Pediatric Health, Medicine and Therapeutics

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Antimicrobial Use and Management of Childhood Diarrhea at Community Drug Retail Outlets in Eastern Ethiopia: A Matched Questionnaire-Based and Simulated Patient-Case Study

Dumessa Edessa[1], Mekonnen Sisay[2], Bisrat Hagos[3], Firehiwot Amare[4]

[1]Department of Clinical Pharmacy, School of Pharmacy, College of Health and Medical Sciences, Haramaya University, Harar, Ethiopia; [2]Department of Pharmacology and Toxicology, School of Pharmacy, College of Health and Medical Sciences, Haramaya University, Harar, Ethiopia; [3]Department of Social Pharmacy, School of Pharmacy, College of Health and Medical Sciences, Haramaya University, Harar, Ethiopia; [4]Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

Correspondence: Mekonnen Sisay, Department of Pharmacology and Toxicology, School of Pharmacy, College of Health and Medical Sciences, Haramaya University, P.O. Box, 235, Harar, Ethiopia, Email mekonnensisay27@yahoo.com

Introduction: Antimicrobial agents have saved millions of lives worldwide. However, inappropriate use has become a global concern leading to the emergence and spread of antimicrobial resistance (AMR). In this regard, the dispensing practices of pharmacy professionals in the community drug retail outlets (CDROs) plays a central role. Therefore, this study was aimed to assess the knowledge and dispensing practices of pharmacy professionals in the management of childhood diarrhea in CDROs of Eastern Ethiopia.

Methods: A community based cross-sectional study was conducted in 100 randomly selected CDROs in Eastern Ethiopia from 1 August to 30 September 2020. Data were collected with a structured questionnaire matched with a simulated patient case. Descriptive statistics were employed to summarize variables. Cohen's Kappa was analyzed to measure the degree of agreement between questionnaire-based and simulated patient-based methods. Binary logistic regression analysis was conducted to determine factors associated with inappropriate dispensing practice.

Results: Majority of the participants were aged 25–34 years (median: 29 years). High proportion of them were male (65%) and had work experiences of two or more years. Majority (61%) of the professionals were knowledgeable about AMR. Out of 2886 scores, 745 scores were agreed on Cohen's Kappa interrater agreement scale with the overall percent agreement between the two methods being 26.0%. Besides, about 67% of dispensing practices to the simulated patient case was found inappropriate. On the multivariate analysis, insufficient knowledge of retailers on AMR was significantly associated with the inappropriate dispensing of antimicrobial agents.

Conclusion: A considerable proportion of retailers had insufficient knowledge regarding the emergence and spread of AMR. Only a quarter of their questionnaire-based knowledge response agreed with simulated-patient-based actual practice, indicating weak agreement between the two methods and high level of inappropriate practice. Besides, insufficient knowledge of retailers was significantly associated with their inappropriate dispensing of antimicrobials.

Keywords: diarrhea, pediatrics, antimicrobial use, CDROs, Ethiopia

Background

One of the major breakthroughs of 20th century was the discovery of antibiotics which are the magic bullets for several infections.[1–3] These agents have saved millions of lives worldwide and transformed the health of the world one step forward.[4] However, emerging and gradually evolving nature of antimicrobial resistance (AMR) has threatened the effectiveness of these agents.[1–3] The AMR is recognized as a serious public health challenge and a global bottleneck in this era.[1,5] As a result, the World Health Organization (WHO) recommended member states to prepare national action plans for containment of AMR and preservation of antimicrobials.[6] On the contrary, there is a dearth of antimicrobial

Received: 6 November 2021
Accepted: 7 March 2022
Published: 18 March 2022

agents in the development pipeline and is alarming the world about the post-antibiotic era which may be realized in the near future unless appropriate measures are taken in advance.[7–9]

Major reasons for the increase of AMR are multi-factorial and include unregulated drug availability, absence of antimicrobial stewardship programs, inadequate surveillance, and widespread attitude to antimicrobial misuse, and self-medication.[2,10–12] Patient-related factors are also major drivers of misuse for antimicrobials.[13,14] The dispensing practices of community pharmacy professionals should play a central role for ensuring the safe use of antimicrobials in the community.[15–17]

The use of antimicrobials is the a major driving factor for AMR.[18] Oral antimicrobials are inappropriately dispensed without prescription for diseases such as malaria, diarrhea, common cold, pneumonia, and mild childhood infections.[10,19] It is an irrational practice which contributes to the emergence and spread of AMR. Globally, it has been estimated that more than 50% of the antimicrobials are sold over the counter despite the fact that such dispensing practice is illegal in several countries.[20–24] Healthcare professionals have a vital role in preserving antimicrobial agents and containing AMR. In this regard, the spread of AMR will be augmented if they lack up-to-date information, cannot identify the causative agent, or dispense antimicrobials without prescription.[25] WHO also estimated that two-thirds of all antimicrobials are sold without prescription through unregulated private drug retail outlets.[26]

Therefore, assessing dispensing practice of professionals in community drug retail outlets (CDROs) of Eastern Ethiopia was found vital to devise appropriate interventional strategies. In addition, it is also meant to generate pertinent baseline data on the relationship between knowledge and practice as well as the agreement between two measurements for the same case. Analyzing the knowledge and actual practice of dispensing antimicrobial agents in CDROs was found mandatory to take evidence-based measures. Therefore, this study was aimed to assess the dispensing practice of professionals in CDROs supported with their management of childhood acute watery diarrhea in Eastern Ethiopia.

Methods

Study Settings and Design

The study was conducted in CDROs of selected towns in Eastern Ethiopia. The CDROs refer to premises registered and licensed by an appropriate government agency for the provision of pharmaceutical services to the public. The study was conducted from 1 August to 30 September 2020. A community based cross-sectional study was conducted with a mixed data collection tools (structured questionnaire matched with simulated patient method). In this case, acute watery diarrhea was presented to CDROs in both tools. A simulated patient was trained to visit CDROs to enact a scenario that tests a specific behavior of the Pharmacy professional. The simulated patient went to CDROs and presented his symptoms to the pharmacy professional. He told to the professionals that he has suffered from watery diarrhea since yesterday morning and defecated six times a day without associated mucus and symptom of fever.

Study Participants

Pharmacy professionals (pharmacists, pharmacy technicians or druggists) who were working in the CDROs of selected towns of eastern Ethiopia during the study period were our study population. For questionnaire-based study, pharmacy professionals who contacted the simulated-patient were intentionally included for the study. This was made to assess the knowledge of professional about antimicrobial use and AMR as well as determine the degree of agreement between the two measurements for the specified therapeutic area. Community pharmacy professionals who did not serve or contact the simulated-patient (the first study) in selected CDROs were excluded from questionnaire-based study.

