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META-ANALYSIS

A systematic literature review and meta-analysis of community pharmacist-led interventions to optimise the use of antibiotics

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Aims: The aim of this systematic review is to assess the effects of community pharmacist-led interventions to optimise the use of antibiotics and identify which interventions are most effective.

Methods: This review was conducted according to the PRISMA guidelines (PROSPERO: CRD42020188552). PubMed, EMBASE and the Cochrane Central Register of Controlled Trials were searched for (randomised) controlled trials. Included interventions were required to target antibiotic use, be set in the community pharmacy context, and be pharmacist-led. Primary outcomes were quality of antibiotic supply and adverse effects while secondary outcomes included patient-reported outcomes. Risk of bias was assessed using the 'Cochrane suggested risk of bias criteria' and narrative synthesis of primary outcomes conducted.

Results: Seventeen studies were included covering in total 3822 patients (mean age 45.6 years, 61.9% female). Most studies used educational interventions. Three studies reported on primary outcomes, 12 on secondary outcomes and two on both. Three studies reported improvements in quality of dispensing, interventions led to more intensive symptom assessment (up to 30% more advice given) and a reduction of over-the-counter supply up to 53%. Three studies led to higher consumer satisfaction, effects on adherence from nine studies were mixed (risk difference 0.04 [−0.02, 0.10]). All studies had unclear or high risks of bias across at least one domain, with large heterogeneity between studies.

Conclusions: Our review suggests some positive results from pharmacist-led interventions, but the interventions do not seem sufficiently effective as currently implemented. This review should be interpreted as exploratory research, as more high-quality research is needed.

KEYWORDS
adherence, antibiotics, drug utilisation, quality use of medicines

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1 | INTRODUCTION

Inappropriate use of antibiotics, such as unnecessary use or suboptimal antibiotic choice, dose or duration is a major contributor to antimicrobial resistance (AMR).[1] Within Europe, the majority of antibiotics are prescribed by healthcare professionals in the primary care setting and supplied via community pharmacies,[2] making general practice and community pharmacies important settings where consumers and healthcare professionals interact around antibiotics. Strategies to improve the quality and safety of antibiotic use in the community setting are well documented, with most focused on intervention studies targeting general practitioners and other physicians[3–8] or studies undertaken in the general practice setting.[9] Understanding the role of community pharmacists in these strategies may provide insight for future interventions to improve antibiotic use in the community setting.

There is limited information regarding the role of the community pharmacist in improving the appropriate use of antibiotics. A scoping review on the attitude of community pharmacists towards antibiotic stewardship found that most pharmacists are aware of the problem of AMR and agree that inappropriate antibiotic usage is one of its main causes.[10] As the gatekeeper of antibiotic use[11] and according to Good Pharmacy Practice Guidelines of the World Health Organization and the International Pharmaceutical Federation,[12] the role of the community pharmacist extends beyond medication supply. The pharmacist should have the skills and knowledge to undertake a patient assessment, collaborate with the prescriber to encourage appropriate prescribing, and give advice to consumers on responsible use to influence their views and behaviours.[13,14] Ideally, the community pharmacist forms the essential link between the prescriber and the consumer, a role that is likely to be critical in ensuring appropriate use of antibiotics. To further complicate the challenge of ensuring rational antibiotic use, across a number of countries antibiotics may be sold from community pharmacist without prescription and studies have shown that community pharmacists may sell antibiotics without a prescription for unjustified reasons, despite good awareness and knowledge of AMR.[10]

Pharmacist-led interventions have been shown to be successful strategies in optimising medicine use across a range of therapeutic areas including diabetes[15] and hypertension.[16] A narrative review by Bishop et al. identified a wide range of community pharmacist interventions aiming to reduce antibiotic misuse.[17] Understanding the impact of different community pharmacist-led strategies to optimise antibiotic use in the community context is important for the development of future strategies to reduce AMR by improving the safety and quality of antibiotic use. Therefore, the aim of this review is to assess the effects of community pharmacist-led interventions to optimise the use of antibiotics and to define which interventions are most effective to achieve this.

2 | METHODS

2.1 | Search strategy

This systematic review was conducted in accordance with the PRISMA guidelines[18] and the protocol was registered with PROSPERO (CRD42020188552). We searched PubMed, EMBASE and The Cochrane Library with key concepts "anti-bacterial agents", "drug utilization", "community pharmacy services" and "clinical trials", using the search strategies provided in Appendix A. All databases were searched from inception until 11 January 2021. Reference lists and citations of included studies were backward searched for additional studies. From the Cochrane Library, only references not published in PubMed or EMBASE were included in the screening. No restrictions were applied in ways of publication language.

2.2 | Review questions and outcomes of interest

This review assessed the effects of community pharmacist-led interventions to optimise the use of antibiotics and how these were effective at improving appropriate antibiotic use. Additionally, it evaluated which of the interventions were most effective in achieving this. Main outcomes were (1) the supply of antibiotics in community pharmacies such as the rate of supplying antibiotics which are not indicated: "wrong decision supply" and "wrong choice supplying", and (2) the rate of adverse events associated with community pharmacy interventions. Secondary outcomes were patient adherence, quality of life, healthcare professional or consumer knowledge of antibiotics, patient perception of outcome of antibiotic treatment, infection severity and volume of antibiotic supply.

2.3 | Eligibility criteria

For inclusion, studies needed to use a randomised controlled trial, cluster randomised trial or other controlled study design. Based on the definition of drug utilisation research by Wettermark et al.,[19] we defined antibiotic use as any aspect of the recommendation, prescribing, supply, consumption or administration of prescribed and non-prescribed antibiotics. Community pharmacies were defined as any place under the direct supervision of a pharmacist, where prescription orders are compounded and/or dispensed, other than hospital pharmacies and limited-service pharmacies.[20] The target populations were persons involved in any aspect of antibiotic use in the community setting including healthcare professionals, health workers, untrained medicine sellers as well as consumers. Included interventions needed to be pharmacist-led but may have been delivered in part by other members of pharmacy staff, other healthcare professionals or consumers. All intervention types according to the EPOC taxonomy[21] within the above-mentioned criteria were included.

Studies were excluded if they were not aimed at or undertaken in community pharmacies or were not directly linked to the community pharmacy setting. Academic detailing, which often uses pharmacists to deliver the intervention, and similar interventions conducted outside of the community pharmacy setting, were excluded. Studies in which the role of the pharmacist/pharmacy in the intervention was not described were also excluded.

Screening of title and abstracts and full text was undertaken independently by M.L. and C.C.H.S., except for Spanish articles which were assessed by M.L. and C.L. Covidence systematic review software[22] was used for screening. Any disagreement between reviewers was resolved by discussion. If consensus could not be reached, review was undertaken by a third reviewer and discussed between all three reviewers until consensus was reached.

2.4 | Data extraction and analysis

From all included studies, we extracted (if applicable) general information (e.g., year of publication, country of study), study characteristics (e.g., design, number of patients included, duration of follow-up), patient characteristics (e.g., age, gender), prescription characteristics (e.g., type of antibiotic), intervention characteristics (e.g., individual or group, healthcare professionals involved), outcome and size of effect and conclusions from the authors. Data were extracted independently by three authors using a fixed data sheet. M.L. and C.C.H.S. extracted all data, and additionally S.d.V. extracted statistical data. Risk of bias was assessed independently by three authors (M.L., C.C.H.S. and S.d.V.), using the 'Cochrane suggested risk of bias criteria'[23] and Cochrane Handbook[24] as relevant to the study design. Interventions in the included studies were classified in three categories: educational, behavioural and technical interventions, as defined by Van Dulmen 2007.[25] Narrative synthesis was conducted for all outcomes except adherence.

2.5 | Meta-analysis

Due to differences in interventions and outcomes between the studies, and the small number of studies included, a meta-analysis to explore the effect of the different interventions was only proposed for treatment adherence, either as a primary or as a secondary outcome. For each study included in the meta-analysis, the number of post-intervention adherent patients was extracted, and a risk difference calculated, where adherence was the event of interest. Heterogeneity was assessed using the I^2 index, and a random effect model for the summary effect size was used when heterogeneity exceeded 30% (based on Cochrane's suggested threshold).[26] Assessment of certainty was performed through confidence intervals. The analysis was performed using Review Manager 5.4.[27]

3 | RESULTS

In total, 5299 studies were identified through the search strategies with 1292 duplicates (Figure 1). Of the 4007 unique studies, 3948 were excluded based on title and abstract screening, full text of 59 studies were screened and 14 studies were included in the final review. Appendix B shows the reasons for exclusion for the full texts. After screening the reference lists and citations of the 14 remaining studies, three additional studies were identified for the final review, giving a total of 17 studies included in the final synthesis.

3.1 | Study characteristics

In all 17 studies combined, 3822 patients were included, with a mean age of 45.6 years. All studies that reported on the sex of the patients included more females than males, with a mean of 61.9% female patients (Table 1). Of the 17 included studies, eight were cluster randomised controlled trials,[28–35] five were randomised controlled trials[36–40] and four were other controlled trials.[41–44] Two studies were published well before 2000,[30,42] all other studies were published between 2002 and 2019. Most studies were conducted in Europe (10),[28,31,33,34,37–39,41,43,44] with others in Asia (3),[29,30,35] North America (3)[36,40,42] and Africa (1).[32] Three studies[38,41,44] were based at a single pharmacy, all others at multiple pharmacies. Only one study has been conducted in a multidisciplinary setting;[34] all others were conducted solely at pharmacies. In five studies[33,34,36,40,42] interventions were specifically aimed at or performed by pharmacists, in two studies[30,38] the staff consisted of a combination of pharmacists and other staff, one study[32] was aimed specifically at counter attendants and nine studies[28,29,31,35,37,39,41,43,44] mentioned pharmacy staff without any further specification. More detailed study characteristics are shown in Appendix C.

3.2 | Risk of bias

None of the included studies have been judged to have a low risk of bias in all nine domains. In three domains, more than half of the studies were judged to have an unclear or high risk of bias: random sequence generation, baseline outcome measurements similar and incomplete outcome data. Six studies[35–39,44] had at least one domain in which the risk of bias was unclear. Eleven studies[28–34,40–43] had at least one domain in which the risk of bias was judged to be high (see Appendix D).

