Extended-Spectrum Beta-Lactamases: an Escalating Concern

APUA Commentary

The Evolution of CTX-M-15 ESBLs in the U.S.

Beta-lactamases are enzymes that hydrolyze the beta-lactam ring of beta-lactam antibiotics. In the 1980s, the emergence of new beta-lactamases produced by certain E. coli and Klebsiella were undermining the efficacy of widely used extended-spectrum cephalosporins, such as cefuroxime, cefotaxime and ceftazidime. These new “extended spectrum beta-lactamases,” or ESBLs, have evolved dramatically in recent decades, such that few treatment options remain for infections caused by these exceptionally resistant pathogens. This issue addresses the current status of, and prospects for combating, these enzymes and the recent emergence of the CTX-M enzyme in the United States.

Michael Feldgarden, Ph.D.
APUA Research Director

A recent study by Doi et al. in Emerging Infectious Diseases documents the first recorded appearance of CTX-M β-lactamases in E. coli in the U.S. 2 This resistance determinant is often specified by plasmids that have multiple resistance genes, resulting in multi-drug resistant infections. CTX-M β-lactamase-specifying plasmids are also commonly associated with chromosomal ciprofloxacin resistance. In Europe, CTX-M β-lactamases account for a large fraction of ESBLs. In Portugal, two-thirds of ESBL producers possessed CTX-M β-lactamases, most of which were CTX-M-15, and the majority of these infections were community-acquired infections.4

In the U.S., CTX-M β-lactamases are far less common. While they have been observed at low frequencies in clinical settings, until the report by Doi et al., there had been no published reports of community-acquired CTX-M β-lactamases in the U.S. The presence of CTX-M β-lactamases in the community, even at very low frequencies, means that the prevention of the evolution of CTX-M β-lactamases in U.S. E. coli is no longer an option. Molecular data suggest that the effective population size of E. coli is roughly 100 million. For a resistance gene to be detected in the community, it would probably be present in 0.01% of isolates. While that number sounds small, 0.01% of one hundred million is sufficiently large that genetic drift will not purge the population of this gene. The disturbing irony of most surveillance systems that look at community or commensal samples is that once they detect resistance, it is already too late to put the genie back in the bottle.”

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ONE ON ONE continued from page 1

amikacin resistance markers. Looking back, it may have been amikacin that was selecting for the plasmids, and the ESBL was just going “along for the ride.” Now we’re seeing plasmids that mediate resistances for multiple drug classes, not just aminoglycosides and beta-lactams. This is especially disconcerting because multiple resistance factors can be transmitted all at once, not just across the genus Klebsiella, but across all the Enterobacteriaceae.

Q: Are ESBL numbers beginning to skyrocket?

A: It really depends on which part of the world you’re living in. There are some regions, such as the Asia-Pacific, where we didn’t hear much about ESBLs for a long time, but now we’re hearing about a lot of them in countries like India and China. The one enzyme family that has probably emerged as the winner is the family of the CTX-M enzymes. At the ESCMID conference on ESBLs in Venice, in May of 2006, I was supposed to talk about ESBLs in the United States. At that time, there had only been one report of five different CTX-M-producing isolates in the United States, whereas in locations such as China, the Far East, and parts of the UK, the CTX-M enzyme had become the predominant ESBL. There were virtually none in the United States that had been reported at that time—well, that has all changed. I have been contacted over the last 6 months by several sites in the United States that are now reporting outbreaks of CTX-M enzyme-producing organisms. Several of these sites will be presenting data at ICAAC about their experience. Worse still, are the KPC carbapenemases that seemed to start in the United States as single isolates, but that are now creeping all over the world. For example, Israel has a major problem with KPC-producing isolates. I’m now hearing that there are a few isolates in hospitals in the Midwest, and that’s quite worrisome.

Q: In all of this, what is your greatest concern?

A: The KPC enzymes themselves. The standard ESBL enzyme-producing organism can be treated with carbapenems. But in doing so, you end up selecting for organisms that produce carbapenemases. These enzymes are plasmid-encoded and are transferred in tandem with other resistance genes. There is nothing reliable to treat those microbes. One of the problems is that they produce multiple beta-lactamas, so if you have a good beta-lactamase inhibitor that works against one enzyme, in vitro, it may not be at all effective in a clinical setting. Thus, when you start trying to treat a patient with a beta-lactamase inhibitor combination,
the APUA World Congress on Identification and Treatment of Infectious Diseases at the Hyatt Regency Boston October 29-30, 2007 (see p.7). Doctors Steven Projan, Robert Moellering, and Ian Gould will join others in sharing the latest opportunities and challenges in drug development and a roundtable discussion will follow. You are welcome to come and weigh in on the consensus and recommendations we expect from this session.

