Antimicrobial Stewardship (AMS) in the Community

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Abstract: The importance of improving outpatient antibiotic use is acknowledged, but no comprehensive recommendations to curb the use in this setting have been made because of the lack of sufficient data to guide such efforts. A targeted application of antimicrobial stewardship (AMS) principles to the ambulatory setting has the potential to affect the most common indications for systemic antibiotic use in that the majority (80%) of antibiotic use occurs in the community, with acute respiratory-tract infections being the most common indication. However, the reasons driving the excessive prescription of antibiotics in the community are complex and include constraints on the consultation time, the lack of appreciation of the impact on resistance, considerable diagnostic uncertainty, and perhaps most importantly patient and parental pressures in conjunction with patient satisfaction surveys. Thus, in contrast to institutionalized AMS, few recommendations for outpatients are offered, largely because of the paucity of data regarding effective interventions to tackle such complex issues in ambulatory care. Prescribing antibiotics for patients with self-limiting conditions is counterproductive as it reinforces the belief that antibiotics are beneficial and encourages repetitive prescriptions and consultations. Hence, one of the ultimate goals of a community AMS program should be "demedicalization" of self-limiting acute infections. In this regard, multifaceted interventions where educational interventions occur on many levels may be applied successfully to communities after addressing local barriers to change. These appear to be the only interventions with effect sizes of sufficient magnitude to potentially reduce the incidence of antibiotic-resistant bacteria.

Key Words: antimicrobial stewardship, community, ambulatory care, outpatients, primary care physicians

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The global increase in resistance to antibiotics is a major public health problem, and antibiotic use is increasingly recognized as the main factor driving this process. The majority (75% to 80%) of the antibiotic prescriptions for systemic use in adults are prescribed in the community, with acute respiratory-tract infections (ARTI) such as bronchitis, pharyngitis, and sinusitis being the most common indication.[1–3] The same applies to children.[4] Inappropriate antimicrobial prescription is a significant problem, with approximately 50% of the antimicrobial usage suboptimal in hospital or ambulatory settings, which is not only unnecessary but is unlikely to benefit patients.[2,3] Inappropriate use of antibiotics for ARTI, most of which are viral, adds to the burden of antimicrobial resistance (AMR) significantly.[2,3,5] Similarly, the economic burden associated with rampant prescription of antibiotics is such that even a decade ago, >$1.1 billion was spent annually on an estimated 41 million unnecessary prescriptions for noninfluenza viral ARTI episodes in the United States (US).[6]

The effect of these prescribing practices in the community on AMR can be observed at the patient level and also at the community level.[1,3,7,8] Antibiotics prescribed to an individual in the community have consistently been found to be associated with resistance of urinary and respiratory pathogens to those antibiotics in that patient, an impact that may last for up to 12 months.[8] In addition, the greater the number or the duration of antibiotic courses prescribed in the previous 12 months, the greater the likelihood that resistant bacteria would be isolated from that patient. Conversely, reducing the number of prescriptions in ambulatory settings is associated with reduced local antibiotic resistance. However, this does not occur immediately. It has been shown that a reduction in AMR among coliforms isolated from patients with urinary tract infections correlated with a collective reduction in antibiotic dispensing over a 7-year period (1.7 million patients served by 240 community practices).[1]

Subsequent to the US Centers for Disease Control and Prevention (CDC) launch of its "Get Smart: Know When Antibiotics Work" campaign in 1995, various reports demonstrated a decline in antibiotic use in the US.[2,3,9] However, it appears that this has not been sustained in all age groups. Despite an overall impressive decrease among children and adolescents, an increase among older adults was recently documented.[2] In addition, rates of broad-spectrum antibiotic prescriptions doubled from 2000 to 2010 across all age groups in 1 survey and confirmed to constitute almost 80% of the visits for respiratory conditions for which antibiotics rarely provide benefit, in another.[2,3] Considering the fact that the development and the spread of AMR is multifactorial, that ARTIs are the most common indication for community use, and that no single intervention can solve the problem, the question is what more could be done?

CURRENT EFFORTS TO ADDRESS AMR

In an unprecedented global call for urgent action to combat AMR, the World Health Assembly on May 17, 2014 adopted the World Health Organization resolution WHA67.25. Subsequently, governments globally responded in different ways, but as political will entered the fray, the pace of reform in antibiotic preservation gained momentum rapidly as AMR is now regarded as a public health crisis and a "threat to national security." As reported by the CDC, the threat of multidrug resistance (defined as resistance to ≥ 3 antibiotic classes), extensive-drug (defined as resistance to all classes except one), and pan-drug resistance (defined as resistance to all antibiotic classes) among common community-acquired pathogens to the public has become a reality.[10]

There is no doubt that the main objectives of the various federal or state antimicrobial stewardship (AMS) programs to limit further development of resistance and improve patient outcomes would be easier to achieve if hospitals were to implement multidisciplinary team-based AMS.[11–13] How

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TABLE 1. A Multimodal Strategy-Based Approach for Antimicrobial Stewardship (AMS) of Acute Respiratory-Tract Infections in the Community

