The Epidemic of Antibiotic-Resistant Infections: A Call to Action for the Medical Community from the Infectious Diseases Society of America

Brad Spellberg,[1,2] Robert Guidos,[5] David Gilbert,[7] John Bradley,[3,4] Helen W. Boucher,[8] W. Michael Scheld,[6] John G. Bartlett,[9] and John Edwards, Jr., [1,2] for the Infectious Diseases Society of America

[1]Division of Infectious Diseases, Harbor–University of California–Los Angeles (UCLA) Medical Center, Torrance, [2]Geffen School of Medicine, UCLA, Los Angeles, and [3]Children's Hospital San Diego and [4]University of California at San Diego, California; [5]Infectious Diseases Society of America, Alexandria, and [6]Division of Infectious Diseases, University of Virginia Health System, Charlottesville, Virginia; [7]Division of Infectious Diseases, Providence Portland Medical Center and Oregon Health Sciences University, Portland, Oregon; [8]Tufts–New England Medical Center, Boston, Massachusetts; and [9]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland

The ongoing explosion of antibiotic-resistant infections continues to plague global and US health care. Meanwhile, an equally alarming decline has occurred in the research and development of new antibiotics to deal with the threat. In response to this microbial "perfect storm," in 2001, the federal Interagency Task Force on Antimicrobial Resistance released the "Action Plan to Combat Antimicrobial Resistance; Part 1: Domestic" to strengthen the response in the United States. The Infectious Diseases Society of America (IDSA) followed in 2004 with its own report, "Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates, A Public Health Crisis Brews," which proposed incentives to reinvigorate pharmaceutical investment in antibiotic research and development. The IDSA's subsequent lobbying efforts led to the introduction of promising legislation in the 109th US Congress (January 2005–December 2006). Unfortunately, the legislation was not enacted. During the 110th Congress, the IDSA has continued to work with congressional leaders on promising legislation to address antibiotic-resistant infection. Nevertheless, despite intensive public relations and lobbying efforts, it remains unclear whether sufficiently robust legislation will be enacted. In the meantime, microbes continue to become more resistant, the antibiotic pipeline continues to diminish, and the majority of the public remains unaware of this critical situation. The result of insufficient federal funding; insufficient surveillance, prevention, and control; insufficient research and development activities; misguided regulation of antibiotics in agriculture and, in particular, for food animals; and insufficient overall coordination of US (and international) efforts could mean a literal return to the preantibiotic era for many types of infections. If we are to address the antimicrobial resistance crisis, a concerted, grassroots effort led by the medical community will be required.

We are in the midst of an emerging crisis of antibiotic resistance for microbial pathogens in the United States and throughout the world [1–4]. Epidemic antibiotic resistance has been described in numerous pathogens in varying contexts, including—but not limited to—a global pandemic of methicillin-resistant *Staphylococcus aureus* (MRSA) infection [5–12]; the global spread of drug resistance among common respiratory pathogens, including *Streptococcus pneumoniae* [13–19] and *Mycobacterium tuberculosis* [20–29]; and epidemic increases in multidrug-resistant (and, increasingly, truly pan-resistant) gram-negative bacilli [30–39]. Infections caused by these and other antibiotic-resistant microbes impact clinicians practicing in every field of medicine. Given their breadth of effect and significant impact on morbidity and mortality, multidrug-resistant microbes are considered a substantial threat to US public health

Received 21 September 2007; accepted 24 September 2007; electronically published 5 December 2007.

Reprints or correspondence: Dr. John Edwards, Jr., Div. of Infectious Diseases, Harbor-UCLA Medical Center, 1124 W. Carson St., RB2, Torrance, CA 90502 (Edwards@humc.edu)

Clinical Infectious Diseases 2008; 46:155–64

1058-4838/2008/4602-0001$15.00
DOI: 10.1086/524891

Table 1. Microbes versus humans.

Variable	Microbes	Humans	Factor
No. on earth	5×10^{31}	6×10^{9}	$\sim 10^{22}$
Mass, metric tons	5×10^{16}	3×10^{8}	$\sim 10^{8}$
Generation time	30 min	30 years	$\sim 5 \times 10^{5}$
Time on earth, years	3.5×10^{9}	4×10^{6}	$\sim 10^{3}$

NOTE. Data are from [54].

and national security by the National Academy of Science's Institute of Medicine [40], the federal Interagency Task Force on Antimicrobial Resistance (Interagency Task Force) [41], and the Infectious Diseases Society of America (IDSA) [4].

At the very moment when increasing antimicrobial resistance has created a critical need to strengthen society's response, especially through the development of new antibiotics with novel mechanisms of action, pharmaceutical companies have been abandoning the development of anti-infectives [42–44]. In response to the overall threat, the Interagency Task Force released an "Action Plan to Combat Antimicrobial Resistance; Part 1: Domestic" (hereafter referred to as "the Action Plan") in 2001 [45]. The Action Plan, which was never fully funded, contained 84 action elements, 13 of which were designated as "top priority." The elements fell into 4 overarching activity areas: surveillance, prevention and control, research, and product development. Unfortunately, since 2001, without any additional, dedicated resources, US federal agencies, including the Centers for Disease Control and Prevention (CDC), the National Institutes of Health, and the US Food and Drug Administration (FDA), have been unable to sufficiently implement the surveillance, prevention and control, and research elements of the Action Plan. Furthermore, despite the fact that it was a top priority in the Action Plan, no additional measures have been proposed by the US government to stimulate research and development (R&D) of new diagnostics, vaccines, or (most critically) antibiotics.

In 2004, because of the growing crisis of antibiotic-resistant infection and the continued egress of pharmaceutical companies from antibiotic R&D, the IDSA released a report, "Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates, A Public Health Crisis Brews" [4], to publicize the problem and advise the US government on potential solutions. Unfortunately, to date, the resulting publicity and efforts to stimulate the adoption of solutions to spur new antibiotic discovery have failed. Despite recent, promising developments on Capitol Hill that may lead to better use of previously developed antibiotics, there are no signs that development of novel, priority antibiotics (i.e., those that can treat serious or life-threatening infections that are resistant to current antibiotics) will be stimulated in the coming decade. The purpose of this article is to review the causes of this societal conundrum, to summarize the IDSA's response to date, and to urge immediate, grassroots action by the medical community to attempt to address the deepening antimicrobial resistance crisis and, in particular, the need to significantly revitalize antibiotic R&D.

WHY HAS THE "PERFECT STORM" OF INCREASING ANTIBIOTIC RESISTANCE AND LACK OF ANTIBIOTIC DEVELOPMENT OCCURRED?

