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Non-prescription antimicrobial use worldwide: a systematic review

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Abstract

In much of the world antimicrobial drugs are sold without prescription or oversight by health-care professionals. The scale and effect of this practice is unknown. We systematically reviewed published works about non-prescription antimicrobials from 1970–2009, identifying 117 relevant articles. 35 community surveys from five continents showed that non-prescription use occurred worldwide and accounted for 19–100% of antimicrobial use outside of northern Europe and North America. Safety issues associated with non-prescription use included adverse drug reactions and masking of underlying infectious processes. Non-prescription use was common for non-bacterial disease, and antituberculosis drugs were available in many areas. Antimicrobial-resistant bacteria are common in communities with frequent non-prescription use. In a few settings, control efforts that included regulation decreased antimicrobial use and resistance. Non-prescription antimicrobial and antituberculosis use is common outside of North America and northern Europe and must be accounted for in public health efforts to reduce antimicrobial resistance.

Introduction

Antimicrobials are among the most commonly purchased drugs worldwide.[1] They are essential treatments, especially in the developing world where infectious diseases are a common cause of death.[2] Crucial to success of antimicrobial treatment is the use of well-tolerated drugs with activity against common pathogens. Antimicrobial resistance is shrinking the range of antimicrobial drugs and is a worldwide public health problem.[3–5] Although resistance is commonly studied in Europe and North America, developing countries also face the threat of antimicrobial resistance. A substantial proportion of healthy

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Search strategy and selection criteria:
These are described in detail in the Methods section.

Contributors
DJM had the original idea for the Review; RL, ENP, and SW helped develop the concept. DJM and SW searched published works. INO, RL, ENP, and SW interpreted data. DJM and INO created the figures. DJM created the tables. All authors wrote the paper.

Conflicts of interest
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people in develop ing countries are colonised with multidrug-resistant bacteria.[6–11] Common bacterial pathogens such as *Escherichia coli, Salmonella* spp, or *Streptococcus pneumoniae* are often multidrug resistant in these settings. *Mycobacterium tuberculosis*, including multidrug-resistant *M tuberculosis,* is also common in low-income to middle-income countries, and extremely drug resistant strains have emerged.[12,13] By contrast with Europe and North America, developing countries have limited access to antimicrobials, particularly to new drug classes, and drugs that are available often lack activity against these multidrug-resistant bacteria that are becoming more common.[14–16]

Antimicrobial resistance is a global issue.[17] Resistance genes spread throughout the world, as shown by the global spread of CTX-M extended spectrum β-lactamase (ESBL), NDM-1, or *Klebsiella pneumoniae* carbapenemase (KPC) producing Enterobacteriaceae.[18–20] Travellers might acquire resistant bacteria that can be transmitted in their home countries.[20–22] Transmission between developed and developing countries is presumably two-way and is rarely identified in developing countries because of inadequate surveillance.[17,19,20]

Antimicrobials, when appropriately targeted to a susceptible pathogen, improve outcomes for patients.[23] However, use and overuse at the population level is associated with the emergence of bacterial resistance.[16,24] Behaviours that promote resistance in one individual or population can have wider consequences for the global community.[25] These behaviours extend beyond human antimicrobial use to areas such as antimicrobial use in livestock production.[26] Although non-prescription antimicrobial use is typically studied within a single country, the effect of widespread antimicrobial overuse is likely to be felt worldwide.[15]

By contrast with northern Europe and North America, where outpatient antimicrobials are largely restricted to prescription-only use, non-prescription access to antimicrobials is common in the rest of the world.[9,14–16] Pharmaceutical surveillance in Spain showed that about 30% of outpatient antimicrobials purchased were not identified by reimbursement data, largely because nonprescription sales were not tracked.[27] In all countries, most antimicrobial use occurs outside of hospitals.[28] Interventions to preserve the effectiveness of antimicrobials have focused on hospitals or providers thereby missing non-prescription antimicrobial use.[29] Previous reviews have broadly described the problem of antimicrobial resistance in developing countries. However, none have expressly addressed nonprescription antimicrobial use.[14,15,30–35] To quantify the global frequency and effect of non-prescription antimicrobial use, we did a systematic review of published work.

Methods

Search strategy and selection criteria

We searched Medline, PubMed, and Google Scholar for articles published in English or Spanish between 1970–2009 using the keywords “antibiotic(s)”, “antimicrobial(s)”, “antituberculosis”, or “antitubercular” combined with “over-the-counter (OTC)”, “nonprescription”, “community pharmacy”, “pharmacies”, “developing country”, “pharmacoepidemiology”, “rational use of medicines”, and “self-medication”, and the corresponding Medical Subject Heading (MeSH) terms for the above keywords.

