

The Future of Antibiotics and Resistance: A Tribute to a Career of Leadership by John Bartlett

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The ways we have developed, used, and protected antibiotics have led, predictably, to our current crisis of rising antibiotic resistance and declining new treatments. If we want to stave off a postantibiotic era, we need to fundamentally change our approach. We need to challenge long-standing assumptions and cherished beliefs. We need to push through the reflexive resistance and excuses (eg, “that’s not how we do things” and “that can’t be done”) that result from challenging established ways. Excuses abound. Action is needed. Ultimately, we need a coordinated national action plan to combat resistance. Herein we discuss 7 tasks and 3 common themes that cut across those tasks, which are necessary to achieve long-term success in dealing with antibiotics and resistance. These principles derive from many years of dialogue with Dr John Bartlett. The field of infectious diseases, and indeed medicine in general, has benefited immeasurably from his remarkable leadership.

Keywords. antibiotics; future; policies; resistance.

National perceptions about antibiotics and resistance have undergone dramatic undulations over many decades, with attitudes shifting back and forth in rapid cycles, with each cycle sadly uninformed by the one before it. The initial availability of antibacterial therapy fundamentally transformed medicine from a diagnosis- and prognosis-focused field to an interventional field in which lives could be routinely saved. As early as 1948, the fate of infected patients had so dramatically improved that initial inklings of hubris arose regarding the potential defeat of bacterial infections [1].

Shortly thereafter, penicillin resistance spread to become a substantial clinical problem, such that, by the 1950s, many of the gains of the prior decade were threatened [2]. In response, investigators and industry discovered, developed, and deployed new antibiotic classes, restoring our overconfidence. By 1962, a Nobel laureate wrote, “One can think of the middle of

the 20th century as the end of one of the most important social revolutions in history, the virtual elimination of the infectious diseases as a significant factor in social life” [3].

Only 3 years later, the pendulum swung back. In 1965, a roundtable of some of the most prominent figures in the history of infectious diseases warned that antibiotic resistance was once again rising and that the pipeline of new antibiotics was waning and was probably insufficient to deal with the threat [4]. Repeating the cycle, industry once again brought along multiple new antibiotics from the late 1960s through the early 1980s, such that the problem of infections was again believed solved. One of the giant figures of 20th century medicine wrote in 1978, “I cannot conceive of the need for . . . more Infectious Disease specialists . . . unless they spend their time culturing each other” [5]. He repeated this sentiment at a keynote address at the annual meeting of the Infectious Diseases Society of America as late as 1985 [6].

Thereafter, the antibacterial pipeline began to dry up. While resistance continued to spread, we no longer had new antimicrobial weapons to deal with the threat. As a result, in 2014, a full 82 years after the first patients were treated with a sulfa antibacterial agent [7], we once again find ourselves at a crossroads in our struggle

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Table 1. Microbes Versus Humans: The Math

Metric	Microbes	Humans	Factor
No. on earth	5×10^{31}	6×10^9	-10^{22}
Mass, metric tons	5×10^{16}	3×10^8	-10^8
Generation length	30 min	30 y	-5×10^5
Time on earth, y	3.5×10^9	4×10^5	-10^4

Reprinted with modification from Spellberg et al [8].

with microbes. It is time to break the cycle of denial and state the plain and simple reality: we will never win a war against microbes; there is no “endgame.”

The math is clear (Table 1). Microbes will never stop adapting to whatever selective pressure we throw at them. As an example of the scope of the problem, recent national data from the United States indicate that among bacteria isolated in intensive care units, 10% of *Klebsiella* spp., 20% of *Pseudomonas aeruginosa*, and an astonishing 50% of *Acinetobacter baumannii* strains are resistant to carbapenems [9]. Furthermore, a 2011 national survey of infectious diseases specialists conducted by the Emerging Infections Network found that more than 60% of specialists had seen a pan-resistant, untreatable bacterial infection within the prior year [10]. In summary, we have learned that antibiotic resistance ranks up there with death and taxes as a third inevitable truth of life.