3.3 | Intervention types

Fourteen of the included studies used educational interventions, of which nine were aimed directly at patients[33,36,38–44] and five at pharmacy staff.[29,30,32,34,35] Two studies dispensed the exact number of pills instead of full containers,[28,31] i.e., technical interventions, and one study targeted patients' behaviour.[37] Seven studies[29,30,32,34,35,37,42] used

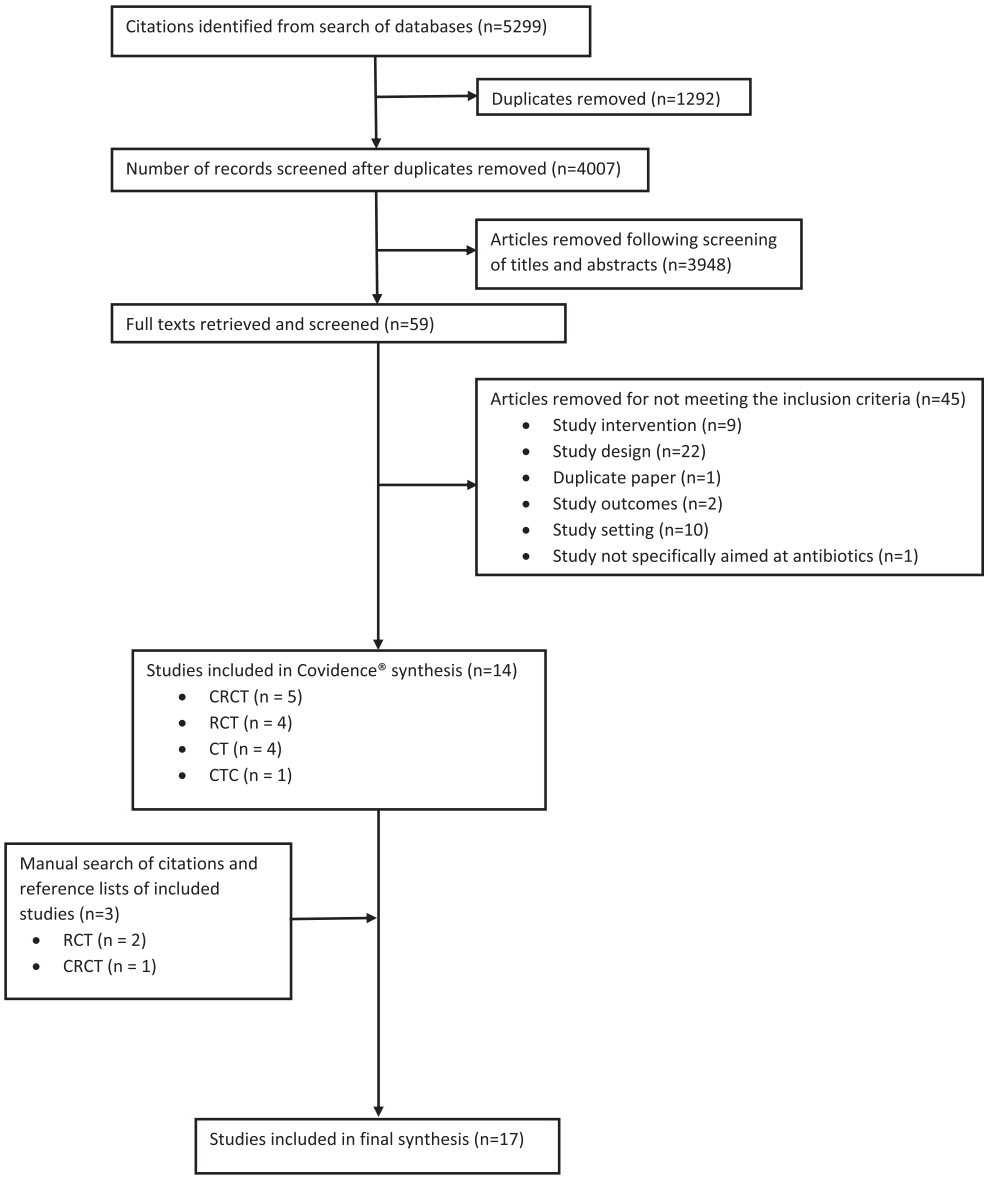

FIGURE 1 Flowchart of study inclusion. CRCT: cluster randomised controlled trial; RCT: randomised controlled trial; CT: controlled trial; CCT: cluster controlled trial

multifaceted interventions; all others were single-component interventions. Eleven studies[28,31,33,36,37,39–44] had a follow-up around the expected end date of the antibiotic course that was prescribed. Three studies had a follow-up after at least 1 month,[29,30,32] one study after 4 months[35] and one after 12 months.[34] One study did not report the moment of follow-up.[38]

Educational interventions were targeted at either individual patients or pharmacy staff. For those targeted at patients, the interventions consisted of oral information,[40,44] written information[38,39,43] or a combination of both oral and written information.[33,36,41,42] Education was focused on different topics, including how to use the antibiotic (i.e., information on treatment duration, dosage, how to take the antibiotic and storage),[33,36,38–40,42–44] patients' general conditions and side effects,[30,36,40] risk of AMR[33,41] and lifestyle habits.[38] Eleven of the educational intervention studies reported the time needed for the interventions, with the time varying between the studies from 2.3 minutes[33] per patient to 20 minutes[44] per patient.

For the educational interventions targeted at pharmacy staff, different strategies were used. In two studies, pharmacy staff were educated during a single two[34]- or three[30]-hour training course. Other studies used more intensive interventions consisting of three morning training sessions,[32] two training sessions of 45 minutes together with a 2-day seminar[29] or multiple peer-to-peer discussion sessions.[29,35] Important topics of these interventions included: enforcement of regulations,[29,35] management of infections,[29,30,32,35] handling requests for antibiotics without prescription,[29,30,35] pathophysiology and clinical characteristics of infections,[30] dispensing practices and non-medication related advice,[30,32] communication with patients[34] and AMR.[34]

The two studies[28,31] dispensing the exact number of tablets defined this as the daily dose multiplied by the number of days for which the antibiotics were prescribed. In one study,[39] the pictograms on the antibiotic container were previously evaluated, the other study[43] did not report on this. The study[37] targeting implementation intentions used a Theory of Planned Behaviour (TPB) questionnaire.

TABLE 1 Characteristics of study populations

Study	Design		*n*	Sex (% female)	Age (yrs) (mean ± SD)	Intervention, antibiotics, population and studied infections	Included outcome
Andrés (Spain, 2004)[28]	CRCT	IG CG	87 94	59.7 NR	38.5 ± 17.0 NR	Single-disciplinary, single-component, technical intervention. Amoxicillin (+ clavulanic acid), all infections.	Patient-reported adherence
Beaucage (Canada, 2006)[36]	RCT	IG CG	126 129	55 60	47 ± 20 49 ± 20	Single-disciplinary, single-component, patient education. Adult patients with a new prescription for any oral antibiotic with a treatment length of 5–14 days.	Change in number of infectious symptoms, change in infection severity score, number of drug-related problems identified, adherence
Chalker (Vietnam, 2002)[35]	RCT	IG CG	NA NA	NA NA	NA NA	Single-disciplinary, multi-component, pharmacy staff education. Included antibiotics not specified except for selling antibiotics without prescription which focused on cephalexin.	Dispensing practices through questionnaire: Asking about fever/quality of breathing, willingness to dispense antibiotics/traditional medicines, selling antibiotics without prescription.
Chalker (Vietnam, Thailand, 2005)[29]	RCT	IG CG	NA NA	NA NA	NA NA	Single-disciplinary, multi-component, pharmacy staff education. Cephalexin in Vietnam, roxithromycin and amoxicillin in Thailand.	Simulated client receiving requested antibiotics without prescription and advice from pharmacy staff
Göktay (Turkey, 2013)[41]	CT	IG CG	30 30	77.4 NR	37.8 ± 16.5 35.0 ± 16.1	Single-disciplinary, single-component, patient education. All adult patients with a prescription for any oral antibiotic for any infection.	Patient self-administration adherence and dose-timing adherence
Gotsch (USA, 1982)[42]	Pilot, CT	IG CG	124 62	51.5 64.0	NR NR	Single-disciplinary, multi-component, patient education. All patients with a new prescription for penicillin V, penicillin G or ampicillin.	Patient satisfaction with information, knowledge of antibiotic, attitude towards patient package inserts, adherence to treatment
Jackson (England, 2005)[37]	RCT	IG CG	157[a] 63	68.7 65.1	48.7 ± 16.4 47.7 ± 15.3	Single-disciplinary, multi-component, behavioural intervention. Patients with a prescription for any oral antibiotic course lasting less than 14 days.	Patient-reported adherence
Machuca (Spain, 2003)[38]	RCT	IG CG	105 109	NR NR	NR NR	Single-disciplinary, single-component, patient education. Patients over 15 years old with a prescription for an antibiotic for an acute infection with a treatment duration of 2–15 days.	Patient-reported adherence, patient-reported state of health
Martín Arias (Spain, 2010)[43]	CT	IG CG	363 383	NR NR	NR NR	Single-disciplinary, single-component, patient education. Patients of 16 years or older with at least one prescription for an oral antibiotic.	Patient-reported adherence
Merks (Poland, 2019)[39]	CRCT	IG CG	97 102	70.1 58.9	48.5 ± 16.8 42.7 ± 16.8	Single-disciplinary, single-component, patient education. Adult patients with a non-liquid prescription for amoxicillin or amoxicillin with clavulanic acid with two daily doses for any infection.	Patient adherence, patient-reported relief of symptoms, perspective on information about treatment
Muñoz (Spain, 2014)[44]	CT	IG CG	64 62	65.6 69.4	44.5 ± 18.2 44.8 ± 17.7	Single-disciplinary, single-component, patient education. All adult patients with a prescription for any oral antibiotic.	Patient adherence, patient-reported health

(Continues)

TABLE 1 (Continued)

Study	Design		*n*	Sex (% female)	Age (yrs) (mean ± SD)	Intervention, antibiotics, population and studied infections	Included outcome
Pham (USA, 2013)[40]	RCT	IG CG	24 26	79 73	39.4 ± 13.6 45.3 ± 16.7	Single-disciplinary, single-component, patient education. English-speaking adult patients without degree in medicine, nursing or pharmacy, receiving one of the 18 medications, including amoxicillin, amoxicillin/clavulanate, penicillin V potassium, cephalexin, cefuroxime, cefdinir, doxycycline, minocycline, tetracycline, ciprofloxacin, moxifloxacin, levofloxacin, azithromycin, clarithromycin, erythromycin, trimethoprim/sulfamethoxazole, nitrofurantoin and clindamycin.	Patient auxiliary label recall, patient-reported adherence
Podhipak (Thailand, 1993)[30]	CRCT	IG CG	NA NA	NA NA	NA NA	Single-disciplinary, multi-component, pharmacy staff education. Assessors were trained to simulate a mother with a child suffering from watery diarrhoea or dysentery.	Percentage of pharmacists and drug sellers supplying antibiotics
Roque (Portugal, 2016)[34]	CRCT	IG CG	NA NA	NA NA	NA NA	Multi-disciplinary, multi-component, pharmacy staff education. All physicians and pharmacies in the study area were included. The following antibiotics were studied: Antibacterials for systemic use, tetracyclines, penicillins, cephalosporins, sulphonamides and trimethoprim, macrolides and quinolones.	Antibiotic consumption in packages per 1000 inhabitants per day
Treibich (France, 2017)[31]	CRCT	IG CG	907[b] 278	62.7 60.8	52.8 ± 17.0 54.3 ± 17.0	Single-disciplinary, single-component, technical intervention. Any patient with an antibiotic prescription for which per-unit dispensing was possible.	Number of antibiotic pills supplied, patient acceptance rate, patient-reported adherence
Tumwikirize (Uganda, 2004)[32]	CCT	IG CG	NA NA	NA NA	NA NA	Single-disciplinary, multi-component, pharmacy staff education. Study personnel posing as mothers of a one-year-old child with either a mild or a severe acute respiratory tract infection for 3 days. Dispensed antibiotics: Co-trimoxazole, amoxicillin and ampicillin.	Assessment of child's conditions, management and dispensing practices for acute respiratory tract infections, information and instruction given with dispensed drugs
West (Malta, 2019)[33]	CRCT	IG CG	200 200	60.5 64.5	44.8 ± 16.1 45.4 ± 15.8	Single-disciplinary, single-component, patient education. Adult patients with a prescription for any oral, solid dosage form, short-term antibiotic.	Patient-reported adherence, beliefs about medicines, knowledge about antibiotic resistance

