APUA Global Network Celebrates Silver Anniversary: Reflections on the Quarter Century Milestone

The year 2006 marks a major milestone for APUA — a celebration of our first quarter century of efforts dedicated toward improving antimicrobial use and curbing antimicrobial resistance worldwide. In the half-decade since our 20th anniversary, drug resistance has continued to permeate the globe, with more and newer multidrug resistance combinations confronting the treatment of bacterial, fungal, viral and parasitic diseases. The world is clearly in need of more accessible first-line agents and discovery of new antimicrobials. APUA has instituted new programs and expanded several ongoing projects over this period of time, including the Global Advisory on Antimicrobial Resistance Data (GAARD) and the Reservoirs of Antibiotic Resistance (ROAR) programs. In 2003 our Shadow Epidemic Executive Report was distributed to public and legislative bodies, presenting the first global snapshot of resistance in the world’s major viral, parasitic and bacterial pathogens. Comprehensive reviews of antimicrobial resistance were published in Clinical Infectious Diseases. Hundreds of individuals have joined our ROAR project list-serv. Since inauguration of this novel collaboration of international investigators, greater attention has focused on commensal bacteria, i.e., those normally unassociated with disease, but which harbor the resistance determinants that can be transferred to more infectious agents. In fact, an important and worrisome development over the past decade is the appearance of many of these commensals.

APUA One-on-Two

The diffuse, yet potent threat of bio-weapons has triggered an “all hands to the pump” response from the biomedical community. In interviews with NIAID and TIGR (The Institute for Genomic Research) leaders we see different, yet integrated, approaches to biodefense.

Tapping the Power of Genomics for Drug Discovery

Interview with Claire Fraser, President The Institute for Genomic Research

Since it was founded in 1992, TIGR has been at the forefront of the genomics revolution, deepening the understanding of life and producing results with wide-ranging applications in medicine, agriculture, energy, the environment and biodefense.

Q: What expectations do you have for creating “model microbial organisms”?
A: I’m not convinced that there is such a thing as a “model microbial organism.” I say that because if one looks at multiple strains of pathogens such as group B streptococci and S. aureus, for

Confronting the Need for New Antimicrobials

Interview with Michael G. Kurilla, Associate Director for BioDefense Product Development DMID, NIAID, NIH, DHHS

Q: What overarching issues in biopreparedness most directly cause you concern?
A: One major issue has been the wholesale exodus of large pharmaceutical companies out of the anti-infective field. There are very few people working on traditional antibiotic development. The antiviral field has collapsed down to HIV, HCV, perhaps HBV, and that’s about it. Very few companies have active programs to come up with a new influenza antiviral — a fact which is independent of biodefense issues, and relates directly to the financing end of the business. It’s very expensive to

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In part, we’ve attempted to stimulate the large companies. We’ve also<br>been supporting the robust biotech industry, which now needs to develop<br>concepts, do product development, and carry it much further down the develop<br>ment pipeline than was required previously. Twenty years ago someone<br>might have come up with a novel screening technology, and that was<br>enough to sell it to a large pharmaceutical. But now, companies want<br>more than “lead compounds,” and they’d like to see it them in pre-clinical studies<br>with some clinical proof of concept. One of our major goals all along has<br>begun to develop the infrastructure to do more product development. The traditional<br>NIH mechanism was to generate extensive basic research with a lot of<br>novel ideas, publish it in the open literature, and then hope that someone else,<br>with other types of funding, picks up the idea and carries it forward. For example, HMG-CoA reductase, which is the rate limiting step in cholesterol<br>biosynthesis, was discovered through<br>interactions. We’re making a wide array of<br>models, particularly biodefense applica<br>tion. A lot of effort has gone into animal models, particularly biodefense applica<br>themselves to the biodefense issue, has reached a point<br>where it’s almost ridiculous not to think of starting with the genome sequence when you approach investiga<br>tion of a new organism. We supported wonderful work looking at multiple group B streptococcal serotypes. If you<br>want to make a vaccine, and target each serotype, you confront a multi-valency<br>issue. The genomics study was able to come up with a combination of just<br>four genetic products that covered all the

