



## Reservoirs of Antibiotic Resistance

### How harmless bacteria turn harmful: Mobile DNA and the recruitment of virulence factors

**Harold W. Stokes**  
Professor and Director, Institute for the  
Biotechnology of Infectious Diseases,  
University of Technology, Sydney, Australia

A major revelation of the genomics era is that much of a bacterium's genome can comprise DNA that is acquired by Lateral Gene Transfer (LGT), a process whereby DNA is accessed from another cell. Over long periods of time, LGT can lead to 25% or more of a specie's DNA being stably imported from other phylogenetic groups.<sup>10</sup> LGT offers many benefits to bacteria because it allows new functions to be acquired quickly, permitting cells to rapidly exploit new environmental niches. The extent of LGT poses a challenge to the "species concept" in bacteria,<sup>7</sup> since populations grouped as the same species can bear large unrelated fractions in their respective genomes, and can manifest very different phenotypes.

Mobile DNA is highly relevant to understanding how pathogens function. For example, the genus *Vibrio* is a ubiquitous component of aquatic environments and even *V. cholerae*, the agent of cholera, can be isolated with relative ease, with most strains being benign. The vibrios however, are very adept at acquiring

mobile DNA, frequently with strains displaying hundreds of foreign kilobases of DNA.<sup>11</sup> It is this strain-specific mobile DNA in which many potentially "pathogenic" factors are found. This DNA is often linked and, in pathogens, the term "pathogenicity island" is often used to describe these clusters, since they commonly include genes that enhance the ability of the cell to cause disease in animals.<sup>14</sup>

#### Mobile DNA and antibiotic resistance

Much of our understanding of mobile DNA comes from attempting to understand and deal with the rise of antibiotic resistance in bacteria. When the first resistant bacterium emerged, it was attributed to spontaneous mutation and assumed that the problem would be manageable.<sup>3</sup> While resistance via this traditional process does occur, it also became obvious early on<sup>13</sup> that other forces were operating and that bacteria had the ability to pass resistance genes to others in a way that is both infectious (more and more cells in a population acquire the gene) and promiscuous (the genes are spread to bacteria of many different unrelated species). Today, drug resistance genes are a common feature of the "mobile genome" of pathogens, including pathogenicity islands, and can give rise to bacteria that are both highly pathogenic and highly resistant. In one notable example, a pathogenic strain of *Acinetobacter baumannii*, a common mediator of nosocomial infections, was found to have 45 distinct resistance genes!<sup>4</sup>

#### How does DNA become mobile?

LGT is a fascinating and complex

*MOBILE DNA continued on page 2*

### Antibiotic innovation on the horizon?

**Ursula Theuretzbacher, Ph.D.**  
Principal, Center for Anti-Infective Agents,  
Vienna, Austria

Innovation in the development of anti-infectives takes place in cycles as the primary discovery of a new class of antimicrobials with novel mechanisms of action leads to modified and improved molecules within the same class.<sup>1</sup> The current phase of modification of known scaffolds has proceeded with hardly a pause since the 1970s, when the empirical usage of broad-spectrum antibiotics became widespread. And, with little applied or apparent concern regarding the inexorable development of resistance, we now find ourselves with a growing, challenging, and threatening resistance problem. From a business point of view, antibacterials constitute a highly competitive market that addresses short-term treatments of acute diseases. With this industry's focus on blockbuster drugs, most large pharma companies prioritize the far more lucrative chronic disease and lifestyle condition markets, and so, in the 1990s, abandoned antibacterial research and development. In the aftermath, the

*INNOVATION continued on page 5*

#### INSIDE:

- Investigating reservoirs of resistance.....p.1-4
- Need for novel antibiotics.....p.1,5-7
- APUA testimony on major US policy initiatives .....p.8-9
- Antibiotic use in food animal production.....p.9
- Social marketing to improve antibiotic use/CDC *Get Smart Week* .....p.10
- APUA field offices and surveys in Zambia and Uganda.....p.11
- Lab capacity building in Sub-Saharan Africa.....p.12
- Ask the Experts: gram-negative infections and AST systems.....p.13

#### Annual APUA Members' Reception Monday, September 14 at ICAAC

Join APUA staff, members and friends at APUA's Annual Members' Reception and Leadership Award Ceremony on Monday, September 14, 2009, in the Franciscan Ballroom at the Westin Hotel, San Francisco from 6:00–8:00 pm. Please RSVP to [jessica.restucci@tufts.edu](mailto:jessica.restucci@tufts.edu).

APUA Newsletter (ISSN 154-1424) is published three times per year by the Alliance for the Prudent Use of Antibiotics; copyright © 2009.

#### Chief Executives

Stuart B. Levy, President  
Thomas F. O'Brien, Vice President  
Kathleen T. Young, Executive Director

#### Board of Directors

Stuart B. Levy, Chairman  
Sherwood Gorbach  
Gordon W. Grundy  
Bonnie Marshall  
Mark Nance  
Thomas F. O'Brien  
Arnold G. Reinhold  
Dennis Signorovich  
Philip D. Walson

#### Advisory Board

Jacques F. Acar, France  
Werner Arber, Switzerland  
Fernando Baquero, Spain  
Michael L. Bennis, USA  
Otto Cars, Sweden  
Patrice Courvalin, France  
Jose Ramiro Cruz, Guatemala  
Iwan Darmansjah, Indonesia  
Julian Davies, Canada  
Abdou Djimdelaye, Mali  
Paul Farmer, Haiti  
Walter Gilbert, USA  
Herman Goossens, Belgium  
Sherwood L. Gorbach, USA  
Ian M. Gould, Scotland  
George Jacoby, USA  
Sam Kariuki, Kenya  
Ellen L. Koenig, Dominican Republic  
Calvin M. Kunin, USA  
Jacobus Kupersztoch, USA  
Stephen A. Lerner, USA  
Jay A. Levy, USA  
Donald E. Low, Canada  
Scott McEwen, Canada  
Jos. W.M. van der Meer, The Netherlands  
Richard P. Novick, USA  
Iruka Okeke, USA & Nigeria  
Maria Eugenia Pinto, Chile  
Vidal Rodriguez-Lemoine, Venezuela  
José Ignacio Santos, Mexico  
Mervyn Shapiro, Israel  
K. B. Sharma, India  
Atef M. Shibl, Saudi Arabia  
E. John Threlfall, United Kingdom  
Alexander Tomasz, USA  
Thelma E. Tupasi, Philippines  
Anne K. Vidaver, USA  
Fu Wang, China  
Thomas E. Wellems, USA  
Bernd Wiedemann, Germany

#### Editorial Staff

Stuart B. Levy, Editor  
Bonnie Marshall, Associate Editor

#### Headquarters

APUA Telephone: 617-636-0966  
75 Kneeland Street Fax: 617-636-3999  
Boston, MA 02111 Email: APUA@tufts.edu  
USA Website: www.APUA.org

#### 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.

### MOBILE DNA *continued from page 1*

process of DNA transfer and incorporation into a new host. The physical movement of DNA from cell to cell occurs by one of three processes—conjugation, transformation or transduction.<sup>6</sup> However, to ensure stable inheritance, the transferred DNA must either be a replicon (i.e., comprise a DNA molecule capable of autonomous replication such as a plasmid), or integrate into a resident replicon (either a chromosome or pre-existing plasmid). Integration is driven by one of two mechanisms. One of these is transposition—a process whereby discrete regions of DNA that often carry resistance genes can randomly insert into a genome. The second is site-specific recombination. As the name implies, this process involves insertion of DNA at a discrete site. It is biochemically differ-

ent from transposition. However, the best example of this system relevant to the antibiotic resistance problem is the integron/gene cassette system. Integrons are a major contributor to the spread of resistance genes in gram-negative bacteria.<sup>2</sup> One of the remarkable features of LGT systems is that they act cooperatively and can rapidly build up tightly linked regions that cluster many resistance genes in a modular format. As illustrated in Fig 1, it is common for resistance gene cassettes to be found in integrons that are embedded in one or more transposons that are in turn, located in a plasmid. As a consequence, the disparate processes of conjugation, transposition and site-specific recombination can work together to mobilize and rearrange genes in a way that was not previously imaginable.<sup>12</sup>

MOBILE DNA *continued on page 3*



APUA is pleased to acknowledge its supporters and partners in  
"Preserving the Power of Antibiotics"<sup>®</sup>

#### APUA Corporate Members

(unrestricted support)

Platinum Level (\$25,000)

bioMérieux, Inc. Bayer AG Pfizer Inc.  
Schering-Plough Co. The Clorox Company Wyeth Pharmaceuticals

Benefactor Level (\$15,000)  
Viropharma Inc.

Partner Level (\$10,000)

GlaxoSmithKline

AstraZeneca

Associate Level (\$5,000)

Trek Diagnostic Systems Inc. Cubist Pharmaceuticals, Inc.  
Alcon Laboratories Ltd.

Affiliate Level (\$2,500)  
Paratek Pharmaceuticals, Inc.