IG: intervention group, CG: control group, NA: not applicable, NR: not reported, CCT: cluster-controlled trial, CRCT: cluster randomised controlled trial, RCT: randomised controlled trial, CT: controlled trial.
[a]Multiple study arms: 54 (Theory of planned behaviour [TPB] only), 53 (TPB and own implementation), 50 (TPB and given implementation intention).
[b]Sample size differs per research question.

This questionnaire consisted of five items about the patients' intentions and plans to take the antibiotics and about their past behaviour on taking antibiotics. Moreover, patients were asked to decide when and where they would take their current antibiotics. Information on how much time this took was not reported.

3.4 | Primary outcomes

Improvements in dispensing practices were reported in three studies.[29,32,35] Pharmacy staff participating in the reported interventions (all were multi-component educational interventions focused on guideline adherence, management of infections, handling over-the-counter [OTC] antibiotic requests and dispensing practices) asked more questions during symptom assessment on certain topics (fever: intervention *vs* control +43%, $P = .01$,[35] patients receiving no advice: intervention *vs* control −30%, $P = .0028$ (Hanoi, Vietnam), −23%, $P = .0181$ (Bangkok, Thailand),[29] and nature of cough in severe acute respiratory tract infections (ARI): −16.2%, $P = .04$),[32] dispensed more first-line antibiotics although not statistically significant ($P = .06$), less second line antibiotics (reduction of 6.8% in intervention group *vs* an increase of 22.2% in control group ($P = .001$)[32] and supplied less OTC antibiotics (intervention versus control −53%, $P = .02$[35] and −24%, $P = .0125$ [Hanoi])[32] than those in the control groups. However, Chalker et al. found that the supply of OTC antibiotics was not consistent, as a decrease in OTC supply was seen only in Hanoi but not in Bankok (−9% supply of OTC antibiotics, $P = .2510$).[29] Moreover, in another study, improvements in dispensing (e.g., giving advice and educating patients) were only seen on the nature of cough for patients suffering from severe ARI not with mild ARI. Additionally, no significant differences were reported for other dispensing-related questions, including questions about duration of illness, age of child, previous medical visits and medication, presence of fever and difficulty breathing.[32] One study reported an increase in traditional medicine (+74%, $P = .02$).[35] Podhipak et al. reported no significant differences in dispensing practices (no confidence intervals or *P*-values reported).[30] The study by Beaucage et al.[36] was the only one that mentioned an increase in adverse effects: patients in the intervention group (who received a phone call from a pharmacist to check patients' general condition, adverse effects and understanding of dosage) reported significantly more drug-related problems than patients in the control group (53% *vs* 8%, $P < .001$). However, there was a difference in design of the study between the intervention and control group, as patients in the intervention group were specifically asked for any adverse effects but patients in the control group had to report this spontaneously.

3.5 | Secondary outcomes

Secondary outcomes were reported in 13 studies.[28,31,33,34,36–44] Roque et al.,[34] in a study of multidisciplinary educational interventions, showed a significant decrease in overall use of antibiotics (−3.71% CI: −8.3, 0, $P = .0459$), specifically for tetracyclines (−15.63% CI: −27.59, −2.94, $P = .0111$), macrolides (−9.37% CI: −17.43, −2.21, $P = .0214$) and cephalosporins (−7.24% CI: −15.80, 0.00, $P = .0206$). However, for penicillins (−2.55% CI: −7.98, 1.22, $P = .1907$), sulphonamides and trimethoprim (−2.90% CI: −10.77, 2.78, $P = .2645$) and quinolones (3.59% CI: 0.00, 6.85, $P = .1160$), no differences were reported between control and intervention groups.

Three studies evaluated patient desire for information or satisfaction with received information, and the impact varied across the different strategies used. Pictograms on antibiotic containers resulted in higher satisfaction with pharmacy services (71.3% *vs* 51.5%, $P < .005$) and a higher score for medical information (76.6% of patients in intervention group *vs* 61.6% in control group, $P = .0239$).[39] Provision of patient package inserts, i.e., written information, with or without oral explanation, was associated with decreased patient desire for additional information during dispensing (63% in control group, 18% and 14% in intervention groups 1 and 2, respectively, no *P*-values reported).[42] The one study[42] that looked at the effect of their intervention on patient knowledge about AMR reported an increase in knowledge associated with the intervention (percentage of correct responses to knowledge items: control: 66%, intervention 1: 90%, intervention 2: 93%, no *P*-values reported). Two other studies[33,44] reported a correlation between increased knowledge and adherence. Additionally, one[33] of those showed a higher score for the General-Benefit beliefs about Medicine Questionnaire in the intervention group (intervention: 14.80 ± 2.09, control: 14.34 ± 2.44, $P = .044$), but this was not related to a difference in adherence. No differences were found for the General-Harm beliefs (intervention: 11.05 ± 2.12 control: 10.74 ± 2.44, $P = .176$) or General-Overuse beliefs (intervention: 11.88 ± 2.69 control: 11.97 ± 2.79, $P = .743$).[33] Pham et al.[40] reported a high recall of auxiliary label information, but there was no significant difference between intervention and control groups (intervention: 88.9%, control: 66.7%, $P = .11$).

Dispensing the exact number of pills led to a lower number of pills to be dispensed on average for the intervention group (20 *vs* 23, $P = .02$), which could be associated with a lower risk of future self-medication.[31] Patient-reported relief of symptoms or perception of health was reported by four studies. Three did not see changes in relief of symptoms (91.7% intervention, 84.3% control, $P = .1127$),[39] number of infectious symptoms (−5.08 ± 3.56 intervention, −4.83 ± 4.03 control),[36] infection severity score (−1.32 ± 1.02 intervention, −1.27 ± 1.28 control)[36] or health perception (patients perceived "totally cured": 54.7% intervention, 46.8% control, $P = .297$).[44] Machuca et al.[38] did show an increase in patient perception of health for patients that were adherent (93.0% for adherent patients, 76.8% for non-adherent patients, $P = .0007$).

3.6 | Meta-analysis

We were unable to undertake a meta-analysis for the defined primary outcomes due to a small number of studies that reported on this and the differences between the studied interventions in those studies. This was also encountered for all secondary outcomes except for adherence. Therefore, one meta-analysis has been performed, to

assess the effect of pharmacist-led interventions on adherence to antibiotics.

A total of nine studies were included in this meta-analysis.[33,36,38–44] These studies reported the effect of an educational intervention on treatment adherence, either as a primary or as a secondary outcome. Some studies included multiple intervention groups or used multiple definitions for adherence. There were differences in adherence definitions between the studies, either focusing on the percentage of patients taking the exact prescribed number of antibiotics,[33,38,39,41,42,44] or taking a number of antibiotics within a range based on the prescribed number (80–110%).[43] One study[36] calculated adherence as the percentage or tablets consumed compared to the prescribed number of antibiotics (e.g., a patient consuming 25 tablets from a course of 30 tablets would be considered 83% adherent). One study used a four-item self-reported adherence scale including forgetting to take medicines, careless about taking medicines, stop taking medicines after feeling better and stop taking medicines after feeling worse[45] together with the exact number of antibiotic pills.[44] In Göktay et al.[41] we used the most stringent definition (where being adherent means timing-adherent and administrative-adherent). In Gotsch and Liguori[42] we compared the control group against intervention II (only patient package inserts [PPIs] without additional verbal counselling). In Jackson et al.[37] we compared control *vs* TPB-only. Since $I^2 = 0.65$, CI = [0.25, 0.84], a random effect model was used to compute a summary effect size. A forest plot of the results is displayed in Figure 2. The summary effect was calculated to be RD = 0.04 (CI = [−0.03, 0.11]), which suggests a lack of efficacy of the educational interventions on treatment adherence. Most of the studies show a wide confidence interval, underlining the uncertainty found in the presented results.

4 | DISCUSSION

In general, community pharmacist-led interventions reported improvements in the quality of antibiotic use in the community setting in three studies;[29,32,35] however, these improvements were only seen for specific indications, antibiotics and settings. One study reported no significant changes in dispensing practices[30] and one study reported an increase in patient-reported adverse effects.[36] Pharmacist-led interventions improved patient perceptions of received information, knowledge about AMR or beliefs about medicine in three studies,[33,39,42] but adherence to antibiotics did not significantly increase after pharmacist-led interventions.

