Confronting Today’s Crisis in Antibiotic Development

Volume 30
Issue 1
The APUA Clinical Newsletter (ISSN 154-1424) is published three times per year by the Alliance for the Prudent Use of Antibiotics; copyright © 2012.

Disclaimer
The Alliance for the Prudent Use of Antibiotics accepts no legal responsibility for the content of any submitted articles, nor for the violation of any copyright laws by any person contributing to this newsletter. The mention of specific companies or of certain manufacturers’ products does not imply that they are endorsed or recommended by APUA in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters. The material provided by APUA is designed for educational purposes only and should not be used or taken as medical advice.

Communications for the editors should be addressed to the Alliance for the Prudent Use of Antibiotics, 136 Harrison Avenue Room 811, Boston, MA 02111; phone (617) 636-0966; email APUA@tufts.edu.

Support APUA’s work by visiting http://www.tufts.edu/med/apua/about_us/support_our_work.shtml.
Partnerships

The Alliance for the Prudent Use of Antibiotics is pleased to acknowledge its supporters and partners in “Preserving the Power of Antibiotics ®.” APUA programs are funded through multi-year contracts and grants from professional societies and other major foundations, as well as unrestricted grants from private corporations.

APUA Corporate Sponsors

Leadership Level ($25,000+)
The Clorox Company

Benefactor Level ($10,000-$15,000)
Alere Inc.
AstraZeneca
Optimer Pharmaceuticals

Partner Level ($5,000-$10,000)
Alcon Laboratories
Bayer Healthcare Pharmaceuticals
bioMérieux Inc.
GlaxoSmithKline

Supporting Level ($2,500-$5,000)
Paratek Pharmaceuticals

APUA Project Partners

The Bill and Melinda Gates Foundation
The Pew Charitable Trusts
U.S. National Institute of Health (NIH)
Pan American Health Organization (PAHO)
U.S. Agency for International Development
U.S. Department of Agriculture
U.S. Office of Homeland Security
National Biodefense Analysis and Countermeasures Center
World Health Organization (WHO)
Centers for Disease Control and Prevention (CDC)
U.S. Food and Drug Administration
World Bank
Ministries of Health
Table of Contents

6 Getting serious about new antibiotics and rational use: introduction to this issue
Kathleen Young
Dr. Stuart Levy honored with 2012 Abbott-ASM Lifetime Achievement Award

8 New antibiotic development: barriers and opportunities in 2012
Brad Spellberg, M.D.

11 Resistant infections: a tragic irony in modern medicine
Barry Eisenstein, M.D. and Elizabeth D. Hermsen, PharmD, M.B.A.

13 All pain, no GAIN: need for prudent antimicrobial use provisions to complement the GAIN Act
Kevin Outterson, J.D.

16 Fewer drugs, more superbugs: strategies to reverse the problem
Jennie Choe, M.S.

20 The lack of novel antibiotic and vaccine development to combat resistance
Victor K.E. Lim, MBBS, M.Sc.

23 APUA One-on-One with Dr. Abraham Sonenshein
Abraham L. Sonenshein, Ph.D.

26 Related initiatives to spur antibiotic development
APUA and ReAct advise new WHO book on antimicrobial resistance
New U.S. FDA guidances on antibiotic use in food animals: mixed reviews
UK-based Antibiotic Action Initiative
BARDA awards $67 million contract to Tetraphase to develop novel antibiotic
April 2012 issue of ICHE dedicated to antimicrobial stewardship
Getting serious about new antibiotics and rational use: introduction to this issue

Kathleen Young

Executive Director, Alliance for the Prudent Use of Antibiotics

The dwindling supply of new antibiotics has become more critical as we face more hyper-virulent, multi-drug-resistant infections in both community and healthcare settings. This issue of the APUA Clinical Newsletter focuses on promising U.S. policy initiatives to promote antibiotic development and to encourage more rational antibiotic use.

In this edition, APUA staff and experts from industry, the nonprofit sector, and academia review the current legislative landscape. We report on the new FDA guidances to minimize antibiotic misuse in food animal production. While some public health advocates consider the FDA action not strong enough, others consider these as bold regulatory steps. We review the draft of the GAIN Act currently before Congress, which provides regulatory incentives to keep drug companies in the antibiotic business but lacks effective incentives for antibiotic stewardship to help extend their useful life. The need for appropriate antibiotic use in human medicine and food animal production must be considered in tandem with promotion of novel antibiotics to ensure that as new antibiotics come on board, they are used appropriately and remain effective as long as possible. Vaccine development is reviewed here as a key preventive strategy to minimize the need for antibiotics. Improved diagnostics and antibiotic resistance surveillance, which are necessary to facilitate more targeted treatment, have been covered in previous issues (see Vol.29 No.2, “Diagnostic Innovation to Contain Resistance,” and Vol.29 No.1, “Antibiotic Stewardship Gaining Traction”).

By implementing a multi-pronged strategy we will emerge out of the antibiotic crisis today and forestall future epidemics of resistant infections. Having been on the front lines of advocacy on these issues for over 30 years, APUA is pleased to be actively supporting current policy initiatives described in this issue, including the Preservation of Antibiotics for Medical Treatment Act, the new FDA guidances, IDSA’s 10x’20 and Limited Population Antibiotic Drug initiatives, the GAIN Act, and others. APUA also played a key role in crafting the new WHO strategy to control antibiotic resistance.

With all these actions as a framework, APUA will continue to work with its global chapter network and all stakeholders to support meaningful action now. We count on the U.S. to take the lead in combating this global crisis by enacting model regulations and payment structures to ensure antibiotic access and affordability for all populations in need for generations to come.
APUA President Dr. Stuart Levy Honored with 2012 Abbott-ASM Lifetime Achievement Award

Congratulations to Dr. Stuart Levy on his selection as the 2012 Abbott-ASM Lifetime Achievement Award Laureate! The award is the highest recognition by the American Society for Microbiology for sustained contributions to the microbiological sciences. The ASM acknowledged Dr. Levy’s co-founding of APUA in 1981, and his tireless efforts through the organization for the past 30 years.

Dr. Hiroshi Nikaido (University of California, Berkeley) nominated Dr. Levy for “not only elucidating the genetics and biochemistry of one of the most important mechanisms for drug resistance, but also striv[ing] to minimize the selection and spreading of resistant bacteria.”

Longtime colleague Dr. Steve Lerner (Wayne State University) also lauds Dr. Levy for “bringing his studies and their implications beyond the laboratory to influence directions in infectious disease research and public health policy worldwide.” Dr. Levy’s pioneering work in fighting antibiotic resistance not only through basic science, but also through industry and government initiatives, inspires all of us who strive to make a difference in public health. Read more about the award on the ASM website.
New antibiotic development: barriers and opportunities in 2012

Brad Spellberg, M.D.
Assistant Professor of Medicine, David Geffen School of Medicine at UCLA; Division of Infectious Diseases, Department of Medicine, Harbor-UCLA Medical Center

In 2012, antibiotic development continues to stagnate. Two systemic antibacterial agents have been approved for use in humans by the US FDA from 2008 through the current year. Compare that to sixteen that were approved from 1983-1987. In particular, we have had no new classes of antibiotics to treat Gram-negative bacilli (GNB) for more than 40 years – amazingly, the fluoroquinolones were the last new class of antibiotics to treat GNB. Meanwhile, antibiotic resistance continues to spread like wildfire, particularly among the GNB. The US and global healthcare systems are encountering on a regular basis extensively drug-resistant (XDR) organisms resistant to all antibiotics except for colistin, a highly toxic agent of questionable efficacy whose use was abandoned in the 1960s when safer and more effective therapies became available.

Even worse, we are seeing pan drug-resistant (PDR) organisms, resistant to all available antibiotics, including colistin. Examples of XDR and PDR bacteria that plague the U.S. and global healthcare systems include carbapenem-resistant bacteria, such as KPC Klebsiella and Acinetobacter. Both of these organisms are increasingly XDR, and are causing increasing infections in the US and worldwide. These infections cause high death rates despite available therapy. They will continue to kill a high percentage of infected patients until new prevention and treatment methods become available.