Pro bono legal services: Holland & Knight LLP

#### Other APUA Project Partners/Contractors

Aetna Foundation, American College of Physicians, American Society of Internal Medicine, Bill and Melinda Gates Foundation, Chiron Foundation, Fundacion Lusara (Mexico, DF), Iowa State University, International Society for Infectious Diseases, Izumi Foundation, the Joyce Foundation, Management Sciences for Health, Massachusetts Department of Public Health, Infectious Diseases Society of America, Michigan State University, National Institute of Allergy and Infectious Diseases, Pan American Health Organization, Pan American Infectious Disease Society, University of Alabama at Birmingham, University of Georgia, University of Illinois, University of Washington, U.S. Agency for International Development, U.S. Army Medical Research Institute on Infectious Diseases, U.S. Centers for Disease Control & Prevention, U.S. Department of Agriculture, U.S. Food and Drug Administration, World Health Organization and APUA Affiliated Chapters working to improve antibiotic access and use in over 60 countries.

MOBILE DNA *continued from page 2****Escherichia coli* and the recruitment of resistance genes into pathogens**

One feature of the mobile genome is that many resistance and virulence genes have been recruited from organisms and environments remote from a clinical context. Thus, the ease with which genes can move through communities means that the entire microbial biosphere is a potential “recruiting ground” of genes useful to pathogens, even if the latter do not venture far from their normal host. *E. coli*, in particular, is well placed to act as a conduit for the “shipment” of mobile DNA. First, *E. coli* is an abundant commensal organism that includes both humans and many other animals as its natural host. It can also persist in natural communities outside animals for relatively extended periods of time and can, itself, produce strains that are pathogenic. *E. coli*, for example, is the single biggest cause of urinary tract infections (UTIs)<sup>14</sup> and is a major health burden to developed and developing countries alike.<sup>5</sup> In the latter group resistant pathogens are a problem particularly felt in children, with mor-

tality rates from gram negative blood borne infections as high as 44%, which, in percentage terms is more than double that of malaria.<sup>1</sup> In general, reports of antibiotic resistance outbreaks are climbing steadily—as is the increase in mortality in all countries.

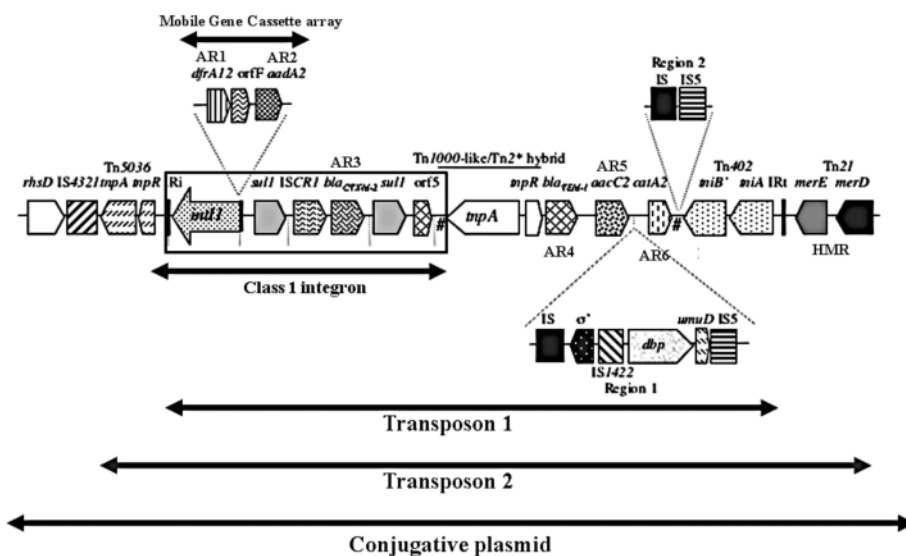
**Mobile DNA and antibiotic resistance in the future**

The unabated rise in *E. coli*-mediated infections, whether manifested as a UTI or other infection, comes about despite the escalating resources spent to contain the problem. This situation indicates the need to tackle the problem of resistance from new perspectives. One of these may be the application of broader molecular epidemiological methods that acknowledges the fact that mobile DNA, the key driver of the evolution of more “pathogenic” strains is a multifaceted, global problem. Traditional clinical microbiological approaches that look at individual resistance genes or groups of genes from specific locations or from the perspective of particular disease-causing organisms is becoming less insightful. For example, how is it that the same resistance gene is found in different locations in different isolates? Is it

because the two genes are embedded in the same mobile DNA backbone or are they two unrelated backbones? Whether the same or different, where did they come from? Did they have a recent common origin geographically or phylogenetically? Answers to questions like these are critical, but can only be achieved by more systematic surveys that look beyond the immediate problem—the resistance gene itself.<sup>8</sup> Also, there is a real need for greater collaboration between countries in the field of molecular epidemiology, possibly modelled after those adopted for international surveillance of resistance outbreaks.

## References

1. Bhutta, ZA (2008) *BMJ* 336:948-9.
2. Boucher Y, Labbate M, Koenig JE, et al (2007) *Trends Microbiol* 15:301-9.
3. Demerec M. (1948) *J Bacteriol* 56:63-74.
4. Fournier, P E, Vallenet D, Barbe V, et al (2006). *PLoS Genet* 2:e7.
5. Foxman, B. (2003), *Dis Mon* 49:53-70.
6. Juhas M, van der Meer JR, Gaillard M, et al (2009) *FEMS Microbiol Rev* 33:376-93.
7. Lawrence, J. G. (2002), *Theor Popul Biol* 61:449-60.
8. Magee, J T, Heginbothom M L, Mason BW (2005) *J Antimicrob Chemother* 55:628-33.
9. Marquez C, Labbate M., Raymondo C, et al (2008) *J Clin Microbiol* 46:3417-25.
10. Ochman, H, Lawrence J G, Groisman E A (2000) *Nature* 405:299-304.
11. Rowe-Magnus D A, Guerout AM, Biskri L et al (2003) *Genome Res* 13:428-42.
12. Walsh T R (2006) *Curr Opin Microbiol* 9:476-82.
13. Watanabe T, and Fukasawa T (1961), *J Bacteriol* 81:669-78.
14. Yamamoto, S. (2007) *Infect Chemother* 13:68-73.

**Figure 1. The cooperative dissemination of resistance genes**

This is an actual example of a multi-resistance plasmid from a UTI-mediating strain of *Klebsiella pneumoniae* revealing a series of gene cassettes inserted into an integron. This integron is embedded into a transposon, which in turn is “piggy backing” on a second transposon. The entire modular element is inserted into a conjugative plasmid. Components of the modular system seen here are commonly recovered from other diverse pathogens in many different parts of the world. AR = Antibiotic resistance gene. HMR = heavy metal resistance region. Figure modified from Marquez et al.<sup>9</sup>

**APUA co-sponsors  
Pan-American Congress**

APUA is pleased to announce that it will be co-sponsoring the XV Pan American Congress of Infectious Diseases to be held April 7-11, 2011 in Punta del Este, Uruguay. The primary topics of discussion will be immunization and new strategies; infections in the pediatric population; emerging and re-emerging diseases; infections in travelers and their prevention; diagnosis and treatment; bacterial resistance; and the rational use of antimicrobials. Dr. Julio Medina, Scientific Committee Coordinator, and Dr. Eduardo Savio, President, will lead the planning activities.

## Microbe publishes APUA article on commensals

APUA's *Reservoirs of Antibiotic Resistance* (ROAR) project was founded on the hypothesis that commensal bacteria can serve as "barometers" of resistance genes in pathogenic strains. The function of commensals and their potential as a reservoir of transferable resistance genes was addressed in the 2009 May issue of the American Society of Microbiology's *Microbe* magazine (see *Commensals: Underappreciated Reservoir of Antibiotic Resistance Vol 4; p.231-238*). The article evolved from a 2008 APUA meeting of expert advisors, supported by the U.S. National Biodefense Analysis and Countermeasures Center (NBACC), who were convened to "address the role of commensals in the problem of antibiotic resistance" (see AMROAR Scientific Meeting

Report at [http://www.tufts.edu/med/apua/AMROAR\\_scientificmeeting.html](http://www.tufts.edu/med/apua/AMROAR_scientificmeeting.html)). APUA authors Marshall, Ochieng and Levy provide an historical overview of the evolution of many once-harmless, antibiotic-susceptible bacteria into worrisome multidrug-resistant pathogens—some of which fail the "drug of last resort." While the earth's total commensal population approaches a staggering number (estimated at  $>10^{29}$ ), little research has been directed to this area. In contrast, much attention has focused on the infinitely smaller populations of "true" pathogens (Fig. 1). The cellular infrastructure of "gene capturing systems" known as integrons (see Fig. 1, page 3), coupled with highly promiscuous bacterial mating (conjugation) systems that know few boundaries, are largely responsible for today's multidrug resistance problem.