Strategy	Components
1. Treat bacterial infection only	Optimize clinical diagnosis and severity assessment
	The use of C-reactive protein and other biomarkers in community practice including point-of-care testing
	Need for tools to reduce diagnostic uncertainty
2. Judicious antibiotic prescribing principles	Target maximum eradication of bacterial pathogens
	Utilize pharmacokinetic/pharmacodynamics to choose the most effective agents and appropriate dosage
	Optimize the duration of therapy
	"Know your bugs": local antibiograms
	Prescribing antibiotics that are associated with less selection of resistant strains
3. Prescription strategies	Immediate prescription
	Delayed prescription
	No prescription
4. Raise the public's "antibiotic threshold"	Community awareness of AMR
	Patient empowerment vs. patient satisfaction
5. Vaccination as a key AMS strategy	Bacterial
	Viral
6. "Covering more territory" to fight resistance in the community	Pharmacists
	Nurses
7. An antibiotic "license" to prescribe?	Educational intervention
	Educational support
8. AMS governance in primary care	Leadership commitment
	Accountability

clinicians implement AMS in the community is a challenging question. As such, the aim of this paper that is to focus on antibiotic use (as opposed to all antimicrobials) and to review multimodal components of an AMS program for ARTI in the community and propose a few new possible strategies (Table 1).

A STRATEGY-BASED APPROACH FOR ARTIs IN THE COMMUNITY

Strategy 1: Treat Bacterial Infection Only

Treating only bacterial ARTI should be self-evident, but is commonly ignored, probably because knowledge of how to distinguish between nonbacterial and/or self-limiting infections is lacking. Viral infections cause the majority of the upper respiratory–tract infections (URTI), and it is widely documented that inappropriate antibiotic prescribing is common in this setting.[14] Similarly, in acute bronchitis, physicians in the US continue to prescribe antibiotics to adults in 60% to 80% of the visits despite guidelines recommending the contrary.[15] Of note, despite the provision of clear evidence, guidelines, quality measures, and >15 years of educational efforts by the CDC, the antibiotic prescribing rate for acute bronchitis, which should be zero, is in fact 71% and this increased during a study period from 2006 to 2010.[16]

This might be because of the fact that in community practices, diagnostic uncertainty prevails, and as a consequence, it is very difficult for clinicians to differentiate between the various manifestations of lower respiratory–tract infections (LRTI). Although there is an overlap in the presentation among each, it is neither feasible nor cost-efficient to perform a full diagnostic work-up in all cases.

Optimize the Clinical Diagnosis and Severity Assessment

Correct clinical diagnosis by utilizing concise, stringent, validated diagnostic criteria based on clinical signs and symptoms is obviously the key to reduce overall antibiotic prescribing. It, however, requires time and clinical acumen for the diagnosis of conditions such as acute otitis media (AOM), where the eardrum has to be visualized to differentiate it from otitis media with effusion, which is unlikely to be due to a bacterial infection.[14] Previous studies have shown that in these circumstances, unnecessary antibiotic use can be reduced by up to two thirds.[17] Another crucial step for clinicians is the recognition and the grading of the symptoms of ARTI, enabling the identification of those with severe disease that requires immediate management, including the initiation of antibiotics and, most importantly, referral.

The Use of C-reactive Protein (CRP) and Other Biomarkers in Community Practice

In community practice, the lack of availability of sensitive and specific, cost-effective diagnostic tests to distinguish viral from bacterial infections perpetuates inappropriate antibiotic use. The problem essentially lies within the predictivity of a biomarker such as CRP that changes along with the prevalence of the disease.

URTI: Increased CRP has been suggested as a diagnostic criterion in URTI, but this has not been the recommendation despite the widespread use without adequate validation of cut-off values. A history of purulent nasal discharge and pus in the nose and throat are better criteria for acute bacterial rhinosinusitis (ABRS) for selecting adult patients for antibiotic treatment than radiography or CRP.

Community-acquired Pneumonia (CAP): The best studied biomarker in community practice is CRP testing for community-acquired pneumonia (CAP). Reviews have found that CRP has limited diagnostic value for pneumonia in the community when the probability of pneumonia is <10%.[18] CRP may be of value in ruling out a diagnosis of CAP in accident and emergency departments because the probability of CAP is higher. In addition, a negative or positive CRP result may produce additional diagnostic information if the patient

presenting has additional symptoms or signs (eg, dry cough, diarrhea, or temperature >38°C) that revise the probability of CAP.

In this regard, the recent GRACE-09 (Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe) study examined the value of CRP and procalcitonin (PCT) concentrations in addition to symptoms and signs to predict pneumonia (diagnostic model) in a large cohort of patients presenting with acute cough.[19] A CRP value of >30 mg/L increased the diagnostic accuracy for pneumonia when doubt remained after the history and physical examination were not conclusive.

Without clinical modeling, the routine use of CRP alone in the community is not recommended as it is unlikely to alter the probability of CAP sufficiently and the positive predictive value too low to generally change subsequent management decisions significantly. Results on the prognostic value of CRP have also been contradictory. PCT concentrations in the GRACE-09 study were higher in patients with pneumonia and comparable to previous findings in patients with LRTIs in the community, but did not add meaningful diagnostic information in the study.[19]

Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): Similarly, CRP alone is neither sufficiently sensitive nor specific to confirm exacerbations of COPD and the magnitude or increase in CRP concentration does not reflect the clinical severity of the event.[20] CRP has shown predictive value, however, in combination with one or more major symptoms (eg, increasing dyspnea, sputum volume, or purulence) or with the white-blood cell count and fibrinogen, and the specificity and the sensitivity may be further improved with the construction of so-called "inflammomas," containing 3 or more easily accessible markers.[21]

In this regard, rapid progress is being made as the search for additional markers continues. Emerging evidence supports the concept of "exacerbation phenotypes" with the ultimate aim to tailor treatment and identify the patients who are most likely to benefit from antibiotics.[22] From an AMS point of view, PCT has been shown to reduce the duration of antibiotic treatment.[22] What will be recommended for the management of acute exacerbations of COPD in the community remains to be seen.