Twelve years ago, Nobel Laureate Dr. Joshua Lederberg wrote that “The future of humanity and microbes will likely evolve…as episodes of our wits versus their genes.” In the 12 years since Dr. Lederberg wrote those prescient words, we have witnessed a continued expansion of antibiotic resistant pathogens due to their genes. Amazingly, we seem to have stopped trying to use our wits to keep up. So, why is this?

There are three principal causes of the antibiotic market failure. The first is scientific: the low-hanging fruit have been plucked. Drug screens for new antibiotics tend to re-discover the same lead compounds over and over again. There have been more than 100 antibacterial agents developed for use in humans in the U.S. since sulfonamides. Each new generation that has come to us has raised the bar for what is necessary to discover and develop the next generation. Thus, discovery and development of antibiotics has become scientifically more complex, more expensive, and more time consuming over time. The second cause is economic: antibiotics represent a poor return on investment relative to other classes of
BARRIERS AND OPPORTUNITIES IN 2012

drugs. The third cause is regulatory: the pathways to antibiotic approval through the U.S. FDA have become confusing, generally infeasible, and questionably relevant to patients and providers over the past decade.

A key concept in dealing with these three causes is to understand that they interact, much like a Venn Diagram, and that they cannot be considered in isolation. For example, the scientific and regulatory challenges markedly increase the cost and timeline of development, which greatly exacerbates the economic disadvantages of antibiotics. Conversely, if antibiotics were billion-dollar-per-year blockbuster drugs, companies would be willing to tolerate high barriers scientifically and from a regulatory perspective. Since antibiotics tend to sell much less than a billion dollars per year, there is instead low tolerance for scientific and regulatory barriers.

There are multiple economic barriers to antibiotic development. The most obvious is that antibiotics are short course therapies, and companies know that they will make much more money selling a drug you have to take very day for the rest of your life. Also, there are many types of infections, and approval for one type gets a company only one slice of the overall market pie. When antihypertensive drugs are approved, they are not approved to treat hypertension of the lung, or hypertension of the kidney. They are approved to treat hypertension. When antifungals are approved, they are approved to treat “invasive aspergillosis,” or “invasive candidiasis.”

Not so for antibacterials, which the FDA continues to approve based on disease state one at a time (pneumonia, urinary tract infection, etc.) rather than based on the organisms the antibiotic is designed to kill. Thus, companies spend $100 million for a phase III program and as a result capture as an indication only one slice of the pie. There is also imbalanced drug pricing in society. We will pay $50,000 for a course of cancer chemotherapy that prolongs life by 3 months, but we don’t want to pay more than $100 for a course of antibiotics that cures the target infection. This pricing difference is neither rational nor data-driven; there is no cost-efficacy analysis that supports cancer drug pricing. Rather, drug pricing in the U.S. is based on public perception and fear. People are terrified of cancer, but not of infections. After all, we’ve had penicillin since 1942. So, we need to educate the public and payors about the true value of antibiotics.

The net effect of these economic barriers has been described in a monograph from the Office of Health Economics (Sharma and Towse, 2011), which found that, at discovery, the net present value of antibiotic to a drug company is minus $50 million. That compares to a positive $1 billion for a new musculoskeletal drug. The Generating Antibiotic Incentives Now (GAIN) Act has recently been introduced into both the House and Senate to address this problem. We owe a debt of gratitude for Representative Gingrey (R-GA) for taking on this issue and to his colleagues, both Democrats and Republicans, in both the House and Senate, for making it a priority. GAIN seeks to use a form of prolonged exclusivity, among other mechanisms, to enhance the value of antibiotics to companies. My own opinion is that the economic incentives in GAIN are a good starting point for discussion, but not strong enough to rekindle pharmaceutical companies’ interest in discovering new antibiotics.

Recently, the Infectious Diseases Society of America proposed a new regulatory pathway, which is hoped to be included in the GAIN Act. The new pathway is called the Special Populations Limited Medical Use (SPLMU) [since renamed the LPAD pathway]. SPLMU would empower the FDA to approve drugs to treat drug-resistant, life-threatening infections with limited available therapies (and possibly drugs to treat other serious diseases with limited available therapies) based on small, rapid, and relatively inexpensive clinical trials. Since the drugs would have a much smaller safety database prior to approval, the indication would be extremely narrow. The drug would only be approved for patients with the highly resistant target pathogens in the setting of the studied diseases. Thus the SPLMU would seek to limit use to the small population of patients in whom the benefits of a

“The future of humanity and microbes will most likely evolve as episodes of our wits versus their genes.”
We seem to have stopped trying to use our wits to keep up.
drug outweigh the risks incurred by its smaller safety database. The goal here is to converge new development with unmet medical need and with stewardship to prolong the useful lives of these critically needed new drugs. It is possible that drugs approved by this mechanism would be able to charge a price premium, given the lack of availability of comparative therapies, the serious nature of the infections, and the smaller scope of patient populations eligible for therapy.

The SPLMU would help overcome the very substantial regulatory challenges that are currently obstructing new antibiotic development. Without going into the specifics of why the FDA has changed the rules governing antibacterial clinical trials, the effect has been a stifling of the new antibiotic pipeline. In the last year, two new draft guidance documents have been released by the FDA governing clinical trials for antibacterial agents with Gram-negative activity: trials for hospital-acquired and ventilator-associated bacterial infections (HABP/VABP), and trials for complicated urinary tract infections (cUTI).

Unfortunately, in my opinion, the trials called for in the guidances are not feasible to conduct, at least with respect to enrolling patients in the U.S. Both guidances require patients to be enrolled in trials before even a single dose of prior treatment is administered to the patients. We cannot make our severely infected patients wait the hours it takes to screen, consent, obtain safety laboratories, randomize, and administer study drug without receiving any therapy. There are other features that also make such trials not feasible to conduct. It may be that physicians in other countries, where patients’ rights are less fully developed, can force their patients to wait hours to receive drug, or can simply abbreviate the process of consenting to enroll such patients. But, a serious ethical dilemma is raised in the encouragement by a U.S. federal agency of the practice of what we would consider to be substandard medicine to support clinical trial conduct. Furthermore, if >90% of patients in such studies are enrolled outside the U.S., it is not clear that the data resulting from the trials would inform providers or patients in the U.S. about how and when to use the drugs. I speak from experience. For many months, I attempted to enroll patients in a cUTI clinical trial recently, and we failed to enroll even a single patient despite the fact that cUTI is a common reason patients are seen in our Emergency Department.

Meanwhile, across the pond, the European Medicines Agency (the FDA equivalent in Europe) has recently released a broad guidance on antibacterial trial conduct that specifies: 1) that patients can be enrolled in trials after receipt of a dose of prior antibiotic therapy, making enrollment possible; 2) the possibility of conducting organism-specific rather than disease-specific studies; 3) the possibility of conducting small studies to support approval of antibiotics that treat resistant, critical infections; 4) and clinical response endpoints at test-of-cure. Each of these principles should be incorporated into FDA guidances, but have not been to date.

Over the past year, several companies have publicly stated, and numerous others have stated to me privately, that given how difficult it is to get antibiotics approved by the FDA, they are considering simply abandoning the U.S. antibiotic market. The European regulatory landscape is more facile (although price-fixing keeps revenues low in Europe). Some have suggested that the Chinese antibiotic market will be larger than the U.S. market in 5 to 10 years. Thus, these companies are saying, we may simply develop antibiotics and sell them overseas and not in the U.S. This begs the question: who will be held accountable when the antibiotics that doctors need to save our patients’ lives are available in Beijing and not in Washington DC?