In all the reviewed studies, more female than male patients were included. This is in accordance with a systematic review which reported that in the community, more antibiotics are dispensed to women between 16 and 54 years than to men.[46] This review reports that women had twice as many medical visits for respiratory tract infections as men, and being a woman was associated with more inappropriate prescribing for multiple infections. This does not necessarily mean that respiratory tract infection incidence is higher for women; the authors mention social and behavioural factors as possible drivers for differences between men and women. It might be that the threshold for visiting general practitioners is lower for women. Other reasons for differences between men and women might be explained by genetic differences; however, the clinical impact of this is not yet sufficiently studied.[46]

All interventions in the included studies aimed at improving the use of antibiotics with the underlying goal of reducing AMR. The inappropriate use of antibiotics has been correlated with increased AMR in different studies and reviews. These report that ease of availability of antibiotics, misdiagnosis,[47] prior antibiotic use, patient clinical history[48] and lower health literacy[49] have all been correlated with AMR. These studies could indicate that some of the small positive results of pharmacist-led interventions that we found in our review may indeed contribute to reducing AMR. Moreover, a review of qualitative studies on patient knowledge and attitudes towards antibiotic use recommended community-based initiatives to improve knowledge on antibiotics and antibiotic resistance as a possible solution to the incorrect use of antibiotics and overdemanding of antibiotics to general practitioners.[50] Additionally, pharmacists and other healthcare professionals should ensure better consumer understanding of antibiotics and tailor patient advice according to patient health literacy.[51]

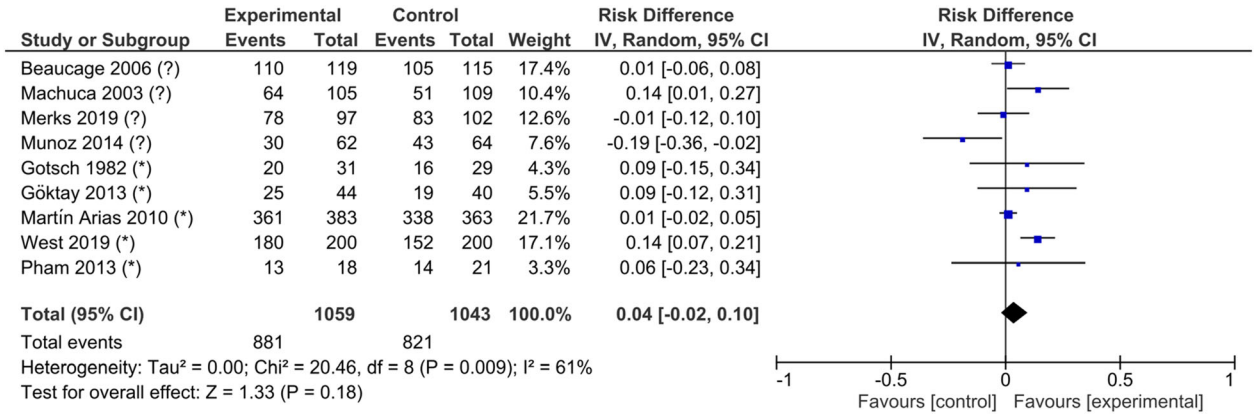

FIGURE 2 Forest plot of risk differences for studies reporting results on educational interventions on treatment adherence. (?): study with unclear risk of bias, (*): study with high risk of bias

Collignon et al.[52] reported a correlation between higher antibiotic usage and antibiotic resistance in Europe, but not in other parts of the world. This might suggest that pharmacist-led interventions could be more successful in developed countries than in developing countries. In our review, the only studies reporting on our primary outcomes were conducted in developing countries. These studies only report small positive effects on quality of care and only on some of the studied outcomes. Chalker et al.[29] conducted their study in Hanoi and Bangkok and found different results for the two cities. This may be due to small differences in the execution of the study in the two cities. The antibiotics studied were not the same, and the peer review intervention was mandatory for participating pharmacists in Hanoi but not in Bangkok. Also, there was a difference in legislation: selling antibiotics without prescription was illegal in Hanoi at the time of the study, while in Bangkok this was considered "bad practice". Another study[30] that reported on our primary outcomes showed no significant differences between intervention and control. In this study, only one staff member of the recruited pharmacies was targeted with the educational intervention. To what extent this staff member informed his/her colleagues in unknown. It is therefore probable that the behaviour of the other staff members was not affected by the intervention, which may have diluted the effects of the intervention. It is difficult to compare the primary outcomes of the studies in this review with studies in other therapeutic areas as most studies on community pharmacist-led interventions focus on chronic diseases and long-term treatment, whereas the included studies in this review focused on short-term antibiotic courses.

We found that educational interventions were the most commonly used pharmacist-led intervention type to change the safety and quality of antibiotic use in community pharmacies. It is notable that even most multifaceted interventions consist of different educational aspects, instead of a combination of different types of interventions. Educational interventions are also mostly used across a range of other therapeutic areas.[15,53] The effect of educational interventions is, however, not the same for different therapeutic areas. For example, Presley et al.[15] found a significant improvement in adherence after educational interventions in diabetic patients, contrary to our results. Among our included studies, we found a large heterogeneity and varying study quality. This was also reported in several other pharmacist-focused intervention reviews in other areas[9,15,16] and it might explain contradictory results between studies.

All in all, this review does not provide sufficient evidence to draw strong conclusions regarding which type of pharmacist-led interventions have the largest impact on antibiotic use, due to large heterogeneity between the included studies. This review should therefore be interpreted as exploratory research to show the possible role of the pharmacist in tackling AMR. Most of the studies in this review focused on interventions that were solely based in the community pharmacy setting. The effects of the different interventions vary, but strong evidence favouring pharmacist-led interventions is not provided in any of the studies. One of the reasons for this could be the lack of multidisciplinary interventions, as different reviews suggest that multidisciplinary interventions in primary care are most effective.[9,15–17] The one study[34] that was conducted in a multidisciplinary setting did report significant effects on lowering the volume of antibiotic consumption. This seems very promising. Possibly, the future role of the pharmacist should be one within a multidisciplinary team. For example, Saha et al.[9] reports the positive effect of community pharmacists as interventionists on antibiotic prescribing by general practitioners in their review. They show different possible roles for the pharmacist, as general practitioner educator, academic detailer and workshop trainer. Moreover, Liaskou et al.[54] already reported on the positive role of the pharmacists in multidisciplinary antimicrobial stewardship programmes in secondary and tertiary care. This emphasises the importance of close collaboration between pharmacists and prescribers.

4.1 | Future research

The evidence of the studies in this review is uncertain due to unclear or high risks of bias, as is reported in several other reviews of pharmacist-led interventions.[9,15,16] Future studies should clearly describe their design, analyses and interpretations, for example according to the CONSORT 2010 Statement[55] or other guidelines. Also, it would be interesting to conduct more research within a multidisciplinary setting. Alternatively, the results of this review seem to indicate that high-quality (cluster) randomised controlled trials might be difficult to set up in the community pharmacy setting. Challenges include lack of long follow-ups, due to predominantly short duration of antibiotic courses and patients before and after interventions are usually not the same patients. Therefore, these study designs might not be the most successful way to define or implement interventions to optimise antibiotic use in the community pharmacy setting.

As the educational interventions reported in this review do not unambiguously favour the intervention groups, future research in community pharmacies could focus on possibly more effective forms of educational interventions or on other intervention types. Such alternative strategies could focus on implementation designs like audit and feedback interventions. Audit and feedback studies have been carried out in general practice,[56] with positive results, but in the community pharmacy such studies are rarely performed. In the community pharmacy setting, such studies could help pharmacists and technicians to gain insight into their dispensing practices and provide targeted feedback for quality improvement. Specifically, such feedback could be aimed at collaborating with general practitioners in the correct choice of antibiotics, at medication safety aspects such as checking for allergies or at counselling patients on correct antibiotic use. Another potentially interesting area for future research could be patients' expectations from and attitudes towards the role of the community pharmacy. This area seems to be underexplored, although several pharmacist-led interventions are targeted at patients. Further exploring patients' needs might make future interventions more appropriate and effective.

4.2 | Strengths and limitations

A strength of this review is that it is the first systematic review focusing on pharmacist-led interventions to optimise the use of antibiotics taking into account the quality of all included studies. We provide a comprehensive overview of different intervention types on a broad range of outcomes. For this review a comprehensive search was conducted in three large databases and in the reference lists of included studies which was a priori documented. Moreover, multiple studies did not favour outcomes in the intervention groups. Together, this makes it unlikely that publication bias has influenced the results of this review.

This review has multiple limitations. Reporting of data was very limited in certain studies and none of the included studies had an overall low risk of bias. Moreover, we did not take into account possible dependencies between observations within pharmacies due to lack of data reported, but we note that this is a possible source of bias. There was a large heterogeneity between the studies, which made it impossible to do a meta-analysis for the primary outcomes and which might explain contradictory results between studies. Finally, differences in primary care systems across countries, e.g., economic differences or varying regulations regarding OTC antibiotic use, make it difficult to extrapolate results from the studies to other parts of the world.

5 | CONCLUSION

Our review shows that pharmacist-led interventions as they are currently implemented lead to mixed results. Some of the studies suggest possible positive effects of pharmacist-led interventions in the community setting, especially on symptom assessment, dispensing first-line antibiotics and decreasing OTC dispensing of antibiotics. Nevertheless, the evidence presented in this review does not point clearly towards improved patient-focused outcomes. Pharmacist-led interventions to improve antibiotic use do not seem sufficiently effective in the way they are currently implemented. The role of the pharmacist in tackling AMR should be further studied, especially within a multidisciplinary team. Moreover, randomised controlled trials may not be the optimal study design in the community pharmacy setting. More attention should be paid to different implementation strategies like audit and feedback, with special attention to patient needs. This should include exploring how to improve interventions to better meet the needs of patients as well as understand the impact of cultural differences between countries.

COMPETING INTERESTS

L.v.D. has received funding from Teva Pharmaceutical Industries for a study not related to this review. C.L. has received research grants from Abbott Diagnostics, unrelated to this review. No other funding was received for writing this review.

CONTRIBUTORS

M.L., C.S., S.d.V., L.P., L.v.D. and K.T. were involved in study conception and design. M.L., C.S., S.d.V., C.L., R.B., L.P., L.v.D. and K.T. analysed and interpreted data. M.L. drafted the article. All authors critically revised the article, approved the manuscript for publication and agreed to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

All extracted data are available in Table 1 and Appendix C of this manuscript.

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APPENDIX A: SEARCH STRATEGY FOR PUBMED, EMBASE AND COCHRANE

PubMed

("Anti-Bacterial Agents"[Mesh] OR antibiotic*[tiab] OR antimicrobial [tiab])

AND

("Drug Utilization"[Mesh] OR "Prescriptions"[Mesh:NoExp] OR "Drug Prescriptions"[Mesh:NoExp] OR "Patient Compliance"[Mesh] OR use [tiab] OR usage[tiab] OR utili*[tiab] OR prescrib*[tiab] OR prescrip* [tiab] OR intake[tiab] OR complian*[tiab] OR adheren*[tiab] OR stewardship[tiab] OR over-the-counter [tiab] OR non-prescription [tiab] OR self-medication [tiab])

AND

("Community Pharmacy Services"[Mesh] OR "Pharmacists"[Mesh] OR "Pharmacies"[Majr] OR "Pharmacy"[Majr:NoExp] OR pharmacy[tiab] OR pharmacies[tiab] OR pharmacist*[tiab])

AND

("Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh] OR random*[tiab] OR ((controlled[tiab] OR control group*[tiab] OR groups[tiab] OR comparative[tiab] OR comparison[tiab]) AND (study[tiab] OR trial[tiab])) OR trial[ti] OR intervention*[tiab] OR program*[ti])

EMBASE

('antibiotic agent'/exp OR [antibiotic* OR antimicrobial]:ab,ti,kw)

AND

('drug utilization'/exp OR 'drug utilization review'/exp OR 'prescription'/exp OR 'drug use'/exp OR 'patient compliance'/exp OR (use OR usage OR utili* OR prescrib* OR prescrip* OR intake OR complian* OR adheren* OR stewardship OR 'over-the-counter' OR 'non-prescription*' OR 'self-medication'):ab,ti,kw)

AND

('pharmacy (shop)'/exp OR 'pharmacist'/exp OR (pharmacy OR pharmacies OR pharmacist*):ab,ti,kw)

AND

('clinical trial'/exp OR 'clinical trial (topic)'/exp OR random*:ab,ti OR ((controlled OR 'control group*' OR groups OR comparative OR comparison) AND (study OR trial)):ab,ti OR trial:ti OR intervention*:ab,ti OR program*:ti)

NOT

'conference abstract'/it.

