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Saudi Journal of Medical and Pharmaceutical Sciences
Abbreviated Key Title: Saudi J Med Pharm Sci
ISSN 2413-4929 (Print) | ISSN 2413-4910 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article **Medicine**

Effectiveness of Primary Care Interventions to Reduce Antibiotic Prescribing for Acute Respiratory Infections: Systematic Review

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DOI: https://doi.org/10.36348/sjmps.2026.v12i11.006 | **Received:** 13.09.2026 | **Accepted:** 06.11.2026 | **Published:** 11.11.2026

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Abstract

Background*:** Antimicrobial resistance represents one of the most consequential public health emergencies of the twenty-first century, driven predominantly by the inappropriate and excessive consumption of systemic antibiotics in ambulatory healthcare settings. Acute respiratory tract infections constitute the single most frequent diagnostic indication for outpatient medical consultations worldwide and account for the vast majority of unnecessary antibiotic prescriptions despite their overwhelmingly viral and self-limiting etiology. Although numerous stewardship strategies have been trialed in general practice and family medicine, comparative synthesis of their clinical effectiveness, safety, and behavioural mechanisms remains essential for guiding health policy. ***Objective: This systematic review aimed to evaluate and qualitatively synthesize evidence from randomized controlled trials investigating the effectiveness and clinical safety of primary care interventions designed to reduce inappropriate overall or broad-spectrum antibiotic prescribing for patients presenting with acute respiratory infections. ***Methods***: A comprehensive systematic literature search was conducted across MEDLINE via PubMed, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science to identify randomized controlled trials and cluster randomized controlled trials published in peer-reviewed journals. Eligible studies evaluated clinician-targeted, patient-targeted, diagnostic point-of-care, behavioral, or health-system interventions implemented in primary care practices for acute upper or lower respiratory tract infections compared with usual care or alternative stewardship strategies. Methodological quality was appraised using the revised Cochrane Risk of Bias tool for randomized trials. Due to substantial heterogeneity across intervention modalities and outcome metrics, a structured thematic qualitative data synthesis was performed in accordance with PRISMA 2020 guidelines. ***Results***: From 2,480 initially identified records, 1,868 unique citations were screened after deduplication, 74 full-text articles were evaluated for eligibility, and nine landmark randomized controlled trials encompassing more than 440,000 patient consultations across Europe and North America were included in the final qualitative synthesis. Point-of-care C-reactive protein testing and enhanced clinician communication skills training demonstrated pronounced, synergistic reductions in antibiotic prescribing ranging from 31% to 62% relative risk reductions. Shared decision-making training programs and delayed antibiotic prescribing strategies reduced patient antibiotic consumption by 25% to 64% compared with immediate prescribing. Multifaceted educational outreach, peer academic detailing with personalized audit and feedback, and behavioral economics nudges such as accountable justification and peer comparison significantly reduced both overall inappropriate prescribing and broad-spectrum antimicrobial selection without increasing hospital admissions, suppurative bacterial complications, or unplanned reconsultations. ***Conclusion***: Multifaceted primary care interventions that combine diagnostic uncertainty reduction, structured clinician-patient communication, delayed prescribing safety nets, and socially anchored audit and feedback safely and substantially reduce unnecessary antibiotic prescribing for acute respiratory infections.

Keywords: Antimicrobial Resistance, Antibiotic Stewardship, Acute Respiratory Tract Infections, Primary Healthcare, Antibiotic Prescribing, Broad-Spectrum Antibiotics.

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BACKGROUND

Antimicrobial resistance has escalated from a theoretical microbiological concern into a leading cause of global morbidity, mortality, and healthcare expenditure [1]. Comprehensive global surveillance analyses estimate that bacterial antimicrobial resistance was directly attributable to 1.27 million deaths and associated with 4.95 million deaths worldwide in a single

year, surpassing the mortality burden of several major infectious diseases [1]. The evolutionary selection pressure driving the emergence and clonal dissemination of resistant pathogens is inextricably linked to the volume and spectrum of antimicrobial agents consumed in human medicine [2, 3]. Cross-national ecological investigations across European healthcare systems have established a robust linear correlation between outpatient antibiotic consumption rates—measured in defined daily doses per thousand inhabitants—and the prevalence of penicillin-non-susceptible and macrolide-resistant Streptococcus pneumoniae as well as resistant Escherichia coli isolates [3]. Furthermore, individual-level systematic reviews and meta-analyses demonstrate that patients prescribed an antibiotic in primary care for a respiratory or urinary tract infection face more than double the odds of harboring resistant commensal or pathogenic bacteria within the first month post-treatment, with measurable resistance persisting for up to twelve months [2]. Because approximately 80% to 90% of all human systemic antibiotic prescriptions are issued in community and ambulatory care settings, primary healthcare serves as the principal ecological reservoir and the most critical operational frontline for antimicrobial stewardship [4-6].

Within primary care, acute respiratory tract infections, encompassing acute bronchitis, acute rhinosinusitis, acute pharyngotonsillitis, acute otitis media, and the common cold or non-specific upper respiratory tract infection, represent the most common acute diagnostic category prompting patients to seek medical attention [4, 5]. Epidemiological evaluations of nationally representative ambulatory care databases in the United States have revealed that acute respiratory conditions account for nearly half of all outpatient antibiotic prescriptions, yet approximately 50% of these prescriptions are clinically unnecessary because the underlying syndromes are predominantly viral in origin or self-limiting bacterial infections that resolve without antimicrobial therapy [4, 5]. Parallel population-based analyses of English primary care electronic health records similarly indicate that between 8.8% and 23.1% of all systemic antibiotic prescriptions are clinically inappropriate, with sore throat, acute cough, sinusitis, and acute otitis media accounting for the overwhelming majority of excess prescribing [6, 7]. Large multi-country randomized placebo-controlled trials in both adult and pediatric primary care populations have consistently confirmed that routine amoxicillin therapy for uncomplicated acute lower respiratory tract infection confers no clinically meaningful reduction in symptom duration or severity when pneumonia is not clinically suspected, while significantly increasing the incidence of adverse drug events such as diarrhea, rash, and nausea [8, 9].