We have to think of antibiotics as a precious, limited resource, like fisheries, forestry, and energy. We have to both conserve and restore the resource. The time has come to admit that the ways we have used, developed, and protected antibiotics over the past 70 years have failed. The time for bickering over half-measures has passed. The time has come for innovative and bold solutions to slow resistance and speed development of new antibiotics.
Resistant infections: a tragic irony in modern medicine

Barry Eisenstein, M.D. and Elizabeth D. Hermsen, PharmD, M.B.A.

1Senior VP, Scientific Affairs, Cubist Pharmaceuticals; Editor, Antimicrobial Agents and Chemotherapy
2Clinical Scientific Director, Cubist Pharmaceuticals

A tragic irony exists in modern medicine. Amidst the vast progress we’ve made against complex illnesses such as heart disease, cancer and diabetes, infections have reemerged as a major public health threat.

More than 1.7 million people acquire bacterial infections in U.S. hospitals annually, and 99,000 die as a result. [1] These numbers are alarming and the causes are complex, but we do know that much of it is related to bacterial resistance to current drugs. About 70% of the bacteria that cause bloodstream or lung infections in the hospital have developed resistance to at least one antimicrobial drug. [2] Moreover, some pathogens are gaining ground. For instance, *Clostridium difficile* killed approximately 6,300 people in 2007, eight times more than it did in 1999. [3]

Our repertoire of antibiotics is waning in efficacy and it is vital that we develop new medicines. The company for which we work – Cubist Pharmaceuticals – is one of only a handful of biopharmaceutical companies that continues to discover, develop and make available new antibiotics. This is in stark contrast to 1990, when nearly 20 biopharmaceutical companies had large antibiotic research and development (R&D) programs. [4]

What happened? The antibiotic pipeline is running dry because antibiotics have come to be viewed by many drug makers as “wasting assets.”

Each new antibiotic likely has a finite lifespan, because the quick evolution of bacteria makes development of resistance inevitable. To preserve their effectiveness for the future, it is common practice to reserve new agents as a last line of defense. This situation paradoxically reduces the commercial returns that a company needs to overcome escalating investment costs in R&D that lead to new medicines approved by the U.S. Food and Drug Administration (FDA). Recent estimates place R&D costs from $800 million to $1.7 billion, and the time commitment is more than a decade to bring a new drug to market. [3,5] Without new medicines, doctors and patients are forced to rely on the currently available antibiotics, and sometimes, they encounter infections due to pathogens that are not susceptible to any such antibiotics.

This vicious cycle has caused many drug makers to abandon antibiotic R&D programs in favor of those for chronic diseases that have a greater potential for long-term financial return. After all, the goal in addressing infections is to use a short treatment course to cure patients as quickly as possible.

One mechanism to help overcome some of the
TRAGIC IRONY IN MODERN MEDICINE

challenges that are paralyzing antibiotic development is approval of the Generating Antibiotic Incentives Now (GAIN) Act. This bipartisan public health measure would undoubtedly help to spur innovation of new anti-infective drugs and diagnostics.

The GAIN Act would extend marketing protection for select “qualified infectious disease products” that significantly improve our ability to fight infections caused by resistant pathogens. The bill also provides for additional exclusivity for those medicines developed with a companion diagnostic test, thus encouraging personalized medicine and thereby optimizing appropriate antibiotic use. It also assures that new types of antibiotics are eligible for expedited review under existing programs at the FDA (Priority Review and Fast Track Status). Finally, the Act calls for the FDA to revise its guidelines for antibiotic clinical trials to reflect the latest developments in science and clinical knowledge.

Another avenue is for stakeholders to work with the FDA to advance regulatory science in this important area. One interesting idea was recently set forth by the Infectious Diseases Society of America (IDSA) – a network of nearly 10,000 infectious diseases doctors and scientists.

The IDSA proposed that the FDA consider a special regulatory pathway for new antibiotics that balances the need to make them quickly available with maintaining the required oversight to ensure these medicines are safe and effective. [6] The idea is modeled on the successful Orphan Drug Act for rare diseases and warrants thoughtful consideration by FDA officials.

The IDSA has also issued guidelines to help doctors make the best treatment decisions for their patients based on the latest science. [7] Aside from the medical benefit, preventing relapse may also reduce the cost-burden of hospital acquired infections. It is estimated that resistant infections account for an estimated $35 billion in additional costs from longer and more complex treatments. [8]

Over the past 30 years we have made tremendous progress against modern causes of human mortality - heart attacks, strokes and cancer. However, we should not forget that human history is peppered with bouts of plagues and pestilence. One must consider, what good is it to perform a life-saving organ transplant only to lose that life to an infection due to a multidrug-resistant pathogen? It will take the collective effort of government, healthcare providers, and the biopharmaceutical industry to ensure development of new antimicrobials and preservation of existing antimicrobials in hopes that we do not have to answer such questions.

Read more about public policy efforts sponsored by Cubist at http://www.battlingsuperbugs.com/.

References
All pain, no GAIN: need for prudent antimicrobial use provisions to complement the GAIN Act

Kevin Outterson, J.D.

Associate Professor of Law & Director of the Health Law Program, Boston University; Editor in Chief, Journal of Law, Medicine & Ethics

The development of new antibiotics without having mechanisms to insure their appropriate use is much like supplying your alcoholic patients with a finer brandy. (Dennis Maki, IDSA meeting, 1998 [1, 2])

Only one health care bill is likely to pass Congress in this election year: the Prescription Drug User Fee Act V (PDUFA V). Every five years, the FDA and the drug and device industries renegotiate the user fees and regulatory priorities for the FDA. PDUFA V is the fifth generation in this process. This bill is very likely to pass Congress this summer because many jobs at the FDA are no longer funded from general federal appropriations, but come from these user fees. If the bill doesn’t pass, many people at the FDA will be furloughed or fired.

Since it is a “must pass” bill with bipartisan support, PDUFA V has attracted additional provisions, hoping to hitch a ride and thus become law. The Generating Antibiotic Incentives Now (GAIN) Act is one prominent example. The GAIN Act is prominently featured in both the House and Senate versions of PDUFA V.

The stated objectives of the GAIN Act include increased surveillance of resistant bacteria, more responsible use of existing antibiotics, and increased incentives to develop new antibiotics. However, the current draft of the GAIN Act does not provide any binding requirements to implement antimicrobial stewardship, appropriate use, and conservation. It focuses exclusively on bringing new antibiotics to market quickly, without any changes whatsoever to patterns of use in either human or animal populations. More brandy for the alcoholics.

It didn’t start out this way. The Infectious Diseases Society of America (IDSA) testified before Congress on March 8, 2012, and asked for both “strong incentives to spur new anti-infective research and development (R&D) and promote antimicrobial stewardship.” [3] While the IDSA’s primary focus has long been on promoting new antimicrobial drugs, this testimony notably included many proposals (advocated by public health organizations such as APUA) for preserving and extending the useful life of existing treatments as well. They suggested creating a new regulatory pathway for “special purpose limited medical use drugs” which would be strictly limited to appropriate antimicrobial use. IDSA called for payors to take a more active role in appropriate use and value-based reimbursement for diagnostics. IDSA called for implementation of effective antimicrobial stewardship programs as a condition of participation in Medicare and Medicaid. IDSA also specifically recom-
mended a robust surveillance system to “promote measurement of antibiotic usage across all health care settings and support adoption and implementation of comprehensive antimicrobial stewardship programs across all health care settings to promote the appropriate use of antibiotics.” Finally, they suggested that drug companies develop a plan for educating health care providers on the appropriate use of new antibiotics and “to reinforce precautions to reduce the risk of resistance.”

As of late April 2012, none of these provisions are included in the latest House or Senate versions. What has survived is an entirely one-sided emphasis on bringing new antibiotics to market quickly, even if the safety data is less complete and without regard to appropriate use. The GAIN Act will add 5 or more years of data exclusivity to the end of patent terms for “qualified infectious disease products,” extending the effective patent period by about 40%, from 12 to 17 years. In economic terms, these extensions in effective patent life will eventually cost the US health care system several billion dollars in prescription drug expenses due to the delayed introduction of generic antibiotics.