Q: How are you addressing the antimicrobial drug deficit problem?
A: In part, we’ve attempted to stimulate the large companies. We’ve also<br>been supporting the robust biotech industry, which now needs to develop<br>concepts, do product development, and carry it much further down the develop<br>ment pipeline than was required previously. Twenty years ago someone<br>might have come up with a novel screening technology, and that was enough to<br>sell it to a large pharmaceutical. But now, companies want more than “lead compounds,” and they’d like to see it them in pre-clinical studies<br>with some clinical proof of concept. One of our major goals all along has<br>begun to develop the infrastructure to do more product development. The traditional NIH mechanism was to generate extensive basic research with a lot of<br>novel ideas, publish it in the open literature, and then hope that someone else,<br>with other types of funding, picks up the idea and carries it forward. For example, HMG-CoA reductase, which is the rate limiting step in cholesterol biosynthesis, was discovered through<br>NIH support. Then Pfizer picked it up and ran with it, making Lipitor®, which generates about $12 billion a year from<br>drug sales. But when someone describes a novel essential bacterial enzyme function,<br>which when knocked out, stops bug growth, we don’t see anyone pursuing that as a target for antimicrobial therapy. So we’ve concentrated on infra<br>structure for assay development, high throughput screens, compound acquisition and collection. We have resources now to do the pre-clinical toxicology, and other non-clinical safety studies. We also have some formulation capability. A lot of effort has gone into animal models, particularly biodefense applications. We’re making a wide array of<br>resources available so that individuals and companies interested in moving their concepts and products along the pipeline will have options to build equity into their intellectual property and hopefully become more attractive<br>to large pharmaceutical companies for further development.

Q: How have genomics and gene function analysis fit into this landscape?
A: Sequencing, which is beyond a biodefense issue, has reached a point where it’s almost ridiculous not to think of starting with the genome sequence when you approach investigation of a new organism. We supported wonderful work looking at multiple group B streptococcal serotypes. If you<br>want to make a vaccine, and target each serotype, you confront a multi-valency issue. The genomics study was able to come up with a combination of just<br>four genetic products that covered all the

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Known serotypes. This was a great example of how genomics could drive a rational approach, rather than a sort of traditional brute force methodology.

Q: What might be the role of a “model organism” for study?
A: Carl Nathan has an interesting tale to tell about the Krebs cycle in *Mycobacterium tuberculosis*. What we read in the biochemistry and microbiology textbooks is largely based on an *E. coli*-oriented world. And the assumption is that what *E. coli* does, all other bacteria also do. It’s turning out that *E. coli* is just one particular example of how the microbial world approaches specific metabolic functions. It may, in fact, not be the dominant way, but it’s what got the most published data. As is typical, people always look where the light shines best. *E. coli* is the best studied and therefore has the most science. Consequently, it justifies continued investigation. Biodefense research has actually shed light on many organisms that have been largely ignored. Anthrax, unless you were specifically doing lethal factor, or protective antigens attracted very little research effort to dissect its biology. But as investigation has progressed, particularly with genomic sequences, we find out that there is considerably more diversity here — which opens a lot of doors to interesting scientific research.

Q: In the war against bioterrorism is antimicrobial resistance a pressing threat?
A: There are two issues here. First, antimicrobial resistance is a naturally occurring thing. It is unfortunate, but the use of antimicrobials brings with it antimicrobial resistance. We know it will continue to be a problem for the medical community. For most new therapeutics, clinicians jump to use them. They're advantageous because you take them less often, there are fewer side effects, and they're more efficacious. When a company comes out with a new antimicrobial, the first thing the infectious disease community says is “We should not use this.” We need to recognize that while no one is advocating indiscriminate use of antibiotics, concerns over antimicrobial resistance do not warrant failure to use under any and all conditions. Antimicrobial resistance will occur over time, and we will have to develop another drug for a particular condition, because no drug will last forever.

Secondly, nations have, or continue to develop, bioweapons programs that attempt to defeat our existing strategies to combat these threats. The simplest way to accomplish this is to engineer in antimicrobial resistance.

Q: What might be the role of a “model organism” for study?
A: The next generation of anti-infective therapy involves identification of host targets. If you inhibit or impair that host target, infection cannot proceed. The pharmaceutical industry, 99% of the time, uses this approach—but for noninfectious disease. The targets relevant to infectious disease are still being defined. We see this most commonly in the virology field. There are particular host cellular functions that are absolutely required to initiate entry of the virus into the cell, for the virus to complete its replication cycle, or for the virus to be able to exit the cell. Another category is cellular antigens, which normally reside in the cell. But upon viral infection, they travel to a different location and now appear on the cell surface, and so become accessible to something like a monoclonal antibody floating around in the blood. We are seeing a number of these targets being pursued, though none has developed to an advanced stage as yet. An example would be the host protein, TSG 101, which is an intracellular antigen. When a virus begins cellular egress, the process of viral encapsidation causes this antigen to translocate to the cell surface. And so we've seen some evidence where both HIV and Ebola can be blocked from producing a viral infection by using a monoclonal antibody against TSG 101. Another example is cisteinal protease inhibition by small molecules, shown by Jim Cunningham in Boston. Two other viral families have also been shown to use cisteinal protease, which gives hope for broad-spectrum applicability.

Dr. Kurilla spoke with APUA Communications Manager Christopher Spivey.

