Urinary Tract Infections: Antibiotic Guidelines for a Global Problem

APUA One-on-One

An interview with Thomas M. Hooton, M.D.

Professor of Clinical Medicine and Director of the Institute for Women’s Health at the University of Miami’s Miller School of Medicine

Dr. Hooton currently serves as a member of the IDSA panel that has been convened to review, update and publish revised guidelines for the treatment of uncomplicated urinary tract infections.

Uncomplicated urinary tract infections (UTI), comprised of episodes of cystitis (infection of the bladder) or pyelonephritis (infection of the kidney), are among the most common infections globally, estimated at over 150 million cases annually. The primary etiological agent is E. coli, followed by the much less common Staphylococcus saprophyticus and occasionally Klebsiella, Proteus or other gram-negative bacilli. On average, a healthy woman will have one to two UTIs in her lifetime. While not contagious, and not presenting a public health threat, UTIs do impose a considerable health and cost burden.

For discussion purposes, uncomplicated UTI should be distinguished from complicated UTI. Uncomplicated UTI tends to occur in young healthy women. Complicated UTIs are by definition associated with functional or anatomic abnormalities of the genito/urinary tract and tend to occur in older individuals, those who are catheterized or institutionalized, or following surgery. For an algorithm of differentiation, see http://www.guideline.gov/algorithm/5173/NGC-5173.pdf. Pyelonephritis in young healthy women can be considered uncomplicated. However, the ratio of uncomplicated cystitis to pyelonephritis is ~30:1, and the treatments are different.

Q. What are the causes and risk factors for UTIs?
A. Among young healthy women, sexual intercourse, diaphragm-spermicide use, and a history of recurrent UTI are strong and independent risk factors for uncomplicated cystitis.1 Risk factors for recurrent uncomplicated cystitis include sexual intercourse, having a

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Monday, September 13, 2010 at ICA

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IDSA issues new guidelines on most common healthcare-associated infection

At some point during their hospitalization, 15-25% of U.S. patients in general hospitals receive urethral catheters. Likewise, as many as 5-10% of nursing home patients are managed with urethral catheters, sometimes for years. Although much catheter use is considered inappropriate, the practice still appears to be increasing. Consequently, urinary tract catheterization has become the most important predisposing factor for healthcare-associated infection (HAI), and catheter-associated bacteriuria, the most common HAI worldwide.

Urinary catheters disturb the body’s infection defense mechanisms and facilitate the access of pathogens to the bladder. They also enhance microbial adhesion by providing a surface to which pathogen binding receptors can attach. The conditions resulting from catheterization include: catheter-associated urinary tract infections (CA-UTI), CA-asymptomatic

IDSA GUIDELINES continued on page 3
**Letter to the Editor**

Dear Editor:

My name is Larry Halperin, M.D., and I am a practicing retina surgeon in Florida. In the early 1980’s, as an undergraduate student, I worked in Stuart Levy’s laboratory at Tufts University. I spoke to Stuart recently about an issue regarding antibiotics, and he suggested that I contact you to post a question to your readership.

In the field of retina care, we do many injections, specifically for exudative (wet) age-related macular degeneration. These injections are performed as frequently as every four weeks. Some, but not all, practitioners use topical ophthalmic antibiotics around the time of the injection. There is tremendous variability as to which antibiotic and the duration of use, but the drops are used several days per month, every month.

My question concerns the development of resistant bacteria on the ocular surface that may develop after topical antibiotic use in this fashion. I would like to know if anyone has studied this, or if anyone has encountered drug resistant bacteria causing endophthalmitis. I would appreciate any input that your readership might provide. Thank you.

Larry Halperin, M.D.
Retina Group of Florida

APUA welcomes letters to the Editor.
To submit your comments, please respond to bonnie.marshall@tufts.edu.

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**IDSA GUIDELINES continued from page 1**

bacteriuria (CA-ASB; bacteria present in the urine but with no symptoms of UTI) and CA-bacteriuria (bacteria in the urine; encompasses both of the former conditions). All of these are considered to represent infection of the urinary tract, since bacteria are not normal inhabitants of this anatomical area.

The most important risk factor for the development of CA-bacteriuria is the duration of catheter treatment. Most hospitalized patients are catheterized for only 2-4 days, but many are catheterized for longer periods. By one month, most patients will be bacteriuric and have their hospital stays extended by 2-4 days. Less than one-quarter of such patients go on to develop overt symptoms of urinary tract infection. Bacteremia (bacteria in the blood) occurs in a small proportion of patients with CA-bacteriuria, but the mortality rate from subsequent bacteremia of UTI origin is ~13%.

Recent studies have estimated each episode of CA-ASB and CA-UTI to cost an additional $589 and $676 respectively, while subsequent bacteremia can cost at least $2,836. In the U.S., these infections may add as much as $500 million to health care costs annually.

CA-bacteriuria constitutes a large reservoir of antimicrobial-resistant organisms, especially in critical care units. It is also an important cause of inappropriate antimicrobial use in both hospitals and long-term healthcare facilities. One study found that 52% of catheterized inpatients with CA-ASB were receiving inappropriate antimicrobial treatment.

These cumulative impacts make CA-bacteriuria a high priority for infection prevention programs. Unfortunately, a lack of clarity in the use of terminology in the literature has hampered efforts to derive effective interventions for this problem. The IDSA guidelines represent a new effort at developing recommendations for the diagnosis, prevention, and treatment of CA-bacteriuria, both symptomatic and asymptomatic, in adults. They were prepared by an Expert Panel from an extensive review of the published literature and rated on strength of recommendation and quality of evidence. The guidelines encompass diagnostic criteria, reduction of inappropriate catheter use, strategies to consider before and after catheter insertion, alternative techniques for catheterization, and strategies for prophylaxis of CA-bacteriuria. Of the 47 recommendations offered, 13 are directly related to the reduction and unnecessary use of antimicrobials and are summarized in Table 1.

The authors conclude that the most effective means for reducing CA-ASB and CA-UTI is the restriction of urinary catheterization to patients who demonstrate clear indications, and the subsequent removal of catheters when they are no longer needed. Implementing such strategies is considered a high priority for all health care facilities.

**Source:**
The above was derived from the IDSA Guidelines: Diagnosis, Prevention, and Treatment of Catheter-Associated Urinary Tract Infection in Adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. (For the full report see http://www.journals.uchicago.edu/doi/pdf/10.1086/650482.)

