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Determinants of Antituberculosis Drug Acceptability among Children with Tuberculosis in Osun State Nigeria

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Abstract

Acceptability of antituberculosis drugs by affected caregivers and children is key to disease elimination. This is affected by many factors including drug, patients, and health institution-related factors. This study aims to assess the influence of the introduction of dispersible formulation on acceptability of antituberculosis drugs. A historical cohort design was used to assess and compare the acceptability of old loose non-dispersible and new dispersible antituberculosis drugs, using a convergent parallel mixed method of data collection. Determinants of tuberculosis drug acceptability were assessed using binary logistic regression. The findings were triangulated with results from the qualitative data. The rate of acceptability of the new dispersible formulation, 112 (88.2%) was significantly higher than the rate of acceptability of old loose non-dispersible drugs, 13 (10.5%), p<0.001. The median age of children with good acceptability, 7.0 (4.0 – 10.0) years was significantly lower than those with poor acceptability, 10.0 (8.0 – 13.0) years, p <0.001. Drug formulation was a significant predictor of acceptability; the fixed-dose dispersible drug had a higher probability of being acceptable relative to lose non-dispersible formulation, (Odd Ratio = 62.3, p <0.001, 95% CI= 25.3 – 153.3). The qualitative data showed that health education about tuberculosis has positive influences on drug acceptability. In conclusion, the formulation of drugs is a key factor in the acceptability of antituberculosis drugs. Hence, there is a need to further promote the recently introduced child-friendly antituberculosis drugs, coupled with strengthening the health education of caregivers to achieve tuberculosis elimination.

Keywords*: Antituberculosis, Acceptability, Fixed-Dose Combination, Dispersible, Tuberculosis.*

Introduction

Drug acceptability is a crucial concept in the achievement of treatment success and control of diseases of public health importance like tuberculosis. Consideration for the acceptability of drugs among paediatric age is essential due to the unique physiological makeup of this age group and poor perception of the benefit of taking a medication which is one of the motivators of drug acceptability and adherence among older age groups [1, 2]. Drug acceptability has varying views from the patients' and physicians' perspectives with some overlapped constructs. Patient drug acceptability refers to the degree to which a patient is willing to use or continue using a particular drug prescribed by their healthcare providers [3]. The acceptability of a drug from a physician's

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perspective on the other hand is viewed as the degree to which a particular drug is deemed acceptable for use by medical professionals, regulatory bodies, and the general public. The commonly identified determinants of drug acceptability from the physician's perspective are the drug's safety profile, efficacy, potential side effects, and the severity of the medical condition it is intended to treat [3].

Determinants of drug acceptability among children are multidimensional; this has been viewed using various frameworks. Three main constructs were identified in a tuberculosis treatment acceptability study conducted among children with tuberculosis: usability, receptivity, and integration [4]. While the construct for usability assessed drug-related factors like the taste of drugs and ease of administration, and how appealing the drugs look; receptivity dwelt on adverse reactions to drugs, perception of the disease, and health generally. The integration construct assessed socioeconomic factors and health system delivery factors that may affect the acceptability of antituberculosis drugs among children. The determinants can also be simply viewed from stakeholders' perspective to comprise the child-related factors, caregivers' factors, and influence of health and social system.

Age of a child is one of the child-related factors that has been established to strongly influence acceptability of a drug formulation [5-9]. The acceptability of tablets was observed to be higher among older children, especially above six years compared to children of younger age groups where syrup and suspensions were more acceptable [10]. The awareness of the benefit of taking a medication among older children has also been attributed to a higher level of acceptability [4].

Among the drug factors that have been identified as determinants of drug acceptability are the taste and odour of the medication. Also, the frequency and dosage of drugs are key factors in drug acceptance [11]. Tuberculosis being a chronic infectious disease that requires a long duration of treatment makes the acceptability of antituberculosis drug imperative, especially among children. Children being more at risk of the disease has drawn much research attention towards drug formulations that will promote antituberculosis acceptability, treatment compliance, and adherence to treatment [12-14]. The efforts aimed at ensuring acceptability, a key step to achieving infection control, have led to varying formulations like fixed-dose combination tablets, syrup, suspension, and dispersible tablets.