We will never “win a war” against microbes. Nor should we want to, because we could not live without them. Our normal microbiome is critical for a variety of required physiological and immunological functions, and environmental bacteria are the foundation on which all life on earth exists; only bacteria can fix nitrogen from the atmosphere into organic solids. Our “us versus them” attitude against microbes must change if we are to preserve the future of antibiotic effectiveness.

THE FUTURE OF ANTIBIOTIC RESISTANCE

Disrupting Dogma

The antibiotic resistance crisis is the predictable outcome of how we have developed and used antibiotics since their discovery. If we continue to develop, use, and protect antibiotics for the next 80 years in the same way we have in the past 80, the future of the resistance problem is easy to predict. Resistance will continue to emerge, our treatment options will continue to dwindle, and we will enter a postantibiotic era for an increasing number of infections. If we want to change the future state, and have long-term availability of effective antimicrobial therapy for infections, we need to think disruptively and challenge long-standing and sometimes cherished assumptions.

We have had the honor of working with Dr Bartlett as members of a team affectionately referred to as “Bartlett’s Renegades” to describe specific changes that are necessary to combat antimicrobial resistance [11, 12]. Our purpose here is not to restate those recommendations but rather to provide context for 7 specific tasks and to highlight 3 common themes that cut across all of these tasks.

The first common theme is that clinicians, academicians, and many public health officials have limited control over how medicine is practiced. Our influence is dependent on educating, building consensus, cajoling, and advocating. These necessary efforts will continue with respect to antibiotic resistance. However, we must have the courage to admit our limits. We believe, as Dr Bartlett has phrased it, that it is time to focus on “crossing the divide that separates us from those who own medicine—payors and regulators” (personal communication). We need to engage those who control medicine (and agriculture), help them understand the causes of and solutions to the antibiotic resistance crisis, and help them create interventions that will work long term.

The second theme is the need to move away from policies and procedures that rely exclusively on convincing persons to change their behavior. Physicians are generally well intentioned and seek to help, not harm, their patients. No one goes to work with an intention to misuse or abuse antibiotics. But we are also imperfect beings, subject to fear, confusion, pressure, and mistakes. We need technologies, automation, and economic incentives that will help hard-wire changes to the ways we develop, use, and protect antibiotics and help us overcome the mistakes individuals inevitably will otherwise continue to make.

The third theme is that the time for excuses has passed. New ideas that challenge the establishment have a tendency to generate an equal and opposite resistance that prevents their consideration or adoption. Excuses like, “it’s too hard,” “that’s not the way we do things,” or “it can’t be done,” are easily conjured, but we must push through them. The alternative is to accept a future that is without effective antimicrobial therapy for an increasing number and diversity of infections. We must expand our thinking and aggressively explore new approaches.

7 TASKS

Collect National Data on Antibiotics and Resistance

The first task is to systematically collect and report in real-time national data on antibiotic resistance rates among different pathogens broadly throughout the United States (and ultimately the world). We need similar data on antibiotic use. It is tempting to make excuses—it cannot be done, the scope is too large, the 50 states are too diverse to enable systematically gathered data, it is too expensive—but we know it must be possible.

During the winter we get weekly reports on influenza activity throughout the United States via the coordinated efforts of

hospitals and public health laboratories from across the country. If it can be done for a virus, why not for bacteria? Furthermore, Europe has done it for bacteria, across 26 countries, 5 languages, and multiple cultures. The European Antibiotic Resistance Surveillance Net (EARS-Net) has provided, over 15 years, a living and country-specific record of antibiotic consumption and resistance, updated monthly and yearly. As Dr Bartlett has written, “It seems unacceptable and embarrassing that the United States at present does not have the necessary support to implement” such a system [12].

Stop Abusing Antibiotics in Agriculture

The second task is to reduce unnecessary agricultural antibiotic usage. A staggering 15 million kg (17 000 tons) of antibiotics are used in the United States every year, 80% in agriculture [12]. This level of environmental contamination is simply unacceptable and will inevitably continue to drive resistance. We cannot continue to let industrial excuses prevent society from acting on the moral imperative to preserve antibiotic effectiveness.