“Biodefense research has actually shed light on many organisms that have been largely ignored.”
Taiwan Confronts Antibiotic Resistance
Po-Ren Hsueh, M.D.
Departments of Laboratory Medicine and Internal Medicine
National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan; Coordinator, APUA-Taiwan

Taiwan has one of the highest levels of antimicrobial resistance in the world. In particular, the resistance of respiratory pathogens (Streptococcus pyogenes, Streptococcus pneumoniae, and Haemophilus influenzae) to macrolides is of great concern.1,6 Prior to 2000, its prevalence among S. pneumoniae (80-90%), S. pyogenes (40-70%) and H. influenzae (30-50%) was remarkably high (40-70%).1,5,6 Since 1996, Taiwan has become one of the epicenters for pneumococcal resistance to both penicillin (60-80%) and macrolides (80-90%).1,3

To control and alleviate the growing problems of antimicrobial resistance, many measures have been instituted, including more-rigorous enforcement of pharmacy dispensing (starting in 1997) and educational programs on appropriate antibiotic use for physicians and patients (starting in 1998).2,3 Furthermore, beginning in February 2001, an additional government restriction was added to deny reimbursement (through the National Health Insurance (NHI) system) for antimicrobial treatment of acute upper respiratory tract infections which demonstrated no evidence of bacterial involvement.2,3 These measures resulted in a decrease in antimicrobial agents in the treatment of all types of infections, as well as respiratory tract infections of ambulatory patients (Fig 1).3 Data obtained from IMS Health (International Marketing Service, Taipei, Taiwan) have demonstrated a 52% decrease in macrolide consumption (from 0.629 DDD [defined daily doses/1000 inhabitants per day] in 1999 to 0.301 DDD in 2003). A 16% decline in rates of penicillin resistance in S. pneumoniae isolates (from 25% in 1998-99 to 9% in 2001) was associated with a 46% decrease in total penicillin and other cephalosporin usage.4,3 A directional relationship was observed between the decline in erythromycin consumption and the decline in erythromycin resistance in S. pyogenes (46% in 1999 vs.17% in 2003)5, and azithromycin resistance in H. influenzae (31% in 2000 vs. 0% in 2003).4 However, erythromycin-resistant S. pneumoniae continued to increase from 80.2% in 1999 to 92% in 2003 (Fig 2).4 With continued antibiotic restriction, the rates of erythromycin resistance in S. pyogenes and H. influenzae and penicillin resistance in S. pneumoniae remained low between 2004 and 2006. However, erythromycin resistance remains high at >90% (unpublished data obtained from SMART [Surveillance of Multicenter Antimicrobial Resistance in Taiwan]). The rates of decline in resistance appear to be slower than rates of resistance emergence, and appear to vary with different classes of agents and different species of bacteria. Appropriate use of antimicrobial agents appears to be the cornerstone for limiting the emergence and spread of drug-resistant pathogens. Continuous enforcement and adherence to governmental policies designed to limit unnecessary use of antimicrobial agents and active surveillance of antimicrobial resistance through a nationwide system (i.e., SMART) are warranted. The adoption of reimbursement restrictions to limit the inappropriate use of antimicrobial agents in countries with national health insurance programs may be an effective method for controlling antimicrobial resistance.

Fig. 1. Frequency of macrolide resistance in Taiwan pathogens

Fig. 2. Macrolide resistance in respiratory pathogens

References
example, you find that each strain contains a set of unique genes and that the collective number of unique genes associated with any species (the pan-genome) can be very large. In collaboration with Chiron Vaccines, we completed a study of eight isolates of group B Strep. We carefully selected these isolates to represent the major serotypes associated with disease worldwide. We anticipated we would define the full gene complement associated with group B Strep, and be able to identify genes that were conserved across all strains, and others that were somewhat more variable. When we did mathematical analysis of the data, it suggested we could go far beyond 8 isolates, and still find new genes associated with group B strep.

Q: Now, is the potential number of genes associated with this, or any species, infinite?
A: I'm not convinced it is, but the number is very large in many cases. I think E. coli is one of the best examples of the kind of diversity that's present in the microbial world. When you look at two different strains you see that they can differ in gene content by as much as 30%. That's an enormous difference. Over time, however, we may begin to get a much better understanding of what types of genes one expects to find associated with E. coli. This concept is critically important in the area of microbial forensics, for which we need to understand the relationship between closely related species. We will be required to look at nearest neighbors of organisms of interest, both pathogens and non-pathogens.

Q: Do the group B strep data point to a need to better understand horizontal gene transfer?
A: Absolutely. The more we look, the more examples of such transfer accumulate — and not just single genes, but multiple genes, pathways that are linked, operons, etc. Many times organisms have been targeted for sequence analysis because some aspect of their biology is of great interest, but when projects are completed and we have to try and explain that interesting biology based on gene content we are at a loss because there are numerous genes in every genome that encode proteins of unknown function. When you stop to think that 25% - 40% of genes in any microbe encode hypothetical proteins — that represents a lot of biology still to be determined.

When you stop to think that 25% - 40% of genes in any microbe encode hypothetical proteins — that represents a lot of biology still to be determined.