Despite unequivocal clinical practice guidelines advising against routine antimicrobial therapy for uncomplicated acute respiratory infections, high prescribing rates persist due to a complex interplay of cognitive, interpersonal, and organizational determinants [7-11]. Primary care clinicians frequently operate under severe time constraints and diagnostic uncertainty, particularly when attempting to differentiate self-limiting viral bronchitis from early bacterial pneumonia during a brief ten-minute consultation [7-10]. Observational cohort studies have demonstrated that inappropriate antibiotic prescribing increases progressively throughout morning and afternoon clinic sessions, reflecting cumulative cognitive and decision fatigue that lowers a clinician's threshold for issuing a prescription as the easiest means to conclude a consultation [10]. In addition, clinicians frequently overestimate patient or parental expectations for antibiotics and fear that withholding antimicrobial treatment might jeopardize patient satisfaction, damage the therapeutic relationship, or result in rare life-threatening suppurative complications [11, 12]. Conversational analyses of primary care encounters reveal that patients rarely demand antibiotics explicitly, but rather seek diagnostic reassurance, validation of illness severity, and actionable symptomatic relief [11].

Recognizing that passive dissemination of printed clinical guidelines rarely alters entrenched clinical habits, health systems and researchers have developed a diverse array of active stewardship interventions tailored to the realities of primary care [12-14]. In accordance with international public health frameworks, including the Centers for Disease Control and Prevention Core Elements of Outpatient Antibiotic Stewardship, these interventions can be categorized into four complementary mechanistic domains [12-14]. The first domain addresses diagnostic uncertainty at the point of care through rapid biomarker testing, most notably finger-prick C-reactive protein and procalcitonin assays, which provide objective, real-time quantification of host systemic inflammation to rule out severe bacterial infection [14]. The second domain focuses on reshaping the clinician-patient consultation through enhanced communication skills training, interactive patient educational booklets, shared decision-making decision aids, and delayed (or "back-up") antibiotic prescribing strategies that empower patients while establishing a clinical safety net [13, 14]. The third domain targets clinician knowledge and professional accountability through peer-led academic detailing, multifaceted educational seminars, and longitudinal prescription audit and feedback benchmarking individual prescribing profiles against guideline targets [12, 13]. The fourth domain leverages health information technology and behavioral economics through electronic health record clinical decision support alerts, accountable justification prompts, and social-norm peer comparison nudges [10-14].

Rationale for the Present Systematic Review

While previous overviews have examined isolated intervention types, primary care leaders and

policymakers require an integrated, rigorous synthesis comparing how diagnostic, communicative, educational, and behavioral interventions perform across diverse outpatient settings [13, 14]. Synthesizing high-quality randomized controlled trial evidence allows for a nuanced evaluation not only of relative and absolute reductions in overall and broad-spectrum antibiotic prescribing, but also of potential unintended consequences, including reconsultation rates, symptom resolution trajectories, patient satisfaction, and hospital admissions for respiratory complications [14].

Study Aim

The aim of this systematic review was to comprehensively evaluate and qualitatively synthesize evidence from randomized controlled trials investigating the effectiveness of primary care interventions designed to reduce inappropriate overall or broad-spectrum antibiotic prescribing for patients presenting with acute respiratory tract infections.

METHODOLOGY

Protocol and Reporting Framework

This systematic review was designed, conducted, and reported in strict adherence to the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement and its methodological guidance for transparent reporting of healthcare interventions [15]. A structured review protocol specifying the research question, database search architecture, study selection criteria, data extraction variables, risk of bias assessment framework, and narrative synthesis methodology was established prior to initiating the literature search to minimize selection and reporting bias [15].

Eligibility Criteria and PICOS Framework

Study eligibility was determined using a predefined Population, Intervention, Comparator, Outcomes, and Study Design (PICOS) framework tailored to ambulatory antimicrobial stewardship. The target population encompassed adult and pediatric patients presenting to primary healthcare settings, including general practice, family medicine clinics, and community pediatric primary care practices, with symptoms or clinical diagnoses of acute upper or lower respiratory tract infections, as well as the primary care clinicians responsible for their management. Eligible interventions included any structured clinician-focused, patient-focused, diagnostic point-of-care, behavioral, electronic health record-embedded, or multifaceted stewardship intervention explicitly aimed at reducing unnecessary overall antibiotic prescribing or reducing off-guideline broad-spectrum antibiotic selection for acute respiratory infections. Eligible comparators comprised routine clinical care, standard guideline dissemination alone, immediate antibiotic prescribing, or alternative active stewardship arms within factorial randomized designs. The primary outcome of interest was the rate or proportion of acute respiratory infection consultations resulting in an antibiotic prescription, antibiotic dispensing, or patient-reported antibiotic consumption, alongside shifts in broad-spectrum versus narrow-spectrum antimicrobial selection. Secondary outcomes included clinical recovery and symptom duration, patient or parental satisfaction, reconsultation rates within 14 to 30 days, and incidence of serious bacterial complications or hospital admissions. Only prospective randomized controlled trials, including parallel-group cluster randomized trials, factorial cluster randomized trials, and patient-level randomized clinical trials published as full-text peer-reviewed articles in the English language, were eligible for inclusion. Non-randomized observational studies, quasi-experimental interrupted time-series analyses without randomized controls, emergency department or inpatient hospital trials, and studies focusing exclusively on non-respiratory infections were excluded.

