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Prevalence and predictors of stunting in children and adolescents aged 1-18 years with nephrotic syndrome attending Mulago Hospital, Uganda

Raihanah Nalubega[1*], Anthony Batte[1] and Sarah Kiguli[1]

Abstract

Background Nephrotic syndrome is the predominant glomerulopathy in children worldwide, particularly in low-income countries. One of the key complications of nephrotic syndrome is stunting. Stunting is the most prevalent form of undernutrition globally; which leads to early and long-term consequences. In this study, we determined the prevalence and predictors of stunting among children and adolescents with nephrotic syndrome at a tertiary nephrology clinic in Uganda.

Methods Between February and August 2022, we conducted a cross-sectional study that enrolled children and adolescents aged 1 to 18 years with nephrotic syndrome. Participants had been undergoing steroid treatment for a minimum of three months and were registered at the paediatric renal clinic of Mulago National Referral Hospital in Kampala, Uganda. Medical history, physical examination and anthropometric assessment were conducted on the enrolled children. The World Health Organisation (WHO) growth reference standards were used to evaluate stunting in the enrolled children. Multivariable logistic regression analysis was performed to determine independent predictors of stunting and a p-value < 0.05 was considered statistically significant.

Results Ninety-four participants were enrolled, with a median age (IQR) at diagnosis of six years (IQR 3–9). Among the participants, 48 (51.1%) were male. The prevalence of stunting was observed in 15 (15.9%) participants (95% confidence interval [CI]: 15.88 — 16.04). Regarding severity, 12 (12.8%) participants were moderately stunted, and 3 (3.2%) were severely stunted. Participants with persistent proteinuria exhibited higher odds of stunting than those without. (OR: 4.11, 95% CI: 1.05 — 15.98, $p < 0.041$).

Conclusions There is a high prevalence of stunting among children with nephrotic syndrome, particularly among those with on-going proteinuria. This underscores the importance of regular growth monitoring and screening for early identification and eventual management of stunting among children receiving care for nephrotic syndrome. Providing nutritional counselling and other interventions is thus crucial in addressing stunting among this specific group of children and adolescents.

*Correspondence:
Raihanah Nalubega
nraihan532@gmail.com

Full list of author information is available at the end of the article

Keywords Nephrotic syndrome, Stunting, Steroids, Proteinuria

Introduction

Nephrotic syndrome is one of the most common glomerular diseases in children [1]. It is a common kidney disorder among children of all ages and has a global prevalence of 2–7 per 100,000 cases worldwide with 5.6 per million children per year in Tropical Africa [2, 3]. In Uganda, it is estimated that the incidence of proteinuric kidney disease in children is estimated at 160 per million population, which is at least eight times higher than the incidence in the United Kingdom [4].

Steroids have been used to treat children with nephrotic syndrome since 1950 [5]. Steroids are currently the first line and mainstay of treatment for children and adolescents with nephrotic syndrome [6, 7]. The initial dosing of steroids lasts about three months, with good outcomes and a low mortality rate of about 3% [8, 9]. The majority of the children with nephrotic syndrome respond to steroids, although about 10–15% of the children with nephrotic syndrome are steroid-resistant, while 71.9% will experience an episode of relapse may further expose them to steroid use [10, 11]. Children who are steroid-resistant, steroid dependent or those with frequently relapsing nephrotic syndrome are given adjunctive medications which offers protection to these children and adolescents from the detrimental effects of long-term steroid use like stunting [12].

Growth stunting has long been linked with steroid treatment in children with nephrotic syndrome [13]. Stunting is maximal in the first three months after diagnosis and the start of treatment and is commensurate with the duration of therapy and frequency of relapses [14]. In many cases, growth stunting can also be attributed to the severity of the underlying disease. Children in sub-Saharan Africa and Asia aged 2–17 years with nephrotic syndrome have a high prevalence of stunting of 11.5–50% as compared to their healthy counterparts who have normal height with a maximum prevalence of stunting of 17.7% [15, 16, 17, 18]. Stunting is the most prevalent form of undernutrition globally [19]. It is associated with several detrimental effects with both short and long-term consequences; like difficulties in achieving physical and cognitive development, increased risk of obesity and other degenerative diseases, susceptibility to infectious diseases due to a weak immune system among others. Stunting in nephrotic syndrome can cause similar complications [20]. Therefore, this study aimed to determine the prevalence of stunting and associated factors among children and adolescents with nephrotic syndrome attending the renal clinic at Mulago Hospital.

