New Data and Resources Advance Study of Reservoirs of Resistance (ROAR)

The Reservoirs of Antibiotic Resistance (ROAR) Project was initiated by APUA in 1997 to foster global research and compile genotypic and phenotypic information on commensal bacteria that serve as potential reservoirs of antibiotic resistance determinants for human pathogens. This multi-year cooperative agreement with the National Institutes of Allergy and Infectious Diseases represents the first systematic effort to compile and disseminate information on reservoir bacteria and examine the flow of resistance genes from commensals to pathogens. The occurrence of antibiotic resistance in commensals may serve as a marker or predictor of emergence in pathogens.

The ROAR-subcontracted Consortium Studies worked in diverse areas, reflecting the enormity of the initiative’s subject, but developed insights with implications for the whole field (Table p.3).

As a result of funded consortium study output as well as other independently solicited data, there are a total of 14 data sets in the ROAR isolate database representing 3352 isolates: 2892 E. coli, 169 Streptococcus, 182 Staphylococcus, 35 Enterococcus, 33 Neisseria, 32 Lactobacillus, and 11 other.

More recently, the concept of developing a standardized method (GETEC, Genome-enabled Typing of E. coli) was conceived and developed at APUA. Multilocus sequence typing data generated by the ROAR project (Dr. D.M. Gordon) are serving as the basis of a collaborative effort between APUA and the Broad Institute’s Microbial Sequencing Center. A white paper has been submitted for review to NIAID to sequence 103 commensal E. coli genomes in order to create a community resource that will provide the foundation for a broad range of research interests including, but not limited to, the genetic mechanisms of pathogenesis, antibiotic resistance, and host adaptation. This project will also enable the determination of the signatures of emerging infectious disease. The resulting standardized method, attributable to ROAR for its initiation and conceptualization, will be a major contribution to the field.

Open Source Resources Now Available to the Scientific Community

ROAR website databases

The ROAR interactive website (www.ROARproject.org) with detailed information on resistance phenotypes and genotypes of reservoir bacteria is open to the public and scientific community with the two linked, quality-controlled databases administered online in a password-protected area: 1) a uniquely synthesized and annotated library of references on antibiotic resistance in commensal flora, and 2) an isolate database of ROAR PROJECT continued on page 2

Annual APUA Members’ Reception

Monday, October 27 at ICAAC

Join APUA staff, members, and friends at the Annual APUA Members’ Reception and Leadership Award Ceremony on Monday, October 27, 2008, at Clyde’s of Gallery Place in Washington, DC from 5:30 - 8:00 pm.

At the reception, APUA members and partners will have a chance to network with international leaders while honoring the SWAB and WIP teams for their model surveillance and infection control programs (see p.7). Please RSVP to jessica.respucci@tufts.edu.

For more information, see www.swab.nl and www.wip.nl and the next issue of APUA Newsletter.

Antimicrobial Resistance in India: Current Scenario

Balaji Veeraraghavan MD, PhD
Christian Medical College and Hospital, Vellore, India
Anne Kane MD, Tufts Medical Center, Boston.

Infectious disease is the most common ailment in India. Every practitioner, irrespective of specialization, will spend a major portion of his/her time treating infections. In India, antimicrobial resistance is a major problem, contributing to increased treatment costs, hospital stay, morbidity and mortality. While resistance is more common among gram-negative than gram-positive organisms, the precise extent of the problem is not known since the majority of the published reports derive from individual units or hospitals. Very few multi-center studies have been reported, and no local or national surveillance programs exist. This report compiles and evaluates the available data in order to present the best estimate of the resistance problem in selected common pathogens from India today.

Staphylococcus aureus

Following the very first report of MRSA prevalence in 1988 (6.9%),1 MRSA fre-
ROAR PROJECT continued from page 1

solicited genomic data from multiple sources to facilitate cross data-set analyses.

The ROAR Literature database library currently contains over 1800 citations with 1100 annotated articles focused specifically on resistance in commensal bacteria. Annotations are ongoing and consist of 53 possible variables, including species, sources, antibiotic susceptibility methods and tests, resistance transfer evaluations, resistance genes and virulence factors.

The ROAR isolate database consists of raw, isolate-by-isolate data, including antibiotic susceptibility, genotype, phenotype, virulence traits and other data. It is currently populated with genetic data from 3352 isolates, which include all data generated by the year 1-5 consortia (see Table). In addition, E. coli data were acquired and added from the National Antimicrobial Resistance Monitoring System (NARMS; http://www.fda.gov/NARMS), provided to us by Steering Committee member David White, past director of the NARMS program.

ROAR Network Listserv

The ROAR Network Listserv (https://elist.tufts.edu/wws/info/roar) has a growing membership of over 350. Comprised of interested investigators from diverse scientific fields, this listserv acts as an active forum for timely discussion of resistance in commensals and has been a valuable resource for the dissemination of ROAR-related scientific news, data solicitations, and announcements and deliberations around controversial scientific policy questions such as antibiotic use in animal feed (see p.6).