Data extraction and analysis

DJM and SW reviewed each paper independently. Articles that studied a community setting (as opposed to hospital) and reported if antimicrobial dispensing was prescription-based were selected. Discrepancies were resolved through discussion between the authors. We classified providers to be either physicians or specially trained nurses. We excluded

antimalarials from this Review because many countries recommend home-based treatment, which often entails non-prescription use as standard practice.[36]

We identified the following general types of studies: community surveys of individuals reporting frequency of prescription and non-prescription antimicrobial use, simulated-client-method pharmacy studies in which actors surveyed antimicrobial dispensing practices of pharmacies, harm or potential harm related to nonprescription antimicrobial use, associations between non-prescription antimicrobial use and bacterial resistance, and non-prescription use of antituberculosis drugs.

Community surveys were assessed for quality on the basis of these criteria: appropriate design, standardised questionnaires, and response rates. Those judged to be of moderate-to-high quality were included.[37] For each region, community surveys of antimicrobial use were combined to report frequency with which patients received antimicrobials. To account for different sample sizes in each survey, the percentage of patients using non-prescription antimicrobials was multiplied by the total number of survey respondents for each survey. Absolute numbers of patients who received non-prescription antimicrobials for a region were then divided by total number of survey respondents. This number is reported as weighted non-prescription antimicrobial use. Similar methods were used to report location from which non-prescription antimicrobials were obtained (when information was available).

Simulated-client-method pharmacy surveys were defined as studies in which individuals identifying themselves as patients or relatives of patients approached pharmacy staffrequesting medical assistance with a predetermined scenario.[38] Surveys of pharmacy bulk purchase or exit interviews with patients, although recommended by WHO for monitoring antimicrobial use, were not included as these do not provide estimates of non-prescription use.[39]

Results

Frequency of non-prescription use

We identified 1434 potential references. 117 articles are included in this Review (figure 1). We identified 35 studies that surveyed use of antimicrobials by patients outside of hospital settings (figure 2). We identified three African surveys; two were surveys of the general population in Nigeria[40] and Sudan[41] and one was a survey of sex workers or soldiers who had sex with them in Nigeria.[42] Both general community surveys focused on non-prescription use of anti microbials and reported frequency of antimicrobial use from 48% over 1 month to 100% lifetime use. Of the antimicrobials used, weighted nonprescription use was 100% (2250 of 2250). Of the nonprescription antimicrobials, 76% were purchased at a pharmacy and 24% were from friends, family, or home (one study enrolled participants at a pharmacy, potentially increasing the proportion of non-prescription antimicrobials purchased at a pharmacy).[42]

Nine surveys from Asia were identified, of which seven were studies of the general population,[8,43–48] one was of sex workers,[49] and one was based on a review of pharmacy records.[50] Frequency of antimicrobial use varied from 4–75%, 4 weeks before each survey. Of antimicrobials used, weighted non-prescription use was 58% (7761 of 13 366). The source of non-prescription antimicrobials was not reported reliably.

Of seven European studies,[51–57] one surveyed 19 countries with at least 200 respondents per country.[52] Sufficient survey data were available to describe individual regions. Northern

Europe, southern Europe, central Europe, and eastern Europe were described separately because of sufficient granularity of data and similarity of practice within each region.

Two surveys of the general population from northern Europe were identified,[52,56] which represented one primary survey of Austria, Belgium, the Czech Republic, Denmark, Ireland, Luxembourg, the Netherlands, Sweden, and the UK.[52] Frequency of antimicrobial use varied from 14–37% in the past year. Of antimicrobials used, weighted non-prescription use was 3% (330 of 9707). Of the non-prescription antimicrobials, 19% were purchased at a pharmacy and 81% were from friends, family, or home.

Four surveys of the general population from southern Europe were identified, with data for Greece, Italy, Malta, and Spain.[51–55] Frequency of antimicrobial use varied from 47–73% in the past year. Of antimicrobials used, weighted non-prescription use was 19% (4113 of 21 599). Of the non-prescription antimicrobials, 47% were bought at a pharmacy and 53% were from friends, family, or home.

Two surveys of the general population from eastern Europe were identified,[52,57] which had data from one primary survey of Lithuania, Poland, and Romania.[52] Frequency of antimicrobial use varied from 23–51% in the past year. Of antimicrobials used, weighted nonprescription use was 30% (625 of 2112). Of the nonprescription antimicrobials, 68% were purchased at a pharmacy and 32% were from friends, family, or home.