Methods

Study design setting

This cross-sectional study was conducted at the outpatient paediatric renal clinic at Mulago Hospital between February and August 2022.

Mulago Hospital is one of Uganda's national referral hospitals. The renal clinic is open once a week (every Monday). This clinic has about 120 children and adolescents with nephrotic syndrome. It has an attendance of about 45 patients with kidney disease per month and an average of 20 patients with nephrotic syndrome weekly. The clinic is run by two Paediatric nephrologists, one paediatric resident, one intern doctor and a nurse.

Study participants

In this study, the inclusion criteria included all children and adolescents aged 1 to 18years who were selected by consecutive sampling. These children and adolescents had been attending the outpatient Paediatric Renal clinic during the study period and had been on steroids for at least three months. For all children aged 1 to 17years, informed consent from parents or caregivers was provided before study enrolment, while adolescents aged 18 years provided informed consent. Additionally, children aged 8 to 17 years were included if they provided assent. Individuals who were too unwell to undergo the study procedure were excluded.

During data management, the principal investigator reviewed all questionnaires for consistency and missing data. Children and adolescents with the missing data were cleaned and if data were not able to be traced, they were dropped. Only cleaned data was considered for the analysis.

Sample size calculation

To determine the prevalence of stunting in children and adolescents 1 year- 18 years with nephrotic syndrome attending the renal clinic at Mulago Hospital.

This sample size calculation was based on previous study by Njugunah, E et al., 2012 who found out that 24.4% of children with nephrotic syndrome on steroids were stunted.

Assuming 95% confidence interval and error within 5% and using Kish Leslie [21] sample size formula; n= $(Z^{2*}p(1\text{-}p)/d^2$. Where Z is the Z value at 95% confidence interval, corresponding to 1.96; $p = 24.4\%$ representing the proportion of children with nephrotic syndrome with stunting; and d represents the sampling error which is 0.05. Even though the sample size was 283, since we have a finite population of about 120 children attending the renal clinic with nephrotic syndrome, we further

adjusted for the sample size using Cochran's formula [22] for determining sample size for a finite population using the formula;

$\text{Final sample size} = \text{S}/\left(1+\left(\text{S}-1\right)/\text{N}\right)$, where; S = sample size calculated = 283,

N = population size which is 120. Using the formula above, we got a sample size of 85 children.

Adjusting for 10% non-response, our final sample size was 94 children.

Study measurements

Anthropometry

To measure the length of children less than two years, a measuring board with a headboard and sliding foot piece (Seca 213 Stadiometer) was used. The measuring board was laid flat, on a stable and level table. A thin cloth was used to cover the board to avoid causing discomfort. For length, the child was positioned on his/her back on the measuring board, supporting the head and placing it against the headboard. The occiput, shoulder blades, gluteus muscle, cuffs and heels touched the board. The length was measured to the last completed 0.1 cm and recorded immediately.

For children two years and above, height was measured using an Ayrton Models 100 stadiometer. The thick socks and shoes of a child were removed. A child stood with his/her back against the measuring surface with feet together flat on the floor, arms at the side and knees and back straight. The head, heels, buttocks and shoulder blades of a child touched the measuring surface. A child was told to look straight ahead; then the headboard was slid gently down to the head of the child, compressing the hair. Hair ornaments or braid buns were removed. When the measurer's eye level met with the indicator, the height of the child was read. Then, the procedure was repeated twice and the average of the three was considered the correct value. Height-for-Age Z-score (HAZ), was calculated using the World Health Organisation Multicentre Growth Reference Standard [23]. One research assistant took the 3 height measurements. The child was classified as stunted if his/her Z score was less than − 2 standard deviation for moderate stunting while less than − 3 standard deviation was considered for severe stunting and not stunted if Z score was ≥ − 2SD. If a diagnosis of stunting was made the child was referred to the endocrinology clinic/nutritionist for counselling and further management.

Tanner staging

This was done for all children aged 10–18 years. Those with delayed puberty were linked to the endocrinology clinic for care.

Sphygmomanometry

Blood pressure was taken three times, at least five minutes apart and the average measurement was recorded [24].

