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% (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 metallo-beta-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, or medical 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...
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 articles were 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.
| 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 |
|-----------|---------|--------|-------------------------|-------------|-------------|-------|----------------|-------------------|----------------------|--------------|--------------|
| [44] Nepal | Asia    | NA     | 239:158                 | 397         | Medical: 397 | NA    | NA            | NA                | 26.2                | NA           | 7            |
| [49] Nepal | Asia    | 20.66 ± 2.33 | 21:54                 | 75          | Medical: 75 | NA    | NA            | NA                | 33.3                | NA           | 5            |
| [52] Nepal | Asia    | 20     | NA                      | 327         | Medical: 327 | Undergraduate: 327 | NA | NA | 90.7 | NA | 6 |
| [58] Congo | Africa   | 16-45 | 265:165                 | 430         | Medical: 45 | Non-medical: 385 | NA | NA | 5.5 | Community pharmacy; Left over; Relative/friend; Online shopping/E-pharmacies | 7 |
| [59] Nepal | Asia    | 21     | 45:123                  | 168         | Medical: 168 | Undergraduate:168 | NA | NA | 35.1 | NA | 4 |
| [63] Ethiopia | Africa | 26-35 | 182:218                 | 400         | Medical: 400 | Undergraduate:100 | NA | NA | 66.8 | NA | 9 |
| [66] Ethiopia | Africa | 21 ± 2.06 | 267:140               | 407         | NA          | NA            | NA            | NA                | 27.5               | Community pharmacy; Drug shop; Relative/friend; Retail pharmacy; Relative/friend; Open market | 6 |
| [69] Ethiopia | Africa | 21.57 ± 2.01 | 397:151              | 548         | NA          | NA            | NA            | NA                | 32.7               | NA | 9 |
| [24] Egypt    | Africa   | 19.1 ± 1.5 | 99:201                | 300         | Medical: 300 | Undergraduate: 300 | NA | NA | 41.5 | NA | 4 |
| [27] Pakistan | Asia    | 23.5 ± 3.6 | 71:79                 | 150         | Medical: 150 | NA            | NA            | NA                | 52.7               | NA | 5 |
| [28] India    | Asia    | 20.4 ± 1.2 | 268:172               | 440         | NA          | Undergraduate: 440 | NA | NA | 63.9 | NA | 6 |
| [31] Ghana    | Africa   | NA     | 300:300                | 600         | Medical: 100 | Non-medical: 500 | NA | NA | 70.3 | NA | 9 |
| [32] Sudan    | Africa   | 21–31 | 536:585                | 1121        | NA          | Undergraduate: 1121 | NA | NA | 76.0 | Retail pharmacy(main) | 8 |
| [16] Sri Lanka | Asia    | 23.2 ± 1.6 | 205:491               | 696         | Medical: 696 | Undergraduate: 696 | NA | NA | 15.8 | Retail pharmacy(main); 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 | NA | 44.8 | Left over | 9 |
| [40] India    | Asia    | 18-25 | 79:121                 | 200         | Medical: 200 | NA            | NA            | NA                | 34.0               | NA | 4 |
| [41] Bangladesh | Asia   | 21.03 ± 4.82 | 372:96               | 468         | Medical: 468 | Undergraduate: 468 | NA | NA | 17.7 | NA | 9 |
| [42] India    | Asia    | 19.90 ± 1.28 | 141:196              | 337         | Medical: 337 | Undergraduate: 337 | NA | 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            | NA                | 26.8               | NA | 5 |
| [48] India    | Asia    | 19.89 ± 1.41 | 230:258              | 488         | Medical: 488 | Undergraduate: 488 | NA | NA | 34.9 | NA | 4 |
| [50] India    | Asia    | NA     | 116:130                | 246         | Medical: 246 | Undergraduate: 246 | NA | NA | 80.9 | Retail pharmacy(main); Left over | 8 |
| [51] India    | Asia    | NA     | 58:21                  | 79          | Medical: 79 | NA            | NA            | NA                | 40.5               | NA | 5 |
| [53] India    | Asia    | 23.32 | 231:85                 | 316         | Medical: 316 | NA            | NA            | NA                | 61.7               | NA | 6 |
| [54] Pakistan | Asia    | 18-25 | 80:120                 | 200         | Medical: 200 | NA            | NA            | NA                | 76.0               | NA | 5 |
| [55] India    | Asia    | 20.3 ± 1.5 | 190:250              | 440         | Medical: 440 | Undergraduate: 440 | Yes:440 | NA | 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          | Patented medicine store; Community pharmacy; Relative/friend; Left over Patent medicine store; Community pharmacy; Relative/friend; NA | 9   |
| [60]      | Nigeria   | Africa | 16-45                    | 188.95:283   | 1000        | NA                    | Undergraduate: 283 | NA   | 56.9          | Patented medicine store; Community pharmacy; Relative/friend; Left over Patent medicine store; Community pharmacy; Relative/friend; NA | 5   |
| [62]      | Indonesia | Asia   | NA                       | 40:56        | 188:95      | NA                    | Undergraduate: 96  | Yes:75 No:21       | 46.9         | 7   |
| [64]      | India     | Asia   | 19-24                    | 188:95       | 1000        | Medical: 100          | NA                | NA   | 71.0          | NA | 6   |
| [65]      | India     | Asia   | 18-25                    | 30:120       | 188:95      | NA                    | Undergraduate: 150 | NA   | 62.7          | Retail pharmacy; Home; medicine cabinet | 5   |
| [23]      | Libya     | Africa | NA                       | 164:199      | 363         | Medical: 180          | Undergraduate: 363 | Yes:97 No:266     | 36.3         | 6   |
| [25]      | China     | Asia   | 22 ± 1.5                 | NA:529       | 731         | Medical: 353          | Undergraduate: 731 | Yes:679 No:52     | 40.2         | 8   |
| [26]      | China     | Asia   | NA                       | 390:341      | 731         | Medical: 353          | Undergraduate: 933 | Yes:64 No:1236    | 47.8         | 8   |
| [20]      | China     | Asia   | 22.3 ± 2.6               | 745:555      | 1300        | Medical: 634          | Undergraduate: 1317 | NA   | 38.7          | NA | 7   |
| [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          | Undergraduate: 581 | 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         | 9   |
| [36]      | Turkey    | Asia   | 21.0 ± 3.0               | 282:390      | 672         | Medical: 61           | NA                | NA   | 44.1          | Left over; Retail pharmacy; Friend; Left over; Health staff | 7   |
| [37]      | Iraq      | Asia   | 19.8 ± 1.6               | 675:760      | 1435        | Medical: 61           | NA                | NA   | 46.1          | NA | 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 | 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           | Undergraduate: 98  | 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 self-medication, and practices concerning SMA were generated from 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.

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.

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

| Subgroups                  | Number of studies | Number of participants | Prevalence (%) | 95% Confidence interval (%) | Heterogeneity across studies | P   |
|----------------------------|-------------------|------------------------|----------------|-----------------------------|-----------------------------|-----|
| **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%, $\hat{p} = 98.4$), South America (38.3%, 95% CI: 0.0% to 91.5%, $\hat{p} = 99.6$), and Europe (41.0%, 95% CI: 35.2% to 46.8%) (Table 2).

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 ($\hat{p} = 0.0$).

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%, $\hat{p} = 0.0$) compared to Master students (65.7%, 95% CI: 61.0% to 70.3%, $\hat{p} = 4.9$) and undergraduates (48.1%, 95% CI: 40.8% to 55.4%, $\hat{p} = 98.8$) (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-
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 self-medication 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 meta-analysis 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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