Research article

Acceptability, adherence, and clinical outcomes, of amoxicillin dispersible tablets versus oral suspension in treatment of children aged 2–59 Months with pneumonia, Kenya: A cluster randomized controlled trial

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ABSTRACT

Amoxicillin dispersible tablet (DT) is now recommended by the WHO as a first-line drug for the treatment of pneumonia in children below 5 years. The study aim was to compare acceptability, adherence and clinical outcome of amoxicillin DT and amoxicillin oral suspension (OS) in the treatment of children aged 2–59 months with pneumonia in Kenya. We conducted a two-arm cluster randomized controlled trial and utilized quantitative methods. The community unit was the unit of randomization. Children aged 2–59 months with pneumonia were enrolled and treated with either amoxicillin DT or OS. Acceptability was defined as the perception of taste of medication as the same or better compared to other medicines and expression of willingness of caregivers to use DT/OS in future, adherence was measured based on the dose, frequency, and duration of treatment, and clinical outcome as complete resolution of symptoms without change of antibiotic treatment. Equivalence was defined as a difference of ≤8% between study arms. We found high levels of acceptability among both DT (93.9%) and OS (96.1%) arms (difference 2.3%, 90% CI -2.6-7.3). The objective measure of adherence on day four and the overall objective measure were significantly higher among children on DT compared to children on OS (88.7% vs. 41.5% (difference 47.2%, 90% CI 31.0–63.3) & 83.5% vs. 39% (difference 44.5%, 90% CI 27.9–60.9), respectively). Cure rates were high in both arms (DT (99.5%), OS (98.1%), difference 1.4%, 90% CI -0.2-3.2). There is reported better adherence to Amoxicillin DT compared to OS and equivalence in acceptability and clinical outcomes.

1. Introduction

Pneumonia is one of the world's leading causes of morbidity and mortality in children, which causes approximately 921,000 child deaths per year [1]. Over 150 million cases of pneumonia occur yearly, with most deaths occurring in sub-Saharan Africa and South Asia [2, 3]. In 2015, approximately 2,500 young lives were lost to pneumonia per day globally [4]. In Kenya, pneumonia is the leading cause of death dislodging malaria as the top killer [5]. Efforts to fight this disease are based on the early and appropriate treatment of pneumonia with antibiotics within the community and if possible within the child's own home.

One of the current challenges in resource-constrained settings is the suitability of existing formulations of amoxicillin for children [6] It is important that the pediatric formulations offer flexibility for dose adjustment, while at the same time remaining within the effective therapeutic range [7]. This will reduce the possible risk of microbial resistance with under-dosing, and of toxicity with over-dosing [8]. With syrups and suspensions, this is often done as full, half, or quarter spoonful, which has been shown to be inaccurate [9]. An alternative is to dispense measured syringes alongside medications. For decades, oral liquid dosage forms, such as syrups and suspensions, have been considered as the favorable type of dosage form in which to administer

medicines to young children [10]. Although they are considered simple to administer and the dose can easily be changed, they also have major disadvantages such as chemical, physical or microbial instability, taste issues, portability problems or refrigerated storage conditions and lack of controlled release properties [11, 12, 13]. Liquid medicines tend to be more expensive than solid medicines and this makes them less accessible to patients who pay for medicines out-of-pocket [14] There would be considerable savings in the cost of drugs if oral liquid formulations were substituted with suitable solid soluble dosage forms [15].

The World Health Organization (WHO) now recommends that where available, dispersible tablets should be chosen above suspensions due to advantages in dosing, stability, storage, cost and transportation [14]. The WHO Essential Medicines List [15], and Priority Medicines List for Children [16], recognize amoxicillin 250 mg scored, dispersible tablet (DT) as a first-line product for the treatment of pneumonia in children below 5 years. All high-burden countries either already have, or are in process of updating national guidelines to amoxicillin DT [17], but despite this, the use of the more established oral suspension (OS) and capsules is still highly prevalent in Africa. With the change in treatment guidelines for pneumonia in children which includes a higher dosage – there is more rationale, now more than ever for the widescale roll -out of Amoxicillin DT.