The effects of antituberculosis drug formulation on the acceptability of the medication among children have been assessed by a few studies [2, 12-14]. A study conducted to compare the acceptability of fixed-dose combination (FDC) dispersible antituberculosis drug and that of loose non-dispersible tablets among children at the intensive phase of treatment showed that the dispersible antituberculosis drug had higher acceptability [12]. In addition, the study also showed that FDC dispersible drug had less hepatotoxicity while maintaining equal efficacy with the single tablets' formulation [12]. A similar comparative study of the acceptability of child-friendly levofloxacin dispersible was conducted among South African children living with Tuberculosis. The study showed good acceptability of the new child-friendly dispersible formulation relative to pre-existing adult tablets.

The World Health Organization commenced the use of a child-friendly dispersible antituberculosis drug in 2015 [15] and was introduced to the Nigeria Health System in 2018. There is, however, a dearth of studies on the acceptability of the new formulation relative to the pre-existing non-dispersible fixed-dose medications since its introduction. This study, therefore, assesses and compares the acceptability of the new child-friendly fixed-dose dispersible antituberculosis drug with a non-dispersible loose formulation. The findings would form the bases for future public health

intervention in Tuberculosis Control Programme.

Methodology

Description of Study Area

The research was conducted in Osun State. Osun State is a land-locked state located in the South-west region of Nigeria, 7°30′N 4°30′E [16, 17]. It has a total population of 3,423,535 million (National Population Figures of 2006) with a 2023 population projection figure of 5,123,586 based on an annual growth rate of 2.4% [18]. Osun state is mainly an agrarian state in the tropical rainforest of Nigeria. The state has 30 local government areas which have been classified into 15 urban local government areas and 15 rural local government areas (LGAs).

Each LGA has between 10 and 11 wards with at least a primary health centre per ward to ensure access to healthcare. All the primary health centres have facilities for vaccination, including BCG, and provision of primary care for locally endemic diseases like diarrheal diseases. There are specific primary health centres spread within each local government area of the state that provide DOTS services for drug-sensitive tuberculosis. All the healthcare facilities providing DOTS services currently use the new child-friendly dispersible fixed-dose antituberculosis drug. Some facilities however still use both the new dispersible and old non-dispersible drugs concurrently. This thus reduces the barrier of physical access to facilities that offer both preventive and curative services for tuberculosis. The state also has referral centres for drug-resistant tuberculosis and other complications resulting from tuberculosis infection.

Study Design

The study was conducted using a historical cohort study design. Quantitative and qualitative data were collected. The retrospective section of the study involved the interview of children that used non-dispersible loose antituberculosis drugs between 2018 to 2020 and their caregivers. The children that took child-friendly dispersible antituberculosis drugs 2020-2022 were also interviewed to determine their acceptability of antituberculosis drug formulation. Study population: children (0 – 14 years) with drug-sensitive pulmonary tuberculosis in Osun State.

Sample size and Sampling Technique

The sample size (N) was calculated to get an absolute precision of ± 5% using the sample size formula for comparison between two proportions [19]. Since the study population is relatively small or finite (i.e., less than 10000), the finite population correction for proportions was used by dividing the sample size N by 1 + [N – 1/10,000] [19]. After correcting for an anticipated non-response rate of 10%, the sample size was 123 for each group. The sample size was calculated based on the proportion of children who developed hepatotoxic-related side effects to child-friendly dispersible antituberculosis drugs (9.6%) and non-dispersible loose antituberculosis drugs (16.4%) in a similar study conducted among children with drug-sensitive pulmonary tuberculosis [12]. The study sample for the qualitative aspect was selected using a convenient sampling technique. The interviewees were representative of mothers whose children are Tuberculosis patients and uptaking dispersible and non-dispersible antituberculosis drugs.

