Published in final edited form as:
BMJ. ; 363: k3047. doi:10.1136/bmj.k3047.

Advances in optimizing antibiotic prescribing in outpatient settings

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Abstract

Inappropriate antibiotic use can increase the likelihood of antibiotic resistance and adverse events. Nearly a third of US outpatient antibiotic prescriptions are unnecessary, and outpatient antibiotic selection and duration are often inappropriate as well. Evidence shows that antibiotic prescribing is influenced by psychosocial factors, including lack of accountability, perceived patient expectations, clinician workload and habit. A varied and growing body of evidence that includes meta-analyses, randomized controlled trials, and qualitative studies has evaluated interventions to optimize antibiotic use. Interventions informed by behavioral science, such as communication skills training, audit and feedback with peer comparison, public commitment posters, and accountable justification, have been associated with improved antibiotic prescribing. Additionally, delayed prescribing and active monitoring and the use of diagnostics are guideline-recommended practices that improve antibiotic use for some conditions. In 2016, the Centers for Disease Control and Prevention released the *Core Elements of Outpatient Antibiotic Stewardship*, which provides a framework for implementing these interventions in the outpatient settings. This review summarizes the varied evidence on drivers of inappropriate outpatient antibiotic prescribing and potential interventions to improve outpatient antibiotic use.

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Contributorship statement and guarantor:
Ms. King, Dr. Fleming-Dutra, and Dr. Hicks all made substantial contributions to the conception of the manuscript, approved the final version of this manuscript, and agree to be accountable for all aspects of the work. Ms. King conceptualized the review, performed the literature review and wrote the article. Dr. Fleming-Dutra and Dr. Hicks conceptualized the review and provided critical revisions for important intellectual content. Dr. Hicks, as guarantor, accepts full responsibility for the work, had access to the references reviewed, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Patient consent: Not applicable.

Conflicts: We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

Introduction

Antibiotics are life-saving drugs that have enabled advances in modern medicine. However, the more antibiotics are used, the less effective they become. Antibiotic resistance is an important global public health threat.[1] Additionally, antibiotics are associated with adverse events ranging from mild gastrointestinal distress to life-threatening *Clostridium difficile* infections. Antibiotic stewardship is the measurement and optimization of antibiotic use and includes not only ensuring that antibiotics are given only when necessary and beneficial, but also, when antibiotics are needed, that the right agent, dose, and duration are used. In addition, antibiotic stewardship emphasizes initiating antibiotics promptly when needed, such as when sepsis is suspected. The goal of antibiotic stewardship is to optimize patient safety and outcomes.

Globally, up to 95% of all antibiotics for humans are prescribed in outpatient settings, including physician offices, urgent care facilities, retail health clinics, and emergency departments.[23] In 2015, in the United States, enough outpatient antibiotic prescriptions were dispensed for five out of every six people to receive an antibiotic course.[4] Historically, much of the focus on antibiotic stewardship has been in hospitals. However, there has been a recent surge of research in outpatient settings and, in 2016, the US Centers for Disease Control and Prevention (CDC) published the *Core Elements of Outpatient Antibiotic Stewardship*[5] (fig 1) to provide a framework for US outpatient clinicians and facilities to improve antibiotic use.

The aim of this review is to synthesize the growing literature examining the causes of inappropriate antibiotic prescribing and potential antibiotic stewardship interventions in outpatient settings. To contextualize this literature, this review also provides a brief overview of the consequences and epidemiology of outpatient antibiotic prescribing.

Sources and selection criteria

The references for this review were identified through PubMed searches, author libraries, and reference lists from CDC publications. Our PubMed search was limited to English-language publications published in peer-reviewed journals from January 2012 to November 2017. Search terms included “antimicrobial stewardship” AND “outpatient”, “antimicrobial stewardship” AND “primary care”, and “antimicrobial stewardship review.” We reviewed relevant titles and abstracts from this search and included meta-analyses, systematic reviews, randomized controlled-trials, and large descriptive and observational studies. Where those types of studies were limited or where other study types yielded richer data, for example in examining the drivers of inappropriate prescribing, we included qualitative and small observational studies. We included older (pre-2012) references from author libraries and CDC reference lists if they were highly cited, complemented or contextualized recent studies, or if recent literature on the topic was limited. We also included relevant government documents and resources from author libraries. We included studies from both US and non-US settings. In discussing drivers of inappropriate prescribing and potential interventions, we note studies from outside the US. During the peer review process, two studies with new information on topics described here were published. Based on the novelty of the information in these studies and their relevance to this topic, we included them in this review.

By its nature, this narrative review may suffer from selection bias. We did not include gray literature or studies published in languages other than English and we limited published studies to those available in PubMed or already in author libraries. Thus, there may be additional references omitted here which provide further insight.

Why outpatient antibiotic use needs to be improved

Antibiotic use selects for antibiotic-resistant bacteria; antibiotic-resistant organisms infect at least 2 million people, cause at least 23,000 deaths, and result in $20 billion in excess direct healthcare costs in the United States each year.[6] For some pathogens, such as carbapenem-resistant Enterobacteriaceae, treatment options are becoming increasingly limited, increasing the risk of patient morbidity and mortality and treatment costs. Antibiotic use and resistance are associated both at population and individual levels. Antibiotic resistance patterns for selected antibiotic-pathogen combinations have been observed to change in parallel with shifting antibiotic consumption patterns in a population.[7–9] At the individual level, the odds of identifying antibiotic-resistant bacteria (colonization or infection) are over twice as high among those with recent antibiotic exposure compared to those without antibiotic exposure.[10] Antibiotic-associated adverse drug events (ADEs) are a threat to patient safety. Antibiotic-associated ADEs include gastrointestinal disturbances, nephrotoxicity, secondary infections (including yeast and *C difficile* infections), neurological or psychiatric effects, sensory or motor disturbances, and allergic reactions. CDC estimates that one emergency department visit for an antibiotic-associated ADE occurs for every 1,000 outpatient antibiotic prescriptions.[11]