Point-of-Care Testing (POCT): The availability of POCT while the patient waits in community practices before the clinician prescribes an antibiotic offers definitive advantages. In fact, recent reviews including a Cochrane review concluded that POCT for CRP to guide antibiotic treatment of ARTIs in primary care can significantly reduce antibiotic use.[23] A POCT for CRP should be considered for patients presenting with a LRTI if it is not clear after clinical assessment whether antibiotics should be prescribed or not. Recently a consensus of collaborators in European and UK consortia have suggested using the results of the CRP to guide antibiotic prescribing as follows[23]:

- Do not routinely offer antibiotic therapy if the CRP concentration is less than 20 mg/L.
- Consider a delayed antibiotic prescription (a prescription for use at a later date if symptoms worsen) if the CRP concentration is between 20 mg/L and 100 mg/L.
- Offer antibiotic therapy if the CRP is greater than 100 mg/L.

Antibiotics for Acute Cough "Illness"

Because the predominant etiology for acute cough "illness," common cold, acute bronchitis, and nonspecific URTI are viruses, antibiotic therapy is not indicated.[14] Despite this, acute cough is one of the most common reasons for the prescription of antibiotics in community practices; 52.7% of the adult patients presenting with acute cough received an antibiotic.[24] The median time for recovery is 11 days, during which time a patient frequently receives another unnecessary antibiotic. The local inflammatory response may persist for prolonged periods after an infection, and coughing is not a reason for the prescription of antibiotics, particularly because there are many other noninfective causes. However, one of the reasons why the recommendations to avoid antibiotics for virtually all patients presenting with acute cough are frequently ignored is that simple diagnostic decision making is very challenging for community physicians.

Whaley et al[15] recently demonstrated that among the patients presenting in primary care with acute cough, the most common infective diagnoses were URTI (46%), sinusitis (10%), acute bronchitis (9%), and pneumonia (8%), and clinicians more often expressed uncertainty when prescribing than when not prescribing antibiotics (30% vs. 12%; $P < 0.001$). As the number of differential diagnoses increased from 1 to 2 and to ≥ 3, they were more likely to express diagnostic uncertainty (5%, 25%, and 40%, respectively; $P < 0.001$) and were consequently more likely to prescribe antibiotics (16%, 25%, and 41%, respectively; $P < 0.001$).

The Need for Tools to Reduce Diagnostic Uncertainty

Considering what was discussed above, the diagnostic complexity and the uncertainty faced by clinicians is acknowledged. Distinguishing viral from bacterial ARTI is no mean feat.[14] Hence, national guidelines in support of AMS in the community should if possible focus rather on the provision of definitive and simple frameworks for clinical decision making regarding antibiotic use. An example of such a clinical tool is shown in Table 2.[25] The aim was to facilitate closing the gap between guideline recommendations and actual practice.

Preferably, the interpretation of laboratory tests such as CRP should also be included where applicable. Guidance regarding the clinical circumstances in which biomarkers and, in the future, rapid molecular POCT tests would reduce diagnostic uncertainty in ARTIs and would assist in making antibiotic decisions is urgently required. Without the validation of the diagnostic modeling in the community and AMS guidance to interpret diagnostic results appropriately, there may be little change in the prescribing behavior of community physicians.

Strategy 2: Judicious Antibiotic-Prescribing Principles

If a bacterial infection is determined to be likely and evidence suggests that antibiotics may provide benefit, several aspects of judicious prescribing should be considered.[14] The term judicious frequently used in the context of AMS is poorly understood. It encompasses all those antibiotic treatment principles required to preserve antibiotics and to reduce AMR and is synonymous with prudent, well advised, well judged, sound, well thought out, insightful, considered, informed, logical, and rational.

The following judicious antibiotic treatment principles are briefly summarized from an ARTI point of view, but may have a broader application for antibiotic use in general.

Target Maximum Eradication of Bacterial Pathogens

Spontaneous recovery, which is the norm for mild-moderate ARTI, masks differences between the use of antibiotics or not, and allows suboptimal agents or dosing to continue to be prescribed. This is referred to as the "Pollyanna"

TABLE 2. Clinical Parameters to Exclude CAP

Pneumonia is unlikely if the following are absent
Fever $\geq 38^{\circ}C$
Tachypnea ≥ 24/min
Tachycardia ≥ 100/min
Evidence of consolidation on examination: crackles, bronchial breathing, fremitus
If any one of above is present or coughing persists >3 wk
Then perform CXR (eg, to exclude TB or lung CA in smokers, etc.)

CA indicates carcinoma; CXR, chest x-ray; TB, tuberculosis.