Accelerating Antimicrobial Development
Initiatives by Wellcome Trust and APUA

The Wellcome Trust is very interested in antibiotic resistance and has recently announced expansion of the eligibility criteria for its Seeding Drug Discovery Initiative for antibacterial drug discovery due to its being a priority interest. Proposals for this initiative will be considered at two funding committee meetings in each 12-month period. Preliminary applications submitted by November 9, 2007 will be short-listed for consideration by the committee in December 2007. Please see the following link for further details: (http://www.wellcome.ac.uk/node2630.html).

On Sunday, October 28, 2007, APUA will hold an international workshop on future strategies in drug development. Cosponsored by the International Society of Chemotherapy, the program will occur in conjunction with

you have multiple beta-lactamases that you need to inhibit. One of the things you could look for in the future would be a much more potent beta-lactamase inhibitor that would be able to control organisms producing five, six, or even seven beta-lactamases.

Q: Currently, that's not available however?
A: That’s correct. Tazobactam does inhibit some of these enzymes, if you test an isolated enzyme in vitro. But when you try to kill an organism expressing multiple beta-lactamases, especially when one is an ESBL, plus an enzyme such as an SHV beta-lactamase, the piperacillin-tazobactam combination doesn’t work. Apparently there isn’t enough tazobactam in the combination to inhibit all the beta-lactamases. I wouldn’t even try to use sulbactam against these kinds of organisms because it’s the weakest of the three beta-lactamase inhibitors. Clavulanic acid also doesn’t seem to work quite as well as tazobactam against some of the ESBLs. It’s a “mixed bag,” however, as both may effectively inhibit an isolated enzyme, but neither works really well when they need to inactivate a group of enzymes in the same organism.

Q: Could you target some secondary enzyme substrate, provided by the mammalian host itself, whose limitation might consequently reduce the activity or virulence of the microbe?
A: I think there is definitely something to that idea. If you have immunocompromised individuals, they are indeed more likely to develop a resistant infection. However, this is not my area of expertise, so I would prefer not to comment in depth.

Q: Short of a new class of antibiotic working through a new biological mechanism, what would be your next best “shot to fire”?
A: Combination therapy, I think, will be a short-term “fix.” With pseudomonal infections, there currently is a tacit understanding that we’ll have to use combination therapy for seriously ill patients, because a single drug is not going to be sufficiently effective because of the high resistance rates for this organism. We will probably need to do the same thing for treating infections caused by Acinetobacter spp. or other non-fermenters. It is likely that clinical trials will be initiated to evaluate combination therapy.

Q: Recently there was a request to use ceftazidime, a 4th generation cephalosporin, in agriculture. Is that something you could support?
A: No. While I was at Lederle working on a carbapenem program, American Cyanamid had an agricultural division. I was approached several times and asked if we had any drugs we were not going to develop for humans: “Please pass them over our way and we’ll see if we can develop them for veterinary use.” However, I was not very cooperative—they didn’t get any from me.

Q: Diagnostically what’s in store for ESBLs?
A: If a laboratory is not using CLSI methods, they will have to use a molecular test, which will tell you which specific enzyme family is present in the genome. But this won’t tell you whether that beta-lactamase is an ESBL or not—some organisms can produce a TEM, an SHV and a CTX-M enzyme, and only one of these may be an ESBL. However, it doesn’t make a lot of difference to the routine clinical laboratory as to which specific ESBL is there.

In the future I expect that well-funded and technically advanced groups will routinely employ PCR and other molecular techniques to determine not only the enzyme family, but the specific enzymes that are in their resistant isolates. For community hospitals, there will have to be a rapid and extensive diagnostic panel devised for ESBLs. The development of this panel will cost a large amount of money, but at some point, this almost certainly will become a commercial product.