Studying commensals as resistance reser-

voirs is complicated for many reasons, including the increased blurring of the border between pathogens and commensals, (especially as manifested in immunocompromised patients) and the large temporal differences in the emergence of resistance among different antibiotics. Moreover, in-depth study has been limited to just a few microbial species, largely ignoring the potentially overwhelming contributions posed by anaerobic genera. Modeling the emergence of commensals as resistant pathogens is a formidable challenge, and attempts have been undermined by large, persisting knowledge gaps. To address the many unanswered questions surrounding this challenge, researchers strongly suggest that a multi-disciplinary, ecological approach is imperative. Further, investigators are encouraged to use gene-based technologies such as DNA fingerprinting to study commensal ecology. A move towards standardizing the methods used in surveillance systems will greatly assist in advancing this field.

The authors describe how the ROAR project ([www.ROARproject.org](http://www.ROARproject.org)), supported by a grant from NIAID and launched by APUA in 1997, became a pioneering attempt to focus more attention on the largely neglected commensals. ROAR's online searchable databases include both an expanding literature library of over 1100 extensively annotated articles, as well as an isolate database of gene-based data. Mining of APUA's databases can help close some of the persisting data gaps and ultimately help address unanswered questions that still impede progress in this area, in particular "whether antibiotic use in agriculture and aquaculture is driving resistance genes from animal-associated bacteria into strains that cause human disease."

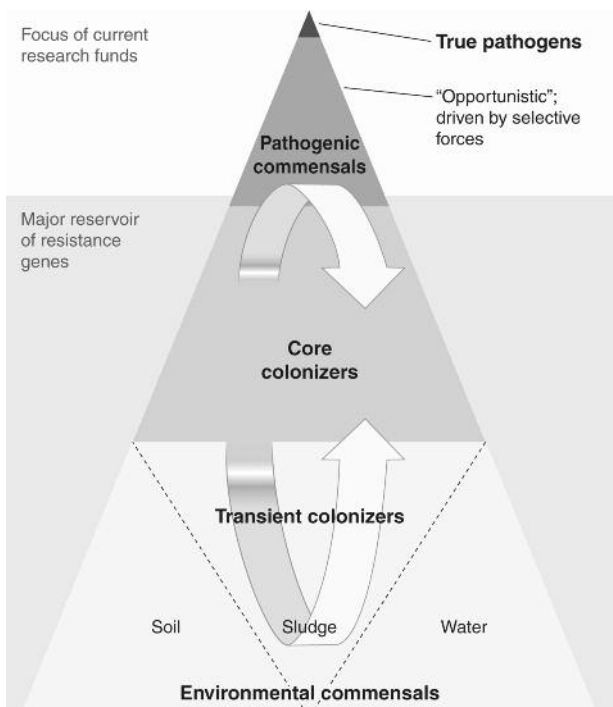
The authors conclude that "probing commensals and understanding the role they play in antibiotic resistance should help toward developing effective interventions to control resistance and preserve the efficacy of antibiotics."

## APUA completes successful pilot surveillance of commensal flora

In collaboration with the United States Army Medical Research Institute on Infectious Diseases (USAMRIID) and NBACC's Biological Threat Characterization Program (BTC), APUA has completed a one-year pilot surveillance project to track and analyze patterns of antibiotic resistance identified in global sources of environmental and animal commensal bacteria that may serve as reservoirs for antibiotic resistance genes. The APUA collaboration and strain collection effort, entitled *International Surveillance of Reservoirs of Antibiotic Resistance: Pilot for a Global Surveillance System*, is viewed as the "core of the antibiotic resistance research project" of NBACC's Biological Threat Characterization Program. During the pilot, 500 strains of *E. coli*, *Streptococcus/Enterococcus*, *Staphylococcus* and *Salmonella* were collected through the efforts of five APUA country chapters (Uganda, Turkey, South Korea, Georgia and India). Isolates were verified and susceptibilities tested with 5-6 antibiotics. The pilot

**SURVEILLANCE** *continued on page 6*

**Figure 1. Hierarchy of commensals**



Reprinted with permission from *Microbe* (2009) Vol 4, p. 234 (not to scale)

Pathogens comprise only a tiny fraction of the total microbial environment. "Opportunistic" or "pathogenic commensals" are considered generally nonpathogenic, but can be propelled to the status of pathogens when imbalances or shifts occur in environmental selective pressures. These can become more problematic if they have acquired resistance or virulence genes from the vast pool of environmental commensals, many of which may become transient colonizers of humans and animals through the food chain and multiple other routes of exposure. The accumulated evidence suggests widespread gene exchange among these groups.

INNOVATION *continued from page 1*

bulk of antibacterial research and early development activities (Figure 1) shifted to small companies. Recently, the growing magnitude and severity of the resistance problem created new business opportunities leading to a renaissance in antibacterial interest, investment, and research. However it will be many years before drugs with novel modes of action will become available for clinical usage. In a world where anti-infective R&D is dominated by the for-profit model, investment and progress will continue to be cyclic.

### New antibiotics against systemic gram-positive infections

Visible and accelerating public health concerns regarding the rapid rise of methicillin-resistant *Staphylococcus aureus* (MRSA) forced open a market niche window resulting in a wave of anti-Gram-positive research and development (R&D). As a result, Pfizer's linezolid, and later Cubist's daptomycin, have become part of the clinical tool box. About 20 other antibacterial compounds are moving through the clinical development and approval process. Over

the next decade many new anti-gram-positive therapeutic options are expected to become available to the clinician. However, most of these antibacterials build on well-known antibiotic groups. Only a few companies are pursuing novel programs with new targets that would avoid potential issues with cross resistance. Three of these novel anti-gram-positives with a new mode of action have reached early clinical development. Should they be approved, treatment options for infections caused by Gram-positive bacteria including MRSA and vancomycin-resistant enterococci will be expanded in 7 to 10 years.

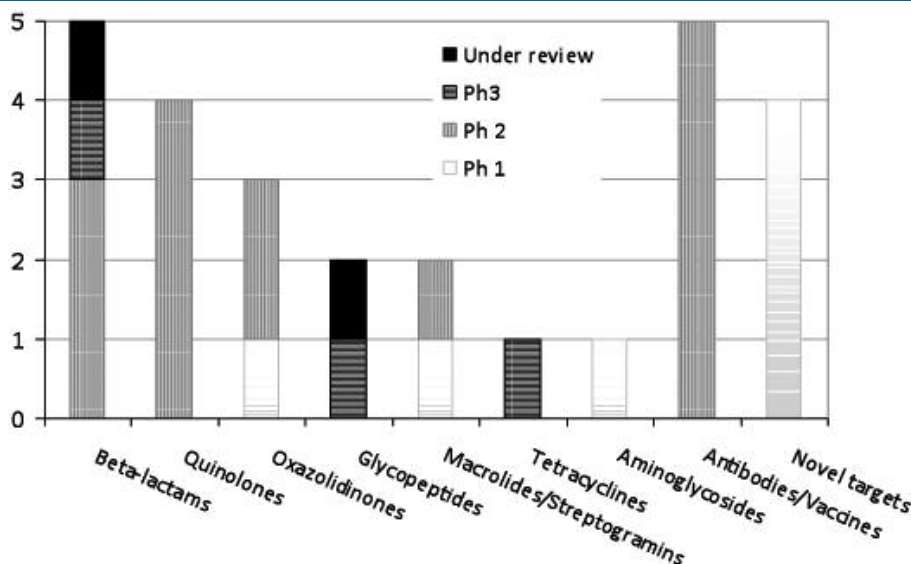
### Antibiotics against systemic gram-negative infections

Lacking the visibility of the MRSA crisis and faced with daunting scientific challenges, novel anti-gram-negative R&D has been relatively neglected (Figure 2). At the same time, gram-negative resistance is a very real health problem and is garnering increasing attention.<sup>2-5</sup> Similar to the activities regarding gram-positive bacteria, most current anti-gram-negative R&D focuses on exploiting existing classes of

antibiotics. Beta-lactams are at the center of these activities as drug developers attempt to overcome selected resistance determinants. However, they are rarely able to solve the multidrug resistance (MDR) problem. To address the enzyme-mediated, beta-lactam resistance, a variety of new and established approaches for protecting beta-lactams against beta-lactamases are being explored. These include both using old and newly developed beta-lactamase inhibitors in combination with both old and new cephalosporins. The monobactam group has also seen a revival, as has the well-known group of aminoglycosides. Another way of utilizing well understood groups is to reformulate them for specific patient populations. For instance, in localized infections such as *Pseudomonas* infections in cystic fibrosis or in ventilated patients in the Intensive Care Unit, a wide range of inhalation forms of old drugs have been pursued as adjunct therapy to systemic treatment. However, in consideration of the widespread resistance problem and the propensity for existing treatment options to intensify the effect of class-specific resistance mechanisms, most specialists would prefer novel chemical classes with no pre-existing cross-resistance.<sup>6,7</sup>