Sample Size Determination and Sampling Procedure

A total of 100 CDROs were randomly selected from CDROs of selected towns in eastern Ethiopia. In which, 90 CDROs were randomly selected from Dire Dawa city administration, Harar and Jigjiga towns (30 CDROs from each) and the remaining 10 CDROs were from the towns of East Hararghe. Then, 100 participants (one professional in each CDROs) were selected for one-time mixed method (matched questionnaire-based and simulated patient methods) study, totaled to 200 responses, for ease of assessing the practitioner response and their actual performance in naturalistic settings.

Data Quality Control

A combination of these methods (simulated patient and questionnaire) was pretested on 5% of the sample size and modifications were made accordingly to enhance the feasibility and consistency. In addition, the quality of the study was maintained by explaining the purpose of the questionnaire to the respondents at the beginning of interview. To avoid recall bias, the simulated-patient himself filled the checklist based on the professional recommendations regarding the case management upon exit from each CDRO.

Data Collection Tools and Methods

A structured and pretested questionnaire, prepared in English language, was administered through face-to-face interview to community pharmacy professionals who were working in CDROs. To minimize bias, a simulated-patient visit was initially implemented in each CDRO to collect data about the same case. The simulated patient case employed for this study was adapted from standard treatment guideline of childhood acute watery diarrhea for general hospitals in Ethiopia[27] and Infectious Diseases Society of America (IDSA) clinical practice guideline.[28]

In this regard, the simulated patient method has become popular in health services research to observe the behavior of healthcare practitioners in a natural setting. This method has primarily been used to assess the actual performance of practitioners in the primary care setting. However, the method does not directly capture knowledge. As we also aimed to examine the knowledge of practitioners in a specific therapeutic area, the simulated patient method alone may not be suitable as it captures the actual behavior of practitioners rather than their knowledge (of course, knowledge may inform behavior). A combination of methods (mixed questionnaire-based and case-based tools) was found to be appropriate.[29]

The data collection tool for the simulated-patient was translated to Amharic, Afan Oromo and Somali languages to consider simulated-patient's primary language preference in each setting. A pharmacy professional working in each CDRO and who served the simulated patient was interviewed. To match the two methods on the same professional, the data collector with questionnaire immediately entered into the CDRO following the exit of the simulated patient. Recommendations of a professional to a simulated patient was discarded when he/she declined to participate in the interview. Details of patient-related information, all medicines dispensed or recommended, queries about possible drug interactions and allergies, and non-pharmacological advices given (including referral) were recorded by the simulated patient himself after he left each CDRO.

Study Variables

Knowledge of the pharmacy professional about antimicrobial use and AMR as well as dispensing practice of the pharmacy professionals in the management of childhood diarrhea were assessed as key outcome variables. In this study, age, sex, marital status, level of education, years of experience, income level of professional, ownership of premise, clinical conditions and drug related information were considered as potential explanatory variables.

Definition of Operational Terms

Data validity (accuracy) of the questionnaire was assessed against the standard simulated patient method on the same clinical condition as follows:

- Sensitivity: proportion of participants with the condition (appropriate practice) and who are correctly identified by the measurement = *true positive*/(*true positive* + *false negative*).
- Specificity: proportion of participants without the condition (no or inappropriate practice) and who are correctly identified by the measurement = *true negative*/(*false positive* + *true negative*).

Cohen's kappa: the degree of agreement of the results of two data collection methods on the same case can be measured by Cohen's kappa (κ), which is given by:

$$K = \frac{\text{Observed agreement} - \text{Chance agreement}}{\text{Maximum agreement} - \text{Chance agreement}} = \frac{p0 - pE}{1 - pE}$$

Perfect agreement is evident when Cohen's kappa equals 1; a value of Cohen's kappa equal to zero suggests that the agreement is no better than that which would be obtained by chance alone. It considers agreement between two measurements on the same samples (repeatability).[30]

Appropriateness: Appropriateness of the antimicrobial dispensing practice for the case was determined based on the national and international guidelines:

- In most people with acute watery diarrhea and without recent international travel, empiric antimicrobial therapy is not recommended. An exception may be made in people who are immunocompromised or young infants who are ill appearing. Empiric treatment should be avoided in people with persistent watery diarrhea lasting 14 days or more. Asymptomatic contacts of people with acute or persistent watery diarrhea should not be offered empiric or preventive therapy, but should be advised to follow appropriate infection prevention and control measures.[27,28]

Data Processing and Analysis

The data from questionnaire and the simulated patient methods were coded and entered into Epi-data version 3.0 and exported to SPSS, version 21.0 for analysis. Descriptive statistics was employed to summarize sociodemographic characteristics and knowledge of professionals about antimicrobial use and AMR related issues. Sensitivity and specificity of questionnaire was assessed against simulated patient method. Cohen's Kappa was also analyzed to measure the agreement between the questionnaire-based and simulated patient-based methods. Note: Cohen's Kappa value indicates level of agreement. So its values < 0 as no agreement; 0–0.20 as none to slight agreement; 0.21–0.39 as fair agreement; 0.41–0.60 as moderate agreement; 0.61–0.80 as substantial agreement; above 0.80 as excellent agreement.[31]

Binary logistic regression analysis was conducted to determine the presence of association between inappropriate antimicrobial dispensing practice for management of diarrhea and explanatory variables. The significance of association was measured using odds ratio with 95% confidence interval and P-value < 0.05. So, explanatory variables which showed potential for association in bivariable logistic regression analyses at $P \leq 0.25$ were considered to enter into multivariable logistic regression analysis to adjust for confounders. The results were presented using tables.

Results

Sociodemographic Characteristics of Study Participants

Out of 100 CDROs included in the study, majority of the practicing professionals were aged 25–34 years with the median age of 29 years. Again, the average monthly income of the professionals was 6652 Ethiopian birr (ETB). Majority of the professionals were male (65%), were employed by the owner (61%), were pharmacy technicians (56%) and had work experiences of 2 or more years (Table 1).