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phenomenon, which applies where antibiotics with poor bacteriological activity appear to be as effective as those with superior or optimal bacteriological efficacy. This translates to "silent" bacteriological failure not recognized by the clinician, but which eventually may culminate in recurrence or relapse and the development of resistance. Bacterial eradication is thus the primary goal of antibiotic therapy and should be the main determinant of the therapeutic outcome.[26]

Utilize Pharmacokinetic/Pharmacodynamics (PK/PD) to Choose the Most Effective Agents and Appropriate Dosage

To achieve maximal bacterial eradication, clinicians need a basic understanding of the PK/PD principles that govern how antibiotics exert their antibacterial action and the indices required for each class to achieve maximal efficacy. A basic understanding of the mechanisms of resistance to these agents is also required. Differences exist between antibiotics in the same PK/PD class in their ability to achieve the required targets: not all cephalosporins (which are time dependent) are equal and similarly not all fluoroquinolones (which are concentration dependent) are comparable.

Optimize the Duration of Therapy

Several studies have shown that low dosage and/or a long treatment duration increase the risk of carriage of resistant strains.[26] The benefits of shorter antibiotic courses (confirmed by several RTI meta-analyses) are reflected not only in an optimal outcome and better patient compliance, but also in fewer side effects and reduced costs and, most importantly, a reduced risk of resistance. Considering the principles of maximal bacterial eradication, utilizing PK/PD, and minimizing the duration, the "mantra" that should be communicated to community clinicians is that where antibiotics are utilized, a "high-dose short-course" strategy is preferred.

"Know Your Bugs"

It has ever been as important for a clinician to take recognizance of the local epidemiology and the prevalence of resistance. Local laboratories should not only provide epidemiology and antibiograms for hospitalized patients, but for selected primary care RTI and urinary tract infection pathogens as a matter of priority. Such data should be interpreted, concise, easy-to-use, and should provide information about appropriate first-line (including alternative) antibiotic choices based on the prevalence of pathogens and resistance patterns geographically (tailored). Antibiograms should be provided to everybody involved in a community AMS program, that is, besides community physicians, physician assistants, nurse practitioners, long-term care facilities, home health care agencies, and pharmacies.

Prescribing Antibiotics That Are Associated With Less Selection of Resistant Strains

Antibiotics differ between and within classes in their potential to select for resistance. Although somewhat ill defined, broad-spectrum agents such as fluoroquinolones and second-generation- and third-generation cephalosporins are regarded as high-risk antibiotics, and the restriction of these agents in Ireland for example (including clindamycin) has contributed to significant reductions in the incidence of *Clostridium difficile* infections and extended-spectrum β-lactamase–producing bacteria and methicillin-resistant *Staphylococcus aureus* in both hospital and community settings.[27]

Similarly, a significant association was found between the consumption of long half-life macrolides (azithromycin, clarithromycin) and temporal and regional macrolide resistance in *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and other oral streptococci.[26] In the community, these agents are used indiscriminately and frequently for their anti-inflammatory and immune-modulatory effects, but because of the confirmed long-term impact (up to 12 mo in exposed patients) on AMR among common RTI pathogens and oral streptococci, their widespread use without specific guidance cannot be endorsed currently.[28]

A recent CDC survey highlighted an important issue. Community health providers widely thought that broad-spectrum agents were more successful for curing an infection than narrow-spectrum antibiotics.[29] Despite the fact that the American Academy of Paediatrics recommends penicillin or amoxicillin as first-line agents for streptococcal pharyngitis, acute sinusitis, and pneumonia, approximately 50% of the children receive broader-spectrum antibiotics for such RTIs.[4,14] The trend was recently confirmed across all age groups.[2,3,14] In 2010, the most frequently prescribed antibiotic agent in the US was azithromycin.[30] It is also important to emphasize that Shapiro et al[3] found that among patients prescribed antibiotics, broad-spectrum agents were more likely to be prescribed than narrow-spectrum antibiotics for respiratory infections for which antibiotics are rarely indicated, for example, bronchitis, and during visits to emergency departments and for patients aged 60 years and older.

A challenge for community AMS programs is therefore intervention to improve antibiotic selection and initiatives to promote first-line, targeted antibiotic therapy.[3,29] One aspect regarding collateral damage that is important to recognize is that although narrow-spectrum targeted therapy is preferable, inappropriate use of all antibiotics is the primary goal of an AMS program.

Strategy 3: Immediate Against Delayed Against No Antibiotic Prescription Strategies

Accumulating evidence suggests that advice to delay filling of an antibiotic prescription for uncomplicated ARTI, for at least the expected duration of the illness, is an effective strategy for reducing antibiotic use.[31,32] It appears that delayed prescriptions are the only interventions with effect sizes of sufficient magnitude to potentially reduce the incidence of AMR bacteria in the community.[31]

There has been some debate as to the efficacy of these strategies with regard to symptom control; however, in the largest study to date, Little et al[33] combined structured advice regarding palliative therapy with no prescriptions, immediate prescriptions, or delayed prescriptions, and confirmed that symptom control was no worse, and that <40% of patients used

antibiotics. In fact, there was little difference in the antibiotic use between those advised to delay filling the prescription and those not given a prescription, because the former had been appropriately informed as to the lack of efficacy of antibiotics in this setting. In contrast, most patients given a prescription without advice used antibiotics (97%) and strongly believed in them (93%), despite no benefit with regard to the severity or the duration of symptoms. Complications (such as quinsy, cervical adenitis, etc.) were slightly more common in the no-prescription group (2.5%) than in the delayed strategy groups (1.4%) and similar to the immediate group (2.5%).

