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Global access to antibiotics without prescription in community pharmacies: a systematic review and meta-analysis

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Abstract

Objective: To estimate the proportion of over-the-counter antibiotic requests or consultations that resulted in non-prescription supply of antibiotics in community pharmacies globally.

Methods: We systematically searched EMBASE, Medline and CINAHL databases for studies published from January 2000 to September 2017 reporting the frequency of non-prescription sale and supply of antibiotics in community pharmacies across the world. Additional articles were identified by checking reference lists and a Google Scholar search. A random effects meta-analysis was conducted to calculate pooled estimates of non-prescription supply of antibiotics.

Results: Of the 3302 articles identified, 38 studies from 24 countries met the inclusion criteria and were included in the review. All the included countries with the exception of one, classified antibiotics as prescription-only medicines. The overall pooled proportion of non-prescription supply of antibiotics was 62% (95% CI 53 – 72). The pooled proportion of non-prescription supply of antibiotics following a patient request was 78% (95% CI 59 - 97) and based on community pharmacy staff recommendation was 58% (95% CI 48 – 68). The regional supply of non-prescription antibiotics was highest in South America, 78% (95% CI 72 - 84). Antibiotics were commonly supplied without a prescription to patients with symptoms of urinary tract infections (68%, 95% CI 42 – 93) and upper respiratory tract infections (67%, 95% CI 55 - 79). Fluoroquinolones and Penicillins respectively were the most commonly supplied antibiotic classes for these indications.

Conclusion: Antibiotics are frequently supplied without prescription in many countries. This overuse of antibiotics could facilitate the development and spread of antibiotic resistance.

Keywords: antibiotics; non-prescription supply; community pharmacies; infections; antibiotic stewardship.

Introduction

Antibiotics are the most frequently prescribed medicines world-wide.[1] Between 2000 and 2010, consumption of antibiotics increased from approximately 50 billion to 70 billion standard units.[1] More than three-quarters of the overall increase in consumption of antibiotics occurred in Brazil, Russia, India, China, and South Africa.[1] This global increase in consumption has been driven by a number of factors including economic growth and access to antibiotics.[1]

However, the growing access to and use of antibiotics (either through prescription or non-prescription) has been linked to antibiotic resistance, which is a significant threat to global public health.[1-3] Antibiotic resistance accounts for more than 2 million infections and at least 23,000 deaths annually in the USA [4] and about 25,000 deaths in Europe [5]. Although reliable estimates of the burden of antibiotic-resistant infections in developing countries are lacking, it is believed to cause many more deaths in these countries. For example, in India alone, about 57,000 neonatal sepsis deaths occurring annually are due to antibiotic-resistant infections.[5]

About 80% of antibiotics are used in the community.[6] These antibiotics are either prescribed by a healthcare professional or purchased directly by consumers without a valid prescription from many sources including community pharmacies. In many countries, the dispensing of antibiotics without a prescription is illegal. Nevertheless, over 50% of antibiotics worldwide are obtained without a prescription and community pharmacies are a major source of non-prescribed antibiotics.[7] This practice is particularly common in developing countries where there are no regulations regarding the sale and distribution of medicines or the enforcement of these regulations is weak.[8, 9] Recent evidence has indicated that dispensing antibiotics without a prescription is becoming a problem in developed countries including Portugal and Spain.[10, 11]

Non-prescription use of antibiotics is often associated with incomplete/shorter treatment courses and inappropriate drug and dose choices.[12-14] Such irrational use of antibiotics could have a number of consequences including the development and spread of resistance to antibiotics, delayed hospital admissions and masking the diagnosis of infectious diseases.[12-15] For example, tuberculosis symptoms suppressed temporarily through the use of fluoroquinolones could delay its diagnosis and lead to the patients receiving several antibiotic courses for the wrong diagnosis.[15] While in recent times, several interventions designed to optimise the use of antibiotics have been developed, they are often targeted at hospitals thereby missing the non-prescription sources of antibiotics.[16]

To address the problem of non-prescription use of antibiotics, an understanding of the magnitude of the practice and circumstances in which it occurs is important in the first instance. Previous reviews have focussed on the frequency of non-prescribed use of antibiotics in the general population and have identified community pharmacies as important sources of these antibiotics.[16, 17] However, the review by Morgan et al.,[16] provided additional analysis on the frequency of community pharmacists' recommendation of non-prescribed antibiotics. The analysis by Morgan et al.,[16] was limited to 13 studies and without specific estimates by country, region or symptom. Hence, a more robust and updated analysis is needed. Therefore, we estimated the frequency of the supply of antibiotics without a prescription in community pharmacies globally identifying regions where this practice commonly occurs, the disease conditions commonly treated with non-prescribed antibiotics and the types of antibiotics commonly supplied without a prescription in community pharmacies.

Methods

Search strategy

We searched EMBASE, Medline and CINAHL to identify studies published from January 2000 to September 2017 that reported the sale and dispensing of non-prescribed antibiotics in community pharmacies. Search terms used including antibiotics, community pharmacy, sales and dispensing were combined using Boolean operators (See Box1). Additional articles were identified by checking reference lists and Google scholar search. No language or geographical restrictions were applied to the search. The research protocol was registered in the PROSPERO international prospective register of systematic reviews (CRD42017058156).

Eligibility criteria for included studies

Two reviewers, AA and DA independently screened studies against the inclusion and exclusion criteria with a Kappa agreement of 91.9%. Discrepancies were resolved through consensus. We included observational and experimental studies that reported the proportion of over-the-counter antibiotic requests or consultations in relation to symptoms of suspected infectious diseases that resulted in non-prescription supply of antibiotics in community pharmacies. Population-based surveys that explored pharmacists' and public opinions on the supply and/or sources of non-prescription antibiotics were excluded. We also excluded qualitative studies (with no quantitative measures of non-prescription supply of antibiotics), reviews, editorials and conference reports.

Assessment of risk of bias of included studies

All studies were assessed for quality and risk of bias on eight criteria modelled largely from the 'Strengthening the Reporting of Observational Studies in Epidemiology framework'.[18] These criteria were: detailed description of research setting, sample size, sampling strategy, clear definition of clinical/product-request scenario, reliability of measurement, social desirability, statistical analysis methods and generalisability of results. Each risk of bias criteria was assessed as low (scored as 1), moderate/high or unclear (scored as 0). The total score for each study was computed. All studies were classified into one of the three levels of bias depending on their total scores, 0-2 (high risk), 3-5 (moderate risk) and 6-8 (low risk).