Knowledge on Antimicrobial Use and AMR

Accordingly, nearly all participants (92%) dispensed antimicrobial agents in response to prescription, 90% of them did it a day before the day of data collection. Ninety nine percent of them advised clients on how to use and handle the antimicrobial agents, more than three-fifths (63%) of them were advising clients not to prematurely discontinue the prescribed antimicrobial agents. Majority of the professionals agreed on how microorganisms develop resistance to antimicrobial agents (81%), increasing number of infections that became resistant to treatment by antimicrobials (96%), challenges of treating resistant bacteria (92%), and impacts of AMR on all community members at large (83%). However, nearly one-third of the professionals had wrong belief and advised clients to use antimicrobials given to family or friends (34%) or those agents that benefited them in the past (39%) and about a quarter of them (27%) thought AMR as not being a problem in the setting. Taking the mean score of correct responses (mean = 5.85) as cut off value for

Table 1 Sociodemographic Characteristics of the Pharmacy Professionals Working in Selected Community Drug Retail Outlets (CDROs), Eastern Ethiopia, 2020

Characteristics	Category	Number/Percent
Age of professionals (years)	≤ 24 25–34 35 −44 > 45 No response	17 45 25 5 8
Monthly income (Ethiopian birr)	< 5000 5000–10,000 >10,000 No response	27 26 5 42
Work experience (years)	Less than 2 2–5 Greater than 5 No response	10 36 32 22
Sex	Male Female	65 35
Qualification of dispensing professional	Pharmacist Pharmacy technician	44 56
Responsibility of the professional in the CDRO	Employee Owner No response	61 36 3

AMR questions, 61% of the professionals who scored above the mean were considered knowledgeable about AMR (Table 2).

Interviewer and Retailer Interaction About Management of Diarrhea

Majority of the retailers responded that they should inquire age of client (94%), onset and duration of diarrhea (94%), presence of vomiting (92%), presence of fever (91%), frequency of diarrhea (90%), presence of blood or mucus (90%), and appearance of diarrhea (86%). Most of them also agreed on the requirement of asking clients about presence of dehydration (73%), medication history (66%) and nutrition condition (61%). Overall, about three-fifths of the retailers (61%) responded sufficiently about the requirements of demographics and patient history in relation to diarrhea symptoms (Table 3).

Simulated-Patient and Retailer Interaction

Majority of the retailers requested the simulated-patient's age (85%), appearance of diarrhea (80%), presence of blood or mucus (76%), and onset and duration of diarrhea (62%). About half of them probed to identify frequency of diarrhea (54%) and presence of fever (51%). However, low proportion of the retailers assessed vomiting symptoms (40%), medication history (11%), dehydration symptom (7%) and nutrition condition which would have been equally important for effective management of diarrhea.

Despite the absence of scientific evidence supporting infectious etiology, about two-thirds of the retailers dispensed antimicrobial agents (67%). Majority of the drug regimen components were addressed in less than 50% settings (Table 4).

Table 2 Knowledge of the Pharmacy Professionals About Antimicrobial Dispensing and AMR in Selected CDROs, Eastern Ethiopia, 2020

Knowledge Related Variables	Category	Number/Percent
Recent time when the professional did antimicrobial agent dispensing	Yesterday In the last week More than a year ago Cannot remember No response	90 7 1 1 1
Did the professional dispense antimicrobial agent in response to prescription?	Yes No Cannot remember No response	92 5 1 2
Did the professional advice clients on how to use/handle antimicrobial agents?	Yes No response	99 1
Did the professional advice clients regarding time When to stop taking antimicrobial agents?	When they feel better When they have taken all of the antimicrobials as directed When they become allergic Do not know No response	33 63 1 2 1
Did the professional advice clients to use antimicrobial agent given to friend or family?	Yes No No response	34 65 1
Did the professional advice clients to take the same antimicrobial agents to that helped them in the past?	Yes No No response	39 60 1
Did the professional thinks that AMR occurs when microorganisms become resistant to antimicrobial agents?	Yes No No response	81 14 5
Did the professional thinks that many infections are becoming increasingly resistant to treatment by antimicrobials?	Yes No	96 4
Did the professional thinks that if bacteria are resistant, it can be difficult or impossible to treat the infection they cause?	Yes No No response	92 3
Did the professional thinks that AMR could affect him/her or his/her family?	Yes No	83 17
Did the professional thinks AMR as not an issue here, but in other countries?	Yes No No response	27 67 6
Did the professional thinks AMR as a sole problem of people who take the antimicrobial agents regularly?	Yes No	44 56
Did the professional thinks that resistant bacteria can spread from person to person?	Yes No No response	81 16 3

(*Continued*)

Table 2 (Continued).

Knowledge Related Variables	Category	Number/Percent
Did the professional thinks that AMR makes medical procedures more dangerous?	Yes No No response	81 14 5
Knowledge status on AMR*	Not knowledgeable Knowledgeable	39 61

Note: Asterisk (*), indicates that the professionals were considered knowledgeable if they correctly answered above the mean value of correct responses (mean=5.85) from eight AMR questions.

Agreement Between Questionnaire-Based and Simulated-Patient Case Studies

Generally, the average sensitivity and specificity of the questionnaire-based study against the standard (simulated-patient study) for management of childhood acute watery diarrhea was found to be 64.90% and 36.24%, respectively. The kappa values indicated that the agreement between responses with two methods was from none to slight level in almost all essential components of the management of diarrhea. There was also no agreement for many variables whereas a moderate agreement was observed with regard to recommendation of professionals for other specific agents. Generally, from a total of 2886 scores, only 745 scores were reliable (agreed between raters). The overall percent agreement between the two data collection methods to the same case was 26%, indicating weak agreement between the two measurements and low specificity of questionnaire-based study. About 67% of practices in response to the childhood diarrhea symptom presented to pharmacy professionals was found inappropriate (Table 5).

Bivariable logistic regression analysis revealed that only retailers' qualification, favoring sharing of antibiotics, thinking AMR as a risk to users only, knowledge and satisfactory interaction with clients in responding to symptoms were associated with inappropriate dispensing of antimicrobial agents. However, after adjusting for covariates, only retailers with insufficient knowledge on AMR were significantly associated with the inappropriate dispensing of antimicrobial agents for the simulated patient (AOR, 2.9; 95% CI: 1.23–6.89) (Table 6).