Of note, Little et al[33] also directly compared different methods to delay antibiotic prescription or antibiotic use. These included recontacting the practice to request a prescription by phone (recontact), postdating the prescription (postdate), collection of the prescription from the practice by the patient (collection), and issuing prescriptions, but asking them to wait for a defined period (patient led). No significant differences were demonstrated although the data favored collection (a slightly lower use of antibiotics) rather than the other delay strategies. It was concluded that if clear advice is given to patients, there is probably little to choose between the different strategies of delayed prescription.

Ultimately, an important question is whether no antibiotics as a prescribing strategy for ARTI should be favored above delayed antibiotics? In fact, results of a recent Cochrane review suggest that should be the preference.[34] Where clinicians feel it is safe not to prescribe antibiotics immediately, no antibiotics with advice to return if symptoms do not resolve is likely to result in the least antibiotic use, while maintaining patient satisfaction and clinical outcomes similar to delayed antibiotics.

However, a crucial consideration is the socioeconomic status of the patient and their access to health care. Systematic reviews suggest that in high-income countries, the benefit of antibiotics for acute pharyngotonsillitis, AOM, and ABRS is extremely limited.[5] In contrast, there are few data from low-income and middle-income countries, where acute rheumatic fever and suppurative complications such as mastoiditis are more common.[5] Despite the fact that most cases of viral and bacterial acute pharyngitis are self-limiting, including those caused by group A β-hemolytic streptococci, the primary reason for considering antibiotic therapy in such societies is to prevent acute rheumatic fever and glomerulonephritis.

Similarly, it is thought that despite the fact that AOM is often viral in etiology and that even bacterial AOM frequently resolve spontaneously, in patients with limited access to health care or follow-up, and particularly in children less than 2 years of age where there is a risk of a serious infections from *S. pneumoniae* and/or *Haemophilus influenzae*, antibiotics should be prescribed at the first visit, provided the AOM is diagnosed correctly.[5]

Strategy 4: Raise the Public's "Antibiotic Threshold"

The reduction of antibiotic prescriptions and consumption is clearly dependent on patient (or parental) involvement and this form of empowerment should be defined as a separate strategy within a multifaceted community AMS program. This would eliminate many of the factors that lead to a physician visit and the prescription of an antibiotic in the first place. Many patients expect to receive an antibiotic at their first visit and as many as 1 in 5 children return during the same RTI illness period and are prescribed another antibiotic. Although the vast majority of these are unnecessary, considerable pressure is placed on clinicians to prescribe antibiotics despite the lack of any real benefit. Patient and parental beliefs and fears and expectations play a crucial role in determining whether or not a prescription will be provided or not.

In fact, it has been shown before that the factors most strongly associated with prescribing were the patient's opinion that antibiotics were required, his/her expectation of receiving them, and the clinician's perception of this expectation, which was confirmed in a recent survey.[35] This comes as no surprise as clinicians have been found to overestimate patient expectations for antibiotics, especially in those presenting with acute cough. It also appears that there are subtle but distinct differences between the "expectation of an antibiotic," "hoping for" an antibiotic, or actually asking for an antibiotic.[36] Patient's expectations and hopes were independently associated with higher prescribing rates, whereas asking for an antibiotic was not.

To raise the "threshold" of the public before consulting a clinician for self-limiting RTIs to obtain an antibiotic script, both community awareness of AMR and patient empowerment is therefore required. What is not needed, however, is the emphasis on patient satisfaction over standards of care, which in fact might have gone too far already. When it comes to antibiotic preservation efforts, physicians cannot be held captive by satisfaction surveys. This would require fundamental changes in managed-care governance from an antibiotic prescribing point of view, which is discussed below briefly. Perhaps another underlying problem lies with poor communication and the quality of the consultations.

Promoting effective communication that is culturally appropriate and provision of evidence-based information on the recognition of signs of severity and the likely duration of the illness is thus required to reduce patient and parenteral anxiety (Table 3).[37] Such a strategy should include patients' or parents'/care givers' concerns and expectations that specifically need to be addressed by the clinician when agreeing on the use of one of the 3 antibiotic-prescribing strategies (no prescribing, delayed prescribing, and immediate prescribing). In this regard, it has been shown that patient information leaflets that describe the expected symptom duration and simple self-help measures reduce antibiotic prescribing and reconsultations significantly.

A unique approach to improve the bed-site management of community-acquired LRTI includes combining interventions that contain enhanced communication skills, training for clinicians (an illness-focused approach aimed at patients),

TABLE 3. The Duration of Respiratory-Tract Infections

For all antibiotic prescribing strategies, patients should be given:
Advice about the usual natural history of the illness, including the average total length of the illness (before and after seeing the doctor)

Infection	Duration (d)
Acute otitis media	4
Acute sore throat/acute pharyngitis/acute tonsillitis	7
Common cold	10-11
Acute rhinosinusitis	17-18
Acute cough/bronchitis	21

Advice about managing symptoms, including fever (particularly analgesics and antipyretics)

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supported by a patient booklet, and/or the use of a POCT for CRP (a disease-focused diagnostic approach). Such creative interventions under the auspices of the GRACE consortium have been found to reduce antibiotic prescription rates significantly in patients with LRTIs.[38,39] Importantly, the significant reduction in antibiotic use that occurred in these patients did not compromise patient recovery or satisfaction with the care provided by the clinician, an important driver for change.[38]

Strategy 5: Vaccination as a Key AMS Strategy

Vaccines are a key component in the fight against AMR and a crucial component of a comprehensive AMS campaign.

