

Original Article

Self-Medication with Antibiotics among University Students in LMIC: A systematic review and meta-analysis

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Abstract

Introduction: Self-medication with antibiotics (SMA) is common among university students in low and middle-income countries (LMICs). However, there has been no meta-analysis and systematic review in the population.

Methodology: A literature search was conducted using PubMed, Embase and Web of Science for the period from January 2000 to July 2018. Only observational studies that had SMA among university students from LMICs were included. A random-effects model was applied to calculate the pooled effect size with 95% confidence interval (CI) due to the expected heterogeneity (I^2 over 50%).

Results: The pooled prevalence of SMA of overall included studies was 46.0% (95% CI: 40.3% to 51.8%). Africa had the highest pooled prevalence of SMA among university students (55.30%), whereas South America had the lowest prevalence (38.3%). Among individual LMICs, the prevalence of SMA among university students varied from as low as 11.1% in Brazil to 90.7% in Congo.

Conclusions: The practice of SMA is a widespread phenomenon among university students in LMICs and is frequently associated with inappropriate use. Effective interventions such as medication education and stricter governmental regulation concerning antibiotic use and sale are required to be established in order to deal with SMA properly.

Key words: Antibiotics; self-medication; university students.

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Introduction

Antibiotics are among the most commonly purchased drugs in the world [1]. They play an indispensable role in the treatment of infectious diseases, especially in developing countries. However, the emergence of super bacteria (New Delhi metallobeta-lactamase-1) has made people around the world aware of the seriousness of bacterial resistance [2]. Antibiotic resistance is one of the world's most serious public health problems this century [3], which not only affects human health, but also increases healthcare costs worldwide [4,5]. Risk analysis of this resistance may be related to higher risk of morbidity and mortality, more resource utilization and cost, and lower flexibility of therapy regimens [6-8]. A review reported that current deaths attributable to antimicrobial resistance every year is 700000 (low estimate). This number is expected to rise to 10 million by 2050, if no effective preventive measures are adopted to reduce people's use of antibiotics [9]. In low and middle-income countries

(LMICs) this issue is increasingly exacerbated due to the rapid economic and population growth [10].

Inappropriate use of antibiotics is considered the single most important cause of antibiotic resistance [11,12]. Self-medication with antibiotics (SMA) is a serious public health problem worldwide [3], with high prevalence among different populations and countries [13-15]. SMA was defined as the use of antibiotics by individuals to treat symptoms/diseases without professional advice, prescriptions, medical or supervision, which can lead to inappropriate use of antibiotics [3]. Most commonly, inappropriate use examples include: change of antibiotic dosage during the course of treatment, change of antibiotic during the course of treatment or discontinuation of antibiotic use. Generally, the sources for antibiotics mainly include purchasing of antibiotics from retail pharmacy (without a prescription or resubmitting old prescription), sharing antibiotics with relatives or friends, and using leftover antibiotics from previous prescription [13,16]. A review

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estimated that over 50% of antibiotics worldwide are commonly purchased without a prescription [13]. The possible consequences of SMA include not only the emergence of antibiotic resistance, but also masking symptoms, treatment failure, drug toxicity, adverse drug events, and even death [17-19].

Since university students are at high risk for SMA due to higher education level, younger age, and better social and economic background, more attention should be focussed on them [20]. Moreover, in low and middle income countries, university students represent practitioners of high-level education and possible opinion leaders in the future. Their medication behavior may have a profound impact on members of their social circle and even their next generation. Especially, medical students are future leaders in healthcare practice, and play an important role in delivering knowledge of appropriate use of antibiotics to patients. University students' medication behavior of antibiotics has attracted widespread attention in the world. In recent years, a number of investigators and authority agencies from different countries have attempted to understand the current situation of SMA in university students. These reports are far-reaching for solving public health problems in the region. However, a systematic review to quantify the frequency and effect of SMA among university students worldwide is necessary. There is a need to provide evidence from well-designed studies on the use of antibiotics among university students to help adopting specific and effective interventions to promote proper development of global public health.

Therefore, we carried out a meta-analysis and systematic review of observational studies to investigate the prevalence of SMA in university students, to explore differences of SMA in different regions, gender, non-medical and medical students, and other subgroups, to identify reasons for SMA, and to evaluate knowledge and attitudes regarding to SMA among university students.

Methodology

Inclusion and exclusion criteria

The inclusion criteria were as follows: 1) study focused on the relationship between SMA and university students; 2) participants were university students (including undergraduate or postgraduate, non-medical and medical students); 3) the prevalence of SMA in university students and total sample size reported; 4) study analyzed all types of antibiotics; 5) only papers written in English were included, 6) Studies were done in LMICs (classified according to the World

Bank classification, low-income economies are defined as those with a GNI per capita of \$995 or less; lower middle-income economies are those with a GNI per capita between \$996 and \$3,895; upper middle-income economies are those between \$3,896 and \$12,055 [21]). Exclusion criteria included letters, reviews, meta-analysis, case reports, editorials and comments.

Information sources and search strategies

Standard search methods and multiple search strategies were adopted to avoid retrieval bias. Two researchers independently carried out literature reviews using three English databases: PubMed, Web of science and Embase for the period from January 2000 to July 2018. The search terms included self-medication or self-medicated or self-prescription or non-prescription, university student or undergraduate or postgraduate or nonmedical student or medical student or college student, antibiotic. According to the inclusion and exclusion criteria, retrieved titles/abstracts, and full-text readings are carried out in sequence to identify those eligible articles.

Data extraction

Two researchers independently extracted the required data from eligible articles and imported the data to a spreadsheet, which included the following contents: first author's name, year of publication, geographic location, mean age of participants, total sample size, gender, education level, source of self-medication, the prevalence of SMA, and the classification of income. Any disagreements were resolved with discussion or a third researcher.

Risk of bias

Multiple search strategies and as many search terms as possible were carried out among three databases to reduce the risk of publication bias. Funnel plots visually and Egger's test statistically were conducted to detect the presence of publication bias.

