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## New Societal Approaches to Empowering Antibiotic Stewardship

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Substantial concern regarding the ever-worsening crisis of antibiotic resistance has been raised by the World Health Organization, US Centers for Disease Control and Prevention (CDC), European Centre for Disease Prevention and Control, European Medicines Agency, Institute of Medicine, World Economic Forum, and the US Presidential Advisory Council on Science and Technology. The question is no longer whether to act, but how.

Antibiotic stewardship is the term used to describe efforts to optimize selection of antibiotic therapy. Formal antibiotic stewardship programs are essential to help society address antimicrobial resistance by reducing the estimated more than 50% of antibiotic use that is unnecessary or inappropriate.<sup>1</sup> The US government has recently emphasized the need for implementation of antibiotic stewardship programs at all hospitals.<sup>2</sup> To be effective, antibiotic stewardship programs must incorporate best practices, which include dedicating sufficient resources to the program, appointing a single leader to be accountable for performance, having appropriate antibiotic expertise, implementing action plans, monitoring bacterial resistance, reporting antibiotic usage to staff, and providing education.<sup>3</sup>

However, further improving antibiotic use will require increased accountability and transparency at the societal level.<sup>2</sup> A parallel can be drawn between antibiotic stewardship and infection prevention. Hospitals have been required to have infection prevention programs for many decades. Yet no transformative progress in reducing health care–

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associated infections occurred until society began requiring public reporting of infection rates and linking such rates to pay-for-performance measures. This shift toward greater accountability and transparency in healthcare-associated infections has led hospitals to vest infection control programs with the authority to implement critical improvements. A similar shift could substantially accelerate efforts to improve antibiotic use.

To further reduce antibiotic use, antibiotic stewardship programs require authority to prevent inappropriate prescription of antibiotics. But how will the persistent tension be resolved between societal governance of how medicine should be practiced and the longstanding, appropriate tradition of autonomy of individual practitioners? This tension may be resolved by re-framing the discussion around a single, under appreciated, core principle: antibiotics are unique because they are the only pharmaceutical agents that have transmissible loss of efficacy over time.

Other drug types should work as well in the future as they do today. However, because of the inevitable occurrence and transmission of antibiotic-resistant bacteria from patient to patient, every patient's use of antibiotics affects the future ability of every other patient to use those same antibiotics. Antibiotics are a shared community property or trust, and clinicians, health care organizations, patients, and the public are bound together in the need to protect these drugs from misuse.<sup>4</sup>

The societal imperative not to tolerate wasting this precious community resource was identified in 1945 by Fleming, who noted, "the microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out.... In such a case the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted."<sup>5</sup> However, in the 70 years since, the "evil" has not been averted, and society has not been accountable for misusing antibiotics.

Individual practitioners understandably perceive that restrictions or enforcement beyond advice impinges on the autonomy to practice medicine. However, misuse of antibiotics does not just harm the individual, it has a negative health effect on everyone in society. The indulgence of individual practitioner freedom regarding antibiotic choices therefore must be tempered by the knowledge that inappropriate use of antibiotics affects society at large. Thus, antibiotic stewardship programs must have authority to implement proven strategies to improve antibiotic use, such as prior approval of certain antibiotics, prospective audits to stop or change in appropriate therapy, and implementing time limits to therapy.<sup>3,6</sup> Making data on antibiotic prescribing patterns publicly available will also help support stewardship initiatives just as it has worked to drive reductions in hospital-acquired infections.

Another key issue that threatens to undermine antibiotic stewardship is that regulatory approval of new antibiotics and treatment guidelines that influence antibiotic usage only consider the efficacy and safety of the antibiotics but do not consider fundamental principles of antibiotic stewardship. The approved indication is critical for an antibiotic because it defines the scope of corporate marketing that will drive use of the drug. Similarly, national treatment guidelines typically serve as the basis for formulary decisions, care pathway

standards, expected practices, core measures of care, and reimbursement standards set by hospital regulatory authorities and payers. Expansive indications drive broad use even for antibiotics that should be kept in reserve for resistant infections, difficult-to-treat infections, or both.