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**Table 1. Recommendations for use of antimicrobials in indwelling urethral catheterization**

<table>
<thead>
<tr>
<th>Practice</th>
<th>Recommendation</th>
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| Antimicrobial (silver alloy or antibiotic)–coated catheters             | May be considered in short-term catheterization for reduction or delay in onset of catheter-associated (CA) bacteriuria
| Prophylaxis with systemic antimicrobials                                | Should not be used for short or long-term catheterization due to concern for selection of antimicrobial resistance |
| Catheter irrigation with antimicrobials                                  | • Should not be used routinely to reduce or eradicate CA-bacteriuria or CA-UTI |
|                                                                           | • May be considered for selected patients undergoing surgical procedures and short-term catheterization |
| Antimicrobials in the drainage bag                                       | Should not be used                                                             |
| Prophylactic antimicrobials (systemically or by bladder irrigation) at time of catheter removal or replacement | Should not be administered routinely                                           |
| Screening for and treatment of: CA-ASB in indwelling catheter           | Not recommended except in 1) pregnant women and 2) patients undergoing urologic procedures with anticipated mucosal bleeding |
| CA-ASB at catheter removal                                               | May be considered in women with CA-ASB persisting for 48h following catheter removal |
| Urine culture before antimicrobial treatment                             | Recommended                                                                  |
| Catheter replacement before antimicrobial treatment                      | For catheters in place >2 weeks at onset of CA-UTI, catheter should be replaced if still needed |
| Antimicrobial treatment for CA-UTI (duration)                            | • 7 days for CA-UTI with prompt resolution of symptoms; 10-14 days for those with delayed response |
|                                                                           | • Levofloxacin (5-day regimen) may be considered for non-severely ill patients |
|                                                                           | • A 3-day regimen may be considered for women <65 yr with no upper UTI symptoms following catheter removal |

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1 Table created from IDSA guidelines found in Clin Infect Dis 2010; 50:625-663 or at http://www.journals.uchicago.edu/doi/pdf/10.1086/650482

2 Data are insufficient to make a recommendation for this practice in order to prevent CA-UTI

3 For recommendations on prophylaxis with methenamine salts or cranberry products see recommendations #30-33 of original document
UTI in developing world increasingly drug-resistant

It is not new that *E. coli* resistant to commonly prescribed antibiotics has been increasing worldwide. Such a pattern threatens the success of UTI treatment, especially in the developing world. As more bacteria become resistant to the standard UTI antibiotic treatment, trimethoprim-sulfamethoxazole (TMP-SMX), some regions recommend prescription of quinolone antibiotics to treat UTI. The prevalence of antimicrobial resistance among uropathogenic *E. coli* to some quinolones is increasingly being reported from numerous countries around the world.

There are efforts to monitor resistance profiles of UTI pathogens in order to guide empirical treatments of UTI in various African countries. Because most reports emanate from very few hospitals and centers with good facilities, available data cannot be used to reflect the situation of the whole region. Antibiotic susceptibility patterns vary greatly, even in a small geographical area. In Asia, changing etiology of UTI, emergence of drug resistance, and high variations in resistance rates have been reported in both urban and rural areas. Table 1 is a partial compilation of reported data on resistance profiles of *E. coli* in the developing world.

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**Table 1. Antibiotic resistance in *E. coli* from uncomplicated urinary tract pathogens in developing countries**

<table>
<thead>
<tr>
<th>Countries reporting</th>
<th>Ampicillin</th>
<th>TMP-SMX</th>
<th>Nitrofurantoin</th>
<th>Gentamicin</th>
<th>Fosfomycin</th>
<th>Cephalosporin 1st generation</th>
<th>Cephalosporin 3rd/4th generation</th>
<th>FQ</th>
</tr>
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<tbody>
<tr>
<td>AFRICA</td>
<td></td>
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<tr>
<td>Senegal (6), Sudan (1), Central Africa Republic (6), Ethiopia (6), Tanzania (6), Madagascar (10)</td>
<td>NR</td>
<td>80</td>
<td>0.4</td>
<td>6.33</td>
<td>2.5</td>
<td>12</td>
<td>06</td>
<td>08</td>
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<tr>
<td>ASIA</td>
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<td></td>
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<tr>
<td>India (6), Japan (13), Hong Kong (7), China (5), Taiwan (16)</td>
<td>53/92</td>
<td>30-50</td>
<td>0.7</td>
<td>13-17</td>
<td>27</td>
<td>27-30</td>
<td>55 (India)</td>
<td>13-66</td>
</tr>
<tr>
<td>SOUTH AMERICA</td>
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<tr>
<td>Brazil (9, Chile (4), Mexico (7), Peru (11), Venezuela (12)</td>
<td>56/73</td>
<td>45-66</td>
<td>2</td>
<td>1-19</td>
<td>1</td>
<td>27-40</td>
<td>3-19</td>
<td>0.38</td>
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NR: Not reported; Not all sites reported all drugs. Testing dates ranged from 1990 - 2008.

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Recent data strongly suggest a possible genetic role for increased susceptibility to both cystitis and pyelonephritis in women and pyelonephritis in children. In addition, uropathogens that cause uncomplicated cystitis and pyelonephritis have been demonstrated to have certain virulence determinants that provide a selective advantage for the ability to colonize and cause infection.

Q. Are there useful strategies that can be recommended to avoid recurrent infection?

A. In general the patient should be informed of risk factors, as described above, and it is reasonable to advise them to increase their fluid intake, avoid restricting undergarments and to urinate soon following sexual intercourse.

Data cannot be used to reflect the situation of the whole region. Antibiotic susceptibility patterns vary greatly, even in a small geographical area. In Asia, changing etiology of UTI, emergence of drug resistance, and high variations in resistance rates have been reported in both urban and rural areas. Table 1 is a partial compilation of reported data on resistance profiles of *E. coli* in the developing world.
managing recurrent infections that utilize antibiotic strategies. First is the daily prophylactic use of low-dose antimicrobials, such as SXT or nitrofurantoin. In healthy women this method has proved very effective. The second is to use an antimicrobial, such as SXT or nitrofurantoin, immediately following sexual intercourse; however, the advisability of this approach is limited by the frequency of intercourse. The third is a self-diagnosis/self-treatment approach in which a single dose or a 3-day prescription is issued to the patient—to be taken at the first sign of classic UTI symptoms. This early treatment strategy, without daily dosing, decreases delays in treatment and reduces antibiotic exposure, as well as overall medical costs associated with repeated doctor or ER visits. This approach works well for college students, but it has not been extensively studied in older females.

