CHAPTER 8

Next **Steps**

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When you want to cook a frog, they say, don't throw it into boiling water—it will only jump out. Instead, place the frog in tepid water and, ever so slowly, increase the heat.

Much like the frog that is unaware that it is being cooked, our reaction to the antibiotic resistance problem has been to wait for a crisis before responding—but the frequency of resistance has been increasing slowly and steadily. When resistance reaches crisis levels, it may be too late. Meanwhile, thousands of people continue to die or suffer from a cause that does not show up on any death certificate. A crisis need not be a sudden, uncontrollable outbreak of a resistant pathogen. Many believe that the emergence and spread of deadly infections like community-acquired MRSA already constitutes a crisis. Perhaps we will see drug-resistant pneumonia and MRSA in large numbers of patients afflicted with avian influenza, or perhaps the prevalence of *Clostridium difficile*, which by itself is not a drug-resistant pathogen but whose survival and proliferation have been facilitated by widespread antibiotic use, will reach epidemic proportions. Many deaths during the influenza epidemic of 1918 are thought to have been caused by untreatable bacterial infections—bacterial pneumonia, and not just pneumonia caused by streptococci but also staphylococcus-associated pneumonia. The combination of today's highly virulent MRSA with an outbreak of avian flu could have devastating consequences.

It is perplexing why so little attention is paid to finding solutions to the antibiotic resistance problem when it has such catastrophic potential. One is reminded of the years of neglect that led to the failure of the levees and the destruction of New Orleans during Hurricane Katrina. Even if policymakers are not motivated to act in preparation for such a medical eventuality, a more immediate concern—the increasing costs of health care and the consequent difficulty of bringing large numbers of uninsured people under the umbrella of pooled-risk financing—may spur action.

Regardless of when policy action is forthcoming, policymakers will need a playbook of carefully considered ideas. Our objective in writing this report has been to sketch the outlines of such a playbook, notwithstanding that more basic science and policy research may be needed on some of the ideas. A summary of policy actions, their pros and cons, and the actors involved is presented in Table 8.1.

This report has outlined a plan to change incentives to address antibiotic resistance in health care, not just in the immediate term (such as by changing Medicare reimbursement rules, subsidizing hospital infection control and diagnostics, or imposing stricter state standards for reporting hospital infections) but also in the longer term, to ensure a sustainable and affordable supply of antibiotics into the foreseeable future. After all, new drugs take at least 10 to 15 years to develop, and policies changing how antibiotics are used will take years to be implemented and have an effect on resistance.

Main messages

Our main conclusion is that antibiotic resistance is an important and growing challenge to health and health care systems. It raises the cost and lowers the effectiveness of health care in the United States and will have potentially serious consequences if not addressed now. Although the underlying causes appear to be, broadly speaking, overuse of antibiotics and inadequate hospital infection control, the deeper reasons relate to incentives. A policy solution will have to address incentives that affect how individuals, physicians, institutions, and pharmaceutical companies demand, use, and produce antibiotics. The changes in the behavior of humans must, in turn, effectively change the microbial world. These issues are not unique to antibiotics, however. Managing incentives is a challenge with the use of any resource, whether oil or fish, and the lessons learned in those contexts can be valuable here.

We have critically and objectively evaluated various policy options to address antibiotic resistance, and on the basis of this evaluation, we make five general observations about the policy solutions.

1. Policy solutions tend to focus either on changing incentives for how individual actors deal with antibiotic use or infection control (by changing how hospitals get reimbursed for hospital acquired infections, for instance), or on exercising federal or state government oversight (by requiring reporting of hospital infections, for instance). This report identifies the incentive problems associated with the latter type of regulatory policy and generally finds greater support for the former, the incentive-altering policies. Government action is needed but is more likely to be effective when focused on changing incentives (say, for new drug development) than on just mandating standards.