What is the cause of antibiotic resistance? In the aftermath of the unprecedented successes of early antibiotic therapies, in the late 1960s, US Surgeon General William H. Stewart is alleged to have made the now infamous declaration that "[it] is time to close the book on infectious diseases and declare the war against pestilence won" [46]. Although this statement may well be apocryphal [46], it clearly reflects the general sentiment in the medical community at the time [47]. Unfortunately, the past 30 years have revealed how grossly inaccurate that sentiment was [4, 47–49]. Indeed, we are further away than ever from "closing the book on infectious diseases," which, despite the availability of antibiotics, remain the second-leading cause of death worldwide [50] and the third-leading cause of death in the United States [51].

The global spread of microbial resistance is a predominant reason why infectious diseases have not been conquered. It is commonly expressed that physician misuse of antibiotics is the cause of antibiotic resistance in microbes and that, if we could only convince physicians to use antibiotics responsibly, we could "win the war against microbes." Unfortunately, this belief is a fallacy that reflects an alarming lack of respect for the incredible power of microbes.

As diverse as human beings are, we pale in comparison with the adaptability of microbes, which inhabit literally every possible climate and environment on the planet, despite extremes of boiling or freezing temperatures, pressures sufficient to crush virtually any human-made submersible, extreme salinity, zero oxygen content, presence or absence of sunlight, etc. Indeed, from the microbial perspective, human beings are nothing more than walking microbial planets; there are 5–10 times more microbes living on and in every human being than there are human cells in our bodies [52]. Bacteria even exist in large numbers miles deep in the midst of solid rock in the earth's crust [53]. Because of this extraordinary diversity of habitat, microbes comprise fully 60% of the biomass on the planet (90% if cellulose is excluded from the calculation), despite their submicron size [54].

Microbes have had 3.5 billion years to adapt to the various environments on planet Earth [55–57]. The power that drives microbial adaptability is genetic plasticity and rapid replication. It takes many bacteria only 20–30 min to replicate; it takes human beings 20–30 years to replicate. Given the above, there

is no doubt that microbes are the most numerous, diverse, and adaptable organisms that have ever lived on the planet.

On reflection, perhaps it would be wise to reconsider the frequently used metaphor of humans being "at war with microbes" [58, 59]. It is absurd to believe that we could ever claim victory in a war against organisms that outnumber us by a factor of 10^{22}, that outweigh us by a factor of 10^{8}, that have existed for 1000 times longer than our species, and that can undergo as many as 500,000 generations during 1 of our generations (table 1) [54]. Furthermore, the weapons in a war against microbes would be antibiotics. We need to remember that human beings did not invent antibiotics; we merely discovered them. Genetic analysis of microbial metabolic pathways indicates that microbes invented both β-lactam antibiotics and β-lactamase enzymes to resist those antibiotics >2 billion years ago [60, 61]. In contrast, antibiotics were not discovered by humans until the first half of the 20th century. Thus, microbes have had collective experience creating and defeating antibiotics for 20 million times longer than *Homo sapiens* have known that antibiotics existed.

From this framework, it is obvious that microbes do not need our help in creating antibiotic resistance. On the other hand, what human beings can do is affect the rate of spread of bacterial resistance by applying selective pressure via exposure to the thousands of metric tons of antibiotics we have used in patients and livestock over the past half century [2]. Methods to control unnecessary use of antibiotics include appropriate regulations on use of antibiotics in agriculture (including elimination of use of antibiotics to promote growth of food animals), restriction of antibiotic use to pathogen-specific agents, and limits on the common practice of using antibacterial agents for viral infections. Clearly, it is desirable to use antibiotics only when appropriate, to try to limit selective pressure that increases the frequency of resistance. Nevertheless, the distinction between causality of microbial resistance and the rate of spread of resistance must be recognized if we are to create a true solution to the problem of antibiotic resistance. If our misuse of antibiotics causes drug resistance, the solution that would allow us to forever defeat microbial resistance would be for us to strictly use antibiotics only when truly indicated. On the other hand, if our misuse of antibiotics affects the rate of spread of resistance but does not actually cause resistance, then using antibiotics correctly will not stop microbial resistance, it will only slow it down so that we can find a real solution to the problem. Framed in this context, it is clear that convincing physicians to use antibiotics properly is an important step to take, not because it is a solution to drug resistance, but because it will buy us more time to create a real solution to the problem.

Antimicrobial effectiveness is a precious, limited resource. Therefore, preserving antibiotic effectiveness can be viewed similar to society's responses to overconsumption and depletion of other precious, limited resources, such as oil and other energy sources, clean water and air, and forests [62]. When supply of these other resources have been threatened, society has stepped in to protect them from further consumption/depletion (e.g., energy conservation and restrictions on factory pollution) and to promote their restoration (e.g., forest restoration). Here, the resource that must be protected and restored is antibiotic "effectiveness." Society has tried to protect this resource against depletion through antimicrobial stewardship, including the placement of appropriate restrictions on antibiotic use, and through infection control. Unfortunately, society has not acted to promote antibiotic restoration (i.e., the development of new antibiotics), and antibiotic restrictions have the unintended, negative consequence of further destabilizing an already fragile market situation for antibiotic R&D.

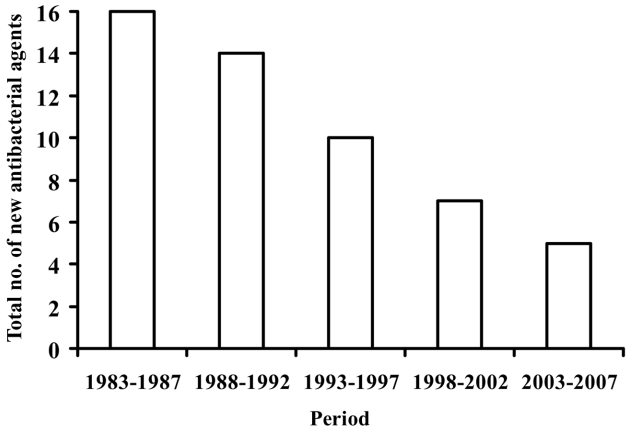

Figure 1. Systemic (i.e., nontopical) antibacterial new molecular entities approved by the US Food and Drug Administration, per 5-year period.

Ultimately, we must concede that we will never truly defeat microbial resistance; we can only keep pace with it. The only viable, long-term solution to the problem of microbial resistance is to have in place in perpetuity a continuing, steady development of new antibiotics and other strategies (including immunotherapeutics and vaccines, diagnostics and antibiotic stewardship programs to improve targeted therapy, and well-coordinated and -funded domestic and international monitoring, tracking, and prevention and control plans) to respond to new drug-resistant threats. Finally, because it takes years to develop a new drug, planning must include consideration of needs that are immediate as well those that are anticipated to occur over the coming decade.

