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By Aaron S. Kesselheim and Kevin Outterson

Fighting Antibiotic Resistance: Marrying New Financial Incentives To Meeting Public Health Goals

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ABSTRACT **The world faces a worsening public health crisis: A growing number of bacteria are resistant to available antibiotics. Yet there are few new antibiotics in the development pipeline to take the place of these increasingly ineffective drugs. We review a number of proposals intended to bolster drug development, including such financial incentives for pharmaceutical manufacturers as extending the effective patent life for new antibiotics. However, such strategies directly conflict with the clear need to reduce unnecessary antibiotic prescriptions and could actually increase prescription use. As an alternative, we recommend a two-prong, "integrated" strategy. This would increase reimbursement for the appropriate, evidence-based use of antibiotics that also met specific public health goals—such as reducing illness levels while limiting antibiotic resistance.**

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Rising rates of antibiotic resistance have become a clear public health crisis.[1] The trend is not limited to the United States but is a worldwide problem—so much so that the World Health Organization considers antibiotic resistance an emerging threat to global stability.[2]

The issue captured headlines in 2007 when Andrew Speaker, a U.S. attorney who flew to Europe for his wedding and honeymoon, potentially exposed hundreds of international travelers to extensively drug-resistant tuberculosis. That form of TB is resistant to first- and second-line drugs.[3]

Over the past two decades, hospitals and other health care institutions have reported more infections that are not treatable by standard therapies.[4,5] Community-acquired infections have also demonstrated escalating patterns of antibiotic resistance. For example, the frequency of community-acquired methicillin-resistant *Staphylococcus aureus* increased more than sevenfold from 1999 to 2006.[6]

Resistant microorganisms have implications for individual patients as well as for health care systems. Patients who acquire such infections are at increased risk for death and disease.[6] Such patients can more than double inpatient hospital costs[7] and account for increased outpatient treatment costs[8] and spending on long-term care.[9]

In recent years, a call to arms has arisen from physicians,[10] public health organizations, governments, and leading academic groups such as the Infectious Diseases Society of America[11] and the Alliance for the Prudent Use of Antibiotics.[12] Many proposals being offered to address the issue of increasing antibiotic resistance emphasize the need for additional incentives to develop new generations of more powerful drugs.

In this paper we review the proposals. We also argue that without an integrated focus on both producing new drugs and making careful and more limited use of existing ones—a strategy called "conservation"—the world will not be able to develop drugs fast enough to get ahead of the resistance problem. We propose that one effective way to achieve this focus would be to tie reimbursement for antibiotics more directly to

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objective evidence of appropriate prescription rates and positive public health outcomes.

Background: The Problem Of Antibiotic Resistance

When penicillin was first used in the United States in 1942, physicians were optimistic about the ability of modern medicine to defeat deadly microorganisms.[13] However, shortly after that came the first report of penicillin-resistant *Staphylococcus*.[14] Since then, researchers have uncovered many biological bases for resistance to antibiotics, including naturally selected genetic mutations in bacteria, the passage of mutations between species, and the decrease in nonpathogenic species of bacteria that allowed deadly microorganisms to flourish.[15]

Societal factors accelerate the spread of resistance. Undertreatment through suboptimal doses or inadequate treatment durations—for example, when a patient does not complete a prescribed course of antibiotics—leads to resistant strains of disease-causing microorganisms. Resistance is also encouraged by unnecessary treatment of viral or noninfectious diseases with antibiotics and the use of broad-spectrum drugs in patients whose infections could be treated with more-targeted drugs.

The misuse of antibiotics in these ways is unfortunately common. Physicians may not be aware of or adhere to clinical practice guidelines for the proper use of drugs.[16,17] Patient factors, such as demand for antibiotics in inappropriate clinical situations, contribute to the use of unnecessary prescriptions.[18]

Pharmaceutical manufacturers also play a role, through marketing campaigns aimed at increasing sales. For example, in 2005 Pfizer was warned by the Food and Drug Administration (FDA) that its "misleading promotion" of linezolid (Zyvox) as a treatment for a wide range of methicillin-resistant *Staphylococcus aureus* (MRSA) infections "poses serious public health and safety concerns because of its potential to result in inappropriate use." The FDA concluded that the clinical trial data did not support linezolid's use for those conditions.[19]

