Height as proxy for weight in mass azithromycin dosing of Kenyan children with active trachoma

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ABSTRACT

Objectives: **To determine whether height can be used as an alternative to weight in mass treatment of children aged 1-15 years with active trachoma using azithromycin and propose a height-based dose stick for Kenyan children.**
Design: **community based operational research**
Subjects: A total of 2,020 children were included: 987(48.9%) male and 1033 (51.1%) female. 369 (18.3%) were from Kajiado, 772 (38.2%) from West Pokot and 879 (43.5%) from Baringo.
Settings: **The study was carried out in three trachoma endemic districts: West Pokot, Baringo and Kajiado. A baseline trachoma survey had been conducted in the three districts in preparation for the implementation of SAFE.**
Results: **Children from West Pokot were heavier and taller than those from Kajiado and Baringo (P < 0.001). The body mass index (BMI) of the children in the three study areas was comparable. There was a close relationship between weight and height and the distribution was near linear. Height explained 92.8% of the variance of weight. A height based dose stick that recommends the use of 40mg/ml suspension and 125mg (half tablet) incremental dosage predicted doses within tolerance limits (15-30mg/kg) to 98.8% of children and 100% with extended dose range (13 -35 mg/kg). If 40mg/ml suspension and 1 tablet (250mg) incremental dosage were to be used, the height stick would predict doses within tolerance limits to 97.5% of the children and 99.9% with extended dose range (13 -35 mg/kg).**
Conclusions: **The theoretical model based on the use of 40mg/ml suspension and 125mg (half tablet) incremental offers better dosing ranges to all the children of West Pokot, Baringo and Kajiado districts when the extended dosage range (13-35mgs/kg) is applied.**
Recommendations: **Similar studies should be conducted in other trachoma endemic communities in Kenya to determine whether a single height-based dose stick can be used in the entire country. The manufacturer should look into the possibility of producing 125mg tablet for mass treatment.**

INTRODUCTION

Trachoma is the leading infectious cause of blindness with six million out of 32 million Kenyans at risk of infection. The worst affected provinces are the Rift valley, Eastern and Northeastern.[2] Following a baseline survey done by University of Nairobi (UON) together with the Ministry of Health (MOH), African Medical and Research Foundation (AMREF), International Trachoma Initiative (ITI) and partners in 2004 in 6 districts[1], the Ministry of Health developed a strategic plan for control of blinding trachoma using the WHO recommended SAFE strategy (S = surgery for trichiasis, A = antibiotics for active disease, F = face washing, E = Environmental cleanliness).[2] The World Health Organization recommends that if the prevalence of active trachoma is more than 10% in children aged 1 to 9 years in a district or 5% for the community, mass distribution of antibiotic in affected. Trachoma control programs in some of districts are currently on going.[2] Antibiotics commonly used for the control of active trachoma are topical tetracycline eye ointment or oral azithromycin.[3] The use of eye ointment for mass treatment is difficult since it is difficult to apply in children, blurs sight, and is applied daily for at least 6 weeks.[4] The dosing of azithromycin in persons weighing less than 50 kg is based on weight and presents logistic problems during mass antibiotic distribution. Scales are cumbersome to carry and can lose calibration. The standard dose of 20 mg /kg of body weight with a tolerance limit of 15 mg/kg to 30 mg / kg recommended in Zithromax product insert was used in this study[5, 8]. Other researchers have safely used an extended dosage of

13- 35mgs/kg.[4, 6] The heavier the child the wider the tolerance limits. The use of height to determine dose has been investigated and found to be feasible as an alternative approach to using weight; it is easier, more economical, safe, effective and convenient alternative.[3] Studies done elsewhere showed that the weight and height of children varied significantly from one region to the other and a single height paradigm cannot therefore, be generalized to the whole country without being scientifically validated.[4]