Clinical success is often determined by the extent to which any patient adheres to a medical regimen [18]. There is strong evidence that non-adherence to medication is prevalent and associated with adverse outcomes and higher costs of care [19]. Dispersible tablets and Orally Disintegrating Tablets (ODTs) may allow improved patient compliance, in particular with pediatric, geriatric, and institutionalized patients [20]. Previous studies on other DTs for other diseases e.g. Coartem for malaria and Zinc for diarrhoea have indicated that the DTs are well accepted in children and have better adherence [21, 22]. However, information about the acceptability, adherence and clinical outcomes of amoxicillin DTs versus the OS prescribed in the rural community among children (2–59 months old) with pneumonia are lacking. The main aim of this study, therefore, was to compare the acceptability, adherence and clinical outcome of amoxicillin DT to that of the conventional Amoxicillin OS in treatment of children aged 2–59 months with pneumonia in Kenya. The study was conducted to inform the national roll-out of the amoxicillin DT in Kenya.

2. Materials and methods

2.1. Study design

We implemented a two-armed, prospective; cluster randomized controlled equivalence trial (RCT) design with the community unit as the unit of randomization (cluster) (ratio 1:1). Fifty-two community units (CUs) in Homa Bay County were randomly selected using computerized simple random sampling and assigned to receive amoxicillin OS or DT. An independent monitoring and evaluation officer who was not directly involved with the amoxicillin study did randomization. This study was nested within a larger quasi-experimental trial looking at the effectiveness of integrated community case management (iCCM) for pneumonia malaria and diarrhoea in Homa Bay County conducted by the Kenya Medical Research Institute (Trial registration: ACTRN 12614000208606) [23,24]. In the parent iCCM study, the delivery of the intervention was at the CU (sub-location) level. We, therefore, used the CU as the level of randomization. Randomization at the CU level allowed us to avoid contamination, i.e. leaking of the intervention to non-intervention areas.

2.2. Study site

The study was conducted between March 2014 and April 2015 in 8 sub-counties within Homa Bay County, Kenya. Pneumonia is one of the leading causes of morbidity in Homa Bay County accounting for 10% of all morbidity [25]. Homa Bay is the only county in Kenya that has been approved to implement integrated community case management of pneumonia with full coverage of community health units.

2.3. Study implementation

This study was implemented within the context of iCCM. iCCM is an initiative of UNICEF, the WHO and the government of Kenya as a blueprint to expand case management of childhood illness beyond health facilities in areas where access to facility-based services is limited so that more children have access to lifesaving treatments. Essential iCCM interventions include oral antibiotics for pneumonia, rapid diagnostic tests (RDTs) and antimalarials (principally artemisinin-based combination therapy) for malaria, and oral rehydration salt (ORS) and zinc for diarrhoea. Community health workers, study quality assurance nurses and their supervisors received training on how to classify acute respiratory infections according to the WHO algorithm, identify danger signs and home case management of pneumonia with oral amoxicillin. Study quality assurance nurses received training on study-specific procedures as appropriate.

Community Health Workers (CHWs) identified children with suspected pneumonia and provided amoxicillin treatment as per the treatment allocation of their community unit. Whenever a CHW identified and treated a case of pneumonia, s/he sent a "Please Call Me" message to a study hotline number. The hotline attendant called the CHW to record what the CHW had diagnosed in an online study database. The online-based system then compared CHWs' classification against the system algorithm and regardless of the diagnosis, sent an automatic SMS with only the child's key location details to the nearest nurse for confirmation. The nurse traced the child within 24 h and independently did an assessment and classification of the child. Caregivers of children in the control arm were given amoxicillin OS and advised to administer 10mls to children aged 2 months up to 12 months and 20mls to children aged 12 months up to 5 years twice daily for 5 consecutive days. Caregivers of children in the intervention arm were given amoxicillin DT and advised to administer 1 tablet to children aged 2 months up to 12 months and 2 tablets to children aged 12 months up to 5 years twice daily for 5 consecutive days. The caregivers received counselling on how to prepare amoxicillin DT in 5–10mls of water and on how to reconstitute the amoxicillin OS to the mark on the bottle. They were informed that a follow-up visit will be made and advised to keep the remaining "tablets" and used blister pack at home and not discard any suspension left after treatment. A second follow-up visit was done on day 4 (after 3 completed days of treatment) to assess for adherence and clinical outcomes, and the last follow-up visit on day 6 (after 5 days of completed treatment) to assess for acceptability, adherence, and clinical outcomes. Clinical assessment was done at each follow-up visit. During the last visit, spoons used by the caregivers to administer the OS were collected and measured for volume appropriateness.