I’m not a big fan of the current ESBL test as approved by CLSI, other than for hospital epidemiology. The fact that hospitals must change all the interpretive criteria to “resistant” for all cephalosporins is a bad message, as I think we’re limiting the use of some of our current cephalosporins—which we probably could still use if they test susceptible by MIC. This forces the use of carbapenems when cephalosporins might be just as effective. By using the carbapenems, we’re driving the selection of organisms like the KPC-producing pathogens.

Karen Bush was interviewed by APUA Communications Manager, Christopher Spivey.
Antibiotic Susceptibility Testing in the ICU: Challenging the Status Quo

The following was excerpted from commentary given by retiring President of AB Biodisk, Anne Yusof, at the APUA World Congress on Antibiotic Resistance and R&D Initiatives, Boston 11-12 Dec. 2006

“So, why does AB BIODISK support APUA and its efforts to organize significant educational events like this First World Congress? Simply this—APUA and Stuart Levy’s personal dedication towards the understanding of antibiotic resistance and the need to preserve our “miracle drugs” echoes the vision and mission of Hans Ericsson (Professor of Microbiology, Karolinska Institute & Hospital, Stockholm), the scientific founder of AB BIODISK. Even as a young clinician in the 1950s, Hans Ericsson was adamant about the crucial importance of promoting the rational clinical use of antibiotics in hospitals.

Stuart Levy’s global key message consistently includes the need to conduct surveillance and find interventions for alleviating resistance at the local level. What can be more local than the critical care bedside—the most important compartment of complex and heavy antibiotic use? Here are found the primary breeding grounds for the development of clinically significant drug resistance—amidst our sickest patients—with invasive procedures and severely compromised immune defenses and where mortality can easily be in excess of 50%! Here, inappropriate and inadequate use of antibiotics can have a direct impact on mortality and morbidity, health care costs, and not in the least, the selection of resistance. This has been proven over and over again.

Have we asked ourselves if we are doing all we can to improve the odds when one out of two patients dies as a consequence of inappropriate therapy today? These are among the most non-standard of patients, yet our practice of antibiotic use remains sub-standard. We continue to throw overly simplistic and crude S-I-R (sensitive-intermediate-resistant) categorical results to guide the treatment of our most vulnerable patients. So, if we have organism susceptibility to multiple drugs—which one is clinically the safest drug to use in the absence of immune defenses in a particular ICU patient?

It has been stated that the US Congress, or any government body for that matter, doesn’t really want to know about MICs. The question is—do they really have a choice? In my personal opinion, the answer is a simple “No!” If that particular critical care patient were ultimately themselves or someone they love—what then? So, I think that we really need to have a “face” to show Congress to make them understand that it is about real people and that it affects you and me.

From a personal perspective, I can assure you that the critical care bedside is a scary place to be, having been there myself. That’s why AB BIODISK continues to support educational efforts to help bring the “PATIENT” into the room where experts continue to elegantly discuss the issues of resistance again and again. When is the time to act, and to improve our medical practices for optimal antibiotic therapy management of the critical care patient?

We can do so much better for our ICU patients today, if only we care to, and dare to question our complacent practices in how we select and dose our antibiotics beyond the simplistic and potentially misleading S-I-R approach, so conveniently embraced by the professions today.

So, how important is all this in the bigger picture? Crucially important—in my personal opinion—is that the clinical drivers of resistance are the strongest in the ICU setting. We must learn to use our “miracle drugs” better. We must stop over-simplifying to the immediate detriment of our patients and we must stop driving the resistance equation even further in the wrong direction. It’s not only about finding new antibiotics—more importantly it’s about using the ones we have left WELL!