METHODS

This community based cross sectional operational research was conducted in the sub-locations with the highest prevalence of trachoma in Kajiado, Baringo and West Pokot districts between March and April 2006. Permission to conduct this operational research was granted by the National prevention of Blindness Committee of the MOH. Informed consent was also obtained form the parents/ guardians of the children. Pretesting of data collection tools and standardization of equipment was done in Kajiado. The same researcher did all the measurements. The estimated minimum sample size for each district was 366 children. The following were excluded: children with physical deformity that would compromise height measurement such as poliomyelitis, congenital anomalies such as achondroplasia and dwarfism, children who were too sick to participate in the study and children without parent/guardian consent. The children who had not reached school going age were selected during a meningitis mass immunization campaign in West Pokot and during a vitamin A supplementation exercise Kajiado and Baringo; using systematic random sampling method. Questionnaires were used to collect demographic and health information on the selected children who were weighed and their height measured. School going children were selected using a two stage random cluster sampling method: In the first stage, the schools were randomly selected. In the second stage, pupils were selected from each class (stratification) with population students selected per class being proportion to the size of the class. The age was obtained as reported by the caretaker/ mother/teacher. Where care-taker /mother /teacher was uncertain of age, vaccination cards, baptism cards or school registers were used.

Weight was measured using Zero calibrated Salter digital scales placed on a flat wooden board. Weight was recorded in kilograms, corrected to the nearest 100 grams. For the children who could not stand on the scale, the mother and the child were weighed together then the mother alone. The weight of the child was the difference of the two weights. Height was measured in centimeters using a straight stick with a tape measure, with the child standing or lying on a flat surface. The distance from the ground to the vertex of the head was recorded. A 250 mg tablet of azithromycin which could be divided into half to provide a dose of 125mg and 200mg / 5ml suspension (40mg/ml) was used. Normal tolerance limit was defined as 15mg – 30 mg / kg body weight (model 1), with extended normal range being 13 mg – 35 mg / kg body weight (model 2).[3]

Data was analyzed using SPSS version 11.5 software package as well as S-plus 2000 package. The raw relationship between height and weight was first evaluated then height and weight were plotted in the log scale for data transformation and smoothed spline calculated. To create the best fitting model, linear regression models were created to predict weight from height and then including variables for sex, study area, illness and age, the variable accounting for the most variance was determined. When the best fit model had been created, height was used to predict weight. The predicted weight was then used to calculate predicted dose. The predicted dose was compared with dose calculated from the actual weight to determine whether the child would have been over dosed, under dosed or received dose within tolerance limits.