The referral was made as per standard of care for children with severe pneumonia or very severe disease or any other classification and children whose caregiver refused home treatment or were already on antibiotics for more than 48hours with no improvement for management. A child was considered as lost to follow-up if contact could not be made after the fourth day.

2.4. Intervention and study population

Children aged 2–59 months with pneumonia who were residents of Homa Bay County were enrolled after the caregivers gave informed consent. In this study, pneumonia was defined as the presence of a cough or difficulty in breathing with chest indrawing or fast breathing. Any child diagnosed with very severe pneumonia, severe disease, or chronic illness (according to the Integrated management of childhood illness algorithm), had used any of the study antibiotics at an appropriate dose during the previous 48 h or whose caregiver refused to give informed consent was excluded from the study.

2.5. Sample size and sampling

Community units were randomly selected and sorted on the Research Randomizer website (https://www.randomizer.org/). Half of the selected community units were randomly selected into the control arm and the other half into the intervention arm. The children in each eligible community unit were selected purposively.

Our primary question was to examine whether a dose of amoxicillin DT is equivalent to that of amoxicillin OS at the 0.10 significance level and power of 80% utilizing a cluster randomized controlled trial design. The sample size was determined using the formula by Allan Donner [26]. We anticipated that there would be about 80% efficacy for both administrations. The calculated sample size was 173 children per arm (Total of 346). Each arm had 26 clusters (Total of 52 clusters) and 7 children were selected from each cluster.

2.6. Data collection

We used a standardized structured questionnaire to collect data. The questionnaires were pre-tested in 6 community units in the presence of the research investigators and were modified according to the feedback received. The interviewers administering the questionnaire received two days of training and orientation. Data was also abstracted from the sick child recording forms adapted from WHO and utilized by both CHWs and the quality assurance nurses.

2.7. Measurement of outcomes

Acceptability: Acceptability was assessed on day 4 and 6, based on the caregivers' observation of their children's behaviour when they were given the OS/DT formulations. Specifically, the mothers were asked about their perception of the taste of the formulation given to their children compared to other medicines (the three options were: better, same, or worse). Good acceptability was defined as the perception of the taste of the formulation as the same or better and expression of willingness of caregivers to use amoxicillin tablet in future.

Adherence: Adherence was described in relation to dosage, treatment duration, frequency of daily administration, and tablet preparation/suspension reconstitution. Adherence was measured on day 4 and 6 by comparing self-reported adherence with a more objective measure of adherence; pill count for dispersible tablet and volume measurement for oral suspension using calibrated measuring cups. Good adherence was defined as twice a day intake of an accurate dose of DT/twice a day intake of an accurate dose of OS for 5 consecutive days.

Clinical outcome: A child was reported to have positive clinical outcome if they had complete resolution of symptoms on day 6 without a change of antibiotic treatment prescribed on day 0. Treatment was considered to have failed if the child had no resolution of the following symptoms presenting on enrollment (presence of a cough or difficulty in breathing with chest indrawing or fast breathing), had a danger sign, had developed severe pneumonia or very severe disease or did not improve after 48 h of antibiotics.