Global Outbreaks: Early Reporting and Response

In July, 2007, Kathy Young, APUA’s Executive Director, attended the Global Health Council/WHO Forum concerning the new International Health Regulations (http://www.who.int/csr/ihr/en/). The regulations provide guidance on identifying and responding to global pandemics and health emergencies and the role of WHO and public health organizations worldwide. David Heymann, WHO Assistant Director-General for Communicable Diseases, reviewed WHO’s leadership in the successful containment of SARS and outlined changes in WHO disease reporting regulations. He assessed H5N1 risks and presented the current global pandemic prevention strategy backed by WHO surveillance collaborations. (See:http://www.globalhealth.org/news/article/8890)
It should be noted that none of the reported studies monitored resistance development to colistin during or following therapy. Our ICU experience with the emergence of colonization or infection with colistin-resistant gram-negatives (Table), as well as the occurrence of seven bloodstream bacteremias with intrinsically colistin-resistant Proteus and Serratia spp., is certainly worrisome. The on the other hand, the emergence of K. pneumoniae producing metallo-beta-lactamas (MBL) in Greek ICUs since 2001 resulted in excessive empirical use of colistin, leading to a cluster of multiclonal pan-drug-resistant Klebsiella strains implicated in bacteremias, VAP and soft tissue infections, mostly in patients with prolonged administration of colistin (median 27 days). Horizontal transmission via hands was demonstrated by REP-PCR. The analysis of risk-factors after a Greek ICU outbreak with pan-drug-resistant P. aeruginosa causing VAP revealed that the sole independent predictors were the administration of colistin for >13 days or the combined use of a carbapenem for >20 days. The outbreak resolved following reduction in the days of colistin therapy, coupled with reinforcement of infection control measures.

**Recommendations**

There is no doubt that we must explore ways for maintaining the utility of colistin. It is now evident that in order to avert resistance development, duration of therapy should be limited to <12 days; co-administration with a carbapenem should be avoided; the relationship of drug activity (PK) to drug efficacy (PD) should be utilized; and hand hygiene measures should be strictly applied. It is clear that colistin is not an ICU “panacea” to be prescribed casually, but rather only under certain strict indications—as in severe ICU infections with pathogens susceptible only to colistin, or empirically in ICU nosocomial sepsis of late onset in settings with high prevalence of MDR isolates. Even then, however, de-escalation should be prompt if susceptibility results permit replacement with another antibiotic. It is highly probable that only the above policy can keep colistin as real ammunition against MDR gram-negative microorganisms.

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**Emergence of colistin resistance in Greek ICUs (2004-2006)**

<table>
<thead>
<tr>
<th>Species</th>
<th>% of total colonized patients having colistin-resistant flora</th>
<th>Infections with COL-R strains (N of patients)</th>
<th>Duration of therapy with colistin (days)</th>
<th>MIC (µg/ml)</th>
<th>ESBL(+) MBL(+)</th>
<th>Susceptibility</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>K. pneumoniae (37%)</td>
<td>Blood stream infection of central venous catheter (1)</td>
<td>27</td>
<td>128</td>
<td>ESBL MBL Tig/Gent</td>
<td>Tig/Gent</td>
<td>Death</td>
<td></td>
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<td>Soft tissues (1)</td>
<td>29</td>
<td>64</td>
<td>Tig</td>
<td>Death</td>
<td></td>
<td></td>
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<tr>
<td>VAP (1)</td>
<td>4</td>
<td>128</td>
<td>ESBL Tig/Gent</td>
<td>Death</td>
<td></td>
<td></td>
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<tr>
<td>Blood stream infection (1)</td>
<td>45</td>
<td>128</td>
<td>ESBL Tig/Gent</td>
<td>Death</td>
<td></td>
<td></td>
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<tr>
<td>Blood stream infection of central venous catheter (1)</td>
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<td>16</td>
<td>Tig</td>
<td>Death</td>
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<tr>
<td>Enterobacter spp (4%)</td>
<td>Postoperative peritonitis (1)</td>
<td>8</td>
<td>32</td>
<td>Chl</td>
<td>Death</td>
<td></td>
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<tr>
<td>A. baumannii (2.5%)</td>
<td>(0)</td>
<td>-</td>
<td>-</td>
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<tr>
<td>P. aeruginosa (4.5%)</td>
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<td>S. maltophilia (44%)</td>
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<td>-</td>
<td>-</td>
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<tr>
<td>E. coli (7.3%)</td>
<td>(0)</td>
<td>-</td>
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APUA to honor Bangladesh’s ICDDR

Annual Members’ Reception
Tuesday, September 18

Join APUA staff, members and friends at the Annual Members’ Reception on Tuesday, September 18 at the Wyndham Hotel in Chicago at 6:30 PM when APUA will bestow its 2007 Leadership Award to the International Centre for Diarrhoeal Disease Research, Bangladesh.

