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ORIGINAL RESEARCH

Evaluating Equity and Coverage in Mass Drug Administration for Soil-Transmitted Helminth Infections among School-Age Children in the Hard-to-Reach Setting of Southern Ethiopia

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Correspondence: Mekuria Asnakew Asfaw Tel +251-91-202-9517 Email maksambaramr23@gmail.com **Background:** Soil-transmitted helminth (STH) infections are prevalent in most developing countries, including Ethiopia, with school-age children (SAC) at high risk of infection. In Ethiopia, despite substantial progress being made on mass drug administration (MDA) coverage for STH infections, its implementation is facing challenges in hard-to-reach areas. This study thus aimed at assessing equity and coverage in MDA and identifying factors associated with drug coverage for STH infections among SAC in the hard-to-reach setting of southern Ethiopia.

Methods: A community-based cross-sectional survey was conducted in the North Ari district, South Omo Zone in July 2019. Sample size was estimated following WHO drug-coverage evaluation guidelines. Factors associated with drug uptake for STH infections were identified using multivariate logistic regression.

Results: Of 956 SAC participating in this study, the overall MDA coverage for STH was found to be 27.5% (95% CI 24.7%–30.5%). The odds of having taken drugs were highest among school-enrolled children and in those who knew the purpose of MDA: about about double their counterparts. In contrast, the odds of drug uptake were lower by 69% among those who had got informed only when the drugs delivered and by 92% among those who needed to travel >30 minutes to reach drug-distribution points than their counterparts.

Conclusion: Achieving effective and equitable MDA coverage is facing serious challenges in the hard-to-reach setting of southern Ethiopia. The very low (27.5%) and inequitable MDA coverage found in this study are associated with school nonenrollment, inaccessibility, and lack of information, awareness, and mobilization. Social mobilization should be scaled up to inform and create awareness in the community ahead of MDA. Further, school-based deworming in settings with low school enrollment needs a modified strategy to reach those in need of drugs.

Keywords: equity, mass drug administration, soil-transmitted helminths, North Ari, hard-toreach setting

Introduction

Soil-transmitted helminths (STHs) are a group of parasitic intestinal worms, ie, roundworm (*Ascaris lumbricoides*), whipworm (*Trichuris trichiura*), and hookworms (*Ancylostoma duodenale and Necator americanus*) that are prevalent in places where the soil is warm and humid and sanitation is lacking.^{1–3} They are among the common neglected tropical diseases (NTDs), which are a diverse group

© 2021 Asfaw et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs A.2 and 5 of our Terms (https://www.dovepress.com/terms.php). of diseases that affect impoverished, marginalized, and remote communities.^{1,2} Risk factors of STH infections include poor hygiene, lack of sanitation, and low socio-economic status.^{4,5}

It is estimated that >2 billion people around the world are affected by $STHs^{2,3}$ and >550 million school-age children (SAC) worldwide at risk of STH infections.⁶ STHs are widespread in most developing countries, including Ethiopia, with high prevalence among SAC.^{3,4,7} STHrelated morbidity associated with moderate or heavy infection intensity results in anemia, stunted growth, loss of education, and cognitive problems in children.^{3,8}

According to the World Health Organization (WHO), at least 75% of SAC should be covered by mass drug administration (MDA) in an endemic area.³ In 2017, it was reported that >500 million SAC (69% of total SAC in need) received preventive chemotherapy (PC) through MDA for STHs globally, with 73% of implementation units reaching the recommended coverage. More than 596 million SAC in 101 countries were estimated to be in need of PC for STH infections in 2017.9 STHs are targeted to be eliminated as a public-health problem by 2030, defined as a <2% proportion of STH infections of moderate and heavy infection intensity, as stated in the new revised WHO's NTD roadmap of 2021-2030.¹⁰ To control and eliminate STH infections, PC using annual or biannual single-dose albendazole (400 mg) or mebendazole (500 mg) has been provided as a public-health intervention for all SAC living in areas where the baseline prevalence of any STH is 20% or higher in children to reduce the worm burden of STHs.^{2,3,7} Controlling NTDs through PC in at-risk populations provides a cost-effective way of improving health equity in endemic countries.¹¹ Furthermore, for sustained solutions, it is advocated that the STH-control program is complemented with measures that ensure access to improve sanitation, health, and hygiene behaviors, such as hand-washing and the use of footwear through health education.³ In 2016, the global NTD program passed the half-billion mark, reaching 531 million children in need of deworming. This accounted for 63% of global needs, an increase from 58.5% in 2015. Of the 103 STH-endemic countries, 77 reported conducting deworming of SAC.¹ However, reaching children who are not attending schools through school-based control programs remains a challenge in remote settings to achieve the required treatment coverage.²