Clostridium difficile infection is a life-threatening antibiotic-associated ADE. *C difficile* caused an estimated 450,000 infections and 15,000 deaths in 2011 in the United States.[12] In 2015, estimated US annual acute-care costs attributable to *C difficile* infection were $1.2–5.9 billion.[13] Antibiotic use is a well-known risk factor for *C difficile* infection[14] and reducing outpatient antibiotic prescription rates by 10% could result in an estimated 17% decrease in *C difficile* infection rates.[15] Reductions in specific antibiotics, including fluoroquinolones and cephalosporins, are especially impactful in preventing *C difficile* infection.[816]

Certain antibiotics commonly used in outpatient settings are of special concern due to their association with severe ADEs. Azithromycin is the most frequently prescribed antibiotic in outpatient settings[17] and is often inappropriately prescribed for conditions for which it is not a recommended first-line treatment or antibiotics are not indicated.[18] In 2013, the US Food and Drug Administration (FDA) warned that azithromycin can lead to potentially fatal heart rhythm irregularities.[19] Fluoroquinolones are also commonly used in outpatient settings, often inappropriately.[20] In 2016, FDA updated its warning on fluoroquinolones due to disabling and permanent side effects, including tendonitis, tendon rupture, worsening of myasthenia gravis, peripheral neuropathy, and central nervous system effects.[21] FDA recommended that fluoroquinolones be avoided in acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections.[21]

An emerging focus is the impact of antibiotics on the microbiome, the population of microorganisms in the body, and related health impacts. Antibiotic use can result in loss of diversity and disturbances in the microbiome that can persist for years. Current evidence is limited, but indicates that early-life antibiotic use may be associated with increased risk of chronic diseases, such as juvenile idiopathic arthritis,[22] celiac disease,[23] inflammatory bowel disease,[24] diabetes,[25] and food allergies,[26] likely mediated through disruption in the microbiome.[27] For these conditions, increasing numbers of antibiotic courses correspond with increasing likelihood of disease.[22–26] Additionally, use of antibiotics in livestock growth promotion has prompted researchers to study the relationship between antibiotics and obesity in humans. Although nascent, much of the data on childhood antibiotic use and body mass, overweight, obesity, and/or weight gain shows an association.[28–33] However, a recent observational study of over 38,000 children followed to age 7 found that antibiotic use within the first 6 months of life was not associated with later weight gain.[34]

US outpatient antibiotic prescribing

In 2015, 269 million antibiotic prescriptions, equivalent to 838 antibiotic prescriptions per 1,000 population, were dispensed from US community pharmacies, making the outpatient setting an important target for improving antibiotic use.[4] In fact, the US National Action Plan for Combating Antibiotic Resistant Bacteria, released in 2015, set a goal to reduce inappropriate antibiotic use in the outpatient setting by 50% by 2020.[35] Inappropriate antibiotic use includes unnecessary use (using antibiotics for conditions for which they are not indicated) and suboptimal antibiotic selection, dosing, and course duration.

Using national outpatient prescribing data, the authors of this review previously estimated that at least 30% of antibiotics prescribed in US physician offices and emergency departments were unnecessary (table 1).[36] Total inappropriate antibiotic use, including selection, dosing and duration, is likely much higher. In outpatient settings, acute respiratory infections (ARIs) are major drivers of inappropriate antibiotic use. ARIs accounted for 44% of antibiotics prescribed in US physician offices and emergency departments in 2010–2011 and half of these prescriptions were unnecessary.[36]

Guideline-concordant antibiotic selection is an important stewardship target as it can improve “drug–bug” match and reduce side effects. In a descriptive study using national prescribing data, Hersh et al. found that among the three most common conditions leading to antibiotic prescriptions in the United States, acute otitis media, sinusitis, and pharyngitis, guideline-recommended first-line antibiotics were prescribed in only 52% (95% confidence interval [CI] 49%−55%) of visits.[37] Accounting for drug allergies and treatment failures, the authors estimated at least 80% of visits should be treated with first-line agents.[37]

Shortening therapy to the minimum effective duration reduces antibiotic exposure and minimizes the risk of resistance and adverse events. Recent editorials have advocated for shorter courses of antibiotic therapy.[38–40] Historically, 7-, 10-, or 14-day courses were the norm for many conditions. However, shorter durations of therapy have been shown to be equally effective in several conditions, including community-acquired pneumonia,[41–44] pyelonephritis,[45] acute chronic obstructive pulmonary disease exacerbations,[46] and sinusitis.[47] However, long courses are still more effective for acute otitis media in young children.[48] High-quality studies defining the minimum effective duration of antibiotic therapy for specific diagnoses and populations are needed. Little evidence exists on duration in actual outpatient prescribing; however, a descriptive study by the authors of this review of over 3.5 million adult sinusitis visits with an antibiotic prescription found that 66.9% (95% CI 61.0–72.8%) of prescriptions were for 10 days, longer than the guideline-recommended 5–7 days of antibiotic therapy for uncomplicated cases.[49]