Cochrane (only those studies not published in PubMed or EMBASE):

#1 MeSH descriptor: [Anti-Bacterial Agents] explode all trees

#2 Antibiotic OR antimicrobial in Trials (Word variations have been searched)

#3 MeSH descriptor: [Drug Utilization] explode all trees

#4 MeSH descriptor: [Prescriptions] this term only

#5 MeSH descriptor: [Drug Prescriptions] this term only

#6 MeSH descriptor: [Patient Compliance] explode all trees

#7 Use OR utilization OR prescribing OR prescription OR intake OR compliance OR adherence OR stewardship OR over-the-counter OR non-prescription OR self-medication in Trials (Word variations have been searched)

#8 MeSH descriptor: [Community Pharmacy Services] explode all trees

#9 MeSH descriptor: [Pharmacists] explode all trees

#10 Pharmacy OR pharmacist in Trials (Word variations have been searched)

#11 (#1 OR #2) AND (#3 OR #4 OR #5 OR #6 OR #7) AND (#8 OR #9 OR 10) in Trials

APPENDIX B: REASONS FOR EXCLUSION OF FULL TEXT ARTICLES

Study	Reason for exclusion
Ajalla 2004[57]	Not specifically aimed at antibiotics
Ashiru-Oredope 2020[58]	Outcomes
Astuti 2017[59]	Setting
Burns 2020[60]	Study design
Chowdhurry 2018[61]	Study design
Demoré 2018[62]	Study design
De Santis 1994[63]	Setting
Dollman 2005[64]	Study design
Dutcher 2020[65]	Setting
Finkelstein 2001[66]	Pharmacist not main intervention
Formoso 2013[67]	Pharmacist not main intervention
Garnett 1981[68]	Setting
Gastelurrutia 2002[69]	Study design
Gastelurrutia 2013[70]	Study design
Heringa 2017[71]	Study design
Hickman 2003[72]	Setting
Huang 2007[73]	Pharmacist not main intervention
Ives 1987[74]	Study design
Kandeel 2019[75]	Study design
Klepser 2019[76]	Study design
Lim 2020[77]	Study design
Linnebur 2011[78]	Setting
Madaras-Kelly 2006[79]	Study design
McCombs 1993[80]	Study design
Mölstad 1994[81]	Study design
Neuner 2011[82]	Setting
Newby 2010[83]	Study design
Papastergiou 2018[84]	Study design
Peñalva 2020[85]	Study design
Peterson 1997[86]	Pharmacist not main intervention
Rodis 2004[87]	Study design
Rodrigues 2019[88]	Setting
Rubin 2005[89]	Study design
Seager 2006[90]	Setting
Smeets 2009[91]	Pharmacist not main intervention
Stevens 2002[92]	Outcomes
Steward 2000[93]	Pharmacist not main intervention
Valimba 2014[94]	Study design
Vervloet 2016[7]	Pharmacist not main intervention
Vervloet 2016[7]	Duplicate
Wakeman 2018[95]	Study design
Welschen 2004[96]	Pharmacist not main intervention
Westfall 1997[97]	Study design
Wong-Beringer 2009[98]	Setting
Worral 2010[99]	Pharmacist not main intervention

APPENDIX C: MAIN CHARACTERISTICS OF THE INCLUDED STUDIES

Author (year) country	**Andrés (2004),[28] Spain (urban or rural setting not reported)**
Study design (intervention type)	Cluster randomised controlled trial (technical intervention)
Outcome category (subcategory)	Patient outcome (adherence) Adherence is defined as no leftovers at the end of treatment, based on prescribed dose.
Antibiotics and target population	Amoxicillin and amoxicillin + clavulanic acid in capsules, tablets or sachets. Target population not further specified, all infections included.
Objective of study	To assess if unit dose dispensing enhances adherence to antibiotics versus traditional packaging (full boxes)
Description of the intervention	The intervention group received the exact number of pills/sachets dispensed. The control group received full packages. Both groups received tailored written and oral information during dispensing.
Number of pharmacies	15 (IG = 7, CG = 8)
Outcome measurement(s) and results	Phone call (max three times, otherwise lost to follow-up) to measure patient-reported adherence. Higher 100% adherence was reported for the control group (73.40%) *vs* the intervention group (62.07%), but this difference was not significant ($P = .1025$)
Conclusion	Unit dose dispensing did not result in higher 100% adherence. The authors suggest that pharmacists may have a key role in actively educating patients since overall adherence to antibiotics improved for both intervention and control.
Author (year) country	**Beaucage (2006),[36] Canada (urban setting)**
Study design (intervention type)	Randomised controlled trial (educational intervention)
Outcome category (subcategory)	Patient outcome (no. of reported symptoms) Outcomes: Change in number of infectious symptoms, change in infection severity score, number of drug-related problems, adherence
Antibiotics and target population	Adult patients with a new prescription of any oral antibiotic with a treatment length of 5–14 days.
Objective of study	To evaluate the impact of a telephone follow-up intervention on clinical outcomes, pharmaceutical care, and costs for patients undergoing antibiotic treatment
Description of the intervention	Both intervention and control group received standardised oral and written information from a pharmacist at the start of the treatment. The intervention group received a phone call from a pharmacist on Day 3 of their antibiotic treatment to check the patients' general condition, adverse effects and understanding of the dosage. They explained the importance of adherence and encouragement was offered. Patients in the control group did not receive the follow-up call but could ask their pharmacist questions when needed. Final evaluation phone call was scheduled at the expected last day of treatment.
Number of pharmacies	6
Outcome measurement(s) and results	Prior to randomisation, the number of symptoms and severity of infection were measured using a measurement scale developed specifically for this study. During the intervention, drug-related problems were identified through telephone intervention. And at the final evaluation adherence to treatment (asking number of pills left) and patient satisfaction were measured by a (non-validated) questionnaire over the telephone. No significant difference in: Change in number of infectious symptoms: −5.08 ± 3.56 (IG), −4.83 ± 4.03 (CG) Change in infection severity score: −1.32 ± 1.02 (IG), −1.27 ± 1.28 (CG) After excluding lower and upper respiratory tract infections: Significant difference in change in number of symptoms, mean difference: −1.26 (CI −0.71–−0.005) No significant difference in change of infection severity score, mean difference: −0.27 (CI −0.71–0.16) Drug-related problems identified: 92 (IG), 11 (CG) Percentage of patients with drug-related problems: 53% (IG), 8% (CG), $P = <.001$ Percentage of patients receiving oral advice: 52% (IG), 6% (CG), $P = <.001$ Over 90% of drug-related problems were identified and 90% of advice was given during pharmacist telephone intervention that the control group did not receive. Adherence (antibiotics taken/antibiotics prescribed *100%): 94% ± 9% (IG), 94% ± 12% (CG), $P = .803$

(Continues)

Author (year) country	Andrés (2004),[28] Spain (urban or rural setting not reported)
	Patient satisfaction questionnaire: Friendly-explanation domain scores: 4.60 ± 0.46 (IG), 4.49 ± 0.56 (CG), $P = .2$ Managing-therapy domain scores: 4.52 ± 0.54 (IG), 4.43 ± 0.60 (CG), $P = .4$
Conclusion	Telephone follow-up was not proven to be effective in improving clinical outcomes (infection severity score, adherence) and pharmaceutical care in terms of patient satisfaction. The study suggests that telephone follow-up could be used as a cost-effective tool in detecting and managing drug-related problems.
Author (year) country	**Chalker (2002),[35] Vietnam (urban setting)**
Study design (intervention type)	Randomised controlled trial (educational intervention)
Outcome category (subcategory)	Quality of care (dispensing antibiotics without prescription) Outcomes: Dispensing practices through questionnaire: Asking about fever/quality of breathing, willingness to dispense antibiotics/traditional medicines, selling antibiotics without prescription.
Antibiotics and target population	Antibiotics included not specified, except for selling antibiotics without prescription which focused on cephalexin. All staff working in the pharmacy were educated.
Objective of study	To assess the effectiveness of a multi-component intervention on knowledge and reported practice amongst staff working in private pharmacies in Hanoi regarding non-prescription requests for antibiotics
Description of the intervention	Three interventions were implemented sequentially (duration of 3 months/intervention) and focused on good practice management of an STD, upper respiratory tract infection, request for an antibiotic and steroids without a prescription. The first intervention included two visits (1 month apart) of four inspectors of the Hanoi health office in which regulations around selling prescription-only drugs was explained, the second intervention consisted of two face-to-face education sessions on the topics (written and oral information) and the third was a one-day seminar for appointed leaders from each intervention pharmacy in which the importance of peer influence was stressed. This was followed by 3-monthly meetings with all the leaders to discuss/review practical cases.
Number of pharmacies	44 (IG = 22, CG = 22)
Outcome measurement(s) and results	Interviews conducted with a semi-structured questionnaire were performed at baseline and after intervention (4 months later) in both control and intervention groups to measure non-prescription requests and sales of antibiotics for acute respiratory tract infections. Additionally, healthcare professionals' knowledge and reported practice of the staff were tested. Questions about breathing Percentage of pharmacies at baseline: 50% (IG), 55% (CG) Percentage of pharmacies at follow-up: 73% (IG), 39% (CG) 0.10 Questions about fever Percentage of pharmacies at baseline: 64% (IG), 75% (CG) Percentage of pharmacies at follow-up: 75% (IG), 43% (CG) 0.01 Pharmacies that would offer antibiotic treatment Percentage of pharmacies at baseline: 16% (IG), 11% (CG) Percentage of pharmacies at follow-up: 9% (IG), 36% (CG) 0.02 Pharmacies that would offer traditional medicines Percentage of pharmacies at baseline: 5% (IG), 45% (CG) Percentage of pharmacies at follow-up: 57% (IG), 23% (CG) 0.03 Would sell cephalexin without prescription Percentage of pharmacies at baseline: 57% (IG), 45% (CG) Percentage of pharmacies at follow-up: 20% (IG), 61% (CG) 0.02
Conclusion	The multi-component intervention resulted in a significant decrease of antibiotics sold without prescription and an improvement of healthcare professionals' knowledge.
Author (year) country	**Chalker (2005),[29] Vietnam/Thailand (urban setting)**
Study design (intervention type)	Randomised controlled trial (educational intervention)
Outcome category (subcategory)	Quality of care (dispensing antibiotics without prescription) Outcomes: Simulated client receiving requested antibiotics without prescription, simulated client receiving advice from pharmacy staff.