Q. What are the drugs of choice for UTI and what is their current utility?
A. That really depends on whether one is speaking domestically, here in the U.S., or elsewhere. In the U.S., the current choices include trimethoprim-sulfamethoxazole, nitrofurantoin, fosfomycin, fluoroquinolones, and augmentin. Resistance to SXT is high in the U.S., but still within the limits of usefulness. Nitrofurantoin, a 55-year old antibiotic, has been revisited recently with some encouraging results. While not as effective in "short course" (3-day) regimens, it performs perfectly well in a 5-day course, with no tendencies thus far towards resistance development.

Q. What are some of the current problems with empiric therapy treatment?
A. Resistance trends are geographically localized and attempts at developing global or even country-wide recommendations are not rational. High resistance rates in the U.S. have outmoded the empiric use of amoxicillin, ampicillin and possibly augmentin. While ciprofloxacin is now commonly used for UTI therapy, fluoroquinolone resistance is increasing and its use as a routine treatment regimen should be discouraged. UTIs are treated empirically for the most part, and the problem with this is that good surveillance data on antimicrobial resistance are relatively scarce. Thus, local rates of resistance are not known because testing is performed so infrequently. Until we have an established system of sentinel site testing for antimicrobial resistance among uropathogens, such as that done by CDC for invasive bacterial pathogens, our ability to make informed decisions about antibiotic selection will be limited. If we had access to local resistance data, we could reserve fluoroquinolones for more serious infections where they are truly needed.

Q. Do you see any innovative approaches toward management of UTI on the horizon?
A. Unfortunately, UTI has not been a research priority in the U.S. Vaccines have generated sporadic interest and could be of some value. The extensive work done by Walter Hopkins’ group on devising a vaginal mucosa vaccine has proved disappointing so far. Some oral and vaginal vaccines with heat-killed uropathogens have been studied in Europe with varying levels of success. These vaccines have not yet received attention in this country. Studies with a vaccine against the fimH adhesion of E. coli looked promising in animal studies but there are no published data in humans.

There persists the chronic question of which populations should be vaccinated if an effective vaccine became available. Since older patients have frequently been exposed to multiple courses of antibiotics, they tend to develop resistant flora. Arguably, a vaccine could be the best approach in such patients. Other possible vaccine targets are young women with very frequent recurrences, women planning pregnancy, children or adults with functional or anatomic abnormalities of the genitourinary tract, or persons in nursing homes. Clearly, a vaccine would be welcomed by those who suffer chronically from repeat infections.

Another very promising antimicrobial-sparing approach to reduce the risk of recurrent UTI is the use of lactobacillus probiotics. The concept behind this approach is based on the observation that the vaginal flora is often abnormal in women with recurrent UTI, with a reduction in lactobacilli and an increase in uropathogen vaginal colonization. Several studies have been presented recently with promising results.

Q. How well do in vitro susceptibility tests correlate with the clinical outcome?
A. There are lots of data with SXT—in general, if the organism is resistant and this drug is used, about half those with uncomplicated cystitis will fail treatment. There are no similar published data for the fluoroquinolones. However, given the high resistance rates in Europe, there should be sufficient cases before long to answer this question with fluoroquinolones.

Q. What is the status of the development of new guidelines for UTI? Can we expect any significant changes?
A. The IDSA is currently reviewing guidelines that were published in 1999. A panel of international experts has been recruited for this, so as to consider both European and U.S. perspectives on susceptibility trends and treatment strategies. Resistance patterns are very different in different parts of the world, and the guidelines will try to present principles for choosing empiric treatment regimens. For example, resistance rates even in uncomplicated cystitis cases are very high with SXT and fluoroquinolones in parts of Europe, and many feel that these drugs should not be used empirically. That is not the case in the U.S.

The IDSA expects to release the new guidelines in late 2010.

Q. What do you see as the most urgent research needs in this field at present?
A. There are a number of deficits in our current knowledge of UTI. We certainly need a better understanding of the adverse consequences of different antibiotics used for UTI (such as FQs and broad-spectrum cephalosporins)—in particular how they select for resistance in gram-negatives, MRSA, and ESBL-products, etc. The role of MRSA in uncomplicated cystitis and pyelonephritis is poorly understood and we still lack adequate knowledge of the role of food as a source of resistant uropathogens. Finally, there is an urgent need for resistance surveillance for outpatient UTI to help guide treatment.

REFERENCES
4Schuchardt AC, Leijonhufvud I, Ragnarsdottr B et al. (2005) J Infect Dis. 182:177
CA-MRSA persists on fomites

Community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) is a growing public health menace, often associated with skin-to-skin contact among populations like athletes and military recruits. But new research elucidates one of the dangers of this infection—that the organism can survive on some inanimate objects for weeks before being transmitted to a new human host.

Dr. Rishi Desai of Children’s Hospital Los Angeles led a study presented last fall at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in San Francisco, Calif. His team tested the transmission of CA-MRSA from nine different fomites starting immediately after they were contaminated with the bacteria and successively for the next ten weeks.

The researchers found that porous surfaces, such as bed sheets and shoulder pads, were able to transmit the infection for an average of 7-10 days following contamination. On non-porous surfaces like plastic and vinyl, however, CA-MRSA bacteria survived and were able to be transmitted to skin for more than five weeks, including over two months on some surfaces. What’s more, skin contact in tests for transmission was brief—only three seconds long. One surface, bar soap, showed no bacterial growth or transmission after the application of CA-MRSA.

The findings show that CA-MRSA can outlive healthcare-associated MRSA (HA-MRSA) on non-porous surfaces, and also suggest implications for the prevention and containment of CA-MRSA infections.

Reflections on H1N1

Genevra Pittman, APUA staff

H1N1 and lung damage

Medical examinations and statistical analysis have given experts insight into how pandemic flu differs from seasonal influenza in its physiological effects. Surveillance conducted by the U.S. Centers for Disease Control and Prevention (CDC) shows that 90 percent of fatalities associated with H1N1 occurred in people with conditions that predisposed them to serious disease, including obesity, heart disease, and asthma.

Autopsies also showed that swine flu victims had lung infections that often included damage to the alveoli. As a result, serious H1N1 virus infection often causes pneumonia. This pattern of lung infection is seen in victims of avian flu and was also common in fatalities associated with the 1918 Pandemic Influenza, but is absent in most cases of seasonal influenza, a virus that is normally confined to the upper respiratory tract.