Antibiotic prescribing rates in the United States are highest in the South compared with other regions.[1750–55] There is also a trend toward higher antibiotic prescription rates in rural, compared with urban, areas.[5256] The reasons for these geographic differences are not known. Prescribing also varies by outpatient setting. A descriptive study of a large convenience sample of employer-group health insurance claims (N=156,015,899) found that antibiotic prescribing rates for antibiotic-inappropriate respiratory conditions were highest among urgent care clinics (45.7% of visits) compared with emergency departments (24.6%), physician offices (17.0%), and retail clinics (14.4%).[57]

Progress has been made in the United States; national antibiotic prescription data shows that outpatient antibiotic prescription rates decreased 4% between 2011 and 2015 — from 877 prescriptions per 1000 population in 2011 to 838 prescriptions per 1000 population in 2015 (fig 2).[58] This decline has been driven by reductions in prescribing to children. US antibiotic prescribing rates for children decreased by 13% from 2011–15, while rates among adults remained stable.[58] The success in improving pediatric antibiotic prescribing is likely due to many factors, including the introduction of 13-valent pneumococcal conjugate vaccine,[59] public health efforts to educate parents and health professionals, and clinician efforts to change behavior.

Drivers of inappropriate antibiotic prescribing

Inappropriate antibiotic prescribing is likely multifactorial. Growing evidence shows that reasons for inappropriate prescribing are at least in part psychologically and socially rooted, meaning that antibiotic prescribing is as much a behavior as a scientific decision. Much of this literature is qualitative and based on surveys or interviews with clinicians with some evidence from observational studies.

Clinicians do not perceive that they prescribe inappropriately. In a qualitative study by Dempsey et al. of semi-structured interviews of 13 clinicians about acute bronchitis management, clinicians agreed with guideline recommendations to not use antibiotics and felt that clinicians other than themselves were inappropriately using antibiotics for treatment of bronchitis.[60] Without information on and oversight of their antibiotic prescribing patterns, clinicians may not understand their role in inappropriate antibiotic prescribing. In this same study, clinicians cited lack of feedback on and accountability as a barrier to appropriate antibiotic prescribing.[60]

Knowledge of guideline recommendations of antibiotic indications is the foundation of appropriate antibiotic prescribing. Lack of knowledge could lead some clinicians to prescribe antibiotics inappropriately. However, a qualitative study by Sanchez et al. of 36 clinician interviews found that clinicians are generally familiar with guideline recommendations for common outpatient conditions.[61] Gaps availability of guideline recommendations may contribute to variation in antibiotic treatment for some conditions. For example, there are few guidelines on dental infection management.

Additionally, evidence from these clinician interview studies by Dempsey et al. and Sanchez et al. show that clinicians frequently cite fear of complications from infections as a reason for prescribing antibiotics when they are not indicated and for prescribing broader-spectrum agents than indicated.[6061] However, for ARIs that commonly lead to unnecessary antibiotic prescribing, infectious complications are rare compared with the frequency of antibiotic-associated ADEs. A cohort study of 3.36 million ARI episodes seen in UK primary care practices found that, overall, the number needed to treat to prevent one case of a serious ARI complication was over 4,000.[62] However, as previously discussed, it is estimated that for every 1,000 outpatient antibiotic prescriptions, there is one emergency department visit for an antibiotic-associated ADE.[11]

The qualitative studies by Dempsey et al. and Sanchez et al. also found that clinicians' perception that patients want antibiotics drives them to inappropriately prescribe antibiotics.[6061] In another qualitative study of clinician attitudes by Szymczak et al., pediatricians reported that they sometimes prescribed antibiotics for social reasons, such as wanting to please parents.[63] Direct requests for antibiotics, i.e., when a patient explicitly asks for antibiotics for their illness, are rare. A qualitative study of 42 German visits to primary care clinics by adult patients with acute cough found that only 2 patients (5%) explicitly requested antibiotics while implicit expectations were observed in 7 visits (17%).[64] A 2001 mixed-methods study by Mangione-Smith et al. of 295 parents at two pediatric practices found that overt requests for antibiotics occurred in only 1% of visits, yet clinicians perceived expectations for antibiotics in 34% of visits.[65] Implied requests for antibiotics are more common, and certain communication behaviors by patients and families can lead clinicians to perceive that antibiotics are desired. Another mixed-methods study of 522 pediatric encounters for cold symptoms found that clinicians were 20.2% (95% CI 6.3–34.0%, p=0.004) more likely to perceive expectations for antibiotics when parents questioned the treatment plan and 9.3% (95% CI 1.8–16.9%, p=0.02) more likely to perceive expectations for antibiotics when parents offered a candidate bacterial diagnosis.[66] An example of questioning the treatment plan would be a parent responding to clinician suggestions of symptomatic therapy, "We have already tried that, and it is not helping." An example of offering a candidate bacterial diagnosis is when a parent says, "I am worried that she might have strep throat." This study also found that clinicians were 31% (95% CI 16.0–47.3%, p<0.001) more likely to prescribe an antibiotic for a viral diagnosis when they perceived parental expectations for antibiotics.[66]

Workload and time constraints are also associated with antibiotic prescribing. In the previously discussed clinician interview studies, clinicians reported prescribing antibiotics because they felt they did not have time to explain why antibiotics were unnecessary[63] or because they perceived that writing a prescription was faster than communicating non-antibiotic treatment plans.[60] Clinicians with high caseloads may be more likely to prescribe antibiotics than those with fewer patients. An observational study of 440 general practitioners in Norway (N=142,900 ARI visits) found that physicians with higher numbers of ARI visits had higher rates of antibiotic prescriptions for ARIs; the odds of prescribing an antibiotic for an ARI among clinicians in the highest visit number quintile were 1.64 (95% CI 1.33–2.03) times higher than among those in the lowest visit number quintile.[67] Additionally, clinicians may face decision fatigue that makes prescribing antibiotics the default approach, even when inappropriate. An observational study of 21,867 adult primary care visits demonstrated that antibiotic prescribing for ARIs increased throughout each shift.[68] This odds of receiving antibiotics for an ARI in the 4th hour of a clinic session was 26% higher than in the 1st hour (adjusted odds ratio [aOR] 1.26, 95% CI 1.13–1.41).[68]