One survey of the general population from central Europe was identified with data for Croatia, Slovakia, and Slovenia.[52] Frequency of antimicrobial use varied from 31–61% in the past year. Of antimicrobials used, weighted non-prescription use was 6% (141 of 2304). Of the nonprescription antimicrobials, 68% were purchased at a pharmacy and 32% were from friends, family, or home.

Six surveys of the general population from the Middle East had data for Turkey,[58,59] Jordan,[60,61] and Israel.[52,62] Two studies[52,62] reported data from the same population, and the most exhaustive study was included.[52] We identified one study of adolescent girls in Saudi Arabia.[63] Antimicrobial use varied from 23–46% in the past year. Of antimicrobials used, overall non-prescription use was 39% (4782 of 12 283), although Israel was an outlier for the region with 4% non-prescription use. Of nonprescription antimicrobials, 44% were purchased at a pharmacy and 56% were from friends, family, or home.

Three surveys of the general population from South America included data for Bolivia,[10] Brazil,[64] and Peru.[65] Frequency of antimicrobial use varied from 23%, in the past 2 weeks, to 62%, in the past 4 months. Weighted non-prescription antimicrobial use was 25% (312 of 1224). The source of non-prescription antimicrobials was not described.

From Central America and the Caribbean, studies from Honduras,[66] Mexico,[67,68] and Trinidad and Tobago[69,70] were available. Four studies[66–70] reported on the same populations and in these cases the more exhaustive study was reviewed.[68,70] Frequency of antimicrobial use varied from 5–55% in the 2 weeks to 6 months before each study. Of antimicrobials used, weighted non-prescription use was 19% (1867 of 9917). Of the non-prescription antimicrobials, 86% were purchased at a pharmacy and 14% were from friends, family, or home.

No surveys of the general population in North America were identified. However, two surveys of Latin American immigrants[71,72] and one survey of patients attending a sexually transmitted disease clinic,[73] all in the USA, discussed non-prescription antimicrobial use. Within these groups, 14–26% reported non-prescription antimicrobial use a year before each study.

We identified no clear temporal trends in proportion of non-prescription antimicrobial use over the 40-year period examined in this Review.

13 studies were identified in which a simulated-client survey was used to assess willingness of pharmacy staffto dispense an antimicrobial in response to specific clinical scenarios (table 1). We did not include simulatedclient surveys without a predefined clinical scenario or direct surveys of pharmacy staffor general national policies, because these have been reported to be less reflective of actual practice.[84] These surveys examined practices of ten to 197 pharmacies. Two studies examined many countries, and country-specific results are shown in table 1.[79,81]

Wide variation was noted between studies, with some studies finding infrequent prescription of antimicrobials. Some of this variation might be ascribed to variations in the clinical scenario presented to pharmacists. However, frequency of antimicrobial dispensing was not always logical: in one study, fewer patients with high fever and sinusitis received antimicrobial than did those in the same scenario with low fever.[77] No obvious temporal or geographical patterns in antimicrobial dispensing were evident. Inappropriate antimicrobial dispensing was common, including use of antituberculosis drugs for standard bacterial infections and anti tuberculosis monotherapy. [74,83,85] No studies comparing frequency of antimicrobial dispensing by pharmacists and providers in the same area were identified. Community surveys have shown that pharmacists were more likely than physicians to dispense inappropriate antimicrobials in Brazil,[63] but less likely in Mexico.[67]

One study,[81] in Vietnam and Thailand, assessed a pharmacy intervention that included enforcement of existing regulation and education in pharmacies randomly assigned to intervention or control. In Vietnam, 71% of patients with cough were given antimicrobials by pharmacies after the intervention compared with 95% without. The same intervention in Thailand resulted in no difference (88% *vs* 92%), showing the importance of culture.[81] Finally, one study surveyed internet-based pharmaceutical sites accessed within the USA, finding that all major classes of antimicrobials were available for purchase without prescription, generally from countries that do not regulate antimicrobials.[86]

Safety

26 studies addressed potential or confirmed patient-safety issues related to non-prescription use of antimicrobials. No standardised method for these studies was identified. Most reported potential adverse events, although four reported actual adverse events including death, in relation to non-prescription use of antimicrobials (table 2).