Data extraction

Data were extracted by two reviewers (AA & DA) and any discrepancy was resolved by consensus. The following data were extracted; author, year of publication, study country, sample size, number of visits/interactions observed, proportion of non-prescribed sale and supply of antibiotics. Other data extracted include; types of symptoms/disease conditions treated, types of antibiotics dispensed and nature of information given during consultation.

Data analysis

Statistical analyses were performed using Stata version 13.1 (StataCorp. LP, College Station, USA). A random effects meta-analysis based on the DerSimonian and Laird approach,[19] was conducted to calculate pooled proportions (with 95% confidence interval) of the supply of non-prescribed antibiotics for all included studies. The proportion of non-prescription supply of antibiotics in this study was calculated as the percentage of over-the-counter antibiotic requests or consultations in relation to symptoms of infectious diseases that resulted in the supply of antibiotics without a prescription. Proportion data were also pooled by symptoms of disease conditions, study period and types of antibiotics dispensed. I-squared (I^2) statistics were determined to assess the degree of heterogeneity across studies. Sub-group and meta-regression analyses were conducted to explore the causes of heterogeneity. The co-variates considered included geographical region, study period, sampling procedure (random vs convenience sampling), number of community pharmacies, type of simulated scenario, category of pharmacy staff, concealment in methodology and each risk of bias criteria. Co-variates were first tested individually and only those with p-values below 0.01 were included in the multivariate model. We performed sensitivity analysis to examine the effect of outliers and test the robustness of our findings.

Results

Study selection and characteristics

We identified 3302 articles through the literature search, of which 38 met the inclusion criteria (see figure 1). The 38 studies were conducted in 24 countries and involved 8085 interactions within 6353 community pharmacies. Antibiotics are classified as prescription-only medicines in all the countries included in this review with the exception of Thailand. In Thailand, pharmacists are legally allowed to supply some antibiotics without a prescription.

The majority of the studies (23 out of 38) included in this review were conducted in Asia. Almost all (37 out of 38) of the included studies were of cross-sectional design (Table 1). All included studies used simulated patient methodology with 35 of the 38 studies involving simulated-patient with concealed identities. The remaining three studies were based on pharmacy staff interviews using simulated scenarios. A range of scenarios were simulated in the included studies with the most common involving symptoms of upper respiratory tract infections (URTI), gastroenteritis and urinary tract infections (UTI) in women of childbearing age (Table 1).

The risk of bias assessment found that 15 (39%) studies had a low risk of bias while the remaining 23 (61%) studies had a moderate risk. The most common source of bias among the included studies was due to sampling (26/38, 68%) and half of the included articles (19/38) did not report a justification for the sample sizes used in their studies.

Pooled estimates of the supply of antibiotics without prescription

The overall pooled estimate of non-prescription supply of antibiotics was 62% (95% CI 53 – 72) (Figure 2). This global estimate was comparable to the estimate for Asia (65%, 95% CI 54 – 76), the most studied region. The pooled estimate for Southern and Eastern Europe (53%, 95% CI 33 – 72) was comparable to that of Africa (57% 95% CI 16 - 99). The pooled estimate for Africa, was lower than those for Asia (65%, 95% CI 54 – 76) and South America (78% 95% CI 72 - 84). This was due to the low prevalence in the Zimbabwean study (Figure 2). Sensitivity analysis conducted by excluding the Zimbabwean study yielded a pooled estimate of 74% (95% CI 63 – 85) for Africa. However, the overall proportion (64%, 95% CI 55 – 73) of non-prescription supply of antibiotics in community pharmacies was similar to the estimate obtained before the sensitivity analysis. Generally, non-prescription supply of antibiotics was more frequent in Indonesia (91%, 95% CI 86 – 94), Syria (87%, 95% CI 82 – 91), Saudi Arabia (85% 95% CI 72 – 99) and Ethiopia (85% 95% CI 75 – 92) (Figure 3).

Seven studies presented data on the proportion of non-prescription supply of antibiotics following a specific product request by patients. The figures ranged from 16% (95% CI 10 – 22) in Spain [20] to 98% (95% CI 94 – 102) in Saudi Arabia [21]. The pooled estimate was 78% (95% CI 59 - 97). Similarly, the proportion of non-prescription supply of antibiotics based on pharmacy staff recommendation following the presentation of clinical symptoms to them ranged from 8% (95% CI 4 -12) in Zimbabwe [22] to 94% (95% CI 92 – 98) in India [23]. The pooled estimate based on pharmacy staff recommendation was 58% (95% CI 48 – 68) (Figure 4).

Subgroup meta-analysis showed a significant difference between the pooled proportions of studies conducted from 2000 -2005 and 2011-2017 with estimates of 80% (95%CI 76 – 85) and 56% (95% CI 43 – 69), respectively (Table 2). Overall, substantial heterogeneity was observed on the pooled estimate of non-prescription supply of antibiotics (X^2 = 4239.0, p < 0.001, I^2= 99.1%). Of the sources of variation investigated through meta-regression, only number of community pharmacies, study period and three quality criteria (reliability of measurement, statistical analysis methods and generalisability of results) had p values below 0.10. These covariates yielded a significant multivariate model (p = 0.0193) that explained 25.3% of between-study variation.

Pooled estimates by symptom category

The proportion of non-prescription supply of antibiotics among patients with symptoms of upper respiratory tract infections (URTI) ranged from 19% (95% CI 15 – 22) in a study in Bosnia and Herzegovina [24] to 99% (95% CI 97 -100) in Vietnam [25]. The pooled estimate for URTI was 67% (95% CI 55 – 79) (Table 3). Penicillins were the most commonly recommended and supplied medicines to treat symptoms of URTI (Figure 5). Pooled analysis by individual type of antibiotics supplied revealed that amoxicillin 53% (95% CI 34-71; I^2=98.0, p<0.001), amoxicillin-clavulanic acid (co-amoxiclav) 39% (95% CI 23-54; I^2 =97.4, p<0.001) and azithromycin 19% (95% CI 11-27; I^2=96.2, p<0.001) were commonly supplied for URTI.