Habit also drives antibiotic-prescribing patterns. In their qualitative study, Sanchez et al. found that clinicians report that they often rely on previous experience and familiarity with antibiotic agents.[61] Additionally, clinician-level variation in antibiotic prescribing for ARIs is seen in studies that control for patient case-mix and comorbidities. An obsevational study of 1,044,523 ARI visits at US Department of Veterans Affairs outpatient clinics found that 59% of observed variation in antibiotic prescribing was attributable to provider-level variation.[53] Similarly, an observational study of almost 400,000 ARI visits to a pediatric primary care network found that antibiotic prescribing varied significantly by practice ($p<0.001$) and that this relationship could not be explained by clinical factors, such as comorbidities or diagnosis, implying provider-level factors contributed to the observed variability.[69]

Interventions to improve outpatient antibiotic prescribing

Improving outpatient antibiotic prescribing requires interventions that target the root causes of inappropriate prescribing and modify clinician behavior. Here, we examine the existing literature on several potential interventions, including patient and clinician education, communication training, point-of-care testing, active monitoring and delayed prescribing, clinical decision support, audit and feedback, accountable justification, and public commitment posters (table 3). Although these interventions are examined individually, they could be implemented in combination, potentially to greater effect. A 2012 systematic review and meta-analysis of outpatient stewardship interventions in ARI management found that multi-part interventions were more likely to be effective than those with only one component (aOR 6.5, 95% CI 1.9–22).[70] These interventions (or combinations of interventions) can be implemented within a framework provided by CDC's *Core Elements of Outpatient Antibiotic Stewardship* (fig 1 and table 2). The Core Elements are *commitment*, *action for policy and practice*, *tracking and reporting*, and *education and expertise* and are based on much of the evidence discussed here.[5]

With increasing awareness of the complex factors involved in antibiotic prescribing, the use of behavioral science to inform antibiotic stewardship interventions has grown[71] and merits special attention in this review. Behavioral science-informed interventions have been of interest to and supported by public health agencies including CDC,[5] Public Health England,[72] and the World Health Organization.[73]

Patient education

Clinicians cite patient demand as a factor in antibiotic prescribing and, as a result, there has been interest in patient education on appropriate antibiotic use. The quality of evidence on targeted patient-facing education is limited with contradictory findings. A 2016 Cochrane systematic review identified two randomized controlled trials (from 2000 and 2009) evaluating written information for patients that included 827 participants.[74] Overall, the studies in this Cochrane review found that written information reduced antibiotic prescribing in ARIs compared with usual care (risk ratio [RR] 0.47, 95% CI 0.28–0.78; RR 0.84, 95% CI 0.81–0.86).[74] However, two other randomized trials in the UK examining educational leaflets, one a 2×2 factorial trial studying two interventions in 1,581 general practitioners practices and the other a single intervention trial in 870 patients presenting to primary care practices with lower respiratory tract infection, found no significant associations between patient educational materials and decreases in antibiotic use (incidence rate ratio [IRR] 1.01, 95% CI 1.00–1.02; IRR 1.27, 95% CI 0.86–1.87).[75,76]

Mass-media campaigns have been associated with reductions in antibiotic use in observational studies, although evaluating causation is difficult. In an observational study of national reimbursement data (N=453,407,458 records), the French campaign, "Antibiotics are not automatic" was associated with a 27% decline in the population-based antibiotic use rate from 2000–2001 to 2002–2007.[77] A media campaign in North East England was associated with a 6% reduction in winter antibiotic prescribing compared with nearby areas with no campaign in an observational study.[78] In the United States, CDC leads a national effort, *Be Antibiotics Aware: Smart Use, Best Care*, to educate patients, caregivers, and clinicians about appropriate antibiotic use (www.cdc.gov/antibiotic-use).[79] Additionally, CDC observes US Antibiotic Awareness Week each November,[80] which coincides with the World Health Organization's Antibiotic Awareness Week[81] and European Antibiotic Awareness Day,[82] as well as other global observances.

Clinician education

Two older systematic reviews have demonstrated that active and intensive clinician educational efforts, such as academic detailing, are more effective than passive education.[83,84] A more recent quasi-experimental study tested academic detailing versus provider and patient mailings and found a significant change in antibiotic prescribing among clinicians who received the academic detailing (odds ratio [OR] 0.49, 95% CI 0.26–0.89) but no significant change among the mailing group.[85] National efforts, such as CDC's *Be Antibiotics Aware*[79] and TARGET in the United Kingdom,[86] provide education and resources on antibiotic use for clinicians.