But, in a perfect Washington game, these expenses will not count against the GAIN Act when the Congressional Budget Office scores the bill. As the IDSA testimony points out: “IDSA’s exclusivity proposals will likely not score a cost to the federal government for the next decade or two, given the average amount of patent life typically remaining on new antibiotics at the time they are approved. Major companies, including GlaxoSmithKline (GSK) and Pfizer, agree with IDSA’s assessment.”

In addition to the IDSA testimony, in early April 2012, several stewardship proposals were made to congressional staff during bipartisan discussions on the GAIN Act. One proposal was to limit the new GAIN incentives to companies that met appropriate use or stewardship targets set by the FDA. In other words, the federal government would agree to spend billions to bring new antibiotics to market, but only if the companies were careful with how they were used. Another proposal called for the Centers for Disease Control and Prevention (CDC) to spend $10 million per year in surveillance, to track the resistance profiles of the new drugs approved under GAIN. Neither proposal made the cut. The only amendment that might be considered friendly to appropriate use is proposed section 906 of the Senate bill, which calls for a study by the National Academies on alternative business models for antimicrobial R&D, including prize funds. [4-5]

At this point, public health would be better served if GAIN did not pass as part of PDUFA V. Any new incentives for rushing antibiotics to market must be matched by similar commitments to stewardship and appropriate use. [6-7] Value-based reimbursement of both antibiotics and companion diagnostics should include strong support for appropriate use. [8-9] Otherwise, we might succeed at meeting the IDSA’s goal of 10 new drugs by 2020, but fail in the ultimate goal of having effective antimicrobials at the moment of need due to accelerating resistance. [10]

The current draft of the GAIN Act does not provide any binding requirements to implement antimicrobial stewardship, appropriate use, and conservation.

The correct policy isn’t simply conservation or new production; we need both, in a balanced approach. As currently drafted, GAIN is not balanced, but this could be corrected this summer in the Conference Committee before Congress passes PDUFA V.

Professor Outterson is an appointed member of the Antimicrobial Resistance Working Group of the OID/Board of Scientific Counselors, CDC and a faculty associate at the Harvard Center for Communicable Disease Dynamics.

References

APUA Clinical Newsletter Vol.30 No.1 • © 2012 APUA
Fewer drugs, more superbugs: strategies to reverse the problem

Jennie Choe, M.S.
Staff Reporter, Alliance for the Prudent Use of Antibiotics

Resistance to antibiotics among the world’s most dangerous pathogens is a serious public health threat, but hardly a new phenomenon. Alexander Fleming himself warned as early as 1945 that penicillin and similar antibiotics would eventually make themselves obsolete, through natural selection and the very nature of bacteria. [1] Today, ever-increasing types of resistant bacteria and fewer new antibiotics being developed against them portend a post-antibiotic era on the horizon rather than a regression to the pre-antibiotic era. [2] A post-antibiotic era would again be plagued by common, potentially fatal medical conditions, but have far less hope of finding effective treatments.

Societal consequences of drug resistance
What would medical treatment look like in a post-antibiotic era? Many types of surgery would become impossible, including organ transplants. So would cancer chemotherapy and care for both premature infants and the critically ill. Two million patients in the U.S. develop drug-resistant healthcare-associated infections every year, of which 99,000 will die. [3] Direct expenses alone cost the healthcare system anywhere from $21 billion to $34 billion. Additional medical expenses, restrictions on international travel, and decreased tourism, trade, and commerce could incur far greater economic losses to society.

Infectious disease and drug resistance is never just one country’s problem. Drug-resistant pathogens like XDR-TB, hypervirulent C. difficile, and multidrug-resistant S. pneumoniae and N. gonorrhoeae incur huge costs not only to human life but also to the global economy and international security. Resistant infections in the U.S. required more than 8 million additional days spent in the hospital compared to non-resistant infections. The same loss of labor (and with higher mortality rates, the loss of working-age citizens) in developing countries such as those in the sub-Saharan region can cost up to 20% GDP. [4] The resulting difficulty in developing resources and creating products for export, and the decreased demand for imports from their trading partners, makes the crisis bleed over from developing countries into industrial ones. Developed countries end up shou-dering much of that burden through both federal funding and private aid from philanthropic organizations, to prevent other countries’ losses from becoming their own. Moreover, the Bipartisan WMD Terrorism Research Center warns that a terrorist attack using a drug-resistant pathogen could cause a “potentially uncontrollable” num-
FEWER DRUGS, MORE SUPERBUGS

The dwindling antibiotic development pipeline

It’s not that all hope is lost just yet. Drugs still exist to treat infections like XDR-TB that are resistant to most drugs – but they are expensive and have serious side effects that can drastically affect quality of life. In the meantime, an alarming number of major pharmaceutical companies are shifting their efforts away from the antibiotic market. Between 1983 and 1987, the FDA approved 16 new antibiotic drugs for use in humans. Between 2003 and 2007, it approved six, and since 2009, only two. More than 20 pharmaceutical companies had large antibiotic R&D programs in 1990, but today only AstraZeneca and GlaxoSmithKline remain. [5]

Why are so many companies losing interest in developing antibiotics just when the demand projected for resistant infections seems highest? Simply put, an antibiotic will not bring enough return on investment on the current market to make it worthwhile to invest the time and effort required to develop one. They are less likely to be approved by the FDA, with a roughly 1 in 72 approval rate compared to 1 in 15 for other types of drugs. Also, there is less to be gained. Antibiotics are priced low, used for short durations, and responsible physicians hold newer antibiotics in reserve and encourage patients to use them sparingly to ward off the development of antibiotic resistance.

The current state of the market leaves pharmaceutical manufacturers with two options, both undesirable from a public health point of view: they can stop wasting their time and money, or they can encourage patients and practitioners to use more antibiotics. The latter strategy is largely responsible for opposing any effort made towards the responsible stewardship of antibiotics. All pharmaceutical manufacturers are in a race to sell as many units of a drug as they can before their 20-year patent period runs out. After lengthy and expensive clinical trials ($50-100 million for phase III trials alone) are finally concluded, they have even less time before competitors get approval for similar drugs or resistance arises to similar drugs already on the market.

At that point manufacturers sometimes tout an antibiotic as a treatment for conditions even when it has not yet been clinically proven to be effective against them, contributing to misuse and driving up resistance to that entire class of antibiotics. It is also unfeasible to prevent misuse by taxing antibiotics or placing tighter FDA regulations on prescriptions. Unilaterally discouraging the use of antibiotics will dis incentivize manufacturers from developing new drugs that are desperately needed against the growing number of cases of resistant infections.

What is being done?

Through PDUFA V

The Infectious Diseases Society of America (IDSA), in collaboration with many medical societies and public health organizations, has been instrumental in urging diverse stakeholders to collaborate in the quest for urgently needed drugs. The Alliance for the Prudent Use of Antibiotics is proud to support initiatives like 10x’20 and IDSA’s newly proposed Limited Population Antibiotic Drugs (LPAD) approval mechanism. [6] Originally called the Special Population Limited Medical Use (SPLMU) mechanism and proposed for inclusion into the GAIN Act, LPAD was presented to the House Energy and Commerce Committee on March 8 and is now under consideration as part of the reauthorization legislation for PDUFA V.

LPAD is an alternative FDA regulatory pathway intended to speed the approval process for drugs that may be the only treatment (or one of few treatments) for patients who have serious resistant infections. If the FDA grants LPAD designation to a drug manufacturer, they will be permitted to conduct fast, cheap clinical trials on a small population. The resulting drug with its LPAD logo will only be sold to the small, specific population for whom the benefits of treatment have been proven to out-

© 2012 APUA • APUA Clinical Newsletter Vol.30 No.1
weigh the risks.

