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ORIGINAL ARTICLE

An observational assessment of the safety of mass drug administration for trachoma in Ethiopian children

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Background: The International Trachoma Initiative (ITI) provides azithromycin for mass drug administration (MDA) to eliminate trachoma as a public health problem. Azithromycin is given as tablets for adults and powder for oral suspension (POS) is recommended for children aged <7 y, children <120 cm in height (regardless of age) or anyone who reports difficulty in swallowing tablets. An observational assessment of MDA for trachoma was conducted to determine the frequency with which children aged 6 mo through 14 y received the recommended dose and form of azithromycin according to current dosing guidelines and to assess risk factors for choking and adverse swallowing events (ASEs).

Methods: MDA was observed in three regions of Ethiopia and data were collected on azithromycin administration and ASEs.

Results: A total of 6477 azithromycin administrations were observed; 97.9% of children received the exact recommended dose. Of children aged 6 mo to <7 y or <120 cm in height, 99.6% received POS. One child experienced choking and 132 (2%) experienced ≥1 ASEs. Factors significantly associated with ASEs included age 6–11 mo or 1–6 y, non-calm demeanor and requiring coaxing prior to drug administration.

Conclusions: There is a high level of adherence to the revised azithromycin dosing guidelines and low incidence of choking and ASEs.

Keywords: airway obstruction, azithromycin, mass drug administration, pharmacovigilance, program evaluation, trachoma

Introduction

Trachoma, a neglected tropical disease (NTD) caused by the bacterium *Chlamydia trachomatis*, is the leading infectious cause of blindness worldwide.[1] An estimated 1.9 million people have trachoma-related visual impairment and 142 million are at risk of the disease.[1] The WHO recommends the SAFE strategy (Surgery, Antibiotics, Face washing and Environmental improvement) for the prevention of blinding trachoma.[1]

The antibiotic component of SAFE involves periodic presumptive treatment with azithromycin of at-risk populations, known as mass drug administration (MDA). The goal of MDA for trachoma is reducing *C. trachomatis* transmission at the community level, leading to elimination of the disease as a public health problem.[2] An estimated 95.2 million people received MDA for trachoma in 2019.[1]

Azithromycin and other drugs given during MDA for NTDs have an excellent safety profile.[3] However, serious adverse events are occasionally reported through national pharmacovigilance.[4] Although the incidence is low, fatal choking has been reported in young children during MDA for soil-transmitted helminthiasis (STH) and other NTDs.[5] Limited evidence suggests that forcing young children to swallow tablets is an important risk factor for fatal choking.[5–7]

Since 1998, azithromycin (Zithromax) has been donated by Pfizer Inc. (New York, NY, USA) for trachoma elimination through the International Trachoma Initiative (ITI).[8] Azithromycin is provided in tablet form for adults and as an age-appropriate formulation—powder for oral suspension (POS)—which is reconstituted to a sweet syrup to minimize the risk of choking in young children.[9] During MDA, the azithromycin dose is determined by both height, using a simple dosing pole, and age. In 2018, to provide an extra level of safety in preventing choking, the ITI revised its MDA azithromycin-dosing recommendations by (1) increasing the upper age for POS administration from 5 to 7 y of age and the upper height limit to 120 cm; and (2) offering POS to anyone who has difficulty with swallowing tablets, regardless of age.

In Ethiopia, MDA is conducted by government staff and health extension workers (HEWs), assisted by volunteer community drug distributors (CDDs) and health professionals, who mobilize communities to participate in MDA and administer drugs to communities at risk. HEWs and CDDs are supervised by district health officers and health center staff. From November 2019 to January 2020, an observational assessment of MDA for trachoma was conducted in Ethiopia to (1) determine the frequency with which children aged 6 mo through 14 y receive the correct dose and form of azithromycin (i.e. tablets or POS) under the revised dosing guidelines; and (2) assess the incidence of, and risk factors for, choking and other adverse swallowing events (ASEs) during MDA.