Communication skills training

Communication skills training for clinicians can improve antibiotic use. These trainings teach clinicians to effectively communicate with patients to understand patient concerns and expectations, provide information on expected disease course and recommended treatment options, and provide a contingency plan if symptoms do not improve.[87] A multi-arm, cluster-randomized trial by Little et al. examined training in communication skills and/or C-reactive protein (CRP) testing among primary care clinicians in 246 practices in 6 European countries.[87] They found that the risk of antibiotic prescribing for ARIs was significantly lower among those who received communication training (adjusted risk ratio [aRR] 0.68, 95% CI 0.50–0.87) or CRP training (aRR 0.53, 95% CI 0.36–0.74) versus controls.[87] The risk of antibiotic prescribing was lowest in the group with both interventions (aRR 0.38, 0.25–0.55).[87] A cluster-randomized controlled trial in 20 Dutch primary care practices (N=379) also assessed the effect of CRP and communication training on antibiotic prescribing for ARIs.[88] Clinicians in the CRP and communication training groups prescribed fewer antibiotics than control groups (CRP: 31% of visits received antibiotics vs. 53% in no-test group, p=0.02; communication training: 27% of visits received antibiotics vs. 54% in no-training group, p<0.01).[88] The group with both CRP testing and communication training prescribed the fewest antibiotics (23% of visits).[88] However, 3.5 years after the interventions were removed, clinicians who received communication training still prescribed fewer antibiotics (antibiotics prescribed in 26.3% of ARI visits, 95% CI 20.6–32.0%) than the control group (39.1%, 95% CI 33.1–45.1%, p=0.02), while the CRP group was not different than the control group at follow-up.[88] In quantitative and qualitative studies, clinicians who received communication skills training provided positive feedback about the training and reported increased confidence in improving antibiotic prescribing.[89–91]

Clinicians may perceive that they are improving patient satisfaction by prescribing antibiotics; however, evidence shows that patients may still be satisfied without antibiotics as long as their communication expectations are met. In a descriptive study of surveys of almost 300 patients with sore throat in Belgian primary care practices, patients listed seeking symptomatic relief, information about disease course, and reassurance of disease cause as their top three reasons for visiting a physician, while obtaining an antibiotic was rated as the 11th (of 13) most important reason.[92] An observational study of 5,169 acute sinusitis encounters in a large integrated health system found that 79.5% of visits in which an antibiotic was prescribed resulted in a favorable patient satisfaction score compared with 75.4% of visits with no antibiotic prescription.[93] This difference was significant (aOR 1.2, 95% CI 1.0–1.6); however the actual difference in the percentage of visits with a favorable score was only 4 percentage points, and the factor with the greatest effect on satisfaction was patient-clinician bonding (aOR 2.0, 95% CI 1.6–2.3).[93] An observational study of 1,285 pediatric ARI visits found that receiving an antibiotic prescription was not significantly associated with a high satisfaction score (adjusted risk ratio [aRR] 1.13, 95% CI 0.95–1.34) while communication was: parents who received both a negative treatment recommendation (i.e., noting that antibiotics won't help the child get better) and a positive treatment recommendation (i.e., providing non-antibiotic strategies to help the child feel better) were more likely to rate the visit highly than patients who received no treatment recommendation (aRR 1.16, 95% CI 1.01–1.34).[94] Even among patients and caregivers who expect antibiotics, providing specific types of communication may maintain satisfaction. The previously discussed 2001 mixed-methods study by Mangione-Smith et al. showed that satisfaction scores increased significantly among caregivers who expected an antibiotic and did not receive one when a contingency plan was provided;[65] the mean satisfaction score for the no contingency plan group was 59 (95% conflidence limit [CL] 53–65) while the mean score for the contingency plan group was 76 (95% CL 66–86).[65]

Rapid and point-of-care diagnostic tests

When rapid diagnostic, including point-of-care, tests are available, have good sensitivity and specificity, and are not cost-prohibitive, they can help guide disease diagnosis and management, thereby improving antibiotic prescribing. Most US patients and clinicians are familiar with the rapid antigen detection test for *group A Streptococcus*, which is recommended in the United States by the Infectious Diseases Society of America to establish a diagnosis of streptococcal pharyngitis prior to prescribing antibiotics.[95] There has been recent interest in procalcitonin and CRP testing. Procalcitonin and CRP are biomarkers that, although not highly specific, may indicate increased risk of bacterial infection. A Cochrane systematic review and meta-analysis of 26 studies examining procalcitonin testing in ARI management found that the per-visit rates of antibiotic prescriptions in primary care were significantly lower among those who used procalcitonin testing compared with controls, 22.9% vs 63.1% (aOR 0.13, 95% CI 0.09–0.18).[96] However, a more recent randomized controlled trial (N=1,656) of procalcitonin testing in adult patients diagnosed with acute lower respiratory tract infection in the emergency department found that there was no significant difference in mean antibiotic exposure days between the procalcitonin intervention group (4.2 days) and the usual-care control group (4.3 days; difference −0.05 day; 95% CI −0.6 to 0.5; p=0.87).[97] A Cochrane meta-analysis examining six trials of CRP in ARI management found that there was a reduction in antibiotic use with CRP testing (pooled RR 0.78, 95% CI 0.66–0.92) compared with usual care.[98] However, the authors of this meta-analysis note that due to heterogeneity in the studies, these results should be interpreted with caution.[98] Although these tests may improve antibiotic prescribing, it is important to note that, as already discussed, communication skills training is as effective as CRP testing at reducing antibiotic prescriptions for ARIs and has sustained benefits that CRP testing does not.[8788] Additionally, using testing appropriately, i.e. diagnostic stewardship, is critical. Testing should only be done if the clinical presentation is consistent with bacterial infection and test results will influence management.[99]