Potential adverse events were common. Pharmacists dispensing non-prescription antimicrobials had no knowledge of patients' allergies 83–100% of the time.[76,82] Potential side-effects were discussed in about 50% of non-prescription antimicrobial purchases.[81,87] Duration of antimicrobial use was shorter without than with a prescription.[100] Many studies of non-prescription dispensing showed short, often single-day, courses of antimicrobials.[41,48,82,85,88,94,101] Dose of antimicrobials was also commonly lower than standard doses.[10,41,85,89] Parenteral antimicrobials were often available without prescription.[52,66,68,89–92]

An additional safety concern was substandard quality of antimicrobials available without prescription. Expired drugs or those that, as a result of degradation, have decreased bioavailability might both predispose a patient to treatment failure and promote antimicrobial resistance.[30,94] Outright counterfeit antimicrobials are available in developing countries and can lead to treatment failure or direct harm;[94,95] non-prescription use of

substandard antimicrobials is probably more common, although low-quality antimicrobials have also been identified through official prescription sources.[102]

Definite adverse effects of non-prescription antimicrobials were rarely reported (table 2), probably due in part to the decentralised health-care systems in most areas with non-prescription sale of antimicrobials. In Taiwan, patients admitted to hospital through the emergency room with detectable anti microbial concentrations in urine were nearly twice as likely to have a masked or missed diagnosis of an infectious disease.[97] Two case reports described severe adverse events in relation to non-prescription antimicrobials (table 2).

Adverse effects of non-prescription antimicrobials are rarely reported, but they are likely at least as common as adverse effects of prescription antimicrobials. In a study from North America, penicillin, cephalosporins, clindamycin, sulphonamides, and fluoroquinolones were the antimicrobials most commonly associated with adverse events. Of adverse events requiring emergency room attendance, 79% were allergic reactions. Antimicrobials accounted for 19% of all visits to the emergency room for adverse drug events, with some associated with a rate of serious adverse events as high as 20 per 10 000 prescriptions.[103]

Resistance

Eight studies assessed bacterial resistance while surveying frequency of non-prescription use of antimicrobials in human beings. Bartoloni and colleagues[10] studied non-pathogenic *E coli* isolates from children under age 5 years in Bolivia. Overall, 40% of children harboured non-pathogenic *E coli* resistant to ampicillin, co-trimoxazole, tetracycline, and chloramphenicol (which were the antimicrobials most commonly used in the communities studied). In this population, antimicrobials were available without a prescription and were frequently used. Bartoloni and colleagues[11] did a larger follow-up study of non-pathogenic *E coli* in Bolivia and Peru and reported that, 8 years after the first study, multidrug resistance had increased to 90% of isolates and that after the introduction of fluoroquinolones resistance to them had increased.[11]

Frequency of resistance has been examined in respiratory pathogens in Vietnamese children and Senegalese adults with urinary tract infections.[8,45,104] In all studies, high rates of community resistance were reported and were associated with patients receiving antimicrobials 6 months before each study, in communities with high non-prescription antimicrobial use. The risk conferred by use of non-prescription antimicrobials in these small studies seems to be roughly equal to that reported for prescription antimicrobial use in a recent meta-analysis (odds ratio 1·4–3·7).[8,104,105]

At a population level, clinically important bacterial resistance including penicillin-resistant and erythromycin- resistant *S pneumoniae* and ciprofloxacin-resistant non-typhi salmonella has been associated with increasing non-prescription use of these antimicrobials in a Thai community.[106]

At least some of these shifts in antimicrobial resistance are potentially reversible: data about pharmaceutical use in Pakistan was combined with data about antimicrobial resistance to show a relation between declining use of antimicrobials and declining resistance in *Salmonella enteric* serotype Typhi.[15] In Chile, as a result of regulation of antimicrobials, consumption decreased and *E coli* antimicrobial resistance seems to have decreased.[6]

Antituberculosis drugs

Essential antituberculosis drugs were available without prescription in many regions (panel). Non-prescription use included monotherapy with rifampicin for urinary tract infection or sexually transmitted diseases,[49,83] isoniazid for general respiratory ailments,[107] or other

antituberculosis drugs, including streptomycin, for many non-tuberculosis indications.[40,52,93,110,112]

Treatment of presumed tuberculosis with nonprescription antituberculosis drugs was common—over half of antimicrobials purchased for treatment of tuberculosis in Manila, Philippines, and Nagpur, India, were dispensed without prescription.[93,108] Pharmacies in Mexico often recommended non-prescription rifampicin monotherapy for tuberculosis.[74] Second-line antituberculosis drugs, including moxifloxacin and aminoglycosides, have been widely available without prescription according to published works,[58,93,108] although this may have improved after recent WHO recommendations.[12]