Bacterial Vaccines

By targeting bacterial pathogens:

- Vaccines directly reduce the need for antibiotics by providing direct protection from a bacterial disease (regardless of whether the bacterium is sensitive to specific antimicrobials).
- Vaccines inhibit the carriage (by decreasing acquisition and colonization) of bacteria, particularly those targeted by the vaccine. Pneumococcal conjugate vaccines (PCV) for example decrease the incidence of URTI such as AOM (including severe or recurrent AOM) and chronic bacterial rhinosinusitis in children,[2,40] with an overall reduction in antibiotic prescriptions.
  - In a study of privately insured children in the US, a 41.9% reduction in antibiotic prescriptions for AOM was demonstrated from 1997 to 2004 after the implementation of the 7-valent PCV (PCV7) immunization program.[41]
  - A recent paper predicted that universal vaccination of children with the 13-valent PCV (PCV13) would reduce AOM by an additional 16.3 million cases in the US compared with PCV7.[42]
- Further reduction in the overall antibiotic consumption occurs due to indirect (herd) immunity. This relates to the prevention/reduction in the transmission of pathogenic bacteria between unvaccinated members of the community.

Thus, one of the best documented examples of the crucial role of vaccination in reducing AMR has been the use of PCVs (PCV7 followed by PCV13) that target the most virulent pneumococcal serotypes, those linked to invasive disease and that are also associated with antibiotic resistance. The introduction in the US and many parts of the world has had a profound and highly significant impact on drug-resistant, invasive pneumococcal disease.[2,14] The most recent data are from South Africa, where Von Gottberg et al[43] demonstrated not only a drastic reduction in penicillin-resistant (−82%) and ceftriaxone-resistant (−85%) pneumococcal infections, for example, but also multidrug resistance disease (−84%) that occurred within only 4 years.

It is crucial that campaigns to increase vaccine uptake should include programs to promote AMS, both of which appear to be synergistic:

- Cohen et al[44] demonstrated that a reduction in antibiotic consumption in the community in conjunction with an increase in PCV uptake had a synergistic effect on the carriage of resistant pneumococcal infections in the cohort studied. Risks for penicillin-nonsusceptible *S. pneumoniae* carriage were as follows: 4.2% for immunized children who had not received antibiotics in the preceding 3 months, 8.6% for immunized children who had received antibiotics, 10.3% for nonimmunized children who had not received antibiotics, and 16.2% for nonimmunized children who had received antibiotics ($P < 0.001$).
- Hicks et al[45] also recently demonstrated that after the introduction of PCV7 vaccination, whereas antibiotic prescribing in US states remained high, the proportion of nonsusceptible IPD due to nonvaccine serotypes also remains high, suggesting that local prescribing practices continue to contribute to local resistance patterns.

Viral Vaccines

In addition to other antibacterial vaccines such as diphtheria, pertussis, *H. influenzae* type b, etc., vaccines against nonbacterial pathogens can also have a direct or indirect effect on antibiotic consumption by reducing the following:

- Viral infections and fever syndromes in which antibiotics are frequently used inappropriately.
- Complications of viral infections (eg, secondary bacterial infection) requiring antibiotics.

In a recent study in Ontario, Canada, the increased use of influenza vaccination after recommendations for universal vaccination resulted in a 64% decrease in antimicrobial prescriptions for influenza-associated respiratory disease.[46] Targeting selected patient groups such as children or postpartum mothers is also beneficial.[2] For example, influenza vaccinations reduced acute respiratory illnesses, febrile episodes, influenza-like illnesses, and health care visits in neonates born to vaccinated mothers by 37.7%, 50.3%, 53.5%, and 41.8% respectively, and also reduced antibiotic prescriptions by 45.4%.[47]

Strategy 6: Covering More Territory to Fight Resistance in the Community

No specific data have been published defining the AMS role of community nurses (or those in hospitals). One randomized controlled study compared nurse with community physician care, and although the focus was not on antimicrobials, the (may be not so) surprising results suggest that nurses would be most suitable for inclusion in a community AMS program.[48] It was found that patients who consulted nurse practitioners were generally more satisfied with their care, consultations were significantly longer, and their patients reported being provided with more information. In addition, there were no notable differences for the other outcomes studied, including the resolution of symptoms, allaying of concerns, and prescribing.

If poor communication with patients or parents lies at the heart of antibiotic abuse for self-limiting and/or viral ARTI, nurses and physician assistants would therefore be ideally suited to decrease antibiotic consumption through informed patient decision making and no or delayed prescription strategies. If adequately trained, they potentially represent a time-efficient and cost-efficient use of resources, particularly in light of the time constraints faced by community clinicians.

Similarly, little or no data exist on the role of community pharmacists. As patients frequently pursue the self-medication route for colds or influenza-like illnesses first, the pharmacist is also well placed to influence the prescribing practice with symptomatic treatment and advice on the self-limiting nature of most ARTIs. They can also reinforce no or delayed prescriptions where applicable. Extending the role of nurses and community pharmacists to include AMS should be investigated and studied, and this should be followed by specific strategies to define their concurrent role in a community AMS program.

