to the public at the community level.

The hospital perspective total mean cost help the hospital administrator know how much it costs to treat one child admitted with RVG per admission. This should help in deciding how much the patient should be charged. The mean total cost of care up to the time of discharge of Kshs. 4,853.95 for hospital perspective using the subsidized KNH bed charge rate, which is below market value, is less than the cost of vaccinating one child for Rotarix® of about Kshs 6,000.00 at current rates in a private hospital in Nairobi. However, the mean total cost up to the time of discharge is higher in the hospital perspective, if the near market rates for daily bed charges proposed by the NHIF and WHO-CHOICE are used, Kshs. 10,627.91 and KShs. 11,229.15 respectively.

The mean total cost of care for RVG is also higher than cost of vaccinating in the hospital and society perspective using any daily bed charge rate (table 17 and table 18). The economic cost is useful to the country's treasury department. It is what can be used in cost effective analysis of vaccines. It defines what the whole economy incurs on average per patient admitted with rotavirus gastroenteritis. Long duration of hospital confinement for the caretakers, most of who are in the productive age group and are relatively educated, takes away a lot of man-hours of production from the economy.

The average cost of care per child admitted with RVG, in the economic/society's perspective, using the WHO-CHOICE recommended costing method up to the point of discharge (Kshs 13,198.46) is more than twice the cost of vaccinating one child in a private hospital in Nairobi (Kshs 6,000.00) and almost thrice up to the point of going home (Kshs 17,416.09). This cost is much higher than the cost of the cheaper Rotarix™ vaccine. The manufacturer's selling price is Kshs 3,524.00 for two doses of Rotarix™ vaccine and Kshs 7,650.00 for three doses of the Rotateq™ vaccine. It costs Kshs 4,700.00 - 6,000.00 in private hospitals for the two doses of Rotarix™ vaccine, and up to Kshs 9,000 for the three doses of Rotateq™ vaccine to the patient. The Global Alliance for Vaccines and Immunization (GAVI) may subsidize the cost by co-financing with the government. The initial government contribution is normally about $0.15 (about Kshs 10.00) per dose. Cost benefit with RVV is likely to be higher if manufacturer's vaccine cost is used instead of the private hospital costs.

Vaccination would reduce the costs of care and treatment of children with RVG and any other gastroenteritis. As a result of economies of scale, the cost of vaccination per child might actually reduce with routine vaccination since there is a possibility of having savings from immunizing many children. There is thus potential for cost saving with routine rotavirus vaccination. However cost effectiveness utility and cost benefit analysis need to be done, since it is not all children who get rotavirus gastroenteritis are hospitalized yet all infants would require immunization!

The costing as done in KNH would be higher than the other government hospitals in Kenya. The other government facilities do not have the human resource and facilities comparable to KNH. The cost calculated from this study would be expected to be lower than that in most private hospitals in Nairobi. This is because the other hospitals do not subsidize their charges. The biggest component of the total cost was from that due to the bed charges for the duration of stay.

The mean (±SD) of length of stay to discharge was 2.9(±1.8) for those with no co-morbidity, comparable to 2.4±1.7 seen in children with no underlying illness in Canada [28] while it was 6.7 (±8.2) for those with co-morbidities. The higher length of stay was also noted in the Canada study for those with underlying illnesses. The inter-quartile

range is wide for those with any underlying/co-morbid illness in this study as some of the children stayed for long before discharge, some stayed for about two weeks and one of them who suffered from hypoxic brain injury, probably as a result of shock, stayed for 60 days.

There was a significant mean difference between length of stay to discharge (P value < 0.001) and length of stay to going home (P value < 0.001) for those who had a co-morbid illness and those who did not have. Those with co-morbidities stayed longer in the hospital before being discharged and also before going home. Longer duration of hospitalization for rotavirus for patients with co-morbidities was also seen from Ford-Jones study in Canada [28] where it was significantly longer (P <0 .001). This could be due to the other illnesses also being treated fully once the patients are admitted even though it is not what made the patients seek medical care. It could also be that they take longer to recover due to a reduced immunity as may be the case in malnourished and HIV infected children.

