Testimony of the Infectious Diseases Society of America (IDSA)

Antibiotic Resistance: Promoting Critically Needed Antibiotic Research and Development and Appropriate Use ("Stewardship") of these Precious Drugs

Presented by Brad Spellberg, MD, FIDSA

Before the House Committee on Energy and Commerce Subcommittee on Health

June 9, 2010

The Infectious Diseases Society of America's (IDSA) Statement on

Antibiotic Resistance: Promoting Critically Needed Antibiotic Research and Development and the Appropriate Use ("Stewardship") of these Precious Drugs

Before the House Committee on Energy and Commerce Subcommittee on Health

June 9, 2010

The Infectious Diseases Society of America (IDSA) appreciates this opportunity to speak in support of the House Energy and Commerce Committee Health Subcommittee's efforts to promote the development of new antibacterial drugs ("antibiotics") for humans, as well as methods to ensure the judicious use of such antibiotics once they are on the market. [1] My name is Brad Spellberg, MD, FIDSA. I am an infectious diseases specialist and an Associate Professor of Medicine at the Geffen School of Medicine at the University of California, Los Angeles (UCLA). I also work within the Division of General Internal Medicine at the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center. I am a member of IDSA's Antimicrobial Availability Task Force and the author of a book titled "Rising Plague: The Global Threat from Deadly Bacteria and Our Diminishing Arsenal to Fight Them."

IDSA represents more than 9,000 infectious diseases physicians and scientists devoted to patient care, prevention, public health, education, and research in the area of infectious diseases. Our members care for patients of all ages with serious infections, including meningitis, pneumonia, tuberculosis (TB) and HIV/AIDS, antibiotic-resistant bacterial infections such as those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and gram-negative bacterial infections such as *Acinetobacter baumannii* (which are attacking brave U.S. soldiers who have served in Iraq and Afghanistan) and *Pseudomonas aeruginosa*, and, finally, emerging infections like the 2009 H1N1 influenza virus.

ANTIBIOTIC RESISTANCE: A MAJOR PUBLIC HEALTH PROBLEM

Antibiotic resistance is a serious public health, patient care and safety, and national security issue. Antibiotic-resistant infections are extremely difficult to treat and frequently recur. These infections result in tremendous pain, suffering, and disfigurement in adults, children and infants, and have caused millions of deaths worldwide. Hospital-acquired antibiotic-resistant infections currently kill nearly one hundred thousand Americans each year (this does not include infections acquired outside of hospitals) and have been estimated to cost the U.S. health care system between $21 billion and $34 billion annually.

> *"The last decade has seen the inexorable proliferation of a host of antibiotic-resistant bacteria, or bad bugs, not just MRSA, but other insidious players as well. ...For these bacteria, the pipeline of new antibiotics is verging on empty. 'What do you do when you're faced with an infection, with a very sick patient, and you get a lab report back and every single drug is listed as resistant?' asked Dr.*

Fred Tenover of the Centers for Disease Control and Prevention (CDC). 'This is a major blooming public health crisis.'"

—*Science* magazine; July 18, 2008 [2]

For the past decade, IDSA has raised concerns about the imbalance between the dwindling antibiotic pipeline and the significant and concomitant need for new antibiotics to treat an increasing number of drug-resistant infections. In 2004, concluding that immediate government action was essential, IDSA published its report "Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates a Public Health Crisis Brews," [3] and launched an advocacy campaign to spur government solutions. Now, six years later, the drug pipeline and resistance problems have only grown worse as more companies have withdrawn from antibiotic research and development (R&D) and ever-more resistant "bad bugs" have spread across the United States in health care settings and communities, devastating the lives of the young and the old, the healthy and the frail.

In response to the expanding crisis, IDSA recently launched the *10 x '20 initiative* [4], endorsed by other prominent medical societies and organizations [5], to provide a measurable goal and a framework for global action. The inaugural statement appears in the April 15th issue of the journal *Clinical Infectious Diseases*. The *10 x '20* goals are simple to articulate, but difficult to achieve. We seek a global commitment by the United States Government, particularly the Department of Health and Human Services (HHS), and other governments to create a sustainable antibiotic R&D enterprise, which in the short-term can produce 10 new safe and effective antibiotics by 2020. The antibiotics we seek are those that can treat the most serious and life-threatening pathogens against which most approved antibiotics are not effective. [6,7]

Today, IDSA's statement before the Subcommittee explores our fundamental premise that:

- Antibiotics are a vital resource and a precious gift from prior generations, and we have a moral obligation to ensure this resource is available for future generations.
- Safe and effective antibiotics are urgently needed to treat serious and life-threatening infections caused by a growing list of drug-resistant bacteria.
- As with other diminishing resources (energy, forests, etc.), Congress and the Administration must establish policy (statutory and administrative) [8,9] to nurture both the conservation and restoration of antibiotics through the development of new, innovative antibiotics and other relevant tools (rapid diagnostics, vaccines, etc.).
- We must adopt, promote, and continue to refine effective strategies to prevent the emergence and transmission of resistant organisms. Antibiotics must be used judiciously in order to limit the emergence of drug-resistant bacteria. Antibiotic stewardship strategies are the best way to achieve this goal, while good infection control practices and immunization policies can prevent transmission of these organisms.

ANTIBIOTICS' TRUE VALUE: "PRECIOUS RESOURCE" OR "A GIVEAWAY MARKETING TOOL"?

Our society takes antibiotics for granted—we do not realize how fortunate we are to have them. Many of our parents, grandparents and great-parents were not so lucky. Prior to the discovery of antibiotics, many injuries and illnesses became death sentences as there was no way to treat the common infections that were often associated with them. Since antibiotics were first discovered and used in the 1930s and then in the 1940s to save American soldiers during World War II, they have saved millions of lives and eased the suffering of an incalculable number of patients. Indeed, antibiotics often are referred to as "miracle drugs," as patients need only take them for a few days to completely resolve most infections.

> *"For most of the infectious diseases on the wards of Boston City Hospital in 1937, there was nothing that could be done beyond bed rest and good nursing care. Then came the explosive news of sulfanilamide [the first antibiotic], and the start of the real revolution in medicine. ... I remember the astonishment when the first cases of [lethal blood infections] were treated with antibiotics in Boston in 1937. The phenomenon was almost beyond belief. Here were moribund patients, who would surely have died without treatment, improving...within a matter of hours...and feeling entirely well within the next day...we became convinced, overnight, that nothing lay beyond reach for the future. Medicine was off and running."*
>
> —Lewis Thomas, MD, "Notes of a Medicine Watcher;" 1983

How have we spiraled from such a high starting point, where antibiotics were recognized as an "awesome acquisition of power" and "a force for change in the 20th century of the same general kind as James Watt's modification of the steam engine," (according to Walsh McDermott, MD, first president of the Medical Board [precursor to the Institute of Medicine] of the National Academy of Sciences) to the low point today where grocery stores and pharmacies give prescribed antibiotics away for free as a marketing ploy to lure customers into their stores? As a society, we need to begin to rethink how we utilize these precious resources.

There is incredible disparity in how our society values antibiotics versus other types of medicines. Most commonly used antibiotics cost only a few dollars for the typical course of treatment. It is arguable that effective antibiotics provide greater value than any other medicine ever created. The most expensive antibiotics (e.g., linezolid and daptomycin) can cost between $1,000 and $3,000 for a seven-day course of treatment (compared to $20,000-$50,000 for a multi-week course of a typical cancer treatment). The investment made in purchasing antibiotics typically leads to a <u>total cure</u> of the target disease or infection and <u>a life saved</u>. One antibiotic course has the potential to provide a sick child <u>70 or more quality years of life</u>. That was not the case prior to the 1940s, when there was a much higher probability that a child with a serious infection would not survive. Antibiotic therapy also reduces the risk that communicable bacteria will spread to other susceptible patients. Hence, a single course of antibiotics has the potential to

protect and preserve many quality years of life for many people. No other type of medicine can claim such an achievement at such a price.