Discussion

The causes and consequences of non-prescription antimicrobial use are varied. Poor regulation of antimicrobials results from absent policies or, more commonly, from absent enforcement of policies, as happens in southern European countries.[51–55] Community antimicrobial resistance was common in several studies that examined communities with frequent use of nonprescription antimicrobials.[6–11] Antimicrobial use, whether it is prescription or non-prescription, exerts antimicrobial selection pressure.[3–5] No studies have shown that non-prescription antimicrobial use is worse than equally frequent prescription antimicrobial use. However, non-prescription antimicrobials are associated with very short courses[41,48,82,85,88,93,101] and inappropriate drug and dose choice.[10,41,74,83,85,88] These factors make non-prescription use a greater concern than prescription use. Of note, most community surveys relied on patient reporting of antimicrobial use (with a variable degree of confirmation). Since some surveys reported that patients often do not know they were prescribed an antimicrobial, the true proportion of patients using antimicrobials is probably higher than reported.[93] In support of this assumption, more widespread antimicrobial use was identified with urine sampling than with patient selfreport. [97,115–118] Expansion of internet commerce provides virtual worldwide access to non-prescription antimicrobials; those available on the internet are diverse and generally seem to originate in countries in which non-prescription antimicrobials are available.[86]

Non-prescription use of antimicrobials is inherently associated with little guidance regarding appropriate antimicrobial selection for individual syndromes and safe practices to minimise adverse drug effects (even when provided by a pharmacist).[76,81,82,87] Appropriate antimicrobial use is complex and must be based on local susceptibility patterns. In areas where antimicrobial susceptibility data is unavailable, antimicrobial selection is difficult, even for skilled providers.[14–16] Uninformed patients or undertrained pharmacy staffrarely have access to basic information regarding appropriate antimicrobial use and do not appreciate the complexity involved in decisions surrounding drug selection.[64,67,76,83] As a result, financial concerns often guide antimicrobial selection resulting in short duration of treatment.[15,35,119] The conflict of interest inherent in the same individual prescribing and dispensing antimicrobials is a potential target for regulatory intervention.

Despite concerns about inappropriate use, nonprescription status of antimicrobials might be an important mechanism of access to antimicrobials in resource-limited settings. Interventions to reduce inappropriate antimicrobial use, be they focused on prescription or non-prescription, must be monitored so as to not limit access to antimicrobials for those patients with true bacterial disease.[120] Receipt of appropriate antimicrobials in a timely fashion is a determinant of good outcome in pneumonia and other serious bacterial illnesses.[121]

Clear evidence that antimicrobials obtained without prescription are used less appropriately than prescription antimicrobials does not exist. Providers, pharmacists, and patients might be equally as likely to overuse antimicrobials in any given setting.[39,64,67] Studies with patients simulated by actors showed that inappropriate antimicrobial dispensing by pharmacists without a prescription occurred frequently.[74–83,85] In low-income to medium-income countries, training of health-care workers as part of WHO's Integrated Management of Childhood Illness strategy has been shown to increase appropriate use of antimicrobials and decrease inappropriate use.[122–125] Non-physician health-care workers trained in integrated management of childhood illness might use antimicrobials more judiciously than physician providers. In resource-limited settings, training of nonphysician providers could increase both access to and appropriate use of antimicrobials; this is especially important in regions where inadequate numbers of physician providers could drive non-prescription antimicrobial use.[126]

Inappropriate antimicrobial use by patients with true bacterial infections is associated with treatment failure and masking of the underlying clinical syndrome.[97] In patients treated inappropriately, either because they do not have an underlying bacterial infection or receive an inappropriate drug or suboptimum duration of treatment, patients are exposed to the risks of an antimicrobial without benefit. Although widely perceived as low-risk drugs, antimicrobials are the second most common cause of adverse drug events in the USA,[103] and nonprescription antimicrobial use has been associated with severe adverse events including death.[98,99]

Non-prescription use of antituberculosis drugs for non-tuberculosis indications was common. Since up to a third of the world's population is estimated to be infected with tuberculosis,[13] substantial use of antituberculosis drugs in countries with a high prevalence of tuberculosis is concerning. Essential firstline antituberculosis drugs include rifampicin, isoniazid, pyrizinamide, ethambutol, and streptomycin.[13] Although these drugs are generally poor antibiotics, they are available and used for tuberculosis and nontuberculosis indications in many countries with a high prevalence of tuberculosis. Previous use of antituberculosis drugs is a risk factor for development of multidrug-resistant tuberculosis. Second-line drugs including fluoroquinolones and aminoglycosides are also available without a prescription in most countries, which could be a factor in the emergence of extremely drug-resistant tuberculosis.