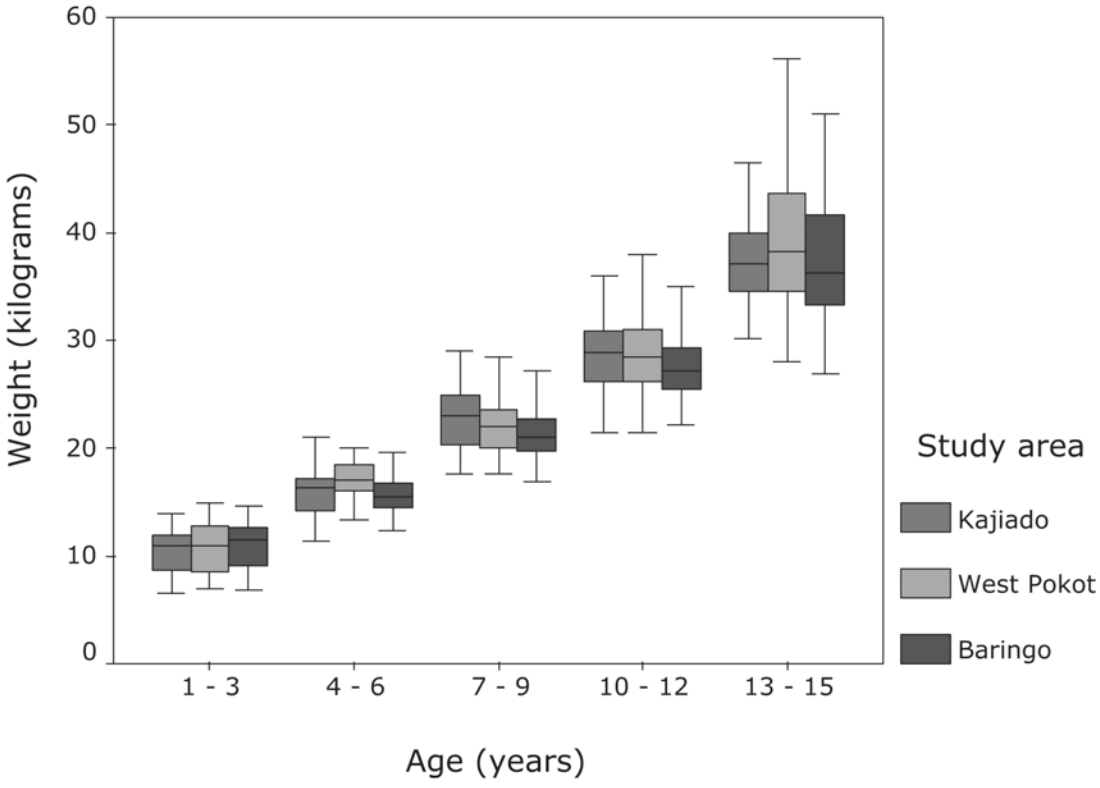
RESULTS

A total of 2020 randomly selected children were studied. Of these 1033 (51.1%) were females and 987 (48.9%) were male.

Table 1: Demographic characteristics of the study population (N = 2020)

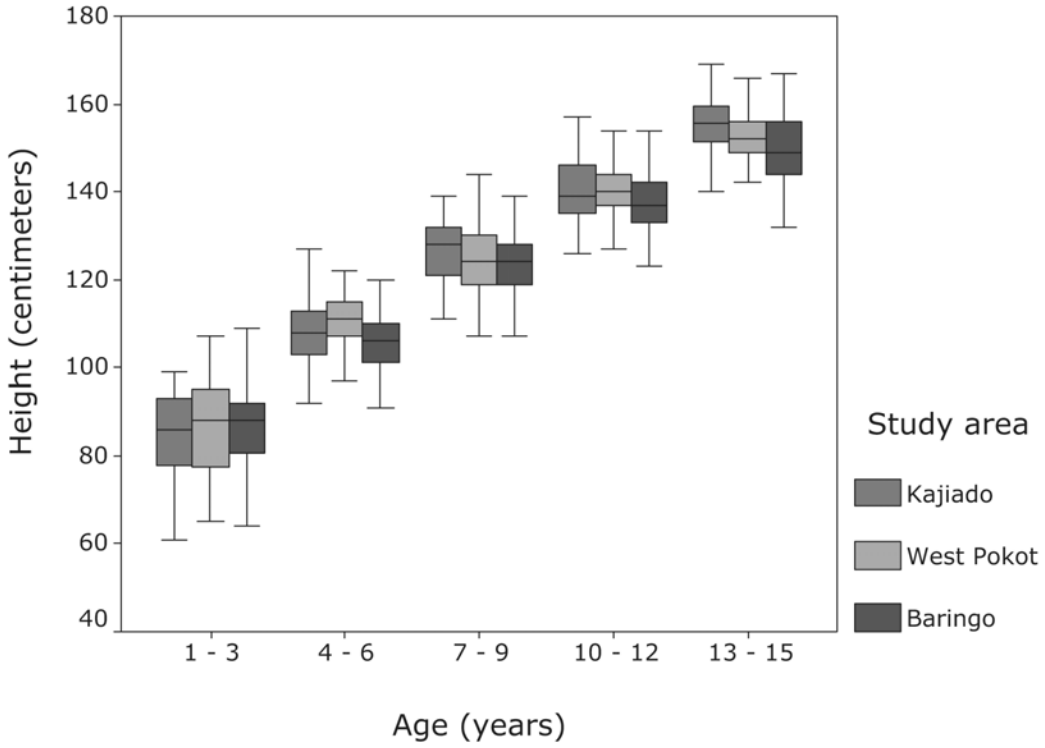
	Districts (study area)							
	Kajiado		West Pokot		Baringo		Total	
Age (years)	Male n (%)	Female n (%)	Male n (%)	Female n (%)	Male n(%)	Female n (%)	Male n (%)	Female n (%)
1 – 3	45 (25)	30 (16)	30 (8)	41 (10)	59 (13)	40 (9)	134 (14)	111 (11)
4 – 6	34 (19)	48 (26)	62 (17)	77 (18)	94 (21)	105 (24)	190 (19)	230 (22)
7 – 9	42 (23)	39 (21)	70 (20)	83 (20)	112 (25)	109 (26)	224 (23)	231 (22)
10 – 12	33 (18)	46 (24)	99 (28)	104 (25)	116 (26)	106 (25)	248 (25)	256 (25)
13 – 15	28 (15)	24 (13)	94 (27)	112 (27)	69 (15)	69 (16)	191 (19)	205 (20)
Total*	182 (100)	187 (100)	355 (100)	417 (100)	450 (100)	429 (100)	987 (100)	1033 (100)