Data Collection

Quantitative data was collected using an interviewer administered questionnaire, administered electronically using an android application, mWater Survey. The first section of the questionnaire assessed the characteristics of the children and their households while the second section comprised questions that assessed the acceptability of antituberculosis drugs. The last two sections assessed the level of knowledge of the caregivers about tuberculosis and the support received while receiving treatment respectively.

The Qualitative aspect adopted Key informant interviews, In-depth interviews, and Focused-Group Discussion Guides to explore the determinants of acceptability of antituberculosis drugs. The guides explore the perception of participants about the disease, treatments, and their experience with antituberculosis drugs. Likewise, common factors that enhance acceptability and adherence to treatment were also investigated by the guides.

Data Analysis Plan

Data were analysed using SPSS version 27 for Windows. The qualitative data were analysed using thematic and content analysis. The data were triangulated, and the qualitative data were used to strengthen the findings from the quantitative data.

Results

The median age of the children that took the new dispersible antituberculosis drugs was 6.0 (4.0 – 10.0) years while the median age of children that took old loose dose non-dispersible drugs was 10.0 (8.0 – 13.0) years, $P < 0.001$. There was a statistically significant difference between the educational status of children in the two drug formulation groups, $p < 0.001$. There were no out-of-school children among the children that took old non-dispersible formulation while 20 (15.7%) were out of school among children that took FDC dispersible formulation. The proportion of caregivers/mothers with good knowledge of tuberculosis was significantly higher among caregivers with children that used old non-dispersible formulation, 54 (56.8%) relative to the proportion with good knowledge among those that use new dispersible formulation, 41 (43.2%), $p = 0.023$. There were no significant associations between drug formulation and other participants' characteristics like religion, level of education of parents/caregivers, and wealth index. (Table 1).

Table 1. Comparison of Participants' Characteristics Across the Study Groups

Variables	**New Dispersible Drug n (%)**	**Old Loose Doses Non-dispersible drugs n (%)**	**Statistics**
Age of the child (years)	6.0 (4.0 – 10.0)	10.0 (8.0 – 13.0)	U = 3853.5
			p < 0.001
Religion			
Christianity	51 (40.2)	62 (50.0)	LR = 4.069
Islam	76 (59.8)	61 (49.2)	p = 0.131
others	0 (0.0)	1 (0.8)	
Mothers' Occupation			
Artisan	31 (24.4)	31 (25.0)	LR = 17.868
Civil Servant	14 (11.0)	6 (4.8)	p = 0.003
Farming	25 (19.7)	44 (35.5)	
Housewife	6 (4.7)	2 (1.6)	
Trading	46 (36.2)	41 (33.1)	
Other (please specify)	5 (3.9)	0 (0.0)	
Child Educational Status			
In school	107 (84.3)	124 (100.0)	$X^2 = 21.218$
Out of School	20 (15.7)	0 (0.0)	p < 0.001
Mothers' Level of Education			
No formal education	16 (12.6)	21 (16.9)	$X^2 = 3.486$
Primary	44 (34.6)	42 (33.9)	p = 0.480

Secondary	37 (29.1)	42 (33.9)	
Diploma	21 (16.5)	13 (10.5)	
University Degree	9 (7.1)	5 (4.8)	
Fathers' Level of Education			
No formal education	12 (9.4)	23 (18.5)	$X^2 = 7.368$
Primary	30 (23.6)	33 (26.6)	$p = 0.118$
Secondary	52 (40.9)	47 (37.9)	
Diploma	17 (13.4)	8 (6.5)	
University Degree	16 (12.6)	13 (10.5)	
Households' Wealth Index			
1	19 (15.0)	30 (24.2)	$X^2 = 4.931$
2	24 (18.9)	27 (21.8)	$p = 0.294$
3	29 (22.8)	22 (17.7)	
4	26 (20.5)	24 (19.4)	
5	29 (22.8)	21 (16.9)	
Knowledge of Tuberculosis			
Poor	86 (67.7)	70 (56.5)	$X^2 = 7.522$
Good	41 (32.3)	54 (43.5)	$p = 0.023$