2. Much of the public debate on dealing with antibiotic resistance has dealt with lowering antibiotic use. There is a need to broaden the discussion of policy alternatives beyond simply educating health care providers to reduce antibiotic use. We know that antibiotic use leads to resistance, but it is unclear to what extent education alone can lower antibiotic use and how much this will slow resistance. Dealing with resistance will require careful rethinking and restructuring of the incentives for infection control within hospitals and vaccination policies in the community.

Lowering antibiotic use involves a tension between what is good for the individual patient—important from the prescriber's perspective—and what is good for the rest of society. Resolving this tension between sound medicine and sound public health is one feature of the problem; preventing the spread of infections and using a diversity of antibiotics, in contrast, are policy options that do not require balancing the individual and the public good.

3. Our policy goal should go beyond minimizing resistance, since that may be best achieved by not using antibiotics at all. Antibiotics serve a useful social purpose, but we have to balance the benefits of their use to individuals and to the rest of society (by lowering the chance that one patient's infection will spread to others) against the costs that are largely borne by society in the form of lower future effectiveness.

4. Successful policy solutions should incorporate an understanding of ecology and evolutionary biology. A sustainable antibiotics policy must recognize that drug resistance and new drug development are two facets of the ongoing process of coevolution between humans and microbes. New drugs can provide a temporary solution only until microbes catch up through the process of evolution. Moreover, new targets for antibiotics may be increasingly difficult to find, and there may be cross-resistance between old and new antibiotics. Antibiotic efficacy is a renewable resource, but only on very long time scales. Meanwhile, policy must focus on extending the useful therapeutic life of existing drugs, and this requires a change in human behavior that leads to change in microbial communities. To be effective, policy must consider population biology and microbial community ecology, and this will require new basic research, including research to identify microbial interactions that can be exploited to manage resistance.

5. We need to integrate our thinking of supply-side and demand-side policy objectives. Efforts to protect new antibiotics from drug resistance by keeping them on the sidelines potentially reduce incentives for new drug development by the pharmaceutical industry. Similarly, having a supply of new antibiotics that are fundamentally different from existing drugs expands our options by lowering selection pressure for resistance to evolve to existing drugs. Solutions that focus only on the supply side or only on the demand side may be less effective in the long term than solutions that are mindful of the interrelatedness between how we use existing antibiotics and incentives to produce new antibiotics.

Empirical research can inform our current understanding of which policy solutions are most likely to improve sustainable antibiotic use. Much of the discussion of ways to change incentives for patients, physicians, and other agents to behave optimally with respect to resistance is based on a theoretical understanding of economics and the law. However, there are knowledge gaps that prevent progression to an implementation stage.

Future policy research and dialogue

This report provides an objective evaluation of various policy alternatives, but the assessment is challenged by important gaps in our understanding of these alternatives. Our call for more data and research is not just a nod to the established norm; our goal is to provide the biological, medical, and economic analysis that can directly inform policy decisions. Although we have evaluated incentives and motivating factors from a theoretical perspective, policymakers will undoubtedly need stronger evidence to act on such policies as subsidizing infection control in hospitals. Policy research is needed to empirically test, using pilot studies and model-based approaches, the effects of some of the more immediate solutions related to changing prescribing behavior and

hospital infection control. Policy pilots will be important for determining the impact of greater cost-sharing for antibiotic prescriptions and patient outcomes, and for calculating the effect of subsidizing substitutes for antibiotics that relieve symptoms, thereby reducing antibiotic use. These studies will be useful in understanding what proportion of antibiotic use can be avoided without harming patient outcomes. Modeling will have to be used for other approaches, such as the overall economic impact of antibiotic use and better reporting of resistance levels in hospitals. A natural outcome of this research will be prioritizing policy changes and identifying those most likely to have a significant impact on resistance.