Fig 1: Weight distribution by age per study area (n = 2020)



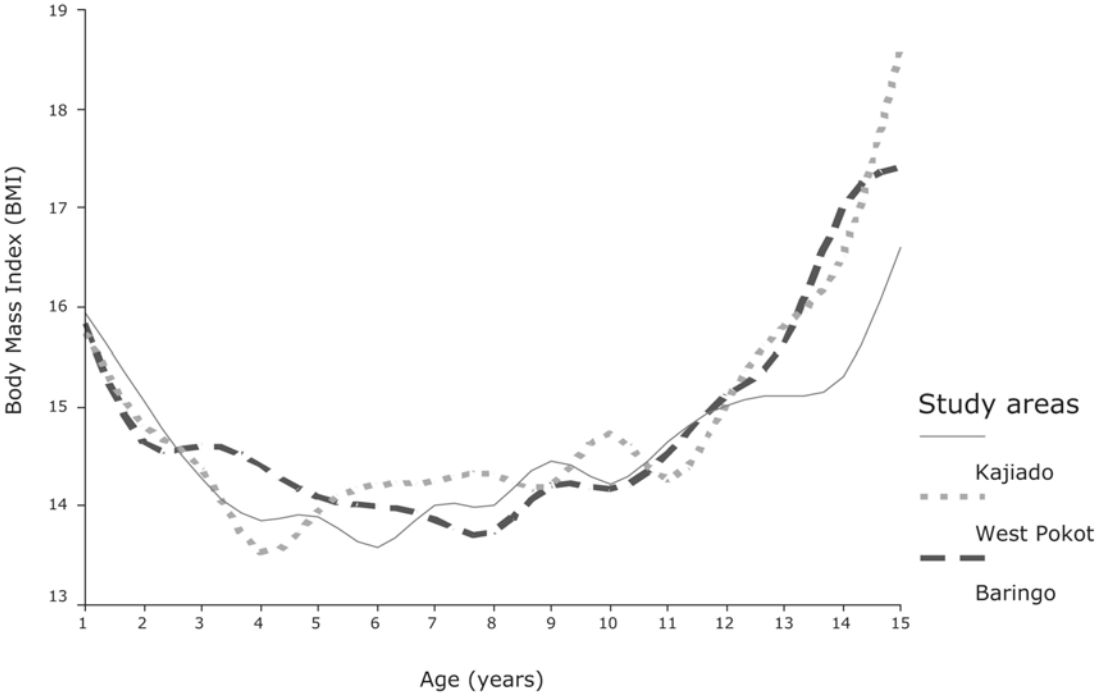
The weights of children in the study were more dispersed with increasing age. Children from West Pokot were heavier than those from Kajiado and Baringo ($P < 0.001$).

Fig 2: Height distribution by age per study area (n = 2020)



