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Epidemiology and economic burden childhood diarrhea in tertiary hospital in Southeast Nigeria

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Abstract: Background

Diarrhea is a major public health problem among children with huge health, and economic burden globally.

Objectives: This study aimed to determine the epidemiology, and economic burden of diarrhea in children in southeast Nigeria a low income country were described.

Methods: The study was conducted in the Children Emergency Ward of Federal Medical Centre, Umuahia, Southeast, Nigeria. Information on their age, medical history, and treatment received, and diagnostic tests were abstracted from medical records, using standard profoma. Both the direct medical costs and indirect cost of the management of diarrhea as in-patient were estimated. The socioeconomic status was determined based on occupation and education of both parents.

Results: Out of 2199 children admitted, 289 (13.1%) had diarrhea. Childhood diarrhea had peak period in January and February

with 73 (26.6%) and 87 (28.2%) cases respectively and highest 66 (68%), among children under 12 months of age, with males 71 (73.2%) preponderance, and affect mainly 32, (62.8%), children from low socioeconomic class. Prevalence of self-medication was 43, (44.7%). and antibiotics was used in 38 (88.4%) of these cases. The average and median costs of in-patient treatment for childhood diarrhea were USD59.3 (31.1), and USD 51.2 respectively. The average cost of diarrhea (in-patient and loss in productivity) was USD83.8. *Conclusion:* The incidence of diarrhea diseases was highest in January/February and among children under 12 months of age, especially those from low socioeconomic class. There is also high economic burden of diarrhea in children. Promotion of the home care for childhood diarrhea especially appropriate use ORS, should be both life and cost saving.

Keywords: Children, Diarrhea, Epidemiology, Economic Cost

Introduction

Acute diarrhea disease (ADD) is one of the most common causes of morbidity and mortality in children worldwide. It is a disease of high public health importance. Over the years, concerted efforts have been made to reduce the burden of ADD through the introduction of preventive rotavirus vaccine^{4,5} and the curative hypo-osmolar rehydration solution^{6,7} with resultant reduction in morbidity and mortality such that an estimated half a million deaths globally due to diarrhea that occurred in 2015¹ compared to previous studies that reported higher mortalities.^{2,3} Nevertheless in Nigeria, acute diarrheal diseases is still the second leading killer of children under five⁶ even when the optimal strategy for the management of childhood diarrhea comprise of correct fluid therapy, correct feeding therapy, and effective education of the mothers or caregivers.⁷ An intervention that can be both timely and appropriately instituted at the com-

munity and primary healthcare levels. Surprisingly, diarrhea cases still constitute significant reason for children out-patient clinics visits and admission in emergency units of most tertiary health facilities. This highlights an obvious gap in both knowledge and implementation of childhood diarrhea management.

Caregivers' response to any diseases is multi-factorial: availability of finance,⁸ knowledge of appropriate intervention,⁹ medications at home, and perception of severity of the illness.¹⁰ According to WHO guideline, complicated diarrhea with severe dehydration, diarrhea in neonates, illiterate mother/caregiver with inability to understand reconstitution of oral rehydration solution, distant place of resident from health facility or severely malnourished are some indicators for in-patient management of children with diarrhea. There is no empirical information on the extent to which this guideline has guided management of childhood diarrhea at the apex

health facilities. Furthermore, management of childhood diarrhea diseases in tertiary health institutions carries an important economic impact on the household of the affected children and the community.¹¹ Information on its cost implication will be a strong advocacy tool in an effort to improve access to universal health coverage and achievement of poverty eradication programmes. Among factors which influence the decision of a household to seek for care are the experienced economic costs (direct and loss in productive) of previously treated illnesses and the responsiveness of the health system. There is dearth of evidence on the cost implication of managing diarrhea in tertiary hospital. Our extensive literature search revealed that few studies on the economic burden of diarrhea disease have been conducted in Bangladesh, Bolivia, and South Africa.¹²⁻¹⁴ This study was aimed at determining the epidemiology of childhood diarrhea and estimate the economic costs (direct and indirect costs) associated with in-patient management of childhood diarrhea diseases. This information will give insight into the burden of diarrhea, an important information that will inform evidence-based decision on treatment of diarrhea. This is especially when the cost of some tropical illnesses like malaria have been widely studied,¹⁵ but there is paucity of information available on cost of treating paediatric diarrhea.