These concepts have been summarized succinctly and precisely by Nobel prize winner Dr. Joshua Lederberg, who stated, "The future of humanity and microbes will likely evolve as…episodes of our wits versus their genes" [63].

What is the cause of decreasing antibiotic development? Three years ago, members of the IDSA, in collaboration with

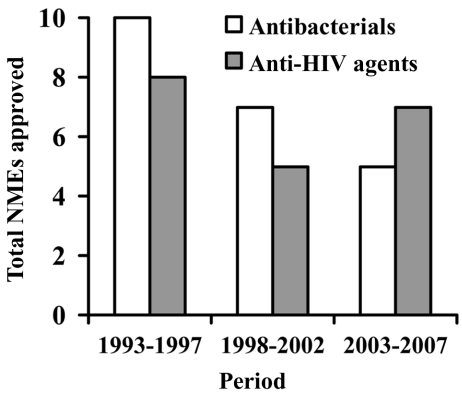

Figure 2. Antibacterial and anti-HIV new molecular entities (NMEs) approved by the US Food and Drug Administration, per 5-year period.

officials at the US FDA, published the first peer-reviewed data confirming the decline in the development of new antibiotics by pharmaceutical companies [42]. However, at that time, the decline had already been going on for >1 decade, as documented by previously published letters to editors, press releases, personal communications, and newspaper stories [40, 44, 64–67]. It is indisputable that antibiotic development has slowed dramatically over the past 25 years. Indeed, as of 2004, there were only 5 systemic antibacterial new molecular entities publicly listed as being in development by the largest pharmaceutical companies, barely beating out the 4 new molecular entities in development to treat erectile dysfunction [42]. A recent follow-up study conducted by the IDSA's Antimicrobial Availability Task Force reaffirmed the ongoing dearth of antibiotic development [43]. Perhaps the most dramatic illustration of the problem is an updated graph documenting the number of systemic antibacterial new molecular entities approved by the FDA over the past quarter-century (figure 1).

The cause of the decline of antibiotic development is multifactorial, but fundamentally, each factor relates to return on investment. Drug development, in general, is facing increasing challenges, given the high costs required, currently estimated to be $400–$800 million per approved agent [68]. Unfortunately, antibiotics have a lower relative rate of return on investment than do other drugs [64]. Antibiotics are short-course therapies that cure their target disease and, therefore, are typically taken for no more than 2 weeks. In contrast, chronic diseases are treated with noncurative therapies that suppress symptoms and are required to be taken for the life of the patient. Ironically, antibiotics are victims of their own success; they are less desirable to drug companies and venture capitalists because they are more successful than other drugs.

A dramatic illustration of the power of long-term therapy in driving interest in drug development is the remarkable and continuing success in developing new therapeutics to treat HIV infection. Antiretrovirals are an excellent example of therapeutic agents that are taken long term for the remainder of a patient's life and are typically initiated in relatively young patients. Perhaps it should not be surprising, therefore, that over the past 15 years, the US FDA has approved virtually the same number of new molecular entities targeting HIV as have been approved for the treatment of all bacterial infections combined (figure 2). These data are extremely important when strategies to stimulate antibiotic development are considered, because they clearly demonstrate, understandably, that if financial advantage is apparent to pharmaceutical companies, they are still capable of and interested in making anti-infective agents.

Another factor that weighs heavily as a disincentive for antibiotic development is the appropriate public health need to limit use of new, broad-spectrum antimicrobials. Antibiotics, alone among all classes of drugs, become less effective the more they are used. Therefore, thought leaders appropriately encourage restriction of the use of new, powerful antibiotics, and this inevitably negatively impacts sales [64, 67]. In direct contrast, when new drugs in other classes become available, their use may be encouraged by thought leaders.

Finally, an issue that is repeatedly cited by both pharmaceutical and biotechnology companies as a major deterrent for the development of antibiotics is the lack of available guidance documents from the FDA regarding which studies (e.g., placebo-controlled vs. noninferiority clinical trials) and evidence the agency considers to be acceptable to demonstrate the safety and efficacy of new anti-infective drugs [69, 70]. Concerns about the lack of formal guidance documents are exacerbated by perceived inconsistencies in protocol requirements for different companies developing drugs for the same disease states, as well as the uncertainty that the trial currently required by the FDA will be accepted in the future when a New Drug Application is ultimately filed. In communications with IDSA task force officials, pharmaceutical and biotechnology representatives have indicated that the availability of such guidances from the FDA would greatly enhance their companies' ability to perform antibiotic development.

WHAT HAS BEEN THE IDSA's RESPONSE TO THE CRISIS IN ANTIBIOTIC-RESISTANT INFECTIONS?

In the past 3 years, IDSA leaders have moved aggressively to highlight the drug-resistance problem, including the need to move aggressively to promote new antibiotic R&D. IDSA leaders have testified at governmental and congressional-level hearings [71], have been interviewed for a significant number of trade and major news stories, and have published opinion and editorial pieces to try to further publicize the problem of antibiotic-resistant infections [72].

The initial public alert to the medical community about the growing crisis in antibiotic development was published in 2002 by IDSA members David Schlaes and Robert Moellering [65]. Their warning was followed shortly thereafter by follow-up communications from IDSA members David Gilbert and John Edwards, Jr. [66], and Steven Projan [64]. In response to such publications, as well as to considerable discussion and communications among the IDSA and pharmaceutical and biotechnology officials, meetings were held between the IDSA, the National Institutes of Health, the FDA, the Pharmaceutical Research and Manufacturer's of America, and the Biotechnology Industry Organization to better understand the barriers to antibiotic R&D. Subsequently, the IDSA established the Antimicrobial Availability Task Force to consider options, to develop recommendations for legislative and administrative action, and to raise public awareness about the problem [43]. In July 2004, the IDSA released its "Bad Bugs, No Drugs" report, which documented the magnitude of the problem and made recommendations to address the complex issues underlying the lack of antibiotic development [4]. The IDSA financed this advocacy campaign with patients' best interests and the public's health in mind. No funding from the pharmaceutical industry or from any other sources were accepted for this effort.

On the regulatory front, for several years, IDSA leadership has urged the FDA to move quickly to publish adequate clinical trials guidances for industry to follow in developing new antiinfectives [69, 70]. As mentioned above, recent experiences related to the FDA's review of antibiotics have been criticized as inconsistent and unpredictable. The guidelines are viewed by industry as critically needed to eliminate regulatory uncertainty. Since 2001, the FDA has stated that guidelines in 5 areas would be published very soon. Fortunately, the first draft guidance document (on acute bacterial sinusitis) has just been published [73]; we are still awaiting the others.

