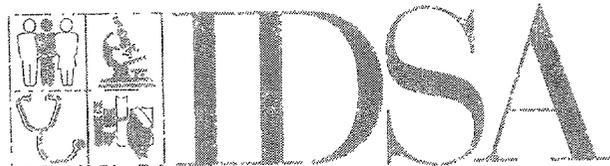
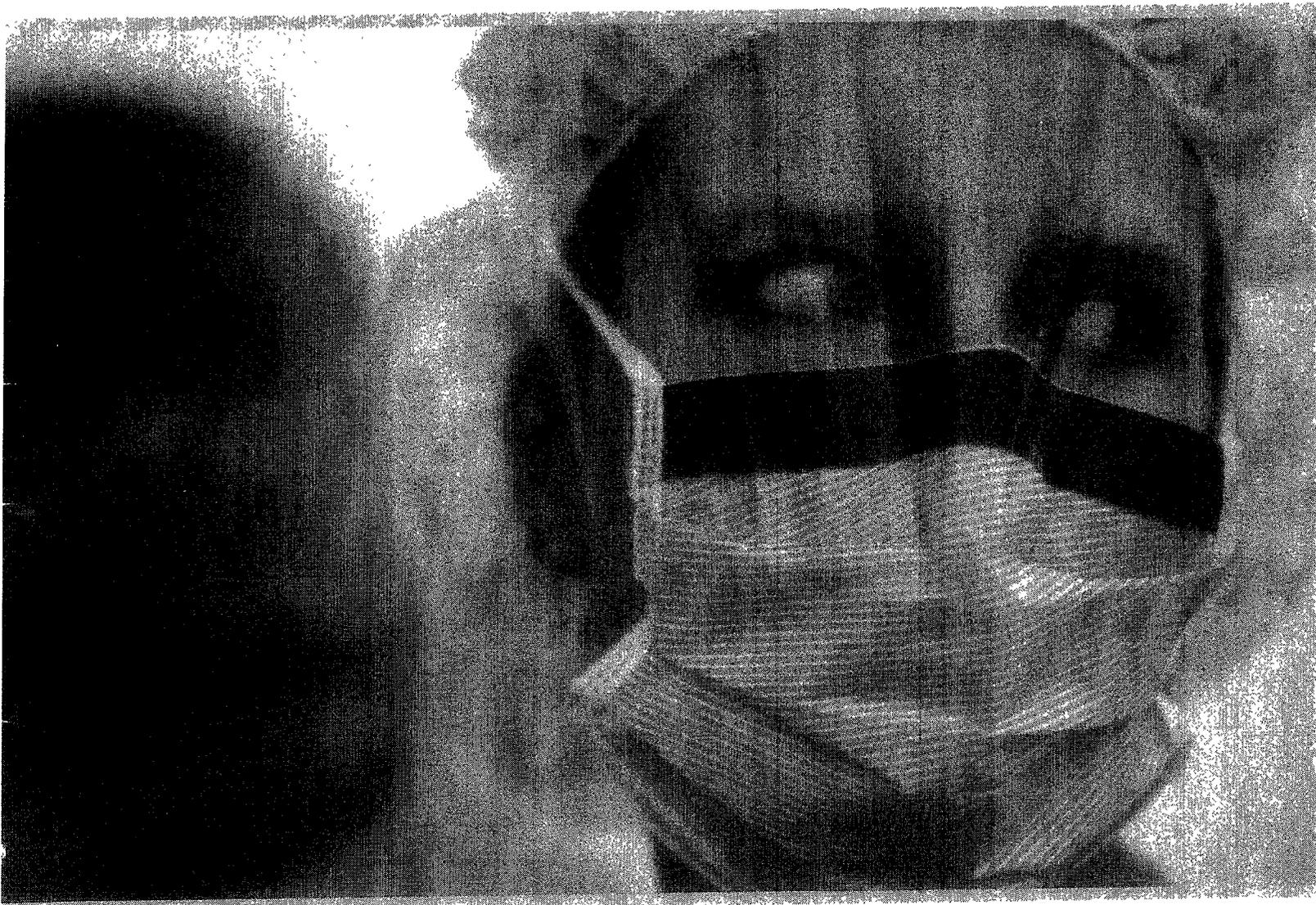




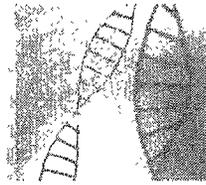
BAD BUGS, NO DRUGS

As Antibiotic Discovery Stagnates ...
A Public Health Crisis Brews



Infectious Diseases Society of America

July 2004



ABOUT IDSA

The Infectious Diseases Society of America (IDSA) represents more than 7,500 physicians, scientists, and other health professionals who specialize in infectious diseases in the United States and internationally.

Acknowledgements

IDSA is grateful to the many individuals who provided expert advice and assistance to the Society in the development of this paper. Most notably, we wish to express our sincere appreciation to the members of IDSA's Task Force on Antimicrobial Availability, who provided enormous contributions to our work over the past year. We also are grateful to the many government and industry officials and others who met with and advised IDSA leaders on the unique technical and business aspects of antibiotic research, development, evaluation, and review.

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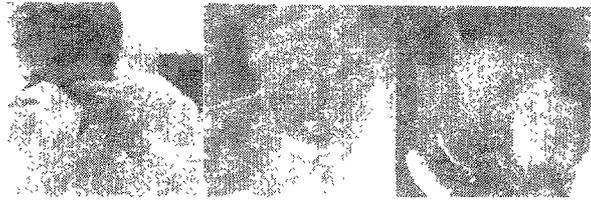
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THE NEXT EPIDEMIC BEGINS...

Day 1 A 34-year-old New Hampshire expectant mother visits her doctor's office complaining of severe stomach pain, vomiting, diarrhea, fever, and chills. She is diagnosed with an intestinal infection, given intravenous fluids and a prescription for a fluoroquinolone—an antibiotic—and is sent home.

Day 2 At a Massachusetts hospital's emergency room, a 2-year-old boy with a severe case of diarrhea, vomiting, dehydration, and fever is given fluids and administered a cephalosporin, another type of antibiotic, and is admitted to the hospital.

Day 4 The boy's lab results come back identifying the cause of his illness as *Salmonella*, a common foodborne bacterial infection, but, in this instance, the "bug" is highly resistant to the antibiotics commonly used to treat such infections, including cephalosporins and fluoroquinolones.

The baby boy dies of dehydration and bloodstream infection. As for the 34-year-old woman, the *Salmonella* infection results in a miscarriage of an otherwise normal baby followed by the woman's death.

Day 5 325 people are dead. Thousands—many of them children, the elderly, and other vulnerable individuals—jam emergency rooms across the Northeast complaining of similar symptoms. Cases have been reported in 15 states along the East Coast and in the Mid-Atlantic region. Isolated cases are reported in other states, including Texas and California. Fourteen cases are reported in Mexico and 27 cases in Canada.

Day 6 1,730 deaths and 220,000 illnesses have occurred in the United States. The epidemic expands in other countries.

Canada, Mexico, and Europe close their borders to U.S. food imports, and travel initiated from the United States is banned around the globe. Economic losses to the U.S. and global economies soon reach tens of billions of dollars.

The Food and Drug Administration and Centers for Disease Control and Prevention identify the source of the infections as a milk distribution facility located in New York state. They confirm that the *Salmonella* not only causes severe illness, but also is resistant to all available antibiotics. Doctors can only provide supportive care, not specific, antibiotic treatment.

Day 7 The number of deaths and illnesses continues to climb.

Think it can't happen? Think again. In 1985, milk contaminated with *Salmonella typhimurium* infected 200,000 people across the Midwest. What distinguishes that case from our scenario is the development of a fully antibiotic-resistant strain of the bacteria as compared to the one that is only partially drug-resistant. Such "bad bugs" are evolving. Some are already here.

Had bioterrorism prompted this scenario, infection rates could have been significantly higher, as several sources could have been intentionally contaminated. The toll on human lives and the U.S. economy would have been substantially worse.

Can we avert this catastrophe? If we act now, the answer is yes.

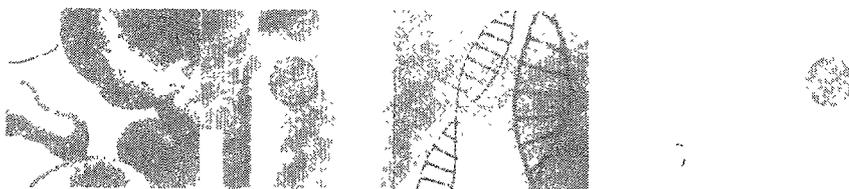


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EXECUTIVE SUMMARY

Antibiotic-Resistant Bacterial Pathogens: Why We Are Concerned

Antibiotics and other antimicrobial drugs have saved millions of lives and eased patients' suffering. Although they have been dubbed "miracle drugs," antibiotics are not always effective. Over time, bacteria can develop resistance to existing drugs, making infections difficult if not impossible to treat.

A multi-pronged approach is needed to limit the impact of antibiotic resistance on patients and the public. These efforts include educating physicians, patients, and parents about the appropriate use of antibiotics, developing and applying infection control and immunization policies and practices to prevent transmission, surveying clinical and prescription data, and developing safer alternatives to antibiotic uses in agriculture.

The purpose of this document, however, is to call attention to a frightening twist in the antibiotic resistance problem that has not received adequate attention from federal policymakers: The pharmaceutical pipeline for new antibiotics is drying up.

Until recently, research and development (R&D) efforts have provided new drugs in time to treat bacteria that became resistant to older antibiotics. That is no longer the case. Unfortunately, both the public and private sectors appear to have been lulled into a false sense of security based on past successes. The potential crisis at hand is the result of a marked decrease in industry R&D, government inaction, and the increasing prevalence of resistant bacteria. Infectious diseases physicians are alarmed by the prospect that effective antibiotics may not be available to treat seriously ill patients in the near future.

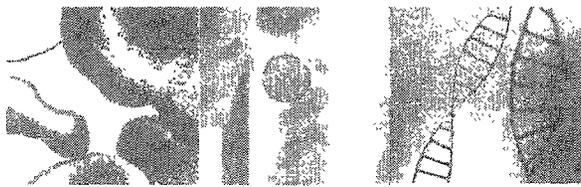
Why Policymakers Should be Concerned Too

Policymakers already have recognized the urgent need to spur R&D related to biodefense. While this concern is appropriate, it is important to keep things in perspective.

There has not been a single case of smallpox anywhere on the planet since the 1970s, but drug-resistant bacterial infections kill tens of thousands of Americans every year, and an epidemic could harm millions.

Why should policymakers care about antibiotic resistance and the lack of new antibiotics to treat resistant infections?

- Infections caused by resistant bacteria can strike anyone—the young and the old, the healthy and the chronically ill. Antibiotic resistance is a particularly serious problem for patients whose immune systems are compromised, such as people with HIV/AIDS and patients in critical care units.
- About 2 million people acquire bacterial infections in U.S. hospitals each year, and 90,000 die as a result. About 70 percent of those infections are resistant to at least one drug. The trends toward increasing numbers of infection and increasing drug resistance show no sign of abating.
- Resistant pathogens lead to higher health care costs because they often require more expensive drugs and extended hospital stays. The total cost to U.S. society is nearly \$5 billion annually.
- The pipeline of new antibiotics is drying up. Major pharmaceutical companies are losing interest in the antibiotics market because these drugs simply are not as profitable as drugs that treat chronic (long-term) conditions and lifestyle issues.
- Drug R&D is expensive, risky, and time-consuming. An aggressive R&D program initiated today would likely require 10 or more years and an investment of \$800 million to \$1.7 billion to bring a new drug to market.
- Resistant bacterial infections are not only a public health problem; they have national and global security implications as well.
- The Institute of Medicine and federal officials have identified antibiotic resistance and the dearth of antibiotic R&D as increasing threats to U.S. public health.