Methods

Study Area and Population

The study was conducted in the Children Emergency ward of Federal Medical Centre (FMC) Umuahia, a tertiary health institution in southeast Nigeria. Umuahia has an estimated population of 369230 people¹⁶ and children under five years of age make up significant proportion of the entire population. The FMC is strategically located and receives referral from within Umuahia and neighboring five states. The hospital has a paediatric department amongst its other departments. The Children Emergency ward renders emergency services to all children. It is open to service round the clock. Approximately over 150 children with emergency problems are attended to in the Children Emergency Ward (CHEW) monthly and they are seen by both resident doctors and consultants. The hospital is government-owned, and relies on both government's periodic subvention and internally-generated revenue as sources of income. There is no form subsidy to the out- and in-patient services, and patients bear the full cost of treatment. The unit cost of different services are suggested by the rendering departments.

Study Design

The study was a retrospective review of the medical records of children seen in the CHEW from October 2017 to September 2018. The admission register for all the patients that presented to the CHEW were reviewed and those with diarrhea were identified. A list of those

with diarrhea was made and their medical folders retrieved. Those that were severely dehydrated on physical examination and thus received intravenous fluid for rehydration were excluded from the study.

Data collection

The logbook of all the paediatric patients that were discharged according to the discharge logbook of children emergency ward during the period under study was reviewed. The folders numbers of 289 diarrhea cases were noted and copied. A systematic sampling method was used to identify the medical folders to review. A list of the folder numbers of the 289 paediatric managed for diarrhea as in-patient was made and the minimum sample size was randomly selected.

The appropriate minimum sample size of 71 was obtained based on standard sample size formula for estimating a population mean of 289. The ratio of the standard deviation to the mean which is the coefficient of variation of treatment cost per person of 0.5 was used based on previous reports.⁷ The level of precision of 10% since out-of-pocket expenses were expected to amount to large proportion of total cost and a total number of in-patient cases in the year being reviewed of 289⁷ patients.

The sampling interval of 3 was determined based on the ratio of the 289 children managed for diarrhea and the targeted sample size of 90 and above. Therefore every third medical folder in the list was selected. After the first patient's record which was the 3rd on the list was selected, the subsequent 3rd medical folder on the list which was the 6th was selected and the pattern was continued until all the medical folder required for the study was selected. In the case the selected number of a medical record was not found in the medical record office, the next patient's folder on the list was selected to replace it.

A proforma adapted from the WHO standardized data abstraction form for patient records⁷ was used to collect from patients' medical records. The patient's specific information: patient's age, gender, educational and occupation level of the parents, history of the present illness, duration of illness before presentation, their health-seeking behavior before presentation, physical findings, duration on admission, and patient-specific resource utilization for direct medical costs for inpatients and indirect costs.

The direct medical costs were the costs of resources incurred for the treatment of diarrhea, including transportation, diagnostic investigations, drugs, and hospital stay obtained using micro-costing techniques.

- The cost of travelling to and fro the health facility was estimated based on the distance of the patients' residence from the hospital, while fuel cost was estimated for those who used their personal cars.
- The type, frequency, quantity, duration and route of

administration of ORS, Intravenous fluid, antibiotics and other medications were obtained. The average of hospital and market purchase price of each was used to estimate the cost.

- The type of laboratory investigations mainly serum electrolyte, urea and creatinine, complete blood count, stool analysis, and urinalysis were documented. The average of unit cost from both the hospital laboratory and the outside private laboratory facilities was used for costing.
- In-patients were those admitted to the hospital for at least an overnight stay. The cost of admission or hospital bed-day did not vary much between patients. Total sum charged each day on admission for bed space, feeding, nursing care and equipment usage was collected.
- Indirect costs was the value of time lost due to caregiving during the illness episode. It was determined based on the fraction of the estimated monthly income for different occupations that would be lost over the days the caregiver spent away from productive activities while taking care of the child on admission.