Blood tests

Blood samples were collected for measurement of kidney function and electrolyte test (creatinine, sodium, potassium and urea) and the Human Immunodeficiency virus (HIV) test was conducted for all enrolled children. Chronic kidney disease (CKD) is defined according to the KDIGO guidelines 2024 as abnormalities of kidney structure or function, present for a minimum of 3 months, with implications for health. However, in our study, a low GFR of < 60 ml/min/1.73m^2 was used as a marker of CKD.

Urinalysis

A urine sample was collected for a urine dipstick and submitted for analysis at the Mulago National Referral Hospital clinical chemistry laboratory.

Statistical analysis

Data was analysed using Stata 14.0. Continuous variables were summarised using median (interquartile range) and means (standard deviations). The prevalence of stunting was calculated as the proportion of children and adolescents with stunting among all those enrolled in the study. Logistic regression was used to determine the factors associated with stunting. Multivariate logistic regression was used to perform all variables found to have a p-value ≤ 0.2 at bivariate analysis. A p-value ≤ 0.05 was considered statistically significant.

Results

Enrolment

Ninety-four study participants were enrolled in the study between February and August 2022 and majority of the were male (n = 48, 51.5%).

Of the ninety-four participants, the median age (IQR) at diagnosis of nephrotic syndrome was six [3, 4, 5, 6, 7, 8, 9] years. Most participants (n = 57, 60.6%) resided in urban areas (Kampala and Wakiso districts). The majority of the caregivers were mothers (n = 65, 69.2%) who had attained secondary and tertiary education. (Table 1)

Among the children with nephrotic syndrome, 2 (2.1%) had hepatitis B infection and almost half suffered relapses (44.9%). The median duration of steroid treatment was 181.1 days (3-]

31.5) months.

Table 1 Baseline characteristics of participants and caregivers

Variables	Frequency (%)
Age of the child	
Under 5 years	16 (17.1)
5–9 years	33 (35.1)
10–17 years	45 (47.8)
Median age at diagnosis, median (IQR), years	6 (3–9)
Sex	
Male	48 (51.1)
Female	46 (48.9)
District of residence	
Kampala	26 (27.7)
Wakiso	31 (32.9)
Others	37 (39.4)
Religion	
Christian	74 (78.7)
Muslim	21 (21.3)
Primary caregiver	
Mother	65 (69.2)
Father	20 (21.3)
Siblings	1 (1.1)
Grandparents	6 (6.3)
Others	2 (2.1)
Education level of care giver	
None	5 (5.3)
Primary	44 (46.8)
Secondary	27 (28.8)
Tertiary and above	18 (19.1)
Classification of nephrotic syndrome	
Primary	92 (97.9)
Chronic Hepatitis B infection	2 (2.1)
Tanner stage	
Stage I	22 (44.9)
Stage II-V	72 (76.6)
Urine protein	
Yes	28 (29.8)
No	56 (70.2)
****BMI for age Z scores**	
≥-2 to ≤ + 1 (Normal)	49 (68.1%)
Z > + 1 (Overweight)	19 (29.7%)
Z > + 2 (Obese)	11 (17.2%)
***Weight for age (WAZ) scores**	
Z ≥ 3 (Obese)	1 (6.1%)
≥-2 to ≤ + 2 (Normal)	15 (93.7%)

**BMI for participants aged 5 to 18 years

*WAZ scores for participants 1 to 4 years

Prevalence of stunting among children and adolescents with nephrotic syndrome

Stunting was observed in 15 (15.9%) participants, (95% confidence interval [CI]: 15.88 — 16.04%). Regarding severity, 12 (12.8%) participants were moderately stunted, and 3 (3.2%) participants were severely stunted. Most participants who were stunted were above five years of age (Fig. 1).

Factors associated with stunting among children and adolescents with nephrotic syndrome

Using bivariate analysis, steroid-resistant nephrotic syndrome, chronic kidney disease, presence of oedema, having been on tacrolimus and ongoing proteinuria were associated with stunting.

However, at multivariable analysis, only persistent proteinuria was independently associated with stunting (aOR: 4.11, 95% CI: 1.05 — 15.98, $p \leq 0.041$). (Table 2)

Discussion

In this study, the prevalence of stunting among children and adolescents with nephrotic syndrome was found to be about 16%, with 12.8% being moderately stunted and 3.2% being severely stunted. This prevalence of stunting in our study is comparable to other prevalence rates reported from studies in Kenya, Nigeria, Iran and India and these range from 11.5–50% [3, 16, 17, 18].