This intensified need for new therapeutic options has created a promising market opportunity for the pharmaceutical industry. Even targeting small patient populations, high price points can provide a satisfying return on investment. Early signs of renewed commercial interest are reflected in the development of novel compounds such as Cubist's lipopeptide, Novexel's non-beta-lactam penicillin-binding protein inhibitor, and Achaogen's membrane biosynthesis inhibitor. Each of these compounds has shown promising activity against enterobacteria and non-fermenters. Other new approaches showing up in the pipelines (Table 1) include drugs with activity against MDR enterobacteria and non-fermenters, as well as drugs targeted specifically to one pathogen only (*Pseudomonas* antibodies). Going a step

**Figure 1. Number of systemic antibiotics and vaccines in clinical development (phase 1, 2, 3 or under review) according to antibacterial group\***



\*Information based on the proprietary database of the Center for Anti-Infective Agents (CEFAIA) 7/2009

## INNOVATION *continued from page 5*

further, the extremely specific approach of targeting only single serotypes of *Pseudomonas* moves rapid diagnostics into the spotlight. Another indicator of this trend towards niche applications is the industry's interest in non-mainstream treatment approaches. While not taken seriously a few years ago, multiple drug resistance and market conditions have also opened the window for innovative R&D projects in areas such as: monoclonal and polyclonal antibodies, therapeutic vaccines, anti-virulence drugs, phage formulations and antibacterial peptides. Some of these activities are in the early phase of discovery and so will not be available for testing in clinical trials for 5-10 years. While it's encouraging to see that new and promising treatment options are on the horizon, many years will pass before new antibiotics against the most problematic gram-negative pathogens will be available for clinical practice. Without a doubt, we need to continue our efforts to slow down the resistance spiral when using existing treatment options.

### Outlook

Assuming that the current economic downturn doesn't kill investment and that the R&D trends mentioned above continue, we should expect to see more

novel, highly priced, small-spectrum antibiotics by the 2020s. Driven by financially challenged health care systems worldwide, usage of such targeted antibiotics will need to be supported by improved rapid diagnostic tools. Enticed by successful examples of applied personalized medicine in the oncology field, the concurrent rise of reliable, easy to use, and rapid molecular diagnostic capabilities points towards a future change in treatment paradigms in everyday clinical practice.<sup>8-10</sup> The success of these advances will require changes to the regulatory, clinical and reimbursement landscape. Considerable challenges are ahead.

The uncertainties of the general economic situation and the changing landscape of regulatory and government initiatives make "prediction very difficult, especially about the future" (Niels Bohr). However, I believe that despite increased pressure for health care cost controls, viably profitable niche segments, coupled with rapid diagnostics, will align to drive antibacterial development. Given the growing urgency of multi-drug resistance and lack of antibiotics with a novel mode of action today, we must intensify every effort to reduce resistance selection pressure, as well as manage spread of resistance using currently available tools.

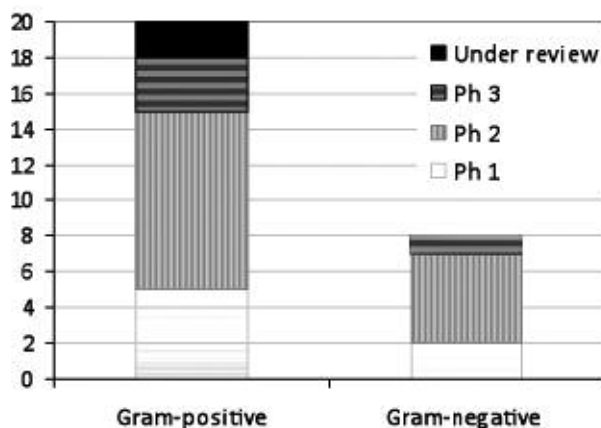
### References

1. Theuretzbacher U. 2009. *Int J Antimicrob Agents* 34:15-20.
2. Boucher HW, Talbot GH, Bradley JS et al. 2009. *Clin Infect Dis* 48:1-12.
3. O'Fallon E, Pop-Vicas A, D'Agata E. 2009. *J Gerontol A Biol Sci Med Sci* 64:138-41.
4. Hawkey PM. 2008. *J Antimicrob Chemother* 62(Suppl. 1):i1-9.
5. Mulvey MR, Simor AE. 2009. *CMAJ* 180: 408-415.
6. Wang YC, Lipsitch M. 2006. *M. Proc Natl Acad Sci USA* 103:9655-60.
7. Rolston KV. 2009. *Hematol Oncol*. Jul 1. [website]
8. Casadevall A. 2009. *Expert Opin Pharmacother*. Jun 28. [Epub ahead of print]
9. Weile J, Knabbe C. 2009. *Anal Bioanal Chem*. 394:731-42.
10. Muldrew KL. 2009. *Curr Opin Pediatr*. 21:102-11.

## SURVEILLANCE *continued from page 4*

study served to establish "proof of principle" and to provide lessons to guide refinement of systems. The successful testing of infrastructure and logistics protocols provides the foundation for study expansion into a larger multi-year project that will include Thailand and Vietnam and also the collection of additional species (*Aeromonas*, *Pseudomonas*, *Stenotrophomonas* and *Acinetobacter*). In collaborative efforts with NBACC and Michigan State University, all isolates will undergo molecular analysis for detection of novel resistance genes. The genetic data will be utilized to populate APUA's ROAR isolate database ([www.ROAR.project.org](http://www.ROAR.project.org)).

**Figure 2. Number of systemic antibiotics and vaccines in clinical development (phase 1, 2, 3 or under review) according to focus of activity \***



\* Information based on the proprietary data base of the Center for Anti-Infective Agents (CEFAIA) 7/2009

## APUA Recommended Reading

*Positive Epistasis Drives the Acquisition of Multidrug Resistance*

Trinidad S., Sousa A, Xavier KB, Dionisio F, Ferreira MG et al (2009), *PLoS Genet* 5

e1000578. doi:10.1371/journal.pgen.1000578

*Squashing Superbugs—The Race for New Antibiotics*

Walsh CT and Fischbach MA

<http://www.scientificamerican.com/article.cfm?id=squashing-superbugs>

**Table 1. Investigational intravenous drugs with a focus on hard-to-treat MDR gram-negative bacteria including *Pseudomonas* in preclinical and clinical development<sup>1</sup>**

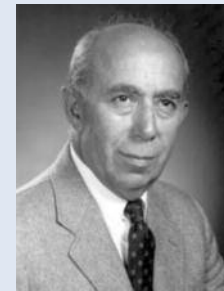
Development phase	Compound (Company)	Group	Notes
Phase 2	Ceftazidime+NXL 104 (Novexel)	Cephalosporin+new $\beta$ -lactamase-inhibitor	Stable against class A (ESBL)- and class C-producing $\beta$ -lactamases. • cUTI
Phase 2	FR 264205= CXA-101 (Astellas/Calixa)	Cephalosporin	Comparable to ceftazidime, more stable against class C- $\beta$ -lactamases • cUTI
Phase 2	IC43 (Chiron/Pelias/Intercell)	Recombinant subunit vaccine	<i>P. aeruginosa</i> specific • VAP
Phase 2	KBPA101 (Kenta Biotech)	Human monoclonal antibody	<i>P. aeruginosa</i> serotype O11-specific; Co-development of a multivalent diagnostic test for rapid serotyping
Phase 1/2	KB001 (Kalobios)	PEGylated monoclonal antibody fragment	<i>P. aeruginosa</i> -specific; Antivirulence-antibody (PcrV protein of the Type III secretion system of <i>P. aeruginosa</i> ) • CF and VAP
Phase 1	ACHN-490 (Achaogen)	Aminoglycoside	Active against aminoglycoside-resistant gram-negative pathogens, MRSA
Phase 1	CB-182804 (Cubist)	Lipopeptide	• <i>E. coli</i> , <i>Acinetobacter</i> , <i>P. aeruginosa</i> and <i>Klebsiella</i>
Preclinical completed	Polyphor	Protein epitope mimetics (novel class)	• <i>P. aeruginosa</i> -specific
Preclinical completed	Ceftaroline+NXL 104 (Forest / Novexel)	Cephalosporin+new $\beta$ -lactamase-inhibitor	Stable against class A (ESBL)- and class C-producing $\beta$ -lactamases • Enterobacteria, <i>P. aeruginosa</i> , MRSA
Preclinical	BAL30072 (Basilea)	Monobactam	Stable against class C and class B enzymes (metallo- $\beta$ -lactamases) • <i>Acinetobacter</i> , <i>P. aeruginosa</i> , enterobacteria
Preclinical	NXL105 (Novexel)	PBP-Inhibitor (novel class)	• Gram-negative bacteria
Preclinical	Aminoglycoside (SelectiX)	Aminoglycoside	More stable against aminoglycoside-modifying enzymes
Preclinical	Achaogen	Membrane biosynthesis inhibitors (novel class)	• Enterobacteria, <i>P. aeruginosa</i>

<sup>1</sup>As of 7/2009; adapted from Theuretzbacher, U., 2009<sup>1</sup>

## Obituaries

It is with great sadness that we inform you of the passing of three of APUA's highly respected colleagues:

**Morton A. Madoff, MD, MPH**, former Dean of Tufts University Medical School, passed away at age 81 on June 16, 2009. He will be remembered by his family, friends, students, and colleagues as a stellar physician, public health leader, innovator and educator. Among numerous brilliant



accomplishments, Dr. Madoff conceived of the Tufts Associated Health Plan that was based on the unique 3-way risk-sharing model, which is a key element of the present Health Plan proposed by Obama's administration under "accountable care organizations" label. Dr. Madoff served for several years as a valued member of APUA's Board of Directors. The eulogy, given by Vice Dean Harris Berman can be found at <http://medical.alumni.tufts.edu/downloads/Mort-eulogy.pdf>.