With this value in mind, as a society we are justified in seeking new and innovative ways to protect the long-term effectiveness and availability of antibiotics.

We must begin to think "outside the box" about this problem. The moral imperative to have effective antibiotics available, combined with the failure of all efforts attempted to date to slow resistance and stimulate R&D, indicates that we need to think more broadly and more creatively about the problem and its solutions.

ANTIBIOTICS ARE UNIQUE

In addition to their extremely high level of effectiveness and the value that they provide to society, antibiotics are unique among all medicines in two critically important ways. First, over time, antibiotics lose their ability to treat the diseases for which they were approved—due to bacteria's ability to mutate and develop resistance to the antibiotic. Second, due to resistance and our desire to prolong antibiotics' effectiveness for as long as possible, physicians and professional societies ask that antibiotics be used appropriately and sparingly and seek ways to limit misuse and abuse of these drugs. We actively discourage non-essential use of newly approved antibiotics.

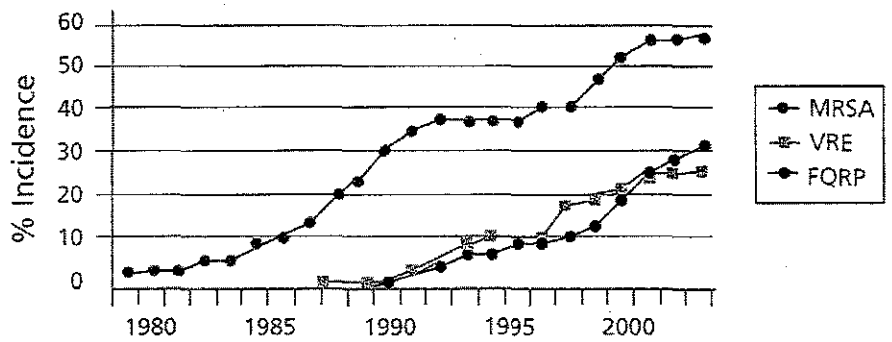
Unfortunately, this combination of factors—antibiotics' ability to cure most infections in just a matter of a few days, antibiotic resistance, and measures to ensure appropriate use ("antibiotic stewardship") to protect antibiotics' effectiveness over time—has resulted in a market failure. Most pharmaceutical companies have withdrawn from antibiotic R&D to pursue more lucrative markets such as treatments for chronic diseases (e.g., heart disease, high blood pressure, anti-cholesterol, etc). The sad result is that the antibiotic pipeline now is drying up, placing Americans and other people around the world at serious risk. [10,11]

In a report [12] published in the January 2009 issue of the journal *Clinical Infectious Diseases* (*CID*), IDSA confirmed that the antibiotic pipeline is nearly bare, particularly for drugs needed to treat high priority pathogens and infections. In September 2009, the European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency (EMA) released their own report [13] affirming IDSA's assessment and found only 15 antibiotics in development that may provide benefit over existing drugs. Based on experience, we know most of these drugs will never make it across the finish line to approval. Furthermore, none of the drugs currently in development is capable of treating bacteria that are resistant to all presently available drugs.

The bottom line: The relentless spread of a growing number of drug-resistant infections in our hospitals and communities (for example, see Chart 1) and the diminishing number of antibiotics being approved (see Table 1) have made it more and more difficult for physicians to protect patients and save lives—morbidity and mortality are on the rise. The dearth of new antibiotics in development is deeply troubling to health experts and has the

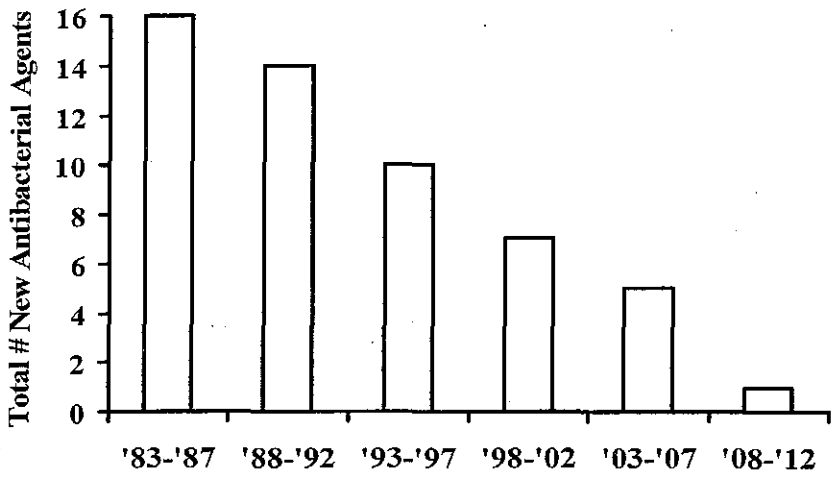
potential to change the practice of medicine as we know it. A number of advanced interventions that we currently take for granted—e.g. surgery, cancer treatment, transplantation and care of premature babies—would be impossible to perform without effective antibiotics.

Chart 1: Resistant Strains Spread Rapidly



Source: Centers for Disease Control and Prevention

Table 1: Antibiotic Approvals (1983-Present)



Source: IDSA's 2004 Bad Bugs, No Drugs report (modified)

ANTIBIOTIC RESISTANCE: THE COSTS ARE TOO GREAT TO WAIT

The U.S. CDC has described antibiotic resistance as "one of the world's most pressing health problems" as "the number of bacteria resistant to antibiotics has increased in the last decade [and] … many bacterial infections are becoming resistant to the most commonly prescribed antibiotic treatments." The World Health Organization (WHO) has identified antibiotic resistance as "one of the three greatest threats to human health."

Infectious diseases physicians agree. The costs due to antibiotic resistance, both in the numbers of lives lost or devastated as well as in economic terms, are exceedingly high.

Deaths and Illnesses

The compelling and heart-wrenching stories witnessed by infectious diseases specialists and other physicians on a daily basis are represented briefly in the patient stories and recent statistics that follow. As you will see, there is urgent need to act.

Patient Stories:

Simon was a healthy baby boy from **Chicago, Illinois** who contracted MRSA and did not survive his infection.

— "At the emergency room, I tried to convince myself that this was all much ado about nothing. Well, I was wrong. Way wrong. As soon as Simon was wheeled in, doctors hooked him up to everything imaginable (oxygen, nebulizer, IVs for medication and pain relievers). And, I kept hearing, "Your child is very, very sick. Your child is very, very sick." At this point, I became absolutely hysterical... Simon kept looking at me with his chocolate-brown eyes, and long, curly eye-lashes, repeating, 'Agua, agua ... agua.' Now I have a window into what so many families experienced 50 years ago–the death of a child caused by a bacterium or virus. It is ironic that the same advances in science that led to healthier and longer lives have resulted in the unintended consequence of the creation of bacteria that no longer respond to antibiotics. As long as we do not treat antibiotics as a precious resource, only to be used in the most extreme cases, we will continue to have a false sense of security in medicine."

— Everly Macario, DrPH, Simon's mother

Rebecca Lohsen was a healthy 17-year old high school honor student and swimmer from **Northern New Jersey** who died of an MRSA infection in 2006.

—"I no longer have the confidence in medicine that I once had...I've watched the dismay in the faces of doctors who are supposed to be the

best in their field as they told me they didn't have any more "cures in their bag."

—Linda Lohsen, Rebecca's mother, a former public health nurse

Carlos Don was a healthy 12-year old football player and skateboarder from **Southern California** who died of pneumonia caused by an MRSA infection.

—"I lost my son Carlos to MRSA on February 4, 2007, only 15 days before his 13th birthday. Carlos was the person I loved most in this entire world. He was my life."