Discussions are archived by date and topic. To join the ROAR listserv, contact APUA@tufts.edu.

Ongoing Work

Most recently a symposium entitled APUA Global Projects on Antimicrobial Resistance was presented at ASM 2008 Boston. APUA is currently engaged in a project funded by The United States Army Medical Research Institute for Infectious Diseases (USAMRIID) to collect and analyze commensal bacterial strains imported from selected APUA-affiliated Chapter countries.

For more information on ROAR please see the website or contact Kathleen Young or Bonnie Marshall at APUA.
### APUA ROAR Consortium Studies

<table>
<thead>
<tr>
<th>PI</th>
<th>Project Title</th>
<th>Project Goal/Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susan Hollingshead University of Alabama</td>
<td>Streptococcus mitis biovar 1 and its potential as a reservoir for <em>Streptococcus pneumoniae</em></td>
<td>A systematic exploration of the long-suspected contribution of commensal mouth flora to the resistance gene complement of <em>Streptococcus pneumoniae</em> was initiated. MLST systems were developed to elaborate the population structure of collections of <em>Streptococcus mitis</em> and delineate their resistance genes. 1,2</td>
</tr>
<tr>
<td>Lisa Nolan and Timothy Johnson Iowa State University</td>
<td>Possible emergence of a plasmid-mediated reservoir of resistance genes among the <em>Escherichia coli</em> of poultry.</td>
<td>Multiple multiplex PCR panels were designed to screen over two thousand isolates of <em>Escherichia coli</em> for plasmid virulence and resistance traits, and to observe presumptive flow of these between commensal and pathogenic isolates from the collections different sources, including poultry and distant humans. While the avian pathogenic <em>E. coli</em> had more resistance genes than those from other sources, the research revealed that all of the populations shared some resistance genes.3a, 3b</td>
</tr>
<tr>
<td>Anne Summers University of Georgia</td>
<td>High throughput molecular genotyping of environmental and human staphylococci carrying class I integrons.</td>
<td>A battery of methods were developed to discriminate strains of staphylococci, including plasmid profiling and fingerprinting, phenotyping and genotyping, planar microarray and leveraged compete plasmid sequencing: the latter now generating further work to explicate the mobility mechanisms of staphylococcal genetic elements.</td>
</tr>
<tr>
<td>David Gordon Australian National University</td>
<td>Antibiotic resistance and genetic relationship of <em>E. coli</em> from Australia.</td>
<td>A classification of <em>E. coli</em> was developed to advance understanding of its population structure, which is needed to understand its major role in commensal-pathogen spread of resistance. A new rapid PCR-based method to identify <em>E. coli</em> phylogroups was compared with the older more laborious method that had been in use.6</td>
</tr>
<tr>
<td>James Tiedje Michigan State University</td>
<td>Exploring transfer, diversity, and distribution of antibiotic resistance genes residing in soil.</td>
<td>Four classes of tetracycline resistance genes as well as aminoglycoside and quaternary ammonium resistance genes were found in DNA extracted from soil, but only in soil managed by tetracycline treated pigs. Numerous integrons were found in all soils, however, indicating that while resistance genes may be concentrated at sites of selection, genetic elements to disseminate them are widespread.</td>
</tr>
<tr>
<td>Marilyn Roberts University of Washington</td>
<td>Profiling of mef and erm resistance genes in oral pediatric isolates.</td>
<td>A variety of each of the two major types of genes expressing macrolide resistance were identified, many of them linked to mercury resistance genes, in many genera of commensal oral flora of children who had mercury dental amalgams. Traces of mercury could thus coselect for greater persistence of the macrolide resistance genes and the chance of their transfer to neighboring pathogens.5a,5b</td>
</tr>
<tr>
<td>Betsy Foxman University of Michigan</td>
<td>Probe hybridization array typing: A high throughput <em>E. coli</em> typing method</td>
<td>Probe Hybridization Array Typing (PHAT) was developed to be a more rapid and readily digitized method that will correlate with MLST typing while also detecting faster evolutionary changes to better monitor events in the real-world spread and transfer of resistance genes.</td>
</tr>
<tr>
<td>Erick Denamur* <em>, Andre Andremont†, David Skurnik‡, Sylvain Brisse</em> INSERM U722*, Institut Pasteur,Université Paris 7*</td>
<td>Phylogenetic analysis of antibiotic resistance in commensal <em>Escherichia coli</em></td>
<td>A collection of 444 commensal <em>E. coli</em> isolates exposed to varying levels of antibiotic selective pressure (wild and domestic animals, pets, humans) was examined by MLST to: 1) assess resistance gene transfer among isolates, 2) compare virulence in sensitive and resistant strains, and 3) attempt to correlate the mechanism of tetracycline resistance with strain phylogeny and isolate host.</td>
</tr>
<tr>
<td>Carlos F. Amabile Cuevas Fundación IUSARA Mexico</td>
<td>Antibiotic resistance in oral commensal streptococci from healthy Mexicans and Cubans: resistance prevalence does not mirror antibiotic usage</td>
<td>No difference in prevalence of resistance were found among oral streptococci between groups presumptively with high and low exposure to antibiotics, although the former has more multiply resistant strains. Further work suggests a selective pressure in the environment that favors emergence of low-level resistance to fluoroquinolones. (ROAR 1)</td>
</tr>
<tr>
<td>David White U.S. Food and Drug Administration</td>
<td>Characterization of chloramphenicol and florfenicol resistance in <em>Escherichia coli</em> associated with bovine diarrhea</td>
<td>Florfenicol and chloramphenicol resistance mechanisms were examined in 48 <em>E. coli</em> from diarrheic calves. AST profiles and assays for the related efflux genes flo and cmaA were determined. DNA sequence analyses showed high homology with flo genes from the pathogen <em>Salmonella Typhimurium</em> DT104 and the environmental commensal, <em>Proteobacterium piscicida</em>, suggesting horizontal gene transfer from these organisms. The findings demonstrated a wider distribution of the flo gene than previously believed, suggesting that the emerging chloramphenicol resistance in <em>E. coli</em> is due to the flo gene. (ROAR 1)</td>
</tr>
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quencies began escalating, and (excepting the occasional report as high as 80%), stabilized around 34% in 1999. For the period 2007-2008, hospital MRSA had an IQR (Inter Quartile Range) of 20-40 %. More than 90% of these MRSA were resistant to gentamicin.