Two researchers also independently determined the methodological quality of included studies using an eleven-item checklist based on Agency for Healthcare Research and Quality (AHRQ) [22]. If the answer was "No" or "unclear", then the item would be scored 0; if "Yes" was answered that would be scored 1. The assessment of article quality was based on the following scores: 0- 3 scores, 4-7 scores and 8-11 scores were regarded as low quality, moderate quality and high quality, respectively. Any disagreements were resolved by discussion or a third researcher.

Table 1. Characteristics of studies included in the meta-analysis and systematic review.

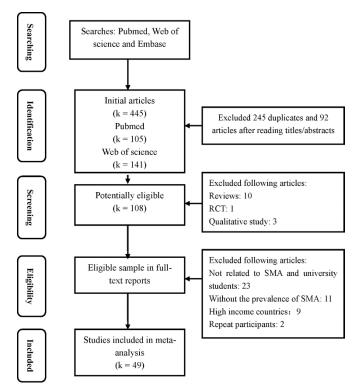
Reference	Country	Region	Mean age ± SD/age range	Male: Female	Sample size	Major	Education level	Medical insurance	Prevalence of SMA (%)	Source of SMA	Study qualit
[44]	Nepal	Asia	NA	239:158	397	Medical: 397	NA	NA	26.2	NA	7
[49]	Nepal	Asia	20.66 ± 2.33	21:54	75	Medical: 75	NA	NA	33.3	NA	5
[52]	Nepal	Asia	20	NA	327	Medical: 327	Undergraduate: 327	NA	50.7	NA	6
[58]	Congo	Africa	16-45	265:165	430	Medical: 45 Non-medical: 385	NA	NA	90.7	NA	7
[59]	Nepal	Asia	21	45:123	168	Medical: 168	Undergraduate:168	NA	35.1	Community pharmacy; Left over; Relative/friend; Online shopping/E- pharmacies	4
[63]	Ethiopia	Africa	26-35	182:218	400	Medical: 400	Undergraduate:100	NA	66.8	NA	9
[66]	Ethiopia	Africa	21 ± 2.06	267:140	407	NA	NA	NA	27.5	Community pharmacy; Drug shop; Relative/friend;	6
[69]	Ethiopia	Africa	21.57 ± 2.01	397:151	548	NA	NA	NA	32.7	Retail pharmacy; Relative/friend; Open market	9
[24]	Egypt	Africa	19.1 ± 1.5	99:201	300	Medical: 300	Undergraduate: 300	NA	41.5	Pharmacy	5
[27]	Pakistan	Asia	23.5 ± 3.6	71:79	150	Medical: 150	NA	NA	52.7	NA	5
[28]	India	Asia	20.4 ± 1.2	268:172	440	NA	Undergraduate: 440	NA	63.9	NA	6
[31]	Ghana	Africa	NA	300:300	600	Medical: 100 Non-medical: 500	NA	NA	70.3	Left over	9
[32]	Sudan	Africa	21-31	536:585	1121	NA	Undergraduate: 1121	NA	76.0	Retail pharmacy(main)	8
[16]	Sri Lanka	Asia	23.2 ± 1.6	205:491	696	Medical: 696	Undergraduate: 696	NA	15.8	Retail pharmacy; Relative/friend; Left over	7
[33]	Pakistan	Asia	20.04 ± 1.74	253:178	431	Non-medical: 431	Undergraduate: 427	Yes: 252 No: 171	47.6	Left over	7
[34]	Pakistan	Asia	23.0 ± 3.4	352:315	727	Non-medical: 727	Undergraduate: 694	NA	44.8	Left over	9
[40]	India	Asia	18-25	79:121	200	Medical: 200	NA	NA	34.0	NA	4
[41]	Bangladesh	Asia	21.03 ± 4.82	372:96	468	Medical: 468	Undergraduate: 468	NA	17.7	NA	9
[42]	India	Asia	19.90 ± 1.28	141:196	337	Medical: 337	Undergraduate: 337	NA	40.4	NA	7
[45]	Palestine	Asia	19.9 ± 1.7	577:1001	1581	Medical: 468 Non-medical: 1112	NA	NA	19.8	NA	8
[46]	Pakistan	Asia	21 ± 1.8	235:337	572	NA	NA	NA	26.8	NA	5
[48]	India	Asia	19.89 ± 1.41	230:258	488	Medical: 488	Undergraduate: 488	NA	34.9	NA	4
[50]	India	Asia	NA	116:130	246	Medical: 246	Undergraduate: 246	NA	80.9	Retail pharmacy(main); Left over	8
[51]	India	Asia	NA	58:21	79	Medical: 79	NA	NA	40.5	NA	5
[53]	India	Asia	23.32	231:85	316	Medical: 316	NA	NA	61.7	NA	6
[54]	Pakistan	Asia	18-25	80:120	200	Medical: 200	NA	NA	76.0	Community pharmacy; Left over; Relative/friend;	5
[55]	India	Asia	20.3 ± 1.5	190:250	440	Medical: 440	Undergraduate: 440	Yes:440	39.3	NA	9