—Amber Don, Carlos' mother

Ricky Lannetti was a healthy 21-year old football player at Lycoming College in **Williamsport, Pennsylvania** who contracted MRSA and did not survive the infection.

—"Like millions of Americans today, I had never heard of MRSA until it claimed my son's life. His sisters, father and I live everyday thinking about Ricky and what he would be doing today if he was here... During a time that I should have been planning for my son's college graduation and helping him prepare for his future, I was burying my only son who only days before had been the picture of health."

—Theresa Drew, Ricky Lannetti's mother

Tom Dukes was a healthy and active father from **Lomita California** whose life was torn apart by a painful and drug-resistant Escherichia coli (E. coli) in December 2009.
—" 'You're going to the operating room right now' the emergency room doctor told me. My family gathered around me...I said goodbye, scared I wouldn't see them again. Months later, I'm still trying to get my life back together after an antibiotic-resistant E. coli infection turned my world upside down."

—Tom Dukes, E. coli survivor

Recent Statistics:

- A CDC-supported study [14,15] published in the *Journal of the American Medical Association* (*JAMA*, October 17, 2007) estimated that invasive MRSA infects more than 94,000 people and kills nearly 19,000 people annually around the country—more deaths than those caused by emphysema, HIV/AIDS, Parkinson's

disease and homicide. These numbers are very conservative, since they only consider infections proven by laboratory culture—many more cases occur for which physicians do not request cultures. Moreover, invasive MRSA infections represent only a segment of the greater MRSA problem in this country. [16]

- CDC reports [17] that nearly 2 million health care-associated infections (HAIs) and 90,000 HAI-related deaths occur annually in the U.S. Many of these infections and deaths are caused by antibiotic-resistant infections.

- A February 2010 [18] study published in the *Archives of Internal Medicine* showed that two common conditions caused by HAIs—sepsis and pneumonia—killed 48,000 people and ramped up health care costs by $8.1 billion in 2006 alone.

- A December 2009 *JAMA* study [19] showed that 1 in every 2 patients in more than 1,000 ICUs in 75 countries were infected—infected patients had twice the risk of death in the hospital than uninfected patients.

In IDSA's estimation, the above patient stories and recent statistics represent only the tip of the iceberg. The United States needs better surveillance and data collection tools (see the STAAR Act discussion below) to adequately understand the full extent of the impact of antibiotic-resistant infections.

Health Care Costs Associated with Antibiotic-Resistant Infections

The direct and indirect economic costs associated with antibiotic-resistant infections are enormous in terms of dollars spent, length of hospital stays, and loss of productivity.

- A recent analysis of antibiotic-resistant infection data conducted at Chicago Cook County Hospital [20] showed that the direct and indirect economic costs of antibiotic resistance are substantial in terms of dollars and length of hospital stays. Extrapolating the analysis nationwide [21], the authors concluded that antibiotic-resistant infections cost the U.S. health care system in excess of $20 billion annually as well as more than $35 billion in societal costs, and more than 8 million additional days spent in the hospital.

- Another recent study [22] published in 2009 in *Antimicrobial Agents and Chemotherapy* comparing HAIs caused by drug-resistant gram negative bacteria versus drug-susceptible gram negative bacteria, found that the drug-resistant infections increased hospital costs by 29.3 percent ($144K vs. $106K) and lengths of stay by 23.8 percent (36 vs. 31 days).

- A 2010 study in *Infection Control and Hospital Epidemiology* [23] found that over a six-month period of assessment the cost of treating patients with MRSA was significantly higher than treating patients with *S. aureus* that responds to methicillin, known as methicillin-susceptible *S. aureus* (MSSA). The median cost for treating an MRSA infection was $34,657 compared to $15,923 for treatment

of an MSSA infection. The higher costs were the result of longer hospital stays, more laboratory and imaging tests, and more rehabilitation services.

PRIORITY ANTIBIOTIC-RESISTANT BACTERIA PATHOGENS

Listed below are some of the current drug-resistant infections of greatest concern.

The ESKAPE Pathogens: The so-called ESKAPE [24] Pathogens (***Enterococcus faecium***, ***Staphylococcus aureus***, ***Klebsiella pneumoniae***, ***Acinetobacter baumannii***, ***Pseudomonas aeruginosa***, and ***ESBL positive bacteria, such as E. coli*** and *Enterobacter* species) represent a grouping of antibiotic-resistant gram-positive and gram-negative bacteria [25] that cause the majority of U.S. HAIs. The group is so-named because these bacteria effectively "escape" the effects of most approved antibacterial drugs.

Take for example, *Acinetobacter baumannii,* an increasingly common drug-resistant bacteria found in health care settings across the United States [26,27] and globally. *Acinetobacter* is multidrug-resistant, and is extremely difficult to kill once it enters the body.[28] In just the past 10 years in the U.S., the frequency of *Acinetobacter* resistant to all first-line antibiotics has risen from less than 5 percent (of isolates studied) to greater than 40 percent. As a result, *Acinetobacter* now often is treatable only with a highly toxic drug, colistin, which was abandoned in the 1960s because it causes kidney damage. Increasingly *Acinetobacter* has become resistant even to colistin, and hence those infections are totally untreatable with any available antibiotic. Of note, *Acinetobacter* has become a particular problem for U.S. soldiers who have served in Iraq and Afghanistan. A 2006 study [29] conducted at Walter Reed Army Medical Center found that of 75 patients who tested positive for the bacteria, 89 percent were resistant to at least three classes of antibiotics and 15 percent were resistant to five classes. The bacteria also are able to live on environmental surfaces in hospitals placing additional soldiers and patients at risk. *Acinetobacter* is commonly found in water and soil in Iraq, Afghanistan and other locations, and the bacteria can enter the body through deep combat wounds or burns. Once inside the bloodstream, the bacteria can wreak havoc causing potentially fatal infections, including pneumonia, meningitis, and shock. A strong soldier may survive a combat injury sustained in Iraq or Afghanistan, only to lose the battle against *Acinetobacter*.

Like MRSA [16], vancomycin-resistant *Staphylococcus aureus* (VRSA) [30], is a strain of *Staph* bacteria that is multi-drug resistant. Although extremely rare at this time, VRSA is especially problematic as it is resistant to vancomycin, the powerful antibiotic physicians often use when others fail. Should this dangerous organism begin to spread further, we will be in dire straits. A patient with a VRSA infection was transferred from a hospital in Delaware to a hospital in Pennsylvania in April 2010. This is the 11th known case of VRSA in the United States. Eight prior cases occurred in Michigan. The others occurred in New York and Delaware.

Clostridium difficile: Another resistant infection receiving increased scrutiny is *Clostridium difficile* (*C. diff*). [31,32,33] C. diff. is an HAI that can lead to severe diarrhea,

rupture of the colon, kidney failure, blood poisoning, and death. CDC estimates there are 500,000 cases of *C. diff.* infection annually in the U.S., contributing to between 15,000 and 30,000 deaths. States have reported increased rates of *C. diff.* nationwide over the past several years noting more severe disease and an associated increase in mortality. Elderly hospitalized patients are at especially high risk.

COMPREHENSIVE U.S. GOVERNMENT ACTION IS URGENTLY NEEDED

> *"The impacts of antibiotic-resistant bacteria can be reduced by preserving the effectiveness of current antibiotics through infection control, vaccination and prudent use of antibiotics, and by developing new antibiotics specifically to treat infections caused by antibiotic-resistant bacteria."*
>
> —Congressional Office of Technology Assessment (OTA), September 1995 [34]

Similar to the OTA, IDSA supports a comprehensive, multi-pronged approach to address the complex problem of antibiotic resistance. We believe success can be achieved if we:

A. fix the broken antibiotic drug pipeline;
B. support the development and utilization of new rapid diagnostic tests;
C. enact the Strategies to Address Antimicrobial Resistance (STAAR) Act (H.R. 2400);
D. promote the judicious use of antibiotics in human medicine (antimicrobial stewardship);
E. implement effective infection prevention and control programs;
F. support the development of new vaccines and appropriate immunization policies;
G. stop non-judicious uses of antibiotics on U.S. farms (animal and plant agriculture); and
H. view antibiotic resistance as a global health issue.