Severely malnourished children, Z score weight for age less than minus 3, had a worse outcome compared to those with a higher weight for age Z score. This was also noted in the studies by Dagan in Israel [13] and Binka in Ghana [14]. Those with a co-morbid or underlying illness had worse outcomes and higher costs of care. Worse outcome for those with underlying illnesses has also been documented in other studies in Israel [13], Ghana [14] and Canada [28] and postulated in Malawi [34]. There was no significant difference in extra days stayed in hospital from point of discharge to day of going home (p value of 0.302). The worse outcome may not be a result of the rotavirus effects alone but also due to the multiple effects of the other illnesses, such as a poor immune system from malnutrition and a natural progression of the the co-morbidities.

Shock was a predictor of a poor outcome on univariate and multivariate analysis (p value <0.001). This could reflect the significant physiological changes that may have resulted from severe dehydration which may be more difficult to reverse than just severe dehydration. The duration the patient had been in shock may be important but the study had not sought this out. This highlights the need for urgent emergency intervention in patients presenting in shock and with co-morbidities.

Being aged six months or less was an independent predictor of poor outcome on multivariate analysis, p value of 0.016. Getting RVG at this early age may be an indicator of low passive immunity from mothers or due to effects of early weaning. Infants getting RVG early may indicate they have lower immunity. Early weaning has been shown in literature to be a risk factor for acquiring RVG [9]. Protection in neonatal period is conferred via transplacental maternal antibodies and by antibodies and other factors such as lactoadherin transferred through breastfeeding. Lactoadherin in human milk is believed to interfere with rotavirus replication [51]. In this study exclusive breastfeeding rate was very low. Early mixed feeding may have reduced the protective effects of exclusive breastfeeding. Those exclusively breastfed for six months were too few to allow any analysis between them and those who were weaned earlier.

Poor outcomes were more likely to occur in those with co-morbidities compared to those who did not have any underlying/co-morbid illness; p value of 0.038 for death and <0.001 for long hospital stay of more than 7 days. Other underlying conditions such as Z score of less than minus 3 (height for age and weight for height), rickets or pneumonia on their own did not influence outcomes. The individual illnesses may not have had an effect on outcome as their numbers may be too small, hence limited power, to bring out any statistical differences.

The other factors, namely; sex, having received prior medical care, whether referred or not, breastfeeding or not, caretakers characteristics (age, occupation or employment status) did not influence the outcome on univariate analysis. The sex of the patient has not been documented to influence outcome in other studies. The caretaker's characteristics have not been documented to influence outcome of RVG.

There were higher mean total costs for those patients with co-morbidities. Those with co-morbidities have a significantly longer hospital stay. Longer duration of stay gives a higher probability of use of more pharmacotherapy, supplies and laboratory investigations. These may have contributed to the higher cost.

The mean of total pre-KNH costs (table 19) were lower for those with a co-morbid/underlying illness (Kshs 195.68) compared to those with no co-morbid/underlying

illness (Kshs 553.18). This could be due to those with co-morbidities being referred earlier to KNH or the caretakers opted to seek treatment in KNH first. This led to spending less money elsewhere before ending up in KNH.

Since patients with co-morbidities have a significantly poor outcome and high costs of care, it might be worthwhile to consider targeted rotavirus vaccination for this group.

Conclusions

1. Rotavirus gastroenteritis has a high morbidity and mortality in terms of long hospital stay and high mortality rate for a preventable illness.

2. The average cost of treating rotavirus gastroenteritis is high compared to the average incomes of the patients. RVG causes considerable resource utilization in all health care settings, both to families and to the economy.

3. The children with co-morbidities and those in shock on admission had a poor outcome compared to those who did not have any co-morbid illness or those who were not in shock.

4. Average cost of caring for children with co-morbidities were higher than the average costs of caring for children who did not have co-morbidities.

Recommendations

1. Children in shock on admission and those with co-morbid conditions should get priority for they have a poor outcome.

2. Rotavirus gastroenteritis has a significant impact on young children, their families and the health care system. Cost effectiveness utility and cost benefit analysis for the whole country for routine rotavirus vaccination should be done. This would show if prevention of severe disease through routine infant vaccination would be potentially cost-effective.