Reference	Country	Region	Mean age ± SD/age range	Male: Female	Sample size	Major	Education level	Medical insurance	Prevalence of SMA (%)	Source of SMA	Study quality
[56]	Nigeria	Africa	NA	896:1104	2000	NA	Undergraduate: 2000	NA	53.8	Patent medicine store; Community pharmacy; Relative/friend; Left over	9
[60]	Nigeria	Africa	16-45	188:95	283	Medical: 107 Non-medical: 176	Undergraduate: 283	NA	56.9	Patent medicine store; Community pharmacy;	5
[62]	Indonesia	Asia	NA	40:56	96	Medical: 96	Undergraduate: 96	Yes:75 No:21	46.9	Retail pharmacy; Relative/friend;	7
[64]	India	Asia	19-24	40:60	100	Medical: 100	NA	NA	71.0	NA	6
[65]	India	Asia	18-25	30:120	150	Medical: 150	Undergraduate: 150	NA	62.7	Retail pharmacy; Home; medicine cabinet	5
[23]	Libya	Africa	NA	164:199	363	Medical: 180 Non-medical: 183	Undergraduate: 363	Yes: 97 No: 266	36.3	Pharmacy; Relative/friend	6
[25]	China	Asia	$22\ \pm 1.5$	NA	529	Medical:529	NA	NA	14.6	NA	9
[26]	China	Asia	NA	390:341	731	Medical: 353 Non-medical: 378	Undergraduate: 731	Yes: 679 No: 52	40.2	Retail pharmacy(main)	8
[20]	China	Asia	22.3 ± 2.6	745:555	1300	Medical: 634 Non-medical: 666	Undergraduate: 933 Master: 343 PhD: 24	Yes: 64 No: 1236	47.8	Community pharmacy	8
[29]	Turkey	Asia	18-23	426:534	960	Non-medical: 960	NA	NA	36.7	NA	7
[30]	China	Asia	18-45	369:291	660	Medical: 279 Non-medical: 305	Undergraduate: 581 Master: 59 PhD: 5	NA	47.9	Left over; Community pharmacy	9
[35]	Jordan	Asia	21.01 ± 1.98	364:953	1317	Medical: 1317	NA	Yes: 1317	46.9	Community pharmacy; Left over; Relative/friend; Herbal shop	9
[36]	Turkey	Asia	21.0 ± 3.0	282:390	672	Medical: 61 Non-medical: 611	NA	NA	44.1	Left over;	7
[37]	Iraq	Asia	19.8 ± 1.6	675:760	1435	NA	NA	NA	46.1	Retail pharmacy; Friend; Left over; Health staff	9
[38]	Iran	Asia	22.07 ± 3.84	69:181	250	Medical: 250	NA	NA	43.6	NA	9
[39]	Brazil	South America	22.03	50:66	116	Medical: 116	NA	NA	11.1	NA	7
[43]	Peru	South America	19.82	492:508	1000	Medical: 206 Non-medical: 794	Undergraduate: 1000	NA	65.4	NA	7
[47]	Iran	Asia	22.61	152:377	529	Medical: 529	Undergraduate: 529	NA	61.8	Retail pharmacy (main); Left over	9
[57]	Turkey	Asia	NA	164:406	570	Medical: 570	Undergraduate: 570	NA	31.1	NA	9
[61]	Iran	Asia	21.8 ± 0.25	97:98	195	Medical: 97 Non-medical: 98	NA	NA	45.1	NA	7
[67]	Romania	Europe	22	56:225	281	NA	NA	NA	41.0	NA	7
[68]	Iran	Asia	18-22	0:160	160	NA	NA	NA	53.0	NA	7

Statistical analysis

A proportion meta-analysis was performed on outcomes of interest in eligible studies, using Stata software version 11.0 (Stata Corporation, College Station, Texas, USA). The descriptive summaries of the reasons for SMA, the sources of antibiotics for selfmedication, and practices concerning SMA were generated form eligible studies. To facilitate the calculation of the pooled prevalence of SMA and other outcomes, primary data in included articles was converted into unified standard (prevalence and standard error). Forest plots were constructed to display the effect size and 95% confidence interval, calculating the I^2 and Q statistic to estimate the heterogeneity among included studies ($I^2 < 25\%$, 25-49%, 50-74%, and $\geq 75\%$ indicating no, low, moderate and high level of heterogeneity, respectively). A random-effects model was chosen to calculate the pooled effect size due to the expected heterogeneity (I^2 over 50%). Potential publication bias across the screened studies was assessed using Egger's and Begg's test and Funnel plot. A P value less than 0.05 on Egger's and Begg's test was considered indicative of statistically significant publication bias.

Figure 1. Flow diagram of study screening and selection process.



Results

Study selection

A total of 445 potentially relevant articles were identified from three databases. After initial screening, 245 articles were duplicates, 92 articles were excluded by reading titles and abstracts. 108 potentially eligible articles were selected for a full text detailed examination. Fifty-nine articles were removed based on the inclusion and exclusion criteria. Finally, 49 eligible articles were identified for the meta-analysis [16,20,23-69] (Figure 1).

Study characteristics

Table 1 details the summaries of 49 eligible studies, of them 10 form Africa, 36 from Asia, 2 from South America and 1 from Europe (most countries in Europe are high-income countries). A total of 25841 participants from 22 LMICs were included. Eight studies were conducted in 3 low income countries, 24 in 10 lower middle income countries and 17 in 9 upper middle income countries. All eligible studies were cross-sectional studies, published between 2007 and 2018, and 45 studies in 2010 or later. 29 studies reported the mean age of participants, with a median age of 21 years. The prevalence of SMA among university students ranged from a minimum of 11.10% to a maximum of 90.70%. Pharmacies, leftovers and relatives/friends are the most reported sources of antibiotics for self-medication. Additional details are shown in Table 1.

Quantitative synthesis

Overall, for all 49 eligible studies, the pooled prevalence of SMA among university students was 46.0% (95% CI: 40.3% to 51.8%, $I^2 = 99.0\%$). A random-effects model was selected to calculate the pooled effect size due to the high heterogeneity among studies (I^2 over 50%). Figure 2 shows the forest plot.

The economic level of the highest reported prevalence of SMA among university students was lower middle income countries (48.9%, 95% CI: 39.8% to 58.0%, I^2 = 99.2%). The economic level of the lowest reported prevalence was upper middle income countries (41.9%, 95% CI: 35.3% to 48.6%, I^2 = 98.2%). The prevalence of low income countries was 45.4% (95% CI: 24.6% to 66.3%, I^2 = 99.4%). The region with the highest reported prevalence of SMA was Africa (55.3%, 95% CI: 42.2% to 68.4%, I^2 = 99.3%).

Figure 2. Forest plot illustrating pooled prevalence of SMA among university students for 49 studies from LMICs.

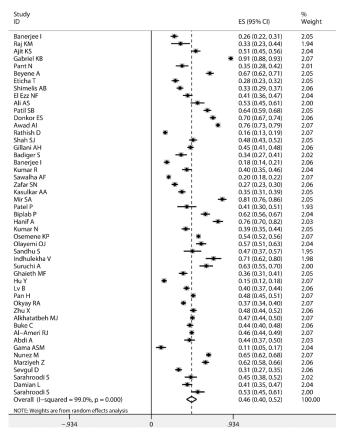


Figure 3. The prevalence of SMA among university students in different LMICs. *P* values indicates heterogeneity (only shown in countries larger than one study).