H1N1 and vaccination

The emergence of H1N1 created pressure for the rapid development of a vaccine that could slow the spread of infection and protect the most vulnerable patient populations. While these populations are generally younger than those that are most vulnerable to seasonal flu, there is overlap: pregnant women, and people with underlying medical conditions are in the most commonly affected brackets for both viruses. To address prophylaxis in these populations, Roberto Gasparini of Genoa University and his colleagues conducted a study on the safety and efficacy of administering vaccines for seasonal and pandemic flu, concomitantly and three months apart.

The data were promising for vaccination against this and future pandemics: prior or concomitant administration of the plain seasonal or MF59-adjuvanted seasonal influenza vaccine did not interfere with responses to the pandemic influenza vaccine in healthy adults or elderly patients. Immunogenicity of the H1N1 vaccine was not affected, and no serious reactions were reported to the vaccines. Reporting of local, transient reactions was similar to former observations, and elderly patients that had previously been administered the MF59-adjuvanted seasonal influenza vaccine actually had a lower rate of local and systemic adverse effects from the pandemic influenza vaccine than those that had not been previously vaccinated.

Recommended Reading

Superbug: The Fatal Menace of MRSA
By Maryn McKenna
Simon & Schuster
March, 2010

Eating Animals
By Jonathan Safran Foer
Little, Brown & Company
November, 2009
Multidrug resistance among mastitis pathogens in India

Manvi Sharma, PhD, FICCI Research and Analysis Centre, New Delhi, India
Ravinder Kumar Malik, PhD, National Dairy Research Institute, Haryana, India

Antimicrobial susceptibility tests help guide the veterinarian in selecting the most appropriate antimicrobial agent for treatment of intra-mammary infections. As a result of indiscriminate use, many mastitic pathogens are multidrug-resistant. The appearance and spread of multidrug-resistant pathogenic bacteria have been recognized as a serious problem by the World Health Organization (WHO). Recent reports have also shown a marked and worrying increase of antibiotic resistance in the mastitis-causing pathogens because of non-rational and excessive antibiotic use. Yet with each passing decade, bacteria that defy multiple antibiotics have become increasingly common. This situation emphasizes the need and importance of periodic study of susceptibility surveillance in order to evaluate current resistance patterns and to modify treatment accordingly. Data were generated on the antibiograms of selected isolates from mastitic milk samples obtained from different villages and belonging to different breeds.

Antibiotic susceptibility of mastitis isolates

Prior to treatment with antibiotic therapy (generally penicillin or tetracycline), 30 mastitic cows from the National Dairy Research Institute’s Cattle Yard (n=17) and nearby villages (Manglora [3], Nagla [3], Pundrak [2], Ranwar [5]) were sampled by plating 0.05 ml of mastitic milk sample onto blood agar. Following incubation at 35-37°C for 24-48h, ~10 phenotypically distinct colonies were sub-cultured for gram stain and catalase tests and identified using standard biochemical assays (Bergey’s Manual of Systematic Bacteriology). They were then tested against those antibiotics that are effective for gram-positive and gram-negative mastitic isolates (see Fig. legend).

Testing was performed on Mueller Hinton agar plates by Kirby-Bauer disk diffusion using the following antibiotic disks: amoxicillin (Am) 30 µg, ampicillin (A) 10 µg, bacitracin (B) 10 units, chloramphenicol (C) 30 µg, ciprofloxacin (Cf) 5 µg, cloxacillin (Cx) 5 µg, erythromycin (E) 1.5 µg, gentamicin (G) 10 µg, kanamycin (K) 30 µg, lincomycin (L) 2 µg, nalidixic acid (Na) 30 µg, neomycin (N) 30 µg, novobiocin (Nv) 30 µg, oxytetracycline (Ot) 30 µg, penicillin G (P) 10 units, polymyxin B (Pb) 300 units, rifampicin® 5 µg, streptomycin (S) 10 µg, tetracycline (T) 30 µg, trimethoprim (Tr) 5 µg and vancomycin (Va) 30 µg. Zones of inhibition were categorized as resistant, sensitive or intermediate as per CLSI (formerly NCCLS) guidelines.

Multidrug resistance

Antibiograms of 150 gram-positive isolates tested against narrow- and broad-spectrum antibiotics revealed that 95% of the isolates were multidrug resistant. The highest frequencies of fully resistant gram-positives were found for penicillin G (88%), vancomycin (83%), streptomycin (70%), ampicillin (66%), and erythromycin (61%). Isolates showed no general susceptibility to any single drug tested. Gram-negatives were highly resistant to ampicillin (100%), novobiocin (89%), ciprofloxacin (83%) and amoxicillin (66%), but demonstrated susceptibility to polymyxin B (83%) and gentamicin (63%) (Fig 1).

Like the findings of other investigators, these studies showed resistance of the Staphylococcus strains to a number of antibiotics including penicillin, ampicillin, erythromycin, tetracycline, neomycin and methicillin. Costa et al reported that 29.5% of Escherichia coli isolates from mastitic milk samples were multidrug resistant. Most isolates were susceptible to cefoperazone, polymyxin B, colistin and gentamicin. In the present study, gram-negative isolates were most susceptible to polymyxin B and gentamicin. The highest frequency of drug resistance emerged against beta-lactam (penicillin, ampicillin) and tetracycline antibiotics, currently used more extensively and indiscriminately in the treatment of mastitis. Nazer and Tavakoli reported that 89 percent of their isolates showed beta-lactamase activity. The difference in the susceptibility pattern of the gram-positive and gram-negative isolates clearly indicated that type of microflora greatly influences the type of antibiotic to be effective in the treatment of mastitis.

Reasons for failure of antibiotic therapy

The failure of antibiotic therapy could be attributed to the lack of contact between bacteria and antibiotics and also to scar tissue formation. The reasons for ineffectiveness of antibiotic therapy are as follows:

Protection within leukocytes

Most antibiotics destroy organisms as they replicate. When the gland, leukocytes, or other enzyme activity affects bacterial growth, this can affect the ability of the antibiotic to kill the microorganisms.
Phagocytized bacteria are also protected from exposure to antibiotic—they may survive phagocytic killing and be released to re-establish an infection.