There is no clear picture of the prevalence of community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA), although a study conducted in seven cities reported that as high as 87.5% of health care associated infections were due to MRSA. Currently resistance among the methicillin-susceptible S. aureus (MSSA) is 45-55% (IQR) for ciprofloxacin, 33-45% for cotrimoxazole, 23-27% for netilmicin and 8-12% for rifampicin. Resistance to linezolid or daptomycin has not yet been reported.

A limited number of reports of VRSA, vancomycin-intermediate S. aureus (VISA),
and heterogeneous vancomycin resistant S. aureus (hVRSA) strains indicate that this is a newly emerging problem in India.

**Enterococcus spp.**

While enterococcal bacteraemia is a significant clinical problem, fortunately, VRE is not yet a major factor, although isolates have been documented from Chandigarh, Lucknow, Mumbai and Vellore (unpublished). Ampicillin-resistant **Enterococcus** spp. (ARE) strains are highly predisposed to acquiring vancomycin resistance determinants and are also believed to be markers for serious underlying conditions and poor outcome. Once ARE become endemic in an institution, they appear as difficult to eradicate as MRSA. In Vellore, a high level of ampicillin resistance (65%) is observed. Data from other centers are not available, but a high prevalence is likely, which suggests that VRE may become a significant problem in the near future. High-level aminoglycoside resistance (HLAR) appears relatively less frequent in the South as compared to North India. When treating Enterococcus spp. with an ampicillin/aminoglycoside combination, the clinician should always remember that successful synergistic activity depends on susceptibility to both antibiotics.

**Streptococcus pneumoniae**

Because of its low cost and accessibility, amoxicillin is extensively used in the community for treatment of upper respiratory tract infections. However, this practice may result in increased penicillin resistance among pneumococci. The neighbor island of Sri Lanka reports close to 90% penicillin resistance, and in India, intermediate-level resistance has increased steadily over the last decade. The South Asian Pneumococcal Network Alliance (SAPNA) has conducted surveillance of invasive pneumococcal disease since 1993. The Indian contingent of SAPNA (the Invasive Bacterial Infection surveillance (IBIS) group reported 1.3% of isolates with Intermediate resistance only between 1993-1997. This increased to 4.6% in 1999. One study from a tertiary care center has reported 11.3% intermediate resistance to penicillin. More recently, IBIS recorded 7.6% intermediate resistance to penicillin (personal communication, Dr. Kurien Thomas, IBIS Vellore). Last year, complete resistance to penicillin was observed for the first time in both Varanasi and Vellore (unpublished data). Over all, 70% of S. pneumoniae were resistant to cotrimoxazole.

**Enterobacteriaceae**

Extended spectrum beta lactamas (ESBLs) have emerged as a major problem, with a prevalence of 30-65% (IQR) in Enterobacteriaceae. In certain intensive care units, isolation reached 80%. Amongst ESBL producers, resistance rates to ciprofloxacin, cotrimoxazole and amikacin are 76%, 70% and 38% respectively. Of the β-lactam and β-lactamase inhibitor combinations, the cefepazone/sulbactam and piperacillin/tazobactam combinations are most useful. Resistance to ticarcillin/clavulanic acid is also very high and deemed unacceptable especially for empiric therapy. While combinations of fourth generation cephalosporins and β-lactam inhibitors are widely available, their efficiency is undocumented.

Genotypic studies show that the ESBL isolates from India are completely dominated by the presence of bla (CTX-M-15) whereas in other countries, multiple ESBL variants are reported. With a carriage rate of 10% for CTX-M-15, fecal *E. coli* represent a major reservoir. In 2008, the presence of nosocomial bla CTX-M-28-producing Enterobacteriaceae strains was documented for the first time.