The pooled estimates of non-prescription supply of antibiotics to patients with symptoms of urinary tract infections (UTI) and acute gastroenteritis were 68% (95% CI 42-93) and 63% (95% CI 46-80), respectively. Fluoroquinolones (69%, 95% CI 50-88) including ciprofloxacin and norfloxacin were commonly supplied for UTI while metronidazole (55%, 95% CI 29-81) was the most commonly supplied non-prescription antibiotic for acute gastroenteritis.

Two studies investigated non-prescription supply of antibiotics in patients with persistent pulmonary tuberculosis. The proportions of non-prescription supply of antibiotics in these studies were 27% (95% CI 25-30) and 24% (95% CI 18-31) in India and Cambodia, respectively.

Nature of consultation and advice given

The proportion of patients that were referred to a medical prescriber without supplying an antibiotic ranged from 3% (95% CI 1 - 6) in a study in Indonesia [26] to 38% (95% CI 35 - 40) in a study in India.[15] The pooled estimate for referral was 21% (95% CI 14 - 28).

Very few consultations that resulted in non-prescription supply of antibiotics enquired about the patients' drug history (12%, 95% CI 4-19) and allergies (32%, 95%CI 11-53) (Table 4). The pooled proportion of the number of consultations with pharmacy staff that resulted in the provision of information regarding the dose and duration of treatment with the supplied antibiotics were 73% (95% CI 52-92) and 49% (95% CI 28-70), respectively. Four studies reported on the proportion of women of childbearing age presenting with symptoms of UTI that were asked about their pregnancy status prior to antibiotics being supplied. The proportion ranged from 0% in a Spainish study [10] to 23% in a Saudi Arabian study.[27]

Discussion

This is the first study to provide pooled estimates of the extent of the supply of antibiotics without prescription. Despite regional variations, supplying antibiotics without prescription remains high globally. About three in four (78%) antibiotic requests and three in five (60%) consultations (in relation to symptoms of infectious diseases) in community pharmacies resulted in the supply of antibiotics without prescription. The majority of these antibiotics were supplied for the treatment of disease conditions that were largely acute and self-limiting including upper respiratory tract infections and gastroenteritis.

Many of the antibiotics supplied without a prescription were broad-spectrum antibiotics including amoxicillin, amoxicillin-clavulanic acid, azithromycin and several fluoroquinolones. The use of broad-spectrum antibiotics increases the risk of the development of resistant infection including meticillin-resistant *Staphylococcus aureus* (MRSA). Broad-spectrum antibiotics were commonly recommended even in conditions where there are equally effective narrow spectrum antibiotics which can be used as first line therapies. For instance, fluoroquinolones were commonly recommended and supplied for uncomplicated urinary tract infections rather than the first-line narrow spectrum antibiotics such as trimethoprim and nitrofurantoin. Such use of fluoroquinolones can promote the development of resistant UTIs. A recent systematic review and meta-analysis estimating the global prevalence of antibiotic resistance in paediatric urinary tract infections caused by *E.coli* reported a pooled prevalence of 53.3% and 79.8% against ampicillin, and 2.1% and 26.8% against ciprofloxacin in OECD countries and countries outside OECD respectively.[28] Over the counter sale of antibiotics in developing countries (outside OECD) was one of the reasons given by the authors to explain the higher prevalence of resistance.[28]

Furthermore, the majority of the commonly supplied non-prescription antibiotics identified in our review including amoxicillin, azithromycin and the fluoroquinolones have been classified by the World Health Organisation as critically important antibiotics.[29] This is because of their unique place in the treatment of infectious diseases including being the sole or one of the limited therapies for serious infections. For instance, macrolides remain part of a limited treatment option for Campylobacter infections especially in children, in whom fluoroquinolones are contraindicated.[29] Therefore, the emergence of resistance to these antibiotics could have a significant impact on population health given the high and increasing incidence of campylobacter infections in children especially *Campylobacter jejuni*.[30]

Results of this study also highlight some concerns around the safe supply and use of antibiotics. Even though the safety of fluoroquinolones in pregnancy have not been fully established, they were commonly supplied for UTIs to simulated patients who were of child-bearing age without any check on their pregnancy status. In addition, only about one in three patients were asked if they have any known drug allergy during consultations. While antibiotics are largely perceived to be generally safe, serious adverse reactions including anaphylaxis have been associated with many of them.[31] Therefore, we recommend that all antibiotics dispensing should have questions about allergy and pregnancy status in cases of women of childbearing age to enhance their safe use.

Strict implementation of restrictions on over-the-counter sales of antibiotics has been shown to be effective in reducing non-prescription antibiotic consumption in Brazil, Chile and South Korea and Mexico.[32-34] Given that many countries have laws prohibiting over-the-counter sales of antibiotics, there is a need to ensure that these laws are strictly enforced. However, it is important to understand that over-the-counter sale of some antibiotics may be supported in certain contexts. For example, in the UK, pharmacists legally supplied using a patient group direction, azithromycin to patients with positive chlamydia test results.[35] Legislative changes in some countries including Canada and New Zealand have given designated pharmacists the authority to prescribe and dispense antibiotics for some conditions. For instance, in New Zealand, pharmacists can prescribe and dispense trimethoprim for short-term treatment of an uncomplicated UTI.[35]

Timely access and appropriate use of antibiotics have been associated with positive patient outcomes in several serious bacterial infections including pneumonia.[36] A significant proportion of deaths caused by infections in many developing countries can be averted with early diagnosis and treatment. However, in many of these countries, access to healthcare facilities and prescribers are limited. Community pharmacies are often the first point of contact for the public.[35, 37] Therefore, community pharmacists trained in antibiotic stewardship in these settings could play a significant role in ensuring prompt access to and rational use of antibiotics. They could deliver treatment for certain bacterial infections using standard treatment protocols, counsel patients on appropriate use of antibiotics, and prevent unnecessary use of antibiotics for non-bacterial infections through appropriate treatment of symptoms and counselling of patients to ensure they have a good understanding of their illness.[35] Hence, promoting rational use of antibiotics rather than just restricting the supply of antibiotics without a prescription may be a more appropriate focus for any relevant policy in these settings.