IDSA's Investigation

IDSA has investigated the decline in new antibiotic R&D for more than a year, interviewing stakeholders from all sectors. Society leaders have met with officials from the Food and Drug Administration (FDA), the National Institute of Allergy and Infectious Diseases (NIAID), the Centers for Disease Control and Prevention (CDC), congressional members and staff, executives from leading pharmaceutical and biotechnology companies, representatives from public-private partnerships that are focused on infectious diseases-related product development, patients, and other stakeholders. Each stakeholder has an important role in furthering future antibiotic discovery and development and limiting the impact of antibiotic resistance. However, based upon past successes, the pharmaceutical and biotechnology industries are clearly best situated to take the lead in developing the new antibiotics needed to treat bacterial diseases. As such, industry action must become the central focus of an innovative federal public health effort designed to stimulate antibiotic R&D.

IDSA's investigation has revealed that the incentives most likely to spur R&D within major pharmaceutical companies include those that provide financial benefits prior to a drug's approval (e.g., tax credits for R&D), commence at the time of approval (e.g., wild-card patent extension), reduce the costs of clinical trials (e.g., FDA flexibility concerning the evidence necessary to demonstrate safety and efficacy, NIAID-sponsored research to develop rapid diagnostics tests, etc.), and reduce companies' risks (e.g., liability protections). R&D at smaller biotechnology companies also could be stimulated through statutory and administrative changes. Finally, new funding for critical federal public health programs, and public and private research efforts, would help to ensure progress as well as limit the public health impact of antibiotic resistance.

Following is a list of specific potential legislative solutions, administrative recommendations, and funding requests

Potential Legislative Solutions To Fuel Innovation

Congress and the Administration must work together to enact statutory incentives that stimulate the discovery and development of new antibiotics to treat drug-resistant and other dangerous infections. Critical priority incentives that will have the greatest impact are indicated.

Commission to Prioritize Antimicrobial Discovery

CRITICAL PRIORITY

Establish and empower an independent Commission to Prioritize Antimicrobial Discovery to decide which infectious pathogens to target using these legislative R&D incentives and administrative solutions:

Supplemental intellectual property protections:

- "Wild-card patent extension."

CRITICAL PRIORITY

A company that develops and receives approval for a priority antibiotic could extend the market exclusivity period of another FDA-approved drug as long as the company commits to invest a portion of the profits derived during the extension period back into antibiotic R&D.

- Restoration of all patent time lost during FDA's review of priority antibiotics
- Extended market exclusivity similar to what has been successfully implemented for pediatric and orphan drugs

Other potential statutory incentives:

- Tax incentives for R&D of priority antibiotics

CRITICAL PRIORITY

- Measured liability protections

CRITICAL PRIORITY

- Additional statutory flexibility at FDA regarding approval of antibiotics, as needed

- Antitrust exemptions for certain company communications

- A guaranteed market



In 2002, out of 89 new drugs, no new antibiotics were approved.

Establish similar statutory incentives to spur R&D for rapid diagnostic tests for targeted pathogens, which will help to reduce the cost of clinical trials

Potential statutory incentives of interest to small biopharmaceutical companies:

- Waive FDA supplemental application user fees for priority antibiotics
- Tax credits specifically targeting this segment of the industry
- Small business grants

In addition to enacting statutory incentives to spur antibiotic R&D, Congress should work with the Administration to implement administrative recommendations at FDA and NIAID.

July 1997. A 7-year-old girl from urban Minnesota was admitted to a hospital with an infected right hip joint. Doctors drained the infected joint and treated the girl with the antibiotic cefazolin. On the third day of her hospital stay, tests showed the girl was infected with methicillin-resistant *Staphylococcus aureus* (MRSA), and the doctors changed her antibiotic to vancomycin, but it was too late: The infection had already invaded too deeply into her lungs. The girl suffered respiratory failure that day and was placed on a ventilator. After five weeks in the hospital, she died from a lung hemorrhage. This girl was previously healthy with no recent hospitalizations.

Food and Drug Administration Recommendations

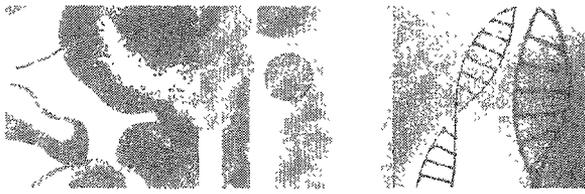
FDA is a pivotal and constructive partner in the process of antibiotic development. In order to effectively implement FDA's plan, *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*, modifications to existing policy, procedures, and guidelines are necessary. Each of the following recommendations is a critical priority.

CRITICAL PRIORITIES

- Accelerate the publication of updated guidelines for antibiotic clinical trials to provide needed clarity, and revisit existing guidelines as appropriate to ensure their relevance
- Encourage imaginative clinical trial designs that lead to a better understanding of drug efficacy against resistant bacterial pathogens
- Provide a clear definition of acceptable surrogate markers as end points for clinical trials of bacterial infections
- Explore and, when appropriate, encourage the use of animal models of infection, in vitro technologies, and valid microbiologic surrogate markers to reduce the number of efficacy studies required for each additional indication while maintaining safe and effective drug dose regimens
- Explore with NIAID all opportunities to streamline antibiotic drug development
- Grant priority antibiotics accelerated review status



Drug-resistant infections can strike anyone, even healthy children.



National Institute of Allergy and Infectious Diseases Recommendations

NIAID could play a central role in the R&D process. To do so, NIAID should implement the following recommendations. Each is a critical priority:

CRITICAL PRIORITIES

- Aggressively encourage translational (bench to bedside) research as described in NIH's *Roadmap for Medical Research*
- Remove roadblocks to antibiotic R&D that may exist in NIAID's structure and guidelines, including any unnecessary restrictions affecting companies' intellectual property rights
- Increase the number and size of grants that support discovery of new drugs that treat targeted pathogens
- Develop and expand collaborations with industry and the infectious diseases research community
- Sufficiently fund and rapidly launch NIAID's newly established Drug Discovery and Mechanisms of Antimicrobial Resistance Study Section
- Engage outside experts in research planning and ensure more transparent decision-making
- Explore with FDA all opportunities to streamline antibiotic drug development
- Encourage research on topics directly related to conduct of clinical trials
- Sponsor research into new rapid diagnostic tests for bacterial infections that, when available, could reduce the cost of clinical trials
- Encourage research on antibiotic use and resistance development
- Fund placebo-controlled trials to evaluate the necessity of antibiotic therapy for selected diseases

New Funding Needed

The increasing threat of drug resistance, concomitant with decreasing antibiotic R&D, requires a dramatic increase in public funding for CDC, FDA, NIAID, and public-private research efforts. At a minimum, Congress and the Administration must work together to invest *new* resources (i.e., not shift funds from other public health efforts) into the following critical program areas:

- Double CDC's antimicrobial resistance program funding to \$50 million in 2005 and continue to increase it by \$25 million increments until 2009 to a total of \$150 million
- Increase FDA's funding by \$25 million to support implementation of the *Critical Path* plan (which would help decrease the cost of antibiotic development), the development of new antibiotic guidelines, and to speed antibiotic reviews
- Significantly increase NIAID's translational and antibiotic resistance research efforts
- Support synergistic public/private partnerships that focus on infectious diseases medicines

Conclusion

Without innovative public policy and additional financial support, fewer and fewer antibiotics will be available to treat the increasing number of drug-resistant and dangerous microbes that threaten Americans and the global community. The proposals advanced in this document are intended to ensure a sustainable supply of safe and effective antibiotics to protect the public's health.

We urge policymakers to act quickly.



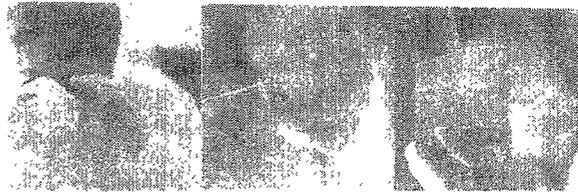
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"Infectious diseases physicians are alarmed by the prospect that effective antibiotics may not be available to treat seriously ill patients in the near future. There simply aren't enough new drugs in the pharmaceutical pipeline to keep pace with drug-resistant bacterial infections, so-called 'superbugs.'"



*Joseph R. Dalovisio, MD
IDSA President*



RESISTANCE ON THE RISE

Antibiotics* have saved millions of lives and eased the suffering of patients of all ages for more than 60 years. These “wonder drugs” deserve much of the credit for the dramatic increase in life expectancy in the United States and around the world in the 20th century. They prevent amputations and blindness, advance our ability to perform surgery, enable new cancer treatments to be used, and protect the lives of our military men and women. A famous infectious disease expert once noted that the discovery of penicillin in the early 1940s gave more curative power to a lone provider than the collective talent of all the physicians in New York City at that time. Unfortunately, it is inevitable that, over time, bacteria develop resistance to existing antibiotics, making infections more difficult to treat.

Antibiotic resistance is not a new phenomenon. National surveillance data and independent studies show that drug-resistant, disease-causing bacteria have multiplied and spread at alarming rates in recent decades. A diverse range of patients is affected. The Institute of Medicine (IOM), Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), and the Food and Drug Administration (FDA) warn that drug-resistant bacteria are a serious public health threat, especially considering that there are few novel drugs in the pipeline to combat them.

Infections that were once easily curable with antibiotics are becoming difficult, even impossible, to treat, and an increasing number of people are suffering severe illness—or dying—as a result. This year, nearly 2 million people in the United States will acquire bacterial infections while in the hospital, and about 90,000 of them will die, according to CDC estimates. More than 70 percent of the bacteria that cause these infections will be resistant to at least one

of the drugs commonly used to fight them. (See Table 1.) In a growing and frightening number of cases, these bacteria are resistant to many approved drugs, and patients have to be treated with new, investigational compounds or older, toxic alternatives. For many patients, there simply are no drugs that work.

The resistance problem “has probably been smoldering for years, but recently it’s almost like a switch got triggered,” medical professor Stuart H. Cohen, MD, of the University of California, Davis, recently told the *Wall Street Journal*.

“Antibiotic resistance is increasing too quickly and in too many organisms,” said Harvard Medical School pediatric infectious disease specialist Jonathan Finkelstein, MD, in the same article.

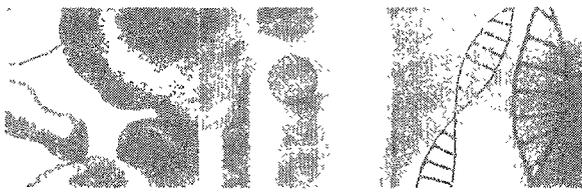
Table 1: Estimated Cases of Hospital-Acquired Infections Caused by Selected Resistant Bacteria in the United States in 2002

Antibiotic-Resistant Bacteria	Estimated Cases
Methicillin/ <i>S. aureus</i>	102,000
Methicillin/CNS	130,000
Vancomycin/enterococci	26,000
Ceftazidime/ <i>P. aeruginosa</i>	12,000
Ampicillin/ <i>E. coli</i>	65,000
Imipenem/ <i>P. aeruginosa</i>	16,000
Ceftazidime/ <i>K. pneumoniae</i>	11,000

Source: Centers for Disease Control and Prevention, Division of Healthcare Quality Promotion

These preliminary estimates were extrapolated by CDC staff from data collected from hospitals that participate in the National Nosocomial Infections Surveillance System. NNIS hospitals are disproportionately large, urban, and affiliated with medical schools and are more likely to have more seriously ill patients. As such, these estimates should be interpreted cautiously. CNS=Coagulase-negative staphylococci

*Antibiotics are a type of antimicrobial, a broad term used to describe any agent that inhibits the growth of microorganisms, including bacteria, viruses, fungi, yeast, protozoa, and parasites. Antibiotics target bacteria—the “bad bugs” addressed in this paper. Bacteria are by far the most common cause of infectious diseases-related deaths in the United States.