Strategy 7: An "Antibiotic License" to Prescribe?

A Cochrane review of interventions designed to improve antibiotic-prescribing practice in ambulatory care concluded that the use of printed educational materials (such as this overview) or audit and feedback alone resulted in no or only small changes in the prescribing practice.[31] In fact, such an intervention does not appear sustainable because after the termination of the audit and feedback, prescribing of antibiotics tend to revert to baseline levels.[49] Interactive educational meetings appeared to be more effective than didactic lectures, whereas educational outreach visits and physician reminders produced mixed results. However, patient-based interventions, particularly the use of delayed prescriptions, effectively reduced antibiotic use as discussed previously, but multifaceted interventions combining physician, patient, and public education in a variety of creative ways were the most successful in reducing inappropriate prescribing.

Ongoing education efforts promoting appropriate antibiotic use among both patients and health care providers with regard to the growing threat of AMR include the CDC's Get Smart: Know When Antibiotics Work Program and the United Kingdom's Royal College of General Practitioners' TARGET Antibiotics Toolkit (Treat Antibiotics Responsibly Guidance, Education and Tools). However, the question remains whether this is enough and whether regulatory authorities should get involved? Studies of US medical school undergraduates and pharmacy students have documented the need for further education regarding AMS, but how do you train qualified clinicians regarding AMS strategies?

The grave threat to the public of extensive-drug resistance and potentially of pan-drug resistance among common community-acquired pathogens may warrant drastic measures such as reeducation with regard to AMS. Although education alone has been shown to be only marginally effective in changing the prescribing practice and also has not demonstrated a sustained impact, it is still considered to be an essential element of any AMS program.[50] Several educational interventions should be considered, which could include an "antibiotic license" for qualified practicing clinicians with the aim of equipping doctors with the appropriate tools to understand, enhance, and increase their acceptance of AMS strategies.[51]

Such "licensing" should preferably be followed by a structured, multifaceted, continuous educational support strategy. In a practice-based, randomized controlled trial that evaluated the effectiveness and costs of a creative and flexible educational program called STAR (Stemming the Tide of Antibiotic Resistance), antibiotic dispensing in the community was reduced.[52] It consisted inter alia of a practice-based seminar reflecting on the practice's own dispensing and resistance data (bug-drug match), multiple online educational elements, and teaching of consulting skills in routine care, specifically time-efficient consultation strategies that empower the patient. Third, as with all forms of licensing, AMS revalidation requirements would have to be determined and specified for all prescribers.

Strategy 8: AMS Governance in Primary Care

Because of the diverse and unique settings in which health care is provided in the community (ie, community or private practice physicians alone or in groups including large managed-care companies), clinicians, despite an awareness of AMS, tend not to be accountable to anyone but themselves. Although many of the core elements of hospital AMS programs such as leadership commitment (eg, appointment of specific staff and ensuring that there is sufficient time to contribute to stewardship activities), accountability (eg, identification of a single leader who will be responsible for program outcomes), and support (eg, organizational improvement) are relevant in the ambulatory setting,[9] empowering such diverse groups to play a crucial role in AMS in the community and involving such prescribers in a sustainable way constitutes a particular challenge.

Gerber et al,[4] however, recently demonstrated that with relatively few resources compared with those of traditional hospital-based programs, the automated use of generic data elements that are increasingly common to all outpatient electronic health records can be utilized in the most effective way to promote AMS. The intervention was performed in a large pediatric primary care network (25 practices in Pennsylvania and New Jersey) and consisted of clinician education along with personalized (tailored) audit and feedback of antibiotic prescription practices to children with ARTIs. This resulted in a significant decrease in the prescription of broad-spectrum antibiotics to children during acute primary care encounters and decreased the use of off-guideline antibiotics for children with pneumonia by 75% one year after the intervention. A pediatrician representative from each practice was specifically chosen to oversee the program and ensure that AMS principles were followed. In fact, it does not have to be a clinician or an infectious disease–trained clinician or pharmacist as other health care and related workers are increasingly tasked with the responsibility of AMS.[53] As stated by Cosgrove et al[53] recently, skills beyond infectious diseases such as an understanding of how to implement change and how to measure the success of a program are critical in the initiation and the maintenance of an AMS program.

Monitoring AMS in Primary Care

If we wish to improve antibiotic use, it is critical to develop the capacity to measure the quality of antibiotic prescription in a community program. Precisely, what quality indicators of antibiotic prescribing means and to whom must first be defined. These indicators should be useful to individual prescribers (eg, patient outcome) rather than just to administrators (eg, acquisition costs), which has been the case historically. Recently, in an effort to create a standardized approach for evaluating the impact of institutionalized AMS programs in the US and Canada, indicators of performance were developed with a focus on antimicrobial consumption, AMR, and very importantly, patient outcomes.[54] However, whereas the optimal metrics to gauge the success of an AMS program in the community are ill defined and need to be investigated, it will most probably similarly involve both the process (eg, determining whether prescribers have the applied diagnostic criteria accurately or whether the recommended agents have been used) and the outcome measures (eg, reduction of AMR, community-acquired *C. difficile* infections, costs, etc.)