The NTD program is an entry point to universal health coverage,¹ and the WHO set a global target to end NTDs by 2030, as mentioned in target 3.3 of the Sustainable Development Goals,¹² leaving no one behind from accessing basic health services by 2030.¹³

In Ethiopia, >81 million people are living in STHendemic areas, of which 25.3 million are SAC. About 1 million SAC got dewormed for STH infections in 2007 in Ethiopia, and in 2013 and 2014, 11.6 million and 7.8 million SAC received treatment, respectively. Following the launch of the countrywide school-based deworming program in November 2015, nearly 13 million SAC received drugs against STHs.¹⁴ Since 2015, MDA for STHs among SAC using a school-based deworming platform has been implemented in Ethiopia and remarkable achievements observed regarding MDA coverage; however, segments of the population are still left behind from accessing PC, especially in the hard-toreach setting of southern Ethiopia.¹⁵

The WHO recommends that all SAC (both enrolled and nonenrolled) be treated through school-based deworming. Implementation of deworming using the school platform is facing challenges, due to a significant proportion of SAC in many developing countries not attending school. Although good results have been obtained by encouraging SAC to bring their nonenrolled siblings and friends to school on a treatment day,¹⁶ this has not brought substantial change insouthern Ethiopia. For example, in South Omo Zone, data obtained from records at the the zonal health department have shown persistently low — <50% — administrative drug coverage for STHs has been reported for >3 years.

To achieve the STH-program goals, effective and equitable coverage is vital. It is thus important to conduct periodic epidemiological surveys to assess equity and coverage in MDA and identify factors associated with drug uptake. The STH program within the health system calculates and reports administrative mass-treatment coverage by adding reports received from drug distributors. However, these reports are often prone to error, and thus evidence is lacking on equity and coverage in MDA and factors associated with drug uptake in southern Ethiopia. Therefore, this study aimed at determining MDA coverage, assessing equity of MDA with respect to sex, age, place of residence, educational level, and school attendance, and identifying factors associated with drug consumption for STH infections in the North Ari district of South Omo Zone, a hard-to-reach area.

Methods Study Design and Period

A community-based cross-sectional study was conducted in July 2019 to assess the coverage, equity, and factors associated with drug uptake for STHs.

Study Setting

This study was conducted in the North Ari district of South Omo Zone, about 940 km southwest of Addis Ababa, the capital Ethiopia. The population in the zone is estimated to be 577,673 (288,638 male and 289,035 female), and that of North Ari was projected to be 18,495 by the central statistical authority in 2007.¹⁷ There are transportation problems in the entire district, and it is very far from regional and zone towns. The absence of roads for four-wheel vehicles and motorcycles makes for hard-to-reach data-collection sites. As such, the study area is defined as hard-to-reach setting. STH infections are a common and prevalent NTD in the district, and have been affecting the community, mainly SAC.14

Study Populations

The study population was selected SAC who lived in the study area during the MDA campaign that was happened head of the survey. Only children aged 5–14 years (according to SAC categorization) were included. Since there is no consistent definition of SAC in the existing literature, in this study all children aged 5–14 years were considered SAC, as per a WHO guideline.^{16,17} Participants were excluded if they were nonresidents (had come to visit their relatives), were seriously ill, or parents were unable to deliver their information.

Sample-Size Determination and Sampling Strategy

As this study adopted coverage-evaluation survey methodology, sample size was estimated using multistage cluster sampling following WHO guidelines to evaluate coverage and equity of MDA.¹⁸ The Survey Sample Builder tool was used, which generates an equal probability proportional to each village of the survey population by assuming expected coverage of 71%¹⁹ by considering desired precision of 5%, α =5%, design effect of 3, and 10% nonresponse rate. Figure 1 shows the sampling strategy. In total, 30 segments were systematically selected from the subunits (villages) by taking probability proportional to estimated population size into consideration, and from each selected segment at least 16 randomly selected households were included. From each selected household, SAC who were resident and available during the MDA campaign participated in the study. To include eligible household members that were absent at the time of the interview, the survey team made an attempt to revisit the household or a primary caretaker was asked to answer on their behalf.