We have not reviewed interventions to improve nonprescription use, because solutions are often specific to a culture, country, or region.[14,15,35] Many groups have described comprehensive guidelines that emphasise development of health-care systems, including a WHO report on containment of antimicrobial resistance.[14,33–35,127] Chile and South Korea are notable examples of countries that improved regulation of non-prescription antimicrobial use and seem to have improved resistance profiles.[128–130] However, whether or how quickly resistance can be reversed in response to a reduction in selective pressure is unknown.[131,132]

The contribution of non-prescription antimicrobial use to the worldwide development and spread of antimicrobial resistance genes and bacteria is not known. Hospital and community prescription use and antimicrobial use in livestock production all exert selection pressure for antimicrobial resistance.[26] Countries with high levels of community antimicrobial resistance often have non-prescription antimicrobial use. Non-prescription use has been speculated to play an important role in selecting and maintaining these high levels of community antimicrobial resistance.[18,20,133,134]

Our Review has limitations including the combination of studies with heterogeneous populations and the analysis of studies over a broad time period. Data might not mirror

current practice in countries included in our Review. Data about dispensing practices in regions were extrapolated, and although many neighbouring countries probably had similar practices, exceptions exist such as Chile in South America. As in any review, a positive publication bias could affect some findings. Our Review is not meant to be a reference for policy or enforcement of such policy in specific countries, but is meant to be a broad overview of general issues associated with non-prescription antimicrobial use. Future studies are needed that include standardised definitions and methods and sample many countries, such as those done in Europe by Grigoryan and colleagues.[52] Studies that focus on individual patients or providers are important to accurately identify practice and not just policy in those regions where substantial differences might exist.[83] Studies of antimicrobial use should assess the appropriateness of prescription and non-prescription use so that local interventions could be best targeted for the greatest effect.

Despite many publications describing the frequency of non-prescription use and the adverse effects of such a practice, high-quality research is scarce. In the absence of rigorous studies, interventions to improve nonprescription antimicrobial use by effective restriction of national formularies to safe antimicrobials should be used; this should include restriction of aminoglycosides and other injectable antimicrobials. Essential first-line antituberculosis drugs should be restricted to prescription-only use in all countries, and secondary antituberculosis should be restricted in countries with a high prevalence of multidrug-resistant tuberculosis. Appropriate labelling of anti microbials including common indications, treatment duration, and side-effects could improve safety. Restriction of dispensing to a set number of pills, ideally in blister packs, could aid in appropriate use when healthcare practitioners are not available. In middle-income to high-income countries with reliable access to health-care practitioners, antimicrobials should be restricted to prescription-only status.

Community antimicrobial stewardship must include a focus on non-prescription antimicrobials. Most methods of monitoring antimicrobial use including pharmacy prescription monitoring or health-care insurance billing do not reliably detect non-prescription use. Pharmacy exit interviews or community surveys more accurately identify total antimicrobial use. In countries with high levels of non-prescription use, interventions to decrease community antimicrobial use should focus on the general public. Countries that have effectively decreased non-prescription use have done so by combining regulation with expanded access to health care.

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Panel: Reports of WHO first-line antituberculosis drugs available without prescription for treatment of tuberculosis and other bacterial infections

First-line drug antituberculosis drugs include rifampicin, isoniazid, pyrizinimide, ethambutol, streptomycin.[12]

Non-tuberculosis infections

- Asia (Thailand,[83] Philippines,[49,107,108] India,[92] Vietnam[8,87])
- Middle East (Saudi Arabia[109])
- Central America (Mexico[74])
- South America (Bolivia[10,110])
- Eastern Europe (Lithuania,[52] Russia,[111] Georgia[112])
- Africa (Nigeria[40,42])

Tuberculosis

- Asia (India,[93] Nepal,[113] Vietnam,[114] Philippines[107])
- Eastern Europe (Russia,[111] Georgia[112])
- Central America (Mexico[74])