Separately, Pfizer has settled a case in which it was charged with promoting the use of the macrolide antibiotic azithromycin (Zithromax) to treat types of infections for which the drug was known to have limited efficacy. Court documents alleged that the company's motivation was to "keep sales for Zithromax consistent over the year."[20]

Efforts To Control Antibiotic Resistance

As resistance rates among microorganisms have risen, so have concerns about whether enough new antibiotics are being developed. The Infectious Diseases Society of America reported that the largest pharmaceutical companies produced only five systemic antibacterial agents during 2003–7.[21] FDA approvals in general have declined in recent years, but given that resistance is a more acute public health threat for infectious diseases than for other medical conditions, a vibrant pipeline of new antibiotics may be more critical than the pipeline of other drugs—such as a new proton-pump inhibitor for acid reflux, or another statin to treat elevated cholesterol.

One industry leader has argued that antibiotic development has slowed because the "low-hanging fruit" has already been picked, and more-substantial investment is required to develop the next generation of products.[22] And in fact, pharmaceutical research and development is dominated by for-profit companies, which are likely to set investment priorities on the basis of projected revenues, rather than perceived public health needs.[23] The major problem in this case is that the development of antibiotics is not well reimbursed relative to that of other drugs, such as treatments for cancer.[24] There is no substantial investment in developing new antibiotics because companies don't expect them to produce a substantial rate of return.[25]

Numerous strategies have been suggested to address rising antibiotic resistance and a limited development pipeline. The three main categories of such strategies are conserving the effectiveness of existing antibiotic drugs, providing additional financial incentives to encourage drug development, and reducing the drug development costs.

Antibiotic Conservation: Infection Control And Rational Use

The most widely employed methods of conservation are improved environmental infection control and rational prescription practices. In terms of environmental infection control, routine hand washing in an intensive care setting has been shown to reduce rates of vancomycin-resistant *Enterococcus* (VRE), a bacterium that can cause deadly blood infections.[26] In some well-regulated environments, rigorous infection control has successfully limited antibiotic resistance.[27] A recent report suggests that hospital-based conservation efforts in the United States have reduced the incidence of certain methicillin-resistant *Staphylococcus aureus* infections.[28]

Encouraging the rational use of antibiotics

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often entails active supervision of physicians' prescribing practices. Such programs include educating physicians about evidence-based prescribing practices, known as "academic detailing";[29] the development of treatment guidelines;[30] and restrictions that exclude certain antibiotics from clinical use or require prior authorization for their use. Rational-use programs impose increased requirements on specialists in infectious diseases but can still be cost-effective and lead to positive public health outcomes. In the decentralized U.S. system, individual institutions may be reluctant to invest in societally advantageous programs because some of the benefits would inevitably accrue to unaffiliated neighboring institutions, perhaps direct competitors.

Experience has also shown that both infection control and rational prescription practices have important limitations. Methicillin-resistant *Staphylococcus aureus* has passed between patients isolated in different rooms or areas of a hospital.[32] In the United States, the varying levels of commitment to conservation on the part of hospitals and other health care institutions can also limit the strategy's overall effectiveness. Notably, infection control measures are generally not reimbursed. To the degree that institutions have financial inducements to engage in infection control, these are largely punitive and occur after the fact, instead of being positive incentives to support infection control ahead of time. Under recent Medicare guidelines, for example, hospitals will be assessed a financial penalty for inpatients who acquire certain catheter-associated infections, whether or not the infection was avoidable.[33]

Supply-Side Incentives For New Drug Development

Policy makers have sought to address rising antibiotic resistance by proposing additional financial incentives for drug manufacturers.

PATENT TERM EXTENSION One proposal is to extend the period of effective patent life granted to new antibiotics. Drug patents have a statutory lifetime of twenty years, but the effective patent length is shorter because of the amount of time the drug approval process takes.

The U.S. Government Accountability Office (GAO) has suggested that patents could be lengthened "to 25 or 30 years" for important antibiotics with "high therapeutic potential."[34] Others have argued for starting the patent period when regulatory approval is granted,[35] or extending antibiotic patents for even longer periods.[36,37]

Longer patent terms would give sponsors more time in which to earn revenues. But the real benefits would not accrue until after the current twenty-year patent term ends, which limits the impact of the extra time on a company's bottom line in the present.[38] Many other troublesome questions are also raised by the idea of extending the patent term, including the difficulty of modifying patent law for a discrete sector such as antimicrobials without creating unanticipated effects in other drug classes.