Discussion

About 61% of community drug retailers had sufficient knowledge on antimicrobial use and AMR. Yet, a considerable number of them had insufficient knowledge about AMR. Indeed, knowledge and formulary management are key aspects to effective antimicrobial stewardships.[32,33] To have sufficient knowledge about antimicrobial use and emergence and spread of resistance, continuous professional development of retailers is mandatory.[34] However, majority of community retailers reported limited training opportunities for their continuous professional development.[32] In line with this gap, dispensing antibiotics without prescription is becoming an increasing practice.[35] In a study conducted in China, the community pharmacy professionals' knowledge about antimicrobials was good, but their practices regarding antimicrobial stewardship were poor. Hence, tailored training shall be provided to the community pharmacy staff on antimicrobial use, and the need and implementation of antimicrobial stewardship programs.[36]

Nevertheless, this indiscriminate use of antibiotics has contributed to the development of resistance to these essential medicines.[37] Some of the key justifications related to irrational antibiotic dispensing practice could be linked to self-medication, lack of regulations and supervision, and readily available antibiotics.[37] Regulations on dispensing antibiotics without prescription should be enforced. Policy makers need to implement antimicrobial stewardship and encourage the use of public educational interventions in community pharmacy.[38] Several community retailers agree that undertaking patient examinations and questioning the rationale for antibiotic prescriptions would allow them to contribute to antimicrobial stewardship activities.[39] Moreover, key other gap is related with a difference in perception and response of retailers on how AMR occurs.[40]

Practice response of retailers in 40% case scenarios of uncomplicated acute childhood diarrhea presented by a trained simulated-patient was accompanied by recommendation of oral rehydration solution (ORS). On top of this, about two-

Table 3 Interviewer and Retailer Interactions Towards the Requirements in the Management of Childhood Diarrhea (Questionnaire Based-Study), Among CDROs, Eastern Ethiopia, 2020

Variable		Response of Retailers	
		Yes (%)	No (%)
Demographic	Age	94	6
	Weight	57	43
History of diarrhea symptom	Onset and duration of diarrhea	94	6
	Frequency of diarrhea	90	10
	Medication history	66	34
	Nutrition condition	61	39
	Presence of blood or mucus in the diarrhea	90	10
	Appearance of diarrhea	86	14
	Presence of vomiting	92	8
	Presence of fever	91	9
	Dehydration symptom	73	27
	Any other related symptoms	14	86
Overall	Response for all variables ≥ their mean value	61	39
Medication recommended	Oral rehydration salt with zinc	54	46
	Oral rehydration salt	67	33
	Antibiotics/antibacterial	69	31
	Antidiarrheal agents	11	89
	Antispasmodics	10	90
Drug-related information provided	Name of medication	75	25
	Dose	84	16
	Frequency	84	16
	Duration	81	19
	Route of administration	78	22
	Common side effects	66	34
	Major interactions	57	43
	Storage condition	74	26
	Procedure on how to prepare ORS	83	17
Dietary recommendation	Increase intake	66	34
Fluid recommendation	Increase intake	83	17

thirds (67%) of the retailers recommended antibiotic medicines to patient cases without any evidence of bacterial ethology nor did clinical and laboratory evaluation. In knowledge response of retailers to the hypothetical case presented, however, ORS and antimicrobial medicines were recommended for 67% and 69%, respectively. For the case, there was no symptomatic hint to suspect infection. Some illogical reasons linked with such inappropriate practice could be patient

Table 4 Simulated-Patient and Retailer Interaction About the Management of Childhood Diarrhea, Eastern Ethiopia, 2020

Variable		Practice Response of Retailers	
		Yes (%)	No (%)
Demographic data inquiry	Age	85	15
	Weight	17	83
History of diarrhea symptom	Onset & duration of diarrhea	62	38
	Frequency of diarrhea	54	46
	Medication history	11	89
	Nutrition condition	2	98
	Presence of blood or mucus in the diarrhea	76	24
	Appearance of diarrhea	80	20
	Presence of vomiting	40	60
	Presence of fever	51	49
	Dehydration symptom	7	93
	Any other related symptoms	4	96
Overall response	Response for all variables ≥ mean value	44	56
Medication recommended	Oral rehydration salt with zinc	8	92
	Oral rehydration salt	40	60
	Antibiotics/antibacterial	67	33
	Antidiarrheal agents	2	98
	Antispasmodics	0	100
Drug-related information provided	Name of medication	41	59
	Dose	37	63
	Frequency	59	41
	Duration	36	64
	Route of administration	57	43
	Common side effects	2	98
	Major interactions	4	96
	Storage condition	12	88
	Procedure on how to prepare ORS	36	64
Dietary recommendation	Increase intake	2	98
Fluid recommendation	Increase intake	11	89
Practice	Inappropriate antibiotic dispensing	67	33

pressure, inclination to business, and lack of tight supervision.[33] Always, retailers felt pressured to respond to clients' demands.[41] Besides, antibiotic treatment was not significantly associated with better treatment outcomes for such diarrheal cases.[42] Despite a similar proportion of retailers who acknowledge AMR and appropriate antibiotic use in

Table 5 Agreement Between Questionnaire-Based and Simulated-Patient Case Studies for Dispensing Practice of Pharmacy Professionals in Response to Childhood Diarrhea Symptom, Eastern Ethiopia, 2020

Variables and Categories		Simulated-Patient Case Study (Standard)			Data Accuracy for Questionnaire		Kappa Value	P-value
Questionnaire-Based Study		**Yes**	**No**	**Total**	**Sensitivity (%)**	**Specificity (%)**		
Professional inquired client's age	Yes	81	13	94	96.43	13.33	0.13	0.112
	No	3	2	5				
	Total	84	15	99				
Professional inquired client's weight	Yes	9	48	57	52.94	41.46	−0.29	0.671
	No	8	34	42				
	Total	17	82	99				
Professional inquired onset and duration of diarrhea	Yes	59	35	94	95.16	5.41	0.07	0.901
	No	3	2	5				
	Total	62	37	99				
Professional inquired frequency of diarrhea	Yes	52	38	90	96.29	13.63	0.107	0.074
	No	2	6	8				
	Total	54	44	98				
Professional inquired client's medication history	Yes	9	57	66	81.81	35.23	0.053	0.258
	No	2	31	33				
	Total	11	88	99				
Professional inquired client's nutritional condition of client	Yes	2	59	61	100.00	39.18	0.025	0.259
	No	0	38	38				
	Total	2	97	99				
Professional inquired for presence of blood or mucus in diarrhea	Yes	71	19	90	93.42	17.39	0.137	0.114
	No	5	4	9				
	Total	76	23	99				
Professional inquired appearance of diarrhea	Yes	72	14	86	90.0	26.32	0.185	0.058
	No	8	5	13				
	Total	80	19	99				
Professional inquired presence of vomiting symptom	Yes	39	53	92	97.50	10.16	0.063	0.144
	No	1	6	7				
	Total	40	59	99				
Professional inquired presence of fever	Yes	48	43	91	94.12	10.42	0.046	0.408
	No	3	5	8				
	Total	51	48	99				

(*Continued*)

Table 5 (Continued).