**Ms. Ruth Bwalya Tembwe** (1959-2009) was the Head of Zambia's National Reference Laboratory for Tuberculosis. Ms. Ruth Bwalya Tembwe received her education with honors in Bradford UK and Diploma Medical Laboratory Technology in Lusaka, Zambia. She was one of the founders of the APUA-Zambia Chapter. Ms. Bwalya Tembwe had made great contributions to the field through extensive work in routine diagnostics, research and teaching.

**Mr. Angelino Manuel** was one of the founding members of the APUA-Mozambique Chapter. Mr. Manuel had extensive experience in microbiology and contributed greatly to the establishment and development of the Mozambique chapter.

## APUA Public Policy Actions

APUA is continually committed to the effort of advising policy makers on policy decisions, based on the latest available research. Riding the recent wave of increased attention to health care reform and amplified research funding promised by the current administration, APUA has been active in several policy related activities:

### APUA provides Congressional testimony on H1N1 pandemic

On May 14, 2009, APUA Vice-president Thomas O'Brien testified before Congressman Lynch and his Committee on issues surrounding the H1N1 (Swine Flu) outbreak. APUA drew on historical lessons of the 1918 influenza pandemic in order to alert the legislators of possible forthcoming challenges, in particular, the potential for life-threatening secondary infections. Multi-resistant MRSA has now spread widely in the community, and will very likely become a major contributor to mortality in future influenza infections. Confronted with an H1N1 pandemic, the potential for multi-resistant secondary infections such as MRSA and pneumonia needs to be addressed as quickly as possible.

APUA emphasized that participation of all sectors that use antibiotics—human medical, veterinary, and horticultural—is essential in slowing down proliferation of antibiotic-resistant bacteria. Alternatives to growth promoting and prophylactic uses of antimicrobials in agriculture include improved management practices, wider use of vaccines, and introduction of probiotics. APUA's testimony recommended the following interventions:

- **Surveillance:** A good public health surveillance system requires local laboratory infrastructure to recognize new or emerging infectious diseases and to track the prevalence of more established ones.
- **Basic Research:** Genetic analysis and bioinformatics accelerate find-



APUA executives recently presented Congressional testimony on the challenges posed by bacterial infection associated with the H1N1 pandemic. From left: Congressman Stephen Lynch, Kathleen Young (Executive Director), Thomas O'Brien (Vice President)

ings critical to public health. This area is seriously underfunded.

- **Vaccines:** While helpful, vaccines should not be viewed as the entire solution due to the frequency of virus mutation.
- **Sanitation:** Clean water supplies, personal hygiene and safe food handling are now fundamental public health practices in the U.S. that can protect us from infectious diseases.
- **Hygiene and antiseptics:** In almost all cases, antiseptics and disinfectants are benevolent agents that, when properly used, make an enormous contribution to protecting people, especially those facing surgery.
- **Antivirals:** Influenza viruses develop resistance quickly, and overuse of Tamiflu or any antimicrobial will hasten drug resistance. Prudent use of these therapeutics means using them only for viral infections and ensuring proper dose and length of treatment.
- **Antibiotics:** The usefulness of antimicrobial drugs can be ensured only if they are used carefully and responsibly. Any investment which will improve antibiotic use and preserve the power of existing drugs is a good one.

The present H1N1 outbreak demonstrates once again the value of an effective U.S. public health infrastructure and the need for a coordinated global surveillance program effort among all health agencies. APUA urged passing of the STAAR Act as an opportunity to take leadership in the preserving the power of antibiotics.

### APUA seeks President Obama's support

Given the magnitude of antimicrobial resistance problem, APUA feels strongly that the government should pay more attention to the issue through policy changes and increased research funding. On May 15, APUA submitted a letter to President Obama requesting an allocation of additional funds that could help combat bacterial infections in resource poor countries. APUA asked the President for his assistance in the appropriate distribution of funds for diagnosis, treatment and improvement of laboratory techniques to fight pneumonia. APUA is currently engaged in this endeavor in the U.S. and countries such as Zambia and Uganda that are in dire need of additional research, education and project funding.

### APUA continues support for PAMTA and STAAR Act

The purpose of the **PAMTA** (*Preservation of Antibiotics for Medical Treatment Act of 2009*; H. R. 1549) is to preserve the effectiveness of medically important antibiotics used in the treatment of human and animal diseases by reviewing the safety of certain antibiotics for non-therapeutic purposes in food-producing animals.

If passed, the Bill would amend the Federal Food, Drug, and Cosmetic Act to deny an application for use of a new critical antimicrobial animal drug. A "critical antimicrobial animal drug" is defined as "a drug intended for use in food-producing animals that contains specified antibiotics or other drugs used in humans to treat or prevent disease or infection caused by microorganisms." An applicant could

**BILLS IN CONGRESS** *continued on page 9*

**BILLS IN CONGRESS** *continued from page 8*

be exempted by demonstrating that there is a reasonable certainty of no harm to human health due to the development of antimicrobial resistance attributable to the non-therapeutic use of the drug. The Bill requires the Secretary to withdraw approval of a non-therapeutic use of such drugs in food-producing animals two years after the date of enactment of this Act unless certain safety requirements are met. It will also direct specified Congressional Committees to hold hearings on the implementation of such a withdrawal of approval.

The bill was introduced to Congress on March 17, 2009 by Louise Slaughter (D-NY) along with 38 co-sponsors.

The **STAAR Act** (*Strategies to Address Antimicrobial Resistance Act*; H.R. 24000), if passed, will establish an Antimicrobial Resistance Office (ARO) within the HHS Office of the Assistant Secretary of Health. The Director of ARO will serve as the director of the existing interagency task force, thus strengthening existing

efforts to control antimicrobial resistance. The Act also establishes a Public Health Antimicrobial Advisory Board (PHAAB) comprised of infectious disease and public health experts who will provide much needed advice about antimicrobial resistance and strategies to address it. Importantly, the STAAR Act will: a) strengthen existing surveillance, data collection, and research activities as a means to reduce the inappropriate use of antimicrobials, b) develop and test new interventions to limit the spread of resistant organisms, and c) create new tools to detect, prevent and treat drug-resistant infections.

The bill was introduced to Congress on May 13, 2009 and sponsored by representative Jim Matheson (D-Utah).

*The text and summary of the Acts are adopted from <http://www.opencongress.org>*

### Policy changes sought for antibiotics in animal feed

APUA has continually expressed its support of the 2006 recommendation by

the USFDA Veterinary Medicine Advisory Committee not to approve the use of cefquinone, a fourth-generation cephalosporin antibiotic, for use in agriculture. On April 1, 2009, APUA submitted a letter to Dr. Sharfstein, Deputy Commissioner of the USFDA, urging the agency to increase its efforts in removing broad-spectrum antibiotics from agriculture and animal feed. It also recommended that the FDA reissue the ban on extra-label use of cephalosporins in agriculture and expressed support for the work that the *Keep Antibiotics Working* group does by offering scientific and clinical guidance. In response to Dr. Sharfstein's request that APUA add its influence to the Administration's new policy positions in the area of antibiotic use in agriculture, APUA has signed on to the letter.

Dr. Sharfstein has testified before the House Committee on Rules on the dire need of preserving the effectiveness of antimicrobials and banning the use of antimicrobial drugs in agriculture for non-judicious purposes, including growth promotion and feed efficiency.

## APUA reactivates "prudent use" efforts in agriculture

The cost of drug resistant infections is of particular concern as the United States Congress considers universal health insurance. APUA's mission is to promote improvement in the use of antibiotics in all sectors—human medical, veterinary, aquaculture, and horticulture. The ultimate goal is cost-effective infectious disease treatment and control.

Towards this end, in 2000, APUA initiated a 2-year project called *Facts about Antimicrobials in Animals and the Impact on Resistance* (FAAIR) to gather evidence about human health impacts of antimicrobial misuse in agriculture. That effort culminated in the 2002, APUA FAAIR report, *The Need to Improve Antimicrobial Use in Agriculture: Ecological and Human Health Consequences* (Clin Infect Dis. Vol. 34, Supplement 3), published as the first comprehensive peer review on the topic since the 1986 IOM report.