For the purpose of today's hearing, IDSA will focus primarily on the first four elements.

A. Fix the Broken Antibiotic Pipeline

In IDSA's view, there is an urgent need to address the factors that have resulted in a dearth of new antibiotics in development: lack of financial incentives of sufficient strength to make companies choose to engage; regulatory uncertainty caused by the lack of consistent approval pathways at the Food and Drug Administration (FDA); insufficient federally supported research; the need for greater public/private collaborations; and lack of adequate rapid, point-of-care diagnostics (see diagnostics discussion in section B below).

Strengthen Financial Incentives

To fix the broken pipeline and create a sustainable, national and global antibiotic R&D enterprise, it is necessary to determine the right combination of financial incentives ("push" and "pull" mechanisms) to entice industry to reengage in antibiotic R&D.[35,36,37] Examples of the push incentives are grants, contracts, and tax credits. Examples of the

pull incentives are guaranteed markets, liability protection, patent extensions or data exclusivity, and prizes. These incentives are intended to change the "return on investment" or net present value calculation of antibiotics to make them more competitive with other drugs. Such incentives were discussed in detail in IDSA's 2004 "Bad Bugs, No Drugs" white paper.[3] More recently, a September 2009 report commissioned by the European Union and produced by Chantal Morel and Elias Mossialos of the London School of Economics and Political Science (LSEPS) provides a comprehensive list of incentives that should be helpful to members of the Subcommittee as they deliberate these issues. The LSEPS incentives are summarized in brief in a newly published (May 2010) *British Journal of Medicine* analysis [38] also authored by Morel and Mossialos.

IDSA supports in particular an extension of patent life for priority antibiotics effective against emerging multidrug resistant bacteria. These drugs are viewed as priority drugs as opposed to low priority drugs ("me-too" drugs) that add little to the existing inventory. IDSA supports the development of an antibacterial orphan-like pathway for drugs shown as safe and effective in the treatment of infections due to the drug-resistant high priority bacteria. This orphan drug-like designation could extend by several years (perhaps up to 15 or 20 years) the period of market exclusivity during which no generic drugs could be approved. The additional years of patent life/market exclusivity could motivate companies to develop drugs against priority pathogens and infections. Obviously, other push/pull incentives listed in the LSEPS paper (tax credits, grants, awards, advanced market commitments, etc.) also should be considered. We emphasize that the failure of antibiotic R&D has occurred along the entire spectrum of drug discovery and development—there is no single rate-limiting step to overcome. Therefore, adopting a single type of incentive will not solve the problem. Rather, a panel of push and pull incentives, which can appeal to the various constituents (e.g., large and small companies, academia, etc.) active along the entire R&D spectrum, must be created.

Advance Regulatory Certainty

FDA must quickly assure a clear regulatory pathway for the development of antibiotics. For many years, industry representatives have identified regulatory uncertainty as one of the primary obstacles to new antibiotic development. IDSA acknowledges the strong commitment expressed by current FDA leaders and staff to address the multi-faceted problem of regulatory uncertainty. Despite good faith meetings, workshops, and advisory committee meetings, the situation today appears no better than it was at this time last year. In some respects, the level of uncertainty has increased.[39,40]

For example, in March 2009, a draft guidance providing an approval pathway for new drugs for community-acquired bacterial pneumonia (CABP) was published and public comment solicited. We were extremely pleased to finally have witnessed some progress. However, the public comments lead to an additional advisory committee meeting last December, which again has engendered uncertainty. We, and the pharmaceutical industry, still are waiting for publication of the final guidance for trials in CABP patients. Similarly, in May 2009, companies were moving forward on clinical trials for new drugs to treat skin and skin structure infections (SSSIs), but, in 2010, companies no longer

know what to do to satisfy FDA on SSSIs even though such a pathway had existed for years. Clear clinical trial design guidance is urgently needed for CABP and complicated SSSIs, as well as for other serious infections such as hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, and bacteremia.

Also, in 2010, FDA has moved no closer to identifying an approval pathway that will lead to new antibiotics to treat multiply drug-resistant and pan-drug-resistant pathogens like *Pseudomonas aeruginosa*, *Acinetobacter*, Extended Spectrum Beta Lactamase (ESBL) – producing *E. coli* and *Klebsiella,* and *Klebsiella pneumoniae carbapenemase (KPC)* producing gram-negative bacteria. According to the CDC, KPC producing bacteria are quickly spreading across the United States. For these life-threatening, multiply drug-resistant bacteria, which occur in critically ill patients that are difficult to enroll in clinical trials, IDSA believes it is time to discuss a new model for the assessment of potentially active new drugs; a model that allows for FDA approval based on a relatively small clinical sample size (< 100 patients) with infections in multiple organ systems. Perhaps Congress also should consider some type of conditional approval mechanism for these drugs.

To quickly implement changes in the regulatory process requires people and money. This spring, IDSA testified [41] in support of an additional $36 million for FDA's antibiotic resistance and antibiotic drug review programs. Specifically, we support an additional $15 million to allow the agency to hire additional staff to develop much needed clinical trial guidance documents and to fund Critical Path initiatives specific to antibiotic drug development. We also requested $13.25 million to support a focus on new antibiotics within FDA's new regulatory science initiative with the National Institutes of Health (NIH). The regulatory science initiative involves the development and use of new tools, standards and approaches to more efficiently develop products and to more effectively evaluate product safety, efficacy and quality.

Finally, industry representatives also have articulated a strong desire for greater harmonization of international regulatory review and approval standards for antibiotics across the U.S., Europe, Japan, etc. as competing standards serve as impediments to approval.

<u>Strengthen Funding for Resistance and Drug and Diagnostics Discovery Research</u>
Significantly increased federal research dollars are urgently needed to advance scientific knowledge about resistance to antibiotics as well as to support drug discovery and development. Given the scope of the antibiotic resistance problem and its potential impact on every American, IDSA supports [42] a substantial funding increase in antibacterial resistance and antibacterial discovery research within NIH's National Institute of Allergy and Infectious Diseases (NIAID) to a total of $500 million in FY2011. We also support a significant boost in funding for HHS' Biomedical Advanced Research and Development Authority (BARDA), including specific funding targeting antibiotic development. IDSA recommends that at least $1.7 billion of multi-year appropriations be allocated to BARDA in FY 2011 to fund therapeutics, diagnostics, vaccines, and other technologies, including antibiotics. IDSA also wishes to see BARDA take a much stronger role in advancing the

development of new antibiotics to treat the ESKAPE pathogens and *C. diff.*, which are affecting a significant number of Americans in hospitals annually. Regardless of whether these particular drug-resistant bacteria present an immediate bioterrorism threat, that potential is always there.

After IDSA performed a preliminary examination of NIAID research funding for Fiscal Year 2009, NIAID officials graciously provided pertinent grant data and undertook a more in-depth review. Of a total NIAID grant budget of roughly $4.7 billion, $242 million funded grants in the areas of antibiotic resistance and discovery or development of new antibacterials. IDSA's analysis of this additional information finds that many of these grants funded pathogenesis, descriptive epidemiology, and other facets of the problem, as opposed to research on resistance mechanisms or new approaches to antibacterial therapy. Further, funding specifically for drug or other treatment modalities was $114 million, of which $94 million was for drugs or other therapies for agents of bioterrorism (e.g., anthrax, plaque, botulism). Only $16 million was provided for grants that focus on efforts to detect and develop new drugs for infections due to the ESKAPE pathogens.