Table 2 compares various components of acceptability among participants that experience the use of new dispersible drugs and old single doses of non-dispersible drugs. Majority of the caregivers that used the new dispersible antituberculosis drugs, 112 (88.2%) were satisfied with the dosage preparation relative to the proportion of caregivers that were satisfied among those that used old single doses of non-dispersible drugs, 20 (16.1%), $p < 0.001$. There was a statistically significant difference between the perceived ease of dissolving the two drug formulations in water for ease of administration to children, $p < 0.001$. Most of the caregivers using the new dispersible drugs, 122 (96.1%) perceived their drugs to be easy to dissolve while only 23 (18.5%) of the caregivers that used the old non-dispersible drugs perceived the drug to be easy to dissolve. Most children that used dispersible drugs perceived the drug as having good taste, 100 (78.7%) while the proportion that reported good taste using old single doses of non-dispersible drugs was low, 19 (15.3%), $p<0.05$. Statistically significantly higher proportions of caregivers using new dispersible drugs felt the taste was good and felt the administration of drugs was easy compared to caregivers using the old non-dispersible drugs, $p < 0.001$ respectively.

Table 2. Association between Drug Formulation Received and Acceptability of Antituberculosis Drugs

Variables	**New Dispersible Drug n (%)**	**Old Loose Doses Non dispersible drugs n (%)**	**Statistics**
Caregivers' feelings about the preparation of the doses			
Poor	15 (11.8)	104 (83.9)	$X^2 = 130.667$
Good	112 (88.2)	20 (16.1)	$p < 0.001$
Ease of dissolving medication in water			
Poor	5 (3.9)	101 (81.5)	$X^2 = 154.523$
Good	122 (96.1)	23 (18.5)	$p < 0.001$
Caregivers' feelings about the administration of the doses			

Poor	6 (4.7)	101 (81.5)	$X^2 = 151.026$
Good	121 (95.3)	23 (18.5)	$p < 0.001$
Caregivers' perception of the taste of the drug			
Poor	32 (25.2)	99 (79.8)	$X^2 = 75.075$
Good	95 (74.8)	25 (20.2)	$p < 0.001$
Child's feeling about the taste of the drug			
Poor	27 (21.3)	105 (84.7)	$X^2 = 101.204$
Good	100 (78.7)	19 (15.3)	$p < 0.001$

The findings above were supported by the submissions from the qualitative data support on the association between acceptability of antituberculosis and drug formulation. Most interviewees and participants in FGD that used new dispersible antituberculosis admitted to the ease of dissolving the tablets in water while those that used old drugs complained of the need to grind the medications for kids that could not swallow pills. The taste of pills was also mentioned by virtually all the participants. This is explicated in the excerpts below:

"My child seems to like the taste of the drug as she does bring it and spoon to me even when I forget" (An IDI participant, a 67 years Grandmother, Dispersible antituberculosis drug).

"Grinding the drugs everyday was tiring, my only consolation was that my son was getting better, that kept me going ... He does not like one of the pills; giving him the drugs is usually a thug of war, but we thank God" (33 years Mother, Old loose doses non-dispersible drugs, an IDI participant).

Figure 1 showed a comparison between the overall acceptability of the new fixed-dose dispersible antituberculosis drug and old loose doses of non-dispersible antituberculosis drugs. The proportion of participants with good acceptability among participants that used new dispersible, 112 (88.2%) was significantly higher than the proportion of participants that had good antituberculosis drug acceptability among participants that used old non-dispersible drugs, 13 (10.5%), $p < 0.001$.