The FAAIR report findings were publicized in scientific journals and in major news outlets such as *USA Today* and the *LA Times* and at a press conference at the National Press Club in Washington, D.C. They were also used as evidence in policy debates, including the successful FDA lawsuit to support the withdrawal of fluoroquinolones in food-animal production.

The FAAIR Report outlined several lines of evidence linking antimicrobial resistant pathogens in humans to the use of antimicrobials in food animals. These include the following: (i) direct epidemiological studies, (ii) temporal evidence for emergence of resistance in animal-associated bacteria before their appearance in related human pathogens, (iii) additional circumstantial evidence, (iv) trends in resistance among *Salmonella*, *Campylobacter*, and *Escherichia coli* isolates, and (v) studies suggesting that farmers and family members may be

more likely than the general population to acquire antimicrobial-resistant bacteria (see <http://www.tufts.edu/med/apua/Ecology/faair.html> for the full FAAIR report).

Since that report, APUA has remained an active advocate for promoting improvement of antibiotic use through correspondence with regulators, congressional testimony, and publicity in the lay media (see the public policy section of APUA.org at [http://www.tufts.edu/med/apua/public\\_policy/legislation.html](http://www.tufts.edu/med/apua/public_policy/legislation.html)).

New funding from the PEW Charitable Trusts Foundation will enable APUA to reactivate its role in improving antibiotic use in agriculture. The project will produce an extensive review of related scientific literature, coordinate meetings with scientific experts and policy makers to update the science, and explore implementation of the EU ban on antibiotic growth promotion use.

## Social marketing framework published in JAC

APUA is partnering with The Centers for Disease Control and Prevention (CDC) in their annual *Get Smart* campaign to raise awareness of improper antibiotic use. The campaign will reach out to pharmacies and health care providers with the goal of educating the public, particularly in light of the H1N1 pandemic. It also comes at a time when APUA has released a publication that resulted in significant findings that behavioral intervention programs can work in social groups when multiple channels of communication are used.



<http://www.cdc.gov/GetSmart/campaign-materials/week/buttons/gsw-web-button.html>

APUA's study, sponsored by an unrestricted grant from Pfizer Inc., was published in the *Journal of Antimicrobial Chemotherapy* (JAC). (*Sustainability for behaviour change in the fight against antibiotic resistance: a social marketing framework* T. Edgar et al. 2009, vol. 63, 230-237—see <http://jac.oxfordjournals.org/cgi/content/full/63/2/230>). The study evaluated the types of campaigns that have been implemented in various countries to reduce antibiotic use for colds, as well as their effectiveness in raising awareness of the general public and health professionals about proper antibiotic use. The main study findings were as follows:

1. Significant changes in social

behavior can be, and have been achieved, in some European countries such as Belgium and in Australia.

2. The interventions are most successful when multiple communication channels are employed.
3. Lasting results for even most successful intervention programs are hard to achieve. To help perpetuate success, programs should adhere to the six criteria of social marketing as developed by Andreasen, leading scholar in social marketing:

- 1) Focus on behavioral change and design an intervention program that is lucid, unambiguous and easy to follow.
- 2) Understand your target audience through studies on population behavior and their perception of the studied issue.
- 3) Consider subpopulations that often have different perspectives on an issue. For instance, doctors will not respond to the same intervention messages as would patients with small children.
- 4) Try to communicate the immediate benefits of behavior change. For example, the fact that antibiotic-resistant bacteria may develop due to inappropriate use of antibiotics is too intangible a motivator to elicit a change in habits.

- 5) To implement interventions, rely on a complete marketing mix to appeal to a wider audience and make a stronger impact in behavioral change. The marketing mix discussed by Andreasen consists of Promotion, Product, Price and Place.
- 6) Consider aspects of competition, i.e., the choice presented between the status quo and changing one's behavior. For example, physicians with time constraints may opt to prescribe an antibiotic for a cold rather than educate a patient on its worthlessness for that illness.

### Schoenbaum retires from APUA Board of Directors

APUA announces the retirement of Dr. Stephen Schoenbaum, executive vice president for programs at The Commonwealth Fund, from the APUA Board of Directors after 9 years of dedicated service. As chairperson of the APUA Development and Nominating Committee, Dr. Schoenbaum provided invaluable strategic leadership and advice which paved the way for several important APUA project grants. He was a uniquely engaged and vibrant board member. We thank him for his generous service and wish him well in his continued role as VP at The Commonwealth Fund, where he is very involved at a high level in the US national health care reform debate.

### New chapter welcomed: APUA-AUSTRIA

APUA announces its newest country chapter, APUA-AUSTRIA, and welcomes the scientists who together lay the foundation for this new endeavor. The chapter will be led by Annegret Frank.

Antimicrobial resistance is already a top priority for public health authorities in this country, with initiatives [e.g., The

Austrian ABS (Antibiotic Stewardship Initiative)] dating back to the year 1998.

The planned objectives of the Austrian APUA chapter are summarized as follows:

- The promotion of all types of activities that aim for the optimization of antibiotic use in hospital and primary care
- The promotion of continuous (further) education of all interest groups in this context (educational programs, workshops, symposia, con-

gresses etc.)

- The development and dissemination of information and educational materials, dissertations and other scientific work
- The promotion of the collaboration and networking of Austrian and international health professionals with research scientists, public authorities, hospital administration, the pharmaceutical industry and scientific organizations

## International Field Research and Interventions

### APUA field teams in Africa conducting Gates Foundation-funded project

Launching of the *Antibiotic Situation Analysis and Needs Assessment* project in Uganda and Zambia was announced in the previous *APUA Newsletter*. The project, funded by the Bill & Melinda Gates Foundation, is in full operation, following approval by the appropriate university ethics committees in both countries and here in Boston. It is designed to conduct a comprehensive analysis and needs assessment to evaluate antibiotic use and the resistance problem in these two countries. The acquired knowledge

O'Brien, met with APUA-Zambia chapter members in early January and identified a project manager (Dr. Chileshe Lukwesa, M.D.) and a pharmaceutical advisor. A project field office and a project administrator have also been identified. Stakeholders were briefed on project activities and goals, and a Country Advisory Team was formed. Dr. Chileshe has assessed the current state of knowledge on antibiotic resistance in Zambia and 17 laboratory sites around Zambia are being visited by a team of three microbiology graduate students in order to assess their potential roles in the surveillance of antibiotic resistance.

In Uganda, the work is also progressing rapidly. A country project manager has been named (Dr. Florence Najjuka, of the Makerere University College of Health Sciences Department of Medical Microbiology), as well as a Project Coordinator (Pharmacist, Ms. Annette Naggayi). In June, fieldwork began with over 90 Makerere University medical,

pharmacy and dental students who received a one-week training program in use of the questionnaires, data entry, and handheld GPS units to mark locations of informal sector drugshops. The students are working under the auspices of the Community Based Education and Services (COBES) Program of Makerere University's College of Health Sciences. Following training, they departed for data collection from 11 sites country-wide. A Boston University intern, Joe Novotny, is overseeing the fieldwork



**Trained students, equipped with computers, scanners, printers and GPS units, depart for field-work assignments**

and assisting with data entry. Equipped with a laptop computer, scanner, printer, and GPS unit, each team is collecting information on the use of antibiotics in the formal sector, as well as among informal sector drugsellers. Over 1000 samples of antibiotics from both sectors and from private pharmacies are being collected for quality and potency testing. A subset of samples which "fail" initial domestic screening assays will be sent to an external, internationally recognized laboratory for confirmation. Pending activities include the assessment of surveillance capacities in over 20 labs by a team of three microbiology graduate students from Makerere University.

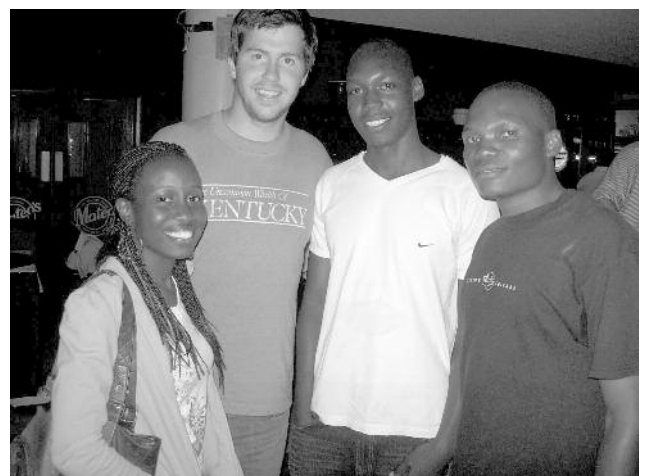


**Susan Foster, APUA Project PI, trains students at Makerere University, Kampala, Uganda.**

is expected to contribute to appropriate healthcare practice and policy in Africa.

APUA's International Advisory Board met in Boston in March, 2009 and convened an eminent group of experts to review plans and provide guidance. Among those attending were Drs. Keith Klugman, Iruka Okeke, Kenneth Lawrence, and Michael Bennish. In Boston, several interns from Boston and Tulane Universities' Schools of Public Health have been recruited to conduct literature reviews on antibiotic resistance and on pharmaceutical distribution and supply systems in Uganda and Zambia.