**Inactivation by milk and tissue proteins**

Milk components such as casein, lipids and other lipoproteins can inhibit antibiotic activity, e.g., casein will link to tetracycline due to calcium binding and inhibit its activity on microorganisms. The acidity of mammary secretion may also render the antibiotic ineffective.8

**Bacterial dormancy**

Metabolically inactive organisms or non-multiplying bacteria are not sensitive to most antibiotics. Bacterial growth is generally slowed down by conditions existing in secretions and an antibiotic may require rapid bacterial growth to be effective.8

**Development of bacterial L-forms**

Microorganisms exposed to some antibiotics that affect cell wall structure form cell-wall deficient L-forms (similar to mycoplasma) that are resistant to betalactam antibiotics.

**Encapsulated bacteria affect opsonization and phagocytosis**

Some antibiotics can affect the polymorphonuclear leucocytes and damage intra-cellular killing. Others are detrimental to phagocytosis.

**Conclusions**

In India villagers generally use tetracycline or penicillin for the treatment of mastitic cows. This study not only demonstrated high levels of resistance to these antibiotics, but multidrug resistance as well. Following the indiscriminate use of antibiotics as therapeutics for treatment of disease and as prophylactic agents or as growth promoters in the livestock, the microorganisms develop new mechanisms to survive, thereby leading to the failure of antibiotic therapy. This illustrates the need to either modify the antibiotics or to discover new antibacterial substances that are helpful in controlling pathogenic bacteria.

REFERENCES


**APUA Policy Actions**

**Triclosan danger tackled by APUA and Congressional Markey**

On January 25, APUA wrote to Rep. Edward Markey (D-MA), commending him for his efforts to communicate with the EPA and FDA on the dangers of triclosan, an antibacterial used in over 1000 household products. Markey asked both administrative authorities about their research into the safety of these products and their plans for regulation. APUA also spoke with Dr. Michal Freedhoff and Dr. Joseph Avenel on Markey’s staff about the risk of antibiotic resistance developing from triclosan use, and has shared Dr. Stuart Levy’s extensive work on the topic with Markey’s office.

The FDA acknowledged Markey’s letter and updated its website on April 8 to reflect questions about the safety of triclosan. The agency is reviewing the available evidence of both the benefits and risks of triclosan in consumer products, and announced that it will share its findings in the spring of 2011. APUA hopes to enhance its collaboration with Rep. Markey to continue influencing policy on this pressing public health issue.

**Antimicrobial resistance funding sought for CDC**

On March 16, APUA sent letters to Rep. David Obey (D-WI) and Senator Tom Harkin (D-IA), Chairs of the House and Senate Labor-HHS Appropriations Subcommittee, addressing cuts to the Centers for Disease Control and Prevention’s antimicrobial resistance budget. The budget was cut 50 percent this year, to $8.6 million. APUA explained the urgency of growing resistance and the toll it takes on patients and healthcare facilities and asked for an increase in the CDC’s antimicrobial resistance budget to $40 million for FY 2011.

**Limiting antibiotics for growth promotion**

APUA to convene EU Roundtable of Experts on antibiotics in agriculture

APUA, with the support of The Pew Charitable Trusts, is convening and co-hosting a Roundtable of Experts, which will be co-chaired by Dr. Herman Goossens and Dr. Christina Greko. The 15 delegates to the Roundtable represent expertise in human and veterinary medicine and microbiology from 10 countries. The European Medicines Agency (EMA), European Food Safety Agency (EFSA) Panel on Biological Hazards, FDA (U.S.), Pasteur Institute, Robert Koch Institute, and the World Health Organization (WHO) are among the organizations that will be represented at the meeting.

The purpose of the Roundtable will be to review the history and impact of both the EU and country-specific bans on the use of antibiotics for growth promotion in animal husbandry and the implications for the

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**Triclosan** is a bisphenol that is accumulating in the environment and is under scrutiny for safety issues. This and other antibacterial products leave behind a residue that possess the ability to promote the development of resistant bacteria. APUA instead recommends using soap and water, bleach, peroxides, or alcohol, which do not contribute to resistance.
United States. The fundamental scientific principles that support a ban on growth promotion are not well-understood or easily conveyed. Since its inception, the effect of the EU ban continues to be misrepresented and misunderstood in the U.S. and elsewhere. The goal of the discussion is to focus on the scientific evidence to address information gaps and misconceptions.

The meeting, to take place in Paris on May 28-29, will be part of APUA’s longstanding campaign to strengthen scientific evidence to control misuse of antibiotics in agriculture (see FAAIR Report at www.apua.org/edu/med/apua/Ecology/faair.html).

PAMTA
APUA continues to support legislative action to protect antibiotics, backing the Preservation of Antibiotics for Medical Treatment Act (PAMTA) that targets antibiotics used nontherapeutically in farm animals. The Keep Antibiotics Working coalition, Union of Concerned Scientists, APUA and 109 other organizations submitted written testimony to the House Committee on Appropriations suggesting funding for essential research relating to antibiotic resistance and the use of antibiotics for growth promotion in animal husbandry.

Rep. Slaughter hosts briefing on antibiotic resistance and PAMTA
On December 2, Rep. Louise Slaughter (D-NY) hosted a congressional briefing on “Antibiotic Resistance: A Multi-Billion Dollar Healthcare Crisis.” The briefing provided scientific evidence from a range of presenters in support of the Preservation of Antibiotics for Medical Treatment Act (PAMTA), sponsored by Rep. Slaughter. At the time of the meeting, PAMTA had 86 co-sponsors in the House and 10 in the Senate. It now has 106 in the House and 17 in the Senate.

Presenters at the briefing included:
Rep. Louise Slaughter (D-NY)—PAMTA sponsor
Dr. Robert Lawrence—Director, Center for a Livable Future, Baltimore, MD

Dr. Ramanan Laxminarayan—Senior Fellow, Center for Disease Dynamics, Economics, and Policy; Resources for the Future, Washington, D.C.

Dr. Lance Price—Director, Center for Metagenomics and Human Health; Translational Genomics Research Institute, Flagstaff, AZ

Dr. Michael Blackwell—Vice Chair, Pew Commission on Industrial Farm Animal Production and veterinarian, Knoxville, TN

Robert Martin—Executive Director, Pew Commission on Industrial Farm Animal Production, Washington, D.C.

Dr. Lawrence opened the briefing by explaining its purpose: presenting testimony to strengthen PAMTA. Rep. Slaughter described the excessive use of antibiotics in farm animal production: Seventy percent of antibiotics used in the U.S. are administered to farm animals for growth promotion and disease prevention—compensating for unsanitary conditions. The EU ban on growth-promoting antibiotics will cause U.S. trade to suffer because these nations can refuse to import meat raised with different standards. PAMTA would phase out the use of seven classes of antibiotics, all critically important for human health, from non-therapeutic use in animals.