According to IOM and FDA, only two new classes of antibiotics have been developed in the past 30 years, and resistance to one class emerged even before FDA approved the drug. (See Table 2.)

Furthermore, some strains of resistant bacteria are no longer confined to hospitals and are occurring in otherwise healthy individuals in communities across the United States and other countries.

As resistant bacteria multiply, so does the burden they place on our health care system. The economic cost has reached billions of dollars annually in the United States, according to estimates from IOM and the former Congressional Office of Technology Assessment. The human cost in terms of pain, grief, and suffering, however, is incalculable.

Table 2: History of Antibiotic Discovery and Approval

Year Introduced	Class of Drug
1935	Sulfonamides
1941	Penicillins
1944	Aminoglycosides
1945	Cephalosporins
1949	Chloramphenicol
1950	Tetracyclines
1952	Macrolides/ Lincosamides/ Streptogramins
1956	Glycopeptides
1957	Rifamycins
1959	Nitroimidazoles
1962	Quinolones
1968	Trimethoprim
2000	Oxazolidinones
2003	Lipopeptides

Source: Food and Drug Administration (modified)

Presented by John H. Powers, MD, at April 15-16, 2004 "Antimicrobial Drug Development Workshop," co-sponsored by FDA, IDSA, and the International Society of Anti-Infective Pharmacology.

Fast-Moving Targets

To understand how quickly disease-causing bacteria can develop resistance to antibiotics, take the example of *Staphylococcus aureus* (staph), a common cause of hospital infections that can spread to the heart, bones, lungs, and bloodstream with fatal results. Penicillin, introduced in the early 1940s, once kept staph bacteria at bay. However, penicillin-resistant staph bacteria were identified as early as 1942. By the late 1960s, more than 80 percent of staph bacteria were penicillin-resistant. Methicillin was introduced in 1961 to combat resistant staph bacteria, but reports of methicillin-resistant *Staphylococcus aureus* (MRSA) rapidly followed. In 1974, 2 percent of the staph bacteria found in U.S. hospitals were methicillin-resistant. By 2002, that figure had jumped to 57.1 percent, according to CDC data. (See Chart 1 and Table 3.)

Staph infections have acquired resistance to many other drugs in addition to penicillin and methicillin. In fact, according to CDC, about half of the identified MRSA strains in U.S. hospitals are resistant to all but a few antibiotics. Causing even greater alarm, staph bacteria partially resistant to vancomycin, a drug of last resort in the treatment of several resistant infections, were discovered in patients in the late 1990s. Two cases of fully vancomycin-resistant *Staphylococcus aureus* (VRSA) were reported in 2002 and a third in 2004.

MRSA is no longer a problem confined to hospitals. One ongoing study of children with community-acquired staph infections at the University of Texas has found nearly 70 percent infected with MRSA. In a 2002 outbreak, 235 MRSA infections were reported among military recruits at a training facility in the southeastern United States. In addition, a total of 12,000 cases of community-acquired MRSA were found in three correctional facilities (Georgia, California, and Texas) between 2001 and 2003.

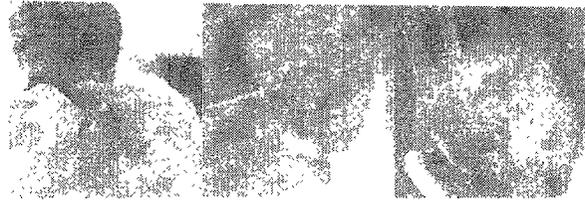
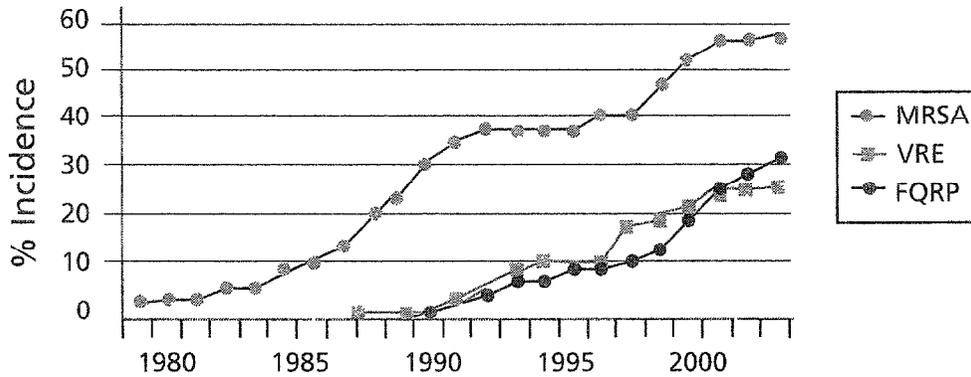


Chart 1: Resistant Strains Spread Rapidly



Source: Centers for Disease Control and Prevention

This chart shows the increase in rates of resistance for three bacteria that are of concern to public health officials: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and fluoroquinolone-resistant *Pseudomonas aeruginosa* (FQRP). These data were collected from hospital intensive care units that participate in the National Nosocomial Infections Surveillance System, a component of the CDC.

Other resistant bacterial infections also are raising significant public health concerns:

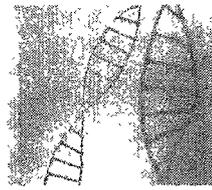
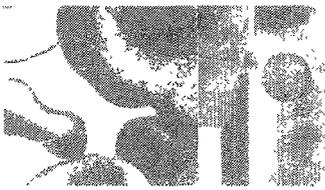
- In 1998, IOM reported an alarming rise in the incidence of infections due to a bacterium called enterococcus, which causes wound infections, infections in blood, the urinary tract and heart, and life-threatening infections acquired in hospitals. Vancomycin has been a core treatment for enterococci. The percentage of enterococci resistant to vancomycin (VRE) has been increasing dramatically since the late 1980s, according to CDC. In 2002, more than 27 percent of tested enterococci samples from intensive care units were resistant to vancomycin. (See Chart 1 and Table 3.)
- The percentage of *Pseudomonas aeruginosa* bacteria resistant to either ciprofloxacin or ofloxacin, two common antibiotics of the fluoroquinolone class (FQRP), has increased dramatically from the late 1980s to the present. Recent CDC data show that in 2002, nearly 33 percent of tested samples from intensive care units were resistant to fluoroquinolones. *P. aeruginosa* causes infections of the urinary tract, lungs, and wounds and other infections commonly found in intensive care units. (See Chart 1 and Table 3.)

Table 3: Percent of Drug Resistance in Hospital-Acquired Infections in 2002

Drug/Pathogen	Resistance (%)
Methicillin/ <i>S. aureus</i>	57.1
Vancomycin/enterococci	27.5
Quinolone/ <i>P. aeruginosa</i>	32.8
Methicillin/CNS	89.1
3 rd -gen. Ceph./ <i>E. coli</i>	6.3
3 rd -gen. Ceph./ <i>K. pneumoniae</i>	14.0
Imipenem/ <i>P. aeruginosa</i>	22.3
3 rd -gen. Ceph./ <i>P. aeruginosa</i>	30.2
3 rd -gen. Ceph./ <i>Enterobacter spp.</i>	32.2
Penicillin/ <i>S. pneumoniae</i>	11.3

Source: CDC National Nosocomial Infections Surveillance System, August 2003 for all, except penicillin resistant *Streptococcus pneumoniae*, which is the Active Bacterial Core Surveillance of the Emerging Infections Network.

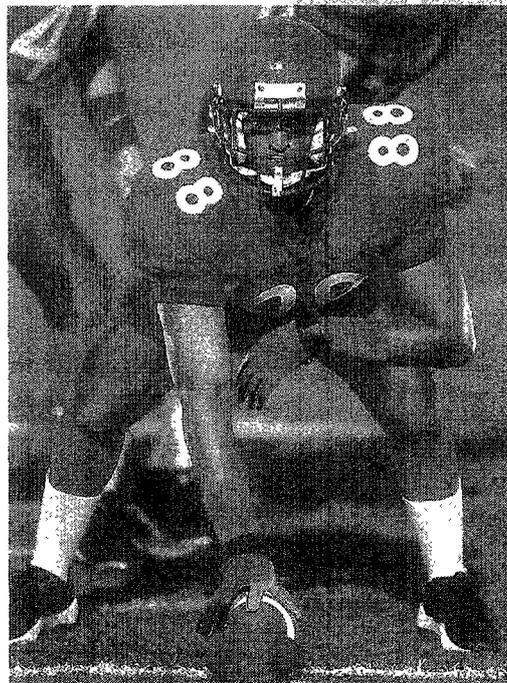
This table provides a snapshot of selected drug-resistant pathogens associated with hospital infections in intensive care unit patients during 2002. CNS=Cocci-negative staphylococci, 3rd Ceph=resistance to 3rd generation cephalosporins (either ceftaxime, cefotaxime, or ceftazidime), Quinolone=resistance to either ciprofloxacin or ofloxacin.



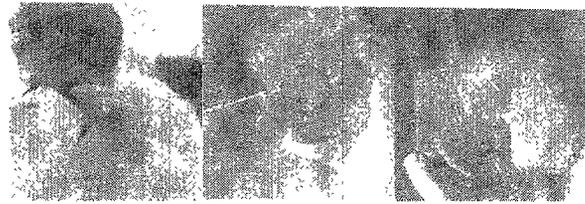
- *Streptococcus pneumoniae* is the most feared bacterium that causes pneumonia. *S. pneumoniae* strains that are resistant to penicillin and other drugs are emerging rapidly in the United States. Up to 40 percent of infections caused by this bacterium are resistant to at least one drug, and 15 percent are resistant to three or more drugs, the CDC reports. Aside from 100,000 cases of pneumonia each year, this bacterium causes childhood ear infections (6 million per year), meningitis (3,300 per year), and sinusitis (thousands of cases)
- Multidrug-resistant *Acinetobacter*, a type of bacteria that has caused stubborn wound infections in U.S. soldiers and civilians stationed in Iraq, has been increasingly reported worldwide. Pneumonia due to *Acinetobacter* infections is now considered one of the most difficult hospital-acquired infections to control and treat, according to a recent study in *Clinical Infectious Diseases (CID)*. An international surveillance study, also reported in *CID*, tested hundreds of *Acinetobacter* samples and found various levels of resistance to 15 drugs. Some *Acinetobacter* strains are resistant to virtually every available drug with the exception of one toxic antibiotic that causes substantial side effects.
- Salmonellosis, a common foodborne infection that causes diarrhea, can cause serious illness and death. Nationally, the incidence of *Salmonella* bacteria resistant to cephalosporins, an antibiotic commonly used to treat severe salmonellosis, rose nearly fivefold (from 0.5 percent to 2.4 percent) between 1998 and 2001, according to a study published in the *Journal of Infectious Diseases*. In Massachusetts during the same time period, the prevalence of drug-resistant *Salmonella* rose from 0 percent to 53 percent.

- Tuberculosis (TB) is becoming increasingly difficult to treat. The World Health Organization estimates that up to 50 million people worldwide may be infected with drug-resistant strains of TB. Treatment for resistant TB strains can take up to 24 months, as opposed to the six months generally required to treat non-resistant strains.