While the risks associated with a drug tested through LPAD might be greater than drugs approved for the general population, this population can tolerate more uncertainty about risk in exchange for the option of treatment where before there was none. Not only will LPAD make it cheaper to develop much needed drugs, but it is also hoped that the small demand for such drugs will drive up prices sufficiently for pharmaceutical companies to start investing in their development. Patients will also be more likely to use expensive drugs carefully and abide by measures such as confirmatory follow-up tests, which will slow the development of resistance.

Fourteen pharmaceutical companies have signed onto a letter of support for inclusion of the LPAD pathway into the PDUFA reauthorization bill. All 14 agree that a major flaw in the current FDA approval pathway is that companies are encouraged to develop antibiotics that are as broad-spectrum as possible and can be used in the largest population possible. This is the worst strategy possible for furthering antibiotics stewardship and combating the development of resistance. The letter has prompted positive reactions from members of the House Energy and Commerce Committee and the Senate Health, Education, Labor, and Pensions Committee. APUA and 22 other nonprofit patient, physician, and stakeholder organizations have signed on to a separate letter in support of LPAD inclusion.

Potential market strategies

Other potential solutions have been put forth but not yet officially proposed before Congress. Kevin Outterson (editor-in-chief of the Journal of Law, Medicine & Ethics) and Aaron Kesselheim (assistant professor of pharmacoeconomics at Harvard Medical School) have long advocated the seemingly simple but radical strategy of making antibiotics more expensive. They pinpoint drug pricing as the reason that pharmaceutical companies are losing interest in development. Antibiotics are currently priced as though they are plentiful and easy to make, when the opposite is true.

Outterson and Kesselheim attest that drugs should be priced in accordance with the “true value” of antibiotics to society. Manufacturers should also be given incentives to use careful marketing and awareness of infection control to slow the development of resistance—namely, by being reimbursed more when fewer units of their antibiotic have been prescribed. This could be accomplished if the CDC set public health goals for how much of any type of antibiotic should be on the market at any given time in order to meet established conservation and resistance targets. Manufacturers would be allowed to retain marketing exclusivity for as long as their sales data met the target. Under this system, it would be in pharmaceutical companies’ best interests to develop diagnostic tests that accurately determine the need for antibiotic use, and other surveillance or infection control products.

Through government oversight

As well as the high-profile LPAD pathway and GAIN Act, groups like the IDSA recommend practical short-term strategies such as strengthening antibiotic R&D through tax credits, grants, and more support for public-private collaborative programs like the ones at NIH and BARDA. Building off of the patent exclusivity extension that the GAIN Act would offer to new antibiotics, antibiotics could also be given additional patent extensions if they are the first of a new class or use a novel mechanism of action. Large-scale measures to slow the development of resistance are still as necessary as ever. The IDSA has strongly urged forceful policies like banning the nontherapeutic use of antibiotics in agriculture and food animal production, and the mandatory implementation of antibiotic stewardship programs in all healthcare facilities as a prerequisite for participating in Medicare and Medicaid.

The current crisis in antibiotics could benefit from strategies being applied in other fields. When shortages occur for drugs that are life-supporting, life-sustaining, or treat a debilitating condition, HHS would be required (under the recently proposed Patient Access to Drugs in Shortage Act) to keep an up-to-date list of drug shortages and address them by increasing production quotas or ingredient availability. HHS should similarly monitor a list of priority infections and resistant
FEWER DRUGS, MORE SUPERBUGS

pathogens that may create an unmet medical need, and act upon antibiotic shortages that are reported. Surveillance of antibiotic resistance should be carried out in real time by a federally funded network of sentinel sites and made available to the public. Also, like the Cancer Human Bio-Bank, NIAID and FDA should establish a centralized repository of human clinical samples to facilitate the development of better diagnostic tools. A repository would quickly identify patients who are eligible for the kind of fast-track clinical trials proposed in LPAD, and serve as controls that diagnostic tools could be tested against.

Conclusions

The U.S. has a responsibility – not only to itself, but also to its allies in the developing world – to lead the search for new drugs against infectious diseases that every day threaten to surpass our ability to treat them. The first step is to incentivize research and innovation at home, but once new drugs have been discovered, they need to be marketed to the developing world at affordable and sustainable prices. Diagnostic and vaccine development are also essential to deal with the current antibiotic crisis. Arguably the most cost-effective medical interventions available today, access to vaccines in the developing world would start to remedy an area of gaping unmet need in which the most virulent, most resistant pathogens are infecting the populations that are least able to afford treatments. [10]

It is difficult to imagine an antibiotic-free future. With financial incentives for novel drug development and nationwide regulation of appropriate antibiotic use in human and veterinary medicine, we can prevent that future from becoming a reality. APUA will continue its efforts at the forefront of this global public health crisis. By sharing the opinions of our distinguished expert contributors in each issue of the APUA Clinical Newsletter, we hope to engage healthcare providers, patients, and policymakers in dialogue that will help us find solutions.

References

8. SHEA, IDSA, PIDS, Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). Infect Control Hosp Epidemiol 33, 322-327 (2012).

© 2012 APUA • APUA Clinical Newsletter Vol.30 No.1
The lack of novel antibiotic and vaccine development to combat resistance

Victor K.E. Lim, MBBS, M.Sc.

Executive Dean of Medicine and Health, International Medical University of Kuala Lumpur

The discovery of antibiotics was one of the most significant events in medical history and is said to have added a decade to the life expectancy of man. [1] Together with vaccination, clean water and other public health measures, mortality from infectious diseases was dramatically reduced to the extent that by the 1950s and 1960s, many thought that infectious diseases were no longer a major public health challenge. In 1967, William Stewart – the Surgeon General of the United States of America – was purported to have said that “The time has come to close the book on infectious diseases and declare the war against pestilence won.” There is now some dispute as to whether Stewart actually made this infamous pronouncement. [2] This optimism has now been shown to be unfounded due to various reasons, among which is the emergence of antibiotic resistance.

Antibiotic resistance

Resistance is not a new phenomenon. Sir Alexander Fleming in his Nobel Lecture warned that, “It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body.” [3] The resistome is defined as the collection of all the antibiotic resistance genes and their precursors both in pathogenic and non-pathogenic bacteria. [4] Recent studies of the soil resistome have revealed the presence of genes encoding antibiotic resistance to a wide variety of antibiotics, including synthetic compounds like quinolones and newer antimicrobials like Synercid and daptomycin. It would appear that the development of antimicrobial resistance had been going on in nature long before antibiotics came into medicinal use. The environment – in particular, the soil – is regarded as an important reservoir of antibiotic resistance determinants. [5]

Antibiotic resistance is a major challenge worldwide. It is seen in Gram-positive as well Gram-negative organisms; in healthcare-associated as well as community-acquired infections. The Infectious Diseases Society of America had identified six organisms as being the most problematic; the so-called ESKAPE organisms (namely Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter sp.)

New antibiotic development

In their 2008 report on the pipeline of new anti-
microbial agents, the IDSA concluded that the number of new agents in the pipeline is disappointing and there were no agents solely for the purposes of countering Gram-negatives or the emerging carbapenemases. It is unlikely that there will be any major advance in ability to treat antibiotic-resistant infections. [6]

A similar European report came to the same conclusions. A gap exists between multidrug-resistant bacteria and the development of new antibiotics. Resistance to antibiotics is high among bacteria that cause serious infections in humans. Resistance is increasing among certain Gram-negative bacteria. Very few antibacterial agents with new mechanisms of action are under development to meet the challenge and there is a particular lack of new agents for multidrug-resistant Gram-negative bacteria. [7]

There is a significant decrease in the involvement of top pharmaceutical companies in the area of antimicrobial drug development. The reasons are understandable. The cost of bringing a product from bench to bedside is prohibitively high. Antibiotics are usually used for short durations, and new potent antibiotics are often kept in reserve to be used only in patients who have not responded to more conventional agents. Many of the novel agents have been developed by small companies which are willing to take higher risks. However, they will still need the involvement and resources of large companies for future clinical trials and commercialization.