The IDSA also has tried to raise public awareness about the resistance problem. The Society actively participated with the public television program Nova, which produced an Emmy award–winning episode, "Rise of the Superbugs," which aired in the winter of 2005. Most recently, *Time* magazine has acknowledged the problems of increasing drug resistance and the lack of new antibiotic development, as well as the role of the IDSA in lobbying Congress to address these problems [74].

HOW HAS CONGRESS RESPONDED TO DATE?

Since 2004, the IDSA has worked with several members of Congress to create legislation that could have gone a long way toward addressing antimicrobial resistance and stimulating antibiotic R&D. As a result, several promising bills were introduced. Unfortunately, as a whole, the 109th Congress focused on other priorities and did not act on these bills before adjourning in December 2006.

However, there are signs that the 110th US Congress has begun to recognize the severe nature of the antibiotic resistance crisis. In September 2007, signed into law the Food and Drug Administration Amendments Act of 2007 (Public Law No. 110-85; 2007). This act focuses on improving the FDA's ability to perform its critical safety monitoring role for drugs, food, and medical devices. Also included in the bill are provisions, developed with IDSA guidance, that will enable the government to begin to gather badly needed data about the extent of the spread of antibiotic resistance among bacteria. For example, there is a provision that requires the US Government Accountability Office (GAO) to study the causes of infections that occur in hospitals and to evaluate hospital infection-control procedures.

Another piece of legislation that was developed with IDSA input, the Strategies to Address Antimicrobial Resistance (STAAR) Act (H.R.3697 and S.2313), has also been introduced to the House of Representatives and the Senate [75]. The STAAR Act calls for creation of an Office of Antimicrobial Resistance in the Department of Health and Human Services and a Public Health Antimicrobial Advisory Board, which are intended to develop coordinated plans and manage a federal effort to combat antibiotic-resistant infection. This coordinated effort would include gathering data on how common such infections are and tracking the spread of such infections in real time. These bills are seen as the first concrete, positive steps toward beginning to address the crisis in antibiotic resistance. Fortunately, the bills have bipartisan support and have been endorsed by several medical and public health organizations, underscoring the universal nature of this issue.

Most recently, new legislation has been introduced into the Senate and House (S.2351 and H.R.4200) that will provide R&D tax credits for critically needed infectious disease products, such as antibiotic and antiviral drugs, medical devices, diagnostic tests, biological products, and vaccines.

The IDSA continues to work with Senators Orrin Hatch (Republican-UT), Edward Kennedy (Democrat-MA), Michael Enzi (Republican-WY), Richard Burr (Republican-NC), Sherrod Brown (Democrat-OH), Charles Schumer (Democrat-NY), Richard Durbin (Democrat-IL), Lamar Alexander (Republican-TN), Christopher Dodd (Democrat-CT), and Barack Obama (Democrat-IL) and with Members of the House of Representatives, including Representatives Jim Matheson (Democrat-UT), Michael Ferguson (Republican-NJ), Henry Waxman (Democrat-CA), Edolphus Towns (Democrat-NY), John Dingell (Democrat-MI), Brian Baird (Democrat-WA), and Barbara Cubin (Republican-WY), as well as with other public health champions in the House and Senate, to develop comprehensive

legislation to address the burgeoning problem of antibiotic-resistant infection.

THE IDSA's "WISH LIST" OF STRATEGIES TO ADDRESS ANTIMICROBIAL-RESISTANT INFECTIONS

The IDSA has developed a set of strategies to address antimicrobial resistant infections. The wish list takes a holistic approach to the problem by recognizing that each of us, including physicians, patients, antibiotic manufacturers, personnel at hospitals and other health care facilities, and others, must act as good partners in keeping antibiotics available and effective for the long term. In so doing, the IDSA's proposals support existing elements of the Interagency Task Force's Action Plan.

IDSA's proposals are as follows.

1. The creation of a Federal Office of Antimicrobial Resistance in the Department of Health and Human Services to coordinate and fund the work of the Interagency Task Force to further strengthen and implement the domestic Action Plan, as well as to develop an international action plan.
2. The creation of a Public Health Antimicrobial Advisory Board comprised of experts, including specialists in infectious diseases, hospital and community-based physicians, public health officers, and veterinary and research specialists, to recommend ways to strengthen the federal Action Plan.
3. The establishment of a federal strategic research plan on antimicrobial resistance that will focus on basic, clinical, translational, epidemiological, and interventional research.
4. The creation of an Antimicrobial Resistance Clinical Research and Public Health Network (with at least 10 sites across the United States) to track and confirm, in near real time, the emergence of antibiotic-resistant pathogens, to conduct research, and to enhance our capacity to prevent, control, and treat infections due to antibiotic-resistant organisms.
5. The collection of relevant antimicrobial consumption data, including antibiotic human and animal antibiotic use data and available prescribing data.
6. Strengthened surveillance programs to monitor and track resistance patterns.
7. A requirement that pharmaceutical manufacturers submit to the FDA, as part of a new antibiotic drug application, a resistance impact statement that predicts how approval and use of the antibiotic may impact the development of resistance, as well as a management plan that aims to slow the development of resistance associated with the drug's use.
8. Sufficient federal funding to implement the federal Action Plan, including for antibiotic stewardship programs to limit the spread of resistance.
9. The establishment and periodic updates by the FDA of antibiotic susceptibility breakpoints for microorganisms based on expert input, to assist physicians in using antibiotics wisely.
10. A reassessment and strengthening of FDA's regulatory authority relating to the use of antibiotics in food-producing animals.
11. More appropriately regulate the use of antibiotics in agriculture, including phasing out the use of antibiotics for growth promotion in food animals.
12. Finally, a requirement that the US GAO audit the success of the aforementioned measures in completing their stated aims.

To ensure the ongoing availability of priority antibiotics and other tools that target infections resistant to currently available drugs, the IDSA supports the adoption of other appropriate "orphan drug"–type incentives that target "priority" antibiotics (as defined above) and other supportive tools. These incentives are as follows.