Limitations

1. The study assumes that all the study patients received standardized care in terms of accurate diagnosis, timing and appropriateness.

2. The subsidized KNH charges used for some services in computation of costs is less than the market charges because KNH is a public hospital.

3. There is a likelihood of extra costs for patients who developed nosocomial infections during the RVG admission. If such patients went home and were then admitted later on, the extra costs of managing the nosocomial infections acquired as a result of RVG admission are not included. The rate of acquiring these infections is unknown in Kenya.

4. Those children with diarrhoea who died or were discharged within 48 hours before provision of a stool sample for rotavirus antigen testing were excluded automatically from the study even though they may have had rotavirus acute gastroenteritis.

5. It was not possible to include all the extra costs of the illness such as; the extra costs of extra baby diapers used during the illness, the extra costs incurred by the patient's visitors who brought gifts to the child and/or caretaker, lost income to patient's visitors who had to stop working to visit the patient and the lost income by caretakers for whom a monetary value for their daily activities was not obtained such as housewives.

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APPENDICES

Appendix 1: PATIENT DATA COLLECTION FORM.

Study number _____ WARD _____.

History

1. Date of 1st interview ___/___/___(dd/mm/yy).
2. Patient name _____.
3. IP No. _____.
4. Sex M F (circle correct answer)
5. Age of child (months)_____
6. Residence (village/estate) _____
7. Has the child been vaccinated for rotavirus (circle correct answer)
   1.Yes 2.No 3.Not known
8. If yes, how much did you pay for it? Kshs _____
9. At what age was he/she immunized? _____months.
10. At what age was the child weaned (even water) _____months.
11. Is the child still breastfeeding? _____ (Y/N)
12. Caretaker's relationship to the patient:
    1. Mother_____
    2. Father_____
    3. Sister_____
    4. Brother_____
    5. Grandmother_____
    6. Grandfather_____
    7. Other relative_____
    8. Friend_____
    9. Other (specify)_____
13. Education of caretaker Nil (0), 1- 8yrs (1), 9-12yrs (2), >12yrs (3)
14. Age of caretaker in years_____
15. Symptoms:
    Vomiting ___ (yes/no) No of episodes/24hrs ____ Duration (days) _____
    Diarrhoea ___ (yes/no) No of episodes/24hrs ____ Duration (days) _____
    Fever ___ (yes/no) Duration _____days
    Convulsions ___ (yes/no) No of episodes/24hrs ____ Duration (days) _____

16. Number of days of illness before hospitalization_____

17. Other household members with diarrhea _____ (Yes/No)

18. Were you referred_____ (Yes/No)

19. Where did the patient receive care prior to arriving at KNH?
    1. Not applicable
    2. Traditional healer/Herbalist
    3. Chemist/Over-the-counter drugs
    4. Private clinic/hospital
    5. Mission clinic/hospital
    6. Health center
    7. District hospital
    8. Provincial General Hospital
    9. Others, specify_____

Clinical evaluation.

1. Weight _____ kilograms.

2. Height _____centimeters.

3. Z - Weight for age _____

4. Z - Weight for height _____

5. Z – Height for age _____

Clinical complications as documented by primary clinicians on admission;
1. Shock
2. Severe dehydration
3. Some Dehydration

How many co-morbidities did the patient have? _____
(Specify the co-morbidities)
_____
_____
_____
_____

Laboratory data

1. HIV test: Exposed (1) Non-exposed (0) Not done/Declined (2)

2. HIV WHO and/or immunological stage:
   (0) PCR negative; (1) stage 1 or 2;
   (2) Stage 3 or 4 (3) Declined PCR/further testing

3. Adenovirus; Y/N

Outcomes

Date of admission ___ /___ /___ (dd/mm/yy)

Date of discharge ___ /___/ ___ (dd/mm/yy)

Date of death ___/ ___ /___ (dd/mm/yy)

Date of going home ___ /___ /___ (dd/mm/yy)

Length of stay to discharge [LoS(d)]_____

Length of stay to going home [LoS(h)]_____

Outcome on going home;