LINKING ANTIBIOTIC DEVELOPMENT TO OTHER RIGHTS Another alternative involves linking antibiotic development to supplementary market exclusivity rights that could be transferred to other drugs, also known as "wildcard patents." For example, if Pfizer developed a new antibiotic, the FDA might grant six months of market exclusivity that Pfizer could apply instead to its blockbuster cholesterol-lowering drug atorvastatin (Lipitor), whose U.S. market exclusivity is scheduled to expire in 2011. An analysis by Kevin Outterson and others estimated that ten wildcard patents could cost as much as $40 billion.[38] An expenditure of this magnitude, however, is likely to be wasteful and would act as a hidden tax on common conditions such as high cholesterol. Shifting funds among disease categories in a haphazard fashion, detached from market signals, might hurt more patients than the strategy would help.[38,39]

OTHER INCENTIVES Finally, some "supply side" proposals focus on non-patent-related incentives.

▶ **ORPHAN DRUG ACT:** The Orphan Drug Act of 1983 encourages research into therapeutic agents for rare conditions and gives manufacturers federal funding and research tax credits, as well as enhanced market exclusivity rights. In recent legislation, Congress asked the FDA to study how the act might be applied to antibiotics developed to treat "serious and life threatening infectious diseases" caused by "antibiotic-resistant bacteria."[40] But many antibiotics and other antimicrobials have already received orphan drug designation, so it is not clear how much extending the law would accomplish.

▶ **PRIZES AND BUYOUTS:** Other analysts and academics have recommended using a prize to encourage research in this area. The public health payoff would come when the ultimate product was dissociated from the patent system and entered the public domain, where it could be sold more cheaply.[41] Sen. Bernie Sanders (I-VT) recently proposed an $80 billion prize fund to encourage research, although the plan did not receive much further attention in the Senate.[42]

Similar to a prize would be offering generous patent buyouts. A patent buyout involves purchasing the patent and marketing exclusivity rights and offering open, nonexclusive, no-

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royalty licenses as necessary. The "first in class" drugs developed could then be held in a "strategic antibiotic reserve" and saved for future crises.[43]

Prize proposals face financing and implementation barriers. However, they may represent a substantial evolution in the thinking behind global pharmaceutical development, especially for fighting high-priority disease-causing microorganisms and where existing drug development pipelines are weak.[44]

Reducing Drug Development Costs

A third category of proposals seeks to reduce the investment expense of creating a new antibiotic. One way of achieving such a goal is through increasing public or nonprofit funding of basic research on infectious diseases. The Bill & Melinda Gates Foundation, for example, funds research on the basic biology of tuberculosis[45] and how to manage the increase of extensively drug-resistant tuberculosis.[46] However, the National Institutes of Health (NIH) spends only about $200 million per year on such "upstream" antimicrobial resistance–related research.[47] Sustained increases in basic research budgets would benefit "downstream" research and ultimately the public's health. Investment at this level could be more cost-effective than extensive changes in patent law—for example, if a new receptor or mechanism is discovered that serves as the basis for numerous subsequent products. Still, the need to incentivize involvement of "downstream" pharmaceutical manufacturers would remain.

Another way to affect development costs is by adjusting certain regulatory standards. Antibiotics are usually tested against a control drug known to be effective against the bacterium in question, to demonstrate that the experimental antibiotic is not inferior to the standard treatment. Such "non-inferiority" trials can be complicated for investigators to design, and achieving useful results often requires enrolling more patients and investing additional time and money than would be required in a placebo-controlled trial. Therefore, industry sources have pointed out that relaxing benchmarks for statistical significance in these trials could cut development costs.[48]

Short of major changes in regulatory standards, some proactive steps can be taken to streamline the regulatory process, including publishing guidelines to reduce uncertainty about FDA expectations for clinical trials and actively working with drug developers early in the process to provide feedback about implementing these recommendations.[49] The Infectious Diseases Society of America and the FDA recently held a joint meeting to consider guidelines for developing new antibiotics to treat pneumonia. Creating such guidelines for emerging infectious disease threats could help make the regulatory process for potential antibiotic sponsors more transparent.[50]

Current programs for antibiotic conservation and production work at cross-purposes to each other.