Since 2000, CDC has reported a new phenomenon—community-acquired outbreaks of MRSA among athletes, including college football players in Pennsylvania, wrestlers in Indiana, and a fencing club in Colorado. Public health officials believe that physical contact and the sharing of clothing or equipment probably leads to the spread of infection in these otherwise healthy people. In September of 2003, this issue was brought to national attention when MRSA broke out in Florida among the Miami Dolphins, sending two players to the hospital for treatment.



Many athletes have developed methicillin-resistant *Staphylococcus aureus* (MRSA), which can infect the heart, bones, lungs, and bloodstream.



The Human Toll

Statistics cannot convey the human toll that resistant organisms take on their victims. Throughout this paper are stories of previously healthy people who became seriously ill or died as a result of drug-resistant infections. These examples, reported by the CDC, the media, and infectious diseases physicians, show that resistant infection can strike anyone, at any time. They serve as examples of what an increasing number of Americans could face as a result of the impending public health crisis.

The Economic Burden

Drug-resistant bacteria impose an economic burden on the United States on the order of billions of dollars annually, according to several authoritative analyses. Drug-resistant infections are significantly more expensive to treat than non-resistant infections because of longer hospitalizations, extra physician visits, the higher cost of alternative antibiotics, more post-hospital care, lost work days, and deaths. For example, resistant TB strains are as much as 100 times more expensive to treat than non-resistant strains, according to Lee B. Reichman, MD, MPH, director of the New Jersey Medical School National Tuberculosis Center. MRSA infections cost an average of \$31,400 per case to treat compared to \$27,700 per case for non-resistant infections, according to a study cited in the IOM report *Antimicrobial Resistance. Issues and Options* (1998).

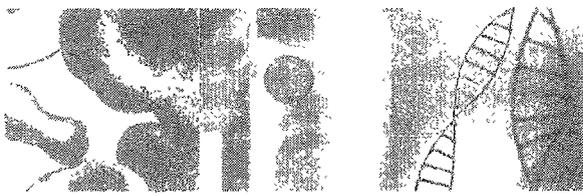
The same IOM report estimated that the total cost to U.S. society of antimicrobial resistance was at least \$4 billion to \$5 billion annually. A 1995 cost analysis by the former Congressional Office of Technology Assessment (OTA) provided similar dollar estimates when factors such as the costs of lost work days and costs for post-hospital care are considered. OTA went further to say that "these costs can be expected to increase rapidly as the numbers of antibiotic resistant bacteria increase."

A multi-pronged approach is essential to limit the impact of antibiotic resistance on patients and public health. Good antibiotic stewardship, infection control and prevention efforts, increased surveillance, and limits on agricultural uses of antibiotics are extremely important. But a more pressing concern is that, as the number of resistant pathogens continues to grow, the pipeline of antibiotics used to treat these "bad bugs" is quickly drying up.



Patients with Compromised Immune Systems at Greater Risk

Antibiotic resistance is a serious problem for people with compromised immune systems, including patients in hospital critical care units and the 40 million people living with HIV/AIDS in the United States and globally. Their weakened immune systems make these patients particularly vulnerable to drug-resistant and other bacterial infections. A recent study published in *Clinical Infectious Diseases* has shown that the very patients most vulnerable to the devastating impact of resistant infections—those with compromised immune systems—also are more likely than other patients to be infected with resistant pathogens. Furthermore, in many areas of the world, patients infected with HIV are more likely to die as a result of bacterial infections, such as tuberculosis, than of the underlying HIV infection. A wider array of antibiotics that treat bacterial infections—particularly drug-resistant strains—could offer significant hope to people with compromised immune systems.



THE PIPELINE OF NEW ANTIBIOTICS IS DRYING UP

In spite of the pressing need for new drugs to treat resistant infections, there simply are not enough new antibiotics in the pharmaceutical pipeline to keep pace. Major pharmaceutical companies with the R&D “muscle” to make progress are losing interest in the antibiotics market, even as they increase their overall R&D budgets. Of greatest concern is the dearth of resources being invested in drug discovery.

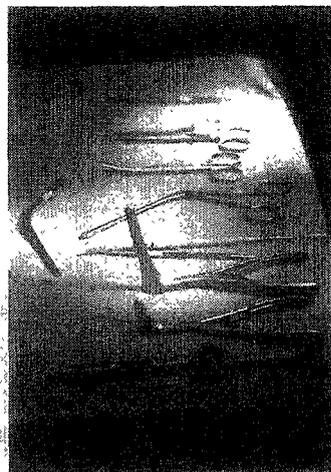
The trend started more than 10 years ago. In 1990, half of the large pharmaceutical companies in the United States and Japan reported that they had halted or significantly decreased their antibiotic discovery efforts. That same year, several companies attempted to get back into the market, spurred on by worsening problems with MRSA and a VRE outbreak. But the enthusiasm was short-lived. In 2000, Roche announced that it was spinning off its anti-infective discovery division. In 2002, Bristol-Myers Squibb Company, Abbott Laboratories, Eli Lilly and Company, and Wyeth all halted or substantially reduced their anti-infective discovery efforts, and Aventis announced plans to spin off its anti-infectives division. Procter & Gamble also appears to be withdrawing from new antibiotic R&D. Other companies appear to have decreased the number of employees assigned to antibiotic discovery and development

A growing number of drug companies appear to be withdrawing from new antibiotic research and development.

An article in the January-February 2004 issue of *Health Affairs* described the impact of these reductions on the ability of pharmaceutical companies to develop new drugs to target antibiotic resistance: “Today there are few champions for the study of infectious diseases mechanisms, and few within the industry are able to interpret the epidemiological data in a way that translates into business decisions.”

Companies’ efforts to downsize antibiotic R&D activities have had a notable impact on the number of antibiotics moving through the pipeline.

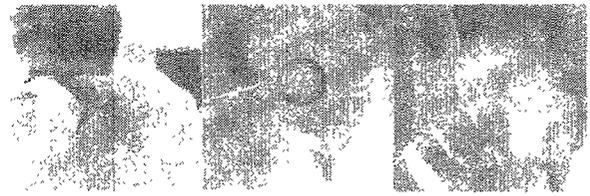
A recent analysis published in *Clinical Infectious Diseases* found only five new antibiotics in the R&D pipeline out of more than 506 drugs in development.* The authors evaluated the websites or 2002 annual reports of 15 major pharmaceutical companies with a track record in antibiotic development and seven major biotechnology companies.** Their analysis revealed four new antibiotics being developed by pharmaceutical companies, and only one antibiotic being developed by a biotech company. By comparison, the analysis found that the pharmaceutical companies were developing 67 new drugs for cancer,



April 2004. A 46-year-old Maryland man received a transplant and was sent to the intensive care unit. His blood cultures grew *Acinetobacter* that was resistant to all antibiotics except colistin, a drug rarely used because it is very toxic. He died.

*“Development” in this context refers to phases 2 and 3 of human testing—the later stages of the R&D process

**Pharmaceutical companies examined were Merck & Co., Johnson & Johnson, Pfizer, GlaxoSmithKline, Bristol-Myers Squibb, Aventis, Pharmacia, Novartis, F. Hoffman-La Roche, AstraZeneca, Abbott Laboratories, Wyeth, Eli Lilly & Company, Schering-Plough, and Bayer. Biotech companies were Amgen, Genentech, Applera, Genzyme, Serono, Chiron, and Biogen. The authors’ list of new drugs in the pipeline also included telithromycin, which was subsequently approved by FDA



33 for inflammation/pain, 34 for metabolic/endocrine disorders, and 32 for pulmonary disease. The biotech companies were developing 24 drugs for inflammation/immunomodulators, 14 drugs for metabolic/endocrine disorders, and 13 for cancer.

The end result of the decline in antibiotic discovery research is that FDA is approving few new antibiotics. Since 1998, only 10 new antibiotics have been approved, two of which are truly novel—i.e., defined as having a new target of action, with no cross-resistance with other antibiotics. In 2002, among 89 new medicines emerging on the market, none was an antibiotic.

IOM's 2003 report on microbial threats reinforces the point, noting that although at first glance the situation with respect to antibiotics currently in clinical development looks encouraging, not one *new class* of antibiotics is in late-stage development. "Rather these 'new' antibiotics belong to existing classes, including macrolides and quinolones, that have been used to treat humans for years," IOM said.

Infectious disease experts are particularly concerned about the dearth of new "narrow-spectrum" agents—that is, drugs that fight a specific infectious organism. Many of the antibiotics in development today are "broad-spectrum"—meaning they are intended to work against a wide range of organisms—which are more likely to contribute to the development of resistance.

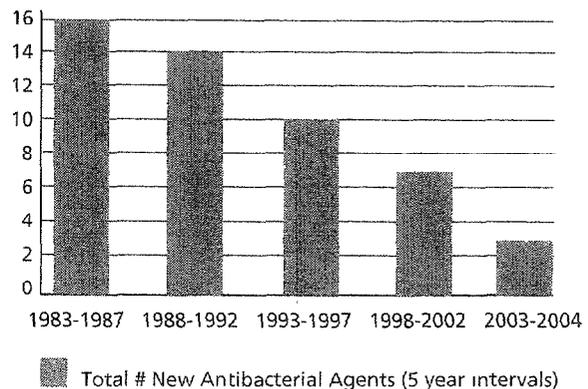
Only about five new antibiotics are in the drug pipeline, out of more than 506 agents in development.

Table 4: New Antibacterial Agents Approved Since 1998

Antibacterial	Year	Novel
rifapentine	1998	No
quinupristin/dalfopristin	1999	No
moxifloxacin	1999	No
gatifloxacin	1999	No
linezolid	2000	Yes
cefditoren pivoxil	2001	No
ertapenem	2001	No
gemifloxacin	2003	No
daptomycin	2003	Yes
telithromycin	2004	No

Source: Spellberg et al, *Clinical Infectious Diseases*, May 1, 2004 (modified)

Chart 2: Antibacterial Agents Approved, 1983-2004



Source: Spellberg et al, *Clinical Infectious Diseases*, May 1, 2004 (modified)



Medical Need Versus Market Realities

There is a growing disconnect between the medical need perceived by those who practice infectious diseases medicine and the market as assessed by the pharmaceutical industry. Infectious diseases physicians see a significant need for new antibiotics to treat a growing number of bacterial infections from which their patients suffer—but antibiotic R&D does not add up from a business perspective. The costs outweigh the benefits to a company's bottom line.



Are Small Biotechnology Companies Engaged?

If major pharmaceutical companies are exiting the field, what about smaller biopharmaceutical companies?

Indeed, several smaller companies are focusing on the development of antibiotic compounds (e.g., Cubist Pharmaceuticals, Basilea, Paratek, Vicuron Pharmaceuticals, and Oscient). However, a substantial number of other small companies simply are pursuing development of drugs that have been licensed from the major companies—i.e., most are not involved in basic discovery research. While some smaller companies are funding antibiotic discovery programs, it remains to be seen whether they can be successful in the absence of the financial support and expertise available at larger companies. In order to advance new classes of antibiotics from discovery to development, they may need the financial support of larger companies or other backers to fund late-stage clinical trials and commercialization. For the economic reasons described in this paper, it is not apparent that such support will be forthcoming.

The pharmaceutical industry, like all other publicly traded industries, must deliver for its shareholders in order to justify their continued investment. The unique nature of antibiotics makes securing investments challenging. Because antibiotics work so well and so fast, they produce a weak return on investment for manufacturers. Antibiotics are commonly prescribed for seven to 14 days. Even for the most serious of infections, these drugs are rarely needed for more than four to six weeks.