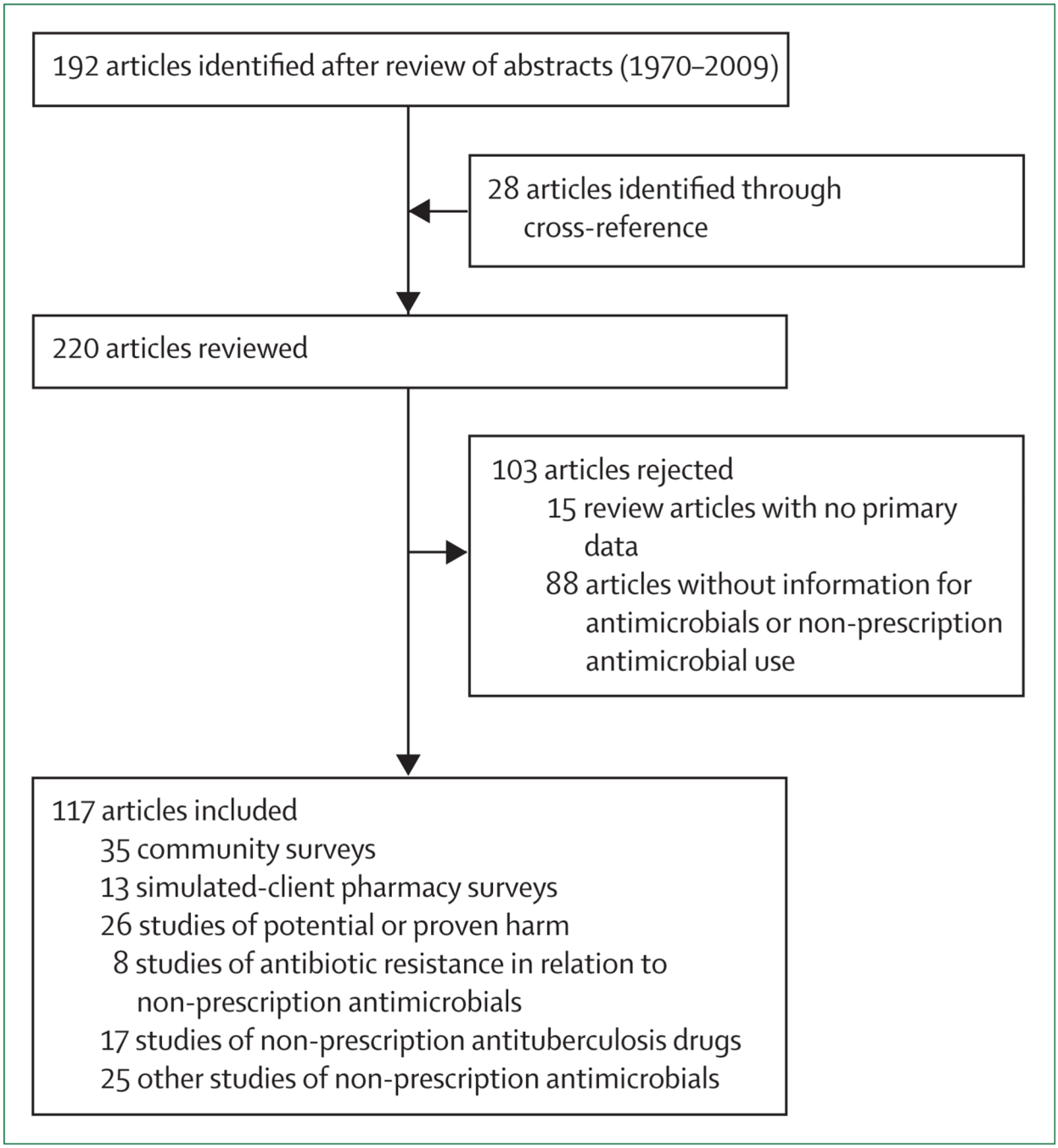

Figure 1. Flowchart of study selection

Some articles were classified as fitting into more than one type of study (eg, simulated client pharmacy surveys and potential or proven harm).