However, adjusting the regulatory process may not have much of an effect. Historically, approved antibiotics have had among the shortest clinical development times of any drug class.[51] There may also be important disadvantages to loosening regulatory requirements, as reduced premarket testing may lead to an increased risk of the emergence of dangerous side effects after approval.[52]

For the most important antibiotics, it may be worth taking these additional risks, but the relaxation of premarketing hurdles would require careful surveillance of drug safety after FDA approval. Although currently in development, effective systems for postmarketing surveillance have not yet been implemented.

An Integrated Response To The Antibiotic Resistance Crisis

One of the primary themes to emerge from the efforts to address growing antibiotic resistance is that current programs for antibiotic conservation and production work at cross-purposes to each other. The growing popularity of infection control and limits on antibiotic use contributes to depressed sales of new products. Depressed sales in turn have prompted large pharmaceutical manufacturers to abandon new antibiotic research.

However, supply-side incentives—particularly those that provide longer periods of market exclusivity or allow drugs to come to market sooner—do not directly address bacterial resistance. Because future spending on pharmaceutical products is unpredictable, patent owners may choose to maximize short-term revenues, wasting antibiotic resources. For example, they

Incentives that include public health goals are essential to avoiding unintended consequences and the misuse of antibiotics.

may encourage the broad use of an antibiotic so they can sell more of the drug. If there are other manufacturers with antibiotics in the same class, this anticonservation pressure will spread to those competitors. The damage in terms of resistance may then be even more acute, because bacteria may develop cross-resistance among drugs with similar mechanisms of action.

Value-Based Reimbursement

A more rational incentive structure would promote conservation while creating a viable market for investment in antibiotic research and development. In the United States, antibiotics have traditionally been low-price products.[53] The societal value of activities such as hospital infection control programs greatly exceeds the value placed on them by private-sector and government payers. We suggest applying the principles of value-based reimbursement to paying for continued antibiotic effectiveness.

Take, for example, a new drug, or a conservation program for an existing drug, that treats or reduces vancomycin-resistant *Enterococcus* and leads to fewer intensive care unit admissions for patients with this infection. A value-based reimbursement plan would allow part of the savings to be shared with the manufacturer of the product and with the hospital that put the infection control program in place. Under such a proposal, the combined increase in antibiotic reimbursement should be substantial—amounting to at least several billion dollars a year. This approach would close some of the gap between the private cost and societal value of antibiotics.

Linking potential revenues to the appropriate use of a product has more and more precedents in pharmaceutical markets. In some markets, government-related expert bodies make value-based assessments of available medical technology. England's National Institute for Health and Clinical Excellence, for example, recently evaluated medications available for Alzheimer's disease and concluded that the evidence did not justify their cost and widespread use.[54] Australia's Pharmaceutical Benefits Scheme has many years of experience in evaluating population-level reimbursement based on health impact.[55]

We envision a similar system for evaluating antibiotic effectiveness and providing fair payments for societal benefit. The resulting dramatic increases in antibiotic reimbursement would jump-start innovation for new antibiotics.

Conservation-Based Market Exclusivity

As we have noted, the current market exclusivity system can contribute to misuse of new antibiotics because manufacturers earn revenue by encouraging the widespread use of their products before their patents expire. Many proposals to increase market exclusivity to spur drug research and development do not address this problem sufficiently.

As an alternative, we suggest a conservation-based market exclusivity strategy, whereby the FDA would set specific effectiveness targets for each antibiotic. Just as the FDA consults with expert advisory committees on the approval of new drugs, it could consult with appropriate experts from the NIH and the Centers for Disease Control and Prevention (CDC). Ideally, these experts would be free from substantial conflicts of interest.

In the deliberations, factors such as disease morbidity, the effectiveness of current treatment strategies, and the rate of emerging resistance would be used to set the public health goals. If the observed data met the target and equitable access to the drug was observed, the company would continue to enjoy marketing exclusivity. For example, for a drug developed to treat vancomycin-resistant *Enterococcus*, the target could be lower resistance rates or reduced morbidity from related illness in a sample of U.S. health care institutions.

Certainly, this strategy would require additional investment in improved surveillance of antibiotic use and development of resistance. Some of the proposed objective criteria for assessing proper antibiotic use may be unpredictable. For example, resistance may emerge at a more accelerated rate than anticipated.

But, as with any regulatory function, there should be some flexibility, and the manufacturer should be given the opportunity to explain its results to the oversight committee. If the marketing practices and usage patterns are appropriate, then the manufacturer could retain market exclusivity. This flexibility should increase the ap-

peal of this scheme to participating pharmaceutical companies.