The unit costs were calculated in Nigeria local currency Naira and converted to United States of American Dollars at the 2018 exchange rate of 360 Naira to one USD. The Statistical Package for Social Sciences, Chicago, IL (SPSS) version 21 was used to enter and analyze the data.

Data Analysis

The Socio-Economic Status (SES) of the patients was determined using Oyedepi's social classification¹⁷ based on the occupation and highest educational level of both parents. The educational status are scored thus: No formal education scored one, completed primary education two, completed secondary education scored three, extra training after secondary school but not tertiary institution scored four and tertiary education scored five. Occupation is scored thus: unemployed and petty trader scored one, artisans and drivers scored two, secretary and secondary school teachers scored three, medium business scored four and contractors, professional and politicians scored five. The SES is generated by summing the score on both maternal and paternal educational and occupational scores and dividing by a factor of four. and graded on a score of one(1) to 5(five), one being the highest and five being the lowest. The SES is classified into high (1&2), medium (3) and Low (4&5).

The loss in productivity due to childhood diarrhea was estimated using human capital method¹⁷i.e. loss in productivity emanating from caregivers stay with the child with diarrhea during admission). Estimated daily income loss of parents/caregivers of the infants due to time spent in the hospital while their children received care was used.¹⁸ The costs used in this study were initially estimated in Nigerian currency (Naira). Afterwards the costs were converted to United States of America Dol-

lars (USD) at the exchange rate as at 2018 of 360 Naira per Dollar. The international purchasing power parity was used to adjust for the discrepancies in the purchasing power and the cost structure of Nigerian naira against the dollar.

Ethical Consideration

The Health Research Ethics Committee of Federal Medical Centre, Umuahia reviewed the proposal and gave consent for the study to be carried out. The medical records were handled with confidentiality. The patients' folders were sorted by the medical records department and released in small units of about 5 folders at a time to ensure that researchers did not unduly hold the folders.

Results

Out of the total of 289 children with diarrhea seen over the review period, 97 medical records were reviewed. The mean age of the subjects was 14.2 month. Majority 65 (67.0%) of the subjects were within the age range of 2month to 12 months and were mainly male 71 (73.2%). Mothers that had tertiary education were 42 (66.6%) and those that live within 1 km radius from the hospital were 81 (83.5%). See Table 1.

Variables	
<i>Age (n= 97)</i>	
Mean (Range)	14.2 months (1 - 96 months)
1 month	1 (1.0%)
>1month - 12 month	65 (67.0%)
> 12 month - 59 month	31 (32.0%)
> 59 month	1 (1.0%)
<i>Gender (n = 97)</i>	
Male	71 (73.2%)
Female	26 (26.8%)
<i>Mothers Education (n=63)</i>	
No formal Education	0 (0.0%)
Primary	2 (3.2%,)
Secondary	19 (30.2%)
Tertiary	42 (66.6%)
<i>SES (n = 51)</i>	
High	4 (7.8%,)
Medium	15 (29.4%)
Low	32 (62.8%)
<i>Resident Distance from the HCF (n = 97)</i>	
Within 1 Kilometer radius	81 (83.5%,)
Within 2 – 3 Kilometer radius	7 (7.2%,)
4 Kilometer radius	9 (9.3%)

The prevalence of diarrhea was high (65 [67%]) among children under 1 year of age. See Table 1. Among these children under 1 year, those between the age range of 7 to 8 months (31.6%) experienced the highest prevalence of 31.6%. This period coincided with the period of transition from exclusive breastfeeding to complementary feeding with risk of bottle feeding and it associated predisposition to diarrhea and malnutrition. Secondly, it is

the period of rapid milestone achievements: crawling and mouthing of picked objects. All these predispose to infection and diarrhea. See Figure 1.