2.8. Statistical analysis

The primary outcome was cure among children aged 2–59 months receiving either Amoxicillin dispersible tablet (DT) or oral suspension (OS) for treatment of pneumonia in HomaBay County. Based on previous equivalency clinical trials and consensus among the investigators, a difference of 8% (-8%–8%) was chosen as a reasonably suitable difference in the endpoints that could be considered bio-equivalent [27]. Using this definition and a two-sided test with a type I error of 10%, and to have >80% power would conclude equivalence. The baseline characteristics included the child's age, child's sex, caregivers' relationship to child, care-givers age, and care-givers education level. These baseline characteristics of the study participants were summarized using descriptive statistics, where appropriate. The analyses for the primary and secondary outcomes was performed based on an intention-to-treat basis. Acceptability of DT and OS was assessed based on the perceived taste of the caregiver and willingness of the caregiver to use the drug in the near future. Treatment adherence to DT and OS was assessed based on the self-reported accurate dose administered, actual pill count/volume measurement verified by the research officers, frequency of treatment administration within a day and duration of treatment at the fourth and sixth day.

Primary and secondary analyses were performed using log-binomial model (GLM) to compute an adjusted risk ratio (RR). Similarly, Linear regression was conducted for the binary outcomes to model differences in treatment rates between children administered on DT compared to those on OS adjusting for clustering using the community unit, while controlling for age and gender in the multivariable analysis. Risk ratios and confidence intervals were reported. A two-sided 90% CI was constructed where the interval should lie entirely between the equivalence margins. Statistical significance was assessed using the two-sided 0.1 level of significance. Statistical analysis was performed using Stata version 13.

2.9. Ethics approval and consent to participate

This study obtained ethical approval from the Kenya Medical Research Institute ethical review committee (SSC 2424) and the Ethics Review Committee of Maseno University (Reference number MSU/DRPI/MUERC/00252/15). Caregivers provided written informed consent prior to all study procedures.

3. Results

A total of 417 children diagnosed with pneumonia were interviewed between March 2014 and April 2015, of which 212 were assigned to DT while 205 were assigned to OS for treatment of pneumonia. The trial was stopped after the sample size was reached and all study procedures including follow up were completed. There were no statistically significant differences in the baseline characteristics of children treated with DT and those treated with OS (Table 1).

3.1. Acceptability of DT and OS among the caregivers

The results show no significant differences in perceived taste of the amoxicillin DT and OS when compared to other medicines (p = 0.25). The difference in percentage was however above our equivalence margin. Specifically, caregivers administering DT perceived the taste to be better than other medicines when compared to those in the OS arm (51.5% vs. 38.5%, difference 13%, 90% CI -8.2-33.1), while more caregivers administering OS to the children believed that the drug tasted the same as other medicine compared to those who administered DT to the children (60.5% vs. 47.6%, difference 12.9%, 90% CI -7.9-32.8). The willingness of caregivers to use DT or OS in the future did not differ significantly between the two treatment arms (p = 0.16). The proportions of 'good acceptability' among both the caregivers administering DT and OS were high (93.9% vs. 96.1%, respectively) (p = 0.44). This represents a difference of 2.3% (90% CI -2.6%–7.3%]) which falls within our preselected definition of equivalence (±8%) indicating equivalence (Table 2).

3.2. Treatment adherence to DT and OS

Children who were administered DT were 6.17 times more likely to have an accurate pill count compared to volume measurement for children on OS (RR = 6.17; 90% CI = 2.74–13.86; p < 0.01) even after adjusting for age, and sex, on the fourth day of treatment. The mean volume of spoons collected was 9.54 ml. On the fourth day, children on DT were 4.10 times more likely to adhere to treatment and 3.12 times more likely to adhere to treatment overall when adherence was

Table 1. Baseline characteristics of children aged 2–59 months with pneumonia and their caregivers.