Finally, because resistance can cross species and diminish the effectiveness of antibiotics both within and across classes of drugs, the implementation of this program would be improved if the Federal Trade Commission and the Department of Justice permitted manufacturers to coordinate the marketing, sale, and proper use of important antibiotics.

Conclusion

As microorganisms resistant to available therapies continue to emerge, there is concern from many sides that the current supply of antibiotics is not sufficient to meet the growing demand. Most proposed solutions provide additional incentives to encourage investment by pharmaceutical manufacturers. Few of the proposals take into account the fact that the profit-making incentives of manufacturers can be at odds with public health programs intended to limit antibiotic use and limit resistance.

As an alternative, we have outlined a way to better align manufacturer and public health incentives. Enhanced reimbursement for antibiotics commensurate with their societal value, along with market exclusivity tied to clinically rational use of the drugs, would allow everyone to benefit from the use of the antibiotics in situations most likely to reduce deaths caused by infection.

These programs would also encourage manufacturers to create programs to restrict clinically inappropriate use of their products, such as cooperating with—and funding—hospital-based infection control efforts. At the same time, enhanced public investment in resistance research could improve knowledge about drug targets and foster more development of antibiotics. For drugs that ultimately emerge from public investment programs, the government should receive an appropriate share of the enhanced reimbursement by payers.

Incentives that include public health goals are essential to avoiding the various unintended consequences and the misuse that have frequently characterized the market for antibiotics. The same incentives may offer legitimate hope for addressing the growing public health crisis posed by antibiotic resistance. ■

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NOTES

1 Maragakis LL, Perencevich EN, Cosgrove SE. Clinical and economic burden of antimicrobial resistance. Expert Rev Anti Infect Ther. 2008; 6(5):751–63.

2 World Health Organization. WHO global strategy for containment of antimicrobial resistance [Internet]. Geneva: WHO; 2001 [cited 2010 Jun 17]. Available from: http://www.who.int/csr/resources/publications/drugresist/en/EGlobal_Strat.pdf

3 Geberding JL. Recent case of extensively drug resistant TB: CDC's public health response [Internet]. Statement in testimony before the House Committee on Homeland Security. Atlanta (GA): Centers for Disease Control and Prevention; 2007 Jun 6 [cited 2010 Jun 17]. Available from: http://hsc.house.gov/SiteDocuments/20070606125418-21114.pdf

4 Munoz-Price LS, Weinstein RA. Acinetobacter infection. N Engl J Med. 2008;358(12):1271–81.

5 Tsuchimochi N, Takuma T, Shimono N, Nagasaki Y, Uchida Y, Harada M. Antimicrobial susceptibility and molecular epidemiological analysis of clinical strains of *Pseudomonas aeruginosa*. J Infect Chemother. 2008;14(2):99–104.

6 Klein E, Smith DL, Laxminarayan R. Hospitalizations and deaths caused by methicillin-resistant *Staphylococcus aureus*, United States, 1999–2005. Emerg Infect Dis. 2007;13(12):1840–6.

7 Evans HL, Lefrak SN, Lyman J, Smith RL, Chong TW, McElearney ST, et al. Cost of Gram-negative resistance. Crit Care Med. 2007; 35(1):89–95.

8 Asche C, McAdam-Marx C, Seal B, Crookston B, Mullins CD. Treatment costs associated with community-acquired pneumonia by community level of antimicrobial resistance. J Antimicrob Chemother. 2008; 61(5):1162–8.

9 Capitano B, Leshem OA, Nightingale CH, Nicolau DP. Cost effect of managing methicillin-resistant *Staphylococcus aureus* in a long-term care facility. J Am Geriatr Soc. 2003; 51(1):10–6.

10 Arias CA, Murray BE. Antibiotic-resistant bugs in the 21st century—a clinical super-challenge. N Engl J Med. 2009;360(5):439–43.

11 Infectious Diseases Society of America. Bad bugs, no drugs: as antibiotic discovery stagnates, a public health crisis brews [Internet]. Alexandria (VA): IDSA; 2004 Jul [cited 2010 Jun 17]. Available from: http://www.fda.gov/ohrms/dockets/dockets/04s0233/04s-0233-c000005-03-IDSA-vol1.pdf

12 Levy SB. Antibiotic and antiseptic resistance: impact on public health. Pediatr Infect Dis J. 2000; 19(10 Suppl):S120–2.