Variable		Prevalence (95% CI)	P
Brazil	-	0.11 (0.05-0.17)	
Sri Lanka	+	0.16 (0.13-0.19)	
Bangladesh	+	0.18 (0.14-0.21)	
Palestine	•	0.20 (0.18-0.22)	
Libya	-	0.36 (0.31-0.41)	
Nepal		0.36 (0.24-0.49)	< 0.001
Turkey	—	0.37 (0.30-0.44)	< 0.001
China		0.38 (0.21-0.54)	< 0.001
Romania	→	0.41 (0.35-0.47)	
Egypt	-	0.42 (0.36-0.47)	
Ethiopia		0.42 (0.19-0.65)	< 0.001
Iraq	+	0.46 (0.44-0.49)	
Jordan	→	0.47 (0.42-0.50)	
Indonesia		0.50 (0.37-0.57)	
Pakistan		0.49 (0.34-0.65)	< 0.001
Iran	-	0.51 (0.41-0.61)	< 0.001
India		0.53 (0.42-0.64)	< 0.001
Nigeria	•	0.54 (0.52-0.562)	0.326
Peru	+	0.65 (0.63-0.68)	
Ghana	+	0.70 (0.67-0.74)	
Sudan	+	0.76 (0.74-0.79)	
Congo		0.91 (0.88-0.93)	
	0.0 0.2 0.4 0.6 0.8 1.0		

Table 2. Subgroup analysis of the prevalence of SMA among university students according to study and participants' characteristics.

6.1	Number of	Number of participants	D	95% Confidence	Heterogeneity across studies	
Subgroups	studies		Prevalence (%)	interval (%)	I ² (%)	Р
Gender						
Male	17	4944	47.9	36.3-59.4	98.8	< 0.001
Female	17	5314	46.1	34.2-58.0	99	< 0.001
Major						
Medical	37	11499	46.4	39.8-53.0	98.4	< 0.001
Non-medical	14	7302	46.7	33.4-60.1	99.4	< 0.001
Education level						
Undergraduate	25	13919	48.1	40.8-55.4	98.8	< 0.001
Master	2	502	65.7	61.0-70.3	4.9	0.305
PhD.	2	29	86.6	74.2-98.9	0	0.695
Health insurance						
Yes	7	2924	43.1	38.7-47.6	77.4	< 0.001
No	5	1746	41.5	34.5-48.5	78.7	0.001
Region						
Africa	10	6452	55.3	42.2-68.4	99.3	< 0.001
Asia	36	17992	43.8	38.5-49.2	98.4	< 0.001
South America	2	1116	38.3	-14.9-91.5	99.6	< 0.001
Europe	1	281	41	35.2-46.8	/	/
Income level						
Low	8	2752	45.4	24.6-66.3	99.4	< 0.001
Lower middle	24	12021	48.9	39.8-58.0	99.2	< 0.001
Upper middle	17	11068	41.9	35.3-48.6	98.2	< 0.001

The regions with the lowest reported prevalence of SMA were Asia (43.8%, 95% CI: 38.5% to 49.2%, I^2 = 98.4%), South America (38.3%, 95% CI: 0.0% to 91.5%, I^2 = 99.6%), and Europe (41.0%, 95% CI: 35.2% to 46.8%) (Table2).

Figure 3 shows the prevalence of SMA among universities of different countries. For over half of the university students SMA was reported in Congo, Sudan, Ghana, Peru, Nigeria, India and Iran, with a prevalence of 90.7%, 76.0%, 70.3%, 65.4%, 54.2%, 52.9% and 51.1%, respectively. The reported prevalence of SMA was less than one-fifth among university students in Brazil, Sri Lanka, Bangladesh and Palestine, with the values of 11.1%, 15.8%, 17.7%, and 19.8%, respectively. Significant heterogeneity was observed for pooled analyses in each country (over two studies), except Nigeria ($I^2 = 0.0\%$).

Gender, major (medical and non-medical), education level and the status of participants' health insurance were used to analyze the difference of prevalence of SMA among university students. The result of prevalence was similar in gender (male: 47.9%, 95% CI:36.3% to 59.4% and female:46.1%, 95% CI: 34.2% to 58.0%), major (medical student: 46.4%, 95% CI: 39.8% to 53.0% and 46.7%, 95% CI: 34.2% to 58.0%) and their health insurance status (participants with health insurance: 43.1%, 95% CI: 38.7% to 47.6% and participants without health insurance: 41.5%, 95% CI:34.5% to 48.5%). In contrast, students with higher education levels showed increased SMA with the highest prevalence among PhD students (86.6%, 95% CI: 74.2% to 98.9%, $I^2 = 0.0\%$) compared to Master students (65.7%, 95% CI: 61.0% to 70.3%, $I^2 = 4.9\%$) and undergraduates (48.1%, 95% CI: 40.8% to 55.4%, $I^2 = 98.8\%$) (Table 2).

The participants' year in university was also analyzed to explore the difference of prevalence of SMA. Figure 4 shows the trend of prevalence of SMA among different grades (P < 0.05). Higher numbers of university years of participants increased prevalence of SMA ranging from the first year to the fifth year (37.5%, 40.2%, 42.2%, 44.4% and 49.7%).

Quality assessment and publication bias

All eligible studies were assessed for methodological quality. The quality assessment of each study is shown in Table 1. Twenty studies were of high quality and twenty-nine were of moderate quality. The scores of all 49 studies were 4 and above.

For the detection of publication bias, visual inspection of the Funnel plot indicated that spots were symmetrical (Figure 5). The finding was confirmed by

Begg's test (P = 0.464 > 0.05) and Egger's test (P = 0.37 > 0.05).

Discussion

The main findings from this meta-analysis show that the practice of SMA is a widespread phenomenon among university students in LMICs. These participants from lower middle income countries and Africa gave higher prevalence of SMA. The prevalence increased with education level and grade (years spent in university). The countries of Congo, Sudan, Ghana, Peru, Nigeria, India and Iran contributed more than half of the participants with SMA.

To the best of our knowledge, the study is the first comprehensive meta-analysis aiming to pool the prevalence of SMA among university students in LMICs. Previous studies were focused on self-

Figure 4. The prevalence of SMA between university students of different grades. LCI: lower 95% CI; UCI: upper 95% CI; n: number of studies; I^2 : heterogeneity statistic.