Characteristics	DT (n = 212), n (%)	OS (n = 205), n (%)	P-value
Age (months)			
Median(IQR)	24 (12, 36)	24 (11, 42)	0.32
2 up to 12	54 (25.5)	58 (28.3)	
12 up to 59	158 (74.5)	147 (71.7)	
Sex			
Male	93 (44.1)	106 (51.7)	0.12
Female	118 (55.9)	99 (48.3)	
Relationship of caregiver to child			
Father	16 (7.6)	18 (8.8)	0.89
Mother	192 (90.6)	184 (89.8)	
Other	4 (1.8)	3 (1.4)	
Caregiver age (Years)			
<30	120 (56.6)	103 (50.2)	0.33
≥30	92 (43.4)	102 (49.8)	
Caregiver highest level of education			
Primary or less	111 (52.4)	106 (51.9)	0.99
Post-primary	101 (47.6)	97 (47.6)	
Declined	0 (0.00)	1 (0.5)	

objectively measured (RR = 4.10, 90% CI = 2.26–7.44, p < 0.01 & RR = 3.12, 90% CI = 1.83–5.31, P < 0.01 respectively). However, there was no significant difference on day 6 when adherence was objectively measured (RR = 1.34, 90% CI = 0.85–2.10). No equivalence in overall adherence was found between children on DT and OS (difference 44.5, 90% CI 27.9–60.9) (Table 3).

3.3. Clinical outcome among children on DT compared to those on OS

Subjects randomized to DT and OS had no significant difference in the cumulative proportion achieving clinical cure by day 6, 99.5% and 98.1%, respectively (difference 1.4, 90% CI -0.2-3.2; p = 0.16). The clinical outcome was equivalent between the two arms with the difference falling within our equivalence margin of ±8%. After adjusting for age and sex, we did not find any significant differences in the appearances of danger signs or fast breathing on the fourth-day or the sixth-day following treatment or receipt of additional antibiotics between children administered on DT compared to children on OS. None of the children in both arms of treatment died while on treatment (Table 4).

4. Discussion

To date, there are no trials directly comparing the acceptability, adherence and clinical outcomes of amoxicillin DT with that of amoxicillin OS in sub-Saharan Africa. The overall aim of this study was to assess the acceptability, adherence and clinical outcome of amoxicillin DT versus the OS in children aged 2–59 months with pneumonia. This study demonstrated that in a population with little experience and no knowledge of amoxicillin DT, the formulation was perceived to taste better, had significantly higher adherence rates but equivalent acceptability and clinical outcomes to the OS.

The study demonstrated that children treated with amoxicillin DT were 3.12 times more likely to adhere to treatment as compared to those treated with OS when adherence was measured objectively per protocol. The importance of adherence cannot be overstated. Lack of adherence to medication is associated with adverse outcomes and higher costs of care [19]. As has been shown in other studies, we found that when adherence was measured by self-report, self-reported adherence was higher when compared to objectively measured adherence [28]. In our study, there are two plausible explanations that explain the discrepancy between self-reported and objectively measured adherence. 1) Lack of accuracy in dose measurement. The caregivers in this study used spoons to measure amoxicillin OS. A measurement of these spoons was done and showed diversity in volume with regard to size and depth. On average the spoons were ~0.6ml smaller than required for each dose. There is evidence that significant under or over-dosing can occur since the accuracy of measuring spoons and other devices supplied with liquid medicines is not guaranteed [9]. 2) Caregivers may not want to admit that they were non-adherent and therefore reported to be adherent. The main reasons cited for non-adherence typically include being away from home, forgetfulness, too busy and improvement of the child have also been reported in other studies [29, 30, 31].

Our study demonstrated that acceptability of DT was equivalent to that of amoxicillin OS, however, caregivers of children on DT perceived its taste to be better than other medicines as compared to those on OS. These results on high acceptability are similar to those done on dispersible tablets for other indications [21, 22, 32, 33], such as zinc for diarrhoea and Coartem for malaria. The results of this study are consistent with studies in high, low and medium income country settings which have proven that DTs are acceptable in children under five years. For example, a study on acceptability of and adherence to Zinc DTs done in Bangladesh showed that dispersible zinc tablets were equally or even more acceptable to their children than other formulations as reported by caretakers of 282 (93.1%) of the treated children [21]. In a similar study in the rural community of Mirzapur, 77% of the mothers/caretakers perceived the taste of the Zinc DTs as same or better than that of other medicines given to their children and expressed willingness to use Zinc DTs in the future [30]. In Netherlands, a study on the acceptability of different oral formulations in infants and pre-school children, all formulations were well accepted but DTs were the best-accepted formulation [34]. Similarly, in Kenya, a study evaluating efficacy and safety of artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DP) in the treatment of uncomplicated falciparum malaria in children below five years of age, found that acceptability of AL dispersible regimen was significantly better than DP non-dispersible pediatric tablets [22].