Salmonella: Traditionally, drugs such as chloramphenicol, ampicillin and cotrimoxazole were effective as first-line drugs for typhoid. However, during the late 1980s and early 1990s, *S typhi* multidrug resistance (MDR) (to ampicillin, chloramphenicol and cotrimoxazole) led to the widespread use of fluoroquinolones (FQ). Recently some nalidixic acid-resistant strains have also been associated with reduced susceptibility to ciprofloxacin (MIC > 0.5 µg/mL), and treatment failure with ciprofloxacin has become a serious concern. Isolation of highly FQ-resistant *S. typhi* and *S. paratyphi* A are increasingly reported. At the same time, in most parts of the country MDR strains commonly seen in the 1980s and 1990s have shown a downward trend. Last year, FQ resistance in the absence of multidrug resistance was reported.

Based on PK/PD breakpoint studies and prevailing FQ resistance to *S. typhi* in India, Rodrigues et al. have recently proposed that the MIC of ciprofloxacin be lowered to ≤ 0.25 µg/mL and that the resistant zone diameter breakpoint be increased to ≥ 28 mm with the susceptible breakpoint ≥ 30 mm. This will help clinicians successfully correlate in-vitro testing results. The increasing finding of susceptibility to cotrimoxazole, ampicillin and chloramphenicol suggests that fluoroquinolones be used sparingly, with a reversion to earlier standard treatments.

Shigella. Across the country, *S. flexneri* was the most prevalent Shigella species, followed by *S. sonnei*, *S. dysenteriae* and *S. boydii*. Most susceptibility surveys show that more than 70% of Shigella are resistant to ampicillin, cotrimoxazole, and tetracycline, while >90% are resistant to nalidixic acid. Previously, single-dose norfloxacin or ciprofloxacin was effective, but now resistance to FQs is
increasing, thus far, only among S. dysentersiae type I and S. flexneri. The newer quinolones, cephalosporin derivatives, or azithromycin are the preferred treatment. S. dysentersiae type I strains are reemerging with MDR.16-27

Carbapenem resistance: Until 2005, resistance to carbapenem in Enterobacteriaeae had not been seen. In 2006, Gupta et al reported that five percent of Delhi study isolates were carbapenem resistant. 11 Recently, at CMC Vellore, we have identified and characterized 20 urine and blood isolates resistant to carbapenem. (This resistance was confirmed by Jean Patel of the CDC, Atlanta and Y. Carmeli, Harvard.) Unfortunately this heralds the end of the reliability of carbapenem, the drug of last resort for Enterobacteriaceae.

Vibrio cholerae

Traditionally, V. cholerae El Tor Ogawa has been more common than serotype Inaba, but Inaba are now isolated more frequently. 20 Both Vibrio cholerae 01 and 0139 are still largely susceptible to tetracycline, while an increasing MIC is seen for ciprofloxacin. These V. cholerae exhibit a fluctuating and unpredictable pattern of resistance to ampicilllin, nalidixic acid, furazolidone and cotrimoxazole. In contrast, V. cholerae non-O1, non-O139 strains exhibit high levels of resistance to every class of antimicrobial agent tested. 20-30

Non fermenting Gram Negative Bacilli (NFGNB)

Both multidrug resistance and pan-drug resistance in NFGNB are appearing concurrently in all the major hospitals. The IQR of P aeruginosa resistant to carbapenem is 20-30%, (with some reports as high as 65%), and that of Acinetobacter spp. is 15%-30%. Overall, 10% more isolates had resistance to meropenen than to imipenem and catheter isolates had 25% more resistance than blood/urine/pus isolates. Amongst NFGNB, up to 60% are resistant to ciprofloxacin, 50% to amikacin and 60% to ceftazidime.

Of the beta-lactam and beta-lactamase inhibitor combinations, cefporezone/ sulbactam and piperacillin/tazobactam (40% resistance reported) are found to be more effective than the ticarcillin/clavulanic acid combination (76% resistance). Overall, resistance in blood culture isolates is 10 to 25% less than in urinary isolates.12-35

Confronting Antibiotic Resistance in India

Irresponsibly prescribed antibiotics and inadequate therapy are two major contributors to the growing problem of antibiotic resistance in India. In order to help reduce this problem and its related morbidity and mortality, revised curriculum with an emphasis on appropriate use of antibiotics need to be adopted for undergraduate medical training. Furthermore, institution of local and national surveillance programs to detect and contain the dissemination of the resistant strains is needed. The current scenario of high antimicrobial resistance demands the development of programs for the training of infectious disease specialists, whose efforts should be integrated with pharmacists and microbiologists.