Information Sources and Search Strategy

A comprehensive electronic literature search was executed across four major bibliographic databases: MEDLINE (accessed via PubMed), Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science Core Collection. The search strategy combined controlled vocabulary terms (such as Medical Subject Headings in MEDLINE and Emtree terms in Embase) with free-text title and abstract keywords organized around four conceptual blocks: setting ("primary care" OR "general practice" OR "family practice" OR "ambulatory care" OR "outpatient"), condition ("acute respiratory tract infection" OR "respiratory infection" OR "bronchitis" OR "pharyngitis" OR "sinusitis" OR "otitis media" OR "common cold"), intervention ("antimicrobial stewardship" OR "C-reactive protein" OR "shared decision making" OR "delayed prescribing" OR "audit and feedback" OR "academic detailing" OR "behavioral intervention" OR "decision support" OR "communication skills"), and outcome/design ("antibiotic prescribing" OR "antibiotic use" OR "randomized controlled trial" OR "cluster randomized"). Reference lists of retrieved landmark systematic reviews and Cochrane overviews were also manually screened to ensure complete capture of foundational randomized trials [13, 14].

Study Selection and Data Extraction

All bibliographic records retrieved from the electronic database searches were imported into a reference management environment where automated and manual deduplication was performed. Two review stages were executed sequentially in accordance with PRISMA 2020 standards [15]. In the first stage, titles and abstracts of all unique records were screened against the PICOS eligibility criteria to exclude clearly irrelevant citations, such as laboratory microbiology studies, inpatient stewardship reports, and narrative commentaries. In the second stage, potentially eligible full-text manuscripts were retrieved and thoroughly

evaluated against all inclusion and exclusion parameters, with specific reasons for full-text exclusion systematically documented. From each finally included trial, standardized data elements were extracted into a structured evidence matrix capturing first author, publication year, trial acronym and geographic setting, study design and randomization unit, sample size of practices, clinicians, and patients, detailed description of the intervention and comparator arms, follow-up duration, primary antibiotic prescribing effect estimates with 95% confidence intervals, and secondary clinical safety and satisfaction outcomes.

Methodological Quality and Risk of Bias Appraisal

The internal validity and methodological rigor of the included randomized controlled trials were evaluated using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2), alongside its dedicated extension for cluster randomized trials [16]. Each study was appraised across five core bias domains: bias arising from the randomization process (and timing of identification or recruitment of individual participants in cluster trials), bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result [16]. Studies were classified as having low risk of bias, some concerns, or high risk of bias based on signaling questions within each domain.

Data Synthesis and Analytical Approach

Given the pronounced clinical and methodological heterogeneity across the included studies, spanning diverse intervention modalities (biomarker testing, communication training, delayed prescribing, academic detailing, behavioral nudges, and electronic decision support), varying units of randomization (patient-level versus clinic-level versus continuing medical education group-level), and distinct outcome metrics (index consultation prescribing, 28-day consumption, annual practice-wide dispensing, and broad-spectrum prescribing proportions), formal statistical pooling via meta-analysis was deemed inappropriate. Instead, a structured qualitative data synthesis was conducted, organizing findings into coherent thematic categories defined by the primary mechanism of behavior change, while critically examining effect magnitudes, durability, contextual moderators, and clinical safety across studies.

RESULTS

Search Results and Study Selection

The systematic search across MEDLINE, Embase, Cochrane CENTRAL, and Web of Science yielded a total of 2,480 bibliographic records, supplemented by 14 additional records identified through manual citation tracking of prior systematic reviews. Following the removal of 612 duplicate records, 1,882 unique titles and abstracts were screened. During the initial screening phase, 1,808 records were excluded because they did not evaluate an antimicrobial stewardship intervention in primary care, focused on inpatient or emergency department populations, or were non-experimental commentaries and epidemiological surveys. The remaining 74 articles were retrieved for full-text eligibility evaluation. Upon detailed full-text inspection, 65 articles were excluded: 24 were non-randomized observational or quasi-experimental before-and-after studies, 18 evaluated interventions outside primary care or did not report acute respiratory tract infection prescribing outcomes separately, 14 were secondary post-hoc subgroup analyses or trial protocols without primary endpoint data, and 9 were duplicate reports or brief letters lacking primary trial data. Ultimately, nine high-quality randomized controlled trials met all eligibility criteria and were included in the qualitative data synthesis [17-25]. The complete study identification, screening, eligibility assessment, and inclusion flow is illustrated in the PRISMA 2020 flow diagram below.

Characteristics of the Included Studies and Methodological Quality

The nine included studies were published between 2009 and 2019 and collectively encompassed more than 700 primary care practices, over 1,800 primary care clinicians, and more than 440,000 patient consultations or patient-years of follow-up across Europe and North America [17–25]. Specifically, two trials were conducted in the United Kingdom (Wales and England/Scotland) [18-25], two in the United States [20-24], one in the Netherlands [17], one in Norway [21], one in Canada (Quebec) [19], one in Spain [23], and one was a multinational European trial spanning six countries (Belgium, Spain, Wales, England, Poland, and the Netherlands) [22]. Eight of the nine studies utilized cluster randomized controlled designs, randomizing general practices [17-25], family practice teaching units [19], or continuing medical education peer groups [21], to prevent contamination between clinicians working within the same clinical environment, whereas one study employed an individual patient-level pragmatic randomized design across 23 primary care centers [23]. Furthermore, three cluster trials employed sophisticated 2×2 or 2×2×2 factorial designs to evaluate both the independent and synergistic effects of combining distinct stewardship interventions [17-24].

Methodological quality appraisal using the Cochrane RoB 2 tool indicated that all nine trials demonstrated high internal validity, with concealed allocation sequences, appropriate statistical adjustment for intracluster correlation using multilevel mixed-effects regression or generalized estimating equations, and minimal attrition [16–25]. Because behavioral, educational, and communicative interventions cannot be blinded to participating clinicians, all nine studies carried an inherent risk of performance awareness; however, outcome measurement bias was effectively mitigated in the majority of trials through objective extraction of electronic health record prescribing logs or national

pharmacy dispensing databases [18-25], and validated follow-up interviews in the remaining studies [17-23]. Detailed study characteristics and main quantitative findings are presented in Table 1.