Materials and Methods

The observational assessment was conducted during routine MDAs organized by health officials in three regions of Ethiopia: Amhara, Oromia and the Southern Nations, Nationalities and Peoples' Region (SNNPR). Within each region, one zone was chosen; within each zone, two districts were selected (known as *woredas* in Amharic), and within each woreda, MDA was observed in five neighborhoods (known as *kebeles* in Amharic), for a total of 30 kebeles. Sites were picked in consultation with regional and local health officials, based on several factors, including representativeness, security and accessibility. In each kebele, data were collected during 5 consecutive days: the duration of the regular MDA in each location. The protocol and sampling design are incorporated in the Supplementary Data.

Each of the three regions was assigned four trained data collectors (a total of 12), who observed MDA and recorded observations on child age, gender, height, azithromycin dose, child demeanor just prior to taking the drug (calm, combative, crying or fearful) and ASEs. ASEs included choking, coughing and gagging (which reflect difficulty in swallowing and may be related to risk of choking), as well as spitting, vomiting or holding the medication in their mouth (which may be associated with ingestion of subtherapeutic doses of medication). As children presented, HEWs checked the MDA household registry to verify the child's name and asked the child or their parent to verbally confirm the child's age (within earshot of the observer). All children aged 6 mo through 14 y were included in the assessment. Observers did not intervene with distribution or interact with staff or MDA participants. Data were collected on electronic tablets using the KoBoToolbox program (Harvard University, Cambridge, MA, USA). Observers were trained in 2-d sessions: 1 d of classroom instruction and 1 d of practice in an MDA setting. The ITI led separate trainings in each region, which focused on the design and conduct of the assessment, operating mobile collection devices and standardizing responses for different ASEs.

Data were analyzed using the SAS University Edition version 3.8 statistical software package (SAS, Cary, NC, USA). Frequency distributions and incidence of ASEs were compared using χ^2 tests and two-sided CIs were calculated using an α of 5%. Variables significantly associated with an ASE in bivariate analyses were entered into a multivariate logistic model with backwards elimination of non-significant variables to arrive at a parsimonious model. Two-sided CIs were also calculated for the multivariate logistic model using an α of 5%. A reference level of $p<0.05$ was used as a cutoff to determine significance. Generalized estimated equations were used to account for clustering by site. Results are reported as ORs with 95% CIs.

Results

A total of 6477 azithromycin administrations were observed, 3174 (49.0%) among girls. Participants included 303 (4.7%) children aged 6–11 mo (defined as children up to their first birthday), 3077 (47.5%) aged 1–6 y (defined as children up to their seventh birthday) and 3097 (47.8%) aged 7–14 y (defined as children up to their 15th birthday). A total of 1994 (30.8%) azithromycin administrations were observed in Amhara, 2546 (39.3%) in Oromia and 1937 (29.9%) in SNNPR.

Azithromycin dose and information

Based on the revised dosing guidelines, 3926 children qualified for POS because they were aged 6 mo to 6 y or were <120 cm in height. Of these, 3910 (99.6%) received POS; this figure was 100.0% among 303 participants aged 6–11 mo, 99.7% among 3077 aged 1–6 y and 98.7% among 546 children aged ≥7 y who were <120 cm in height. Of the 16 children who received tablets when they should have received POS, nine were aged <7 y and seven were aged ≥7 y but <120 cm in height. There was only one participant who was both aged <7 y and <120 cm tall who received tablets. Of 2538 participants aged ≥7 y and ≥120 cm, for whom azithromycin tablets are recommended, 309 (12.2%) were given POS instead. This aligns with dosing guidelines to offer POS to anyone who reports difficulty in swallowing tablets, regardless of age.

Overall, 6341 (97.9%) children received the exact recommended dose of azithromycin. An additional 102 (1.6%) received a dose that was within one category of the recommended dose on the height-based dosing pole. For POS, each dose category is equivalent to 2 ml for children up to 130 cm in height, and larger (3–6 ml) for children >130 cm in height. For tablets, one dose category is equivalent to one tablet (250 mg) (Figure 1). Thirteen (0.2%) participants were not measured using the dosing pole, so whether they received the recommended dose could not be determined (Figure 2). Of the remaining 21 children (<0.1%) who did not receive azithromycin within one recommended dose category, four received less than the recommended dose, eight received more and the correct dose could not be determined for