Variables and Categories		Simulated-Patient Case Study (Standard)			Data Accuracy for Questionnaire		Kappa Value	P-value
Questionnaire-Based Study		**Yes**	**No**	**Total**	**Sensitivity (%)**	**Specificity (%)**		
Professional inquired presence of dehydration symptom	Yes	5	68	73	71.43	26.09	−0.005	0.886
	No	2	24	26				
	Total	7	92	99				
Professional inquired presence of other symptoms	Yes	1	13	14	25.00	86.32	0.051	0.525
	No	3	82	85				
	Total	4	95	99				
Professional recommended oral rehydration solution (ORS) with zinc	Yes	2	52	54	25.00	43.48	−0.087	0.086
	No	6	40	46				
	Total	8	92	100				
Professional recommended ORS	Yes	25	42	67	62.50	28.81	−0.078	0.365
	No	15	17	32				
	Total	40	59	99				
Professional recommended antibiotics	Yes	45	24	69	67.16	27.27	−0.025	0.805
	No	22	9	31				
	Total	67	33	100				
Professional recommended specific antibacterial agent	Yes	42	25	67	66.67	32.43	−0.009	0.926
	No	21	12	33				
	Total	63	37	100				
Professional recommended antidiarrheal agents	Yes	1	10	11	50.00	89.79	0.124	0.075
	No	1	88	89				
	Total	2	98	100				
Professional recommended specific antidiarrheal agent	Yes	0	7	7	0.00	9.78	−0.018	0.783
	No	1	92	93				
	Total	1	99	100				
Professional recommended antispasmodics	Yes	0	10	10	0.00	90.0	0.000	1.00
	No	0	90	90				
	Total	0	100	100				
Professional recommended specific antispasmodics	Yes	0	10	10	0.00	90.0	0.000	1.00
	No	0	90	90				
	Total	0	100	100				

(*Continued*)

Table 5 (Continued).

Variables and Categories		Simulated-Patient Case Study (Standard)			Data Accuracy for Questionnaire		Kappa Value	P-value
Questionnaire-Based Study		**Yes**	**No**	**Total**	**Sensitivity (%)**	**Specificity (%)**		
Professional recommended another specific agent	Yes	2	2	4	66.67	97.94	0.556	0.000
	No	1	95	96				
	Total	3	97	100				
Professional told name of medication given	Yes	32	43	75	78.05	27.12	0.046	0.557
	No	9	16	25				
	Total	41	59	100				
Professional told dose of medication given	Yes	31	53	84	83.78	15.87	−0.003	0.964
	No	6	10	16				
	Total	37	63	100				
Professional told duration of treatment	Yes	31	50	81	86.11	21.88	0.063	0.328
	No	5	14	19				
	Total	36	64	100				
Professional told route of medication administration	Yes	45	33	78	78.95	30.23	0.023	0.792
	No	12	10	22				
	Total	57	43	100				
Professional told common side effects of medication recommended	Yes	1	65	66	50.00	33.67	−0.01	0.629
	No	1	33	34				
	Total	2	98	100				
Professional told major drug interactions	Yes	1	56	57	25.00	41.67	−0.045	0.187
	No	3	40	43				
	Total	4	96	100				
Professional told about appropriate storage condition of medication recommended	Yes	7	67	74	58.33	23.86	−0.055	0.187
	No	5	21	26				
	Total	12	88	100				
Professional told client on how to prepare ORS	Yes	32	51	83	88.89	20.31	0.072	0.240
	No	4	13	17				
	Total	36	64	100				
Average sensitivity and specificity of questionnaire-based method (%)					64.90	36.24		
Number of agreement scores							745	
Total number of scores							2886	
Percent agreement between measurements on diarrheal case							26	

Table 6 Factors Associated with Inappropriate Dispensing of Antimicrobial Agents in Response to Childhood Acute Watery Diarrhea Symptom

Factors	COR (95% CI)	P-value	AOR (95% CI)	P-value
Retailer's qualification				
Pharmacist	1		1	
Pharmacy Technician	1.94 (0.81–4.6)	0.134	1.35 (0.52–3.54)	0.53
AMR understanding of retailer				
Sufficient knowledge	1		1	
Insufficient knowledge	2.78 (1.18–6.55)	0.02	2.9 (1.23–6.89)	0.015*
Retailer's dispensing behavior favors sharing antimicrobials				
Yes	1		1	
No	0.40 (0.17–0.95)	0.038	0.80 (0.21–3.07)	0.75
Retailer thinks AMR as a risk to users only				
Yes	1		1	
No	0.63 (0.27–1.47)	0.248	0.76 (0.26–2.2)	0.61
Satisfactory interaction for responding to symptoms				
Yes	1		1	
No	1.8 (0.77–4.20)	0.17	1.44 (0.59–3.5)	0.42

Note: *Statistically significant at p-value < 0.05.

this study, very small proportion of them aligned appropriate matching of their knowledge and dispensing practice. In line with this, previous study indicated that history taking by CDROs for diarrheal case is poor with key patient assessment questions for decision-making missed. Referral decision and the use of ORS is a rare practice. Majority of the dispensaries issued antimicrobials illegally.[43]

The number of scores matched for Cohen's interrater agreement was 745 out of 2886 scores. That means, the percent agreement between questionnaire-based and simulated-patient based study was 26%. Particularly, the low specificity value had an overwhelming effect on the kappa-values of the two measurements. This indicates professionals who responded "yes" in the questionnaire-based study (false positives) did not actually practice the appropriate management of childhood diarrhea in simulated-patient study. To obtain substantial or excellent agreement between methods on the same case, there must be a maximum combined sensitivity and specificity. This is also a ringing bell for those using questionnaire-based studies for assessing the actual performance of practitioners in specific therapeutic area.