1. An R&D tax credit for priority antibiotics and other tools.
2. Grants to encourage clinical development of priority antibiotics and other tools.
3. Extension of the patent life or market exclusivity for priority antibiotics. In November 2006, the US GAO issued a report on new drug development [76] that looked at the effect of including financial incentives or disincentives on the innovative potential of drugs produced by the pharmaceutical industry. One idea noted in the GAO's report supports extending patent life for critically needed products, noting that "a patent could be extended to 25 or 30 years for drugs considered innovative, or offering high therapeutic potential; while patents for drugs offering less innovative benefits could be only 10 years" (p. 36). Also worthy of consideration is full restoration of patent time lost while the FDA evaluates and reviews priority antibiotic drug applications.
4. Federally funded advanced purchase commitments or other "promised markets" for priority antibiotics and other tools.
5. Expansion of the definition of "countermeasures" found in the newly enacted Biomedical Advanced Research and Development Authority (BARDA; December 2006) to include priority antibiotics that treat "resistant bacterial pathogens that threaten the lives of a significant number of U.S. citizens annually." BARDA is intended to enhance and accelerate the R&D and procurement of promising new countermeasures (defined as "therapeutics, vaccines, and diagnostics") by infusing federal funds during critical stages in a product's testing and development. BARDA's current scope includes funding the development of countermeasures against agents that "may cause a public health emergency affecting national security," such as pandemic influenza or bioterrorism agents.

6. Transferable priority review vouchers. Such vouchers would be provided to pharmaceutical companies that receive FDA approval for a priority antibiotic or related diagnostic product. The company could use the voucher to expedite FDA review of another product of its choice.

One additional proposal, known as "transferable patent extensions" (also known as "wild card patent extensions"), would grant companies receiving FDA approval for a priority antibiotic an extension on patent time of 6 months to 2 years on another drug that the company markets. IDSA currently is not aggressively pursuing adoption of the transferable patent extension concept because of the extreme controversy that has been associated with this idea. However, of all of the potential solutions, transferable patent extensions are generally acknowledged by pharmaceutical companies to be, by far, the incentives most likely to successfully stimulate new antibiotic development. Although many fear the costs to society incurred by extending the patent on blockbuster drugs, such as atorvastatin, it is possible that a compromise could be reached by capping the earnings resulting from patent extension.

Opponents of transferable patent extensions have characterized the idea as a boondoggle for the pharmaceutical industry. What has been generally underappreciated in this controversy is the potential for newly developed antibiotics to mitigate the dramatic costs posed to society by antimicrobial resistance, estimated to be in the tens of billions of dollars annually [1, 77]. Indeed, an academic analysis of the transferable patent extension concept has indicated that it likely will result in a net savings of billions of dollars in health care costs by promoting the availability of antibiotics to fight costly multidrug-resistant infections [78].

There may be a sense on Capitol Hill and among the public (including physicians) that pharmaceutical companies are to blame for the problem of lack of antibiotic development and, therefore, should not be rewarded with financial incentives to fix the problem. IDSA's premise from the beginning of its Bad Bugs, No Drugs advocacy campaign has been that the dearth of new antibiotics is a societal problem requiring a collective solution and that it is nobody's fault. Pharmaceutical companies do not have a constitutional or corporate responsibility to produce antibiotics. Rather, corporate directors have a fiduciary responsibility to invest their R&D dollars in a manner that maximizes the likelihood of return on investment [79, 80]. Indeed US corporations have been successfully sued by their shareholders for pursuing corporate policies that favor public good over corporate profits [79, 80]. Thus, it is completely unrealistic to expect pharmaceutical companies to be solely responsible for developing drugs that, although beneficial to the public good, do not maximize return on investment.

Private, large pharmaceutical companies have discovered, developed, manufactured, and brought to market nearly all of the ~150 antibiotics available today. Unfortunately, their motivation in this regard has deteriorated over time as more lucrative markets, including those for therapeutics to treat cancer, hypertension, hypercholesterolemia, arthritis, inflammatory diseases, and dementia, have arisen [42]. A critical void now exists, and it is incumbent on society and our government—which holds the great responsibility of protecting the public's health—to step up to the plate with incentives to fill that void.

It is perhaps not surprising that the most vocal critics of providing incentives to spur pharmaceutical R&D are generic drug manufacturers and their lobbyists [81]. Generic drug manufacturers perceive that extension of patents will delay their ability to begin profiting from the sales of generic copies of those drugs. However, generic manufacturer criticism of patent extensions likely will prove to be short-sighted; if pharmaceutical companies do not discover, develop, and seek regulatory approval for new antibiotics, generic manufacturers will have no new antibiotics to manufacture as generics in the future, even as sales of old generic antibiotics decrease precipitously as a result of increasing antibiotic resistance. Furthermore, making cheaper generic versions of already existing drugs does not address the problem of rising drug resistance and the increasing incidence of pan-resistant, lethal infections; only innovative discovery of new antibiotics can address this problem.

IMMUNO-ENHANCEMENT IS A COMPLEMENTARY, NOT AN ALTERNATIVE, STRATEGY

Another mechanism to address antibiotic resistance is to continue and enhance R&D of novel immunotherapies and immunoprophylactic strategies, such as vaccines, antibody-based therapies, and cytokines or other small molecules. Development of immunotherapeutics and immunoprophylactics has tremendous potential to reduce the overall burden of infection and infection-related deaths, and it should be a major focus of both government and industrial R&D. The enactment of S.2351 and H.R.4200 should be helpful in this regard. It should be acknowledged that, despite some extensive efforts, there are virtually no immune-based treatments available for common infections other than the vaccines and immunoglobulins that have been used for decades. Thus, it is naive to believe that immunological strategies will be able to completely eliminate the need for new antibiotics. Rather, new antibiotics and immunological strategies complement one another, and both are needed.

WHAT CAN THE GREATER MEDICAL COMMUNITY DO TO HELP SOLVE THE PROBLEM?

For relevant legislation to be viable, politicians need to be convinced that the problem is critical and—equally important—

to hear from their well-informed constituents who believe the problem is significant. Therefore, a grassroots movement spearheaded by the medical community could serve as an invaluable catalyst to raise awareness of the problem.

It is critically important that members of the broader medical community become advocates in this campaign and work with the IDSA to put a "human face" on the problem of drug-resistant infections. The IDSA needs your help in finding Health Information Privacy Protection Act–compliant patient cases and personal stories to demonstrate the negative impacts of antibiotic resistance. The IDSA's Web site (http://www.idsociety.org/STAARAct.htm) contains several sample patient stories. You may submit additional such stories to the IDSA (rguidos@idsociety.org). We also urge you to reach out to your congressional representatives and to urge your patients to do the same. Please visit the IDSA Web site, which contains sample letters to send to Congress, as well as additional information about legislative opportunities to tackle the antimicrobial resistance problem.