Finally, our study was limited by a lack of data from many countries. In addition, in countries where data were available, we included many small local/regional studies which may not necessarily reflect the extent of non-prescription supply of antibiotics across the whole nation. Geographical variations (urban vs rural) within the same country in terms of non-prescription supply of antibiotics cannot be ruled out. Therefore, our findings may have over or underrepresented the actual extent of non-prescription supply of antibiotics. Our findings could not take into account the impact of any national/regional policies targeted at reducing the supply of antibiotics without prescription, which was implemented after the publication of the included papers and has resulted in the reduction of non-prescription supply of antibiotics. We only looked at the supply of antibiotics without prescription but not antifungals or antivirals, which will be the focus of future research. Also, our aim was to estimate the global frequency of supplying antibiotics without a prescription but not to assess the association between non-prescription supply of antibiotics and development of antibiotic resistance, an important area for future research.

Conclusion

This review provides the most robust and up-to-date global estimate of the proportion of over-the-counter consultations and antibiotic requests that resulted in the dispensing of antibiotics without a prescription. Despite the limitation of our review, the findings suggest that antibiotics are frequently supplied without prescription in many countries even where this supply remains illegal. This overuse of antibiotics could facilitate the development and spread of antibiotic resistance. Our findings underscore the need for countries to enforce laws that limit the supply of antibiotics without prescription in community pharmacies.

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Conflicts of interests

The authors declare that they have no conflicts of interests.

Contributors

AA conceived and designed the study. All authors oversaw its implementation. AA, DA, MAH & EO were involved in the review activities including searches, study selection, data extraction and quality assessment. AA & DA planned and carried out the meta-analyses and meta-regressions. AA and MAH wrote the initial draft and all authors contributed writing to subsequent versions of the manuscript. All authors reviewed the study findings and read and approved the final version of the manuscript before submission.

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Box 1: Search strategy

#	Searches
1	(antibiotic* or antimicrobial* or antibacterial*).af.
2	(Non-prescri* or Sale* or Supply* or over the counter or Dispens* or Self-medication).af.
3	(community pharmac* or Pharmacy or pharmacies or Pharmacy shop* or Retail pharmac* or Shop* or Drug store* or Drug shop*).af.
4	1 and 2 and 3
5	limit 4 to year="2000 -Current"

Tables and figures

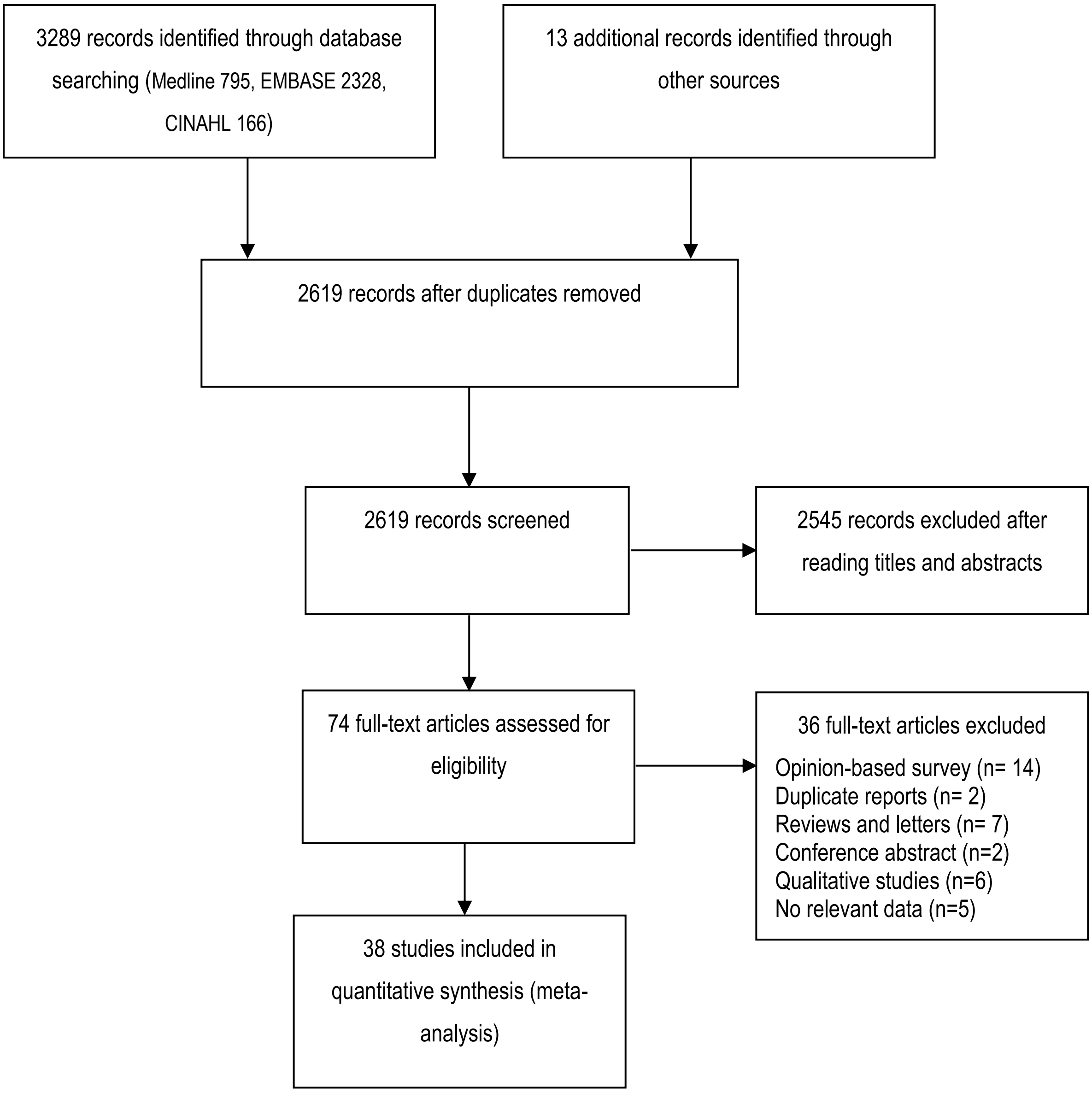

Figure 1: Flow diagram of article selection process

Table 1 Characteristics of included studies

Authors	Study location	Study design	Methods	Number of community pharmacies involved	Number of interactions or consultations	Proportion of dispensing of non-prescribed antibiotics (%)	Risk of bias classification
Hussain et al.,[38]	Pakistan	Cross-sectional	Simulated patient visits involving scenarios of symptom of upper respiratory tract infections (URTI)	371	371	57.4	Moderate
Puspitasari et al.,[26]	Indonesia	Cross-sectional	Simulated patient visits involving specific product request (ciprofloxacin tablets and tetracycline capsules)	88	176	90.9	Low
Almaaytah et al.,[39]	Jordan	Cross-sectional	Simulated patient visits involving scenarios of symptom of URTI, gastroenteritis and urinary tract infection (UTI) in women of childbearing age	202	202	74.3	Low
Gastelurrutia et al.,[20]	Spain	Cross-sectional	Simulated patient visits involving specific product requests and scenarios of symptoms of UTI in women of childbearing age	280	280	Product requests (16.3) and symptom-based scenarios (18.7)	Moderate
Marković-Peković and Grubisa,[40]	Bosnia and Herzegovina	Cross-sectional	Simulated patient visits involving scenarios of symptoms of URTI	131	131	58	Moderate