Observing global research reports, approximately 47.2% community pharmacists dispensed antibiotics to simulated clients without a prescription in the country of Belize.[44] In Pakistan, of the 386 visits for acute diarrhea, nonprescription antibiotic dispensing occurred in 67.1% visits. Inappropriate dispensing practices were prevalent largely at the drug-stores, and antibiotics were effortlessly obtainable without prescription.[45] Consistent to this, illegal supply of antibiotics without a prescription was reported in about 50% of simulated-patients with acute diarrhea presented to retailers in Sri Lanka.[46] Again, 15 out of 50 (30%) for simulated-patient visits to community retailers in Gondar town, Ethiopia, led to metronidazole dispensing.[47] In the same town, 23.9% of retailers dispensed mebendazole to simulated-patients with diarrheal illnesses.[48] In India, 40.24% antibiotics were dispensed for management of simulated-patients with childhood diarrhea.[49] More importantly, antibiotics were dispensed to simulated-patients in 62.4% and 52.2% of the cases presented with acute diarrhea in Nigeria and Thailand, respectively.[50,51] Likewise, antibiotic over-prescription occurred in 52.5% of Kenyan children with diarrhea.[52] Moreover, the proportion of antibiotic dispensing without prescription most commonly for diarrhea and upper respiratory infections account for above 60.0%.[53] Along with this varying extent of practice, antibiotic dispensing without prescription is alarmingly an inappropriate practice.[54] Indeed, irrational antibiotic use in early childhood is considered as a major distractor of gut microbiota, which is linked with reduced floral species diversity, altered metabolic activity, and the selection of resistance.[54,55] Besides, this early childhood exposure to antibiotics can also lead to several gastrointestinal, immunologic, and neurocognitive problems.[55] Key behaviors justified

for antibiotic dispensing without prescription are lack of clinical training and awareness gaps of the community.[48] The antibiotic dispensing behavior can also be influenced by pressure from patients if customer satisfaction is the most important factor motivating their work.[56]

Retailers with insufficient knowledge on issues around antimicrobials and AMR were 2.9 times more likely to dispense antimicrobials inappropriately to simulated-patient with case of diarrhea. Consistent to this, knowledge of dispensers about antibiotics and AMR was linked with reduced likelihood of illegal dispensing for acute diarrhea (AOR: 0.76, 95% CI: 0.58–0.99; P=0.048).[57] Non-prescription dispensing of antibiotic agents for diarrhea was one of the most frequently presented case scenario in CDROs[58] Knowledge of what AMR is and how it occurs are quite rational to influence the practice of retailers.[59] A study conducted in Jordan emphasized that educational level is a significant predictor of good knowledge about antibiotic use and AMR.[60] In line with this, continuing education of dispensers, monitoring, and supervision are suggested aspects beneficial to combat resistance.[61] Again, periodic refresher training is crucial in helping dispensers deal with clients who demand antibiotics.[62]

This study tried to address the knowledge of retailers about antimicrobial use and AMR as well as assess the actual practice of managing diarrhea with a combination of simulated patient and questionnaire-based tools. Indeed, the finding highlights a profound discrepancy in actual practice and knowledge responses towards the management of acute diarrhea as observed from low agreement score. Again, a higher proportion of CDROs was taken from major towns that may not represent practice of smaller towns in eastern Ethiopia. Therefore, interpretation of findings should be made in the context of such limitation.

Conclusion

The study revealed that a considerable proportion of retailers had insufficient knowledge about antimicrobial use and AMR. Nearly a quarter of their response agreed with their actual practice towards the management of acute childhood diarrhea. The study also revealed that there was low sensitivity and specificity of questionnaire against the standard simulated-patient, reinforcing the notion that the low kappa-value is largely influenced by poor specificity of the questionnaire in assessing the actual performance. Insufficient knowledge of retailers was significantly associated with their inappropriate dispensing of antimicrobial medicines. To fill this gap, designing and implementing antimicrobial stewardship programs, applying tight regulation of antimicrobial use in CDROs, conducting targeted and overarching refresher trainings, and holding public awareness campaigns regarding rational antimicrobial use and AMR are highly recommended.

Data Sharing Statement

All the data used for the study are contained within the paper.

Ethics Approval and Consent to Participate

This study was conducted following the Declaration of Helsinki. Before starting data collection and preliminary study, the investigating team obtained a formal letter of ethical approval from the Institutional Health Research Ethics Review Committee of College of Health and Medical Sciences, Haramaya University (letter's reference number: IHRERC/100/2019). A letter of support, written from the College of Health and Medical Sciences to Regional Health Bureaus and health facilities, was delivered to the study settings prior to initiation of the study. Relevant information about the study was highlighted to the respondents about the purposes and procedures, potential risk and benefits of the study. In this respect, participation in the study was ensured voluntary and participants were told to have the right to withdraw from the study without giving justification, and all responses were kept confidential. Verbal informed consent was approved by the Institutional Health Research Ethics Review Committee of College of Health and Medical Sciences, Haramaya University.

Acknowledgment

The authors thank data collectors and staff of all healthcare settings for their substantial help to realize this research work. The authors also extend their thank to Haramaya University for granting this research work.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Funding

The authors disclosed reception of financial support from Haramaya University for conducting this research work.

Disclosure

The authors have declared that no competing interests exist.