Q: Does any single approach stand out for gene functional analysis?
A: We need more emphasis on large-scale approaches. For example, microarray analysis is helpful because it tells you when a gene is expressed, and you can make some inferences about potential function based on this information. But that still leaves a lot to be done. Sequencing and bioinformatics alone, are never going to be enough; however, they can narrow down a long list of genes to a subset, that might be responsible for phenotypic differences between strains. Another large scale approach is the Protein Structural Initiative, PSI II, run by NIGMS, which is working to take a very high throughput approach to protein structure determination. That's going to be very helpful, but knowing a protein fold does not necessarily reveal function. Another approach that could be considered would be to select some small number of bacterial species, and put a concerted effort together that involved small and large labs around the world. By a target date the goal might be to understand the function of all of the proteins encoded in a particular genome. Investigators could approach this question many different ways. I'd be very excited to see a targeted effort on some limited number of organisms, probably both pathogens and non-pathogens, to see what we could do, in terms of determining function.

Q: Has genomics fit well into drug discovery for antimicrobials?
A: It's been disappointing to me that the availability of pathogen genome sequence information, which has helped to identify potential targets, has not been more fully exploited in the design of novel antibiotics. It's not the panacea to this problem — I don't for a second want to imply that it is. But it's very unfortunate that the economics of drug development are such that there's not sufficient financial incentive for industry to go after further development of novel targets. I think we had all naively hoped that might happen ten years ago, when microbial genomics really started.

Q: In biopreparedness, is transparency and openness still the best defense?
A: Yes, but that approach comes with risk, and that risk is very difficult to quantify. But we can't deal with information in a more limited way, and still expect the same level and amount of research. The information on many of the threat agents has already been out in the public domain for quite awhile. It's an international issue — the technology has spread around the world to generate, or regenerate, this information. United States guidelines and regulations need to acknowledge this fact.

Dr. Fraser spoke with APUA Communications Manager Christopher Spivey
sals as pathogens, such as *Staphylococcus epidermidis* and *S. aureus* that cause skin diseases and septicemia, *E. coli* and enterococci associated with systemic and urinary tract problems, and certain non-invasive species of *Hemophilus* and streptococci involved in respiratory tract infections.

APUA was created as an alliance of individuals, groups and countries with a common concern and vision. In the last five years alone, we have birthed 20 new country-based chapters, bringing the total to 56, more than half of which are in the developing world. Importantly, we have shouldered the difficult challenge of chapter-building in the continent of Africa. We have also attracted new members from broader disciplines, including not only microbiology and infectious diseases, but also public health policy, epidemiology, ecology and economics.

What are the fruits of this growing alliance? First, antimicrobial resistance has become a priority focus for organizations such as WHO, CDC, FDA and USAID. We now see a better understanding among physicians and the need to respect our valuable antimicrobial agents. There is a broader comprehension among physicians and patients that antibiotics are not always to be expected or needed. Finally there is increased reluctance by the prescriber to dispense antimicrobials unless absolutely necessary. Encouraged by this increased awareness, APUA now seeks to develop tools and implement concrete interventions that can significantly reduce morbidity and mortality.

APUA’s mission remains steadfast — to improve and strengthen society’s defenses against infectious diseases through improved antimicrobial availability and use. We have extended our focus beyond bacteria to include other microbial agents, namely viruses, parasites and fungi.

By building coordinated global partnerships, APUA has laid the groundwork for a more aggressive campaign to curb resistance and improve access to appropriate antibiotics. APUA counts on its national and international partners and countrywide members to work with us in our continuing efforts to achieve our goals. As we enter the next quarter century, we recognize the vital role of our partners: our chapters, public health organizations and corporate sponsors supporting the mission of the Alliance. Our professional, expert staff has grown and crafted new initiatives to advance our mission. We thank all members and friends of APUA for your past support and look forward to working with you as we encounter new opportunities to conserve and build an antimicrobial armamentarium that will meet the infectious disease challenges worldwide.

Stuart B. Levy
President, APUA

APUA members are cordially invited to attend the Anniversary Members’ Reception at the Annual ICAAC meeting. (see p. 7)

APUA’s commitment: Global ID resources

This edition of the APUA Newsletter marks 23 years of continuous publication as a uniquely objective source of information to guide antimicrobial policy and clinical practice around the world. The focus of this edition is on biopreparedness. This new threat compounds the problems associated with the natural evolution of drug-resistant microbes and related diminution of the effectiveness of antimicrobials. As we move into our next 25 years, APUA, along with its affiliated chapters and other public health collaborators, stands ready to face these challenges. Based on current demographic trends, we will be operating in a future full of new opportunities for diseases to spread. On the bright side, this era will also present new opportunities for advances in the technology and science required to meet these challenges. Larger investment by governments worldwide and more coordinated action by all stakeholders are key to keeping ahead of these threats.