Active monitoring and delayed prescribing

Active monitoring (also called watchful waiting) and delayed prescribing are treatment strategies that engage patients/caregivers to observe illness progression and return (active monitoring) or fill an antibiotic prescription (delayed prescribing) if symptoms do not improve or worsen. These strategies are guideline-recommended in the United States for the management of acute otitis media in children[100] and acute sinusitis,[101102] and have been shown to reduce unnecessary antibiotic use. Delayed prescribing and active monitoring should not be used in conditions where antibiotics are not indicated or are immediately indicated. A Cochrane meta-analysis of delayed prescribing for ARIs found that delayed prescribing resulted in significantly lower odds of antibiotic use than immediate prescribing based on 7 studies (N = 1,963; OR 0.04, 95% CI 0.03–0.05) with no significant difference in patient satisfaction (6 studies, N = 1,633, OR 0.65, 95% CI 0.39–1.10).[103] A 2016 randomized trial in 405 adult ARI visits in 23 Spanish family practice clinics examined the effect of antibiotic prescription strategies on several outcomes, including antibiotic use.[104]

Antibiotic use was significantly different among groups: 91% of patients who received immediate antibiotic prescriptions used antibiotics, compared with 33% of patients with delayed antibiotic prescriptions, 23% of patients instructed to return to the clinic to pick up a prescription if needed, and 12% of patients not prescribed antibiotics ($p<0.001$).[104] In this trial, there were no differences in patient satisfaction, complications, adverse events, or unscheduled return visits among groups.[104] Furthermore, in a mixed-methods study of children with acute otitis media, a majority of parents who utilized pain management and delayed prescribing instead of immediate antibiotic therapy reported that they would be willing to treat future episodes without antibiotics.[105]

Clinical decision support

Studies examining clinical decision support (CDS), which provides information and decision support at the time of diagnosis or treatment, have shown mixed results. A cluster-randomized trial of 33 primary clinics utilized both printed and electronic CDS for acute bronchitis in otherwise healthy adolescents and adults with 9,808 visits during the baseline and 6,242 visits during the intervention period.[106] Antibiotic prescribing for acute bronchitis decreased significantly in printed CDS sites, from 80.0% to 68.3%, and at electronic CDS sites, from 74.0% to 60.7%, but not at control sites (72.5% to 74.3%).[106] Prescribing was not significantly different between printed and electronic CDS sites.[106] However, notably, the appropriate rate of antibiotic prescribing for acute bronchitis in patients included in this study is zero. Another cluster-randomized trial of a CDS intervention in 27 primary care clinics with 21,961 ARI visits found that the CDS tool was used in as few as 6% of visits in the intervention group and was not effective.[107] Additionally, a cluster-randomized trial in 104 family practice facilities in England and Scotland found that about 25% of intervention practices used the CDS tool rarely or not at all.[108] CDS design is important in its uptake and effectiveness; a 2015 systematic review of CDS randomized trials found that CDS tools that provided decision support integrated into existing processes were more likely to improve prescribing than systems that required active initiation by the clinician.[109] Finally, any achieved benefits may not be sustainable once the intervention is removed. A quasi-experimental study in the US Department of Veterans Affairs health system (N = 1,131 ARI visits) found that a CDS tool for ARI management improved guideline-concordant prescribing; however, after the tool was removed, inappropriate prescribing increased.[110]

Audit and feedback with peer comparisons

There is strong evidence to support the use of tracking antibiotic prescribing practices and reporting them back to clinicians, called audit and feedback, and this practice is recommended by CDC's *Core Elements*.[5] The *Core Elements* also specify that effective audit and feedback interventions include comparisons of clinician prescribing with their peers.[5] A cluster-randomized trial in 18 pediatric primary care practices (N=1,291,824 visits) evaluated an intervention in which pediatricians received education and prescribing pattern feedback for themselves, their practice, and their network.[111] The intervention was associated with a 12.5% decrease in broad-spectrum prescribing for ARIs, with a statistically significant difference of differences of 6.7% ($p=0.01$) versus controls.[111] Unnecessary prescribing for ARIs was low at baseline and did not change significantly during the intervention for any group ($p=0.93$).[111] However, a follow-up observational study found that when the intervention was removed, antibiotic prescribing patterns returned to pre-intervention levels.[112]

Behavioral science has been used in two recent audit and feedback studies to increase the effectiveness of the intervention.[75113] In the first, a randomized trial, Hallsworth and colleagues sent 3,227 letters with peer comparisons to UK general practitioners. The letter informed physicians that they were prescribing antibiotics at higher rates than 80% of general practitioners in their area, i.e., provided social norm information; was signed by a high-profile figure, England's Chief Medical Officer, to increase credibility; and gave three specific actions clinicians could take to reduce unnecessary antibiotic prescribing.[75] Prescribing rates in the letter intervention group were significantly lower than controls, 126.98 (95% CI 125.68–128.27) antibiotics per 1,000 weighted population versus 131.25 (95% CI 130.22–132.16) (IRR 0.97, 95% CI 0.96–0.98, p<0.001).[75] In the second study, a cluster-randomized trial in 47 primary care practices in Boston and Los Angeles, Meeker et al. examined three stewardship interventions designed using behavioral science principles: peer comparison, accountable justification, and suggested alternatives.[113] In the peer comparison intervention arm, clinicians with the lowest inappropriate antibiotic prescribing rates for ARIs received an email informing them that they were top performers, reinforcing desired behavior, while all other clinicians received emails informing them that they were "not a top performer."[113] The intervention was designed to drive performance to a goal, instead of to the mean, and therefore did not include an average prescribing comparison. This peer comparison was associated with a significant decrease in inappropriate antibiotic prescribing for ARIs from 19.9% to 3.7% (difference in differences compared to controls, −5.2, 95% CI −6.9% to −1.6%).[113] One year after the interventions were discontinued, the peer comparison was the only intervention arm (of three) that had significantly lower prescribing rates than the control group.[114]