In the meantime, physicians must take care to prescribe antibiotics appropriately, to minimize the rate of spread of drug resistance. Indeed, the IDSA has recently released guidelines on appropriate antibiotic stewardship to try to minimize antibiotic misuse [82]. Most importantly, we must educate each other, our patients, the media, and politicians about this problem. Only the medical community can provide an accurate perspective and rational balance to this issue. For example, although bioterrorism is an important theoretical threat, the total death toll from the anthrax scare of several years ago was 5 people, and the last death due to smallpox in the United States occurred almost 60 years ago. In contrast, as of the year 2000, the CDC reported that ~70,000 deaths due to nosocomially acquired, drug-resistant infections occurred per year in hospitals throughout the United States [4]. The number is almost certainly dramatically higher in 2007. We must not let appropriate concern for important theoretical threats that overshadow the importance of threats that are already striking heavy blows. It is up to each of us to be the voice of reason in this debate and to continue fighting on behalf of our patients and the public's health.

CONCLUSIONS

The consequences of the failure to create new antibiotics could be catastrophic. Availability of effective antibiotics has revolutionized public health and has been responsible for enabling countless advancements in medical care. For example, antibiotics have been critical to the development of advances in surgery and of myeloablative therapies for cancer and to the transplantation of both solid organs and hematopoeitic stem cells. Effective antibiotics have also been critical for advanced medical treatment of patients with trauma and battlefield injuries, as well as myocardial infarctions, strokes, and other illnesses that require intensive care with catheters, hyperalimentation, and mechanical ventilation. Ironically, the very advances in medical care enabled by effective antibiotic therapies have, in turn, created enormous populations of increasingly immunocompromised hosts, who develop infections caused by increasingly resistant microbes that require treatment with newer, more powerful antibiotics. As global and US populations continue to age, this upwardly spiraling need for intensive care with catheters and ventilators, for increasingly aggressive cancer chemotherapy, and for cardiac, abdominal, and other complicated surgeries are all going to continue to increase. Although we have come to take for granted such elements of modern medical care, their continued utility depends in large part on the continued availability of effective antimicrobial therapy.

It is incumbent on physicians to lead the fight to address this societal conundrum. Educate your colleagues and your patients. Write to your Senators and Congresspersons. The time for action is now.

Acknowledgments

The IDSA's Board of Directors expresses its gratitude to the members of IDSA's Antimicrobial Availability Task Force for their contributions in developing this manuscript. The Board also expresses its appreciation to the members of IDSA's Antimicrobial Resistance Work Group and Research on Resistance Work Group, as well as IDSA staff, including Robert J. Guidos, Julie Hantman, and Beth Rada, for their work in developing strategies to address antimicrobial resistance, many of which have been incorporated in this manuscript. Finally, the Board is most appreciative to Brad Spellberg for his ongoing commitment to finding workable solutions to the "Bad Bugs, No Drugs" dilemma.

Potential conflicts of interest. B.S. has received consulting fees from Pfizer; has received research support from Astellas, Gilead, Elan, Enzon, Novartis, Merck, and Pfizer; and is on the speakers' bureaus for Merck, Pfizer, and Astellas. D.G. serves on the speakers' bureau of Abbott Laboratories, Bayer, GlaxoSmithKline, Lilly, Merck, Pfizer, Roche, Schering-Plough, and Wyeth. J.B.'s employer has received research grants from AstraZeneca, Elan, Glaxo SmithKline, Johnson & Johnson, and Novartis and reimbursement for J.B.'s role in consulting for Johnson & Johnson, Trius Therapeutics, Cerexa, and Wyeth. H.W.B. serves as an advisor/consultant to Cubist, Johnson & Johnson, Pfizer, Schering-Plough, and Targanta; serves as a speaker for Cubist, Pfizer, and Schering-Plough; and owns or has owned shares of Pfizer and Cubist. W.M.S. serves on advisory boards for Pfizer, Cubist, and GlaxoSmithKline and serves on speakers' bureaus of these same companies, plus those of Schering-Plough and Bristol-Myers Squibb. J.G.B. serves on the HIV advisory boards for Bristol-Myers Squibb, Abbott Laboratories, and GlaxoSmithKline. J.E.E. serves on the scientific advisory boards of Pfizer, Merck, and Gilead; has participated in educational programs regarding fungal infections funded by Pfizer, Merck, and Astellas; has received research laboratory support from Pfizer, Merck, and Gilead; and has participated in the Bristol-Myers Squibb Freedom to Discovery research program. R.G.: no conflicts. These funding sources played no role in the preparation of this manuscript. The Antimicrobial Availability Task Force receives no financial support from outside sources for any of its activities, and the authors received no financial support for preparation of this manuscript.

References

1. Division of Healthcare Quality Promotion, National Center for Infectious Diseases, Centers for Disease Control. Antimicrobial resistance:

a growing threat to public health. Atlanta: Division of Healthcare Quality Promotion, National Center for Infectious Diseases, Centers for Disease Control, **2002**.
2. Palumbi SR. Humans as the world's greatest evolutionary force. Science **2001**; 293:1786–90.
3. Alanis AJ. Resistance to antibiotics: are we in the post-antibiotic era? Arch Med Res **2005**; 36:697–705.
4. Infectious Diseases Society of America. Bad bugs, no drugs: as antibiotic discovery stagnates, a public health crisis brews. Alexandria, VA: Infectious Diseases Society of America, **2004**.
5. Chambers HF. Community-associated MRSA—resistance and virulence converge. N Engl J Med **2005**; 352:1485–7.
6. Fridkin SK, Hageman JC, Morrison M, et al. Methicillin-resistant *Staphylococcus aureus* disease in three communities. N Engl J Med **2005**; 352:1436–44.
7. Miller LG, Perdreau-Remington F, Rieg G, et al. Necrotizing fasciitis caused by community-associated methicillin-resistant *Staphylococcus aureus* in Los Angeles. N Engl J Med **2005**; 352:1445–53.
8. Moran GJ, Amii RN, Abrahamian FM, Talan DA. Methicillin-resistant *Staphylococcus aureus* in community-acquired skin infections. Emerg Infect Dis **2005**; 11:928–30.
9. Moran GJ, Krishnadasan A, Gorwitz RJ, et al. Methicillin-resistant *S. aureus* infections among patients in the emergency department. N Engl J Med **2006**; 355:666–74.
10. Eady EA, Cove JH. Staphylococcal resistance revisited: community-acquired methicillin resistant *Staphylococcus aureus*—an emerging problem for the management of skin and soft tissue infections. Curr Opin Infect Dis **2003**; 16:103–24.
11. Kazakova SV, Hageman JC, Matava M, et al. A clone of methicillin-resistant *Staphylococcus aureus* among professional football players. N Engl J Med **2005**; 352:468–75.
12. Sattler CA, Mason EO Jr, Kaplan SL. Prospective comparison of risk factors and demographic and clinical characteristics of community-acquired, methicillin-resistant versus methicillin-susceptible *Staphylococcus aureus* infection in children. Pediatr Infect Dis J **2002**; 21:910–7.
13. File TM Jr. Clinical implications and treatment of multiresistant *Streptococcus pneumoniae* pneumonia. Clin Microbiol Infect **2006**; 12(Suppl 3):31–41.
14. File TM Jr. *Streptococcus pneumoniae* and community-acquired pneumonia: a cause for concern. Am J Med **2004**; 117(Suppl 3A):39S-50S.
15. Centers for Disease Control and Prevention. Resistance of *Streptococcus pneumoniae* to fluoroquinolones—United States, 1995–1999. MMWR Morb Mortal Wkly Rep **2001**; 50:800–4.
16. Gordon KA, Biedenbach DJ, Jones RN. Comparison of *Streptococcus pneumoniae* and *Haemophilus influenzae* susceptibilities from community-acquired respiratory tract infections and hospitalized patients with pneumonia: five-year results for the SENTRY antimicrobial surveillance program. Diagn Microbiol Infect Dis **2003**; 46:285–9.
17. Hyde TB, Gay K, Stephens DS, et al. Macrolide resistance among invasive *Streptococcus pneumoniae* isolates. JAMA **2001**; 286:1857–62.
18. Kays MB, Smith DW, Wack ME, Denys GA. Levofloxacin treatment failure in a patient with fluoroquinolone-resistant *Streptococcus pneumoniae* pneumonia. Pharmacotherapy **2002**; 22:395–9.
19. Whitney CG, Farley MM, Hadler J, et al. Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States. N Engl J Med **2000**; 343:1917–24.
20. Grant GR, Lederman JA, Brandstetter RD. T. G. Heaton, tuberculosis, and artificial pneumothorax: once again, back to the future? Chest **1997**; 112:7–8.
21. Kir A, Tahaoglu K, Okur E, Hatipoglu T. Role of surgery in multidrug-resistant tuberculosis: results of 27 cases. Eur J Cardiothorac Surg **1997**; 12:531–4.
22. Nachega JB, Chaisson RE. Tuberculosis drug resistance: a global threat. Clin Infect Dis **2003**; 36:S24–30.
23. Strambu I. Therapeutic pneumothorax—an effective adjuvant method in treating multidrug-resistant tuberculosis. Pneumologia **2000**; 49: 129–36.
24. Sung SW, Kang CH, Kim YT, Han SK, Shim YS, Kim JH. Surgery increased the chance of cure in multi-drug resistant pulmonary tuberculosis. Eur J Cardiothorac Surg **1999**; 16:187–93.
25. Zignol M, Hosseini MS, Wright A, et al. Global incidence of multidrug-resistant tuberculosis. J Infect Dis **2006**; 194:479–85.
26. Zazueta-Beltran J, Muro-Amador S, Flores-Gaxiola A, Llausas-Magana E, Leon-Sicairos N, Canizalez-Roman A. High rates of multidrug-resistant *Mycobacterium tuberculosis* in Sinaloa State, Mexico. J Infect **2006**; 54:411–2.
27. Centers for Disease Control and Prevention. Multidrug-resistant tuberculosis in Hmong refugees resettling from Thailand into the United States, 2004–2005. MMWR Morb Mortal Wkly Rep **2005**; 54:741–4.
28. Granich RM, Oh P, Lewis B, Porco TC, Flood J. Multidrug resistance among persons with tuberculosis in California, 1994–2003. JAMA **2005**; 293:2732–9.
29. Nettleman MD. Multidrug-resistant tuberculosis: news from the front. JAMA **2005**; 293:2788–90.
30. Mirza SH, Beeching NJ, Hart CA. Multi-drug resistant typhoid: a global problem. J Med Microbiol **1996**; 44:317–9.
31. Douglas MW, Mulholland K, Denyer V, Gottlieb T. Multi-drug resistant *Pseudomonas aeruginosa* outbreak in a burns unit—an infection control study. Burns **2001**; 27:131–5.
32. Levin AS, Barone AA, Penco J, et al. Intravenous colistin as therapy for nosocomial infections caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Clin Infect Dis **1999**; 28: 1008–11.
33. Muller M, McGeer A, Willey BM, et al. Outbreaks of multi-drug resistant *Escherichia coli* in long-term care facilities in the Durham, York and Toronto regions of Ontario, 2000–2002. Can Commun Dis Rep **2002**; 28:113–8.
34. Zansky S, Wallace B, Schoonmaker-Bopp D, et al. From the Centers for Disease Control and Prevention: outbreak of multi-drug resistant *Salmonella* Newport—United States, January–April 2002. JAMA **2002**; 288:951–3.
35. McGowan JE Jr. Resistance in nonfermenting gram-negative bacteria: multidrug resistance to the maximum. Am J Med **2006**; 119:S29–36; discussion S62–70.
36. Rhomberg PR, Fritsche TR, Sader HS, Jones RN. Clonal occurrences of multidrug-resistant gram-negative bacilli: report from the Meropenem Yearly Susceptibility Test Information Collection Surveillance Program in the United States (2004). Diagn Microbiol Infect Dis **2006**; 54:249–57.
37. Wright MO. Multi-resistant gram-negative organisms in Maryland: a statewide survey of resistant *Acinetobacter baumannii*. Am J Infect Control **2005**; 33:419–21.
38. McDonald LC. Trends in antimicrobial resistance in health care–associated pathogens and effect on treatment. Clin Infect Dis **2006**; 42(Suppl 2):S65–71.
39. Paterson DL. The epidemiological profile of infections with multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter* species. Clin Infect Dis **2006**; 43(Suppl 2):S43–8.
40. Smolinski MS, Hamburg MA, Lederberg J. Microbial threats to health: emergence, detection, and response. Washington, DC: Institute of Medicine, **2003**.
41. Antibiotic/antimicrobial resistance: action plan. Atlanta: US Department of Health and Human Services Centers for Disease Control and Prevention, **1999**. Available at: http://www.cdc.gov/drugresistance/actionplan.
42. Spellberg B, Powers JH, Brass EP, Miller LG, Edwards JE. Trends in antimicrobial drug development: implications for the future. Clin Infect Dis **2004**; 38:1279–86.
43. Talbot GH, Bradley J, Edwards JE Jr, et al. Bad bugs need drugs: an update on the development pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America. Clin Infect Dis **2006**; 42:657–68.
44. Wenzel RP. The antibiotic pipeline—challenge, costs, and values. N Engl J Med **2004**; 351:523–6.