The number of new agents is therefore unsurprisingly small. New agents which have entered Phase II and Phase III development include a novel aminoglycoside, ACHN-490. ACHN-490 has been shown to be active in vitro against multi-resistant Klebsiella pneumoniae and E.coli, including strains which are carbapenem-resistant. [8] A new fluoroketolide, CEM-101, has been shown to be active against macrolide-resistant Streptococcus pneumoniae and Streptococcus pyogenes. [9] This agent could be potentially useful in the treatment of community-acquired pneumonia in regions where the prevalence of macrolide resistance is high. NXL-104, a beta-lactamase inhibitor, effectively inhibits Class A ESBLs, Class C enzymes, and Class A carbapenemases. This would make it a promising agent to combine with current beta-lactam agents against multidrug-resistant Gram-negatives including those that produce the KPC carbapenemase. [10] A new cephalosporin, CXA-101, has been found to have good activity against Pseudomonas aeruginosa, including strains which were resistant to imipenem. [11] TP-434 is a fluorocycline derivative of tetracycline and has activity against multidrug-resistant Gram-positive and Gram-negative organisms – including tetracycline-resistant Enterobacteriaceae. [12] Radezolid and torezolid are novel oxazolidinones which have activity against linezolid-resistant strains. [13]

Vaccine development

A logical approach, in the face of increasing antibiotic resistance, would be the development of vaccines to prevent the infections. An early trial of a conjugated Staphylococcus aureus vaccine (StaphVAX) had shown some promise in conferring partial protection to patients on hemodialysis. [14] Results from a later, larger Phase III trial were unfortunately not as encouraging. A clinical trial of another staphylococcal vaccine (V710) was abandoned in 2011 after it failed to show any benefit. There have been numerous attempts to develop a vaccine against Pseudomonas aeruginosa. Although many preclinical trials have been conducted, there are very few clinical trials and no Pseudomonas aeruginosa vaccine is currently licensed for clinical use. [15] A Pseudomonas aeruginosa flagella vaccine had been shown to reduce the occurrence of pseudomonas infection among vaccinated subjects. [16] It would appear that the use of vaccines to combat increasing antibiotic resistance, especially among nosocomial infections, still has some way to go.

Conclusions

The emergence of resistance is threatening the usefulness of antibiotics. There is a dearth of new agents to meet the challenge of resistant strains. Vaccines are an
alternative strategy, but it will still be some time before these vaccines can be in routine clinical use. Antibiotic stewardship is therefore crucial to contain resistance and to prolong the useful lives of available agents. A concerted effort employing a multifaceted strategy is essential at international, national and institutional levels, and we need to work together to meet this challenge.

References
Q. What are some factors that make vaccines so expensive?

All currently available vaccines require refrigeration or freezing from the moment of manufacture until delivery to the patient. In addition, most are delivered by injection. As a result, they require technology and expertise for manufacture, storage and delivery that are not available to a very large fraction of the world’s population. In addition, most vaccines are purified protein antigens or purified, inactivated (or attenuated) pathogenic bacteria or viruses. Preparing purified antigens is expensive because large amounts of cell culture must be obtained and extracted, followed by rigorous elimination of all other proteins and other contaminating substances. Inactivating pathogens or using attenuated (mutant) pathogens requires the producer to verify rigorously that each batch of the pathogen has been truly inactivated or, if attenuated, that it has not reacquired virulence properties.

Q. You and Dr. Hanping Feng at Tufts are working on a vaccine against C. difficile infections that could potentially replace antibiotic treatments. Why are antibiotics an unsustainable treatment for C. difficile?

[Dr. Feng has moved to the University of Maryland. Although I had advised him on some of his work, he was the one developing novel vaccines against C. difficile. Our vaccine work at Tufts has been entirely in collaboration with Dr. Saul Tzipori.]

C. difficile infection is usually precipitated by treatment with antibiotics to deal with a previous infection. As a result, the intestinal microbial flora, which normally protects against C. difficile infection, becomes compromised and is unable to prevent colonization and growth of C. difficile. Current treatment depends on either vancomycin or metronidazole. Not only is neither fully effective in eradicating C. difficile infection, but they also prevent the re-establishment of the normal flora. In addition, recently appearing strains of C. difficile are not only more virulent but also resistant to several antibiotics, including fluoroquinolones, ruling out this class of antibiotics for future use. Moreover, the spore form of C. difficile is completely resistant to all antibiotics. Hence, many patients who appear to have been cured of C. difficile infection become re-infected within a few weeks. Some newer antibiotics appear to be somewhat more effective at preventing re-infection, but other, non-antibiotic treatments are also on the horizon. For instance, fecal transplants from healthy individuals have
been used effectively to restore the flora of *C. difficile* patients who have not been treated successfully with antibiotics.

Q. Tell us about the work that your lab has done in mapping out the genes that bacteria express during nutritional stress, and the ones that they express during active growth.

Most Gram-positive bacteria use a common regulatory protein, CodY, to control the expression of dozens of genes that are turned on when the bacteria experience nutrient limitation. Most of these genes code for proteins involved in nutrient uptake and metabolism, but pathogenic bacteria use the same protein to control their major virulence genes. For instance, in *C. difficile*, the CodY protein represses during active growth the genes that code for the major toxin proteins TcdA and TcdB. It does so indirectly by repressing the synthesis of another protein, TcdR, that directs RNA polymerase to the toxin gene promoters. When cells experience nutrient limitation, CodY loses activity, TcdR is synthesized and the toxin genes are expressed.

Q. What made you think of using the dormant state of bacterial spores as a vehicle for delivering vaccine antigens?

The original idea came from Jerry Keusch, formerly Chief of Infectious Disease at Tufts Medical Center and now Professor of International Health at Boston University. In 1996, Jerry came back from a childhood vaccination meeting and asked me if it would be possible to use bacterial spores as vaccine delivery systems that wouldn’t need refrigeration. That phone call stimulated a collaborative project that continues to this day. In 2004 we enlisted Saul Tzipori to direct the animal studies and together were able to obtain a large grant from the Bill and Melinda Gates Foundation to move the project forward in a significant way.

Q. When you first engineered the *B. subtilis* vaccine, you envisioned the bacterium expressing a fragment of the tetanus toxin protein as an antigen on its surface, then being induced to take its dormant spore form in the lab, then being shipped all over the world to be taken as an oral vaccine, after which the bacterium would germinate in the gastrointestinal tract. In an article in *Tufts Journal* you say that “Almost every aspect of that plan turned out not to work.” What went wrong?

The original idea was to engineer bacteria to express antigens on the surface of vegetative cells, induce the cells to form spores and ship the spores around the world. A patient would drink the spores, which would germinate in the intestinal tract and display the antigens. The main problem turned out to be that *B. subtilis* spores don’t germinate very well in the GI tract. As a result, there was very little display of antigen and very little immunity.

Q. Then you re-engineered the vaccine so that the tetanus antigen was expressed on the surface of the dormant spore instead. Did that eliminate those setbacks?

Our current approach sounds similar but is different in many fundamental ways. We engineer the bacteria to express the antigens on the surface of the spores and vaccinate by adding a few drops into the nose or under the tongue. Germination of the spores isn’t necessary since the cells of the immune system interact directly with the surface-exposed antigens in the nose or mouth. By freeze-drying the spores, we can store them at any temperature between -20°C and 45°C (113°F) for more than a year without any loss of potency. Thus, we now have needle-free vaccines that don’t need to be refrigerated. In addition, since growing *B. subtilis* industrially is relatively inexpensive and no purification is needed, the vaccine can be produced at minimal cost.