References

1. World Health Organization. *The Evolving Threat of Antimicrobial Resistance: Options for Action*. World Health Organization; 2012.
2. World Health Organization. *Antimicrobial Resistance: Global Report on Surveillance*. World Health Organization; 2014.
3. Ameko E, Achio S, Alhassan S. Effects of antibiotic self-medication on the efficacy of four antibiotics commonly used in Ghana on clinically isolated micro organisms. *Int J Pure Appl Sci Technol*. 2012;10:62.
4. Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance—the need for global solutions. *Lancet Infect Dis*. 2013;13(12):1057–1098. doi:10.1016/S1473-3099(13)70318-9
5. Solomon SL, Oliver KB. Antibiotic resistance threats in the United States: stepping back from the brink. *Am Fam Physician*. 2014;89(12):938–941.
6. Seale AC, Gordon NC, Islam J, Peacock SJ, Scott JAG. AMR Surveillance in low and middle-income settings - A roadmap for participation in the Global Antimicrobial Surveillance System (GLASS). *Wellcome Open Res*. 2017;2:92. doi:10.12688/wellcomeopenres.12527.1
7. Provenzani A, Hospodar AR, Meyer AL, et al. Multidrug-resistant gram-negative organisms: a review of recently approved antibiotics and novel pipeline agents. *Int J Clin Pharm*. 2020;42(4):1016–1025. doi:10.1007/s11096-020-01089-y
8. Okeke IN, Edelman R. Dissemination of antibiotic-resistant bacteria across geographic borders. *Clin Infect Dis*. 2001;33(3):364–369. doi:10.1086/321877
9. Tse BN, Adalja AA, Houchens C, Larsen J, Inglesby TV, Hatchett R. Challenges and opportunities of nontraditional approaches to treating bacterial infections. *Clin Infect Dis*. 2017;65(3):495–500. doi:10.1093/cid/cix320
10. World Health Organization. Medicines use in primary care in developing and transitional countries: fact book summarizing results from studies reported between 1990 and 2006; 2009. Available from: http://appswhoint/medicinedocs/documents/s16073e/s16073epdf. Accessed May 20, 2019.
11. Okeke IN, Laxminarayan R, Bhutta ZA, et al. Antimicrobial resistance in developing countries. Part I: recent trends and current status. *Lancet Infect Dis*. 2005;5(8):481–493. doi:10.1016/S1473-3099(05)70189-4
12. Okeke IN, Klugman KP, Bhutta ZA, et al. Antimicrobial resistance in developing countries. Part II: strategies for containment. *Lancet Infect Dis*. 2005;5(9):568–580. doi:10.1016/S1473-3099(05)70217-6
13. Cars O, Nordberg P. Antibiotic resistance–The faceless threat. *Int J Risk Saf Med*. 2005;17:103–110.
14. Cars O, Högberg LD, Murray M, et al. Meeting the challenge of antibiotic resistance. *BMJ*. 2008;337:337. doi:10.1136/bmj.a1438
15. Abuirmeileh A, Samara S, Alkhodari A, Bahnassi A, Talhouni A, Hayallah AM. Antibiotic dispensing without prescription in Jordanian community pharmacies: a pharmacist's perspective. *Bull Pharmaceut Sci Assiut*. 2014;37(1):51–63. doi:10.21608/bfsa.2014.62622
16. Al-Faham Z, Habboub G, Takriti F. The sale of antibiotics without prescription in pharmacies in Damascus, Syria. *J Infect Dev Ctries*. 2011;5(05):396–399. doi:10.3855/jidc.1248
17. Sabry NA, Farid SF, Dawoud DM. Antibiotic dispensing in Egyptian community pharmacies: an observational study. *Res Soc Adm Pharm*. 2014;10(1):168–184. doi:10.1016/j.sapharm.2013.03.004
18. Chacko CT, Prakash D, Hafsa P, Lallu J, Sarabaya A. A review on the attitude and practice on self medication, storage and disposal of drugs in a community. *Int J Res Rev*. 2020;7:122–129.
19. Noah D, Fidas G. *The Global Infectious Disease Threat and Its Implications for the United States*. Washington DC: National Intelligence Council; 2000.
20. Apisarnthanarak A, Tunpornchai J, Tanawitt K, Mundy LM. Nonjudicious dispensing of antibiotics by drug stores in Pratumthani, Thailand. *Infect Control Hosp Epidemiol*. 2008;29(6):572–575. doi:10.1086/587496
21. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet*. 2005;365(9459):579–587. doi:10.1016/S0140-6736(05)17907-0
22. Hadi U, Duerink DO, Lestari ES, et al. Survey of antibiotic use of individuals visiting public healthcare facilities in Indonesia. *Int J Infect Dis*. 2008;12(6):622–629. doi:10.1016/j.ijid.2008.01.002
23. Livermore DM. Minimising antibiotic resistance. *Lancet Infect Dis*. 2005;5(7):450–459. doi:10.1016/S1473-3099(05)70166-3
24. Plachouras D, Kavatha D, Antoniadou A, et al. Dispensing of antibiotics without prescription in Greece, 2008: another link in the antibiotic resistance chain. *Eurosurveillance*. 2010;15(7):19488. doi:10.2807/ese.15.07.19488-en
25. World Health Organization. Antimicrobial resistance: draft global action plan on antimicrobial resistance. Geneva, Switzerland; 2015.
26. World Health Organization. The world medicines situation: rational use of medicines. Geneva, Switzerland; 2011.
27. FMHACA. Standard treatment guidelines for general hospitals. Addis Ababa, Ethiopia: FMHACA; 2014.
28. Shane AL, Mody RK, Crump JA, et al. 2017 Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. *Clin Infect Dis*. 2017;65(12):e45–e80. doi:10.1093/cid/cix669
29. Collins JC, Chong WW, de Almeida Neto AC, Moles RJ, Schneider CR. The simulated patient method: design and application in health services research. *Res Soc Adm Pharm*. 2021;17(12):2108–2115. doi:10.1016/j.sapharm.2021.04.021