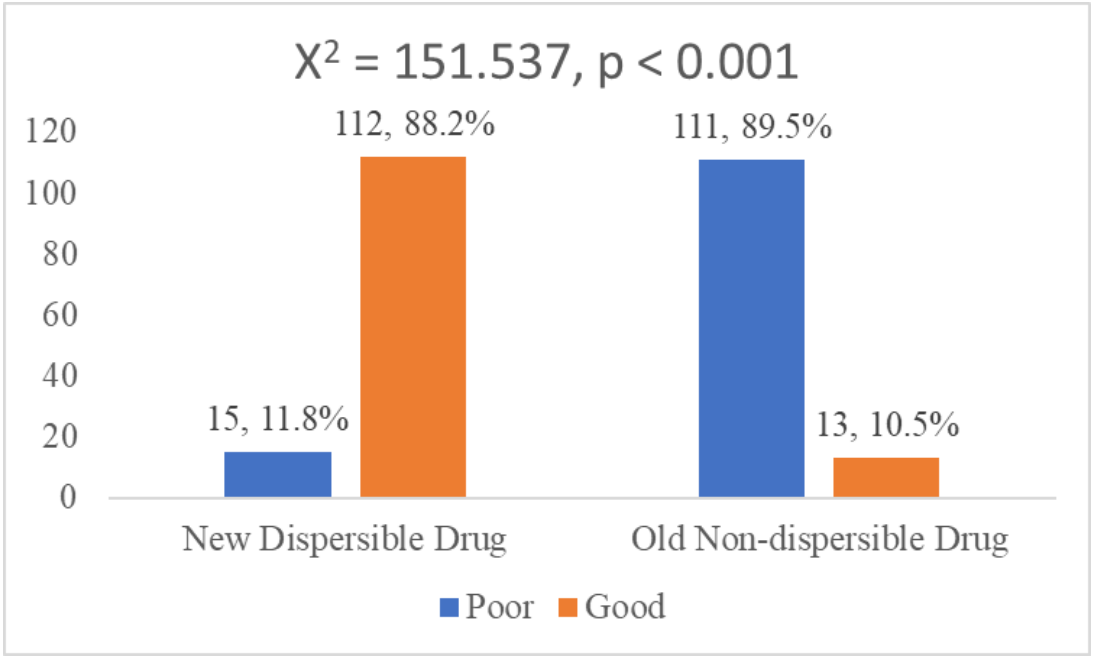

Figure 1. Comparison between the Acceptability of New Dispersible and Old Loose Doses Non-dispersible Drugs

Table 3 assessed the associations between the acceptability of antituberculosis drugs and participants' characteristics. There was a significant association between the age of children and the acceptability of antituberculosis drugs, $p < 0.001$. A younger age group, 7.0(4.0 – 10.0) years had good acceptability while an older age group, 10.0(8.0 – 13.0) years had poor acceptability. There was also a significant association between the child's educational status and acceptability of drugs, $p = 0.001$. A higher proportion of out-of-school children was observed to be higher among children with good acceptability, 17(85.0%) compared to the proportion among people with poor acceptability, 3(15.0%). There was no significant association between the acceptability of antituberculosis drugs and other participants' characteristics – religion, mothers' education, caregivers' level of education, wealth index, and the knowledge of tuberculosis among caregivers.

Table 3. Association between Participants' Characteristics and Acceptability of Antituberculosis Drugs

Variables	**Acceptability of Antituberculosis Drugs**		**Statistics**
	Poor n (%)	**Good n (%)**	
Age	10.0 (8.0 – 13.0)	7.0 (4.0 – 10.0)	U = 4289.5
			p < 0.001
Religion			
Christianity	63 (55.8)	50 (44.2)	LR = 4.117
Islam	62 (45.3)	75 (54.7)	p = 0.128
Others	1 (100.0)	0 (0.0)	
Mothers' Occupation			
Artisan	30 (48.4)	32 (51.6)	LR = 8.356
Civil Servant	7 (35.0)	13 (65.0)	p = 0.133
Farming	44 (63.8)	25 (36.2)	
Housewife	3 (37.5)	5 (62.5)	
Trading	2 (40.0)	3 (60.0)	
Other (please specify)	40 (46.0)	47 (54.0)	
Child Educational Status			
In school	123 (53.2)	108 (46.8)	$X^2 = 10.770$
Out of School	3 (15.0)	17 (85.0)	p = 0.001
Mothers' Level of Education			
No formal education	21 (56.8)	16 (43.2)	$X^2 = 2.344$
Primary	44 (51.2)	42 (48.8)	p = 0.673
Secondary	35 (44.3)	44 (55.7)	
Diploma	17 (50.0)	17 (50.0)	
University Degree	9 (60.0)	6 (40.0)	
Fathers' Level of Education			
No formal education	22 (62.9)	13 (37.1)	$X^2 = 2.653$
Primary	31 (49.2)	32 (50.8)	p = 0.617
Secondary	47 (47.5)	52 (52.5)	
Diploma	12 (48.0)	13 (52.0)	
University Degree	14 (48.3)	15 (51.7)	
Households' Wealth Index			
1	28 (57.1)	21 (42.9)	$X^2 = 3.638$