There were 43 (44.7%) of the subjects that received care before presentation to the hospital. The proportion that received: antibiotics, ORS, Zinc and antimalarial were 38 (88.4%), 13 (30.2%), 10 (23.3%) and 5 (11.6%) respectively. The proportion with indicators of an underlying health conditions such as: dehydration 77 (83.7%), hepatomegaly 17 (33.3%), splenomegaly 9 (18.0%), pallor 16 (18.6%), crepitation 4 (6.5%) and none had jaundice, lymphadenopathy and edema 0 (0.0%). Tonsillitis (23; 23.7%) and malaria (20; 20.6%) were the main identified co-morbidities. See Table 2.

The proportion of admission fee, investigations and drugs were 59.1% (USD36.8), 19.8% (USD12.3) and 19.3% (USD12.0) respectively. The estimated cost of loss in productivity was USD24.5. Thus the estimated total cost for in-patient management of childhood diarrhea was USD83.8. See Table 3.

Although seemingly two peaks were observed over the 12 month review, first was in January - February, while the second peak was in June with incidence of 28% and 23% respectively. See Figure 2.

Table 2: History of the present illness and patients' clinical evaluation

Variables	
<i>Duration of illness before presentation (n= 97)</i>	
Mean (SD)	4.1 days (2.6)
Range	1 – 9 days
Median	2 days
1 day	19 (19.6%)
2 days	19 (19.6%)
3 – 4 days	13 (13.4%)
5 days	46 (47.4%)
<i>Previous treatment received (n = 97)</i>	
Yes	43 (44.7%)
No	54 (65.3%)
<i>What was the components of medications received prior to presentation (n = 43)</i>	
Antibiotics	38 (88.4%)
Zinc	13 (30.2%)
ORS	10 (23.3%)
Analgesics	10 (23.3%)
Antimalarial	5 (11.6%)
<i>Presenting Symptoms</i>	
Fever	83 (85.6%)
Vomiting	83 (85.6%)
Loose stool	63 (64.9%)
Weakness	13 (13.4%)
<i>Physical Examinational Findings</i>	
Febrile	69 (71.1%)
Pallor (n = 86)	16 (18.6%)
Jaundice (n = 84)	0 (0.0%)
Lymphadenopathy (n = 62)	0 (0.0%)
Dehydrated (n = 92)	77 (83.7%)
Edema (n = 60)	0 (0.0%)
Hepatomegaly (n = 52)	17 (33.3%)
Splenomegaly (n = 50)	9 (18.0%)
Crepitation (n = 62)	4 (6.5%)
<i>Was there another co-existing illness</i>	
Yes	55.3%
No	44.7%
<i>What are these existing illnesses</i>	
Tonsillitis	23 (23.7%)
Malaria	20 (20.6%)
Severe Acute Malnutrition	5 (5.2%)
Bronchopneumonia	2 (2.1%)
Enteric fever	2 (2.1%)

Table 3: Expenditure on In-patient management of diarrhea in Tertiary Health facility

Variables	US dollars	%
Average cost of previous treatment (SD)	5.3 (3.2)	
Average cost of in-patient treatment (SD)	59.3 (31.1)	
Median cost of in-patient treatment	51.2	
Transportation	1.2 (1.1)	1.9
Drugs	12.0 (9.7)	19.3
Investigations	12.3 (8.8)	19.7
Admission	36.8 (16.7)	59.1
<i>Duration on admission (n = 97)</i>		
Mean (Range)	2.9 days (1–5)	
Median	3 days	
Loss in productivity due in-patient management of diarrhea		
Average income loss (SD)	24.5 (19.4)	
Range	7.7 – 68.6.	
Total cost of diarrhea (in-patient + Loss in productivity) USD	83.8	