45. Interagency Task Force on Antimicrobial Resistance. Action plan to combat antimicrobial resistance; part 1: domestic. **2001**. Available at: http://www.cdc.gov/drugresistance/actionplan/aractionplan.pdf.
46. The Office of the Public Health Service Historian. Frequently asked questions. US Public Health Service, Office of the Librarian, **2006**. Available at: http://lhncbc.nlm.nih.gov/apdb/phsHistory/faqs.html.
47. Fauci AS. Infectious diseases: considerations for the 21st century. Clin Infect Dis **2001**; 32:675–85.
48. Fauci AS. Emerging and reemerging infectious diseases: the perpetual challenge. Acad Med **2005**; 80:1079–85.
49. Morens DM, Folkers GK, Fauci AS. The challenge of emerging and re-emerging infectious diseases. Nature **2004**; 430:242–9.
50. World Health Organization. Deaths by cause, sex and mortality stratum in WHO regions, estimates for 2002: World Health Report—2004. Geneva: World Health Organization, **2004**.
51. Pinner RW, Teutsch SM, Simonsen L, et al. Trends in infectious diseases mortality in the United States. JAMA **1996**; 275:189–93.
52. Berg RD. The indigenous gastrointestinal microflora. Trends Microbiol **1996**; 4:430–5.
53. Fisk MR, Giovannoni SJ, Thorseth IH. Alteration of oceanic volcanic glass: textural evidence of microbial activity. Science **1998**; 281:978–80.
54. Schaechter M, Kolter R, Buckley M. Microbiology in the 21st century: where are we and where are we going? Washington, DC: American Society for Microbiology, **2004**. Available at: http://www.asm.org/Academy/index.asp?bid=29245.
55. Altermann W, Kazmierczak J. Archean microfossils: a reappraisal of early life on Earth. Res Microbiol **2003**; 154:611–7.
56. Schopf JW. Microfossils of the Early Archean Apex chert: new evidence of the antiquity of life. Science **1993**; 260:640–6.
57. Schopf JW, Packer BM. Early Archean (3.3-billion to 3.5-billion-year-old) microfossils from Warrawoona Group, Australia. Science **1987**; 237:70–3.
58. Spellberg B. Bad bugs, no drugs: a failing police action (i.e. NOT a war). In: Harold C. Neu Conference (Scottsdale, AZ). **2005**.
59. Ending the war metaphor: the changing agenda for unraveling the host-microbe relationship—workshop summary. National Academies Press, **2006**. Available at: http://www.iom.edu/CMS/3783/3924/35346.aspx.
60. Hall BG, Salipante SJ, Barlow M. Independent origins of subgroup Bl + B2 and subgroup B3 metallo-β-lactamases. J Mol Evol **2004**; 59:133–41.
61. Hall BG, Barlow M. Evolution of the serine β-lactamases: past, present and future. Drug Resist Updat **2004**; 7:111–23.
62. Laxminarayan R, Malani A, Howard D, Smith DL. Extending the cure: policy responses to the growing threat of antibiotic resistance. Antibiotic effectiveness as a natural resource. Vol. July 19, 2007: Resources for the future, **2007**:19–21.
63. Lederberg J. Infectious history. Science **2000**; 288:287–93.
64. Projan SJ. Why is big Pharma getting out of antibacterial drug discovery? Curr Opin Microbiol **2003**; 6:427–30.
65. Shlaes DM, Moellering RC Jr. The United States Food and Drug Administration and the end of antibiotics. Clin Infect Dis **2002**; 34:420–2.
66. Gilbert DN, Edwards JE Jr. Is there hope for the prevention of future antimicrobial shortages? Clin Infect Dis **2002**; 35:215–6; author reply 216–7.
67. Powers JH. Development of drugs for antimicrobial-resistant pathogens. Curr Opin Infect Dis **2003**; 16:547–51.
68. DiMassa JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. J Health Econ **2003**; 22:151–85.
69. Blaser MJ, Bartlett JG. Letter to FDA Commissioner Andrew C. von Eschenbach, MD.: Infectious Diseases Society of America, **2006**. Available at: http://www.idsociety.org/WorkArea/downloadasset.aspx?id=3384.
70. Boucher HW. Open public forum. In: FDA Anti-Infective Drugs Advisory Committee: Joint with Drug Safety and Risk Management Advisory Committee. Silver Spring, MD.
71. Blaser M. The Honorable Richard Burr: Health, Education, Labor and Pensions Committee. Bioterrorism and Public Health Preparedness Subcommittee. Vol. 2006, **2006**.
72. Bradley JS, Guidos R, Baragona S, et al. Anti-infective research and development—problems, challenges, and solutions. Lancet Infect Dis **2007**; 7:68–78.
73. Guidance for industry: acute bacterial sinusitis. Developing drugs for treatment. US Department of Health and Human Services. Rockville, MD: US Food and Drug Administration, Center for Drug Evaluation and Research (CDER), **2007**.
74. Bjerklie D, Gorman C, Kluger J, et al. The year in medicine from A to Z: it was a year of old scourges and new drugs, from the first vaccine that prevents cancer to a bug that spoiled an entire crop of California spinach. Time **2006**. Available at: http://www.time.com/time/specials/2007/article/0,28804,1685055_1685070,00.html.
75. Strategies to address Antimicrobial Resistance Act: patient stories. Arlington, VA: Infectious Diseases Society of America, **2007**.
76. US Government Accountability Office. New drug development: science, business, regulatory, and intellectual property issues cited as hampering drug development efforts. Report GAO-07-49. Washington, DC: US Government Accountability Office, **2006**.
77. Antimicrobial resistance: data to assess public health threat from resistant bacteria are limited. RCED-99–132. Washington D.C.: United States General Accounting Office, **1999**.
78. Spellberg B, Miller LG, Kuo MD, Bradley J, Scheld WM, Edwards JE. Societal costs versus savings from wild-card patent extension legislation to spur critically needed antibiotic development. Infection **2007**; 35:167–74.
79. Frankel T. Fiduciary law. California Law Review **1983**; 71:795–836.
80. Diamond J. Chapter 15. Big business and the environment. In: Collapse. New York: Penguin, **2005**:483–4.
81. Generic Pharmaceutical Association. Legislation promoted as a countermeasure against bioterrorism would counter bipartisan measures to constrain prescription costs. Arlington, VA: Generic Pharmaceutical Association, **2006**.
82. Dellit TH, Owens RC, McGowan JE Jr, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis **2007**; 44:159–77.