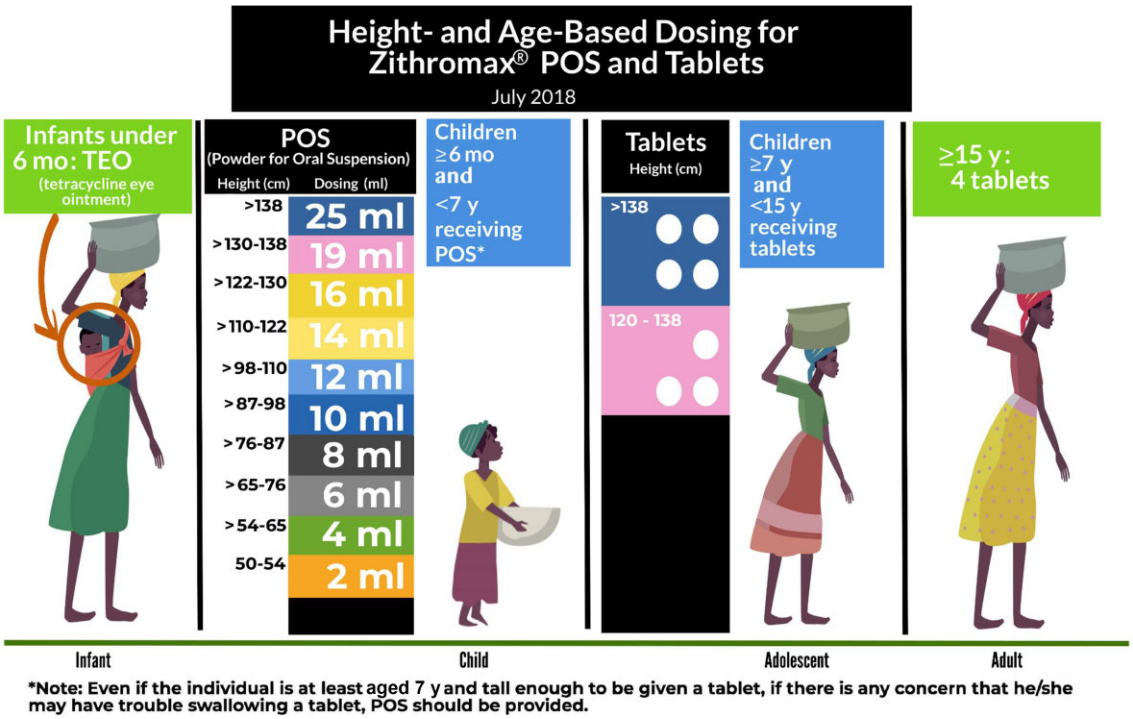

Figure 1. Height- and age-based dosing for Zithromax powder for oral suspension and tablets. Recommended dose of Zithromax by height and age for mass drug administrations to prevent blinding trachoma. Infants aged <6 mo receive tetracycline eye ointment (TEO) (not included in the assessment). Children aged 6 mo through 6 y receive powder for oral suspension (POS), regardless of height, while children aged 7–14 y receive tablets, if at least 120 cm in height. Children aged ≥15 y receive tablets regardless of height (also not included in the assessment). Figure provided by the International Trachoma Initiative.[14]

nine (those children were either measured using the POS side of the dosing pole but received tablets or vice versa). Fifteen participants (<0.1%) received two tablets when they should not have, as one- and two-tablet doses were removed from the revised guidelines and dosing poles in 2018. Six of these children were <120 cm in height and should have received POS, while the remaining nine were in the 120–138 cm height range and should have been offered three tablets. The proportion of children given the exact recommended dose differed by age: 289 (95.4%) for those aged 6–11 mo, 3024 (98.3%) for those aged 1–6 y and 3028 (97.8%) for those aged 7–14 y (X^2=11.7, p=0.0028).

Choking and other ASEs

One child (<0.1%) experienced choking, a boy aged 6–11 mo in Oromia. He resisted taking POS; the first attempt was unsuccessful and he experienced choking on the second. Choking was reported to be momentary and transient, and did not require medical attention.