Those in opposition try to confound the national dialogue by raising doubts as to whether the massive amounts of agricultural antibiotic use contributes to resistance or by suggesting that banning growth-promotional antibiotics in livestock will drive up the cost of meat production, but it has been well established that agricultural use of antibiotics contributes to resistance in human patients [12]. Excuses about economic disaster or extensive harm to animals are belied by the experience in Europe. For example, Denmark banned growth-promotional antibiotics for livestock 15 years ago and not only experienced no disaster but had a nearly 15-fold increase in hog production after the ban [13]. Excuses abound. Action is needed.

Stop Abusing Antibiotics in Humans

The third task is to modernize approaches to antimicrobial stewardship. The alarm that physicians and patients overuse antibiotics was first raised by Sir Alexander Fleming as early as 1945 [14]. In the 69 years since, a variety of means of stewardship have been devised, but they primarily revolve around devising ways to change human behavior (eg, education, restriction). We need to continue such efforts.

We also need to recognize that inappropriate antibiotic use is an example of the Tragedy of the Commons, which results from tension between what individuals perceive as being to their own short-term benefit weighed against a small collective longer-term harm to society [15]. It is difficult to convince persons to act against what they perceive to be their own benefit, especially in a sustainable way. There are new psychological approaches to overcoming this problem, such as the gentle “nudge” that results from public commitment [16]. Such new approaches merit additional study.

We also need to bring technology to bear. Perhaps the most effective way to reduce inappropriate antibiotic use is to eliminate the diagnostic fear and uncertainty that drives the inappropriate use. The development, implementation, and clinical use of rapid molecular diagnostics can empower providers to withhold antibiotics when no bacterial pathogen is identified. For example, use of rapid strep tests dramatically reduces antibiotic prescriptions in the management of pharyngitis.

Aligning the economics of self-interest with the public interest also can help preserve antibiotic effectiveness. For example, antibiotic usage should be publicly reported across healthcare systems, and possibly across providers, to enable benchmarking of reimbursement from prominent payer sources [11].

Finally, the science of antibiotic usage will advance greatly with additional studies of short-course therapies across disease areas. Clinical trials have consistently showed that shorter courses of therapy are as effective as longer ones [12]. Furthermore, emerging data support tailoring the duration of therapy to normalization of biomarkers for activation of innate immunity (eg, serum procalcitonin levels), as opposed to treating for arbitrary and generally more conservative durations, set forth in guidelines. Ultimately, as pointed out by Rice [17], the inaccurate dogma that patients should continue to take antibiotics to complete their full course even after they feel better should be replaced by a much simpler dogma: “shorter is better.”

Ramp Up Infection Prevention

The fourth task is to modernize approaches to infection prevention. Efforts to improve hand washing rates are critical and must continue. We must also relieve the pressure on hand washing by employing automation and disinfection technology so that disaster does not ensue when individuals forget to wash their hands. We have had self-cleaning ovens for decades—we need self-cleaning hospital rooms. Robotic and automated disinfection technologies are now available for deployment in healthcare settings. Further study is necessary to assess and optimize their real-world efficacy.

Rekindle the Antimicrobial Pipeline and Find New Treatments That Do Not Require Killing Microbes

The fifth and sixth tasks are, respectively, to rekindle antimicrobial discovery and development and to complement antimicrobials with new approaches to treatment of infection that do not require killing the microbe. Examples of latter approaches include disarming pathogens so that they do not cause disease even when they are present (eg, inhibiting synthesis of endotoxin by the bacteria), passively starving microbes of nutrients (eg, iron) so they cannot proliferate in the host, directly modulating the host response to pathogens without attacking targets on the microbes, and protecting the microbiota with probiotics [11].