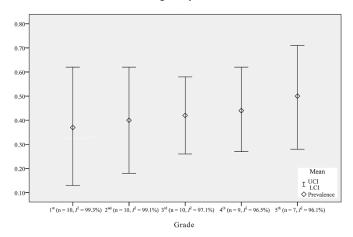
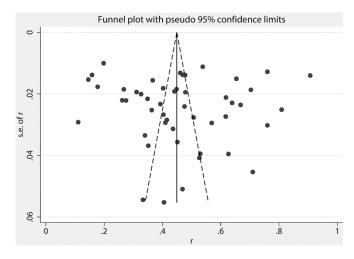


Figure 5. Funnel plot to evaluate potential publication bias. r: mean difference of SMA prevalence of each study. s.e. of r: standard error of SMA prevalence.



medication with antimicrobials among the general population [14], and SMA among the general population in Middle East [13], or self-medication among different population [70,71].

The prevalence of SMA among university students in LMICs of 46.0% determined in this meta-analysis is higher than that in the general population (38.8%) in LMICs, which was reported in a previous meta-analysis [14]. Moreover, our study reports that increasing education level presented a higher prevalence of SMA for undergraduates, master students, and PhD students. This is an interesting finding compared to the previous finding that illiteracy is a high risk for SMA, which was reported by Abdelmoneim et al. [72] and Moses et al [14]. In addition, researchers from Europe, Turkey and Jordan also reported similar finding of higher education level as a risk factor of self-medication with antibiotics among local adults [73-75]. A slightly increased trend of SMA was found among the first- to fifth-grade participants (P < 0.05). Although 6/10 studies reported no association among participants of different years in university. The pooled result still showed that increasing university performance seems to have a significant positive impact on SMA.

The prevalence of SMA among university students in Africa was higher than in other regions. The top three countries with the highest prevalence are in Africa (Congo, Sudan and Ghana). These findings reveal that some countries in Africa were poorly controlled for antibiotics use among university students. Of the pooled results of different countries, the highest prevalence of SMA among university students was 90.7% compared to the lowest of 11.1%. Differences in the effectiveness of policies on SMA in different resource-limited countries could explain this. Although university students in Europe and South America showed a lower prevalence, but were only represented in three studies, which might increase the risk of publication bias. However, it seems unlikely that there is a high risk of a publication bias because a low proportion of countries in Europe is the classification of LMICs, and both high and low prevalences of SMA are of interest. Participants from lower middle countries were reported to have a higher prevalence of SMA, which revealed that the economic status of a country may influence the practice of SMA among university students.

Under supervision, precise practices of selfmedication might become an important substitute for the formal health care system, providing an opportunity for access to immediate healthcare for patients [76]. In particular, medical students, who are more knowledgeable in medication use, should consciously do precise practices of SMA, even without physician's advice. However, in most universities or colleges in LMICs, inappropriate practices of SMA were frequently reported with high prevalence among medical and nonmedical students. These practices included change of dosage during the course of treatment, change of antibiotic during the course of treatment, discontinuation of antibiotic use and using antibiotics to treat viral infections, sleep problems, allergic reactions, or muscle pain. Inappropriate antibiotic medication practices potentially increase the risk of treatment failure, antibiotic resistance, drug toxicity, adverse drug events, and even death [17,18].

Previous experience was the most frequently reported reason for university students for SMA. They were confident to use antibiotics to treat similar symptoms based on previous experience [16,31,33,34]. The behavior would not only increase the risk of antibiotics resistance, but might also lead to treatment failure. The wish to save time or a lack of time were major reasons for SMA [33,34,40]. University students reported to lack of free time for seeking medical advice, getting a prescription and purchasing the correct antibiotic due to their burdensome school tasks. Using leftover or others' antibiotics would save their time [33,40]. Moreover, some students reported that they did not consider their illness serious enough for medical consultation [35,38]. The behavior might be associated with discontinuation of antibiotic use and reducing dosage during the course. In addition, lack of trust in prescribers, a wish to save money and confidence with self-medication were also reported in some studies [30,35]. We generally think that medical students are more medically knowledgeable than non-medical students, which should make medical students use antibiotics strictly as recommended by medical experts. However, the meta-analysis revealed that the prevalence of SMA among medical students (46.4%) was similar to non-medical students (46.7%). Previous studies have reported the close prevalence among medical and nonmedical students [46,77]. Some studies have shown a significantly higher prevalence of SMA among medical students compared to non-medical students [26,45]. One possible explanation is that medical students feel more confident about the practice of SMA based on their medical knowledge [35,40].

Effective interventions are needed to be adopted to reduce the prevalence and inappropriate practice of SMA among university students. Pharmacological education could be effective as an intervention to lower the prevalence of SMA. Studies show that pharmacological education could improve students'

knowledge of appropriate self-medication [51], but the prevalence of SMA among university students has not been effectively reduced [16]. Pharmacological education may be successful in increasing medical knowledge, but the contents may not be sufficient to teach students how to appropriately practice SMA. Therefore, educational intervention is indispensable, but it cannot be the only way. Multiple interventions need to be adopted to address this problem. This includes not only changes in personal knowledge and attitude, but also support from national policy and law. Considering the various reasons for SMA among university students, authority agencies such as the World Health Organization (WHO), the Ministry of Health and the Ministry of Education of LMICs are needed to establish novel approaches and to continuously reinforce education on inappropriate practices of SMA among university students. On the one hand, strengthened training programs are needed to be carried out among university students. Rational use of antibiotics must be highlighted in medical students' pharmacology courses. Meetings and promotional activities for rational use of antibiotics and other drugs should be conducted regularly in non-medical and medical universities. On the other hand, governments must issue relevant policies and laws to prohibit sale of antibiotics without prescription by retail pharmacies [25,26]. Doctors who work in school hospital should improve the service efficiency to enhance students' trust in them and save students' time. School hospital need to reduce the medical costs for students, especially for minor ailments, since students are more likely to practice SMA due to high medical cost for minor ailments.