Author (year) country	Andrés (2004),[28] Spain (urban or rural setting not reported)
Antibiotics and target population	Cephalexin in Vietnam, roxithromycin and amoxicillin in Thailand, population characteristics NA
Objective of study	To study the effectiveness of a multi-faceted intervention on the dispensing practices of drug sellers in Hanoi and Bangkok
Description of the intervention	The research consisted of a baseline measurement followed by three different interventions (1) enforcement of regulations with local inspectors (two in Hanoi, six in Bangkok) visiting to emphasise the importance of prescription-only medicine legislation; (2) education (on dealing with request for antibiotic without prescription), performed face-to-face in Hanoi and in a large group in Bangkok; and (3) peer review, voluntary in Bangkok and compulsory in Hanoi, consisting of five meetings in which client case reports were discussed.
Number of pharmacies	Hanoi: 55 (IG = 28, CG = 27), Bangkok: 69 (IG = 34, CG = 35)
Outcome measurement(s) and results	Practice was studied through simulated client method (SCM), by five visits per pharmacy per dispensing practice at baseline and a month after each intervention. The visits consisted of customers asking for a few capsules of an antibiotic. Dispensing of antibiotics without prescription, questions and advice given at dispensing were recorded. Mean difference (IG-CG) after each phase of the interventions, no confidence intervals reported: Hanoi (all pharmacies), mean difference in percentage of simulated customers that received antibiotics: – baseline: 2% ($P = .1625$) – post regulatory intervention: 0% ($P = .7389$) – post educational intervention: −21% ($P = .0471$) – post peer review: −24% ($P = .0125$) Bangkok (all pharmacies), mean difference in percentage of simulated customers that received antibiotics: – baseline: 1% ($P = .8925$) – post regulatory intervention: −9% ($P = .3770$) – post educational intervention: −3% ($P = .4795$) – post peer review: −4% ($P = .5525$) Bangkok (only pharmacies that completed peer review intervention): – baseline: 4% ($P = .6998$) – post regulatory intervention: −9% ($P = .3705$) – post educational intervention: −8% ($P = .1152$) – post peer review: −9% ($P = .2510$) Hanoi (all pharmacies), mean difference in percentage of simulated customers that received no advice from pharmacy: – baseline: −3% ($P = .6027$) – post regulatory intervention: 0% ($P = .9597$) – post educational intervention: −26% ($P = .0025$) – post peer review: −30% ($P = .0028$) Bangkok (all pharmacies), mean difference in percentage of simulated customers that received no advice from pharmacy: – baseline: −4% ($P = .4165$) – post regulatory intervention: −2% ($P = .5526$) – post educational intervention: 0% ($P = .9447$) – post peer review: −9% ($P = .1927$) Bangkok (only pharmacies that completed peer review intervention): – baseline: −6% ($P = .3158$) – post regulatory intervention: −5% ($P = .1598$) – post educational intervention: −10% ($P = .0914$) – post peer review: −23% ($P = .0181$)
Conclusion	The intervention showed positive results in Hanoi by a reduction in the number of antibiotics dispensed without prescription and more questions (e.g., asking for a prescription)/advice given at time of dispensing. In Bangkok there was no significant improvement in antibiotic management suggesting further research needs to be tailored to cultural and societal settings.
Author (year) country	**Göktay (2013),[41] Turkey (urban setting)**
Study design (intervention type)	Controlled trial (educational intervention)
Outcome category (subcategory)	Patient outcome (adherence) Patient self-adherence (patients with a pill count of 100% were defined as adherent) and timing adherence (patients who answered 'yes' to the question 'did you take your antibiotic at the correct times?' were considered timing adherent).
Antibiotics and target population	Patients that had been prescribed oral antibiotics for any type of infection

(Continues)

Author (year) country	Andrés (2004),[28] Spain (urban or rural setting not reported)
Objective of study	To assess the impact of patient education on adherence to prescribed antibacterial agents
Description of the intervention	All patients were instructed to take their medication according to the prescribers' advice and pharmacists gave additional verbal and written information on antibiotic usage, with instruction and warning stickers on each container. The intervention group received additional information from the pharmacist around the risk of antibacterial resistance in relation to the prescribed dosage regimen.
Number of pharmacies	1
Outcome measurement(s) and results	Two questionnaires of which the first took place at initial visit to the pharmacy and consisted of questions around socio-demographic characteristics of the patients. The second questionnaire was conducted the day after completing the antibiotic treatment and included questions to test self-administration adherence and timing adherence Percentage of patients who were adherent: Administration adherence: 83.9% (IG), 75.9% (CG), $P = .438$ Timing adherence: 80.6% (IG), 65.5% (CG), $P = .185$ Administration and timing adherence: 64.5% (IG), 55.2% (CG), $P = .460$ Differences between adherent and non-adherent groups: Minutes of examination: 14.30 ± 9.63 (adherent), 13.70 ± 8.14 (not adherent), $P = .798$ Number of pills received: 8.87 ± 4.32 (adherent), 12.33 ± 4.35 (not adherent), $P = .003$ Number of days of therapy: 5.69 ± 2.20 (adherent), 7.07 ± 2.23 (not adherent), $P = .007$
Conclusion	This small study showed no overall differences in adherence between the intervention and control groups. Increased adherence was reported in cases of shorter antibiotic courses, lower dosing frequencies (once a day) and older age of patients (> 30 years old). The time of examination did not influence adherence. Pharmacists may have a role in educating younger patients receiving multi-dose, long-term antibiotics.
Author (year) country	**Gotsch (1982),[42] USA (one pharmacy serves a rural population, one pharmacy an urban population)**
Study design (intervention type)	Pilot study, controlled trial (educational intervention)
Outcome category (subcategory)	Patient outcome/quality of care (adherence) Outcomes: Patient satisfaction with information, knowledge of antibiotics, attitude towards patient package inserts, adherence to treatment (number of leftover antibiotics is the same as expectation based on prescription).
Antibiotics and target population	Patients who presented with a new prescription for penicillin V, penicillin G or ampicillin.
Objective of study	To evaluate the effects of patient package inserts (PPIs) on the knowledge, attitudes and adherence of patients on a short course of therapy with either penicillin V, penicillin G or ampicillin.
Description of the intervention	Quasi-experimental study executed in two pharmacies. Both pharmacies took part in being the control first, then in intervention 1 and finally intervention 2, requiring an increasing amount of involvement by the pharmacist. The PPIs included information on possible side effects, interactions, adherence and instructions on how to take the antibiotics. Intervention consisted of a control group: No PPI or verbal information; intervention 1: PPIs were given together with dispensed drugs but without verbal reinforcement; and intervention 2: PPI and verbal information.
Number of pharmacies	2
Outcome measurement(s) and results	Telephone follow-up with standardised questionnaire to test patient knowledge and adherence (reported number of doses remaining in medicine container) of antibiotic therapy and attitude towards drug information received. Percentage of respondents desiring more information: 63% (CG), 18% (IG1), 14% (IG2) Percentage of correct responses to knowledge items: 66% (CG), 90% (IG1), 93% (IG2) Positive towards helpfulness of PPIs: 90% (IG1), 91% (IG2) Percentage of respondents adherent: 48% (CG), 57% (IG1), 72% (IG2)
Conclusion	Results of this small quasi-experimental study suggest that providing PPI with/without verbal consultation provides patients with a satisfactory amount of information about their antibiotic treatment. It additionally increases their knowledge and adherence.
Author (year) country	**Jackson (2005),[37] England (urban setting)**
Study design (intervention type)	Randomised controlled trial (behavioural intervention)
Outcome category (subcategory)	Patient outcome (adherence) Adherence defined as 100% intake of prescribed antibiotics
Antibiotics and target population	Patients with a prescription for any oral antibiotic course lasting less than 14 days
Objective of study	To test whether implementation intentions increase adherence to short-term antibiotics

Author (year) country	Andrés (2004),[28] Spain (urban or rural setting not reported)
Description of the intervention	Implementation intentions are defined as "specific plans that outline exactly when, where and how performance of a behaviour is to be achieved and are presented as 'I intend to do X at time Y in place Z'". The study consisted of four groups. All participants were asked a series of questions (about antibiotic and other medicines they are taking) and were all asked to take the antibiotic as prescribed (control group). Theory of planned behaviour group (TPB): Had to complete a five-item theory of planned behaviour and past behaviour questionnaire. TPB + own implementation intention: Had to form their own implementation intention for each daily dose. TPB + given: Researcher provided an implementation intention.
Number of pharmacies	10
Outcome measurement(s) and results	Telephone follow-up after completing the antibiotic course to record adherence (pill count measure, dichotomised as "no tablets remaining" versus "one or more tablets remaining"), intention, perceived behavioural control and past behaviour. No *P*-values reported. Self-reported pill count by number of daily doses 2 daily doses: No tablets remaining (100%), one or more remaining (0%) 3 daily doses: No tablets remaining (78.4%), one or more remaining (21.6%) 4 daily doses: No tablets remaining (66.7%), one or more remaining (33.3%) Self-reported pill count by intervention group Control: No tablets remaining (74.1%), one or more remaining (25.9%) TPB only: No tablets remaining (78.4%), one or more remaining (21.6%) TPB + own: No tablets remaining (73.1%), one or more remaining (26.9%) TPB + given: No tablets remaining (78.3%), one or more remaining (21.7%)
Conclusion	Completing a TPB questionnaire or forming an implementation intention (by oneself or with a healthcare professional) did not enhance adherence. Results from this study suggest that pharmacists might increase adherence to prescribed medicines by a telephone follow-up only.
Author (year) country	**Machuca (2003),[38] Spain (urban setting)**
Study design (intervention type)	Randomised controlled trial (educational intervention)
Outcome category (subcategory)	Patient outcome (adherence) Outcomes: Adherence (100% adherence to the prescribed dose), patient perception of health.
Antibiotics and target population	Patients over 15 years old with a prescription for an antibiotic for an acute infection with a duration of 2–15 days. Over 70% of patients had a respiratory tract infection. Largest groups of antibiotics were macrolides (22.4%), penicillin (20.1%) and penicillin + clavulanic acid (16.8%).
Objective of study	Determine the influence of written information on patient adherence to antibiotic treatment, verify the correlation of adherence to patient's perception of his/her state of health and to identify the possible causes of non-adherence.
Description of the intervention	All patients were given information about their treatment, as well as the lifestyle habits that would favour the cure of their infections. Only patients in the intervention group received the reinforcement of this information in writing.
Number of pharmacies	1
Outcome measurement(s) and results	Telephone follow-up interview to check for adherence to treatment and patient's perception of his/her health. Treatment adherence: 61% (IG), 46.8% (CG), $P = .038$ Patient perception of health (percentage of patients who felt better or cured): Adherent patients (93.0%), non-adherent patients (76.8%), $P = .0007$
Conclusion	Written information resulted in higher adherence to antibiotic regimes. In the majority of cases, patients who complied felt better and adherence was higher with fewer daily doses (1–2 daily doses). Abatement of symptoms was a principal reason for non-adherence.
Author (year) country	**Martín Arias (2010),[43] Spain (setting unclear)**
Study design (intervention type)	Controlled trial (educational intervention)
Outcome category (subcategory)	Patient outcome (adherence) Adherence is defined as taking between 80% and 110% of the prescribed antibiotics.
Antibiotics and target population	Patients of 16 years or older with at least one prescription for an oral antibiotic, excluding pregnant and lactating women, patients with mental illness, alcohol or drug addiction or patients who did not pick up their antibiotic at the pharmacy themselves.
Objective of study	To evaluate the antibiotic adherence after active dispensing antibiotics and patient follow-up