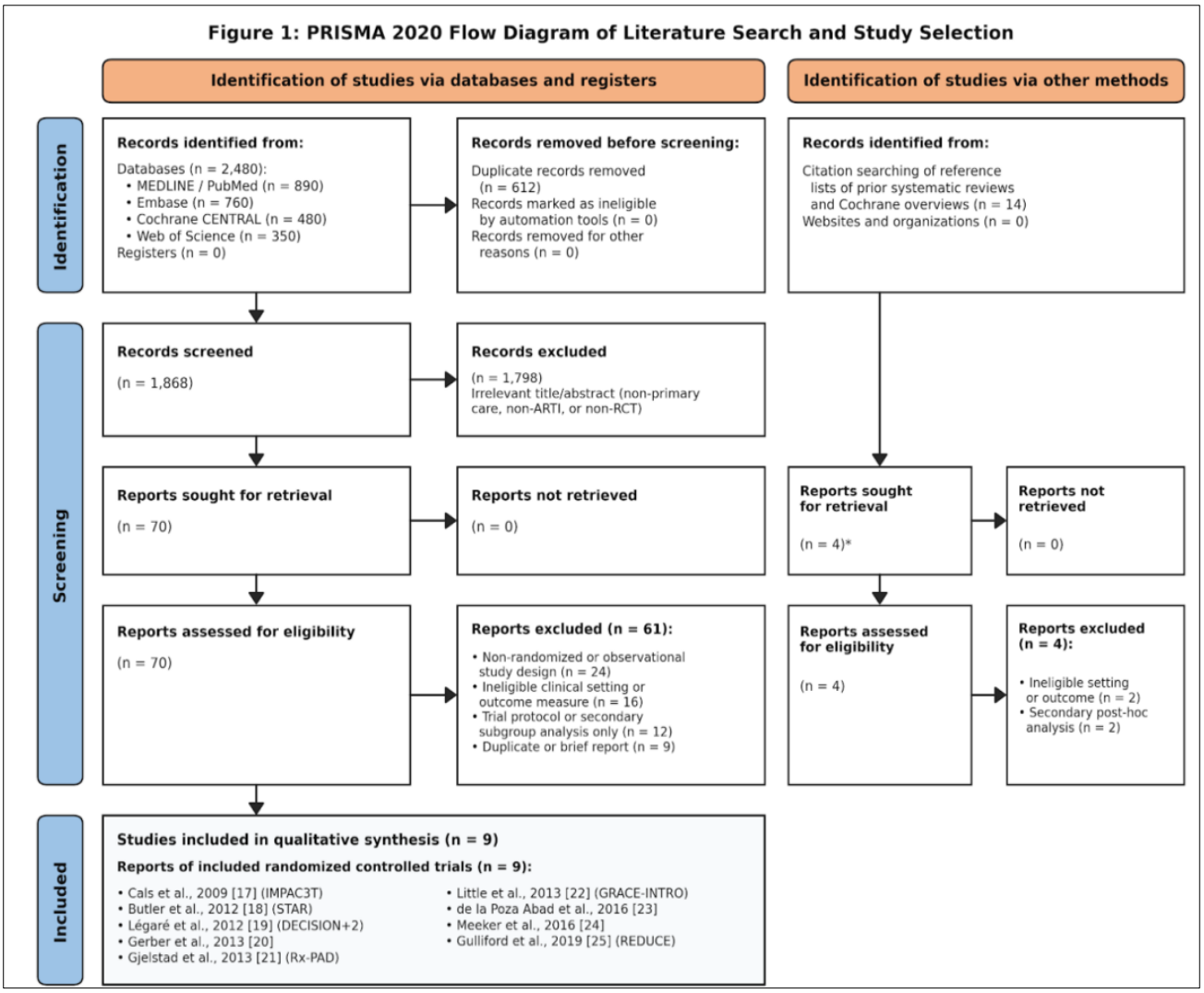


Table 1: Characteristics and Main Findings of the Included Primary Care Randomized Controlled Trials (n = 9)

Study Citation & Country	Study Design & Population	Intervention Arms	Comparator	Primary Prescribing Outcome & Effect Size	Clinical Safety & Secondary Outcomes
Cals *et al*., 2009 [17] (IMPAC3T); Netherlands	Cluster 2×2 factorial RCT; 20 general practices, 40 GPs, 431 adults with acute lower RTI	(1) Point-of-care CRP testing; (2) Enhanced communication skills training; (3) Combined CRP + communication	Usual care (no CRP test, no communication training)	Index antibiotic prescribing: CRP 31% vs no-CRP 53% (p = 0.02); Communication 27% vs no-training 54% (p < 0.01); Combined group 23%	28-day prescribing remained significantly reduced; patient recovery time and satisfaction were similar across all four arms
Butler *et al*., 2012 [18] (STAR); United Kingdom (Wales)	Practice-based cluster RCT; 68 general practices (~480,000 registered patients)	Multifaceted educational program (online reflection, communication skills, outreach seminar, web forum)	Usual care	Total oral antibiotic dispensing reduced by 4.2% (95% CI: 0.6% to 7.7%, p = 0.02) over 1 year; penicillin V reduced by 7.3%, macrolides by 7.7%	No significant differences in hospital admissions for RTIs or 7-day reconsultations; 5.5% trend toward lower dispensing costs