Accountable justification

Accountable justification, in which clinicians must document explanations for non-indicated antibiotic prescriptions, was associated with a reduction in inappropriate antibiotic prescribing in the previously mentioned study by Meeker et al.[113] The intervention was designed based on the behavioral science principles that accountability improves decision making and public justification creates social and reputational concerns that improve behavior.[113] Clinicians knew that antibiotic justification notes in the medical record would be visible to other clinicians, thus increasing accountability for inappropriate prescribing. The intervention was associated with a significant reduction in prescribing for ARIs from over 23.2% to 5.2% (difference in differences, −7.0%, 95% CI −9.1% to −2.9%; p<0.001).[113] In contrast, the suggested alternatives intervention in this study, where the electronic health record suggested non-antibiotic treatments, did not significantly improve prescribing compared with the control group (p=0.66).[113]

Public commitment posters

Lastly, evidence shows that using public commitment posters, a simple, low-cost intervention, reduces inappropriate antibiotic prescribing. Commitment posters are behavioral nudges for clinicians that are designed to utilize clinicians' desire to remain consistent with previous public commitments.[115] A randomized controlled trial in 954 visits by adults with ARIs in 5 outpatient clinics tested the use of public commitment posters in patient exam rooms.[115] The posters included a letter from the clinician committing to use antibiotics appropriately and the clinician's picture and signature.[115] The public commitment poster intervention was associated with an absolute reduction in inappropriate prescribing for ARIs of 19.7% (95% CI 5.8%−33.0%) compared with the control group (p=0.02).[115] Commitment posters have been adopted by state health departments, healthcare systems, and CDC.[5116]

Emerging interventions

A study of clinicaltrials.gov for the terms "antibiotic" and "outpatient" yielded 24 active studies. Three of these 24 studies examine interventions to improve antibiotic prescribing in outpatient settings. The first, a randomized controlled trial in Switzerland is in the enrollment phase and will evaluate a nationwide antibiotic stewardship program that uses routine feedback and clinician and patient education on overall and broad-spectrum antibiotic use and hospitalization rates (NCT03379194). The second is a randomized controlled trial that will examine education and communication skills interventions among clinicians, looking at the outcomes of parental ratings of shared decision-making and satisfaction, inappropriate antibiotic prescribing, re-visits, and adverse drug events (NCT03037112). This trial is currently in the recruitment phase with estimated study completion in June 2019. The third study is recruiting clinicians in France to investigate the effect of regional antibiotic consumption and bacterial resistance data on prescribing practices and antibiotic resistance (NCT02816528); however, information on this study has not been updated since June 2016.

Guidelines

CDC's *Core Elements of Outpatient Stewardship* offers guidance for implementation of outpatient antibiotic stewardship.[5] Additionally, many guidelines for common outpatient conditions provide specific recommendations on antibiotic prescribing that, if followed, could reduce unnecessary antibiotic prescribing and improve agent selection and therapy duration when antibiotics are indicated. The Healthcare Infection Control Practices Advisory Committee (HICPAC) has provided recommendations on incorporating antibiotic stewardship principles into treatment guidelines, emphasizing diagnostic testing and infectious disease treatment.[117] In addition, the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America developed guidelines for the implementation of antibiotic stewardship programs in inpatient settings,[118] and some of the strategies in these guidelines may be beneficial in outpatient settings as well.

Conclusion

Approximately 270 million outpatient antibiotics are dispensed in the United States each year and at least 30% of these are unnecessary.[436] Antibiotic use is not without risks, including antibiotic resistance and adverse events. Antibiotics should be considered when the clinical benefits outweigh the risks, such as for sepsis or suspected sepsis. Using antibiotics only when needed, and, when needed, using the right agent, dose, and duration at the right time is a matter of patient safety.

In addition to clinical factors, outpatient antibiotic prescribing is also driven by psycho-social factors including lack of self-awareness, fear of complications, perceived patient expectations, and time constraints and fatigue. Many different outpatient antibiotic stewardship interventions have shown some success and using multiple, complementary intervention strategies can reduce inappropriate antibiotic use. The most effective combination of interventions will depend upon the outpatient setting and practice; however, behavioral-science based interventions (public commitment posters, accountable justification, and feedback with peer comparison) and communications training have shown promising results and should be included in any antibiotic stewardship intervention package. The *Core Elements of Outpatient Antibiotic Stewardship* can facilitate the implementation of stewardship interventions in outpatient settings. Using antibiotics appropriately is an important component of best patient care and should be a cornerstone of effective outpatient practice.

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Questions for future research (box)

- What is the effect of outpatient antibiotic stewardship interventions on adverse events?
- What is the effect of outpatient antibiotic stewardship interventions on antibiotic resistance?
- What is the return on investment of outpatient antibiotic stewardship interventions?
- What antibiotic stewardship interventions work to improve agent selection, dose, and duration in conditions where antibiotics are indicated?
- Is there a correlation between inappropriate antibiotic prescribing and inappropriate prescribing of other medications, such as opioids?
- Do pay-for-performance or other financial incentives, similar to the Quality Premium program in the UK, improve antibiotic prescribing in US outpatient practices?