(Continues)

Author (year) country	Andrés (2004),[28] Spain (urban or rural setting not reported)
Description of the intervention	The intervention consisted of active dispensing which was extra information in the form of a label with pictograms on the antibiotic box. Patients were asked to visit the pharmacy after 10 days to count their pills, patients who did not show up were contacted by telephone.
Number of pharmacies	4
Outcome measurement(s) and results	Patient adherence was measured by pill counting. Percentage of adherent patients: 94.4% (IG), 93.2 (CG), $P = .04$ Percentage of adherent patients, based on daily dose (no *P*-value): One daily dose: 96.1% Two daily doses: 93.8% Three daily doses: 93% Four daily doses: 100% Percentage of adherent patients, based on treatment length (no *P*-value): One week: 95.5% Two weeks: 92.4% Three weeks: 84%
Conclusion	Labels containing pictograms resulted in a small (significant) increase in adherence. Patients finishing secondary school were more adherent, while more complex dosing regimens resulted in a decrease in adherence.
Author (year) country	**Merks (2019),[39] Poland (setting unclear)**
Study design (intervention type)	Cluster randomised controlled trial (educational intervention)
Outcome category (subcategory)	Patient outcome (adherence) Outcomes: Complete use of whole package of antibiotics, following recommended daily dose, patient perspective on medical information about antibiotic treatment.
Antibiotics and target population	Adult patients with a non-liquid prescription for amoxicillin or amoxicillin with clavulanic acid with two daily doses for any infection.
Objective of study	To evaluate the practical utility of pharmaceutical pictograms in routine practice of dispensing antibiotics in community pharmacy
Description of the intervention	The intervention group received an antibiotic with pictograms placed on the external packaging of the antibiotic containing information about drug regimen, whereas the control group received their antibiotic according to usual practice. Patients were interviewed during the initial visit to the pharmacy (demographic and antibiotic regime-related questions). A second interview was conducted via telephone or in the community pharmacy after completing the antibiotic therapy and included questions regarding resolution of symptoms, adherence, reasons for non-adherence and adverse reactions.
Number of pharmacies	64
Outcome measurement(s) and results	Semi-structured interview to assess patient's adherence (complete use of the whole package of medication), taking the recommended dose twice a day and subjective assessment of patients' perspective on medical information about antibiotic therapy obtained during the pharmacy consultation. Percentage of patients reporting relief of symptoms: 91.7% (IG), 84.3% (CG), $P = .1127$ Percentage of patients finishing entire package: 86.6% (IG), 83.3% (CG), $P = .6271$ Taking recommended daily dose: 80.4% (IG), 81.3% (CG), $P = .8633$ Patients who were advocates of pharmacy care: 76.6% (IG), 61.6% (CG), $P = .0239$
Conclusion	No statistical difference between the study and control groups in the context of symptom relief, completion of antibiotic therapy as recommended and taking the recommended dose twice a day. However, pictograms are highly accepted by patients and have a positive impact on the patient's perspective of services available in community pharmacies.
Author (year) country	**Muñoz (2014),[44] Spain (urban setting)**
Study design (intervention type)	Controlled trial (educational intervention)
Outcome category (subcategory)	Patient outcome (adherence) Outcomes: Adherence (not missing any dose in self-reported pill count and Morisky-Green test), patient perceived health
Antibiotics and target population	All adult patients who came to the pharmacy with a prescription for any antibiotic
Objective of study	To assess the effectiveness of an educational intervention on antibiotic adherence and patient-reported resolution of symptoms

Author (year) country	Andrés (2004),[28] Spain (urban or rural setting not reported)
Description of the intervention	The intervention focused on providing individualised verbal information to the patient or carer about treatment duration, dosage and how to use the antibiotic. Written information was not provided. The 20 minute counselling session took place in a separate area. In the control group, any questions on initiative of the patient or carer were answered but no extra counselling was provided.
Number of pharmacies	1
Outcome measurement(s) and results	Baseline knowledge on antibiotics were tested both for the intervention group and control group prior to receiving intervention and treatment. Telephone follow-up was used for the final evaluation of resolution of symptoms and adherence. Complete adherence to treatment: 67.2% (IG), 48.4% (CG), $P = .033$ Missing more than one dose: 38.1% (IG), 81.2% (CG), $P = .001$ Patient perceived 'totally cured': 54.7% (IG), 46.8% (CG), $P = .297$
Conclusion	The results show that medication knowledge is correlated to greater adherence and lower non-adherence (missing more than one dose) rates. No significant difference in health perception/resolution of symptoms were reported.
Author (year) country	**Pham (2013),[40] USA (urban setting)**
Study design (intervention type)	Randomised controlled trial (educational intervention)
Outcome category (subcategory)	Patient outcome (adherence) Outcomes: Auxiliary label recall, adherence (patients not missing any dose)
Antibiotics and target population	Literate, English-speaking adult patients receiving one of the 18 medications, including amoxicillin, amoxicillin/clavulanate, penicillin V potassium, cephalexin, cefuroxime, cefdinir, doxycycline, minocycline, tetracycline, ciprofloxacin, moxifloxacin, levofloxacin, azithromycin, clarithromycin, erythromycin, trimethoprim/sulfamethoxazole, nitrofurantoin and clindamycin. Subjects were excluded from the study if they were obtaining or had obtained a degree in medicine, nursing or pharmacy; were receiving chronic antibiotic therapy; or received the same antibiotic within the last 3 months.
Objective of study	To evaluate whether medication counselling with emphasis on auxiliary labels improves recall of auxiliary label information and adherence to medication schedule
Description of the intervention	The intervention consisted of a 10–15 minute counselling session from one pharmacist using a prescription-specific counselling form (not tailored to the patient's regime). Counselling included pertinent information on the antibiotic from the medication label and the information on the auxiliary labels. The control group did not receive additional counselling.
Number of pharmacies	2
Outcome measurement(s) and results	A follow-up call was conducted to collect data on the subject's short-term recall of medication instructions (auxiliary label recall) and self-reported adherence to the antibiotic schedule and duration of use. Rates of correct and incorrect recall of auxiliary label content were reported. Complete auxiliary label recalled correctly: 88.9% (IG), 66.7% (CG), $P = .11$ Patients being adherent: 72.2% (IG), 66.7% (CG), $P = .7$
Conclusion	Due to the small size of the study, strong conclusions cannot be drawn; however, results suggest that counselling does increase the level of auxiliary label recall and adherence. However, correctly recalling information does not directly translate into improved patient adherence.
Author (year) country	**Podhipak (1993),[30] Thailand (urban setting)**
Study design (intervention type)	Cluster randomised controlled trial (educational intervention)
Outcome category (subcategory)	Quality of care (healthcare professionals' adherence to guidelines) Outcome: Percentage of pharmacists and drug sellers supplying antibiotics for watery diarrhoea or dysentery
Antibiotics and target population	Twelve assessors were trained to simulate a mother with a child suffering from watery diarrhoea or dysentery.
Objective of study	To assess the impact of an intervention programme on the dispensing of oral rehydration salts (ORS), antibiotics and antidiarrhoeal drugs
Description of the intervention	Pharmacists in the intervention area were invited to attend a 3-hour training course organised by the investigators. Pharmacists who did not come to the course received educational material by registered mail which was followed up by a telephone call. Pharmacists were advised to convey the information to other personnel in their store. Drug sellers in the intervention area received the educational material by mail, followed by a telephone call. Drugstores/pharmacies in the control area received no information.
Number of pharmacies	191 pharmacists (IG = 123, CG = 68)90 drug sellers (IG = 44, CG = 46)

(Continues)

Author (year) country	Andrés (2004),[28] Spain (urban or rural setting not reported)
Outcome measurement(s) and results	Assessors recorded all the advice obtained from pharmacists/drug sellers immediately after leaving on a structured form and did this both for the intervention and control group. The investigators executed spot checks periodically to ensure the reliability of data obtained. Prescribing of ORS, antibiotics and anti-diarrhoeal drugs was recorded. No confidence intervals or *P*-values were reported. Percentage of cases in which antibiotics were supplied by pharmacists: Pre-intervention watery diarrhoea: 82.1% (IG), 91.0% (CG) Post-intervention watery diarrhoea: 79.7% (IG), 90.2% (CG) Pre-intervention dysentery: 86.8% (IG), 94.1% (CG) Post-intervention dysentery: 85.3% (IG), 94.1% (CG) Percentage of cases in which antibiotics were supplied by drug sellers: Pre-intervention watery diarrhoea: 54.5% (IG), 65.9% (CG) Post-intervention watery diarrhoea: 52.3% (IG), 68.2% (CG) Pre-intervention dysentery: 56.5% (IG), 54.3% (CG) Post-intervention dysentery: 43.5% (IG), 50.0% (CG)
Conclusion	The intervention resulted in a non-significant reduction of antibiotic dispensing for both pharmacist and drug sellers for diarrhoea and dysentery. Mixed results are reported for both control groups. Firm conclusions cannot be drawn due to flaws in study design (e.g., percentage of pharmacists informing colleagues not reported) and system influences (e.g., financial competition).
Author (year) country	**Roque (2016),[34] Portugal (mixed setting)**
Study design (intervention type)	Cluster randomised controlled trial (educational intervention)
Outcome category (subcategory)	Quality of care (population antibiotic use) Outcome: Consumption of antibiotics in packages per 1000 inhabitants per day
Antibiotics and target population	The study population comprised all physicians working at public national health system outpatient centres (~1100 physicians) and all pharmacists working at community pharmacies (~1200 pharmacists) in the study area. The consumption of antibiotics was measured for the following groups: Antibacterials for systemic use, tetracyclines, penicillins, cephalosporins, sulphonamides and trimethoprim, macrolides and quinolones.
Objective of study	To decrease population antibiotic use through an educational intervention targeting primary care physicians' and community pharmacists' attitudes and knowledge
Description of the intervention	The educational intervention targeting inappropriate antibiotic prescribing and dispensing consisted of a presentation (targeting physicians and pharmacists) followed by an explanation of flyers and posters (targeting patients). Sessions ended with a discussion about the role of pharmacists in promoting the rational use of antibiotics. The control group did not receive the educational intervention.
Number of pharmacies	507 (IG = 106 pharmacies [173 pharmacists], CG = 401 pharmacies [888 pharmacists])
Outcome measurement(s) and results	Consumption of antibiotics obtained from national data was expressed in packages per 1000 inhabitants and compared between baseline and post intervention for both intervention as control group. Mean difference. Overall consumption (−3.71% CI: −8.3, 0), $P = .0459$ Tetracyclines (−15.63% CI: −27.59, −2.94), $P = .0111$ Penicillins (−2.55% CI: −7.98, 1.22), $P = .1907$ Cephalosporins (−7.24% CI: −15.80, 0.00), $P = .0206$ Sulphonamides and trimethoprim (−2.90% CI: −10.77, 2.78), $P = .2645$ Macrolides (−9.37% CI: −17.43, −2.21), $P = .0214$ Quinolones (3.59% CI: 0.00, 6.85), $P = .1160$
Conclusion	The educational intervention showed a small (statistical) reduction in the overall antibiotic consumption (3.71% decrease at 1 year of the intervention) for all antibiotic types except for quinolones, and thus showed to be a feasible non-time-consuming (2-hour education) way to reduce antibiotic use.
Author (year) country	**Treibich (2017),[31] France (mixed setting)**
Study design (intervention type)	Cluster randomised controlled trial (technical intervention)
Outcome category (subcategory)	Patient outcome/quality of care (adherence) Outcomes: Number of antibiotic pills supplied, patient acceptance rate, patient-reported adherence
Antibiotics and target population	Any patient with an antibiotic prescription for which per-unit dispensing was possible, who agreed to participate.