A total of 132 (2.0%) children experienced ≥1 ASEs, including choking (1), holding medication in the mouth (1), gagging (8), vomiting (8), coughing (35) or spitting (103). Multiple ASEs were reported for 24 children. ASEs were more frequently reported in Amhara (3.7%) than in Oromia (1.1%) or SNNPR (1.6%). Risk of an ASE was highest in children aged 6–11 mo (10.9%) and lowest in those aged 7–14 y (0.2%) (Table 1). ASE risk was also elevated in children receiving POS (3.1%) compared with those receiving tablets (0.1%), and in children whose demeanor was combative, crying or fearful immediately before azithromycin administration (33.2%) compared with those who were calm (0.4%). Of 149 children who required 'coaxing' or 'time out' before receiving azithromycin, 56 (37.6%) experienced an ASE compared with 76 (1.2%) of the 6252 who took azithromycin without any problem. Lastly, the risk of having an ASE was highest in children who were administered medication by a caregiver (usually a family member, most often the mother) alone (11.1%) and was lowest among children who administered their own medication (0.5%). Reported incidence of ASEs by MDA site ranged from 0.0% to 13.3%, median 1.27% (IQR=0.00–2.72%). Amhara accounted for more than half the ASEs. Reported ASE incidence also varied by observer. Observers did not consistently report ASEs at the same frequency from one day (i.e. MDA site) to another (data not shown).

Variables significantly associated with ASEs in bivariate analysis were entered into a multiple logistic regression model, using GENMOD to account for clustering of ASEs by site. Factors significantly associated with ASEs include: age 6–11 mo; children with a combative, crying or fearful demeanor; and requiring 'coaxing' or 'time out' prior to drug administration (Table 2). After backwards stepwise elimination of variables that were not significantly associated with ASEs, all three previously mentioned variables remained, in addition to the ages of 1–6 y (Table 3).

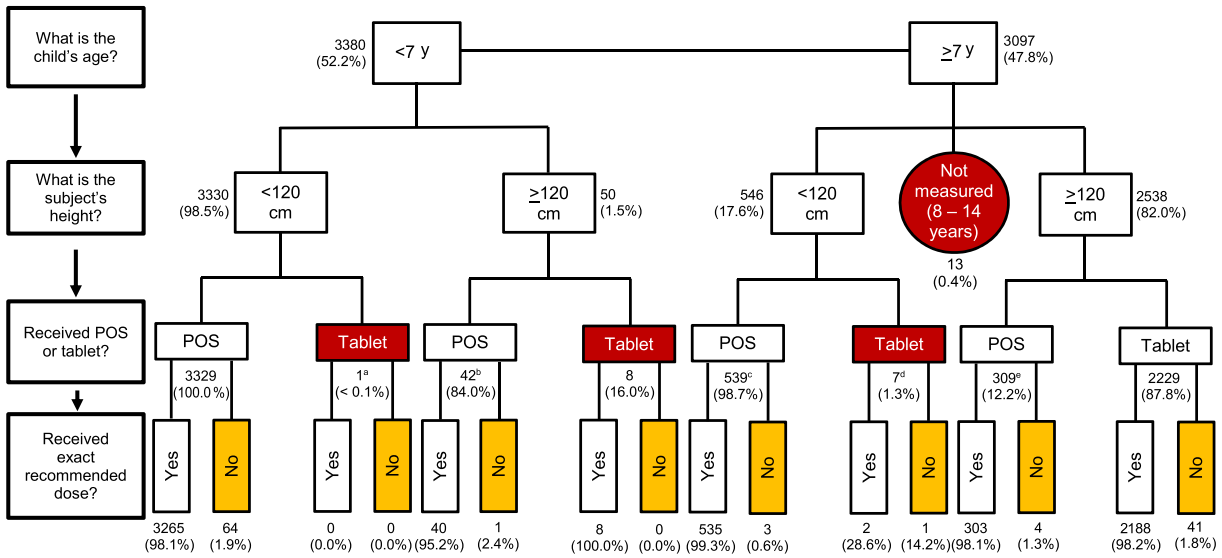

Figure 2. Distribution of participants by age, height, receipt of azithromycin tablets or powder for oral suspension, and receipt of exact recommended dose. The figure tracks the decision points in the revised azithromycin-dosing guidelines (Figure 1) based on age (<7 or ≥7 y), height (<120 or ≥120 cm), drug form (powder for oral suspension [POS] or tablets) and whether the exact recommended dose was received (yes or no). Areas of highest concern are shown in red and areas of some concern are shown in yellow. Nine children were measured by the wrong side of the pole and we were unable to determine if the recommended dose was received. [a]Unable to determine if the recommended dose was received for one child. [b]Unable to determine if the recommended dose was received for one child. [c]Unable to determine if the recommended dose was received for one child. [d]Unable to determine if the recommended dose was received for four children. [e]Unable to determine if the recommended dose was received for two children.