Study Variables

The dependent variable was STH-drug uptake and independent variables sex, age, place of residence, school attendance, educational level, information-, social mobilization-, and awareness-related characteristics, place of drug distribution, availability of drug distributors while taking the drugs, participants informed about MDA ahead of time, ways participants were informed, and time taken to reach drug-distribution points.

Data Collection

Data were collected using a pretested questionnaire by experienced and trained health professionals who were members of the community, but not involved in the MDA campaign through home visits. Data collectors used a sample of albendazole or mebendazole tables to show and confirm the type of drug the children received so that recall bias was minimized. Children or their primary caregivers were asked for information regarding each variable. If there were no SAC in the selected household or if the entire household was absent and not expected to return later in the day, the survey team moved to the next



Figure I Sampling strategy.

household. Moreover, the survey team attempted to revisit the household if children were absent, but expected to return later in the same day. Data from very young children (<7 years old) were collected from their parents or caregivers.

Data Analysis

Data were coded, entered into EpiData 4.4.2, and exported to SPSS 25 for analysis. Factors associated with STH-drug uptake were assessed using multivariate logistic regression. Bivariate analysis, interaction effects, multicollinearity, and assumption of $#x1D712;^2$ were checked before fitting to the multivariate model. Goodness of model fitness was checked for the full model using the Hosmer–Lemeshow test at P>0.05.

Equity in MDA coverage was assessed by disaggregating data by sex, age, place of residence, school enrollment, and educationlevel, and presented in tables. Differences in coverage of MDA between or among groups was checked using #x1D712;² tests (*P*<0.05).

In this study, drug coverage was defined as the proportion of individuals who had taken a drug, calculated as such:

Total number of interviewed individuals that swallowed the target drug Total number of interviewed individuals *100%

Equity is defined as preventable, unfair, or remediable differences among groups of people, whether those groups are defined socially, economically, demographically, or geographically.¹¹ In this study, it was defined as all individuals in need of PC regardless of sex, age, place of residence, education level, school enrollment, place of education, and other differences.

Ethics

Ethics approval was granted by the Institutional Research Ethics Review Board of Arba Minch University, College of Medicine and Health Sciences, Ethiopia (CMHS-12032750/111). The study was conducted in accordance with the Declaration of Helsinki. All participants were informed about the purpose of the study. Oral and written informed consent was obtained from parents or legal guardians, with informed assent from the children before data collection, and participation was totally voluntary. The study team had a meeting with the district health office head and village chiefs, where the purpose of the survey was explained and verbal permission obtained to perform the survey.

Results

Sociodemographic Characteristics

In total, 956 participants were involved in this study. Of these, the proportion of boys was higher than girls (55.9% versus 44.1%), almost two-thirds (645) were aged 5–10 years of age group, a majority (96.4%) were living in rural area, three-quarters (718) were attending school, most (92.2%), most at the primary level, and >95% at government schools (Table 1). Table 1 summarizes the socio-demographic characteristics of participants.

MDA-Implementation Strategies Information, Social Mobilization, and Awareness Regarding MDA

Ahead of the actual MDA campaign, it was recommended that the district health office in collaboration with healthextension workers perform health education in schools and communities to create awareness and improve knowledge, attitudes, and practice related to MDA and STH prevention and control. However, in this study, of the total study participants (956), more than half (52.8%) did not know anything about MDA, only 50.4% had heard about the MDA campaign. Of those informed, a majority (68.7%) had heard 1 day prior, more than half (53.5%) had been informed on the location and time of MDA, and 47.2% knew about the purpose of taking the drugs (Table 2).