Author (year) country	**Andrés (2004),[28] Spain (urban or rural setting not reported)**
Objective of study	To assess the environmental, economic and health effects of dispensing the exact number of pills for 14 antibiotics.
Description of the intervention	Intervention pharmacies dispensed the exact number of pills for patients' antibiotic regime prescriptions. Control pharmacies provided usual care (full boxes).
Number of pharmacies	100 (IG = 75, CG = 25)
Outcome measurement(s) and results	Respondents were retrospectively questioned about their antibiotic treatment by a telephone follow-up call. Adherence was measured through the Morisky scale indicating patients' adherence: No pills left (strict adherence criterion), less than four pills left (one-day tolerance criterion) and a mixed indicator using both pill counts and self-declared scale (mixed adherence criterion). No confidence interval reported: Patient acceptance rate for per-unit dispensing: 80.6% Average number of pills dispensed: 20 (IG), 23 (CG), $P = .02$ Strict adherence 91.4% (IG) *vs* 65.6% (CG), $P = .00$ One-day tolerance 92.3% (IG) *vs* 71.1% (CG), $P = .00$ Mixed adherence 77.8% (IG) *vs* 57.5% (CG), $P = .00$
Conclusion	Dispensing the exact number of pills increased adherence to treatment and the majority of the patients accepted the per-unit dispensing (80.6%). In 60% of the cases, the initial drug packaging had to be modified, indicating opportunities to reduce risks associated with self-medicating with left-over antibiotic pills.
Author (year) country	**Tumwikirize (2004),[32] Uganda (mixed setting)**
Study design (intervention type)	Cluster controlled trial (educational intervention)
Outcome category (subcategory)	Quality of care (dispensing behaviour) Outcomes: Appropriate assessment of child's conditions, appropriate management and dispensing for acute respiratory tract infections, information and instruction given with dispensed drugs.
Antibiotics and target population	Study personnel posing as mothers of a 1-year-old child with either a mild or a severe acute respiratory tract infection for 3 days. Dispensed antibiotics: Co-trimoxazole, amoxicillin and ampicillin.
Objective of study	To investigate the impact of a face-to-face educational intervention on counter attendants' dispensing behaviour for mild and severe acute respiratory infections (ARI) in children at private pharmacies and drug shops.
Description of the intervention	The intervention involved two elements: (1) three morning sessions of face-to-face educational training of counter attendants on appropriate management of ARI in children; and (2) the distribution of written materials (brochures, posters, guidelines) to assist counter attendants' practices. Counter attendants were instructed on advice to give with dispensing the drugs and were asked to educate patients on how to use the drugs appropriately.
Number of pharmacies	147 drug shops (IG = 72 drug shops, CG = 75 drug shops)25 pharmacies (IG = 12 pharmacies, CG = 13 pharmacies)
Outcome measurement(s) and results	Baseline and after intervention data collection were the same and included the counter attendant's assessment of the child's condition and the dispensing practices for ARI. The latter covered two areas: The commonly dispensed drugs and the advice and instructions given with dispensed drugs. Mean difference (intervention – control) in assessment of child's conditions (no *P*-values reported): Mild AMR: History of illness −0.4 (CI: −0.2, 0.7) Mild AMR: Signs and symptoms −0.3 (CI: 0.4,0.7) Severe AMR: History of illness −0.4 (CI: −0.3, 0.8) Severe AMR: Signs and symptoms −0.1 (CI: −0.3, 0.5) Mean difference (intervention – control) in questions asked: Mild acute respiratory tract infections Age of child: −2.3%, $P = .79$ Duration of illness: −7.8%, $P = .62$ Previous medical visits: −14.4%, $P = .08$ Previous medication: −3.6%, $P = .77$ Presence of fever: −15.3%, $P = .08$ Difficulty in breathing: −9.4%, *P*-value not reported Nature of cough: −9.4%, $P = .27$ Severe acute respiratory tract infections Age of child: −1.5%, *P*-value not reported Duration of illness: −14.4%, $P = .15$ Previous medical visits: −7.5%, $P = .26$ Previous medication: −17.9%, $P = .10$ Presence of fever: −5.2%, $P = .58$ Difficulty in breathing: 3.6%, $P = .49$ Nature of cough: −16.2%, $P = .04$ Mean difference (intervention – control) in dispensing patterns of antibiotics:

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Author (year) country	Andrés (2004),[28] Spain (urban or rural setting not reported)
	Mild acute respiratory tract infections An antibiotic: 2.2%, $P = .75$ Co-trimoxazole: 2.1%, $P = .82$ Amoxicillin: 2.6%, $P = .65$ Ampicillin: 3.4%, $P = .90$ Severe acute respiratory tract infections An antibiotic: −11.6%, $P = .21$ Co-trimoxazole: 17.7%, $P = .06$ Amoxicillin: −29%, $P = .00$ Ampicillin: 2.5%, $P = .70$
Conclusion	Despite the education, management of mild and severe ARI did not improve the assessment of the condition; additional appropriate instructions given with dispensing and high levels of inappropriate dispensing were still present. Barriers identified were related to the system (competition between drug stores) and financial and behavioural components of patients.
Author (year) country	**West (2019),[33] Malta (mixed setting)**
Study design (intervention type)	Cluster randomised controlled trial (educational intervention)
Outcome category (subcategory)	Patient outcome (adherence) Outcomes: Adherence (defined as no tablets/capsules left at end of treatment), beliefs about medicines, knowledge about antibiotic resistance.
Antibiotics and target population	Adults with a prescription for oral, solid dosage form, short-term antibiotics.
Objective of study	To assess whether an intervention supported by an educational leaflet enhances adherence and reduces cost in relation to wastage of unused antibiotics amongst patients taking short-term antibiotics in community; and to determine a possible association between adherence and patients' general medicines' beliefs
Description of the intervention	An educational leaflet formed the basis of the educational intervention containing information based on 'Get smart: Know when antibiotics work' by Centers for Disease Control and Prevention. The pharmacists in the intervention group were asked to fill the instructions on the top section of the leaflet, provide oral counselling based on information from the leaflet, and hand the leaflet to the patient together with their antibiotic package and other counselling they deemed necessary. Pharmacists within the control group provided counselling as usual.
Number of pharmacies	14 (IG = 7, CG = 7)
Outcome measurement(s) and results	Adherence and association between adherence and patients' general medicines' beliefs (perception of the outcome of their infection, knowledge about antibiotic resistance) were measured through a phone interview. Percentage of patients adherent: 90%% (IG), 76% (CG), $P < .0005$ Knowledge about antibiotic resistance: Patients with more knowledge were more adherent, $P < .0005$ Beliefs about medicines: General-benefit beliefs: 14.80 ± 2.09 (IG), 14.34 ± 2.44 (CG), $P = .044$ General-harm beliefs: 11.05 ± 2.12 (IG), 10.74 ± 2.44 (CG), $P = .176$ General-overuse beliefs: 11.88 ± 2.69 (IG), 11.97 ± 2.79 (CG), $P = .743$ There was no statistically significant association between adherence and beliefs about medicines.
Conclusion	The leaflet significantly increased adherence and the study showed that adherence was correlated with patients who have a healthcare professional in the family and older age. Patients' general beliefs around antibiotic use (e.g., general overuse) could assist in developing tailored strategies.

APPENDIX D: RISK OF BIAS

	Random sequence generation	Allocation concealment	Baseline outcome measurements similar	Baseline characteristics similar	Incomplete outcome data	Knowledge of interventions adequetely prevented	Protection against contamination	Selective outcome reporting	Other risks of bias	Overall risk of bias
Andrés 2004	?	?	-	-	+	-	-	-	-	+
Beaucage 2006	-	-	?	-	-	-	-	-	-	?
Chalker 2002	?	?	-	?	-	?	-	-	-	?
Chalker 2005	?	-	-	+	-	?	-	-	+	+
Göktay 2013	+	?	?	?	+	?	?	-	+	+
Gotsch 1982	+	+	+	+	+	?	-	+	-	+
Jackson 2005	-	?	?	-	?	-	-	-	-	?
Machuca 2003	-	?	?	?	-	-	?	-	-	?
Martín Arias 2010	+	?	-	-	+	-	?	-	-	+
Merks 2019	?	-	?	-	-	?	-	-	-	?
Muñoz 2014	-	?	?	-	-	-	?	-	-	?
Pham 2013	?	-	?	-	-	-	+	-	+	+
Podhipak 1993	?	-	?	+	?	?	-	-	+	+
Roque 2016	-	-	-	+	?	-	-	-	-	+
Treibich 2017	-	-	?	-	?	+	-	-	-	+
Tumwikirize 2004	?	-	-	?	+	-	-	-	+	+
West 2019	-	-	?	-	-	+	-	-	-	+

Risk of bias assessment, based on low risk (-), unclear risk (?) and high risk (+) of bias.