Plachouras et al., [41]	Greece	Cross-sectional	Simulated patient visits involving specific product requests (amoxicillin/clavulanate acid or ciprofloxacin)	174	174	72.4	Moderate
Quagliarello et al., [25]	Vietnam	Cross-sectional	Simulated patient visits involving scenarios of symptoms of URTI and gastroenteritis in children	75	150	86.7	Low
Shet et al., [42]	India	Cross-sectional	Simulated patient visits involving scenarios of symptoms of URTI in adults and gastroenteritis in children	261	261	66.7	Low
Volpato et al.,[43]	Brazil	Cross-sectional	Simulated patient visits involving scenarios of symptoms of URTI	107	107	74	Moderate
Llor & Cots,[44]	Spain	Cross-sectional	Simulated patient visits involving scenarios of symptoms of URTI, acute bronchitis and UTI in women of childbearing age	197	197	45.2	Low
Bin Abdulhak et al., [27]	Saudi Arabia	Cross-sectional	Simulated patient visits involving scenarios of symptoms of URTI, acute bronchitis, otitis media, gastroenteritis and UTI in women of childbearing age women) aged women)	327	327	77.6	Moderate
Al-Faham et al., [45]	Syria	Cross-sectional	Simulated patient visits involving scenarios of symptoms of URTI	200	200	87	Moderate

Erku et al., [37]	Ethiopia	Cross-sectional	Simulated patient visits involving specific product requests (amoxicillin and clavulanic acid capsule) and scenarios of symptoms of URTI	31	62	Product requests (93.5) and symptom-based scenarios (77.4)	Moderate
Diwan et al.,[46]	India	Cross-sectional	Simulated patient visits involving scenarios of symptoms of gastroenteritis in children	164	164	40.2	Moderate
Hoxha et al., [47]	Albania	cross-sectional	Specific product request	323	323	80.2	Moderate
Chang et al., [48]	China	cross-sectional	Simulated patient visits involving scenarios of symptoms of URTI in adults and gastroenteritis in children	256	512	68.8	Low
Saengcharoen et al., [49]	Thailand	Cross-sectional	Simulated patient visits involving scenarios of symptoms of URTI	32	128	87.5	Low
Contopoulos-Ioannidis et al., [50]	Greece	Cross-sectional	Simulated patient visits involving scenarios of symptoms of URTI	98	98	77.6	Low
Vacca et al., [51]	Columbia	cross-sectional	Simulated patient visits involving specific product requests (amoxicillin, azithromycin, ciprofloxacin and trimethoprim / sulfamethoxazole) and scenarios of symptoms of URTI, gastroenteritis, otitis media and UTI	200	239	80.3	Low

Saengcharoen & Lerkiatbundit,[14]	Thailand	cross-sectional	Simulated patient visits involving scenarios of symptoms of acute gastroenteritis in children	115	115	52.2	Low
Al-Mohamadi et al., [21]	Saudi Arabia	Cross-sectional	Simulated patient visits involving specific product requests (co-amoxiclav or cefaclor).	60	60	97.6	Moderate
Guinovart et al., [10]	Spain	Cross-sectional	Simulated patient visits involving scenarios of symptoms of URTI, acute bronchitis and UTI in women of childbearing age.	220	220	54.1	Moderate
Chalker et al., [52]	Vietnam	cross-sectional	Simulated patient visits involving scenarios of symptoms of sexually transmitted diseases (STD)	60	295	81.5	Moderate
Kalungia et al.,[53]	Zambia	Cross-sectional	structured interviewer-administered questionnaire with simulated case scenarios of symptoms of URTI and UTI in pregnancy	73	146	71.2	Moderate
Ibrahim et al.,[54]	Qatar	cross-sectional	Simulated patient visits involving scenarios of symptoms of acute gastroenteritis	30	60	43.9	Moderate
Chuc et al., [55]	Vietnam	Randomized controlled trial	Simulated patient visits involving specific product requests and scenarios of symptoms of uncomplicated URTI in a child and STD in an adult in an adult man	58	116	Product requests (94.8) and symptom-based scenarios (41.1)	Low

Salunkhe et al., [23]	India	cross-sectional	Simulated patient visits involving scenarios of symptoms of URTI or diarrhoea	263	263	94.3	Moderate
Jaganathan et al., [56]	India	Cross-sectional	Simulated patient visits involving scenarios of symptoms of acute gastroenteritis and URTI	120	120	72.5	Moderate
Amin et al., [57]	Egypt	Cross-sectional	Simulated patient visits involving scenarios of symptoms of URTI	104	104	65.4	Low
Satyanarayana et al., [15]	India	Cross-sectional	Simulated patient visits involving scenarios of symptoms of pulmonary tuberculosis (TB)	622	1200	27	Low
Nyazema et al., [22]	Zimbabwe	Cross-sectional	Simulated patient visits involving scenarios of symptoms of STD and gastroenteritis	87	184	8.2	Moderate
Alabid et al., [58]	Malaysia	Cross-sectional	Simulated patient visits involving scenarios of symptoms of URTI	50	100	32	Moderate
Malik et al., [59]	Pakistan	Cross-sectional	Simulated patient visits involving scenarios of symptoms of malaria	238	238	28.6	Moderate
Bell et al., [60]	Cambodia	Cross-sectional	Interviewer-administered questionnaire with simulated case scenarios of TB	170	170	24.1	Low
Al-Ghamdi [61]	Saudi Arabia	Cross-sectional	Simulated patient visits involving scenarios of symptoms of UTI	88	88	81.8	Moderate