All APUA members and partners are invited to join in honoring ICDDR,B for its international leadership in infectious disease research, treatment and advocacy to promote appropriate antimicrobial access and practice. Located in one of the world’s poorest countries and working at the local and international levels, the Centre employs 250 scientists and clinicians along with 800 research staff and attends 1,200,000 patients per year, primarily for diarrheal disease and pneumonia. ICDDR,B has pioneered successful real time treatment strategies as well long term research on the causes of diseases, effective vaccines and use of rapid diagnostic tests (RDTs).

The APUA leadership looks forward to greeting Dr. Wasif Ali Kahn and his colleague Sabeena Ahmed, M.Sc., who will receive the award and present a brief video featuring footage of the remarkable daily work of the Centre and a message from its new Executive Director, Dr. Alejandro Cravioto. For more information, see www.icddrb.org and next issue.

New Scientific Advisory Board Member appointed from Mali

APUA Board Members and Staff welcome Abdoulaye Djimde, Pharm.D., Ph.D. as the newest member of the APUA Scientific Advisory Board. Dr. Djimde, an EDCTP Senior Fellow & HHMI International Scholar, is Head of the Molecular Epidemiology and Drug Resistance Unit of the Malaria Research and Training Center in the Department of Epidemiology of Parasitic Diseases. He is also a member of the Faculty of Medicine, Pharmacy and Odonto-Stomatology at the University of Bamako in Mali.

ROAR projects set to build large commensal E. coli databank

The Reservoirs of Antibiotic Resistance (ROAR) project, funded by the NAIAD and coordinated by APUA, is an unprecedented effort to improve scientific understanding of the role of commensal bacteria in the spread of antibiotic resistance. Two of its annually funded research projects were recently completed:

• “Probe Hybridization Array Typing: A High Throughput E. coli Genotyping Method Suitable for Phylogenetic Analysis” by Dr. Betsy Foxman, University of Michigan
• “Antibiotic Resistance and Genetic Relationship of E. coli from Australia” by Dr. David Gordon, Australian National University

A third project, “Phylogenetic Analysis of Antibiotic Resistance in Commensal Escherichia coli,” will be completed in September. In conjunction with data from a previously completed project, “Possible Emergence of a Plasmid-Mediated Reservoir of Resistance Genes Among the Escherichia coli of Poultry” (Dr. Lisa Nolan, Iowa State University), these data will form one of the largest sets of commensal E. coli isolates that have been characterized genetically and for antibiotic resistance phenotypes. For more information about the projects, see http://www.roarproject.org/ROAR/html/projects.htm. To join the ROAR Scientific Network listserv, or to submit commensal isolate data to the ROAR database, please see www.ROARProject.org.

New data emerging on costs of antibiotic resistance

APUA’s Director of Public Policy and Education, Susan Foster, Ph.D. presented preliminary Massachusetts-based data from the Economic Burden of Drug Resistance project at the New England APUA NEWS

2nd World Congress
Boston, October 28-30, 2007
Hyatt Regency Hotel, Boston

Session Topics:
• Drug Policy/Economic Burden
• Infection Control
• Immunomodulation
• Diagnostics
• Biodefense
• Drug Innovation & Development

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• Arturo Casadevall, MD, PhD, AECM
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• Patrick Doyle, PhD, MIT
• David Gorenstein, PhD, Univ. of Texas
• Janet Hindler PhD, UCLA Med. Ctr.
• Sally Hojvat, PhD, CDHR, FDA
• Ramanan Laxminarayan, PhD, RFF
• Helen Lee, PhD, Univ. Cambridge
• Carol Linden, PhD, DHHSt
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Phone: 617.636.0866
Fax: 617.636.3999
Visit the APUA website for preliminary program and Registration information: www.apua.org
New guidelines released on antimicrobial stewardship

Teaming up with several other key healthcare organizations, The Infectious Disease Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) have jointly sponsored the production of Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship.

A key feature of the new guidelines is a well-supported, multidisciplinary approach that recommends a hospital team consisting of an ID physician, a clinical pharmacist with ID training, a clinical microbiologist, an information system specialist, an infection control professional and a hospital epidemiologist.

Antibiotic stewardship programs are aimed at improving patient care, while simultaneously reducing drug resistance as well as costs.