1. Alive, well
2. Alive, partially recovered
3. Died
4. Discharged against medical advice
5. Absconded

Costing

LOST INCOME

1. Are you (caretaker) unemployed/housewife (1), business/self employed (2), casual worker/daily wage earner (3), salaried employee (4), Others (5) specify_____

2. Are you paid or earning when not on duty? _____ (Yes/No)

3. How many days, before admission, had you been out of work due to child's illness? _____ Days.

4. How much are you losing out per day (a day's pay) due to taking care of child here? _____ .

5. Total lost income (total days work missed before admission and while in the ward x4) to discharge _____ to going home _____

TRANSPORT:

1. How much did you (and the people who escorted you) pay to get to the hospital and back for those who went back? _____ Kshs.

2. How many trips did other household members make to visit your child and how many people visited you?

Day	1	2	3	4	5	6	7	8	9	10	11	12
Visitors												
Trips												
Total												

3. Total numbers of round trips _____
(Examples: 3 relatives' visit twice [n = 6 trips] One relative visits thrice [n = 3 trips])

4. How much is (one way) fare to the hospital? _____ Kshs. (per person)

5. Total cost of traveling to hospital *(include fare for going back on discharge)* to discharge _____ to going home _____

PRE KNH COSTS

How much did it cost you for Drugs, Tests, Consultation and other financial costs?

Facility	Consultation	Tests	Drugs	Other costs	Total
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____

Total costs incurred in other facilities prior to visiting KNH _____

KNH Total Bill _____ Kshs.

PFC total costs not included in KNH bill above _____Kshs

Amount waived by the KNH (PFC and Inpatient) _____ Kshs

Amount paid by patient to hospital _____Kshs

Total costs to the patient. _____Kshs.
(Includes amount incurred by the patient prior to visiting KNH, opportunity costs and the charges the patient actually paid KNH excluding waivers)

KNH CALCULATED COSTS

LABORATORY TESTS DONE			KSHS/TEST
Haemogram	_____ (yes/no)	No. done_____	_____
Blood gas analysis	_____ (yes/no)	No. done_____	_____
U/E/C	_____ (yes/no)	No. done_____	_____
Malaria blood slide	_____ (yes/no)	No. done_____	_____
Blood culture	_____ (yes/no)	No. done_____	_____
Urine culture	_____ (yes/no)	No. done_____	_____
Urinalysis	_____ (yes/no)	No. done_____	_____
LP Biochemistry	_____ (yes/no)	No. done_____	_____
LP M/C/S	_____ (yes/no)	No. done_____	_____

Others (specify)

1. _____ No. done _____ _____
2. _____ No. done _____ _____
3. _____ No. done _____ _____

Total cost of KNH tests _____

TREATMENT GIVEN.

Medication use: *Include any drugs prescribed on discharge. Write "missing" for any data not there (e.g. if number of days administered is missing).Exclude drugs for chronic illnesses.*

Drug name	Route*	Dose units (e.g. µg/ml, ml, mg)	Dose amount (e.g. 50,100) 1	Freq of administering per day 2	No. of days admin (e.g. 3days) 3	Total dose adm. 1x2x3 4	Cost of dose adm 5	Cost of drugs 4x5
Total								

* 1 = intravenous; 2 = IM injection; 3 = oral; 4 = nasal/gastric tube; 5 = rectal; 6 = topical (ointments); 7 = drops for ear, nose, throat; 8 = inhalation

Consumable	Size	No used	KSHS/UNIT
IV canulas	yellow	____	_____
	blue	____	_____
Syringes	2cc	____	_____
	5cc	____	_____
	10cc	____	_____
	20cc	____	_____
Needles			
	23g	____	_____
	21g	____	_____
	18g	____	_____
NG tube	6g	____	_____
	8g	____	_____
	10g	____	_____
IV giving sets		____	_____
Others	_____	____	_____
	_____	____	_____
Total			_____
Other costs;			
1. _____			_____
2. _____			_____
3. _____			_____
Total			_____

Total computed KNH costs (Consult + drugs + hosp charge + tests) _____

Appendix 2: CONSENT FORM.