Because of the rapid escalation in the problem of resistance, new initiatives must be developed. Significantly increasing funding both related to antibacterial resistance research and antibacterial drug discovery will enable NIAID to support a better understanding of mechanisms of resistance as well as expanding joint ventures between academia and industry that will identify new drug targets and drugs with activity for those targets. In the end, we hope this will lead to the development of a library of target drug compounds that will support industry's efforts to find new antibiotics that treat infections caused by ESKAPE pathogens and *C. diff.*, etc. Increased funding for NIAID and BARDA also will help federal officials work with industry and academia to create a seamless approach to new antibiotic drug R&D.

New funding also is needed to support the development of new vaccines and rapid diagnostics (see diagnostics discussion in Section B below). It is well-known that the development and use of pneumococcal conjugate vaccine has lead to a reduction in drug-resistant *Streptococcus pneumoniae* as well as a reduction in antibiotic use.[43] Development of new vaccines for MRSA and other multi-drug resistant organisms would be very useful in preventing diseases caused by these organisms as well as in reducing antibiotic use.

Establish Public Private Collaborations

For multiply drug-resistant bacteria and other high priority bacterial infections, where market challenges are extreme, we should explore the establishment of a non-profit, public-private partnership (PPP). Since a PPP would not be profit-driven, it could focus on developing critically needed drugs for indications where markets are very small (e.g. drugs to treat *Acinetobacter*, *Klebsiella*). Removing profit motives from the equation also will help to limit the marketing of the "priority" antibiotic to the more serious and life-threatening indication for which it is approved. This will support the appropriate stewardship of these drugs and will prolong their effectiveness. Thus, the advantage of

the PPP is that it could merge antibiotic conservation efforts with new antibiotic R&D efforts.

It is important to note that the PPP idea is not meant to replace the essential activities of private companies in drug discovery and development. Rather the PPP is intended to complement efforts to reinvigorate market driven, for-profit antibiotic development. Private companies' R&D activities must still be strengthened through strong, new incentives and other companies must be lured back into this field. We cannot rely on an unproven PPP model to fix the current situation.

Create an Antibiotic Innovation and Conservation Fee

One idea we propose for funding new antibiotic innovations and the uptake of good antimicrobial stewardship practices is the creation of an Antibiotic Innovation and Conservation (AIC) fee. Such a fee would be placed on every course of antibiotic treatment prescribed both on human and veterinary prescriptions (branded and generic). Perhaps 75 percent of the AIC fee could be allocated to the development of promising, high priority candidate antibiotics under a PPP arrangement while 25 percent of the fee could go to a fund overseen by the CDC, which would support the promotion and establishment of antibiotic stewardship programs in health care facilities across the country. In addition to funding new R&D, an advantage to such a fee is that it could help to limit non-judicious uses of these drugs in both human and animal settings. Finally, the AIC fee would recognize the value of these essential drugs and the need to use them wisely.

B. Support the Development and Utilization of New Rapid Diagnostic Tests

Rapid, point-of-care diagnostic tests are an important part of the solution and are urgently needed for three reasons:

1. The biggest driver of inappropriate antibiotic use is the inability of physicians to be certain whether or not patients have a bacterial infection, and if so, what type of bacteria is causing the infection. Using existing test methods (culture tests) requires days or weeks to identify bacterial organisms, and the tests often fail to detect bacteria that are present (i.e. the culture tests are not "sensitive"). The power of a rapid, accurate diagnostic that could inform the physician that the disease is not, in fact, a bacterial infection cannot be overestimated. Such a test would dramatically reduce inappropriate antibiotic prescriptions. Furthermore, if the patient did have a bacterial infection and the test could identify which bacteria was causing the infection, it would enable more accurate, narrow spectrum antibiotics to be prescribed, further improving antibiotic stewardship efforts.

2. New rapid diagnostic tests would greatly facilitate clinical trials of critically needed new antibiotics. The tests would enable investigators to identify potential study subjects more easily, which would permit smaller and less expensive studies of antibiotics as they move through development. Smaller and less expensive studies would facilitate development of new antibiotic agents.

3. New diagnostics would make it easier to identify and track the spread of new and dangerous drug-resistant pathogens (e.g., KPC-producing bacteria) as they spread across the country. Once we are better able to track the spread of these organisms, we can begin to study and implement interventions to slow their pace.

Unfortunately, while some other areas of medicine have made tremendous strides in advancing technological sophistication, there has been little impetus for diagnostics companies to develop new tests to detect and identify resistant bacteria. This is partly due to the fact that physicians have come to treat infections empirically, often not utilizing microbiologic diagnostic tests to confirm their diagnoses. With the low cost of currently available generic antibiotics, it actually costs more to test patients than to just give them a prescription. As we have seen above, the failure to establish a precise cause of infection results in guesswork in antibiotic use, overprescribing, and less than optimal patient care.

For these reasons, we believe it is necessary to enact incentives that spur the development and utilization of rapid diagnostics tests. The LSEPS report can be helpful in this regard, but we also need to consider how the Center for Medicare and Medicaid Services (CMS) and Joint Commission can support the uptake and use of these essential tools.

To support the development of new diagnostics, we ask Congress to establish and fund a reference library of culture-positive clinical specimens, perhaps maintained by NIH or FDA's Center for Devices and Radiological Health. Such a reference library would allow sponsors of new diagnostics to quickly determine the sensitivity and specificity of their new test to detect pertinent pathogens (viruses and bacteria) in clinically relevant specimens. The library would consist of clinical specimens that are fully characterized as to the presence, or absence, of relevant microorganisms as determined by current standards of laboratory diagnosis.

C. Enact the Strategies to Address Antimicrobial Resistance (STAAR) Act

IDSA and 25 other organizations [44,45] representing physicians, hospitals, pharmacists, health care epidemiologists, infection prevention and control professionals, and public health experts and advocates have strongly endorsed the Strategies to Address Antimicrobial Resistance (STAAR) Act, H.R. 2400, and launched the STAAR Act Coalition to support the bill's enactment.

The STAAR Act [46,47,48,49,50] builds upon the solutions identified in the OTA report as well as on existing federal efforts that have been highlighted in the Public Health Action Plan to Combat Antimicrobial Resistance. The Action Plan was published in January 2001 by an interagency task force, co-chaired by CDC, FDA and NIAID, and authorized under Section 319E [51] of the Public Health Service Act. This authorization expired September 30, 2006. Thirteen key elements (out of a total of 84 elements) highlighted within the Action Plan were deemed critically necessary to address the growing resistance crisis. Unfortunately, neither the interagency task force nor the Action Plan

has received adequate resources to accomplish its goals. Moreover, there exists no centralized office to facilitate the coordination of activities, prioritize the federal response, or provide a platform for on-going discussion and action. Nor is there a sufficient process for engaging outside experts to provide input into federal policymaking in this area.

The STAAR Act strengthens existing efforts by establishing an Antimicrobial Resistance Office (ARO) within the HHS Office of the Assistant Secretary of Health. The Director of ARO will serve as the director of the existing interagency task force. The Act also establishes a Public Health Antimicrobial Advisory Board (PHAAB) comprised of infectious diseases and public health experts who will provide much-needed advice to the ARO Director and task force about antimicrobial resistance and strategies to address it. The STAAR Act will strengthen existing surveillance, data collection, and research activities as a means to reduce the inappropriate use of antimicrobials, develop and test new interventions to limit the spread of resistant organisms, and create new tools to detect, prevent and treat drug-resistant "bad bugs."

Public reporting of infections and access to data provides the opportunity for states and the CDC to rapidly identify problems and work toward corrections and improvements that save lives. Such data on antibiotic-resistant infections and antibiotic use are needed to inform our development of antibiotic stewardship programs, to limit the emergence and prevent transmission of resistant bacteria, and to guide development of new and effective therapies. The U.S. desperately needs transparent and accurate data with respect to antibiotic resistance and antibiotic use.