Discussion

Fatal choking during MDA rarely occurs, but it is both tragic and preventable. Available evidence suggests that an age-appropriate formulation for young children, such as POS, and not forcing children to take medicine during MDA, can significantly reduce the risk of fatal choking.[5–7] To minimize the choking risk during MDA for trachoma, the ITI originally provided POS to children aged <5 y or <74 cm in height. Out of an abundance of caution, in 2018, the ITI expanded the recommended age group to include 5- and 6-y-olds and those who are <120 cm in height. Treatment guidelines were adjusted accordingly and the one- and two-tablet doses, originally for children of 88–119 cm in height, were removed from the height-based dosing pole completely to ensure that children in that height bracket were offered oral suspension.[9] These changes necessitated revised training of CDDs and new, or recalibrated, dosing poles in the 40 countries that received azithromycin from the ITI at the time.

This large observational assessment in three regions of Ethiopia indicates that adherence to the new azithromycin dosing guidelines is very high. Nearly all the children for whom POS is recommended received it, while 97.8% of them also received the correct dose of azithromycin. With one exception, the relatively few (16) children who received tablets instead of the recommended POS met one of the criteria (age <7 y or height <120 cm) for POS, but not both of them. This suggests that while both height and age can be used successfully during MDA to administer the recommended form and dose of azithromycin, particular attention may be needed when children meet one, but not both of these criteria.

Of the 2538 children who were eligible to take tablets, 309 (12.2%) were given POS instead. The 'elective' provision for receiving POS in the revised Zithromax Management Guide offers an extra measure of safety for persons who may have difficulty swallowing.[9] It is not clear whether these children requested POS because of personal preference, anticipated difficulty in swallowing tablets or an abundance of caution by the distributor.

Fifteen (0.2%) participants received two tablets even though the two-tablet dosing option was removed from the guidelines and dosing poles in 2018, to be replaced with an equivalent dose of POS. Only two (13.3%) of these 15 were given the exact recommended dose of azithromycin. These events were clustered at three sites involving four HEWs, and occurred sporadically throughout the day. It seems likely that experienced distributors in these cases were following the outdated version of the dosing guidelines, which recommended two tablets for children of height 88–119 cm.[10] Refresher training of HEWs should ensure that they are aware of and can follow new recommendations.

It may be beneficial to reinforce, with a written message on the tablet side of the dosing pole, that children <120 cm in height should be measured using the other side of the pole. The need to assess both height and age should be reinforced. Eight of the nine (88.9%) 1–6-y-old children who were given tablets were 120–138 cm in height.

Only one child experienced choking: an infant boy whose demeanor was not calm before being given POS. The incident represents 0.02% of all children observed and 0.1% of children

Table 1. Factors associated with adverse swallowing events, mass drug administration for trachoma, Ethiopia