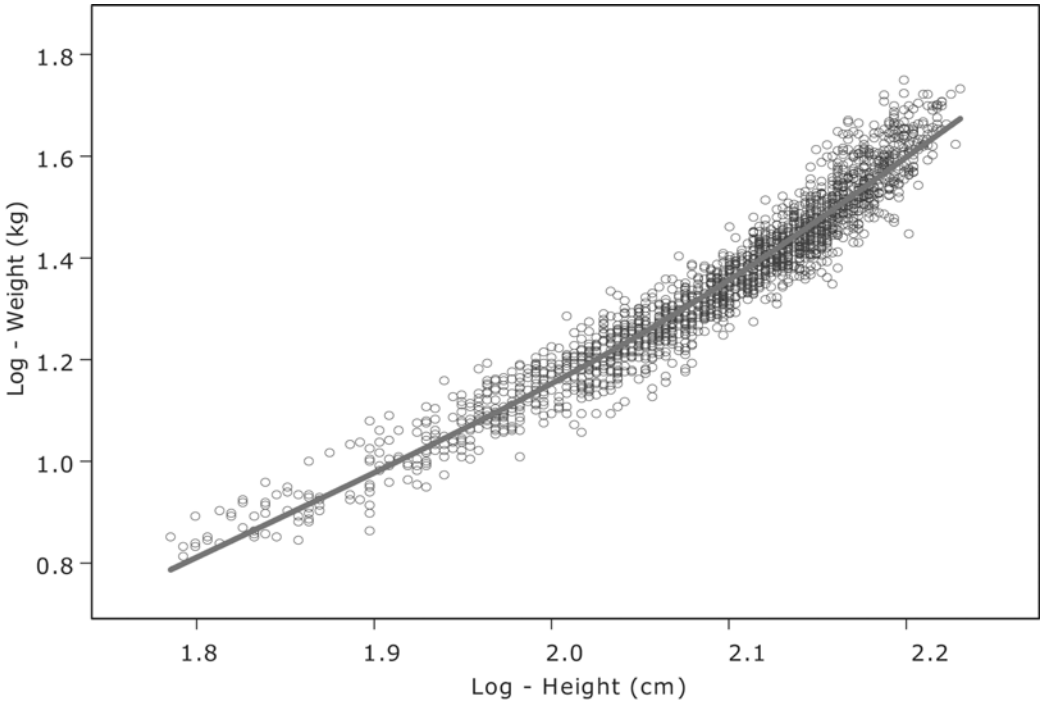
The heights of younger children were more dispersed than those from older children. Children from West Pokot were taller than those from Kajiado and Baringo ($P < 0.001$).

Figure 3: Body mass index (BMI) by age per study area (n =2020)



The body mass index (BMI) of the children in the three districts was comparable to each other.

Figure 4: Scatter plot of $\log_{10}$ (weight) $_{vs}$ $\log_{10}$ (height) of the study population (n = 2020)



There was a close relationship between weight and height and the distribution was near linear with most points clustering near the 45^0 line.

Table 2: Predicting Weight from height using a spline regression model in the log scale

Model	*Variable*	*Parameter Estimate**	*95% CI*	*P*	*R2*
General	Intercept	-2.9899	(-3.049, -2.942)	<0.001	
	Log10 (height)	2.0751	(2.05, 2.100)	<0.001	0.9283
Adding other Specific variables	Intercepts	-2.9721	(-3.051, -2.944)	<0.001	
	Log10 (height)	2.0662	(2.052, 2.102)	<0.001	0.9288
	Study area	0.000	(- 0.003, 0.003)	0.915	
	Sex	0.0043	(0.0000, 0.0049)	0.049	
	Illness	0.0018	(-0.004, 0.008)	0.545	

The height of the children in the model accounted for 92.8% of the variance of weight (adjusted R squared). The study area and illness did not account for any significant variance in the model. However, sex accounted for some variance but very small in the general equation (4.279×10^{-03}). Therefore sex, study area and illness were not included in the creation of the general model equation. The final model equation was:

$$y = m x + c$$

Where
$y = \log_{10}$ weight
$X = \log_{10}$ height
$M = 2.075$
$C = -2.9899$

Using this general model, the proportion of children who would be under dosed, overdosed or receive azithromycin within tolerance levels was determined.

Table 3: Dosing of azithromycin using height instead of weight if 40mg/ml suspension and 125mg (1/2 tablet) incremental is used

	MODEL 1 (Tolerance limits 15 – 30mg /kg)			MODEL 2 (Tolerance limits 13 – 35mg/kg)			
Age (years)	**Under Dose,** *N (%)*	**Normal Dose** *n (%)*	**Over Dose,** *n (%)*	**Under Dose,** *n (%)*	**Normal Dose** *n (%)*	**Over Dose,** *n (%)*	**Total**
1 – 3	0 (0.0%)	245 (100.0%)	0 (0.0%)	0 (0.0%)	245 (100.0%)	0 (0.0%)	245
4 – 6	13 (3.1%)	404 (96.2%)	3 (0.7%)	0 (0.0%)	420 (100.0%)	0 (0.0%)	420
7 – 9	2 (0.4%)	451 (99.2%)	2 (0.4%)	0 (0.0%)	455 (100.0%)	0 (0.0%)	455
10 – 12	0 (0.0%)	502 (99.6%)	2 (0.4%)	0 (0.0%)	504 (100.0%)	0 (0.0%)	504
13 – 15	3 (0.8%)	393 (99.2%)	0 (0.0%)	0 (0.0%)	396 (100.0%)	0 (0.0%)	396
Total	18 (0.9%)	1995 (98.8%)	7 (0.3%)	0 (0.0%)	2020 (100.0%)	0 (0.0%)	2020