Table 2. Acceptability of DT and OS among caregivers of children aged 2–59 months with pneumonia.

Characteristics	DT (n = 212), n (%)	OS (n = 205), n (%)	Adjusted Risk Ratios (90% CI)	% Difference, (90% CI)	P-value
The taste perceived by caregivers					
Same as other medicines	97 (47.6)	121 (60.5)	0.78 (0.51–1.18)	12.9 (-7.9–32.8)	0.31
Better than other medicines	105 (51.5)	77 (38.5)		13 (-8.2–33.1)	0.32
Worse than other medicines	2 (1.0)	2 (1.00)	0.86 (0.29–2.52)	0 (-2.1–2.1)	0.10
The willingness of caregivers to use the drug in future[‡]					
Willing	197 (96.1)	198 (98.5)	0.65 (0.42–1.00)	2.4 (-0.4–5.3)	0.16
Not willing/depends	8 (3.9)	3 (1.5)		2.4 (-0.4–5.3)	0.16
Good acceptability	199 (93.9)	197 (96.1)	1.27 (0.81–1.98)	2.3 (-2.6–7.3)	0.44

Data are n (%) or risk ratio (90%CI) or p-values.

[‡] Numbers are only for those who have an answer to the questions.

Table 3. Treatment adherence to DT and OS among children aged 2–59 months with pneumonia.

	Characteristics	DT (n = 212), n (%)	OS(n = 205), n (%)	Adjusted Risk Ratio[§] (90% CI)	% Difference, (90% CI)	P-value
Day 4	**Dose**					
	Self-reported accurate dosage	204 (96.2)	195 (95.1)	1.18 (0.78–1.80)	1.1 (-1.9–4.1)	0.55
	Pill count/volume measurement accurate dosage	197 (92.9)	86 (42.0)	6.17 (2.74–13.86)	50 (34.8–67.1)	<0.01*
	Frequency of administration:					
	Administered drugs two times/day	206 (97.2)	201 (98.1)	0.94 (0.52–1.71)	0.9 (-2.1–3.9)	0.633
	Duration:					
	Administered drugs for 3 days	203 (95.8)	196 (95.6)	0.97 (0.61–1.53)	0.2 (-3.7–3.9)	0.95
	Self-reported adherence at day 4	194 (91.5)	184 (89.8)	1.12 (0.76–1.63)	1.7 (-4.4–7.9)	0.64
	Objective measure of adherence at day 4	188 (88.7)	85 (41.5)	4.10 (2.26–7.44)	47.2 (31.0–63.3)	<0.01*
Day 6	**Dose**					
	Self-reported accurate dosage	201 (94.8)	195 (95.1)	1.00 (0.66–1.50)	0.3 (-3.6–4.3)	0.90
	Finished tablet/syrup at day 6	203 (95.8)	190 (92.7)	1.33 (0.71–2.51)	3.1 (-2.4–8.6)	0.36
	Frequency of administration:					
	Administered drugs two times/day	210 (99.1)	201 (98.1)	1.70 (0.62–4.67)	1.0 (-3.1–1.1)	0.44
	Duration:					
	Administered drugs for 5 days	200 (94.3)	187 (91.2)	1.27 (0.69–2.36)	3.1 (-3.5–9.8)	0.44
	Self-reported adherence at day 6	192 (90.6)	176 (85.9)	1.28 (0.81–2.03)	4.7 (-3.2–12.6)	0.32
	Objective measure of adherence at day 6	190 (89.6)	171 (83.4)	1.34 (0.85–2.10)	6.2 (-2.2–14.6)	0.23
Overall	Overall self-reported adherence	184 (86.8)	169 (82.4)	1.19 (0.84–1.68)	4.4 (-3.9–12.7)	0.39
	Overall objective measure ofadherence	177 (83.5)	80 (39.0)	3.12 (1.83–5.31)	44.5 (27.9–60.9)	<0.01*

Data are n (%) or risk ratio (90%CI) or p-values.
[§] Adjusted for age and sex in the model.
* Significant at α = 0.05.