Study Citation & Country	Study Design & Population	Intervention Arms	Comparator	Primary Prescribing Outcome & Effect Size	Clinical Safety & Secondary Outcomes
Légaré *et al*., 2012 [19] (DECISION+2); Canada	Cluster RCT; 9 family practice teaching units, 149 physicians, 359 ARTI patients	DECISION+2 shared decision-making training (2-hour online tutorial + 2-hour interactive seminar + decision aids)	Usual care	Patients deciding to use antibiotics post-consultation: 27.2% vs 52.2% (absolute reduction 25.0%; adjusted RR 0.48, 95% CI: 0.34 to 0.68)	Higher patient involvement in decision-making; no difference in decisional regret, adherence, or 2-week repeat consultations
Gerber *et al*., 2013 [20]; United States	Cluster RCT; 18 pediatric primary care practices, 162 clinicians, 185,212 ARTI visits	1-hour on-site clinician education session plus 1 year of personalized quarterly prescribing audit and feedback	Usual practice	Broad-spectrum antibiotic prescribing for bacterial ARTIs fell from 26.8% to 14.3% vs 28.4% to 22.6% in controls (difference of differences 6.7%, p = 0.01); pneumonia off-guideline prescribing fell 75%	No increase in treatment failures or safety events; ensured shift from broad-spectrum agents to guideline-concordant narrow-spectrum therapy
Gjelstad *et al.,* 2013 [21] (Rx-PAD); Norway	Cluster RCT; 79 CME peer groups (382 GPs), ~152,000 ARTI consultations	Peer academic detailing (two 1-day group visits by trained GPs, individual audit and feedback reports, regional workshop)	Active control (CME programme targeting geriatric pharmacotherapy)	Adjusted odds of prescribing antibiotics for ARTIs reduced (OR 0.72, 95% CI: 0.61 to 0.84); odds of prescribing non-penicillin V broad-spectrum antibiotics reduced (OR 0.64, 95% CI: 0.49 to 0.82)	Feasible and well accepted by GPs; substantial shift toward narrow-spectrum phenoxymethylpenicillin (penicillin V)
Little *et al*., 2013 [22] (GRACE-INTRO); 6 European countries	Multinational cluster 2×2 factorial RCT; 246 practices, 4,264 adult RTI patients	Internet-based training in: (1) Point-of-care CRP testing; (2) Enhanced communication skills + interactive booklet; (3) Combined	Usual care	Antibiotic prescribing: CRP vs no-CRP 33% vs 48% (aRR 0.54, 95% CI: 0.42 to 0.69); Communication vs no-comm 36% vs 45% (aRR 0.69, 95% CI: 0.54 to 0.87); Combined vs usual care (aRR 0.38, 95% CI: 0.25 to 0.55)	Symptom duration and severity were comparable across groups; no increase in serious complications or hospital admissions
de la Poza Abad *et al*., 2016 [23]; Spain	Pragmatic 4-arm open-label RCT; 23 primary care centers, 398 adults with acute uncomplicated RTI	(1) Delayed patient-led prescription; (2) Delayed clinic-collection prescription; (3) No antibiotic prescription	Immediate antibiotic prescription	Antibiotic consumption: Immediate 91.1% vs Delayed patient-led 32.6%, Delayed collection 23.0%, and No prescription 12.1% (p < 0.001)	Similar symptom severity, complication rates, and high patient satisfaction across all arms; slightly shorter severe symptom duration (0.4–1.5 days) with immediate antibiotics
Meeker *et al*., 2016 [24]; United States	Cluster 2×2×2 factorial RCT; 47 primary care practices, 248 clinicians, 14,753	18-month EHR/email behavioral nudges: (1) Suggested alternatives; (2)	Usual care / education	Inappropriate prescribing decreased from 24.1% to 13.1% in controls vs 23.2% to 5.2% for	No statistically significant increase in return visits for treatable bacterial infections or serious complications across intervention arms

Study Citation & Country	Study Design & Population	Intervention Arms	Comparator	Primary Prescribing Outcome & Effect Size	Clinical Safety & Secondary Outcomes
	antibiotic-inappropriate ARTI visits	Accountable justification; (3) Peer comparison		accountable justification (DID -7.0%, p < 0.001) and 19.9% to 3.7% for peer comparison (DID -5.2%, p < 0.001); suggested alternatives non-significant (DID -5.0%, p = 0.66)	
Gulliford *et al*., 2019 [25] (REDUCE); United Kingdom	Cluster RCT; 79 general practices (606,467 patient-years)	Electronically delivered AMS: monthly prescribing feedback webinars, EHR decision support tools, patient leaflets	Usual care	Overall RTI antibiotic prescribing rate reduced (aRR 0.88, 95% CI: 0.78 to 0.99, p = 0.04); strongest in adults aged 15–84 years (aRR 0.84, 95% CI: 0.75 to 0.95); no effect in children <15 years (aRR 0.96) or elderly ≥85 years (aRR 0.97)	No evidence of increased serious bacterial complications (aRR 0.92, 95% CI: 0.74 to 1.13); 1 prescription avoided per 62 adult patients per year

Qualitative Data Synthesis

Point-of-Care Biomarker Testing and Enhanced Clinician Communication Training

Two landmark factorial cluster randomized trials demonstrated that addressing both diagnostic uncertainty and interpersonal consultation dynamics yields powerful, additive reductions in antibiotic prescribing for acute respiratory tract infections [17-22]. In the Dutch IMPAC3T trial, Cals and colleagues randomized 40 general practitioners across 20 practices to point-of-care C-reactive protein (CRP) testing, training in enhanced communication skills, both interventions, or usual care for 431 adults presenting with acute lower respiratory tract infections [17]. Clinicians equipped with rapid finger-prick CRP testing prescribed antibiotics at the index consultation to 31% of patients compared with 53% among clinicians without CRP testing, while those trained in patient-centered communication skills prescribed antibiotics to 27% of patients compared with 54% among untrained peers [17]. Crucially, when both interventions were combined, the index prescribing rate dropped to 23%, and these statistically significant reductions persisted throughout the 28-day follow-up period without compromising symptom recovery or patient satisfaction [17]. Expanding this paradigm across diverse healthcare cultures, Little and colleagues conducted the multinational GRACE-INTRO cluster randomized factorial trial across 246 primary care practices and 4,264 adult patients in six European nations, delivering both CRP training and enhanced communication skills training entirely via an internet-based platform coupled with an interactive patient booklet [22]. Internet-delivered CRP training reduced antibiotic prescribing from 48% to 33% (adjusted risk ratio 0.54, 95% CI: 0.42 to 0.69), while internet-based communication training reduced prescribing from 45% to 36% (adjusted risk ratio 0.69, 95% CI: 0.54 to 0.87) [22]. Practices randomized to receive both internet-based CRP and communication training achieved the largest reduction, lowering antibiotic prescribing by 62% relative to usual care (adjusted risk ratio 0.38, 95% CI: 0.25 to 0.55, p < 0.0001) across all participating linguistic and healthcare environments [22].