If suspension (children below 5 years were considered to be unable to swallow tablets) and 125mg incremental tablets were to be used, 98.8% of the children would receive normal dose while 1.2% would receive doses outside the tolerance limits with most of them being under dosed (MODEL 1).

Of the children who received doses outside the tolerance limit, none received doses less than 13 mg / kilogram body weight or more than 35 mg / kilogram body weight (MODEL 2). 72.2% of those children who would be under dosed were aged between four and six years.

Table 4: Dosing of azithromycin using height instead of weight if 40mg/ml suspension and 250mg tablet incremental were to be used

	MODEL 1 (Tolerance limits 15 – 30mg /kg)			**MODEL 2** (Tolerance limits 13 – 35mg/kg)			
Age (years)	*Under Dose,* n (%)	*Normal Dose* n (%)	*Over Dose,* n (%)	*Under Dose,* n (%)	*Normal Dose* n (%)	*Over Dose,* n (%)	*Total*
1 – 3	0 (0.0%)	245 (100.0%)	0 (0.0%)	0 (0.0%)	245 (100.0%)	0 (0.0%)	245
4 – 6	0 (0.0%)	404 (96.2%)	16 (3.8%)	0 (0.0%)	420 (100.0%)	0 (0.0%)	420
7 – 9	0 (0.0%)	443 (97.4%)	12 (2.6%)	0 (0.0%)	455 (100.0%)	0 (0.0%)	455
10 – 12	0 (0.0%)	482 (95.6%)	22 (4.4%)	0 (0.0%)	503 (99.8%)	1 (0.2%)	504
13 – 15	0 (0.0%)	395 (99.7%)	1 (0.3%)	0 (0.0%)	396 (100.0%)	0 (0.0%)	396
Total	**0 (0.0%)**	**1969 (97.5%)**	**51 (2.5%)**	**0 (0.0%)**	**2019 (99.99%)**	**1 (0.01%)**	**2020**

The main problem with using 40mg /ml suspension and 250mg tablet incremental would be over dosage. About 97.5% of the children would receive doses within normal limits while 2.5 % of them would be over dosed (MODEL 1).

There was one case of over dosage when the extended dosage (13 – 35 mg/ kg) was applied. The child was twelve years old and 159 cm tall. This would mean a dose of more than 35 mg per kilogram body weight (MODEL 2).

DISCUSSION

Mass antibiotic distribution for active trachoma is an expensive exercise and among of the major logistical handicaps is the weighing of children in order to accurately calculate the dosage of oral azithromycin. The use of height to determine the dose of azithromycin has been accepted as an economical, safe, effective and convenient alternative to weight–based dosing [3]. In this study, it was established that height could explain up to 92.8 % of the variance of weight and hence could be used as a near alternative to weight in determining the dosage. Similar results were obtained from a multi-center study carried out in Ghana, Tanzania and Sudan where height accounted for 94% of the variance of weight[4].

For trachoma control purposes, the recommended dose of azithromycin is a single dose of 20mg per kilogram body weight to a maximum dose of 1 gramme [3]. The drug has a large therapeutic range, usually between 15mg and 30 mg per kilogram body weight which has been utilized to determine doses from height without significantly under dosing or overdosing children[5]. Occurrence of side effects such as diarrhea and vomiting is related to the dose received. Doses above normal levels are associated with increased side effects while those below the normal range may lead to sub-therapeutic treatment. An ideal height based model, is that which predicts all the doses within the normal accepted limits. Doses based on actual weight are still be required among children who are less than 60 centimeters tall or less than one year of age, those with physical deformities where height determination would be inaccurate and among those children who appear unusually short, tall or fat [4].