Going forward, it is important not just to engage in policy research but also to reconcile diverse viewpoints among the broad range of stakeholders, ranging from consumer groups and physicians to pharmaceutical companies and health insurers. All of these stakeholders are committed to a long-term future for antibiotics: after all, no one is better off with drugs that do not work. However, specific policy proposals may be more or less palatable to different groups, and it will therefore be important to engage multiple stakeholder groups, such as the Interagency Task Force on Antimicrobial Resistance, the Infectious Diseases Society of America, the Academy of Managed Care Pharmacy, the American Hospitals Association, and the Joint Commission on Accreditation of Health care Organizations, in an expanded, multidisciplinary consultation process to develop consensus around policy solutions that will have a significant impact on how we use and develop antibiotics.

CONCLUSION

At this time, death from a drug-resistant pathogen, although increasing in frequency, is not yet a concern for most Americans. Many infections that are resistant to common antibiotics typically respond to other, more expensive drugs. However, running out of the cheapest antibiotics is somewhat like running out of oil. Just as oil is relatively cheap and convenient but not our only energy source, so generic antibiotics are inexpensive and available but may not be the only way to treat infectious diseases. Losing drugs that cost pennies a dose and moving to more expensive antibiotics, the newest of which can cost thousands of dollars, can have a profound impact on the health care system as a whole and especially on the poor and uninsured, who are most likely to have to pay directly for their care.

Nevertheless, the time may come when even our most powerful antibiotics will fail. The proposals in this report are meant to offer a guide to policy and research to address this crisis now, rather than waiting until the pressure on policymakers to act —even in the absence of information—is unavoidable. The proposals in this report are meant to offer a guide to prepare for and respond to such a crisis, when there will undoubtedly be far greater pressure on policymakers to act. The ultimate goal should be to develop and implement policy solutions that will ensure the sustainability of antibiotic effectiveness for the next hundred years.

TABLE 8.1 EXTENDING THE CURE: SUMMARY OF POLICY OPTIONS

POLICY	DESCRIPTION	ACTORS	PROS	CONS
CONTROLLING ANTIBIOTIC USE IN HOSPITALS AND OUTPATIENT SETTINGS				
Increase cost-sharing for prescriptions	• Increase copayments • Restrict prescribing through formularies • Impose delay for fulfillment of some prescriptions for certain infections	• Insurance companies • Pharmacies • State and federal governments	• Patients will use fewer antibiotics	• May not distinguish between "appropriate" and "inappropriate" use
Use public information campaigns	• Educate physicians and patients to discourage inappropriate prescribing	• Doctors (professional societies) • Patient and consumer groups • State and federal government	• Is inexpensive and simple to implement	• May not yield sufficiently large or permanent reductions in use
Restrict prescribing by physicians	• Require preapproval for some or all antibiotics • Restrict ability of physicians to prescribe antibiotics	• Doctors and hospitals • State and federal governments	• Circumvents current lack of incentives to reduce inappropriate prescribing	• May inhibit patient-physician relationship • May discourage appropriate antibiotic use
Change prescribing patterns in hospital and outpatient settings	• Monitor and present feedback of prescribing patterns compared with peers • Use pay-for-performance measures	• Professional medical associations • Hospitals	• Creates incentives, since physicians care about their reputation and performance	• May discourage all antibiotic use unless feedback distinguishes between appropriate and inappropriate use
	• Conserve new and powerful antibiotics for cases where first-line drugs do not work	• Professional medical associations • CDC • Hospitals	• Maintains viability of new antibiotics longer	• Increases resistance to first-line drugs • Is inefficient from ecological standpoint because diversity of antibiotics may be helpful • Decreases incentive to develop new antibiotics
	• Switch from broad-spectrum to narrow-spectrum antibiotics	• Doctors	• Reduces opportunities for resistance to arise	• Few rapid tests to determine pathogen are available • Doctors have few incentives to use narrow-spectrum drugs • Is difficult to switch from broad- to narrow-spectrum drugs once therapy has begun • Pharmaceutical industry has few incentives to develop narrow-spectrum antibiotics
	• Cycle or rotate drugs	• Doctors and hospitals	• Ecological models suggest this may reduce risks of resistance	• Has not yet been validated in limited trials • Could be costly to implement • Resistance may reemerge rapidly when drug is reintroduced • There may not be enough antibiotics for rotation in each case