13 Grossman CM. The first use of penicillin in the United States. Ann Intern Med. 2008;149(2):135–6.

14 Barber M. Staphylococcal infection due to penicillin-resistant strains. Br Med J. 1947;2:863–5.

15 Levy SB, Marshall B. Antibacterial resistance worldwide: causes, challenges, and responses. Nat Med.

2004;10(12 Suppl):S122–9.
16 Switzer GE, Halm EA, Chang CC, Mittman BS, Walsh MB, Fine MJ. Physician awareness and self-reported use of local and national guidelines for community-acquired pneumonia. J Gen Intern Med. 2003;18(10):816–23.
17 Saver R. In tepid defense of population health: physicians and antibiotic resistance. Am J Law Med. 2008;34(4):431–91.
18 Coenen S, Michiels B, Renard D, Denekens J, Van Royen P. Antibiotic prescribing for acute cough: the effect of perceived patient demand. Br J Gen Pract. 2006;56(524):183–90.
19 U.S. Food and Drug Administration, Division of Drug Marketing, Advertising, and Communication. Warning letter [Internet]. Silver Spring (MD): FDA; 2005 Jul 20 [cited 2010 Jun 17]. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/ucm054813.pdf
20 United States et al. ex rel. Blair Collins v. Pfizer, Inc. Civ. No. 04-11780-DPW (D. Mass).
21 Spellberg B, Guidos R, Gilbert D, Bradley J, Boucher HW, Scheld WM, et al. The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. Clin Infect Dis. 2008; 46:155–64.
22 Leeb M. Antibiotics: a shot in the arm. Nature. 2004;431(7011):892–3.
23 Wenzel RP. The antibiotic pipeline: challenges, costs, and values. N Engl J Med. 2004;351:523–6.
24 Finch R, Hunter PA. Antibiotic resistance: action to promote new technologies. J Antimicrob Chemother. 2006;58(Suppl 1):i3–22.
25 Pollack A. For profit, industry seeks cancer drugs. New York Times. 2009 Sep 2.
26 Malik RK, Montecalvo MA, Reale MR, Li K, Maw M, Munoz JL, et al. Epidemiology and control of vancomycin-resistant enterococci in a regional neonatal intensive care unit. Pediatr Infect Dis J. 1999;18: 352–6.
27 Wertheim HF, Vos MC, Boelens HA, Voss A, Vandenbroucke-Grauls CM, Meester MH, et al. Low prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) at hospital admission in the Netherlands. J Hosp Infect. 2004;56:321–5.
28 Burton DC, Edwards JR, Horan TC, Jernigan JA, Fridkin SK. Methicillin-resistant *Staphylococcus aureus* central line–associated bloodstream infections in U.S. intensive care units, 1997–2007. JAMA. 2009;301: 727–36.
29 Solomon DH, Van Houten L, Glynn RJ, Baden L, Curtis K, Schrager H, et al. Academic detailing to improve use of broad-spectrum antibiotics at an academic medical center. Arch Intern Med. 2001;161(15):1897–902.
30 Schaffer K, Fitzgerald S, Gonzalez-Sanchez Z, Fenelon L. Do educational interventions improve management of patients with community-acquired pneumonia? J Healthc Qual. 2006;28(6):7–12.
31 Lesprit P, Brun-Buisson C. Hospital antibiotic stewardship. Curr Opin Infect Dis. 2008;21(4):344–9.
32 Cepeda JA, Whitehouse T, Cooper B, Hails J, Jones K, Kwaku F, et al. Isolation of patients in single rooms or cohorts to reduce spread of MRSA in intensive-care units. Lancet. 2005;365(9456):295–304.
33 Wald HL, Kramer AM. Nonpayment for harms resulting from medical care: catheter-associated urinary tract infections. JAMA. 2007;298: 2782–4.
34 U.S. Government Accountability Office. New drug development. Washington (DC): GAO; 2006 Nov [cited 2010 Jun 17]. Available from: http://www.gao.gov/new.items/d0749.pdf
35 Livermore D. Can better prescribing turn the tide of resistance? Nat Rev Microbiol. 2004;2:73–8.
36 Outterson K. The vanishing public domain: antibiotic resistance, pharmaceutical innovation, and intellectual property law. Univ Pittsbg Law Rev. 2005;67:67–123.
37 Kades E. Preserving a precious resource: rationalizing the use of antibiotics. Northwest Univ Law Rev. 2005;99:611–75.
38 Outterson K, Samora JR, Keller-Cuda K. Will longer antimicrobial patents improve global public health? Lancet Infect Dis. 2007; 7:559–66.
39 Sonderholm J. Wild-card patent extensions as a means to incentivize research and development of antibiotics. J Law Med Ethics. 2009;37: 240–6.
40 Food and Drug Administration Amendments Act of 2007, section 1112 (2007).
41 Love J, Hubbard T. The big idea: prizes to stimulate R&D for new medicines. Chic Kent Law Rev. 2007;82:1519–54.
42 Medical Innovation Prize Act, S. 2210, 110th Cong., 1st sess. (2007).
43 Outterson K. The legal ecology of resistance: the role of antibiotic resistance in pharmaceutical innovation. Cardozo Law Rev. 2010;31: 613–78.
44 Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. J Infect Dis. 2008;197:1079–81.
45 Smith I, Nathan C, Peavy HH. Progress and new directions in genetics of tuberculosis: an NHLBI working group report. Am J Respir Crit Care Med. 2005;172(12):1491–6.
46 Keshavjee S, Gelmanova IY, Farmer PE, Mishustin SP, Strelis AK, Andreev YG, et al. Treatment of extensively drug-resistant tuberculosis in Tomsk, Russia. Lancet. 2008;372: 1403–9.
47 Peters NK, Dixon DM, Holland SM, Fauci AS. The research agenda of the National Institute of Allergy and Infectious Diseases for antimicrobial resistance. J Infect Dis. 2008;197(8): 1087–93.
48 Norrby SR, Nord CE, Finch R. Lack of development of new antimicrobial drugs: a potential serious threat to public health. Lancet Infect Dis. 2005;5:115–9.
49 Powers JH. Antimicrobial drug development: the past, the present, and the future. Clin Microbiol Infect. 2004;10(Suppl 4):23–31.
50 Tillotson G. Pneumonia workshop raises more questions than answers. Lancet Infect Dis. 2008;8:221.
51 Reichert JM. Trends in development and approval times for new therapeutics in the United States. Nat Rev Drug Discov. 2003;2:695–702.
52 Outterson K, Powers JH, Gould IM, Kesselheim AS. Questions about the "10 X 20" initiative. Clin Infect Dis. Forthcoming 2010.
53 Currently, consumers can purchase a generic antibiotic for $4 in many retail pharmacies, and a few pharmacies have experimented with offering the same antibiotics at no charge. Parker-Pope T. Free antibiotics may contribute to drug resistance, officials say. New York Times. 2009 Mar 4;A22.
54 Kmietowicz Z. NICE proposes to withdraw Alzheimer's drugs from NHS. BMJ. 2005;330:495.
55 Doran E, Alexander HD. Australian pharmaceutical policy: price control, equity, and drug innovation in Australia. J Public Health Policy. 2008; 29(1):106–20.