According to the Uganda Nutrition Profile 2021, the prevalence of stunting decreases with increasing levels of the mother's education. About 4 in 10 children born to mothers with no education (37%) are stunted as compared with 1 in 10 children born to mothers with more than a secondary education (10%) [25]. In this study, most of the caretakers were mothers who had attained at least secondary or tertiary education status, which could explain the lower prevalence of stunting.

Compared with other developing countries, this prevalence of stunting in our study was reported in a similar study conducted in Nigeria [17]. Solarin and colleagues found a prevalence of stunting among children with nephrotic syndrome of 11.5% [17]. However, a smaller sample size of 61 subjects was used which could have been responsible for the slightly lower prevalence compared to the current study. Another study carried out in Kenya showed the prevalence of stunting among children with nephrotic syndrome to be at 24.4% [16] This divergence is probably due to the better management and follow-up of children and adolescents in the Mulago Renal Clinic, nutritional counselling started early, where a high protein diet is advised as affected children and adolescents are encouraged to take boiled eggs to counter the effect of protein loss in urine. The relatively earlier initiation of steroid sparing agents in Mulago Renal Clinic could also have led to a lower prevalence of stunting as seen in our study.

In this study, children and adolescents above five years were more likely to be stunted than those below five years. The majority of the studies done show that stunting is more prevalent in subjects below five years [19]. However, this was different for our study. The possible explanation of this is that children and adolescents above five years could have had prolonged exposure to steroid

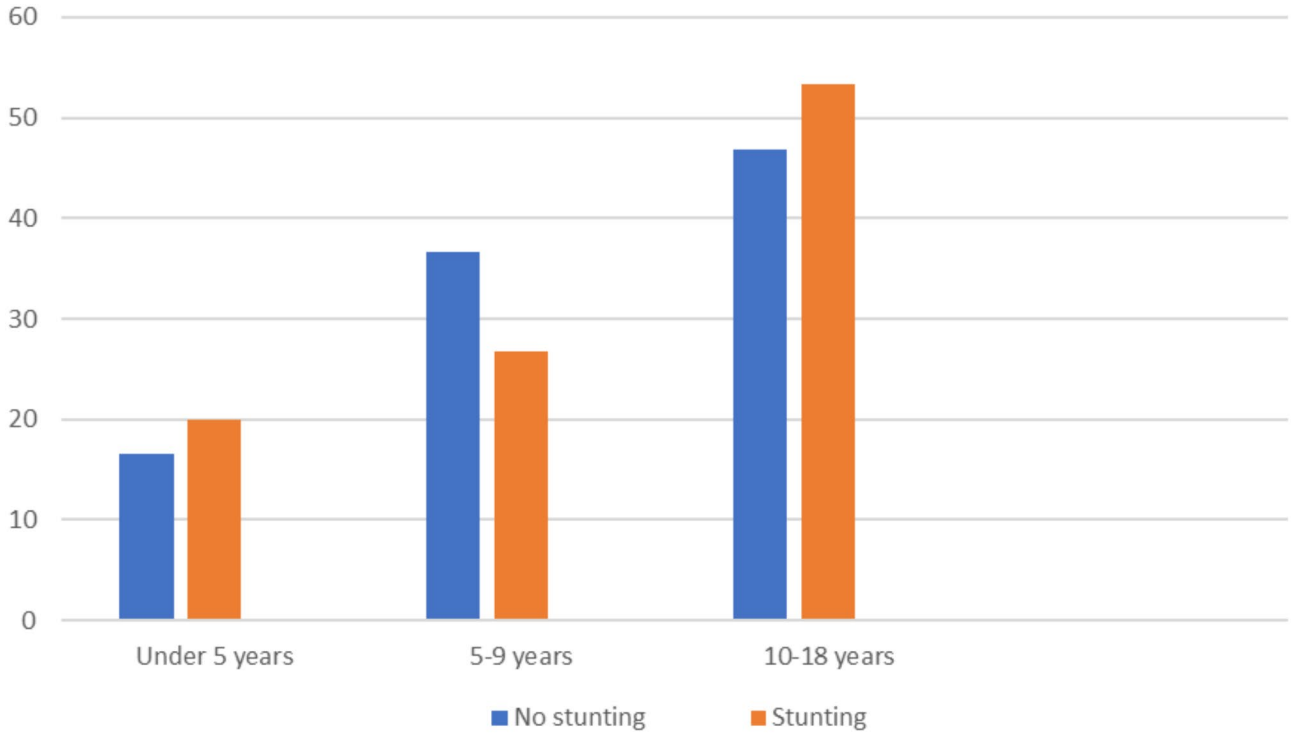

Fig. 1 Distribution of stunting by age

treatment than those below five years especially if the diagnosis of nephrotic syndrome was made earlier in life.