Perhaps the major factor contributing to antimicrobial resistance is the problem of counterfeit drugs. According to the World Health Organization’s 2001 statistics, 35 per cent of the world’s counterfeit drugs are produced in India, with antibiotics at the top of the list. The Economic Times (Feb. 2008) quoted the Associated Chambers of Commerce and Industry in India as reporting that the counterfeit drug market is growing at a rate of 25% annually and has absorbed 20-25% of the total market share. India has emerged as the leading distributor of these drugs and contributes 75% of the total fake drugs supplied all over the world. While the health ministry estimates that only 5% of the drugs in India are spurious, the ready availability of these over-the-counter antibiotics represents an enormous selection pressure for antimicrobial resistance. In the interests of public health, legislation to ban the distribution of such antibiotics may be necessary.

Only selected references have been cited.

Reference:
Testimony on Antibiotic Use in Animals Spurs Lively Debate on APUA’s ROAR Listserv

As part of its mission to contain drug resistance, APUA is involved in education and advocacy to improve antibiotic use in human and veterinary medicine. The Reservoirs of Antibiotic Resistance (ROAR) Scientific Network provides a discussion forum to distribute and integrate information concerning the ecology of antibiotic resistance in commensal, clinical and environmental bacteria via the ROAR website and its electronic listserv.

On June 24, 2008, the Senate Committee on Health, Education, Labor & Pensions held a hearing titled “Emergence of the Superbug: Antimicrobial Resistance in the U.S.” Dr. Lyle P. Vogel, assistant executive vice president of The American Veterinary Medical Association (AVMA), presented testimony that scientific data do not support a ban on the preventative use of antibiotics in food animals. Those testifying also included Mr. Brandon Noble, former NFL player and MRSA survivor, Dr. Jay P. Graham, consultant, The Pew Commission on Industrial Farm Animal Production, Dr. Patrick J. Brennan, president, The Society for Healthcare Epidemiology of America, and Dr. Barry I. Eisenstein, senior vice president of Scientific Affairs, Cubist Pharmaceuticals, Inc.

Vogel also testified that the Food & Drug Administration evaluations of antibiotic use in livestock are more stringent than for human antibiotics evidence, suggesting that when livestock are not given antimicrobials for prevention of disease, an increase in illnesses is likely to occur.

“Risk assessments demonstrate a very low risk to human health from the use of antimicrobials in food animals, and some models predict an increased human health burden if the use is withdrawn,” Vogel testified. “Non-risk-based bans of approved uses of antimicrobials will negatively impact animal health and welfare without predictably improving public health.”

Vogel’s comments sparked controversial debate on APUA’s ROAR listserv amongst specialists in the infectious disease and agricultural microbiology sectors, who expressed concern regarding the increasing exposure of ceftiofur and similar drugs in food animals on a global basis. There is escalating concern regarding the extensive use of ceftiofur (used to inject very large numbers of eggs before chickens hatch) at hatcheries worldwide. A recent study by the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) provided data that “off-label” use of ceftiofur was associated with increasing numbers of 3rd generation cephalosporin resistant salmonella in both animals and in people in Quebec. Of particular concern is the high number of resistant extended spectrum beta-lactamase (ESBLs) in the poultry isolates causing infections in people. Specialists have also articulated concern about the ambiguity of “off-label” terminology and the increasing abuse of Federal law which restricts the use of ceftiofur by a licensed veterinarian.

Consensus suggested that critical evaluation of the association between 3rd generation cephalosporin use in food animals and resistance in humans be pursued more extensively. Existing data that suggest antimicrobial usage leads to resistance emergence need to be verified and supported through additional studies. Discussions continue in the wake of the recent Order of Prohibition issued by the FDA’s Center for Veterinary Medicine (CVM) on extralabel use of the cephalosporin class of antimicrobial drugs in food-producing animals, in effect on October 1, 2008.

To join the ROAR Scientific Network and Listserv and follow these discussions, please sign up at the following link: http://www.roarproject.org/ROAR/html/network.htm

In 2002, the Alliance for the Prudent Use of Antibiotics (APUA) published a report, “Facts about Antimicrobials in Animals and the Impact on Resistance” (FAAIR) titled “The Need to Improve Antimicrobial Use in Agriculture” in the medical journal Clinical Infectious Diseases, (Vol. 34, Suppl. 3), calling for immediate action by government and the agriculture industry to reduce the human health risks identified in the report. The national scientific experts involved in the APUA report also recommended elimination of antibiotic use for growth promotion and limiting farm use of critically important drugs, such as fluoroquinolones and third generation cephalosporins, which are needed for hard-to-treat human infections. The World Health Organization, the Institute of Medicine, the American Medical Association (AMA), APUA, and now the Pew Commission, have called for a ban on those growth-promoting drugs that are essential in human medicine.