Understandably, pharmaceutical and biotechnology companies and their investors are drawn to develop products that provide greater returns on investments. The favored drugs include those that patients take for life, like insulin for diabetes, statins for elevated cholesterol, and drugs that treat hypertension and arthritis. Although these drugs do address significant medical needs, other drugs—like those used to treat impotence, baldness, and other lifestyle issues—have little to no medical benefit at all but are likely to reap huge profits.

Experts in industry, government, and academia understand the problem and have acknowledged it for years:

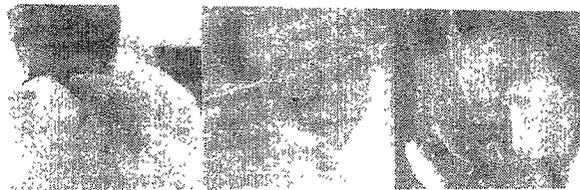
- “Product development in areas crucial to public health goals, such as antibiotics, has slowed significantly during the past decade.” (U.S. Food and Drug Administration. *Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*. March 2004.)
- “To describe drug research in trendy terms: chronic disease medications are in; anti-infectives are out.” When it comes to annual sales potential, antibiotics don't measure up. An industry representative speaking at a scientific conference noted that a musculoskeletal drug is worth about \$1.150 billion, a neuroscience treatment is rated at \$720 million, and a medicine for resistant Gram-positive cocci is worth only \$100 million. (Sellers, L.J. Big pharma bails on anti-infectives research. *Pharmaceutical Executive* December 2003, 22.)

- “As a consumer, you want a drug [that] you don’t have to take very long and works very well. But that isn’t the most profitable type of drug. . . . [I]n some cases the economics and the public health imperative do not match up.” (Mark Goldberger, acting deputy director of FDA’s Center for Drug Evaluation and Research, quoted in Service, RF. Orphan drugs of the future? *Science* March 19, 2004, Vol 303, 1798.)
- U.S. demographics shifting toward an increasingly older population will lure even more investors and companies to the chronic diseases market. As generics compete with existing products, companies face additional pressure to develop new blockbusters, which account for most of their revenue. (Health Care Industry Market Update: Pharmaceuticals, Centers for Medicare and Medicaid Service January 10, 2003.)

Limiting Resistance—and Profitability, Too

Antibiotic resistance—and public health measures to combat resistance—also pose unique challenges to securing investment in antibiotic R&D. Resistance limits the effectiveness of antibiotics over time and therefore decreases a drug’s long-term profitability. Antibiotics and other antimicrobials are the only drugs where extensive use leads to loss of benefit.

In addition, infectious diseases physicians and other public health experts often hold new antibiotics in reserve, hoping to avoid fostering the rapid emergence of resistant bacteria and saving them for when they are most needed. This unusual practice is unique to anti-infective drugs. From a public health perspective, the strategy is sensible. However, in pharmaceutical industry terms, this practice translates into a “slow commercial uptake” that limits the potential market for new antibiotics. Drug company representatives have said that physicians’ efforts to preserve antibiotics for the treatment of resistant infections serve as a disincentive to antibiotic discovery and development.



August 2003. A 7-year-old Texas boy came down with a fever of nearly 103 degrees and complained of severe pain in his leg. He was taken to Hermann Children’s Hospital in Houston, where doctors discovered that a virulent, drug-resistant staph infection was causing a potentially fatal blood clot in the boy’s leg. Fortunately, in this case, surgery was life-saving.

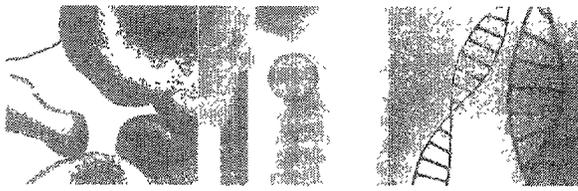


Infectious disease doctors often hold new antibiotics in reserve because of concerns about resistance.

Technical Hurdles

In addition to the lack of effective market incentives, antibiotic R&D is hampered by technical challenges as well. As IOM’s microbial threats report noted, “the discovery of new antibiotics is not as easy as was once believed.”

Until the early 1990s, pharmaceutical companies tended to develop new infectious diseases drugs by randomly screening natural products to identify those demonstrating antimicrobial activity. New technologies in use since then, such as combinatorial chemistry, X-ray crystallography, high throughput screening, and molecular modeling, have not been as successful in identifying new antibiotics as might have been hoped.



Moreover, industry representatives speaking about these challenges at a recent scientific meeting said that genomic data have “failed to deliver the expected flood of novel targets.”

Assuming one has a novel target of action within the bacterium, there is still the challenge of finding a chemical entity that can reach the target site and inhibit growth, without being too highly toxic to patients. “The technical hurdles, coupled with competition for resources within pharmaceutical companies from other significant medical needs with larger market opportunities, have led to reduced investment in or, in the case of most companies, elimination of antibiotic drug discovery programs,” concluded IOM.

Additional Hurdles for Clinical Trials of New Antibiotics

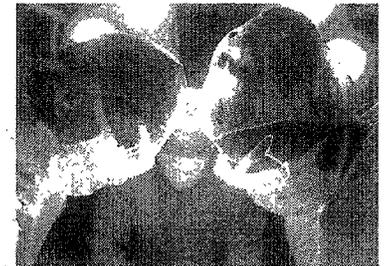
In addition to market and technical challenges, industry representatives cite scientific and regulatory hurdles as impediments to antibiotic approvals.

Because antibiotics are used to treat various types of infection (e.g., pneumonia, urinary tract infection, skin and soft tissue infection), the drug approval process requires clinical trials for each of these indications (one trial or often more per indication), with enrollment of large numbers of patients to ensure an understanding of a drug’s safety and effectiveness against specific bacterial pathogens.

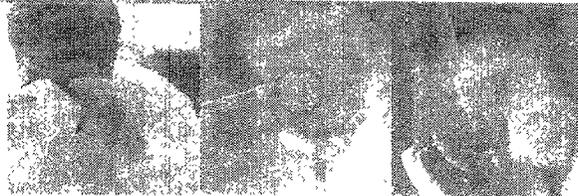
Finding enough patients to enroll in clinical trials of new drugs to treat resistant pathogens is no easy task. By contrast, when enrolling patients in a clinical trial to test a new cancer drug, researchers know from the start whether a specific patient has the specific type of cancer they are targeting. With antibiotic clinical trials, that is not necessarily the case. For many resistant pathogens, there are no rapid diagnostic tests available to help researchers to identify patients who would be eligible for their studies.

As one industry consultant explained, in order to test a drug that is intended to treat resistant strains, “You have to wait for epidemics to break out in hospital wards, and you can’t predict when that will happen. It may take five years to complete a clinical study.”

One company’s experience in trying to develop a new drug to treat vancomycin-resistant enterococci (VRE) illustrates some of the challenges. Researchers used entry criteria that were developed in consensus with FDA and academia. With 54 research sites open for two years, only three patients enrolled in the study—it was closed for insufficient enrollment. When a second study was launched, only 45 subjects enrolled over a period of 18 months. This does not mean that there are few VRE infections; indeed, according to CDC, there are estimated to be 26,000 hospital-acquired cases each year in the United States. (See Table 1.) The problem is in the ability to anticipate their presence and to enroll critically ill patients in clinical trials.



July 2001. An 11-year-old boy struck by a resistant staph infection first spent seven weeks in the hospital, two of those weeks in intensive care, and then underwent 12 surgeries over the next two years to excise the infection and repair the damage it inflicted on his thigh bone. After two years of operations, body casts, wheelchairs, and crutches, this boy is finally able to walk and run again, although with a limp because his previously infected leg is now shorter than the other.



Updated FDA guidance documents defining the investigational approaches for each type of infection, some of which are currently in review, will bring needed clarity to drug development teams within industry. Such guidance would provide a better understanding about the type of safety and efficacy data that FDA could find to be scientifically compelling and acceptable when evaluating new antibiotic applications.

Lengthy, Costly, and Risky Process

As with any other drug, antibiotic R&D is a lengthy, costly, and risky process.

According to a September 2003 review by the Tufts Center for the Study of Drug Development, the median time from the beginning of clinical testing through FDA review for new antibiotics and similar drugs was just over six years (55.8 months in the clinical phase; 18.6 months in the review phase) * Preclinical identification and testing of potential candidate drugs may add several more years to the process.

During the pre-approval phases of drug discovery and development, a product's patent clock is ticking away. Most patents are filed during the pre-clinical phase, which means that the effective patent life of a new compound once it is brought to market is less (sometimes substantially so) than the 20 years provided by law. Although current law allows for restoration of some patent time lost during FDA's period of review, not all lost time is restored.

Because antibiotics work so well and so fast, they produce a weak return on investment for manufacturers.

The 2003 IOM report acknowledged this challenge, noting that "the development of an antibiotic is an expensive and risky process; no guarantee can be made that the antibiotic will remain effective and the investment will be regained before the patent period has ended." As for the cost, according to a recent FDA report, bringing a new drug to market can cost \$800 million to \$1.7 billion.

The pharmaceutical industry's risks are high. According to the Pharmaceutical Research and Manufacturers of America, only five in 5,000 compounds that enter preclinical testing make it to human testing, and only one of these five is approved. If a product is not going to produce strong profits, then other products with greater market potential will get the "green light" for the next phase of development.

Pharmaceutical Charity Helps, But Is Not the Solution

The pharmaceutical industry participates in many areas of public health and provides many good works *pro bono*. Some examples include Merck & Co.'s efforts related to River Blindness; efforts by Bristol-Myers Squibb, Pfizer, and other drug companies related to global AIDS; and GlaxoSmithKline's malaria and AstraZeneca's TB drug discovery initiatives. Nevertheless, industry cannot alter its fundamental business strategy in any way that would place its bottom line at risk. Policymakers and the public should have no illusions that future pharmaceutical charity will be sufficient to address the existing and emerging pathogens that threaten public health.

*The study looked at small molecule anti-infectives approved between 1982 and 2001



THE FEDERAL GOVERNMENT'S RESPONSE

Much has been written about antibiotic resistance and the decline in R&D. Many groups have supported strengthening the U.S. and international governments' response to this growing public health crisis, including IOM, the World Health Organization, the Congressional Office of Technology Assessment, the American Society for Microbiology, and the Alliance for the Prudent Use of Antibiotics.

To date, the U.S. government's action has been inadequate to address the brewing crisis, but the Administration and Congress recently have announced several proposals, which, if successfully and fully implemented, could make a difference.

- **NIH's Roadmap for Medical Research**

NIH's *Roadmap*, issued in September 2003, outlines a series of initiatives to "speed the movement of research discoveries from the bench to the bedside." After

decades of investment in basic biomedical research, the *Roadmap* is intended to widen NIH's mission to include *translational research*—i.e., translating basic discoveries from concept into clinical evaluation, focusing on specific diseases or therapies.

- **FDA's Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products**

In March 2004, FDA issued its *Critical Path* report to complement the NIH *Roadmap* initiative. In FDA's view "applied sciences have not kept pace with the tremendous advances in basic sciences." The *Critical Path* plan is FDA's attempt to encourage the creation of new tools to get fundamentally better answers about how the safety and effectiveness of new drugs can be demonstrated, in faster time frames, with more certainty, and at lower costs. FDA's report has been called "timely and significant" and "courageous" by

National Security and Antibiotic Resistance

Antibiotic resistance not only threatens public health, but may have national and global security implications as well. Virtually all of the antibiotic-resistant pathogens that exist naturally today can be bio-engineered through forced mutation or cloning. In addition, genetic manipulation of existing pathogens could render them resistant to currently available antibiotics. A better understanding of the mechanisms related to drug resistance and tools that could be derived from such research may help U.S. public health officials as they monitor and respond to any future bioterrorism episodes that involve genetically engineered resistant pathogens. Moreover, antibiotic resistance may limit the effectiveness of antibiotics during future bioterrorism events, outbreaks, and other emergencies.