Our study also found 22 children in Tanner stage 1, with only 1 male participant above 14 years and 4 female participants above 13 years which correlates with delayed puberty. Delayed puberty causes stunting, and this could have been responsible for stunting in these adolescents. However, our study did not set out to check for hormonal levels and therefore, this cause could not be ascertained.

Using multivariable analysis, only urine protein (proteinuria) was found to have a significant association with stunting. Children who presented with persistent proteinuria had a four-fold higher odds of being stunted compared to those who had no proteinuria. The possible explanation could be proteins are among osteotrophic nutrients and play an important role in bone development thereby influencing peak bone mass; hence their deficiency will impair bone health and growth, causing stunting. The proteinuria was mainly manifested in children and adolescents with steroid-resistant nephrotic syndrome, non-responsive to steroid sparing agents as well as those who were lost to follow-up and had been off treatment for a long time. This might have led to prolonged periods of protein loss as well as prolonged exposure to steroids in some subjects hence the stunting seen in this group of children and adolescents. Furthermore, children and adolescents with a low GFR of < 60 ml/min/1.73m^2 which was used as a marker of chronic kidney disease in our study also presented with proteinuria, yet chronic kidney disease affects bone mineralisation which further predisposes these children and adolescents to stunting. It is also important to note that majority of the participants who had an estimated GFR < 60 had SRNS (77.8%). SRNS is the most severe form of childhood nephrotic syndrome and has an increased risk of progressing to chronic kidney disease. Children with SRNS have a prolonged nephrotic state characterized by proteinuria, which is an independent risk factor for the progression to CKD in children hence stunting in these children and adolescents.

Findings like the duration of steroid therapy did not affect stunting in our study yet prolonged use of steroids is associated with stunting [8]. Children and adolescents who required prolonged use of steroids like those have steroid-resistant nephrotic syndrome, steroid dependent nephrotic syndrome and those with frequently relapsing nephrotic syndrome are given adjunctive medications soon after diagnosis which reduces steroid exposure hence stunting. Finally, about 30% of the participants were obese and this could be attributed to steroid use.

Study strengths and limitations

In this study, we did not assess the mid-parental height as we only relied on the current child's height on the day of evaluation. Mid-parental height should have been calculated to determine the relationship of the child's current height to the parent's height. Equally, bone age was not assessed mainly due to financial limitations. The sample

Table 2 ; factors associated with stunting at bivariate and multivariate analysis