Related links:
- AVMA: antibiotic use in food animals:
  - 03 JUL 2008 Press Release: Scientific data does not support a ban on the preventative use of antibiotics in food animals, according to The American Veterinary Medical Association (AVMA)
  - http://www.worldpoultry.net/news/id_2205–50410/avma_questions_antibiotic_ban_in_animals.html

- AVMA’s food safety testimony:
  - Testimony and information is posted on AVMA’s food safety advocacy website
  - http://www.keepourfoodsafe.org:80/

- CIPARS cefitiofur study:
  - The Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) provided data to stakeholders leading to a voluntary withdrawal in Quebec chicken hatcheries of the extra-label use of cefitiofur

- FDA’s Cephalosporin Order of Prohibition:
  - http://www.fda.gov/cvm/CVMupdateCepha_QA.htm

A copy of the Federal Register document is available at: http://edocket.access.gpo.gov/2008/E8-15052.htm

Recent APUA Public Policy Actions

The Alliance for the Prudent Use of Antibiotics (APUA) has long served as a respected resource to guide policy decisions throughout the United States and throughout the world. Executing its dedication to improve institutional and governmental antimicrobial policies, the organization has recently been involved in numerous public policy developments.

Calls for Accelerated Drug Development and Stronger Antibiotic Stewardship

On June 24, 2008, APUA submitted a statement of support to the Senate Committee on Health, Education, Labor and Pensions hearing, the Emergence of the Superbug: Antimicrobial Resistance in the U.S. In its statement, APUA called for urgent federal action to fill the antibiotic pipeline and curb antibiotic misuse, and supported new legislative proposals to curb antibiotic misuse in animals and accelerate new drug development. APUA also outlined a three-pronged approach to contain antibiotic resistance: economic incentives for new antibiotic development, improved monitoring of resistance rates of antibiotics in humans and animals, and stronger stewardship requirements to protect antibiotics already on the market. APUA offered the novel approach of designating antibiotics as a special regulatory class of drugs to enable unique economic incentives for antibiotic development and foster better stewardship of marketed drugs.

Opposes Home Stockpiling of Prophylactic Antibiotics

APUA also submitted a statement for consideration at the National Biodefense Science Board meeting, June 18-20, 2008, in which the organization strongly opposed the proposal of consumer home storage of antibiotics for post exposure prophylaxis for a biological warfare threat. APUA stated that the idea of safeguarding antibiotics is highly inadvisable because putting active antibiotics in the hands of consumers would likely lead to drug misuse and the ultimate emergence and spread of resistance to that drug. Additionally, the public, widespread distribution of antibiotics would give potential terrorists the ability to identify which medication American citizens will rely on and therefore introduce resistance genes for that medication into their bioterrorist agent of choice. APUA claimed that better monitoring of resistance rates and antibiotic use in humans and animals is needed to extend the life of current antimicrobials.

Renews Pleas for Controlling Antibiotics as Growth Promotants

Amidst heightened recognition and concern that the use of antibiotics in food-producing animals contributes to the development of resistance in bacteria that find their way into food and humans, APUA helped fuel an awareness campaign to support the findings of the Pew Commission on Industrial Farm Animal Production’s final report, “Putting Meat on The Table: Industrial Farm Animal Production in America.” Released in Washington DC on April 29, 2008, the policy report called for the elimination of antibiotic use for growth promotion in animals and, like other policy reports, is contested by the animal food industry, which has an economic stake in improving efficiency in food animal production.

In 2002, APUA published a similar report, “The Need to Improve Antimicrobial Use in Agriculture,” (Clin. Inf. Dis. Vol 34, Suppl 3). The World Health Organization, the Institute of Medicine, the American Medical Association (AMA), APUA, and now the Pew Commission have called for a ban on those growth-promoting drugs that are essential in human medicine.

APUA Supports STAAR Act initiative

In its press release supporting the PEW Commission’s recent findings, APUA commends the legislative leadership of Senators Kennedy, Brown, and Hatch and Representatives Matheson, Ferguson and Lynch for their committed efforts to contain antimicrobial resistance. In the face of this intensifying crisis, APUA, the Infectious Diseases Society of America (IDSA), AMA, and others are currently advocating legislative action in 2008 through the Strategies to Address Antimicrobial Resistance (STAAR) Act, the Prescription Drug User Fee Act (PDUFA), and the Preservation of Antibiotics for Human Treatment Act (PAMTA) to provide incentives to new drug development and ensure better stewardship of existing life-saving crucial antibiotics.

- The STAAR Act would strengthen federal antimicrobial resistance surveillance, prevention and control in the U.S.
- The reauthorization of PDUFA significantly broadens and upgrades the agency’s drug safety program, increases resources for review of television drug advertising, and facilitates more efficient development of safe and effective new medications for the American public.
- PAMTA serves to phase out the use of non-therapeutic antibiotics in livestock. The act provides for Federal payments to farmers to defray their costs in switching to antibiotic-free husbandry practices.

2008 APUA Leadership Award Recipients:


Inge C. Gysens
Jos van der Meer
Henri S. Verbrugh
John Degener
Christina M. Vandenbroucke-Grauls
Peter J.M. van den Broek

The APUA Newsletter Vol. 26 No. 1
APUA submits testimony to FDA

On April 28, 2008, APUA submitted a written testimony for the FDA hearing on antimicrobial resistance [Docket No. FDA-2008-N-0225]. In its statement, the organization outlined numerous approaches needed to better contain antimicrobial resistance, including the novel approach of antibiotics being considered a special, “protected” regulatory class to enable unique economic incentives and better antibiotic stewardship requirements. APUA also advocated heightened surveillance of resistance rates and antibiotic use in humans and animals that is needed to extend the life of current antimicrobials. Additionally, APUA expressed the urgent need for economic incentives for new antibiotic development and stewardship of existing life-saving crucial antibiotics, as well as increased funding for agencies and private organizations working on the problem.