Fig 1: The proportion of the children with diarrhea under 1 year of age

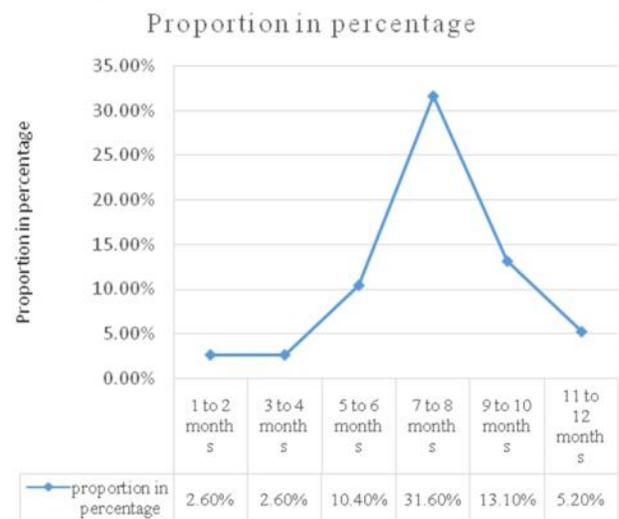
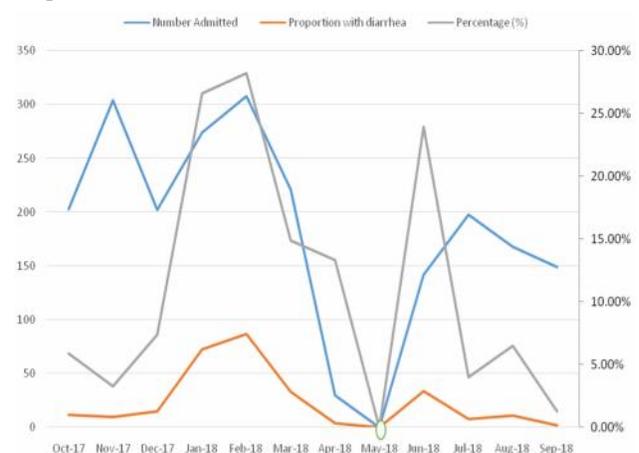


Fig 2: Annual distribution of cases of childhood diarrhea



Discussion

The 68% incidence of diarrhea among children less than one year was higher than 47.9% in children less than 5 years reported in Yenegoa by Efealukwu *et al*,¹⁹ 37% was reported among children of market women in Ibadan by Omokhodion *et al*²⁰ and 40.9% reported by Vu Nguyen *et al*²¹ among children in Hamoi, Vietnam. Although people of all ages irrespective of their socio-economic status can be affected by diarrhea diseases but it is more among children under 12 months of age especially for those who sought for care in the public hospital. Mortality from diarrheal diseases is high among this age group if the diarrhea is not adequately managed. Studies have shown that rotavirus and diarrheagenic *E. coli* are the predominant cause of diarrhea in children less than two years of age.^{22,23} Unfortunately, high prevalence of resistance to ampicillin, chloramphenicol, and trimethoprim/sulfamethoxazole has been reported in the diarrheagenic *E. coli*.²⁴ This highlights the need to discourage excessive use of antibiotics in the home management of diarrheal diseases as reported in this study, where 88.4% used antibiotics prior to presentation at the hospital while another study reported 27.6% antibiotic use prior to hospital visits. Emphasis should be principally on the use of ORS and zinc in the management of diarrhea.

The incidence of diarrhea diseases was highest during cool, dry months of December to March, peaking during January and February and this has been documented in other studies that have shown seasonal variation.²⁵⁻²⁷ Humidity and temperature as well as latitude and rainfall may drive the distribution of diarrhea.²⁸ The seasonality in diarrhea may be related to temporal oscillation in the pathogenic agents and host susceptibility vis-à-vis fluctuation of neuroendocrine functions and immune response.²⁹ One of the peak seasons was during dry and cold weather and majority of the subjects were infants and rotavirus is the predominant aetiology of diarrhea in this age group^{30,31} and rotavirus favors low temperature.^{32,33} In a study by Ojoobor *et al*³⁴ in Enugu, showed 31.5% prevalence of rotavirus among children with acute gastroenteritis (AGE) and Odimuya *et al* in Ilorin, reported 55.9% of children with diarrhea to be positive for rotavirus.³⁵ There is no local study to compare the seasonal variation of childhood diarrhea, but study by Farrar *et al* in India reported diarrhea mortality peaked in July and January, while deaths with fever and bloody diarrhea which indicate enteroinvasive bacterial etiology, showed little seasonality.³⁶ There is similarity between tropical rainforest (equatorial) climate in the southern Nigerian, and the Indian tropical monsoon in the south and the temperate in North.³⁷