To view the new guidelines, see www.journals.uchicago.edu/IDSA/guidelines/

APUA International launches APUA-Tanzania chapter

APUA’s Dr. Anibal Sosa will attend the inauguration ceremony of the new APUA-Tanzania chapter in Dar es Salaam, Tanzania on November 12-16, 2007, when APUA-Tanzania will hold the first AMR symposium sponsored by the Izumi Foundation. The new chapter is led by Dr. Faustine Ndugulile, Head of Diagnostic Services at the Ministry of Health in Dar es Salaam.

Left to right: Dr. Mabula J. Kasubi, Dr. Sayoki D. M. Mfinanga and a colleague at the National Institute for Medical Research, Dar es Salaam, Tanzania

APUA-Dominican Republic

APUA Director of Global Chapter Network, Dr. Anibal Sosa, chaired a symposium on New Advances in Antimicrobial Resistance at the XIII Pan American Congress of Infectious Diseases held August 22-25, 2007, in Punta Cana. The president of the Congress, Dr. Jesús Ferís Iglesias, APUA-Dominican Republic chapter leader and the Infectious Disease Society of Dominican Republic assembled one of the most comprehensive and exciting programs for updating knowledge to improve the diagnosis and treatment of infectious diseases in Latin America and the Caribbean. APUA President, Dr. Stuart B. Levy, spoke on new approaches toward preventing and treating bacterial infections. For more information contact anibal.sosa@tufts.edu.

APUA-The Gambia


• With sponsorship from the Izumi Foundation, APUA International continues to provide technical assistance to sustain AMR interventions in The Gambia. Dr. John Stelling, Senior Consultant for APUA, traveled to Banjul the week of July 8-14, 2007 to establish WHONET technology (http://www.who.int/drugresistance/whonetsoftware/en/) and training for the microbiology laboratories of Royal Victoria Teaching Hospital and the Medical Research Council-Fajara.

Left to right: Dr. Mabula J. Kasubi, Dr. Sayoki D. M. Mfinanga and a colleague at the National Institute for Medical Research, Dar es Salaam, Tanzania

APUA staff, Boston, MA. From left to right, front row: Stuart B. Levy, Kathleen Young, Thomas O’Brien. Middle row: Susan Foster, Leakan Ung, Amelie Peryea, Stephanie Boyd, Katherine Corso. Back row: Bonnie Marshall, Michael Feldgarden, Karrie-Ann Toews, Michael Hricz, Jona Muhameti, Christopher Spivey

Microbiology Laboratory Directors meeting held in Sturbridge, MA on April 25, 2007. Using Massachusetts Hospital Discharge Data, Dr. John Cai of the Massachusetts Division of Health Care Finance and Policy, has examined patient discharges with drug-resistant microorganisms (based on ICD-9 V09 codes for antibiotic resistance). In 2005, 1.1% of Massachusetts discharges recorded a V09 code. About 30% of those resistance are thought to be caused by antibiotic use (n=2865). Discharges with resistance required a length of stay 3.61 days longer (5.45d vs. 9.06d), or 66% more days. They cost 46% more than hospitalizations without resistance, a difference of $7,620. The incremental cost of resistance in Massachusetts is thus estimated at a minimum of $72 million in 2005. Because the V09 codes are infrequently used, efforts are underway to improve the accuracy of estimates through collection of additional lab-based data points.

This project is supported by an unrestricted grant from BioMérieux. For more information, contact Susan.Foster@tufts.edu.
Alliance for the Prudent Use of Antibiotics
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If you are concerned about the public health threat of antibiotic resistance, become part of the solution. Make a tax-deductible contribution and join our global network of citizens, clinicians, researchers and policy makers.

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Founded in 1981 as a nonprofit organization, APUA is the only organization in the world solely dedicated to strengthening society’s defenses against infectious diseases through research and education on antibiotic use and antibiotic resistance. APUA’s mission is to improve infectious disease treatment and control worldwide through promoting appropriate antibiotic access and use and reducing antibiotic resistance. With members in over 100 countries and over 55 affiliated country chapters, APUA provides a unique network to support country-based activities and facilitate international planning and communication. APUA’s resources include an international scientific advisory board with members of national academies of medicine and science and a professional staff with specialized expertise. APUA’s global network of affiliated chapters serves to tailor interventions to local customs and practices.

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... containing global antibiotic resistance through local action

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- CHAPTERS IN DEVELOPMENT: Azerbaijan, Botswana, Egypt, Ethiopia, Mozambique