Q. What experimental work with animals have you conducted so far with the *B. subtilis* tetanus vaccine?

The tetanus vaccine, our test case, has been given to mice and piglets either intranasally or sublingually. In both cases, the animals developed high levels of antibodies against tetanus. No deleterious effects of the vaccine have been seen in the hundreds of animals we have tested so far.
Q. The next step in the regulatory process for the approval of the *B. subtilis* tetanus vaccine and rotavirus vaccine is to demonstrate that they are not toxic to humans. What are your opinions on the duration and complexity of the FDA regulatory process for vaccines?

We are working with a group at MGH headed by Elizabeth Hohmann and Patricia Hibberd (formerly at Tufts and a collaborator on the Gates-funded project). They are seeking FDA approval for a Phase I clinical trial of the tetanus vaccine. Even a small trial is very expensive to carry out and the Phase II and Phase III trials require a huge investment. Therefore, we are trying to find governmental and industrial partners in the US and in the developing world who would be interested in helping support the trials as well as collaborate on development of additional vaccines.

Q. How does the cost of a vaccine delivered via a dormant bacterial spore compare to the cost of an injected vaccine today?

We estimate that the spore vaccines can be produced for less than 40 cents per dose.

Q. What other approaches are you working on to block *C. difficile* infections without resorting to antibiotics?

A few years ago, Joseph Sorg, then a postdoc here, found that certain bile acids are required to activate germination of *C. difficile* spores whereas other bile acids inhibit germination by competing with the pro-germinant bile acids for binding to an apparent receptor. The inhibitory bile acids could potentially be useful in blocking infection but they are metabolized by the normal intestinal flora and recirculated from the intestine to the liver. In collaboration with Joe (now an Assistant Professor at Texas A&M) and Med-Chem Partners, a medicinal chemistry company, we are designing analogs of the inhibitory bole acids that are neither metabolized nor reabsorbed. We hope that these compounds can be sued either to prevent initial *C. difficile* infections or to block recurrence. They would have a very narrow spectrum of activity (as far as we can tell only *C. difficile* germinates in response to bile acids).

We have also been studying for many years the bacterial regulatory protein called CodY that controls many aspects of metabolism in Gram-positive bacteria. In pathogens, it also regulates the expression of key virulence genes. For instance, in *C. difficile*, CodY is the predominant regulatory protein (repressor) for the toxin genes. CodY is activated as a DNA-binding protein by interaction with isoleucine, valine and leucine, the so-called branched-chain amino acids (BCAAs). We are searching for analogs of the BCAAs that activate CodY but are not metabolized by bacteria or human cells. If given orally, such compounds would, in principle, repress toxin gene expression in *C. difficile* cells in the intestinal tract. Since these compounds are expected to affect gene expression but not growth, they will probably not give rise to resistant mutants.

[Please note that the *C. difficile* work described above and the *B. subtilis* vaccine project are not linked at the moment. Dr. Hanping Feng has begun to attempt to use the *B. subtilis* system as one of his approaches to creating new vaccines, but he is not very far along and it is not his major effort in the vaccine field.]
Related initiatives to spur antibiotic development

APUA News Staff

Alliance for the Prudent Use of Antibiotics

APUA and ReAct advise new WHO book on antimicrobial resistance

Dr. Stuart Levy (APUA President) and Dr. Otto Cars (Executive Director of ReAct) coauthored a chapter and contributed their expert opinions on measures to ensure better access to antibiotics in the World Health Organization’s (WHO) latest book, “The Evolving Threat of Antimicrobial Resistance – Options for Action.” Dr. Cars stated that “WHO’s ambitious global plan [to contain antimicrobial resistance] could truly be informed by the content of the book.”

Launched in Geneva on March 8, the open-access book (available for download from the ReAct website) builds on recommendations from the 2001 WHO Global Strategy for Containment of Antimicrobial Resistance and is the result of collaboration between WHO and 50 international experts in the field. The book aims to raise awareness and stimulate coordinated efforts by describing various global policy activities that have addressed antimicrobial resistance and preservation of medicine efficacy in infectious disease.

A few of the most notable case studies of successful actions taken by governments, healthcare facilities, and providers to slow development of resistance include:

- A program in Thailand that reduced antibiotic prescriptions by up to 46% while maintaining treatment efficacy at 97%;
- A program in Vietnam to regulate antibiotics more strictly for treatment of acute respiratory infections;
- The reduction of antibiotic use in farmed fish in Norway by 98% between 1987 and 2004, by the effective use of vaccines; and
- Bringing antimicrobial stewardship and rational use of medicines to the forefront of medical education in medical universities and graduate schools around the world.

New U.S. FDA guidances on antibiotic use in food animals: mixed reviews

On April 11, 2012, the FDA issued three long-awaited documents containing their strategy for regulating antibiotic use in food animal production – final Guidance #209, draft Guidance #213, and the draft of proposed Veterinary Feed Directive regulation. Draft Guidance #213 and the draft Veterinary Feed Directive regula-
tion are open for public comment until July 12, 2012, after which final versions will be drawn up.

Final Guidance #209, also known as “The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals,” recommends that food animal producers phase out the use of medically important drugs for growth promotion or feed efficiency purposes. It also recommends phasing in, over a period of three years, veterinary oversight of all medically important drugs being used in therapeutic situations (which include disease treatment, control, and prevention).

Draft Guidance #213 is titled “Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with Guidance for Industry #209.” It calls on drug companies to comply with Guidance #209 by removing any uses associated with growth promotion from the ones listed on their products’ FDA-approved labels. Within three months of issuance of the final Guidance #213, the companies will have the option of applying to list therapeutic uses (including disease treatment, control, and prevention) on their products’ FDA labels instead. After three years the FDA plans to evaluate how many companies have adopted Guidance #213, and how long it took them to do so, as they consider their next actions.

The draft regulation of the Veterinary Feed Directive program proposes establishing broad veterinary oversight of all drug use in animal feed, with clearly outlined ways in which veterinarians can authorize the use of drugs in certain situations. Such regulation would be necessary to make the veterinary oversight component proposed in Guidance #209 possible.

The FDA’s issuance of these guidances has stirred up many differing opinions concerning their feasibility and effectiveness. The FDA has acknowledged that the voluntary aspect of the guidances is a limitation. However, the FDA also claims that enforcing an outright ban on nontherapeutic antibiotic use in food animal production would require a long-winded formal process, in which drug companies would have the opportunity to demand evidentiary hearings to try to prove the safety of their products – in sum, that decades would pass before any real action could happen. In that sense, voluntary recommendations – while not as far-reaching and effective as could be desired – might at least start the process of achieving the desired goals.

Other organizations’ opinions about the guidances fall into three broad camps. The most negative opinion holds that the FDA guidances are tragically flawed, empty gestures for not requiring the food animal industry to take action. The guidances could also be seen as going against the decision made by the court in March that penicillin and tetracycline use in food animal production is in fact unsafe, and that the FDA must uphold the proposed ban against them. Another concern has been raised that if the industry does not even obey the law (as was seen when traces of banned fluoroquinolones were found in chicken feathers), how can producers be expected to comply with voluntary recommendations? The sheer volume of antibiotic use in animals (accounting for 80% of all antibiotics sold in the U.S.) can only be reduced through cooperation from the entire industry. The organizations that take this attitude (including the NRDC and the Center for Science in the Public Interest) insist that a more productive move would be for the FDA to support the Preservation of Antibiotics for Medical Treatment Act, which was introduced in Congress in 2009.

Groups like Keep Antibiotics Working, and Congresswoman Louise Slaughter of New York, the author of PAMTA legislation, hold a more neutral position. While they commend the FDA for recognizing the seriousness of problems posed by unregulated antibiotic use and for taking a step in the right direction, they are skeptical that the step will lead to tangible results in the near future. Slaughter calls the FDA’s pace “nothing short of glacial.” They criticize the lack of a plan for monitoring drug use under the guidances, which is necessary as a measure of their effectiveness.