Members of Congress are beginning to see the connection and to understand our vulnerability. In their reports on Project Bioshield in 2003, both the House Government Reform Committee and the Energy and Commerce Committee linked *natural conditions*, including antimicrobial resistance and dangerous viruses, to national security concerns. The Energy and Commerce Report stated "advancing the discovery of new antimicrobial drugs to treat resistant organisms ... may well pay dividends for both national security and public health."

[See also the report, *Beyond Anthrax: Confronting the Biological Weapons Threat*, issued May 4, 2004, by the Democrats of the House Select Committee on Homeland Security simultaneously with the introduction of the Rapid Pathogen Identification to Delivery of Cures Act (H.R. 4258).]



industry leaders who have praised the report for “recognizing the serious problems that are preventing new, innovative drugs and biologics from getting to the patients who need them ”

• **Project Bioshield**

Following the 2001 anthrax attacks, the Administration and congressional leaders moved rapidly to introduce the Project Bioshield Act.* The legislation is intended to spur R&D of new drugs, vaccines, and diagnostics for use against potential bioterrorism agents by establishing a guaranteed market for these products with the federal government serving as purchaser. Project Bioshield focuses on the six category A bioterrorism agents of greatest concern (smallpox, anthrax, botulism, tularemia, viral hemorrhagic fevers, and plague).

The legislation does not include incentives to spur R&D of new antibiotics to treat drug-resistant infections that threaten public health, despite IDSA’s pleas that they be included.

• **Public Health Service Action Plan to Combat Antimicrobial Resistance**

In January 2001, a federal interagency task force including CDC, FDA, NIH, and other agencies published the *Public Health Service Action Plan to Combat Antimicrobial Resistance*. The action plan is a comprehensive strategy that includes efforts to reverse the stagnation in antibiotic R&D. Other key action items target antimicrobial resistance surveillance, prevention and control, and research. Due to limited appropriations, the Administration’s implementation of the plan thus far has been slow, not well coordinated, and incomplete

• **General Accounting Office Study**

In May 2003, Senators Judd Gregg (R-NH) and Jack Reed (D-RI) asked the General Accounting Office (GAO) to study the antimicrobial availability problem. The senators stated:

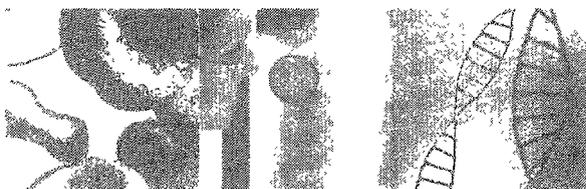
“With the threat of bioterrorism, the growing number of microorganisms resistant to drug therapy, the reemergence of previously deadly infectious diseases, such as tuberculosis, and the emergence of new infectious diseases in the United States, such as severe acute respiratory syndrome and West Nile virus, there is an urgent need for new antimicrobials.”

A year later, GAO has yet to begin the study, and their analysis of the many challenges to antibiotic R&D may be years away. ... **The time for studying the problem is over.**



January 1999. A 13-year-old girl from rural Minnesota was brought to a local hospital with fever and respiratory distress. She was coughing up blood. A chest X-ray revealed fluid in the lungs. The girl was treated with the antibiotics ceftriaxone and nafcillin. Within five hours of arriving at the hospital, the girl’s blood pressure dropped, and she was transferred to a pediatric hospital, intubated, and treated with vancomycin and cefotaxime. Despite intensive medical care, the girl’s health deteriorated, and she died on the seventh hospital day from multiple organ failures and excessive fluid and swelling in the brain. An autopsy and tests revealed that MRSA had destroyed her left lung. The girl had no chronic medical conditions and no recent hospitalizations.

*Although not enacted at the time this paper went to press, the Act likely will have been enacted by its publication date



INNOVATIVE FEDERAL POLICY AND IMMEDIATE ACTION ARE NEEDED

The federal government must take decisive action now. Primarily, policymakers must focus on adopting incentives to stimulate investment in this area of discovery by pharmaceutical and biotechnology companies. Any antibiotic R&D plan that does not include industry action at its core will yield hollow promises. Government-sponsored research and refinement of existing regulations, policies, and guidance can help to address the overall problem of antibiotic resistance, fill in some of the gaps in research, and reduce the cost of antibiotic discovery and development. But industry must take the lead to ensure success. Industry decision-making is not perfect from a public health perspective, but the focus on financial incentives has made industry successful in the past, and new incentives can lead to future successes.

The past two decades of antibiotic development clearly have demonstrated that we no longer can rely on existing market forces to keep companies engaged in this area of drug discovery and development. Should additional companies' antibiotic R&D infrastructures be dismantled, it will take years to establish new programs—or this expertise could simply be lost forever. Moreover, given the 10-year time gap that it takes for new antibiotics to move from concept to market, time for action is running out.

April 2004. A 52-year-old Maryland man, previously healthy, was hospitalized complaining of cough, fever, and shortness of breath. His sputum culture grew MRSA. A chest X-ray showed pneumonia involving almost all segments of the lung. He was treated aggressively with antibiotics, transferred to the intensive care unit, and placed on a ventilator but died on the second hospital day.

Creative thinking and innovative policy will solve both the antibiotic R&D and antibiotic resistance problems. IDSA has explored with industry, government officials, academics, patient representatives, and congressional staff the long-term value of many potential solutions. Our investigation has revealed that the incentives most likely to spur R&D within major pharmaceutical companies include those that provide financial benefits prior to a drug's approval (e.g., tax credits for R&D), commence at the time of approval (e.g., wild-card patent extension), reduce the costs of clinical trials (e.g., FDA flexibility concerning the evidence necessary to demonstrate safety and efficacy; National Institute of Allergy and Infectious Diseases [NIAID] sponsored research to foster the development of rapid diagnostics tests, etc.); and reduce companies' risks (e.g., liability protections). R&D at smaller companies also could be stimulated through statutory and administrative changes. Finally, new funding could help to ensure a better understanding about biological mechanisms related to antibiotic resistance, limit the public health impact of antibiotic resistance, and spur public-private R&D efforts.

IDSA does not claim to possess all of the answers, but a combination of the solutions listed in the next section will help. Policymakers should use these recommendations to shape a framework for governmental action.



Resistant infections can lead to longer hospital stays.

RECOMMENDATIONS FOR CONGRESS

Legislative action is necessary to stem the tide of pharmaceutical company departures from antibiotic R&D and to stimulate the involvement of non-active companies. Critical priorities that will have the greatest impact are indicated.

Commission to Prioritize Antimicrobial Discovery

CRITICAL PRIORITY

To begin to address the "bad bugs, no drugs" problem, Congress should establish and empower an independent Commission to Prioritize Antimicrobial Discovery (CPAD). CPAD's specific focus would be to identify the targeted pathogens that are (or are likely to become) a significant threat to public health due to drug resistance and other factors. The statutory R&D incentives that follow would apply to drugs that treat these pathogens. CPAD's decision-making would be based on an analysis of risks as well as benefits to public health.

An expert independent commission is needed to address the public health and R&D issues unique to antimicrobial R&D. Similar entities in other areas of medicine include the National Vaccine Advisory Committee and the National Cancer Advisory Board.

CPAD would make recommendations directly to the Secretary of Health and Human Services (HHS) and would be comprised of experts from the infectious diseases medical and research communities, representatives from relevant government agencies (CDC, FDA, NIH), and representatives from industry and relevant patient advocacy groups.

Companies would register with HHS to become eligible for the incentives. Once HHS certified a company as eligible, it could receive tax credits (R&D, capital formation, etc.). When a company successfully developed a product that met HHS predetermined specifications, it would become eligible for other incentives (intellectual property, liability, etc.)

Proposed Statutory Incentives

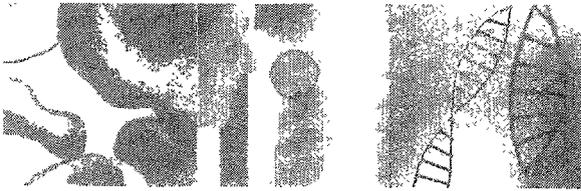
Congress must enact a robust set of statutory incentives to stimulate private sector investment and innovation. Unless such incentives are established, Americans will be at even greater risk from infectious disease threats in the future.

The Project Bioshield Act and pending legislation, such as the Biological, Chemical, and Radiological Weapons Countermeasures Research Act (S. 666), introduced by Senators Lieberman and Hatch in 2003, provide good starting points for congressional discussions about what incentives are appropriate. Like Project Bioshield, S. 666 includes progressive ideas to spur R&D for bioterrorism countermeasures. S. 666 goes further, however, providing tax credits, special intellectual property incentives, and antitrust and indemnification provisions.

Existing law offers other models to consider. The Best Pharmaceuticals for Children Act, for example, provides an additional six months of market exclusivity for new or already-marketed drugs and priority review status for pediatric supplements to a drug application, if the holder of an approved application undertakes studies of these drugs in children. Under the Orphan Drug Act,* qualifying drugs receive seven years of market exclusivity protection against generics and innovator drugs, tax incentives (up to 50 percent for clinical research), and research grants.

Following is a list of potential statutory incentives for Congress to consider:

*Orphan diseases or conditions must affect fewer than 200,000 individuals in the United States or provide no reasonable expectation that the sales of the drug will recover the costs of development.



RECOMMENDATIONS FOR CONGRESS (CONTINUED)

1. Supplemental intellectual property protections for companies that invest in R&D for priority antibiotics

- **Establishment of a "wild-card patent extension" linked to R&D for antibiotics to treat targeted pathogens**

CRITICAL PRIORITY

The original concept of a wild-card patent extension is provided in S. 666. Under this proposal, a company that receives approval for a new antibiotic, or a new indication for an existing antibiotic, that treats a targeted pathogen would be permitted to extend the market exclusivity period for another of the company's FDA-approved drugs. S. 666 supports a patent extension of two years.

The wild-card incentive may not be acceptable to all policymakers. For that reason, Congress should explore the feasibility of modifying the wild-card concept to require that the company commit a substantive portion (10 percent-20 percent) of the profits derived from the patent extension to additional targeted antibiotic R&D. This incentive is unlikely to help small biopharmaceutical companies, but would be a significant lure to major pharmaceutical firms.

- **Restoration of all patent time lost during FDA's review of applications for antibiotics that treat targeted pathogens**

FDA's review time for new antibiotic applications can vary, but the mean time is as long as 18 months. Although some of the patent time lost during FDA's review may be restored under current law, the specter of losing any patent time can have dramatic implications for companies' decision-making. S. 666 permits a company to select either this incentive or the wild-card patent extension incentive, but not both. Because the profit potential of most antibiotics is not very high and is likely to decline as the patent runs out, this is unlikely to be a very strong incentive in most cases.

- **Extension of market exclusivity for antibiotics that treat targeted pathogens similar to what has been successfully implemented for pediatric and orphan drugs**

Extended periods of market exclusivity can be an incentive to the original sponsor of a drug, as generic copies of the drug may not be approved or marketed during this time. Lengths of market exclusivity used or proposed in the past include six months under the Best Pharmaceuticals for Children Act (BPCA), seven years under the Orphan Drug Act, and 10 years under S. 666. Several pharmaceutical companies have indicated that an additional six months of market exclusivity would not provide a sufficient draw for them to invest in the development of new antibiotics or to seek a new indication for an existing antibiotic. For that reason, new legislation should include the longer periods of exclusivity as available under the Orphan Drug Act or as proposed in S. 666.