2	29 (56.9)	22 (43.1)	p = 0.457
3	22 (43.1)	29 (56.9)	
4	22 (44.0)	28 (56.0)	
5	25 (50.0)	25 (50.0)	
Knowledge of Tuberculosis			
Poor	76 (48.7)	80 (51.3)	$X^2 = 0.362$
Good	50 (52.6)	45 (47.4)	p = 0.548

The findings from the qualitative data expatiate on the role of health education from the healthcare workers which was also observed to influence the caregiver's acceptability and perception of the disease severity as shown in the excerpt below:

"When I came to the health center the nurse told me that the cough my child had was different from the common cough other children use to have and it can kill my child. She said only the drug at the center can cure the baby, not medicine at chemists. I had no option than to force the baby to take the drug; my baby must not die" (35 years old mother of a child that took an old single loose non-dispersible drug and one of the selected IDI participants).

Table 4 showed the factors affecting the acceptability of antituberculosis drugs using a binary logistic regression. The probability of having good acceptability of antituberculosis drugs was 62.3 times higher among participants that used fixed-dose dispersible drugs compared to participants that used loose doses non-dispersible antituberculosis drugs, (Odds Ratio = 62.3, p < 0.001, 95%CI = 25.3 – 153.3. The ages of the children, levels of knowledge of caregivers, and educational status of children were not significant predictors of acceptability of antituberculosis drugs.

Table 4. Binary Logistic Regression of Association Between Selected Participants' Characteristics and Acceptability of Antituberculosis Drugs

Variables	**Odds Ratio**	**p-value**	**95% CI**
Educational status of the child			
Out of school	Ref	0.238	0.541 – 11.821
In school	2.5		
Knowledge of Tuberculosis			
Poor	Ref	0.188	0.755 – 4.207
Good	1.9		
Type of drugs			
Loose doses non-dispersible	Ref	< 0.001	26.247 – 156.620
Fixed-dose dispersible	64.1		
Age (years)	-0.105	0.102	0.794 – 1.021

Finding from the qualitative data showed that the major side effect observed across the two study groups was discouloration of urine which was a threat to acceptability and compliance with treatment. Majority of the caregivers interviewed acknowledge the important role of health education received from the healthcare providers and other sources in allaying the resulting fear. This is supported by the following excerpts:

"a note from my son's teacher that he passed red urine got me so scared that I could not sleep. I was confused if it was the drug that caused it or if the cough has damaged the organs. Though I was sceptical about continuing the drug, the reassurance of our matron really helped me to

keep the hope alive and complete the treatment" (an IDI participant, a 32 years old mother in Aiyedire LGA).

"I was not so scared on seeing my son passing reddish urine because our mind has been prepared against the common side effects of the drugs in the clinic" (an IDI participant, a 52 years old grandmother in Ife-North LGA).

Discussion

There was a significant difference in the age of participants across the two study groups. This could be due to the period when the new dispersible antituberculosis formulation was introduced, 2018. Only a few children born after the period of introduction of the new drug formulation used old single doses of non-dispersible drugs, especially in rural areas where there are logistic challenges with drug supply. All out-of-school children were observed to be among children using new dispersible antituberculosis drugs. This could be due to a younger age of a proportion of children in this drug formulation group; a significant proportion of the children were in the preschool age group. The caregivers that used the old non-dispersible formulation had better knowledge of tuberculosis relative to caregivers that used the new dispersible formulation. This could be due to variations in the mode and intensity of health education exposure over the years when the caregivers' children were on treatment.