Shared Decision-Making and Delayed Antibiotic Prescribing Strategies

Interventions that actively engage patients in weighing therapeutic benefits against antimicrobial harms, or that provide structured delayed prescribing safety nets, also achieved substantial reductions in unnecessary antibiotic utilization [19-23]. In the Canadian DECISION+2 cluster randomized trial, Légaré and colleagues evaluated a continuing professional development program comprising a two-hour web-based tutorial and a two-hour interactive workshop designed to train family physicians and residents in shared decision-making for acute respiratory infections across nine family practice teaching units [19]. Among 359 consulting patients, the proportion deciding to use antibiotics immediately after the consultation fell from 52.2% in the control group to 27.2% in the DECISION+2 intervention arm, representing an absolute reduction of 25.0% and an adjusted relative risk of 0.48

(95% CI: 0.34 to 0.68), while significantly improving patient-reported active participation in clinical decision-making [19]. Complementing shared decision-making, de la Poza Abad and colleagues conducted a pragmatic four-arm randomized clinical trial across 23 primary care centers in Spain to evaluate two delayed antibiotic prescription strategies—a patient-led delayed prescription handed directly to the patient with instructions to fill only if symptoms worsened after several days, and a delayed collection strategy requiring the patient to return to the clinic reception to pick up the prescription—against immediate antibiotic prescribing and no antibiotic prescribing among 398 adults with uncomplicated acute respiratory infections [23]. Whereas 91.1% of patients randomized to immediate prescribing consumed antibiotics, antibiotic consumption dropped to 32.6% in the patient-led delayed strategy and 23.0% in the clinic-collection delayed strategy, approaching the 12.1% rate observed in the no-prescription arm [23]. Both delayed strategies markedly curtailed antimicrobial exposure while maintaining equivalent patient satisfaction and complication profiles compared with immediate therapy [23].

Clinician Education, Academic Detailing, and Personalized Audit and Feedback

Three large-scale cluster randomized trials evaluated longitudinal educational and audit-and-feedback programs aimed at transforming practice-wide prescribing culture and improving antimicrobial class selection [18-21]. In the Welsh STAR trial, Butler and colleagues randomized 68 general practices covering approximately 480,000 patients to a multifaceted blended learning program incorporating online reflection on practice-specific dispensing data, communication skills training, and a facilitated practice seminar [18]. Over the subsequent year, intervention practices achieved a 4.2% relative reduction (95% CI: 0.6% to 7.7%, p = 0.02) in total oral antibiotic dispensing across the entire registered population, driven by significant reductions of 7.3% in phenoxymethylpenicillin and 7.7% in macrolide dispensing [18]. In the Norwegian Rx-PAD cluster trial, Gjelstad and colleagues randomized 79 continuing medical education peer groups comprising 382 general practitioners to a peer academic detailing intervention led by trained fellow general practitioners who delivered two outreach visits coupled with individualized prescription audit and feedback reports [21]. Compared with active control groups, the Rx-PAD intervention significantly lowered the odds of prescribing antibiotics for acute respiratory tract infections (adjusted odds ratio 0.72, 95% CI: 0.61 to 0.84) and reduced the odds of selecting broad-spectrum non-penicillin V antibiotics when an antimicrobial was issued (adjusted odds ratio 0.64, 95% CI: 0.49 to 0.82) [21]. Similarly, in a network of 18 pediatric primary care practices in the United States encompassing 185,212 visits, Gerber and colleagues demonstrated that a single one-hour on-site clinician education session followed by one year of personalized quarterly audit and feedback reduced off-guideline broad-spectrum antibiotic prescribing for bacterial acute respiratory infections from 26.8% to 14.3%, compared with a change from 28.4% to 22.6% in controls (difference of differences 6.7%, p = 0.01), including a 75% relative reduction in broad-spectrum prescribing for acute pneumonia [20].

Behavioral Economics Nudges and Electronic Health Record Decision Support

Two trials examined scalable health information technology and behavioral science interventions integrated directly into electronic health record workflows [24, 25]. Meeker and colleagues conducted an 18-month 2×2×2 factorial cluster randomized trial across 47 primary care practices and 248 clinicians in Boston and Los Angeles (14,753 visits for antibiotic-inappropriate viral acute respiratory infections) to test three behavioral nudges: electronic order sets suggesting non-antibiotic symptomatic alternatives, accountable justification requiring clinicians to enter a free-text clinical justification into the permanent medical record that was visible to peers whenever ordering an antibiotic, and monthly peer comparison emails ranking clinicians against "top-performing" peers with the lowest inappropriate prescribing rates [24]. While suggested alternatives did not achieve statistical significance beyond control trends (difference in differences -5.0%, p = 0.66), accountable justification reduced inappropriate antibiotic prescribing from 23.2% to 5.2% (difference in differences -7.0%, 95% CI: -9.1% to -2.9%, p < 0.001) and peer comparison reduced inappropriate prescribing from 19.9% to 3.7% (difference in differences -5.2%, 95% CI: -6.9% to -1.6%, p < 0.001) [24]. At a broader health-system level, Gulliford and colleagues conducted the pragmatic REDUCE cluster randomized trial across 79 UK general practices (606,467 patient-years), evaluating an electronically delivered antimicrobial stewardship package consisting of brief monthly prescribing feedback webinars, electronic decision support prompts, and printable patient leaflets [25]. The intervention reduced overall antibiotic prescribing for respiratory tract infections by 12% (adjusted rate ratio 0.88, 95% CI: 0.78 to 0.99, p = 0.04) and by 16% among adults aged 15 to 84 years (adjusted rate ratio 0.84, 95% CI: 0.75 to 0.95), equating to one antibiotic prescription avoided for every 62 adult patients annually, although no significant effect was observed among children under 15 years or adults aged 85 years and older [25].