The APUA team, comprised of Drs. Susan Foster, Anibal Sosa, and Tom



**Boston University intern, Joseph Novotny, and students in Kololo, Uganda**

## APUA building lab capacity in Sub-Saharan Africa

The APUA chapter network provides an international support structure for improving local capacity for disease surveillance, diagnostics and control with a focus on acute bacterial diseases—the leading cause of deaths in children under five in Sub-Saharan Africa.

APUA International Chapter Director, Dr. Anibal Sosa and Executive Director Kathleen Young attended an IZUMI foundation Grantees meeting on June 16. APUA reported on its progress in establishing the APUA chapter network in Africa—a project partially sponsored by this foundation and by USAID and WHO.

Antimicrobial resistance is considered one of the top global health threats and is particularly devastating in sub-Saharan Africa. Of particular concern in Africa are the absence of essential antimicrobials in the national drug formularies; lack of access to antibiotics medicines; inappropriate antibiotic prescribing and dispensing practices; the availability of counterfeit and sub-standard drugs; and the unregulated or uncon-

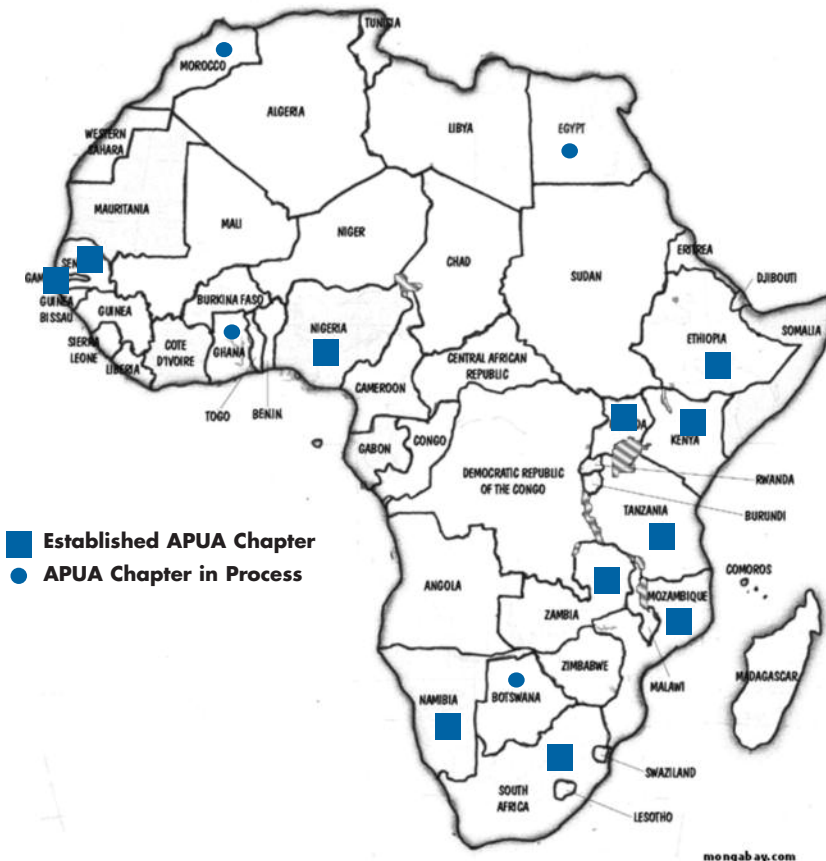
trolled sale of drugs, all of which, along with many other factors, contribute to an accelerated antimicrobial resistance (AMR) rate as described by Okeke and Sosa.<sup>1</sup>

With the support of the Izumi Foundation, APUA set out to decrease morbidity and mortality for the patients in the region through education and capacity building. Targeted countries were Namibia, Gambia, Tanzania and Mozambique. The objectives were to: (1) improve treatment of acute respiratory infections and diarrheal diseases at the community level; (2) improve access and use of antimicrobials and decrease antimicrobial resistance; and (3) establish an APUA chapter organization in targeted countries as a sustainable resource to educate health care practitioners in disease management and antimicrobial prescribing practice. Activities included antibiotic resistance surveillance training and targeted antimicrobial use education and the development of a multi-disciplinary, multi-sectorial APUA chapter capable of sustaining related efforts for the foreseeable future.

### Project benefits at the community level:

- Improvement of antibiotic treatment of acute respiratory tract infections (ARI) and diarrheal diseases through introduction of laboratory training and surveillance capacity
- Country-specific assessment of the AMR situation and work plan based on local priorities
- Improved and standardized protocols for antimicrobial susceptibility testing and quality control
- Identification of the most prevalent resistant pathogens and temporal trends to guide healthcare practitioners
- “Targeted approaches for antibiotic management in the developing world,” an article published in the *APUA Newsletter*
- Inclusion of new APUA-Chapter members on the International APUA clinical list-serve, which provides regular up-dates from APUA headquarters on antibiotic resistance and use
- Ongoing provision of *APUA Newsletter* and other APUA links following the project completion

### APUA Country Chapters in Africa



### Examples of chapter activities

**APUA-The Gambia:** Conducted the 1st Symposium on Prudent Use of Antibiotics and Control/Prevention of Antimicrobial Resistance. A survey of practitioners' prescribing practices and microbiological assessment is underway.

**APUA-Namibia:** Installed antimicrobial resistance surveillance software (WHONET) at the Namibian Institute of Pathology and PathCare. Chapter leadership is currently assisting the Windhoek Central Hospital with its development of antibiotic policy.

**APUA-Tanzania:** Chapter leadership has published relevant articles—among them, “Surveillance of antimicrobial resistance at a tertiary hospital in Tanzania.”<sup>2</sup>

#### References

- 1 Okeke I & Sosa A. *Africa Health*. 2003. 25(3): p10-15.
- 2 Blomberg B, Mwakagile DSM, Urassa WK et al. <http://www.biomedcentral.com/1471-2458/4/45>

## Ask the Experts

APUA's scientific advisors provide their expert opinions on key questions in diagnostic and antibiotic development and public policy response.

**Q. What is the real medical need for new gram-negative hospital agents in the U.S. and abroad for Enterobacteriaceae, Pseudomonas, and Acinetobacter?**

**A.** There is a definite medical need for new antibiotics for infections by gram-negative bacilli due to lack of effective hospital infection control methods, as well as a paucity of effective antibiotics to treat these infections. While MRSA is the major form of hospital infection, it can be managed with infection control measures and there are several effective new drugs in development. In the UK and in several hospitals in the USA, MRSA infections have been reduced significantly by environmental measures. Similarly, *C. difficile* can be brought under control in some centers, particularly in the UK, using stringent environmental measures and antibiotic restriction policies and there are some new drugs under development (see Table 1, page 7).

Environmental control of gram-negative infections is much more difficult. A variety of different species are causing widespread hospital infections, including *Pseudomonas*, *Klebsiella*, and *Acinetobacter*. Each organism has its particular epidemiology and multiple strains can cause disease in a single hospital. These gram-negative bacilli are ubiquitous in the hospital: sinks, bedpans, beds, and other inanimate objects. Infection control measures are difficult to implement and enforce. Furthermore, few new antibiotics are available in the pipeline for treating these infections. We are now relying on antibiotics from fifty years ago to treat certain highly resistant infections, e.g., colistin and polymyxin.

The gram-negative infection problem is widespread and highly virulent. It poses challenges in all regions of the world due to a lack of good infection control measures and few new effective antibiotics.

*Responder: Sherwood Gorbach, MD Chief, Nutrition/Infection Unit, Dept of Family Medicine & Community Health, Tufts University School of Medicine*

**Q. What is the status of evolving resistance among gram-negative organisms and the accuracy of automated methodologies in detecting these mechanisms?**

**A.** Acquired antimicrobial resistance among gram-positive and gram-negative bacteria isolated from colonized or infected patients is a continuing problem. It is important for clinical laboratories to utilize antimicrobial susceptibility test (AST) systems that allow accurate recognition of resistant bacteria. The options for AST include reference methods such as those described by the Clinical and Laboratory Standards Institute (CLSI) or commercial test systems. Some commercial test systems are similar to reference methods in that results are generated after overnight incubation and some commercial test systems are automated and generate results in as little as 6-8 hours.

Advantages of automated systems include: labor savings for the laboratory; objective interpretation of endpoints and interpretation of results; incorporation of "expert" software that automatically flags unusual results and applies important testing and reporting rules; and capability of interfacing with a laboratory's information system, thereby eliminating potential transcription errors when reports are generated. In an era when there is a shortage of qualified and trained personnel to perform laboratory tests, it is critical that information technology (IT) be utilized to the maximum. The IT component, in addition to testing accuracy and adequate staff training, are essential to the success of any AST system.