MDA Coverage and Self-Reported Reasons for Not Being Offered Drugs

Overall MDA coverage for STHs was 27.5% (95% CI 24.7%–30.5%), much lower than the WHO's recommended coverage (at least 75%). Self-reported cases of drugs was not

Table I	Sociodemographic	characteristics	of	participants
(n=956)				

	Category	n	%
Sex	Male	534	55.9
	Female	422	44.1
Age (years)	5–10	645	67.5
	11–14	311	32.5
School enrollment	Yes	688	72
	No	268	28
Education (n=688)	Primary	634	92.2
	Secondary	54	7.8
Place of education (n=688)	Private	13	1.9
	Government	675	98.1

	Category	n	%
Heard of MDA ahead	Yes	482	50.4
of time	No	474	49.6
Before how many days	One	331	68.7
informed about MDA	Two	128	26.5
(n=482)	Three	23	4.8
How informed on MDA (n=482)	Teacher Community meeting Health professional Crier	118 7 228 129	24.5 1.5 47.5 26.8
Informed about	Location	192	39.8
location and time of	Time	32	6.6
MDA (n=482)	Location and time	258	53.5
Do you know about	Yes	45 I	47.2
MDA?	No	505	52.8
What do you know about MDA (n=451)?	About the disease given for Color and amount of drugs	280 171	62.1 37.9

 $\label{eq:constraint} \begin{array}{c} \textbf{Table 2} \\ \textbf{Information, social mobilization, and awareness regarding MDA \end{array}$

being offered/given came to 98.7% (684 of 693), and the main self-reported reason for this was not being informed (42.8%, 293 of 684) and long distance to drug-distribution points (26%, 178 of 684; Table 3). With regard to place of distribution, we found health posts (43%) and schools (42.6%) were the main distribution points, while 41.8% of participants needed to for >30 minutes to reach the distribution points. In most (97.1%) drug-distribution points, community drug distributors (CDDs) were available (Table 3).

MDA Coverage for STHs

The survey showed that MDA coverage for STHs was 27.5% (95% CI 24.7%-30.5%).

Equity in MDA Coverage for STHs among SAC

This study showed inequities in MDA coverage based on coverage data disaggregated by gender, age, place of residence, school enrollment, and education level. There was a a significant difference in drug uptake based on schoolenrollment status (#x1D712;²=52.01, *P*=0, Table 4).

Factors Associated with STH-Drug Uptake

On univariate analysis, variables identified with $P \le 0.25$ for STH-drug uptake were place of residence, school

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Table 3 MDA coverage, implementation, and self-reported rea	-
sons for not being offered drugs (n=956)	

	Category	n	%
Offered drugs	Yes	272	28.5
	No	684	71.5
Took drugs	Yes	263	27.5
	No	693	72.5
MDA-distribution point	Home	12	4.4
(n=272)	School	116	42.6
	Health post	117	43.0
	Central point	27	9.9
Time taken to reach drug-	>60 minutes	234	24.5
distribution points	30–60 minutes	165	17.3
	<30 minutes	557	58.3
CDDs available while	Yes	264	97.1
drugs were offered (n=272)	No	8	2.9
Perceived reasons for not	Fear of side effect	7	1.0
taking drugs (n=693)	Do not like test	2	0.3
	Not offered/given	684	98.7
Perceived reasons for not	Not informed	293	42.8
being offered drugs (n=684)	Felt healthy	107	15.6
	Long distance to	178	26.0
	MDA site		
	Do not attend school	106	15.5

attendance, informed of MDA ahead of time, knowledge about MDA, what known about MDA, how informed on MDA, informed about location and time of distribution, CDDs available while drugs were offered, and time taken to reach distribution sites. To improve the likelihood of the remaining variables being included in the multivariate model, we used a cutoff of $P \le 0.25$ to select candidate variables.

Following univariate analysis, all variables with $P \le 0.25$ that met the #x1D712;² assumptions were entered into a multivariate logistic regression model using the backward-stepwise method. The variable "availability of CDDs while drugs were offered" was not entered into the model, since it did not meet the #x1D712;² assumptions (one cell [25%] with expected count <5). After adjustment for confounding variables, the multivariate model identified the following variables as potential factors associated with STH-drug uptake. The odds of STH-drug uptake were highest among those SAC who were enrolled in school (AOR 2.29, 95% CI 1.13–4.61) and among those who knew the purpose of the drug (AOR 2.27, 95% CI 1.44–3.59). On the other hand, the odds of STH-drug uptake were lower by 69% among SAC who were informed only