As Dr Bartlett has said, “The lesson of history is that we need a pipeline” (personal communication, 2008). Three barriers have contributed to the antibiotic market failure in the modern era: scientific, economic, and regulatory. These barriers and ways to overcome them have been discussed at length elsewhere [11, 12, 18, 19]. We emphasize that the solutions will require challenging long-standing dogma (eg, the dogma dating from 1913 that to successfully treat infection one must kill the bacteria [20]).

In addition to scientific innovation, we must employ novel economic approaches that align corporate interest with societal interest. We also need strong leadership at the regulatory level that reflects a practical, patient-centered approach to trial designs and enables international harmonization of regulatory standards. Statistics are important tools to help us arrive at rigorous scientific conclusions. However, statistics must not replace a patient-centered focus. For example, setting the requirement that skin infection studies declare treatments successful if they cause skin lesions to regress by only 20% in size after 3 days of therapy may be statistically desirable [21], but no patient would agree that such a metric reflects a successful treatment outcome.

Develop a Plan

Finally, the seventh task is to develop an organized and coordinated national plan to combat antibiotic resistance. As Dr Bartlett has written, “Antibiotic resistance has been a recognized crisis for 15 years, but most of the proposed interventions in the United States have nibbled at the edge of the problem. The problem will increase unless the United States adopts a national antibiotic resistance plan to deal with all the complex elements” [22]. We need coordinated leadership across diverse government agencies, academia, practitioners, and industry. New government reporting structures are probably required to facilitate such coordination (eg, an undersecretary of antimicrobial resistance reporting to the secretary of the Department of Health and Human Services).

Ultimately, we must cross the line between experts and agencies that have declared that antibiotic resistance is a public health crisis but have no authority to act to fix the problem and the agencies and payers that have the ability to turn medical practice on a dime. Over the years, Dr Bartlett has reminded us that medicine is a business. We need to frame our concerns in a manner that payers and regulators can understand.

CONCLUSIONS

Microbes have been creating and defeating antibiotics for billions of years. Microorganisms are more tempered and judicious in their use of these molecules, perhaps explaining the long-term viability of antibiotics as effective growth inhibitors in nature. In contrast, in just 80 years of clinical use, humans have so abused antibiotics that we threaten their availability

for future generations. Multiple generations of clinicians, scientists, and leaders have attempted to deal with complex forces that drive overuse and misuse of these drugs and the need to continue discovering new ones, but we have not yet achieved long-term solutions. It took billions of years for microbes to get it right. Perhaps 80 years on the scale of human societal evolution is simply not enough time for us to figure out how to optimally handle antibiotics.

Nearly 15 years ago, Nobel laureate Joshua Lederberg wrote, “The future of humanity and microbes will likely evolve as . . . episodes of our wits vs their genes” [23]. With respect to our wits, despite past failings, there is reason for future optimism. The current high frequency of inappropriate antibiotic use could lessen dramatically over the coming decade thanks to major and rapidly evolving scientific advances among diagnostic and biomarker technology, and new policies and research reflecting a better understanding of the psychology driving inappropriate use. Future therapy could consist of some combination of specific antibody, organism-specific bacteriophage, small molecules (or antisense small interfering micro-RNAs) that inhibit specific virulence factors, and drugs that counter antibiotic resistance mechanisms (eg, new β -lactamase inhibitors, and blockade of efflux pumps).

In short, humans will have the tools to behave like bacteria that produce antibiotics. When threatened, the potential could exist for a short course, narrowly focused, customized, treatment package. Such an approach offers the promise of enhanced efficacy and reduced collateral damage in the form of drug-related adverse effects and resistance. Ultimately, long-term success may depend on a complete reconceptualization of our relationship with microbes, so that the eventual goal is to stop seeking their destruction and instead seek to achieve peaceful coexistence.

These principles are the result of innumerable hours of thought and dialogue, in large part driven by Dr Bartlett. No one in our field can claim to have done more to combat resistance, to educate policy makers and regulators, and to promote the principles herein laid out. We are indebted to him in ways that are difficult to describe and defy limit. We are card-carrying members of “Bartlett’s Renegades,” and we call on others to join the movement to preserve and restore the life-saving public resource that is effective antibiotic therapy.

Notes

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