Dr. Laxminarayan discussed antibiotics as a shared resource, different from other kinds of drugs in that each use, both necessary and unnecessary, contributes to resistance and impacts the global community. He presented data on the toll of MRSA, and on the cost of resistance: the U.S. has the third-highest MRSA rate in the world, and the number of MRSA infections tripled between 1995 and 2004; meanwhile, the annual cost of drug resistance may be anywhere from $378 million to $30 billion. Antibiotic use in farm animals creates a huge selection pressure towards resistance—therefore, banning the use of growth promoters in animals is an intuitive decision. We do not need to wait for more evidence linking use in animals to resistance in humans before implementing PAMTA.

Dr. Price explained how applying antibiotics to a mixed community of bacteria selects for the survival and multiplication of resistant ones. He argued that a farm system based on Concentrated Animal Feeding Operations (CAFOs), which requires farmers to use as many antibiotics as they do to prevent disease, is a broken system. Dr. Price also presented data from the EU and Canada that showed decreases in resistance in human infections after cessation of growth promoter use.

Dr. Blackwell offered a veterinary perspective, explaining his frustration that veterinarians cannot control antibiotic use in the food supply because so many drugs are available to lay people. In fact, pet owners have less access to antibiotics than farmers because food animals are classified as “unprocessed food.” Like Dr. Price, he made the case for improved animal husbandry practices. Better surveillance, monitoring and reporting to obtain drug use data and conduct risk assessments are needed, as well as more public financing of resistance research to reduce the bias and continued on next page
way to control the spread of resistance. They thought would be the most effective resistance in their communities, and what magnitude of the threat of antibiotic resistance pneumonia. They were asked about such as how they would treat a cold or resistance and their prescribing practices, conveyed on their thoughts on antibiotic resistance. The survey was also designed to determine whether employees, and sources of funding. Surveys have been collected from health facilities, pharmacies, and laboratories in urban and rural areas of Uganda and Zambia.

At health facilities, clinicians were surveyed on their thoughts on antibiotic resistance and their prescribing practices, such as how they would treat a cold or pneumonia. They were asked about the magnitude of the threat of antibiotic resistance in their communities, and what they thought would be the most effective way to control the spread of resistance.

Pharmacy workers, like doctors, were interviewed to see what medication they offer for different conditions and how they interact with patients. Pharmacies in Uganda and Zambia are allowed to sell antibiotics to customers without a prescription, and so could be an appropriate target for interventions. Protocols are still being examined to perform quality testing of antibiotics on the market to see if they meet standards for the type and amount of active drug ingredients.

As part of the project, laboratories were also surveyed to determine their capabilities to do antibiotic susceptibility testing, the number and workload of lab employees, and sources of funding. Surveys were also designed to determine whether labs had a system or network in place to report data on antibiotic resistance to local clinicians and how this information was generally communicated.

Immunization records collected by the World Health Organization are being examined for all districts in Uganda and Zambia to determine childhood immunization rates for respiratory and enteric diseases, two major causes of antibiotic use. These rates are being compared with mortality and infection rates throughout the countries. Finally, a literature review of the resistance situation in Uganda and Zambia is being completed, looking at a range of drug classes to determine what antibiotics are being used to treat different conditions.

The wide variety of data that will come from this project should help determine the types of interventions needed to control drug resistance in Uganda and Zambia at patient, provider, and laboratory levels. Implementation of more informed policy in these countries could provide a model for the prevention of drug resistance in other developing nations and lessen the global burden of resistance.

**APUA finds cost of resistance shifting from public to private payers**

By Miriam E. Tucker, Elsevier Global Medical News

This story appears courtesy of IMNG/Elsevier. It has been adapted from one that first appeared in print in the March 2010 issue of Hospitalist News. The studies cited were initiated and funded by APUA.

The overall cost burden of antimicrobial resistance—as high as $38 billion in one 2009 hospital estimate—has shifted dramatically from Medicare to private payers over the last decade.

Medicare still pays the majority of the costs for excess length of stay, increased use of more expensive drugs, and poorer health attributable to treatment-resistant infections. However, the rise in infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), which largely affects younger, healthier individuals, has meant that the overall cost per patient has declined but more is being borne by private HMOs and PPOs, Susan D. Foster, Ph.D., said at the 2010 Conference on Antimicrobial Resistance sponsored by the National Foundation for Infectious Diseases.

“There’s been a major shift in who’s actually paying. I don’t think the insurance companies are quite aware of this,” said Dr. Foster, director of public policy and education for the Alliance for the Prudent Use of Antibiotics in Boston, and professor of international health at Boston University.

Supported in part by an unrestricted educational grant from bioMérieux Inc., Dr. Foster analyzed data from three studies. The first study reviewed Massachusetts hospital discharge data from 2000 to 2007 to look for ICD9 “VO9” codes, which are specific for drug-resistant infections. Although these codes are complex and difficult to use and therefore represent a study limitation, they do allow for analysis of trends over time, she explained.

Overall, the number of hospital dis-
charges reporting antibiotic resistance in Massachusetts increased from 3,861 in 2000 to 11,218 in 2007. The inflation-adjusted total cost more than doubled over the 7 years, from $135 to $285 million. However, the length of stay (LOS) per patient for drug-resistant infections dropped by 4.5 days, and the cost per patient fell by nearly $10,000.

In contrast, the length of stay for drug-susceptible infections didn’t change during the study period (just under 5 days), while the cost per patient with susceptible infections rose only slightly.

The drop in LOS and cost per patient with drug-resistant infections is largely explained by the dramatic shift in patient age, particularly among 19- to 64-year-olds: In 2000, that age group accounted for 50% of drug-resistant infection discharges, whereas in 2007 the proportion had risen to 45.5%. At the same time, the 65- to 80-year-old group dropped from 38% to 25%. While the proportion of infections due to drug-resistant organisms rose in all age groups, the greatest rise was among working-age adults, Dr. Foster noted.

Not surprisingly, then, was the concurrent payer shift: Medicare’s proportion of the cost dropped from 73% in 2000 to 58% in 2007, while Medicaid’s rose from 6% to 15%. The proportion paid by “Other,” including private insurance, rose from 20.5% to 28%, she said.