There are several limitations in this meta-analysis. First, although we believe our search strategy was adequate to cover all relevant search terms, it is still possible that some eligible articles may have been overlooked. Second, the proportion (8/49) of studies conducted in low income countries is lowest among the three classifications. Low quality is also a characteristic feature of these studies. However, these countries are most in need of our attention, only more high-quality research data can reflect the real situation of the region. Third, self-report was the main measurement method in these studies included in the meta-analysis, which might increase risk of recall bias. Non-uniform data collection tools could also potentially have an effect on outcomes, such as online questionnaire and paper questionnaire. Finally, the studies included in the metaanalysis rarely proposed a substantive strategy to address the issue.

Conclusions

The practice of SMA is a widespread phenomenon among university students in LMICs. There is a great difference in the prevalence among different countries due to the difference in the effectiveness of policies on SMA. Increased education level and grade were associated with a higher prevalence of SMA. At present, there is still no substantive and effective strategy to solve the issue of high prevalence of SMA and inappropriate practice. Authority agencies need to be aware of the seriousness of the issue, and take substantive actions to control antibiotic use and inappropriate use among universities in LMICs.

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References

- Col NF, O'Connor RW (1987) Estimating worldwide current antibiotic usage: report of Task Force 1. Rev Infect Dis 9 Suppl 3: 232-243.
- Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, Chaudhary U, Doumith M, Giske GC, Irfan S, Krishnan P, Kumar AV, Maharjan S, Mushtaq S, Noorie T, Paterson DL, Pearson A, Perry C, Pike R, Rao B, Ray U, Sarma JB, Sharma M, Sheridan E, Thirunarayan MA, Turton J, Upadhyay S, Warner M, Welfare W, Livermore DM, and Woodford N. (2010) Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. Lancet Infect Dis 10: 597-602.
- Morgan DJ, Okeke IN, Laxminarayan R, Perencevich EN, Weisenberg S (2011) Non-prescription antimicrobial use worldwide: a systematic review. Lancet Infect Dis 11: 692-701.
- Stocker M, Ferrao E, Banya W, Cheong J, Macrae D, Furck A (2012) Antibiotic surveillance on a paediatric intensive care unit: easy attainable strategy at low costs and resources. BMC Pediatr 12: 196.
- Centres for Disease Control and Prevention (2013) Antibiotic Resistance Threats in the United States. Avaliable: https://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf access: 29 August 2018
- Holmberg SD, Solomon SL, Blake PA (1987) Health and economic impacts of antimicrobial resistance. Rev Infect Dis 9: 1065-1078.
- Friedman ND, Temkin E, Carmeli Y (2016) The negative impact of antibiotic resistance. Clin Microbiol Infect 22: 416-422.
- 8. Fischbach L, Evans EL (2007) Meta-analysis: the effect of antibiotic resistance status on the efficacy of triple and quadruple first-line therapies for *Helicobacter pylori*. Aliment Pharmacol Ther 26: 343-357.
- Tagliabue A, Rappuoli R (2018) Changing priorities in vaccinology: Antibiotic resistance moving to the top. Front Immunol 9: 1068.

- Hamers RL, van Doorn HR (2018) Antibiotic consumption in low-income and middle-income countries. Lancet Glob Health 6: e732.
- Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, Vlieghe E, Hara GL, Gould IM, Goossens H, Greko C, So AD, Bigdeli M, Tomson G, Woodhouse W, Ombaka E, Peralta AQ, Qamar FN, Mir F, Kariuki S, Bhutta ZA, Coates A, Bergstrom R, Wright GD, Brown ED, Cars O (2013) Antibiotic resistance-the need for global solutions. Lancet Infect Dis 13: 1057-1098.
- Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M (2014) A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. BMC Infect Dis 14: 13.
- 13. Alhomoud F, Aljamea Z, Almahasnah R, Alkhalifah K, Basalelah L, Alhomoud FK (2017) Self-medication and selfprescription with antibiotics in the Middle East-do they really happen? A systematic review of the prevalence, possible reasons, and outcomes. Int J Infect Dis 57: 3-12.
- 14. Ocan M, Obuku EA, Bwanga F, Akena D, Richard S, Ogwal-Okeng J, Obua C (2015) Household antimicrobial self-medication: a systematic review and meta-analysis of the burden, risk factors and outcomes in developing countries. BMC Public Health 15: 742.
- Bretagne JF, Richard-Molard B, Honnorat C, Caekaert A, Barthelemy P (2006) Gastroesophageal reflux in the French general population: national survey of 8000 adults. Presse Med 35: 23-31. [Article in French]
- Rathish D, Wijerathne B, Bandara S, Piumanthi S, Senevirathna C, Jayasumana C, Siribaddana S (2017) Pharmacology education and antibiotic self-medication among medical students: a cross-sectional study. BMC Res Notes 10: 337.
- Isturiz RE, Carbon C (2000) Antibiotic use in developing countries. Infect Control Hosp Epidemiol 21: 394-397.
- 18. Ceyhan M, Yildirim I, Ecevit C, Aydogan A, Ornek A, Salman N, Somer A, Hatipoğlu N, Camcioglu Y, Alhan E, Celik U, Hacimustafaoglu M, Celebi S, Inan D, Kurt N, Oner AF, Gulumser O, Gunes A, Coskun Y (2010) Inappropriate antimicrobial use in Turkish pediatric hospitals: a multicenter point prevalence survey. Int J Infect Dis 14: e55-61.
- Scuri S, Petrelli F, Tanzi E, Thi Thu CN, Grappasonni I (2019)
 European university students of pharmacy: survey on the use of pharmaceutical drugs. Acta Biomed 90: 83-91.
- Pan H, Cui B, Zhang D, Farrar J, Law F, Ba-Thein W (2012)
 Prior knowledge, older age, and higher allowance are risk factors for self-medication with antibiotics among university students in southern China. PLoS One 7: e41314.
- The World Bank (2018) World Bank country and lending groups. Available: https://datahelpdesk.worldbank.org/knowledgebase/articles/9 06519-world-bank-country-and-lending-groups. Assessed: August 30, 2018.
- 22. Hu J, Dong Y, Chen X, Liu Y, Ma D, Liu X, Zheng R, Mao X, Chen T, He W (2015) Prevalence of suicide attempts among Chinese adolescents: A meta-analysis of cross-sectional studies. Compr Psychiatry 61: 78-89.
- Ghaieth MF, Elhag SM, Hussien ME, Konozy EE (2015)
 Antibiotics self-medication among medical and nonmedical students at two prominent Universities in Benghazi City, Libya. J Pharm Bioallied Sci 7: 109-115.