Since its founding in 1981, APUA’s mission has remained remarkably relevant, yet adaptable to emerging public health problems. The goal of conserving the effectiveness of lifesaving medicines has become even more timely as global aid projects have accelerated distribution of medicines into the least developed nations. These countries bear the greatest burden of infectious diseases; however, they lack adequate financial resources, infrastructure and health personnel to ensure medicines are used effectively. To address this crisis, APUA has accelerated its chapter development program in low-resource countries, building grassroots organizations to conduct the education, research and advocacy programs needed to contain antimicrobial resistance. Working alongside WHO and other partners, APUA’s chapter network in 56 countries is a global force working to ensure that antimicrobials are accessible and used wisely. While we continue to address the major scourges of HIV, TB and malaria, we advocate for increased attention to acute bacterial infections—the leading cause of morbidity and death for children
under 5 in developing countries.

APUA will continue to play a leadership role in addressing politically sensitive issues, just as our FAAIR project convened reluctant stakeholders to develop a national consensus concerning misuse of antibiotics in agriculture. Of particular concern now are the need for equal access to essential medicines and the need to foster innovation in drug and diagnostics development. To begin this debate, APUA is convening the first World Congress on December 11 and 12 to consider legislative incentives and public-private initiatives to spur industry in the development of new antimicrobials, diagnostics and vaccines. Building on its ROAR and GAARD projects, APUA will continue to advocate for increased resources for basic and applied scientific research that helps inform interventions. Using a multidisciplinary approach, we will continue to promote needed research which informs clinical interventions. We hope you will join us on September 27 at ICAAC for an interactive symposium on this topic, at which top population biologists will share their latest research findings and implications for the treatment of HIV, TB and acute bacterial infections.

Many thanks to our founder, Dr. Stuart Levy for his foresight and leadership, and to APUA staff members for their dedication. Together, with our esteemed global, national and local partners, we will continue to make the case for increased and more coordinated use of our limited resources to hasten control of infectious diseases over the next 25 years.

Kathleen T. Young, Executive Director

APUA Staff

Stuart B. Levy, M.D., is President and founder of APUA, and a past president of the American Society for Microbiology. He is currently Professor of Medicine and Molecular Biology/Microbiology at Tufts University School of Medicine.

Thomas F. O’Brien, M.D., Vice President of APUA, is an infectious disease specialist and microbiologist who has helped develop the WHONET surveillance program at the Brigham and Women’s Hospital.

Kathleen T. Young serves as Executive Director of APUA, overseeing development, implementation, and evaluation of APUA’s operations and programs. Ms. Young was formerly a Director of Planning at the Massachusetts Office of Health Planning and the Massachusetts Hospital Association.

Susan Foster, Ph.D., Director of Public Policy and Education, has a background in pharmaceutical policy and has worked as an economist in Geneva with the WHO Essential Drugs Programme and with the World Bank.

Christopher Spivey, M.A., Manager for Business Development and Communications earned a master’s degree in communication from Christchurch Technical College in New Zealand. He co-founded the Human Proteome Organisation (HUPO).

Michael Feldgarden, Ph.D., is the Research Director and the P.I. for the ROAR project. Dr. Feldgarden received his Ph.D. in Biology from Yale University where he researched the evolution of resistance to colicins.

Bonnie Marshall, M.T., Research Scientist for ROAR and editorial consultant to the APUA Newsletter, serves as a Research Associate in the Department of Molecular Biology and Microbiology at Tufts University School of Medicine.

Amelie Peryea, B.S., the Program Manager for the ROAR project, received APUA Staff continued on page 8

The Alliance for the Prudent Use of Antibiotics (APUA) 25th Anniversary Symposium

ICAAC 2006, San Francisco, September 27th, 2:00 PM

REVERSING ANTIMICROBIAL RESISTANCE: Population biology suggests different resistance management strategies for different pathogens

• Convener: Stuart B. Levy, President, Alliance for the Prudent Use of Antibiotics, Tufts University School of Medicine, Boston, MA
• Anticipating resistance management problems: Examples from Staphylococcus aureus and nosocomial Enterobacteriaceae. Thomas F. O’Brien, Vice President, Alliance for the Prudent Use of Antibiotics, Brigham and Women’s Hospital, Boston MA.
• The effects of antiretroviral therapy on mixed populations of resistant HIV viruses. Miguel E. Quinones-Mateu, Cleveland Clinic, Cleveland, OH.
• Transmission dynamics of drug-resistant tuberculosis. Megan Murray, Harvard School of Public Health, Boston, MA.
• Lessons from the Intercontinental spread of pyrimethamine-resistant malaria from southeast Asia and the dissemination of its alleles across Africa. Cally Roper, London School of Hygiene and Tropical Medicine, London, U.K.
• Major clones of penicillin-nonsusceptible pneumococci, their serotype-switch variants, and their variable acquisition of other resistance genes. Bernard Beall, Centers for Disease Control, Atlanta, GA

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a BS in Microbiology from the University of Washington. She has worked on research projects at several large universities.