I, Dr B. O. Osano of the Department of Paediatrics and Child Health, University of Nairobi, am conducting a study to find out clinical outcomes of children aged 0 to 35 months suffering from gastroenteritis due to rotavirus infection and the costs you as the parent or guardian will incur in their treatment for this admission. Rotavirus is a virus that causes gastroenteritis in a majority of the children admitted with gastroenteritis. I am also studying the relation of such patients' outcomes with other conditions that your child may or may not have such as state of nutrition and HIV status.
When compiled together the information will be useful to us in planning interventional measures and monitoring progress in children's healthcare provision.
Answers to questions asked will be filled in a questionnaire. The child will then be examined; his weight and height will also be taken. A stool sample in a container will be requested for from the child to test for the virus and other organisms that may be found in the stool in the laboratory. A blood sample may be taken from a needle prick on the finger which may cause slight temporary discomfort for HIV laboratory testing, if the test has not been done prior.
If you would not want to know the results of any/either of the tests, I will remove the identifying labels on the sample in your presence and they will be tested as anonymous. The information you give and the test results obtained shall be treated with strict confidence and used only for the study and your child's care. Any useful information and results for her/his treatment shall be communicated to the attending doctors.
You may opt not to participate in the study and the treatment and care of your child will not be altered in any way.

If you wish your child to take part in the study please acknowledge.

Mr./Mrs./Miss..... who is the parent/guardian of the child .....is giving permission for the above mentioned procedures to be carried out on my child. I acknowledge that a thorough explanation of the nature and consequences of the procedures to which I am consenting to has been explained to me by Dr.....
I clearly understand that my participation is completely voluntary.

Date .....

Parent/guardian signature.....

Doctor's signature.....

Researcher – 0722-646720.

Appendix 3: Laboratory tests and other consumables price list used.

TEST	COST/TEST Kshs	Discounted amount Kshs
LABORATORY		
Haemogram	200	302.52
Haemogram + ESR	240	363.02
Blood gas analysis	600	907.55
U/E/C	350	831.92
Malaria blood slide	100	151.26
Blood culture	400	605.04
Urine culture	300	453.78
Urinalysis	120	181.51
LP Biochemistry	200	302.52
LP M/C/S	350	453.78
PCV	200	302.52
ESR	40	60.50
RBS	160	242.01
Widal test	200	302.52
LFT	380	574.78
RADIOLOGICAL		
Wrist X-ray	1000	
Chest X-ray	1000	
CT Scan Brain	4500	

OTHER SUPPLIES	Size	PRICE in Kshs
Needles	21g	1.50
	23g	1.00
Syringes	2cc	1.40
	5cc	1.50
	10cc	3.00
	20cc	4.80
IV Canulas	24G	14.50
	22G	12.50
IV Fluid giving set		14.50
IV Blood giving set		13.50
A pair of clean gloves		1.68
A pair of sterile gloves		26.00
Nasogastric tubes	6g	8.25
	8g	8.80
	10g	9.00

Appendix 4: Supplies/consumables usage guide schedule

Drug	Dosage	Syringe type	Needle type	Comment
Crystalline penicillin	≤1megaunit	2cc	21G	To dilute – 21G To inject - 23G
	> 1megaunit	5cc	21G	
Gentamicin	≤ 80mg	2cc	21G	To dilute – 21G To inject - 23G
	> 80mg	5cc	21G	
Amikacin		2cc	21G	
Ceftriaxone or Flucloxacillin	≤ 250mg	2cc	21G	5cc used for dilution
	250 – 500 mg	5cc	21G	
	500m – 1g	10cc	21G	
Chloramphenicol or Ceftazidime	≤ 250mg	2cc	21G	10cc syringe used to dilute chloramphenicol
	250 – 500mg	5cc	21G	
	>500mg	10cc	21G	
Amoxycillin – clavulinic acid	≤ 500 mg	5cc	21G	10 cc used for dilution
	>500mg	10cc	21G	
Ringer's lactate		20cc	21G	For shock treatment

1. Needle use: bear in mind injection safety rules. One needle for dilution and another one for injection. In children the 23G needles are used for intramuscular injections. For drug dilution, one needle was used for diluting one vial. 21G needle was used for drug dilution.
2. One intravenous giving set per one bottle of intravenous fluid. With a change of intravenous fluid bottle, the fluid giving set was changed too.
3. One pair of gloves was used per injection time, if more than one drug is given to a patient at a time, then one pair of gloves was used for the multiple drugs given to a patient.
4. One pair of gloves per procedure, for example, in fixing intravenous drip.