		Adverse swallowing event experienced				
Risk factor	Level	Yes (% of total)	No (% of total)	Total	Incidence (per 1000) (95% CI)	Risk rate ratio
Region	Amhara	73 (3.7)	1921 (96.3)	1994	36.6 (29.2 to 45.8)	3.2
	SNNPR	30 (1.6)	1907 (98.5)	1937	15.5 (10.8 to 22.1)	1.4
	Oromia	29 (1.1)	2517 (98.9)	2546	11.4 (7.9 to 16.4)	-
Age	6–11 mo	33 (10.9)	270 (89.1)	303	108.9 (78.3 to 149.3)	68.1
	1–6 y	94 (3.1)	2983 (97.0)	3077	30.5 (25.0 to 37.3)	19.1
	7–14 y	5 (0.2)	3092 (99.8)	3097	1.6 (0.6 to 3.9)	-
Drug form	Powder for oral suspension	129 (3.1)	4090 (96.9)	4219	30.6 (25.8 to 36.2)	23.5
	Tablet	3 (0.1)	2255 (99.9)	2258	1.3 (0.3 to 4.1)	-
Demeanor	Combative, crying or fearful	109 (33.2)	219 (66.8)	328	332.3 (283.5 to 385.0)	89.8
	Calm, content	23 (0.4)	6126 (99.6)	6149	3.7 (2.5 to 5.6)	-
Ease drug taken	Required 'coaxing' or 'timeout'	56 (37.6)	93 (62.4)	149	375.8 (282.2 to 429.2)	31.3
	No problem	76 (1.2)	6252 (98.8)	6328	12.0 (9.6 to 15.0)	-
Who administered drug	Caregiver alone	60 (11.1)	482 (88.9)	542	110.7 (86.8 to 140.0)	22.1
	Caregiver + another distributor	13 (8.7)	137 (91.3)	150	86.7 (50.2 to 143.8)	17.3
	Child alone	15 (0.5)	2981 (99.5)	2996	5.0 (3.0 to 8.3)	0.4
	HEW + another distributor	22 (2.5)	863 (97.5)	885	24.9 (16.3 to 37.6)	5.0
	Other combination	1 (1.2)	84 (98.8)	85	11.8 (0.0 to 70.0)	2.4
	HEW alone	21 (1.2)	1 798 (98.9)	1819	11.5 (7.5 to 17.7)	-

Abbreviations: HEW, health extension worker; SNNPR, Southern Nations, Nationalities and People's Region.

Table 2. Risk factors for adverse swallowing events, logistic regression model adjusting for clustering by site

Risk factor	Level	OR (95% CI)	p
Age	6–11 mo	7.3 (2.4 to 22.1)	0.0005
	1–6 y	2.9 (0.8 to 9.7)	0.0913
	7–14 y	Reference	-
Drug form	Powder for oral suspension	1.5 (0.3 to 8.4)	0.6210
	Tablets	Reference	-
Demeanor	Combative, crying, or fearful	52.2 (22.9 to 119.1)	<0.0001
	Calm, content	Reference	-
Ease drug taken	Required 'coaxing' or 'time out'	2.8 (1.3 to 6.3)	0.0101
	No problem	Reference	-
Who administered drug	Caregiver alone	1.1 (0.3 to 3.2)	0.9317
	Caregiver + another distributor	0.7 (0.2 to 2.8)	0.5600
	Child alone	0.7 (0.2 to 2.3)	0.5809
	HEW + another distributor	0.6 (0.2 to 2.0)	0.4236
	Other combination	1.1 (0.2 to 5.1)	0.8922
	HEW alone	Reference	-

Abbreviation: HEW, health extension worker.

aged <3 y, who are usually considered at a higher risk of choking during MDA.[5,6] By contrast, about 1% of 1- to 3-y-olds are reported to experience choking on deworming tablets.[6,7] While a side-by-side comparison on choking risk during MDA has not been performed for deworming and trachoma, these findings suggest that POS reduces the risk of choking (and, by extension, fatal choking) in young children. Criteria for assessing choking and other ASEs in this observational assessment were identical to those used in a recent assessment for deworming for soil-transmitted helminths, which reported a 1% incidence of choking and a 14.8% incidence of ASEs.[7] The overall ASEs reported here for trachoma were infrequent (2.0%) and not serious.

Table 3. Risk factors for adverse swallowing events, parsimonious logistic regression model adjusting for clustering by site

Risk	Level	OR (95% CI)	p
Age	6–11 mo	10.5 (3.8 to 29.0)	<0.0001
	1–6 y	4.0 (1.6 to 10.3)	0.0040
	7–14 y	Reference	-
Demeanor	Combative, crying or fearful	55.1 (28.7 to 105.9)	<0.0001
	Calm, content	Reference	-
Ease drug taken	Required 'coaxing' or 'time out'	2.6 (1.2 to 5.5)	0.0144
	No problem	Reference	-

However, they are of potential interest because gagging and coughing may be proxies for choking risk, while spitting, vomiting and holding the medication in the mouth may indicate that the child did not receive an adequate dose of azithromycin.