Also not surprising—though perhaps not considered previously—were the declines in inpatient mortality due to drug-resistant infections (from 11% to 5%) and in patients being discharged to nursing homes (32% to 28%), with a concomitant increase in patients returning home from the hospital (33% to 48%).

The second study, from the Chicago Antimicrobial Resistance Project, analyzed discharge data at Cook County Hospital (currently the John H. Stroger, Jr. Hospital of Cook County) for a random sample of 1,391 high-risk (more than five ICD9 codes, excluding trauma, burn, or obstetric care) adult patients, of whom 13.5% (188) had an antibiotic-resistant infection (ARI). Societal costs for the study year 2000 were estimated at $10.7-$15 million, which extrapolated to $13.35 million in 2008 dollars (Clin. Infect. Dis. 2009;49:1175-84).

In that study, conducted by Dr. Rebecca Roberts and her associates, LOS was three times longer for the patients with ARIs (24 vs. 8 days) and mortality rates six times higher (18% vs. 3%). Total inpatient costs were $58,029, compared with $13,210 for non-ARI patients, even the daily cost was $517 greater for the ARI group, Dr. Foster noted.

The most common type of ARI was MRSA (43%), followed by vancomycin-resistant enterococci (VRE, 31%), Escherichia coli/Klebsiella species (16%), and multiple infections (6%). By cost, however, VRE accounted for the greatest proportion (36%), followed by MRSA (34%), and multiple infections (16%).

Dr. Foster and Dr. Roberts extrapolated the Chicago data to the entire United States: In 2000, there were 900,000 admissions with the same criteria the study used. Applying the costs found in that study gives $16.6-$26 billion in additional health care costs (the range reflects different types of infection adjustments). Updating the figure to 2009 costs using the Consumer Price Index gives an estimated $21-$34 billion, while using medical inflation rates boosts the figures to as high as $24-$38 billion, “a substantial burden,” she commented.

The third study, also from Dr. Foster’s group, was an Internet-based survey of more than 300 respondents recruited from MRSA chatrooms, listservs, and Google Adwords. Acknowledging the limitations of such surveys—particularly the bias toward those who are younger, healthier, and more likely to Internet access as well as to have strong opinions—she noted that there were “some heart-rending responses,” including one from a 52-year-old woman who felt completely isolated from friends and family, a teacher who was fired when her MRSA diagnosis became known, and parents who felt they had to send their children away to prevent transmission.

Respondents reported a mean out-of-pocket expenditure of $2,251, including copays for office visits, prescription drugs, and hospital stays. Nearly 70% reported having private insurance (HMO or PPO), and 14% said they were uninsured, which approximately reflects the national average, Dr. Foster noted.

“Individuals and households affected by drug resistance bear a large uncompensated burden in terms of out-of-pocket expenses and lost wages,” she concluded.

APUA bench, field and public health skills propel international biosecurity project

APUA’s International Surveillance of Reservoirs of Antibiotic Resistance (ISRAR) project has entered its third year of collaboration with the U.S. NBACC’s National Biological Threat Characterization Center (NBACC). A pilot phase, organized to establish collaborative contracts with APUA-Chapter countries, has succeeded in collecting, identifying, and performing susceptibility testing on over 700 isolates to date. Recently Dr. Anibal Sosa visited the ICCDRB Bangladesh where he met with APUA chapter leaders to expand the collection into that country.

The data from the ISRAR isolate collection, which represents six different countries and includes species of E. coli, Streptococcus, Staphylococcus, Aeromonas, Pseudomonas, Acinetobacter, Salmonella and Stenotrophomonas have been incorporated into APUA’s Reservoirs of Antibiotic Resistance (ROAR) isolate database. The ROAR website (see ROARproject.org), which consists of an isolate database and an annotated library, is currently undergoing reconstruction. The isolate database is being modified to permit the entry of genetic data anticipated from this study. The literature library is actively being updated and now contains over 1,100 entries on antimicrobial resistance

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in commensals.

APUA invites investigators to submit their isolate-based phenotypic and genotypic data to this online web resource. For further details, please contact bonnie.marshall@tufts.edu.

APUA contributes to deliberations on resistance problem

Recognizing the importance of antimicrobial resistance, the Wellcome Trust sponsored a meeting in Cape Town, South Africa on February 11-13, 2010. APUA was a featured presenter at the meeting.

APUA Board Member Philip Walson, M.D. presented “The Prudent Use of Antibiotics” on behalf of Dr. Stuart Levy during the first session. Dr. Anibal Sosa discussed policy issues learned from the APUA chapters, especially those in Africa, in a session on Case Studies from networks, sentinel labs, and developing country researchers. In addition, a number of APUA Chapter leaders gave presentations, including Dr. Otto Cars from ReAct.

The conference brought together researchers, funders and policy makers from around the globe and marked the emergence of antimicrobial resistance as a major focus of the Wellcome Trust’s planning activities. The presentations were followed by lively panel discussions and then productive break-out sessions which generated specific recommendations for funding and program focus in this area by the Trust. Details and slides from the presentation are available on-line through the Wellcome Trust.

From audience comments it was evident that the work of APUA and its chapters is at the forefront of what is needed to control resistance, but also that these activities have received insufficient recognition by the global infectious disease and public health communities.

The meeting generated a number of opportunities for APUA and its chapters in terms of funding, education and public policy. It is hoped that the meeting heralds the entry of another major player and funder into the area of antimicrobial resistance and that many of the suggestions made will become realities through collaboration between APUA, its chapters and all of the researchers and organizations represented at the meeting.

GARP holds inaugural meeting

The Global Antibiotic Resistance Partnership held its inaugural meeting of GARP-South Africa in Stellenbosch, South Africa on February 8-9, 2010. The University of Witwatersrand and Resources for the Future (RFF) convened 30-40 experts from a variety of disciplines and sectors in the first meeting, followed by a one-day meeting on global strategies for antibiotic resistance surveillance.

GARP is a five-country (South Africa, China, India, Kenya, Vietnam) project conducted by RFF and funded by the Bill & Melinda Gates Foundation to establish a framework for policy action to moderate the spread of antibiotic resistance. Presenters, including APUA’s Dr. Anibal Sosa, shared their understanding of what is known about antibiotic resistance in South Africa, antibiotic use practices, levels and types of antibiotic resistance, and the larger social system in which this all fits. The meeting outcome will include a blueprint for continuing work to develop policy alternatives that will brighten the outlook for continued antibiotic efficacy.