Homedes and Ugalde, [62]	Mexico	Cross-sectional	Interviewer-administered questionnaire with simulated case scenarios of URTI and gastroenteritis	25	49	71.4	Moderate
Marković-Peković et al [24]	Bosnia and Herzegovina	Cross-sectional	Simulated patient visits involving scenarios of symptoms of URTI	383	383	18.5	Low
Okuyan et al [63]	Turkey	Cross-sectional	Simulated patient visits involving scenarios of symptoms of URTI	70	70	45.7	Moderate

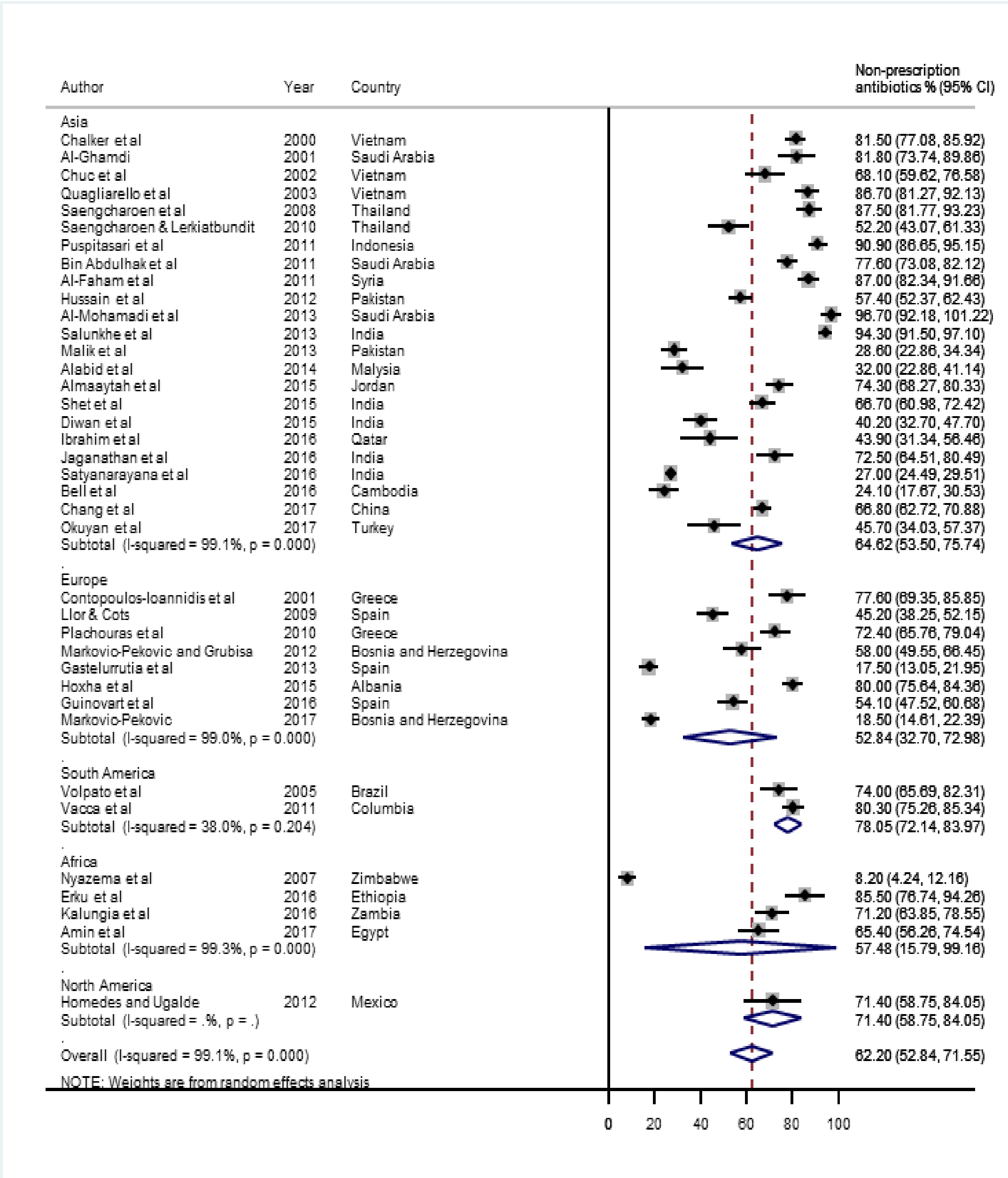

Figure 2: Meta-analysis for the overall pooled proportion of non-prescription supply of antibiotics

