Published in final edited form as:
N Engl J Med. 2013 January 24; 368(4): 299–302. doi:10.1056/NEJMp1215093.

The Future of Antibiotics and Resistance

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In its recent annual report on global risks, the World Economic Forum (WEF) concluded that "arguably the greatest risk … to human health comes in the form of antibiotic-resistant bacteria. We live in a bacterial world where we will never be able to stay ahead of the mutation curve. A test of our resilience is how far behind the curve we allow ourselves to fall."[1]

Traditional practices in infection control, antibiotic stewardship, and new antibiotic development are cornerstones of society's approach to combating resistance and must be continued. But the WEF report underscores the facts that antibiotic resistance and the collapse of the antibiotic research- and-development pipeline continue to worsen despite our ongoing efforts on all these fronts. If we're to develop countermeasures that have lasting effects, new ideas that complement traditional approaches will be needed.

New ideas are often based on the recognition of old truths. Prokaryotes (bacteria) "invented" antibiotics billions of years ago, and resistance is primarily the result of bacterial adaptation to eons of antibiotic exposure. What are the fundamental implications of this reality? First, in addition to antibiotics' curative power, their use naturally selects for preexisting resistant populations of bacteria in nature. Second, it is not just "inappropriate" antibiotic use that selects for resistance. Rather, the speed with which resistance spreads is driven by microbial exposure to all antibiotics, whether appropriately prescribed or not. Thus, even if all inappropriate antibiotic use were eliminated, antibiotic-resistant infections would still occur (albeit at lower frequency).

Third, after billions of years of evolution, microbes have most likely invented antibiotics against every biochemical target that can be attacked — and, of necessity, developed resistance mechanisms to protect all those biochemical targets. Indeed, widespread antibiotic resistance was recently discovered among bacteria found in underground caves that had been geologically isolated from the surface of the planet for 4 million years.[2] Remarkably, resistance was found even to synthetic antibiotics that did not exist on earth until the 20th century. These results underscore a critical reality: antibiotic resistance already exists, widely disseminated in nature, to drugs we have not yet invented.

Thus, from the microbial perspective, all antibiotic targets are "old" targets. Yet since the early 1930s, when Gerhard Domagk and colleagues discovered that chemical red dyes (the sulfonamides) can kill bacteria, the singular arc of antibiotic research and development has been to discover "new" targets to attack in order to kill the microbes. This strategy has saved

countless lives. Ironically, it has also driven the resistance that threatens the very miracle of antibiotics. Ultimately, over centuries or millennia of selective pressure, we will run out of targets, and resistance mechanisms will become so prevalent as to preclude effective clinical deployment of antibiotics.

Promising future strategies to combat resistance can be divided into five categories, each of which requires additional societal investment in basic and applied research and policy activities (see table). These interventions aim to prevent infections from occurring in the first place, to encourage new economic models that spur investment in anti-infective treatments, to slow the spread of resistance in order to prolong the useful lives of antibiotics, to discover new ways to directly attack microbes in a manner that does not drive resistance, or to alter host–microbe interactions in order to modify disease without directly attacking microbes.

Infection prevention eliminates the need to use antibiotics. Traditional infection-prevention efforts must be buttressed by new technologies that can more effectively disinfect environmental surfaces, people, and food. We also need technology that enables intensive health care without requiring the implantation of foreign materials such as plastic or metal (e.g., improved drug delivery by means of the gut, skin, or respiratory mucosa to replace intravenous therapy and regenerative-tissue technology that obviates the need for prosthetic implants). Improvements in population health and health care delivery systems can reduce admissions to hospitals and skilled nursing facilities, thereby reducing infections. Finally, new vaccines hold great promise for preventing antibiotic-resistant infections.

Despite preventive efforts, though, infections will always occur, and we will always need safe and effective therapy for them. The collapse of the antibiotic research- and-development pipeline is the result of both economic and regulatory barriers. The solution is better alignment of economic and regulatory approaches to antibiotic development.[3] For example, public–private partnerships could align the research- and-development focus of industry with unmet medical needs. Also, a new regulatory approach, such as the Limited Population Antibiotic Drug (LPAD) proposal from the Infectious Diseases Society of America, could allow drugs to be approved on the basis of small, relatively inexpensive clinical superiority trials focused on lethal infections caused by highly resistant pathogens.[3] The antibiotic would receive a very narrow label, helping to protect against overuse. Thus, the LPAD would simultaneously empower antibiotic stewardship and provide economic incentives for investment by reducing the cost of clinical trials and creating the conditions for a pricing premium.