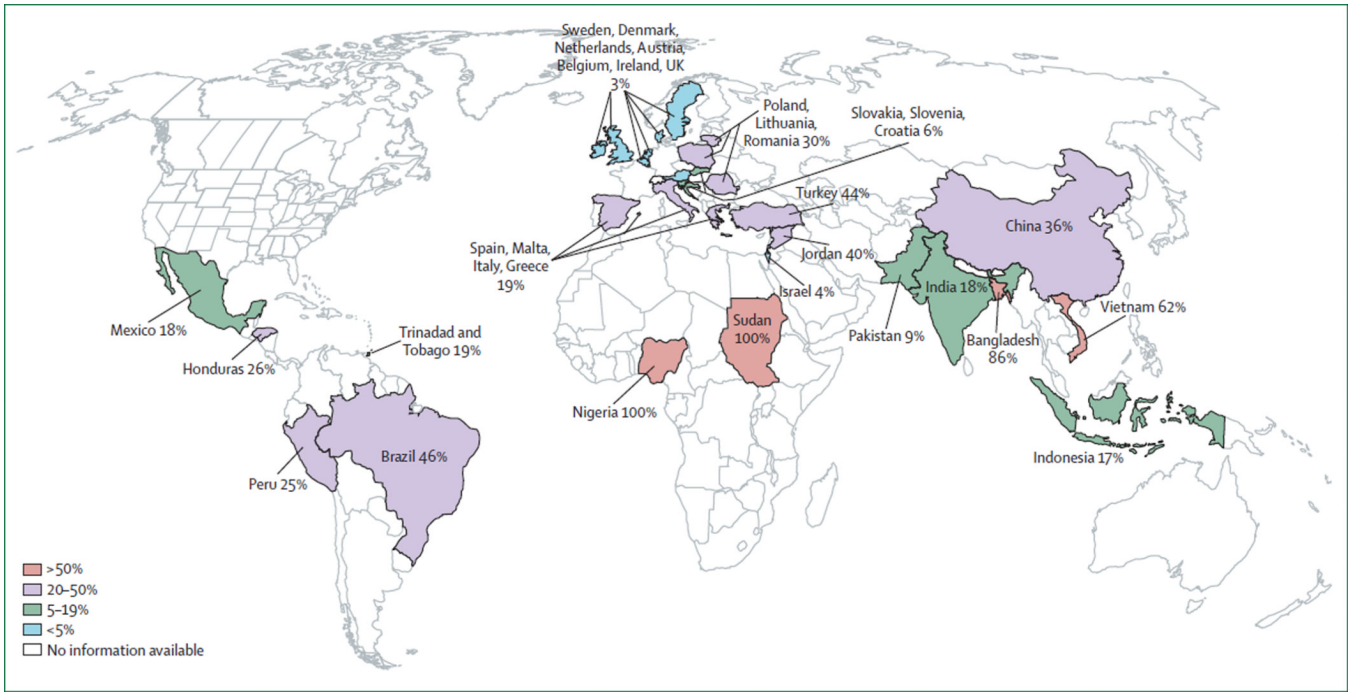

Figure 2. Frequency of non-prescription use of antimicrobials in the general population based on published works

In small areas, countries with similar frequency of non-prescription antimicrobial use have been grouped.

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Table 1

Frequency of pharmacist recommendation of antimicrobial based on simulated client method surveys

Country (year)	Cough or runny nose	Pharyngitis (afebrile)	Upper respiratory infection or influenza	Acute sinusitis	Diarrhoea	Urinary tract infection
Americas						
Mexico (1994)[74]	100% * †	..	..	..	..	..
Bolivia (1992)[10]	16%	91% ‡	24%	..	92% §	63%
Brazil (2002)[75]	..	..	..	74%	..	..
Europe						
Spain (2007)[76]	..	35%	16%	..	..	80%
Greece (2000)[77]	..	..	..	80%	..	..
Middle East						
Iran (1975)[78]	..	60%	..	..	40%	..
Yemen (1985)[79]	..	..	..	..	9%	..
Africa						
Zimbabwe (2004)[80]	..	..	..	..	9%	8%
Asia						
Sri Lanka (1985)[79]	..	..	..	..	41%	..
Bangladesh (1985)[79]	..	..	..	..	68%	..
Bangladesh (2004)[43]	..	..	..	..	40%	..
Vietnam (1999)[45]	..	..	99%	..	75%	..
Vietnam (1999)[81]	98%	..	..	..	..	..
Nepal (1996)[82]	..	..	..	..	97%	38%
Thailand (1999)[81]	76%	..	..	..	9%	..
Thailand (2006)[83]	..	74%	65%	80%	76%	100% †

*Cough duration 1 month.

†Rifampicin recommended.

‡Pharyngitis with high fever.

§40% of children and 92% of adults received an antimicrobial for diarrhoea.

Table 2

Potential and proven adverse events associated with antimicrobials taken without prescription

	Frequency	Description
No questioning by pharmacists regarding allergies[76,82]	>80%	No advice or questions from pharmacy staff regarding allergies, side-effects, or drug interactions
No explanation of potential side-effects[87,88]	About 50%	No advice or questions from pharmacy staff regarding allergies, side-effects, or drug interactions
Contraindicated antimicrobials	Up to 8% of antimicrobials used for children	Tetracyclines and fluoroquinolones dispensed for children[8,50]
Parenteral antimicrobials for home use[52,66,68,89–92]	Unknown	Injectable streptomycin, gentamicin, and penicillin provided
Inadequate treatment (of true bacterial infections)		
Short course[41,79,82,88,93]	Many treatment courses <1 day	··
Inadequate dose[10,41,85,88]	Common	··
Inappropriate antimicrobial[74,83]	Common	Inappropriate drug for indication
Low-quality medication[30,94–96]	Unknown	··
Documented adverse events		
Diarrhoea[51,64]	5–11%	As reported by patients
Rash[51]	4%	··
Masked diagnosis of infectious disease[97]	90% increased risk	Emergency room patients with detectable antimicrobials in urine had higher risk than those without for masked or missed diagnosis of infections
Renal failure[98]	Case report	Non-prescribed rifampicin used for cough resulting in renal failure
Aplastic anaemia and death[99]	Case report	Woman vacationing in Spain took chloramphenicol for upper respiratory infection