The variation in reported ASEs by observers could reflect individual differences in assessment, but they likely also reflect clustering of ASEs by site, because observers reporting frequent ASEs did not consistently do so across sites (data not shown). Actual differences in ASE frequency by site could reflect overzealous 'encouragement' to take the medicine by CDDs, variation in levels of training or other factors related to conditions during MDA, such as orderliness of the site.

Several variables were significantly associated with ASEs in bivariate analyses, including receiving POS rather than tablets. This association was driven by the fact that POS was given primarily to young children, who developmentally have more difficulty swallowing. Only three variables remained significant in logistic regression models. One of these, young age, is well known as a risk factor for choking.[5,6] The other two risk factors are related to how the drug is administered, particularly to children who are not calm or require 'coaxing' or 'time out' prior to taking drug.

These findings expand on those by Kernell et al., who identified non-calm child demeanor just before drug administration to be the most significant risk factor for choking during MDA for STH.[7] Our findings argue against 'forcing' children to participate in MDA when they are struggling to avoid taking medicine. Both the ITI's Zithromax Management Guide and WHO guidance for STH MDAs strongly recommend against this practice.[6,9] However, during MDA, factors beyond the training and manuals may come into play: distributors may feel under pressure to attain high drug coverage, while parents may feel peer pressure from neighbors, or push their child to be treated out of a concern for the child's health and a desire to cooperate with MDA. MDA safety will require that CDDs have the skills to maintain order and minimize error, recognize when children are resisting or struggling to take the drugs, and convey to parents that treatment of such children will be delayed—until the subsequent MDA, if needed.

As noted, the incidence of choking in our assessment of trachoma MDA was markedly lower than that reported by Kernell et al. for STH, in which chewable tablets were administered. Age-appropriate formulations have been developed for other drugs donated for NTD MDAs, notably mebendazole and, very recently, praziquantel.[7,11–13] Consistent with previous assessments of MDA for STH, we observed that forcing children to take medication, especially after refusing on a first attempt, was a significant risk factor for ASEs.[6,7]

However, this assessment also highlights that coercing fussy children to take medication is a risk factor for ASEs during MDAs other than deworming campaigns. These data support the revisions made in the Zithromax Management Guide about refraining from forcing children to take azithromycin.[7] The higher risk of ASEs among children who required 'coaxing' or 'time out' prior to drug administration suggests that efforts to calm such children are not always effective and require further attention.

The potential limitations of this assessment include the possibility of imperfect standardization of criteria for ASEs across 12 observers, even though this was minimized through training and ongoing supervision during the assessment. In addition, although sites were selected to be representative, choices were necessitated by the timing of MDAs planned by regional health bureaus; they were not randomly selected. Therefore, our findings on MDA coverage and risk factors for ASEs may not be representative of other countries, or even other regions of Ethiopia. In this case, our sampling may not be generalizable to all instances of MDA coverage. The assessment was limited to children. Difficulty swallowing also tends to increase in older people and we were unable to evaluate the need for POS or frequency of ASEs in older adults. Additional work is needed to assess MDA safety in older people and for others who may have difficulty swallowing. Finally, because the observational assessment did not include interviews with caregivers, we were unable to determine reasons for some observed patterns, such as why a proportion of children who were eligible for tablets were given POS.

Conclusions

Fatal choking is a rare, but tragic, occurrence in young children during MDA. To minimize this risk, the ITI offers age-appropriate POS to young children during MDA for trachoma and recently changed its dosing guidelines to increase the age for which POS is recommended up to 7 y. Our results indicate a high level of adherence to these recommended changes and an extraordinarily low incidence of choking and other ASEs. Continued vigilance and additional work are needed to equip CDDs with the skills to further reduce the risk of choking and to better understand how to calm children who appear resistant or fearful during MDA so that drugs can be administered even more safely.

Supplementary data

Supplementary data are available at *Transactions* online.

Author's contributions: DGA, PJH, PME and TG designed the assessment. FK, FS, GK, MA, MJS, MS, TG and TT implemented the assessment. AMC, DGA, GL, PJH, PME, SKW, TG and TT analyzed and interpreted the data. AMC, DGA, GL and SKW provided major contributions to writing.

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Ethical approval: This project was approved by the Ethiopian Federal Ministry of Health and Regional Health Bureaus of the Amhara, Oromia and SNNPR as program evaluation.

Data availability: The data will be shared on request to the corresponding author.

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