The fundamental principle behind the passage of BPCA and the Orphan Drug Act is that the government has a public health interest in spurring the discovery of new treatments to assist vulnerable populations. This same principle should prompt Congress to address the problem of drug-resistant infections.

Because the profit potential of most antibiotics is not high and is likely to decline over time, this solution is unlikely to be a very strong incentive in most cases.

2. Other potential statutory incentives to spur antibiotic R&D

- **Provide tax incentives** (as provided in S. 666) The company seeking to fund research would be eligible to elect among the following tax incentives:

- Claim tax credits for R&D of

CRITICAL PRIORITY

- antibiotics that treat targeted pathogens



RECOMMENDATIONS FOR CONGRESS (CONTINUED)

- Allow R&D limited partnerships to conduct research on drugs to treat targeted pathogens. The partnerships would pass through all business deductions and credits to the partners.
- Issue a special class of stock for the entity to conduct the research. The investors would be entitled to a zero capital gains tax rate on any gains realized on the stock.
- Receive a special tax credit for research conducted at a non-profit and academic research institution

- **Provide FDA with additional statutory flexibility to approve antibiotics that treat targeted pathogens as opposed to types of infection (e.g., resistant *S. aureus* vs. pneumonia) and encourage the agency to use that authority**
- **Create a guaranteed market with the federal government as purchaser and sufficient appropriations to stimulate R&D for antibiotics that treat targeted pathogens** (as provided for biodefense in Project Bioshield and S. 666)

The “bad bugs, no drugs” problem highlights the need for an open and flowing pipeline of antibiotics to treat patients on a daily basis in hospitals and communities across the United States. A guaranteed market that prompts stockpiling of drugs is unlikely to have much applicability in this regard.

- 3. **Establish similar statutory incentives (as listed previously) to spur R&D for rapid diagnostic tests to identify targeted pathogens, which will help to reduce the cost of clinical trials**

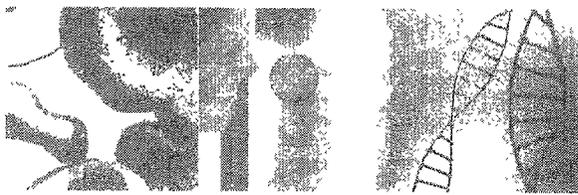
Policymakers should consider applying the incentives outlined above as potential solutions to encourage R&D for rapid diagnostic tests. New rapid diagnostics would greatly reduce the cost and time needed to conduct clinical trials for new antibiotics. For many resistant pathogens, there currently are

no rapid diagnostic tests available to assist in identifying eligible patients for clinical trials. Cutting costs and time will serve as incentives for greater investment in and more speedy approval of targeted antibiotics. In addition, new rapid diagnostics will permit physicians to diagnose specific bacterial infections in their patients. This will enable physicians to prescribe the most appropriate antibiotics, which will slow the evolution of new resistance.

- 4. **Potential statutory incentives of interest to small biopharmaceutical companies that have far less up-front capital to invest in R&D for antibiotics that treat targeted pathogens**

- **Provide tax incentives to form capital from investors and retained earnings for biopharmaceutical companies that cannot use tax credits, because they have no tax liability, or permit the small company to save or sell its credits** (as provided in S. 666)
- **Significantly increase the number and amount of Small Business Innovation Research (SBIR) grants that NIH can provide for these antibiotics**
- **Waive user fees for supplemental new drug applications submitted to FDA for the treatment of targeted pathogens**

Currently, companies can submit supplemental applications for new indications of drugs that have already been approved by FDA—for example, if an existing drug is found to be effective in treating a different bacterial infection or the same infection located in a different area of the body. Under current law, the user fee is waived for the original new drug application that an eligible “small company” submits to FDA for review. However, the company is charged a user fee for supplemental applications submitted for each new indication even if the new indication will treat an organism that threatens public health.



RECOMMENDATIONS FOR CONGRESS (CONTINUED)

5. Liability protections afforded to companies that receive FDA approval for antibiotics that treat targeted pathogens (as provided in S. 666)

CRITICAL PRIORITY

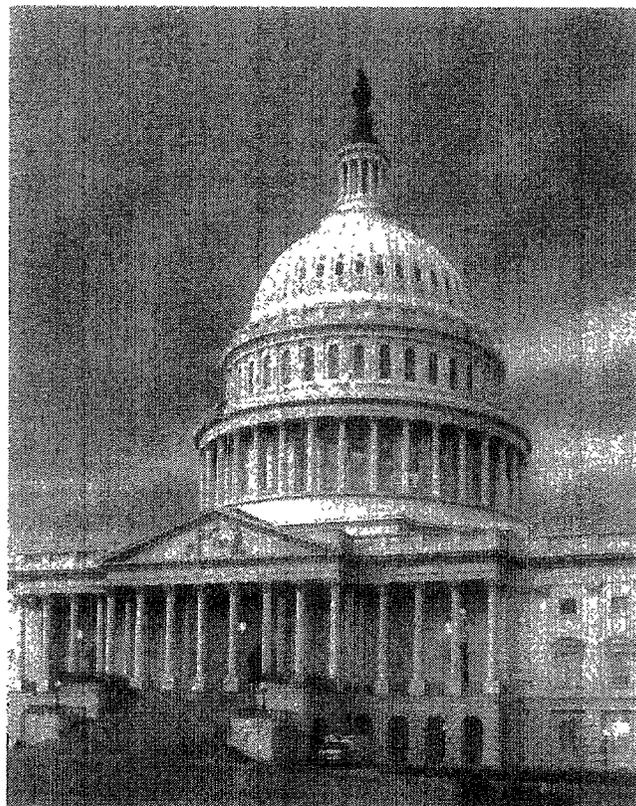
For obvious reasons, the pharmaceutical company representatives with whom IDSA met each saw government indemnification, similar to what has been afforded childhood vaccines, as a powerful incentive to develop new antibiotics. IDSA's recommendation is limited to antibiotics as they are being used to treat pathogens targeted by the Commission to Promote Antimicrobial Discovery.

6. Limited antitrust exemptions for companies that seek to work together to expedite research on targeted antibiotics (as provided in S. 666)

February 2004. A 34-year-old Maryland woman had the flu and went to an emergency room where a chest X-ray showed pneumonia. Laboratory studies confirmed it was due to MRSA. She developed shock and required a ventilator and tracheostomy to support breathing. As a complication of shock, both legs were amputated. She remained in the hospital for more than two months.

Next Steps for Congress

Hearings should be scheduled as soon as possible to highlight the human consequences of the "bad bugs, no drugs" problem and to determine which combination of incentives are most appropriate. The Senate and House leadership should work together in a bipartisan manner to enact sufficient statutory incentives to stimulate new antibiotic R&D. Congress should work cooperatively with the Administration to encourage greater antibiotic R&D and to limit the public health impact of antibiotic resistance.



Congress must act now to encourage pharmaceutical and biotech companies to invest in the antibiotics market.

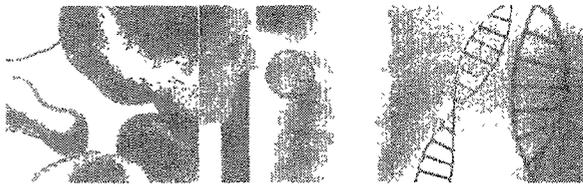


RECOMMENDATIONS FOR FDA

The Food and Drug Administration's (FDA) high standards for evaluating antibiotics' safety and efficacy must be maintained. However, avenues must be explored to better address the unique nature of antibiotic discovery and stimulate industry-sponsored antibiotic R&D. As FDA implements its new *Critical Path* plan, the agency should implement the following recommendations. Each of the recommendations should be considered a critical priority

CRITICAL PRIORITIES

- **Publish updated guidelines for clinical trials of anti-infectives.** Industry is understandably hesitant to initiate new clinical trials in areas where the standards for safety and efficacy are unclear. FDA should issue, as soon as possible, guidelines for resistant pathogens, bacterial meningitis, acute bacterial sinusitis, acute bacterial otitis media, and acute exacerbation of chronic bronchitis. These guidelines have been in revision or development for some time. FDA also should move quickly to identify additional areas of uncertainty in antibiotic drug development and develop or update guidelines in those areas as well. Review of these guidance documents at appropriate intervals also would be extremely useful in ensuring their continued relevance and accuracy.
- **Encourage imaginative clinical trial designs that lead to a better understanding of drug efficacy against resistant pathogens.** For example, clinical trial data on resistant pathogens are time-consuming and costly to accrue. FDA could define ways in which an antibiotic's efficacy against drug-sensitive types of bacteria could be used to extrapolate efficacy against drug-resistant strains.
- **Provide a clear definition of acceptable surrogate markers as endpoints for clinical trials of bacterial infections.** In other words, FDA needs to define new ways to determine an antibiotic's effectiveness, such as clearing bacteria from blood or other body sites (e.g., hip and knee implants) or resolving fever. This concept has been accepted for antiviral agents, but has had limited application to bacterial infections.
- **Explore, and when appropriate encourage, the use of animal models of infection, in vitro technologies (e.g., test tube), and valid microbiologic surrogate markers (e.g., clearance of bacteremia) to reduce the number of efficacy studies required for each additional indication.** These data are easier and less costly to obtain than full results of safety and efficacy testing in human subjects, and therefore, when appropriate, could result in a more timely and efficient approval process. Of course, safe and effective drug dose regimens must be maintained.
- **Explore with NIAID all opportunities to streamline antibiotic drug development.** (See examples outlined under NIAID recommendations.)
- **Grant accelerated approval status for antibiotics that treat targeted pathogens.** This regulatory pathway allows FDA to grant approval prior to completion of full human testing, based upon a demonstration of efficacy using surrogate endpoints with a commitment for post-approval human testing to confirm the effect on disease outcomes. Moving beyond the current scenario, FDA could give provisional approval for antibiotics that treat targeted pathogens followed by a post-approval study of the drug by a select group of investigators certified to treat patients with the drug. The certified investigators would collect additional efficacy data needed to lead to a full approval, while providing patients with earlier access to the drug. Health care payers would offset the costs of the clinical trials, which may prompt companies to pursue candidate drugs that they otherwise might not.