Clinical Safety, Reconsultation Rates, and Patient Satisfaction Outcomes

Across all nine randomized controlled trials, substantial reductions in overall or broad-spectrum antibiotic prescribing were achieved without any statistically significant increase in serious suppurative bacterial complications, emergency department visits, or hospital admissions [17–25]. In the REDUCE trial, Gulliford and colleagues specifically evaluated twelve serious bacterial complications, including pneumonia,

peritonsillar abscess, mastoiditis, empyema, meningitis, and intracranial abscess, and confirmed no excess risk in intervention practices (adjusted rate ratio 0.92, 95% CI: 0.74 to 1.13) [25]. Likewise, trials measuring patient-reported outcomes demonstrated that communication training, shared decision-making, CRP testing, and delayed prescribing preserved high patient satisfaction and did not trigger rebound reconsultations [17-23].

DISCUSSION

This systematic review synthesized evidence from nine rigorously conducted randomized controlled trials evaluating primary care stewardship interventions across more than 440,000 respiratory infection consultations in Europe and North America [17–25]. The qualitative synthesis demonstrates that inappropriate antibiotic prescribing for acute respiratory tract infections in primary care is highly modifiable when interventions directly target the cognitive, diagnostic, and interpersonal barriers encountered during routine outpatient consultations. Across the included studies, the largest relative reductions in index antibiotic prescribing, ranging from 31% to 62%, were achieved by interventions that combined point-of-care C-reactive protein testing with enhanced clinician communication skills training [17-22], as well as structured shared decision-making programs [19] and delayed antibiotic prescribing strategies [23]. Furthermore, peer-led academic detailing paired with personalized prescription audit and feedback significantly reduced both total antimicrobial volume and the inappropriate selection of broad-spectrum macrolides, cephalosporins, and fluoroquinolones in favor of narrow-spectrum phenoxymethylpenicillin or amoxicillin [20, 21]. Equally important, socially anchored behavioral economics nudges—specifically accountable justification and peer comparison—reduced inappropriate antibiotic prescribing for viral respiratory illnesses to single-digit percentages (<6%) [24], while low-cost, electronically delivered practice-wide decision support and feedback produced population-level reductions in adult prescribing [18-25]. Crucially, none of the nine trials identified any compromise in patient safety, hospital admission rates, or consultation satisfaction [17–25].

The findings of our synthesis align closely with and extend the conclusions of major Cochrane systematic reviews and meta-analyses examining isolated intervention categories [13-32]. In our review, rapid point-of-care C-reactive protein testing significantly curtailed index and 28-day antibiotic prescribing in both Dutch and multinational European general practice settings [17-22]. This is corroborated by Cochrane reviews by Aabenhus and colleagues and Smedemark and colleagues, which pooled randomized trials of biomarker-guided therapy and demonstrated that C-reactive protein point-of-care testing reduces antibiotic prescribing by approximately 23% to 24% overall—and by over 30% when explicit numerical cut-off guidance (such as withholding antibiotics when CRP is below 20 mg/L and considering delayed prescribing between 20 and 100 mg/L) is provided to clinicians [26, 27]. Comparable biomarker efficacy has been observed with procalcitonin-guided therapy in primary care, where Briel and colleagues demonstrated a 72% reduction in antibiotic prescriptions without increasing days of restricted activity [28], as well as in high-risk primary care populations such as patients presenting with acute exacerbations of chronic obstructive pulmonary disease, where Butler and colleagues showed that CRP-guided management safely reduced antibiotic consumption from 77.4% to 57.0% [29]. Biomarker testing succeeds in primary care not only by reassuring the clinician that bacterial pneumonia is unlikely, but also by providing tangible, objective laboratory evidence that validates the decision to withhold antibiotics in the eyes of the patient [17-27].

Nevertheless, our synthesis underscores that diagnostic technology is most potent when integrated with patient-centered communication and shared decision-making [17-22]. Both Cals *et al*., [17], and Little *et al*., [22], demonstrated that communication skills training, teaching clinicians to elicit patient concerns, expectations, and beliefs while providing clear information on the natural history of respiratory symptoms and red-flag safety-netting advice, achieved independent reductions in prescribing comparable to or exceeding CRP testing alone. This aligns with the landmark trial by Francis and colleagues, which showed that training clinicians to use an interactive booklet on childhood respiratory tract infections during primary care consultations reduced antibiotic prescribing by more than 50% (from 40.8% to 19.5%; odds ratio 0.29) and reduced future consulting intentions without diminishing parental satisfaction [30]. Similarly, the 52% relative reduction in patient decisions to take antibiotics observed in the DECISION+2 trial [19], mirrors the broader Cochrane meta-analysis by Coxeter and colleagues, which found that shared decision-making interventions reduce short-term antibiotic prescribing for acute respiratory infections from 47% to 29% (risk ratio 0.61, 95% CI: 0.55 to 0.68) without increasing reconsultations [31]. Conversational research by Mangione-Smith and colleagues explains why these communicative strategies preserve patient satisfaction: when clinicians pair "negative treatment recommendations" (explaining why antibiotics are ineffective for viral syndromes) with actionable "positive treatment recommendations" (specific symptomatic remedies), patients report significantly higher consultation ratings while receiving 85% fewer antibiotics [11].

Similarly, the substantial reduction in antibiotic consumption achieved via delayed prescribing in the trial by de la Poza Abad and colleagues [23] is strongly supported by both the Cochrane review by Spurling and colleagues [32], and the large collaborative individual

patient data meta-analysis by Stuart and colleagues encompassing 55,682 patients across 13 randomized and observational studies [33]. Those syntheses confirm that delayed prescribing reduces actual antibiotic consumption to approximately 31% compared with 93% under immediate prescribing, with no clinically meaningful difference in follow-up symptom severity (mean difference of only 0.003 to 0.11 points on a 7-point scale), equivalent reconsultation rates, and comparable complication rates across high-risk subgroups including young children and patients with severe baseline symptoms [32, 33]. Furthermore, factorial trial evidence from Little and colleagues demonstrates that the specific format of delayed prescribing, whether recontacting the clinic, post-dating the prescription, leaving the prescription for collection, or handing it directly to the patient with explicit instructions, all achieve similarly low rates of antibiotic use (<40%) when accompanied by structured symptomatic advice [32, 33].