The lack of comprehensive data on use and resistance is a problem that is unique to the United States, among developed nations. In contrast, the European Union has a robust data collection system that has been able to track antimicrobial use and resistance trends, by country, since 1999. Data also are available by specific antimicrobial drug and specific pathogen. Having comparable data is critically important if the U.S. is to tackle the antibiotic resistance problem. We strongly support including within the STAAR Act language to ensure that we have the data needed to make the best decisions possible regarding antibiotic use, both in human health and agricultural settings.

D. Promote the Judicious Use of Antibiotics in Human Medicine

Inappropriate use of antibiotics is one of the biggest contributors to the problem of resistance. It has been estimated that up to 50 percent of antibiotic use is either unnecessary or inappropriate, and this holds true across all health care settings, including acute care academic and community hospitals, long-term care facilities, private physician offices, and at the retail pharmacy and consumer level. (Inappropriate use also is an enormous problem in food animal/agricultural settings, but we have not been asked to focus on this significant issue.[52,53]) As mentioned earlier, in the past several years there have been a variety of campaigns by retail pharmacies that offer "free" antibiotics. The intent is to attract customers, but it further contributes to a public perception that

antibiotics can be used for any type of illness and that there are no health-related repercussions associated with their use.

Promoting Antibiotic Stewardship Strategies in Health Care Facilities

The primary strategy for preserving antibiotics and preventing the development of drug resistance is antibiotic stewardship, which is intended to ensure that antibiotics are used appropriately.[54] Antibiotic stewardship has been a major focus for both IDSA and the Society for Healthcare Epidemiology of America (SHEA); both societies are collaborating to promote good stewardship practices in health care, but practical implementation has been challenging.

The goal of antibiotic stewardship is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the emergence of resistance, and the selection of pathogenic organisms such as *C. diff.* The combination of effective antibiotic stewardship along with comprehensive infection prevention and control efforts has been shown to limit the emergence and transmission of antibiotic-resistant bacteria. A secondary goal of antibiotic stewardship is to reduce health care costs without adversely affecting quality of care. Indeed, many studies have demonstrated that antibiotic stewardship can decrease health care costs while improving the quality of care. Antibiotic stewardship strategies directly improve cure rates by ensuring that patients receive the correct antibiotic in a timely fashion. Improved cure rates result in decreased intensive care unit and overall length of stay. Antibiotic stewardship programs are typically directed by a physician and/or a clinical pharmacist with relevant (infectious diseases, etc.) training.

IDSA and SHEA issued guidelines for developing an institutional program to enhance antibiotic stewardship in 2007.[55] These guidelines provide an extensive blueprint for designing and implementing a successful stewardship program. However, establishing an antibiotic stewardship program can be a costly endeavor that eludes many health care facilities that lack adequate resources. While stewardship programs have demonstrated a long-term cost savings, they require staff resources that some health care facilities may not have. Specifically, not every health care facility has an infectious diseases physician or an infectious diseases pharmacist on staff that can help to develop, monitor, and oversee a stewardship program. Other facilities may have staff with appropriate training, but the facility may be unable—or unwilling—to compensate the physician or pharmacist for the extra time required to establish and maintain these programs. Regardless of the costs of establishing and maintaining a stewardship program, in this age of resistance, it is too costly not to practice stewardship.

It is possible for health care facilities to implement stewardship strategies and embrace a philosophy of stewardship without having to implement an expensive comprehensive program. While most research has focused on comprehensive efforts, they may not be practical in smaller community hospitals and practice settings. In these instances, there are a fair number of administrative and practice strategies that can be employed to pick the "low hanging fruit."

Essential Components of Successful Antibiotic Stewardship Programs

There are several essential components of a successful stewardship program: leadership and dedicated staff; training and education; mechanisms that serve to improve antibiotic usage; diagnostic utilization (see Section B above for a discussion on diagnostics); and a mechanism to pay for establishing and maintaining these programs and practices and the staff's services.

Leadership and Dedicated Staff

To assure the success of stewardship programs, the hospital administrator must be an active proponent to ensure that the programs have the necessary infrastructure, the ability to track and manage use data and that the staff working on stewardship are compensated for their time. Also critical is the support of medical staff leadership—or physician champions—to develop and maintain stewardship programs, while also encouraging staff buy-in and adherence to the stewardship philosophy.

Training and Education

Training and educating health care professionals on the appropriate use of antibiotics must include appropriate selection, dosing, route, and duration of antibiotic therapy. To ensure that training and education is working, there should be extensive collaboration between the antibiotic stewardship and hospital infection prevention and control teams. Without benchmarks, it is difficult to track successes and weaknesses.

Education must occur at all levels, including the executive and administrative levels. The training and education component also should include a mechanism for quality control audits and feedback.

Improving Use

Another critical component of successful stewardship efforts is conserving our limited antibiotic resources. Once health care facility staff is trained and educated about antibiotic stewardship strategies, including appropriate use, dose and duration, there are additional strategies to further improve the use of certain antibiotics. This can take the form of restricting which antibiotics are included in the formulary or requiring that prescribing a specific therapy may require a preauthorization. Additional mechanisms can include antibiotic order forms, formal prospective audit and feedback, de-escalation of therapy based upon microbiology data, an evaluation of dose optimization, or the conversion from intravenous to oral therapy.

Antibiotic usage also can be improved by changing prescribing requirements, so that prescriptions include the type of antibiotic, the quantity, dose, duration and indication. Including all of these items on a prescription could allow for their capture by electronic health records, which in turn, allows for public reporting and monitoring by the health care facility or by an outside entity. The special labeling also can be restricted to certain antibiotics that are directed toward our most resistant pathogens, have a greater potential to cause resistance, or have increased potential for toxicity.

Paying for Antibiotic Stewardship
Given the importance of antibiotics to public health, patient care and safety, and national security, we need to think of novel ways to promote the uptake of good antibiotic stewardship practices. Government-supported enticements would go a long way to promote the adoption of stewardship programs and practices by health care facilities, to help to ensure quality across these programs nationwide, and to promote leadership in this field. The Antibiotic Innovation and Conservation fee we mentioned above is one potential funding option. Adoption of antibiotic stewardship strategies also could be a component of value-based purchasing.

CDC Programs Related to Antibiotic Stewardship, Use and Resistance
To combat inappropriate use of antibiotics, the CDC launched the program, Get Smart: Know When Antibiotics Work, to educate the public and providers about the judicious use of antibiotics. Physicians sometimes admit that they inappropriately prescribe antibiotics to patients who insist on receiving them. As part of CDC's effort to help health care professionals, the Get Smart program includes tools to educate patients as well as tools to assist physicians in explaining to their patients why antibiotics would be unnecessary in a particular treatment protocol. Information is disseminated in a manner accessible to the greater public, such as podcasts and health e-cards, but there is still a need for a more aggressive campaign targeted at consumers.

Building on the success of the existing "Get Smart" program, the CDC recently launched a new antibiotic stewardship initiative —"Get Smart for Healthcare"— in hopes of advancing adherence to stewardship practices in health care facilities. CDC officials are collaborating with physicians and hospitals about the best ways to implement the campaign, which aims to clearly define the roles of physicians, pharmacists and other health care workers in antibiotic stewardship initiatives. The CDC is working with SHEA to develop simple implementation tools to facilitate adoption of these efforts.

The CDC also is collaborating with the Institute for Healthcare Improvement (IHI) and SHEA to develop a driver diagram with practical antibiotic stewardship implementation strategies with the intent of promoting aspects of care in places where improvement is needed. A long-term goal of this partnership is to encourage more facilities to engage in appropriate antibiotic use and stewardship efforts.

In an effort to more adequately capture antibiotic use data the CDC will pilot an Antimicrobial Use and Resistance (AUR) Module in the fall of 2010 as part of the National Healthcare Safety Network (NHSN) system. The module likely will include a pharmacy option, which measures antibiotic use by days of therapy, and a microbiology option, which will assist health care facilities by providing data that allows for benchmarking.