	Category	Drug uptake		Mean difference in	#x1D712; ²	Р
		Yes	No	drug coverage		
Sex	Male Female	5 (28.3%) 12 (26.5%)	383 (71.7%) 310 (73.5%)	1.8%	0.36	0.56
Age (years)	5–10 11–14	179 (27.8%) 84 (27%)	466 (72.2%) 227 (73%)	0.8%	0.06	0.81
School level	Primary Secondary	218 (34.4%) 16 (29.6%)	416 (65.6%) 38 (70.4%)	4.8%	0.50	0.48
School enrollment	Yes No	234 (34%) 29 (10.8%)	454 (66%) 239 (89.2%)	23.2%	52.01	0
Place of education	Government Private	187 (29.5%) I (12.5%)	447 (70.5%) 7 (87.5%)	17%	1.10	0.29

Table 4 Equity in MDA coverage (n=956)

when the drug would be delivered compared to those who were informed of the location and time of MDA (AOR 0.31, 95% CI 0.12–0.82). In addition, the STH-drug uptake was lower among SAC who needed to travel >90 minutes to reach drug-distribution points by 88% (AOR 0.22, 95% CI 0.14–0.35 and 92%, AOR 0.08, 95% CI 0.04–0.17, respectively) compared to the reference category (Table 5).

Discussion

Despite the significant progress that has been made in terms of reaching STH-affected communities through MDA, the findings of this study showed low and inequitable MDA coverage for STHs in SAC in the hard-to-reach setting of southern Ethiopia. We identified school enrollment, accessibility, and information, awareness, and mobilization as associated factors with STH-drug uptake among SAC.

MDA coverage was found to be very low (27.5%) compared to the target coverage set by the WHO (at least 75%)³ and also less than PC coverage estimated on a global level in 2017 (68.8%).¹⁸ Likewise, it was much lower than the coverage estimated by a study done in ten districts of Ethiopia (71%).¹⁹ However, coverage was in alignment with that in different countries using 2016 WHO PC data, where 31 countries achieved <75% MDA coverage, including Ethiopia. On the other hand, 57 countries achieved \geq 75% PC coverage¹⁸ Similarly, in 2017, a WHO report noted that 36 countries met the target.⁹

We found very low MDA coverage (27.5%) in this study, lower than the administration-reported coverage

(34.5%). This may have been due to the fact that reported coverage is often subject to error. The finding collaborates with studies conducted in other parts of Ethiopia,¹⁹ in other countries,²⁰ and in Bangladesh.²¹

In this study, slightly higher MDA coverage in boys was observed thangirls (28.5% versus 26.5%). On the contrary, evidence from 16 countries indicated that female coverage was slightly higher than male coverage.²² The difference in this finding might be due a norm that may prevail in the study area that favors male individuals in terms of a higher chance of attending school and taking drugs than their female counterparts.

Evidence showed that exclusive school-based deworming was unable to reach children not attending school.²¹ In the present survey, treatment coverage in school-attending children was 34%, significantly higher than coverage among nonenrolled children (10.8%). Low school enrollment and a high dropout rate in the study area could be reasons for the low drug coverage in nonenrolled children. This is consistent with studies conducted in Ethiopia¹⁹ and Bangladesh.²¹ In addition, a finding of a previous coverage survey conducted in Ethiopia showed that only about half of nonenrolled children received drugs for STHs, whereas >95% of school-attending children did.²³

The difference in of MDA coverage for STHs among SAC living in urban areas was notable compared to children living in rural areas (58.2% versus 26.4%). The low rural coverage might be due to geographical inaccessibility related to the hard-to-reach setting of the study area where limited infrastructure exists, eg, lack of roads would make it difficult to reach all individuals in need of PC.