Furthermore, in a survey of seven countries by Chao *et al*³⁸, although an annual periodicity of diarrhea based on different pathogens was reported, but of the seven sites, Kenya had pathogens with a significant 6-month periodicity: rotavirus and norovirus GII. There is no study in

Nigeria that has evaluated the periodic incident of diarrhea. A study has shown that some bacterial pathogens were more prevalent during hot and rainy weather, which is favourable for the thriving of bacteria in the environment or the contaminated water sources.³⁹ The enterotoxigenic *E. coli* (ETEC) was associated with warmer weather condition (in Mozambique, Pakistan, India, and Bangladesh), consistent with the observed association between ETEC and higher temperatures but not rainfall.^{40,41} A significant association between *Cryptosporidium* and rainy weather was identified in The Gambia, Mali, and Mozambique, which is consistent with the finding that precipitation may drive cryptosporidiosis in the tropics.⁴² Contrarily to the above findings, rotavirus was found to be more prevalent during the drier winter months, which in Nigeria can be likened to dry season on December to February, with reported rotavirus seasonality in the tropics.^{43,44,45} Notwithstanding, some studies have detected secondary peaks of rotavirus activity during monsoon/rainy seasons in tropical settings,^{44,46,47,48,49} which reported that rotavirus peaked in the winter in the temperate and dry season in the tropics, cholera in the monsoon/rainy season, and ETEC in the summer at three sites in Bangladesh. However, it is difficult to identify the combination of components of weather that drives each pathogen, since weather covariates can be highly correlated (e.g., heat and humidity). In this study, although there was evidence of two peaks of diarrhea outbreak January/February and in June, the outbreak in January/February was much higher than that of June. What made the incident in June prominent was the return to hospital services after one month industrial action by healthcare workers, but the proportion of children admitted which had diarrhea was high.

There was high level of poor treatment practices: 88.4% used antibiotics, 69.2% and 76.3% did not use zinc and ORS respectively, in their home management of diarrhea before presentation to the hospital, this resembles the 69.3% harmful practices Carter *et al*⁵⁰ reported in their systematic review. Many children with symptoms of illnesses may have been empirically treated with antibiotics without advice from medical staffs.⁵¹ There are associated negative health outcomes with harmful practices such as incorrect use of orthodox medicine, that conflict with World Health Organization (WHO) treatment guidelines in the management of childhood diarrhea. These incorrect practices can affect correct management of childhood diarrheal disease and result in failure in treatment, nutritional deficits, and diarrheal associated mortality.

Appropriate management of most cases of diarrheal diseases irrespective of whether bacterial or viral, consists of correcting fluid management to replenish lost fluid and electrolyte using either oral or parenteral rehydration, sustained breastfeeding and/or food intake during the diarrheal episodes and correct use of antimicrobial therapy especially in bloody diarrhea or suspected cholera with severe dehydration, and supplementary zinc and probiotics.^{52,53,54} The factors that sustain these harmful

practices during diarrhea treatment could be: caregivers concern for their child's health and caregiver action to treat the illness to the best of their knowledge and abilities. In a systematic review by Carter *et al*,⁵⁰ caregivers reported that their actions were based on the advice of healthcare providers, community members, or elderly relatives, as well as their own observations or understanding of the efficacy of certain treatment for diarrhea. In view of the aforementioned, majority of the diarrhea cases can be managed with low cost home-based interventions, most still sought care from the public hospital as already reported.⁵⁵ This comes at a huge financial cost of USD 59.3 to the households and majority of which are out-of-pocket spendings.^{18,56,57} The location of the hospital gives easy geographical accessibility to inhabitants of the municipality. The distance of place of residence from the facilities has been observed to influence reporting of diarrheal diseases to health facilities.⁵⁸ The cost of facility use was USD36.8 and contributed highest (59.1%) to the cost of diarrheal diseases management and it is similar to what has been reported.⁵⁹ It can be argued that most diarrheal diseases could have been managed on out-patient basis. Most of these children presented with fever, vomiting and dehydration but none was life threatening situation that will warrant admission.