Finally, related to CDC's funding, we call to your attention the Administration's proposed budget for FY 2011, in which CDC's already severely strapped Antimicrobial Resistance budget would be cut dramatically by $8.6 million—just over 50 percent! This vital program is necessary to help combat the rising crisis of antibiotic resistance. Yet the

President's FY2011 budget would allow only 20 state and local health departments and health care systems to be funded for surveillance, prevention, and control of antibiotic resistance, down from 48 this past year. It would also eliminate all grants to states for the Get Smart in the Community program to combat improper uses of antibiotics. IDSA believes CDC's antimicrobial resistance activities are so important to protecting Americans from serious and life-threatening infections that we should boost funding for these activities to at least $40 million in FY2011.

CONCLUSION

As we have outlined above, the problems of antibiotic resistance and the dry antibiotic pipeline are complex and multi-factorial. No one single strategy can begin to address these problems—a multi-pronged approach is required. We must conserve antibiotics' effectiveness through the adoption of appropriate antibiotic stewardship practices. We must prevent the emergence and transmission of resistant infections through effective infection prevention and control initiatives and effective immunization policies. And we must continue to replenish this precious resource through heightened investments in innovative antibiotics and related rapid diagnostics, and through the adoption of strong, well-considered incentives.

Last November, President Barack Obama and Swedish Prime Minister Fredrik Reinfeldt, representing the European Union (EU), agreed to establish a Transatlantic Task Force to address antibiotic resistance. The Task Force will focus on appropriate therapeutic use of antibiotics in the medical and veterinary communities, prevention of both health care- and community-associated drug-resistant infections, and strategies for improving the pipeline of new antibiotics. IDSA strongly supports [56] this comprehensive approach, but it must move forward with a sense of extreme urgency to strengthen the antibiotic and related diagnostics pipelines.

The Subcommittee on Health has a long history of leading the way to address our nation's most pressing public health issues. Today, we call on you to adopt strong measures to build and sustain a global antibiotic (and related rapid diagnostics) R&D enterprise. It is our hope that the resulting enterprise will spur the development of 10 new safe and effective antibiotics by 2020. Such an achievement would be of immense benefit to the health of the citizens of the United States and the world. Further, a sustained infrastructure would help to reestablish the highly skilled scientific workforce that has been lost over the past two decades as many companies abandoned antibiotic development. We also urge the Committee to move with haste to enact the Strategies to Address Antimicrobial Resistance Act, which we believe will significantly strengthen U.S. antibiotic resistance surveillance, research, prevention and control efforts as well as provide the necessary data we need to save lives and protect public health.

Thank you again for the opportunity to testify on this incredibly important issue. IDSA looks forward to assisting the Subcommittee in any way that we can.

References/Attachments

1. Highlights of Past U.S. Response to Antimicrobial Resistance; accessed online at: <http://www.idsociety.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=16627>.

2. Taubes G. The Bacteria Fight Back. *Science* 18 July 2008: 321(5887):356 – 61. <http://www.sciencemag.org/cgi/content/summary/321/5887/356>

3. Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates…A Public Health Crisis Brews. Infectious Diseases Society of America. July 2004. <http://www.idsociety.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=5554>

4. Gilbert DN, Guidos RJ, et al. (for the Infectious Diseases Society of America). The 10 x '20 Initiative: Pursuing a Global Commitment to Develop 10 New Antibacterial Drugs by 2020. *Clin Infect Dis* 2010; 50:1081–1083. <http://www.idsociety.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=16264>

5. Organizations that Endorse the 10 x '20 initiative, May 30, 2010. <http://www.idsociety.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=16606>

6. Arias CA, Murray BE. Antibiotic-Resistant Bugs in the 21st Century — A Clinical Super-Challenge. *N Engl J Med* 360;5:439-43. <http://content.nejm.org/cgi/reprint/360/5/439.pdf>

7. Andrew Pollack, "Rising Threat of Infections Unfazed by Antibiotics," *New York Times*, 26 Feb 2010. <http://www.nytimes.com/2010/02/27/business/27germ.html>

8. Spellberg B, Guidos RJ, Gilbert DN, et al. The Epidemic of Antibiotic-Resistant Infections: A Call to Action for the Medical Community from the Infectious Diseases Society of America; *Clin Infect Dis* 2008; 46:155–64. <http://www.idsociety.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=9048>

9. So AD, Gupta N, Cars O. Tackling Antibiotic Resistance – Editorial. *BMJ* 2010;340:1091-96. <http://www.bmj.com/cgi/section_pdf/340/may18_2/c2071.pdf>

10. Eben Herrell, "The Desperate Need for New Antibiotics," *Time*, 1 October 2009. <http://www.time.com/time/printout/0,8816,1926853,00.html>

11. Nathan C, Goldberg FM. The profit problem in antibiotic R&D. *Nat Rev Drug Discovery* 4, 887-91 (November 2005). <http://www.nature.com/nrd/journal/v4/n11/abs/nrd1878.html?lang=en>

12. Boucher HW, Talbot GH, Bradley JS, et al. Bad Bugs, No Drugs: no ESKAPE! an Update from the Infectious Diseases Society of America. *Clin Infect Dis* 2009; 48:1–12. <http://www.idsociety.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=13478>

13. European Centre for Disease Prevention and Control/European Medicines Agency Joint Technical Report. The bacterial challenge: time to react. Updated September 2009. <http://www.emea.europa.eu/pdfs/human/antimicrobial_resistance/EMEA-576176-2009.pdf>

14. United States, Centers for Disease Control and Prevention, "CDC estimates 94,000 invasive drug-resistant staph infections occurred in the U.S. in 2005" October 16, 2007. <http://www.cdc.gov/media/pressrel/2007/r071016.htm?s_cid=mediarel_r071016>

15. Klevens RM, Morrison MA, Nadle J, et al. Invasive Methicillin-Resistant *Staphylococcus aureus* Infections in the United States. ***JAMA.*** 2007; 298:1763-71. <http://jama.ama-assn.org/cgi/content/abstract/298/15/1763>

16. Frederik Joelving, "Faster, stronger, deadlier: the MRSA superbug" Reuters Health, 14 May 2010. Accessed online at: <http://www.reuters.com/article/idUSTRE64D66L20100514>.

17. Klevens RM, Edwards JR, Richards CL, et al. Estimating Health Care-Associated Infections and Deaths in U.S. Hospitals. *Public Health Reports*; March-April, 2007; p. 160-66. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1820440/pdf/phr122000160.pdf>

18. Eber MR, Laxminarayan R, Perencevich EN, et al. Clinical and Economic Outcomes Attributable to Health Care–Associated Sepsis and Pneumonia. *Arch Intern Med.* 2010;170(4):347-53. <http://www.extendingthecure.org/press-release/new-study-shows-sepsis-and-pneumonia-caused-hospital-acquired-infections-kill-48000-pa>

19. Vincent JL, Rello J, Marshall J, et al. International Study of the Prevalence and Outcomes of Infection in Intensive Care Units. *JAMA*. 2009; 302(21):2323-29. <http://jama.ama-assn.org/cgi/content/abstract/302/21/2323>

20. Roberts RR, Hota B, Ahmad I, et al. Hospital and Societal Costs of Antimicrobial-Resistant Infections in a Chicago Teaching Hospital: Implications for Antibiotic Stewardship. *Clin Infect Dis* 2009;49:1175–84. <http://www.journals.uchicago.edu/doi/abs/10.1086/605630>

21. PRNewswire press release: "Antibiotic-Resistant Infections Cost the U.S. Healthcare System in Excess of $20 Billion Annually." October 19, 2009. <http://www.prnewswire.com/news-releases/antibiotic-resistant-infections-cost-the-us-healthcare-system-in-excess-of-20-billion-annually-64727562.html>