Table 4. Clinical outcome among children aged 2–59 months with pneumonia.

Clinical Outcome	DT (N = 212)	OS (N = 205)	Adjusted Risk Ratio[§] (90% CI)	% Difference, (90% CI)	P-value
Appearance of danger signs on day 4	3 (1.4)	2 (1.0)	1.21 (0.66–2.21)	0.4 (-1.2–2.1)	0.16
Appearance of danger signs on day 6	0 (0.00)	0 (0.00)	0 (0.00)		
Fast breathing on day 4	2 (0.9)	2 (1.0)	1.01 (0.45–2.25)	0.1 (-1.5–1.5)	0.67
Fast breathing on day 6	0 (0%)	0 (0%)			
Received additional antibiotics	1 (0.5)	4 (2.0)	0.39 (0.08–1.69)	1.5 (-0.2–3.2)	0.97
Cured	211 (99.5)	201 (98.1)	2.55 (0.58–11.1)	1.4 (-0.2–3.2)	0.16
Deaths	0 (0%)	0 (0%)			

Data are n (%) or risk ratio (90%CI) or p-values.
[§] Adjusted for age and sex in the model.

Lastly, our study showed equivalence in clinical outcomes for pneumonia after 3 and 5 days of completed treatment using DT or OS in children aged 2–59. The high cure rates among children on amoxicillin OS despite low objectively measured adherence can be attributed to the fact that the administered dose of 80 mg/kg/day is more effective than the standard dose of 45 mg/kg/day [6]. It is also likely that some patients with fast breathing enrolled in the study did not have pneumonia, as the sensitivity and specificity of fast breathing (as defined by the WHO to categorize non-severe pneumonia), is approximately 80% [35]. In addition, previous research shows that a three-day course of antibiotics is as efficacious as a five-day course in treating children with fast breathing pneumonia. The studies recommended a shorter course of antibiotic therapy since they found no significant difference in either the treatment failure or relapse rates between groups [36, 37].

The main limitation of our study was that it relied on the iCCM and Integrated Management of Childhood Illness (IMCI) clinical criteria to make a diagnosis, with no microbiological or other supportive laboratory or radiological data for confirmation. However, in many parts of Africa IMCI and iCCM are the hallmark methods of diagnosis of pneumonia as many communities do not have access to microbiological or other supportive laboratory or radiological diagnostic methods. The study had several strengths: We achieved high rates of follow-up in all study sites. The health workers were trained to identify signs of clinical deterioration, and their ability to do so resulted in zero mortality rates. Moreover, we conducted the study within the existing health system and made use of existing health centers and groups of community health workers and nurses, which increases the chances of generalizability and transportability of the results as well as meaningful dialogue with policy makers.

5. Conclusion

This study demonstrated that DT is equivalent to OS in terms of acceptability and clinical outcome but has better adherence. Given that poor adherence can lead to adverse outcomes, drug resistance and higher cost of care, DT should be chosen preferentially over OS. These results are further strengthened by the potential benefit of improving the acceptability of the formulation once in the market. It is our strong recommendation from this study that the Kenyan government mobilize resources for procurement, promotion and scale-up of the use of amoxicillin dispersible tablets in both public and private sectors in sick children under 5 years with pneumonia.

Declarations

Author contribution statement

L. Angwa, C. Ouma and M. Onono: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

K. Mutai: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

P. Okoth, R. Nyamai and N. Kamau: Contributed reagents, materials, analysis tools or data.

Competing interest statement

The authors declare no conflict of interest.

Additional information

The clinical trial described in this paper was registered at the Australian New Zealand Clinical Trials Registry under the registration number ACTRN 12614000208606.

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