RECOMMENDATIONS FOR NIAID

NIH has shown leadership in developing the *Roadmap* initiative. The true test is still to come as the plan is implemented. The National Institute of Allergy and Infectious Diseases (NIAID) has primary responsibility for implementing the *Roadmap* in the infectious diseases arena. To achieve success, NIAID should implement the following recommendations. Each of these recommendations should be considered a critical priority:

CRITICAL PRIORITIES

- **Move aggressively to expand the translational (bench to bedside) research concepts contained in the *Roadmap* to strengthen antibiotic R&D, remove roadblocks that may exist in NIAID's structure and guidelines, and accelerate antibiotic resistance research activities**
- **Increase the number and size of grants to small businesses, academic institutions, and non-profit organizations that focus on R&D of antibiotics to treat targeted pathogens**
- **Seek greater opportunities to work with pharmaceutical and biotechnology companies to advance antibiotic R&D, and ensure that NIAID staff who oversee technology-transfer efforts understand industry's motivations and goals**
- **Engage more aggressively the infectious diseases research community in research planning efforts and create a more transparent decision-making process**
- **Sufficiently fund and rapidly implement NIAID's newly launched Drug Discovery and Mechanisms of Antimicrobial Resistance Study Section**
- **Encourage research on topics directly related to the implementation of clinical trials (e.g., surrogate endpoints of response to therapy, animal models, and analytical methods)**
- **Sponsor research into new rapid diagnostic tests for bacterial infections that, when available, could reduce the cost of clinical trials**
- **Re-examine NIH's 1999 research tool guidelines and modify or waive the guidelines where necessary.** NIH's guidelines have been criticized for unnecessarily restricting companies' intellectual property rights and revenue generation where research tools have been developed in conjunction with federally funded research. Critics believe the guidelines should be modified to breathe new life into research tool development, particularly to help fight emerging infectious pathogens. Research tools include cell lines, drug delivery technologies, laboratory animals, clones and cloning tools, databases, and other technologies.
- **Develop a fellowship curriculum designed for clinician investigators to provide expertise in clinical trials of new antibiotics.** FDA and the National Cancer Institute (NCI) announced an analogous program for anti-cancer drugs in 2003.
- **Explore joint programs with FDA to streamline antibiotic drug development similar to programs initiated by NCI and FDA in 2003.** The NCI/FDA programs are intended to inform and harmonize all phases of cancer drug discovery, development, and regulatory review.
- **Encourage research on antibiotic use patterns and their impact on resistance, specifically the impact of use restrictions on newly approved antibiotics**
- **Fund placebo controlled trials to determine if certain diseases require antibiotic therapy (e.g., acute otitis media, acute exacerbation of chronic bronchitis, and acute bacteria sinusitis).** There is reasonable concern that antibiotics frequently are prescribed to treat diseases that are not caused by bacteria (e.g., are viral in origin). This inappropriate use of antibiotics promotes antibiotic resistance with no benefit to patients. Definitive placebo-controlled studies are needed to elucidate this point.



NEW FUNDING NEEDED

Public and private efforts that target the growing problem of drug resistance and lack of antibiotic R&D are drastically under-funded. An infusion of new resources (i.e., not shifting funds from other public health efforts) in several critical program areas will go a long way toward assuring Americans that they will soon be protected from dangerous and drug-resistant pathogens.

- **Double CDC's antimicrobial resistance program to \$50 million in 2005 and continue to increase it by \$25 million increments until 2009 to a total of \$150 million**

CDC is the primary coordinator of much of the *Public Health Service Action Plan to Combat Antimicrobial Resistance*. Increasing CDC's funding will enable the agency to expand its surveillance of clinical and prescribing data that are associated with drug-resistant infections, which would assist the Commission to Prioritize Antimicrobial Discovery (referenced above), CDC, and other public health agencies in setting priorities. Funding also is needed to educate physicians and parents about the need to protect the long-term effectiveness of antibiotics as well as to strengthen infection control activities across the United States. Finally, broadening the number of CDC's extramural grants targeting applied research at academic-based centers would harness the brainpower of our nation's researchers and assist the agency in developing practical and successful antimicrobial resistance prevention and control strategies.

- **Increase by \$25 million funding for FDA's programs that support antibiotic development and reduce the costs of clinical trials**

New funding will enable the anti-infective review group within FDA's Center for Drug Evaluation and Research to begin to implement the *Critical Path* plan, including funding research efforts envisioned under the plan and creating guidelines that clarify for industry the standards FDA will apply to antibiotic R&D. New funding also would strengthen the anti-infective review group's ability to

evaluate antibiotics for the treatment of targeted pathogens, by permitting them to contract with companies that provide national, real-time microbiological data related to relevant antibiotics and all clinically relevant strains of bacteria. This information is not available through government sources. New funding also would enhance the Center for Devices and Radiological Health's ability to support the review of rapid diagnostics to detect resistant microorganisms.

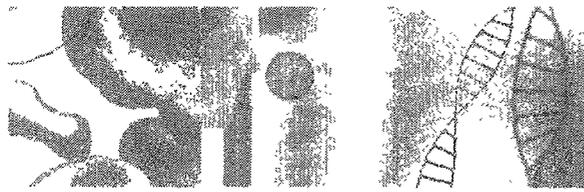
- **Significantly increase NIAID's critical translational and antibiotic resistance research efforts**

IDSA and other organizations have called for a 10 percent across-the-board funding increase for NIH in 2005. Such funding is necessary to allow NIAID to move aggressively to implement the *Roadmap* initiative in the area of antibiotic R&D as well as to support research that will lead to a better understanding of mechanisms related to antibiotic resistance.

February 1999: A 12-month-old boy from rural North Dakota was admitted to a hospital with vomiting, dehydration, and inflammation of his airway. He had a

temperature of slightly more than 105 degrees. Tests and X-rays revealed an infection in his right lung. Doctors transferred the boy to the intensive-care unit, inserted a chest tube, and treated him with the antibiotics vancomycin and cefuroxime. The next day the boy developed severe respiratory distress and falling blood pressure, and he died. The boy had not been hospitalized since birth and had no known medical problems. However, his 2-year-old sister had been treated for a culture-confirmed MRSA infection three weeks earlier.





NEW FUNDING NEEDED (CONTINUED)

• Support Synergistic Public/Private Solutions

A growing number of international public-private partnerships are focusing on the discovery of medicines to treat infectious diseases in the United States and globally. Initiatives like the International AIDS Vaccine Initiative (formed in 1996), the Medicines for Malaria Venture (1999), and the Global Alliance for TB Drug Development (2000) offer promising opportunities to advance product R&D in areas that have languished in the past. Public-private partnerships have adopted business models that exploit the venture capital approach to investment in new product R&D. Such initiatives receive the bulk of funding from the public and philanthropic sectors. They involve for-profit partners by seeking in-kind contributions from industry. The commitment of U.S. public dollars for these and similar initiatives would take advantage of the

entrepreneurial spirit possessed by many researchers and humanitarians.

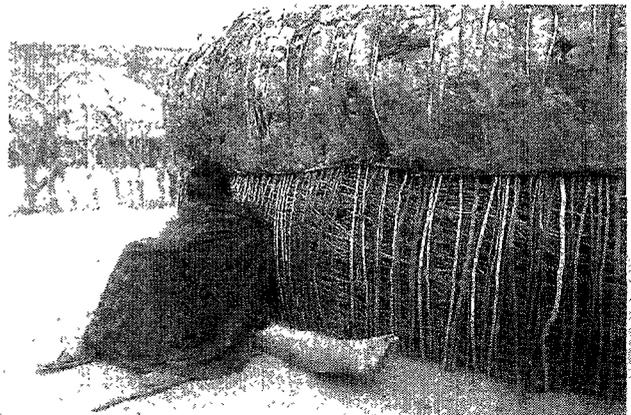
In addition to funding public-private partnerships, policymakers should seriously consider ways to prompt companies to inventory their shelves for promising drug candidates that could be donated to the partnerships for development. Such candidates exist, and companies recently have shown some interest in donating them. This is not a current priority for companies, however, because the resources required would have to be diverted from other efforts.

Emerging and Re-Emerging Infections

Robust research and development programs are needed to respond successfully to existing infectious diseases as well as new threats on the horizon.

More than three dozen new infectious diseases have been identified since the 1970s that have impacted the United States and more vulnerable countries. The list includes HIV/AIDS, severe acute respiratory syndrome (SARS), Lyme disease, hepatitis C, a new form of cholera, waterborne disease due to *Cryptosporidium*, foodborne disease caused by *E. coli* 0157:H7, and a plethora of neglected diseases that primarily affect patients in the developing world.

Some of these diseases have no treatment except for supportive care. For diseases that do have effective treatments, complacency can stifle new research and allow us to be caught off guard when current treatments become less effective due to resistance. This has been the case with tuberculosis (TB). It has been 30 years since a new class of antibiotic was approved to treat TB despite the fact that it is the second most common microbial cause of death in the world. Doctors also are concerned about the rapid rate at which other bacterial infections, such as gonorrhea and syphilis, are becoming resistant to drugs. Finally, for diseases such as TB, AIDS, and malaria, which have notoriously complex and sometimes toxic treatment regimens, there is a substantial need for new drugs that are not only more effective but easier to deliver to the patient so that greater drug adherence and, ultimately, successful care and treatment will be achieved.



CONCLUSION

The time for talk has passed—it's time to act. The "bad bugs, no drugs" problem is growing more severe, and patients are suffering. Government-sponsored research and refinement of existing regulations, policies, and guidance can help to address the overall problem of antibiotic resistance, fill in some of the gaps in drug development, and help reduce the cost of drug discovery and development. However, industry action must remain policymakers' central focus. Incentives that encourage pharmaceutical companies to remain active in this area of discovery or stimulate additional investment by inactive pharmaceutical and biotechnology companies must be a critical part of any solution.

New drugs are desperately needed to treat serious as well as common infections (e.g., blood, heart, and urinary tract infections; pneumonia; childhood middle-ear infections; boils; food poisoning, gonorrhea, sore throat, etc.). The bacteria that cause these infections are becoming increasingly resistant to the antibiotics that for years have been considered standard of care, and the list of resistant pathogens keeps growing. It is not possible to predict when an epidemic of drug-resistant bacteria will occur—but we do know it will happen.

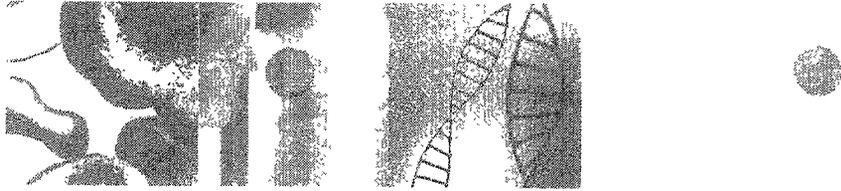
January 1998. A 16-month-old girl from rural North Dakota was taken to a local hospital with a temperature of over 105 degrees. She was suffering from seizures and was in shock. Doctors treated her with the antibiotic ceftriaxone, but the girl died within two hours of heart and lung failure. An autopsy and tests revealed that MRSA had spread to her brain, heart, liver, and kidneys. One month earlier, the patient had been treated with amoxicillin for otitis media (an ear infection). Neither the girl nor her family members had been hospitalized during the previous year.

Congress and the Administration have a window of opportunity to act now—*before a catastrophe occurs*—to spur both R&D of antibiotics to treat dangerous and drug-resistant infections and to promote a better understanding of antibiotic resistance and its implications for both public health and national and global security. Time is running out. Even if all of the incentives outlined in this paper were implemented today, it likely would take 10 or more years for companies to move safe and effective new drugs to market.

Federal officials have worked tirelessly over the past few years to help improve U.S. defenses against, and treatments for, bioterrorism agents. Although this work is needed and appropriate, it also is necessary to keep risks in perspective. Drug-resistant bacterial infections kill tens of thousands of Americans every year and a growing number of individuals are succumbing to community-acquired infections. An epidemic may harm millions. Unless Congress and the Administration move with urgency to address these infections now, there is a very good chance that U.S. patients will suffer greatly in the future.



Drug-resistant infections are more difficult to treat.



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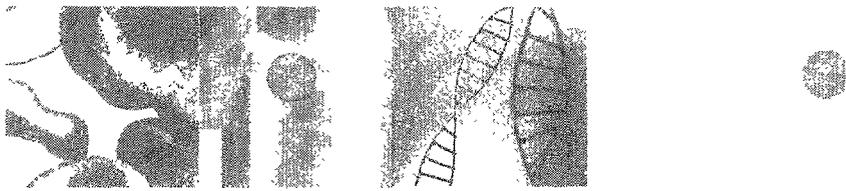
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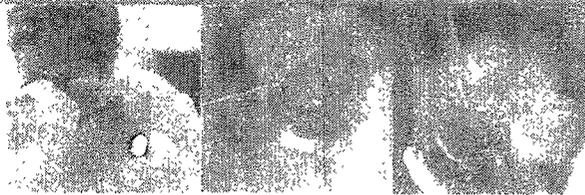
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