- 24. El Ezz NF, Ez-Elarab HS (2011) Knowledge, attitude and practice of medical students towards self medication at Ain Shams University, Egypt. J Prev Med Hyg: 52: 196-200.
- Hu Y, Wang X, Tucker JD, Little P, Moore M, Fukuda K, Zhou X (2018) Knowledge, Attitude, and Practice with Respect to Antibiotic Use among Chinese Medical Students: A Multicentre Cross-Sectional Study. Int J Environ Res Public Health 15.
- Lv B, Zhou Z, Xu G, Yang D, Wu L, Shen Q, Jiang M, Wang X, Zhao G, Yang S, Fang Y (2014) Knowledge, attitudes and practices concerning self-medication with antibiotics among university students in western China. Trop Med Int Health 19: 769-779.
- Ali AS, Ahmed J, Ali AS, Sonekhi GB, Fayyaz N, Zainulabdin Z, Jindani R (2016) Practices of self-medication with antibiotics among nursing students of Institute of Nursing, Dow University of Health Sciences, Karachi, Pakistan. J Pak Med Assoc 66: 235-237.
- Patil SB, S H V, B V P, Santoshkumar J, Binjawadgi AS, Kanaki AR (2014) Self-Medication Practice and Perceptions Among Undergraduate Medical Students: A Cross-Sectional Study. J Clin Diagn Res 8: 20-23.
- Okyay RA, Erdogan A (2017) Self-medication practices and rational drug use habits among university students: a crosssectional study from Kahramanmaras, Turkey. Peer J 5: e3990.
- Zhu X, Pan H, Yang Z, Cui B, Zhang D, Thein WB (2016) Self-medication practices with antibiotics among Chinese university students. Public Health 130: 78-83.
- Donkor ES, Tetteh-Quarcoo PB, Nartey P, Agyeman IO (2012) Self-medication practices with antibiotics among tertiary level students in Accra, Ghana: a cross-sectional study. Int J Environ Res Public Health 9: 3519-3529.
- Awad AI, Eltayeb IB (2007) Self-medication practices with antibiotics and antimalarials among Sudanese undergraduate university students. Ann Pharmacother 41: 1249-1255.
- Shah SJ, Ahmad H, Rehan RB, Najeeb S, Mumtaz M, Jilani MH, Rabbani MS, Alam MZ, Farooq S, Kadir MM (2014) Self-medication with antibiotics among non-medical university students of Karachi: a cross-sectional study. BMC Pharmacol Toxicol 15: 74.
- 34. Gillani AH, Ji W, Hussain W, Imran A, Chang J, Yang C, Fang Y (2017) Antibiotic self-medication among non-medical university students in Punjab, Pakistan: A cross-sectional survey. Int J Environ Res Public Health 14: 1152.
- Alkhatatbeh MJ, Alefan Q, Alqudah MA (2016) High prevalence of self-medication practices among medical and pharmacy students: a study from Jordan. Int J Clin Pharmacol Ther 54: 390-398.
- 36. Buke C, Hosgor-Limoncu M, Ermertcan S, Ciceklioglu M, Tuncel M, Köse T, Eren S (2005) Irrational use of antibiotics among university students. J Infect 51: 135-139.
- Al-Ameri RJ, Abd Al-Badri HJ, Lafta RK (2017) Prevalence of self-medication among university students in Baghdad: a cross-sectional study from Iraq. East Mediterr Health J 23: 87-93.
- Abdi A, Faraji A, Dehghan F, Khatony A (2018) Prevalence of self-medication practice among health sciences students in Kermanshah, Iran. BMC Pharmacol Toxicol 19: 36.
- Gama ASM, Secoli SR (2017) Self-medication among nursing students in the state of Amazonas - Brazil. Rev Gaucha Enferm 38: e65111. [Article in Portuguese]
- Badiger S, Kundapur R, Jain A, Kumar A, Pattanshetty S, Thakolkaran N, Bhat N, Ullal N (2012) Self-medication

- patterns among medical students in South India. Australas Med J 5: 217-220.
- 41. Banerjee I, Bhadury T (2012) Self-medication practice among undergraduate medical students in a tertiary care medical college, West Bengal. J Postgrad Med 58: 127-131.
- Kumar R, Goyal A, Padhy BM, Gupta YK (2016) Selfmedication practice and factors influencing it among medical and paramedical students in India: A two-period comparative cross-sectional study. J Nat Sci Biol Med 7: 143-148.
- Nú~nez M, Ayala MT, Olivares FG (2017) Antibiotic selfmedication in university students from Trujillo, Peru. Medicina Universitaria 18: 205-209.
- 44. Banerjee I, Sathian B, Gupta RK, Amarendra A, Roy B, Bakthavatchalam P, Saha A, Banerjee I (2016) Self-medication practice among preclinical university students in a medical school from the city of Pokhara, Nepal. Nepal J Epidemiol 6: 574-581.
- 45. Sawalha AF (2008) A descriptive study of self-medication practices among Palestinian medical and nonmedical university students. Res Social Adm Pharm 4: 164-172.
- 46. Zafar SN, Syed R, Waqar S, Zubairi AJ, Vaqar T, Shaikh M, Yousaf W, Shahid S, Saleem S (2008) Self-medication amongst university students of Karachi: prevalence, knowledge and attitudes. J Pak Med Assoc 58: 214-217.
- 47. Marziyeh Z, Maryam D, Farzaneh BH (2016) Prevalence and causes of self medication among medical students of Kerman university of medical sciences, Kerman, Iran. Glob J Health Sci 8: 150-159.
- Kasulkar AA, Gupta M (2015) Self Medication Practices among Medical Students of a Private Institute. Indian J Pharm Sci 77: 178-182.
- Raj KM, Sujata S (2015) Knowledge, attitude and practice of self-medication among medical students. IOSR J Nurs Health Sci 4: 89-96.
- 50. Mir SA (2015) A cross-sectional study on knowledge, attitude, and behavior related to antibiotic use among undergraduate medical students in a tertiary care medical college, Kashmir. Int J Basic Clin Pharmacol 4: 1156-1162.
- Patel P, Prajapati A, Ganguly B, Gajjar B (2013) Study on impact of Pharmacology Teaching on Knowledge, Attitude and practice on self-medication among medical students. Int J Med Sci Public Health 2: 173-178.
- Ajit KS, Rajesh KJ, Dev KS (2016) Self-medication with antibiotics among nursing students of Nepal. Int J Pharma Sci Res 7: 427-430.
- Biplab P, Krishna M, Ashok KG, Choudhury U, Rastogi M, Pandey H, Lal CS, Pandey K, Das P (2016) Self medication with antibiotics among medical and pharmacy students in North India. Current Res Med 7: 7-12.
- Hanif A, Ashar SM, Rabnawaz R, Yasmeen S (2016) Selfmedication of antibiotics among the students of Hamdard university, Pakistan. J Public Health Dev Ctries 2: 145-148.
- 55. Kumar N, Kanchan T, Unnikrishnan B, Rekha T, Mithra P, Kulkarni V, Papanna MK, Holla R, Uppal S (2013) Perceptions and practices of self-medication among medical students in coastal South India. PLoS One 8: e72247.
- Osemene KP, Lamikanra A (2012) A Study of the prevalence of self-medication practice among university students in Southwestern Nigeria. Trop J Pharm Res 11: 683-689.
- Sevgül D, Kivanç G, Pinar G (2018) Knowledge, attitude and practice of self-medication with antibiotics among nursing students. Int J Pharmacol 14: 136-143.