U.S. national security requires incentives for antibiotic development and stewardship. APUA remains committed to preserving the power of antibiotics through needed policy work and legislative advocacy to forestall a future of unaffordable drugs and untreatable infections.

All public policy transcripts can be found on APUA’s Public Policy Actions Web page: http://www.tufts.edu/med/apua/public_policy/legislation.html

APUA Studies MRSA from Patient’s Perspective

MRSA is an increasingly common diagnosis among the non-hospitalized population, but little is known about patient knowledge regarding MRSA or the effects that this knowledge has on patient experience and behavior. In order to address these questions, APUA fielded a 73-question online survey between Aug.-Dec. 2007; 395 responses were collected and analyzed using regression analysis (see Table.)

On June 17, APUA delivered an oral presentation at the annual meeting of the Association for Professionals in Infection Control and Epidemiology (APIC). The presentation evaluated the relationships between patient experience with MRSA and receipt of MRSA information at time of diagnosis: 53% of respondents reported receiving no information, and an additional 5% received only a fact sheet, with no opportunity for discussion with a health professional. Those who received fact sheets were similar in their experiences and behaviors to those who received no information at all, with the following differences being noted between the two groups: Patients who received no information were also more likely to report undertaking excessive cleaning or isolation procedures, often as a result of advice that came from the Internet, newspapers, or other sources of information less valid than health care professionals. Some of those who did not receive information also reported that they were unaware that MRSA was contagious and had passed it on to other family members before they learned that they should take contact precautions.

These data indicate a need for further research into this issue, and education of health care providers regarding the potential problems associated with failure to provide valid, science-based information to patients.

This work was funded by grants from Clorox and bioMérieux.

APUA Convenes Expert Panel on Resistance in Commensals

On June 2, 2008, APUA convened an expert panel at Tufts University School of Medicine in Boston to share presentations of recent work and discuss the current state of commensals as “reservoirs” of resistance genes for emerging pathogens. This AMROAR scientific meeting was follow-up activity emanating from APUA’s NIH-funded ROAR (Reservoirs of Antibiotic Resistance) project and was supported by the CORE Support group of the Battelle National Biodefense Institute. A meeting summary report and peer-reviewed article on the subject of commensals as reservoirs will be forthcoming from this effort.

New APUA Chapter under Development

Dr. Anibal Sosa visited Maputo, Mozambique in July 2008 to meet with Dr. Americo Assan, Director Nacional de Assistencia Medica, and other key opinion leaders who are engaged in the formation of a new APUA chapter in Mozambique.

MRSA: The Patient’s Perspective

<table>
<thead>
<tr>
<th>Reported Behavior or Experience</th>
<th>Received Information</th>
<th>No Information or Fact Sheet Only</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceived stigma from MRSA</td>
<td>69%</td>
<td>78%</td>
<td>.05</td>
</tr>
<tr>
<td>VERY worried about MRSA in general</td>
<td>68%</td>
<td>77%</td>
<td>.05</td>
</tr>
<tr>
<td>VERY concerned about transmitting to family members</td>
<td>54%</td>
<td>64%</td>
<td>.05</td>
</tr>
<tr>
<td>Didn’t want ANYONE to know about MRSA status</td>
<td>2%</td>
<td>16%</td>
<td>.0001</td>
</tr>
<tr>
<td>Didn’t want to tell coworkers about MRSA</td>
<td>18%</td>
<td>31%</td>
<td>.02</td>
</tr>
<tr>
<td>Didn’t want to tell boss about MRSA</td>
<td>8%</td>
<td>26%</td>
<td>.0004</td>
</tr>
<tr>
<td>Missed work due to fear of disclosing MRSA status</td>
<td>8%</td>
<td>17%</td>
<td>.02</td>
</tr>
<tr>
<td>Didn’t want to tell about MRSA because of job security fear</td>
<td>23%</td>
<td>40%</td>
<td>.04</td>
</tr>
</tbody>
</table>

From Left to Right, Mr. Rafael Joaquim, Laboratorio de Microbiologia, Hospital Central de Maputo, Dr. Elizabeth Coelho, Head, National TB Laboratory Program, Dr. César Palha de Sousa, Universidade E. Mondlane (UEM), Dr. Sam Patel, Head of the Comité Tecnico de Terapeutica e Farmacia (CTTF)
South American Infectious Disease Initiative in Bolivia, Paraguay and Peru

Under the sponsorship of USAID, and with the assistance of APUIA International, the APUIA chapters in Bolivia, Paraguay and Peru have begun implementing a multi-pronged action plan: to 1) design training modules for undergraduate students and post graduate medical residents regarding guidelines for the use of antibiotics for acute respiratory infections in children under five years of age; 2) formulate policy that will categorize antibiotic use in third level hospitals as “restricted, controlled or authorized”; and 3) revise, analyze and translate AMR surveillance data for clinicians and policy makers.