Interestingly, all the parameters for management of diarrhea as out-patient are met in most of the subjects: firstly, majority of the subjects resides in close proximity to the health facility and can easily bring the child back to the healthcare facility for monitoring and follow-up, secondly, most of their mothers were educated thus can comprehend directives on the management of childhood diarrhea, thirdly, the proportion that were neonates was few, and fourthly, most of the subjects were stable with no obvious threat to life. Medication, and laboratory investigation costs contributed less to the total cost of management of diarrheal disease in children compared to the facility cost and is similar to what have been reported.^{52,58} However, considering the direct and indirect cost of treatment, it represents a substantial economic burden for the affected households.⁵⁹ All of these results have shown that the economic burden of diarrhea is considerable and there is a need to reduce these costs.⁶⁰ This can be achieved through vaccination program that will build immunity in children, resulting to fewer cases and thus alleviating the economic burden of diarrhea. This cost analysis will assist government in determining the cost-effectiveness of a rotavirus vaccine program as it is newly introduced in Nigeria.

The mean duration of hospital stay was 2.9 days and similar to 2.4 days and 2.1 days reported by Fischer *et al*⁶¹ and Giaquinto *et al*⁶² respectively in their studies in developed countries. The duration of hospital stay was also similar to 2.3 days – 4.9 days and 3.7 days reported by Aikins *et al*⁶³ in Ghana and by Breurec *et al*⁶⁴ in Central African Republic respectively. Yilgwan *et al* in Jos reported duration of diarrhea of 4 ± 3.6 days.⁶⁵ Most of the episodes of diarrhea managed in the public hospi-

tals does not require hospital treatment and can be managed at home.⁶⁶ Home management of childhood diarrhea where appropriate could be both life and cost saving. This can save a household up to an average of USD83 in economic cost. The impact of this is huge considering that majority of the households are living below poverty line and out-of-pocket spendings (OOP) ranged from 85% to 100%^{18,56,57} due to existing lack accessible health insurance scheme that is available to less than 5% of the population and presently available to those caregivers employed in Federal parastatals. Anecdotal evidence suggests that the treatment of diarrhea relies heavily on household treatment patterns and resources.

One of the limitations of this study is that the single center design may not have given adequate coverage of all the possible social economic scenarios that would have been the case if the study was multi-centered. However, insight on the cost implication of in-patient management of childhood diarrhea has been gained. Another limitation is the small sample size used in this study. Among the factors that contributed to the small sample size were: (i) the poor filing practices in the hospital that led to the folders of some patients whose name were on the admission register not able to be traced, (ii) some patients upon review of the folder found to be dehydrated such that intravenous therapy were required, thus a good justification for their hospital admission, were not included in the study. Since the review aimed also at the seasonal/periodicity of diarrhea, extending the review beyond 12 calendar period or one year, would affect the outcome. However in view of this, future studies, may consider a comparative study of multiple years.

Conclusion

The incidence of diarrheal diseases was highest in January/February and among children under 12 months of age, especially those from low socioeconomic class. There is also high economic burden of diarrhea in children. Promotion of the home care for childhood diarrhea especially appropriate use ORS, should be both life and cost saving.

Authors' Contributions

Authors' Information. MDU. Conceptualized the study, Data collection and analysis, Draft of initial manuscript, approved the final manuscript. CI. Data collection, reviewed manuscript and approved final manuscript. SO. Data collection, reviewed the manuscript and approved the final manuscript. UM. Reviewed the manuscript and approved the final manuscript. EN. Data collection, reviewed the manuscript and approved the final version.

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