22. Mauldin PD, Salgado CD, Hansen IS, et al. Attributable Hospital Cost and Length of Stay Associated with Health Care-Associated Infections Caused by Antibiotic-Resistant Gram-Negative Bacteria. *Antimicrob Agents Chemother*, 2010; 54(1):109-15. <http://aac.asm.org/cgi/content/short/54/1/109>

23. Filice GA, Nyman JA, Lexau C, et al. Excess Costs and Utilization Associated with Methicillin Resistance for Patients with *Staphylococcus aureus* Infection. *Infect Control Hosp Epidemiol* 2010; 31:365-73. <http://www.idsociety.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=16277>

24. Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: No ESKAPE. *J Infect Dis* 2008; 197:1079–81. <http://www.journals.uchicago.edu/doi/pdf/10.1086/533452>

25. Peleg AY, Hooper DC. Hospital-Acquired Infections Due to Gram-Negative Bacteria; *N Engl J Med* 2010; 362:1804-13. <http://content.nejm.org/cgi/content/short/362/19/1804>

26. Sengstock DM, Thyagarajan R, Apalara J, et al. Multidrug-Resistant *Acinetobacter baumannii:* An Emerging Pathogen among Older Adults in Community Hospitals and Nursing Homes. *Clin Infect Dis* 2010; 50(12):1611–16. <http://www.journals.uchicago.edu/doi/pdf/10.1086/652759>

27. de Medina T, Carmeli Y. The Pivotal Role of Long-Term Care Facilities in the Epidemiology of *Acinetobacter baumannii:* Another Brick in the Wall. *Clin Infect Dis* 2010; 50(12):1617–18. <http://www.journals.uchicago.edu/doi/pdf/10.1086/652760>

28. Fishbein J, Peleg AY. Treatment of *Acinetobacter* Infections. *Clin Infect Dis* 2010; 51(1):79–84. <http://www.journals.uchicago.edu/doi/pdf/10.1086/653120>

29. Hujer KM, Hujer AM, Hulten EA, et al. Analysis of Antibiotic Resistance Genes in Multidrug-Resistant *Acinetobacter* sp. Isolates from Military and Civilian Patients Treated at the Walter Reed Army Medical Center. *Antimicrob Agents Chemother*, 2006; 50(1):4114–23. <http://aac.asm.org/cgi/reprint/50/12/4114>

30. CDC Clinical Reminder on Vancomycin-Resistant Staphylococcus Aureus, May 5, 2010. <http://www.cdc.gov/ncidod/dhqp/ar_vrsa_labUpdate.html>

31. CDC Update: Information about the Current Epidemic Strain of *Clostridium difficile*, March 2010. <http://www.cdc.gov/ncidod/dhqp/id_CdiffFAQ_newstrain.html>

32. Jump RL, Riggs MM, Sethi AK, et al. Multi-hospital Outbreak of C. diff. Infection in Cleveland, Ohio, USA. *Emerg Infect Dis*; Vol. 16, No. 5, May 2010; p. 827-29. <http://www.cdc.gov/EID/content/16/5/pdfs/827.pdf>

33. Elizabeth Weise, "Lesser-known C-diff a bigger hospital threat than MRSA?" *USA Today*, 22 March 2010. <http://www.usatoday.com/news/health/2010-03-20-c-diff-bacteria_N.htm>

34. U.S. Congress, Office of Technology Assessment, *Impacts of Antibiotic-Resistant Bacteria,* OTA-H-629 (Washington, DC: U.S. Government Printing Office, September 1995). < http://www.theblackvault.com/documents/ota/Ota_1/DATA/1995/9503.PDF>

35. Anders Ekblom, "How law could help to fight antibiotic resistance," *Times of London*, 31 December 2009. <http://business.timesonline.co.uk/tol/business/law/article6972691.ece>.

36. Shlaes DM. New Antibiotics—Government Intervention Versus Market Forces. *Microbe*; Volume 2, Number 2, 2007; p. 56-7. <http://www.antiinfectivesconsulting.com/PDF/Antibiotics.pdf>

37. "Financial Incentives Seen as a Path to Resurgence of Antibiotics," *The Pink Sheet*, 26 April 2010. <http://sis.windhover.com/buy/abstract.php?id=00720170012>

38. Morel CM, Mossialos E. Stoking the Antibiotic Pipeline. *BMJ* 2010;340:1115-18. <http://www.bmj.com/cgi/section_pdf/340/may18_2/c2115.pdf>

39. Viral Gandhi, Kirsty Barnes, and Jennifer C. Smith, "FDA mulls change to anti-infectives trials" *Financial Times*, 20 April 2010. <http://www.ft.com/cms/s/2/f7dd3986-4cba-11df-9977-00144feab49a.dwp_uuid=e8477cc4-c820-11db-b0dc-000b5df10621.html>

40. Matthew Herper, "The FDA's Infection," *Forbes*, 2 March 2009. <http://www.forbes.com/2009/03/02/fda-antibotics-mrsa-business-health-care_fda.html>

41. IDSA Testimony to the Senate Appropriations Subcommittee on Agriculture; March 26, 2010. <http://www.idsociety.org/WorkArea/DownloadAsset.aspx?id=16261>

42. IDSA Testimony to the House Appropriations Subcommittee on Labor, Health and Human Services, and Education; April 16, 2010. <http://www.idsociety.org/WorkArea/DownloadAsset.aspx?id=16493>

43. Dagan R, Klugman KP. Impact of conjugate pneumococcal vaccines on antibiotic resistance. *Lancet Infect Dis* 2008; 8: 785–95. <http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(08)70281-0/fulltext#article_upsell>

44. Organizations that Endorse the Strategies to Address Antimicrobial Resistance Act, May 15, 2010; accessed online at: http://www.idsociety.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=15947.

45. STAAR Act Coalition letter to Speaker Pelosi urging co-sponsorship of H.R. 2400; May 18, 2009; accessed online at: http://www.idsociety.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=14478.

46. STAAR Act Backgrounder; accessed online at: http://www.idsociety.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=14464.

47. STAAR Act Section-by-Section Summary; accessed online at: http://www.idsociety.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=14466.

48. STAAR Act Options for Improving Access to Antimicrobial Consumption Data in the United States; accessed online at: http://www.idsociety.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=14476.

49. STAAR Act Rationale for Establishing the Antimicrobial Resistance Surveillance and Research Network (ARSRN); accessed online at: http://www.idsociety.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=14472.

50. Rep. Matheson's Statement in Congressional Record upon STAAR Act Introduction, May 13, 2009; accessed online at: http://www.idsociety.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=14474.

51. Public Health Service Act, Section 319 E: Combating Antimicrobial Resistance; accessed online at: http://www.idsociety.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=16628.

52. Infectious Diseases Society of America (IDSA): Summary of Existing Policy on the Use of Antimicrobial Drugs in Food Animals; November 1, 2009. accessed online at http://www.idsociety.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=15841

53. 20 organization letter to White House Domestic Policy Advisor Melody Barnes on FDA's public health approach to antimicrobial use in animals; July 24, 2009. <http://www.idsociety.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=14986>

54. MacDougall C, Polk RE. Antimicrobial Stewardship Programs in Health Care Systems. *Clinical Microbiology Reviews* 2005; 18(4):638–56. <http://cmr.asm.org/cgi/reprint/18/4/638>

55. Dellit TH, Owens RC, McGowan JE, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines on Institutional Antimicrobial Stewardship Programs. *Clin Infect Dis* 2007; 44:159–77. <http://www.journals.uchicago.edu/doi/pdf/10.1086/510393>

56. IDSA letter to President Obama and Swedish Prime Minister Reinfeldt. Published 20 November 2009. Accessed online at: http://www.idsociety.org/WorkArea/DownloadAsset.aspx?id=15752.