One disadvantage of automated AST systems involves cost to the laboratory, which may be offset by cost savings outside of the laboratory if rapid results enable more rapid use of directed antimicrobial therapy. A major criticism of rapid automated AST systems has focused on their inability to detect some types of acquired resistance during their short incubation cycle. This criticism has been voiced since the

inception of rapid automated AST systems back in the 1970s. A number of papers reference several current testing accuracy concerns, and there is also concern that AST systems that were cleared by FDA for use in diagnostic testing several years ago may not adequately detect any new resistance that emerges. Despite these facts, many clinical laboratories in the USA and beyond use rapid automated AST systems for diagnostic testing, and there are limited data to suggest there have been adverse patient outcomes directly related to use of these systems. This may be due in part to the fact that it would be difficult to prove that an AST system is at fault when many factors may contribute to failure of an antimicrobial agent in treating an infected patient.

Clinical microbiology laboratories should be aware of any limitations of the AST system they use, whether it be a rapid automated system or manual reference system. They should also take advantage of all IT features available to help avert potential errors in reporting. Finally, it would seem prudent for the FDA to mandate periodic reassessment of commercial AST systems to ensure they can accurately detect any new resistance that emerges.

*Responder: Janet Hindler, MCLS MT (ASCP) Sr. Specialist, Clinical Microbiology UCLA Medical Center*

### Recent References on Automated AST

1. Brigante GR, Luzzaro FA, Pini B et al. (2007) BMC Microbiol 7:46.
2. Hsieh WS, Sung LL, Tsai KC et al. (2009). APMIS 117:241-7.
3. Juretschko S, Labombardi VJ, Lerner SA et al (2007) J Clin Microbiol 45:1339-42.
4. Kerremans JJ, Verboom P, Stijnen T, et al (2008). J Antimicrob Chemother 61:428-35.
5. Kulah C, Aktas E, Comert F, et al (2009). BMC Infect Dis 9:30.
6. Pitout, JD, Le P, Church DL, (2008). Int J Antimicrob Agents 32:333-8.
7. Richter SS, Howard WJ, Weinstein MP, et al (2007). J Clin Microbiol 45:2863-71.
8. Sader HS, Fritsche TR, Jones RN. (2006). J Clin Microbiol 44:1101-4.
9. Snyder JW, Munier GK, Johnson CL (2008). J Clin Microbiol 46:2327-33.
10. Stone ND, O'Hara CM, Williams PP, et al (2007). J Clin Microbiol 45:340-6.
11. Tenover, FC, Kalsi RK, Williams PP, et al (2006). Emerg Infect Dis 12:1209-13.

**Alliance for the Prudent Use of Antibiotics**  
**75 Kneeland Street**  
**Boston, MA 02111 U.S.A.**

NONPROFIT ORG.  
 U.S. POSTAGE  
 PAID  
 BROCKTON, MA  
 PERMIT NO. 782

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.

Name \_\_\_\_\_

Address \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Areas of Interest \_\_\_\_\_

Telephone \_\_\_\_\_ E-mail Address \_\_\_\_\_


- |   |   |  |
|---|---|--|
| Individual Member*                                  | Supporting Member**                               | Corporate Member                               |
| <input type="checkbox"/> 1 Year Individual (\$45)   | <input type="checkbox"/> 1 Year Supporting (\$55) | <input type="checkbox"/> Associate (\$5,000)   |
| <input type="checkbox"/> 2 Year Individual (\$70)   | <input type="checkbox"/> 2 Year Supporting (\$95) | <input type="checkbox"/> Partner (\$10,000)    |
| <input type="checkbox"/> Student (\$20)             | <input type="checkbox"/> Friend (\$250)           | <input type="checkbox"/> Benefactor (\$25,000) |
| <input type="checkbox"/> Library/Non-Profit (\$100) |   | <input type="checkbox"/> Platinum (\$50,000+)  |

Payment method is in US dollars (please check one):  
 Check drawn on a US affiliate or international money order, payable to APUA  
 Mastercard  Visa

Card Number \_\_\_\_\_

Expiration Date \_\_\_\_\_ Signature \_\_\_\_\_

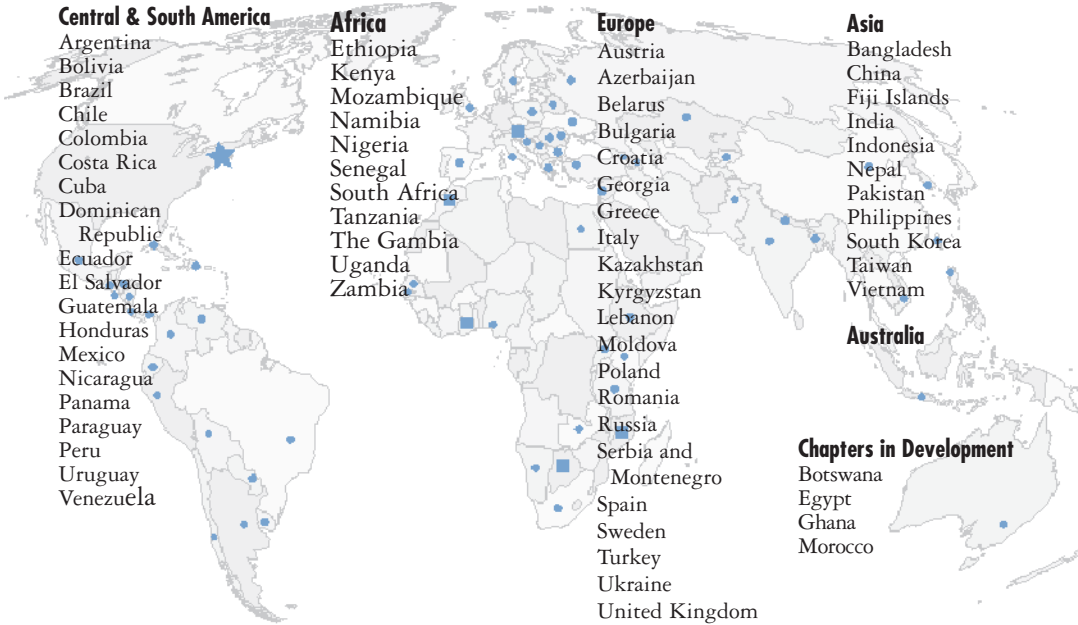
**\*Membership is complimentary in the developing world.**  
**\*\*Supporting memberships sponsor members in a developing country.**  
 APUA is a 501(c)3 non-profit, donations are US tax-deductible.



**APUA**<sup>®</sup>  
ALLIANCE FOR THE PRUDENT USE OF ANTIBIOTICS

**“Preserving the Power of Antibiotics”<sup>®</sup>**

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 60 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.



<p><b>Central &amp; South America</b></p> <ul style="list-style-type: none"> <li>Argentina</li> <li>Bolivia</li> <li>Brazil</li> <li>Chile</li> <li>Colombia</li> <li>Costa Rica</li> <li>Cuba</li> <li>Dominican Republic</li> <li>Ecuador</li> <li>El Salvador</li> <li>Guatemala</li> <li>Honduras</li> <li>Mexico</li> <li>Nicaragua</li> <li>Panama</li> <li>Paraguay</li> <li>Peru</li> <li>Uruguay</li> <li>Venezuela</li> </ul>	<p><b>Africa</b></p> <ul style="list-style-type: none"> <li>Ethiopia</li> <li>Kenya</li> <li>Mozambique</li> <li>Namibia</li> <li>Nigeria</li> <li>Senegal</li> <li>South Africa</li> <li>Tanzania</li> <li>The Gambia</li> <li>Uganda</li> <li>Zambia</li> </ul>	<p><b>Europe</b></p> <ul style="list-style-type: none"> <li>Austria</li> <li>Azerbaijan</li> <li>Belarus</li> <li>Bulgaria</li> <li>Croatia</li> <li>Georgia</li> <li>Greece</li> <li>Italy</li> <li>Kazakhstan</li> <li>Kyrgyzstan</li> <li>Lebanon</li> <li>Moldova</li> <li>Poland</li> <li>Romania</li> <li>Russia</li> <li>Serbia and Montenegro</li> <li>Spain</li> <li>Sweden</li> <li>Turkey</li> <li>Ukraine</li> <li>United Kingdom</li> </ul>	<p><b>Asia</b></p> <ul style="list-style-type: none"> <li>Bangladesh</li> <li>China</li> <li>Fiji Islands</li> <li>India</li> <li>Indonesia</li> <li>Nepal</li> <li>Pakistan</li> <li>Philippines</li> <li>South Korea</li> <li>Taiwan</li> <li>Vietnam</li> </ul> <p><b>Australia</b></p>
---	---	--	--

**Chapters in Development**

- Botswana
- Egypt
- Ghana
- Morocco

★ Headquarters: Boston, MA   ● Chapters   ■ Chapters in Development

APUA, 75 Kneeland Street, Boston, MA 02111-1901, USA • Telephone: 617-636-0966 • Fax: 617-636-3999 • [www.APUA.org](http://www.APUA.org)