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TABLE 8.1 EXTENDING THE CURE: SUMMARY OF POLICY OPTIONS (CONTINUED)

POLICY	DESCRIPTION	ACTORS	PROS	CONS
Change prescribing patterns in hospital and outpatient settings (continued)	• Use two or more antibiotics in combination	• Doctors (professional societies)	• Ecological models suggest this may be effective at slowing down evolution of resistance	• Empirical work has not yet validated many combinations • May compound side effects
	• Employ antibiotic heterogeneity (concurrent use of multiple antibiotics on different patients)	• Doctors (professional societies)	• Ecological models suggest this may be effective at slowing down evolution of resistance • Heterogeneity may already be at work since not all patients receive same antibiotic	• Multiple antibiotics may not always be available to treat all conditions
	• Increase doses while shortening length of therapy	• Doctors	• May reduce risks of resistance	• Still leaves long tail for recrudescence
Provide substitutes	• Promote antibiotic substitutes (e.g., cold packs) in cases where antibiotics are not necessary (e.g., flu) • Shift some remedies from prescription to over the counter • Rethink limited access to pseudoephedrine	• Managed-care organizations • Insurance companies • State and federal governments	• Simple, does not require major changes, lets physicians reduce antibiotic use without reducing patient satisfaction	• Substitutes lack effectiveness • Impact on antibiotic use has not been widely studied
Impose tax, quota, or permit	• Tax antibiotic use either generally or selectively	• State and federal governments	• Creates strong incentive to reduce use	• Does not differentiate between appropriate and inappropriate use • Insurance shields intended targets from tax burden
Improve diagnostic accuracy	• Improve diagnostic tests • Improve decision rules on when to use antibiotics	• Doctors (professional societies) • Hospitals • Medical schools • State and federal governments	• Delays drug therapy until need for antibiotics is certain • Encourages use of narrow-spectrum drugs when appropriate • Decision rules are inexpensive and can easily be incorporated into clinical therapy	• Decision rules lack specificity • Some diagnostic tests are expensive and invasive
Research novel ecological approaches	• Test all novel approaches	• NIH • Drug companies	• Many ecological strategies (at both population level and patient level) would use existing antibiotics more effectively	• Who should bear cost of developing these strategies is not clear
	• Explore probiotics ("good bacteria")	• Doctors • Drug companies	• Can be used to fill niche left by antibiotic use	• Public health value of probiotics is uncertain and not well studied
	• Employ bacteriophages ("bacteria eaters") or other biological control agents	• Drug companies	• Bacteriophages can attack and adapt to resistant bacteria and reduce need for antibiotics	• Approach is largely speculative • Bacteriophages may themselves cause toxicity
	• Interfere with bacterial quorum sensing (which facilitates invasion of host)	• Drug companies	• Could prevent bacteria from "attacking" or cause bacteria to "attack" prematurely	• May not work for all bacteria • May have side effects on helpful bacteria • Feasibility is unknown