Table 5 Univariate and multivariate analyses of factors	associated with drug uptake
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	Category	•		Univariate analysis, COR (95% CI)	Multivariate analysis, AOR (95% CI)
Sex	Male Female	151 112	383 310	1.09 (0.82–1.45) Reference	-
Age (years)	5–10 11–14	179 84	466 227	1.04 (0.77–1.41) Reference	-
Enrolled in school	Yes No	216 47	530 163	2.40 (2.80–6.44)** Reference	2.29 (1.13–4.61)* Reference
School level	Primary Secondary	218 16	416 38	1.25 (0.68–2.28) Reference	-
Informed about MDA ahead of time	Yes No	228 35	254 439	11.26 (7.64–16.59)** Reference	-
How many days before did you get informed about MDA? (n=482)	One Two Three	150 66 12	181 62 11	I.32 (0.56–3.07) I.03 (0.42–2.49) Reference	-
Do you know about MDA?	Yes No	210 53	241 452	7.43 (5.29–10.44)** Reference	
What do you know about MDA?	About the disease given for Color and drug	147 63	133 108	I.89 (I.28–2.80)** Reference	2.27 (1.44–3.59)* Reference
How informed about MDA (n=482)	Teacher Community meeting Health professional	73 2 93	45 5 135	0.54 (0.32–0.89)** 2.17 (0.41–11.62) 1.26 (0.82–1.95)	
	Town crier	60	69	Reference	
Informed about location and time of MDA (n=482)	Where When Where and when	78 20 130	114 12 128	I.48 (I.02–2.16)** 0.61 (0.29–1.30)** Reference	I.42 (0.92–2.26) 0.31 (0.12–0.82)* Reference
Time taken to reach distribution site	>60 minutes 30–60 minutes <30 minutes	143 66 54	91 99 503	0.07 (0.05–0.10)** 016 (0.11–0.25)** Reference	0.22 (0.14–0.35)* 0.08 (0.04–0.17)* Reference
CDD available while drug being offered (n=272)	Yes No	259 4	5 4	51.80 (10.01–268.19)** Reference	-

Notes: **P≤0.25 on univariate analysis. Reference = comparison group. *P<0.05 on multivariate analysis. **Abbreviations:** COR, Crude odd ratio; AOR, Adjusted odd ratio.

On the other hand, our study indicated that the treatment coverage those aged5–10 years was 27.8%, a little bit higher than the coverage within those aged 11–14 years (27%). The possible reason for this could be older children staying outside the home to keep cattle, which may have resulted in them missing out on the drugs. On the contrary, a study conducted in another part of Ethiopia showed that children aged >10 years had a higher chance of obtaining drugs.¹⁹

In this study, children who were informed on the location and time of MDA had a higher chance of drug uptake than those informed only of the time the drug was planned to be delivered. It is obvious that those participants who got information on the place and time of deworming would be able to access the drugs effectively and efficiently. A study conducted in Bangladesh supports this finding, where lack of adequate information was found to be a barrier to the utilization and coverage of MDA for ${\rm STHs.}^{21}$

The findings of the current study demonstrate that the chance of drug uptake was higher among individuals who knew the purpose of MDA than those who did. A possible reason for this is communities that know why drugs are delivered would have more opportunity to accept and take the drugs. In line with this, previous research has shown showed that community knowledge and perceptions about the disease influenced the uptake of MDA.^{24,25}

It is known that accessibility in terms of remoteness to reach drug-distribution points can affect uptake of drugs.¹¹ In agreement with this, our study showed that individuals who needed to travel long distances to drug-distribution points were less likely to take drugs than those able to reach drug-distribution sites within 30 minutes.

Some limitations in this study should be taken into consideration. First, recall bias may have been a source of error if participants did not remember whether they had taken the drug or not. Second, cross-sectional studies have limitations in identifying cause–effect relationships.

Conclusion

Achieving effective and equitable MDA coverage is facing serious challenges in the hard-to-reach setting of southern Ethiopia. The findings of this study showed that the MDA coverage for STHs was much lower than the WHO's recommendation. In addition, the survey coverage was lower than the reported administrative drug coverage. School enrollment, accessibility, information, awareness, and mobilization were important risk factor of inequitable MDA coverage. Social mobilization should be scaled up to create awareness and inform the community ahead of MDA rollout. Further, exclusive school-based deworming in settings with low school enrollment needs a modified strategy to reach those in need of PC, and challenges related to implementation of MDA need further investigation.

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Author Contributions

MA wrote the original draft and was also involved in the study's conception. All authors made significant

contributions to the work reported, whether in study design, execution, acquisition of data, analysis, interpretation, or all these areas, revising or critically reviewing the article, gave final approval to the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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