For drugs other than antibiotics, appropriate use generally mirrors the way the drug was proven to be effective and safe in clinical trials. In contrast, effective and safe are necessary but not sufficient to define appropriate use of an antibiotic. For example, consider an antibiotic that has a broad spectrum of activity that includes both highly resistant bacteria and also more common susceptible bacteria for which many other antibiotics already exist. Use of such a drug to treat common susceptible bacteria drives resistance to the drug among bacteria that are more difficult to treat and for which no other options are available. Thus, even if the new antibiotic is safe and effective against susceptible bacteria, if it can also be used to treat more-resistant bacteria, its use to treat infections caused by susceptible bacteria would seem inappropriate as a first-line option (but may be appropriate in specific circumstances such as intolerance to or practical inability to use narrower-spectrum agents). Consideration should be given to including such information in prescribing information of indications. This information could be embedded within the electronic health record, making it more readily available to physicians.

One of many tangible examples of this phenomenon is the fluoroquinolones, which are the only oral antibiotics that reliably can be used to treat infections caused by gram-negative bacilli, including antibiotic-resistant bacteria such as *Pseudomonas* and *Acinetobacter*. Routine use of these agents to treat skin, urinary tract, or respiratory tract infections caused by susceptible bacteria, when other treatment options are available, conflicts with fundamental antibiotic stewardship principles. The consequence is selection of resistant bacteria such that fluoroquinolones can no longer be reliably used to treat common infections or infections caused by more resistant bacteria. Yet the fluoroquinolones are approved to treat skin, urinary tract, and respiratory tract infections, and national guidelines recommend these agents to treat such infections, making it difficult for stewardship programs at the hospital level to prevent such use.

Given that antibiotics represent a shared societal trust, the regulatory approval process and national practice treatment guidelines governing use of antibiotics should not be based solely on considerations of efficacy and safety, as they are for all other drugs. Rather, for antibiotics, the regulatory approval process and national practice guidelines should incorporate fundamental principles of antibiotic stewardship, in addition to safety and efficacy of the drug, in defining approved indications and treatment recommendations.

Changing national treatment guidelines to incorporate antibiotic stewardship principles into prioritizing antibiotic options is conceptually simple and should be implemented immediately across all infectious disease areas. Incorporating stewardship principles in to the antibiotic development process is more challenging. Options include incorporating stewardship principles into clinical trial guidances, asking advisory panels to consider stewardship principles in their recommendations, and asking thought leaders working with companies to refine the indications being sought during the development process. Another

key aspect will involve engaging the public. Learned behavior is difficult to change, and for decades, some patients have expected to receive antibiotics for certain conditions.

In 1982, McDermott wrote, “It is not too much to state that the introduction of [antibiotics] has represented a force for change in the 20th century of the same general kind as James Watt’s modification of the steam engine did in the 18th. The crossing of the historic watershed could be felt at the time. One day we could not save lives, or hardly any lives; on the very next day we could do so across a wide spectrum of diseases. This was an awesome acquisition of power.”<sup>7</sup> It is a tragedy with serious societal consequences to continue wasting that awesome power that he and his generation bestowed on medicine.

The crisis of antibiotic resistance continues to worsen. The alternative to meaningful change is a continuation of the problem and entry into a prolonged postantibiotic era. The result will be increased morbidity and mortality from antibiotic-resistant infections and an end to many aspects of modern medical care that are now taken for granted (eg, treatment within intensive care units, complex surgeries, cancer chemotherapy, care for premature infants, organ transplantation). It is time to develop and incorporate new clinical and societal approaches to empower effective and sustainable antibiotic stewardship.

## References

1. Centers for Disease Control and Prevention. [Accessed November 16, 2013] Antibiotic Resistance Threats in the United States. 2013. <http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf>
2. Executive Office of the President. [Accessed January 2, 2015] Report to the President on Combating Antibiotic Resistance. Sep. 2014 [https://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast\\_carb\\_report\\_sept2014.pdf](https://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf)
3. Centers for Disease Control and Prevention. [Accessed January 5, 2016] Core Elements of Hospital Antibiotic Stewardship Programs. 2015. <http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html>
4. Spellberg B. Antibiotic judo: working gently with prescriber psychology to overcome inappropriate use. *JAMA Intern Med.* 2014; 174(3):432–433. [PubMed: 24474306]
5. New York Times. Jun 26. 1945 Penicillin’s finder assays its future; p. 21
6. Dellit TH, Owens RC, McGowan JE Jr, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis.* 2007; 44(2):159–177. [PubMed: 17173212]
7. McDermott W, Rogers DE. Social ramifications of control of microbial disease. *Johns Hopkins Med J.* 1982; 151(6):302–312. [PubMed: 6757513]