In the third camp, organizations including APUA, the Pew Charitable Trusts, and the American
Academy of Pediatrics applaud the guidances as an important step forward and call on major drug companies and food producers to comply with them. In a press release through Elsevier Global Medical News, Dr. Stuart Levy of APUA states “These voluntary FDA guidances will hopefully promote leadership by the large food producers to reduce antibiotic overuse on the farm, but there is a need for strong monitoring of their implementation.” The Pew Charitable Trusts also commends the FDA for “the most sweeping action the agency has taken in this area,” but warns that “if these measures do not bring down antibiotic use and drug-resistant bacteria, then FDA will have to take additional steps.”

Find the full text of final Guidance #209, draft Guidance #213, and draft VFD regulation at www.fda.gov.

UK-based Antibiotic Action Initiative

Antibiotic Action was launched in 2011 to provide a global platform from which to inform all about the need for discovery, research and development of antibiotics. Antibiotic Action calls for immediate action to ensure replenishment of the pipeline of new antibacterial agents. The initiative is clear that the time for discussion is over and that the time for action is now, and with the tagline “Determined to Succeed” Antibiotic Action is calling on colleagues across the world to help ensure it does.

Two recent articles published in The Lancet [1] and Nature Reviews Microbiology [2] present overviews of the pending crisis of no new antibiotics, and say more about the need for Antibiotic Action than can be reported here.
The initiative is directed by Professor Laura Piddock, Professor of Microbiology at the University of Birmingham, UK and has received considerable support from professional societies and charities from around the world. A major mechanism for stimulating political activities has been the petition on the website. This remains open and as a tool to maintain pressure on governments, policy makers and national agencies to address the various issues in antimicrobial chemotherapy and not just regenerate antibacterial drug discovery, research and development.

Antibiotic Action’s long term aspiration is the establishment of a public-private global alliance to meet its aims, and particularly a model by which antimicrobial development can be successfully taken forward. There is no intention to “reinvent wheels,” but rather to capitalize on or adapt those that are already in existence, such as the models employed by the GAVI Alliance and Bill & Melinda Gates Foundation for the successful delivery of vital vaccines worldwide.

APUA is coordinating with the Antibiotic Action Initiative to strengthen our efforts and assist WHO in implementing their new global plan. We are now inviting all members of APUA to promote Antibiotic Action and ask their colleagues, friends and family to visit www.antibiotic-action.com and sign the petition now.

If you wish to promote Antibiotic Action nationally or globally or become an Antibiotic Action Champion, please contact Tracey Guise at tguise@bsac.org.uk.

References
1. Piddock LJV. Lancet Infect Dis. 2011 Nov 17

BARDA awards $67 million contract to Tetraphase to develop novel antibiotic

The Biomedical Advanced Research and Development Authority (BARDA) of the U.S. HHS is now more than ever taking on the burden of funding novel antibiotic drug development. On February 16, 2012, BARDA chose Tetraphase Pharmaceuticals to be awarded a contract for up to $67 million. Tetraphase specializes in developing antibiotics against pathogens that are resistant to other drugs. The lead product candidate in their clinical pipeline is TP-434, an antibiotic against a broad spectrum of multidrug-resistant Gram negative pathogens that is currently in Phase II clinical trials. TP-434 could potentially be an empiric, once-daily antibiotic against pathogens such as Bacillus anthracis and Yersinia pestis, and it is hoped that is will also be a therapeutic agent against serious healthcare-associated infections.

In combination with funding from other federal sources, funding for TP-434 could reach $100 million. The BARDA contract exemplifies the type of funding commitment necessary to supplement legislation like the GAIN Act and PDUFA if antibiotic development is to be significantly incentivized. Past BARDA awardees that manufacture antibiotics include Achaogen, who develop broad-spectrum antibiotics against potential bioterrorism pathogens; Elusys Therapeutics, the makers of an anthrax anti-toxin; and GlaxoSmithKline, which focuses its pipeline on bioterrorism pathogens, ventilator-associated pneumonia, and abdominal infections. Find out more about this award in the Tetraphase press release.

April 2012 issue of Infection Control and Hospital Epidemiology dedicated to antimicrobial stewardship

Dr. Neil Fishman (Associate Chief Medical Officer for the University of Pennsylvania Health System) and Dr. Arjun Srinivasan (Associate Director for Healthcare Associated Infection Prevention Programs at the CDC) were guest editors for the April 2012 issue of Infection Control and Hospital Epidemiology, the first ICHE issue focused entirely on antimicrobial stewardship. The issue advocated for making antimicrobial stewardship maximally effective through powerful, immediate interventions that will improve quality of care and reduce wasteful healthcare spending. In a companion post on the CDC blog “Safe Healthcare,” Dr. Fishman applauded growing recognition of the vital nature of antimicrobial stewardship in hospitals nationwide, but pointed out that “truly effective stewardship means more than just an...
The 24 articles in the April issue of ICHE present a “snapshot” of the current state of the science in antimicrobial stewardship. Some articles addressed the financial impacts of antimicrobial stewardship business models. Stewardship programs, after all, represent a unique type of healthcare quality initiative that improves both clinical and institutional outcomes, as opposed to many other programs that increase the cost of care. Standiford et al. conducted a study entitled “Antimicrobial stewardship at a large tertiary care academic medical center: cost analysis before, during, and after a 7-year program” at the University of Maryland Medical Center. During its seven year existence, the antimicrobial stewardship program described in the paper made possible a 46% decrease in antibiotic expenditures. These costs increased again by 32% within two years of terminating the program, mostly due to resurgence in the use of broad-spectrum antibiotics. Total unnecessary costs in those two years amounted to $2 million. This case study provides a cautionary tale against eliminating stewardship programs, and may serve as a useful model for institutions implementing them.

Other articles focused on the need for stewardship programs to reflect the broadening of medical practice by including not only adult acute-care settings, but also outpatient and post-discharge therapy, transitions in care, long-term institutions, pediatric facilities, and intensive care settings. And despite many advances in stewardship program implementation, some articles pointed out room for improvement and for further data collection – especially in the “low-hanging fruit” areas such as the parenteral-oral conversion for fluoroquinolones. Cosgrove et al. also gave an account of a first-of-its-kind multicenter trial of an antimicrobial stewardship intervention initiated by the CDC Prevention Epicenter. The results of the trial emphasized the benefits of performing both large-scale, multicenter studies, and smaller, simpler trials.

A joint policy statement from SHEA, IDSA, and PIDS outlined recommendations for a national approach to antimicrobial stewardship. These included adopting economic incentives and new regulatory approaches to encourage antimicrobial development, enhancing surveillance systems, investing in diagnostic development, and eliminating the non-judicious use of antibiotics in plants and animals. A position paper from SHEA and APIC focused on multidrug-resistant organisms as a grave threat to patient safety by causing a significant proportion of HAIs, and highlighted the need for collaboration between epidemiologists and infection preventionists.

More information on APUA’s advocacy of antibiotic stewardship can be found in the APUA Clinical Newsletter Vol.29 No.3 (“Enhancing Infection Control with Antibiotic Stewardship”) and Vol.29 No.1 (“Antibiotic Stewardship Gaining Traction: Recommended Models and Resources”). See also the April issue of ICHE, and Dr. Neil Fishman’s CDC blog post.
About Us

Antibiotics are humanity's key defense against disease-causing microbes. The growing prevalence of antibiotic resistance threatens a future where these drugs can no longer cure infections and killer epidemics run rampant. The Alliance for the Prudent Use of Antibiotics (APUA) has been the leading global non-governmental organization fighting to preserve the effectiveness of antimicrobial drugs since 1981. With affiliated chapters in more than 66 countries, including 30 in the developing world, we conduct research, education and advocacy programs to control antibiotic resistance and ensure access to effective antibiotics for current and future generations.

Our global network of infectious disease experts supports country-based activities to control and monitor antibiotic resistance tailored to local needs and customs. The APUA network facilitates the exchange of objective, up-to-date scientific and clinical information among scientists, health care providers, consumers and policy makers worldwide.