Prescribing Drug-Specific Indicators

To date, consumption expressed in either defined daily dose measurement or days of therapy probably best indicates the extent to which prescriptions drive antibiotic resistance, that is, the size of antibiotic pressure. Benchmarking by comparing consumption with other countries or states is an important stimulus to quality improvement. Comparisons allow entities to assess their position in relation to others and identify temporal trends and regional differences, all of which could trigger corrective actions where necessary. If antibiotic prescription dosing and duration data, a requirement for

defined daily dose or days of therapy measurement, are not available, alternative metrics may be used for comparisons.[2,3]

In this regard, significant differences in outpatient antibiotic-prescribing rates have been observed within the US, in particular a large geographical variation in antibiotic use for ARTI for which antibiotics are rarely indicated, especially between the south and the west.[3,30] Judgments about the quality of care made by any metric should, however, be made with caution as patient demographics and case mix may vary and risk adjustments would need to be made.[55]

Prescribing Quality Indicators (PQI)

Perhaps even more relevant than the above, primary care clinicians might prefer disease-specific quality indicators rather than drug-specific indicators for outpatient prescribing. A PQI is a measurable element of prescribing performance for which there is evidence or consensus that can be used to assess the quality and to modify the care provided. Usually, a PQI is defined as the percentage of patients receiving the recommended drug treatment, with the numerator comprising the total number receiving treatment. Such PQIs were recently proposed for the 7 main indications for antibiotic prescribing (AOM, acute URTI, ABRS, acute tonsillitis, acute bronchitis/bronchiolitis, cystitis/other UTIs) and for pneumonia as depicted in Table 4.[7]

An alternative method of evaluating antimicrobial prescription patterns would be for each practice to record the numbers of consultations for ARTI and the proportion of those that resulted in an antibiotic prescription. An age-standardized and sex-standardized consultation ratio and standardized prescription ratio can then be calculated to monitor longitudinal trends or compare practice differences. Lee et al[2] had shown that although the number of ARTI visits in the US decreased by 19%, patients with ARTI visits were more likely to receive an antibiotic in 2010 than in 2000 ($P < 0.001$).

Enhanced measurement of the quality of antibiotic prescribing requires correct and appropriate coding, for example, the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) or 10th Revision (ICD-10). Alternatively, the revised 2nd edition of the International Classification of Primary Care (ICPC-2-R) codes has received increasing world recognition as an appropriate and comprehensive classification for community practice and primary care, and has been used extensively in some parts of the world. However, the link between a diagnostic label or code and the actual disease might not always be reliable. Misclassification will continue to be a major limitation in monitoring success of a community AMS program.

The challenge is to develop and validate disease-specific quality indicators that include quality-of-care metrics while considering other contextual factors. Perhaps this may facilitate greater physician buy-in of AMS recommendations.

TABLE 4. A List of Proposed Disease-Specific Antibiotic-Prescribing Quality Indicators

No.	Title	Acceptable Range (%)
1a	Percentage of patients aged between 18 and 75 y with acute bronchitis/bronchiolitis prescribed antibacterials for systemic use	0-30
1b	1a receiving the recommended antibacterials	80-100
1c	1a receiving quinolones	0-5
2a	Percentage of patients older than 1 y with acute upper respiratory infection prescribed antibacterials for systemic use	0-20
2b	2a receiving the recommended antibacterials	80-100
2c	2a receiving quinolones	0-5
3a	Percentage of female patients older than 18 y with cystitis/other urinary infection prescribed antibacterials for systemic use	80-100
3b	3a receiving the recommended antibacterials	80-100
3c	3a receiving quinolones	0-5
4a	Percentage of patients older than 1 y with acute tonsillitis prescribed antibacterials for systemic use	0-20
4b	4a receiving the recommended antibacterials	80-100
4c	4a receiving quinolones	0-5
5a	Percentage of patients older than 18 y with acute/chronic sinusitis prescribed antibacterials for systemic use	0-20
5b	5a receiving the recommended antibacterials	80-100
5c	5a receiving quinolones	0-5
6a	Percentage of patients older than 2 y with acute otitis media/myringitis prescribed antibacterials for systemic use	0-20
6b	6a receiving the recommended antibacterials	80-100
6c	6a receiving quinolones	0-5
7a	Percentage of patients between 18 and 65 y with pneumonia prescribed antibacterials for systemic use	90-100
7b	7a receiving the recommended antibacterials	80-100
7c	7a receiving quinolones	0-5

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CONCLUSIONS

Considering the frequency of ARTI and the large proportion of antibiotic prescribing attributable to ARTI consultations, these infections represent a high-impact target for AMS programs in ambulatory care. To decrease AMR in the community, it is evident that similar to institutionalized AMS, multimodal approaches are necessary. Reduction of antibiotic prescriptions, combined with the implementation of vaccination programs, probably represents the most efficient strategy. In addition, assuming an antibiotic script is justified for an ARTI and appropriate, dispensing of less selective antibiotic compounds and the use of optimal dosage and duration is required.

Communication with and education of patients is the key. A long-term strategy of multidisciplinary, collaborative, educational programs and interventions at many levels in society are required. For these reasons, community clinicians, nurses, physician assistants, and pharmacists play a pivotal role in ensuring support for initiatives that seek to enhance patient empowerment and informed decision making. Synergy between them might create a whole that is greater than the sum of its parts. However, the success would depend to a large degree on the barriers to change not only among community health care providers but also the public. Tailored interventions to overcome identified barriers to change might be needed to effect change.

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