Even though the children from West Pokot were both taller and heavier than those from Kajiado and Baringo, their weight and height did not affect the general formula. Sex of the child contributed some variance in the equation but its exclusion from the final equation did not significantly affect the doses of the children received.

If the 250mg (1 tablet) incremental height cut offs were applied, the main draw back would be over dosing : none of the children would be under dosed while 2.5% would be overdosed, but when the tolerance limit is extended to 13 – 35 mgs / kg one child would be over dosed. Sheila K. et al, using tolerance limit of 20 – 35 mgs /kg found 5.4% of the children who would be under dosed and 7.1% overdosed[6]. If the height cut offs proposed by Sheila K. et al were to be used in the study population, about 6.5% of the children would be over dosed using the extended tolerance limit. This finding further strengthens the need for a specific height based model for the targeted community.

The alternative is to use 125mg (1/2 tab) incremental which predicted doses within normal limits in 98.8 % of the children: 1.2% of the children would receive doses outside the tolerance limits with 0.9% of them being under dosed and 0.3% being overdosed, none of these children would received doses out side the extended tolerance limit. These findings were in accordance with a similar study done in Sudan, Ghana and Tanzania where 98.6% would receive doses within normal limits[4]. Children between four and six years old were more likely to receive doses outside the tolerance limits.

The use of 125 mg incremental height cut offs appear to offer better dose adjustments in the community as well as predict doses within tolerance limits for majority of children than the 250mg incremental height cut offs. However, the use of 125 mg incremental height cut offs is still controversial. The splitting of 250mg tablet to half to achieve 125mg dose may not guarantee an accurate split through the centre. Furthermore, splitting the tablet may also alter the pharmacokinetic properties of azithromycin, making it more susceptible to gastric acid[7]. Bioavailability of the drug is therefore uncertain and this may result in sub-therapeutic blood levels.

The use of suspension for the children who were less than four years old or less than 115 cm tall may be a solution for the dosing problem as well as the risks associated with splitting azithromycin tablets, but some logistical problems of transporting, diluting and dispensing the suspension would still be experienced.

For this reason, the health workers and health planners will still be facing the dilemma on whether to use suspension with 125 mg (½ tablet) incremental or 250 mg (1 tablet) incremental height models. They will have to decide or develop a model that best suits their situation and local needs.
The manufacturers of azithromycin should look into the possibility of producing 125mg tablets for mass community treatment in various communities.

CONCLUSIONS

For dosing children from West Pokot, Baringo and Kajiado districts, theoretical models suggest that the dose stick based on the use of 40mg/ml suspension and 125mg (half tablet) incremental which could accurately predicted doses within tolerance limits (15 – 30mg /kg) in 98.8% of children or 100% with extended dose range (13 -35 mg/kg), is preferred. However, aspects concerning bioavailability with splitting of tablets need to be addressed further. An alternative stick based on 250mg (1 full tablet) incremental predicted accurate doses in 97.5% of the children (table 6).

Proposed height-stick parameters in the studied population

Table 5: Proposed height categories for dosing azithromycin if 40mg/ml suspension and 125mg (1/2 tablet) incremental is used in the study population.

Height range (cm)	Recommended Dose (mg)
Less than 60 cm	weigh the child
60 – 63	120 mg (3ml suspension)
64 – 70	160 mg (4ml suspension)
71 – 79	200 mg (5ml suspension)
80 – 105	250 mg (1 tablet)
106 – 119	375 mg (1 ½ tablets)
120 – 130	500 mg (2 tablets)
131 – 144	625 mg (2 ½ tablets)
145 – 154	750 mg (3 tablets)
155 – 164	875 mg (3 ½ tablets)
165cm and more	1000 mg (4 tablets)

Table 6: Proposed height categories for dosing azithromycin if 40mg/ml suspension and 250mg tablet incremental were to be used in the study population.

Height Range (cm)	Recommended Dose (mg)
Less than 60 cm	weigh the child
60 – 63	120 mg (3ml suspension)
64 – 71	160 mg (4ml suspension)
72 – 80	200 mg (5ml suspension)
81 – 94	240 mg (6ml suspension)
95 – 114	280 mg (7ml suspension)
115 – 135	500 mg (2 tablets)
136 – 155	750 mg (3 tablets)
≥ 156	1000 mg (4 tablets)

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