Figure 1.
US Centers for Disease Control and Prevention's *Core Elements of Outpatient Antibiotic Stewardship*[5]

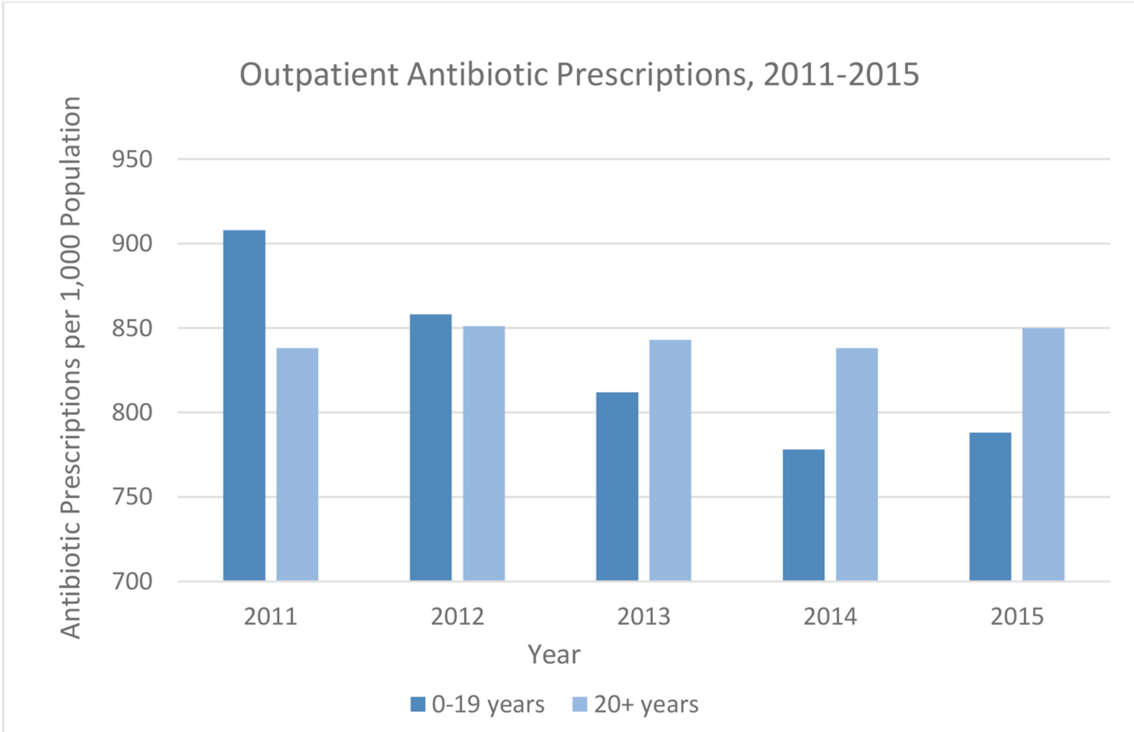

Figure 2.
Outpatient antibiotic prescriptions in the United States by age group, 2011–2015

Table 1.

Percent of antibiotic prescriptions that were unnecessary, United States, 2010–2011

Age group	All conditions	Acute respiratory conditions
0–19 years	29%	34%
20–64 years	35%	70%
≥65 years	18%	54%
All ages	30%	50%

As presented in the US Centers for Disease Control and Prevention’s 2017 Antibiotic Use in the United States: Progress and Opportunities Report,[119] original data from Fleming-Dutra et al., 2016.[36]

Table 2.

Relationship between the US Centers for Disease Control and Prevention's *Core Elements of Outpatient Antibiotic Stewardship* and examined interventions

CDC Core Element of Outpatient Antibiotic Stewardship	Related Interventions
Commitment	Public Commitment Posters
Action for Policy and Practice	Diagnostics and Point of Care Testing, Accountable Justification, Active Monitoring / Delayed Prescribing, Clinical Decision Support, Communication Skills Training
Tracking and Reporting	Audit and Feedback, Peer Comparison
Education and Expertise	Communication Skills Training, Clinician Education, Patient Education

Table 3.

Summary of outpatient antibiotic stewardship interventions and considerations

Intervention	Considerations
Patient Education	• Effectiveness of smaller-scale interventions uncertain • Mass-media campaigns may be effective
Clinician Education	• Active, in-person education more effective than passive education • Factors influencing prescribing go beyond knowledge gaps, so should be provided in combination with other interventions
Communication Skills Training	• Effective with sustained benefits over time • May improve patient satisfaction • Effective elements of communication in conditions where antibiotics are not needed include: – Using both a negative and positive treatment recommendation – Providing a contingency plan
Diagnostics and Point of Care Testing	• Can be useful in diagnosing bacterial etiologies – Accurate diagnosis decreases inappropriate antibiotic use for viral infections • Diagnostic stewardship is needed in any intervention where diagnostics or point of care testing are used
Active Monitoring/Delayed Prescribing	• Can reduce antibiotic use for conditions where antibiotics are sometimes indicated • Guideline recommended for some conditions (acute otitis media in children and acute sinusitis) • Should never be used in conditions where antibiotics are not indicated or are immediately indicated
Clinical Decision Support	• Evidence on effectiveness is mixed • Can range from low-tech (such as printed clinical pathways) to high-tech (integrated into EHR) • Low uptake can be a barrier to effectiveness – More effective if integrated into existing systems and easy to use
Audit and Feedback + Peer Comparison	• Peer comparison rooted in behavioral science • Effective in reducing inappropriate prescribing • Should provide an appropriate prescribing target (not mean) to prevent regression to the mean effect
Accountable Justification	• Based in behavioral science • Effective in reducing inappropriate prescribing • Must be integrated into EHR
Public Commitment Posters	• Based in behavioral science • Low-cost, effective intervention • Intended effect is for clinician rather than patient – Should be placed in exam room (not waiting room)

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Intervention	Considerations
	• Templates available from CDC and some state health departments

A full discussion of these interventions and supporting evidence is available in the “Interventions to improve outpatient antibiotic prescribing” section of the text.