Aníbal Sosa, M.D., APUA’s Project Director for International Chapter Programs and Clinical Advisor, has a technical background as a clinician, microbiologist, and infectious disease specialist, and considerable experience managing public health programs. Dr. Sosa’s career has included managing HIV/AIDS services.

Mike Hricz, M.P.A., Manager for Contract Compliance and Strategic Planning, has over ten years experience in program design, management and implementation. He served as program manager at the Harvard Institute of International Development.

Karrie-Ann E. Toews, M.P.H., is an epidemiologist for the ROAR project. She received her Master’s in Public Health degree from Tufts University and has worked as an epidemiologist at the State Laboratory Institute of Massachusetts.

Stephanie Boyd, M.A., is APUA’s Ecology Program Coordinator. She is a PhD candidate in cognitive anthropology at SUNY Buffalo, and was an educator at the Wilds, a wildlife conservation and research facility.

Katherine Corso, B.S., is the Project Assistant for the ROAR project. She received a BS and is currently working on a Masters in Public Health at Tufts University.

Katherine Gillespie, B.A., is a Public Health Program Assistant, supporting the International Chapter program, the ROAR project, and development. She has a BA in International Affairs and Global Public Health from the George Washington University.

Leakna Ung, B.A., is the Executive Special Project’s Coordinator, supporting the Executive Director in development and partnership building. She is currently working on her Masters in Biology at Harvard University.

Ronald Lanoue, M.B.A., is the APUA Operations Manager, implementing systems to support program activities. Mr. Lanoue has held senior administrative positions with various medical provider organizations.

Antimicrobial Pipeline Failure: the case of Acinetobacter baumannii

Dr. Michael Feldgarden, APUA Research Director

Acinetobacter baumannii is an emerging bacterial pathogen that causes severe hospital outbreaks worldwide. It gained popular notoriety in the U.S. after a severe A. baumannii outbreak in U.S. military hospitals. These recent outbreaks are particularly troubling because roughly 35% percent of isolates were susceptible only to imipenem, and four percent were resistant to all drugs tested. Outbreaks of A. baumannii have also been prevalent in France, Israel, Japan, Korea, and Turkey. While Acinetobacter infections have been rising in the U.S., so far, there do not appear to be epidemic outbreaks in the U.S. That may change, however, as U.S. troops return from the Gulf Region.

A. baumannii are often multidrug resistant, with several widely distributed strains possessing extended-spectrum, ß-lactamas. Genome sequencing of a French epidemic clone “AYE” revealed that this multidrug-resistant clone has over 50 resistance loci, most of which are clustered in an 86kb region resembling a pathogenicity island. This raises the spectre of a single gene transfer event converting other Acinetobacter or even other species to a multidrug-resistant phenotype. While data are limited, these isolates also appear to be metal resistant, which may provide a selective advantage for resistance outside of the clinical setting and within the environmental reservoir. The long-term prospects for treatment of Acinetobacter are cause for concern. For MDR infections, only tigecycline is currently being recommended for treatment; it is unlikely to be used in children because of concerns about toxicity. An
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IDSA taskforce was unable to identify any drugs in the development pipeline to treat A. baumannii and it concluded that “A. baumannii is a prime example of a mismatch between unmet medical needs and the current antimicrobial research and development pipeline.”

References:

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APUA Unveils New Website

The Reservoirs of Antibiotic Resistance (ROAR) project, funded by the National Institute of Allergy and Infectious Diseases and coordinated by APUA, is an unprecedented effort to improve scientific understanding of the role of commensal bacteria in the spread of antibiotic resistance. To optimize access to the ROAR Isolate Database, a new website was developed this spring. The new ROAR website at www.ROARproject.org went live on April 1, 2006. Content includes summaries of past and current ROAR-funded projects, links to ROAR publications, and mechanisms for accessing the ROAR Isolate Database (see http://db.roarproject.org/ROAR/account/databases.htm). The ROAR Database is currently accepting commensal isolate data. Interested investigators should contact ROAR staff (see below) for submission guidelines.

In 2006, ROAR initiated three projects that use phylogenetic methods to better understand the linkage between virulence and antibiotic resistance (see http://www.roarproject.org/ROAR/html/projects.htm). These projects will serve to better describe commensal organisms and illustrate the continuum between non-pathogen and pathogen with respect to antibiotic resistance.

Dr. Betsy Foxman at University of Michigan, will develop a rapid, high-throughput technique, probe hybridization array typing (PHAT), to genotype E. coli. This will allow fine-scale mapping of evolutionary events, including the acquisition of resistance genes.

Dr. David Gordon of the Australian National University is examining a collection of commensal E. coli isolates exposed to varying levels of antibiotic selective pressure (animals in tropical rainforests versus mammals in high-intensity agricultural settings). This project will assess resistance gene transfer among these isolates, compare virulence in sensitive and resistant isolates, and attempt to correlate the mechanism of tetracycline resistance with strain phylogeny and isolate host.