Appendix 5: drugs used and their unit costs.

Drugs	Units	Amp/Vial size	Cost/vial
ANTIBIOTICS			**KShs**
Crystalline penicillin	Vial	1megaunit	3.80
Gentamicin 80mg/2ml	Amp	80mg	1.40
Chloramphenicol	Vial	1gram	38.50
Erythromycin syrup	bottle	250mg/5ml	37.00
Ceftriaxone (Rocephine)	Vial	500mg	280.00
Amikacin	Amp	500mg	330.00
Ceftazidime (Fortum)	Vial	1gram	300.00
Cefuroxime (Zinnat)	bottle	250mg/5ml	900.00
Amoxycillin/Clavulinate	mg	228mg/5ml	200.00
Flucloxacillin inj.	vial	250mg	33.00
Flucloxacillin oral	bottle	125mg/5ml	250.00
Metronidazole inj.	mg	500mg	104.00
Metronidazole(Flagyl)	bottle	250mg/5ml	38.00
Amoxycillin	bottle	250mg/5ml	57.00
Nitrofurantoin	tabs	100mg	1.70
ANALGESICS			
Paracetamol syrup	bottle	160mg/5ml	27.50
Paracetamol suppository		100mg	12.00
ANTIMALARIALS			
Artemether	Amp	80mg	44.00
Artemether	Amp	20mg	30.00
Quinine Hydrochloride inj.	Amp	300mg/ml	2.60
INTRAVENOUS FLUIDS			
Ringer's lactate	Bottle	500mls	30.00
Normal saline	Bottle	500mls	31.50
10 % Dextrose	Bottle	500mls	14.00
50% Dextrose	Bottle	50mls	50.00
Half Strength Darrow's	Bottle	500mls	32.00

OTHERS			
Multivitamins syrup	Bottle	60mls	22.00
Folic acid	Tabs	5mg	0.30
Ferrous sulphate/folic acid syrup	Bottle	60mls	105.00
ORS	satchet		3.00
ReSoMal (cost of reconstituted)	mls	500mls	77.00
Potassium Chloride inj	Amp	10mls	24.00
Albendazole	tabs	200mg	3.95
Phenobarbitone	tabs	30mg	0.30
Phenobarbitone inj	Amp	200mg/ml	330.00
Nystatin oral drops (100,000units/ml)	Bottle	60mls	27.00

Appendix 6: KNH Ethics approval

KENYATTA NATIONAL HOSPITAL
Hospital Rd. along, Ngong Rd.
P.O. Box 20723, Nairobi.
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP", Nairobi.
Email: KNHplan@Ken.Healthnet.org

Ref: KNH-ERC/ 01/ 4841

23rd October 2007

Dr. B. Ombaba Osano
Dept. of Paediatrics & Child Health
School of Medicine
University of Nairobi

Dear Dr. Osano

RESEARCH PROPOSAL: "SHORT TERM OUTCOMES AND COST ANALYSIS OF CHILDREN ADMITTED WITH ROTAVIRUS GASTROENTERITIS" (P291/10/2007)

This is to inform you that the Kenyatta National Hospital Ethics and Research Committee has reviewed and **approved** your above cited research proposal for the period 23rd October 2007 – 22nd October 2008.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimen must also be obtained from KNH-ERC for each batch.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely

PROF A N GUANTAI
SECRETARY, KNH-ERC

c.c. Prof. K.M. Bhatt, Chairperson, KNH-ERC
The Deputy Director CS, KNH
The Dean, School of Medicine, UON
The Chairman, Dept. of Paediatrics, UON
Supervisors: Dr. Rose Kamenwa, Dept.of Paediatrics, KNH
Dr. Dalton Wamalwa, Dept. of Paediatrics, UON
Prof. J. Wang'ombe, Dept. of Community Health, UON