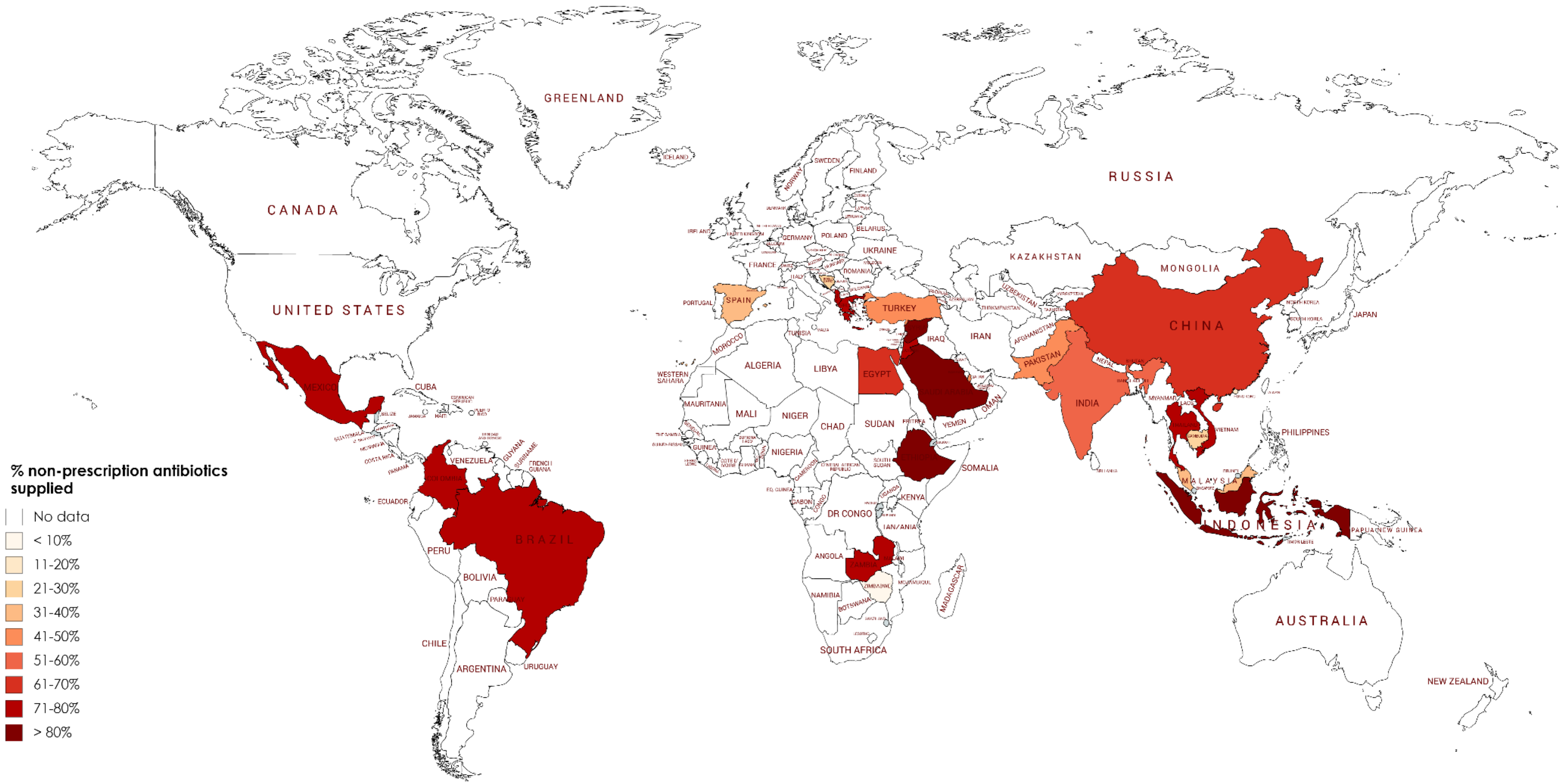

Figure 3: Country level estimates of non-prescription supply of antibiotics

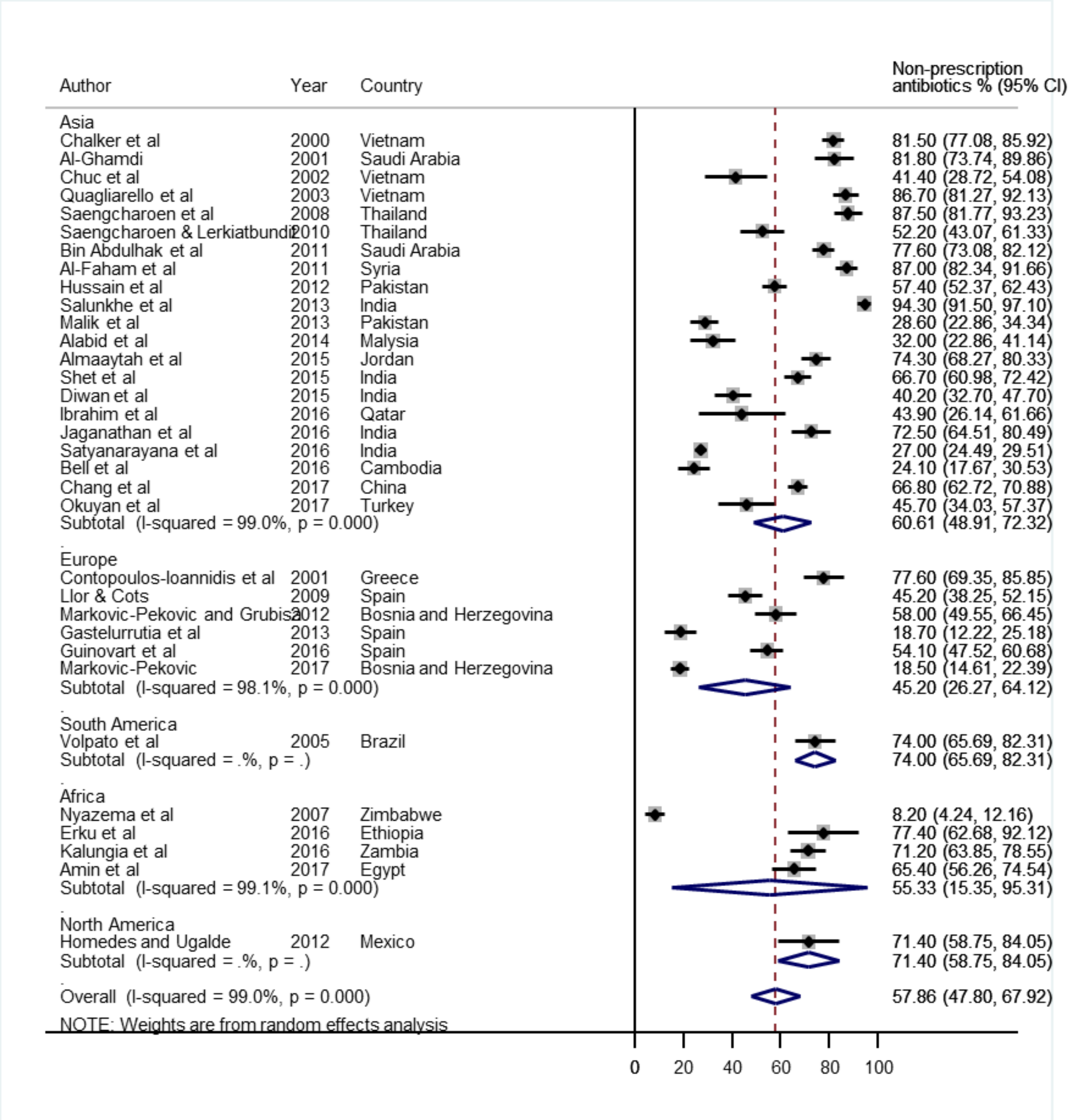

Figure 4: Meta-analysis for the proportion of non-prescription supply of antibiotics based on pharmacy staff recommendation

Table 2: Subgroup meta-analysis of the proportion of non-prescription supply of antibiotics