30. Watson PF, Petrie A. Method agreement analysis: a review of correct methodology. *Theriogenology*. 2010;73(9):1167–1179. doi:10.1016/j.theriogenology.2010.01.003
31. McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med*. 2012;22:276–282. doi:10.11613/BM.2012.031
32. Baraka MA, Alsultan H, Alsalman T, Alaithan H, Islam MA, Alasseri AA. Health care providers' perceptions regarding antimicrobial stewardship programs (AMS) implementation-facilitators and challenges: a cross-sectional study in the Eastern province of Saudi Arabia. *Ann Clin Microbiol Antimicrob*. 2019;18(1):26. doi:10.1186/s12941-019-0325-x
33. Kotwani A, Joshi PC, Jhamb U, Holloway K. Prescriber and dispenser perceptions about antibiotic use in acute uncomplicated childhood diarrhea and upper respiratory tract infection in New Delhi: qualitative study. *Indian J Pharmacol*. 2017;49(6):419–431. doi:10.4103/ijp.IJP_508_17
34. Muloi D, Fèvre EM, Bettridge J, et al. A cross-sectional survey of practices and knowledge among antibiotic retailers in Nairobi, Kenya. *J Glob Health*. 2019;9(2):010412. doi:10.7189/jogh.09.020412
35. Chanvatik S, Kosiyaporn H, Lekagul A, et al. Knowledge and use of antibiotics in Thailand: a 2017 national household survey. *PLoS One*. 2019;14(8):e0220990. doi:10.1371/journal.pone.0220990
36. Feng Z, Hayat K, Huang Z, et al. Knowledge, attitude, and practices of community pharmacy staff toward antimicrobial stewardship programs: a cross-sectional study from Northeastern China. *Expert Rev Anti Infect Ther*. 2021;19(4):529–536. doi:10.1080/14787210.2021.1826307
37. Darj E, Newaz MS, Zaman MH. Pharmacists' perception of their challenges at work, focusing on antimicrobial resistance: a qualitative study from Bangladesh. *Glob Health Action*. 2019;12(sup1):1735126. doi:10.1080/16549716.2020.1735126
38. Darwish RM, Baqain GN, Aladwan H, Salamah LM, Madi R, Al Masri RM. Knowledge, attitudes, and practices regarding antibiotic use and resistance among community pharmacists: a cross sectional study in Jordan. *Int J Clin Pharm*. 2021;1–10. doi:10.1007/s11096-020-01222-x
39. Jones LF, Owens R, Sallis A, et al. Qualitative study using interviews and focus groups to explore the current and potential for antimicrobial stewardship in community pharmacy informed by the Theoretical Domains Framework. *BMJ open*. 2018;8(12):e025101. doi:10.1136/bmjopen-2018-025101
40. Gebretekle GB, Haile Mariam D, Abebe W, et al. Opportunities and barriers to implementing antibiotic stewardship in low and middle-income countries: lessons from a mixed-methods study in a tertiary care hospital in Ethiopia. *PLoS One*. 2018;13(12):e0208447. doi:10.1371/journal.pone.0208447
41. Kaae S, Malaj A, Hoxha I. Antibiotic knowledge, attitudes and behaviours of Albanian health care professionals and patients - a qualitative interview study. *J Pharmaceut Policy Pract*. 2017;10(1):13. doi:10.1186/s40545-017-0102-1
42. Vandepitte WP, Ponthong R, Srisarang S. treatment outcomes of the uncomplicated upper respiratory tract infection and acute diarrhea in preschool children comparing those with and without antibiotic prescription. *J Med Assoc Thai*. 2015;98(10):974–984.
43. Wondimsigegn D, Woldegerima B, Taddese AA. History taking and response to an adult diarrheal case among community drug retail outlets in Gondar town, north-west Ethiopia: a simulated-client survey. *J Pharmaceut Policy Pract*. 2021;14(1):26. doi:10.1186/s40545-021-00310-1
44. Husaini DC, Abubakar Y, Harris-Thurton L, Mphuthi DD. Over-the-counter sales of antibiotics at community pharmacies in Belize: a cross-sectional simulated client visit study. *Int J Integr Med Sci*. 2021;8. doi:10.15342/ijms.2021.455
45. Malik UR, Chang J, Hashmi F, et al. A simulated client exploration of nonprescription dispensing of antibiotics at drugstores for pediatric acute diarrhea and upper respiratory infection in Lahore, Pakistan. *Infect Drug Resist*. 2021;14:1129–1140. doi:10.2147/IDR.S301812
46. Zawahir S, Lekamwasam S, Aslani P. Community pharmacy staff's response to symptoms of common infections: a pseudo-patient study. *Antimicrob Resist Infect Control*. 2019;8(1):60. doi:10.1186/s13756-019-0510-x
47. Erku DA, Aberra SY. Non-prescribed sale of antibiotics for acute childhood diarrhea and upper respiratory tract infection in community pharmacies: a 2 phase mixed-methods study. *Antimicrob Resist Infect Control*. 2018;7(1):92. doi:10.1186/s13756-018-0389-y
48. Ayele AA, Mekuria AB, Tegegn HG, Gebresillassie BM, Mekonnen AB, Erku DA. Management of minor ailments in a community pharmacy setting: findings from simulated visits and qualitative study in Gondar town, Ethiopia. *PLoS One*. 2018;13(1):e0190583. doi:10.1371/journal.pone.0190583
49. Diwan V, Sabde YD, Byström E, De Costa A. Treatment of pediatric diarrhea: a simulated client study at private pharmacies of Ujjain, Madhya Pradesh, India. *J Infect Dev Ctries*. 2015;9(05):505–511. doi:10.3855/jidc.5694
50. Ogbo PU, Aina BA, Aderemi-Williams RI. Management of acute diarrhea in children by community pharmacists in Lagos, Nigeria. *Pharm Pract (Granada)*. 2014;12(1):376. doi:10.4321/S1886-36552014000100002
51. Saengcharoen W, Lerkiatbundit S. Practice and attitudes regarding the management of childhood diarrhoea among pharmacies in Thailand. *Int J Pharm Pract*. 2010;18(6):323–331. doi:10.1111/j.2042-7174.2010.00066.x
52. Rhee C, Aol G, Ouma A, et al. Inappropriate use of antibiotics for childhood diarrhea case management - Kenya, 2009–2016. *BMC Public Health*. 2019;19(S3):468. doi:10.1186/s12889-019-6771-8
53. Batista AD, Arodrigues D, Figueiras A, Zapata-Cachafeiro M, Roque F, Herdeiro MT. Antibiotic dispensation without a prescription worldwide: a systematic review. *Antibiotics*. 2020;9(11). doi:10.3390/antibiotics9110786
54. Khamsarn S, Nampoonsak Y, Busamaro S, et al. Epidemiology of antibiotic use and antimicrobial resistance in selected communities in Thailand. *J Med Assoc Thai*. 2016;99(3):270–275.
55. Ramirez J, Guarner F, Bustos Fernandez L, Maruy A, Sdepanian VL, Cohen H. Antibiotics as major disruptors of gut microbiota. *Front Cell Infect Microbiol*. 2020;10:572912. doi:10.3389/fcimb.2020.572912
56. Acharya Y, Nepal P, Yang D, et al. Economic and social drivers of antibiotic dispensing practices among community pharmacies in Nepal. *Trop Med Intl Health*. 2021;26(5):557–571. doi:10.1111/tmi.13555
57. Zawahir S, Lekamwasam S, Aslani P. A cross-sectional national survey of community pharmacy staff: knowledge and antibiotic provision. *PLoS One*. 2019;14(4):e0215484. doi:10.1371/journal.pone.0215484
58. Belachew SA, Hall L, Selvey LA. Non-prescription dispensing of antibiotic agents among community drug retail outlets in Sub-Saharan African countries: a systematic review and meta-analysis. *Antimicrob Resist Infect Control*. 2021;10(1):13. doi:10.1186/s13756-020-00880-w
59. Viberg N, Kalala W, Mujinja P, Tomson G, Lundborg CS. "Practical knowledge" and perceptions of antibiotics and antibiotic resistance among drugsellers in Tanzanian private drugstores. *BMC Infect Dis*. 2010;10(1):270. doi:10.1186/1471-2334-10-270
60. Abdel-Qader DH, Albassam A, Ismael NS, et al. Community pharmacists' knowledge of and attitudes toward antibiotic use, resistance, and self-medication in Jordan. *Drugs Ther Perspect*. 2021;37(1):44–53. doi:10.1007/s40267-020-00797-9

61. Chareonkul C, Khun VL, Boonshuyar C. Rational drug use in Cambodia: study of three pilot health centers in Kampong Thom Province. *Southeast Asian J Trop Med Public Health*. 2002;33(2):418–424.
62. Dillip A, Embrey M, Shekalaghe E, et al. What motivates antibiotic dispensing in accredited drug dispensing outlets in Tanzania? A qualitative study. *Antimicrob Resist Infect Control*. 2015;4(1):30. doi:10.1186/s13756-015-0073-4