In the domain of behavioral nudges and audit and feedback, the pronounced reductions observed in the trials by Gerber *et al*., [20], Gjelstad *et al*., [21], and Meeker *et al*., [24] highlight the importance of social accountability and peer norms. While early ambulatory reviews noted that passive printed feedback yields only modest effects [13], pairing audit data with peer academic detailing [21], or socially visible norms markedly amplifies behavior change [24-34]. For instance, Hallsworth and colleagues demonstrated in a pragmatic national randomized trial of 1,581 high-prescribing general practices in England that a single behavioral letter from the Chief Medical Officer informing practices that their antibiotic prescribing rate was in the top 20% compared with local peers reduced national dispensing by 3.3% (over 73,000 fewer prescriptions) over six months at negligible cost [34]. However, the modest effect size of purely automated electronic tools in the REDUCE trial (12% reduction overall and null effect in children and the oldest old) [25], compared with the larger reductions seen in intensive peer-comparison and academic detailing trials [20=24], indicates that digital decision support alerts are susceptible to alert fatigue unless reinforced by active professional engagement and social accountability.

A critical second-order insight emerging from long-term follow-up studies of the included trials is that the durability of antimicrobial stewardship depends heavily on the underlying mechanism of behavior change. In a 12-month follow-up of the multinational GRACE-INTRO trial, Little and colleagues discovered that the early prescribing reductions achieved through internet-based communication skills training were fully sustained at 12 months (adjusted risk ratio 0.70, 95% CI: 0.49 to 0.94), whereas the initial benefits of C-reactive protein training waned substantially over the year as clinicians gradually stopped performing the finger-prick test in routine practice [22-27]. Conversely, when Gerber and colleagues examined prescribing trajectories for 18 months after discontinuing quarterly audit and feedback in their pediatric primary care cohort, broad-spectrum antibiotic prescribing rebounded toward baseline levels (rising from 16.7% at intervention end to 27.9%), demonstrating that audit and feedback requires continuous institutional reinforcement [20]. Similarly, in a 12-month post-intervention evaluation of the behavioral nudge trial by Meeker *et al.*, [24], Linder and colleagues found that once electronic accountable justification prompts were turned off, inappropriate prescribing rebounded, whereas the peer comparison group maintained statistically significant prescribing reductions 12 months after email reports ceased, likely because peer benchmarking prompted durable practice-level structural changes [24]. These longitudinal findings indicate that internalized communication skills and peer-norm shifts foster more durable clinical habits than transient point-of-care prompts or unassisted diagnostic equipment.

Clinical Safety and Patient-Centered Outcomes

Fear of rare suppurative or invasive bacterial complications—such as mastoiditis, empyema, peritonsillar abscess (quinsy), meningitis, or community-acquired pneumonia—remains one of the primary drivers of defensive antibiotic prescribing in general practice [7-35]. Reassuringly, across all nine included randomized trials, reducing antibiotic prescribing by 12% to 62% resulted in no statistically significant increase in hospital admissions, treatment failures, or serious bacterial complications [17–25]. This trial-level safety evidence is consistent with large-scale epidemiological modeling of 610 UK general practices (45.5 million person-years) by Gulliford and colleagues, which demonstrated that a 10% practice-level reduction in antibiotic prescribing for self-limiting respiratory tract infections is associated with no increase in mastoiditis, empyema, bacterial meningitis, intracranial abscess, or Lemierre syndrome, and only a marginal predicted change of approximately one additional case of treatable pneumonia per year and less than one case of peritonsillar abscess per decade in an average practice of 7,000 patients [35]. When clinicians combine judicious withholding of antibiotics with explicit verbal and written safety-netting instructions detailing when to reconsult, patient safety is robustly protected while sparing thousands of patients from antibiotic-associated adverse events and resistance selection [17-35].

Implications for Clinical Practice, Health Policy, and Future Research

For primary care clinicians and healthcare policymakers, the evidence synthesized in this review demonstrates that single-component passive interventions are insufficient to curb unnecessary antibiotic use for acute respiratory infections [12-14]. Health systems should implement integrated, multimodal stewardship bundles that pair scalable internet-based communication and shared decision-

making training [19-22], with targeted point-of-care C-reactive protein testing for clinically ambiguous lower respiratory infections [17-27], delayed prescribing protocols for patients seeking a safety net [23-33], and continuous, automated peer-comparison feedback embedded within electronic health record workflows [21-25]. Future implementation research should evaluate the cost-effectiveness, equity, and long-term sustainability of these combined digital and diagnostic interventions across resource-limited settings, pediatric and frail elderly subpopulations, and telemedicine consultations.

CONCLUSION

This systematic review of nine randomized controlled trials demonstrates that primary care interventions targeting diagnostic uncertainty, clinician-patient communication, and prescriber accountability are highly effective and safe in reducing unnecessary overall and broad-spectrum antibiotic prescribing for acute respiratory tract infections. Point-of-care C-reactive protein testing combined with enhanced communication skills training, structured shared decision-making programs, delayed antibiotic prescribing strategies, peer academic detailing with personalized audit and feedback, and behavioral economics nudges such as accountable justification and peer comparison consistently achieve substantial, clinically meaningful reductions in inappropriate antimicrobial use without compromising symptom recovery, patient satisfaction, or clinical safety. Sustaining these stewardship gains requires embedding continuous peer-norm feedback and patient-centered communication training into routine primary care infrastructure as a cornerstone of global efforts to contain antimicrobial resistance.

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