POLICY	DESCRIPTION	ACTORS	PROS	CONS
HOSPITAL INFECTION CONTROL				
Clear colonizing infections in incoming patients	• Use alternative antibiotic to clear resistant colonized bacteria in patients susceptible to infection	• Doctors (professional societies) • Hospitals	• Reduces the number of antibiotic resistant infections	• Resistance to alternatives may develop
Employ surveillance and patient isolation	• Screen all patients on admission (active surveillance) and isolate patients who test positive	• Hospitals	• Reduces likelihood of antibiotic-resistant pathogens entering hospital • Reduces chances of transmission	• Is costly and time consuming • Stigmatizes infected patients • Does not completely eliminate possibility of transmission
	• Screen only patients at risk (selective active surveillance): those who were recently hospitalized or had previous resistant infections	• Hospitals	• Reduces likelihood of antibiotic-resistant pathogens entering hospital • Is less costly than screening everyone	• Is costly and time consuming • Requires electronic medical records
Reduce transmission by health care workers	• Reduce patient cohorting (number of patients seen by each nurse)	• Hospitals • Health care workers • Doctors	• Could reduce transmission	• Is costly and difficult to implement and enforce
	• Improve hygiene through education (on hand washing, gloves, gowns)	• Hospitals	• Could reduce transmission	• May require installation of hand-washing stations • Incentives to follow guidelines are lacking • Long-term impact of interventions is unclear
	• Improve hygiene through pay-for-performance measures (such as for achieving certain target rates for hand washing)	• Hospitals	• Could change incentives for health care workers and doctors	• May require installation of hand-washing stations • Effect of changing incentives may wear off
Reduce transmission by patients and visitors	• Improve cleaning of visitors' and patients' rooms	• Hospitals	• Removes pathogens, reducing likelihood of transmission • Does not affect clinical practice	• Is expensive but may be cost-effective if carried out in many or all health care institutions
Promote regional cooperation	• Enforce regional cooperation and information sharing to improve hospital infection control at regional level	• Hospitals • State and local governments	• Ensures coordinated infection control • Reduces free-riding by individual facilities	• Hospitals may not cooperate • May be difficult and costly to ensure cooperation
Require hospital infection and resistance reporting	• Require hospitals to report levels of hospital-acquired infections and resistance	• Hospitals • State and federal governments	• Increases transparency • Creates incentive to reduce levels of infection	• Creates disincentive to monitoring among hospitals with high levels of infection • Creates incentive to cherry-pick patients • May encourage lawsuits by patients with hospital-acquired infections • Is difficult to enforce

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TABLE 8.1 EXTENDING THE CURE: SUMMARY OF POLICY OPTIONS (CONTINUED)

POLICY	DESCRIPTION	ACTORS	PROS	CONS
Change hospital incentives	• Link hospital reimbursement to levels of infection	• Hospitals • Insurance companies	• Creates incentive to reduce levels of infection to get full reimbursement	• Is difficult to implement • Creates incentive to cherry-pick patients
	• Examine legal avenues for responding to resistance	• Lawyers • Hospitals	• Creates incentive to reduce levels of infection to avoid medical malpractice lawsuits	• Creates disincentive to monitor levels of infection • Legal system may be inappropriate and expensive for determining medical causation • Is politically infeasible because of pushback from providers
	• Consider impact of infections on hospital budgets and organizational structure	• Hospitals • Medical research institutions • Government agencies	• Multidisciplinary research could identify organizational issues that reduce hospital incentives to conduct surveillance	• Actors are nonspecific • Mandate is unclear
	• Include infection control in hospital accreditation and health care quality ratings	• Hospitals • JCAHO • Health care quality organizations (e.g., Leapfrog)	• Coverage would be comprehensive • Quality indicators are increasingly important in health care purchasing decisions	• JCAHO monitors only hospital protocols, not levels of infection • Current process is designed to catch egregious violators of medical practice • Infections are only one consideration in determining quality of health care facility
ROLE OF GOVERNMENT				
Incentives to encourage development of new antibiotics	• Fund basic scientific research to identify new organisms	• NIH	• Reduces cost of creating new antibiotics	• Introduces issues of patent ownership and royalties
	• Speed up approval of antibiotics	• FDA	• Reduces cost and increases return from creating new antibiotics	• Safety may be traded off for speed
	• Increase financial incentives for companies developing new antibiotics	• Congress	• Increases incentive for pharmaceutical companies to create new antibiotics	• Is costly • Does not solve the common property problem (many firms exploiting the same pool of effectiveness) • Does not encourage innovation
	• Tie financial incentives for companies to efficacy of drug	• Congress	• Gives pharmaceutical companies incentive to maintain efficacy of their drugs	• Appropriate standards for efficacy must be developed • Is costly
	• Create new agency to fund research	• Congress • Proposed Biomedical Advanced Research and Development Agency • Other government agency	• Lowers cost of creating new antibiotics • Could solve common property and innovation problems through oversight	• Government may not be best positioned to pick winners • Is costly