Significant differences were observed in various drug factors across the two study groups. Majority of the caregivers were satisfied with the new antituberculosis formulation relative to the old formulations. This could be attributed to various drug factors that were considered in making the new antituberculosis drug. Rather than loose doses of pills that could not easily be dissolved in water. The new drug formulation had the characteristics of being a fixed-dose combination of multiple drugs in a single tablet. In addition, it is easier to dissolve in water, thus making it available in suspension form before administration. The use of a single tablet rather than multiple tablets in old loose doses, coupled with the ability to dissolve the drug easily into suspension which is more child-friendly contributes to the acceptability and satisfaction experienced with the use of new dispersible antituberculosis drugs compared with the loose doses non-dispersible formulation.

A similarly high level of acceptability of fixed-dose combination was observed in a qualitative study conducted among caregivers of children with tuberculosis in South Africa [13]. Most of the participants in the study identified inability to dissolve the FDC formulation and the time required for the drug administration as challenges, thus resulting in the manipulation of drugs to ease administration. The new dispersible FDC formulation is an improvement on the drug used in the South African study as the new formulation is dispersible and the dosage is once a day. Previous studies on the effects of drug formulations on acceptability of drugs for the treatment of other chronic disease conditions were in agreement with the findings of this study that fixed-dose combination was more acceptable relative to single loose dose formulations [20-23]. The domain of solubility of drug formulation was however not considered in some of the studies since they were mainly conducted among adults.

The taste of drugs is an important factor in drug formulations for children. Both the caregivers and children had good perceptions of the taste of the new dispersible drug. This could account for the higher acceptability of the new dispersible formulation because it was sweetened to make it child-friendly compared to the old loose doses' formulation, hence the ease of administration by caregivers with minimal resistance from the child. Age of the child also had a significant association with the acceptability of antituberculosis drugs. The acceptability was good among the younger age group and poor among older children. This could be due to variations in the drug formulation used by the children. The older children that were managed before the introduction of new

dispersible drugs may not have good acceptability of the antituberculosis drugs due to the many pills to use per dose, solubility, and tastes of the medications. Many previous studies among children were in agreement with the importance of taste on the acceptability of antituberculosis medications underscored by this study [4, 14, 23, 24].

Also, a dispersible formulation of the new FDC antituberculosis serves as a cost-effective approach to tuberculosis treatment among the paediatric age group. The dispersible formulation is acceptable to all paediatric age groups which profer a better solution to the age-specific formulation recommended by a study conducted among caregivers in India where oral liquid and tablets were recommended for children below six years and children that are six years and above respectively [10].

Health education from service providers and its influence on the caregivers' perception of tuberculosis was identified as a driver of acceptability. Perception of antituberculosis drugs as the only solution to child's illness based on the education received from healthcare workers influences acceptability irrespective of the drug formulation and frequency of administration. Though most similar studies focused on adherence to medication [25, 26], it could be deduced that they had similar findings of a positive relationship between health education and acceptability of medication since acceptability of medication is a precursor to adherence to treatment [27].

Conclusion

Overall, the drug factor was the only observed significant predictor of antituberculosis drug acceptability. The probability of having good acceptability was more with the usage of a child-friendly dispersible formulation. This could be attributed to properties of the drug like being tasty, fixed-dose combination, and being soluble in water hence, it can easily be converted to a form that is easier to administer to children of younger age groups. Ensuring universal access to this new formulation, coupled with the intensification of health education of caregivers are key to tuberculosis elimination.

Limitations of the Study

Majority of participants in the two study groups were on treatments at different periods as the new dispersible antituberculosis drug was introduced into Nigerian Health System in 2018. The acceptability of antituberculosis formulations available at the different periods could have been affected by other circumstantial factors peculiar to that period, Findings from those that are still using old non-dispersible drugs due to shortage of new formulation in some areas of study were however not different from those that used it before the introduction of the new formulation in 2018. The study period was limited to between 2018 and 2020 for those that used old non-dispersible drugs and 2021 – 2022 for those that used new dispersible drugs to limit the effect of recall bias on participants' responses.

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