Drs. Antoine Andremont, David Skurnik, Sylvain Brisse, and Erick Denamur will examine a collection of commensal E. coli isolates exposed to varying levels of antibiotic selective pressure. This project uses multi-locus sequence typing to assess resistance gene transfer among these isolates, compare virulence in sensitive and resistant isolates, and correlate the mechanism of tetracycline resistance with strain phylogeny and isolate host. For more details on these projects, see http://www.roarproject.org/ROAR/html/projects.htm.

APUA Research Director and ROAR Principal Investigator Dr. Michael Feldgarden presented a poster at the 106th American Society for Microbiology General Meeting in Orlando, Florida entitled “The analysis of integrated antimicrobial susceptibility datasets: a case study using the ROAR database.” In addition, Dr. Feldgarden presented a talk entitled “The Determinants of Antibiotic Resistance Phenotypes in Enterococcus: Possible Evidence of Equilibrium and Non-Equilibrium States” at the Evolution 2006 meeting on Monday, June 26.

For more information or to join the ROAR Scientific Network listserv please see www.ROARProject.org or contact Amelie Peryea (amelie.peryea@tufts.edu).

APUA Website “Top-ranked”

A July 1 invited article in Clinical Infectious Diseases categorizes the APUA website as “high interest” to target user groups and rated it “excellent” for ease of navigation and overall quality. Authors S. Harbarth and S. Emonet performed exhaustive World Wide Web searches for antimicrobial resistance information and evaluated sites for the quality of information provided to patient and consumer groups. The APUA site was one of two sites noted to be “the most user-friendly for lay persons, scientifically correct, and concise among the countless Web sites available.” For more details on their evaluations, see Navigating the World Wide Web in Search of Resources on Antimicrobial Resistance in Clinical Infectious Diseases 2006;43:72-78.

APUA Launches Consumer Education Campaign

APUA has launched a new research and public education campaign entitled...
Antibiotics and the Consumer: Perceptions and Use. The project, funded by an unrestricted educational grant by Pfizer Incorporated, brings together an advisory board of experts from the fields of clinical medicine, managed care, epidemiology, and health communications to develop a national survey on consumer antibiotic use patterns.

Patients use antibiotics incorrectly in a variety of ways. They may request antibiotic prescriptions for viral infections, stop taking antibiotics before the prescription is finished, share antibiotics with friends and family, or completely avoid taking them even when they are necessary. The *Antibiotics and the Consumer* project aims to learn more about the prevalence of these practices, and will also move beyond the goal of simply measuring rates to examine the driving forces behind these behaviors. The advisory panel is designing a survey that will probe consumers’ beliefs, concerns, and past experiences regarding antibiotic use and general health care. The survey will also examine consumer responses to existing messages and guidelines for proper antibiotic use, with the goal of identifying potential new ways of targeting at-risk populations and refining messages to be more effective.

The survey will be fielded by Links Media, and will include 1,000 English-speaking respondents from across the United States. With the collaboration of Chamberlain Healthcare Public Relations, survey results will be used to launch a media campaign. Results will also be translated into educational messages for a variety of audiences, with the dual aims of more effectively educating consumers on the relevant issues and of educating physicians about communication methods that can facilitate this outcome. For more information on this project, visit [http://www.tufts.edu/med/apua/Research/antibiotics_consumer.htm](http://www.tufts.edu/med/apua/Research/antibiotics_consumer.htm) or contact Stephanie Boyd at Stephanie.Boyd@tufts.edu.

**APUA Partnership to Further Research on the Clinical and Financial Implications of Antibiotic Resistance**

BioMérieux has committed a sizeable unrestricted education grant to support APUA in an independent research and educational project entitled, “Measuring the Economic Burden of Drug Resistance in the U.S.”

This research project is expected to produce the first in-depth analysis of the burden of resistant infections in U.S. hospitals and encourage cost-effective interventions to control the problem. The BioMérieux grant will support APUA in establishing a think tank of national and international experts from the fields of microbiology, clinical medicine and economics. Their findings will be offered for publication in peer-reviewed journals and serve as policy guidance for legislators, provider groups, and HMOs.

Resistance to antibiotics has become a serious concern for hospitals. The selective pressures caused by inappropriate antibiotic use jeopardize both the effective treatment of bacterial infections and the hospital’s bottom line. Quantifying the economic cost of antibiotic resistance is therefore of vital interest to healthcare payers, administrators and clinicians.

Determineding the cost of resistant infections is extremely complex, involving diverse disciplines and a variety of hospital departments,” explained Kathleen Young, Executive Director of APUA.

“We are pleased to partner with BioMérieux on this research project as we strive to document the cost of drug resistant infections in the U.S. and to explore measures needed to improve antibiotic use,” said Stuart B. Levy, M.D., president, APUA and professor of molecular biology and microbiology at Tufts University School of Medicine.