In a 1945 interview with the *New York Times*, Alexander Fleming called for stopping the overuse of penicillin in order to slow the development of resistance. Nearly 65 years later, in 2009, more than 3 million kg of antibiotics were administered to human patients in the United States alone; in 2010, a staggering 13 million kg were administered to animals. The majority of the animal antibiotic use was meant to promote the growth of livestock. We cannot confront resistance unless we stop exposing the environment to massive quantities of antibiotics and their resulting selective pressure. Promising but untapped strategies for slowing resistance include transparent, public reporting of data on antibiotic use across medical centers and individual providers to enable national benchmarking and reimbursement modification, development and use of rapid diagnostic and biomarker tests that empower providers to withhold antibiotics from patients who don’t have bacterial infections and shorten antibiotic courses for those who do, elimination of antibiotic use for the promotion of growth in animals, bioengineering efforts to degrade antibiotics in sewage so as to avoid environmental contamination and selection for resistance, and conducting of studies to determine the shortest effective course of therapy for common infections.

A more innovative form of stewardship is the development of therapies that do not drive resistance. For example, the infusion of monoclonal antibodies (a modern advance on serum therapy, which is more than a century old) or white cells that attack microbes holds promise for treating infections. Finally, what if we were able to treat infections without seeking to kill the microbe? Casadevall and Pirofski's damage-response framework of microbial pathogenesis underscores the concept that clinical signs, symptoms, and outcomes of infection result as much, or more, from the host response to the microbe as from a direct effect of the microbe itself.[4] Thus, we should be able to treat infections by attacking host targets rather than microbial targets. Indeed, recent preclinical research demonstrates that we can successfully deploy therapies that either moderate the inflammatory response to infection or that limit microbial growth by blocking access to host resources without attempting to kill microbes. For example, an antibiotic of a novel class (LpxC inhibitors), which blocks synthesis of gram-negative lipopolysaccharide, could not kill *Acinetobacter baumannii* but prevented the microbe from causing disease in vivo.[5] Other examples include antiinflammatory monoclonal antibodies, probiotics to compete with microbial growth, and sequestration of host nutrients (e.g., iron) to create a resource-limited environment in which microbes cannot reproduce. Such strategies require clinical validation but have the potential to reduce resistance when pursued in concert with traditional antibiotic therapy.

The converging crises of increasing resistance and collapse of antibiotic research and development are the predictable results of policies and processes we have used to deal with infections for 75 years. If we want a long-term solution, the answer is not incremental tweaking of these policies and processes. Novel approaches, based on a reconceptualization of the nature of resistance, disease, and prevention, are needed.

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Table 1

New Interventions to Address the Antibiotic-Resistance Crisis.*

Intervention	Status
Preventing infection and resistance	
"Self-cleaning" hospital rooms; automated disinfectant application through misting, vapor, radiation, etc.	Some commercially available but require clinical validation; more needed
Novel drug-delivery systems to replace IV catheters; regenerative-tissue technology to replace prosthetics; superior, noninvasive ventilation strategies	Basic science and conceptual stages
Improvement of population health and health care systems to reduce admissions to hospitals and skilled nursing facilities	Implementation research stage
Niche vaccines to prevent resistant bacterial infections	Basic and clinical development stage
Refilling antibiotic pipeline by aligning economic and regulatory approaches	
Government or nonprofit grants and contracts to defray up-front R&D costs and establish nonprofits to develop antibiotics	Models in place, expansion needed in number and scope; new nonprofit corporations needed
Institution of novel approval pathways (e.g., Limited Population Antibiotic Drug proposal)	Proposed, legislative and regulatory action needed
Preserving available antibiotics, slowing resistance	
Public reporting of antibiotic-use data as a basis for benchmarking and reimbursement	Policy action needed to develop and implement
Development of and reimbursement for rapid diagnostic and biomarker tests to enable appropriate use of antibiotics	Basic and applied research and policy action needed
Elimination of use of antibiotics to promote livestock growth	Legislation proposed
New waste-treatment strategies; targeted chemical or biologic degradation of antibiotics in waste	One strategy approaching clinical trials
Studies to define shortest effective courses of antibiotics for infections	Some trials completed
Developing microbe-attacking treatments with diminished potential to drive resistance	Preclinical, proof-of-principle stage
Immune-based therapies, such as infusion of monoclonal antibodies and white cells that kill microbes	
Antibiotics or biologic agents that don't kill bacteria but alter their ability to trigger inflammation or cause disease	
Developing treatments attacking host targets rather than microbial targets to avoid selective pressure driving resistance	Preclinical, proof-of-principle stage
Direct moderation of host inflammation in response to infection (e.g., cytokine agonists or antagonists, PAMP receptor agonists)	
Sequestration of host nutrients to prevent microbial access to nutrients	
Probiotics that compete with microbial growth	

* IV denotes intravenous, PAMP pathogen-associated molecular pattern, and R&D research and development.