- Gabriel KB, Mupenzi M, François KM (2017) Assessment of antibiotic self-medication pattern among university students in Eastern Democratic Republic of the Congo. J Pharm Res Int 18: 1-7.
- Pant N, Sagtani RA, Pradhan M, Bhattarai A, Sagtani A (2015)
 Self-medication with antibiotics among dental students of Kathmandu -prevalence and practice. Nepal Med Coll J 17: 47-53.
- Olayemi OJ, Olayinka BO, Musa AI (2010) Evaluation of antibiotic Self-Medication Pattern Amongst Undergraduate Students of Ahmadu Bello University (Main Campus), Zaria. Res J Appl Sci Eng Technol 2: 35-38.
- 61. Sarahroodi S, Arzi A, Sawalha AF, Ashtarinezhad A (2010) Antibiotics Self-Medication among Southern Iranian university students. Int J Pharmacol 6: 48-52.
- Sandhu S, Suryani Y, Dwiprahasto I, Atthobari J (2017) A Survey of Antibiotics Self-Medication and Over the Counter Drug Use among Undergraduate Medical Students in Yogyakarta, Indonesia. Southeast Asian J Trop Med Public Health 48: 1290-1298.
- 63. Beyene A, Getachew E, Doboch A, Poulos E, Abdurahman K, Alebachew M (2017) Knowledge, attitude and practice of self medication among pharmacy students of rift valley university, Abichu campus, Addis Ababa, Ethiopia. J Health Med Informat 8: 1-6.
- Indhulekha V, Anirudha K, Kumar MPS (2018) Selfmedication with antibiotics among dental undergraduate students. Drug Invention Today 10: 1335-1339.
- 65. Suruchi A, Aditya R (2013) Self- medication among dental undergraduate students with antibiotics: Looking beyond the known. Asian J Pharm Clin Res 6: 132-135.
- Eticha T (2014) Prevalence and predictors of selfmedication with antibiotics among Adi-haqi Campus students of Mekelle University, Ethiopia. Int J Pharma Sci Res 5: 678-684.
- 67. Damian L, Lupusoru CE, Ghiciuc CM (2014) Self-medication with antimicrobial drugs among university students in a Northeast region of Romania. Rev Med Chir Soc Med Nat Iasi 118: 160-164.
- 68. Sarahroodi S, Arzi A (2009) Self-medication with antibiotics, Is it a problem among Iranian college students in Tehran? J of Biol Sci 9: 829-832.
- 69. Shimelis AB, Mesele DA, Alemayehu WY (2016) Magnitude and factors associated with self-medication practices among university students: The case of Arsi university, college of health science, Asella, Ethiopia: Cross-sectional survey based study. Open Access Libr J 3: e2738.
- Gomez GB, Garnett GP, Ward H (2009) Self-medication prevalence for sexually transmitted diseases: meta-analysis and meta-regression of population level determinants. Sex Transm Dis 36: 112-119.
- Gualano MR, Bert F, Passi S, Stillo M, Galis V, Manzoli L, Siliquini R (2015) Use of self-medication among adolescents: a systematic review and meta-analysis. Eur J Public Health 25: 444-450.
- Awad A, Eltayeb I, Matowe L, Thalib L (2005) Self-medication with antibiotics and antimalarials in the community of Khartoum State, Sudan. J Pharm Pharm Sci 8: 326-331.
- Ilhan MN, Durukan E, Ilhan SO, Aksakal FN, Ozkan S, Bumin MA (2009) Self-medication with antibiotics: questionnaire survey among primary care center attendants. Pharmacoepidemiol Drug Saf 18: 1150-1157.
- 74. Al-Azzam SI, Al-Husein BA, Alzoubi F, Masadeh MM, Al-Horani MA (2007) Self-medication with antibiotics in

- Jordanian population. Int J Occup Med Environ Health 20: 373-380.
- 75. Grigoryan L, Haaijer-Ruskamp FM, Burgerhof JG, Mechtler R, Deschepper R, Tambic-Andrasevic A, Andrajati R, Monnet DL, Cunney R, Di Matteo A, Edelsein H, Valinteliene R, Alkerwi A, Scicluna E, Grzesiowski P, Bara AC, Tesar T, Cizman M, Campos J, Lundborg CS, Birkin J (2006) Self-medication with antimicrobial drugs in Europe. Emerg Infect Dis 12: 452-459.
- Bennadi D (2013) Self-medication: A current challenge. J Basic Clin Pharm 5: 19-23.
- 77. Alshogran OY, Alzoubi KH, Khabour OF, Farah S (2018) Patterns of self-medication among medical and nonmedical

University students in Jordan. Risk Manag Healthc Policy 11: 169-176.

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