POLICY	DESCRIPTION	ACTORS	PROS	CONS
Make federal government steward of antibiotic effectiveness	• Create separate agency within FDA to handle antibiotic effectiveness	• FDA • Congress	• Empowers FDA to better control antibiotics • Provides greater financial support for federal antibiotic stewardship	• May require congressional authorization
	• Pass comprehensive legislation to protect antibiotic effectiveness	• Congress	• Recognizes vital national interest in effectiveness of antibiotics • Funds programs to help conserve effectiveness of existing drugs and support investments in new drugs • Coordinates actions to manage antibiotic effectiveness and develop new antibiotics	• Congressional action to protect natural resources has mixed track record
	• Mandate use of pneumococcal vaccine	• State and federal governments	• Lowers rates of infection and thus use of antibiotics	• Vaccine is currently expensive
	• Promote and subsidize best practices to lower hospital infections and resistance	• Medicare • Medicaid	• Makes better use of hospital resources	• Is expensive • Mandate to do this is unclear
	• Facilitate innovation by conducting field experiments	• Medicare • Medicaid	• Creates significant societal benefits through large-scale experiments to slow evolution of resistance	• Is expensive • Mandate to do this is unclear
	• Require broad infection control programs as condition of participation	• Medicare • Medicaid	• Benefits all patients	• May deny coverage to segment of population
	• Require specific techniques to qualify	• Medicare • Medicaid	• Improves care for all patients • Establishes standard of care for medical malpractice suits	• May deny coverage to segment of population
	• Create codes (hospitals' diagnosis-related group and physicians' common procedure terminology) to track resistant infections and prescribing patterns	• Medicare • Medicaid	• Creates transparency • Provides more data on problem	• Is difficult to change codes • Hospitals may engage in "creative" coding

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TABLE 8.1 **EXTENDING THE CURE: SUMMARY OF POLICY OPTIONS** (CONTINUED)

POLICY	DESCRIPTION	ACTORS	PROS	CONS
Change patent and antitrust laws to alter incentives for pharmaceutical companies to conserve anitbiotic effectiveness	• Allow infinite patents for antibiotics	• Congress	• Increases incentives to develop antibiotics and maintain their efficacy	• Patent law is intended to encourage innovation, not solve commons problem
	• Define patent law for antibiotics over functional resistance groups	• Congress	• Reduces likelihood of resistance arising to classes of drugs under competing patents • Increases incentive to maintain efficacy of antibiotics	• Reduces incentives for companies to create new antibiotics in functional resistance groups they don't own
	• Grant *sui generis* rights over antibiotics	• Congress	• Reduces number of competing drugs in same functional group	• Creates issue of ownership of rights • Generic drug makers may protest
	• Relax antitrust law	• Congress	• Allows patenting of functional resistance groups	• Is politically difficult • Loss of efficiency may be great
	• Harmonize property rights and antitrust laws across countries	• International treaty organizations (such as WTO)	• Transcends national boundaries for this international problem	• Other countries cannot be forced to comply
	• Create wildcard patent extension (for developer of antibiotic to use on existing patent or sell to another company)	• Congress	• Increases incentive to develop new antibiotics	• Is costly • May raise objections from other drug makers

CDC = Centers for Disease Control

FDA = Food and Drug Administration

NIH = National Institutes of Health

JCAHO = Joint Commission on Accreditation of Health care Organizations

WTO = World Trade Organization