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AcademyHealth awarded Kesselheim its Alice S. Hersh New Investigator Award in 2010. The award recognizes scholars early in their careers as health services researchers who show exceptional promise for future contributions.

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Outterson was a practicing attorney for a decade before joining the faculty at Boston University. His practice included health care transactions domestically, as well as tax and corporate issues for nonprofit health systems and international business. He has a law degree from Northwestern University and a master of laws degree from the University of Cambridge.

His research interests focus on global pharmaceutical markets, health disparities, and corporate governance. His scholarship addresses ways to bridge the gap between drug companies and low-income populations, in order to achieve equitable access to pharmaceuticals without harming incentives for innovation.

In their paper in this month's *Health Affairs*, Kesselheim and Outterson analyze a combination of financial incentives and changes in medical practice that could help tackle the public health crisis of multidrug-resistant bacteria. Kesselheim says that he chose the topic as a result of his "specific research interest in the incentives we provide for drug development and how well these incentives work to generate drugs that have the greatest impact on public health."

Kesselheim and Outterson have coauthored two earlier *Health Affairs* articles. The most recent, published in the September/October 2009 issue of the journal, explored how Medicare could obtain better prices on prescription drugs. A previous article in January/February 2008 dealt with licensing human papilloma virus (HPV) vaccines in developing countries and reflected the collaborators' interest in promoting equity and access to pharmaceuticals in lower-income populations.