Variable	No stunting 79 (84%)	Stunting 15 (16%)	Odds Ratio (95% CI)	*P*-value	Adjusted Odds Ratio (95% CI	*P*-value
Age of the child						
Under 5 years	13(16.4)	3(20.0)	1.00			
Above 5 years	66(83.5)	12(80.0)	1.27(0.31,5.14)	0.738		
Sex						
Female	40(50.6)	6(40.0)	1.00			
Male	39(49.4)	9(60.0)	1.54(0.50,4.73)	0.452		
Education level of care giver						
Primary and below*	40(50.6)	9(60.0)	1.46(0.47,4.49)	0.507		
Secondary and above	39(49.4)	6(40.0)	1.00			
Distance to the health facility						
< 5 km	9(11.4)	1(6.7)	1.00			
≥ 5 km	70(88.6)	14(93.3)	1.80(0.21,15.36)	0.591		
Relapses						
No	43(54.4)	9 (60.0)	1.00			
Yes	36(45.6)	6(40.0)	0.79(0.25,2.45)	0.691		
Steroid resistant nephrotic syndrome						
No	65(82.3)	8(53.3)	1.00		1.00	
Yes	14(17.7)	7(46.7)	4.06 (1.26,13.05)	0.019	1.53(0.25,9.39)	0.648
Steroid dependent nephrotic syndrome						
No	47(59.5)	9(60.0)	1.00			
Yes	32(40.5)	6(40.0)	0.97(0.32,3.02)	0.971		
Estimated GFR						
≥ 60 ml/min/1.73m^2	69(88.5)	9(60.0)	1.00		1.00	
< 60 ml/min/1.73m^2	9(11.5)	6(40.0)	5.11(1.47,17.75)	0.010	2.05(0.44,9.43)	0.358
Dietary diversity score						
≥ 4 food groups	5(6.3)	1(6.7)	1.00			
< 4 food groups	74(93.7)	14(93.3)	0.95(0.10.8.72)	0.961		
Oedema						
No	71(89.9)	10(66.7)	1.00		1.00	
Yes	8(10.1)	5(33.3)	4.44(1.12,16.26)	0.025	3.48(0.81,14.99)	0.091
Tacrolimus						
No	71(89.9)	10(66.7)	1.00		1.00	
Yes	8(10.1)	5(33.3)	4.44(1.21,16.26)	0.025	1.34(0.19,9.67)	0.769
Urine protein						
Nil	61(77.2)	5(33.3)	100		1.00	
Present	18(22.8)	10(66.7)	**6.78 (2.05,22.39)**	**0.002**	**4.11(1.05,15.98)**	**0.041**
Steroid therapy duration	19.8(14.5–21.1)	14.7(3.7–25.6)	0.98(0.96,1.02)	0.422		
Cumulative dose	400.1(255.5-544.6)	266.5(107.9-425.1)	0.99(0.99,1.01)	0.427		

size was small hence this may have affected our ability to evaluate associations. Hormonal levels were not done yet hormones like thyroid hormones, growth hormones and androgens further influence the growth of children above three years. However, this is the first study to describe the prevalence of stunting among Ugandan children and adolescents with nephrotic syndrome in a hospital setting. This study was conducted at a national referral hospital receiving patients from different areas of the country; therefore, the study population was diverse, and the findings may be generalised to other children and adolescents with nephrotic syndrome in a hospital setting.

Conclusions

In this study, nearly one in every six children with nephrotic syndrome experienced stunting, particularly among those with persistent proteinuria. There is a need to have routine growth monitoring for children and adolescents with nephrotic syndrome and plotting of standard WHO growth charts. In management of children with persistent proteinuria, there is need for nutritional counselling and support for children who are stunted. Further studies with a relatively bigger sample size, assessing mid-parental height and bone age are recommended. Finally, it is important to note that height is a

dynamic parameter and cannot be captured in a cross-sectional study. A prospective cohort study would be ideal to assess stunting in children with a chronic disease.

Abbreviations

ARF	Acute Renal Failure
CKD	Chronic Kidney Disease
FRNS	Frequently Relapsing Nephrotic Syndrome
FSGS	Focal Segmental Glomerulosclerosis
ICF	International Classification of Functioning, Disability and Health
KDIGO	The Kidney Disease Improving Global Outcomes
MN	Membranous Nephropathy
MCNS	Minimal Change Nephrotic Syndrome
NS	Nephrotic Syndrome
SDNS	Steroid Dependent Nephrotic Syndrome
SRNS	Steroid Resistant Nephrotic Syndrome
SSNS	Steroid Sensitive Nephrotic Syndrome
UBOS	Uganda Bureau of Statistics
UNFPA	United Nations Population Fund

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Author contributions
All authors significantly contributed to the conceptualization of this research article throughout proposal development, data collection, analysis of the data as well as in preparation and reviewing of this manuscript.

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Data availability
Data that supports the findings of this study has been deposited in the Makerere University Institutional Repository-School of Medicine (Sch. of Med.) Collections under the URI-http://hdl.handle.net/10570/11174.

Declarations

Ethics approval and consent to participate
The School of Medicine Research Ethics Committee of Makerere University provided approval for this study (MAK-SOMREC 2021 – 192) and administrative clearance was got from Mulago Hospital. Caregivers provided written informed consent and all children aged 8 years and above provided assent on addition to the written informed consent provided by their caretakers, The study adhered to the ethical principles outlined in the Declaration of Helsinki.

Consent for publication
The consent for publication was not required by IRB or ethics committee.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Paediatrics and Child Health, School of Medicine, College of Health Sciences, Makerere University, P.O. Box 7072, Kampala, Uganda

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