Global Surveillance Project Begins Isolate Collection

As part of the USAMRIID project “International Surveillance of Reservoirs of Antibiotic Resistance (ROAR): Pilot for Global Surveillance System in Selected Countries,” APUIA Project Manager, Anibal Sosa, recently visited microbiology laboratories in Uganda, Turkey, Georgia, South Korea and India for the purposes of laboratory and protocol evaluations.

Guidelines for Control of Antibiotic Resistance


Prevent Antimicrobial Resistance in Healthcare Settings http://www.cdc.gov/drugresistance/healthcare/default.htm contains tools for clinicians treating
- Hospitalized Adults http://www.cdc.gov/drugresistance/healthcare/ha/12steps_HA.htm
- Dialysis Patients http://www.cdc.gov/drugresistance/healthcare/dialysis/12steps_dialysis.htm
- Surgical Patients http://www.cdc.gov/drugresistance/healthcare/surgery/12steps_surgery.htm
- Long-term Care residents http://www.cdc.gov/drugresistance/healthcare/ltc/12steps_ltc.htm

Multi-level Antimicrobial Susceptibility Testing Resources (MASTER)
http://www.cdc.gov/dls/master/default.aspx
This website contains information on antimicrobial susceptibility testing issues related to clinical microbiology laboratory practice. This site updates and provides,
- A Case Study which addresses a contemporary antimicrobial susceptibility testing issue.
- Q&A: answers to five or more questions asked by you or other visitors to our website.
- Hot Papers: features list of recent papers related to antimicrobial susceptibility testing.
- Important News: includes new information and upcoming continuing education offerings on antimicrobial susceptibility testing.
- Reference Materials: lists of antimicrobial susceptibility testing information (primarily books and links to other websites).

National guidelines clearing house (NGC)
http://www.guideline.gov/
The National Guidelines Clearinghouse is a public resource for evidence-based clinical practice guidelines, including infectious disease. The notable feature of this interactive website is the ability to generate a side-by-side comparison of any two or more guidelines. Comparisons feature guideline objective(s), major outcomes considered and description of methods used to collect/select the evidence. In addition the guide rates strength of the evidence, confirms the validation, provides a clinical algorithm and offers major recommendations. http://www.guideline.gov/compare/compare.aspx

National Resource for Infection Control, UK.
NRIC is a project developed by healthcare professionals, aimed at being a single-access point to existing resources within infection control for both Infection Control and all other healthcare staff. http://www.nrnic.org.uk/IntegratedCRD.nsf/NRNIC_Policy_AntimicrobialPrescribing?OpenForm

For veterinary personnel
American Veterinary Medical Association on Judicious Therapeutic Use of Antimicrobials http://www.avma.org/issues/jtua/default.asp


WHO’s general information on antimicrobial resistance http://www.who.int/mediacentre/factsheets/fs194/en/


National Institute of Allergy and Infectious Disease- on antimicrobial resistance http://www3.niaid.nih.gov/topics/antimicrobialresistance/

For community physicians
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.

Name ____________________________
Address ___________________________________________________________
________________________________________________________
________________________________________________________
________________________________________________________

Areas of Interest ______________________________________________________

Telephone __________________________ E-mail Address ______________________

<table>
<thead>
<tr>
<th>Membership Type</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual Member</td>
<td>$45</td>
</tr>
<tr>
<td>1 Year Individual</td>
<td>$45</td>
</tr>
<tr>
<td>2 Year Individual</td>
<td>$70</td>
</tr>
<tr>
<td>Student ($20)</td>
<td></td>
</tr>
<tr>
<td>Library/Non-Profit</td>
<td>$100</td>
</tr>
<tr>
<td>Supporting Member</td>
<td>$55</td>
</tr>
<tr>
<td>1 Year Supporting</td>
<td>$55</td>
</tr>
<tr>
<td>2 Year Supporting</td>
<td>$95</td>
</tr>
<tr>
<td>Friend ($250)</td>
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</tr>
<tr>
<td>Corporate Member</td>
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</tr>
<tr>
<td>Associate ($5,000)</td>
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</tr>
<tr>
<td>Partner ($10,000)</td>
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<tr>
<td>Benefactor ($25,000)</td>
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</tr>
<tr>
<td>Platinum ($50,000+)</td>
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</tbody>
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Payment method is in US dollars (please check one):
☐ Check drawn on a US affiliate or international money order, payable to APUA
☐ Mastercard
☐ Visa

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Expiration Date __________________________ Signature __________________________

*Membership is complimentary in the developing world.

APUA is a 501(c)3 nonprofit, donations are US tax-deductible.

**Supporting memberships sponsor members in a developing country.

... containing global antibiotic resistance through local action

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.

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