Subgroup	Estimate % (95%CI)	No. studies	Heterogeneity
Region			
Asia	65 (54 – 76)	23	$I^2 = 99.1\%$, $p < 0.001$
Africa	57 (16 – 99)	4	$I^2 = 99.3\%$, $p < 0.001$
Europe	53 (33 – 73)	8	$I^2 = 98.7\%$, $p < 0.001$
South America	78 (72 – 84)	2	$I^2 = 38.0\%$, $p = 0.204$
North America	71 (59 – 84)	1	ND
Study period			
2011 - 2017	56 (43 – 69)	7	$I^2 = 99.1\%$, $p < 0.001$
2006 - 2010	62 (43 – 81)	12	$I^2 = 99.4\%$, $p < 0.001$
2000 - 2005	80 (76 – 85)	19	$I^2 = 71.8\%$, $p = 0.002$
Number of community pharmacies included			
≥ 100	58 (46 – 70)	23	$I^2 = 99.2\%$, $p < 0.001$
< 100	69 (52 – 85)	15	$I^2 = 99.0\%$, $p < 0.001$
Type of scenario			
Direct product request	85 (75 – 94)	4	$I^2 = 93.9\%$, $p < 0.001$
Symptom-based	59 (49 – 70)	30	$I^2 = 99.1\%$, $p < 0.001$
Mixed*	63 (26 – 99)	4	$I^2 = 99.3\%$, $p < 0.001$
Category of pharmacy staff			
Pharmacist only	59 (32 – 87)	5	$I^2 = 98.2\%$, $p < 0.001$
Mixed**	58 (42 – 74)	12	$I^2 = 99.0\%$, $p < 0.001$
Unspecified	65 (52 - 78)	21	$I^2 = 99.3\%$, $p < 0.001$
Concealment in methodology			
Yes	63 (53 - 73)	35	$I^2 = 99.1\%$, $p < 0.001$
No	55 (21 – 90)	3	$I^2 = 98.1\%$, $p < 0.001$

*studies that employed both direct product request and symptom-based scenario. **studies that included a variety of pharmacy staff, ND – not determined

Table 3: Pooled estimates on the proportion of antibiotics supplied without a prescription by disease category

Symptom category	Estimate % (95% CI)	No. studies	Heterogeneity
URTI	67 (55–79)	23	$I^2 = 98.7\%$, $p < 0.001$
Bronchitis	42 (34-49)	2	$I^2 = 98.5\%$, $p < 0.001$
Otitis media	57 (47-68)	2	$I^2 = 57.0\%$, $p = 0.127$
Gastroenteritis	63 (46-80)	12	$I^2 = 98.6\%$, $p < 0.001$
UTI	68 (42-93)	6	$I^2 = 97.8\%$, $p < 0.001$
STD	47 (44-51)	2	$I^2 = 99.8\%$, $p < 0.001$
Pulmonary TB	27 (24-29)	2	$I^2 = 0.0\%$, $p = 0.410$
Malaria	29 (23-34)	1	ND

ND – not determined

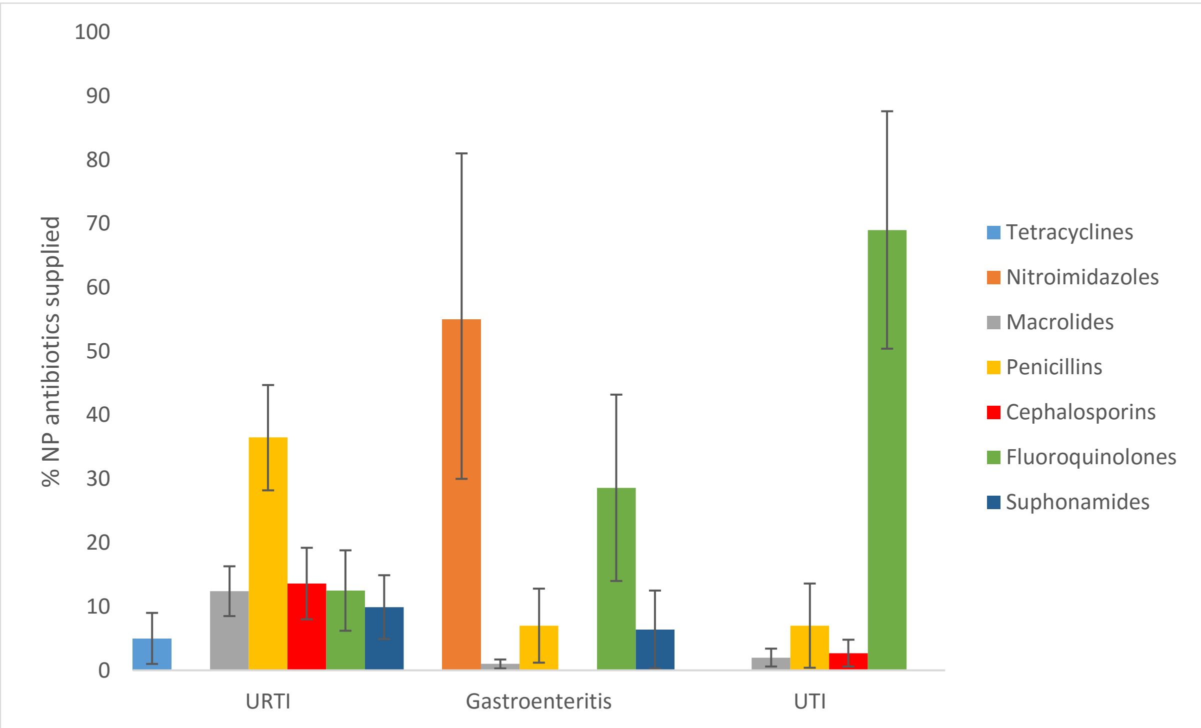

Figure 5: Classes of antibiotics supplied without prescription for Gastroenteritis, URTI and UTI

Table 4: Nature of counselling provided during consultation

Nature of counselling	Estimate % (95% CI)	No. studies	Heterogeneity
Asked patients about allergy	32 (11-53)	10	$I^2 = 99.4\%$, $p < 0.001$
Asked patients about any medicines they are taking	12 (4-19)	6	$I^2 = 96.1\%$, $p < 0.001$
Asked female patients of child-bearing age about pregnancy status	8 (1-18)	4	$I^2 = 82.5\%$, $p = 0.003$
Explained the dose of antibiotics	73 (52-92)	11	$I^2 = 99.2\%$, $p < 0.001$
Explained how long to take the antibiotics	49 (28-70)	12	$I^2 = 99.2\%$, $p < 0.001$
Referred patients to a physician	21 (14-28)	16	$I^2 = 97.8\%$, $p < 0.001$