The International Congress on Infectious Diseases (ICID)

APUA Executive Director Kathleen Young attended the recent ICID Congress held in Miami, Mar 9-12, 2010. Below are relevant excerpts from the program abstracts.

Pneumococcal infection and colonization in children and its impact on pneumococcal disease in adults by K. Klugman, Emory University, Atlanta, GA, USA

The introduction of the 7-valent pneumococcal conjugate vaccine in children in the U.S. in 2000 has been followed by evidence not only of direct protection from invasive pneumococcal disease, meningitis and pneumonia in immunized infants, but also by a reduction in serotype-specific infections in adults, particularly the elderly. Replacement disease has occurred, particularly among Alaska natives, HIV-infected adults, and adults with underlying chronic diseases. The replacing serotypes are less invasive and therefore the replacement has not eliminated the benefits of vaccination in most groups. Antibiotic resistant infections have diminished, but resistance is emerging among important serotypes such as 19A and G.

Lessons from 1918 and the current H1N1 pandemic on the role of bacterial infections during pandemic influenza by K. Klugman, Emory University, Atlanta, GA, USA

The current pandemic of H1N1 influenza has features reminiscent of 1918 influencing infections and excess morbidity in young adults. The impact in terms of mortality, however, has been far less severe. This is due, in part, to lesser virulence of the virus, but also to the introduction of antibiotics, and most recently, to the introduction of conjugate pneumococcal vaccines in some countries that have reduced the morbidity of influenza-associated pneumonia. The great majority of individuals hospitalized with H1N1 pneumonia have received antibiotics, and it is probable that widespread availability of antibiotics has contributed to the reduction in mortality associated with this pandemic, by reducing bacterial superinfections in susceptible individuals.

Global Burden of Neonatal Sepsis by E.K. Mulholland, E. Fenn, and A. Zaidi, London School of Hygiene and Tropical Medicine, London, U.K., Menzies School of Health Research, Darwin, Australia, Aga Khan University, Karachi, Pakistan

Globally, neonatal mortality constitutes about 40% of child deaths. Neonatal mortality rates are being systematically underestimated, especially in the poorest, most marginalized communities. Data on
The causes of neonatal deaths in the community are seriously inadequate, as deaths occur outside the health service, and post mortem questionnaires are very difficult to interpret in this age group. From a review of 52 community-based studies published since 1990, between 8% and 80% of all neonatal deaths in different regions of the developing world are reported as being due to infectious causes.

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APUA-Indonesia

The PhD thesis of Usman Hadi, M.D., an Executive Committee member of APUA-Indonesia, provides the first look into the quantity and quality of antibiotic use in Indonesia. The 2009 report, Antibiotic usage and antimicrobial resistance in Indonesia, (2009, Airlangga University Press) suggests common inappropriate usage of antibiotics and high levels of resistant bacteria in patients following hospital stays. A review of medical records from two hospitals showed that almost 60% of antibiotic prescriptions qualified as unjustified or inappropriate. In addition, one out of five antibiotic samples acquired from a variety of sources was found to be substandard, another factor that contributes to poor outcomes and increased resistance in developing nations.

A series of interventions aimed at implementing guidelines for antibiotic use showed mixed success: there was improvement in the number of patients treated with antibiotics, both immediately upon hospital admission and in the five days following, but there was no change in the percentage of correct prescriptions given for antibiotics. Dr. Hadi suggests efficiency testing for a range of intervention methods, both with doctors to prevent inappropriate diagnoses and with patients to promote better usage. He also recommends improvements in the development and implementation of infection control guidelines and enhanced communication and collaboration between clinicians and microbiologists.

On March 12, 2010, APUA-Cuba leadership attended a workshop on sepsis in La Havana, Cuba, which was co-sponsored by APUA and the Pan American Society of Infectious Diseases. Left to right - Dr. Sollet (head of the National Group of Internal Medicine), Dr. Morejon (APUA-Cuba President), Dr. Cordoves (University Director), Dr. Peña (Director of CDF), Dr. Delgado (President of the Cuban Pharmacology Society), Dr. Dotres (former Minister of Health), and Dr. Escobedo (Cuba’s API representative).

APUA-Mexico

APUA-Mexico recently collaborated on the Mexican National Institute of Public Health’s publication, Regulación y promoción para el uso adecuado de antibióticos en México, or Regulation and promotion of the appropriate use of antibiotics in Mexico. The document laid out a set of priorities for improving the use of antibiotics and containing antibiotic resistance, in line with recommendations from the World Health Organization that each member country undertake such a strategy. Implementation of the regulations will be discussed by Congress. The actions identified as priorities include the creation of a multidisciplinary advisory committee on the use of antibiotics and antibiotic resistance, regulation of antibiotic use in agriculture, surveillance of antibiotic use and resistance patterns, and enforcement of legislation on prescriptions and quality requirements of antibiotics marketed in Mexico.

APUA Leadership Awardees*

2009 Dr. Martin Blaser, Dr. Neil Fishman (Infectious Diseases Society of America)
2008 Dr. Inge C. Gyssens, Prof. Jos W. M. van der Meer, Prof. Henri S. Verbrugh, Prof. John E. Degener, Prof. Christina M. Vandenbroucke-Grauls, Prof. Peter J. M. van der Broek (Dutch Working Party on Antibiotic Policy)
2007 Dr. Wasif Ali Khan, Sabeena Ahmed (International Centre for Diarrheal Disease Research, Bangladesh)
2006 Dr. Anna Lönroth, Dr. Herman Goosens (European Research Commission Program; University Hospital, Antwerp)
2005 Dr. Richard Besser (U.S. Centers for Disease Control & Prevention)
2004 Dr. Gabriel Schmunis (The Pan American Health Organization)
2003 Dr. Frank M. Aarestrup, Dr. Henrik C. Wegener, Robert L. Langer (Danish Veterinary Institute; McDonald’s Corporation)
2002 Dr. David Bell, Dr. Marissa Miller, Dr. Murray Lumpkin (U.S. Centers for Disease Control & Prevention; National Institute of Allergy & Infectious Diseases; U.S. Food & Drug Administration)
2001 Dr. Rosamund Williams (World Health Organization)

* see 2010 Leadership Award ceremony invitation on p. 1
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 63 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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- Costa Rica
- Cuba
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- El Salvador
- Guatemala
- Honduras
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- Nicaragua
- Panama
- Paraguay
- Peru
- Uruguay
- Venezuela

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- Namibia
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- South Africa
- Tanzania
- The Gambia
- Uganda
- Zambia

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