“BioMérieux is delighted to join forces with the APUA through support of this critical research on the clinical and economic implications of antibiotic resistance,” said Eric Bouvier, BioMérieux North American president and CEO.

“This issue is even more critical today given the numerous pilot programs that link reimbursement and quality measures, such as programs like Pay for Performance. We feel that microbiology data are a critical component in better patient management and we are pleased to offer our support to such an outstanding organization as the APUA,” continued Bouvier.

The 18 month study will conclude in June 2007 with recommendations which will be cited in several media outlets and peer reviewed scientific journals. The National Scientific Advisory Board assembled for this project includes: Dr. Jennifer Brower (RAND), Richard Dew (SIDP), Dr. Sara Cosgrove (Johns Hopkins University Hospital), Dr. Joseph DiMasi (Tufts Center for the Study of Drug Development), Dr. David Howard (Emory University), Thomas O’Brien (VP of APUA), Dr. Douglas Salvador (IDSA), Dr. Douglas Scott (CDC), John Cai (MA, Health & Human Services), Dr. Susan Foster (APUA) and administrator Michael Hricz of APUA.
Household Hygiene Project

On May 17th, the advisory board of APUA’s Hygiene for a Healthy Household project convened for the first time. The new initiative is funded by an unrestricted grant from The Clorox Company. The board includes representatives from the fields of clinical medicine, social epidemiology, public health, risk analysis, and microbiology. This diversity of expertise facilitated productive conversation on the relevant issues and participants narrowed the initiative’s focus, working to identify household areas that represent the greatest burden of risk in infection transmission. The next meeting, scheduled for September 19, will focus on the further clarification of guidelines and the identification of potential audiences that can be reached in educational messages. For more information visit http://www.tufts.edu/med/apua/Research/hygiene.html or contact Stephanie Boyd at Stephanie.Boyd@tufts.edu.

New Chapter: APUA-Namibia

Dr. Anibal Sosa, Director of APUA International Chapter Network, visited Namibia and South Africa in February, 2006 to meet with government officials of both countries and finalize development of APUA’s newest chapter, APUA-Namibia. The chapter is formed by Mrs. Dawn Pereko, B. Pharm, Chapter President, Mrs. Joyce Namuhuja, Mr. Sherif Moustafa, Dr. Braum van Gruwen and Dr. Alec S. Bishi.

National Antibiotic Resistance Surveillance Forum

On February 25, 2006, the Sixth NASF Meeting convened in Johannesburg, South Africa, led by Forum chairperson, Dr. Olga Perovic. Invited guest, Dr. Anibal Sosa (APUA), spoke on the APUA Global Chapter Network.

EU Workshop on AMR

On June 7-9, 2006, an EU-sponsored Workshop on International Collaboration on Antibiotic Resistance, organized by the European Commission Research Directorate-General, was held in Brussels, Belgium. APUA Staff members, Drs. Anibal Sosa and Susan Foster participated, along with many experts from around the globe. The objectives of the “Burden of Resistance” workshop were: a) To explore, critically examine, and summarize available knowledge regarding burden of antibiotic resistance in relation to major hospital and community infections in health and economic terms; b) To map known ongoing projects regarding different aspects of burden of antibiotic resistance; c) To map the burden of resistance in relation to innovation in the field of antibacterial treatments and identify priority gaps in innovation; d) To develop fact sheets on current knowledge in relation to burden of antibiotic resistance; and e) To produce a research priority agenda for international collaboration in the field for the next three years.

SAIDI (South American Infectious Disease Initiative)

The USAID’s Regional Bureau for Latin America and the Caribbean has organized the “South American Infectious Disease Initiative” (SAIDI) to develop sound strategies to contain the advance of AMR in Peru, Bolivia and Paraguay. The APUA-Paraguay chapter, led by its President, Dr. Wilma Basualdo, organized a symposium entitled “Prudent Use of Antibiotics and Control and Prevention of Resistance.” The event took place on May 6, 2006 at the auditorium of Laboratorios Lasca with more than 200 health professionals in attendance.

APUA-Bolivia


APUA-Philippines

APUA congratulates Dr. Jaime C. Montoya, who has been elected the new APUA-Philippines chapter coordinator.

APUA-Nepal

Monica Raymond, MPH, MS, RN, and APUA Scientific Consultant, visited the APUA-Nepal Chapter in June, 2006 and interviewed chapter leader, Prof. K. K. Kafle, with whom she exchanged ideas on reducing the incidence of antimicrobial resistance and improving treatment outcomes in Nepal. Topics of discussion also included recent Chapter activities, the anticipated approval of treatment guidelines by the Minister of Health, and plans for dissemination of the latter to selected districts.
Alliance for the Prudent Use of Antibiotics  
75 Kneeland Street  
Boston, MA 02111 U.S.A.

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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*Membership is complimentary in the developing world.

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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.

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 numerous foreign affiliated 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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